Title
Understanding the Molecular Basis of Trace Amine-Associated Receptor 1 Activation by Thyronamines and Related Analogs

Author
Tan, Edwin Saavedra

Publication Date
2007-12-21

Peer reviewed|Thesis/dissertation

Understanding the Molecular Basis of Trace Amine-Associated Receptor 1 Activation by Thyronamines and Related Analogs

by

Edwin Saavedra Tan

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry and Chemical Biology

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

UMI Number: 3289321

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

Acknowledgements

I dedicate this dissertation to my parents, Ismael and Thelma, and my siblings, Irene, Samuel, Annabel and Richard for their unwavering love, support, and encouragement. My parents have taught me the value of a good education and work ethic, being resourceful, and performing to the best of my abilities. They have been by my side throughout my life and have helped me through the tough times and celebrate accomplishments. I am thankful for the sacrifices they have made to give me and my siblings the opportunity to pursue a career that we are passionate about. I want to thank my brothers and sisters for being available when I wanted to get away from work and for listening to me when I needed to talk.

I would like to thank my research advisor, Thomas Scanlan, for being an excellent mentor. His advice, guidance, and expertise have been invaluable throughout my graduate career. I have cherished the opportunity to conduct research in his lab and greatly appreciate the creative freedom he has provided in allowing me to dictate the direction of my research project. The knowledge, skills, and experiences I have gained in Tom's lab will serve me well in my academic endeavors beyond graduate school.

I have enjoyed working with and getting to know all past and present members of the Scanlan lab. They have provided a wonderful work environment and have been a great source of advice, entertainment, and interesting conversations. I am especially grateful to Ngoc-Ha Nguyen, Matthew Hart, Benjamin Lin, Sandra Tobias, Dmitry Kadnikov, and Motonori Miyakawa. Ha was very patient and taught me many basic synthetic chemistry techniques during my rotation. Matt helped me get started with my

project and was a great resource for chemistry related questions. I learned a great deal of biology and cell culture from observing and interacting with Ben. During the four years the lab was at Mission Bay in San Francisco, I became very good friends with Sandra and Dmitry. My daily interactions with both of them were rewarding and have made me less shy become more social. I have been fortunate to work with Motonori Miyakawa, an exceptional chemist who was a visiting scientist in the lab for two years. Motonori synthesized and tested compounds that were included in the Journal of Medicinal Chemistry article I published in 2007 and chapter 2 of this thesis.

I thank Eli Groban from Matthew Jacobson's lab for his enthusiasm and interest in building a homology model of rat $TAAR_1$. The model he built gave me a visual representation of the target receptor and provided insights into the appropriate groups that should be explored in my scaffolds. I am also grateful to James Bunzow from David Grandy's group at OHSU for generating the rat and mouse $TAAR_1$ mutants I needed to experimentally test the specificity issues of $TAAR_1$ delineated in Chapter 6 of this thesis. David himself has also been helpful in addressing biology questions I had about TAARs and GPCRs.

I have to give thanks to Julie Zorn and John Naylor for performing experiments. Julie explored a revised synthetic route to ET-69 and scaled up its the synthesis during her rotation in the lab. John has been testing compounds on the $TAAR_1$ mutants on my behalf. I also thank Warren Wood for advice on the informal process of applying for postdoctoral positions.

I owe a debt of gratitude to Christine Olson, the CCB program coordinator, for her support and encouragement. Chris has always been there to ensure that I have

fulfilled requirements and am progressing through program in a timely manner. Additionally, I would never have had the opportunity to study at UCSF if Chris had not contacted me about my incomplete application several days before the admissions committee was going to evaluate the CCB graduate program applicants.

I would like to thank my orals and thesis committee members Mark von Zastrow, David Julius, Kevan Shokat and R. Kip Guy for critically evaluating my project. They asked challenging questions during my oral examination and offered insightful suggestions and different perspectives to the project during thesis committee meetings.

Lastly, I thank the NIH and Ikaria, Inc for providing grants to support this research.

Chapter 2 is adapted with the permission of the American Chemical Society from Tan, E.; Miyakawa, M.; Bunzow, J.; Grandy, D.; Scanlan, T., Exploring the structure-activity relationship of the ethylamine portion of 3-iodothyronamine for rat and mouse trace amine-associated receptor 1. *J. Med. Chem.* **2007,** 50, (12), 2787-2798.

Abstract

Understanding the Molecular Basis of Trace Amine-Associated Receptor 1 Activation by Thyronamines and Related Analogs

Edwin Saavedra Tan

Thyroid hormone is known to increase metabolism, core body temperature, and cardiac performance by regulating gene expression through the thyroid hormone nuclear receptors. These transcriptional effects have a slow onset and occur within hours to days. 3-Iodothyronamine (**T_1AM**) is an endogenous, decarboxylated, and deiodinated metabolite of the thyroid hormone thyroxine that is found in the brain, heart, liver, and blood. When administered to mice intraperitoneally, **T_1AM** rapidly induces hypothermia, anergia, and bradycardia; effects of which are opposite those observed with hyperthyroidism. *In vitro*, **T_1AM** potently activates the orphan G-protein coupled receptor (GPCR) known as the trace amine-associated receptor 1 ($TAAR_1$), inhibits neurotransmitter reuptake by the dopamine (DAT) and norepinephrine transporter (NET), and inhibits vesicular packaging by the vesicular monoamine transporter 2 (VMAT2). To understand the role of $TAAR_1$ in mediating the effects of **T_1AM**, we sought to develop small molecules that regulate the activity of $TAAR_1$.

Structure–activity relationship studies on the ethylamine portion of **T_1AM** showed that $TAAR_1$ can tolerate prominent structural features found in existing GPCR agonists and antagonists. A closer investigation of the ligand-receptor interactions of existing catecholamine receptor drugs revealed a relationship between the functional

properties of the ligand and how it interacts with the rotamer toggle switch residues of the receptor. Allowing the rotamer switch residues to toggle to their active conformation was associated with agonism while interfering with this conformational transition resulted in antagonism.

The rotamer toggle switch model of aminergic GPCR activation was a useful guideline in the design and synthesis of rat $TAAR_1$ agonists and antagonists. It provided an insightful approach to understanding the molecular basis of rat $TAAR_1$ activation by **T_1AM** and related analogs, and guided the successful development of rat $TAAR_1$ superagonists **ET-36**, **ET-64**, and **ET-69** and lead antagonists **ET-78**, **ET-92**, and **ET-93**.

Table of Contents

List of Figures xii

List of Schemes xiv

List of Tables xvi

Chapter 1: Introduction to Thyroid Hormones and Thyronamines

1.1 Biosynthesis and Metabolism of Thyroid Hormone 2

1.2 Physiological Effects of Thyroid Hormone 4

1.3 Molecular Basis of Thyroid Hormone Action 6

1.4 Thyronamines and the Trace Amine-Associated Receptor 1 8

1.5 References 12

Chapter 2: Structure–Activity Relationship of T_1AM for the Rat and Mouse Trace Amine-Associated Receptor 1

2.1 Previous T_1AM Structure–Activity Relationship 16

2.2 SAR of the Ethylamine Portion of T_1AM 18

2.2.1 Synthesis 18

2.2.2 Receptor Activation 29

2.2.2.1 Functional Assay Format 29

2.2.2.2 Activity of Synthetic Compounds 33

2.3 Discussion 41

2.4 Conclusion 44

2.5 References ……..….. 45

Chapter 3: Insights into Aminergic G-Protein Coupled Receptor Drug Design

3.1 Molecular Mechanism of GPCR Activation …… 49

3.2 Insights into β_2-Adrenergic and Dopamine 1 Receptor Activation ……. 50

3.3 Insights into Dopamine 1 and Dopamine 2 Receptor Antagonism …….. 55

3.4 Conclusion …… 59

3.5 References …… 60

Chapter 4: Agonist Design Principles

4.1 Development of $rTAAR_1$ Superagonists …….. 64

4.1.1 SAR of ET-13 …… 64

4.1.1.1 Synthesis of ET-13 Analogs ……. 68

4.1.1.2 Receptor Activation of ET-13 Analogs …… 71

4.1.2 SAR of ET-36 …… 72

4.1.2.1 Synthesis of ET-36 Analogs ……. 72

4.1.2.2 Receptor Activation of ET-36 Analogs …… 75

4.2 Discussion …… 76

4.3 Conclusion …… 79

4.4 References …… 81

Chapter 5: Antagonist Design Principles

5.1 Development of $rTAAR_1$ Lead Antagonist ……... 86

5.1.1 Synthesis of ET-13 Position 2 Analogs ……. 87

5.1.2 Receptor Activation of ET-13 Position 2 Analogs …… 88

5.1.3 Synthesis of ET-14 Position 2 Analogs ……. 92

5.1.4 Receptor Activation of ET-14 Position 2 Analogs …… 98

5.2 SAR of rTAAR$_1$ Lead Antagonist …… 99

5.2.1 Synthesis of ET-78 Analogs ……..….. 101

5.2.2 Receptor Activation of ET-78 Analogs ……..…. 104

5.3 Discussion ……..… 105

5.4 Conclusion …… 108

5.5 References …… 110

Chapter 6: Exploring the Specificity Determinant Residues of TAAR$_1$

6.1 Mouse TAAR$_1$ Binding Site ……. 114

6.2 Selectivity of ET-13 and ET-14 for rTAAR$_1$ …… 116

6.3 Potency Disparities of Thyronamines in Rat and Mouse TAAR$_1$ ……..…… 120

6.4 Binding Modes of Tyramine and T$_1$AM in TAAR$_1$ …….. 122

6.5 References ……. 125

Appendix A: Experimental Procedures …… 127

A.1 Chemistry ……..…… 128

A.1.1 General Methods ……..…. 128

A.1.2 General Synthetic Procedures ……..…. 129

A.1.3 Synthesis ……..…. 138

A.1.3.1 Chapter 2 Compounds …….. 138

A.1.3.2 Chapter 4 Compounds …….. 174

A.1.3.3 Chapter 5 Compounds ……. 201

A.1.3.4 Appendix A Compounds …….. 251

A.2 $TAAR_1$ *in vitro* cAMP Functional Assay ……. 261

A.2.1 Agonist Activity Assay …… 261

A.2.2 Antagonist Activity Assay ……...…. 262

A.2.3 Cytotoxicity Assay …… 262

Appendix B: ^{1}H and ^{13}C NMR Spectra of Final Compounds …… 264

Appendix C: Final Compounds Inventory and Summary of $TAAR_1$ Activity …. 369

C.1 Final Compounds Inventory ……. 370

C.2 Summary of $TAAR_1$ Activity ……...… 387

Appendix D: Sequence Alignment of Aminergic GPCRs ……... 398

List of Figures

Figure 1-1 The hypothalamic-pituitary-thyroid axis 2

Figure 1-2 Biosynthesis of thyroid hormone 3

Figure 1-3 Thyroid hormone metabolism by enzymatic deiodination 5

Figure 1-4 Thyroid hormone metabolism by conjugation or alanine side chain metabolism 6

Figure 1-5 Thyroid hormone nuclear receptor (TR) subtypes and isoforms 7

Figure 1-6 TR-mediated gene transcription 8

Figure 1-7 Biosynthesis of biogenic amines 9

Figure 2-1 Structures of endogenous trace amines, psychoactive phenethylamines, ergot alkaloids, and biogenic amine GPCR drugs 16

Figure 2-2 Structures of β-adrenergic receptor (propranolol) and dopamine Receptor (sulpiride and SCH 233990) antagonists used as a model for $TAAR_1$ ligand design 19

Figure 2-3 Functional activity assay 31

Figure 2-4 Representative dose-response curves of agonists in $rTAAR_1$ and $mTAAR_1$ stably expressed in HEK293 cells 32

Figure 2-5 Antagonist activity assay results of non-agonists on $rTAAR_1$ and $mTAAR_1$ 36

Figure 3-1 Schematic representations of GPCRs and the rotamer toggle switch model of aminergic GPCR activation 51

Figure 3-2 Sequence alignment of TM5 and TM6 of aminergic GPCRs 52

Figure 3-3 Binding orientations of catecholamines to their receptors 53

Figure 3-4 Proposed pharmacophore model and map of β_2AR agonists 54

Figure 3-5 Proposed pharmacophore model and map of D_1R agonists 55

Figure 3-6 Proposed pharmacophore model and map of D_1R antagonists 57

Figure 3-7 Proposed pharmacophore model and map of D_2R antagonists 58

Figure 4-1 Proposed pharmacophore model and map of rTAAR$_1$ agonists 65

Figure 4-2 Representative dose-response curves of agonists for rTAAR$_1$ stably expressed in HEK293 cells 72

Figure 5-1 Structure of ET-13 and its proposed binding mode in rTAAR$_1$ 87

Figure 5-2 Conformers of ET-13 position 2 analogs 92

Figure 5-3 Representative dose-response curves of antagonists for rTAAR$_1$ stably expressed in HEK293 cells 100

Figure 5-4 ET-78 SAR and proposed binding mode in rTAAR$_1$ 107

Figure 6-1 Sequence comparison of rat and mouse TAAR$_1$ 115

Figure 6-2 Binding site of rTAAR$_1$ and mTAAR$_1$ 115

List of Schemes

Scheme 2-1	Synthesis of Aryloxypropanolamines (ET-1, ET-6, ET-11, and ET-12)	20
Scheme 2-2	Synthesis of Benzamidoalkylamines (ET-2–ET-5 and ET-7–ET-10)	21
Scheme 2-3	Synthesis of Orthopramide-alkylamines (ET-22–ET-30)	22
Scheme 2-4	Synthesis of β-Phenylphenoxyphenethylamines (ET-13 and ET-14)	23
Scheme 2-5	Synthesis of Tetrahydrobenzazepines (ET-15–ET-20)	24
Scheme 2-6	Synthesis of β-Substituted Phenoxyphenethylamines (MM-7, MM-10, and MM-13–MM-15)	25
Scheme 2-7	Synthesis of Phenoxynaphethylamine (ET-21)	26
Scheme 2-8	Synthesis of Naphethylamines (1-NEA, 4-OH-NEA, and ET-102)	28
Scheme 2-9	Synthesis of β-Phenylnaphethylamines (ET-31–ET-33)	29
Scheme 4-1	Synthesis of ET-34–ET-38 and ET-47	66
Scheme 4-2	Synthesis of ET-65–ET-67	67
Scheme 4-3	Synthesis of ET-50 and ET-71	68
Scheme 4-4	Synthesis of ET-64	73
Scheme 4-5	Synthesis of ET-68–ET-70	74
Scheme 5-1	Synthesis of ET-51	90
Scheme 5-2	Synthesis of ET-52–ET-63	91
Scheme 5-3	Synthesis of ET-72 and ET-79	93
Scheme 5-4	Synthesis of ET-73–ET-78, ET-80–ET-83, ET-90, and ET-95–ET-98)	94
Scheme 5-5	Synthesis of ET-84–ET-86 and ET-99–ET-101	96
Scheme 5-6	Synthesis of ET-87 and ET-88	100

Scheme 5-7 Synthesis of ET-89 102

Scheme 5-8 Synthesis of ET-90 102

Scheme 5-9 Synthesis of ET-91–ET-94 103

Scheme A-1 Synthesis of ET-39–ET-45 251

Scheme A-2 Synthesis of ET-46 257

Scheme A-3 Synthesis of ET-48 and ET-49 259

List of Tables

Table 2-1 Structure–activity relationship of T_1AM 17

Table 2-2 Activity of T_1AM and PTA on $rTAAR_1$ and $mTAAR_1$ 32

Table 2-3 Activity of Aryloxypropanolamines ET-1, ET-6, ET-11, and ET-12 on $rTAAR_1$ and $mTAAR_1$ 33

Table 2-4 Activity of Benzamidoalkylamines ET-2–ET-5 and ET-7–ET-10 on $rTAAR_1$ and $mTAAR_1$ 35

Table 2-5 Activity of Orthopramide-alkylamines ET-22–ET-30 on $rTAAR_1$ and $mTAAR_1$ 37

Table 2-6 Activity of β-phenylphenoxyphenethylamines ET-13 and ET-14 on $rTAAR_1$ and $mTAAR_1$ 37

Table 2-7 Activity of tetrahydrobenzazepines ET-15–ET-20 on $rTAAR_1$ and $mTAAR_1$ 38

Table 2-8 Activity of β-substituted phenoxyphenethylamines MM-7, MM-10, and MM-13–MM-15 on $rTAAR_1$ and $mTAAR_1$ 39

Table 2-9 Activity of naphethylamines 1-NEA, 4-OH-NEA, ET-21, ET-102, and ET-31–ET-33 on $rTAAR_1$ and $mTAAR_1$ 40

Table 4-1 Activity of ET-13 analogs on $rTAAR_1$ 70

Table 4-2 Activity of ET-36 analogs on $rTAAR_1$ 76

Table 4-3 Activity of phenethylamine based compounds on $rTAAR_1$ 78

Table 4-4 Activity of naphethylamine based compounds on $rTAAR_1$ 79

Table 5-1 Activity of ET-13 position 2 analogs on $rTAAR_1$ 89

Table 5-2 Activity of ET-14 position 2 analogs on $rTAAR_1$ 97

Table 5-3 Activity of β-phenyl and outer ring analogs of ET-78 and ET-79 on $rTAAR_1$ 104

Table 5-4 Activity of ET-78 analogs on $rTAAR_1$ 105

Table 6-1 Activity of ET-13 analogs on $mTAAR_1$ 116

Table 6-2 Activity of ET-36 analogs on $mTAAR_1$ 117

Table 6-3 Activity of ET-13 position 2 analogs on $mTAAR_1$ 118

Table 6-4 Activity of ET-14 position 2 analogs on $mTAAR_1$ 119

Table 6-5 Activity of β-phenyl and outer ring analogs of ET-78 and ET-79 on $mTAAR_1$ 120

Table 6-6 Activity of ET-78 analogs on $mTAAR_1$ 120

Table 6-7 Activity of thyronamines on $rTAAR_1$ and $mTAAR_1$ 121

Table C1 Agonist activity of T_1AM, PTA, Tyramine, and PEA on $rTAAR_1$ and $mTAAR_1$ 387

Table C2 Agonist activity of Aryloxypropanolamines on $rTAAR_1$ and $mTAAR_1$ 387

Table C3 Agonist activity of Benzamidoalkylamines on $rTAAR_1$ and $mTAAR_1$ 388

Table C4 Agonist activity of Tetrahydrobenzazepines on $rTAAR_1$ and $mTAAR_1$ 388

Table C5 Agonist activity of β-Phenylphenoxyphenethylamines on $rTAAR_1$ and $mTAAR_1$ 389

Table C6 Agonist activity of Naphethylamines on $rTAAR_1$ and $mTAAR_1$ 390

Table C7 Agonist activity of Orthopramide-alkylamines on $rTAAR_1$ and $mTAAR_1$ 390

Table C8 Agonist activity of ET-39–ET-46, ET-48 and ET-49 on $rTAAR_1$ and $mTAAR_1$ 391

Table C9 Agonist activity of ET-50 and ET-71 on $rTAAR_1$ and $mTAAR_1$ 392

Table C10 Agonist activity of ET-13 position 2 analogs on $rTAAR_1$ and $mTAAR_1$ 392

Table C11 Agonist activity of ET-14 position 2 analogs on $rTAAR_1$ and $mTAAR_1$ 393

Table C12 Agonist activity of β-phenyl and outer ring analogs of ET-78 and ET-79 on $rTAAR_1$ and $mTAAR_1$ 394

Table C13 Agonist activity of ET-78 analogs on $rTAAR_1$ and $mTAAR_1$ 394

Table C14 Antagonist activity of ET-13 position 2 analogs on $rTAAR_1$ and $mTAAR_1$ 395

Table C15 Antagonist activity of ET-33 and ET-89 on $rTAAR_1$ and $mTAAR_1$ 395

Table C16 Antagonist activity of ET-14 position 2 analogs on $rTAAR_1$ and $mTAAR_1$ 396

Table C17 Antagonist activity of ET-78 analogs on $rTAAR_1$ and $mTAAR_1$ 397

Chapter 1

Introduction to

Thyroid Hormones and Thyronamines

The thyroid gland is a bilobular organ located from the base of the pharynx to the upper part of the trachea. It absorbs dietary iodide, and synthesizes and secretes 3,5,3',5'-*L*-tetraiodothyronine (thyroxine, $\mathbf{T_4}$) and small amounts of 3,5,3'-*L*-triiodothyronine ($\mathbf{T_3}$) when stimulated by the thyroid stimulating hormone (TSH), a glycoprotein synthesized in the anterior pituitary **(Fig. 1-1)**.[1] Serum levels of $\mathbf{T_4}$ and $\mathbf{T_3}$ feedback into the hypothalamic-pituitary axis to regulate the levels of TSH and thyroid releasing hormone (TRH). TRH is a tripeptide synthesized in the hypothalamus that can control the synthesis and release of TSH.

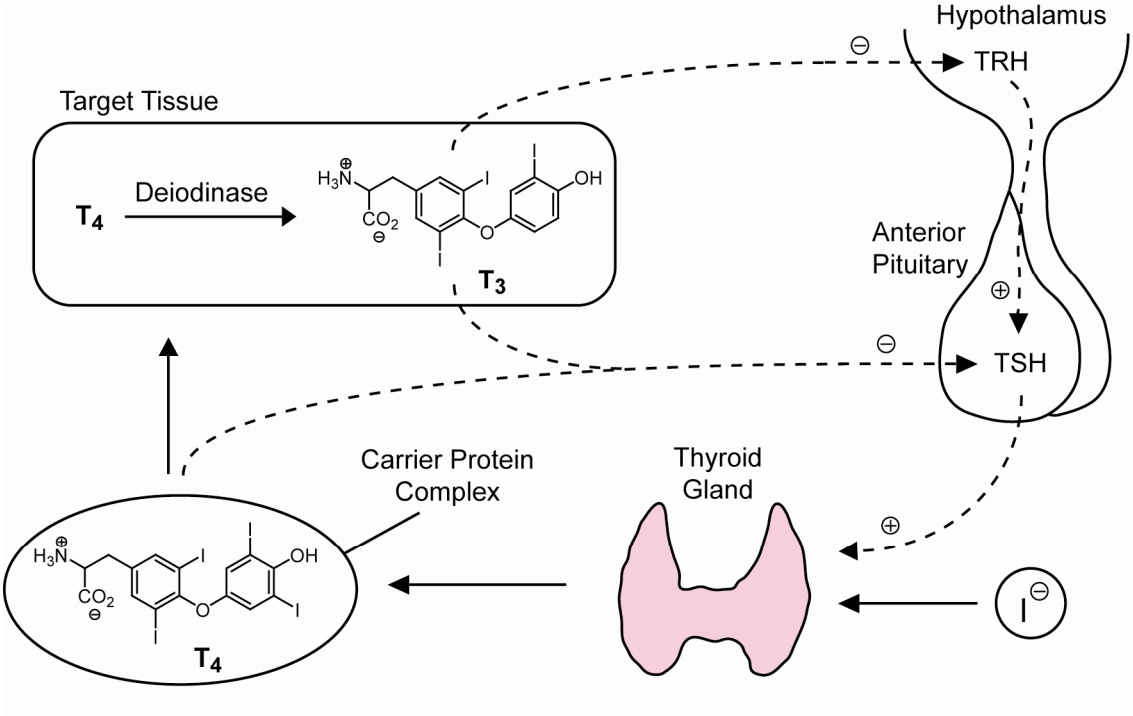


Figure 1-1. The hypothalamic-pituitary-thyroid axis. Adapted from The Thyroid Gland in *Basic and Clinical Endocrinology*, 7th Edition © 2007, Ed. D.G. Gardner and D. Shoback; Lange Medical Books/McGraw-Hill, New York.

1.1 Biosynthesis and Metabolism of Thyroid Hormone

$\mathbf{T_4}$ and $\mathbf{T_3}$ are biosynthesized from tyrosine residues on the glycoprotein thyroglobulin (Tg) by the enzyme thyroperoxidase (TPO).[2] TPO catalyzes (1) the

oxidation of iodide ions (I^-) to iodine (I_2) by hydrogen peroxide, (2) the iodination of tyrosine residues, and (3) the coupling of iodinated tyrosines to form thyroglobulin bound **T_4** and **T_3** (**Fig. 1-2**). TSH stimulation then leads to proteolysis of thyroglobulin and secretion of **T_4** and **T_3** from the follicular cells of the thyroid gland. The secreted thyroid hormones are bound to transport proteins (e.g. thyroxine binding globulin, thyroxine binding prealbumin, and albumin) and delivered to their target tissues via the circulatory system.

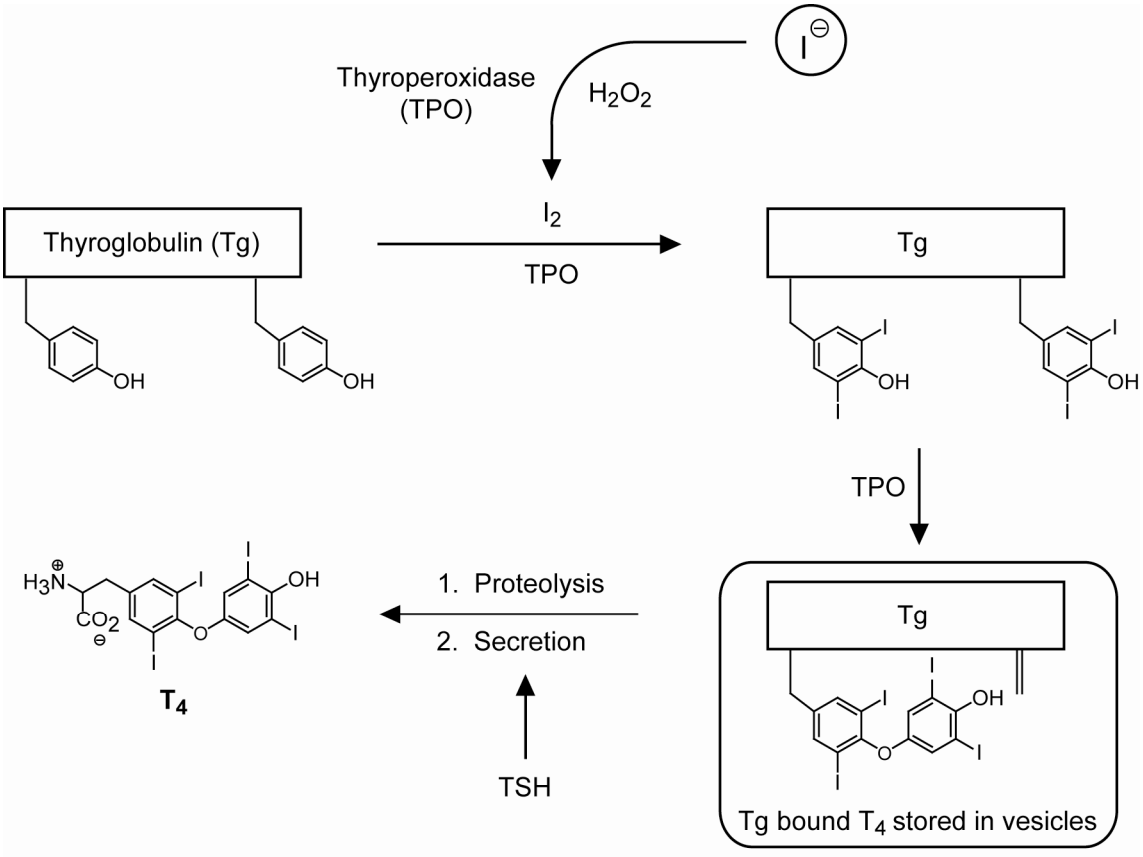


Figure 1-2. Biosynthesis of thyroid hormone.

T_4 is the predominant form of thyroid hormone secreted. It can be enzymatically deiodinated by type 1 5'-deiodinase or type 2 5'-deiodinase to form the more active **T_3**,

and by type 3 5-deiodinase to form the metabolically inactive 3,3`,5`-*L*-triiodothyronine (**rT$_3$**) (**Fig. 1-3**). Further deiodination of **T$_3$** and **rT$_3$** give less active metabolites and eventually lead to *L*-thyronine (**T$_0$**), the fully deiodinated thyroid hormone. Alternatively, **T$_4$** and **T$_3$** can also be inactivated by glucuronidation and sulfation of its phenol, and by metabolism of its alanine side chain through oxidative deamination and oxidative decarboxylation to form thyroacetic acids (**Fig. 1-4**).[3]

1.2 Physiological Effects of Thyroid Hormone

Thyroid hormones regulate many physiological processes. Stimulation of Na^+-K^+ ATPase increases oxygen consumption and metabolic rate, resulting in higher metabolism and body temperature.[1] It affects lipid homeostasis increasing cholesterol clearance and regulating enzymes involved in lipolysis and lypogenesis.[4] Hyperthyroidism increases intestinal glucose uptake, hepatic gluconeogenesis and glycogenolysis, and promotes glucose utilization in muscle and adipose tissues.[1, 5] In bone, thyroid hormones stimulate osteoblast and osteoclast activities leading to bone formation and resorption.[4] Thyroid hormone is necessary for normal brain development. Insufficient amounts of thyroid hormone during fetal development can lead to cretinism, a disorder characterized by mental retardation and dwarfism.[1] In the heart, **T$_3$** increases heart rate and cardiac contractility by enhancing the expression levels of myosin heavy chain (MHC) proteins and sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2).[4, 6] It also increases cardiac output by lowering peripheral vascular resistance and can regulate the number of β adrenergic receptors present in the heart. Overall these effects have a slow onset, requiring hours to days to achieve maximal effects, and are mediated by the actions of the thyroid hormone nuclear receptor on gene transcription.

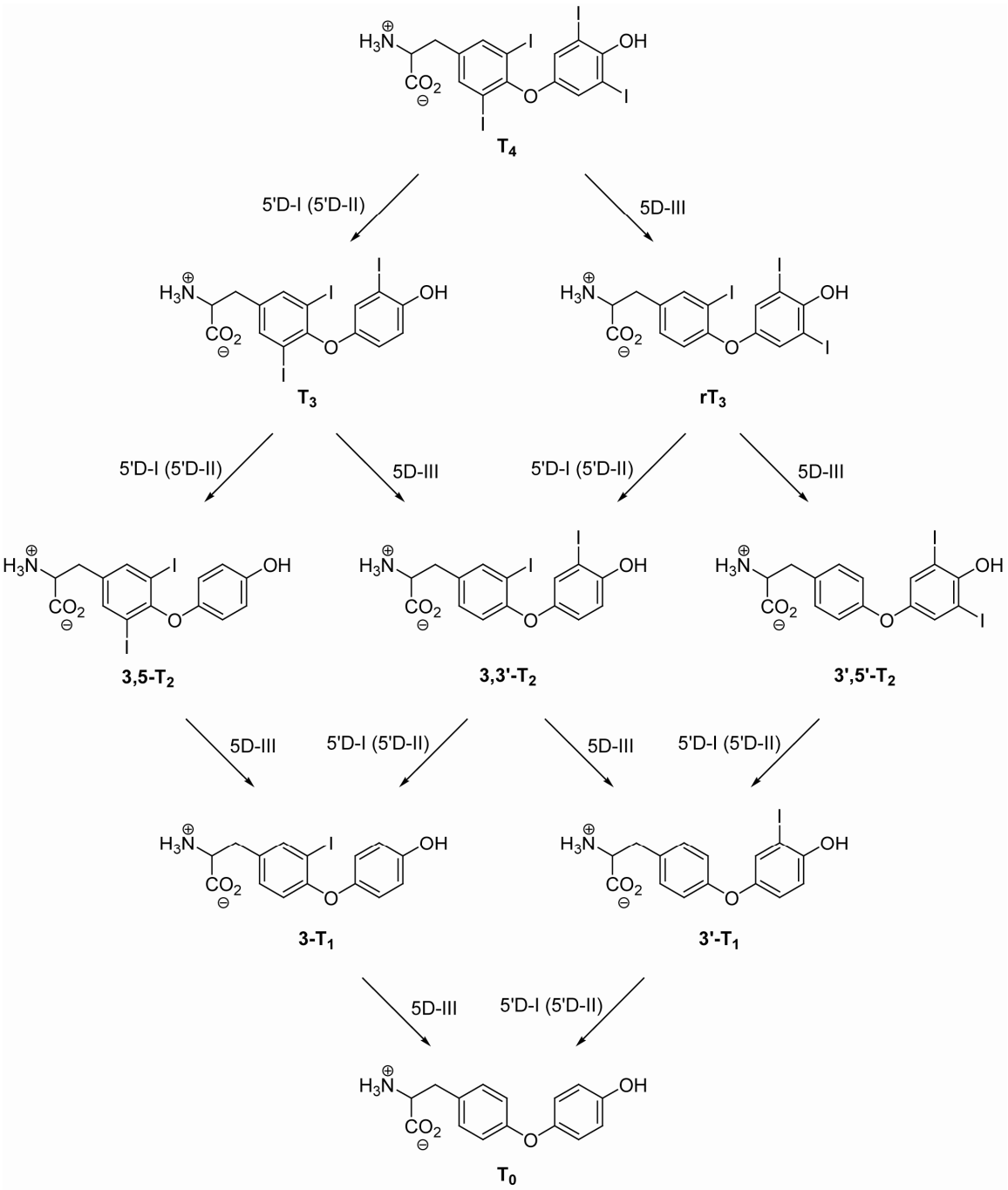


Figure 1-3. Thyroid hormone metabolism by enzymatic deiodination. Type 1 5'-deiodinase (5'-DI), type 2 5'-deiodinase (5'-DII), and type 3 5-deiodinase (5-DIII).

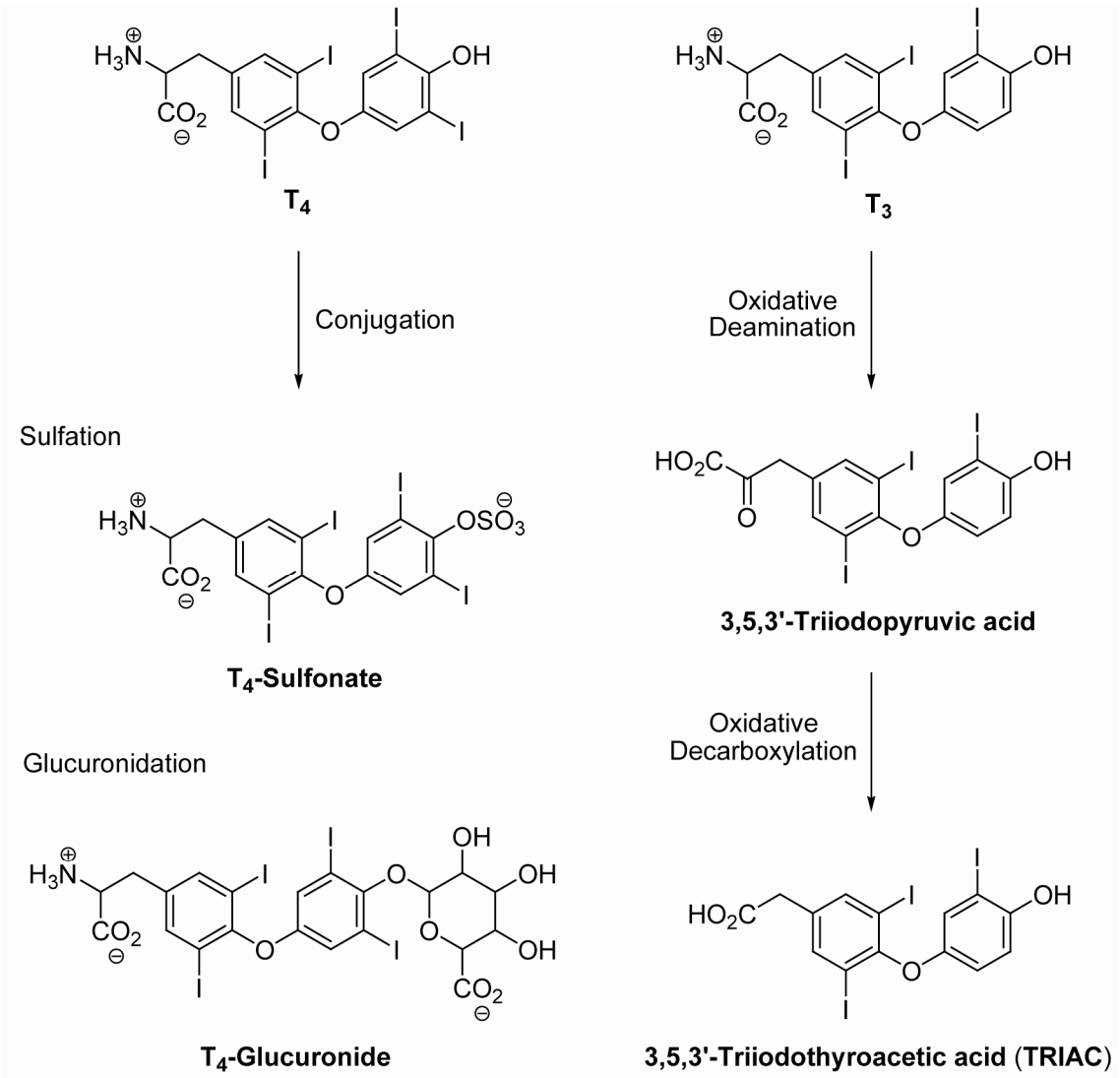


Figure 1-4. Thyroid hormone metabolism by conjugation or alanine side chain metabolism.

1.3 Molecular Basis of Thyroid Hormone Action

There are two types of thyroid hormone receptors (TRs), TRα and TRβ, each consisting of two isoforms, TRα 1 and 2 and TRβ 1 and 2, arising from alternative splicing.[1] The genes for TRα and TRβ are located in chromosome 17 and 3, respectively. TR has a modular structure consisting of 3 domains, N-terminal domain, DNA binding domain (DBD), and the C-terminal ligand binding domain (LBD) (**Fig. 1-5**).[7] The N-

terminal domain is the least conserved domain across the nuclear receptor superfamily and it contains the ligand independent activation function 1 (AF-1). The DBD is the most highly conserved region and is composed of two zinc finger motifs that recognize thyroid hormone response elements (TRE) in the promoter regions of the target genes. The C-terminal LBD interacts with $\mathbf{T_3}$, coactivators, and corepressors and is composed of 12 helices and 3 short β strands. All isoforms except TRα2 are ligand responsive. The four isoforms have different tissue distribution, giving rise to tissue specific action.

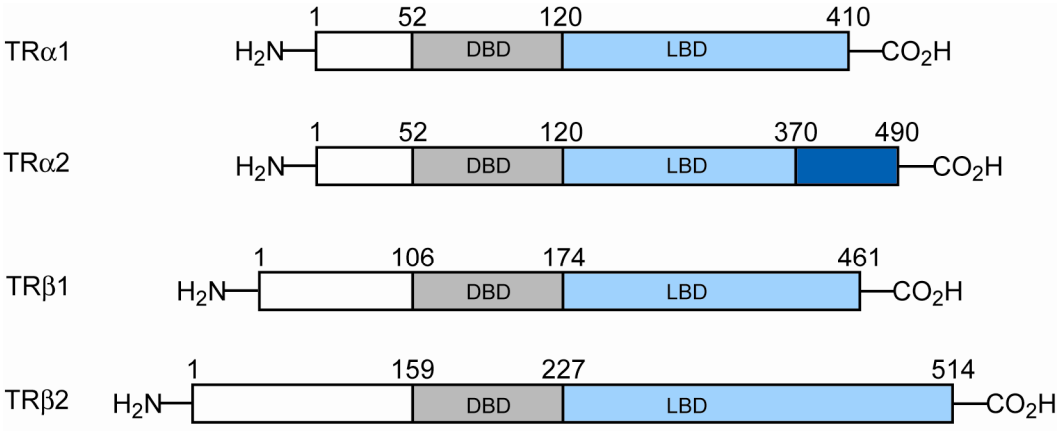


Figure 1-5. Thyroid hormone nuclear receptor (TR) subtypes and isoforms.

Unliganded TR is localized in the nucleus bound to TRE as a monomer, homodimer, or heterodimer with the retinoid X receptor (RXR). It is typically associated with corepressor proteins to repress thyroid hormone responsive genes (**Fig. 1-6**). Upon $\mathbf{T_3}$ binding, the thyroid hormone receptor undergoes a conformational change that releases corepressors, recruits coactivators and interacts with the cellular transcription machinery to upregulate gene expression.

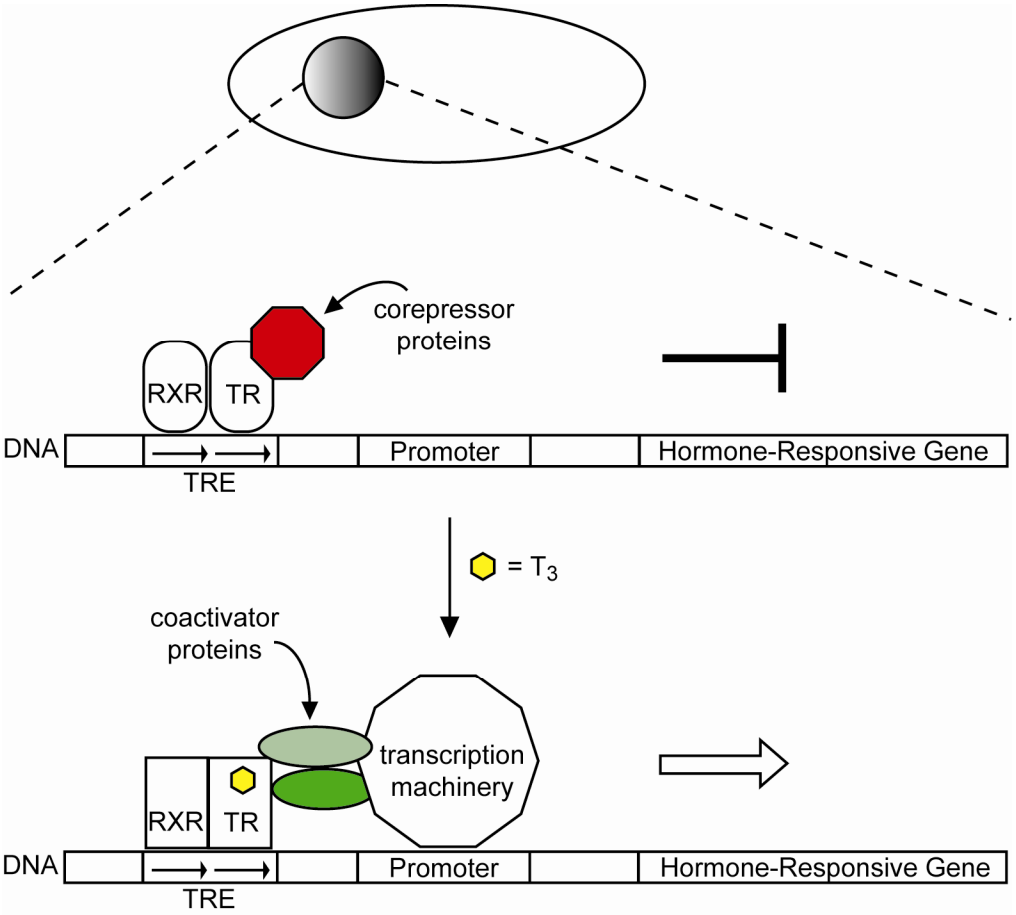


Figure 1-6. TR-mediated gene transcription. RXR (retinoid X receptor); TRE (thyroid response element).

1.4 Thyronamines and the Trace Amine-Associated Receptor 1

In addition to the slow occurring genomic effects, thyroid hormone also has rapid effects that occur within seconds to minutes. These include increasing 2-deoxyglucose and Ca^{2+} uptake, and stimulating sarcoplasmic-/endoplasmic reticulum Ca^{2+} ATPase and Na^{+}/H^{+} antiporter activity.[8-11] These rapid effects are difficult to attribute to transcription mediated by thyroid hormone receptors due to the slow onset of gene expression. These responses suggest the possible existence of thyroid hormone receptors other than TRα/TRβ and the presence of thyroid hormones other than $\mathbf{T_3}$.

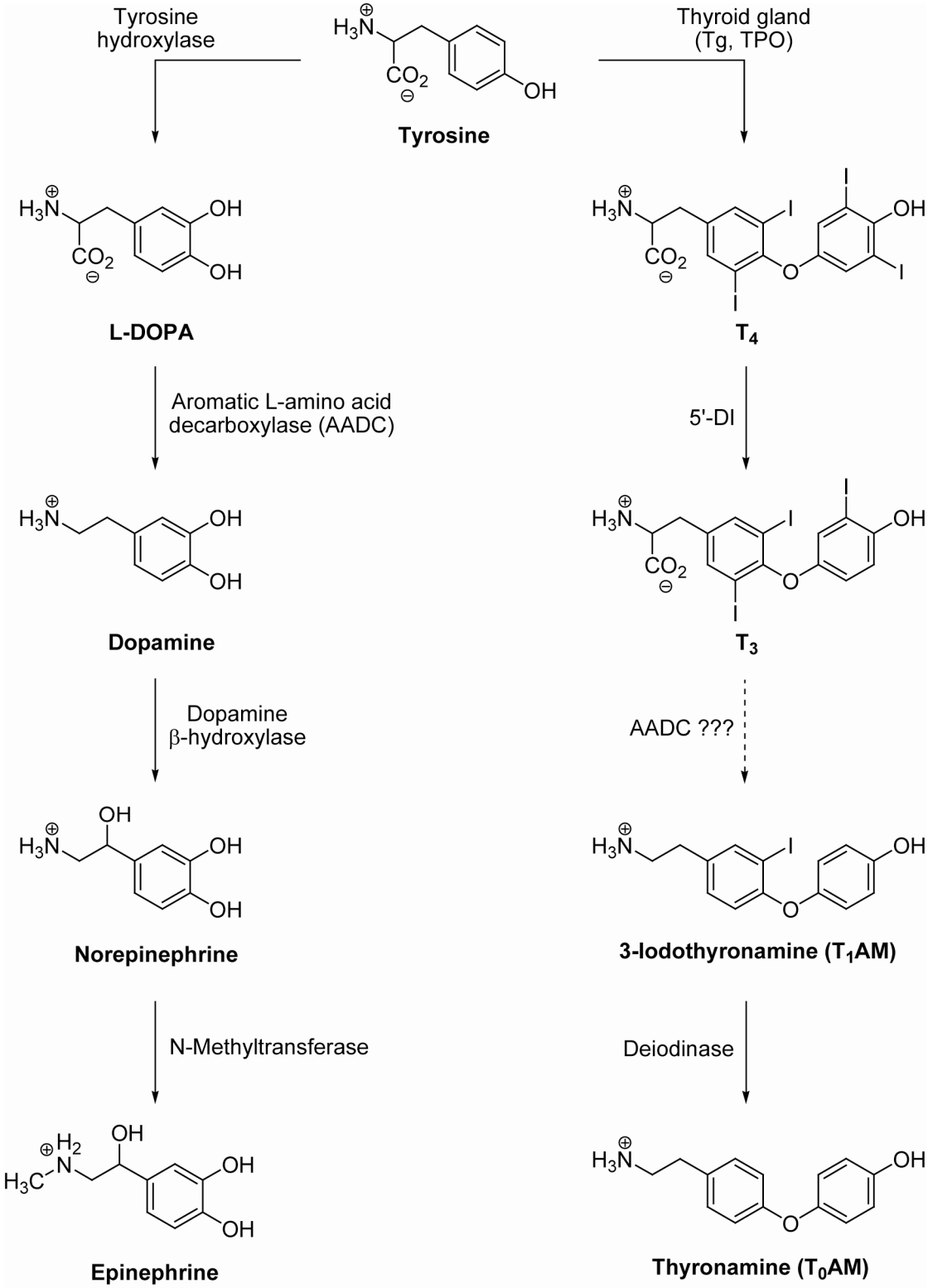


Figure 1-7. Biosynthesis of biogenic amines.

Recently, it was found that 3-iodothyronamine (**T_1AM**) and thyronamine (**T_0AM**) are endogenous molecules present in the brain, heart, liver, and blood (**Fig. 1.7**).[12] Thyronamines are the decarboxylated metabolites of thyroid hormones proposed to arise from enzymatic processing by deiodinases and aromatic amino acid decarboxylase (AADC). Expressed in the brain, kidney, liver, and other tissues, AADC plays an important role in the biosynthesis of the monoamine neurotransmitters dopamine, norepinephrine, and epinephrine from L-DOPA, and serotonin from 5-hydroxytryptophan (**Fig. 1.7**).[13] AADC is fairly nonspecific and can catalyze the decarboxylation of a variety of aromatic amino acids using pyridoxal phosphate as a cofactor.[14] Since thyroid hormones are also biosynthesized from tyrosines and are essentially aromatic amino acids, it's plausible that they could be substrates for AADC and can be enzymatically decarboxylated to generate thyronamines.

When tested *in vitro*, some thyronamines were found to be potent agonists of an orphan G-protein coupled receptor (GPCR) known as the trace amine-associated receptor 1 ($TAAR_1$).[12] Of the nine possible thyronamines varying in the iodination state of the inner and outer ring, **T_1AM** was found to be the most potent at activating rat and mouse $TAAR_1$ with effective concentrations for half-maximal stimulation (EC_{50}) of 14 nM and 112 nM, respectively. When administered to mice, **T_1AM** rapidly induced anergia, bradycardia, and hypothermia; effects of which are opposite those observed with hyperthyroidism. In isolated rat heart preparations, **T_1AM** rapidly decreased cardiac output, aortic pressure, coronary flow, and heart rate.[15] Additionally, **T_1AM** has been found to inhibit neurotransmitter reuptake by the dopamine (DAT) and norepinephrine

transporters (NET), and inhibit vesicular packaging by the vesicular monoamine transporter 2 (VMAT2).[16]

A member of the trace amine-associated receptor family of orphan GPCRs, $TAAR_1$ is one of 19 rat, 16 mouse, 9 human, and 9 chimpanzee subtypes.[17-19] $TAAR_1$ is homologous to β-adrenergic, dopamine, and serotonin receptors and belongs to the biogenic amine subfamily of class A rhodopsin like GPCRs.[20, 21] $TAAR_1$ is coupled to a stimulatory G-protein (G_s) and is activated by endogenous trace amines such as β-phenethylamine, *p*-tyramine, and tryptamine. $TAAR_1$ mRNA transcripts have been detected in many tissues including the brain, heart, lung, kidney, liver, spleen, and pancreas.[20-22] Recently, some mouse TAARs (e.g. TAARs 3, 4, 5, and 7f) have been implicated as a secondary class of chemosensory receptors expressed in the mouse olfactory epithelium.[23]

To understand the role of $TAAR_1$ in mediating the physiological effects of **T_1AM**, we sought to develop small molecules that regulate the activity of $TAAR_1$. The overall objectives of this thesis are to understand the molecular basis of $TAAR_1$ activation and to use this information to develop rat and mouse $TAAR_1$ agonists and antagonists.

1.5 References

1. Cooper, D.; Greenspan, F.; Ladenson, P., The Thyroid Gland. In *Greenspan's basic and clinical endocrinology*, 8th ed.; Gardner, D.; Shoback, D., Lange Medical Books/McGraw-Hill: New York, 2007; pp 209-280.
2. Norman, A.; Litwack, G., *Hormones*. 2nd ed.; Academic Press: San Diego, 1997; p 558.
3. Wu, S. Y.; Green, W. L.; Huang, W. S.; Hays, M. T.; Chopra, I. J., Alternate pathways of thyroid hormone metabolism. *Thyroid* **2005,** 15, (8), 943-958.
4. Yen, P. M., Physiological and molecular basis of thyroid hormone action. *Physiological Review* **2001,** 81, (3), 1097-1142.
5. Banijamali, A., Thyroid function and thyroid drugs. In *Principles of Medicinal Chemistry*, 4th ed.; Foye, W.; Lemke, T.; Williams, D., 'Ed.'^'Eds.' Williams & Wilkins: Baltimore, 1995; 'Vol.' p^pp 688-704.
6. Dillmann, W. H., Cellular action of thyroid hormone on the heart. *Thyroid* **2002,** 12, (6), 447-452.
7. Weatherman, R. V.; Fletterick, R. J.; Scanlan, T. S., Nuclear-receptor ligands and ligand-binding domains. *Annu. Rev. Biochem.* **1999,** 68, 559-581.
8. Davis, P. J.; Davis, F. B., Nongenomic actions of thyroid hormone on the heart. *Thyroid* **2002,** 12, (6), 459-466.
9. Falkenstein, E.; Tillmann, H.; Christ, M.; Feuring, M.; Wehling, M., Multiple actions of steroid hormones - A focus on rapid, nongenomic effects. *Pharmacol. Rev.* **2000,** 52, (4), 513-555.

10. Losel, R.; Wehling, M., Nongenomic actions of steroid hormones. *Nat. Rev. Mol. Cell Biol.* **2003,** 4, (1), 46-56.

11. Losel, R. M.; Falkenstein, E.; Feuring, M.; Schultz, A.; Tillmann, H. C.; Rossol-Haseroth, K.; Wehling, M., Nongenomic steroid action: controversies, questions, and answers. *Physiological Review* **2003,** 83, (3), 965-1016.

12. Scanlan, T.; Suchland, K.; Hart, M.; Chiellini, G.; Huang, Y.; Kruzich, P.; Frascarelli, S.; Crossley, D.; Bunzow, J.; Ronca-Testoni, S.; Lin, E.; Hatton, D.; Zucchi, R.; Grandy, D., 3-iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat. Med.* **2004,** 10, (6), 638-642.

13. Zhu, M. Y.; Juorio, A. V., Aromatic L-amino acid decarboxylase: biological characterization and functional role. *Gen. Pharmacol.* **1995,** 26, (4), 681-696.

14. Lovenberg, W.; Weissbach, H.; Udenfriend, S., Aromatic L-amino acid decarboxylase. *J. Biol. Chem.* **1962,** 237, 89-93.

15. Chiellini, G.; Frascarelli, S.; Ghelardoni, S.; Carnicelli, V.; Tobias, S.; DeBarber, A.; Brogioni, S.; Ronca-Testoni, S.; Cerbai, E.; Grandy, D.; Scanlan, T.; Zucchi, R., Cardiac effects of 3-iodothyronamine: a new aminergic system modulating cardiac function. *FASEB J.* **2007,** 21, (7), 1597-1608.

16. Snead, A. N.; Santos, M. S.; Seal, R. P.; Miyakawa, M.; Edwards, R. H.; Scanlan, T. S., Thyronamines inhibit plasma membrane and vesicular monoamine transport. *ACS Chem Biol* **2007,** 2, (6), 390-398.

17. Lindemann, L.; Ebeling, M.; Kratochwil, N.; Bunzow, J.; Grandy, D.; Hoener, M., Trace amine-associated receptors form structurally and functionally distinct

subfamilies of novel G protein-coupled receptors. *Genomics* **2005,** 85, (3), 372-385.

18. Lindemann, L.; Hoener, M., A renaissance in trace amines inspired by a novel GPCR family. *Trends Pharmacol. Sci.* **2005,** 26, (5), 274-281.

19. Zucchi, R.; Chiellini, G.; Scanlan, T.; Grandy, D., Trace amine-associated receptors and their ligands. *Br. J. Pharmacol.* **2006,** 149, (8), 967-978.

20. Borowsky, B.; Adham, N.; Jones, K.; Raddatz, R.; Artymyshyn, R.; Ogozalek, K.; Durkin, M.; Lakhlani, P.; Bonini, J.; Pathirana, S.; Boyle, N.; Pu, X.; Kouranova, E.; Lichtblau, H.; Ochoa, F.; Branchek, T.; Gerald, C., Trace amines: Identification of a family of mammalian G protein-coupled receptors. *Proc. Natl. Acad. Sci. U. S. A.* **2001,** 98, (16), 8966-8971.

21. Bunzow, J.; Sonders, M.; Arttamangkul, S.; Harrison, L.; Zhang, G.; Quigley, D.; Darland, T.; Suchland, K.; Pasumamula, S.; Kennedy, J.; Olson, S.; Magenis, R.; Amara, S.; Grandy, D., Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. *Mol. Pharmacol.* **2001,** 60, (6), 1181-1188.

22. Regard, J. B.; Kataoka, H.; Cano, D. A.; Camerer, E.; Yin, L.; Zheng, Y. W.; Scanlan, T. S.; Hebrok, M.; Coughlin, S. R., Probing cell type-specific functions of G(i) in vivo identifies GPCR regulators of insulin secretion. *J. Clin. Invest.* **2007,** 117, (12), 4034-4043.

23. Liberles, S.; Buck, L., A second class of chemosensory receptors in the olfactory epithelium. *Nature* **2006,** 442, (7103), 645-650.

Chapter 2

Structure–Activity Relationship of T_1AM for the Rat and Mouse Trace Amine-Associated Receptor 1

2.1 Previous T_1AM Structure–Activity Relationship

The initial pharmacological study by Bunzow *et al.*[1] showed that rat $TAAR_1$ ($rTAAR_1$) can be activated by a diverse class of amines. Rat $TAAR_1$ is stimulated by structurally simple, psychoactive phenethylamines (e.g. amphetamine, 4-hydroxy-amphetamine, and methamphetamine) and endogenous trace amines (e.g. β-phenethylamine, *p*-tyramine, and tryptamine); and by structurally complex ergot alkaloid natural products (e.g. agroclavine and dihydroergotamine) (**Fig. 2-1)**. Interestingly, some biogenic amine receptor drugs can also activate $rTAAR_1$. These include *R*-(–)-apomorphine, naphazoline, and 1-(3-chlorophenyl)piperazine (mCPP) (**Fig. 2-1)**.

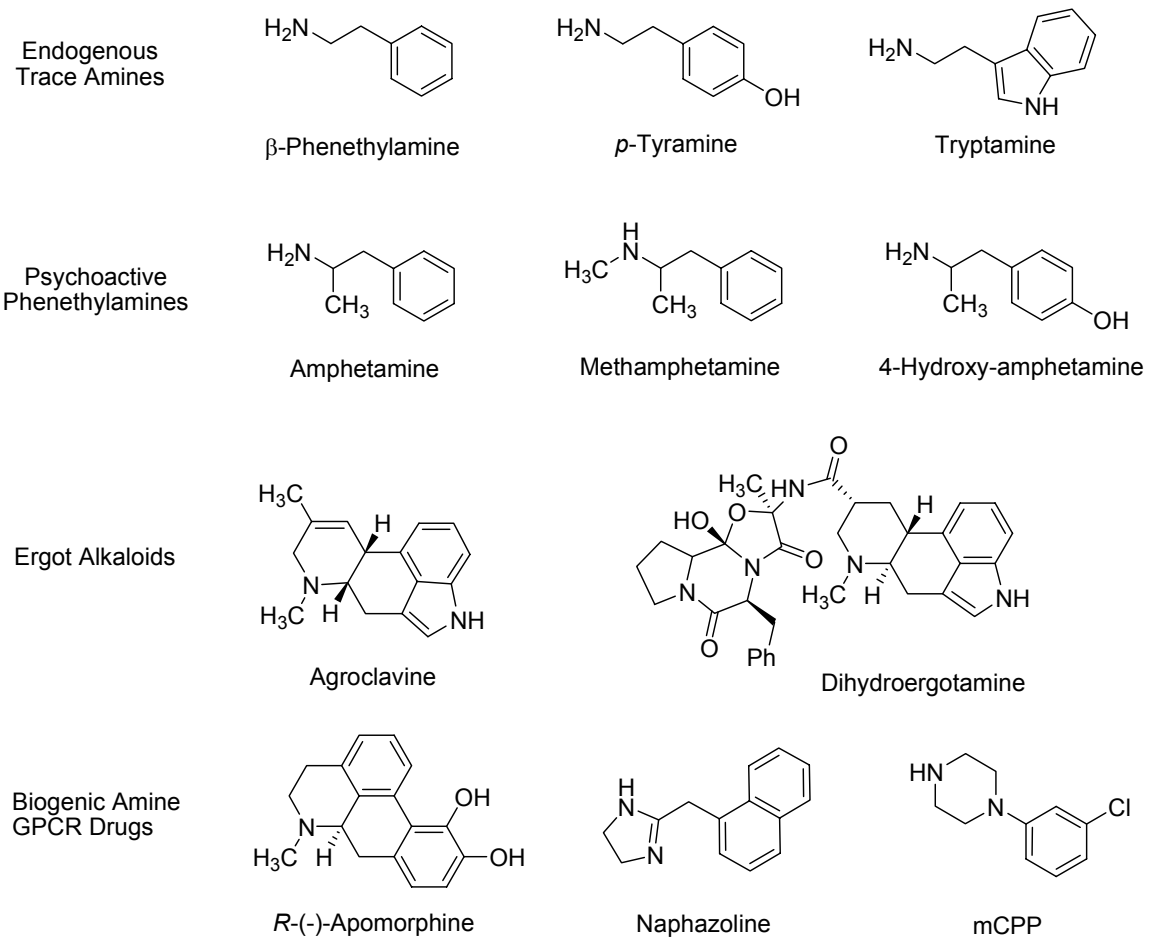
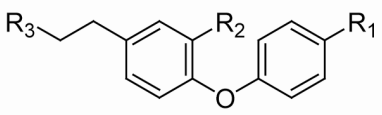


Figure 2-1. Structures of endogenous trace amines, psychoactive phenethylamines, ergot alkaloids, and biogenic amine GPCR drugs.

Similar to $rTAAR_1$, the simple phenethylamine analogs β-phenethylamine, *p*-tyramine, amphetamine, methamphetamine, and 4-hydroxy-amphetamine are also agonists for mouse $TAAR_1$ ($mTAAR_1$).[2] The activities of ergot alkaloids and biogenic amine receptor drugs on $mTAAR_1$ have yet to be determined.

Previous structure–activity relationship (SAR) studies on T_1AM have shown the charged amine to be required for rat and mouse $TAAR_1$ activation.[3] When replaced with an alcohol group (**desamino-T_1AM**), the resulting compound was inactive against both receptors (**Table 2-1).** Removing the outer ring hydroxyl (**deshydroxy-T_1AM**) was beneficial, enhancing the potency for $rTAAR_1$ and $mTAAR_1$ ~5- and ~3-fold, respectively. Deletion of the iodine group alone (**T_0AM**) was more detrimental to both receptors than deletion of both the iodine and hydroxyl substituents (**PTA**). Replacing the inner ring iodine with a methyl group (**3-methylthyronamine**) decreased the potency for $rTAAR_1$ ~2-fold but had no effect on the potency for $mTAAR_1$. The opposite trend was observed with monomethylation of the charged amine; **N-Methyl-T_1AM** was ~2-fold less potent for $mTAAR_1$ but equipotent with **T_1AM** for $rTAAR_1$.

Table 2-1. Structure–Activity Relationship of **T_1AM**



Compd	R_1	R_2	R_3	EC_{50} (nM)	
				$rTAAR_1$	$mTAAR_1$
T_1AM	OH	I	NH_2	14	112
Desamino-T_1AM	OH	I	OH	>1000	>1000
Deshydroxy-T_1AM	H	I	NH_2	2.4	35
T_0AM	OH	H	NH_2	131	~1000
PTA	H	H	NH_2	38	296
3-Methylthyronamine	OH	CH_3	NH_2	33	116
N-Methyl-T_1AM	OH	I	CH_3NH	18	221

In thyronamine related analogs, increasing the linker length between the inner and outer rings by inserting up to four methylene groups between the oxygen atom and the outer ring, was tolerated by both rat and mouse $TAAR_1$.[3] Some functionalized *O*-arylalkyl-tyramine derivatives were up to ~5.5-fold more potent than **T_1AM** for $mTAAR_1$. In $rTAAR_1$, these *O*-arylalkyl-tyramine compounds were ≥ 3-fold less potent compared to **T_1AM**. In the *O*-benzyl-tyramine series, a *N*-methyl group was beneficial but larger alkyl substituents were detrimental for both $rTAAR_1$ and $mTAAR_1$ activation. An *N*-ethyl group was an exception for $mTAAR_1$; the *N*-ethyl substituted *O*-benzyl-tyramine derivative was equipotent to the N-methyl substituted compound.

2.2 SAR of the Ethylamine Portion of T_1AM

2.2.1 Synthesis

To expand the SAR of **T_1AM**, we synthesized a variety of compounds with structural modifications in the ethylamine portion of **T_1AM**. Since rat and mouse $TAAR_1$ are homologous to the β-adrenergic (βAR) and dopamine receptors, we explored their tolerance for structural elements commonly found in existing βAR and dopamine receptor antagonists (**Fig. 2-2)**. We chose to focus on an antagonist based drug design approach to determine if incorporating prominent structural features from catecholamine receptor antagonists would be sufficient to generate $TAAR_1$ lead antagonists. These structural motifs were incorporated into **PTA** (**Table 2-1)** rather than the more potent **T_1AM** because omitting the outer-ring hydroxyl and inner-ring iodine significantly simplified the syntheses.

The aryloxypropanolamines (**Scheme 2-1**) contain an oxymethylene bridge between the aromatic and ethylamine groups as found in the β blocker propranolol (**Fig.**

2-2). **ET-1** and **ET-11** were readily synthesized by coupling Boc-3-bromopropylamine (**2.2**) with *para*- and *meta*-phenoxyphenol to provide ethers **2.5** and **2.6**, respectively. Boc deprotection with 3 N anhydrous HCl gave the hydrochloride salts of **ET-1** and **ET-11** in good yields. Mono-*N*-methyl **ET-12** was obtained by reacting **2.5** with NaH and MeI followed by acid deprotection. Di-*N*-methyl **ET-6** was synthesized by Eschweiler–Clarke reaction of the free amine of **ET-1**.[4]

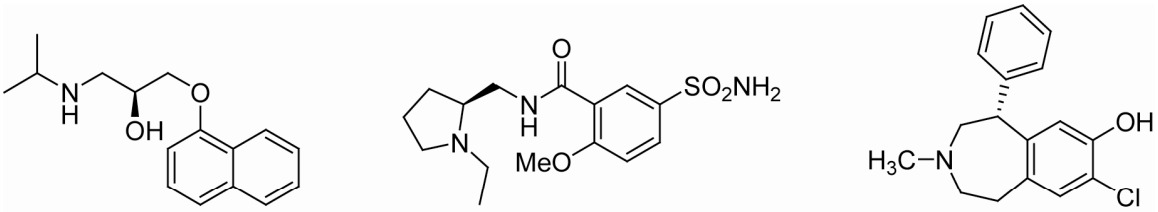


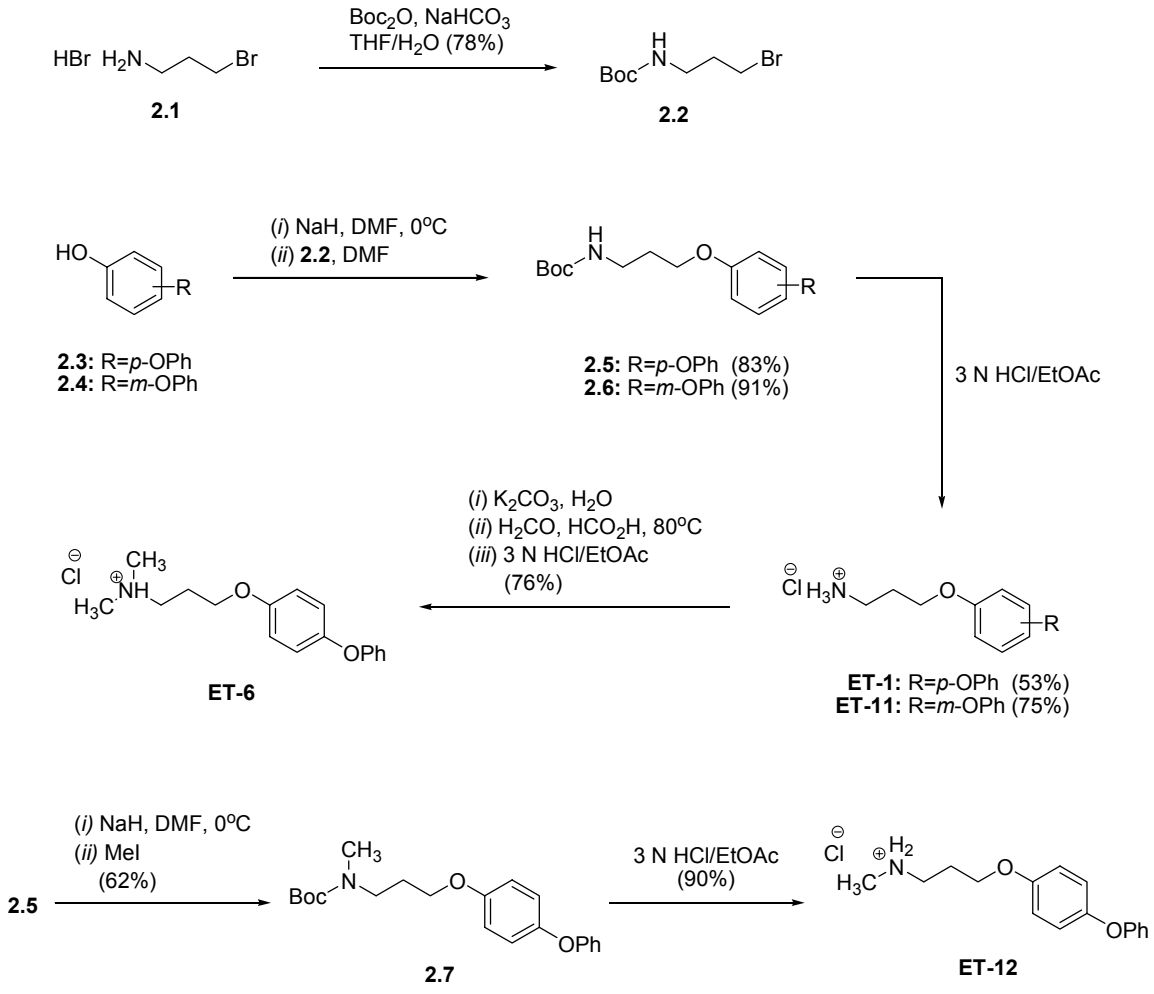
Figure 2-2. Structures of β-adrenergic receptor (propranolol) and dopamine receptor (sulpiride and SCH 23390) antagonists used as a model for $TAAR_1$ ligand design.

The benzamidoalkylamines (**Scheme 2-2**) contained an amide linker between the aromatic and ethylamine portion of the phenoxyphenethylamine scaffold, similar to dopamine receptor antagonist sulpiride (**Fig. 2-2**). The length of the carbon chain connecting the basic and amide nitrogen was varied from two to five carbons. Reaction of the acyl chloride of 4-phenoxybenzoic acid (**2.8**) and previously reported monoprotected alkyldiamines **2.9-2.12**[5] provided amides **2.13-2.16**. Boc deprotection yielded the hydrochloride salts of **ET-2** through **ET-5** in poor to excellent yields. Dimethylated **ET-7**–**ET-10** were synthesized through an Eschweiler–Clarke reaction.

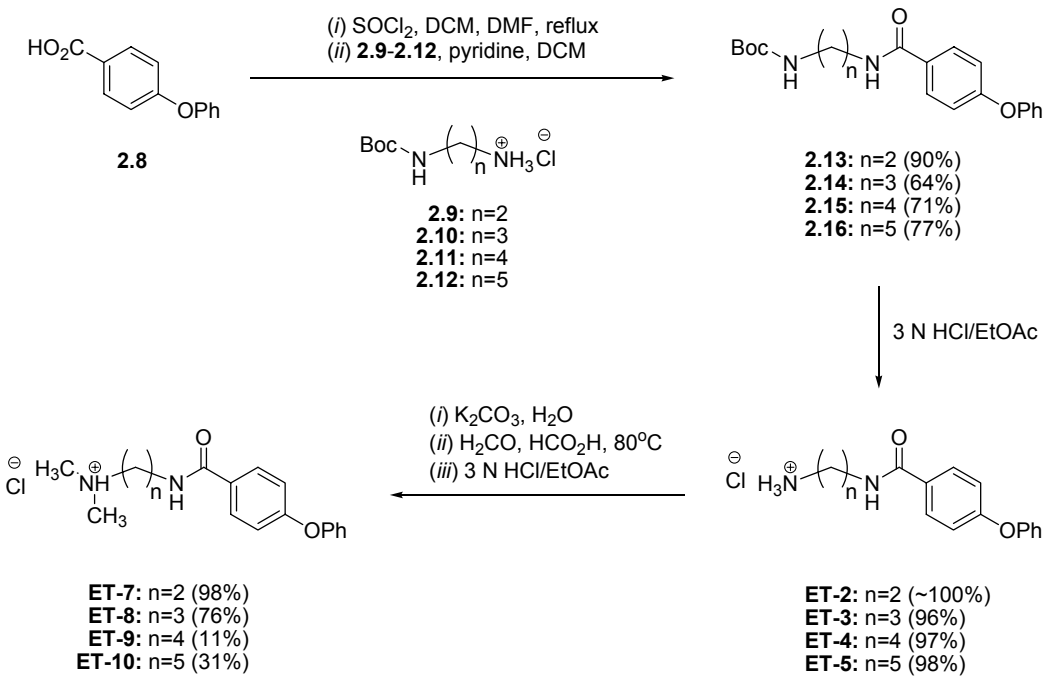
The orthopramide-alkylamines (**Scheme 2-3**) contain the *ortho*-methoxy group found in sulpiride (**Fig. 2-2**) in addition to the amide linker. In this scaffold, the methylene spacer between the two nitrogen atoms was also varied from two to five carbons. Regioselective copper (II) mediated coupling of methyl-2,4-dihydroxybenzoic

acid (**2.17**) with phenylboronic acid yielded biaryl ether **2.18** in modest yield.[6] Reaction of **2.18** with NaH and MeI followed by saponification provided benzoic acid **2.20** in excellent yield. The acyl chloride of **2.20** was coupled to monoprotected diamines **2.9-2.12** and 1-Boc-piperazine to provide **2.21-2.24**. Acid deprotection gave **ET-22**–**ET-26** quantitatively. Reaction of the free amines of **ET-22**–**ET-25** under Eschweiler–Clarke reaction conditions gave dimethylated **ET-27**–**ET-30** in modest to good yields.

Scheme 2-1. Synthesis of Aryloxypropanolamines (**ET-1**, **ET-6**, **ET-11**, and **ET-12**)



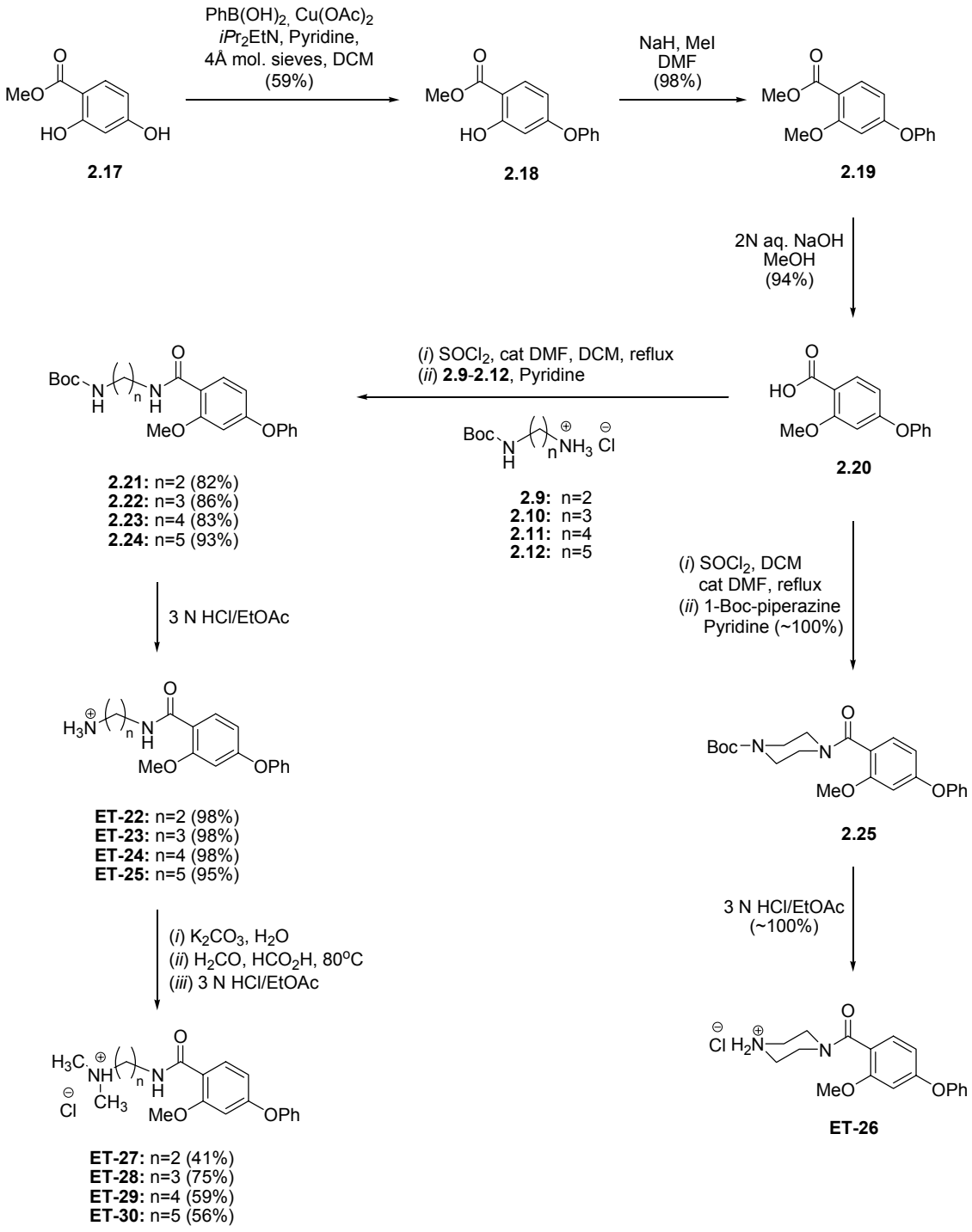
Scheme 2-2. Synthesis of Benzamidoalkylamines (**ET-2**-**ET-5** and **ET-7**-**ET-10**)



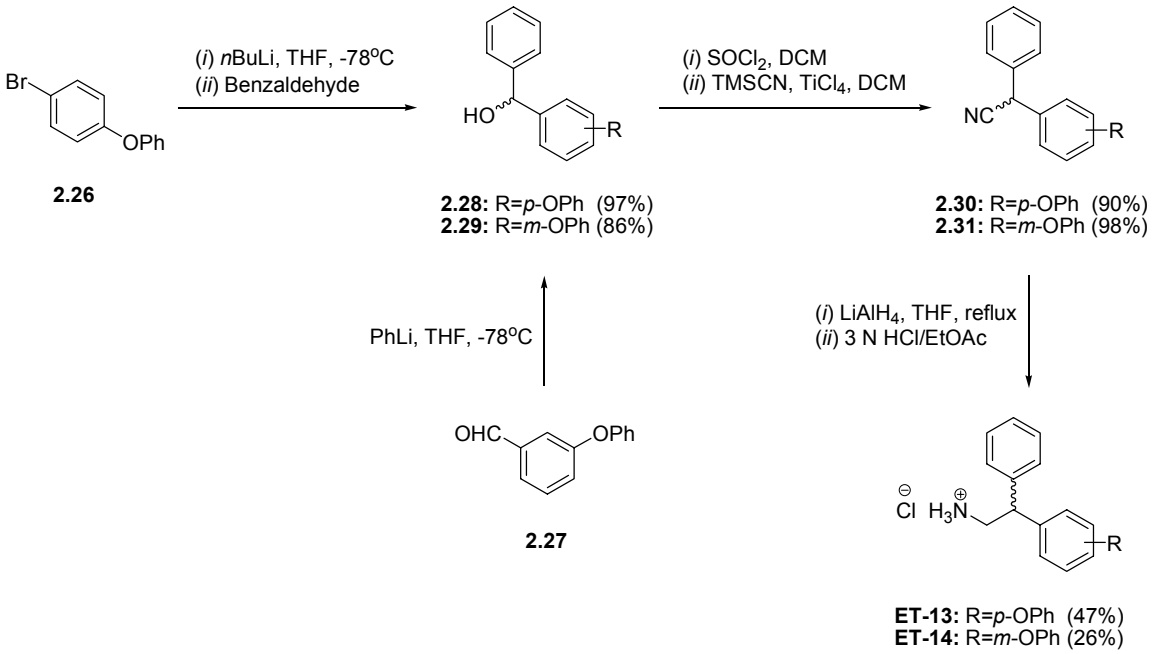
The β-phenylphenoxyphenethylamines (**Scheme 2-4**) and tetrahydro-benzazepines (**Scheme 2-5**) were modeled after the prototypical dopamine receptor antagonist SCH 23390 (**Fig. 2-2**). **ET-13** and **ET-14** have a β-phenyl ring alone while **ET-15**–**ET-20** possesses a seven membered ring in addition to the β-phenyl ring. The reaction of the organolithium species of 4-bromodiphenyl ether (**2.26**) with benzaldehyde and phenyl lithium with 3-phenoxybenzaldehyde (**2.27**) gave the dibenzylic alcohols **2.28** and **2.29**, respectively. Initial attempts at converting this alcohol into a nitrile group by nucleophilic displacement of the corresponding mesylate with sodium cyanide were unsuccessful due to the sterically congested nature of the dibenzylic alcohol. Generating the chloride followed by reaction with $TiCl_4$ and trimethylsilylcyanide (TMSCN) successfully provided nitriles **2.30** and **2.31**.[7] Nitrile reduction with lithium aluminum hydride and treatment with acid yielded the hydrochloride salts **ET-13** and **ET-14** as a

racemic mixture in poor to modest yield. Attempts to resolve the enantiomers of **ET-13** by formation of diastereomeric salts with *L*- or *R*-tartaric acids were unsuccessful.

Scheme 2-3. Synthesis of Orthopramide-alkylamines (**ET-22**-**ET-30**)

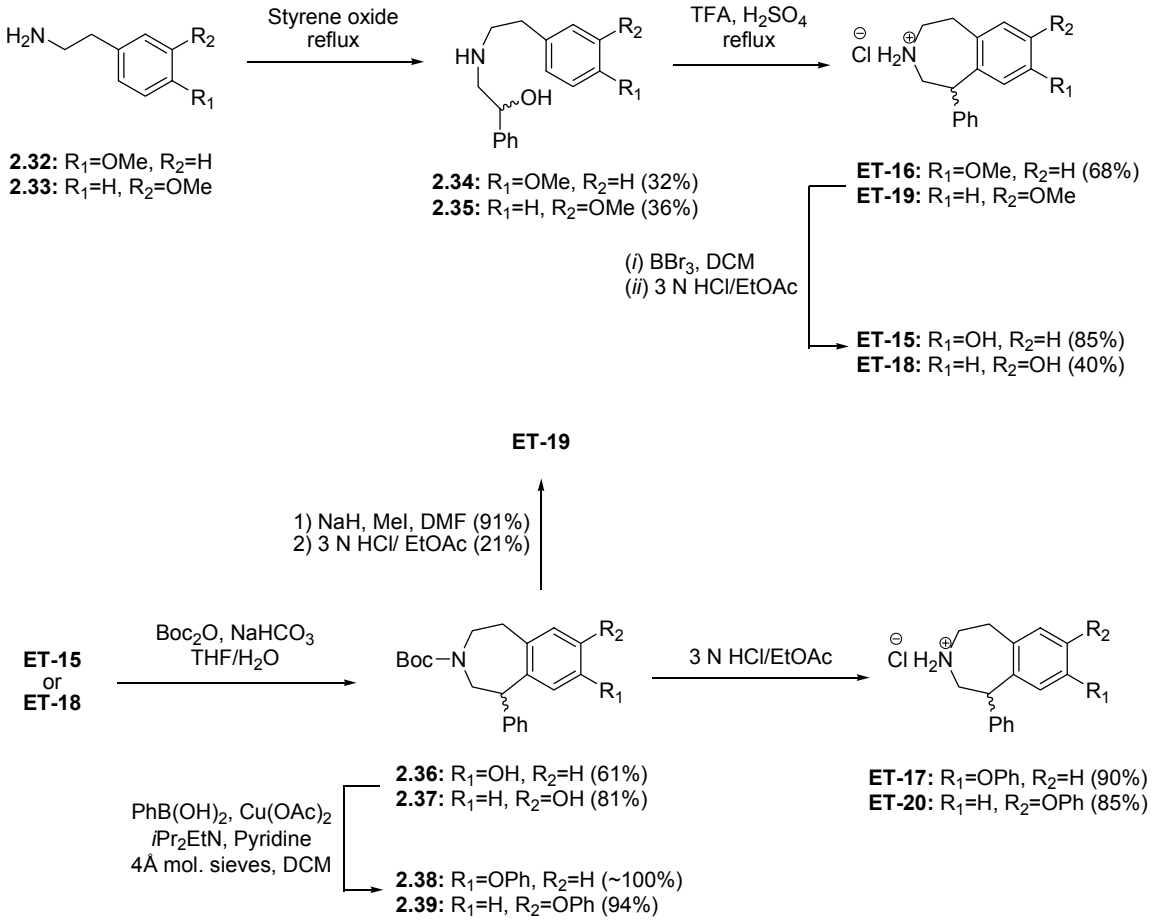


Scheme 2.4. Synthesis of β-Phenylphenoxyphenethylamines (**ET-13** and **ET-14**)



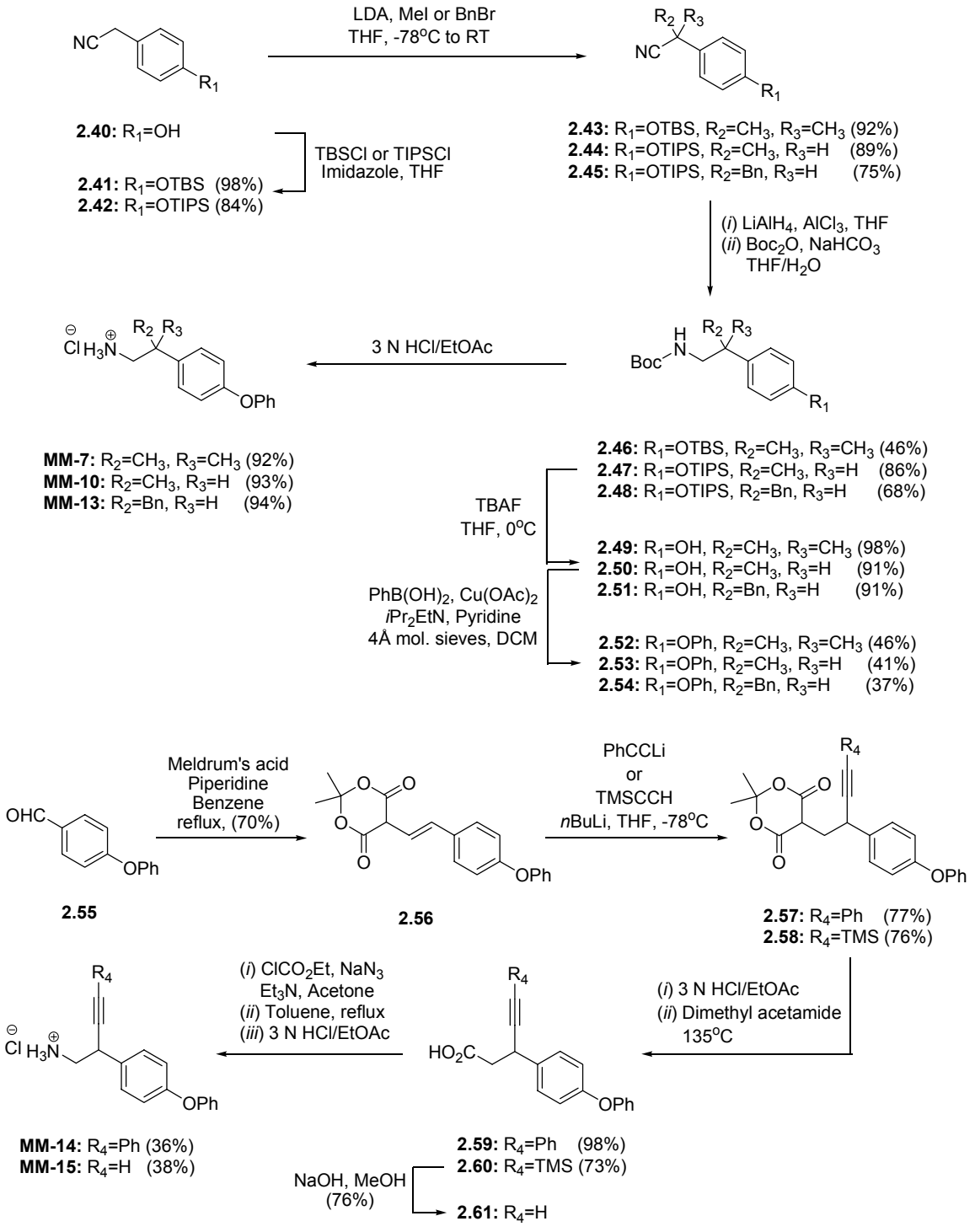
Tetrahydro-benzazepines **ET-19** and **ET-18** were synthesized following the published procedure for known compounds **ET-16** and **ET-15** (**Scheme 2-5**).[8] Reacting 3-methoxyphenethylamine (**2.33**) with neat styrene oxide gave benzylic alcohol **2.35**. Treatment with trifluoroacetic acid in the presence of catalytic amounts of sulfuric acid induced cyclization to form **ET-19**. **ET-19** was obtained as an inseparable mixture with an unknown product. Methyl ether deprotection with boron tribromide followed by acid exposure gave pure hydrochloride salts of **ET-18**. Boc protection of **ET-15** and **ET-18** followed by copper (II) mediated coupling with phenyl boronic acid provided biaryl ethers **2.38** and **2.39**. Boc deprotection yielded **ET-17** and **ET-20** as hydrochloride salts. Methyaltion of **2.37** with NaH and MeI, followed by acid deprotection provided pure hydrochloride salts of **ET-19**.

Scheme 2-5. Synthesis of Tetrahydrobenzazepines (**ET-15**-**ET-20**)



To further explore the steric constraints around the β-carbon, additional phenoxyphenethylamine derivatives possessing smaller and bulkier substituents at the β-carbon were synthesized (**Scheme 2-6**). Triisopropyl (**2.42**) or t*ert*-butyldimethylsilyl (**2.41**) protected 4-hydroxybenzylnitrile was treated with lithium diisopropylamine and methyl iodide or benzyl bromide to give **2.43**, **2.44** or **2.45**. The nitrile was reduced with $LiAlH_4$-$AlCl_3$[9] and subsequently reacted with Boc anhydride to provide Boc protected amines **2.46-2.48**. Silyl deprotection with TBAF followed by copper (II) mediated biaryl ether formation with phenyl boronic acid yielded **2.52-2.54**. Acid deprotection resulted in biaryl ether HCl salts **MM-7**, **MM-10** and **MM-13** in excellent yields.

Scheme 2-6. Synthesis of β-Substituted Phenoxyphenethylamines (**MM-7**, **MM-10**, and **MM-13**-**MM-15**)

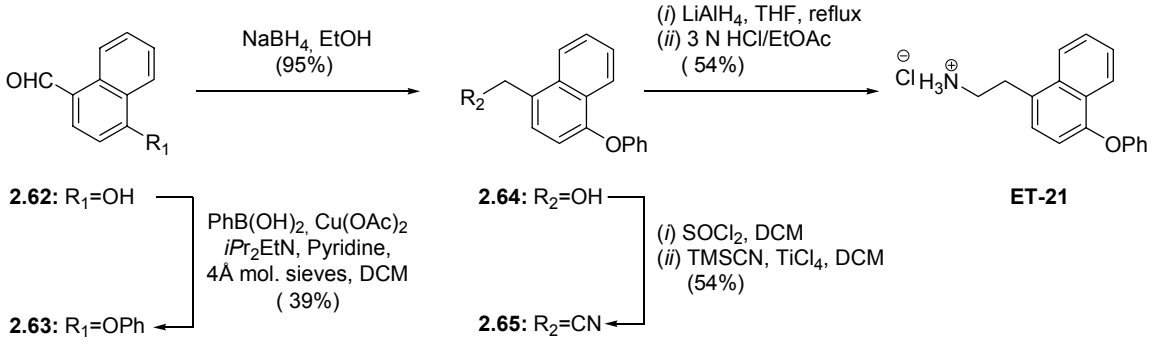


Compounds **MM-14** and **MM-15** (**Scheme 2-6**) were both synthesized from commercially available 4-phenoxybenzaldehyde (**2.55**). Piperidine catalyzed

condensation reaction with Meldrum's acid provided intermediate (**2.56**). Michael addition of phenylacetylide and trimethylsilyl acetylide gave **2.57** and **2.58**, respectively, in good yields.[10] Acetal deprotection and thermal decarboxylation yielded acids **2.59** and **2.60**. Base mediated deprotection of **2.60** gave terminal alkyne **2.61**. Curtius rearrangement followed by acid exposure resulted in hydrochloride salts **MM-14** and **MM-15** in low yields.

As mentioned above (**Table 2-1**), a methyl group rather than an iodine group at the 3 position of **T_1AM** was well tolerated in both $rTAAR_1$ and $mTAAR_1$.[3] The naphethylamines (**Schemes 2-7** and **2-8**) were developed as another halogen free derivative to further probe the binding pocket occupied by the iodine group of **T_1AM**. 1-Naphethylamine (**1-NEA**) and 4-hydroxy-naphetylamine (**4-OH-NEA**) are the naphthyl counterparts to β-phenethylamine and *p*-tyramine, which are both agonists for rat and mouse $TAAR_1$. Copper (II) mediated coupling of 4-hydroxynaphthadehyde (**2.62**) with phenyl boronic acid provided biaryl ether aldehyde **2.63**. Following $NaBH_4$ reduction, the resulting alcohol was converted into a nitrile by treatment with thionyl chloride followed by reaction with $TiCl_4$ and TMSCN. Nitrile **2.65** was then reduced with $LiAlH_4$ and exposed to acid to generate hydrochloride salt **ET-21** in modest yield.

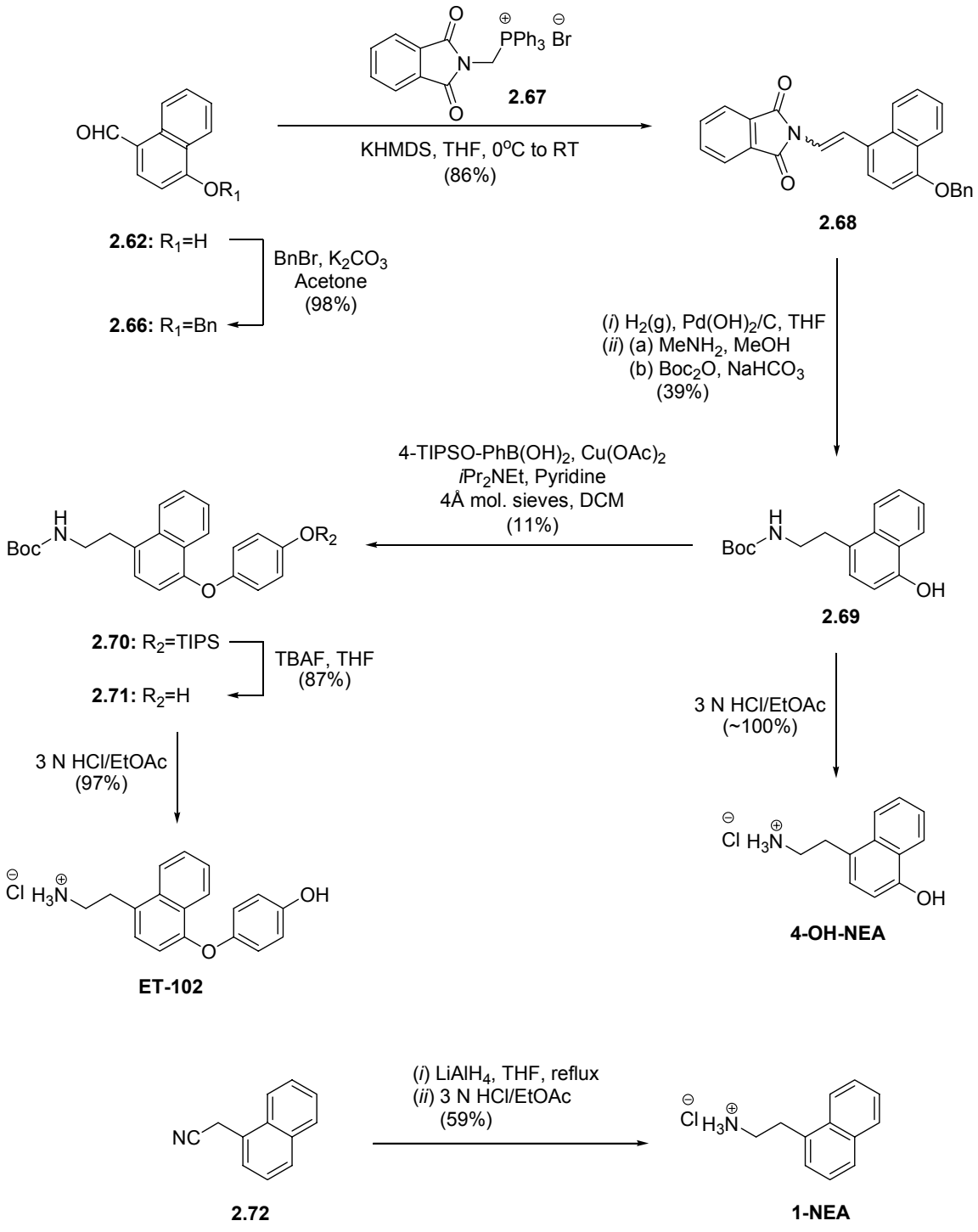
Scheme 2-7. Synthesis of Phenoxynaphethylamine (**ET-21**)



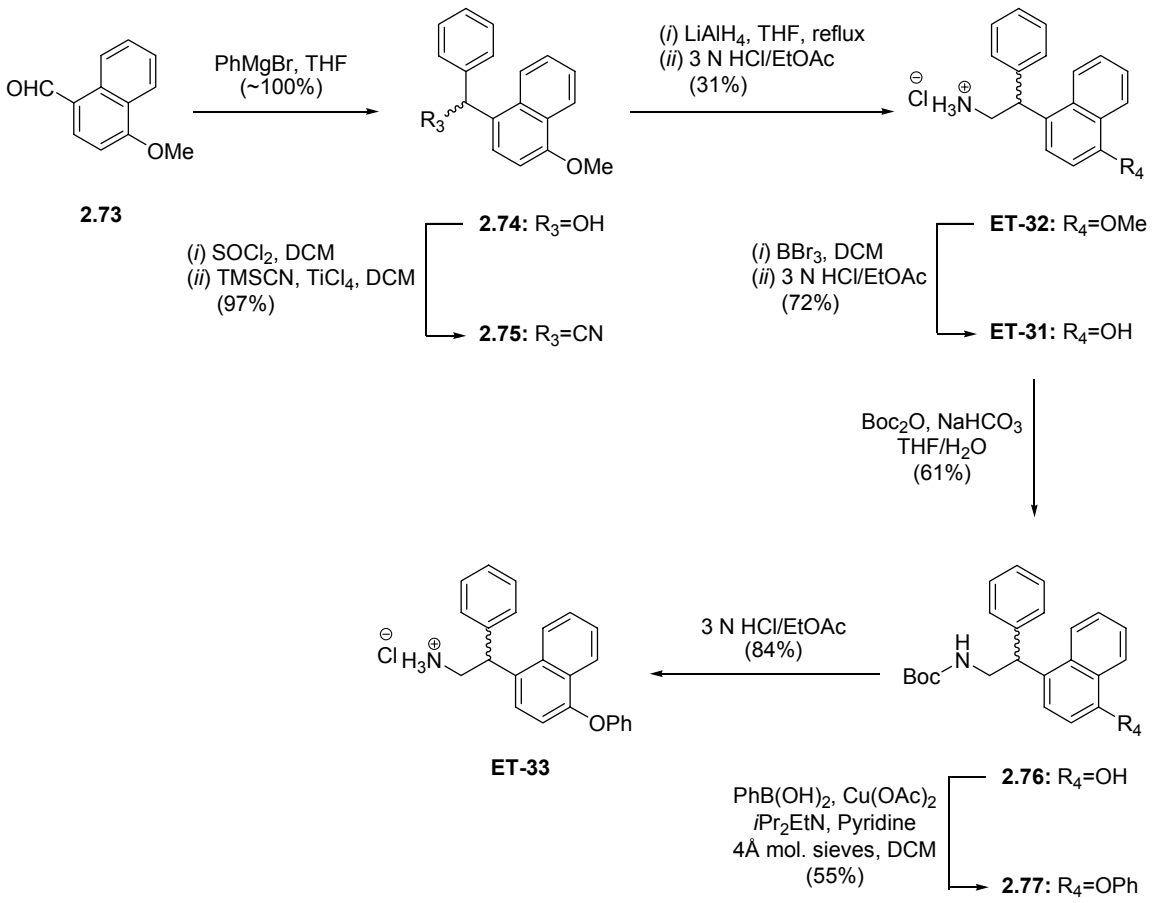
Wittig reaction of benzyl protected **2.62** (**2.66**) with phosphonium bromide **2.67** provided enamine **2.68** in excellent yield (**Scheme 2-8**). This reaction was very sensitive to the concentration of **2.67** in THF; a concentration of 0.11 M gave 86-100% yield, whereas a concentration of 0.24 M gave 15-26% yield. Reagent **2.67** was prepared by refluxing a solution of N-(bromomethyl)phthalimide and PPh_3 in toluene for 24 h. Catalytic hydrogenation of **2.68** with Pearlman's catalyst ($Pd(OH)_2/C$), followed by phthalimide deprotection and immediate Boc protection gave alcohol **2.69** in 39% yield over 3 steps. Boc deprotection provided **4-OH-NEA** as a hydrochloride salt in quantitative yield. Copper (II) mediated coupling of **2.69** with triisopropylsilyl protected 4-hydroxy-phenyl boronic acid formed biaryl ether **2.70** in very poor yield. Treatment with TBAF and subsequent acid deprotection provided the hydrochloride salt of **ET-102**. **1-NEA** was obtained from commercially available 1-naphthylacetonitrile (**2.72**) by reduction with $LiAlH_4$.

A phenyl group was incorporated into the β-carbon of the naphethylamine scaffold (**Scheme 2-9**) to determine if adding a phenyl ring would enhance the potency of the naphethylamine scaffold as observed with **ET-13** and **ET-14**. Reaction of commercially available 4-methoxynaphthaldehyde (**2.73**) with phenylmagnesium bromide quantitatively provided dibenzylic alcohol **2.74**. Treatment with thionyl chloride followed by $TiCl_4$ and TMSCN provided nitrile **2.75**. Nitrile reduction with $LiAlH_4$ and exposure to acid gave the primary amine hydrochloride salt **ET-32**. Methyl ether deprotection with BBr_3 and acid treatment precipitated naphthol **ET-31**. The Boc protected amine **2.76** was subjected to copper (II) mediated coupling to install the biaryl ether group (**2.77**). Acid deprotection provided hydrochloride salt **ET-33** in good yield.

Scheme 2-8. Synthesis of Naphethylamines (**1-NEA**, **4-OH-NEA**, and **ET-102**)



Scheme 2-9. Synthesis of β-Phenylnaphethylamines (**ET-31**-**ET-33**)



2.2.2 Receptor Activation

2.2.2.1 Functional Assay Format

The synthetic compounds were screened for agonist activity through a functional assay using HEK293 cells stably transfected with either rat or mouse $TAAR_1$. The amount of cAMP produced in the cell upon compound stimulation was measured using the HitHunter™ cAMP XS assay by DiscoveRx.[11, 12] This kit is an *in vitro* based competitive immunoassay using enzyme fragment complementation (EFC) technology. In this assay, free cAMP (cAMP from the cell) and labeled cAMP (cAMP conjugated to a small peptide fragment of β-galactosidase) compete for cAMP binding sites on an antibody (**Fig. 2-3a**). When free cAMP binds to the antibody, labeled cAMP is available

to interact with the inactive EFC enzyme. This forms an active β-galactosidase EFC enzyme that can now hydrolyze a substrate to produce a chemiluminescent signal. In the absence of free cAMP, the labeled cAMP is captured by the antibody and unable to reconstitute the galactosidase activity. When plotted as a percentage of positive control (**T_1AM**), agonists will activate in a dose dependent manner while non-agonists will have zero to basal levels of activation (**Fig. 2-3b**).

Representative dose-response curves of agonists for $rTAAR_1$ and $mTAAR_1$ are shown in Figure 2-4. It should be noted that the measured EC_{50} values of **T_1AM** (**Table 2-2**) in this assay are 2- and 3-fold higher in $rTAAR_1$ (EC_{50} = 33 ± 3 nM) and $mTAAR_1$ (EC_{50} = 314 ± 43 nM), respectively, compared to the previously reported values (14 nM and 112 nM for $rTAAR_1$ and $mTAAR_1$, respectively) which were obtained with the classical radioligand/cAMP binding protein assay.[3, 13] However, the rank order potency of compounds was consistent between the radioimmunoassay and EFC assay. In addition to its adaptability for high throughput format, the EFC assay appears to have a better signal range, providing the capacity to distinguish compounds that are more efficacious than **T_1AM**.

Since there are currently no binding assays available for both rat and mouse $TAAR_1$, the antagonist activity of non-agonists was determined by testing for the inhibition of cAMP production of $TAAR_1$ in stably transfected HEK293 cells treated with an EC_{50} concentration of **T_1AM** (**Fig. 2-3b**). This competition assay was validated with β_2AR where the antagonist propranolol was able to inhibit the cAMP production induced by the agonist isoproterenol (data not shown). If the non-agonist is an antagonist, it will

dose-dependently inhibit **T_1AM** induced activity; if it's a non-binding compound, it will have no effect on the **T_1AM** signal.

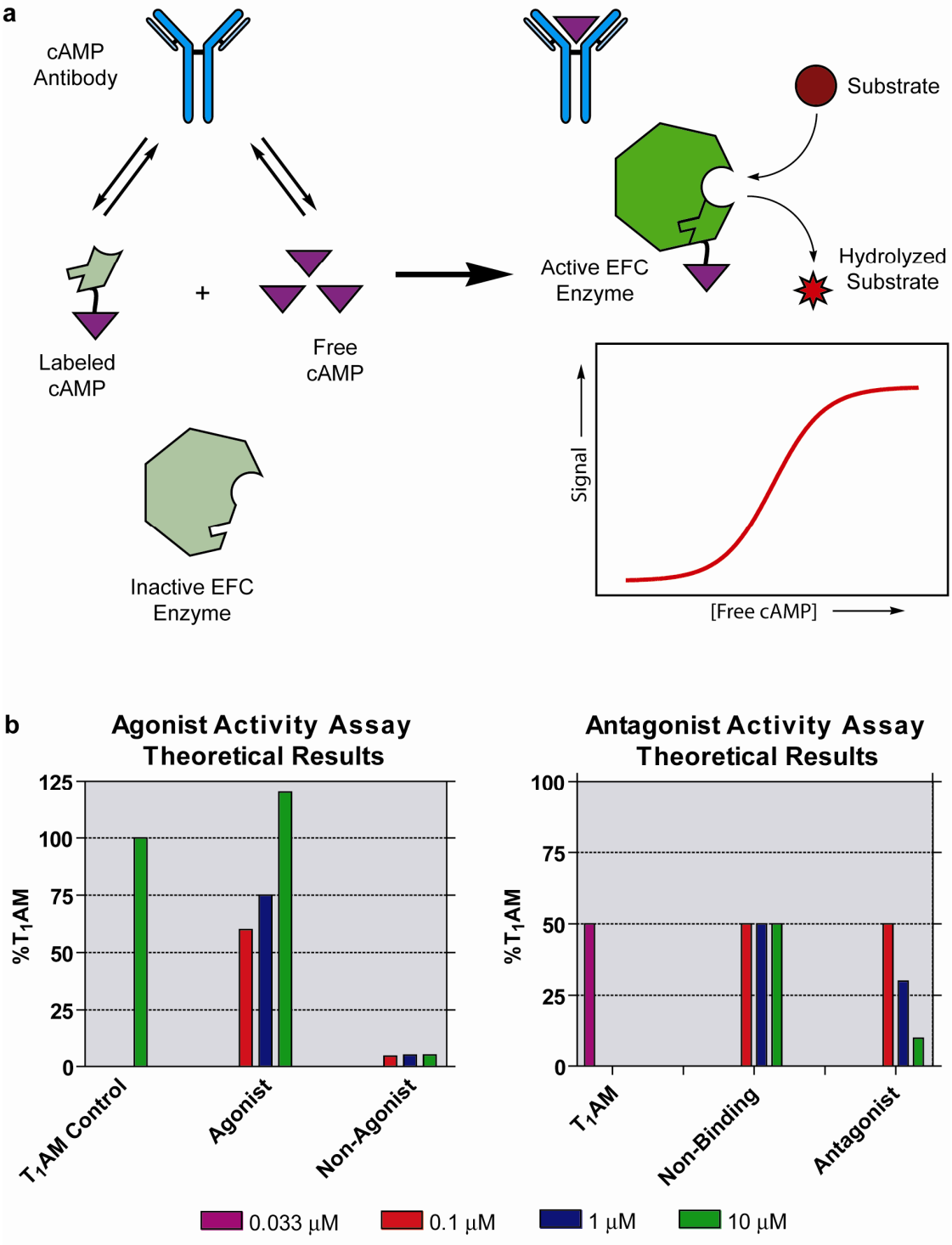


Figure 2-3. Functional activity assay. (**a**) Principle of the Hithunter^{TM} enzyme fragment complementation assay. (**b**) Theoretical results for agonist and antagonist activity assays.

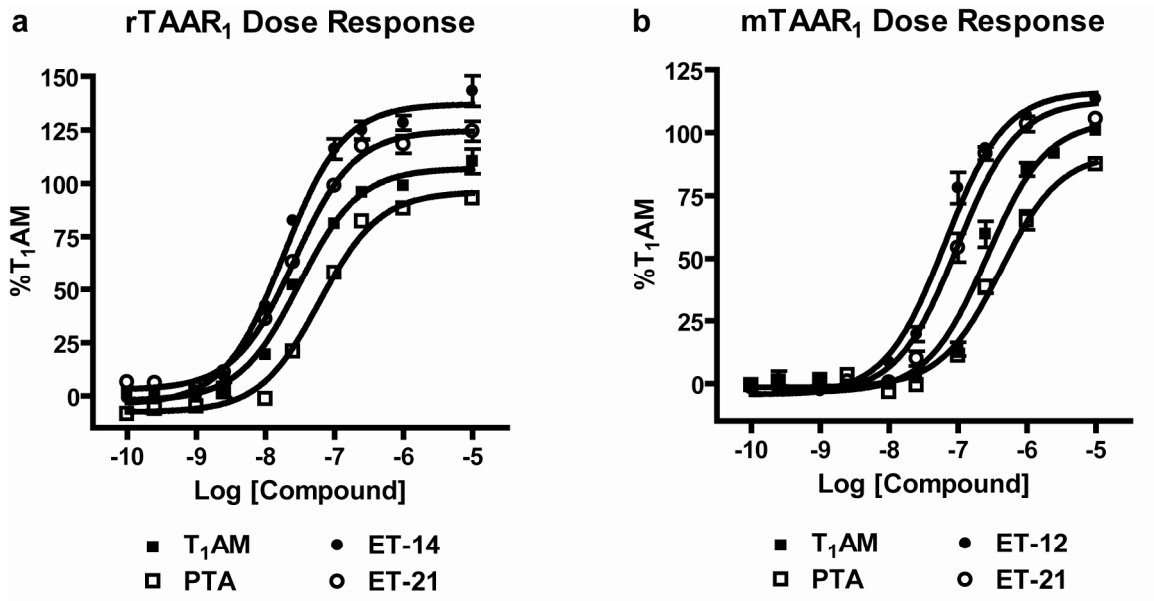
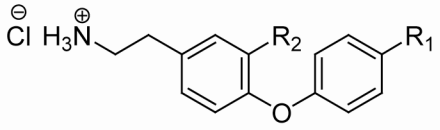


Figure 2-4. Representative dose-response curves of agonists in $rTAAR_1$ and $mTAAR_1$ stably expressed in HEK293 cells. (**a**) Dose-response curves of **T_1AM** (■), **PTA** (□), **ET-14** (●), and **ET-21** (○) for $rTAAR_1$. (**b**) Dose-response curves of **T_1AM** (■), **PTA** (□), **ET-12** (●), and **ET-21** (○) for $mTAAR_1$. Data reported were normalized to **T_1AM** and expressed as a percentage of the activity of **T_1AM** (% T_1AM). Dose-response curves were plotted and EC_{50} values were calculated with use of Prism software as described in the Appendix.

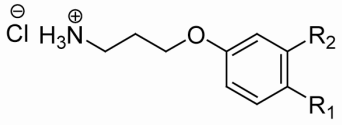
Table 2-2. Activity of **T_1AM** and **PTA** on $rTAAR_1$ and $mTAAR_1$



Compd	R_1	R_2	$rTAAR_1$			$mTAAR_1$		
			EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
T_1AM	OH	I	33 ± 3	100 ± 0	5	314 ± 43	100 ± 0	5
PTA	H	H	63 ± 7	93 ± 4	3	420 ± 66	85 ± 4	3

[a]EC_{50} is the half-maximal effective concentration of a compound. [b]E_{max} is the maximum stimulation achieved at a concentration of 10 μM. EC_{50} and E_{max} values represent the average of *N* independent experiments in triplicate and were calculated by use of Prism software as described in the Appendix. E_{max} = 100 % is defined as the activity of **T_1AM** at 10 μM. [c]*N* is the number of independent experiments in triplicate that were performed and used to calculate the EC_{50} and E_{max} values.

Table 2-3. Activity of Aryloxypropanolamines **ET-1, ET-6, ET-11, and ET-12** on $rTAAR_1$ and $mTAAR_1$



Compd	R_1	R_2	R_3	R_4	$rTAAR_1$			$mTAAR_1$		
					EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-1	OPh	H	H	H	758 ± 104	80 ± 3	2	433 ± 154	92 ± 2	2
ET-6	OPh	H	CH_3	CH_3	>1000	36 ± 6	2	463 ± 173	62 ± 2	2
ET-11	H	OPh	H	H	373 ± 9	90 ± 7	2	885 ± 549	78 ± 13	2
ET-12	OPh	H	CH_3	H	370 ± 70	46 ± 12	2	66 ± 12	113 ± 2	3

[a-c] See footnotes for Table 2-2.

2.2.2.2 Activity of Synthetic Compounds

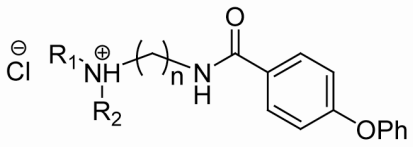
Inserting an oxymethylene bridge between the aromatic and the ethylamine portion of **PTA** had different effects on $rTAAR_1$ and $mTAAR_1$ (**Table 2-3**). For $rTAAR_1$, having an oxymethylene bridge was detrimental. Compared to **PTA**, the potency of **ET-1** decreased ~12 fold (EC_{50} = 758 ± 104 nM and E_{max} = 80 ± 3 %). Mono methylating the amine of **ET-1** (**ET-12**) improved the potency ~2-fold but decreased efficacy (EC_{50} = 370 ± 70 nM and E_{max} = 46 ± 12 %). Dimethylation of **ET-1** decreased both potency and efficacy (EC_{50} > 1 μM and E_{max} = 36 ± 6 %). This trend was consistent with previous SAR for $rTAAR_1$ suggesting that mono methylation of the amine can enhance potency and is preferred over dimethylation.[3] Interestingly, moving the phenoxy group of **ET-1** from the *para* to the *meta* position (**ET-11**) increased potency ~2-fold and efficacy ~10 % (EC_{50} = 373 ± 9 nM and E_{max} = 90 ± 7 %).

For $mTAAR_1$, the oxymethylene bridge was well tolerated (**Table 2-3**). Compound **ET-1** (EC_{50} = 433 ± 154 nM and E_{max} = 92 ± 2 %) was just as potent and efficacious as **PTA**. Mono methylation of the amine (**ET-12**) was very beneficial,

enhancing the potency ~6.5-fold and increasing efficacy by ~21 % (EC_{50} = 66 ± 12 nM and E_{max} = 113 ± 2 %). **ET-12** was also more potent than **T_1AM** by ~4-fold. Dimethylated **ET-6** activated $mTAAR_1$ with the same potency as **ET-1** but had a lower efficacy (EC_{50} = 464 ± 173 nM and E_{max} = 62 ± 2 %). This is also consistent with our previous results showing that $mTAAR_1$ can better accommodate a dimethylamine moiety compared to $rTAAR_1$.[3] The decrease in efficacy without a concomitant reduction in potency observed by dimethylating the amine of **ET-1** (**ET-6**) suggests that it may be possible to convert $mTAAR_1$ agonists into antagonists by simply adjusting the alkylation state of the amine. This may also apply to $rTAAR_1$ as mono-N-methylation of **ET-1** (**ET-12**) decreased the efficacy but improved potency. Contrary to $rTAAR_1$, having the phenoxy group at the *meta* position appears to be detrimental for $mTAAR_1$ since the potency and efficacy of **ET-11** decreased ~2 fold and ~14 % (EC_{50} = 885 ± 549 nM and E_{max} = 78 ± 13 %), respectively, compared to **ET-1**.

In general, compounds based on the benzamidoalkylamine scaffold were poor agonists for $rTAAR_1$ (**Table 2-4**). All primary and secondary amine derivatives (**ET-2**–**ET-5** and **ET-7**–**ET-10**) activated $rTAAR_1$ with EC_{50} values greater than 1 μM and efficacies equal to or less than 69 %. These benzamidoalkylamine analogs were also poor agonists for $mTAAR_1$ except for **ET-10**. **ET-10** was ~4- and ~3- fold more potent (EC_{50} = 109 ± 6 nM) for $mTAAR_1$ compared to **PTA** and **T_1AM,** respectively. The efficacy of **ET-10** (E_{max} = 82 ± 4 %) was comparable to that of **PTA**. All of the benzamidoalkylamine non-agonists, which are defined as compounds with $E_{max} \leq$ 10 %, did not inhibit **T_1AM** induced activity in competition assays and are therefore non-binding compounds for either rat or mouse $TAAR_1$ (**Fig. 2-5**).

Table 2-4. Activity of Benzamidoalkylamines **ET-2**–**ET-5** and **ET-7**–**ET-10** on $rTAAR_1$ and $mTAAR_1$



Compd	n	R_1	R_2	$rTAAR_1$			$mTAAR_1$		
				EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-2	2	H	H	>1000	4 ± 2	2	>1000	17 ± 5	2
ET-3	3	H	H	>1000	2 ± 1	2	>1000	2 ± 1	2
ET-4	4	H	H	>1000	31 ± 2	2	>1000	1 ± 1	2
ET-5	5	H	H	>1000	69 ± 7	2	905 ± 261	96 ± 5	2
ET-7	2	CH_3	CH_3	>1000	5 ± 4	2	>1000	7 ± 2	2
ET-8	3	CH_3	CH_3	>1000	2 ± 4	2	>1000	0 ± 2	2
ET-9	4	CH_3	CH_3	>1000	1 ± 4	2	>1000	3 ± 1	2
ET-10	5	CH_3	CH_3	>1000	44 ± 8	2	109 ± 6	82 ± 4	3

[a-c] See footnotes for Table 2-2.

The orthopramide-alkylamines were also poor agonists for both receptors. **ET-22**–**ET-30** had potencies greater than 1 μM and only activated up to 43 % efficacy (**Table 2-5**). When screened for antagonist activity, none of the inactive orthopramide-alkylamine compounds were antagonists for either $rTAAR_1$ or $mTAAR_1$ (**Fig. 2-5**).

Appending a phenyl ring from the β-carbon of **PTA** was preferred by $rTAAR_1$ but not $mTAAR_1$ (**Table 2-6**). The potency of **ET-13** (EC_{50} = 28 ± 2 nM and E_{max} = 103 ± 4 %) for $rTAAR_1$ was equivalent to that of **T_1AM**, and ~2-fold more potent than **PTA**. Moving the phenoxy group to the *meta* position (**ET-14**) further increased potency (EC_{50} = 19 ± 2 nM) and efficacy (E_{max} = 131 ± 7 %). For $mTAAR_1$, the β-carbon phenyl substituent was unfavorable giving compounds with potencies greater than 1 μM and efficacies equal to or less than 35 % for both receptors.

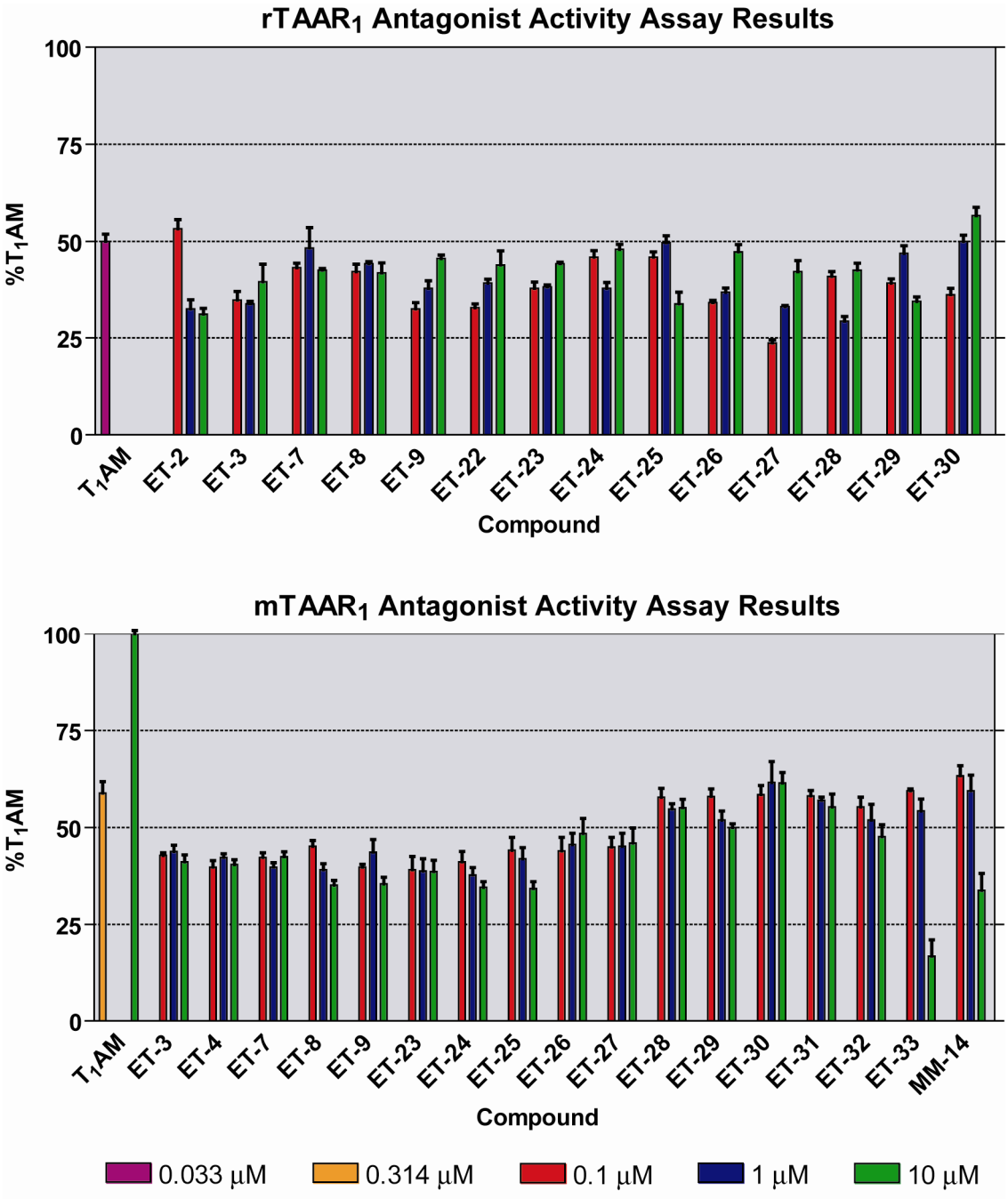
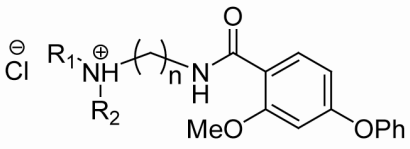
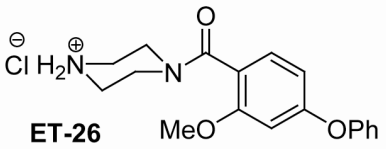


Figure 2-5. Antagonist activity assay results of non-agonists on $rTAAR_1$ and $mTAAR_1$.

Cyclizing the amine to conformationally restrict the β-carbon phenyl group gave tetrahydrobenzazepines (**ET-15**–**ET-20**) that were all weak agonists for both $rTAAR_1$ and $mTAAR_1$ (**Table 2-7**). The potencies of **ET-15**–**ET-20** were ≥ 561 nM and the efficacies did not surpass 86 % for either receptor.

Table 2-5. Activity of Orthopramide-alkylamines **ET-22**–**ET-30** on rTAAR$_1$ and mTAAR$_1$



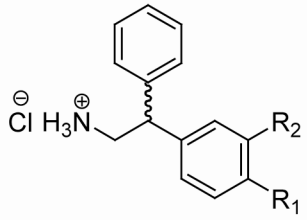


ET-26

Compd	n	R_1	R_2	rTAAR$_1$			mTAAR$_1$		
				EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-22	2	H	H	>1000	25 ± 4	2	>1000	36 ± 2	2
ET-23	3	H	H	>1000	5 ± 2	2	>1000	6 ± 1	2
ET-24	4	H	H	>1000	8 ± 2	2	>1000	2 ± 0	2
ET-25	5	H	H	>1000	12 ± 6	2	>1000	6 ± 1	2
ET-26	-	-	-	>1000	5 ± 8	2	>1000	0 ± 2	2
ET-27	2	CH_3	CH_3	>1000	4 ± 3	2	>1000	12 ± 4	2
ET-28	3	CH_3	CH_3	>1000	6 ± 7	2	>1000	0 ± 1	2
ET-29	4	CH_3	CH_3	>1000	0 ± 1	2	>1000	0 ± 1	2
ET-30	5	CH_3	CH_3	>1000	9 ± 2	2	>1000	43 ± 6	2

[a-c] See footnotes for Table 2-2.

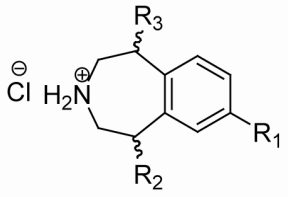
Table 2-6. Activity of β-Phenylphenoxyphenethylamines **ET-13** and **ET-14** on rTAAR$_1$ and mTAAR$_1$



Compd	R_1	R_2	rTAAR$_1$			mTAAR$_1$		
			EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-13	OPh	H	28 ± 2	103 ± 4	3	>1000	35 ± 8	3
ET-14	H	OPh	19 ± 2	131 ± 7	3	>1000	15 ± 4	3

[a-c] See footnotes for Table 2-2. Compounds with stereogenic centers were evaluated as racemic mixtures.

Table 2-7. Activity of Tetrahydrobenzazepines **ET-15**–**ET-20** on $rTAAR_1$ and $mTAAR_1$



Compd	R_1	R_2	R_3	$rTAAR_1$			$mTAAR_1$		
				EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-15	OH	Ph	H	>1000	64 ± 7	2	>1000	51 ± 4	2
ET-16	OMe	Ph	H	561 ± 45	29 ± 9	2	>1000	79 ± 1	2
ET-17	OPh	Ph	H	>1000	32 ± 8	2	>1000	22 ± 3	2
ET-18	OH	H	Ph	>1000	24 ± 7	2	>1000	41 ± 2	2
ET-19	OMe	H	Ph	>1000	31 ± 4	2	>1000	31 ± 1	2
ET-20	OPh	H	Ph	>1000	86 ± 2	2	>1000	45 ± 5	2

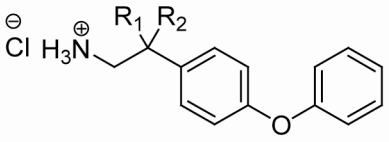
[a-c] See footnotes for Table 2-2. Compounds with stereogenic centers were evaluated as racemic mixtures.

Increasing the size of the substituent at the β-carbon of **PTA** to a benzyl (**MM-13**) or phenylethynyl (**MM-14**) was well tolerated by the $rTAAR_1$ but not $mTAAR_1$ (**Table 2-8**). Compound **MM-13** was ~2-fold less potent (EC_{50} = 140 ± 77 nM) but equally efficacious (E_{max} = 92 ± 3 %) to **PTA** for $rTAAR_1$. Compound **MM-14** was equipotent (EC_{50} = 62 ± 15 nM) and more efficacious (E_{max} = 119 ± 3 %) compared to **PTA**. In $mTAAR_1$ both **MM-13** and **MM-14** were weak agonists.

Smaller β-carbon substituents were also better tolerated in $rTAAR_1$ compared to $mTAAR_1$ (**Table 2-8**). Adding one or two methyl groups to the β-carbon of **PTA** decreased the potency for $rTAAR_1$ by 4-fold (EC_{50} = 250 ± 132 nM and > 1 μM for **MM-10** and **MM-7** respectively). Mono-methyl **MM-10** was comparably efficacious (E_{max} = 94 ± 7 %) to **PTA**, whereas dimethyl **MM-7** was significantly less efficacious (E_{max} = 13 ± 2 %). Interestingly, a small unsaturated acetylene group at the β-carbon (**MM-15**)

slightly enhanced the potency (EC_{50} = 41 ± 4 nM) without significantly changing the efficacy (E_{max} = 105 ± 14 %) of **PTA** for $rTAAR_1$. For $mTAAR_1$, all of these derivatives activated poorly ($EC_{50} \geq 1$ μM) and had lower efficacies ($E_{max} \leq$ 72 %). It should be noted that **MM-14** displayed some level of antagonist activity in competition assays with **T_1AM,** decreasing cAMP induction of **T_1AM** at $mTAAR_1$ ~50% at a dose of 10μM (**Fig. 2-5**).

Table 2-8. Activity of β-Substituted Phenoxyphenethylamines **MM-7**, **MM-10**, and **MM-13**–**MM-15** on $rTAAR_1$ and $mTAAR_1$



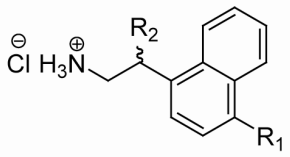
Compd	R_1	R_2	$rTAAR_1$			$mTAAR_1$		
			EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
MM-7	CH_3	CH_3	>1000	13 ± 2	2	>1000	18 ± 4	2
MM-10	CH_3	H	250 ± 132	94 ± 7	2	>1000	72 ± 7	2
MM-13	Bn	H	140 ± 77	92 ± 3	2	>1000	31 ± 9	2
MM-14	CCH	H	41 ± 4	105 ± 14	3	>1000	2 ± 5	2
MM-15	CCPh	H	62 ±15	119 ± 3	3	929 ± 314	79 ± 9	2

[a-c] See footnotes for Table 2-2. Compounds with stereogenic centers were evaluated as racemic mixtures.

The naphethylamine scaffold was favorable to $rTAAR_1$ and $mTAAR_1$ (**Table 2-9**). **1-NEA** and **4-OH-NEA** were full agonists for $rTAAR_1$ with potencies of 65 ± 6 nM and 46 ± 6 nM, and efficacies of 115 ± 2 % and 111 ± 5 %, respectively. Converting the inner ring of **PTA** from a benzene to naphthalene (**ET-21**) increased its potency ~2-fold (EC_{50} 26 ± nM) and efficacy ~20 % (E_{max} = 113 ± 5 %). Adding a *para*-hydroxyl group to the outer ring **ET-21** (**ET-102**) had a modest effect on potency (EC_{50} = 19 ± 3 nM) but decreased the efficacy ~17 % (E_{max} = 96 ± 2). A phenyl ring at the β-carbon (**ET-33**)

decreased the potency of **ET-21** for rTAAR$_1$ ~2-fold. **ET-33** activated rTAAR$_1$ with a potency of 52 ± 4 nM and an efficacy of 100 ± 5 %. Changing the phenoxy group of **ET-33** to a methoxy (**ET-32**) or hydroxyl (**ET-31**) group decreased the potency of **ET-31** and **ET-32** ~5-14-fold (EC_{50} = 716 ± 269 nM and 270 ± 66 nM, respectively) and efficacy ~10 to 30 % (E_{max} = 89 ± 3 % and 71 ± 4 %, respectively).

Table 2-9. Activity of Naphethylamines **1-NEA**, **4-OH-NEA**, **ET-21**, **ET-102**, and **ET-31**–**ET-33** on rTAAR$_1$ and mTAAR$_1$



Compd	R_1	R_2	rTAAR$_1$			mTAAR$_1$		
			EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
1-NEA	H	H	65 ± 6	115 ± 2	2	82 ± 17	112 ± 3	2
4-OH-NEA	OH	H	46 ± 6	111 ± 5	3	649 ± 71	109 ± 2	2
ET-21	OPh	H	26 ± 1	113 ± 5	3	100 ± 22	104 ± 3	3
ET-102	OPh-(*p*-OH)	H	19 ± 3	96 ± 2	3	171 ± 13	98 ± 1	2
ET-31	OH	Ph	716 ± 269	89 ± 3	2	>1000	14 ± 4	2
ET-32	OMe	Ph	270 ± 66	71 ± 4	2	>1000	14 ± 4	2
ET-33	OPh	Ph	52 ± 4	100 ± 6	3	>1000	0 ± 2	2

[a-c] See footnotes for Table 2-2. Compounds with stereogenic centers were evaluated as racemic mixtures.

For mTAAR$_1$, **1-NEA** and **4-OH-NEA** were also full agonists with maximal efficacies of 112 ± 3 % and 109 ± 2 %, respectively (**Table 2-9**). However, **4-OH-NEA** (EC_{50} = 649 ± 71 nM) was ~8-fold less potent than **1-NEA** (82 ± 17 nM). **ET-21** and **ET-102** were ~2.5-4-fold more potent (EC_{50} = 100 ± 22 nM and 171 ± 13 nM, respectively) and ~13-19% more efficacious (E_{max} = 104 ± 3 % and 95 ± 1 %, respectively) than **PTA**. All of the β-carbon phenyl derivatives of **ET-21** (**ET-31**–**ET-**

33) were at least 10-fold less potent at $mTAAR_1$ (EC_{50} > 1 μM) and ≥ 71 % less efficacious compared to **PTA.** When **ET-31** through **ET-33** were screened for antagonist activity in competition assays, only **ET-33** displayed some degree of antagonism inhibiting compound **T_1AM** induced cAMP production at $mTAAR_1$ ~75 % at a dose of 10μM (**Fig. 2-4**). The approximate half maximal inhibitory concentration (IC_{50}) was ~7 μM. The observed activity of all compounds tested were found to be $TAAR_1$ dependent as all compounds showed no cAMP accumulation when screened in an empty vector control cell line (data not shown).

2.3 Discussion

We have previously shown that the potency of **T_1AM** for both rat and mouse $TAAR_1$ can be improved by changing the methylation state of the amine and/or modifying the outer ring portion of the phenoxyphenethylamine core scaffold.[3] The pharmacological survey by Bunzow *et al.*[1] showed that $rTAAR_1$ could be activated by phenethylamine analogs, amphetamines, ergolines, and aminergic GPCR (adrenergic, dopamine, and serotonin receptors) drugs with a structurally diverse range of ethylamine segments (**Fig 2-1**). In this chapter, a number of **PTA** derivatives with structural modifications in the ethylamine section were synthesized to explore the SAR and determine if structural variations in this region would provide more potent agonists and some lead antagonists for rat and mouse $TAAR_1$.

The $TAAR_1$ activity data showed that rat and mouse $TAAR_1$ can tolerate prominent structural features commonly found in the alkylamine fragment of existing βAR and dopamine receptor agonists and antagonists; however, distinct $TAAR_1$ species

preferences are evident. Extending the distance between the charged amine and the aromatic ring of **PTA** by inserting an oxymethylene bridge or an amide linker was tolerated by $mTAAR_1$ but not $rTAAR_1$. On the other hand, appending a phenyl ring at the β-carbon of **PTA** was detrimental for $mTAAR_1$ activation but beneficial for $rTAAR_1$ activation. The preference for hydrocarbon functional groups with some degree of unsaturation at the β-carbon indicates that the binding pocket of $rTAAR_1$ around this position is primarily hydrophobic in nature. Conversely, the tolerance for ether and amide groups in the ethylamine chain of **PTA** suggests a more polar binding pocket in the same region of $mTAAR_1$.

The two receptors also responded differently to changes in the position of the phenoxy group. In general, the potency and efficacy of compounds increased when the phenoxy group was shifted from the *para* to the *meta* position in $rTAAR_1$ as observed with the change in activity from **ET-1** to **ET-11** and **ET-13** to **ET-14**. The same modification gives the opposite effect in $mTAAR_1$ leading to less potent and efficacious compounds. Confining the ethylamine chain of **ET-13** and **ET-14** in a seven membered ring (**ET-15**–**ET-20**) to restrict the conformational orientations of the β-carbon phenyl group was extremely detrimental to $rTAAR_1$ decreasing potency greater than 35-fold.

Transforming the phenethylamine ring of **PTA** into a naphthyl ring was equally beneficial improving the potency and efficacy for $rTAAR_1$ and $mTAAR_1$ to the level of **T_1AM** or better. The additional benzene ring in the naphthyl group of **ET-21** and **ET-102** most likely occupies the iodine binding pocket in $TAAR_1$ and is thus a good isosteric replacement for the iodine present in **T_1AM**. Contrary to the phenoxyphenethylamine scaffold, appending a phenyl group at the β-carbon of the phenoxynaphethylamine

scaffold decreased the potency for rTAAR$_1$. Having the bulkier naphthyl group for an inner ring could possibly limit the available torsional conformations of **ET-33** and affect its ability to position the β-phenyl ring in the optimal orientation inside the binding pocket of rTAAR$_1$ resulting in decreased potency. The considerable decrease in potency observed with hydroxyl (**ET-31**) or methoxy (**ET-32**) substituents in place of the phenoxy group illustrates the significant contribution of the biaryl ether moiety to the potency of the phenoxynaphethylamine scaffold. The same trend was observed when the phenoxy group of **ET-21** was substituted with an alcohol; **4-OH-NEA** was ~2- and ~6.5 fold less potent for rTAAR$_1$ and mTAAR$_1$, respectively. However, the efficacy of **4-OH-NEA** was unaffected as it was comparable to that of **ET-21**. Removing the hydroxyl group of **4-OH-NEA** (**1-NEA**) had no effects on rTAAR$_1$ but significantly increased the potency in mTAAR$_1$. **1-NEA** was ~8 fold more potent than **4-OH-NEA**, activating at the level of **ET-21**.

The antagonist activity of **MM-14** and **ET-33** in mTAAR$_1$ was interesting because these compounds are potent full agonists for rTAAR$_1$. The opposite functional properties suggest different modes of binding between the two receptors. The observed SAR preferences between the rat and mouse TAAR$_1$ was quite interesting given that the two receptors are 93% similar. This species variability is suspected to be caused by non-conserved, specificity determinant residues within the binding site of TAAR$_1$ and is discussed in Chapter 6. Since the rodent receptors are only 83-85% similar to the human receptor, the SAR of the ethylamine portion of **T$_1$AM** for the human TAAR$_1$ (hTAAR$_1$) may be different from that of the rat or mouse TAAR$_1$. Compound **T$_1$AM** has recently

been found to be significantly less potent for $hTAAR_1$ by Wainscott *et al.*[14] when they investigated the pharmacological profile of $hTAAR_1$.

2.4 Conclusion

The data presented in this chapter demonstrates that it is possible to enhance the potency of thyronamines for both rat and mouse $TAAR_1$ by incorporating functionalities in the ethylamine portion of the phenoxyphenethylamine scaffold. Rat and mouse $TAAR_1$ have different structural preferences in this region of the scaffold with $rTAAR_1$ favoring unsaturated hydrocarbon groups and $mTAAR_1$ preferring functional groups that are polar and hydrogen bond acceptors. Despite this species variability, transforming the inner ring of the phenoxyphenethylamine scaffold into a naphthyl group was equally beneficial to both receptors mostly likely acting as an excellent isosteric replacement for the iodophenyl inner ring of **T_1AM**. Lastly, incorporating prominent structural features found in existing antagonistic GPCR drugs into a $TAAR_1$ agonist does not necessarily generate an antagonist.

2.5 References

1. Bunzow, J.; Sonders, M.; Arttamangkul, S.; Harrison, L.; Zhang, G.; Quigley, D.; Darland, T.; Suchland, K.; Pasumamula, S.; Kennedy, J.; Olson, S.; Magenis, R.; Amara, S.; Grandy, D., Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. *Mol. Pharmacol.* **2001,** 60, (6), 1181-1188.
2. Reese, E.; Bunzow, J.; Arttamangkul, S.; Sonders, M.; Grandy, D., Trace amine-associated receptor 1 displays species-dependent stereoselectivity for isomers of methamphetamine, amphetamine, and para-hydroxyamphetamine. *J. Pharmacol. Exp. Ther.* **2007,** 321, (1), 178-186.
3. Hart, M.; Suchland, K.; Miyakawa, M.; Bunzow, J.; Grandy, D.; Scanlan, T., Trace amine-associated receptor agonists: Synthesis and evaluation of thyronamines and related analogues. *J. Med. Chem.* **2006,** 49, (3), 1101-1112.
4. Pine, S. H.; Sanchez, B. L., Formic acid-formaldehyde methylation of amines. *J. Org. Chem.* **1971,** 36, (6), 829-832.
5. Mattingly, P. G., Mono-Protected Diamines-N^{α}-*tert*-Butoxycarbonyl α,ω-Alkanediamine Hydrochlorides from Amino-alcohols. *Synthesis* **1990**, (4), 366-368.
6. Evans, D. A.; Katz, J. L.; West, T. R., Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998,** 39, (19), 2937-2940.

7. Kraxner, J.; Hubner, H.; Gmeiner, P., Azepino- and diazepinoindoles: Synthesis and dopamine receptor binding profiles. *Arch. Pharm. (Weinheim, Ger.)* **2000,** 333, (9), 287-292.

8. Shah, J. H.; Izenwasser, S.; Geter-Douglass, B.; Witkin, J. M.; Newman, A. H., (+/-)-(N-Alkylamino)benzazepine analogs: novel dopamine D1 receptor antagonists. *J. Med. Chem.* **1995,** 38, (21), 4284-4293.

9. Finholt, A. E.; Bond, A. C.; Schlesinger, H. I., Lithium Aluminum Hydride, Aluminum Hydride and Lithium Gallium Hydride, and Some of their Applications in Organic and Inorganic Chemistry. *J. Am. Chem. Soc.* **1947,** 69, (5), 1199-1203.

10. Kruse, L. I.; Kaiser, C.; DeWolf, J., W. E.; Chamber, P. A.; Goodhart, P. J.; Ezekiel, M.; Ohlstein, E. H., β-Substituted Phenethylamines as High-Affinity Mechanism-Based Inhibitors of Dopamine β-Hydroxylase. *J. Med. Chem.* **1988,** 31, (4), 704-706.

11. Eglen, R. M., Enzyme fragment complementation: a flexible high throughput screening assay technology. *Assay Drug Dev. Technol.* **2002,** 1, (1 Pt 1), 97-104.

12. Eglen, R. M.; Singh, R., Beta galactosidase enzyme fragment complementation as a novel technology for high throughput screening. *Comb. Chem. High Throughput Screening* **2003,** 6, (4), 381-387.

13. Scanlan, T.; Suchland, K.; Hart, M.; Chiellini, G.; Huang, Y.; Kruzich, P.; Frascarelli, S.; Crossley, D.; Bunzow, J.; Ronca-Testoni, S.; Lin, E.; Hatton, D.; Zucchi, R.; Grandy, D., 3-iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat. Med.* **2004,** 10, (6), 638-642.

14. Wainscott, D.; Little, S.; Yin, T.; Tu, Y.; Rocco, V.; He, J.; Nelson, D., Pharmacologic characterization of the cloned human trace amine-associated receptor1 (TAAR1) and evidence for species differences with the rat TAAR1. *J. Pharmacol. Exp. Ther.* **2007,** 320, (1), 475-485.

Chapter 3

Insights into Aminergic G-Protein Coupled Receptor Drug Design

The antagonist based drug design strategy of incorporating prominent structural features found in existing GPCR antagonists into the structure of $TAAR_1$ agonists provided distinct scaffolds that were potent agonists for rat and mouse $TAAR_1$, a weak antagonist (**ET-33**) for $mTAAR_1$, but no lead antagonists for $rTAAR_1$. Interestingly, **ET-33** is a full agonist of $rTAAR_1$. The disparate functional property of **ET-33** and the inability to convert $TAAR_1$ agonists into antagonists suggest that mimicking structural motifs is not a viable approach to developing $TAAR_1$ antagonists. This approach has been limited by a lack of knowledge regarding the nature of the drug-receptor interaction and insights into the code of aminergic GPCR drug design. Presently, it is unclear what inherent structural features of a ligand are responsible for endowing agonistic or antagonistic properties or how and why those structural elements lead to receptor activation or inhibition. Insights into the molecular basis of compound induced receptor activation and inhibition was obtained by analyzing the structure–activity relationships and mapping the pharmacophores of existing GPCR drugs into the binding site of their target receptors.

3.1 Molecular Mechanism of GPCR Activation

The biogenic amine GPCRs are seven transmembrane (TM) proteins with an extracellular amino terminus and an intracellular carboxy terminus (**Fig. 3-1a,b**).[1, 2] The β_2-adrenergic receptor (β_2AR) is the model system for investigating the molecular mechanism of GPCR activation. Previous work with β_2AR suggests that agonist binding toggles a rotamer switch to its active configuration and induces a conformational change in transmembrane 6 (TM6) (**Fig. 3-1d**).[3] The movement of the cytoplasmic end of TM6 away from TM3 is thought to break an ionic lock interaction that is present in the inactive

state of the receptor (**Fig. 3-1c**). This exposes G-protein recognition sites in the intracellular surface of the receptor that activate G-proteins and initiate the signaling cascade.[4, 5] The rotamer switch is partly composed of a tryptophan (W6.48) and phenylalanine (F6.52) residues in TM6 that toggle concertedly between their inactive (**Fig. 3-1c**) and active (**Fig. 3-1d**) rotamer configurations to modulate the bend angle of the kink in TM6 formed by proline 6.50 (P6.50). The ionic lock involves highly conserved aspartic acid (D3.49) and arginine (R3.50) residues in TM3 and a glutamic acid (E6.30) residue in TM6.

Residues are labeled relative to the most conserved amino acid in the transmembrane segment in which it is located.[6] Tryptophan 6.48, for example, is located in TM6 and precedes the most conserved residue by 2 positions. Arginine 3.50 is the most conserve residue in TM3. This system simplifies the identification of aligned residues in different GPCRs.

Sequence alignment of adrenergic, dopamine, and $TAAR_1$ receptors show the ionic lock residues and rotamer switch residues to be absolutely conserved (**Fig. 3-2)**. This conservation suggests that the rotamer switch may be a general mechanism for aminergic GPCR activation.

3.2 Insights into β_2-Adrenergic and Dopamine 1 Receptor Agonism

Based on this mechanism, we hypothesized that the functional properties of a compound are determined by the nature of its interaction with the rotamer switch residues. If a compound allows the rotamer switch to toggle and/or has more favorable interactions with the active state of the receptor, it will act as an agonist (**Fig. 3-1d**). In contrast, a compound will behave as an antagonist if it can sterically occlude the rotamer

switch and/or has more favorable interactions with the inactive state of the receptor (**Fig. 3-1c**).

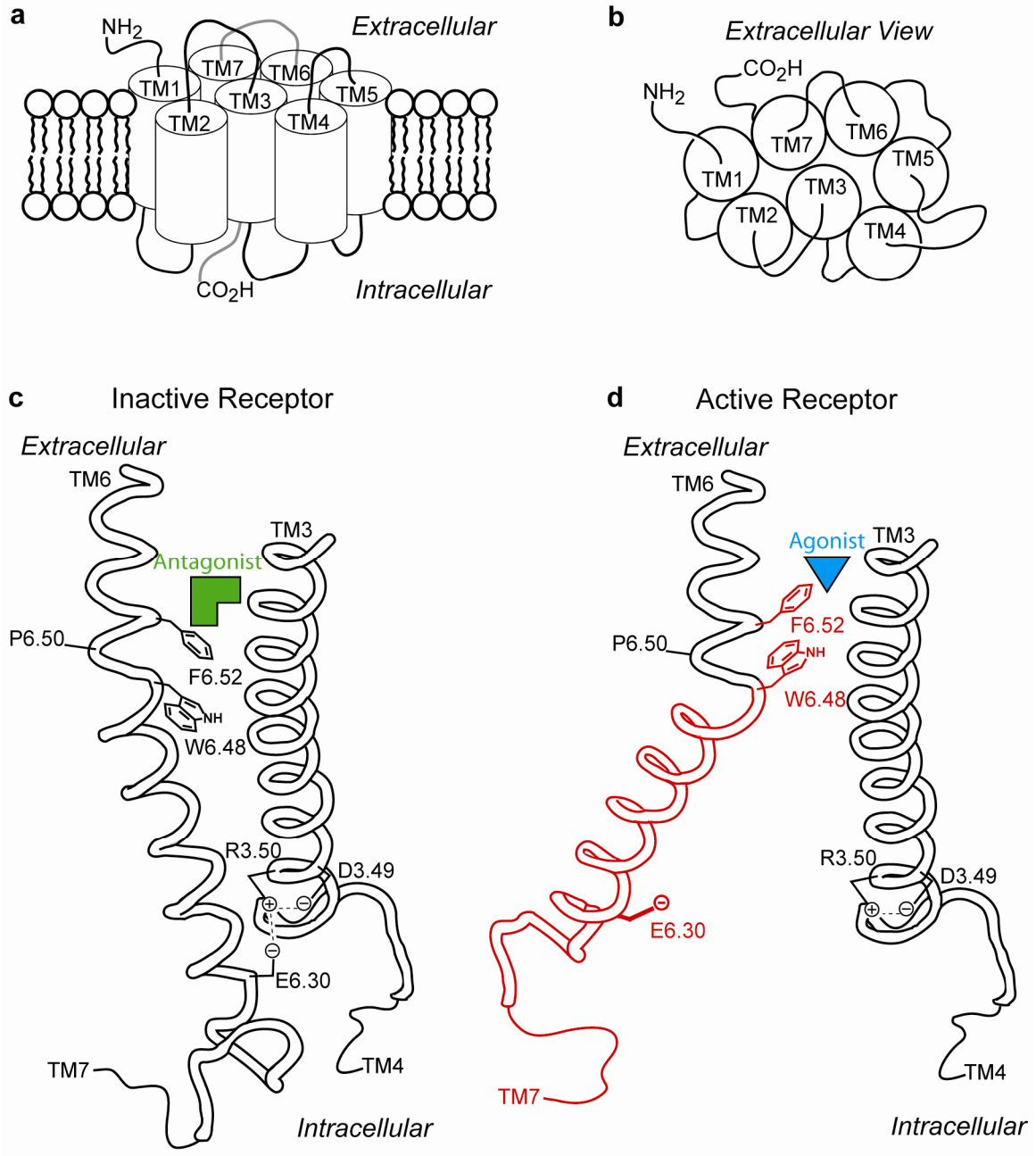


Figure 3-1. Schematic representations of GPCRs and the rotamer toggle switch model of aminergic GPCR activation. (**a**) Helical arrangement of GPCRs viewed form the cell membrane and (**b**) extracellular surface. (**c**) Inactive state of the receptor with an antagonist sterically occluding the rotamer switch residues (W6.48 and F6.52) from assuming their active conformation. (**d**) Agonist binding toggles the rotamer switch to its active conformation and induces a conformational change in TM6 that breaks the ionic lock interaction (D3.49, R3.50, & E6.30) present in the inactive state of the receptor. (**c**) and (**d**) are viewed from the perspective of TM7.

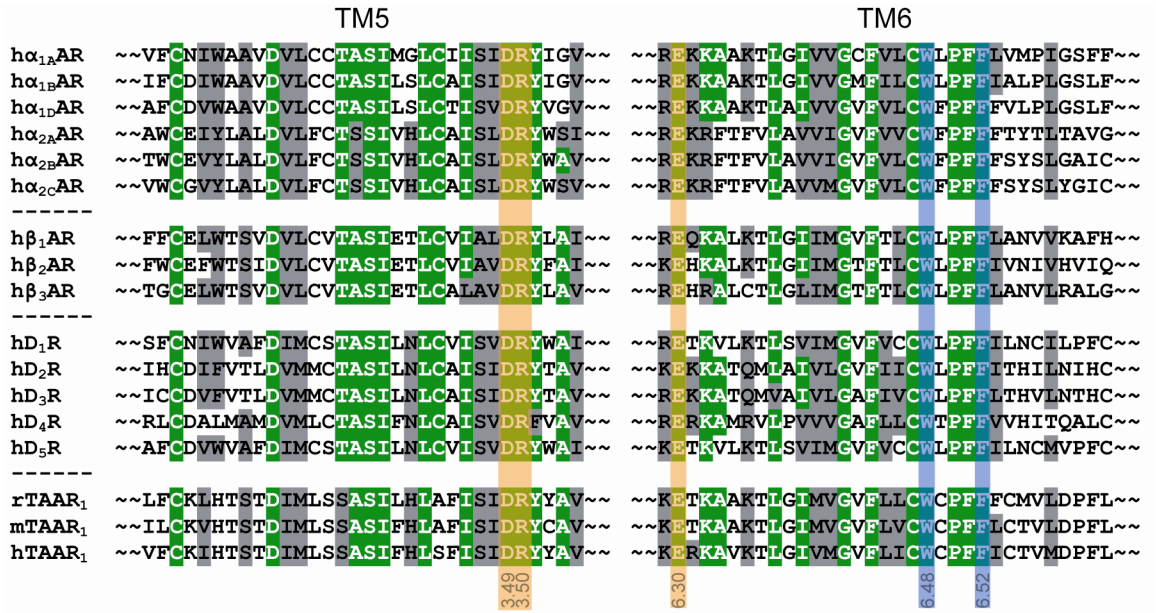


Figure 3-2. Sequence alignment of TM5 and TM6 of aminergic GPCRs. Ionic lock and toggle switch residues are highlighted in orange and blue, respectively.

The binding site of aminergic GPCRs is located within the TM region and is primarily composed of the extracellular half of transmembranes 3, 5, 6, and 7.[7-10] Elegant pharmacological and mutagenesis studies on β_2AR suggest that epinephrine binds to β_2AR with aspartic acid 3.32 (D3.32) acting as the counter ion for the charged amine, serines 5.42, 5.43, and 5.46 (S5.42, S5.43, and S5.46, respectively) interacting with the catechol hydroxyls, phenylalanines 6.51 and 6.52 (F6.51 and F6.52) interacting with the catechol ring, and asparagine 6.55 (N6.55) as the partner for the β-hydroxy group (**Fig. 3-3a**).[11-18] Dopamine binds to the dopamine receptors (DR) in the same orientation because the binding determinant residues (D3.32, S5.42, S5.43, and S5.46) are conserved (**Fig. 3-3b**). Within the binding site, the rotamer switch residues are located in the vicinity of the intracellular *ortho* position adjacent to the ethylamine chain of epinephrine and dopamine.

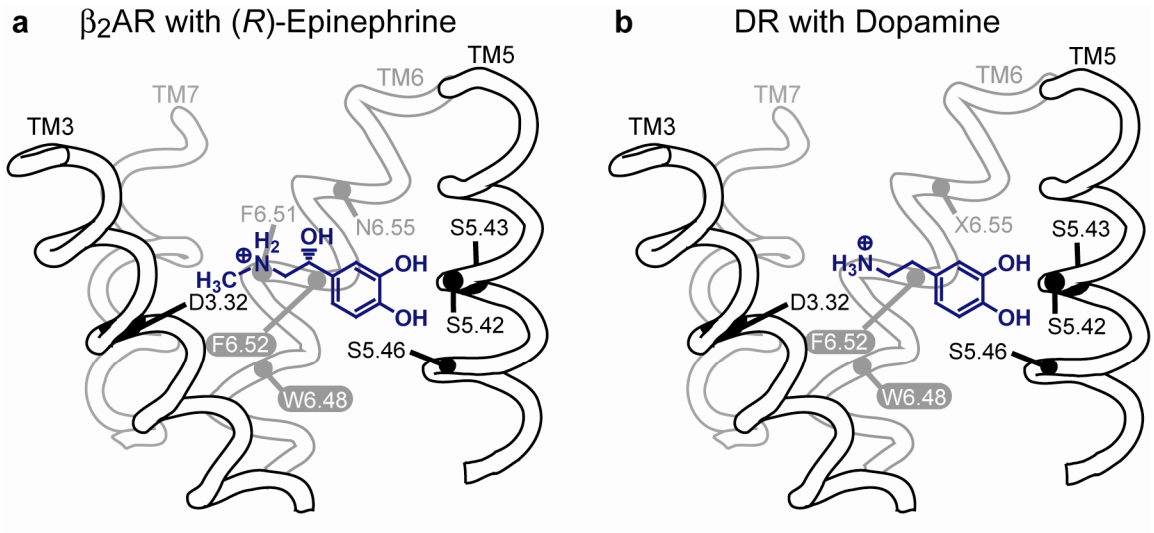


Figure 3-3. Binding orientations of catecholamines to their receptors. (**a**) Binding orientation of (*R*)-epinephrine (blue) in the binding site of the β_2AR. (**b**) Binding orientation of dopamine (blue) in the binding site of DR. Receptors are viewed from the perspective of TM4. The location of the rotamer switch residues (white letters) (see **Fig. 3-1cd**) and residues known to interact with (*R*)-epinephrine and dopamine are labeled.

Figure 3-4a shows the structures of synthetic β-adrenergic receptor agonists. A prominent structural feature shared amongst these agonists is the lack of functional groups in one of the *ortho* positions in the phenethylamine core of the molecules. The pharmacophore of these agonists optimally complements the physicochemical properties of the binding and specificity determinant residues within the binding site of β_2AR in the docking orientation shown in Figure 3-4b. A potential reason why a simple hydrogen atom is preferred at the intracellular *ortho* position of these agonists may be attributed to the possibility that incorporating functional groups here would interfere with the rotamer switch residues and therefore be detrimental for receptor activation.

The same hypothesis can be applied to the dopamine 1 receptor (D_1R) synthetic agonists (**Fig. 3-5a**). Although some of these compounds do have groups built into the proposed intracellular *ortho* position of the phenethylamine core, none of these substituents are thought to be large enough to interfere with the rotamer switch residues.

When bound to D_1R (**Fig. 3-5b**), there is sufficient space for the rotamer switch to toggle to their active conformation.

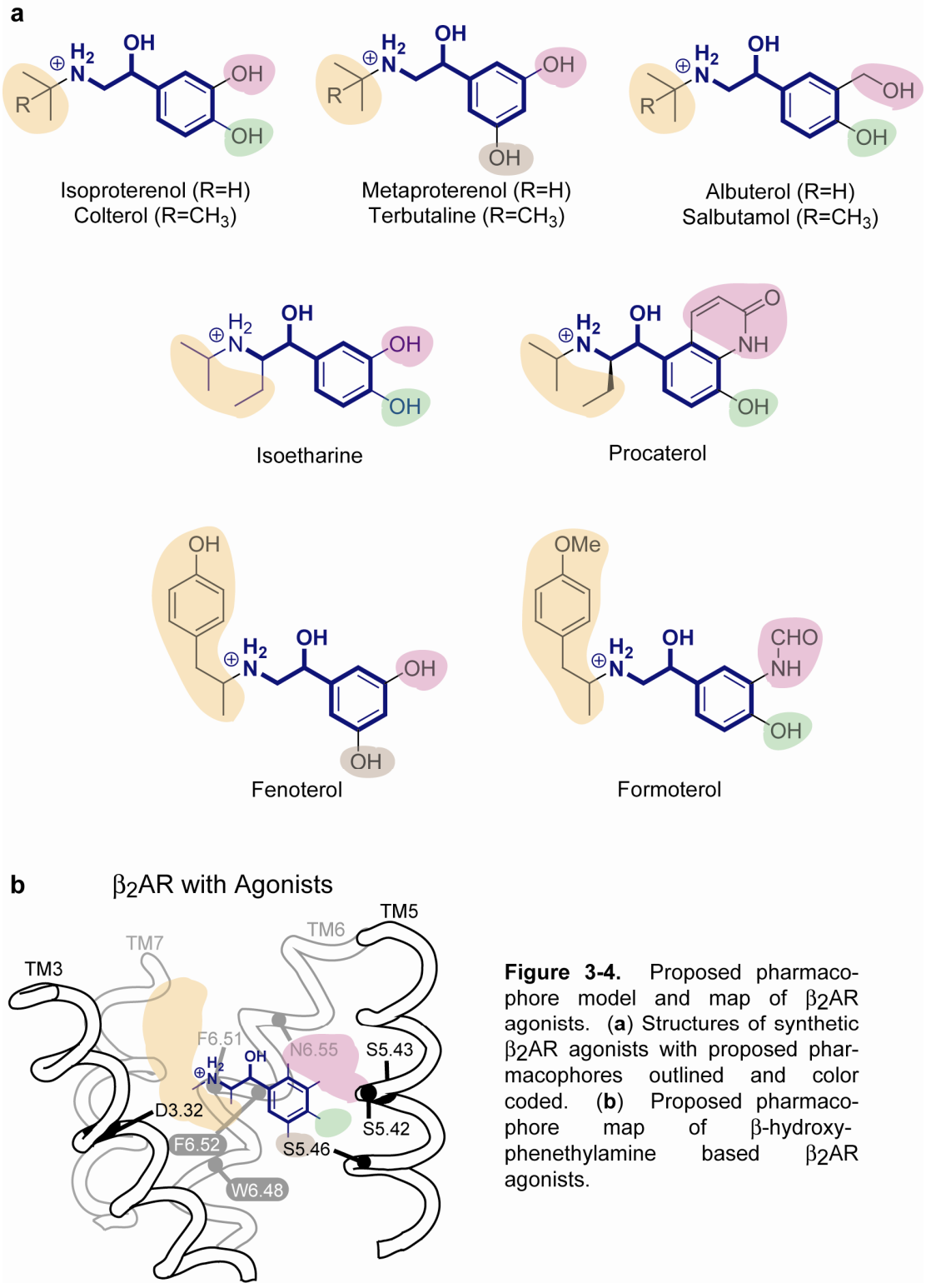


Figure 3-4. Proposed pharmacophore model and map of β_2AR agonists. (**a**) Structures of synthetic β_2AR agonists with proposed pharmacophores outlined and color coded. (**b**) Proposed pharmacophore map of β-hydroxyphenethylamine based β_2AR agonists.

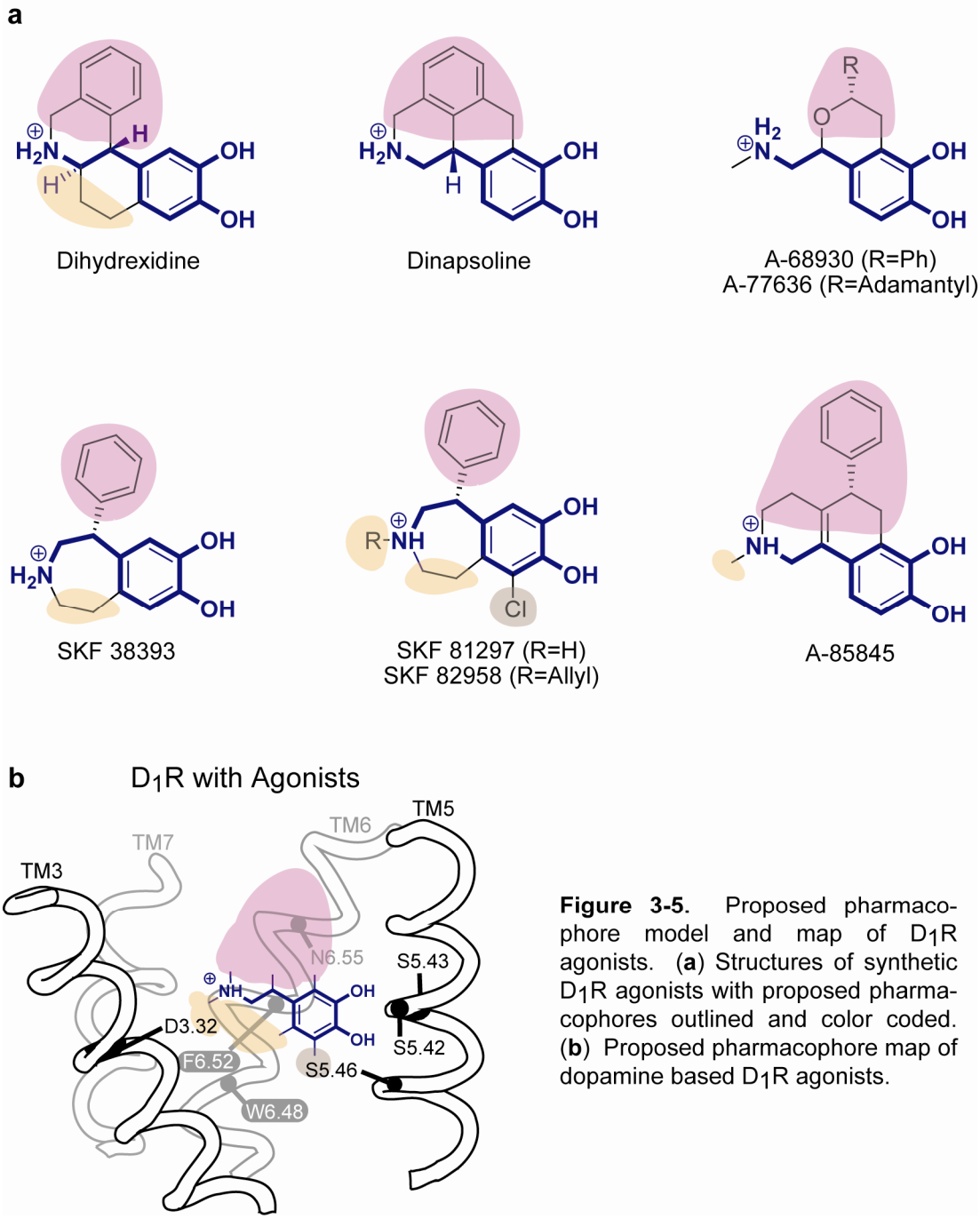


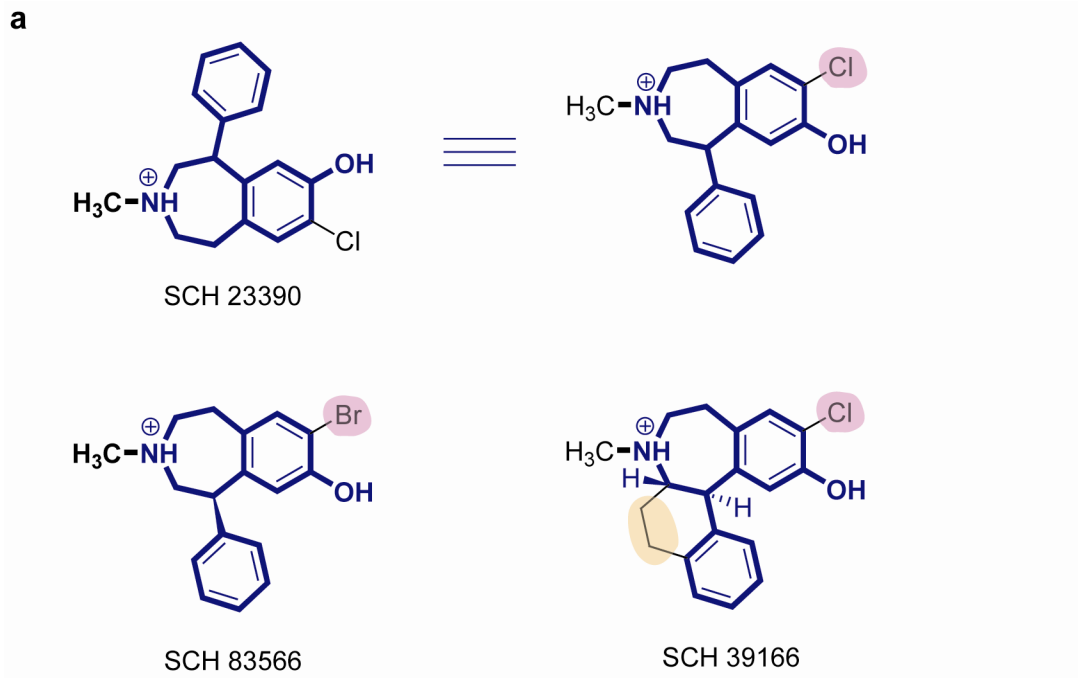
Figure 3-5. Proposed pharmacophore model and map of D_1R agonists. (**a**) Structures of synthetic D_1R agonists with proposed pharmacophores outlined and color coded. (**b**) Proposed pharmacophore map of dopamine based D_1R agonists.

3.3 Insights into Dopamine 1 and Dopamine 2 Receptor Antagonism

SCH 23390 is a prototypical dopamine 1-like receptor antagonist (**Fig. 3-6a**). It is interesting to note that methylating the amine and substituting a chlorine group for one of

the catechol hydroxyls is sufficient to convert SKF 38393 (**Fig. 3-5a**) from a dopamine receptor agonist into an antagonist. Between the two simple structural modifications, the methyl group is predicted to be more important for improving binding affinity and potency while the chloro group is thought to be responsible for conferring antagonist properties. The chloro group was probably incorporated to eliminate the catechol moiety and help decrease the rate of drug metabolism by the enzyme catechol O-methyl transferase. Without a catechol moiety, we speculate that the binding orientation of SCH 23390 to be significantly different from that of SKF 38393. Instead of docking with the β-phenyl ring projected towards the extracellular side of the receptor, we surmise SCH 23390 to bind with the β-phenyl ring oriented towards the cytoplasmic side of the receptor (**Fig. 3-6b**). This inverted orientation allows the phenol to interact with S5.42 and S5.43, and favorably prevent the chloro group from being surrounded by the polar hydroxyls of S5.42, S5.43, and S5.46. As a consequence, the β-phenyl ring would now be adjacent to the rotamer switch residues and can theoretically occlude these residues from assuming its active conformation. Other related D_1R antagonists, SCH 83566 and SCH 39166, are also expected to bind in the same orientation and antagonize the receptor in the same manner (**Fig. 3-6**).

For the orthopramide based dopamine 2 receptor (D_2R) antagonists (e.g. sulpiride, amisulpiride, sultopride, raclopride, metoclopramide, and nafadotride) (**Fig. 3-7a**), they best satisfy the binding and specificity determinant residues of D_2R when mapped as shown in Figure 3-7b. In this orientation, the *ortho* methoxy group, which is present in all of these compounds, is hypothesized to sterically occlude the toggle switch residues and keep it in its inactive conformation.



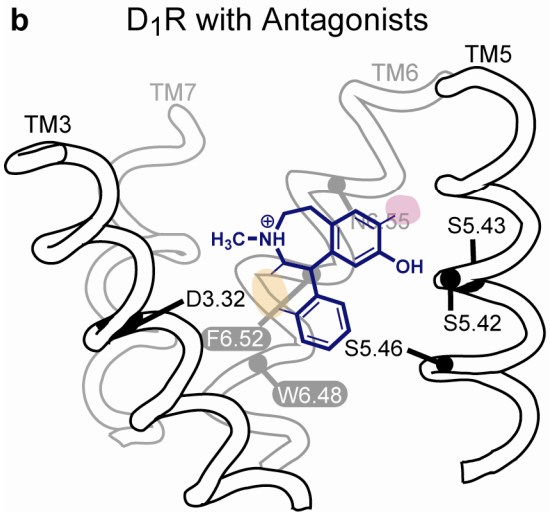


Figure 3-6. Proposed pharmacophore model and map of D_1R antagonists. (**a**) Structures of synthetic D_1R antagonists with proposed pharmacophores outlined and color coded. (**b**) Proposed pharmacophore map of β–phenyl-tetrahydrobenzazepine based D_1R antagonists.

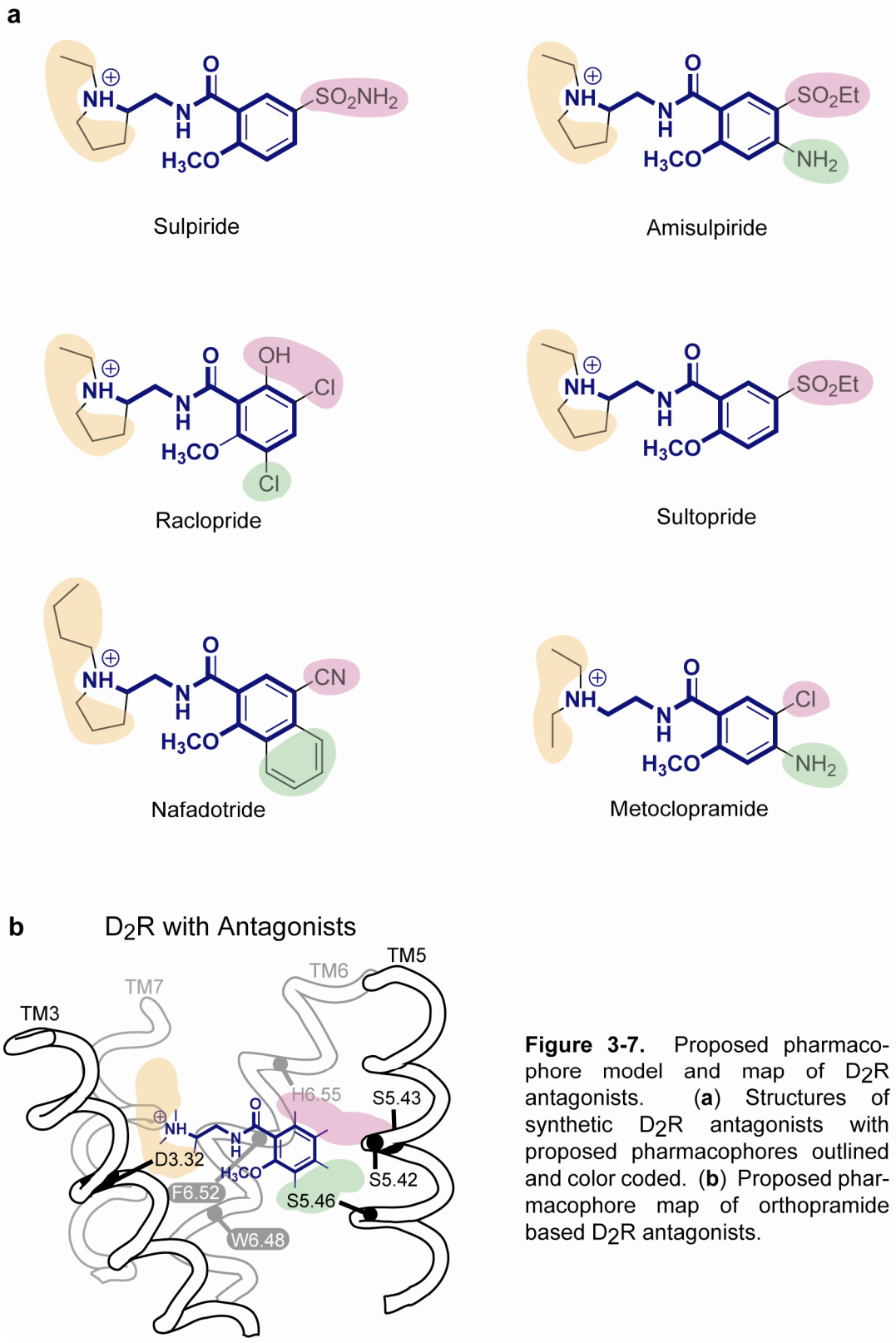


Figure 3-7. Proposed pharmacophore model and map of D_2R antagonists. (**a**) Structures of synthetic D_2R antagonists with proposed pharmacophores outlined and color coded. (**b**) Proposed pharmacophore map of orthopramide based D_2R antagonists.

3.4 Conclusion

The antagonist based drug design strategy was of limited utility to the development of $TAAR_1$ antagonists because the underlying principles of agonism and antagonism are not fully understood. A closer analysis of the ligand-receptor interactions of existing GPCR drugs revealed a relationship between the functional properties of the ligand and how it interacts with the rotamer toggle switch residues. Allowing the rotamer switch residues to toggle to their active conformation was associated with agonism while interfering with this conformational transition resulted in antagonism.

3.5 References

1. Gether, U., Uncovering molecular mechanisms involved in activation of G protein-coupled receptors. *Endocr. Rev.* **2000,** 21, (1), 90-113.
2. Wess, J., Molecular basis of receptor/G-protein-coupling selectivity. *Pharmacol. Ther.* **1998,** 80, (3), 231-264.
3. Shi, L.; Liapakis, G.; Xu, R.; Guarnieri, F.; Ballesteros, J.; Javitch, J., Beta(2) adrenergic receptor activation - Modulation of the proline kink in transmembrane 6 by a rotamer toggle switch. *J. Biol. Chem.* **2002,** 277, (43), 40989-40996.
4. Ballesteros, J.; Jensen, A.; Liapakis, G.; Rasmussen, S.; Shi, L.; Gether, U.; Javitch, J., Activation of the beta(2)-adrenergic receptor involves disruption of an ionic lock between the cytoplasmic ends of transmembrane segments 3 and 6. *J. Biol. Chem.* **2001,** 276, (31), 29171-29177.
5. Yao, X.; Parnot, C.; Deupi, X.; Ratnala, V.; Swaminath, G.; Farrens, D.; Kobilka, B., Coupling ligand structure to specific conformational switches in the beta(2)-adrenoceptor. *Nat. Chem. Biol.* **2006,** 2, (8), 417-422.
6. Ballesteros, J.; Wienstein, H., Integrated methods for the construction of three-dimensional models of structure-function relations in G protein-coupled receptors. *Methods Neuroscience* **1995,** 25, 366-428.
7. Cherezov, V.; Rosenbaum, D. M.; Hanson, M. A.; Rasmussen, S. G.; Thian, F. S.; Kobilka, T. S.; Choi, H. J.; Kuhn, P.; Weis, W. I.; Kobilka, B. K.; Stevens, R. C., High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science* **2007,** 318, (5854), 1258-1265.

8. Rasmussen, S. G.; Choi, H. J.; Rosenbaum, D. M.; Kobilka, T. S.; Thian, F. S.; Edwards, P. C.; Burghammer, M.; Ratnala, V. R.; Sanishvili, R.; Fischetti, R. F.; Schertler, G. F.; Weis, W. I.; Kobilka, B. K., Crystal structure of the human beta2 adrenergic G-protein-coupled receptor. *Nature* **2007,** 450, (7168), 383-387.

9. Rosenbaum, D. M.; Cherezov, V.; Hanson, M. A.; Rasmussen, S. G.; Thian, F. S.; Kobilka, T. S.; Choi, H. J.; Yao, X. J.; Weis, W. I.; Stevens, R. C.; Kobilka, B. K., GPCR engineering yields high-resolution structural insights into beta2-adrenergic receptor function. *Science* **2007,** 318, (5854), 1266-1273.

10. Tota, M. R.; Candelore, M. R.; Dixon, R. A.; Strader, C. D., Biophysical and genetic analysis of the ligand-binding site of the beta-adrenoceptor. *Trends Pharmacol. Sci.* **1991,** 12, (1), 4-6.

11. Liapakis, G.; Ballesteros, J.; Papachristou, S.; Chan, W.; Chen, X.; Javitch, J., The forgotten serine - A critical role for Ser-203(5.42) in ligand binding to and activation of the beta(2)-adrenergic receptor. *Journal of Biological Chemistry* **2000,** 275, (48), 37779-37788.

12. Shi, L.; Javitch, J., The binding site of aminergic G protein-coupled receptors: The transmembrane segments and second extracellular loop. *Annu. Rev. Pharmacol. Toxicol.* **2002,** 42, 437-467.

13. Strader, C.; Candelore, M.; Hill, W.; Sigal, I.; Dixon, R., Identification of 2 serine residues involved in agonist activation of the beta-adrenergic-receptor. *J. Biol. Chem.* **1989,** 264, (23), 13572-13578.

14. Strader, C.; Fong, T.; Tota, M.; Underwood, D.; Dixon, R., Structure and function of G-protein coupled receptors. *Annu. Rev. Biochem.* **1994,** 63, 101-132.

15. Strader, C.; Sigal, I.; Candelore, M.; Rands, E.; Hill, W.; Dixon, R., Conserved aspartic-acid residue-79 and residue-113 of the beta-adrenergic-receptor have different roles in receptor function. *J. Biol. Chem.* **1988,** 263, (21), 10267-10271.

16. Strader, C.; Sigal, I.; Dixon, R., Structural basis of beta-adrenergic-receptor function. *FASEB J.* **1989,** 3, (7), 1825-1832.

17. Wieland, K.; Zuurmond, H.; Krasel, C.; Ijzerman, A.; Lohse, M., Involvement of Asn-293 in stereospecific agonist recognition and in activation of the beta(2)-adrenergic receptor. *Proc. Natl. Acad. Sci. U. S. A.* **1996,** 93, (17), 9276-9281.

18. Zuurmond, H.; Hessling, J.; Bluml, K.; Lohse, M.; Ijzerman, A., Study of interaction between agonists and Asn293 in helix VI of human beta(2)-adrenergic receptor. *Mol. Pharmacol.* **1999,** 56, (5), 909-916.

Chapter 4

Agonist Design Principles

The study expanding the SAR of the ethylamine segment of **T_1AM** provided four structurally distinct agonist scaffolds that were equipotent or more potent than **T_1AM**; three of the scaffolds showed a clear preference for either rat or mouse $TAAR_1$ and one was equally beneficial to both receptors.[1] Despite these species variability, the molecular basis of agonism for all these compounds appears to be in accord with the agonist design principles gleaned from the analysis of the agonist-receptor interaction in biogenic amine GPCRs discussed in Chapter 3. To understand the molecular basis of $TAAR_1$ activation by thyronamines and related analogs, we utilized the toggle switch model as a guiding principle in the rational design and synthesis of rat $TAAR_1$ superagonists, which is defined as compounds that are more potent and/or efficacious than **T_1AM**.

4.1 Development of $rTAAR_1$ Superagonists

5.1.1 SAR of ET-13

The ligand binding site of rat $TAAR_1$ differs from that of the β_2AR in that two hydrophobic residues, alanine (A5.42) and phenylalanine (F5.43) (**Fig. 4-1b**), replace the serine residues S5.42 and S5.43 in TM5 (**Fig. 3-3a**). Additionally, the residue at 6.55 is a methionine rather than an asparagine. By analogy to the catecholamines (epinephrine, norepinephrine, and dopamine), we speculate that potent $rTAAR_1$ agonists **T_1AM**,[2, 3] **ET-13** and **ET-21**[1] (**Fig. 4-1a**) are anchored into the binding site by the salt bridge interaction between the charged amine and D3.32, and the hydrogen bond interaction between the biaryl ether oxygen and S5.46. In this docking orientation, the iodo and naphthyl groups of **T_1AM** and **ET-21**, respectively, would be located around F5.43 and methionine 6.55 (M6.55) while the β-phenyl ring of **ET-13** would be positioned near the interface of TM6 and TM7.

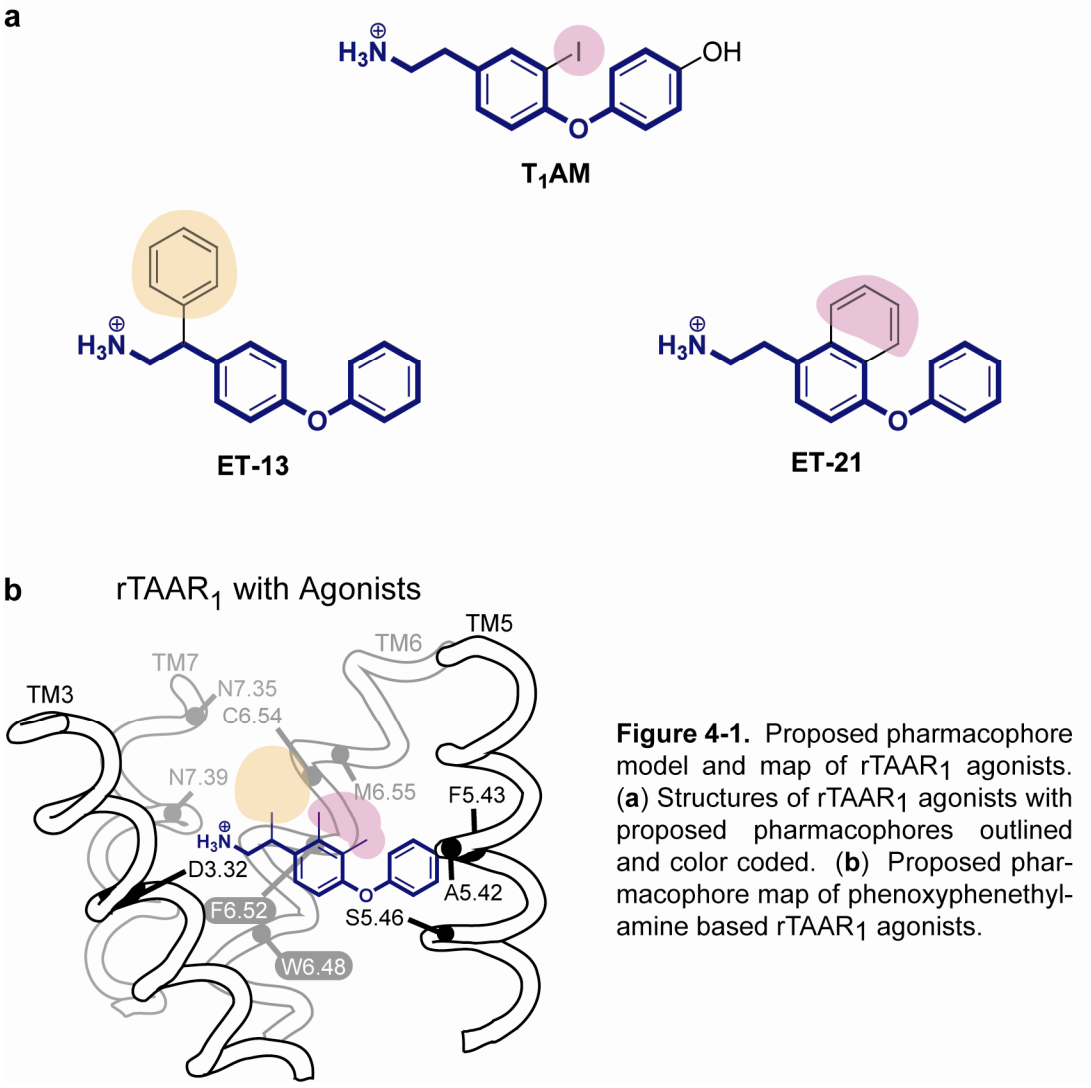
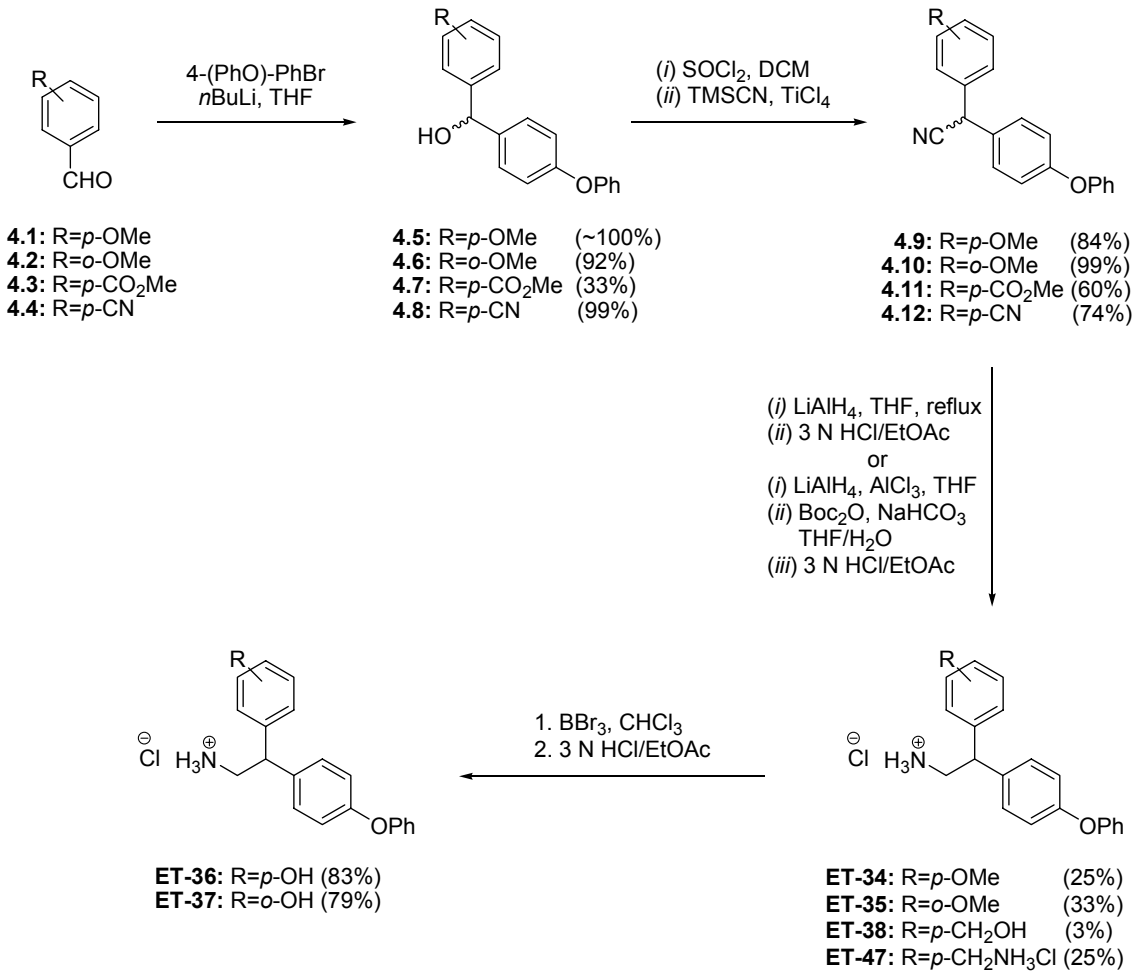


Figure 4-1. Proposed pharmacophore model and map of $rTAAR_1$ agonists. (**a**) Structures of $rTAAR_1$ agonists with proposed pharmacophores outlined and color coded. (**b**) Proposed pharmacophore map of phenoxyphenethylamine based $rTAAR_1$ agonists.

To experimentally test this hypothesis, a series of **ET-13** derivatives containing functional groups at the β-phenyl ring were synthesized. We specifically incorporated polar functional groups (**ET-34–ET-38**, **ET-47**, and **ET-65**) (**Scheme 4-1** and **4-2**) capable of forming hydrogen bond interactions because our homology model of $rTAAR_1$ showed the surrounding residues around the β-phenyl ring are asparagines (N7.35 & 7.39), a methionine (M6.55), and a cysteine (C6.54) (**Fig. 4-1b**). Therefore, if **ET-13** binds in this orientation, having functional groups that can interact with these residues should theoretically enhance binding affinity and thus increase potency. The homology

model of $rTAAR_1$ was based on the crystal structure of bovine rhodopsin[4] and constructed using the software PLOP (commercially available as Prime from Schrödinger Inc). Additionally, fluorine substituted analogs of **ET-13** (**ET-66** and **ET-67**) (**Scheme 4-2**) were also synthesized to determine the effects of decreasing the electron density of the β-phenyl ring on $rTAAR_1$ activation. Furthermore, the outer ring of **ET-13** was removed (**ET-71**) (**Scheme 4-3**) to assess the importance of this group for receptor activation.

Scheme 4-1. Synthesis of **ET-34-ET-38** and **ET-47**



4.1: R=*p*-OMe
4.2: R=*o*-OMe
4.3: R=*p*-CO_2Me
4.4: R=*p*-CN

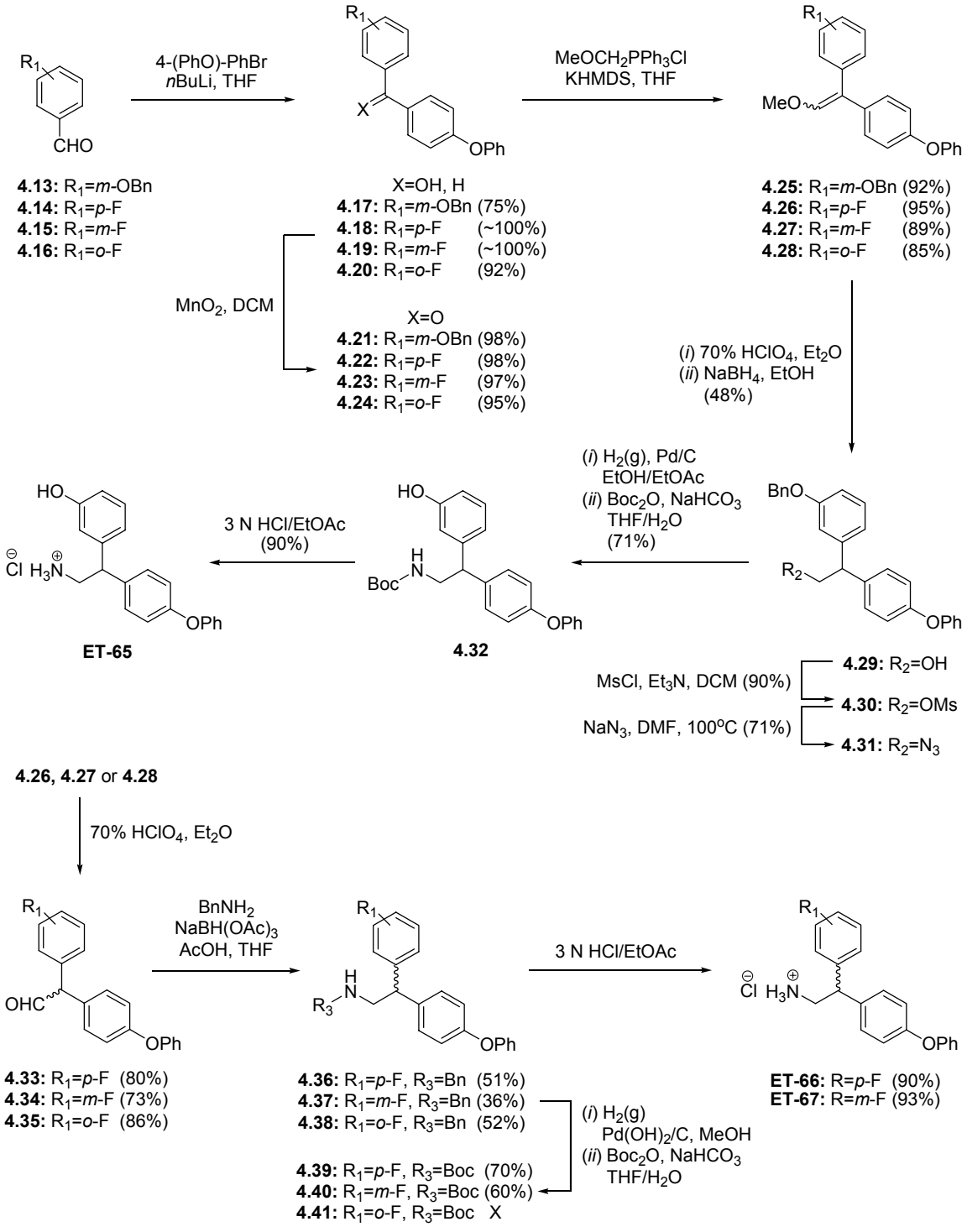
4.5: R=*p*-OMe (~100%)
4.6: R=*o*-OMe (92%)
4.7: R=*p*-CO_2Me (33%)
4.8: R=*p*-CN (99%)

4.9: R=*p*-OMe (84%)
4.10: R=*o*-OMe (99%)
4.11: R=*p*-CO_2Me (60%)
4.12: R=*p*-CN (74%)

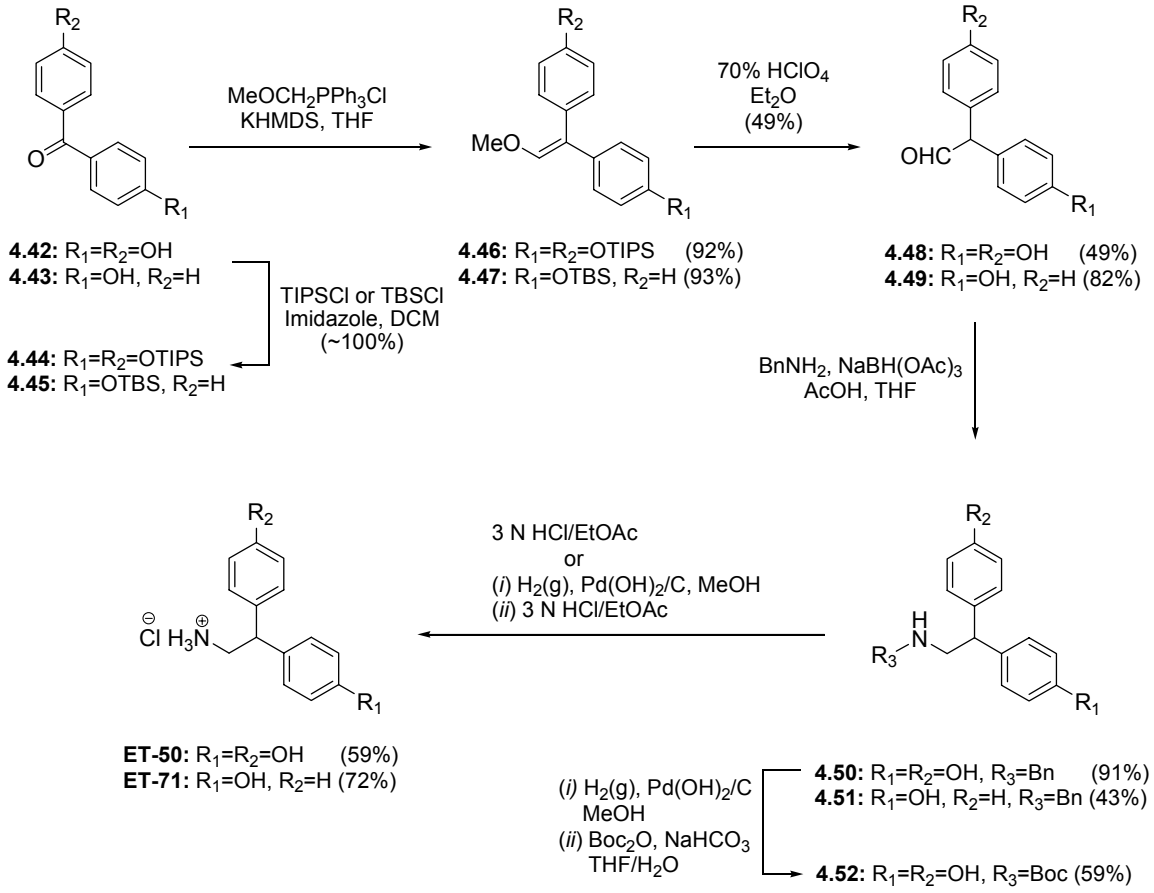
ET-36: R=*p*-OH (83%)
ET-37: R=*o*-OH (79%)

ET-34: R=*p*-OMe (25%)
ET-35: R=*o*-OMe (33%)
ET-38: R=*p*-CH_2OH (3%)
ET-47: R=*p*-CH_2NH_3Cl (25%)

Scheme 4-2. Synthesis of **ET-65-ET-67**



Scheme 4-3. Synthesis of **ET-50** and **ET-71**



4.1.1.1 Synthesis of ET-13 Analogs

ET-34–**ET-38** and **ET-47** (**Scheme 4-1**) were synthesized following the same general scheme as **ET-13** and **ET-14** (**Scheme 2-4**). Reaction of the organolithium species of 4-bromodiphenyl ether with a mono-substituted benzaldhyde (**4.1-4.4**) provided dibenzylic alcohols **4.5-4.8** in poor to excellent yields. Treatment with thionyl chloride followed by $TiCl_4$ and TMSCN converted the dibenzylic alcohols (**4.5-4.8**) into the corresponding nitriles (**4.9-4.12**).[5] Reduction with $LiAlH_4$ and treatment with anhydrous acid gave the hydrochloride salts of **ET-34**, **ET-35**, and **ET-38** as a racemic mixture in poor yields. Methyl ether deprotection with boron tribromide and subsequent

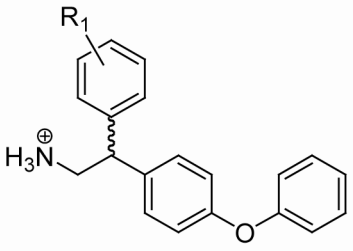
exposure to anhydrous acid precipitated the hydrochloride salts of phenols **ET-36** and **ET-37**.[6] Reaction of **4.12** with $LiAlH_4$ alone proved unsuccessful. Diamine **ET-47** was eventually obtained by reducing **4.12** with $LiAlH_4$-$AlCl_3$.[7]

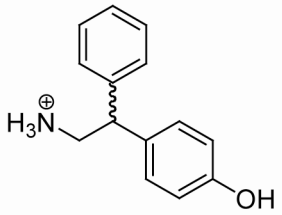
The low yields in the reduction of dibenzylic nitrile intermediates (**4.9-4.12**) led us to explore reductive amination and nucleophilic substitution as alternative approaches to installing the primary amines in **ET-65**–**ET-67** (**Scheme 4-2**). Lithium halogen exchange with 4-bromodiphenyl ether and reaction with substituted aldehydes (**4.13-4.16**) afforded alcohols **4.17-4.20**. After oxidizing the dibenzylic alcohols with manganese dioxide, the resulting benzophenones (**4.21-4.24**) were subjected to Wittig reaction with methoxymethyl triphenylphosphonium chloride to give enol ether **4.25-4.28** in excellent yields.[8, 9] Deprotection of the enol ether was unsuccessful with aqueous HCl. Aldehydes **4.33-4.35** were eventually obtained by perchloric acid treatment.[10] Reductive amination with benzylamine and $NaBH(OAc)_3$ provided secondary amines **4.36-4.38** in poor to modest yield.[11] Formation of the Boc protected amine following catalytic hydrogenation proceeded smoothly for the *para*- and *meta*-fluoro intermediates (**4.36** and **4.37**, respectively) but proved problematic for the *ortho*-fluoro **4.38**. Catalytic hydrogenation of **4.38** and subsequent Boc protection generated a side product that was inseparable from the desired Boc protected intermediate. Acid deprotection of **4.39** and **4.40** yielded racemic **ET-66** and **ET-67** as hydrochloride salts.

The aldehyde intermediate from enol ether deprotection of **4.25** appeared to have degraded under reductive amination conditions with benzylamine and $NaBH(OAc)_3$. Thus the deprotected product of **4.25** was immediately reduced to the more stable primary alcohol **4.29**. Conversion to a mesylate, substitution with an azide, reduction to a

primary amine, and Boc protection gave **4.32** in 45 % yield over 3 steps.[12] Treatment with acid generated the hydrochloride salts of **ET-65** as a racemic mixture in 90 % yield.

Table 4-1. Activity of **ET-13** analogs on $rTAAR_1$





ET-71

Compd	R_1	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-13	H	28 ± 2	103 ± 4	3
ET-34	*p*-OMe	142 ± 40	68 ± 8	3
ET-35	*o*-OMe	163 ± 18	84 ± 2	3
ET-36	*p*-OH	6 ± 1	114 ± 9	4
ET-37	*o*-OH	467 ± 107	70 ± 6	3
ET-38	CH_2OH	728 ± 88	98 ± 2	3
ET-47	CH_2NH_3	>1000	25 ± 12	2
ET-65	*m*-OH	212 ± 39	106 ± 7	3
ET-66	*p*-F	28 ± 6	99 ± 9	3
ET-67	*m*-F	57 ± 6	110 ± 7	3
ET-71	-	78 ± 9	122 ± 16	3

[a]EC_{50} is the half-maximal effective concentration of a compound. [b]E_{max} is the maximum stimulation achieved at a concentration of 10 μM. EC_{50} and E_{max} values represent the average of *N* independent experiments in triplicate and were calculated by use of Prism software as described in the Appendix. E_{max} = 100 % is defined as the activity of **T_1AM** at 10 μM. [c]*N* is the number of independent experiments in triplicate that were performed and used to calculate the EC_{50} and E_{max} values. Compounds with stereogenic centers were evaluated as racemic mixtures.

ET-71 was synthesized from commercially available 4-hydroxybenzophenone (**4.43**) (**Scheme 4-3**). Wittig reaction of TBS protected benzophenone **4.45** with methoxymethyl triphenylphosphonium chloride provided enol ether **4.47** in 93 % yield. Perchloric acid deprotection followed by reductive amination gave secondary amine

4.51.[13] Catalytic hydrogen and acid treatment then afforded the hydrochloride salt of **ET-71** as a racemic mixture.

4.1.1.2 Receptor Activation of ET-13 Analogs

Representative dose-response curves of agonists for $rTAAR_1$ are shown in Figure 4-2. Appending a methoxy group at the *para* (**ET-34**) or *ortho* (**ET-35**) position of the β-phenyl ring in **ET-13** was detrimental, decreasing the potency ~5-6-fold and the efficacy 19-35 % (**ET-34**, EC_{50} = 142 ± 40 nM, E_{max} = 68 ± 8 %, and **ET-35**, EC_{50} = 163 ± 18 nM, E_{max} = 84 ± 2 %) (**Table 4-1**). A hydroxyl group at the β-phenyl ring was well tolerated by $rTAAR_1$ but only at the *para* position. The potency of the *para* hydroxy derivative **ET-36** increased ~4.5-fold (EC_{50} = 6 ± 1 nM) and its efficacy was slightly enhanced (E_{max} = 114 ± 9 %). When the hydroxyl substituent was located at the *ortho* (**ET-37**) or *meta* (**ET-65**) position, the potency decreased ~7.5-16.5-fold (EC_{50} = 467 ± 107 nM and 212 ± 39 nM, respectively) while the efficacy either decreased or was unaffected (E_{max} = 70 ± 6 % and 106 ± 7 %, respectively). The hydroxymethyl (**ET-38**) and aminomethyl (**ET-47**) substituted analogs were also poor agonists being ≥ 26-fold less potent (EC_{50} = 728 ± 88 nM and > 1 μM, respectively). **ET-38** (E_{max} = 98 ± 2 %) was as efficacious as **ET-13** while **ET-47** (E_{max} = 25 ± 12 %) was 78 % less active. Similarly, $rTAAR_1$ somewhat prefers a fluorine group at the *para* over the *meta* position as the potency was the same for **ET-66** (EC_{50} = 28 ± 6 nM) but decreased 2-fold for **ET-67** (EC_{50} = 57 ± 6 nM). The efficacy of **ET-66** and **ET-67** (E_{max} = 99 ± 9 % and 110 ± 2 %, respectively) were unaffected by fluorination and were similar to that of **ET-13**. Losing the outer ring of **ET-13** (**ET-71**) was somewhat beneficial increasing efficacy up to 19 % but decreasing potency ~3-fold (EC_{50} = 78 ± 9 nM and E_{max} = 122 ± 16 %). The

observed activities of all compounds tested were found to be $rTAAR_1$-dependent, as all compounds showed no cAMP accumulation when exposed to an empty vector control cell line (data not shown).

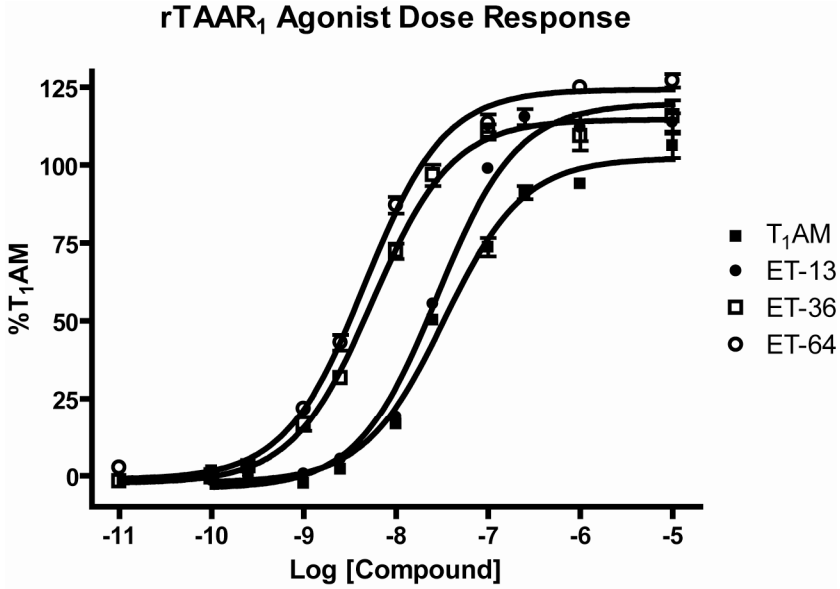


Figure 4-2. Representative dose-response curves of agonists for $rTAAR_1$ stably expressed in HEK293 cells. Dose-response curves of **T_1AM** (■), **ET-13** (●), **ET-36** (□), and **ET-64** (○). Data reported were normalized to **T_1AM** and expressed as a percentage of the activity of **T_1AM** (% T_1AM). Dose-response curves were plotted and EC_{50} values were calculated with use of Prism software as described in the Appendix.

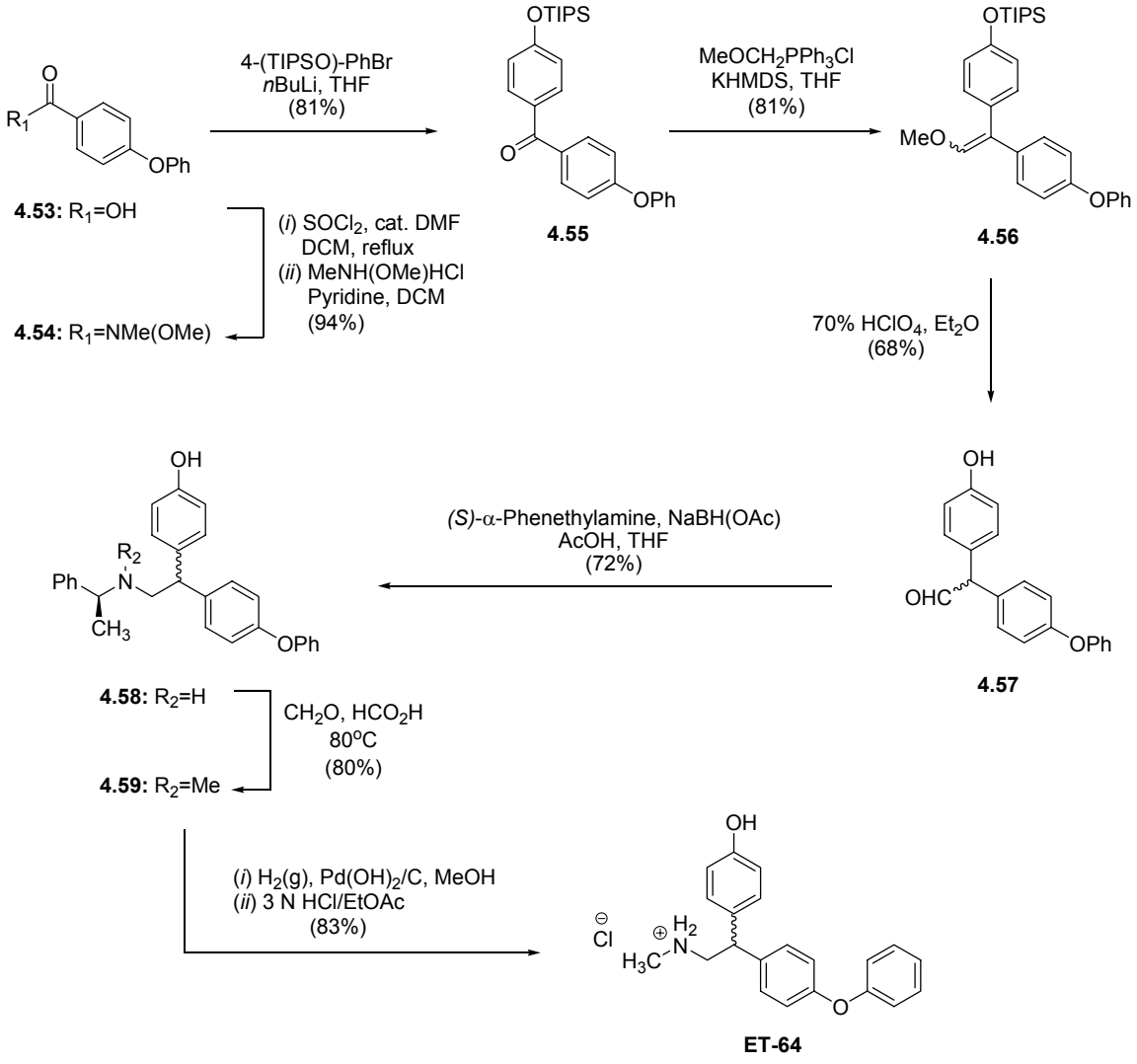
4.1.2 SAR of ET-36

In an effort to improve the potency of **ET-36**, its tolerance for methylation at the amine, iodination of the inner ring, and hydroxylation of the outer ring were explored (**ET-64**, and **ET-68–ET-70**) (**Scheme 4-4** and **4-5**). These modifications, individually or in combination, have previously been found to be beneficial for $rTAAR_1$ activation. **ET-50** was synthesized to explore the contribution of the outer ring to the functional activity of **ET-36**.

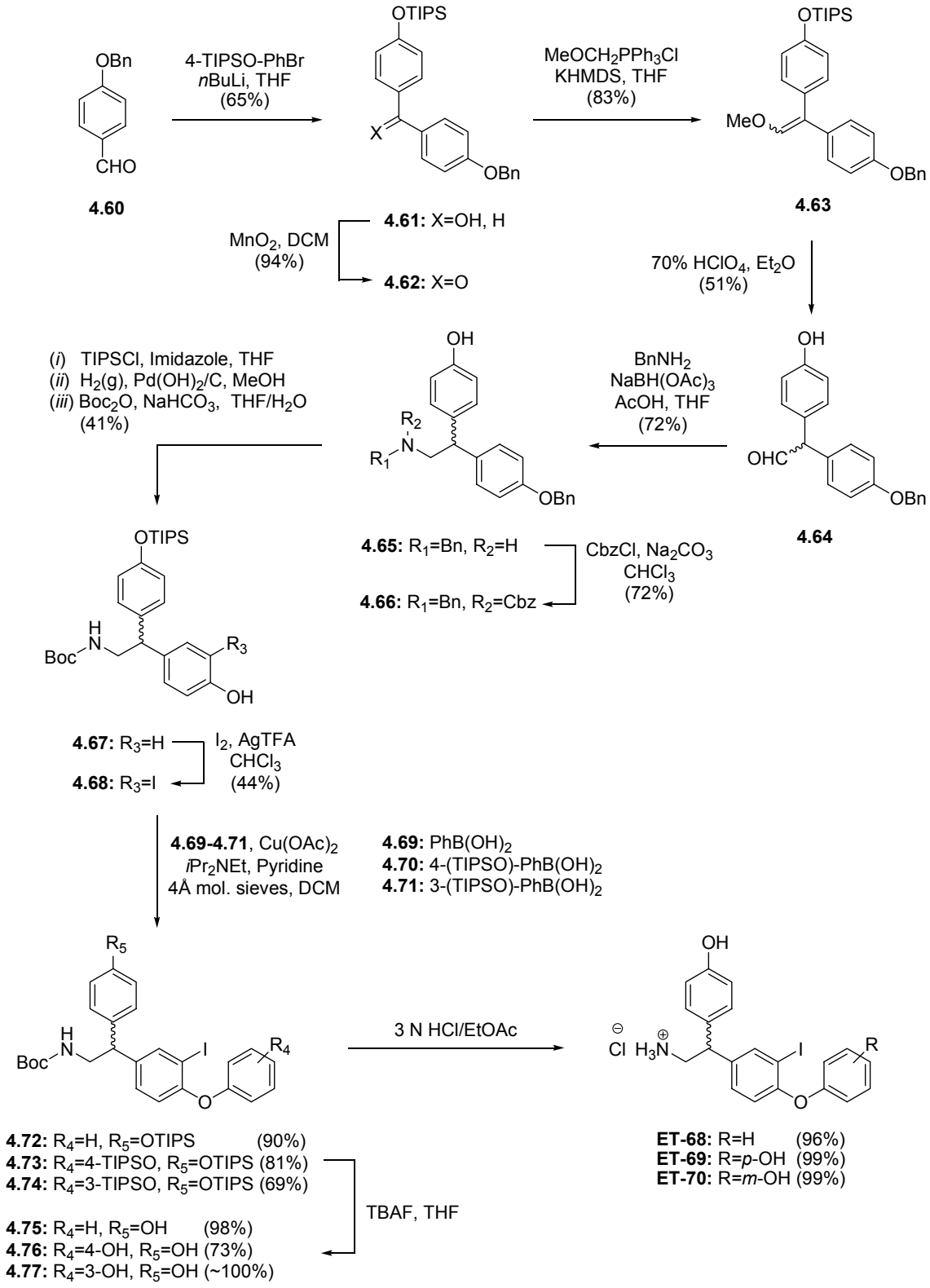
4.1.2.1 Synthesis of ET-36 Analogs

4-Phenoxybenzoic acid (**4.53**) was converted to the Weinreb's amide (**4.54**) by reacting the acid chloride with *N*,*O*-dimethylhydroxylamine hydrochloride under basic condition to give benzophenone **4.55** (**Scheme 4-4**).[14] Wittig homologation generated aldehyde **4.57** in 55 % yield over 2 steps. Reductive amination with enantiopure (*S*)-α-phenethylamine and subsequent Eschweiler Clark reaction provided tertiary amine **4.59**. Unfortunately, the two diastereomers of **4.58** and **4.59** were irresolvable by chromatography. Catalytic hydrogenation with Pearlman's catalyst followed by acid exposure gave **ET-64** as a racemic hydrochloride salt.

Scheme 4-4. Synthesis of **ET-64**



Scheme 4-5. Synthesis of **ET-68-ET-70**



ET-68–**ET-70** (**Scheme 4-5**) were synthesized from *para*-benzyloxy-benzaldehyde and triisopropylsilyl protected *para*-bromophenol. Oxidation of dibenzylic alcohol **4.61**, followed by Wittig homologation and reductive amination with benzylamine provided intermediate **4.65**. Protecting group manipulation and subsequent iodination with iodine and silver trifluoroacetate eventually led to monoiodinated **4.68**.[15, 16] Boc protection of **4.65** was avoided because this presented problems with removing the *N*-benzyl group by catalytic hydrogenation. Copper (II) mediated coupling of **4.68** with boronic acids **4.69-4.71** resulted in biaryl ethers **4.72-4.74**.[17] Reaction with TBAF and anhydrous HCl removed all protecting groups and provided the hydrochloride salts of **ET-68**–**ET-70** in good to excellent yields.

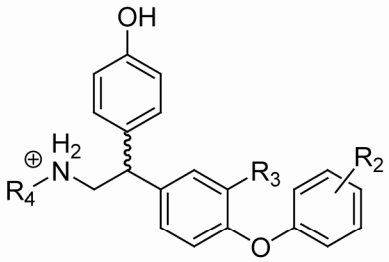
ET-50 (**Scheme 4-3**) was readily synthesized from commercially available 4,4`-dihydroxybenzophenone (**4.42**). Intermediate **4.50** was obtained by TIPS protection of **4.42** followed by Wittig homologation and reductive amination with benzylamine. Exchanging the *N*-benzyl for a Boc protecting group was necessary to allow the removal of all impurities via column chromatography. Boc deprotection then gave **ET-50** as a hydrochloride salt in modest yield.

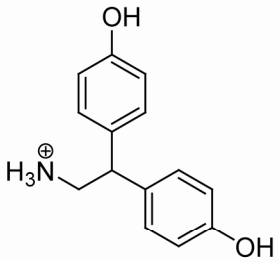
4.1.2.2 Receptor Activation of ET-36 Analogs

When screened for agonist activity, some **ET-36** derivatives were more efficacious but none were more potent. N-Methylation of **ET-36** (**ET-64**) was beneficial increasing the efficacy 13 % (E_{max} = 127 ± 2 %) but it did not improve potency (EC_{50} = 5 ± 1 nM) (**Table 4-2**). Mono-iodination of the inner ring (**ET-68**) was unfavorable decreasing potency ~3-fold (EC_{50} = 17 ± 2 nM) without significantly affecting efficacy (E_{max} = 107 ± 8 %). In the presence of an outer ring *para* hydroxyl group (**ET-69**), the

rTAAR$_1$ activity improved back to the level of **ET-36** (EC_{50} = 4 ± 1 nM, E_{max} = 115 ± 2 %). In contrast, a *meta* hydroxyl group on the outer ring of **ET-68** (**ET-70**) had no effect on potency and efficacy (EC_{50} = 22 ± 2 nM and E_{max} = 111 ± 9 %). Removing the outer ring of **ET-36** (**ET-50**) significantly decreased its potency (EC_{50} = 115 ± 12 nM) but not efficacy (E_{max} = 105 ± 5 %).

Table 4-2. Activity of **ET-36** analogs on rTAAR$_1$





ET-50

Compd	R_2	R_3	R_4	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-36	H	H	H	6 ± 1	114 ± 9	4
ET-64	H	H	Me	5 ± 1	127 ± 2	4
ET-68	H	I	H	17 ± 2	107 ± 8	4
ET-69	*p*-OH	I	H	4 ± 1	115 ± 2	6
ET-70	*m*-OH	I	H	22 ± 2	111 ± 9	4
ET-50	-	-	-	115 ± 12	105 ± 5	3

[a-c] See footnotes for Table 4-1. Compounds with stereogenic centers were evaluated as racemic mixtures.

4.2 Discussion

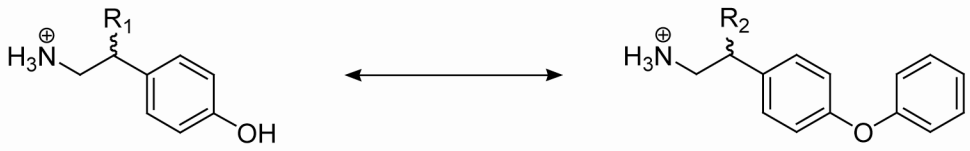
The rotamer toggle switch model of aminergic GPCR activation (**Fig. 3-1cd**) is a useful guideline in the design and synthesis of rTAAR$_1$ agonists. Previous SAR studies on the ethylamine portion of **T$_1$AM** for rTAAR$_1$ provided **ET-13** as a promising scaffold for developing rTAAR$_1$ superagonists.[1] In addition to being as potent and efficacious as

T_1AM, **ET-13** provides the added benefit of having many potential sites for derivitization. By analogy to the docking orientation of epinephrine to β_2AR (**Fig. 3-3a**), we deduced **ET-13** to bind to $rTAAR_1$ in a similar fashion with the charged amine forming a salt bridge interaction with D3.32 and the biaryl ether oxygen hydrogen bonding to S5.46 (**Fig. 4-1**). The β-phenyl ring is proposed to occupy a pocket near the interface of TM6 and TM7.

In the context of the rotamer toggle switch model, our analysis of the ligand-receptor interaction of β_2AR and D_1R showed that agonists lack functional groups in the region of the molecule that is predicted to be located in the vicinity of the rotamer switch residues (See Chapter 3). Structurally, most of these agonists appear to have functional groups that complement the physicochemical properties of the residues within the binding site. Following this lead, we attempted to improve the agonist properties of **ET-13** by incorporating functional groups in the regions of the molecule (e.g. β-phenyl ring, charged amine, outer ring, and position 5 of the inner ring) away from rotamer switch residues. In the β-phenyl ring, SAR studies presented in this chapter showed a clear preference for a hydroxyl group at the *para* position. The *para* hydroxyl analog (**ET-36**) was 24-78-fold and 8-46 % more potent and efficacious, respectively, compared to the *ortho* or *meta* hydroxyl analogs (**ET-37** and **ET-65**) and *ortho* or *para* methoxy (**ET-34** and **ET-35**) analogs (**Table 4-1**). Additionally, the *para* hydroxyl improved the potency and efficacy of **ET-13** ~4.5-fold and 11 %, respectively. We believe that this enhancement in agonist activity is a reflection of an increase in the binding affinity of **ET-13** for $rTAAR_1$ due to hydrogen bond interactions of the *para* hydroxyl with N7.39 and/or N7.35 (**Fig. 4-1b**). Residue 7.39 in the α_2-adrenergic receptor and β_2AR has

previously been shown to make interactions with ligands.[18] In the recently determined crystal structure of the β_2AR, N7.39 of β_2AR was involved in hydrogen bond interactions with the β-carbon hydroxyl group of the partial inverse agonist carazolol.[19-22]

Table 4-3. Activity of Phenethylamine based compounds on rTAAR$_1$



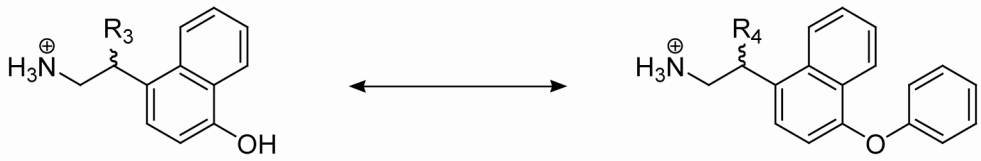
Compd	R_1	EC_{50} ± SEM E_{max} ± SEM	ΔEC_{50} ΔE_{max}	EC_{50} ± SEM E_{max} ± SEM	R_2	Compd
Tyramine	H	65 ± 1 nM 119 ± 7 %	1-fold 26%	63 ± 7 nM 93 ± 4 %	H	**PTA**
ET-71	Ph	78 ± 9 nM 122 ± 16 %	~3-fold 19%	28 ± 2 nM 103 ± 4 %	Ph	**ET-13**
ET-50	*p*-OH-Ph	115 ± 12 nM 105 ± 5 %	~19-fold 9%	6 ± 1 nM 114 ± 9 %	*p*-OH-Ph	**ET-36**

In the presence of the *para* hydroxyl (**ET-36**), mono-methylating the charged amine (**ET-64**) or incorporating a **T_1AM** moiety into the molecule (**ET-69**) was tolerated but it had modest effects on agonist activity, if any at all. N-methyl **ET-64** was equipotent to **ET-36** but 13 % more efficacious. On the other hand, **ET-69** essentially has the same potency and efficacy as **ET-36**. The comparable levels of agonist activity of **ET-36**, **ET-64**, and **ET-69**, suggest that these compounds have similar interactions with rTAAR$_1$ and possibly elicit the same final active conformation of the receptor.

Consistent with previous results, the outer ring was beneficial to receptor activation predominantly affecting potency more than efficacy. When absent in **ET-13**

(**ET-71**) and **ET-36** (**ET-50**), the potency decreased ~3- and ~19-fold, respectively, while the efficacy was only modestly affected when the standard error is considered (**Table 4-3**). The pronounced effect of the outer ring on potency appears to be scaffold dependent. In scaffolds without a β-phenyl ring (**PTA** and **ET-21**), losing the outer ring (**tyramine** and **4-OH-NEA**, respectively) had minimal effects only reducing potency up to 2-fold (**Table 4-3** and **4-4**).[1, 2] When a β-phenyl ring is present in the scaffold (**ET-13**, **ET-36**, and **ET-33**), the potency decreased ~3-19-fold when the outer ring was removed (**ET-71**, **ET-50**, and **ET-31**, respectively).

Table 4-4. Activity of Naphethylamine based compounds on $rTAAR_1$



Compd	R_3	EC_{50} ± SEM E_{max} ± SEM	ΔEC_{50} ΔE_{max}	EC_{50} ± SEM E_{max} ± SEM	R_4	Compd
4-OH-NEA	H	46 ± 6 nM 111 ± 5 %	~2-fold 2%	26 ± 1 nM 113 ± 5 %	H	**ET-21**
ET-31	Ph	716 ± 269 nM 89 ± 3 %	14-fold 11%	52 ± 4 nM 100 ± 6 %	Ph	**ET-33**

4.3 Conclusion

By analogy to the binding orientation of epinephrine to β_2AR, we deduced **ET-13** to bind with its β-phenyl ring in a pocket near the interface of TM6 and TM7. Inserting a *para*-hydroxy group into this ring enhanced the agonist properties of **ET-13** by presumably forming hydrogen bond interactions with the surrounding asparagines

residues in TM7. In the presence of a *para*-hydroxy group in the β-phenyl ring (**ET-36**), methylating the amine or iodinating and hydroxylating the inner and outer rings, respectively, gave modest gains in potency and efficacy. Overall, the agonist design principle of avoiding the rotamer switch and complementing the physicochemical properties of residues within the binding site was an insightful approach to agonist development generating $rTAAR_1$ superagonists **ET-36**, **ET-64**, and **ET-69**.

4.4 References

1. Tan, E.; Miyakawa, M.; Bunzow, J.; Grandy, D.; Scanlan, T., Exploring the structure-activity relationship of the ethylamine portion of 3-iodothyronamine for rat and mouse trace amine-associated receptor 1. *J. Med. Chem.* **2007,** 50, (12), 2787-2798.
2. Hart, M.; Suchland, K.; Miyakawa, M.; Bunzow, J.; Grandy, D.; Scanlan, T., Trace amine-associated receptor agonists: Synthesis and evaluation of thyronamines and related analogues. *J. Med. Chem.* **2006,** 49, (3), 1101-1112.
3. Scanlan, T.; Suchland, K.; Hart, M.; Chiellini, G.; Huang, Y.; Kruzich, P.; Frascarelli, S.; Crossley, D.; Bunzow, J.; Ronca-Testoni, S.; Lin, E.; Hatton, D.; Zucchi, R.; Grandy, D., 3-iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat. Med.* **2004,** 10, (6), 638-642.
4. Palczewski, K.; Kumasaka, T.; Hori, T.; Behnke, C. A.; Motoshima, H.; Fox, B. A.; Le Trong, I.; Teller, D. C.; Okada, T.; Stenkamp, R. E.; Yamamoto, M.; Miyano, M., Crystal structure of rhodopsin: A G protein-coupled receptor. *Science* **2000,** 289, (5480), 739-745.
5. Kraxner, J.; Hubner, H.; Gmeiner, P., Azepino- and diazepinoindoles: Synthesis and dopamine receptor binding profiles. *Arch. Pharm. (Weinheim, Ger.)* **2000,** 333, (9), 287-292.
6. Shah, J. H.; Izenwasser, S.; Geter-Douglass, B.; Witkin, J. M.; Newman, A. H., (+/-)-(N-Alkylamino)benzazepine analogs: novel dopamine D1 receptor antagonists. *J. Med. Chem.* **1995,** 38, (21), 4284-4293.

7. Finholt, A. E.; Bond, A. C.; Schlesinger, H. I., Lithium Aluminum Hydride, Aluminum Hydride and Lithium Gallium Hydride, and Some of their Applications in Organic and Inorganic Chemistry. *J. Am. Chem. Soc.* **1947,** 69, (5), 1199-1203.

8. Paquette, L.; Wang, T.; Philippo, C.; Wang, S., Total Synthesis of the Cembranoid Diterpene Lactone (+)-Cleomeolide. Some Remarkable Conformational Features of Nine-Membered Belts Linked in 2,6-Fashion to a Methylenecyclohexane Core. *J. Am. Chem. Soc.* **1994,** 116, 3367-3374.

9. Poschalko, A.; Welzig, S.; Treu, M.; Nerdinger, S.; Mereiter, K.; Jordis, U., Synthesis of (+/-)-6H-benzofuro[3a,3,2,ef][3]benzazepine: an unnatural analog of (-)-galanthamine. *Tetrahedron* **2002,** 58, (8), 1513-1518.

10. Sorensen, U.; Bleisch, T.; Kingston, A.; Wright, R.; Johnson, B.; Schoepp, D.; Ornstein, P., Synthesis and structure-activity relationship studies of novel 2-diarylethyl substituted (2-carboxycycloprop-1-yl)glycines as high-affinity group II metabotropic glutamate receptor ligands. *Bioorganic & Medicinal Chemistry* **2003,** 11, (2), 197-205.

11. Abdel-Magid, A.; Carson, K.; Harris, B.; Maryanoff, C.; Shah, R., Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. *J. Org. Chem.* **1996,** 61, (11), 3849-3862.

12. Wijdeven, M.; Botman, P.; Wijtmans, R.; Schoemaker, H.; Rutjes, F.; Blaauw, R., Total synthesis of (+)-epiquinamide. *Org. Lett.* **2005,** 7, (18), 4005-4007.

13. Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S., Asymmetric synthesis of (+)- and (-)-latifine. *Tetrahedron: Asymmetry* **2003,** 14, (10), 1309-1316.

14. Faul, M.; Ratz, A.; Sullivan, K.; Trankle, W.; Winneroski, L., Synthesis of novel retinoid X receptor-selective retinoids. *J. Org. Chem.* **2001,** 66, (17), 5772-5782.

15. Nicolaou, K.; Boddy, C.; Li, H.; Koumbis, A.; Hughes, R.; Natarajan, S.; Jain, N.; Ramanjulu, J.; Brase, S.; Solomon, M., Total synthesis of vancomycin - Part 2: retrosynthetic analysis, synthesis of amino acid building blocks and strategy evaluations. *Chem.--Eur. J.* **1999,** 5, (9), 2602-2621.

16. Nicolaou, K.; Snyder, S.; Huang, X.; Simonsen, K.; Koumbis, A.; Bigot, A., Studies toward diazonamide A: Initial synthetic forays directed toward the originally proposed structure. *J. Am. Chem. Soc.* **2004,** 126, (32), 10162-10173.

17. Evans, D. A.; Katz, J. L.; West, T. R., Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998,** 39, (19), 2937-2940.

18. Suryanarayana, S.; Daunt, D.; von Zastrow, M.; Kobilka, B., A point mutation in the 7th hydrophobic domain of the alpha-2-adrenergic-receptor increases its affinity for a family of beta-receptor-antagonists. *J. Biol. Chem.* **1991,** 266, (23), 15488-15492.

19. Cherezov, V.; Rosenbaum, D. M.; Hanson, M. A.; Rasmussen, S. G.; Thian, F. S.; Kobilka, T. S.; Choi, H. J.; Kuhn, P.; Weis, W. I.; Kobilka, B. K.; Stevens, R. C., High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science* **2007,** 318, (5854), 1258-1265.

20. Rasmussen, S. G.; Choi, H. J.; Rosenbaum, D. M.; Kobilka, T. S.; Thian, F. S.; Edwards, P. C.; Burghammer, M.; Ratnala, V. R.; Sanishvili, R.; Fischetti, R. F.; Schertler, G. F.; Weis, W. I.; Kobilka, B. K., Crystal structure of the human beta2 adrenergic G-protein-coupled receptor. *Nature* **2007,** 450, (7168), 383-387.

21. Rosenbaum, D. M.; Cherezov, V.; Hanson, M. A.; Rasmussen, S. G.; Thian, F. S.; Kobilka, T. S.; Choi, H. J.; Yao, X. J.; Weis, W. I.; Stevens, R. C.; Kobilka, B. K., GPCR engineering yields high-resolution structural insights into beta2-adrenergic receptor function. *Science* **2007,** 318, (5854), 1266-1273.

22. Tota, M. R.; Candelore, M. R.; Dixon, R. A.; Strader, C. D., Biophysical and genetic analysis of the ligand-binding site of the beta-adrenoceptor. *Trends Pharmacol. Sci.* **1991,** 12, (1), 4-6.

Chapter 5

Antagonist Design Principles

Our initial attempt at developing $TAAR_1$ antagonists employing an antagonist based drug design strategy (Chapter 2) was unsuccessful because the molecular basis of antagonism is not fully understood. It was uncertain if the prominent structural features of propranolol, sulpiride, and SCH 23390 (**Fig. 2-2**) that were mimicked played any role in endowing antagonistic properties to these molecules. In the context of the rotamer toggle switch model of GPCR activation, sulpiride and SCH 23390 appear to inhibit receptor activation by sterically occluding the rotamer switch residues from assuming its active conformation (**Figs. 3-1cd**, **3-6**, and **3-7**). Following this insight, we were able to develop lead antagonists for $rTAAR_1$ by incorporating functional groups into a $rTAAR_1$ agonist that theoretically interfere with the rotamer switch residues.

5.1 Development of $rTAAR_1$ Lead Antagonist

According to our proposed binding orientation of **ET-13** in $rTAAR_1$ (**Fig. 5-1b**), the rotamer switch residues are located in the vicinity of position 2 of the inner ring (ring B in **Fig. 5-1a**). Using the toggle switch model of aminergic GPCR activation as a guideline (**Fig. 3-1cd**), we attempted to convert **ET-13** into an antagonist by appending functional groups at the 2 position to theoretically disrupt the rotamer switch residues. An alcohol group was installed into the 2 position of **ET-13** (**ET-51**) (**Scheme 5-1**) to serve as a handle for synthesizing a panel of ethers (**ET-52**–**ET-61**) and esters (**ET-62** and **ET-63**) (**Scheme 5-2**) varying in steric bulk, rigidity, topology and polarity.

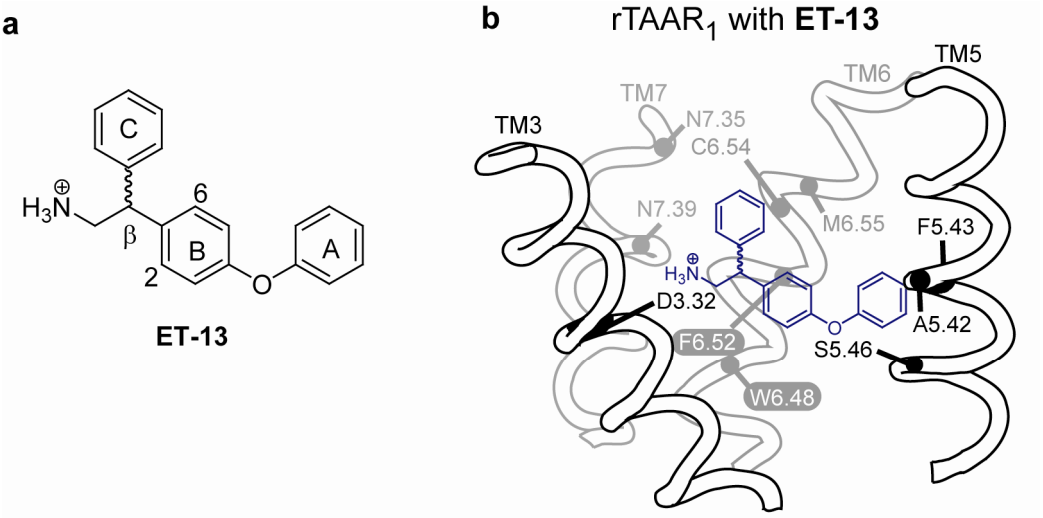


Figure 5-1. Structure of **ET-13** and its proposed binding mode in rTAAR$_1$. (**a**) Structure of **ET-13**. The A, B, and C rings corresponds to its outer, inner, and β-phenyl rings, respectively. (**b**) Proposed binding orientation of **ET-13** in the binding site of rTAAR$_1$, viewed from the perspective of TM4. The rotamer switch residues (white letters), proposed binding and specificity determinant residues are labeled.

5.1.1 Synthesis of ET-13 Position 2 Analogs

The synthetic route to **ET-51**–**ET-63** diverged two steps away from final product at intermediate **5.15** (**Scheme 5-1**). After differentially protecting the *para*- and *ortho*-phenols of methyl-2,4-dihydoxybenzoic acid (**5.1**) with TIPS chloride and benzyl bromide, respectively, the methyl ester was reduced with $LiAlH_4$ and oxidized to afford aldehyde **5.5**.[1, 2] Reaction with phenyl magnesium bromide and subsequent manganese dioxide oxidation of the dibenzylic alcohol provided differentially protected benzophenone **5.7** in quantitative yield. Starting from 2,4-dihydroxybenzaldehyde, intermediate **5.7** was obtained in modest yields after two protection steps. As documented in the literature, the 1,3 relationship of the two alcohols in **5.1** and **5.8** led to the formation of an undesired side product resulting from migration of the TIPS protecting group under the basic conditions of the benzyl protection reaction.[3] After treatment with TBAF, phenol **5.10** was subjected to copper (II) mediated coupling with

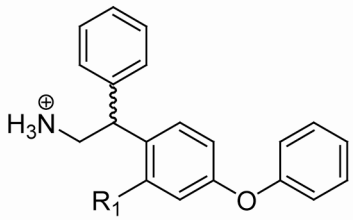
phenyl boronic acid to give biaryl ether **5.11** in good yield.[4] Wittig homologation reaction and subsequent reductive amination with benzylamine afforded secondary amine **5.14**.[5-8] It's worth noting that reductive amination of aldehyde **5.13** with enantiopure (*S*)-α-phenethylamine followed by Boc protection gave diastereometric intermediates that appeared to be resolvable by thin layer chromatography. Catalytic hydrogenation of **5.14** followed by Boc protection provided the key intermediate **5.15**. Acid deprotection of **5.15** provided **ET-51** as a hydrochloride salt in excellent yield. Reaction of **5.15** with alkyl halides (**5.16-5.25**) or acid chlorides (**5.26** and **5.27**) provided ethers (**5.28-5.37**) and esters (**5.38** and **5.39**) in good to excellent yields (**Scheme 5-2**). Boc deprotection gave the hydrochloride salts of **ET-52**–**ET-63** quantitatively.

5.1.2 Receptor Activation of ET-13 Position 2 Analogs

The effects of the ether and ester substituents on receptor agonist activity were variable. The core scaffold **ET-51** and ethyl ether **ET-53** were decent agonists activating to the same efficacy level as **ET-13** (E_{max} = 108 ± 1 % and 95 ± 5 %, respectively) but at ~3-5-fold lower potency (EC_{50} = 96 ± 10 nM and 144 ± 31 nM, respectively) (**Table 5-1)**. On the other hand, the methyl ether **ET-52** showed the opposite trend being equipotent to **ET-13** (EC_{50} = 35 ± 4 nM) but less efficacious (E_{max} = 82 ± 8 %). The unsaturated alkene and alkyne counterparts of the propyl ether **ET-54** appear to be well tolerated by $rTAAR_1$ as **ET-59** (EC_{50} 169 ± 6 nM) and **ET-60** (EC_{50} = 138 ± 37 nM) were at least 6-fold more potent than **ET-54** (EC_{50} > 1 μM). The efficacies of **ET-54**, **ET-59**, and **ET-60** were comparable to each other (E_{max} = 69 ± 5 %, 71 ± 4 %, and 78 ± 1 %, respectively). Further increasing the size of the ether substituents (**ET-55**–**ET-58** and **ET-61**) desirably decreased potency (EC_{50} > 1 μM) but it did not completely abolish the

agonist activity ($E_{max} \leq$ 10 %) of the compounds. These compounds activated $rTAAR_1$ between 15 % and 62 % efficacy. Similarly the ester substituents (**ET-62** and **ET-63**) decreased the potency of **ET-13** (EC_{50} = 143 ± 4 nM and 234 ± 43 nM, respectively) but did not reduce its efficacy below 10 % (E_{max} = 57 ± 5 % and 74 ± 3 %, respectively) (**Table 5-1**).

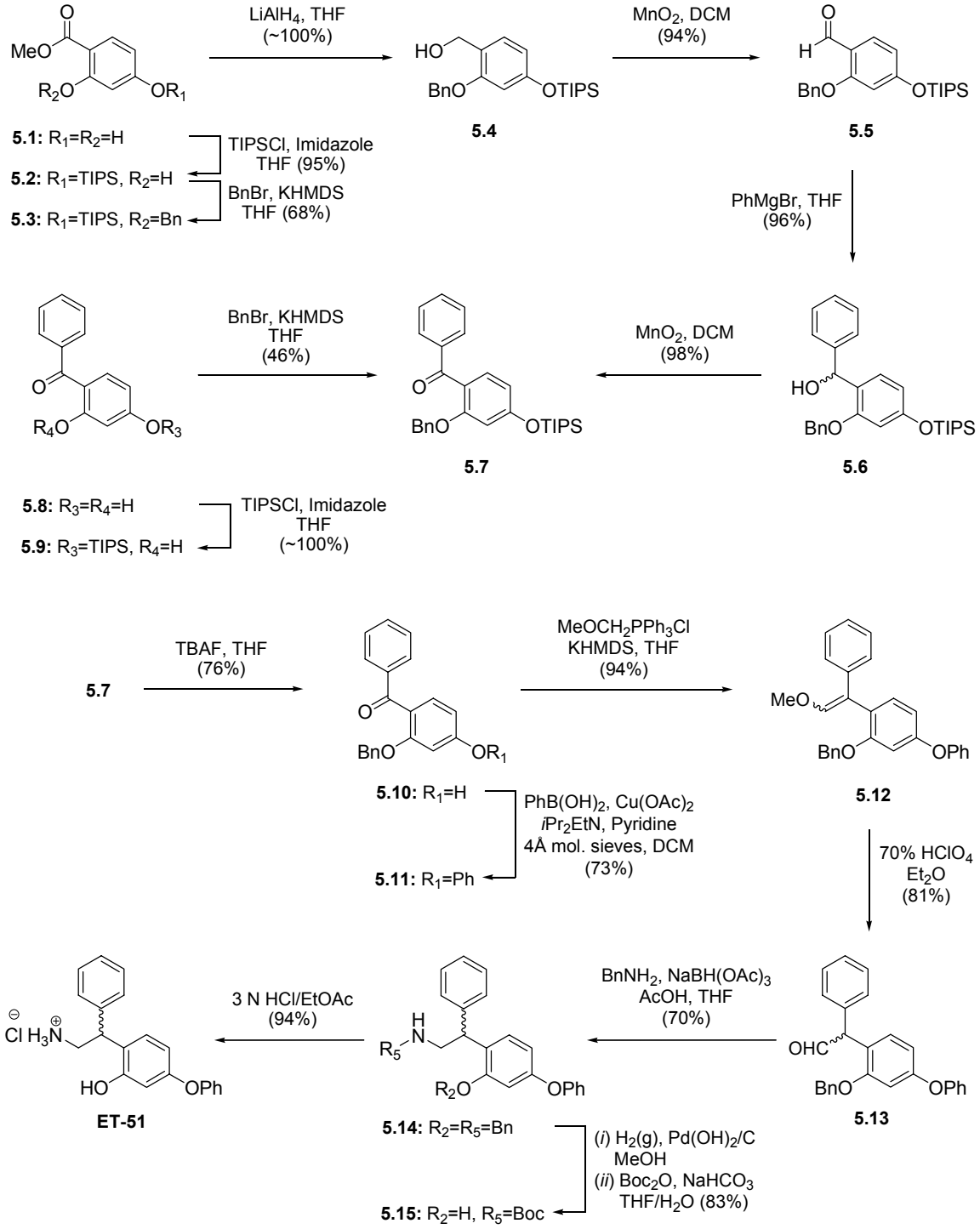
Table 5-1. Activity of **ET-13** position 2 analogs on $rTAAR_1$



Compd	R_1	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-13	H	28 ± 2	103 ± 4	3
ET-51	OH	96 ± 10	108 ± 1	3
ET-52	OMe	35 ± 4	82 ± 8	3
ET-53	OEt	144 ± 31	95 ± 5	3
ET-54	OPr	>1000	69 ± 5	2
ET-55	OBu	>1000	31 ± 1	2
ET-56	OBn	>1000	58 ± 2	2
ET-57	O-*i*Pr	>1000	62 ± 2	2
ET-58	O-*i*Bu	>1000	15 ± 4	2
ET-59	OCH_2CHCH_2	169 ± 6	71 ± 4	2
ET-60	OCH_2CCH	138 ± 37	78 ± 1	2
ET-61	$OCH_2CO_2CH_3$	>1000	56 ± 0	2
ET-62	$O_2CCH_2CH_2Cl$	143 ± 4	57 ± 5	2
ET-63	O_2CCH_3	234 ± 43	74 ± 3	2

[a]EC_{50} is the half-maximal effective concentration of a compound. [b]E_{max} is the maximum stimulation achieved at a concentration of 10 μM. EC_{50} and E_{max} values represent the average of *N* independent experiments in triplicate and were calculated by use of Prism software as described in the Appendix. E_{max} = 100 % is defined as the activity of **T_1AM** at 10 μM. [c]*N* is the number of independent experiments in triplicate that were performed and used to calculate the EC_{50} and E_{max} values. Compounds with stereogenic centers were evaluated as racemic mixtures.

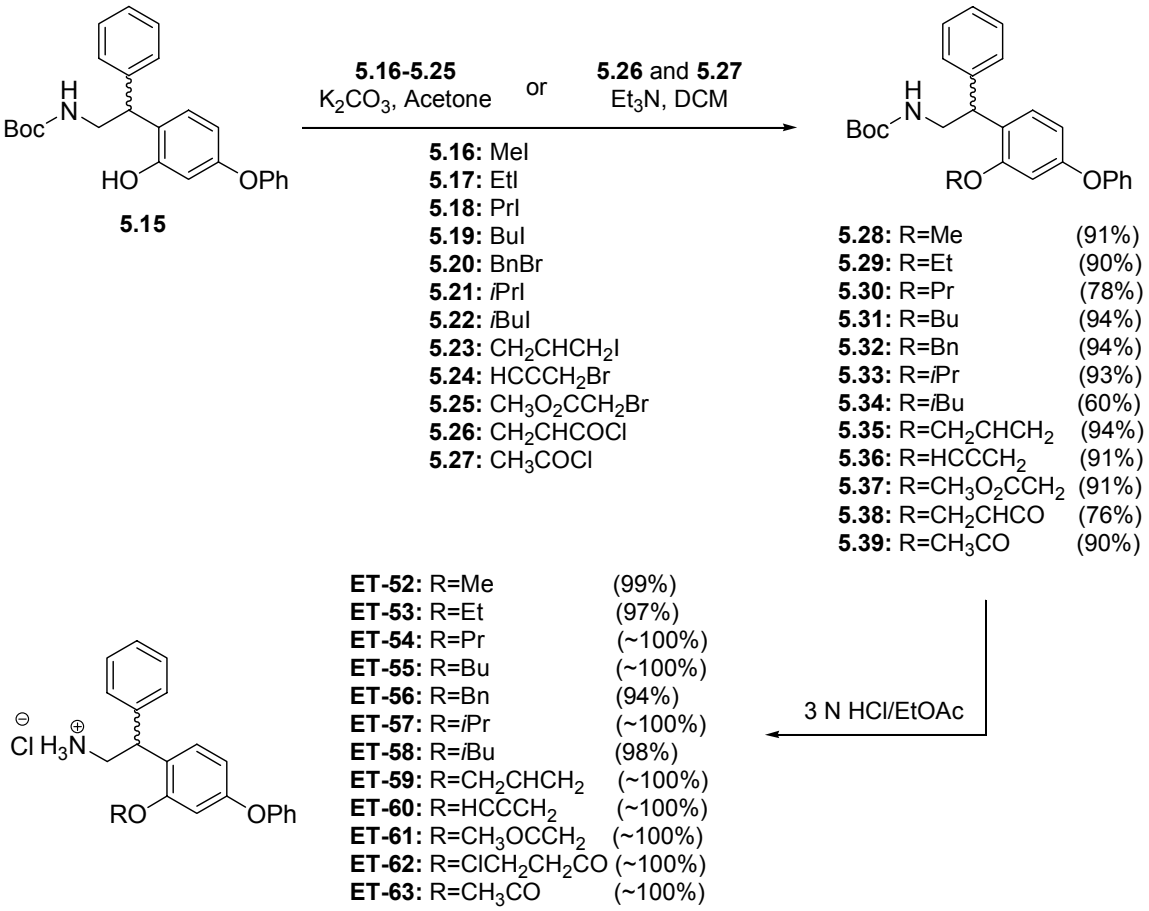
Scheme 5-1. Synthesis of **ET-51**



The observed agonist activities of **ET-51**–**ET-63** were consistent with the idea that the inner ring functional groups of these compounds were not properly interfering

with the rotamer switch residues. In compound **ET-51**, rotation of the inner ring about the β carbon and the biaryl ether oxygen axis renders position 2 and 6 indistinguishable (**Fig. 5-2**). Within the binding site, it's possible that the inner rings of **ET-52–ET-63** have rotated 180^{o} and are actually orienting the position 2 functional group towards the extracellular surface of rTAAR$_1$ around methionine 6.55 (M6.55) instead of the intracellular region near the rotamer switch residues (**Fig. 5-1b**). In this alternate binding orientation, these compounds would be predicted to have some agonist activity as the ether or ester appendage would not be able to interfere with the rotamer switch residues.

Scheme 5-2. Synthesis of **ET-52-ET-63**



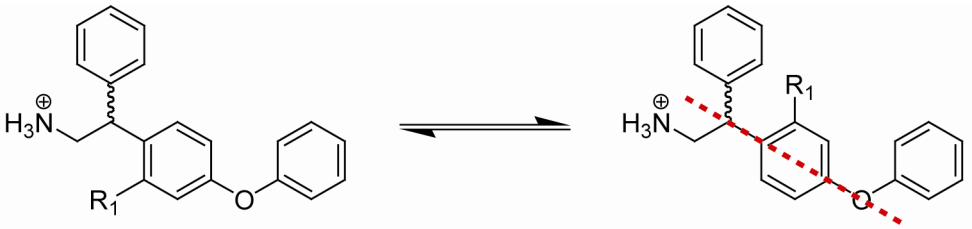


Figure 5-2. Conformers of **ET-13** position 2 analogs. Rotation of the inner ring about the β-carbon and biaryl ether oxygen axis (red dash line) renders position 2 and 6 indistinguishable.

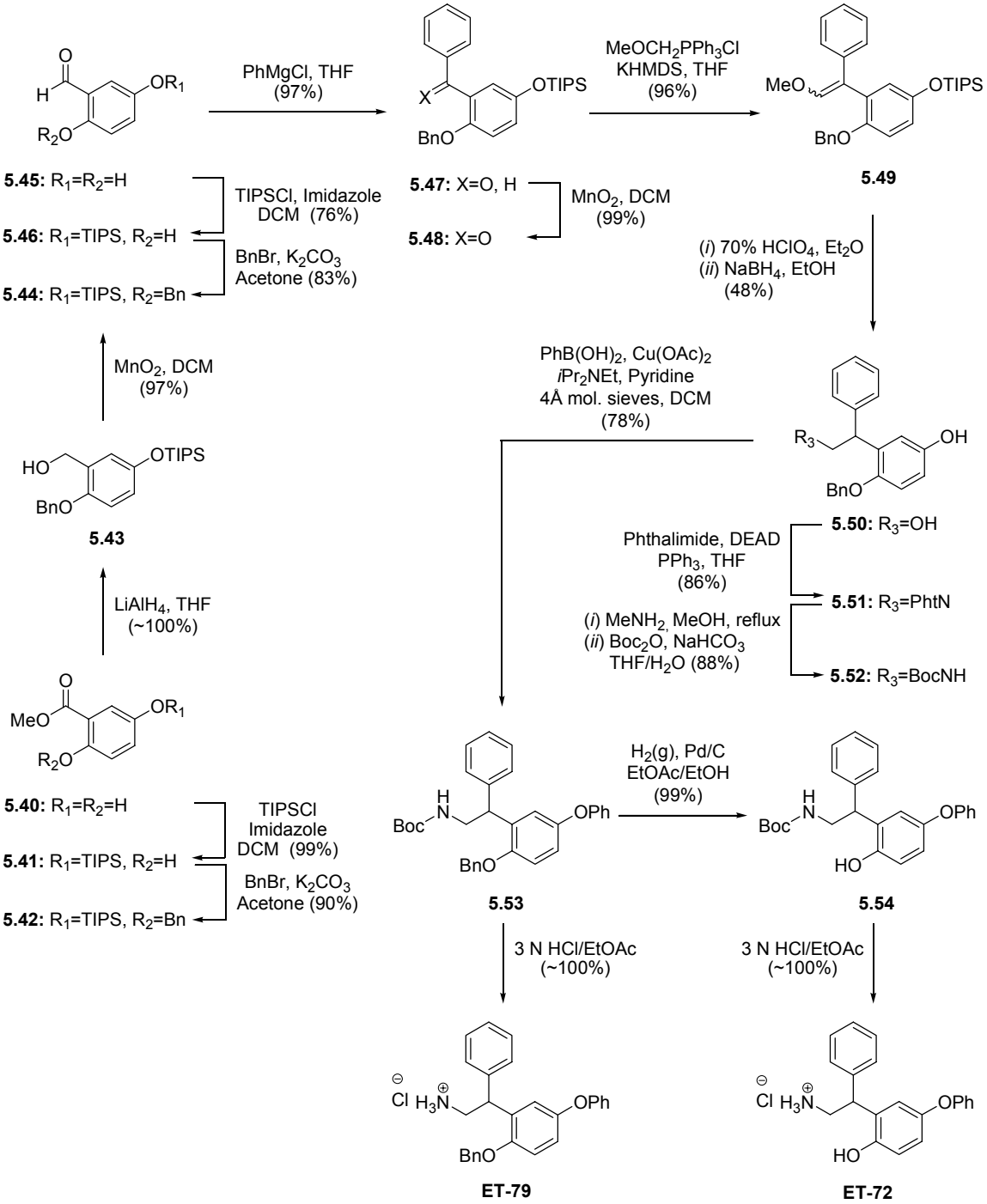
To test this hypothesis, the core scaffold of **ET-51** was modified to have the phenoxy group moved one carbon over to the *meta* position with respect to the ethylamine chain (**ET-72**) (**Scheme 5-3**). In this orientation, the 2 and 6 positions of the inner ring are now structurally distinct. Having a *meta* phenoxy group should not be detrimental to binding affinity because the isomer of **ET-13** with the phenoxy group at the *meta* position (**ET-14**) was found to be a slightly better agonist than **ET-13** for rTAAR$_1$ (EC_{50} = 19 ± 2 nM, E_{max} = 131 ± 7 %).[9] With this modification we synthesized 21 compounds (**ET-73**–**ET-86** and **ET-95**–**ET-101**) with an ether or ester appendage at the 2 position that again varied in steric bulk, rigidity, topology, and polarity (**Schemes 5-3**–**5-5**).

5.1.3 Synthesis of ET-14 Position 2 Analogs

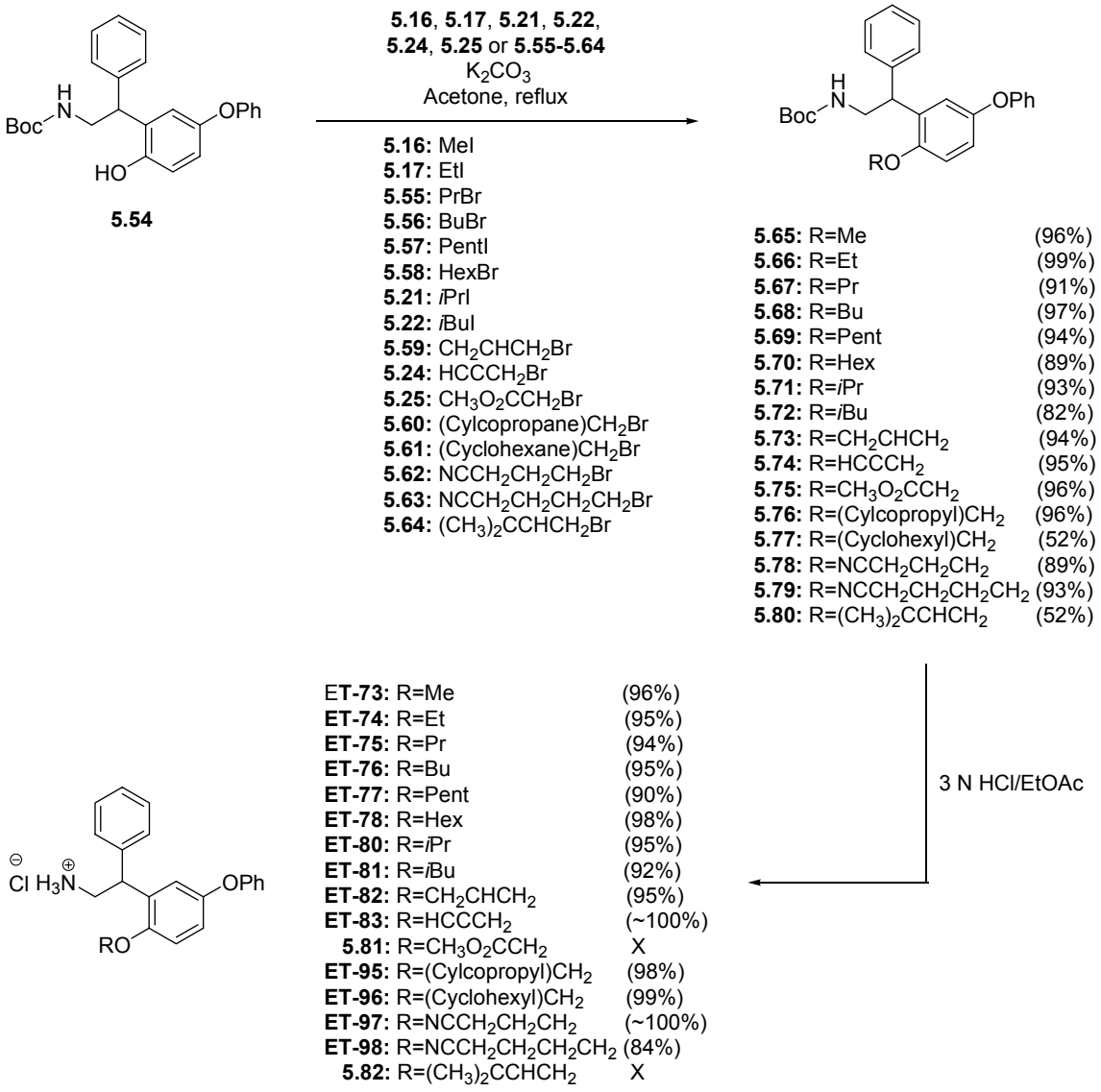
Phenol **5.54**, an isomer of **5.15**, was the key branch point intermediate in the synthetic route to **ET-73**–**ET-86** and **ET-95**–**ET-101** (**Scheme 5-3**). Initially, intermediate **5.54** was synthesized from methyl-2,5-dihydroxybenzoic acid (**5.40**). Following the protection of the *para*- and *ortho*-phenols of **5.40** with TIPS chloride and benzyl bromide, respectively, the methyl ester was reduced with $LiAlH_4$ and oxidized with MnO_2 to provide aldehyde **5.44**. In scaling up, we reduced the number of steps by

synthesizing **5.44** from 2,5-dihydroxybenzaldehyde (**5.45**). Since the phenols of **5.40** and **5.45** had a 1,4 relationship, TIPS migration was not observed in the benzyl protection of **5.41** or **5.46** .

Scheme 5-3. Synthesis of **ET-72** and **ET-79**



Scheme 5-4. Synthesis of **ET-73-ET-78**, **ET-80-ET-83**, **ET-90**, and **ET-95-ET-98**

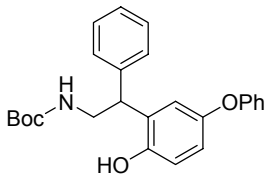


Treatment of **5.44** with phenylmagnesium chloride and oxidation with MnO_2 then provided benzophenone **5.48** quantitatively. The resulting aldehyde from a Wittig homologation reaction of **5.48** with methoxytriphenylphosphonium chloride afforded an intermediate that was unstable to silica and reductive amination with benzylamine. This led us to immediately reduce the aldehyde to primary alcohol **5.50** without any purification. Although transforming the primary alcohol of **5.50** to an amine could be

accomplished by conversion to a bromide, substitution with an azide, and catalytic hydrogenation, we chose to abandon this route because the nucleophilic substitution reaction with sodium azide also produced significant amounts of 1,1 disubstituted alkene through the competing elimination reaction. Instead the amine group was incorporated via a Mitsunobu reaction using phthalimide as the nucleophile.[10, 11] Treatment of **5.51** with methylamine followed by Boc protection provided intermediate **5.52** in excellent yield.[12] Copper (II) mediated coupling with phenyl boronic acid and subsequent catalytic hydrogenation reaction furnished the key intermediate **5.54**. Boc deprotection of **5.54** and **5.53** quantitatively provided the hydrochloride salts of **ET-72** and **ET-79**, respectively. Reaction of **5.54** with alkyl halides followed by acid deprotection afforded **ET-73**–**ET-78**, **ET-80**–**ET-83**, and **ET-95**–**ET-98** as hydrochloride salts (**Scheme 5-4**). Boc deprotection of **5.75** and **5.80** gave an inseperable mixture of esters (methyl and ethyl) and the removal of the 3,3-dimethylallyl substituent, respectively.

Esterification of **5.54** with acid chlorides gave esters **5.87-5.92** in modest to excellent yields (**Scheme 5-5**). Boc deprotection of **5.87-5.92** provided **ET-84**–**ET-86** or product degradation. The ester groups of **5.87**, **5.89**, and **5.92** fell of during acid deprotection and provided **ET-72**. Heterocylic ethers **5.104-5.111** were obtained by Mitsunobu reaction of **5.54** with heterocyclic methyl alcohols (**5.96-5.103**) (**Scheme 5-5**). Upon acid deprotection, only the three pyridine heterocyles (**ET-99**–**ET-101**) survived. The remaining compounds either gave **ET-72** alone or a mixture of **ET-72** and the corresponding heterocyclic ether.

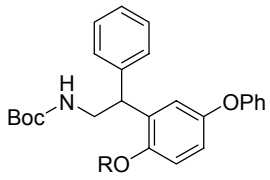
Scheme 5-5. Synthesis of **ET-84-ET-86**, **ET-99-ET-101**



5.54

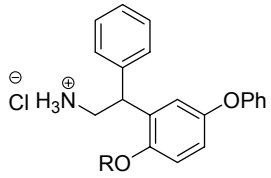
5.26, **5.27**, or **5.83-5.86**
Et_3N
DCM

5.27: CH_3COCl
5.26: $CH_2CHCOCl$
5.83: $ClCH_2COCl$
5.84: $(CH_3)_2CHCOCl$
5.85: $(CH_3)_2CHCH_2COCl$
5.86: $CH_3CO_2CH_2COCl$

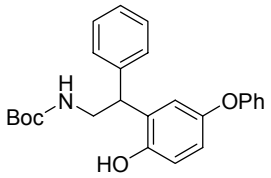


5.87: R=CH_3CO (91%)
5.88: R=CH_2CHCO (86%)
5.89: R=$ClCH_2CO$ (48%)
5.90: R=$(CH_3)_2CHCO$ (91%)
5.91: R=$(CH_3)_2CHCH_2CO$ (~100%)
5.92: R=$CH_3CO_2CH_2CO$ (75%)

3 N HCl/EtOAc



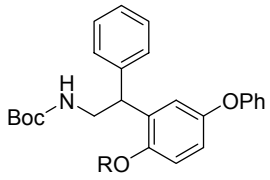
5.93: R=CH_3CO X
ET-84: R=$ClCH_2CH_2CO$ (94%)
5.94: R=$ClCH_2CO$ X
ET-85: R=$(CH_3)_2CHCO$ (~100%)
ET-86: R=$(CH_3)_2CHCH_2CO$ (86%)
5.95: R=$CH_3CO_2CH_2CO$ X



5.54

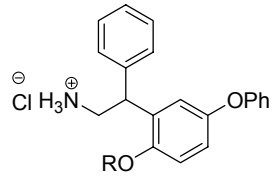
5.96-5.103, PPh_3
DEAD, THF

5.96: 4-Pyridine-CH_2OH
5.97: 3-Pyridine-CH_2OH
5.98: 2-Pyridine-CH_2OH
5.99: Furfuryl-OH
5.100: 3-Furan-CH_2OH
5.101: 2-Thiophene-CH_2OH
5.102: 3-Thiophene-CH_2OH
5.103: 2-(4-Morpholinyl)CH_2CH_2OH



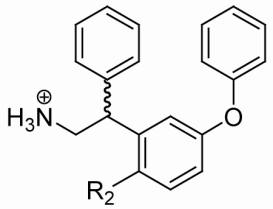
5.104: R=4-Pyridinyl-CH_2 (70%)
5.105: R=3-Pyridinyl-CH_2 (92%)
5.106: R=2-Pyridinyl-CH_2 (75%)
5.107: R=Furfuryl (61%)
5.108: R=3-Furan-CH_2 (89%)
5.109: R=2-Thiophene-CH_2 (59%)
5.110: R=3-Thiophene-CH_2 (52%)
5.111: R=2-(4-Morpholinyl)CH_2CH_2 (76%)

3 N HCl/EtOAc



ET-99: R=4-Pyridinyl-CH_2 (~100%)
ET-100: R=3-Pyridinyl-CH_2 (~100%)
ET-101: R=2-Pyridinyl-CH_2 (95%)
5.112: R=Furfuryl X
5.113: R=3-Furan-CH_2 X
5.114: R=2-Thiophene-CH_2 X
5.115: R=3-Thiophene-CH_2 X
5.116: R=2-(4-Morpholinyl)CH_2CH_2 X

Table 5-2. Activity of **ET-14** position 2 analogs on $rTAAR_1$



Compd	R_2	Agonist Activity			Antagonist Activity		
		EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	I_{max}[e] ± SEM (%)	N[c]
ET-14	H	19 ± 2	131 ± 7	3	-	-	-
ET-72	OH	232 ± 8	88 ± 9	2	-	-	-
ET-73	OMe	102 ± 26	88 ± 1	3	-	-	-
ET-74	OEt	>1000	66 ± 3	2	-	-	-
ET-75	OPr	>1000	41 ± 0	2	-	-	-
ET-76	OBu	>1000	3 ± 0	2	7 ± 2	12 ± 3	2
ET-77	OPent	>1000	0 ± 3	2	5 ± 0	6 ± 1	2
ET-78	OHex	>1000	0 ± 1	2	4 ± 0	3 ± 1	4
ET-79	OBn	>1000	9 ± 1	2	5 ± 1	6 ± 3	2
ET-80	O-*i*Pr	>1000	40 ± 1	2	-	-	-
ET-81	O-*i*Bu	>1000	6 ± 1	2	>10	23 ± 6	2
ET-82	OCH_2CHCH_2	602 ± 10	79 ± 5	2	-	-	-
ET-83	OCH_2CCH	182 ± 46	103 ± 0	2	-	-	-
ET-84	$O_2CCH_2CH_2Cl$	>1000	50 ± 8	2	-	-	-
ET-85	$O_2CCH(CH_3)_2$	599 ± 165	53 ± 6	2	-	-	-
ET-86	$O_2CCH_2CH(CH_3)_2$	>1000	33 ± 7	2	-	-	-
ET-95	OCH_2-Cyclopropyl	>1000	26 ± 7	3	-	-	-
ET-96	OCH_2-Cyclohexyl	>1000	0 ± 3	2	5 ± 1	9 ± 1	3
ET-97	$OCH_2CH_2CH_2CN$	>1000	3 ± 4	2	>10	30 ± 2	3
ET-98	$OCH_2CH_2CH_2CH_2CN$	>1000	2 ± 2	2	>10	23 ± 4	3
ET-99	OCH_2-(4-Pyridinyl)	>1000	4 ± 2	2	7 ± 1	15 ± 2	3
ET-100	OCH_2-(3-Pyridinyl)	>1000	9 ± 0	2	>10	33 ± 1	3
ET-101	OCH_2-(2-Pyridinyl)	>1000	6 ± 1	2	7 ± 0	16 ± 2	3

[a-b] See footnotes for Table 5-1. [c]*N* is the number of independent experiments in triplicate that were performed and used to calculate the EC_{50}, IC_{50}, E_{max}, and I_{max} values. [d]IC_{50} is the half-maximal inhibitory concentration of a compound at inhibiting the signal of fixed concentration of **T_1AM** (33 nM) in a competition assay. [e]I_{max} is the maximum stimulation achieved by a fixed concentration of **T_1AM** (33 nM) when competed with a 10 μM dose of a compound. IC_{50} and I_{max} values represent the average of *N* independent experiments in triplicate and were calculated by use of Prism software as described in the Appendix. I_{max} = 100 % is defined as the activity of **T_1AM** at 10 μM. I_{max} of **T_1AM** at 33 nM was 45 ± 5 %. Compounds with stereogenic centers were evaluated as racemic mixtures.

5.1.4 Receptor Activation of ET-14 Position 2 Analogs

For the ether series (**ET-73**–**ET-83** and **ET-95**–**ET-101**), an interesting correlation was observed between the size of the position 2 substituent and the agonist activity of the compound. The core scaffold **ET-72** was ~12-fold less potent (EC_{50} = 232 ± 8 nM) and 43 % less efficacious (E_{max} 88 ± 9 %) compared to **ET-14** (**Table 5-2**). Methylating the phenol of **ET-72** (**ET-73**) increased the potency ~2-fold (EC_{50} = 102 ± 26 nM) but had no effect on efficacy (E_{max} = 88 ± 1 %). When the ether group was an ethyl ether or larger (**ET-74–ET-81**), the potency of the compound was poor (> 1 μM). The efficacy showed a different profile. When the ether group was less than 5 atom units long (**ET-74**, **ET-75**, **ET-80**, and **ET-95**), the compound still had some degree of agonist activity (E_{max} = 26-66 %). As the ether group increased in size equal to or greater than 5 atom units long (**ET-76–ET-79** and **ET-96–ET-101**), the compounds became non-agonists activating $rTAAR_1$ at less than 10 % efficacy. An exception to this trend was **ET-81**. Although its isobutoxy group is only four atom units long, **ET-81** activated below 10 % efficacy (E_{max} = 6 ± 1 %). Compared to **ET-75** (EC_{50} = > 1000 nM, E_{max} = 41 ± 0 %), introducing an unsaturated alkene (**ET-82**) or alkyne (**ET-83**) into the position 2 group increased both potency (EC_{50} = 602 ± 10 nM and 182 ± 46 nM, respectively) and efficacy (E_{max} = 79 ± 5 % and 103 ± 0 %, respectively).

In the ester series (**ET-84–ET-86**), the potency of the compounds was greater than 1 μM when the position 2 functional group was 5 atom units long (**ET-84** and **ET-86**) but less than 1 μM when 4 atom units long (**ET-85**, EC_{50} = 599 ± 165 nM) (**Table 5-2**). The efficacy of the **ET-84–ET-86** were between 33-53 %.

When the 11 non-agonists (**ET-76–ET-79** and **ET-96–ET-101**) were tested for antagonist activity in a competition assay (as described in Chapter 2), all of the compounds antagonized **T_1AM** induced $rTAAR_1$ activation in HEK293 cells to varying degrees. Representative dose-response curves of antagonists in $rTAAR_1$ are shown in Figure 5-3. The butyl ether **ET-76** showed ca. 75 % antagonism with a half maximal inhibitory concentration (IC_{50}) of 7 ± 2 μM (**Table 5-2**). Isobutyl ether **ET-81** was also a weak antagonist showing 50 % inhibition and a potency of > 10 μM. The longer pentyl and hexyl ethers (**ET-77** and **ET-78**, respectively) were better antagonists reducing the **T_1AM** signal to 3-6 % at a potency of ~4-5 μM. The cyclohexylmethyl ether **ET-96** was equally potent (IC_{50} = 5 ± 1 μM) but somewhat less inhibitory (I_{max} = 9 ± 1 %). Compared to the benzyl ether **ET-79** (IC_{50} = 5 ± 1 μM, I_{max} = 6 ± 3 %), the heterocyclic pyridine methyl ethers (**ET-99–ET-101**) were less potent ($IC_{50} \geq$ 7 μM) and inhibitory ($I_{max} \geq$ 15 %). The cyanoalkyl ethers **ET-97** and **ET-98** were poor antagonists inhibiting the **T_1AM** signal no lower than 23 % with an IC_{50} value > 10 μM. The inhibitory effects of these compounds were neither due to inhibition of adenyl cylcase nor cytotoxicty (data not shown); suggesting that these compounds are *bona fide* $rTAAR_1$ antagonists.

5.2 SAR of $rTAAR_1$ Lead Antagonist

The agonist and antagonist properties of **ET-14** and **ET-78**, respectively, suggested that the hexyloxy group is essential for antagonism. To determine if the outer ring (ring A in **Fig. 5-1a**) and β-phenyl ring are also necessary for antagonism, we synthesized analogs of **ET-78** lacking the outer ring (**ET-88**) or the β-phenyl ring (**ET-89**) (**Schemes 5-6** and **5-7**). For comparison, the outer ring of **ET-79** was also removed (**ET-87**). In an attempt to improve the potency of **ET-78**, we also explored the effects of

N-methylation (**ET-90**) and functionalization of the outer ring (**ET-91–ET-94**) (**Schemes 5-8** and **5-9**).

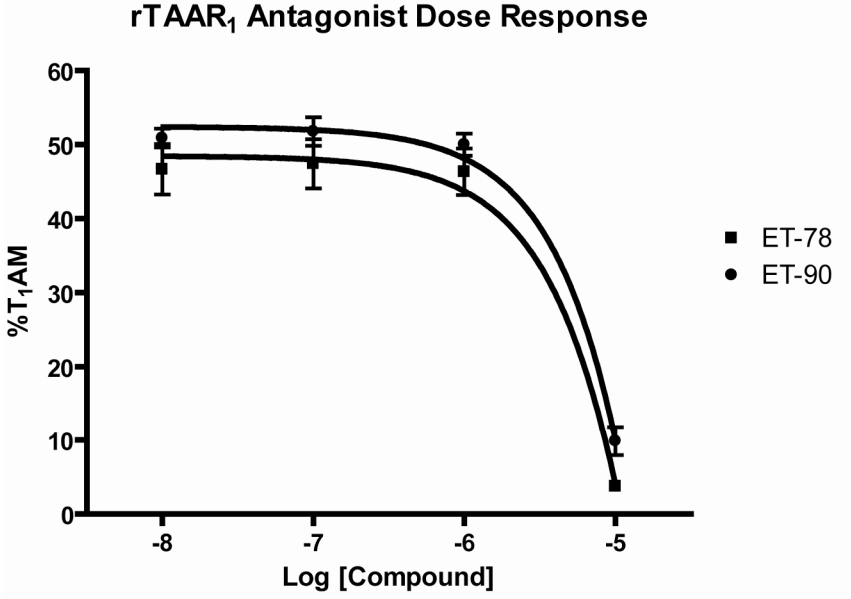
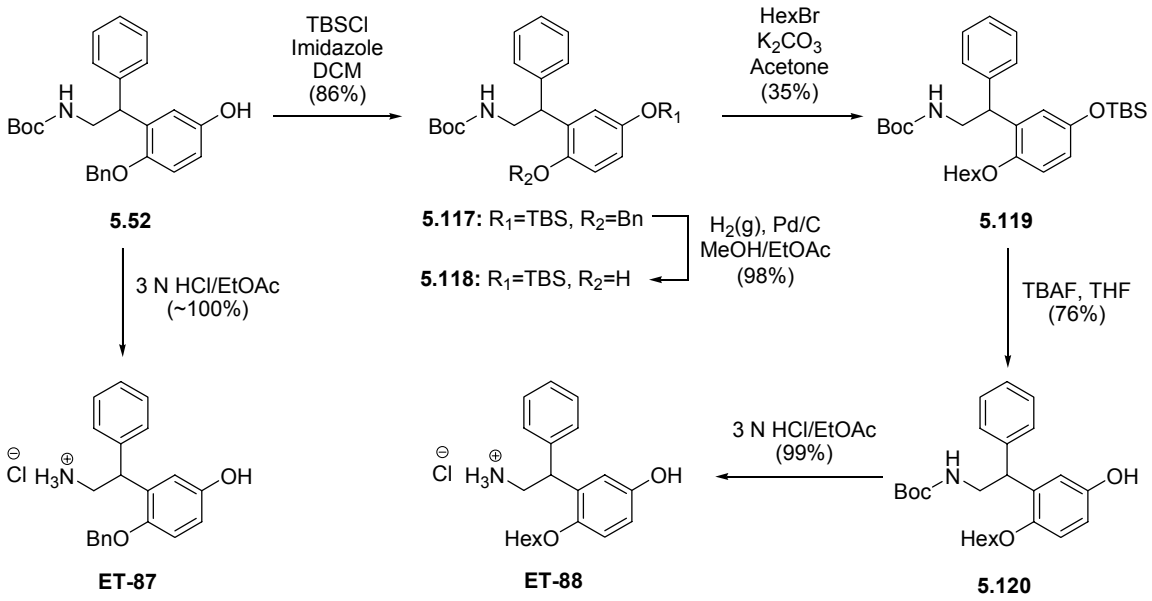


Figure 5-3. Representative dose-response curves of antagonists for rTAAR$_1$ stably expressed in HEK293 cells. Dose-response curves of **ET-78** (■) and **ET-90** (●) in competition with a fixed concentration of **T$_1$AM** (33 nM). Data reported were normalized to **T$_1$AM** and expressed as a percentage of the activity of **T$_1$AM** (% T$_1$AM). Dose-response curves were plotted and IC_{50} and I_{max} values were calculated with use of Prism software as described in the Appendix.

Scheme 5-6. Synthesis of **ET-87** and **ET-88**



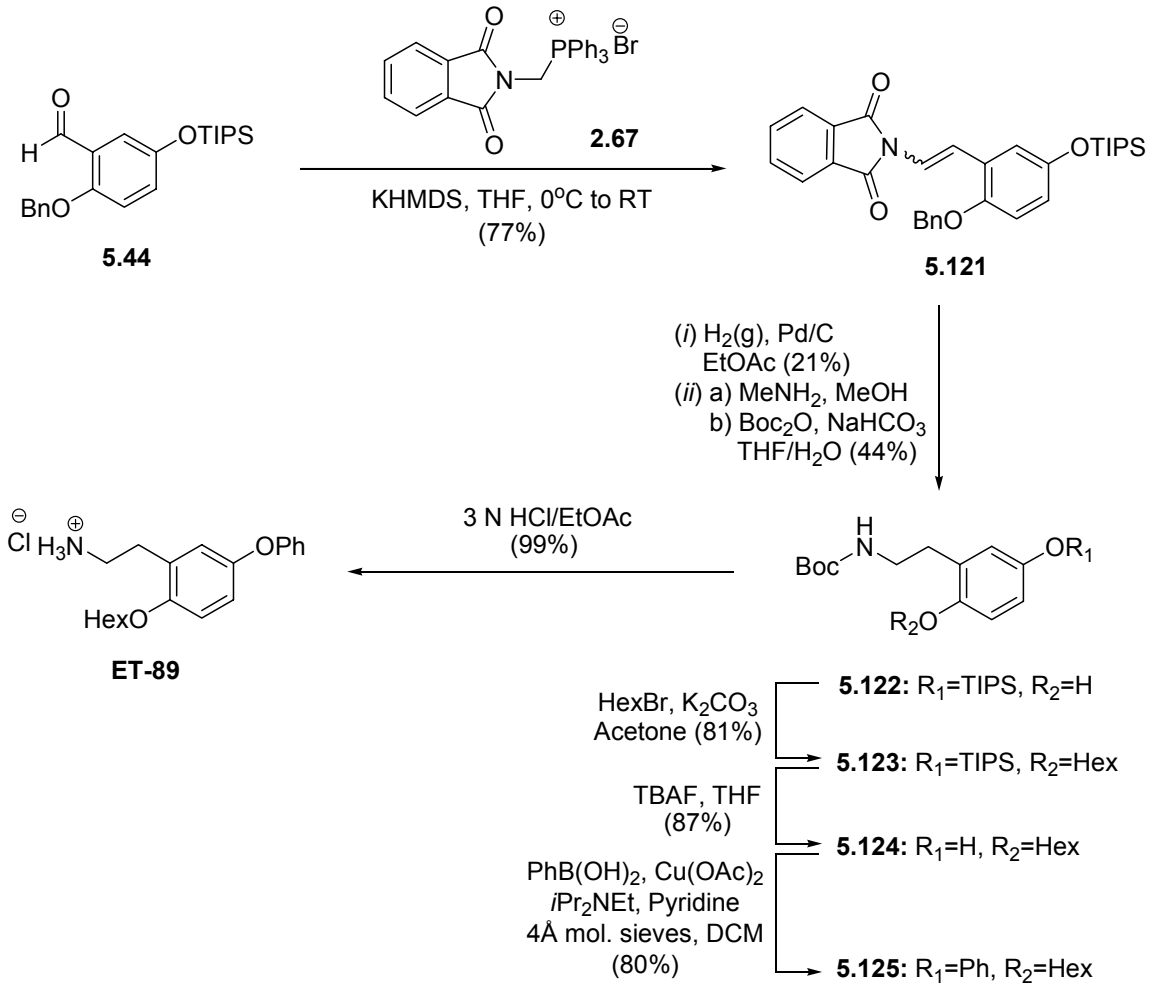
5.2.1 Synthesis of ET-78 Analogs

Boc deprotection of **5.52** provided the hydrochloride salts of **ET-87** quantitatively (**Scheme 5-6**). Protecting group manipulation and subsequent alkylation of the *ortho*-phenol with hexylbromide provided intermediate **5.119**. Deprotection of the TBS and Boc groups in **5.119** afforded **ET-88** as a hydrochloride salt in good yield.

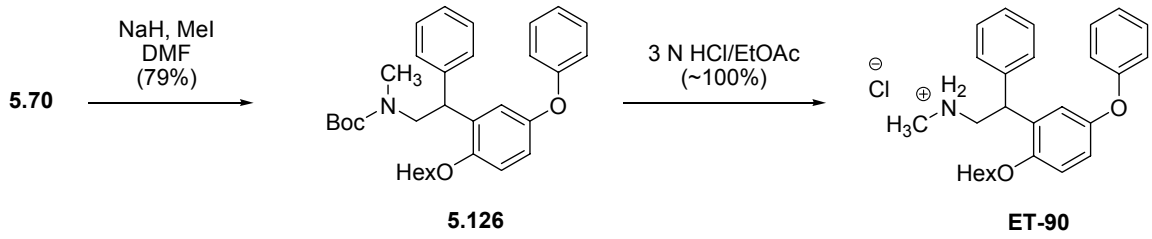
Since **ET-89** lacked the β-phenyl ring, it was synthesized from intermediate **5.44** (**Scheme 5-7**). Wittig reaction with phosphonium bromide **2.67** provided enamine **5.121** in 77 % yield. Catalytic hydrogenation and subsequent deprotection and reprotection of the amine group afforded **5.122** in poor yield. The same poor yields were also obtained for the same sequence of transformations in the synthesis of the naphethylamines (see Chapter 2). At this time, this reaction sequence does not seem to be a good choice for installing a Boc protected methylamine unit into an aromatic aldehyde. Alkylation with hexylbromide, TIPS deprotection, and copper (II) mediated coupling converted **5.122** into biaryl ether **5.125**. Acid deprotection gave **ET-89** as a hydrochloride salt in quantitative yield.

N-Methylation of Boc protected **5.70** afforded mono-methyl **5.126** (**Scheme 5-8**). Boc deprotection with acid provided the hydrochloride salts of **ET-90** quantitatively. Copper (II) mediated coupling of **5.52** with boronic acids **5.127-5.132** was followed by catalytic hydrogenation and alkylation gave ethers **5.144-5.148** (**Scheme 5-9**). The heterocyclic ether **5.138** was not hydrogenated because of concerns that the sulfur group would poison the palladium catalyst. TIPS deprotection of **5.144** gave the corresponding alcohol but deprotection of **5.145** only gave degradation products. Acid deprotection of **5.146-5.149** provided the hydrochloride salts of **ET-91**–**ET-94**.

Scheme 5-7. Synthesis of **ET-89**



Scheme 5-8. Synthesis of **ET-90**



Scheme 5-9. Synthesis of **ET-91-ET-94**

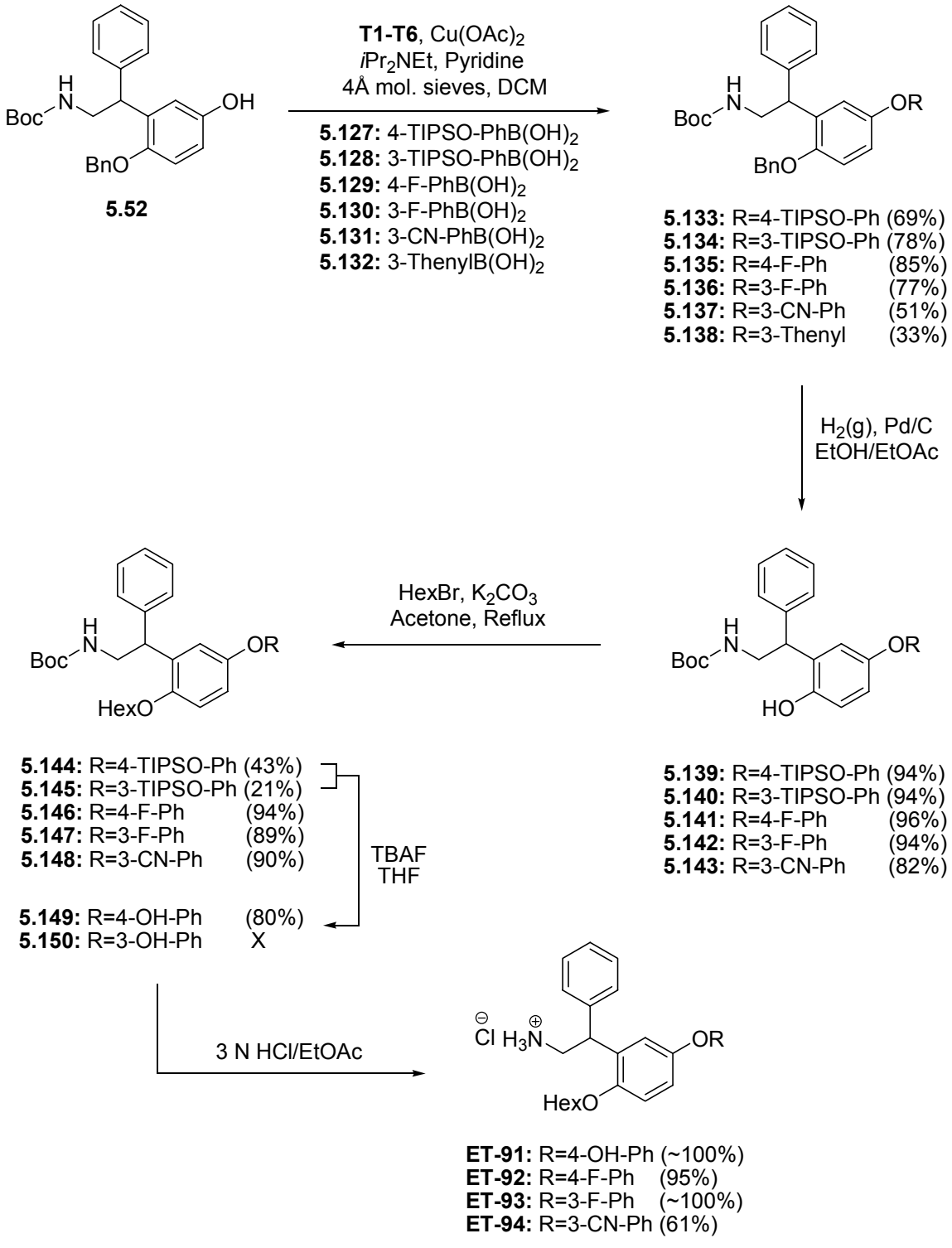
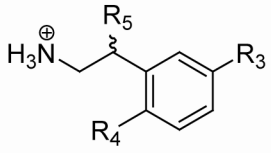


Table 5-3. Activity of β-phenyl and outer ring analogs of **ET-78** and **ET-79** on $rTAAR_1$



Compd	R_3	R_4	R_5	EC_{50} [a] ± SEM (nM)	E_{max} [b] ± SEM (%)	N [c]
ET-87	OH	OBn	Ph	>1000	16 ± 3	2
ET-88	OH	OHex	Ph	>1000	37 ± 9	2
ET-89	OPh	OHex	H	201 ± 23	59 ± 6	2

[a-c] See footnotes for Table 5-1. Compounds with stereogenic centers were evaluated as racemic mixtures.

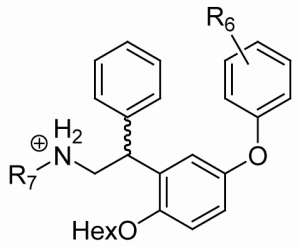
5.2.2 Receptor Activation of ET-78 Analogs

Removing the outer ring or β-phenyl ring of **ET-78** was detrimental to $rTAAR_1$ antagonism. In the absence of the outer ring (**ET-87** and **ET-88**), **ET-78** and **ET-79** were converted into weak agonists (**Table 5-3**). The efficacy of **ET-87** and **ET-88** were 16 ± 3 % and 37 ± 9 %, respectively, and their potency was > 1 μM. Similarly, **ET-78** became an agonist without the β-phenyl ring (**ET-89**, EC_{50} = 201 ± 23 nM, EC_{50} = 59 ± 6 %).

Mono-methylating the amine (**ET-90**) or inserting electron withdrawing groups on the outer ring (**ET-91**–**ET-94**) preserved the antagonist activity of **ET-78**. When screened for agonist activity, these compounds did not activate $rTAAR_1$ (**Table 5-4**). In the antagonist assay, the potency of **ET-90** was unaffected (IC_{50} = 5 ± 1 μM) but the antagonist activity slightly decreased (IC_{50} = 10 ± 4 %). The potency and inhibitory capacity of **ET-78** was also not significantly affected by introducing a *para*-fluoro, *meta*-fluoro, or *meta*-cyano group into the outer ring (**ET-92**, **ET-93**, and **ET-94** respectively). The IC_{50} and I_{max} values of these compounds were ~3 μM and ≤ 2 %, respectively.

Interestingly, inserting a *para*-hydroxy group into the outer ring (**ET-91**) endowed some agonist activity to **ET-78** activating $rTAAR_1$ at > 1 μM potency and 16 ± 3 % efficacy.

Table 5-4. Activity of **ET-78** analogs on $rTAAR_1$



Compd	R_6	R_7	Agonist Activity			Antagonist Activity		
			EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	I_{max}[e] ± SEM (%)	N[c]
ET-90	H	CH_3	>1000	0 ± 3	2	5 ± 1	10 ± 4	3
ET-91	*p*-OH	H	>1000	16 ± 3	3	-	-	-
ET-92	*p*-F	H	>1000	0 ± 3	2	3 ± 0	0 ± 3	3
ET-93	*m*-F	H	>1000	0 ± 4	2	3 ± 1	0 ± 5	3
ET-94	*m*-CN	H	>1000	0 ± 4	2	3 ± 1	2 ± 4	3

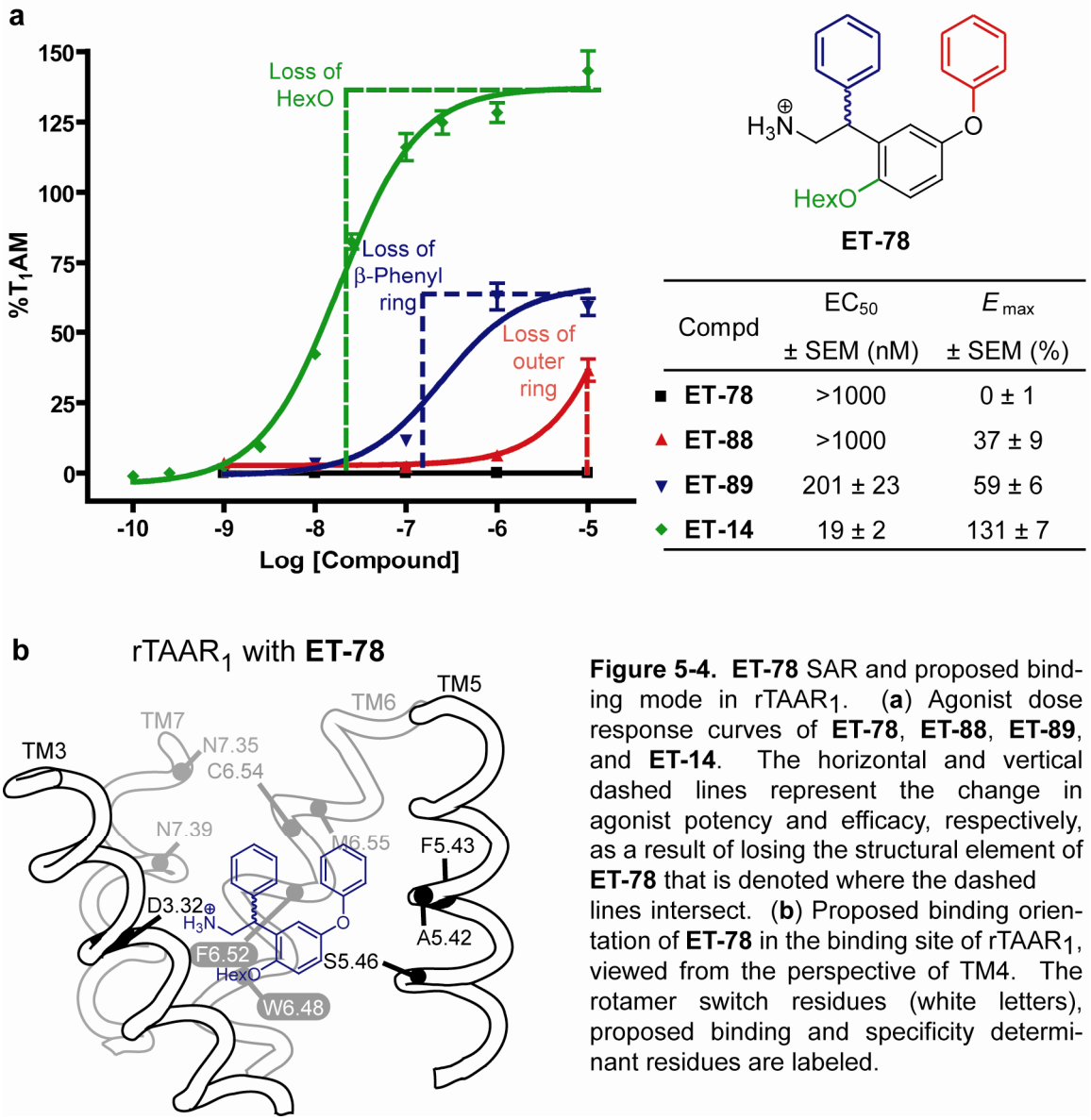
[a-e] See footnotes for Table 5-2. Compounds with stereogenic centers were evaluated as racemic mixtures.

5.3 Discussion

In contrast to the β_2AR and D_1R agonists, our analysis of the SAR and potential binding modes of antagonists for the D_1R and D_2R revealed the presence of structural moieties within these compounds that could conceivably sterically occlude the rotamer toggle switch residues from assuming their active conformation (see Chapter 2). Applying this hypothesis to $rTAAR_1$ we attempted to convert **ET-13** into an antagonist by installing ethers and esters at the 2 position of the inner ring that varied in steric bulk, rigidity, topology, and polarity (**ET-52–ET-63**). Based on our proposed binding

orientation of **ET-13** (**Fig. 5-1b**), this position was identified to be the prime location for presenting groups that could interfere with the rotamer switch residues in $rTAAR_1$. Unfortunately, none of these compounds turned out to be antagonists. Presumably **ET-52–ET-63** were still able to activate $rTAAR_1$ between 15 % and 95 % efficacy because the variable position 2 groups (R_1, **Table 5-1**) are positioned away from the rotamer switch residues within the binding site due to rotation of the inner ring about the β-carbon and biaryl ether oxygen axis (**Fig. 5-2**).

To circumvent this problem, we modified the core scaffold by moving the phenoxy group from the *para* (**ET-51**) to the *meta* (**ET-72**) position (**Tables 5-1** and **5-2**). With this modification, the agonist activity of the compound decreased as the size of the ether substituent increased. When the ether group was ≥ 5 atom units long (**ET-76–ET-79** and **ET-96–ET-101**), the agonist activity of the compound was completely abolished (≤ 10 % efficacy). Compounds with substituents less than 5 atom units long (**ET-73**–**ET-75**, **ET-80**, and **ET-95**) were weak agonists activating $rTAAR_1$ between 26 to 88 % efficacy. The composition of the substituent appears to be important as an ester group that is 5 atom units long (**ET-84** and **ET-86**) was still an agonist (EC_{50} = 33 to 53 %). When the non-agonists (**ET-76–ET-79** and **ET-96–ET-101**) were screened for antagonist activity in a competition assay with **T_1AM** at its EC_{50} concentration (33 nM), all compounds were found to inhibit **T_1AM** induced cAMP production to varying degrees at 10 μM. Compound **ET-78** was the best antagonist showing > 90 % inhibition of $rTAAR_1$ activation with an IC_{50} value of 4 μM. The antagonist activity of **ET-76–ET-79** and **ET-96–ET-101** are thought to arise from the ether substituents sterically occluding F6.52 and/or W6.48 of the rotamer switch residues from assuming their active conformations.



Compd	EC_{50} ± SEM (nM)	E_{max} ± SEM (%)
■ **ET-78**	>1000	0 ± 1
▲ **ET-88**	>1000	37 ± 9
▼ **ET-89**	201 ± 23	59 ± 6
◆ **ET-14**	19 ± 2	131 ± 7

Figure 5-4. ET-78 SAR and proposed binding mode in $rTAAR_1$. (**a**) Agonist dose response curves of **ET-78**, **ET-88**, **ET-89**, and **ET-14**. The horizontal and vertical dashed lines represent the change in agonist potency and efficacy, respectively, as a result of losing the structural element of **ET-78** that is denoted where the dashed lines intersect. (**b**) Proposed binding orientation of **ET-78** in the binding site of $rTAAR_1$, viewed from the perspective of TM4. The rotamer switch residues (white letters), proposed binding and specificity determinant residues are labeled.

The hexyloxy group, outer ring, and β-phenyl ring of **ET-78** are all necessary for antagonism. In the absence of any one of these groups, the resulting compounds lose their antagonist activity and become agonists. Since the transformation of **ET-78** to **ET-14** yielded the greatest increase in agonist potency and efficacy, the hexyloxy group is the most important of the three structural elements in terms of decreasing agonist activity and conferring antagonist properties to **ET-78** (**Fig. 5-4a**). This is consistent with the notion

that the outer ring and β-phenyl ring are essential scaffolding elements that assures **ET-78** docks into the $rTAAR_1$ binding site in the proper orientation to position the hexyloxy group, the molecular basis of antagonism, to interfere with the rotamer switch residues (**Fig. 5-4b**).

5.4 Conclusion

The rotamer toggle switch model of aminergic GPCR activation is a useful model for understanding the molecular basis of $rTAAR_1$ activation by **T_1AM** and related analogs. It has proven helpful in the development of $rTAAR_1$ agonists and antagonists providing superagonists **ET-36**, **ET-64**, and **ET-69** (see Chapter 4) and lead antagonists **ET-78**, **ET-92** and **ET-93**. This proof of concept study shows that the agonist or antagonist properties of aminergic GPCR drugs arise from drug interactions with the rotamer switch residues. Agonists complement the physicochemical properties of the binding site residues without disrupting the rotamer switch residues while antagonists interfere with the rotamer switch residues in addition to optimizing the interactions within the binding site.

These agonist and antagonist design principles have the potential to accelerate and increase the efficiency of the drug discovery and development process for GPCRs. Having insights into the critical ligand-receptor interactions important for receptor activation or inhibition facilitates the interpretation of SAR data and correlation of pharmacophore models with the molecular properties of the receptor binding site. This information then provides a map of the binding site landscape and presents a drug design blueprint for identifying promising scaffolds, recognizing compatible functional groups

to incorporate, and evaluating the contribution of individual structural elements of a given compound towards its binding affinity, selectivity, and functional properties. We envision these principles to supplement all current GPCR drug design strategies (e.g. ligand-based drug design, focused library screening, virtual screening, structure based drug design, etc.)[13-16] and help generate predictive rules and guidelines that would prove to be a useful and general method for designing activators or inhibitors for biogenic amine GPCRs and possibly other rhodopsin like GPCRs.

5.5 References

1. Fauq, A.; Ziani-Cherif, C.; Richelson, E., Synthesis of (S)- and (R)-enantiomers of p-(4-hydroxybenzoyl)phenylalanine, useful photoaffinity labeling probes for peptide-protein binding sites. *Tetrahedron: Asymmetry* **1998,** 9, (13), 2333-2338.
2. Haseltine, J.; Cabal, M.; Mantlo, N.; Iwasawa, N.; Yamashita, D.; Coleman, R.; Danishefsky, S.; Schulte, G., Total synthesis of calicheamicinone - new arrangements for actuation of the reductive cycloaromatization of aglycon congeners. *J. Am. Chem. Soc.* **1991,** 113, (10), 3850-3866.
3. Greene, T.; Wuts, P., *Protective groups in organic synthesis*. Third ed.; John Wiley & Sons, Inc: New York, 1999; 'Vol.' p 1-779.
4. Evans, D. A.; Katz, J. L.; West, T. R., Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998,** 39, (19), 2937-2940.
5. Abdel-Magid, A.; Carson, K.; Harris, B.; Maryanoff, C.; Shah, R., Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. *J. Org. Chem.* **1996,** 61, (11), 3849-3862.
6. Paquette, L.; Wang, T.; Philippo, C.; Wang, S., Total Synthesis of the Cembranoid Diterpene Lactone (+)-Cleomeolide. Some Remarkable Conformational Features of Nine-Membered Belts Linked in 2,6-Fashion to a Methylenecyclohexane Core. *J. Am. Chem. Soc.* **1994,** 116, 3367-3374.

7. Poschalko, A.; Welzig, S.; Treu, M.; Nerdinger, S.; Mereiter, K.; Jordis, U., Synthesis of (+/-)-6H-benzofuro[3a,3,2,ef][3]benzazepine: an unnatural analog of (-)-galanthamine. *Tetrahedron* **2002,** 58, (8), 1513-1518.

8. Sorensen, U.; Bleisch, T.; Kingston, A.; Wright, R.; Johnson, B.; Schoepp, D.; Ornstein, P., Synthesis and structure-activity relationship studies of novel 2-diarylethyl substituted (2-carboxycycloprop-1-yl)glycines as high-affinity group II metabotropic glutamate receptor ligands. *Bioorganic & Medicinal Chemistry* **2003,** 11, (2), 197-205.

9. Tan, E.; Miyakawa, M.; Bunzow, J.; Grandy, D.; Scanlan, T., Exploring the structure-activity relationship of the ethylamine portion of 3-iodothyronamine for rat and mouse trace amine-associated receptor 1. *J. Med. Chem.* **2007,** 50, (12), 2787-2798.

10. Kato, T.; Ozaki, T.; Tamura, K.; Suzuki, Y.; Akima, M.; Ohi, N., Novel calcium antagonists with both calcium overload inhibition and antioxidant activity. 1. 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(aminopropyl)thiazolidinones. *J. Med. Chem.* **1998,** 41, (22), 4309-4316.

11. Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K., Chiral synthesis of (+)-eburnamine, (-)-eburnamenine, and (-)-eburnamonine. *J. Chem. Soc., Perkin Trans. 1* **1985**, (2), 305-309.

12. Statsuk, A.; Liu, D.; Kozmin, S., Synthesis of bistramide A. *J. Am. Chem. Soc.* **2004,** 126, (31), 9546-9547.

13. Evers, A.; Hessler, G.; Matter, H.; Klabunde, T., Virtual screening of biogenic amine-binding G-protein coupled receptors: Comparative evaluation of protein-

and ligand-based virtual screening protocols. *J. Med. Chem.* **2005,** 48, (17), 5448-5465.

14. Evers, A.; Klabunde, T., Structure-based drug discovery using GPCR homology modeling: Successful virtual screening for antagonists of the Alpha1A adrenergic receptor. *J. Med. Chem.* **2005,** 48, (4), 1088-1097.

15. Klabunde, T.; Evers, A., GPCR antitarget modeling: Pharmacophore models for biogenic amine binding GPCRs to avoid GPCR-mediated side effects. *ChemBioChem* **2005,** 6, (5), 876-889.

16. Klabunde, T.; Hessler, G., Drug design strategies for targeting G-protein-coupled receptors. *ChemBioChem* **2002,** 3, (10), 929-944.

Chapter 6

Exploring the Specificity

Determinant Residues of $TAAR_1$

Although rat and mouse $TAAR_1$ are 93 % similar, the two receptors have distinct structural preferences. In the ethylamine region of the phenoxyphenethylamine scaffold, $rTAAR_1$ favored unsaturated hydrocarbon groups while $mTAAR_1$ preferred functional groups that are polar and hydrogen bond acceptors.[1] Additionally the β-phenylnaph-ethylamine **ET-33** had opposite functional properties being a good agonist for $rTAAR_1$ but a weak antagonist for $mTAAR_1$.[1] Since the rodent receptors are only 83-85 % similar to human $TAAR_1$, understanding the molecular basis of species variability will undoubtedly have important implications in the development of small molecule modulators for human $TAAR_1$. We suspect the disparate ligand preferences between $rTAAR_1$ and $mTAAR_1$ to be strongly influenced by non-conserved specificity determinant residues within the binding site. This chapter discusses the observed species dependent pharmacological properties of ligands and delineates experimental strategies to explore the underlying cause behind the species variability.

6.1 Mouse $TAAR_1$ Binding Site

Only 44 of the 332 amino acids that make up the rat and mouse $TAAR_1$ are not identical (**Fig. 6-1**). In the binding site, the two receptors are very similar. The binding determinant residues in TM3 and TM5 (D3.32 and S5.46) as well as the toggle switch residues (F6.52 and W6.48) are conserved (**Fig. 6-2**). However, there are important differences in TM6 and TM7 at residues 6.55 and 7.39. The residues at these positions have previously been shown to make contacts with the ligand in the β_2AR.[2-6] In place of a methionine and an asparagine at 6.55 and 7.39 (M6.55 and N7.39), respectively, $mTAAR_1$ has a threonine (T6.55) and a tyrosine (Y7.39).

```
          N-Terminus                TM1                          1.50          IL1
rTAAR1    MHLCHNSANISHTNSNWSR  DVRASLYSLISLIILTTLVGNLIVIISIS  HFKQLHTPTN
mTAAR1    .....AIT....R..D...  E.Q......M.....A.............  ..........

          TM2          2.50                  EL1          TM3          3.32
rTAAR1    WLLHSMAVVDFLLGCLVMPYSMVRTV  EHCWYFGE  LFCKLHTSTDIMLSSASILHLAFI
mTAAR1    .......I........I..C......  .R......  IL..V.............F.....

               3.50      IL2              TM4          4.50     4.56      EL2
rTAAR1    SIDRYYAV  CDPLRYKAKIN  LAAIFVMILISWSLPAVFAFGMIF  LELNLEGVEEQYH
mTAAR1    .....C..  ...........  IST.L....V.......Y......  .....K....L.R

                         TM5       5.42 5.43  5.46  5.50                IL3
rTAAR1    NQVFCLRGCFPFF  SKVSGVLAFMTSFYIPGSVMLFVYYRIY  FIAKGQARSINRANLQV
mTAAR1    S..SD.G..S...  ............................  ............T.V..

                         TM6                          6.48  6.50  6.52  6.55     EL3
rTAAR1    GLEGESRAPQS  KETKAAKTLGIMVGVFLLCWCPFFFCMVLDPFL  GYVIPP
mTAAR1    ....K.Q....  ................V......L.T......  ......

               7.35  7.39      TM7          7.50                  C-Terminus
rTAAR1    TLNDTLNWFGYLNSAFNPMVYAFFYPWFRRALKMVLF    GKIFQKDSSRSKLFL
mTAAR1    S...A.Y........L.....................L    ...............
```

Figure 6-1. Sequence comparison of rat and mouse $TAAR_1$. Dots represent conserved residues. Amino and carboxy termini (N-Terminus and C-Terminus, respectively), intracellular loops (IL), extracellular loops (EL) and transmembrane regions (TM) are labeled. The most conserved residue in each TM region is labeled X.50.

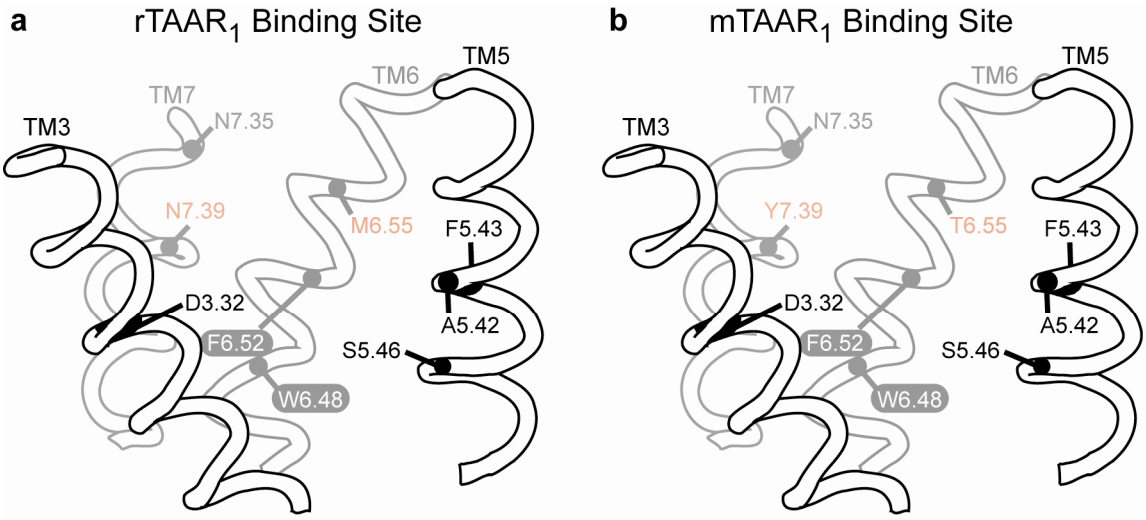
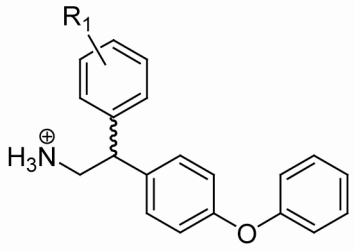
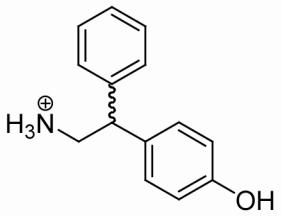


Figure 6-2. Binding site of $rTAAR_1$ (**a**) and $mTAAR_1$ (**b**). The rotamer switch residues (white letters), proposed binding and specificity determinant residues are labeled.

Table 6-1. Activity of **ET-13** analogs on $mTAAR_1$





ET-71

Compd	R_1	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-13	H	>1000	35 ± 8	3
ET-34	*p*-OMe	>1000	31	1
ET-35	*o*-OMe	>1000	4	1
ET-36	*p*-OH	>1000	62 ± 6	3
ET-37	*o*-OH	>1000	2	1
ET-38	CH_2OH	>1000	1	1
ET-47	CH_2NH_3	>1000	0	1
ET-65	*m*-OH	>1000	8	1
ET-66	*p*-F	>1000	29	1
ET-67	*m*-F	>1000	56	1
ET-71	-	>1000	49	1

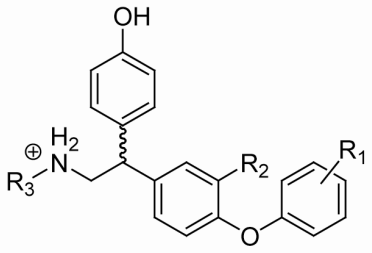
[a]EC_{50} is the half-maximal effective concentration of a compound. [b]E_{max} is the maximum stimulation achieved at a concentration of 10 μM. EC_{50} and E_{max} values represent the average of N independent experiments in triplicate and were calculated by use of Prism software as described in the Appendix. E_{max} = 100 % is defined as the activity of **T_1AM** at 10 μM. [c]N is the number of independent experiments in triplicate that were performed and used to calculate the EC_{50} and E_{max} values. Compounds with stereogenic centers were evaluated as racemic mixtures.

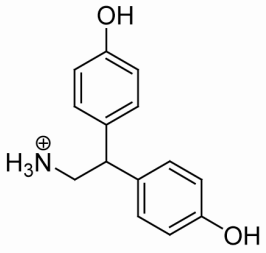
6.2 Selectivity of ET-13 and ET-14 for $rTAAR_1$

The β-phenylphenoxyphenethylamines **ET-13** and **ET-14** were found to be potent agonists for $rTAAR_1$ but poor agonists for $mTAAR_1$.[1] Compared to $mTAAR_1$, **ET-13** and **ET-14** are at least 357- and 526-fold more potent for $rTAAR_1$ (**Table 2-6**). All **ET-13** and **ET-14** derivatives described in Chapters 4 and 5 were also poor agonists for

mTAAR$_1$ with potencies > 1 μM and efficacies ≤ 72 % (**Tables 6-1–6-6**). Of the analogs with zero to basal levels of activity, some compounds were found to antagonize **T$_1$AM** induced cAMP production at mTAAR$_1$ in competition assays (**Tables 6-3–6-6**). The best antagonists were **ET-82** (IC_{50} ~ 3 μM and I_{max} = 7 ± 7 %) and **ET-86** (IC_{50} ~ 4 μM and I_{max} = 3 ± 3 %). Although some **ET-13** and **ET-14** derivatives appeared to be cytotoxic at 10 μM, killing up to 50 % of the mTAAR$_1$ HEK293 stable cells as measured with the CellTiter-Glo luminescent cell viability assay by Invitrogen, **ET-82** and **ET-86** were not cytotoxic at that concentration (data not shown).

Table 6-2. Activity of **ET-36** analogs on mTAAR$_1$





ET-50

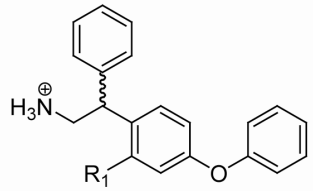
Compd	R_1	R_2	R_3	EC_{50} [a] ± SEM (nM)	E_{max} [b] ± SEM (%)	N [c]
ET-64	H	H	Me	>1000	42 ± 1	2
ET-68	H	I	H	>1000	43	1
ET-69	*p*-OH	I	H	>1000	34 ± 5	3
ET-70	*m*-OH	I	H	>1000	6	1
ET-50	-	-	-	>1000	72	1

[a-c] See footnotes for Table 6-1. Compounds with stereogenic centers were evaluated as racemic mixtures.

In Chapter 4, we deduced **ET-13** to bind to rTAAR$_1$ with the charged amine and biaryl ether oxygen interacting with D3.32 and S5.46, respectively (**Fig. 4-1b** and **5-1b**). Since the β-phenyl ring is located near M6.55 and N7.39, we hypothesize that one or both of these residues are specificity elements that influence compatibility with the β-phenyl ring of **ET-13**, and possibly **ET-14**. To test this hypothesis, we propose to test **ET-13**,

ET-14, and related analogs against rat and mouse $TAAR_1$ single and double swap mutants (M6.55T, N7.39Y, and M6.55T/N7.39Y for $rTAAR_1$; T6.55M, Y7.39N, and T6.55M/Y7.39N for $mTAAR_1$). If residues 6.55 and 7.39 are specificity determinant residues, we expect **ET-13** and **ET-14** to become poor agonists (EC ≥ 1 μM) for the $rTAAR_1$ 6.55 and/or 7.39 mutants and excellent agonists (EC ~20-30 nM) for the $mTAAR_1$ 6.55 and/or 7.39 mutants. For each mutant, a control agonist (**T_1AM**) will be included to demonstrate that the mutant receptors are fully functional and not disabled by the point mutation(s).

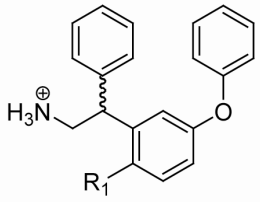
Table 6-3. Activity of **ET-13** position 2 analogs on $mTAAR_1$



Compd	R_1	Agonist Activity			Antagonist Activity			
		EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-51	OH	>1000	11	1	-	-	-	-
ET-52	OMe	>1000	1	1	-	-	-	-
ET-53	OEt	>1000	7	1	>10	1	31	1
ET-54	OPr	>1000	0	1	>10	1	19	1
ET-55	OBu	>1000	1	1	-	-	-	
ET-56	OBn	>1000	0	1	>10	1	19 ± 2	2
ET-57	O-*i*Pr	>1000	3	1	>10	1	30	1
ET-58	O-*i*Bu	>1000	0	1	>10	1	18	1
ET-59	OCH_2CHCH_2	>1000	2	1	>10	1	17	1
ET-60	OCH_2CCH	>1000	11	1	>10	1	24	1
ET-61	$OCH_2CO_2CH_3$	>1000	5	1	-	-	-	-
ET-62	$O_2CCH_2CH_2Cl$	>1000	1	1	>10	1	28	1
ET-63	O_2CCH_3	>1000	4	1	-	-	-	-

[a-b] See footnotes for Table 6-1. [c]*N* is the number of independent experiments in triplicate that were performed and used to calculate the EC_{50}, IC_{50}, E_{max}, and I_{max} values. [d]IC_{50} is the half-maximal inhibitory concentration of a compound at inhibiting the signal of fixed concentration of **T_1AM** (314 nM) in a competition assay. [e]I_{max} is the maximum stimulation achieved by a fixed concentration of **T_1AM** (314 nM) when competed with a 10 μM dose of a compound. IC_{50} and I_{max} values represent the average of *N* independent experiments in triplicate and were calculated by use of Prism software as described in the Appendix. I_{max} = 100 % is defined as the activity of **T_1AM** at 10 μM. I_{max} of **T_1AM** at 314 nM was 45 ± 5 %. Compounds with stereogenic centers were evaluated as racemic mixtures.

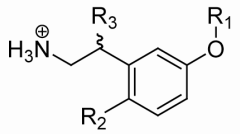
Table 6-4. Activity of **ET-14** position 2 analogs on mTAAR$_1$



Compd	R_1	Agonist Activity			Antagonist Activity			
		EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-14	H	>1000	15 ± 4	3	-	-	-	-
ET-72	OH	>1000	1 ± 2	2	-	-	-	-
ET-73	OMe	>1000	2	1	~10	1	12	1
ET-74	OEt	>1000	0	1	-	-	-	-
ET-75	OPr	>1000	0	1	~10	1	14	1
ET-76	OBu	>1000	0	1	7	1	10 ± 5	2
ET-77	OPent	>1000	0	1	10	1	13 ± 11	2
ET-78	OHex	>1000	0	1	5 ± 0	2	7 ± 4	4
ET-79	OBn	>1000	0	1	8	1	14 ± 6	2
ET-80	O-*i*Pr	>1000	0	1	6	1	12 ± 7	2
ET-81	O-*i*Bu	>1000	0	1	8	1	11 ± 11	2
ET-82	OCH_2CHCH_2	>1000	0	1	3	1	7 ± 7	2
ET-83	OCH_2CCH	>1000	0	1	10	1	18 ± 10	2
ET-84	$O_2CCH_2CH_2Cl$	>1000	0	1	-	-	-	-
ET-85	$O_2CCH(CH_3)_2$	>1000	0	1	7	1	9 ± 9	2
ET-86	$O_2CCH_2CH(CH_3)_2$	>1000	0	1	4	1	3 ± 3	2
ET-95	OCH_2-Cyclopropyl	>1000	0	1	7	1	25 ± 3	2
ET-96	OCH_2-Cyclohexyl	>1000	0	1	6	1	18 ± 5	2
ET-97	$OCH_2CH_2CH_2CN$	>1000	1	1	>10	1	36 ± 5	2
ET-98	$OCH_2CH_2CH_2CH_2CN$	>1000	0	1	>10	1	29 ± 4	2
ET-99	OCH_2-(4-Pyridinyl)	>1000	0	1	>10	1	33 ± 4	2
ET-100	OCH_2-(3-Pyridinyl)	>1000	0	1	-	-	-	-
ET-101	OCH_2-(2-Pyridinyl)	>1000	0	1	8	1	21 ± 2	2

[a-e] See footnotes for Table 6-3. Compounds with stereogenic centers were evaluated as racemic mixtures.

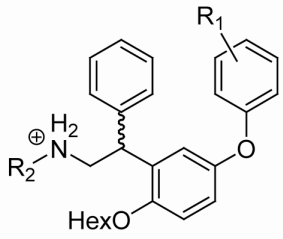
Table 6-5. Activity of β-phenyl and outer ring analogs of **ET-78** and **ET-79** on mTAAR$_1$



Compd	R_1	R_2	R_3	Agonist Activity			Antagonist Activity			
				EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-87	OH	OBn	Ph	>1000	0	1	-	-	-	-
ET-88	OH	OHex	Ph	>1000	0	1	-	-	-	-
ET-89	OPh	OHex	H	>1000	0	1	8	1	23	2

[a-e] See footnotes for Table 6-3. Compounds with stereogenic centers were evaluated as racemic mixtures.

Table 6-6. Activity of **ET-78** analogs on mTAAR$_1$



Compd	R_1	R_2	Agonist Activity			Antagonist Activity			
			EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-90	H	CH_3	>1000	0	1	6	1	24 ± 5	2
ET-91	*p*-OH	H	>1000	0	1	-	-	-	-
ET-92	*p*-F	H	>1000	0	1	7	1	8 ± 1	2
ET-93	*m*-F	H	>1000	0	1	6	1	9 ± 4	2
ET-94	*m*-CN	H	>1000	0	1	6	1	9 ± 3	2

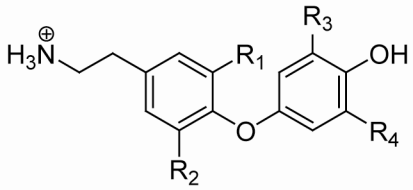
[a-e] See footnotes for Table 6-3. Compounds with stereogenic centers were evaluated as racemic mixtures.

6.3 Potency Disparities of Thyronamines in Rat and Mouse TAAR$_1$

The rank order potency of the thyronamines for rat and mouse TAAR$_1$ are similar but the potency values of individual compounds for the two receptors are not the same

(**Table 6-7**).[7, 8] In general, thyronamines are ~10-fold less potent for $mTAAR_1$ compared to $rTAAR_1$. A possible explanation for this potency disparity can be attributed to a lower G-protein coupling efficiency for $mTAAR_1$ versus $rTAAR_1$. If this were the case, then it's impossible to have an equipotent compound for both receptors because $mTAAR_1$ would be inherently less active than $rTAAR_1$. Since 1-naphethylamine (**1-NEA**, **Table 2-9**) is equipotent for both $rTAAR_1$ (EC_{50} = 65 ± 6 nM and E_{max} = 115 ± 2 %) and $mTAAR_1$ (EC_{50} = 82 ± 17 nM and E_{max} = 112 ± 3 %), the G-protein coupling efficiency of $mTAAR_1$ is comparable to that of $rTAAR_1$.

Table 6-7. Activity of thyronamines on $rTAAR_1$ and $mTAAR_1$



					EC_{50} (nM)[a]	
Compd	R_1	R_2	R_3	R_4	$rTAAR_1$	$mTAAR_1$
T_0AM	H	H	H	H	131	~1000
T_1AM	I	H	H	H	14	112
T_2AM	I	I	H	H	56	371
T_3AM	I	I	I	H	87	>1000
T_4AM	I	I	I	I	>1000	>1000
3,3'-T_2AM	I	H	I	H	41	~1000
rT_3AM	I	H	I	I	>1000	>1000
3',5'-T_2AM	H	H	I	I	>1000	>1000
3'-T_1AM	H	H	I	H	800	>1000

[a] Scanlan et al, *Nat Med* 2004 and Hart et al, *J Med Chem* 2006.

We believe that the potency disparities of thyronamines can be attributed to nonconserved amino acids at key specificity determinant residues within the binding site.

In particular, we speculate that tyrosine 4.56 (Y4.56) is primarily responsible for the ~10-fold lower potency of thyronamines for $mTAAR_1$ (**Fig. 6-1**). This residue was deduced through a process of elimination using the following logic: (1) since the binding sites of GPCRs are located within the transmembrane regions of the receptor, all the intracellular and extracellular loops as well as the amino- and carboxy-terminus are eliminated;[9] (2) amino acid differences in TM1 and TM2 are eliminated because the binding site is primarily composed of TM3, TM4, TM5, TM6 and TM7;[10] (3) since the ethylamine chain of thyronamines and **1-NEA** are exactly the same, non-conserved residues in TM3, TM6, and TM7 cannot be responsible; (4) TM5 is eliminated because it is absolutely conserved between the two species; (5) Y4.56 was the only non-conserved residue remaining when intracellular half of TM4 was eliminated because the binding site of GPCRs is located in the extracellular half of the transmembrane region. The importance of the residue at 4.56 can be experimentally determined by measuring the potency of thyronamines on mouse and rat $TAAR_1$ swap mutants (Y4.56F for $mTAAR_1$ and F4.56Y for $rTAAR_1$). If Y4.56 is important, the thyronamines should become ~10-fold more potent for the $mTAAR_1$ mutant. **1-NEA** would be included as a control to show that the single mutants are fully functional.

6.4 Binding Modes of tyramine and T_1AM

In addition to being a superagonist for $rTAAR_1$, **ET-69** (EC_{50} = 4 ± 1 nM, E_{max} = 115 ± 2 %) is also an interesting compound because it embodies both **tyramine** (EC_{50} = 65 ± 1 nM, E_{max} = 119 ± 7 %) and **T_1AM** (EC_{50} = 33 ± 3 nM, E_{max} = 100 ± 0 %) (**Fig. 6-3a**). **ET-69** potentially explains how two molecules with very different molecular volumes can elicit similar responses. If the β-phenyl ring of **ET-69** represents the

aromatic ring of **tyramine**, then **tyramine** and **T_1AM** would have distinct binding modes in $rTAAR_1$ (**Fig. 6-3b**). On the other hand, if the inner ring of **ET-69** represents the **tyramine** aromatic ring, then **tyramine** and **T_1AM** have similar binding modes. The $rTAAR_1$ agonist activity of **ET-50** (EC_{50} = 115 ± 12 nM, E_{max} = 105 ± 5 %) suggests that **tyramine** has two binding modes in $rTAAR_1$ (**Fig. 6-3c**).

To determine if **tyramine** and **T_1AM** have similar or distinct binding modes in $rTAAR_1$, we propose to examine the effects of mutating A5.42 to a threonine, leucine, isoleucine, or phenylalanine on the potency of **tyramine** and **T_1AM**. The idea behind these single mutants is to abolish the pocket occupied by the outer ring of **ET-69** and **T_1AM** by introducing sterically encumbering residues. If the A5.42 mutants only affect the potency of **T_1AM** and not **tyramine**, then the two compounds have distinct binding modes. If the potencies of both compounds are affected, then they have similar binding modes.

Additionally, the potency of tyramine would also be measured in the $rTAAR_1$ N7.39Y and/or M6.55T single and double mutants to determine if abolishing the binding pocket of the β-phenyl ring in **ET-69** would affect the agonist activity of **tyramine** (**Fig. 6-3a**). If the potency is affected, this would suggest that **tyramine** has two binding modes in $rTAAR_1$. Appropriate control compounds would be included in the test sets to verify that all observed decreased in potency are not caused by a functionally disabled receptor.

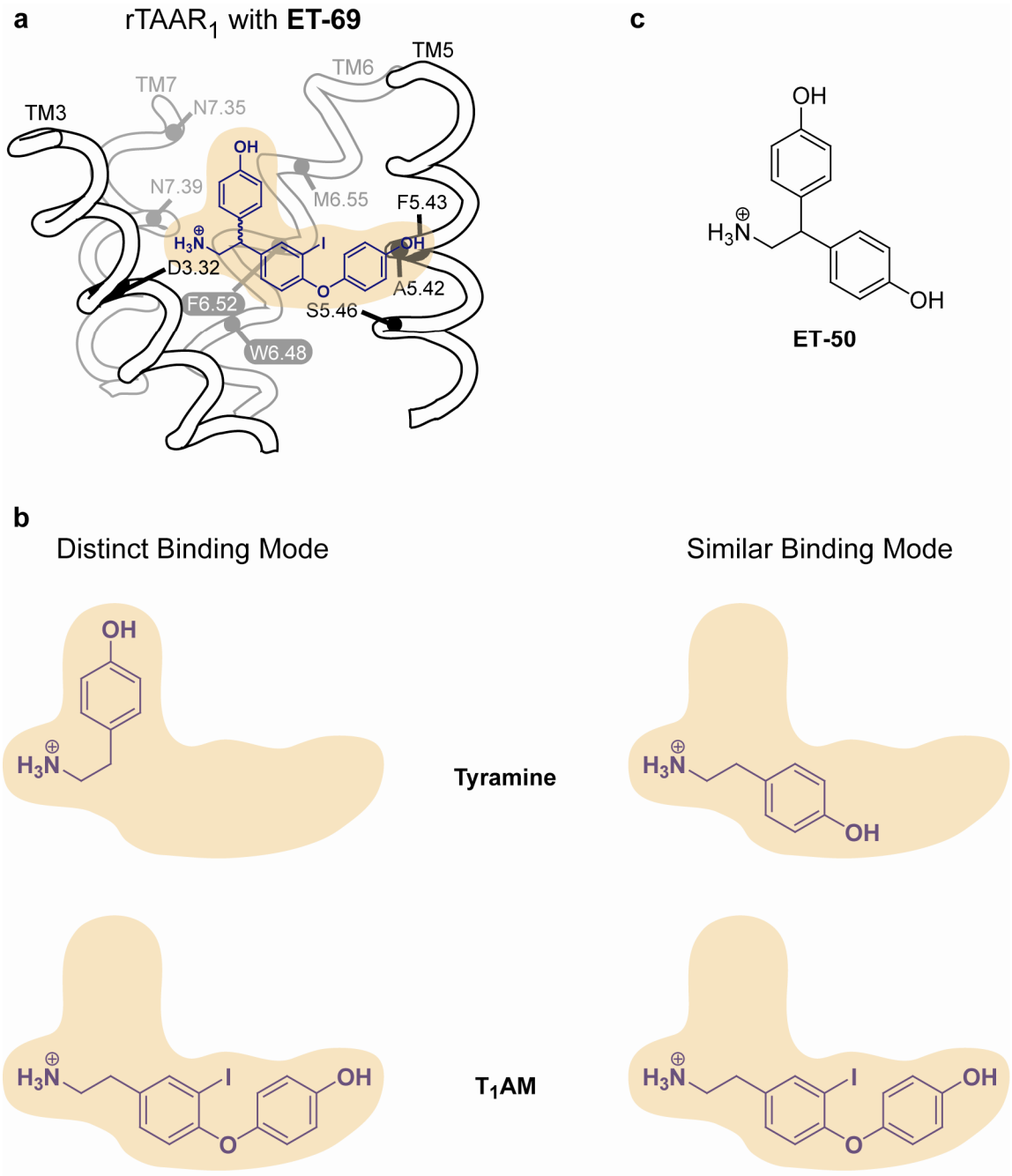


Figure 6-3. Proposed binding modes of **ET-69**, **tyramine**, and **T$_1$AM** in rTAAR$_1$. (**a**) Proposed binding mode **ET-69** in rTAAR$_1$. The rotamer switch residues (white letters), proposed binding and specificity determinant residues are labeled. (**b**) Distinct versus similar binding modes of **tyramine** and **T$_1$AM** in rTAAR$_1$. (**c**) Structure of **ET-50.**

6.5 References

1. Tan, E.; Miyakawa, M.; Bunzow, J.; Grandy, D.; Scanlan, T., Exploring the structure-activity relationship of the ethylamine portion of 3-iodothyronamine for rat and mouse trace amine-associated receptor 1. *J. Med. Chem.* **2007,** 50, (12), 2787-2798.
2. Cherezov, V.; Rosenbaum, D. M.; Hanson, M. A.; Rasmussen, S. G.; Thian, F. S.; Kobilka, T. S.; Choi, H. J.; Kuhn, P.; Weis, W. I.; Kobilka, B. K.; Stevens, R. C., High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science* **2007,** 318, (5854), 1258-1265.
3. Rasmussen, S. G.; Choi, H. J.; Rosenbaum, D. M.; Kobilka, T. S.; Thian, F. S.; Edwards, P. C.; Burghammer, M.; Ratnala, V. R.; Sanishvili, R.; Fischetti, R. F.; Schertler, G. F.; Weis, W. I.; Kobilka, B. K., Crystal structure of the human beta2 adrenergic G-protein-coupled receptor. *Nature* **2007,** 450, (7168), 383-387.
4. Rosenbaum, D. M.; Cherezov, V.; Hanson, M. A.; Rasmussen, S. G.; Thian, F. S.; Kobilka, T. S.; Choi, H. J.; Yao, X. J.; Weis, W. I.; Stevens, R. C.; Kobilka, B. K., GPCR engineering yields high-resolution structural insights into beta2-adrenergic receptor function. *Science* **2007,** 318, (5854), 1266-1273.
5. Suryanarayana, S.; Daunt, D.; von Zastrow, M.; Kobilka, B., A point mutation in the 7th hydrophobic domain of the alpha-2-adrenergic-receptor increases its affinity for a family of beta-receptor-antagonists. *J. Biol. Chem.* **1991,** 266, (23), 15488-15492.

6. Wieland, K.; Zuurmond, H.; Krasel, C.; Ijzerman, A.; Lohse, M., Involvement of Asn-293 in stereospecific agonist recognition and in activation of the beta(2)-adrenergic receptor. *Proc. Natl. Acad. Sci. U. S. A.* **1996,** 93, (17), 9276-9281.

7. Hart, M.; Suchland, K.; Miyakawa, M.; Bunzow, J.; Grandy, D.; Scanlan, T., Trace amine-associated receptor agonists: Synthesis and evaluation of thyronamines and related analogues. *J. Med. Chem.* **2006,** 49, (3), 1101-1112.

8. Scanlan, T.; Suchland, K.; Hart, M.; Chiellini, G.; Huang, Y.; Kruzich, P.; Frascarelli, S.; Crossley, D.; Bunzow, J.; Ronca-Testoni, S.; Lin, E.; Hatton, D.; Zucchi, R.; Grandy, D., 3-iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat. Med.* **2004,** 10, (6), 638-642.

9. Tota, M. R.; Candelore, M. R.; Dixon, R. A.; Strader, C. D., Biophysical and genetic analysis of the ligand-binding site of the beta-adrenoceptor. *Trends Pharmacol. Sci.* **1991,** 12, (1), 4-6.

10. Shi, L.; Javitch, J., The binding site of aminergic G protein-coupled receptors: The transmembrane segments and second extracellular loop. *Annu. Rev. Pharmacol. Toxicol.* **2002,** 42, 437-467.

Appendix A

Experimental Procedures

A.1 Chemistry

A.1.1 General Methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 (400 MHz and 100 MHz respectively) or Bruker Avance 400 MHz NMR. Data reported were calibrated to internal TMS (0.0 ppm) for all solvents unless otherwise noted and were reported as follows: chemical shift, multiplicity (app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = double of triplets, tt = triplet of triplets, dq = doublet of quartets, quin = quintet, sext = sextet, sep = septet), coupling constant, and integration. High resolution mass spectrometry (HRMS) using electrospray ionization was performed by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign.

Inert atmosphere operations were conducted under argon passed through a drierite drying tube in flame dried or oven dried glassware unless otherwise noted. Anhydrous THF, DCM, diethyl ether, pyridine, and diisopropyl ethyl amine were filtered through two columns of activated basic alumina and transferred under an atmosphere of argon gas in a solvent purification system designed and manufactured by Seca Solvent Systems. Anhydrous DMF was obtained by passing through two columns of activated molecular sieves. All other anhydrous solvents and reagents were purchased from Aldrich, Sigma-Aldrich, Fluka, Alfa Aesar, Acros, Fisher or VWR and were used without any further purification unless otherwise stated.

Compounds were purified by flash column chromatography (using Gelduran silica gel: 60Å pore size, 40-64 μm particle size, and 7.0 ± 0.5 pH), Biotage SP1™ purification system (FLASH+® silica cartridge: 500 m^2/g surface area, 60 Å pore size,

and 40-63 μm particle size), or preparatory thin layer chromatography (Analtech prep TLC plates (20x20 cm, 1000 μm). During purification, crude products were typically dissolved in DCM to improve solubility and facilitate loading onto the silica gel. Final compounds were judged to be >95 % pure by ^{1}H NMR analysis and confirmed by HPLC. HPLC was performed on an Agilent 1200 Series LC system (using a Waters XTerra® Phenyl 3.5 μm (3.0 x 50 mm column) with a gradient of 0-90 % acetonitrile (0.1 %TFA) over 8 min and 0-100 % methanol (0.05 % TFA) over 8 or 10 min.

A.1.2 General Synthetic Procedures

General Procedure for *t*-Boc Protection of an Amine Hydrochloride or Hydrobromide Salt. To a solution of the amine hydrochloride or hydrobromide (4.57 mmol) in THF (33 mL) was added an aqueous solution of $NaHCO_3$ (9.14 mmol in 10 mL of water) followed by addition of di-*tert*-butyl dicarbonate (4.57 mmol). After stirring at room temperature overnight, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for *t*-Boc Protection of a Free Amine. To a solution of amine (9.69 mmol) in THF (33 mL) was added an aqueous solution of $NaHCO_3$ (9.69 mmol in 21 mL of water) followed by addition of di-*tert*-butyl dicarbonate (9.69 mmol). After stirring at room temperature overnight, the reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Alkylation of a Phenol with NaH. To a suspension of sodium hydride (5.36 mmol) in DMF (30 mL) was added a solution of phenol (3.58

mmol) in DMF (5 mL). The reaction was stirred under argon at 0°C for 15 minutes before adding a solution of alkyl halide (3.58 mmol) in DMF (5 mL). After stirring under argon at room temperature for 2 hrs, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for N-Methylation of a *t*-Boc Protected Amine. To a suspension of sodium hydride (0.75 mmol) in DMF (6 mL) was added *t*-Boc protected amine (0.60 mmol). The reaction was stirred under argon at 0°C for 15 minutes before adding iodomethane (1.65 mmol) within 2-3 min. After stirring under argon at room temperature for 2 h, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Amide Bond Formation with an Acid Chloride. To a solution of thionyl chloride (0.97 mmol) and carboxylic acid (0.64 mmol) in DCM (3 mL) was added a drop of DMF. After refluxing for 2 hrs, the reaction was concentrated under reduced pressure to give the acid chloride. A solution of the crude acid chloride (0.64 mmol) in DCM (3 mL) was then added to a solution of amine hydrochloride (0.71 mmol) in pyridine (2 mL). After stirring under argon at room temperature for 2 h, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product.

General Procedure for Amide Bond Formation with an Acid. To a solution of carboxylic acid (1.95 mmol) and HBTU (2.14 mmol) in dichloromethane (20 mL) was

added dimethylaminopyridine (0.001 mmol). The solution was stirred under argon at 0°C for 30 minutes before adding the amine hydrochloride (2.14 mmol) and Hunig's base (0.68 mL). The reaction was slowly warmed to room temperature and stirred under argon for 2 hrs. The reaction was diluted with EtOAc (40 mL), washed with 5% aqueous HCl (2 x 35 mL), saturated aqueous $NaHCO_3$ (35 mL), and brine (35 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Formation of a Nitrile. A solution of thionyl chloride (10.80 mmol) and dibenzylic alcohol (7.20 mmol) in DCM (2 mL) was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure to give the dibenzylic chloride. To a solution of the dibenzylic chloride (7.20 mmol) in DCM (33.12 mL) was added trimethylsilyl cyanide (7.20 mmol) and titanium tetrachloride (7.20 mL, 1 M solution in dichloromethane). After stirring under argon at room temperature for 2 h, the reaction was quenched with MeOH (13.90 mL) and water (41.62 mL) and diluted with DCM (104 mL). The organic layer was washed with saturated, aqueous $NaHCO_3$ (68.25 mL) and water (68.25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product.

General Procedure for Formation of a Biaryl Ether. To a solution of phenol (0.53 g, 1.73 mmol), phenyl boronic acid (0.43 g, 3.47 mmol), copper (II) acetate (0.31 g, 1.73 mmol) and dried 4Å molecular sieves (2.64 g, 5 equiv by starting material weight, flame dried under high vacuum for ~5 min) in DCM (20 mL) was added pyridine (0.70 mL, 8.66 mmol) and Hunig's base (1.50 mL, 8.66 mmol). After stirring under dry air atmosphere at room temperature for 24 h or longer, the reaction was filtered through

celite and silica gel, rinsed with EtOAc and washed with 0.5 M HCl, water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Nitrile Reduction and Subsequent *t*-Boc Protection of an Amine. To a suspension of $LiAlH_4$ (195 mg, 5.1 mmol) in THF (10 mL) at 0°C was added aluminum chloride (682 mg, 5.1 mmol) in THF (5 mL). After stirring for 10 minutes at 0ºC, a solution of nitrile (620 mg, 2.1 mmol) in THF (1 mL) was added, and the mixture was allowed to stir for 1 h at ambient temperature before quenching with water. The reaction mixture was then diluted with Et_2O and filtered through celite. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To a stirred solution of the crude mixture in THF (5 mL) were added di-*tert*-butyl dicarbonate (492 mg, 2.3mmol) and an aqueous solution of K_2CO_3 (190 mg in 2.5mL, 2.3 mmol). After overnight stirring, the reaction mixture was diluted with Et_2O, washed with 1N HCl, water, brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product.

General Procedure for *t*-Butyldimethylsilyl or Triisopropylsilyl Deprotection. To a stirred solution of *t*-butyldimethylsilyl protected phenol (155mg, 0.41 mmol) in THF (4 mL) was added dropwise TBAF (0.45 mL, 1M in THF, 0.45 mmol). The reaction mixture was stirred for 15 min at room temperature and diluted with Et_2O. The mixture was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for *t*-Boc Deprotection. The *t*-Boc protected amine (1.40 mmol) was dissolved in a 3N anhydrous HCl solution in EtOAc (3 mL), and the reaction

mixture was stirred at room temperature for 2-16 h. The reaction was exposed to Et_2O and the resulting amine hydrochloride salts were washed with Et_2O. If the amine hydrochloride salts did not form a precipitate, the Et_2O/EtOAc solution was concentrated under reduced pressure and triturated with Et_2O or hexanes to give the hydrochloride salts.

General Procedure for N,N-Dimethylation of an Amine Hydrochloride Salt. The amine hydrochloride salt (0.22 mmol) was dissolved in water, treated with K_2CO_3(>0.22 mmol) and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the free amine. A solution of free amine (0.22 mmol), formic acid (>1.10 mmol, 88% in water solution), and formaldehyde (>1.10 mmol, 37 in water solution) was then stirred at 80^{o}C for ~20 hrs. After cooling to room temperature, the reaction was diluted with water, made basic (pH ~10) with K_2CO_3, and extracted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product. The crude mixture was treated with a solution of 3N anhydrous HCl in EtOAc (1 mL), exposed to Et_2O, and the resulting amine hydrochloride salts were washed with Et_2O. If the amine hydrochloride salts did not form a precipitate, the Et_2O/EtOAc solution was concentrated under reduced pressure and rinsed with Et_2O to give the hydrochloride salt.

General Procedure for Reduction of a Nitrile to an Amine Hydrochloride. To a suspension of lithium aluminum hydride (26.7 mmol) in THF (56 mL) at 0^{o}C, was added a solution of nitrile (6.66 mmol) in THF (10 mL). After refluxing under argon for 24 h, the reaction was quenched with water (1.014 mL), 10% aqueous NaOH (2.028 mL) and water (3.043 mL). The reaction was filtered to remove the precipitated aluminum

salts. The filtrate was washed with water and brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was treated with a 3N anhydrous HCl solution in EtOAc (5-10 mL), exposed to Et_2O, and the resulting amine hydrochloride salts were washed with Et_2O. If the amine hydrochloride salts did not form a precipitate, the Et_2O/EtOAc solution was concentrated under reduced pressure and rinsed with Et_2O to give the hydrochloride salts.

General Procedure for Regioselective Formation of a Biaryl Ether. To a solution of phenol (1.19 mmol), phenyl boronic acid (1.78 mmol), copper (II) acetate (1.19 mmol) and dried 4Å molecular sieves (1 g) in DCM (12 mL) was added pyridine (0.48 mL) and Hunig's base (0.77 mL). After stirring under dry air atmosphere at room temperature for 1-2 days, the reaction was filtered through celite and silica gel, rinsed with EtOAc and washed with 0.5 M HCl, water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Formation of an Organolithium and Reaction with an Aldehyde. To a solution of aromatic halide (2.01 mmol) in THF (15 mL) at -78^{o}C was added *n*-BuLi (2.61 mmol, 2.5M in hexanes) over 10 min. The reaction was stirred at -78^{o}C for another 20 min before adding a solution of aldehyde (2.01 mmol) in THF (5 mL). After stirring at -78^{o}C for 15 min, the reaction was warmed to room temperature and allowed to stir for another 15 min. The reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for *t*-Butyldimethylsilyl or Triisopropylsilyl Protection. To a solution of alcohol (4.67 mmol) and imidazole (10.5 mmol) in DCM (50 mL) was added TBSCl or TIPSCl (5.13 mmol). After stirring overnight at room temperature, the reaction was diluted with DCM, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Formation of a Methyl Enol Ether. To a solution of (methoxymethyl)triphenylphosphonium chloride (27.97 mmol) in THF (80 mL) at 0^oC was added KHMDS (27.97 mmol, 0.5M in Toluene) over 15 min. After stirring at 0^oC for 30 min, a solution of benzophenone (9.32 mmol) in THF (10 mL) was added over 10 min. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with water and diluted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was triturated with hexanes (or cold Et_2O) and filtered to remove the precipitated triphenylphosphine oxide by products. The crude product was then dissolved in DCM, absorbed to silica, and dry loaded into a SiO_2 column equilibrated with 100% hexanes. The column was then flushed with 100% hexanes (recycling solvents) until all of the triphenylphosphine has eluted.

General Procedure for Methyl Enol Ether Deprotection. To a solution of methyl enol ether (8.58 mmol) in Et_2O (30 mL) was added dropwise 70% aq $HClO_4$ (8.75 mL). After stirring at room temperature for ~2-24 hr, the reaction was quenched with saturated $NaHCO_3$ (91 mL) and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Reductive Amination. To a solution of aldehyde (3.09 mmol) and amine (3.39 mmol) in THF (15 mL) was added $NaBH(OAc)_3$ (4.63 mmol) and acetic acid (3.09 mmol). After stirring at room temperature for 24 h, the reaction was quenched with saturated $NaHCO_3$, made basic with K_2CO_3 (pH ~8-10) and diluted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Catalytic Hydrogenation with Pd/C or $Pd(OH)_2/C$. To a solution of benzyl amine, benzyl ether, alkene, or alkyne (1.57 mmol) in MeOH (36 mL) was added Pd/C or $Pd(OH)_2/C$ (0.24 g). After purging all of the air in the reaction by exposure to vacuum, the reaction was stirred overnight at room temperature under H_2(g) atmosphere (1 atm). The Pd/C or $Pd(OH)_2/C$ was filtered through celite and rinsed with MeOH or EtOAc. The filtrate was concentrated under reduced pressure.

General Procedure for Mn_2O Oxidation of an Alcohol. To a solution of alcohol (2.9 mmol) in DCM (10 mL) was added MnO_2 (29-58 mmol). The reaction was stirred at room temperature until all of the alcohol has been consumed (~1-14 days). The Mn_2O was filtered through celite and rinsed with DCM. The filtrate was concentrated under reduced pressure to give the crude product.

General Procedure for Reaction of a Grignard Reagent with an Aldehyde. To a solution of aldehyde (2.02 mmol) in THF (20 mL) was added PhMgBr (2.42 mmol) dropwise. After stirring at room temperature for 30 min, the reaction was quenched with water, saturated NH_4Cl, and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Alkylation of a Phenol with K_2CO_3. To a solution of phenol (0.18 mmol) in acetone (10 mL) was added K_2CO_3 (0.55 mmol) and alkyl halide (0.55 mmol). After stirring under reflux for 24 hrs, the reaction was diluted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Reaction of a Phenol with an Acid Chloride. To a solution of phenol (0.12 mmol) in DCM (3 mL) was added Et_3N (0.18 mmol) and acid chloride (0.18 mmol). After stirring at room temperature for 2 h, the reaction was quenched with water and diluted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

General Procedure for Mitsunobu Reaction. To a solution of phenol (0.37 mmol) in THF (5 mL) was added alcohol (0.74 mmol) and PPh_3 (0.74 mmol) The reaction was cooled to 0^oC and DEAD (0.74 mmol, 40% in toluene) was added dropwise. After stirring at room temperature for 3 h, the reaction was concentrated under reduced pressure.

General Procedure for Phthalimide Deprotection and Subsequent *t*-Boc Protection. To a solution of phthalimide (9.08 mmol) in MeOH (30 mL) was added $MeNH_2$ (181.54 mmol, 40% in H_2O). After refluxing for 3 h, the reaction was concentrated under reduced pressure and placed under high vacuum to remove all the $MeNH_2$. To a solution of the crude product (9.03 mmol) in THF (30 mL) was added an aqueous solution of $NaHCO_3$ (9.08 mmol in 15 mL of water) followed by addition of di-*tert*-butyl dicarbonate (9.08 mmol). After stirring at room temperature overnight, the

reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product.

A.1.3 Synthesis

A.1.3.1 Chapter 2 Compounds

Scheme 2-1. Synthesis of Aryloxypropanolamines (**ET-1**, **ET-6**, **ET-11**, and **ET-12**)

N-*t*-Boc-3-bromopropylamine (2.2). Refer to general procedure for *t*-Boc protection of an amine hydrochloride or hydrobromide salts. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (10%/90%) to (15%/85%)) to give **2.2** as a white solid (0.85 g, 78% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.65 (s, 1H), 3.44 (t, *J*=6.6 Hz, 2H), 3.28 (q, *J*=6.4 Hz, 2H), 2.05 (m, 2H), 1.46 (s, 9H).

N-*t*-Boc-3-(4-phenoxyphenol)-propylamine (2.5). Refer to general procedure for alkylation of a phenol with NaH. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (5%/95%) to (15%/85%)) to give **2.5** (1.02 g, 83% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (app t, *J*=8.0 Hz, 2H), 7.04 (t, *J*=7.6 Hz, 1H), 6.95 (m, 4H), 6.87 (app d, *J*=9.2 Hz, 2H), 4.76 (br s, 1H), 4.01 (t, *J*=6.4 Hz, 2H), 3.34 (br q, *J*=6.0 Hz, 2H), 1.98 (t, *J*=6.2 Hz, 2H), 1.45 (s, 9H).

N-*t*-Boc-3-(3-phenoxyphenol)-propylamine (2.6). Refer to general procedure for alkylation of a phenol with NaH. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (5%/95%) to (15%/85%)) to give **2.6** (2.55 g, 91% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (t, *J*=7.8 Hz, 2H), 7.21 (t, *J*=8.2 Hz, 1H), 7.11 (t, *J*=6.8 Hz, 1H), 7.02 (d, *J*=8.4 Hz, 2H), 6.62 (d, *J*=8.0 Hz, 1H), 6.58 (d,

J=8.0 Hz, 1H), 6.55 (s, 1H), 4.73 (br s,1H), 3.98 (t, *J*=6.0 Hz, 2H), 3.30 (br q, *J*=6.8 Hz, 2H), 1.95 (t, *J*=6.2 Hz, 2H), 1.43 (s, 9H).

N-Methyl, N-*t*-Boc-3-(4-phenoxyphenol)-propylamine (2.7). Refer to general procedure for N-methylation of a *t*-Boc protected amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (5%/95%) to (15%/85%)) to give **2.7** (0.21 g, 62% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29(t, *J*=8.0 Hz, 2H), 7.04 (t, *J*=6.8 Hz, 1H), 6.96 (d, *J*=9.2 Hz, 2H), 6.93 (d, *J*=8.4 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 3.96 (t, *J*=6.2 Hz, 2H), 3.41 (t, *J*=7.0 Hz, 2H), 2.88 (s, 3H), 2.00 (br t, *J*=3.0 Hz, 2H), 1.44 (s, 9H).

3-(4-Phenoxyphenol)-propylamine Hydrochloride (ET-1). Refer to general procedure for *t*-Boc deprotection: 0.12 g, 53% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.29 (t, *J*=8.0 Hz, 2H), 7.04 (t, *J*=7.4 Hz, 1H), 6.96 (s, 4H), 6.89 (d, *J*=7.6 Hz, 2H), 4.11 (t, *J*=5.8 Hz, 2H), 3.16 (t, *J*=7.2 Hz, 2H), 2.14 (m, 2H). HRMS (EI^+) *m/z* for $C_{15}H_{17}NO_2$ $[M + H]^+$: calcd, 244.1338; found, 244.1343.

N,N-Dimethyl-3-(4-phenoxyphenol)-propylamine Hydrochloride (ET-6). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.17 g, 76% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.30 (t, *J*=8.0 Hz, 2H), 7.04 (t, *J*=7.4 Hz, 1H), 6.96 (s, 4H), 6.89 (d, *J*=8.0 Hz, 2H), 4.10 (d, *J*=5.8 Hz, 2H), 3.32 (m, 2H), 2.92 (s, 6H), 2.21 (m, 2H). HRMS (EI^+) *m/z* for $C_{17}H_{21}NO_2$ $[M + H]^+$: calcd, 272.1651; found, 272.1641.

3-(3-Phenoxyphenol)-propylamine Hydrochloride (ET-11). Refer to general procedure for *t*-Boc deprotection: 0.76 g, 75% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.35 (t, *J*=8.2 Hz, 2H), 7.24 (t, *J*=8.4 Hz, 1H), 7.12 (t, *J*=7.4 Hz, 1H), 6.98 (d, *J*=7.6 Hz,

2H), 6.70 (app d, J=7.6 Hz, 1H), 6.57 (app s, 1H), 6.56 (app s, 1H), 4.08 (t, *J*=5.8 Hz, 2H), 3.13 (t, *J*=7.2 Hz, 2H), 2.12 (m, 2H). HRMS (EI^+) *m/z* for $C_{15}H_{17}NO_2$ $[M + H]^+$: calcd, 244.1338; found, 244.1339.

N-Methyl-3-(4-phenoxyphenol)-propylamine Hydrochloride (ET-12). Refer to general procedure for *t*-Boc deprotection: 0.94 g, 90% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.29 (t, *J*=8.0 Hz, 2H), 7.04 (t, *J*=7.4 Hz, 1H), 6.96 (s, 4H), 6.90 (app t, *J*=7.4 Hz, 2H), 4.11 (t, *J*=5.8 Hz, 2H), 3.23 (t, *J*=7.2 Hz, 2H), 2.74 (s, 3H), 2.17 (m, 2H). HRMS (EI^+) *m/z* for $C_{16}H_{18}NO_2$ $[M + H]^+$: calcd, 258.1494; found, 258.1503.

Scheme 2-2. Synthesis of Benzamidoalkylamines (**ET-2**–**ET-5** and **ET-7**–**ET-10**)

N-*t*-Boc-2-(4-phenoxybenzamido)-ethylamine (2.13). Refer to general procedure for amide bond formation with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (10%/90%) to (50%/50%)) to give **2.13** (0.30 g, 90% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 7.75 (d, *J*=8.8 Hz, 2H), 7.34 (t, *J*=8.0 Hz, 2H), 7.12 (t, *J*=7.4, 1H), 6.98 (d, *J*=7.6 Hz, 2H), 6.92 (d, *J*=8.8 Hz, 2H), 3.37 (t, *J*=6.0, 2H), 3.20 (t, *J*=6.0 Hz, 2H), 1.35 (s, 3H).

N-*t*-Boc-3-(4-phenoxybenzamido)-propylamine (2.14). Refer to general procedure for amide bond formation with an acid. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (10%/90%) to (50%/50%)) to give **2.14** (0.61 g, 64% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 7.83 (d, *J*=8.0 Hz, 2H), 7.37 (t, *J*=7.8 Hz, 2H), 7.17 (t, *J*=6.8, 1H), 7.05 (d, *J*=8.0 Hz, 2H), 7.01 (d, *J*=8.8 Hz, 2H), 4.87 (br s, 1H), 3.50 (q, *J*=6.1 Hz, 2H), 3.25 (q, *J*=5.2 Hz, 2H), 1.72 (m, 2H), 1.55 (s, 9H).

N-*t*-Boc-4-(4-phenoxybenzamido)-butylamine (2.15). Refer to general procedure for amide bond formation with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (20%/90%) to (50%/50%)) to give **2.15** (0.35 g, 71% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.77 (d, *J*=8.4 Hz, 2H), 7.37 (t, *J*=8.0 Hz, 2H), 7.17 (t, *J*=7.4, 1H), 7.04 (d, *J*=7.6 Hz, 2H), 7.00 (d, *J*=8.8 Hz, 2H), 6.42 (br s, 1H), 4.63 (br s, 1H), 3.48 (q, *J*=6.2 Hz, 2H), 3.17 (app q, *J*=6.4 Hz, 2H), 1.64 (m, 4H), 1.44 (s, 9H).

N-*t*-Boc-5-(4-phenoxybenzamido)-pentylamine (2.16). Refer to general procedure for amide bond formation with an acid. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (25%/90%) to (50%/50%)) to give **2.16** (0.78 g, 77% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.74 (d, *J*=8.8 Hz, 2H), 7.37 (t, *J*=8.0 Hz, 2H), 7.17 (t, *J*=7.6, 1H), 7.04 (d, *J*=8.0 Hz, 2H), 7.00 (d, *J*=8.8 Hz, 2H), 6.14 (br s, 1H), 4.57 (br s, 1H), 3.45 (q, *J*=6.5 Hz, 2H), 3.13 (app q, *J*=6.4 Hz, 2H), 1.63 (m, 2H), 1.52 (m, 4H), 1.44 (s, 9H).

2-(4-Phenoxybenzamido)-ethylamine Hydrochloride (ET-2). Refer to general procedure for *t*-Boc deprotection: 0.25 g, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.88 (d, *J*=8.8 Hz, 2H), 7.41(t, *J*=7.8 Hz, 2H), 7.20 (t, *J*=7.4 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 2H), 7.01 (d, *J*=8.8 Hz, 2H), 3.66 (t, *J*=5.8 Hz, 2H), 3.17 (t, *J*=6.0 Hz, 2H); ^{13}C NMR (400 MHz, methanol-d_4) δ 170.5, 162.5, 157.2, 131.2, 130.6, 129.1, 125.6, 121.0, 118.4, 41.4, 38.8. HRMS (EI$^+$) *m/z* for $C_{15}H_{16}N_2O_2$ $[M + H]^+$: calcd, 257.1290; found, 257.1293.

3-(4-Phenoxybenzamido)-propylamine Hydrochloride (ET-3). Refer to general procedure for *t*-Boc deprotection: 0.23 g, 96% yield. ^{1}H NMR (400 MHz,

methanol-d_4) δ 7.84 (d, J=8.8 Hz, 2H), 7.41 (t, J=8.1 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 7.06 (d, J=7.8 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 3.49 (t, J=6.6 Hz, 2H), 2.98 (t, J=7.3 Hz, 2H), 1.94 (quintet, J=7.0 Hz, 2H). HRMS (EI^+) *m/z* for $C_{16}H_{18}N_2O_2$ $[M + H]^+$: calcd, 271.1447; found, 271.1447.

4-(4-Phenoxybenzamido)-butylamine Hydrochloride (ET-4). Refer to general procedure for *t*-Boc deprotection: 0.21 g, 97% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.82 (d, J=9.3 Hz, 2H), 7.41 (t, J=8.1 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 7.05 (d, J=8.8 Hz, 2H), 7.00 (d, J=8.8 Hz, 2H), 3.42 (t, J=6.6 Hz, 2H), 2.98 (t, J=7.1 Hz, 2H), 1.71 (m, 4H). HRMS (EI^+) *m/z* for $C_{17}H_{20}N_2O_2$ $[M + H]^+$: calcd, 285.1603; found, 285.1603.

5-(4-Phenoxybenzamido)-pentylamine Hydrochloride (ET-5). Refer to general procedure for *t*-Boc deprotection: 0.13 g, 98% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.81 (d, J=8.8 Hz, 2H), 7.41 (t, J=8.1 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 7.05 (d, J=8.8 Hz, 2H), 7.00 (d, J=9.3 Hz, 2H), 3.39 (t, J=6.8 Hz, 2H), 2.93 (t, J=7.8 Hz, 2H), 1.69 (m, 4H), 1.46 (m, 2H). HRMS (EI^+) *m/z* for $C_{18}H_{22}N_2O_2$ $[M + H]^+$: calcd, 299.1760; found, 299.1767.

N,N-Dimethyl 2-(4-phenoxybenzamido)-ethylamine Hydrochloride (ET-7). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.09 g, 98% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.87 (d, J=8.8 Hz, 2H), 7.42(t, J=7.8 Hz, 2H), 7.21 (t, J=7.6 Hz, 1H), 7.05 (d, J=8.8 Hz, 2H), 7.02 (d, J=9.2 Hz, 2H), 3.74 (t, J=5.8 Hz, 2H), 3.37 (t, J=5.8 Hz, 2H), 2.98 (s, 6H). HRMS (EI^+) *m/z* for $C_{17}H_{20}N_2O_2$ $[M + H]^+$: calcd, 285.1603; found, 285.1609.

N,N-Dimethyl 3-(4-phenoxybenzamido)-propylamine Hydrochloride (ET-8). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.12 g,

76% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.86 (d, J=8.8 Hz, 2H), 7.41 (t, J=8.1 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 7.05 (d, J=7.8 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 3.48 (t, J=6.6 Hz, 2H), 3.19 (t, J=7.6 Hz, 2H), 2.91 (s, 6H), 2.03 (m, 2H) ; ^{13}C NMR (100 MHz, methanol-d_4) δ 170.1, 162.4, 157.3, 131.2, 130.5, 129.3, 125.6, 121.0, 118.5, 56.7, 43.5, 37.4, 26.3. HRMS (EI$^+$) *m/z* for $C_{18}H_{22}N_2O_2$ [M + H]$^+$: calcd, 299.1760; found, 299.1757.

N,N-Dimethyl 4-(4-phenoxybenzamido)-butylamine Hydrochloride (ET-9). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.16 g, 11% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.82 (d, J=8.8 Hz, 2H), 7.41 (t, J=7.8 Hz, 2H), 7.20 (t, J=7.4 Hz, 1H), 7.06 (d, J=7.6 Hz, 2H), 7.00 (d, J=8.8 Hz, 2H), 3.43 (t, J=6.8 Hz, 2H), 3.19 (t, J=8.0 Hz, 2H), 2.89 (s, 6H), 1.77 (m, 2H), 1.69 (m, 2H). HRMS (EI$^+$) *m/z* for $C_{19}H_{24}N_2O_2$ [M + H]$^+$: calcd, 313.1916; found, 313.1925.

N,N-Dimethyl 5-(4-phenoxybenzamido)-pentylamine Hydrochloride (ET-10). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salts: 0.09 g, 31% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.82 (d, J=8.8 Hz, 2H), 7.41 (t, J=8.0 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 7.04 (d, J=8.4 Hz, 2H), 7.00 (d, J=8.8 Hz, 2H), 3.40 (t, J=6.0 Hz, 2H), 3.13 (t, J=7.8 Hz, 2H), 2.88 (s, 6H), 1.78 (m, 2H), 1.69 (m, 2H), 1.46 (m, 2H). HRMS (EI$^+$) *m/z* for $C_{20}H_{26}N_2O_2$ [M + H]$^+$: calcd, 327.2073; found, 327.2087.

Scheme 2-3. Synthesis of Orthopramide-alkylamines (**ET-22**–**ET-30**)

Methyl-2-hydroxy-4-phenoxybenzoate (2.18). Refer to general procedure for regioselective formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (loaded with DCM, eluted with EtOAc/hexanes (0%/100%) to

(2%/98%)) to give **2.18** as a colorless oil (0.29 g, 59% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.91 (s, 1H), 7.78 (d, *J*=8.7 Hz, 1H), 7.39 (t, *J*=7.8 Hz, 2H), 7.21 (t, *J*=7 Hz, 1H), 7.08 (d, *J*=8.3 Hz, 2H), 6.51 (dd, *J*=8.8, 2.4 Hz, 1H), 6.45 (d, *J*=2.4 Hz, 1H), 3.93 (s, 3H).

Methyl-2-methoxy-4-phenoxybenzoate (2.19). Refer to general procedure for alkylation of a phenol with NaH. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (5%/95%) to (10%/90%)) to give **2.19** (0.19 g, 93% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.81 (d, *J*=8.8 Hz, 1H), 7.39 (t, *J*=8.0 Hz, 2H), 7.19 (t, *J*=7.3 Hz, 1H), 7.07 (d, *J*=7.8 Hz, 2H), 6.62 (d, *J*=2.4 Hz, 1H), 6.49 (dd, *J*=8.8, 2.4 Hz, 1H), 3.87 (s, 1H), 3.85 (s, 1H).

2-Methoxy-4-phenoxybenzoic acid (2.20). To a solution of methyl-2-methoxy-4-phenoxybenzoate (**2.19**) (0.18 g, 0.691 mmol) in methanol (1.38 mL) was added 2N aqueous NaOH solution (1.72 mL, 3.45 mmol). The reaction was refluxed for 3 hrs. After cooling to room temperature, the MeOH was evaporated and the reaction was acidified to pH ~3 with 3N HCl. The reaction was extracted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (50%/50%)) to give **2.20** (0.169 g, 93% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.12 (d, *J*=8.8 Hz, 1H), 7.43 (t, *J*=8.0 Hz, 2H), 7.24 (m, *J*=8.0, 8.0 Hz, 1H), 7.09 (d, *J*=7.3 Hz, 2H), 6.67 (d, *J*=2.4 Hz, 1H), 6.6 (dd, *J*=8.8, 2.4 Hz, 1H), 4.01 (s, 3H).

N-*t*-Boc-2-(2-methoxy-4-phenoxybenzamido)-ethylamine (2.21). Refer to general procedure for amide bond formation with an acid chloride. The crude product

was purified via flash SiO_2 chromatography (EtOAc/hexanes (25%/90%) to (50%/50%)) to give **2.21** (0.25 g, 82% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.15 (d, *J*=8.3 Hz, 1H), 8.03 (br s, 1H), 7.39 (t, *J*=7.3 Hz, 2H), 7.18 (t, *J*=7.3 Hz, 1H), 7.06 (d, *J*=7.8 Hz, 2H), 6.63 (d, *J*=1.9 Hz, 1H), 6.59 (dd, *J*=8.6, 2.2 Hz, 1H), 4.98 (br s, 1H), 3.92 (s, 3H), 3.57 (q, *J*=5.9 Hz, 2H), 3.37 (br q, *J*=5.9 Hz, 2H), 1.43 (s, 9H).

N-*t*-Boc-3-(2-methoxy-4-phenoxybenzamido)-propylamine (2.22). Refer to general procedure for amide bond formation with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (25%/90%) to (50%/50%)) to give **2.22** (0.33 g, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.15 (d, *J*=8.3 Hz, 1H), 8.07 (s, 1H), 7.38 (t, *J*=8.1 Hz, 2H), 7.18 (t, *J*=7.3 Hz, 1H), 7.06 (d, *J*=7.3 Hz, 2H), 6.64 (d, *J*=1.9 Hz, 1H), 6.59 (dd, *J*=8.6, 2.2 Hz, 1H), 5.04 (s, 1H), 3.93 (s, 3H), 3.51 (q, *J*=6.2 Hz, 2H), 3.21 (q, *J*=5.5 Hz, 2H), 1.73 (m, *J*=12.6, 6.2, 6.1 Hz, 2H), 1.45 (s, 9H).

N-*t*-Boc-4-(2-methoxy-4-phenoxybenzamido)-butylamine (2.23). Refer to general procedure for amide bond formation with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (25%/90%) to (50%/50%)) to give **2.23** (0.34 g, 83% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.15 (d, *J*=8.8 Hz, 1H), 7.77 (s, 1H), 7.38 (t, *J*=8.0 Hz, 2H), 7.18 (t, *J*=7.6 Hz, 1H), 7.06 (d, *J*=7.3 Hz, 3H), 6.63 (d, *J*=2.4 Hz, 2H), 6.60 (dd, *J*=8.8, 2.4 Hz, 2H), 4.59 (s, 1H), 3.91 (s, 8H), 3.47 (q, *J*=6.5 Hz, 2H), 3.17 (q, *J*=5.9 Hz, 2H), 1.63 (m, 4H), 1.44 (s, 9H).

N-*t*-Boc-5-(2-methoxy-4-phenoxybenzamido)-pentylamine (2.24). Refer to general procedure for amide bond formation with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (25%/90%) to (50%/50%)) to give **2.24** (0.35 g, 93% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.16 (d, *J*=8.8 Hz,

1H), 7.75 (br s, 1H), 7.38 (t, *J*=8.1 Hz, 2H), 7.18 (t, *J*=7.3 Hz, 1H), 7.06 (d, *J*=7.8 Hz, 2H), 6.63 (d, *J*=2.0 Hz, 1H), 6.60 (dd, *J*=8.6, 2.2 Hz, 1H), 4.58 (br s, 1H), 3.91 (s, 3H), 3.46 (dd, *J*=6.8, 5.9 Hz, 2H), 3.13 (q, *J*=6.2 Hz, 2H), 1.59 (m, 4H), 1.44 (s, 9H), 1.41 (m, 2H).

N-*t*-Boc-(2-methoxy-4-phenoxyphenyl)(piperazin-1-yl)methanone (2.25). Refer to general procedure for amide bond formation with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (25%/75%) to (30%/70%)) to give **2.25** (0.34 g, 100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.37 (t, *J*=8.1 Hz, 1H), 7.19 (d, *J*=8.3 Hz, 2H), 7.15 (t, *J*=7.3 Hz, 1H), 7.05 (d, *J*=7.8 Hz, 2H), 6.60 (d, *J*=2.0 Hz, 1H), 6.56 (dd, *J*=8.3, 2.0 Hz, 1H), 3.78 (s, 3H), 3.36 (m, 4H), 1.47 (s, 9H).

2-(2-Methoxy-4-phenoxybenzamido)-ethylamine Hydrochloride (ET-22). Refer to general procedure for *t*-Boc deprotection: 0.09 g, 98% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.97 (d, *J*=8.8 Hz, 1H), 7.42 (t, *J*=7.6 Hz, 2H), 7.22 (t, *J*=7.3 Hz, 1H), 7.08 (d, *J*=8.8 Hz, 2H), 6.76 (d, *J*=2.4 Hz, 1H), 6.56 (dd, *J*=8.8, 2.4 Hz, 1H), 3.93 (s, 3H), 3.69 (t, *J*=5.9 Hz, 2H), 3.17 (t, *J*=5.9 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 168.8, 163.9, 161.0, 156.9, 134.3, 131.2, 125.8, 121.2, 116.5, 110.4, 102.6, 56.7, 41.3, 38.7.

3-(2-Methoxy-4-phenoxybenzamido)-propylamine Hydrochloride (ET-23). Refer to general procedure for *t*-Boc deprotection: 0.24 g, 98% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.90 (d, *J*=8.8 Hz, 1H), 7.41 (t, *J*=8.1 Hz, 2H), 7.20 (t, *J*=7.3 Hz, 1H), 7.07 (d, *J*=7.3 Hz, 2H), 6.75 (d, *J*=2.4 Hz, 1H), 6.55 (dd, *J*=8.6, 2.2 Hz, 1H), 3.91 (s, 3H), 3.52 (t, *J*=6.6 Hz, 2H), 2.98 (t, *J*=7.1 Hz, 2H), 1.95 (m, 2H); ^{13}C NMR (100 MHz,

methanol-d_4) δ 167.4, 162.4, 159.6, 155.8, 132.7, 130.0, 124.5, 119.9, 115.8, 109.3, 101.5, 55.5, 37.0, 35.9, 27.8.

4-(2-Methoxy-4-phenoxybenzamido)-butylamine Hydrochloride (ET-24). Refer to general procedure for *t*-Boc deprotection: 0.24 g, 98% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.89 (d, *J*=8.8 Hz, 1H), 7.41 (t, *J*=8.6 Hz, 2H), 7.20 (t, *J*=7.6 Hz, 1H), 7.07 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=2.0 Hz, 1H), 6.55 (dd, *J*=8.8, 2.4 Hz, 1H), 3.91 (s, 3H), 3.45 (t, *J*=6.6 Hz, 2H), 2.99 (t, *J*=6.8 Hz, 2H), 1.72 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 167.8, 163.4, 160.7, 157.1, 133.81, 131.2, 125.7, 121.0, 117.5, 110.5, 102.7, 56.7, 40.4, 39.8, 27.6, 25.9.

5-(2-Methoxy-4-phenoxybenzamido)-pentylamine Hydrochloride (ET-25). Refer to general procedure for *t*-Boc deprotection: 0.28 g, 58% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.88 (d, *J*=8.8 Hz, 1H), 7.41 (t, *J*=8.1 Hz, 2H), 7.20 (t, *J*=7.3 Hz, 1H), 7.07 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=2.0 Hz, 1H), 6.55 (dd, *J*=8.6, 2.2 Hz, 1H), 3.90 (s, 3H), 3.42 (t, *J*=7.1 Hz, 2H), 2.94 (t, *J*=7.6 Hz, 2H), 1.69 (m, 4H), 1.47 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 167.8, 163.3, 160.7, 157.1, 133.8, 131.2, 125.6, 121.0, 117.6, 110.5, 102.8, 56.7, 40.7, 40.3, 30.1, 28.2, 24.8.

(2-Methoxy-4-phenoxyphenyl)(piperazin-1-yl)methanone Hydrochloride (ET-26). Refer to general procedure for *t*-Boc deprotection: 0.29 g, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.40 (t, *J*=8.8 Hz, 2H), 7.26 (d, *J*=8.3 Hz, 1H), 7.18 (t, *J*=7.3 Hz, 1H), 7.06 (d, *J*=7.3 Hz, 2H), 6.74 (d, *J*=2.0 Hz, 1H), 6.58 (dd, *J*=8.6, 2.2 Hz, 1H), 4.00 (br d, *J*=28.8 Hz, 2H), 3.83 (s, 3H), 3.60 (br s, 2H), 3.32 (br s, 2H), 3.22 (br t, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 169.9, 162.2, 158.5, 157.5, 131.1, 130.9, 125.4, 120.8, 119.5, 111.1, 103.0, 56.4, 45.0, 44.8, 44.4, 39.7.

N,N-Dimethyl 2-(2-methoxy-4-phenoxybenzamido)-ethylamine Hydrochloride (ET-27). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.09 g, 41% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.98 (d, J=8.8 Hz, 1H), 7.43 (t, J=8.1 Hz, 2H), 7.22 (t, J=7.3 Hz, 1H), 7.08 (d, J=7.3 Hz, 2H), 6.76 (d, J=2.4 Hz, 1H), 6.56 (dd, J=8.8, 2.4 Hz, 1H), 3.93 (s, 3H), 3.80 (t, J=5.9 Hz, 2H), 3.38 (t, J=5.9 Hz, 2H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, methanol-d_4) δ 168.8, 164.0, 161.0, 156.9, 134.3, 131.2, 125.8, 121.2, 116.3, 110.4, 102.6, 59.2, 56.7, 44.0, 36.4.

N,N-Dimethyl 3-(2-methoxy-4-phenoxybenzamido)-propylamine Hydrochloride (ET-28). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.23 g, 75% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.92 (d, J=8.6 Hz, 1H), 7.42 (m, 2H), 7.21 (t, J=7.6 Hz, 1H), 7.07 (d, J=7.8 Hz, 2H), 6.76 (d, J=2.4 Hz, 1H), 6.56 (dd, J=8.6, 2.2 Hz, 1H), 3.92 (s, 3H), 3.52 (t, J=6.6 Hz, 2H), 3.18 (t, J=7.3 Hz, 2H), 2.91 (s, 6H), 2.04 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 168.6, 163.6, 160.8, 157.0, 134.0, 131.1, 125.7, 121.1, 116.9, 110.5, 102.6, 56.7, 43.5, 37.1, 26.3, 20.5.

N,N-Dimethyl 4-(2-methoxy-4-phenoxybenzamido)-butylamine Hydrochloride (ET-29). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.25 g, 59% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.88 (d, J=8.8 Hz, 1H), 7.42 (t, J=9.0 Hz, 2H), 7.21 (t, J=7.3 Hz, 1H), 7.07 (d, J=7.3 Hz, 2H), 6.75 (d, J=2.0 Hz, 1H), 6.55 (dd, J=8.8, 2.4 Hz, 1H), 3.91 (s, 3H), 3.46 (t, J=6.6 Hz, 2H), 3.19 (t, J=8.1 Hz, 2H), 2.89 (s, 6H), 1.79 (m, 2H), 1.69 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 166.8, 162.2, 159.5, 155.9, 132.5, 130.0, 124.5, 120.0, 116.3, 109.3, 101.5, 57.4, 55.4, 42.2, 38.4, 26.4, 21.8.

N,N-Dimethyl 5-(2-methoxy-4-phenoxybenzamido)-pentylamine Hydrochloride (ET-30). Refer to general procedure for N,N-dimethylation of an amine hydrochloride salt: 0.26 g, 56% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.88 (d, J=8.8 Hz, 1H), 7.42 (t, J=7.6 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 7.07 (d, J=8.8 Hz, 2H), 6.75 (d, J=2.0 Hz, 1H), 6.55 (dd, J=8.8, 2.4 Hz, 1H), 3.90 (s, 3H), 3.43 (t, J=7.1 Hz, 2H), 3.13 (t, J=8.3 Hz, 2H), 2.88 (s, 6H), 1.79 (m, 2H), 1.69 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 166.6, 162.1, 159.4, 155.9, 150.2, 132.5, 130.0, 124.4, 120.0, 109.3, 101.5, 57.7, 55.5, 42.21, 38.9, 28.8, 24.0, 23.4.

Scheme 2-4. Synthesis of β-Phenylphenoxyphenethylamines (**ET-13** and **ET-14**)

4-Phenoxyphenyl-phenylmethanol (2.28). To a solution of 4-bromodiphenyl ether (2.0 g, 8.03 mmol) in THF (15 mL) at -78^{o}C was added *n*-butyllithium (3.85 mL, 2.6 M solution in hexanes). The reaction was stirred under argon for 2 h before a solution of benzaldehyde (0.85 g, 8.03 mmol) in THF at -78 ^{o}C was added. After stirring at 78^{o}C for 2 h, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was purified via flash SiO_2 chromatography (EtOAc/hexanes (10%/90%) to (15%/85%)) to give **2.28** (2.22 g, 97% yield). ^{1}H NMR (400 MHz, chloroform-d) δ 7.28-7.40 (m, 9H), 7.10 (t, J=7.6, 1H), 6.94-7.01 (m, 4H), 5.84 (d, J=3.6 Hz, 1H), 2.17 (d, J=3.6 Hz, 1H).

3-Phenoxyphenyl-phenylmethanol (2.29). To a solution of 3-phenoxybenzaldehyde (2 g, 10.09 mmol) in THF (15 mL) at -78^{o}C was added dropwise phenyllithium (6.73 mL, 1.8M solution in cyclohexane-ether). After stirring under argon

at -78°C for 4 h, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was purified via flash SiO_2 chromatography (EtOAc/hexanes (10%/90%) to (20%/80%)) to give **2.29** (2.79 g, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.87-7.38 (m, 10H), 7.09 (m, 1H), 6.99 (app d, *J*=7.3 Hz, 1H), 6.88 (m, *J*=8.6, 2.2 Hz, 1H), 5.81 (s, 4H).

2-(4-Phenoxyphenyl)-2-phenylacetonitrile (2.30). Refer to general procedure for formation of a nitrile. The crude mixture was purified via flash SiO_2 chromatography (EtOAc/hexanes 5%/95%) to (10%/90%)) to give **2.30** (0.49 g, 90% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.25-7.40 (m, 9H), 7.13 (t, *J*=7.4, 1H), 6.99 (m, 4H), 5.12 (s, 1H).

2-(3-Phenoxyphenyl)-2-phenylacetonitrile (2.31). Refer to general procedure for formation of a nitrile. The crude mixture of **C7** (2.45 g, 98% yield) was not purified. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.27-7.42 (m, 10H), 7.13 (app t, *J*=6.4 Hz, 1H), 7.01 (app d, *J*=8.8 Hz, 1H), 6.90 (m, 1H), 6.08 (s, 1H).

2-(4-Phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-13). Refer to general procedure for the reduction of a nitrile to an amine hydrochloride: 0.24 g, 47% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.22-7.35 (m, 9H), 7.04 (t, *J*=7.6 Hz, 1H), 6.89-6.92 (m, 4H), 4.22 (t, *J*=8.0 Hz, 1H), 3.56 (d, *J*=8.0 Hz, 1H) ; ^{13}C NMR (100 MHz, methanol-d_4) δ 158.4, 158.2, 141.6, 136.3, 130.9, 130.4, 130.2, 128.9, 128.6, 124.6, 120.2, 120.0, 49.9, 44.5. HRMS (EI$^+$) *m/z* for $C_{20}H_{19}NO$ $[M + H]^+$: calcd, 290.1545; found, 290.1559.

2-(3-Phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-14). Refer to general procedure for the reduction of a nitrile to an amine hydrochloride: 2.79 g, 26% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.34 (m, 10H), 7.12 (app t, J=7.3 Hz, 1H), 6.98 (m, 1H), 6.86 (dd, J=8.1, 2.7 Hz, 1H), 4.26 (t, J=8.1 Hz, 1H), 3.62 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 159.4, 158.3, 143.7, 141.2, 131.6, 130.9, 130.2, 128.9, 128.7, 124.6, 123.5, 120.0, 119.3, 118.5, 50.4, 44.3. HRMS (EI$^+$) *m/z* for $C_{20}H_{19}NO$ $[M + H]^+$: calcd, 290.1545; found, 290.1548.

Scheme 2-5. Synthesis of Tetrahydrobenzazepines (**ET-15**-**ET-20**)

2-(4-Methoxyphenethylamino)-1-phenylethanol (2.34). 4-methoxyphenethylamine (5.0 g, 33.1 mmol) and styrene oxide (3.97 g, 33.1 mmol) were mixed in a pressure tube and heated to 90-95^{o}C for 24 h. The hot reaction mixture was added to a cold solution of EtOAc/Hexanes (25%/75%) and the resulting precipitate was filtered, rinsed with hexanes, and dried under reduced pressure to give **2.34** as a white solid (3.06 g, 32% yield). ^{1}H NMR (400 MHz, chloroform-d) δ 7.35 (s, 2H), 7.34 (d, J=2.9 Hz, 2H), 7.28 (m, 1H), 7.11 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 4.69 (dd, J=9.3 Hz, 3.4 Hz, 1H), 3.79 (s, 3H), 2.84-2.98 (m, 4H), 2.76 (m, 1H), 2.71 (dd, J=12.2 Hz, 9.3 Hz, 1H), 1.68 (br s, 1H).

8-Hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-15). To a solution of **ET-16** (0.08 g, 2.77 mmol) in dry $CHCl_3$ (25 mL) @ 0^{o}C was added BBr_3 (2.21 g, 8.81 mmol, 1.0 M solution in DCM). After stirring for 1 h at room temperature, the reaction was cooled to 0^{o}C and anhydrous MeOH (27.7 mL) was added. The reaction was refluxed in an open mouth flashed for 20 min before evaporating the

solvent. The crude mixture was diluted with EtOAc and made alkaline with K_2CO_3. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Treatment with 3N anhydrous HCl solution in EtOAc and exposure to Et_2O precipitated the hydrochloride salts of **ET-15** (0.64 g, 85% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.42 (t, J=7.6 Hz, 2H), 7.33 (t, J=7.3 Hz, 1H), 7.22 (d, J=7.3 Hz, 2H), 7.08 (d, J=8.3 Hz, 1H), 6.62 (dd, J=7.8 Hz, 2.4 Hz, 1H), 6.22 (d, J=2.4 Hz, 1H), 4.60 (dd, J=8.3 Hz, 2.0 Hz, 1H), 3.62-3.75 (m, 2H), 3.44 (dd, J=11.7 Hz, 7.3 Hz, 1H), 3.23 (dd, J=14.7 Hz, 9.3 Hz, 1H), 3.10 (m, 1H), 3.02 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 157.8, 143.8, 141.0, 132.5, 130.3, 130.1, 129.3, 128.6, 117.5, 115.0, 51.4, 47.8, 47.6, 32.5.

8-Methoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-16). To a solution of **2.34** (1.12 g, 4.17 mmol) in TFA (12.5 mL) was added dropwise H_2SO_4 (0.31 mL, 6.25 mmol). After stirring at reflux for 7 h, the TFA was evaporated under reduced pressure and the crude reaction mixture was poured into ice cold water. The solution was made alkaline with 40% NaOH and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was treated with a 3N anhydrous HCl solution in EtOAc and exposure to Et_2O precipitated the hydrochloride salts of **ET-16** (0.83 g, 68% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.42 (t, J=7.3 Hz, 2H), 7.34 (t, J=7.3 Hz, 1H), 7.22 (d, J=7.3 Hz, 2H), 7.20 (d, J=8.3 Hz, 1H), 6.77 (dd, J=8.3 Hz, 2.9 Hz, 1H), 6.30 (d, J=2.4 Hz, 1H), 4.68 (dd, J=8.5 Hz, 2.2 Hz, 1H), 3.65-3.78 (m, 2H), 3.62 (s, 3H), 3.45 (dd, J=12.2 Hz, 7.3 Hz, 1H), 3.29 (m, 1H), 3.15 (app t, J=11.2 Hz, 1H),

3.05 (dd, *J*=16.2 Hz, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 160.3, 143.9, 140.8, 132.5, 131.5, 130.2, 129.3, 128.6, 116.8, 112.9, 55.6, 51.3, 47.7, 47.5, 32.5.

7-Methoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-19). To a suspension of NaH (0.007 g, 0.18 mmol) in DMF (2.5 mL) cooled to 0^{o}C was added a solution of **2.37** (0.05 g, 0.15 mmol) in DMF (0.5 mL). After 15 min at 0^{o}C, MeI (0.023 g, 0.162 mmol) was added and the reaction was stirred for 1 h slowly warming to room temperature. The reaction was quenched with MeOH and diluted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified via flash SiO_2 column chromatography (EtOAc/hexanes (10%/90%)) to give the *t*-Boc protected amine (48 mg, 91% yield). The *t*-Boc protected amine was then deprotected following the general procedure for *t*-Boc deprotection: 8 mg, 21% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.41 (t, *J*=7.6 Hz, 2H), 7.33 (t, *J*=7.1 Hz, 1H), 7.20 (d, *J*=7.8 Hz, 2H), 6.86 (s, 1H), 6.70 (s, 2H), 4.60 (d, *J*=8.8 Hz, 1H), 3.77 (s, 3H), 3.77 (m, 1H), 3.63 (d, *J*=13.2 Hz, 1H), 3.44 (m, 1H), 3.21 (m, 2H), 3.07 (m, 1H).

2-(3-Methoxyphenethylamino)-1-phenylethanol (2.35). A solution of 3-methoxyphenethylamine (2.0 g, 13.23 mmol) and styrene oxide (1.539 g, 13.23 mmol) was heated @ 90-95^{o}C for 16 h. The hot reaction mixture was added to a 25% EtOAc/75% Hexanes and a fluffy precipitate formed. The solid filtered and washed with 25% EtOAc/75% hexanes to give **2.35** (31.30 g, 36% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35 (m, 3H), 7.32 (m, 1H), 7.27 (m, 1H), 7.22 (t, *J*=8.0 Hz, 1H), 6.79 (d, *J*=7.3 Hz, 1H), 6.76 (m, 2H), 4.67 (dd, *J*=9.0, 3.7 Hz, 1H), 3.80 (s, 3H), 2.90 (m, 3H), 2.78 (m, 2H), 2.70 (m, 1H).

7-Hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-18). To a solution of **2.35** (1.30 g, 4.79 mmol) in trifluoroacetic acid (14.38 mL) was added dropwise sulfuric acid (0.36 mL, 7.19 mmol). The reaction was refluxed for ~3 h. After evaporating the trifluoroacetic acid under reduced pressure, the resulting crude mixture was poured into ~100 mL of ice cold water. The solution was made alkaline with 40% NaOH and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude mixture of benzazepine **ET-19** and an unknown product (0.91 g). To a solution of the crude mixture in dry $CHCl_3$ (30 mL) @ 0^oC was added BBr_3 (9.99 mL, 1.0 M solution in DCM). After stirring for 1 h at room temperature, the reaction was cooled to 0^oC and anhydrous MeOH (28.5 mL) was added. The reaction was refluxed in an open mouth flashed for 20 min before evaporating the solvent. The crude mixture was diluted with EtOAc and made alkaline with K_2CO_3. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Treatment with 3N anhydrous HCl solution in EtOAc and exposure to Et_2O precipitated the hydrochloride salts of **ET-18** (0.35 g, 40%). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.41 (t, J=7.3 Hz, 2H), 7.33 (t, J=7.3 Hz, 1H), 7.20 (d, J=7.3 Hz, 2H), 6.73 (d, J=2.4 Hz, 1H), 6.61 (d, J=8.3 Hz, 1H), 6.57 (dd, J=8.8, 2.44 Hz, 1H), 4.56 (dd, J=8.8, 2.0 Hz, 1H), 3.77 (m, 1H), 3.63 (dd, J=13.4, 2.2 Hz, 1H), 3.42 (m, 1H), 3.19 (m, 2H), 3.03 (m, 1H).

N-*t*-Boc-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (2.36). Refer to general procedure for *t*-Boc protection of an amine hydrochloride. The crude mixture was purified via flash SiO_2 column chromatography (EtOAc/hexanes (20%/80%)) to give **2.36** (0.76 g, 61% yield). ^{1}H NMR (400 MHz, chloroform-d) δ 7.28 (m, 2H), 7.21 (s,

1H), 7.11 (app d, *J*=8.0 Hz, 2H), 7.02 (d, *J*=8.4 Hz, 1H), 6.63 (app d, *J*=9.6 Hz, 1H), 6.40 (s, 1H), 4.63 (br s, 1H), 3.61 (app q, *J*=10.0 Hz, 2H), 3.02 (m, 2H), 3.02 (m, 2H), 2.83 (br m, 2H), 1.36 (s, 9H).

N-*t*-Boc-7-hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (2.37). Refer to general procedure for *t*-Boc protection of an amine hydrochloride. The crude mixture was purified via flash SiO_2 column chromatography (EtOAc/hexanes (10%/90%) to (25%/75%)) to give **2.37** (0.41 g, 81% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.27 (t, *J*=7.3, 2H), 7.18 (t, *J*=7.3, 1H), 7.10 (app t, *J*=9.3 Hz, 2H), 6.75 (d, *J*=8.8 Hz, 1H), 6.63 (s, 1H), 6.54 (d, *J*=8.3 Hz, 1H), 4.38 (br s, 1H), 3.83 (m, 2H), 3.04 (m, 2H), 2.80 (m, 2H), 1.36 (s, 9H).

N-*t*-Boc-8-phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (2.38). Refer to general procedure for formation of a biaryl ether. The crude mixture was purified via flash SiO_2 column chromatography (EtOAc/hexanes (20%/80%)) to give **2.38** (0.57 g, 100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.37 (t, *J*=7.8 Hz, 4H), 7.32 (d, *J*=7.3 Hz, 1H), 7.10 (m, 4H), 7.05 (t, *J*=7.3 Hz, 1H), 6.92 (d, *J*=8.3 Hz, 1H), 6.78 (dd, *J*=8.1, 2.7 Hz, 1H), 6.66 (d, *J*=2.4 Hz, 1H), 4.40 (br d, *J*=35.2 Hz, 1H), 3.90 (br m, 2H), 3.62 (br m, 2H), 2.95 (br m, 2H).

N-*t*-Boc-7-phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine (2.39). Refer general procedure for formation of a biaryl ether. The crude mixture was purified via flash SiO_2 column chromatography (EtOAc/hexanes (0%/100%) to (5%/95%)) to give **2.39** (0.12 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.26-7.35 (m, 4H), 7.22 (app t, *J*= 8.4 Hz, 1H), 7.12 (m, 4H), 7.01 (d, *J*=7.6 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 1H), 6.83

(d, *J*=2.4 Hz, 1H), 6.74 (dd, *J*=8.4 Hz, 1H), 4.41 (br m, 1H), 4.79 (br d, *J*=36.4 Hz, 2H), 3.62 (br s, 2H), 2.92 (br m, 2H).

8-Phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-17). Refer to general procedure for *t*-Boc deprotection: 0.50 g, 90% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.40 (t, *J*=7.6 Hz, 2H), 7.32 (app t, *J*=7.4 Hz, 2H), 7.27 (m, 2H), 7.19 (d, *J*=7.6 Hz, 2H), 7.07 (t, *J*=7.4 Hz, 1H), 6.87 (d, *J*=7.6 Hz, 2H), 6.81 (dd, *J*=8.4, 2.4 Hz, 1H), 6.40 (d, *J*=1.6 Hz, 1H), 4.61 (d, *J*=8.4 Hz, 1H), 3.72 (m, 2H), 3.48 (dd, *J*=11.8, 7.6 Hz, 2H), 3.18 (m, 2H) ; ^{13}C NMR (100 MHz, methanol-d_4) δ 158.1, 158.0, 144.6, 140.5, 134.2, 132.8, 130.8, 130.3, 129.2, 128.7, 124.6, 120.6, 120.0, 118.0, 51.2, 47.7, 47.2, 32.6. HRMS (EI$^+$) *m/z* for $C_{22}H_{21}NO$ $[M + H]^+$: calcd, 316.1701; found, 316.1713.

7-Phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-20). Refer to general procedure for *t*-Boc deprotection: 0.10 g, 85% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.44 (t, *J*=7.6 Hz, 3H), 7.35 (app t, *J*=8.1 Hz, 3H), 7.23 (d, *J*=8.1, 2H), 7.12 (t, *J*=7.3 Hz, 1H), 7.00 (dd, *J*=8.8, 1.0 Hz, 1H), 6.90 (s, 1H), 6.77 (s, 2H), 4.60 (dd, *J*=8.6, 1.7 Hz, 1H), 3.66-3.84 (m, 2H), 3.22 (m, 2H), 3.09 (m, 2H). HRMS (EI$^+$) *m/z* for $C_{22}H_{21}NO$ $[M + H]^+$: calcd, 316.1701; found, 316.1702.

Scheme 2-6. Synthesis of β-Substituted Phenoxyphenethylamines (**MM-7**, **MM-10**, and **MM-13**–**MM-15**)

2-(4-*tert*-Butyldimethylsilyloxyphenyl)acetonitrile (2.41). To a stirred solution of 4-hydroxybenzyl cyanide (2.0 g, 15.0 mmol) in DCM (10mL) was added *t*-butyl-dimethylsilyl chloride (2.5 g, 16.5 mmol). The reaction mixture was cooled to 0 ºC and

imidazole (2.3 g, 33.0 mmol) was added. After warming to ambient temperature and stirring for 3 h, the reaction mixture was diluted with diethyl ether. The organic layer was washed with 0.5 M HCl, saturated aqueous $NaHCO_3$, water, brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (8:1)) to give **2.41** as a clear oil (3.6 g, 98% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.87 (d, J = 8.5 Hz, 2 H), 6.86 (d, J = 8.5 Hz, 2 H), 3.54 (s, 2 H), 0.98 (s, 9 H), 0.23 (s, 6 H).

2-(4-Triisopropylsilyloxyphenyl)acetonitrile (2.42). To a stirred solution of 4-hydroxybenzyl cyanide (1.3 g, 10 mmol) in DCM (5 mL) was added triisopropylsilyl chloride (2.1 mL, 10 mmol). The reaction mixture was cooled to 0 ºC and imidazole (1.7g, 25 mmol) was added. The mixture was stirred at 0 ºC for 30 minutes and then allowed to warm to ambient temperature over 24 hours. The reaction mixture was diluted with diethyl ether, washed with 1 N HCl, saturated aqueous $NaHCO_3$, brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (20:1)) to give **2.42** as a slightly yellow oil (2.4 g, 84 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.16 (d, J = 8.4 Hz, 2 H), 6.87 (d, J = 8.4 Hz, 2 H), 3.67 (s, 2 H), 1.25 (m, 3 H), 1.10 (d, J = 8.4 Hz, 18 H); HRMS (EI+) for $C_{17}H_{27}NOSi$ calcd. 289.1862 found 298.1859.

2-(4- *tert*-Butyldimethylsilyloxyphenyl)-2-methylpropanenitrile (2.43). To a solution of 2-(4-*tert*-butyldimethylsilyloxyphenyl)acetonitrile (**2.41**) (1.2 g, 5.0 mmol) in THF (10 mL) at -78 ºC was added dropwise LDA (2.75 mL, 2.0 M in heptane, THF, and ethylbenzene, 5.5 mmol). Iodomethane (0.37 mL, 6.0 mmol) was added dropwise and the mixture was stirred at -78 ºC for 30 minutes. After stirring at room temperature for 4h,

the reaction was cooled to -78 ºC and LDA (2.75 mL, 2.0 M in heptane, THF, and ethylbenzene, 5.5 mmol) was added dropwise. Iodomethane (0.37 mL, 6.0 mmol) was added to the reaction dropwise and the mixture was stirred at -78 ºC for 30 minutes then allowed to warm to ambient temperature over 16 hours. The reaction mixture was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were sequentially washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (20:1)) to give **2.43** as a slightly yellow oil (1.3 g, 91% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.31 (d, J = 8.3 Hz, 2 H), 6.83 (d, J = 8.3 Hz, 2 H), 1.69 (s, 6 H), 0.98 (s, 9 H), 0.20 (s, 6 H).

2-(4-Triisopropylsilylphenyl)propanenitrile (2.44). To a solution of 2-(4-triisopropylsilyloxyphenyl)acetonitrile **(V3)** (1.0 g, 3.5 mmol) in THF (30 ml) at -78 ºC was added dropwise LDA (2.9 mL, 1.8 M in heptane, THF, and ethylbenzene, 5.2 mmol). Iodomethane (0.24 mL, 3.8 mmol) was added dropwise to the reaction and the mixture was stirred at -78 ºC for 1 h. The reaction was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were sequentially washed with water, and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (20:1)) to give **2.44** as a slightly yellow oil (930 mg, 89% yield). ^{1}H-NMR (400 MHz, chloroform-*d)* δ 7.16 (d, J = 8.8 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 3.82 (m,1 H), 1.63 (d, J = 7.3 Hz, 3 H), 1.26 (m, 1 H), 1.07 (d, J = 7.2 Hz, 18 H).

2-(4-Triisopropylsilylphenyl)-3-phenylpropanenitrile (2.45). To a solution of 2-(4-triisopropylsilyloxyphenyl)acetonitrile **(2.42)** (1.0 g, 3.5 mmol) in THF (30 ml) at -78 ºC was added dropwise LDA (2.9 mL, 1.8 M in heptane, THF, and ethylbenzene, 5.2 mmol). Benzyl bromide (0.45 mL, 3.8 mmol) was added dropwise to the reaction and it was stirred at -78 ºC for 1 h. The reaction mixture was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 (eluted with ether/ethyl acetate (20:1)) to give **2.45** as a slightly yellow oil (985 mg, 75% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.26 (m, 4 H), 7.09 (m, 1 H), 7.06 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 3.93 (m, 1H), 3.17 (m, 1 H), 3.09 (m, 1 H), 1.24 (m, 1 H), 1.09 (d, J = 7.1 Hz, 12 H).

***tert*-Butyl 2-(4- *tert*-butyldimethylsilyloxyphenyl)-2-methylpropylcarbamate (2.46)** To a solution of 2-(4- *tert*-butyldimethylsilyloxyphenyl)-2-methylpropanenitrile (**2.43**) (1.0 g, 3.6 mmol) in THF (15 mL) at 0 ºC was added lithium aluminum hydride (207 mg, 5.5 mmol). The mixture was stirred at 0 ºC for 15 minutes and then refluxed for 2 h. The resulting solution was cooled to 0 ºC, quenched with 2 M NaOH and stirred for 15 minutes at 0 ºC. The crude mixture was filtered through celite and the filtrate was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The crude mixture was dissolved in THF (10 mL) and it was added to a solution of $NaHCO_3$ (337 mg, 4.0 mmol) in water (5 ml) and di-*t*-butyldicarbonate (865 mg, 4.0 mmol). After stirring for 15 h, the reaction mixture was diluted with ether and washed with 0.5 M HCl. The aqueous layer was extracted with ether and the combined organic layers were sequentially washed

with water, brine, dried over $MgSO_4$ and concentrated to dryness. The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (30:1)) to give **2.46** as a slightly yellow solid (627 mg, 46% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.33 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 3.28(s, 2H), 1.69 (s, 6 H), 1.41 (s, 9 H), 0.98 (s, 9 H), 0.20 (s, 6 H).

***tert*-Butyl 2-(4-triisopropylsilyloxyphenyl)propylcarbamate (2.47).** Refer to general procedure for nitrile reduction and subsequent *t*-Boc protection of amine described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (10:1)) to give the pure product **2.47** as a slightly yellow solid (720 mg, 86 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.03 (d, J = 8.1 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 2 H), 4.38 (s, 1 H), 3.36 (m, 1 H), 3.12 (m, 1 H), 2.85 (m,1 H), 1.41 (s, 9H), 1.27 (m, 1 H), 1.22 (d, J = 7.0 Hz, 3 H),1.10 (s, J = 7.2 Hz,18 H).

***tert*-Butyl 2-(4-triisopropylsilyloxyphenyl)-3-phenylpropylcarbamate (2.48).** Refer to general procedure for nitrile reduction and subsequent *t*-Boc protection of amine described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (15:1)) to give the pure product **2.48** as a slightly yellow solid (350 mg, 68 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.14 (m, 4 H), 6.96 (d, J = 6.8 Hz, 1 H), 6.93 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 8.6 Hz, 2 H), 4.13 (s, 1 H), 3.55 (m, 1 H), 3.21 (m, 1 H), 2.96 (m, 1 H), 2.91 (m, 1 H), 2.79 (m, 1 H), 1.38 (s, 9 H), 1.21 (m, 1 H), 1.08 (d, J = 6.6 Hz, 12 H).

***tert*-Butyl 2-(4-hydroxyphenyl)-2-methylpropylcarbamate (2.49).** Refer to general procedure for *t*-butyldimethylsilyl deprotection described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate

(10:1)) to give **2.49** as a white solid (107 mg, 98% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 6.97 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 8.4 Hz, 2 H), 3.25 (s, 2 H), 1.71 (s, 6 H), 1.44 (s, 9 H).

***tert*-Butyl 2-(4-hydroxyphenyl)propylcarbamate (2.50)**. Refer to general procedure for triisopropylsilyl deprotection described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (5:1)) to give **2.50** as a white solid (405 mg, 91% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.06 (d, J = 8.2 Hz, 2 H), 6.79 (d, J = 8.2 Hz, 2 H), 4.45 (s, 1 H), 3.35 (m, 1 H), 3.14 (m, 1 H), 2.86 (m,1 H), 1.43 (s, 9H), 1.22 (d, J = 7.1 Hz, 3 H).

***tert*-Butyl 2-(4-hydroxyphenyl)-3-phenylpropylcarbamate (2.51).** Refer to general procedure for triisopropylsilyl deprotection described above. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (4:1)) to give **2.51** as a white solid (215 mg, 91% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.18 (m, 2 H), 7.13 (d, J = 7.0 Hz, 1 H), 7.01 (d, J = 7.1 Hz, 2 H), 6.96 (d, J = 8.4 Hz, 2 H), 6.74 (d, J = 8.4 Hz, 2 H), 5.42 (s, 1 H), 4.38 (s, 2 H), 3.51 (m, 1 H), 3.22 (m, 1 H), 2.98 (m, 1 H), 2.91 (m, 1H), 2.82 (m, 1H), 1.39 (s, 9H).

***tert*-Butyl 2-methyl-2-(4-phenoxyphenyl)propylcarbamate (2.52).** Refer to general procedure for biaryl ether formation described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (4:1)) to give **2.52** as a slightly yellow solid (63 mg, 46% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.32 (app t, J = 8.2 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H), 7.10 (app t, J = 8.2 Hz, 1 H), 6.97 (d, J = 8.2 Hz, 2 H), 6.89 (app d, J = 8.2 Hz, 2 H), 4.60 (brd s, 1H), 3.27 (s, 2 H), 1.70 (s, 6 H), 1.34 (s, 9 H).

***tert*-Butyl 2-(4-phenoxyphenyl)propylcarbamate (2.53).** Refer to general procedure for biaryl ether formation described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (10:1)) to give **2.53** as a slightly yellow solid (130 mg, 41% yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.33 (app t, *J* = 8.2 Hz, 2 H), 7.16 (d, *J* = 7.0 Hz, 2 H), 7.10 (app t, *J* = 8.2 Hz, 1 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 6.96 (d, *J* = 8.2 Hz, 2 H), 4.45 (brd s, 1H), 3.39 (m, 1 H), 3.18 (m, 1 H), 2.91 (m, 1 H), 1.43 (s, 9 H), 1.26 (d, *J* = 7.0 Hz, 3 H).

***tert*-Butyl 2-(4-phenoxyphenyl)-3-phenylpropylcarbamate (2.54).** Refer to general procedure for biaryl ether formation described above. The crude product was purified via SiO_2 flash chromatography (eluted with hexane/ethyl acetate (10:1)) to give **2.54** as a slightly yellow solid (95 mg, 37 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.33 (m, 2 H), 7.20 (d, *J* = 7.3 Hz, 2 H), 7.15 (d, *J* = 7.0 Hz, 2 H), 7.11 (m, 1 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 6.8 Hz, 2 H), 6.98 (d, *J* = 7.9 Hz, 2 H), 6.93 (d, *J* = 8.2 Hz, 2 H), 4.38 (s, 1 H), 3.55 (m, 1 H), 3.26 (m, 1 H), 3.05 (m, 1 H), 2.94 (m, 1H), 2.85 (m, 1H), 1.40 (s, 9 H).

2-Methyl-2-(4-phenoxyphenyl)propan-1-amine hydrochloride (MM-7). Refer to general procedure for *t*-Boc deprotection described above. Compound **MM-7** was obtained as a white solid (46 mg, 92% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (brd s, 3 H), 7.44 - 7.37 (m, 4 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.02 - 6.99 (m, 4 H), 3.32 (s, 2 H), 1.35 (s, 6 H); ^{13}C-NMR (100MHz, methanol-d_4) δ 158.45, 157.91, 139.98, 130.91, 128.65, 124.61, 119.99, 51.74, 38.03, 26.97. HRMS (EI$^+$) *m/z* for $C_{16}H_{19}NO$ $[M + H]^+$: calcd, 241.1467; found, 241.1457.

2-(4-Phenoxyphenyl)propan-1-amine hydrochloride (MM-10). Refer to general procedure for *t*-Boc deprotection described above. Compound **MM-10** was obtained as a white solid (95 mg, 93% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 2 H), 7.40 (app t, J = 8.2 Hz, 2 H), 7.31 (d, J = 7.0 Hz, 2 H), 7.14 (app t, J = 8.2 Hz, 1 H), 7.00 (m, 4 H), 3.02 (m, 1 H), 1.26 (d, J = 6.0 Hz, 3 H); ^{13}C-NMR (100MHz, methanol-d_4) δ 158.59, 158.14, 137.99, 130.88, 129.71, 124.49, 120.33, 119.89, 46.88, 38.94, 19.99. HRMS (EI$^+$) *m/z* for $C_{15}H_{17}NO$ $[M + H]^+$: calcd, 227.1310; found, 227.1306.

2-(4-Phenoxyphenyl)-3-phenylpropan-1-amine hydrochloride (MM-13). Refer to general procedure for *t*-Boc deprotection described above. Compound **MM-13** was obtained as a white solid (70 mg, 94% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 2 H), 7.38 (t, J = 8.0 Hz, 2 H), 7.25 (d, J = 8.6 Hz, 2 H), 7.22 (d, J = 7.5 Hz, 2 H), 7.14 (m, 2 H), 7.07 (d, J = 7.5 Hz, 2 H), 6.95 (t, J = 7.5 Hz, 4 H), 3.29 (m, 1 H), 3.11 (m, 3 H), 2.82 (dd, J = 8.6, 13.6 Hz, 1 H); ^{13}C-NMR (100MHz, methanol-d_4) δ 158.58, 158.23, 139.94, 135.54, 130.87, 130.64, 130.17, 129.37, 127.46, 124.49, 120.28, 119.84, 46.95, 45.01, 41.78. HRMS (EI$^+$) *m/z* for $C_{21}H_{21}NO$ $[M + H]^+$: calcd, 303.1623; found, 303.1621.

5-(4-Phenoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.56). To a solution of 4-phenoxybenzaldehyde (3.9 g, 20 mmol) in benzene (50 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (2.9 g, 20 mmol), piperidine (35 mg, 0.4 mmol), and acetic acid (0.17 mL, 2.9 mmol). The reaction was refluxed for 2 h using a Dean-Stark. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and sequentially washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified via SiO_2 flash chromatography (eluted

with hexane/ethyl acetate (4:1)) to give the pure product **2.56** as a yellow solid (4.6 g, 70 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 8.39 (s, 1 H), 8.18 (d, J = 9.2 Hz, 2 H), 7.43 (m, 2 H), 7.23 (d, J = 6.4 Hz, 2 H), 7.10 (d, J = 7.5 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 1.79 (s, 6 H).

2,2-Dimethyl-5-(1-(4-phenoxyphenyl)-3-phenylprop-2-ynyl)-1,3-dioxane-4,6-dione (2.57). To a solution of 5-(4-phenoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.56**) (800 mg, 2.5 mmol) in THF (20 mL) at -78 ºC was added lithium phenylacetylide (3.0 mL, 1.0 M in THF, and 3.0 mmol) and the mixture was stirred at -78 ºC for 1 h. The reaction mixture was diluted with diethyl ether and washed with 0.5 M HCl. The aqueous layer was extracted with diethyl ether and the combined organic layers were sequentially washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (3:2)) to give the pure product **2.57** as a white solid (810 mg, 77 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.58 (d, J = 8.8 Hz, 2 H), 7.47 (m, 2 H), 7.32 (m, 5 H), 7.11 (t, J = 7.1 Hz, 2 H), 7.01 (d, J = 8.6 Hz, 2 H), 6.98 (d, J = 8.6 Hz, 2 H), 5.14 (d, J = 2.6 Hz, 1 H), 3.98 (d, J = 2.6 Hz, 1 H), 1.76 (s, 3 H), 1.66 (s, 3 H).

2,2-Dimethyl-5-(3-(trimethylsilyl)-1-(4-phenoxyphenyl)prop-2-ynyl)-1,3-dioxane-4,6-dione (2.58). To a solution of ethynyltrimethylsilane (0.4 mL, 2.29 mmol) in THF (20 mL) in -78 ºC was added butyl lithium (1.2 mL, 2.5 M in hexane, 3.0 mmol) and stirred for 30 minutes. 5-(4-phenoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2.56**) (800 mg, 2.5 mmol) in THF (5 mL) was then added and the reaction mixture was allowed to stir for 1 h. The reaction mixture was diluted with diethyl ether and washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure.

The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (3:2)) to give the pure product **2.58** as a white solid (790 mg, 76 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.49 (d, J = 9.0 Hz, 2 H), 7.34 (t, J = 7.6 Hz, 2 H), 7.32 (m, 5 H), 7.11 (t, J = 7.4 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 4.94 (d, J = 2.6 Hz, 1 H), 1.74 (s, 3 H), 1.67 (s, 3 H), 0.19 (s, 9 H).

3-(4-Phenoxyphenyl)-5-phenylpent-4-ynoic acid (2.59). Refer to general procedure for acetal deprotection and subsequent decarboxylation. The crude product was purified via flash SiO_2 chromatography (eluted with ethyl acetate) to give the pure product **2.59** as a yellow solid (577 mg, 98 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.42 (m, 4 H), 7.34 (m, 1 H), 7.29 (m, 4 H), 7.10 (t, J = 7.2 Hz, 1 H), 7.02 (d, J = 7.7 Hz, 2 H), 6.98 (d, J = 8.6 Hz, 2 H), 4.37 (t, J = 7.3 Hz, 1 H), 2.97 (dd, J = 6.8, 16 Hz, 1 H), 2.86 (dd, J = 6.8, 16 Hz, 1 H).

5-(Trimethylsilyl)-3-(4-phenoxyphenyl)pent-4-ynoic acid (2.60). Refer to general procedure for acetal deprotection and subsequent decarboxylation. The crude product was purified via flash SiO_2 chromatography (eluted with hexane/ethyl acetate (3:1)) to give the pure product **2.60** as a slightly yellow solid (410 mg, 73 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.35 (d, J = 6.6 Hz, 2 H), 7.32 (d, J = 6.8 Hz, 1 H), 7.11 (m, 1 H), 7.01 (dd, J = 1.1, 8.6 Hz, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 4.16 (t, J = 7.5 Hz, 1 H), 2.87 (dd, J = 7.1, 16 Hz, 1 H), 2.76 (dd, J = 7.1, 16 Hz, 1 H), 0.16 (s, 9 H).

3-(4-Phenoxyphenyl)pent-4-ynoic acid (2.61). To a solution of 5-(Trimethylsilyl)-3-(4-phenoxyphenyl)pent-4-ynoic acid **(2.60)** in methanol (5 mL) and water (2 mL) was added 10 % NaOH (5 mL) and stirred for 2 h at ambient temperature. The reaction mixture was concentrated and diluted with 3 N HCl. The aqueous layer was

extracted with ether and the combined organic layers were sequentially washed with water, and brine, then dried over $MgSO_4$. The crude product was purified via flash SiO_2 (eluted with hexane/ethyl acetate (3:2)) to give the pure product **2.61** as a yellow solid (210 mg, 76 % yield). ^{1}H-NMR (400 MHz, chloroform-*d*) δ 7.34 (m, 4 H), 7.11 (t, J = 7.1 Hz, 1 H), 7.01 (d, J = 7.7 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 4.15 (m, 1 H), 2.90 (dd, J = 8.4, 16 Hz, 1 H), 2.79 (dd, J = 8.4, 16 Hz, 1 H), 2.32 (s, 1 H).

2-(4-Phenoxyphenyl)-4-phenylbut-3-yn-1-amine hydrochloride (MM-14). Refer to general procedure for Curtius rearrangement described above. The crude product was purified via flash SiO_2 chromatography (eluted with methanol/ethyl acetate (1:4)) to give the pure product **MM-14** as a white solid (185 mg, 36 % yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 4 H), 7.53 (t, J = 8.3 Hz, 4 H), 7.41 (m, 5 H), 7.16 (t, J = 7.4 Hz, 1 H), 7.05 (t, J = 8.9 Hz, 4 H), 4.36 (t, J = 6.9 Hz, 1 H), 3.21 (m, 2 H); ^{13}C-NMR (100MHz, methanol-d_4) δ 158.85, 158.29, 132.84, 130.95, 130.36, 129.76, 129.48, 124.74, 123.75, 120.17, 120.12, 86.95, 46.29, 37.23. HRMS (EI$^+$) *m/z* for $C_{22}H_{19}NO$ [M + H]$^+$: calcd, 313.1467; found, 313.1367.

2-(4-Phenoxyphenyl)but-3-yn-1-amine hydrochloride (MM-15). Refer to general procedure for Curtius rearrangement described above. The crude product was purified via flash SiO_2 chromatography (eluted with methanol/ethyl acetate (1:4)) to give the pure product **MM-15** as a white solid (71 mg, 38 % yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 3 H), 7.44 (t, J = 8.8 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.16 (t, J = 7.4 Hz, 1 H), 7.03 (m, 4 H), 4.08 (t, J = 6.0 Hz, 1 H), 3.50 (d, J = 2.6 Hz, 1 H), 3.12 (m, 2 H). HRMS (EI$^+$) *m/z* for $C_{16}H_{15}NO$ [M + H]$^+$: calcd, 237.1154; found, 237.1149.

Scheme 2-7. Synthesis of Phenoxynaphethylamine (**ET-21**)

4-Phenoxynaphthaldehyde (2.63). Refer to general procedure for formation of a biaryl ether described above. The crude product was purified via flash SiO_2 chromatography (loaded with DCM, eluted with EtOAc/hexanes (0%/100%) to (5%/95%)) to give **2.63** (0.72 g, 39% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.15 (s, 1H), 9.24 (d, *J*=8.3 Hz, 1H), 8.34 (d, *J*=9.3 Hz, 1H), 7.69 (m, 3H), 7.63 (t, *J*=6.8 Hz, 1H), 7.39 (app t, *J*=8.1 Hz, 2H), 7.18 (t, *J*=7.3 Hz, 1H), 7.06 (d, *J*=8.8 Hz, 1H), 6.66 (s, 1H).

4-Phenoxynaphthalenylmethanol (2.64). To a solution of **2.63** (0.28 g, 1.12 mmol) in ethanol (20 mL) was added sodium borohydride (0.042 g, 1.12 mmol). After stirring at room temperature for 15 min, the reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was purified via flash SiO_2 chromatography (EtOAc/hexanes (25%/75%) to give **2.64** (0.28 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.29 (d, *J*=8.3 Hz, 1H), 8.17 (d, *J*=8.3 Hz, 1H), 7.61 (m, 1H), 7.53 (m, 1H), 7.41 (d, *J*=7.8 Hz, 1H), 7.35 (t, *J*=7.8 Hz, 2H), 7.13 (t, *J*=7.3 Hz, 1H), 7.05 (dd, *J*=8.6, 1.2 Hz, 2H), 6.88 (d, *J*=7.8 Hz, 1H), 5.12 (s, 2H).

4-Phenoxynaphthalenylacetonitrile (2.65). Refer to general procedure for formation of a nitrile. The crude mixture was purified via flash SiO_2 chromatography (loaded with DCM, eluted with EtOAc/hexanes (10%/90%)) to give **2.65** (0.21 g, 54% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.36 (d, *J*=7.8 Hz, 1H), 7.67 (app t, *J*=7.1

Hz, 1H), 7.59 (app t, *J*=8.1 Hz, 1H), 7.47 (d, *J*=7.8 Hz, 1H), 7.38 (app t, *J*=8.1 Hz, 2H), 7.16 (t, *J*=7.6 Hz, 1H), 7.07 (d, *J*=7.8 Hz, 2H), 6.87 (d, *J*=7.8 Hz, 1H), 4.11 (s, 2H).

4-Phenoxynaphthalenethylamine (ET-21). Refer to general procedure for reduction of a nitrile to an amine hydrochloride: 0.13 g, 54% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.24 (d, *J*=8.8 Hz, 1H), 8.12 (d, *J*=8.8 Hz, 1H), 7.66 (app t, *J*=7.6 Hz, 1H), 7.55 (app t, *J*=7.6 Hz, 1H), 7.36 (m, 3H), 7.13 (app t, *J*=7.3 Hz, 1H), 7.02 (d, *J*=7.3 Hz, 2H), 6.88 (d, *J*=7.8 Hz, 1H), 3.43 (t, *J*=7.6 Hz, 2H), 3.27 (t, *J*=7.3 Hz, 2H) ; ^{13}C NMR (100 MHz, methanol-d_4) δ 159.1, 154.3, 134.2, 131.0, 129.1, 128.7, 128.4, 128.2, 127.1, 124.5, 124.4, 123.9, 119.6, 113.9, 41.3, 31.4. HRMS (EI$^+$) *m/z* for $C_{18}H_{17}NO$ [M + H]$^+$: calcd, 264.1388; found, 264.1393.

Scheme 2-8. Synthesis of Naphethylamines (**1-NEA**, **4-OH-NEA**, and **ET-102**)

(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-triphenyl phosphonium bromide (2.67). To a solution of N-(bromomethyl)phtalimide (24.49 g, 102.02 mmol) in toluene (500 mL) was added PPh_3 (26.76 g, 102.02 mmol). After stirring under reflux for 24 h, the white precipitate that formed were filtered, washed with hexanes, and dried under vacuum.

4-Benzyloxy-naphthaldehyde (2.66). To a solution of 4-hydroxynaphthaldehyde (3.96 g, 23.02 mmol) in acetone (60 mL) was added K_2CO_3 (3.50 g, 25.32 mmol) and BnBr (5.91 g, 34.53 mmol). After stirring at room temperature for 24 h, the reaction was concentrated under reduced pressure and diluted with water and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via Biotage® purification system

(EtOAc/Hexanes (0%/100%) to (25%/75%)) to give **2.66** as a yellow oil (5.90 g, 98% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.21 (s, 1H), 9.31 (d, *J*=8.6 Hz, 1H), 8.41 (dd, *J*=8.3 Hz, 0.8 Hz, 1H), 7.91 (d, *J*=8.1 Hz, 1H), 7.71 (dd, *J*=6.8 Hz, 1.5 Hz, 1H), 7.58 (dd, *J*=6.3 Hz, 1.3 Hz, 1H), 7.52 (d, *J*=7.3 Hz, 2H), 7.44 (t, *J*=7.2 Hz, 2H), 7.39 (tt, *J*=8.6 Hz, 7.2 Hz, 1.4 Hz, 1H), 7.00 (d, *J*=8.1 Hz, 1H), 5.35 (s, 2H).

2-(Isoindolinyl-1,3-dione)-(1-(4-benzyloxy)naphthyl)ethene (2.68). To a solution of (1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-triphenyl phosphonium bromide (20.79 g, 41.39 mmol) in THF (376 mL) at 0^{o}C was added KHMDS (82.78 mL, 41.39 mmol, 0.5M in toluene) over 10 min. After stirring at 0^{o}C for 10 min, a solution of **2.66** (4.52 g, 17.25 mmol) in THF (10 mL) was added and the reaction was warmed to room temperature. After 24 h, the reaction was quenched with water and diluted with EtOAc. The organic layer was washed with brine and saturated NH_4Cl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via Biotage® purification system (DCM/Hexanes (50%/50%) to (80%/20%)) to give **2.68** as an orange solid (6.01 g, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.40 (dq, *J*=8.3 Hz, 0.7 Hz, 1H), 8.33 (d, *J*=14.9 Hz, 1H), 8.14 (d, *J*=8.6 Hz, 1H), 7.92 (dd, *J*=5.6 Hz, 3.0 Hz, 2H), 7.78 (dd, *J*=5.6 Hz, 3.0 Hz, 2H), 7.50-7.61 (m, 5H), 7.44 (t, *J*=7.3 Hz, 2H), 7.37 (tt, *J*=8.3 Hz, 7.3 Hz, 1.4 Hz, 1H), 7.27 (d, *J*=14.9 Hz, 1H), 6.92 (d, *J*=8.1 Hz, 1H), 5.29 (s, 2H).

N-*t*-Boc-2-(4-hydroxy-naphthyl)ethylamine (2.69). Refer to general procedure for phthalimide deprotection and subsequent *t*-Boc protection. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (40%/60%)) to give **2.69** as a brownish white solid (1.65 g, 31% yield). ^{1}H NMR (400 MHz,

chloroform-*d*) δ 8.24 (d, *J*=8.3 Hz, 1H), 8.01 (d, *J*=8.1 Hz, 1H), 7.55 (dd, *J*=6.8 Hz, 1.6 Hz, 1H), 7.50 (dd, *J*=6.8 Hz, 1.4 Hz, 1H), 7.14 (d, *J*=7.3 Hz, 1H), 6.76 (d, *J*=7.6 Hz, 1H), 5.53 (s, 1H), 4.60 (br s, 1H), 3.46 (q, *J*=6.6 Hz, 2H), 3.19 (t, *J*=6.7 Hz, 2H), 1.45 (s, 9H).

N-*t*-Boc-2-(4-(4-triisopropylsiloxy)phenoxynaphthyl)ethylamine (2.70). Refer to general procedure to formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (10%/90%)) to give **2.70** as a colorless oil (0.11 g, 11% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.35 (d, *J*=8.3 Hz, 1H), 8.06 (d, *J*=8.1 Hz, 1H), 7.58 (dd, *J*=6.7 Hz, 1.3 Hz, 1H), 7.51 (dd, *J*=6.9 Hz, 1.4 Hz, 1H), 7.17 (d, *J*=7.7 Hz, 1H), 6.95 (dd, *J*=6.6 Hz, 2.5 Hz, 2H), 6.88 (dd, *J*=6.5 Hz, 2.4 Hz, 2H), 6.70 (d, *J*=7.9 Hz, 1H), 4.60 (br s, 1H), 3.48 (q, *J*=6.5 Hz, 2H), 3.22 (t, *J*=7.0 Hz, 2H), 1.44 (s, 9H), 1.25 (m, 3H), 1.11 (d, *J*=7.0 Hz, 18H).

N-*t*-Boc-2-(4-(4-hydroxy)phenoxynaphthyl)ethylamine (2.71). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (20%/80%)) to give **2.71** as a colorless oil/white foam (66 mg, 87% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.34 (d, *J*=8.3 Hz, 1H), 8.06 (d, *J*=7.8 Hz, 1H), 7.58 (dd, *J*=7.1 Hz, 1.4 Hz, 1H), 7.52 (t, *J*=7.1 Hz, 1H), 7.17 (d, *J*=7.8 Hz, 1H), 6.97 (d, *J*=8.8 Hz, 2H), 6.84 (d, *J*=8.8 Hz, 2H), 6.72 (d, *J*=7.3 Hz, 1H), 5.07 (br s, 1H), 4.63 (br s, 1H), 3.48 (q, *J*=6.6 Hz, 2H), 3.22 (t, *J*=6.8 Hz, 2H), 1.44 (s, 9H).

2-(4-(4-Hydroxy)phenoxynaphthyl)ethylamine Hydrochloride (ET-102). Refer to general procedure for *t*-Boc deprotection: white solid, 66 mg, 97% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.36 (dd, *J*=8.3 Hz, 0.8 Hz, 1H), 8.08 (d, *J*=8.3 Hz, 1H), 7.65 (dd, *J*=6.8 Hz, 1.4 Hz, 1H), 7.56 (dd, *J*=6.8 Hz, 1.1 Hz, 1H), 7.28 (d, *J*=7.8 Hz, 1H),

6.93 (d, *J*=8.8 Hz, 2H), 6.82 (d, *J*=9.1 Hz, 2H), 6.68 (d, *J*=7.8 Hz, 1H), 3.39 (d, *J*=7.1 Hz, 1H), 3.37 (d, *J*=6.1 Hz, 1H), 3.26 (d, *J*=8.3 Hz, 1H), 3.24 (dd, *J*=10.2 Hz, 1.1 Hz, 1H). HRMS (EI^+) *m/z* for $C_{18}H_{18}NO_2$ $[M + H]^+$: calcd, 280.1338; found, 280.1332.

2-(4-Hydroxy-naphthyl)ethylamine Hydrochloride (4-OH-NEA). Refer to general procedure for *t*-Boc deprotection: white solid, 73 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 8.27 (dq, *J*=8.5 Hz, 1.4 Hz, 0.8 Hz, 1H), 7.97 (d, *J*=8.6 Hz, 1H), 7.55 (dd, *J*=6.8 Hz, 1.5 Hz, 1H), 7.46 (dd, *J*=6.8 Hz, 1.3 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 6.78 (d, *J*=7.8 Hz, 1H), 3.33 (m, 2H), 3.21 (t, *J*=7.6 Hz, 2H). HRMS (EI^+) *m/z* for $C_{12}H_{14}NO$ $[M + H]^+$: calcd, 188.1075; found, 188.1079.

2-(Naphthyl)ethylamine Hydrochloride (1-NEA). Refer to general procedure for reduction of a nitrile to an amine hydrochloride: yellowish brown solid, 0.36 g, 59% yield. ^1H NMR (400 MHz, methanol-d_4) δ 8.09 (d, *J*=8.4 Hz, 1H), 7.90 (dd, *J*=8.2 Hz, 0.6 Hz, 1H), 7.82 (dd, *J*=6.0 Hz, 3.3 Hz, 1H), 7.58 (dd, *J*=6.8 Hz, 1.4 Hz, 1H), 7.51 (dd, *J*=6.8 Hz, 1.1 Hz, 1H), 7.45 (d, *J*=9.5 Hz, 1H), 7.44 (d, *J*=6.2 Hz, 1H), 3.46 (t, *J*=8.0 Hz, 2H), 3.27 (m, 2H). HRMS (EI^+) *m/z* for $C_{12}H_{14}N$ $[M + H]^+$: calcd, 172.1126; found, 172.1127.

Scheme 2-9. Synthesis of β-Phenylnaphethylamines (**ET-31**–**ET-33**)

(1-Methoxynaphthalen-4-yl)(phenyl)methanol (2.74). To a solution of 4-methoxynaphthaldehyde (0.50 g, 2.69 mmol) in THF @ 0°C was added PhMgBr (3.22 mL, 1.0 M in THF). After stirring at room temperature for 2 h, the reaction was quenched with MeOH and extracted with Et_2O. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give

the crude product. The crude mixture was purified via flash SiO_2 chromatography (EtOAc/hexanes (5%/95%) to (15%/85%)) to give **2.74** as a slightly yellow oil (0.72 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.31 (m, 1H), 8.03 (m, 1H), 7.45 (m, 5H), 7.33 (t, *J*=7.42 Hz, 2H), 7.26 (m, 1H), 6.79 (d, *J*=8.1 Hz, 1H), 6.47 (d, *J*=4.0 Hz, 1H), 4.01 (s, 3H), 2.25 (d, *J*=4.0, 1H).

(1-Hydroxynaphthalen-4-yl) phenylacetonitrile (2.75). Refer to general procedure for formation of a nitrile. No purification was necessary. **2.75** was obtained as a yellowish solid (0.73 g, 97% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.34 (m, 1H), 7.79 (m, 1H), 7.51 (m, 3H), 7.33 (m, 5H), 6.82 (d, *J*=8.1 Hz, 1H), 5.74 (s, 1H), 4.03 (s, 3H).

N-*t*-Boc-2-(1-hydroxynaphthalen-4-yl)-2-phenylethylamine (2.76). Refer to general procedure for *t*-Boc protection of an amine hydrochloride. The crude mixture was purified via flash SiO_2 column chromatography (EtOAc/hexanes (5%/95%) to (15%/85%)) to give **2.76** as a yellow foam (0.12 g, 61% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.22 (m, 1H), 8.02 (m, 1H), 7.45 (m, 2H), 7.26 (m, 4H), 7.19 (d, *J*=8.1 Hz, 2H), 6.81 (d, *J*= 7.9 Hz, 1H), 5.70 (br s, 1H), 4.85 (t, *J*=7.5 Hz, 1H), 4.62 (br s, 1H), 3.84 (m, 2H), 1.15 (s, 9H).

N-*t*-Boc-2-(1-phenoxynaphthalen-4-yl)-2-phenylethylamine (2.77). Refer to general procedure for formation of a biaryl ether. The crude mixture was purified via flash SiO_2 column chromatography (EtOAc/hexanes (10%/90%)) to give **2.77** as a slightly yellow oil (0.08 g, 55% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.26 (d, *J*=7.9 Hz, 1H), 8.11 (d, *J*=8.2 Hz, 1H), 7.49 (m, 3H), 7.35 (m, 2H), 7.28 (m, 4H), 7.21

(m, 1H), 7.12 (t, *J*=7.4 Hz, 1H), 7.06 (dd, *J*=8.6, 0.9 Hz, 2H), 6.91 (d, *J*=7.9 Hz, 1H), 4.94 (t, *J*=7.9 Hz, 1H), 4.61 (br s, 1H), 3.88 (m, 2H), 1.41 (s, 9H).

2-(1-Hydroxynaphthalen-4-yl)-2-phenylethylamine Hydrochloride (ET-31). To a solution of **ET-32** (0.24 g, 0.77 mmol) in dry $CHCl_3$ (7 mL) @ 0^oC was added BBr_3 (2.43 mL, 1.0 M solution in DCM). After stirring for 1 h at room temperature, the reaction was cooled to 0^oC and anhydrous MeOH (7.65 mL) was added. The reaction was refluxed in an open mouth flashed for 20 min before evaporating the solvent. The crude mixture was diluted with EtOAc and made alkaline with K_2CO_3. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Treatment with 3N anhydrous HCl in EtOAc and exposure to Et_2O precipitated the hydrochloride salts of **ET-31** as a brownish solid (0.16 g, 72% yield). ^1H NMR (400 MHz, methanol-d_4) δ 8.27 (d, *J*=8.4 Hz, 1H), 8.01 (d, *J*=9.0 Hz, 1H), 7.44 (m, 3H), 7.35 (m, 4H), 7.23 (m, 1H), 6.89 (d, *J*=7.9 Hz, 1H), 5.03 (t, *J*=8.0 Hz, 1H), 3.70 (m, 2H). HRMS (EI^+) *m/z* for $C_{18}H_{17}NO$ $[M + H]^+$: calcd, 264.1388; found, 264.1388.

2-(1-Methoxynaphthalen-4-yl)-2-phenylethylamine Hydrochloride (ET-32). Refer to general procedure for the reduction of a nitrile to an amine hydrochloride: 0.26 g, 31% yield. ^1H NMR (400 MHz, methanol-d_4) δ 8.28 (m, 1H), 8.04 (d, *J*=7.9 Hz, 1H), 7.47 (m, 3H), 7.35 (m, 4H), 7.24 (m, 1H), 6.97 (d, *J*=8.1 Hz, 1H), 5.05 (t, *J*=8.0 Hz, 1H), 4.03 (s, 3H), 3.72 (m, 2H). HRMS (EI^+) *m/z* for $C_{19}H_{19}NO$ $[M + H]^+$: calcd, 278.1545; found, 278.1550.

2-(1-Phenoxynaphthalen-4-yl)-2-phenylethylamine Hydrochloride (ET-33). Refer to general procedure for *t*-Boc deprotection: Slightly yellow solid, 0.58 g, 84% yield. ^1H NMR (400 MHz, methanol-d_4) δ 8.24 (m, 1H), 8.16 (d, *J*=7.9 Hz, 1H), 7.56

(m, 1H), 7.50 (m, 2H), 7.37 (m, 6H), 7.25 (m, 1H), 7.14 (m, 1H), 7.04 (m, 2H), 6.95 (d, *J*=8.1 Hz, 1H), 5.13 (t, *J*=7.9 Hz, 1H), 3.74 (m, 2H). HRMS (EI^+) *m/z* for $C_{24}H_{21}NO$ [M + H]$^+$: calcd, 340.1701; found, 340.1716.

A.1.3.2 Chapter 4 Compounds

Scheme 4-1. Synthesis of **ET-34–ET-38** and **ET-47**

(4-Methoxyphenyl)-(4-phenoxyphenyl)methanol (4.5). Refer to general procedure for formation of an organolithium and reaction with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (25%/75%)) to give **4.5** as a colorless oil (0.71 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28-7.24 (m, 6H), 7.09 (t, *J*=7.3 Hz, 1H), 6.90 (dd, *J*=8.6 Hz, 0.9 Hz, 2H), 6.97 (dt, *J*=8.6 Hz, 2.8 Hz, 2.0 Hz, 2H), 6.88 (dt, *J*=8.8 Hz, 2.94 Hz, 2.1 Hz, 2H), 5.80 (d, *J*=3.3 Hz, 1H), 3.80 (s, 3H), 2.12 (d, *J*=3.5 Hz, 1H).

(2-methoxyphenyl)-(4-phenoxyphenyl)methanol (4.6). Refer to general procedure for formation of an organolithium and reaction with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **4.6** as a slightly yellow solid (0.51 g, 92% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35 (d, *J*=9.0 Hz, 2H), 7.33 (dd, *J*=7.3 Hz, 1.3 Hz, 2H), 7.30 (m, 1H), 7.26 (m, 1H), 7.08 (t, *J*=7.4 Hz, 1H), 7.00 (dd, *J*=8.8 Hz, 1.1 Hz, 2H), 6.96 (d, *J*=8.8 Hz, 2H),6.96 (m, 1H), 6.90 (d, *J*=8.1 Hz, 1H), 6.05 (d, *J*=3.9 Hz, 1H), 3.83 (s, 3H), 2.99 (d, *J*=5.7 Hz, 1H).

Methyl-4-(hydroxy-(4-phenoxyphenyl)methyl)benzoate (4.7). To a solution of 4-Br-diphenyl ether (1.00 g, 4.01 mmol) in THF (30 mL) at -78^{o}C was added *n*-BuLi (2.09 mL, 5.22 mmol, 2.5M in hexanes). After stirring at -78^{o}C for 2 h, the reaction was

cooled to -100°C (Et_2O and dry ice bath) for 15 min. The reaction was then transferred via cannula to a solution of methyl-4-formylbenzoate (0.66 g, 4.01 mmol) in THF (10 mL) in a separate round bottom flask cooled to -100°C. The reaction was stirred at -100°C for 1 h and then warmed to -78°C for another hour. The reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **4.7** as a yellowish oil (0.44 g, 33% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.48 (d, *J*=8.2 Hz, 2H), 7.33 (t, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.11 (t, *J*=7.4 Hz, 1H), 7.00 (d, *J*=8.1 Hz, 2H), 6.97 (d, *J*=8.6 Hz, 2H), 5.89 (d, *J*=2.6 Hz, 1H), 3.91 (s, 3H), 2.25 (d, *J*=3.3 Hz, 1H).

(4-Cyanophenyl)-(4-phenoxyphenyl)methanol (4.8). To a solution of 4-Br-diphenyl ether (1.00 g, 4.01 mmol) in THF (30 mL) at -78°C was added *n*-BuLi (2.09 mL, 5.22 mmol, 2.5M in hexanes). After stirring at -78°C for 2 h, the reaction was cooled to -100°C (Et_2O and dry ice bath) for 15 min. The reaction was then transferred via cannula to a solution of 4-cyanobenzaldehyde (0.53 g, 4.01 mmol) in THF (10 mL) in a separate round bottom flask cooled to -100°C. The reaction was stirred at -100°C for 1 h and then warmed to -78°C for another hour. The reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **4.8** as a yellowish white solid (1.20 g, 99% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.64 (d, *J*=8.6 Hz, 2H), 7.52 (d, *J*=8.1 Hz, 2H), 7.34 (dd, *J*=8.4 Hz, 4.2 Hz, 2H), 7.28 (d, *J*=8.2 Hz, 2H),

7.12 (t, *J*=7.4 Hz, 1H), 7.00 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 5.87 (d, *J*=2.8 Hz, 1H), 2.28 (d, *J*=3.1 Hz, 1H).

2-(4-Methoxyphenyl)-2-(4-phenoxyphenyl)acetonitrile (4.9). Refer to general procedure for formation of a nitrile. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.9** as a yellowish solid (0.61 g, 84% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35 (t, *J*=7.9 Hz, 2H), 7.27 (t, *J*=7.2 Hz, 4H), 7.13 (t, *J*=7.3 Hz, 1H), 7.01 (d, *J*=8.2 Hz, 2H), 6.98 (d, *J*=8.8 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 5.08 (s, 1H), 3.81 (s, 3H).

2-(2-Methoxyphenyl)-2-(4-phenoxyphenyl)acetonitrile (4.10). Refer to general procedure for formation of a nitrile. The crude product was carried through with any further purification. Yellowish solid (0.52 g, 99% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.84 (m, 2H), 7.33 (dd, *J*=8.6 Hz, 2.8 Hz, 4H), 7.12 (t, *J*=7.4 Hz, 1H), 6.98-7.02 (m, 3H), 6.96 (d, *J*=8.6 Hz, 2H), 6.91 (d, *J*=8.2 Hz, 1H), 5.52 (s, 1H), 3.86 (s, 3H).

Methyl-4-(cyano-(4-phenoxyphenyl)-methyl)benzoate (4.11). Refer to general procedure for formation of a nitrile. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (10%/95%)) to give **4.11** as a yellowish solid (0.27 g, 60% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.05 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=8.2 Hz, 2H), 7.35 (t, *J*=7.9 Hz, 2H), 7.27 (d, *J*=8.6 Hz, 2H), 7.14 (t, *J*=7.4 Hz, 1H), 7.00 (t, *J*=8.9 Hz, 4H), 5.16 (s, 1H), 3.92 (s, 3H).

2-(4-Cyanophenyl)-2-(4-phenoxyphenyl)acetonitrile (4.12). Refer to general procedure for formation of a nitrile. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (10%/95%)) to give **4.12** as a colorless

oil (0.64 g, 74% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.69 (d, *J*=8.2 Hz, 2H), 7.49 (d, *J*=8.2 Hz, 2H), 7.36 (t, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.6 Hz, 2H), 7.15 (t, *J*=7.3 Hz, 1H), 7.01 (t, *J*=7.5 Hz, 4H), 5.16 (s, 1H).

2-(4-Methoxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-34). Refer to general procedure for reduction of a nitrile to an amine hydrochloride: brownish white solid, 88 mg, 25% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.33 (d, *J*=5.1 Hz, 2H), 7.31 (dd, *J*=7.0 Hz, 1.7 Hz, 2H), 7.27 (d, *J*=8.4 Hz, 2H), 7.09 (tt, *J*=7.3 Hz, 7.1 Hz, 1.1 Hz, 1H), 6.95 (dd, *J*=8.8 Hz, 1.1 Hz, 4H), 6.92 (d, *J*=8.8 Hz, 2H), 4.27 (t, *J*=8.2 Hz, 1H), 3.76 (s, 3H), 3.59 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 160.5, 158.1, 136.7, 133.4, 130.9, 130.3, 129.9, 124.5, 120.4, 120.1, 120.0, 115.5, 55.7, 49.1, 44.7. HRMS (EI$^+$) *m/z* for $C_{21}H_{22}NO_2$ [M + H]$^+$: calcd, 320.1651; found, 320.1653.

2-(2-Methoxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-35). Refer to general procedure for reduction of a nitrile to an amine hydrochloride: yellowish solid, 0.19 g, 33% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32 (d, *J*=8.4 Hz, 4H), 7.27 (m, 1H), 7.24 (m, 1H), 7.08 (t, *J*=7.4 Hz, 1H), 6.99 (d, *J*=9.0 Hz, 2H), 6.93-6.96 (m, 4H), 4.72 (t, *J*=8.1 Hz, 1H), 3.83 (s, 3H), 3.60 (dd, *J*=7.9 Hz, 5.7 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 153.5, 158.4, 157.9, 135.9, 130.9, 130.7, 129.9, 129.4, 129.0, 124.5, 122.0, 120.0, 119.9, 112.4, 56.0, 43.9, 43.4. HRMS (EI$^+$) *m/z* for $C_{21}H_{22}NO_2$ [M + H]$^+$: calcd, 320.1651; found, 320.1651.

2-(4-Hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-36). To a solution of **ET-34** (0.07 g, 0.20 mmol) in $CHCl_3$ (2 mL) at 0^{o}C was added dropwise BBr_3 (0.63 mL, 0.63 mmol, 1M in DCM). After stirring at room temperature for 1h, the reaction was cooled to 0^{o}C and diluted with anhydrous MeOH (2 mL). The

reaction was refluxed in an open mouthed flask for 20 min, diluted with EtOAc, and made basic (pH~8-10) with K_2CO_3. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was treated with a 3N anhydrous HCl solution in EtOAc (1 mL), exposed to Et_2O, and the resulting amine hydrochloride salts were washed with Et_2O. **ET-36** was obtained as a brownish solid (56 mg, 83% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.33 (dd, J=8.8 Hz, 7.6 Hz, 2H), 7.30 (d, J=8.6 Hz, 2H), 7.17 (d, J=8.6 Hz, 2H), 7.10 (t, J=7.5 Hz, 1H), 6.96 (d, J=8.6 Hz, 4H), 6.79 (d, J=8.8 Hz, 2H), 4.19 (t, J=8.2 Hz, 1H), 3.56 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 158.5, 158.1, 136.9, 132.0, 130.9, 130.2, 129.9, 124.6, 120.1, 120.0, 116.9, 48.8, 44.8. HRMS (EI$^+$) *m/z* for $C_{20}H_{20}NO_2$ $[M + H]^+$: calcd, 306.1494; found, 306.1490.

2-(2-Hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-37). To a solution of **ET-35** (0.17 g, 0.48 mmol) in $CHCl_3$ (5 mL) at 0^{o}C was added dropwise BBr_3 (1.53 mL, 1.53 mmol, 1M in DCM). After stirring at room temperature for 1h, the reaction was cooled to 0^{o}C and diluted with anhydrous MeOH (4.8 mL). The reaction was refluxed in an open mouthed flask for 20 min, diluted with EtOAc, and made basic (pH~8-10) with K_2CO_3. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was treated with a 3N anhydrous HCl solution in EtOAc (1 mL), exposed to Et_2O, and the resulting amine hydrochloride salts were washed with Et_2O. **ET-37** was obtained as a yellowish solid (0.13 g, 79% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.38 (d, J=8.8 Hz, 2H), 7.35 (dd, J=8.6 Hz, 7.6 Hz, 2H), 7.10-7.16 (m, 3H), 6.98-7.01 (m, 4H), 6.86 (d, J=7.6 Hz, 1H), 6.84 (m, 1H), 4.70 (t, J=8.1 Hz, 1H), 3.68 (dd, J=12.6 Hz, 7.8 Hz, 1H),

3.58 (dd, *J*=12.8 Hz, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 158.6, 158.0, 156.3, 136.1, 130.9, 130.8, 129.6, 129.4, 127.6, 124.5, 121.0, 120.0, 119.9, 116.6, 48.8, 43.9. HRMS (EI$^+$) *m/z* for $C_{20}H_{20}NO_2$ $[M + H]^+$: calcd, 306.1494; found, 306.1490.

2-(4-Hydroxymethylphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-38). Refer to general procedure for reduction of a nitrile to an amine hydrochloride: yellowish solid, 9.5 mg, 3% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.35 (d, *J*=5.7 Hz, 4H), 7.32 (d, *J*=8.6 Hz, 4H), 7.10 (tt, *J*=7.1 Hz, 6.7 Hz, 1.1 Hz, 1H), 6.96 (dd, *J*=8.6 Hz, 1.7 Hz, 4H), 4.58 (s, 2H), 4.28 (t, *J*=8.2 Hz, 1H), 3.61 (d, *J*=8.2 Hz, 2H).

2-(4-Aminomethylphenyl)-2-(4-phenoxyphenyl)ethylamine Dihydrochloride (ET-47). Refer to general procedure for nitrile reduction and subsequent *t*-Boc protection of amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)). The desired product was treated with a 3N anhydrous HCl solution in EtOAc (0.5 mL), exposed to Et_2O, and the resulting amine hydrochloride salts were washed with Et_2O. **ET-47** was obtained as a white solid (12 mg, 25% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.46 (d, *J*=1.3 Hz, 4H), 7.34 (t, *J*=8.7 Hz, 4H), 7.11 (tt, *J*=7.4 Hz, 7.1 Hz, 1.1 Hz, 1H), 6.94-6.98 (m, 4H), 4.35 (t, *J*=8.2 Hz, 1H), 4.10 (s, 2H), 3.65 (dq, *J*=23.4 Hz, 12.7 Hz, 8.4 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 158.5, 158.3, 143.1, 135.7, 133.7, 130.9, 130.8, 130.5, 129.6, 124.7, 120.2, 120.1, 49.7, 44.3, 43.9.

Scheme 4-2. Synthesis of **ET-65–ET-67**

(3-Benzyloxyphenyl)-(4-phenoxyphenyl)methanol (4.17). Refer to general procedure for formation of an organolithium and reaction with an aldehyde. The crude

product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (2%/98%) to (15%/85%)) to give **4.17** as a white solid (6.56 g, 75% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.42 (dd, *J*=8.2 Hz, 2.1 Hz, 2H), 7.38 (dd, *J*=8.4 Hz, 1.5 Hz, 2H), 7.30-7.36 (m, 6H), 7.26 (t, *J*=7.9 Hz, 1H), 7.10 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.04 (t, *J*=2.1 Hz, 1H), 6.99 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.96 (d, *J*=8.8 Hz, 2H), 6.88 (dq, *J*=8.1 Hz, 2.7 Hz, 0.8 Hz, 1H), 5.80 (s, 1H), 5.05 (s, 2H), 2.17 (d, *J*=2.8 Hz, 1H).

(4-Fluorophenyl)-(4-phenoxyphenyl)methanol (4.18). Refer to general procedure for formation of an organolithium and reaction with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (20%/80%)) to give **4.18** as a colorless oil (1.25 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38-7.31 (m, 4H), 7.31 (d, *J*=8.8 Hz, 2H), 7.10 (t, *J*=7.4 Hz, 1H), 7.04 (d, *J*=8.8 Hz, 2H), 6.99-7.02 (m, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 5.83 (s, 1H), 2.17 (d, *J*=2.2 Hz, 1H).

(3-Fluorophenyl)-(4-phenoxyphenyl)methanol (4.19). Refer to general procedure for formation of an organolithium and reaction with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **4.19** as a yellow oil (1.18 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28-7.36 (m, 5H), 7.15 (d, *J*=8.6 Hz, 1H), 7.12 (m, 1H), 7.11 (tt, *J*=7.7 hz, 7.4 Hz, 1.1 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.2 Hz, 2H), 6.97 (d, *J*=8.6 Hz, 2H), 6.95 (m, 1H), 5.82 (s, 1H), 2.22 (s, 1H).

(2-Fluorophenyl)-(4-phenoxyphenyl)methanol (4.20). Refer to general procedure for formation of an organolithium and reaction with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to

(20%/80%)) to give **4.20** as a yellow oil (1.10 g, 92% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.53 (dt, *J*=7.4 Hz, 1.6 Hz, 1H), 7.36 (d, *J*=8.8 Hz, 2H), 7.32 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.24-7.30 (m, 1H), 7.17 (dt, *J*=7.5 Hz, 1.2 Hz, 1H), 7.10 (tt, *J*=7.7 Hz, 7.3 Hz, 1.1 Hz, 1H), 7.01-7.05 (m, 1H), 7.00 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 6.13 (d, *J*=2.2 Hz, 1H), 2.25 (d, *J*=3.3 Hz, 1H).

(3-Benzyloxyphenyl)-(4-phenoxyphenyl)methanone (4.21). Refer to general procedure for Mn_2O oxidation of an alcohol. Crude product of **4.21** was obtained as a colorless oil (6.51 g, 98% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.79 (d, *J*=8.8 Hz, 2H), 7.30-7.45 (m, 10H), 7.18-7.23 (m, 2H), 7.09 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 7.00 (d, *J*=9.0 Hz, 2H), 5.12 (s, 2H).

(4-Fluorophenyl)-(4-phenoxyphenyl)methanone (4.22). Refer to general procedure for Mn_2O oxidation of an alcohol. Crude product of **4.22** was obtained as a colorless oil (1.22 g, 98% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.82 (dd, *J*=8.6 Hz, 5.5 Hz, 2H), 7.79 (d, *J*=8.6 Hz, 2H), 7.41 (t, *J*=7.9 Hz, 2H), 7.21 (t, *J*=7.4 Hz, 1H), 7.16 (t, *J*=8.6 Hz, 2H), 7.10 (d, *J*=8.2 Hz, 2H), 7.04 (d, *J*=8.6 Hz, 2H).

(3-Fluorophenyl)-(4-phenoxyphenyl)methanone (4.23). Refer to general procedure for Mn_2O oxidation of an alcohol. Crude product of **4.23** was obtained as a yellowish solid (1.14 g, 97% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.81 (d, *J*=8.8 Hz, 2H), 7.55 (d, *J*=7.5 Hz, 1H), 7.39-7.48 (m, 4H), 7.27 (dt, *J*=8.3 Hz, 2.7 Hz, 1H), 7.22 (t, *J*=7.2 Hz, 1H), 7.10 (d, *J*=8.2 Hz, 2H), 7.04 (d, *J*=8.6 Hz, 2H).

(2-Fluorophenyl)-(4-phenoxyphenyl)methanone (4.24). Refer to general procedure for Mn_2O oxidation of an alcohol. Crude product of **4.24** was obtained as a colorless oil (1.04 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.82 (dd, *J*=8.9

Hz, 1.2 Hz, 2H), 7.48-7.55 (m, 2H), 7.40 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 7.26 (dt, *J*=7.5 Hz, 0.9 Hz, 1H), 7.21 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.15 (t, *J*=9.0 Hz, 1H), 7.09 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 7.00 (d, *J*=9.0 Hz, 2H).

2-Methoxy-(1-(3-benzyloxyphenyl)-1-(4-phenoxyphenyl))ethene (4.25). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (6%/94%)) to give **4.25** as a yellow oil (6.52 g, 92% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29-7.43 (m, 8H), 7.18-7.26 (m, 1H), 7.16 (d, *J*=8.6 Hz, 1H), 7.09 (t, *J*=7.4 Hz, 1H), 7.05 (dd, *J*=8.5 Hz, 1.0 Hz, 2H), 7.00 (m, 1H), 6.93 (dd, *J*=9.8 Hz, 8.7 Hz, 2H), 6.85 (t, *J*=7.6 Hz, 2H), 6.43; 6.41 (s, 1H), 5.03 (s, 2H), 3.76; 3.75 (s, 3H).

2-Methoxy-(1-(4-fluorophenyl)-1-(4-phenoxyphenyl))ethene (4.26). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (2%/98%)) to give **4.26** as a white solid (1.27 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31-7.38 (m, 4H), 7.18 (dd, *J*=9.0 Hz, 5.5 Hz, 1H), 7.15 (d, *J*=8.8 Hz, 1H), 7.10 (m, 1H), 7.03 (m, 2H), 7.00 (dd, *J*=8.8 Hz, 1.8 Hz, 2H), 6.94 (dd, *J*=8.8 Hz, 6.8 Hz, 2H), 6.41; 6.36 (s, 1H), 3.77; 3.76 (s, 3H).

2-Methoxy-(1-(3-fluorophenyl)-1-(4-phenoxyphenyl))ethene (4.27). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (1%/99%)) to give **4.27** as a yellow oil (1.18 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (m, 1H), 7.33 (d, *J*=8.6 Hz, 2H), 7.16 (d, *J*=8.6 Hz, 2H), 7.15 (m, 1H), 7.10 (t, *J*=7.4 Hz, 1H), 7.04

(dt, *J*=7.6 Hz, 1.2 Hz, 2H), 7.01 (m, 1H), 6.95 (t, *J*=8.5 Hz, 2H), 6.91 (m, 1H), 6.46; 6.42 (s, 1H), 3.79; 3.78 (s, 3H).

2-Methoxy-(1-(2-fluorophenyl)-1-(4-phenoxyphenyl))ethene (4.28). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (1%/99%)) to give **4.28** as a yellow oil (1.11 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38 (d, *J*=9.0 Hz, 1H), 7.32 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.19-7.29 (m, 2H), 7.13 (d, *J*=9.0 Hz, 2H), 7.09 (d, *J*=7.3 Hz, 1H), 7.06 (m, 1H), 7.01 (m, 2H), 6.92 (dd, *J*=10.3 Hz, 9.0 Hz, 2H), 6.61; 6.39 (s, 1H), 3.80; 3.75 (s, 3H).

2-(3-Benzyloxyphenyl)-2-(4-phenoxyphenyl)ethanol (4.29). Refer to general procedure for methyl enol ether deprotection. The crude product was subsequently dissolved in EtOH/Et_2O (75 mL/25 mL) and treated with $NaBH_4$ (1 equiv). After stirring at room temperature for 10 min, the reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **4.29** as a colorless oil (2.05 g, 48% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41 (m, 2H), 7.38 (m, 2H), 7.33 (m, 1H), 7.32 (dd, *J*=8.8 Hz, 7.3 Hz, 2H), 7.25 (t, *J*=8.2 Hz, 1H), 7.20 (d, *J*=8.6 Hz, 2H), 7.09 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.99 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.95 (d, *J*=8.6 Hz, 2H), 6.88 (dd, *J*=6.2 Hz, 1.6 Hz, 2H), 6.86 (dq, *J*=8.1 Hz, 2.6 Hz, 0.9 Hz, 1H), 5.04 (s, 2H), 4.11-4.18 (m, 3H), 1.47 (br s, 1H).

2-(3-Benzyloxyphenyl)-2-(4-phenoxyphenyl)ethyl Methanesulfonate (4.30). To a solution of **4.29** (19 mg, 0.04 mmol) in DCM (0.5 mL) at 0^{o}C was added Et_3N (5.4

mg, 0.05 mmol) and methanesulfonyl chloride (6.1 mg, 0.05 mmol). After stirring at room temperature for 15 min, the reaction was quenched with water and diluted with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%)) to give **4.30** as a colorless oil (21 mg, 90% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31-7.42 (m, 7H), 7.25 (t, *J*=7.9 Hz, 1H), 7.18 (d, *J*=8.6 Hz, 2H), 7.10 (t, *J*=7.7 Hz, 1H), 6.99 (d, *J*=8.6 Hz, 2H), 6.94 (d, *J*=8.4 Hz, 2H), 6.85-6.88 (m, 3H), 5.04 (s, 2H), 4.68 (d, *J*=7.7 Hz, 2H), 4.36 (t, *J*=7.5 Hz, 1H), 2.77 (s, 3H).

2-(3-Benzyloxyphenyl)-2-(4-phenoxyphenyl)ethyl Azide (4.31). To a solution of **4.30** (0.18 g, 0.37 mmol) in DMF (4 mL) was added NaN_3 (0.12 g, 1.87 mmol). After stirring at 100^{o}C for 21 h, the reaction was diluted with DCM. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (1%/99%) to (5%/95%)) to give **4.31** as a colorless oil (0.11 g, 71% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41 (m, 2H), 7.37 (m, 2H), 7.32 (m, 3H), 7.25 (m, 1H), 7.18 (d, *J*=8.6 Hz, 2H), 7.09 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 6.85-6.88 (m, 3H), 5.03 (s, 2H), 4.17 (t, *J*=7.7 Hz, 1H), 3.83 (d, *J*=8.1 Hz, 2H).

N-*t*-Boc-2-(3-hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine (4.32). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. Compound **4.31** was hydrogenated in a solution of EtOH/EtOAc (10 mL/3 mL). The crude product was immediately *t*-Boc protected following the general procedure for *t*-Boc protection for a

free amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (25%/75%)) to give **4.32** as a white foam (0.90 g, 71% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.5 Hz, 7.6 Hz, 2H), 7.18 (m, 1H), 7.17 (d, *J*=8.8 Hz, 2H), 7.09 (t, *J*=7.4 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=7.9 Hz, 1H), 6.69-6.71 (m, 2H), 5.05 (br s, 1H), 4.52 (br s, 1H), 4.06 (t, *J*=7.2 Hz, 1H), 3.71 (t, *J*=6.7 Hz, 2H), 1.41 (s, 9H).

2-(3-Hydroxyoxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-65). Refer to general procedure for *t*-Boc deprotection: white solid, 30 mg, 90% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.34 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 7.32 (d, *J*=8.6 Hz, 2H), 7.19 (t, *J*=7.7 Hz, 1H), 7.11 (t, *J*=7.4 Hz, 1H), 6.98 (d, *J*=8.6 Hz, 2H), 6.97 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.82 (d, *J*=7.5 Hz, 1H), 6.74 (t, *J*=2.0 Hz, 1H), 6.71 (dq, *J*=8.1 Hz, 2.4 Hz, 0.7 Hz, 1H), 4.19 (t, *J*=8.2 Hz, 1H), 3.58 (d, *J*=8.2 Hz, 2H). HRMS (EI^+) *m/z* for $C_{20}H_{20}NO_2$ $[M + H]^+$: calcd, 306.1494; found, 306.1494.

2-(4-Fluorophenyl)-2-(4-phenoxyphenyl)acetaldehyde (4.33). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (15%/85%)) to give **4.33** as a yellow oil (0.97 g, 80% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.91 (d, *J*=2.2 Hz, 1H), 7.35 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.10-7.21 (m, 5H), 7.08 (t, *J*=8.7 Hz, 2H), 7.02 (dd, *J*=8.7 Hz, 1.2Hz, 2H), 7.01 (d, *J*=8.8 Hz, 2H), 4.86 (d, *J*=2.0 Hz, 1H).

2-(3-Fluorophenyl)-2-(4-phenoxyphenyl)acetaldehyde (4.34). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.34** as a yellowish oil (0.77 g, 73% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.91 (d, *J*=2.4 Hz, 1H), 7.32-7.38

(m, 2H), 7.35 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H), 7.11-7.15 (m, 2H), 7.03 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 7.02 (d, *J*=8.8 Hz, 2H), 6.93 (dq, *J*=9.3 Hz, 2.1 Hz, 1H), 4.87 (d, *J*=2.2 Hz, 1H).

2-(2-Fluorophenyl)-2-(4-phenoxyphenyl)acetaldehyde (4.35). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.35** as a colorless oil (0.82 g, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.95 (t, *J*=1.5 Hz, 1H), 7.34 (dd, *J*=8.3 Hz, 7.6 Hz, 2H), 7.31 (m, 1H), 7.19 (d, *J*=8.6 Hz, 2H), 7.10-7.16 (m, 4H), 7.04 (d, *J*=7.5 Hz, 2H), 7.01 (d, *J*=8.6 Hz, 2H), 5.13 (s, 1H).

N-Benzyl -2-(4-fluorophenyl)-2-(4-phenoxyphenyl)ethylamine (4.36). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **4.36** as a colorless oil (0.64 g, 51% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29-7.35 (m, 4H), 7.23-7.25 (m, 2H), 7.17 (dd, *J*=8.8 Hz, 5.5 Hz, 2H), 7.16 (m, 1H), 7.14 (d, *J*=8.6 Hz, 2H), 7.09 (t, *J*=7.3 Hz, 1H), 6.96-7.01 (m, 4H), 6.92 (d, *J*=8.6 Hz, 2H), 4.18 (t, *J*=7.7 Hz, 1H), 3.82 (s, 2H), 3.18 (d, *J*=7.9 Hz, 2H).

N-Benzyl -2-(3-fluorophenyl)-2-(4-phenoxyphenyl)ethylamine (4.37). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (15%/85%)) to give **4.37** as a colorless oil (0.38 g, 36% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28-7.35 (m, 4H), 7.22-7.25 (m, 3H), 7.15 (d, *J*=8.8 Hz, 2H), 7.09 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.01 (m, 1H), 6.99 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 6.87-6.93 (m, 3H), 4.19 (t, *J*=7.6 Hz, 1H), 3.82 (s, 2H), 3.19 (d, *J*=7.7 Hz, 2H).

N-Benzyl -2-(2-fluorophenyl)-2-(4-phenoxyphenyl)ethylamine (4.38). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (15%/85%)) to give **4.38** as a colorless oil (0.60 g, 52% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.18-7.35 (m, 11H), 7.08 (dt, *J*=7.4 Hz, 1.0 Hz, 2H), 7.02 (m, 1H), 6.98 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.92 (d, *J*=8.8 Hz, 2H), 4.55 (t, *J*=7.7 Hz, 1H), 3.83 (s, 2H), 3.23 (d, *J*=7.5 Hz, 2H).

N-*t*-Boc-2-(4-fluorophenyl)-2-(4-phenoxyphenyl)ethylamine (4.39). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. The crude product was immediately *t*-Boc protected following the general procedure for *t*-Boc protection for a free amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **4.39** as a colorless oil/white solid (0.44 g, 70% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 7.19 (dd, *J*=8.6 Hz, 5.4 Hz, 2H), 7.16 (d, *J*=8.6 Hz, 2H), 7.10 (t, *J*=7.4 Hz, 1H), 7.01 (d, *J*=8.6 Hz, 2H), 7.00 (m, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 4.49 (br s, 1H), 4.13 (t, *J*=7.9 Hz, 1H), 3.71 (t, *J*=6.8 Hz, 2H), 1.41 (s, 9H).

N-*t*-Boc-2-(3-fluorophenyl)-2-(4-phenoxyphenyl)ethylamine (4.40). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. The crude product was immediately *t*-Boc protected following the general procedure for *t*-Boc protection for a free amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.40** as a colorless oil (0.23 g, 60% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.28 (m, 1H), 7.17 (d, *J*=8.4 Hz, 2H), 7.10 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.03 (d, *J*=8.6 Hz,

1H), 7.00 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.95 (d, *J*=8.8 Hz, 2H), 6.90-6.93 (m, 2H), 4.50 (br s, 1H), 4.15 (t, *J*=7.4 Hz, 1H), 3.72 (t, *J*=6.8 Hz, 2H), 1.41 (s, 9H).

N-*t*-Boc-2-(2-fluorophenyl)-2-(4-phenoxyphenyl)ethylamine (4.41). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was immediately *t*-Boc protected following the general procedure for *t*-Boc protection for a free amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.41** as a colorless oil (0.43 g, 70% yield). The purified product appears to be a mixture of **4.41** and an unidentified product.

2-(4-Fluorophenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-66). Refer to general procedure for *t*-Boc deprotection: white solid, 0.33 g, 90% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.37 (dd, *J*=8.8 Hz, 5.3 Hz, 2H), 7.34 (m, 2H), 7.32 (d, *J*=8.8 Hz, 2H), 7.11 (m, 1H), 7.11 (t, *J*=8.8 Hz, 2H), 6.98 (d, *J*=8.6 Hz, 2H), 6.97 (m, 2H), 4.28 (t, *J*=8.2 Hz, 1H), 3.61 (d, *J*=8.3 Hz, 2H). HRMS (EI^+) *m/z* for $C_{20}H_{19}NOF$ $[M + H]^+$: calcd, 308.1451; found, 308.1448.

2-(3-Fluorophenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-67). Refer to general procedure for *t*-Boc deprotection: white solid, 0.18 g, 93% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32-7.42 (m, 3H), 7.34 (d, *J*=8.6 Hz, 2H), 7.18 (d, *J*=7.7 Hz, 1H), 7.09-7.14 (m, 2H), 7.03 (m, 1H), 6.99 (d, *J*=8.6 Hz, 2H), 6.98 (m, 2H), 4.29 (t, *J*=8.2 Hz, 1H), 3.63 (d, *J*=8.4 Hz, 2H). HRMS (EI^+) *m/z* for $C_{20}H_{19}NOF$ $[M + H]^+$: calcd, 308.1451; found, 308.1444.

Scheme 4-3. Synthesis of **ET-50** and **ET-71**

Bis(4-Triisopropylsiloxyphenyl)methanone (4.44). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.44** as a colorless oil (4.91 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.72 (dt, *J*=9.0 Hz, 2.7 Hz, 2.2 Hz, 4H), 6.93 (dt, *J*=8.8 Hz, 2.7 Hz, 2.2 Hz, 4H), 1.30 (m, 6H), 1.12 (d, *J*=7.3 Hz, 36H).

(4-(*tert*-Butyldimethylsiloxy)phenyl)-(phenyl)methanone (4.45). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.45** as a colorless oil (1.59 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.77 (d, *J*=8.4 Hz, 2H), 7.76 (dd, *J*=8.4 Hz, 1.3 Hz, 2H), 7.56 (tt, *J*=8.2 Hz, 7.4 Hz, 1.2 Hz, 1H), 7.47 (t, *J*=7.4 Hz, 2H), 6.90 (dt, *J*=8.6 Hz, 2.8 Hz, 1.9 Hz, 2H), 1.00 (s, 9H), 0.25 (s, 6H).

2-Methoxy-(1,1-bis(4-Triisopropylsiloxyphenyl))ethene (4.46). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (2%/98%)) to give **4.46** as a yellow oil (4.76 g, 92% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.24 (d, *J*=9.2 Hz, 2H), 7.05 (dt, *J*=8.6 Hz, 2.9 Hz, 2.1 Hz, 2H), 6.79 (dd, *J*=8.8 Hz, 7.0 Hz, 4H), 6.29 (s, 1H), 3.73 (s, 3H), 1.26 (sep, *J*=7.4 Hz, 6H), 1.10 (d, *J*=7.1 Hz, 36H).

2-Methoxy-((1-(4-(tert-butyldimethylsiloxy)phenyl))-1-(phenyl))ethene (4.47). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (2%/98%)) to give **4.47** as a yellow oil (1.61 g, 93% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.37

(dd, *J*=8.2 Hz, 1.5 Hz, 1H), 7.20-7.33 (m, 5H), 7.06 (dt, *J*=8.6 Hz, 2.9 Hz, 2.1 Hz, 1H), 6.78 (dt, *J*=8.6 Hz, 2.9 Hz, 2.0 Hz, 1H), 6.75 (dt, *J*=8.4 Hz, 2.9 Hz, 2.0 Hz, 1H), 6.37; 6.39 (s, 1H), 3.76; 3.74 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H).

2,2-Bis(4-hydroxy)phenylacetaldehyde (4.48). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (30%/70%)) to give **4.48** as a reddish yellow oil (0.95 g, 49% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.87 (d, *J*=2.4 Hz, 1H), 7.07 (dt, *J*=8.6 Hz, 2.9 Hz, 1.9 Hz, 4H), 6.84 (dt, *J*=8.6 Hz, 2.9 Hz, 2.1 Hz, 4H), 6.72 (s, 1H), 4.76 (d, *J*=2.4 Hz, 1H), 4.73 (s, 1H).

2-(4-Hydroxyphenyl)-2-(phenyl)acetaldehyde (4.49). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%)) to give **4.49** as a yellow oil (0.66 g, 82% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.91 (d, *J*=2.6 Hz, 1H), 7.38 (tt, *J*=7.3 Hz, 7.2 Hz, 1.6 Hz, 2H), 7.31 (tt, *J*=8.3 Hz, 7.3 Hz, 1.4 Hz, 1H), 7.21 (dd, *J*=7.1 Hz, 1.7 Hz, 2H), 7.09 (dt, *J*=8.2 Hz, 3.1 Hz, 1.9 Hz, 2H), 6.84 (dt, *J*=8.8 Hz, 2.9 Hz, 2.2 Hz, 2H), 4.91 (s, 1H), 4.83 (t, *J*=2.6 Hz, 1H),

N-Benzyl-2,2-di-(4-hydroxy)phenylethylamine (4.50). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%) to (50%/50%)) to give **4.50** as a brownish foam (1.21 g, 91% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.19-7.32 (m, 5H), 7.00 (dt, *J*=8.4 Hz, 2.9 Hz, 1.8 Hz, 4H), 6.70 (dt, *J*=8.6 Hz, 3.0 Hz, 2.1 Hz, 4H), 4.00 (t, *J*=7.8 Hz, 1H), 3.74 (s, 2H), 3.07 (d, *J*=8.1 Hz, 2H).

N-Benzyl-2-(4-hydroxyphenyl)-2-phenylethylamine (4.51). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%) to (50%/50%)) to give **4.51** as a brownish foam (0.40 g, 43% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.17-7.31 (m, 10H), 7.03 (d, *J*=8.6 Hz, 2H), 6.68 (d, *J*=8.6 Hz, 2H), 4.16 (t, *J*=7.8 Hz, 1H), 3.81 (s, 2H), 3.19 (d, *J*=7.7 Hz, 2H).

N-*t*-Boc-2,2-di-(4-Hydroxy)phenylethylamine (4.52). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$. The crude product was *t*-Boc protected following the general procedure for *t*-Boc protection of free amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%) to (40%/60%)) to give **4.52** as a clear oil/white foam (0.33 g, 59% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.03 (dt, *J*=8.3 Hz, 2.9 Hz, 1.7 Hz, 4H), 6.76 (dt, *J*=8.6 Hz, 2.8 Hz, 2.1 Hz, 4H), 5.27 (br s, 2H), 4.52 (br s, 1H), 4.00 (t, *J*=7.8 Hz, 1H), 3.66 (t, *J*=6.5 Hz, 2H), 1.41 (s, 9H).

2,2-Di-(4-hydroxy)phenylethylamine Hydrochloride (ET-50). Refer to general procedure for *t*-Boc deprotection: white solid, 0.15 g, 59% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.12 (dt, *J*=8.4 Hz, 3.1 Hz, 2.0 Hz, 4H), 6.77 (dt, *J*=8.6 Hz, 2.9 Hz, 2.0 Hz, 4H), 4.08 (t, *J*=8.3 Hz, 1H), 3.49 (d, *J*=8.2 Hz, 2H). HRMS (EI^+) *m/z* for $C_{14}H_{16}NO_2$ $[M + H]^+$: calcd, 230.1181; found, 320.1176.

2-(4-Hydroxyphenyl)-2-phenylethylamine Hydrochloride (ET-71). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$. The crude product treated with a 3N anhydrous HCl solution in EtOAc (1 mL), exposed to Et_2O, and the resulting amine hydrochloride salts were washed with Et_2O. **ET-71** was obtained as a

brownish powder (0.24 g, 72% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.27-7.34 (m, 4H), 7.22 (tt, *J*=7.5 Hz, 6.9 Hz, 1.7 Hz, 1H), 7.12 (dt, *J*=8.6 Hz, 3.0 Hz, 2.1 Hz, 2H), 6.75 (dt, *J*=8.6 Hz, 3.0 Hz, 2.0 Hz, 2H), 4.17 (t, *J*=8.2 Hz, 1H), 3.53 (d, *J*=8.2 Hz, 2H). HRMS (EI$^+$) *m/z* for $C_{14}H_{16}NO$ $[M + H]^+$: calcd, 214.1232; found, 214.1227.

Scheme 4-4. Synthesis of **ET-64**

N-Methoxy-N-methyl-4-phenoxybenzamide (4.54). Refer to general procedure for amide bond formation with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%)) to give **4.54** as a yellow oil (0.52 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.72 (d, *J*=9.0 Hz, 2H), 7.37 (dd, *J*=8.4 Hz, 7.5 Hz, 2H), 7.17 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.06 (dd, *J*=8.7 Hz, 1.2 Hz, 2H), 6.98 (d, *J*=9.0 Hz, 2H), 3.58 (s, 3H), 3.36 (s, 3H).

(4-Phenoxyphenyl)-(4-(triisopropylsiloxy)phenyl)methanone (4.55). To a solution of 4-(TIPSO)PhBr (2.82 g, 8.55 mmol) in THF (30 mL) at -78^{o}C was added *n*-BuLi (4.14 mL, 10.34 mmol) dropwise over 10 min. After stirring at -78^{o}C for 20 min, the reaction was transferred via cannula to a separate round bottom flask containing a solution of **4.54** (2.0 g, 7.77 mmol) in THF (15 mL) at -78^{o}C. After stirring at -78^{o}C for 15 min and at room temperature for 15 min, the reaction was quenched with 1N HCl (90 mL) and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (3%/97%) to (5%/95%)) to give **4.55** as a yellow oil (2.81 g, 81% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.78 (d, *J*=9.0 Hz, 2H), 7.74 (d, *J*=8.8 Hz, 2H), 7.40 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 7.19 (tt, *J*=7.7

Hz, 7.4 Hz, 1.1 Hz, 1H), 7.09 (dd, *J*=8.7 Hz, 1.2 Hz, 2H), 7.03 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 1.30 (sep, *J*=7.4 Hz, 3H), 1.12 (d, *J*=7.3 Hz, 18H).

2-Methoxy-(1-(4-phenoxyphenyl)-1-(4-(triisopropylsiloxy)phenyl))ethene (4.56). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (1%/99%)) to give **4.56** as a yellow oil (2.242 g, 81% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35 (d, *J*=8.8 Hz, 1H), 7.32 (dd, *J*=7.3 Hz, 2.2 Hz, 2H), 7.26 (d, *J*=8.6 Hz, 1H), 7.17 (d, *J*=8.6 Hz, 1H), 7.01-7.11 (m, 4H), 6.93 (dd, *J*=8.8 Hz, 6.8 Hz, 2H), 6.81 (t, *J*=8.7 Hz, 2H), 6.35; 6.33 (s, 1H), 3.75 (s, 3H), 1.26 (sep, *J*=7.4 Hz, 3H), 1.10 (d, *J*=7.3 Hz, 18H).

2-(4-Hydroxyphenyl)-2-(4-phenoxyphenyl)acetaldehyde (4.57). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **4.57** as a yellow oil (0.98 g, 68% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.89 (d, *J*=2.4 Hz, 1H), 7.34 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 7.15 (m, 1H), 7.10 (d, *J*=8.2 Hz, 2H), 7.01 (t, *J*=8.8 Hz, 4H), 6.85 (d, *J*=8.6 Hz, 2H), 4.85 (s, 1H), 4.81 (d, *J*=2.4 Hz, 1H).

N-(1-(*S*)-Phenylethyl)-2-(4-hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine (4.58). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (40%/60%)) to give **4.58** as a pink foam (0.95 g, 72% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28-7.33 (m, 4H), 7.21-7.25 (m, 3H), 7.09 (m, 1H), 7.09 (dd, *J*=8.6 Hz, 4.2 Hz, 2H), 7.02 (t, *J*=8.1 Hz, 2H), 6.97 (tt, *J*=7.7 Hz, 1.1 Hz, 2H), 6.89 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 6.72 (t, *J*=8.4 Hz, 2H),

4.08 (q, *J*=7.8 Hz, 1H), 3.78 (dq, *J*=13.2 Hz, 6.6 Hz, 2.3 Hz, 1H), 3.04 (dq, *J*=11.7 Hz, 7.3 Hz, 3.5 Hz, 1H), 2.98 (dd, *J*=11.6 Hz, 8.5 Hz, 1H), 1.31 (d, *J*=6.6 Hz, 3H).

N-Methyl-N-(1-(*S*)-phenylethyl)-2-(4-hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine (4.59). To a solution of **4.58** in formic acid at 0°C was added formaldehyde. After stirring the reaction at 80°C for 22 hrs, the reaction was cooled, diluted with DCM, and made basic (pH ~8-10) with K_2CO_3. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%)) to give **4.59** as a yellowish foam/colorless oil (0.16 g, 80% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29-7.38 (m, 3H), 7.22 (dd, *J*=12.5 Hz, 6.7 Hz, 2H), 7.15 (d, *J*=6.6 Hz, 2H), 7.07-7.11 (m, 3H), 6.97-7.05 (m, 4H), 6.89 (dd, *J*=8.8 Hz, 6.8 Hz, 2H), 6.73 (dd, *J*=8.6 Hz, 6.6 Hz, 2H), 4.08 (t, *J*=7.4 Hz, 1H), 3.65 (quin, *J*=5.6 Hz, 1H), 2.81-2.99 (m, 2H),2.20 (s, 3H), 1.30 (d, *J*=6.6 Hz, 3H).

N-Methyl-2-(4-hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-64). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$. The crude product treated with a 3N anhydrous HCl solution in EtOAc (1 mL), exposed to Et_2O, and the resulting amine hydrochloride salts were washed with Et_2O. **ET-64** was obtained as a brownish solid (0.12 g, 83% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.33 (dd, *J*=8.5 Hz, 7.4 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.18 (d, *J*=8.6 Hz, 2H), 7.11 (tt, *J*=7.5 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.97 (d, *J*=8.8 Hz, 2H), 6.97 (m, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 4.26 (t, *J*=8.1 Hz, 1H), 3.66 (d, *J*=8.1 Hz, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, methanol-d_4) δ 158.4, 158.1, 136.7, 131.8, 130.9, 130.2, 129.9, 124.6,

120.1, 120.0, 117.0, 54.5, 48.3, 34.3. HRMS (EI^+) *m/z* for $C_{21}H_{22}NO_2$ $[M + H]^+$: calcd, 320.1651; found, 320.1645.

Scheme 4-5. Synthesis of **ET-68–ET-70**

(4-Benzyloxyphenyl)-(4-(triisopropylsiloxy) phenyl)methanol (4.61). Refer to general procedure for formation of an organolithium and reaction with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.61** as a yellow oil (7.08 g, 65% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 7.42 (d, *J*=7.7 Hz, 2H), 7.37 (t, *J*=7.4 Hz, 2H), 7.31 (t, *J*=7.0 Hz, 1H), 7.26 (d, *J*=8.8 Hz, 2H), 7.19 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 5.75 (d, *J*=3.3 Hz, 1H), 5.05 (s, 2H), 2.06 (d, *J*=3.7 Hz, 1H), 1.24 (sep, *J*=7.4 Hz, 3H), 1.08 (d, *J*=7.3 Hz, 18H).

(4-Benzyloxyphenyl)-(4-(triisopropylsiloxy) phenyl)methanone (4.62). Refer to general procedure for Mn_2O oxidation of an alcohol. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (3%/97%) to (4%/96%)) to give **4.62** as a colorless oil (6.63 g, 94% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 7.78 (d, *J*=9.0 Hz, 2H), 7.72 (d, *J*=8.8 Hz, 2H), 7.45 (d, *J*=7.9 Hz, 2H), 7.41 (t, *J*=7.4 Hz, 2H), 7.35 (tt, *J*=8.3 Hz, 7.1 Hz, 1.6 Hz, 1H), 7.03 (d, *J*=9.0 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 5.15 (s, 2H), 1.30 (sep, *J*=7.4 Hz, 3H), 1.12 (d, *J*=7.3 Hz, 18H).

2-Methoxy-(1-(4-benzyloxyphenyl)-1-(4-(triisopropylsiloxy)phenyl))ethene (4.63). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (1%/99%)) to give **4.63** as a yellow oil (5.37 g, 83% yield). ^1H NMR (400 MHz,

chloroform-*d*) δ 7.44 (d, *J*=7.7 Hz, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 7.31 (d, *J*=8.8 Hz, 1H), 7.23 (d, *J*=8.8 Hz, 1H), 7.13 (d, *J*=8.8 Hz, 1H), 7.05 (d, *J*=8.6 Hz, 1H), 6.91 (dd, *J*=9.9 Hz, 8.9 Hz, 2H), 6.80 (t, *J*=8.4 Hz, 2H), 6.33; 6.29 (s, 1H), 5.06 (s, 2H), 3.74; 3.73 (s, 3H), 1.26 (sep, *J*=7.3 Hz, 3H), 1.10 (d, *J*=7.2 Hz, 18H).

2-(4-Benzyloxyphenyl)-2-(4-hydroxyphenyl)acetaldehyde (4.64). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (20%/80%)) to give **4.64** as a yellowish solid (1.78 g, 51% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.87 (d, *J*=2.6 Hz, 1H), 7.43 (dd, *J*=8.2 Hz, 2H), 7.38 (t, *J*=7.4 Hz, 2H), 7.32 (tt, *J*=8.2 Hz, 7.1 Hz, 1.7 Hz, 1H), 7.12 (d, *J*=9.0 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H), 6.98 (d, *J*=8.8 Hz, 2H), 6.83 (d, *J*=8.8 Hz, 2H), 5.06 (s, 2H), 4.77 (d, *J*=2.6 Hz, 1H), 4.76 (s, 1H).

N-Benzyl -2-(4-benzyloxyphenyl)-2-(4-hydroxyphenyl)ethylamine (4.65). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%) to (50%/50%)) to give **4.65** as a yellowish white solid (1.65 g, 72% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35-7.42 (m, 5H), 7.22-7.33 (m, 5H), 7.10 (d, *J*=8.6 Hz, 2H), 7.05 (d, *J*=8.4 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 6.72 (d, *J*=8.4 Hz, 2H), 5.02 (s, 2H), 4.11 (t, *J*=7.7 Hz, 1H), 3.81 (s, 2H), 3.15 (d, *J*=7.9 Hz, 2H).

N-Cbz-N-benzyl-2-(4-benzyloxyphenyl)-2-(4-hydroxyphenyl)ethylamine (4.66). To a solution of **4.65** (1.43 g, 3.5 mmol) and Na_2CO_3 (2.06 mL, 3.5 mmol, 1.7M) in $CHCl_3$ (20 mL) at 0^{o}C was benzyl chloroformate (0.50 mL, 3.5 mmol) and more Na_2CO_3 (1.85 mL, 3.15 mmol, 1.7M) sequentially. After stirring at room temperature for 3 h, the reaction was quenched with water and diluted with Et_2O. The organic layer was

washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.66** (1.98 g, 72% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32-7.39 (m, 7H), 7.18-7.30 (m, 6H), 7.09 (d, *J*=7.3 Hz, 2H), 7.03 (d, *J*=7.0 Hz, 2H), 6.98 (d, *J*=7.9 Hz, 1H), 6.92 (d, *J*=8.1 Hz, 1H), 6.83 (dd, *J*=13.6 Hz, 8.1 Hz, 2H), 6.68 (t, *J*=7.9 Hz, 2H), 5.12 (s, 2H), 4.99 (s, 2H), 4.29 (t, *J*=7.7 Hz, 1H), 4.14 (s, 2H), 3.70 (m, 2H).

N-*t*-Boc-2-(4-hydroxyphenyl)-2-(4-(triisopropylsiloxy)phenyl)ethylamine (4.67). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was subsequently hydrogenated following the general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. After hydrogenation, the crude product was then *t*-Boc protected following the general procedure for *t*-Boc protection of a free amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **4.67** as a white foam (0.68 g, 41% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.05 (d, *J*=8.6 Hz, 2H), 7.04 (d, *J*=8.4 Hz, 2H), 6.81 (d, *J*=8.4 Hz, 2H), 6.76 (d, *J*=8.6 Hz, 2H), 4.99 (br s, 1H), 4.46 (br s, 1H), 4.02 (t, *J*=8.2 Hz, 1H), 3.65 (t, *J*=6.7 Hz, 2H), 1.40 (s, 9H), 1.23 (sep, *J*=6.9 Hz, 3H), 1.08 (d, *J*=7.0 Hz, 18H).

N-*t*-Boc-2-(4-hydroxy-3-iodophenyl)-2-(4-(triisopropylsiloxy)phenyl)-ethylamine (4.68). To a solution of **4.67** (1.03 g, 2.13 mmol) in $CHCl_3$ (32 mL) was added AgTFA (1.03 g, 4.68 mmol) and I_2 (0.65 g, 2.55 mmol) successively. After stirring at room temperature for 12 h, the reaction was quenched with a saturated solution of Na_2SO_3 (12.52 mL) and diluted with $CHCl_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude product was purified via flash SiO_2 chromatography (EtOAc/DCM (1%/99%) to (5%/95%)) to give **4.68** as a yellow foam (0.58 g, 44% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.47 (d, *J*=1.8 Hz, 1H), 7.07 (dd, *J*=8.4 Hz, 2.0 Hz, 1H), 7.02 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.4 Hz, 1H), 6.82 (d, *J*=8.6 Hz, 2H), 5.23 (s, 1H), 4.45 (br s, 1H), 4.00 (t, *J*=7.9 Hz, 1H), 3.63 (dd, *J*=11.4 hz, 5.7 Hz, 2H), 1.41 (s, 9H), 1.24 (sep, *J*=7.4 Hz, 3H), 1.08 (d, *J*=7.1 Hz, 18H).

N-*t*-Boc-2-(4-phenoxy-3-iodophenyl)-2-(4-(triisopropylsiloxy)phenyl)-ethylamine (4.72). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.72** as a colorless oil (0.19 g, 90% yield).

N-*t*-Boc-2-(4-((4-triisopropylsiloxy)phenoxy)-3-iodophenyl)-2-(4-(triisopropylsiloxy)phenyl)ethylamine (4.73). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **4.73** as a colorless oil (0.22 g, 81% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.64 (d, *J*=2.2 Hz, 1H), 7.05 (dd, *J*=8.6 Hz, 2.0 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 2H), 6.82-6.88 (m, 3H), 6.85 (d, *J*=1.5 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 1H), 6.64 (d, *J*=8.4 Hz, 1H), 4.46 (br s 1H), 4.02 (t, *J*=7.67 Hz, 1H), 3.64 (dd, *J*=12.4 Hz, 6.0 Hz, 2H), 1.41 (s, 9H), 1.25 (m, 6H), 1.10 (d, *J*=4.2 Hz, 18H), 1.08 (d, *J*=3.9 Hz, 18H).

N-*t*-Boc-2-(4-((3-triisopropylsiloxy)phenoxy)-3-iodophenyl)-2-(4-(triisopropylsiloxy)phenyl)ethylamine (4.74). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (2%/98%) to (5%/95%)) to give **4.74** as a colorless oil (0.18 g, 69% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.66 (d, *J*=1.8 Hz, 1H), 7.14 (t, *J*=8.2 Hz,

1H), 7.11 (dd, *J*=8.0 Hz, 2.0 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 2H), 6.83 (m, 1H), 6.82 (dd, *J*=9.6 Hz, 8.5 Hz, 2H), 6.61 (dd, *J*=8.2 Hz, 2.3 Hz, 1H), 6.53 (dd, *J*=8.2 Hz, 2.4 Hz, 1H), 6.44 (t, *J*=2.3 Hz, 1H), 4.47 (br s, 1H), 4.05 (t, *J*=8.1 Hz, 1H), 3.66 (q, *J*=7.0 Hz, 2H), 1.41 (s, 9H), 1.23 (m, 6H), 1,09 (d, *J*=7.1 Hz, 18H), 1.06 (d, *J*=7.3 Hz, 18H).

N-*t*-Boc-2-(4-phenoxy-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine (4.75). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%)) to give **4.75** as a white foam (0.15 g, 98% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.69 (d, *J*=1.8 Hz, 1H), 7.32 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 7.11 (m, 2H), 7.09 (m, 1H), 7.04 (d, *J*=8.4 Hz, 2H), 6.94 (dd, *J*=8.7 Hz, 1.2 Hz, 2H), 6.79 (d, *J*=8.4 Hz, 2H), 5.54 (s, 1H), 4.54 (br s, 1H), 4.04 (t, *J*=7.4 Hz, 1H), 3.67 (t, *J*=6.8 Hz, 2H), 1.42 (s, 9H).

N-*t*-Boc-2-(4-((4-hydroxy)phenoxy)-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine (4.76). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%) to (35%/65%)) to give **4.76** as a yellowish foam (0.13 g, 73% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.65 (d, *J*=2.0 Hz, 1H), 7.05 (d, *J*=8.4 Hz, 2H), 7.05 (m, 1H), 6.87 (d, *J*=9.2 Hz, 2H), 6.80 (d, *J*=5.5 Hz, 2H), 6.78 (d, *J*=5.0 Hz, 2H), 6.66 (d, *J*=8.4 Hz, 1H), 5.00 (br s, 1H), 4.51 (br s, 1H), 4.02 (t, *J*=7.9 Hz, 1H), 3.66 (q, *J*=7.4 Hz, 2H), 1.42 (s, 9H).

N-*t*-Boc-2-(4-((3-hydroxy)phenoxy)-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine (4.77). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%) to (35%/65%)) to give **4.77** as a yellowish

foam (0.12 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.66 (d, *J*=2.2 Hz, 1H), 7.16 (t, *J*=8.2 Hz, 1H), 7.09 (dd, *J*=8.4 Hz, 2.2 Hz, 1H), 7.05 (d, *J*=8.6 Hz, 2H), 6.83 (d, *J*=8.2 Hz, 1H), 6.80 (d, *J*=8.6 Hz, 2H), 6.57 (dq, *J*=8.2 Hz, 2.4 Hz, 0.8 Hz, 1H), 6.51 (dd, *J*=8.2 Hz, 2.3 Hz, 1H), 6.41 (t, *J*=2.3 Hz, 1H), 4.55 (br s, 1H), 4.03 (t, *J*=7.7 Hz, 1H), 3.66 (m, 2H), 1.42 (s, 9H).

2-(4-Phenoxy-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine Hydrochloride (ET-68). Refer to general procedure for *t*-Boc deprotection: white foam, 0.12 g, 96% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.83 (d, *J*=2.2 Hz, 1H), 7.33 (dd, *J*=8.7 Hz, 7.4 Hz, 2H), 7.30 (dd, *J*=8.9 Hz, 2.3 Hz, 1H), 7.17 (d, *J*=8.4 Hz, 2H), 7.11 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.90 (dd, *J*=8.8 Hz, 1.1 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 1H), 6.81 (d, *J*=8.6 Hz, 2H), 4.15 (t, *J*=7.9 Hz, 1H), 3.56 (d, *J*=8.2 Hz, 2H). HRMS (EI$^+$) *m/z* for $C_{20}H_{19}NO_2I$ $[M + H]^+$: calcd, 432.0461; found, 432.0475.

2-(4-((4-Hydroxy)phenoxy)-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine Hydrochloride (ET-69). Refer to general procedure for *t*-Boc deprotection: white foam, 0.11 g, 99% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.77 (d, *J*=2.0 Hz, 1H), 7.22 (dd, *J*=8.7 Hz, 1.9 Hz, 1H), 7.14 (d, *J*=8.4 Hz, 2H), 6.76-6.82 (m, 6H), 6.70 (d, *J*=8.6 Hz, 1H), 4.11 (t, *J*=8.2 Hz, 1H), 3.53 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 158.6, 158.1, 155.3, 150.2, 140.1, 138.3, 131.5, 129.9, 121.6, 118.4, 117.3, 117.0, 88.5, 48.6, 44.6. HRMS (EI$^+$) *m/z* for $C_{20}H_{19}NO_3I$ $[M + H]^+$: calcd, 448.0410; found, 448.0417.

2-(4-((3-Hydroxy)phenoxy)-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine Hydrochloride (ET-70). Refer to general procedure for *t*-Boc deprotection: white foam, 0.10 g, 99% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.81 (d, *J*=2.2 Hz, 1H), 7.30 (dd,

J=8.6 Hz, 2.2 Hz, 1H), 7.17 (d, *J*=8.6 Hz, 2H), 7.11 (t, *J*=8.2 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 6.81 (d, *J*=8.6 Hz, 2H), 6.53 (dq, *J*=8.2 Hz, 2.3 Hz, 0.8 Hz, 1H), 6.35 (dq, *J*=8.0 Hz, 2.3 Hz, 0.8 Hz, 1H), 6.31 (t, *J*=2.4 Hz, 1H), 4.15 (t, *J*=8.2 Hz, 1H), 3.55 (d, *J*=8.1 Hz, 2H). HRMS (EI^+) *m/z* for $C_{20}H_{19}NO_3I$ $[M + H]^+$: calcd, 448.0410; found, 448.0418.

A.1.3.3 Chapter 5 Compounds

Scheme 5-1. Synthesis of **ET-51**

Methyl-2-hydroxy-4-triisopropylsiloxybenzoate (5.2). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (2%/98%)) to give **5.2** as a colorless oil (9.12 g, 95% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 10.85 (s, 1H), 7.70 (d, *J*=8.8 Hz, 1H), 6.44 (d, *J*=2.4 Hz, 1H), 6.40 (dd, *J*=8.7 Hz, 2.3 Hz, 1H), 3.90 (s, 3H), 1.28 (sep, *J*=7.1 Hz, 3H), 1.10 (d, *J*=7.3 Hz, 18H).

Methyl-2-benzyloxy-4-triisopropylsiloxybenzoate (5.3). To a solution of **5.2** (1.94 g, 5.98 mmol) in THF (60 mL) was added KHMDS (17.92 mL, 8.96 mmol, 0.5M in toluene). The reaction was stirred for 5 min before adding benzyl bromide (1.53 g, 8.96 mmol). After stirring overnight at room temperature, the reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **5.3** as a yellowish oil (1.67 g, 68% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 7.79 (d, *J*=8.6 Hz, 1H), 7.47 (d, *J*=7.5 Hz, 2H), 7.37 (t, *J*=7.5 Hz, 2H), 7.29 (t, *J*=7.3 Hz, 1H), 6.48 (dd, *J*=8.4 Hz, 2.2 Hz, 1H), 6.45 (d, *J*=2.2 Hz, 1H), 5.17 (s, 2H), 3.87 (s, 3H), 1.17 (sep, *J*=7.3 Hz, 3H), 1.05 (d, *J*=7.0 Hz, 18H).

2-Benzyloxy-4-triisopropylsiloxybenzyl alcohol (5.4). To a suspension of $LiAlH_4$ (89 mg, 2.34 mmol) in THF (10 mL) at 0°C was added dropwise a solution of **5.3** (0.88 g, 2.13 mmol) in THF (5 mL). After stirring at 0°C for 30 min, the reaction was quenched with dropwise addition of water and diluted with EtOAc. A 1N HCl solution was added until reaction became clear. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellowish oil (0.83 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39 (m, 4H), 7.32 (m, 1H), 7.10 (d, *J*=8.8 Hz, 1H), 6.46 (s, 1H), 6.45 (dd, *J*=8.0 Hz, 2.2 Hz, 1H), 5.09 (s, 2H), 4.65 (s, 2H), 1.18 (sep, *J*=7.3 Hz, 3H), 1.06 (d, *J*=7.0 Hz, 18H).

2-Benzyloxy-4-triisopropylsiloxybenzaldehyde (5.5). Refer to general procedure for Mn_2O oxidation of an alcohol. Crude product of **5.5** was obtained as a yellowish oil (0.78 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.39 (d, *J*=0.7 Hz, 1H), 7.77 (d, *J*=8.6 Hz, 1H), 7.41 (m, 4H), 7.34 (m, 1H), 6.51 (dd, *J*=8.6 Hz, 0.7 Hz, 1H), 6.44 (d, *J*=2.2 Hz, 1H), 5.16 (s, 2H), 1.20 (sep, *J*=7.3 Hz, 3H), 1.06 (d, *J*=7.0 Hz, 18H).

(2-Benzyloxy-4-(triisopropylsiloxy)phenyl)-(phenyl)methanol (5.6). Refer to general procedure for reaction of a Grignard reagent with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **5.6** as a yellowish oil (0.89 g, 96% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29-7.36 (m, 7H), 7.26 (m, 1H), 7.17 (dd, *J*=7.3 Hz, 2.2 Hz, 2H), 7.06 (d, *J*=8.6 Hz, 1H), 6.46 (dd, *J*=8.2 Hz, 2.2 Hz, 1H), 6.45 (s, 1H), 6.00 (d, *J*=5.3 Hz, 1H), 5.00 (d, *J*=2.4 Hz, 2H), 1.18 (sep, *J*=7.3 Hz, 3H), 1.05 (d, *J*=7.0 Hz, 18H).

(2-Benzyloxy-4-(triisopropylsiloxy)phenyl)-(phenyl)methanone (5.7). Refer to general procedure for Mn_2O oxidation of an alcohol. Crude product of **5.7** was obtained as a colorless oil (0.88 g, 98% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.79 (dd, *J*=8.2 Hz, 1.0 Hz, 2H), 7.62 (t, *J*=7.4 Hz, 1H), 7.41 (t, *J*=7.4 Hz, 2H), 7.39 (d, *J*=8.2 Hz, 1H), 7.20 (t, *J*=3.3 Hz, 3H), 6.97 (m, 2H), 6.56 (dd, *J*=8.3 Hz, 2.1 Hz, 1H), 6.49 (d, *J*=2.0 Hz, 1H), 4.95 (s, 2H), 1.23 (m, 3H), 1.09 (d, *J*=7.3 Hz, 18H).

(2-Hydroxy-4-(Triisopropylsiloxy)phenyl)-(phenyl)methanone (5.9). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (3%/97%)) to give **5.9** as a yellow oil (35.96 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.63 (dt, *J*=6.6 Hz, 1.9 Hz, 1.4 Hz, 2H), 7.55 (tt, *J*=8.4 Hz, 7.4 Hz, 1.4 Hz, 1H), 7.48 (dd, *J*=6.8 Hz, 0.7 Hz, 2H), 7.47 (d, *J*=9.0 Hz, 1H), 6.51 (d, *J*=2.4 Hz, 1H), 6.37 (dd, *J*=8.8 Hz, 2.4 Hz, 1H), 1.29 (m, 3H), 1.12 (d, *J*=7.3 Hz, 18H).

(2-Benzyloxy-4-hydroxyphenyl)-(phenyl)methanone (5.10). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%)) to give **5.10** as a yellow oil/foam (0.53 g, 76% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.78 (d, *J*=7.1 Hz, 2H), 7.52 (t, *J*=7.3 Hz, 1H), 7.42 (dd, *J*=7.8 Hz, 1.4 Hz, 2H), 7.41 (m, 1H), 7.18 (dd, *J*=5.1 Hz, 1.8 Hz, 2H), 7.17 (m, 1H), 6.92 (dd, *J*=7.7 Hz, 3.3 Hz, 2H), 6.52 (s, 1H), 6.51 (dd, *J*=8.0 Hz, 2.0 Hz, 1H), 4.92 (s, 2H), 2.69 (br s, 1H).

(2-Benzyloxy-4-(phenoxy)phenyl)-(phenyl)methanone (5.11). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%)) to give **5.11** as a yellowish solid (0.56 g,

73% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.81 (dd, *J*=8.3 Hz, 1.4 Hz, 2H), 7.54 (tt, *J*=8.0 Hz, 7.4 Hz, 1.3 Hz, 1H), 7.45 (d, *J*=8.4 Hz, 1H), 7.44 (d, *J*=7.9 Hz, 2H), 7.39 (t, *J*=7.6 Hz, 2H), 7.19 (m, 4H), 7.07 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.91 (dd, *J*=7.6 Hz, 2.1 Hz, 2H), 6.67 (d, *J*=2.2 Hz, 1H), 6.61 (dd, *J*=8.4 Hz, 2.2 Hz, 1H), 4.92 (s, 2H).

2-Methoxy-((1-(2-benzyloxy-4-(phenoxy)phenyl))-1-(phenyl))ethene (5.12). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (5%/95%)) to give **5.12** as a yellowish solid (0.55 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43; 7.36 (dd, *J*=8.4 Hz, 1.9 Hz, 2H), 7.16-7.35 (m, 8H), 7.12; 7.05 (m, 4H), 6.91; 6.83 (dd, *J*=7.4 Hz, 7.1 Hz, 2H), 6.65: 6.64 (d, *J*=2.4 Hz, 1H), 6.57; 6.60 (dd, *J*=8.2 Hz, 2.4 Hz, 1H), 6.60; 6.34 (s, 1H), 4.86; 4.83 (s, 2H), 3.74; 3.70 (s, 3H).

2-(2-(Benzyloxy)-4-phenoxyphenyl)-2-phenylacetaldehyde (5.13). Refer to general procedure for methyl enol ether deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (2%/98%)) to give **5.13** as a colorless oil (0.41 g, 81% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.93 (d, *J*=1.5 Hz, 1H), 7.30-7.38 (m, 8H), 7.26 (dd, *J*=7.5 Hz, 1.8 Hz, 2H), 7.21 (dd, *J*=7.9 Hz, 1.4 Hz, 2H), 7.12 (tt, *J*=7.4 Hz, 1.1 Hz, 1H), 7.00 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.97 (d, *J*=8.2 Hz, 1H), 6.68 (d, *J*=2.4 Hz, 1H), 6.54 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 5.16 (s, 1H), 4.99 (s, 2H).

N-Benzyl-2-(2-(benzyloxy)-4-phenoxyphenyl)-2-phenylethylamine (5.14). Refer to general procedure for reductive amination. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (20%/80%)) to give **5.14** as a colorless oil (3.69 g, 70% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.20-7.34 (m, 16H), 7.18 (m, 1H), 7.12 (d, *J*=8.2 Hz, 1H), 7.09 (tt, *J*=8.0 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.97

(dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.58 (d, *J*=2.4 Hz, 1H), 6.52 (dd, *J*=8.2 Hz, 2.4 Hz, 1H), 4.91 (dd, *J*=14.7 Hz, 2.9 Hz, 2H), 4.67 (t, *J*=7.6 Hz, 1H), 3.80 (s, 2H), 3.20 (dq, *J*=11.8 Hz, 7.7 Hz, 0.6 Hz, 2H), 1.58 (br s, 1H).

N-t-Boc-2-(2-(hydroxy)-4-phenoxyphenyl)-2-phenylethylamine (5.15). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was then *t*-Boc protected following the general procedure for *t*-Boc protection of free amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (15%/85%)) to give **5.15** as a yellow foam (2.56 g, 83% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.37 (t, *J*=7.4 Hz, 2H), 7.31 (m, 5H), 7.08 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.99 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.76 (d, *J*=7.9 Hz, 1H), 6.55 (s, 1H), 6.43 (d, *J*=7.9 Hz, 1H), 4.84 (br s, 1H), 4.44 (dd, *J*=8.9 Hz, 4.0 Hz, 1H), 3.72; 3.60 (m, 2H), 1.43 (s, 9H).

2-(2-(Hydroxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-51). Refer to general procedure for *t*-Boc deprotection: white solid, 24 mg, 94% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.36 (m, 4H), 7.33 (m, 2H), 7.27 (m, 1H), 7.10 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.05 (d, *J*=8.4 Hz, 1H), 6.97 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.47 (d, *J*=2.6 Hz, 1H), 6.44 (dd, *J*=8.3 Hz, 2.5 Hz, 1H), 4.63 (t, *J*=8.0 Hz, 1H), 3.64; 3.55 (dd, *J*=12.5 Hz, 8.2 Hz, 2H). HRMS (EI^+) *m/z* for $C_{20}H_{20}NO_2$ $[M + H]^+$: calcd, 306.1494; found, 306.1490.

Scheme 5-2. Synthesis of **ET-52–ET-63**

N-t-Boc-2-(2-(methoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.28). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was

purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.28** as a yellow oil (28 mg, 91% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33 (dd, *J*=8.6 Hz, 1.3 Hz, 2H), 7.27 (m, 4H), 7.20 (m, 1H), 7.09 (t, *J*=7.3 Hz, 2H), 7.07 (d, *J*=8.2 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.0 Hz, 1H), 6.56 (d, *J*=2.4 Hz, 1H), 6.50 (dd, *J*=8.2 Hz, 2.4 Hz, 1H), 4.52 (t, *J*=7.9 Hz, 1H), 3.73 (s, 3H), 3.73 (2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(ethoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.29). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.29** as a yellow oil (72 mg, 90% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=7.3 Hz, 1.3 Hz, 2H), 7.28 (m, 4H), 7.19 (m, 1H), 7.09 (d, *J*=8.2 Hz, 1H), 7.09 (t, *J*=7.4 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.53 (d, *J*=2.4 Hz, 1H), 6.50 (dd, *J*=8.2 Hz, 2.4 Hz, 1H), 4.57 (br s, 1H), 4.49 (t, *J*=8.0 Hz, 1H), 3.90 (m, 2H), 3.75 (q, *J*=6.7 Hz, 2H), 1.40 (s, 9H), 1.34 (t, *J*=7.0 Hz, 3H).

N-t-Boc-2-(2-(propoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.30). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.30** as a yellowish oil (65 mg, 78% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.6 Hz, 1.3 Hz, 2H), 7.28 (m, 4H), 7.19 (m, 1H), 7.09 (d, *J*=8.4 Hz, 1H), 7.09 (t, *J*=7.4 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.54 (d, *J*=2.2 Hz, 1H), 6.50 (dd, *J*=8.3 Hz, 2.3 Hz, 1H), 4.56 (br s, 1H), 4.49 (t, *J*=7.9 Hz, 1H), 3.79 (m, 2H), 3.75 (m, 2H), 1.75 (sext, *J*=7.0 Hz, 2H), 1.40 (s, 9H), 0.97 (t, *J*=7.4 Hz, 3H).

N-t-Boc-2-(2-(butoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.31). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified

via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.31** as a yellow oil (81 mg, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 7.23-7.28 (m, 4H), 7.19 (tt, *J*=7.5 Hz, 6.9 Hz, 1.7 Hz, 1H), 7.09 (t, *J*=7.3 Hz, 1H), 7.09 (d, *J*=8.2 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.54 (d, *J*=2.4 Hz, 1H), 6.50 (dd, *J*=8.2 Hz, 2.4 Hz, 1H), 4.56 (br s, 1H), 4.48 (t, *J*=7.8 Hz, 1H), 3.82 (m, 2H), 3.74 (br t, *J*=8.2 Hz, 2H), 1.69 (quin, *J*=7.0 Hz, 2H), 1.41 (m, 2H), 1.40 (s, 9H), 0.93 (t, *J*=7.4 Hz, 3H).

N-t-Boc-2-(2-(benzyloxy)-4-phenoxyphenyl)-2-phenylethylamine (5.32). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.32** as a yellow foam (86 mg, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29-7.34 (m, 6H), 7.20-7.27 (m, 6H), 7.14 (d, *J*=8.4 Hz, 1H), 7.10 (t, *J*=7.3 Hz, 1H), 6.98 (dd, *J*=8.5 Hz, 1.0 Hz, 2H), 6.61 (d, *J*=2.2 Hz, 1H), 6.54 (dd, *J*=8.3 Hz, 2.3 Hz, 1H), 4.93 (dd, *J*=17.8 Hz, 11.5 Hz, 2H), 4.53 (t, *J*=7.8 Hz, 1H), 3.74 (br q, *J*=7.9 Hz, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(isopropoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.33). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.33** as a yellow oil (77 mg, 93% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.5 Hz, 7.4 Hz, 2H), 7.22-7.29 (m, 4H), 7.18 (tt, *J*=7.4 Hz, 1.8 Hz, 1H), 7.09 (d, *J*=8.4 Hz, 1H), 7.09 (t, *J*=7.4 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.54 (d, *J*=2.4 Hz, 1H), 6.49 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 4.60 (br s, 1H), 4.46 (t, *J*=7.9 Hz, 1H), 4.41 (sep, *J*=6.0 Hz, 1H), 3.74 (t, *J*=6.7 Hz, 2H), 1.40 (s, 9H), 1.28 (d, *J*=6.0 Hz, 3H), 1.13 (d, *J*=6.0 Hz, 3H).

N-t-Boc-2-(2-(isobutoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.34). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.34** as a yellow oil (51 mg, 60% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (t, *J*=8.1 Hz, 2H), 7.23-7.28 (m, 4H), 7.19 (t, *J*=7.0 Hz, 1H), 7.10 (d, *J*=8.1 Hz, 1H), 7.09 (t, *J*=7.3 Hz, 1H), 7.00 (d, *J*=8.4 Hz, 2H), 6.54 (d, *J*=2.2 Hz, 1H), 6.50 (dd, *J*=8.3 Hz, 2.3 Hz, 1H), 4.56 (br s, 1H), 4.51 (t, *J*=7.6 Hz, 1H), 3.74 (t, *J*=6.6 Hz, 2H), 3.60 (dd, *J*=6.3 Hz, 2.8 Hz, 2H), 2.03 (sep, *J*=6.4 Hz, 1H), 1.40 (s, 9H), 0.96 (dd, *J*=8.7 Hz, 6.7 Hz, 6H).

N-t-Boc-2-(2-(allyloxy)-4-phenoxyphenyl)-2-phenylethylamine (5.35). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.35** as a yellowish oil (78 mg, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.24-7.29 (m, 4H), 7.19 (m, 1H), 7.10 (d, *J*=8.3 Hz, 1H), 7.09 (t, *J*=7.3 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.2 Hz, 2H), 6.54 (s, 1H), 6.53 (dd, *J*=10.0 Hz, 2.4 Hz, 1H), 5.96; 5.91 (dd, *J*=10.5 Hz, 5.2 Hz, 1H), 5.30 (dq, *J*=17.4 Hz, 1.6 Hz, 1H), 5.22 (dq, *J*=10.6 Hz, 1.4 Hz, 1H), 4.54 (t, *J*=7.9 Hz, 1H), 4.41 (m, 2H), 3.75 (br s, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(propargyloxy)-4-phenoxyphenyl)-2-phenylethylamine (5.36). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.36** as a yellowish oil (75 mg, 91% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.27 (m, 4H), 7.20 (m, 1H), 7.11 (d, *J*=8.1 Hz, 1H), 7.10 (t, *J*=7.1 Hz, 1H), 7.01 (dd, *J*=4.6 Hz, 1.1 Hz, 2H), 6.68 (d, *J*=2.4 Hz, 1H), 6.56 (dd, *J*=8.4 Hz, 2.4 Hz,

1H), 4.59 (d, *J*=2.4 Hz, 2H), 4.53 (t, *J*=7.9 Hz, 1H), 3.75 (t, *J*=6.2 Hz, 2H), 2.47 (t, *J*=2.4 Hz, 1H), 1.40 (s, 9H).

N-t-Boc-2-(2-(methoxycarbonylmethoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.37). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.37** as a yellowish oil (80 mg, 91% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.5 Hz, 7.4 Hz, 2H), 7.29 (d, *J*=5.1 Hz, 4H), 7.20 (m, 1H), 7.10 (d, *J*=8.6 Hz, 1H), 7.10 (t, *J*=7.4 Hz, 1H), 6.98 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.55 (dd, *J*=8.4 Hz, 2.2 Hz, 1H), 6.43 (d, *J*=2.4 Hz, 1H), 4.77 (br s, 1H), 4.61 (t, *J*=8.0 Hz, 1H), 4.54 (s, 2H), 3.80 (m, 2H), 3.77 (s, 3H), 1.39 (s, 9H).

N-t-Boc-2-(2-(acryloxy)-4-phenoxyphenyl)-2-phenylethylamine (5.38). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.38** as a colorless oil (57 mg, 76% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (dd, *J*=8.5 Hz, 7.4 Hz, 2H), 7.27 (m, 4H), 7.20 (t, *J*=7.5 Hz, 1H), 7.16 (d, *J*=7.3 Hz, 1H), 7.12 (t, *J*=7.4 Hz, 1H), 7.05 (dd, *J*=8.5 Hz, 1.0Hz, 2H), 6.88 (dd, *J*=8.6 Hz, 2.4 Hz, 1H), 6.74 (d, *J*=2.6 Hz, 1H), 6.50 (dd, *J*=17.3 Hz, 1.2 Hz, 1H), 6.23 (dd, *J*=17.2 Hz, 10.4 Hz, 1H), 5.98 (dd, *J*=10.4 Hz, 1.1 Hz, 1H), 4.55 (br s, 1H), 4.21 (t, *J*=7.7 Hz, 1H), 3.73 (t, *J*=6.8 Hz, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(acetoxy)-4-phenoxyphenyl)-2-phenylethylamine (5.39). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%)) to give **5.39** as a colorless oil (75 mg, 90% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (dd, *J*=8.6

Hz, 7.5 Hz, 2H), 7.30 (t, *J*=7.3 Hz, 2H), 7.17-17.24 (m, 4H), 7.13 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.04 (dd, *J*=8.7 Hz, 1.2 Hz, 2H), 6.85 (dd, *J*=8.4 Hz, 2.6 Hz, 1H), 6.70 (d, *J*=2.6 Hz, 1H), 4.56 (br s, 1H), 4.25 (t, *J*=7.8 Hz, 1H), 3.71 (t, *J*=6.6 Hz, 2H), 2.19 (s, 3H), 1.41 (s, 9H).

2-(2-(Methoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-52). Refer to general procedure for *t*-Boc deprotection: white solid, 82 mg, 99% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32-7.38 (m, 6H), 7.27 (m, 1H), 7.16 (d, *J*=8.4 Hz, 1H), 7.11 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.99 (dd, *J*=8.8 Hz, 1.1 Hz, 2H), 6.68 (d, *J*=2.4 Hz, 1H), 6.52 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 4.65 (t, *J*=8.1 Hz, 1H), 3.78 (s, 3H), 3.58 (dd, *J*=8.1 Hz, 5.6 Hz, 2H). HRMS (EI$^+$) *m/z* for $C_{21}H_{22}NO_2$ $[M + H]^+$: calcd, 320.1651; found, 320.1647.

2-(2-(Ethoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-53). Refer to general procedure for *t*-Boc deprotection: white solid, 60 mg, 97% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32-7.36 (m, 6H), 7.26 (m, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 7.11 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.98 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.64 (d, *J*=2.4 Hz, 1H), 6.52 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 4.63 (t, *J*=7.9 Hz, 1H), 3.96 (m, 2H), 3.64; 3.57 (dd, *J*=12.8 Hz, 8.1 Hz, 2H), 1.37 (t, *J*=7.0 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{22}H_{24}NO_2$ $[M + H]^+$: calcd, 334.1807; found, 334.1804.

2-(2-Propoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-54). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 56 mg, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32-7.37 (m, 6H), 7.26 (m, 1H), 7.22 (d, *J*=8.4 Hz, 1H), 7.11 (tt, *J*=7.7 Hz, 7.4 Hz, 1.0 Hz, 1H), 6.98 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.64 (d, *J*=2.4 Hz, 1H), 6.53 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 4.64 (t, *J*=8.2 Hz, 1H), 3.85

(m, 2H), 3.64; 3.57 (dd, *J*=12.8 Hz, 8.1 Hz, 2H), 1.78 (q, *J*=6.8 Hz, 2H), 1.00 (t, *J*=7.4 Hz, 3H). HRMS (EI^+) *m/z* for $C_{23}H_{26}NO_2$ $[M + H]^+$: calcd, 348.1964; found, 348.1960.

2-(2-(Butoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-55). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 70 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.30-7.36 (m, 6H), 7.26 (m, 1H), 7.22 (d, *J*=8.4 Hz, 1H), 7.11 (t, *J*=7.4 Hz, 1H), 6.98 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.64 (d, *J*=2.4 Hz, 1H), 6.53 (dd, *J*=8.4 Hz, 2.2 Hz, 1H), 4.62 (t, *J*=8.1 Hz, 1H), 3.89 (m, 2H), 3.63; 3.57 (dd, *J*=12.6 Hz, 8.1 Hz, 2H), 1.72 (quin, *J*=6.7 Hz, 2H), 1.43 (sext, *J*=7.5 Hz, 2H), 0.95 (t, *J*=7.4 Hz, 3H). HRMS (EI^+) *m/z* for $C_{24}H_{28}NO_2$ $[M + H]^+$: calcd, 362.2120; found, 362.2122.

2-(2-(Benzyloxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-56). Refer to general procedure for *t*-Boc deprotection: white solid, 71 mg, 94% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.22-7.35 (m, 13H), 7.11 (tt, *J*=7.7 Hz, 7.3 Hz, 1.0 Hz, 1H), 6.94 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.70 (d, *J*=2.4 Hz, 1H), 6.56 (d, *J*=8.4 Hz, 2.2 Hz, 1H), 5.00 (dd, *J*=15.9 Hz, 11.7 Hz, 2H), 4.65 (t, *J*=8.2 Hz, 1H), 3.63; 3.56 (dd, *J*=12.7 Hz, 8.0 Hz, 2H). HRMS (EI^+) *m/z* for $C_{27}H_{26}NO_2$ $[M + H]^+$: calcd, 396.1964; found, 396.1975.

2-(2-(Isopropoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-57). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 68 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.30-7.37 (m, 6H), 7.27 (m, 1H), 7.21 (d, *J*=8.6 Hz, 1H), 7.11 (tt, *J*=7.9 Hz, 7.3 Hz, 1.1 Hz, 1H), 6.98 (dd, *J*=8.8 Hz, 1.1 Hz, 2H), 6.63 (d, *J*=2.4 Hz, 1H), 6.52 (dd, *J*=8.3 Hz, 2.2 Hz, 1H), 4.58 (t, *J*=8.1 Hz, 1H), 4.51 (sep, *J*=6.0 Hz, 1H), 3.63; 3.57 (dd, *J*=12.7 Hz, 7.8 Hz, 2H), 1.27 (d, *J*=6.0 Hz, 3H),

1.15 (d, *J*=5.9 Hz, 3H). HRMS (EI^+) *m/z* for $C_{23}H_{26}NO_2$ $[M + H]^+$: calcd, 348.1964; found, 348.1966.

2-(2-(Isobutoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-58). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 44 mg, 98% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.30-7.37 (m, 6H), 7.27 (m, 1H), 7.23 (d, *J*=8.4 Hz, 1H), 7.12 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.99 (dd, *J*=8.7 Hz, 1.2 Hz, 2H), 6.63 (d, *J*=2.4 Hz, 1H), 6.54 (dd, *J*=8.3 Hz, 2.5 Hz, 1H), 4.65 (t, *J*=8.3 Hz, 1H), 3.66 (m, 2H), 3.63; 3.56 (dd, *J*=12.6 Hz, 8.2 Hz, 2H), 2.04 (sep, *J*=6.6 Hz, 1H), 0.98 (dd, *J*=6.3 Hz, 3.3 Hz, 6H). HRMS (EI^+) *m/z* for $C_{24}H_{28}NO_2$ $[M + H]^+$: calcd, 362.2120; found, 362.2125.

2-(2-(Allyloxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-59). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 67 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.32-7.36 (m, 6H), 7.26 (m, 1H), 7.22 (d, *J*=8.4 Hz, 1H), 7.12 (t, *J*=7.4 Hz, 1H), 6.98 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.65 (d, *J*=2.4 Hz, 1H), 6.54 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 6.01: 5.95 (dd, *J*=10.4 Hz, 5.3 Hz, 1H), 5.30 (dq, *J*=17.3 Hz, 1.7 Hz, 1H), 5.23 (dq, *J*=10.6 Hz, 1.3 Hz, 1H), 4.67 (t, *J*=8.1 Hz, 1H), 4.50 (m, 2H), 3.64; 3.58 (dd, *J*=12.7 Hz, 8.0 Hz, 2H). HRMS (EI^+) *m/z* for $C_{23}H_{24}NO_2$ $[M + H]^+$: calcd, 346.1807; found, 346.1820.

2-(2-(Propargyloxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-60). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 64 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.33-7.36 (m, 6H), 7.27 (sext, *J*=4.2 Hz, 1H), 7.20 (d, *J*=8.6 Hz, 1H), 7.12 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.99 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.79 (d, *J*=2.4 Hz, 1H), 6.57 (dd, *J*=8.5 Hz, 2.3 Hz, 1H), 4.72 (d,

J=2.4 Hz, 2H), 4.66 (t, *J*=8.1 Hz, 1H), 3.63; 3.58 (dd, *J*=12.8 Hz, 7.9 Hz, 2H), 3.00 (t, *J*=2.5 Hz, 1H). HRMS (EI^+) *m/z* for $C_{23}H_{22}NO_2$ $[M + H]^+$: calcd, 344.1651; found, 344.1653.

2-(2-(Methoxycarbonylmethoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-61). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 69 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.33-7.40 (m, 6H), 7.27 (tt, *J*=7.5 Hz, 6.9 Hz, 1.8 Hz, 1H), 7.16 (d, *J*=8.4 Hz, 1H), 7.12 (t, *J*=7.4 Hz, 1H), 6.97 (dd, *J*=8.7 Hz, 1.0 Hz, 2H), 6.61 (d, *J*=2.4 Hz, 1H), 6.56 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 4.76 (s, 2H), 4.73 (t, *J*=8.1 Hz, 1H), 3.77 (s, 3H), 3.76; 3.61 (dd, *J*=12.7 Hz, 7.4 Hz, 2H). HRMS (EI^+) *m/z* for $C_{23}H_{24}NO_4$ $[M + H]^+$: calcd, 378.1705; found, 378.1711.

2-(2-(Chloromethylacetoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-62). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 54 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.45 (d, *J*=8.6 Hz, 1H), 7.35-7.39 (m, 4H), 7.31 (dd, *J*=7.0 Hz, 1.5 Hz, 2H), 7.28 (m, 1H), 7.16 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.03 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.94 (dd, *J*=8.6 Hz, 2.6 Hz, 1H), 6.76 (d, *J*=2.6 Hz, 1H), 4.44 (t, *J*=8.1 Hz, 1H), 3.83 (t, *J*=6.4 Hz, 2H), 3.60 (dd, *J*=8.1 Hz, 3.4 Hz, 2H), 3.08 (t, *J*=6.5 Hz, 2H). HRMS (EI^+) *m/z* for $C_{23}H_{23}NO_3Cl$ $[M + H]^+$: calcd, 396.1366; found, 396.1373.

2-(2-(Acetoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-63). Refer to general procedure for *t*-Boc deprotection: white foam/colorless oil, 68 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.44 (d, *J*=8.6 Hz, 1H), 7.35-7.39 (m, 4H), 7.28-7.31 (m, 2H), 7.28 (m, 1H), 7.15 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.02 (dd, *J*=8.6 Hz, 1.1 Hz, 2H), 6.92 (dd, *J*=8.5 Hz, 2.8 Hz, 1H), 6.74 (d, *J*=2.6 Hz, 1H), 4.40 (t,

J=8.1 Hz, 1H), 3.60 (dd, *J*=8.1 Hz, 2.4 Hz, 2H), 2.26 (s, 3H). HRMS (EI^+) *m/z* for $C_{22}H_{22}NO_3$ $[M + H]^+$: calcd, 348.1600; found, 348.1601.

Scheme 5-3. Synthesis of **ET-72** and **ET-79**

Methyl-2-hydroxy-5-triisopropylsiloxybenzoate (5.41). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (3%/97%)) to give **5.41** as a colorless oil (9.54 g, 99% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 10.34 (s, 1H), 7.29 (d, *J*=2.9 Hz, 1H), 7.03 (dd, *J*=8.9 Hz, 3.0 Hz, 1H), 6.85 (d, *J*=9.0 Hz, 1H), 3.94 (s, 3H), 1.24 (m, 3H), 1.09 (d, *J*=7.1 Hz, 18H).

Methyl-2-benzyloxy-5-triisopropylsiloxybenzoate (5.42). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (1%/99%) to (2%/98%)) to give **5.42** as a colorless oil (10.94 g, 90% yield). ^1H NMR (400 MHz, chloroform-*d*) δ 7.46 (d, *J*=7.1 Hz, 2H), 7.37 (t, *J*=7.4 Hz, 2H), 7.33 (d, *J*=2.9 Hz, 1H), 7.30 (t, *J*=7.2 Hz, 1H), 6.95 (dd, *J*=8.9 Hz, 3.0 Hz, 1H), 6.87 (d, *J*=9.0 Hz, 1H), 5.11 (s, 2H), 3.89 (s, 3H), 1.24 (m, 3H), 1.09 (d, *J*=7.1 Hz, 18H).

2-Benzyloxy-5-triisopropylsiloxybenzyl alcohol (5.43). To a suspension of $LiAlH_4$ (1.10 g, 29.02 mmol) in THF (145 mL) at 0^oC was added dropwise a solution of **5.42** (10.94 g, 26.39 mmol) in THF (20 mL). After stirring at 0^oC for 30 min, the reaction was quenched with dropwise addition of water and diluted with EtOAc. A 1N HCl solution was added until reaction became clear. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the

crude product as a colorless oil (10.39 g, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31-7.42 (m, 5H), 6.84 (d, *J*=2.9 Hz, 1H), 6.80 (d, *J*=8.8 Hz, 1H), 6.74 (dd, *J*=8.7 Hz, 2.8 Hz, 1H), 5.05 (s, 2H), 4.65 (s, 2H), 1.24 (m, 3H), 1.09 (d, *J*=7.0 Hz, 18H).

2-Benzyloxy-5-triisopropylsiloxybenzaldehyde (5.44). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (10%/90%)) to give **5.44** as a colorless oil (0.70 g, 83% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.48 (s, 1H), 7.34-7.44 (m, 5H), 7.32 (d, *J*=3.3 Hz, 1H), 7.06 (dd, *J*=8.8 Hz, 3.3 Hz, 1H), 6.93 (d, *J*=8.8 Hz, 1H), 5.13 (s, 2H), 1.25 (m, 3H), 1.09 (d, *J*=7.1 Hz, 18H).

2-Hydroxy-5-triisopropylsiloxybenzaldehyde (5.46). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (3%/97%)) to give **5.46** as a light yellow solid (0.68 g, 76% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.61 (d, *J*=0.5 Hz, 1H), 9.81 (d, *J*=0.5 Hz, 1H), 7.10 (dd, *J*=8.7 Hz, 3.3 Hz, 1H), 7.00 (d, *J*=2.3 Hz, 1H), 6.87 (d, *J*=9.1 Hz, 1H), 1.25 (m, 3H), 1.10 (d, *J*=7.1 Hz, 18H).

(2-Benzyloxy-5-(triisopropylsiloxy)phenyl)-(phenyl)methanol (5.47). Refer to general procedure for reaction of a Grignard reagent with an aldehyde. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **5.47** as a colorless oil (11.47 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.19-7.35 (m, 10H), 6.80 (d, *J*=2.8 Hz, 1H), 6.79 (d, *J*=9.0 Hz, 1H), 6.74 (dd, *J*=8.8 Hz, 2.9 Hz, 1H), 5.97 (d, *J*=5.7 Hz, 1H), 4.95 (d, *J*=3.5 Hz, 2H), 2.97 (d, *J*=5.7 Hz, 1H), 1.18 (m, 3H), 1.05 (dd, *J*=7.1 Hz, 1.7 Hz, 18H).

(2-Benzyloxy-5-(triisopropylsiloxy)phenyl)-(phenyl)methanone (5.48). Refer to general procedure for Mn_2O oxidation of an alcohol. The crude product was obtained as a yellow oil (11.35 g, 99% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.81 (dd, *J*=8.3 Hz, 1.4 Hz, 2H), 7.55 (tt, *J*=8.1 Hz, 7.4 Hz, 1.3 Hz, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 7.18-7.20 (m, 3H), 6.95-6.97 (m, 4H), 6.88 (dd, *J*=7.5 Hz, 1.8 Hz, 1H), 4.92 (s, 2H), 1.24 (m, 3H), 1.09 (d, *J*=7.1 Hz, 18H).

2-Methoxy-((1-(2-benzyloxy-5-(triisopropylsiloxy)phenyl))-1-(phenyl))ethene (5.49). Refer to general procedure for formation of a methyl enol ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (0%/100%) to (1%/99%)) to give **5.49** as a yellow oil (10.79 g, 96% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41 (dd, *J*=8.2 Hz, 1.1 Hz, 1H), 7.28 (m, 2H), 7.16-7.24 (m, 6H), 6.90 (m, 2H), 6.77-6.80 (m, 2H), 6.59; 6.36 (s, 1H), 4.83; 4.81 (s, 2H), 3.73; 3.67 (s, 3H), 1.23 (m, 3H), 1.10; 1.08 (d, *J*=2.2 Hz, 18H).

2-(2-Benzyloxy-5-hydroxyphenyl)-2-(phenyl)ethanol (5.50). To a solution of methyl enol ether (9.68 g, 19.81 mmol) in Et_2O (298 mL) was added dropwise 70% aq $HClO_4$ (20.21 mL). After stirring at room temperature for ~22 hr, the reaction was quenched with saturated $NaHCO_3$ (210 mL) and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was subsequently dissolved in EtOH (80 mL) and treated with $NaBH_4$ (0.75 g, 19.81 mmol). After stirring at room temperature for 1 h, the reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%)

to (30%/70%)) to give **5.50** as a brownish solid (3.31 g, 48% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.20-7.36 (m, 10H), 6.80 (d, *J*=8.6 Hz, 1H), 6.74 (d, *J*=3.1 Hz, 1H), 6.65 (dd, *J*=8.7 Hz, 3.0 Hz, 1H), 4.95 (d, *J*=7.0 Hz, 2H), 4.65 (t, *J*=7.0 Hz, 1H), 4.13 (t, *J*=5.2 Hz, 2H).

N,N-Phthalyl-2-(2-benzyloxy-5-hydroxyphenyl)-2-(phenyl)ethylamine (5.51). To a solution of **5.50** (7.28 g, 22.72 mmol) in THF (273 mL) was added phthalimide (6.69 g, 45.45 mmol) and PPh_3 (11.92 g, 45.45 mmol) The reaction was cooled to 0^{o}C and DEAD (7.91 g, 45.45 mmol) was added dropwise. After stirring at room temperature for 3 h, the reaction was concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%) to (25%/75%)) to give **5.51** as a yellow foam/oil (8.26 g, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.72 (dd, *J*=5.2 Hz, 3.2 Hz, 2H), 7.63 (dd, *J*=5.6 Hz, 3.0 Hz, 2H), 7.21-7.33 (m, 9H), 7.16 (tt, *J*=7.9 Hz, 7.0 Hz, 1.7 Hz, 1H), 6.90 (d, *J*=2.9 Hz, 1H), 6.68 (d, *J*=8.8 Hz, 1H), 6.60 (dd, *J*=8.7 Hz, 3.0 Hz, 1H), 5.16 (t, *J*=8.2 Hz, 1H), 4.85 (d, *J*=4.6 Hz, 2H), 4.83 (s, 1H), 4.34 (dd, *J*=13.6 Hz, 9.0 Hz, 1H), 4.22 (m, 1H).

N-*t*-Boc-2-(2-benzyloxy-5-hydroxyphenyl)-2-(phenyl)ethylamine (5.52). Refer to general procedure for phthalimide deprotection and subsequent *t*-Boc protection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (20%/80%)) to give **5.52** as a yellow foam (3.37 g, 88% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.30-7.36 (m, 4H), 7.23-7.28 (m, 3H), 7.17-7.20 (m, 3H), 6.78 (d, *J*=8.8 Hz, 1H), 6.73 (d, *J*=2.9 Hz, 1H), 6.65 (dd, *J*=8.6 Hz, 2.9 Hz, 1H), 5.28 (s, 1H), 4.93 (d, *J*=8.6 Hz, 2H), 4.59 (br s, 1H), 4.55 (t, *J*=8.0 Hz, 1H), 3.70 (m, 2H), 1.39 (s, 9H).

N-*t*-Boc-2-(2-benzyloxy-5-phenoxyphenyl)-2-(phenyl)ethylamine (5.53). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (10%/90%)) to give **5.53** as a colorless oil/white solid (1.44 g, 78% yield). When exposed to MeOH, **5.53** formed a white solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.24-7.38 (m, 10H), 7.17-7.21 (m, 3H), 7.04 (t, *J*=7.3 Hz, 1H), 6.98 (d, *J*=2.2 Hz, 1H), 6.93 (d, *J*=8.4 Hz, 1H), 6.86 (d, *J*=8.8 Hz, 1H), 6.83 (dd, *J*=8.9 Hz, 2.7 Hz, 1H), 4.98 (d, *J*=7.3 Hz, 2H), 4.58 (t, *J*=7.9 Hz, 1H), 4.53 (br s, 1H), 3.71 (q, *J*=6.4 Hz, 2H), 1.39 (s, 9H).

N-*t*-Boc-2-(2-hydroxy-5-phenoxyphenyl)-2-(phenyl)ethylamine (5.54). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. Compound **5.53** was dissolved in EtOAc/EtOH (4/5) instead of MeOH during the hydrogenation reaction. The crude product was obtained as a white solid (1.08 g, 99% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (t, *J*=7.3 Hz, 2H), 7.24-7.29 (m, 6H), 7.01 (t, *J*=7.3 Hz, 1H), 6.87 (d, *J*=8.4 Hz, 2H), 6.84 (s, 1H), 6.77 (dd, *J*=8.6 Hz, 2.9 Hz, 1H), 6.64 (br s, 1H), 4.82 (br s, 1H), 4.48 (dd, *J*=8.8 Hz, 5.1 Hz, 1H), 3.72 (m, 1H), 3.60 (m, 1H), 1.43 (s, 9H).

2-(2-Hydroxy-5-phenoxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-72). Refer to general procedure for *t*-Boc deprotection: white solid, 42 mg, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.33-7.36 (m, 4H), 7.28 (m, 1H), 7.25 (dd, *J*=8.8 Hz, 7.3 Hz, 2H), 7.00 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.82-6.85 (m, 3H), 6.80 (d, *J*=2.8 Hz, 1H), 6.77 (dd, *J*=8.5 Hz, 2.8 Hz, 1H), 4.68 (t, *J*=8.1 Hz, 1H), 3.65 (dd, *J*=12.6 Hz, 7.9 Hz, 1H), 3.56 (dd, *J*=12.8 Hz, 8.4 Hz, 1H). HRMS (EI^+) *m/z* for $C_{20}H_{20}NO_2$ $[M + H]^+$: calcd, 306.1494; found, 306.1490.

2-(2-Benzyloxy-5-phenoxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-79). Refer to general procedure for *t*-Boc deprotection: white solid, 80 mg, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.25-7.40 (m, 12H), 7.03-7.08 (m, 3H), 6.90 (dd, *J*=7.7 Hz, 1.1 Hz, 2H), 6.89 (dd, *J*=8.6 Hz, 3.0 Hz, 1H), 5.07 (d, *J*=5.1 Hz, 2H), 4.69 (t, *J*=8.1 Hz, 1H), 3.61 (dd, *J*=12.7 Hz, 7.7 Hz, 1H), 3.55 (dd, *J*=13.1 Hz, 8.8 Hz, 1H). HRMS (EI$^+$) *m/z* for $C_{27}H_{26}NO_2$ $[M + H]^+$: calcd, 396.1964; found, 396.1963.

Scheme 5-4. Synthesis of **ET-73–ET-78**, **ET-80–ET-83**, **ET-90**, and **ET-95–ET-98**

N-t-Boc-2-(2-(methoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.65). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.65** as a colorless oil (50 mg, 96% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.23-7.30 (m, 6H), 7.19 (tt, *J*=7.4 Hz, 6.9 Hz, 1.7 Hz, 1H), 7.03 (t, *J*=7.3 Hz, 1H), 6.90-6.93 (m, 3H), 6.86 (dd, *J*=8.8 Hz, 2.7 Hz, 1H), 6.81 (d, *J*=8.8 Hz, 1H), 4.56 (t, *J*=7.9 Hz, 1H), 4.52 (br s, 1H), 3.77 (s, 3H), 3.70 (t, *J*=6.5 Hz, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(ethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.66). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.66** as a colorless oil (53 mg, 99% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.23-7.31 (m, 6H), 7.18 (tt, *J*=7.3 Hz, 6.6 Hz, 2.0 Hz, 1H), 7.03 (t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=2.6 Hz, 1H), 6.91 (d, *J*=7.9 Hz, 2H), 6.83 (dd, *J*=8.7 Hz, 2.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 4.56 (br s, 1H), 4.54 (t, *J*=7.8 Hz, 1H), 3.95 (m, 2H), 3.72 (t, *J*=6.7 Hz, 2H), 1.39 (s, 9H), 1.36 (t, *J*=7.0 Hz, 3H).

N-t-Boc-2-(2-(propoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.67). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.67** as a colorless oil (50 mg, 91% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.22-7.31 (m, 6H), 7.18 (t, *J*=6.9 Hz, 1H), 7.03 (t, *J*=7.3 Hz, 1H), 6.94 (d, *J*=2.6 Hz, 1H), 6.91 (d, *J*=8.1 Hz, 2H), 6.84 (dd, *J*=8.8 Hz, 1H), 6.79 (d, *J*=9.0 Hz, 1H), 4.56 (br s, 1H), 4.55 (t, *J*=7.9 Hz, 1H), 3.84 (m, 2H), 3.71 (t, *J*=6.5 Hz, 2H), 1.77 (sext, *J*=6.9 Hz, 2H), 1.39 (s, 9H), 1.00 (t, *J*=7.4 Hz, 3H).

N-t-Boc-2-(2-(butoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.68). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.68** as a white solid (55 mg, 97% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.20-7.31 (m, 6H), 7.18 (t, *J*=7.1 Hz, 1H), 7.03 (t, *J*=7.3 Hz, 1H), 6.94 (d, *J*=2.8 Hz, 1H), 6.91 (d, *J*=8.1 Hz, 2H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 6.79 (d, *J*=8.8 Hz, 1H), 4.56 (br s, 1H), 4.53 (t, *J*=7.8 Hz, 1H), 3.88 (m, 2H), 3.71 (t, *J*=7.0 Hz, 2H), 1.73 (m, 2H), 1.42 (m, 2H), 1.40 (s, 9H), 0.95 (t, *J*=7.4 Hz, 3H).

N-t-Boc-2-(2-(pentyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.69). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.69** as a colorless oil (55 mg, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.22-7.31 (m, 6H), 7.18 (tt, *J*=7.5 Hz, 7.0 Hz, 1.7 Hz, 1H), 7.03 (t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=2.6 Hz, 1H), 6.91 (d, *J*=7.7 Hz, 2H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H),

4.56 (br s, 1H), 4.53 (t, *J*=7.9 Hz, 1H), 3.87 (m, 2H), 3.71 (t, *J*=6.2 Hz, 2H), 1.74 (quin, *J*=6.8 Hz, 2H), 1.40 (s, 9H), 1.37 (m, 4H), 0.92 (t, *J*=7.1 Hz, 3H).

N-t-Boc-2-(2-(hexyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.70). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.70** as a colorless oil (50 mg, 89% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28 (dd, *J*=8.4 Hz, 7.5 Hz, 2H), 7.21-7.27 (m, 4H), 7.18 (tt, *J*=7.5 Hz, 7.0 Hz, 1.7 Hz, 1H), 7.03 (t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=2.6 Hz, 1H), 6.91 (d, *J*=8.1 Hz, 2H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 6.78 (d, *J*=9.0 Hz, 1H), 4.56 (br s, 1H), 4.53 (t, *J*=7.9 Hz, 1H), 3.87 (m, 2H), 3.70 (t, *J*=5.4 Hz, 2H), 1.73 (dt, *J*=14.8 Hz, 6.6 Hz, 2H), 1.39 (s, 9H), 1.39 (m, 2H), 1.30-1.33 (m, 4H), 0.91 (t, *J*=7.0 Hz, 3H).

N-t-Boc-2-(2-(isopropoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.71). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.71** as a yellowish oil (51 mg, 93% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (dd, *J*=8.5 Hz, 7.5 Hz, 2H), 7.21-7.28 (m, 4H), 7.18 (tt, *J*=7.5 Hz, 6.9 Hz, 1.7 Hz, 1H), 7.03 (t, *J*=7.4 Hz, 1H), 6.94 (m, 1H), 6.92 (d, *J*=8.8 Hz, 2H), 6.83 (dd, *J*=8.8 Hz, 2.6 Hz, 1H), 6.79 (d, *J*=8.8 Hz, 1H), 4.60 (br s, 1H), 4.51 (t, *J*=8.0 Hz, 1H), 4.46 (sep, *J*=6.0 Hz, 1H), 3.70 (t, *J*=6.6 Hz, 2H), 1.40 (s, 9H), 1.31 (d, *J*=6.0 Hz, 3H), 1.15 (d, *J*=6.1 Hz, 3H).

N-t-Boc-2-(2-(isobutoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.72). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.72** as a colorless oil (46 mg, 82% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28 (dd, *J*=7.9

Hz, 6.8 Hz, 2H), 7.22-7.26 (m, 4H), 7.18 (tt, *J*=7.4 Hz, 7.0 Hz, 1.7 Hz, 1H), 7.03 (t, *J*=7.3 Hz, 1H), 6.94 (d, *J*=2.6 Hz, 1H), 6.91 (d, *J*=7.9 Hz, 2H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 4.56 (t, *J*=7.6 Hz, 1H), 3.70 (t, *J*=6.8 Hz, 2H), 3.65 (dd, *J*=6.4 Hz, 2.2 Hz, 2H), 2.05 (sep, *J*=6.6 Hz, 1H), 1.39 (s, 9H), 0.98 (dd, *J*=9.7 Hz, 6.8 Hz, 6H).

N-t-Boc-2-(2-(allyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.73). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.73** as a colorless oil (52 mg, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (dd, *J*=8.2 Hz, 7.4 Hz, 2H), 7.23-7.26 (m, 4H), 7.19 (t, *J*=6.7 Hz, 1H), 7.04 (t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=2.4 Hz, 1H), 6.92 (d, *J*=8.1 Hz, 2H), 6.83 (dd, *J*=8.8 Hz, 2.6 Hz, 1H), 6.79 (d, *J*=9.0 Hz, 1H), 6.00; 5.95 (q, *J*=5.3 Hz, 1H), 5.34 (dq, *J*=17.3 Hz, 1.4 Hz, 1H), 5.24 (dq, *J*=10.6 Hz, 1.1 Hz, 1H), 4.59 (t, *J*=7.9 Hz, 1H), 4.65 (br s, 1H), 4.46 (m, 2H), 3.72 (t, *J*=6.3 Hz, 2H), 1.39 (s, 9H).

N-t-Boc-2-(2-(propargyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.74). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.74** as a colorless oil (52 mg, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.24-7.28 (m, 4H), 7.19 (tt, *J*=7.1 Hz, 6.7 Hz, 2.2 Hz, 1H), 7.05 (t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=8.8 Hz, 1H), 6.94 (d, *J*=2.9 Hz, 1H), 6.93 (d, *J*=8.2 Hz, 2H), 6.84 (dd, *J*=8.9 Hz, 2.8 Hz, 1H), 4.61 (d, *J*=2.4 Hz, 2H), 4.57 (t, *J*=8.0 Hz, 1H), 4.53 (br s, 1H), 3.72 (t, *J*=6.6 Hz, 2H), 2.50 (t, *J*=2.4 Hz, 1H), 1.39 (s, 9H).

N-t-Boc-2-(2-(methoxycarbonylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.75). Refer to general procedure for alkylation of a phenol with

K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (20%/80%)) to give **5.75** as a colorless oil (57 mg, 96% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 7.27 (d, *J*=4.4 Hz, 4H), 7.19 (sext, *J*=4.2 Hz, 1H), 7.05 (t, *J*=7.4 Hz, 1H), 6.95 (d, *J*=2.7 Hz, 1H), 6.92 (d, *J*=7.9 Hz, 2H), 6.80 (dd, *J*=8.8 Hz, 2.9 Hz, 1H), 6.70 (d, *J*=8.8 Hz, 1H), 4.75 (br s, 1H), 4.66 (t, *J*=7.9 Hz, 1H), 4.57 (s, 2H), 3.80 (s, 3H), 3.75 (dd, *J*=13.9 Hz, 7.7 Hz, 2H), 1.39 (s, 9H).

N-t-Boc-2-(2-(cyclopropylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.76). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.76** as a colorless oil (0.17 g, 96% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (dd, *J*=8.8 Hz, 7.6 Hz, 2H), 7.27 (d, *J*=4.5 Hz, 4H), 7.19 (sext, *J*=4.2 Hz, 1H), 7.03 (t, *J*=7.3 Hz, 1H), 6.94 (d, *J*=2.5 Hz, 1H), 6.91 (d, *J*=8.1 Hz, 2H), 6.82 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 6.75 (d, *J*=8.8 Hz, 1H), 4.62 (br s, 1H), 4.58 (t, *J*=7.8 Hz, 1H), 3.75 (m, 2H), 3.76; 3.69 (dd, *J*=9.9 Hz, 6.8 Hz, 2H), 1.39 (s, 9H), 1.24 (m, 1H), 0.60 (dd, *J*=8.1 Hz, 1.0 Hz, 2H), 0.28 (dd, *J*=8.2 Hz, 4.9 Hz, 2H),

N-t-Boc-2-(2-(cyclohexylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.77). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.77** as a colorless oil (97 mg, 52% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.31 (m, 6H), 7.19 (tt, *J*=7.6 Hz, 6.9 Hz, 1.5 Hz, 1H), 7.03 (t, *J*=7.3 Hz, 1H), 6.93 (d, *J*=2.8 Hz, 1H), 6.91 (d, *J*=8.6 Hz, 2H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 4.58 (br s, 1H), 4.55 (t, *J*=7.8 Hz, 1H), 3.70 (m, 2H), 3.68 (dd, *J*=5.8 Hz, 3.0 Hz, 2H), 1.69-1.82 (m, 6H), 1.40 (s, 9H), 1.16-1.34 (m, 3H), 1.02 (q, *J*=11.6 Hz, 2H).

N-t-Boc-2-(2-(3-cyanopropoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.78). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (6%/94%) to (40%/60%)) to give **5.78** as a colorless oil/white solid (0.156 g, 89% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (m, 2H), 7.29 (dd, *J*=7.6 Hz, 1.8 Hz, 2H), 7.22 (tt, *J*=8.3 Hz, 7.3 Hz, 1.4 Hz, 1H), 7.19 (d, *J*=7.1 Hz, 2H), 7.06 (t, *J*=7.3 Hz, 1H), 6.95 (d, *J*=2.5 Hz, 1H), 6.93 (d, *J*=8.1 Hz, 2H), 6.87 (dd, *J*=8.9 Hz, 2.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 4.57 (t, *J*=6.3 Hz, 1H), 4.48 (t, *J*=7.7 Hz, 1H), 4.02; 3.93 (m, 2H), 3.74 (quin, *J*=6.8 Hz, 1H), 3.62 (m, 1H), 2.31 (t, *J*=6.7 Hz, 2H), 2.04 (m, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(4-cyanobutyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.79). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (6%/94%) to (40%/60%)) to give **5.79** as a colorless oil (0.169 g, 93% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (m, 4H), 7.21 (d, *J*=7.8 Hz, 2H), 7.21 (m, 1H), 7.05 (t, *J*=7.5 Hz, 1H), 6.96 (d, *J*=2.0 Hz, 1H), 6.93 (d, *J*=7.8 Hz, 2H), 6.86 (dd, *J*=8.6 Hz, 2.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 4.55 (br s, 1H), 4.49 (t, *J*=7.7 Hz, 1H), 3.95; 3.87 (m, 2H), 3.74 (quin, *J*=6.8 Hz, 1H), 3.63 (quin, *J*=6.8 Hz, 1H), 2.32 (t, *J*=6.9 Hz, 2H), 1.88 (m, 2H), 1.69 (m, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(3,3-(dimethyl)allyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.80). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.80** as a colorless oil (92 mg, 52% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (t, *J*=7.6 Hz, 2H), 7.22-7.27 (m, 4H), 7.18 (tt, *J*=7.0 Hz, 6.7 Hz, 2.1 Hz, 1H), 7.03 (t,

J=7.3 Hz, 1H), 6.92 (m, 1H), 6.91 (d, *J*=8.1 Hz, 2H), 6.82 (s, 1H), 6.81 (m, 1H), 5.41 (m, 1H), 4.56 (t, *J*=7.8 Hz, 1H), 4.44 (m, 2H), 3.71 (t, *J*=6.7 Hz, 2H), 3.65 (br s, 1H), 1.78 (s, 3H), 1.67 (s, 3H), 1.39 (s, 9H).

2-(2-(Methoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-73). Refer to general procedure for *t*-Boc deprotection: white solid, 40 mg, 96% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.31-7.38 (m, 4H), 7.28 (dd, *J*=8.7 Hz, 7.4 Hz, 2H), 7.29 (m, 1H), 7.04 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.01 (d, *J*=8.4 Hz, 2H), 6.86-6.92 (m, 3H), 4.69 (t, *J*=8.1 Hz, 1H), 3.85 (s, 3H), 3.58 (dd, *J*=8.0 Hz, 3.2 Hz, 2H). HRMS (EI$^+$) *m/z* for $C_{21}H_{22}NO_2$ [M + H]$^+$: calcd, 320.1651; found, 320.1648.

2-(2-(Ethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-74). Refer to general procedure for *t*-Boc deprotection: white solid, 43 mg, 95% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32-7.38 (m, 4H), 7.29 (dd, *J*=8.7 Hz, 7.4 Hz, 2H), 7.27 (m, 1H), 7.04 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.98 (d, *J*=9.0 Hz, 1H), 6.96 (d, *J*=2.6 Hz, 1H), 6.87-6.90 (m, 3H), 4.68 (t, *J*=8.1 Hz, 1H), 4.04 (m, 2H), 3.63 (dd, *J*=12.7 Hz, 7.6 Hz, 1H), 3.57 (dd, *J*=12.7 Hz, 8.5 Hz, 1H), 1.40 (t, *J*=7.0 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{22}H_{24}NO_2$ [M + H]$^+$: calcd, 334.1807; found, 334.1804.

2-(2-(Propoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-75). Refer to general procedure for *t*-Boc deprotection: white solid, 41 mg, 94% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.33-7.37 (m, 4H), 7.29 (dd, *J*=8.8 Hz, 7.3 Hz, 2H), 7.28 (m, 1H), 7.04 (tt, *J*=7.6 Hz, 7.3 Hz, 1.1 Hz, 1H), 6.99 (d, *J*=1.8 Hz, 1H), 6.97 (d, *J*=4.0 Hz, 1H), 6.87-6.91 (m, 3H), 4.68 (t, *J*=8.2 Hz, 1H), 3.93 (m, 2H), 3.63 (dd, *J*=12.7 Hz, 7.6 Hz, 1H), 3.57 (dd, *J*=12.8 Hz, 8.6 Hz, 1H), 1.82 (sext, *J*=7.0 Hz, 2H), 1.04 (t,

J=7.4 Hz, 3H). HRMS (EI^+) *m/z* for $C_{23}H_{26}NO_2$ $[M + H]^+$: calcd, 348.1964; found, 348.1960.

2-(2-(Butoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-76). Refer to general procedure for *t*-Boc deprotection: white solid, 45 mg, 95% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.32-7.37 (m, 4H), 7.29 (dd, *J*=8.8 Hz, 7.3 Hz, 2H), 7.28 (m, 1H), 7.04 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.98 (d, *J*=2.9 Hz, 1H), 6.97 (d, *J*=8.8 Hz, 1H), 6.89 (dd, *J*=8.8 Hz, 1.1 Hz, 2H), 6.89 (m, 1H), 4.67 (t, *J*=8.2 Hz, 1H), 3.97 (m, 2H), 3.62 (dd, *J*=12.7 Hz, 7.6 Hz, 1H), 3.56 (dd, *J*=12.8 Hz, 8.6 Hz, 1H), 1.77 (m, 2H), 1.47 (sext, *J*=7.5 Hz, 2H), 0.98 (t, *J*=7.4 Hz, 3H). HRMS (EI^+) *m/z* for $C_{24}H_{28}NO_2$ $[M + H]^+$: calcd, 362.2120; found, 362.2120.

2-(2-(Pentyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-77). Refer to general procedure for *t*-Boc deprotection: white solid, 43 mg, 90% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.30-7.37 (m, 4H), 7.29 (dd, *J*=8.7 Hz, 7.4 Hz, 2H), 7.27 (m, 1H), 7.04 (t, *J*=7.4 Hz, 1H), 7.00 (d, *J*=2.8 Hz, 1H), 6.97 (d, *J*=9.1 Hz, 1H), 6.88-6.91 (m, 3H), 4.67 (t, *J*=8.2 Hz, 1H), 3.96 (m, 2H), 3.62 (dd, *J*=12.7 Hz, 7.7 Hz, 1H), 3.56 (dd, *J*=12.6 Hz, 8.6 Hz, 1H), 1.79 (quin, *J*=6.9 Hz, 2H), 1.41 (m, 4H), 0.95 (t, *J*=7.2 Hz, 3H). HRMS (EI^+) *m/z* for $C_{25}H_{30}NO_2$ $[M + H]^+$: calcd, 376.2277; found, 376.2277.

2-(2-(Hexyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-78). Refer to general procedure for *t*-Boc deprotection: white solid, 43 mg, 98% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.30-7.37 (m, 4H), 7.29 (dd, *J*=8.7 Hz, 7.4 Hz, 2H), 7.28 (m, 1H), 7.04 (tt, *J*=7.7 Hz, 7.4 Hz, 1.4 Hz, 1H), 7.01 (d, *J*=3.0 Hz, 1H), 6.98 (d, *J*=8.8 Hz, 1H), 6.88-6.92 (m, 3H), 4.67 (t, *J*=8.1 Hz, 1H), 3.96 (m, 2H), 3.62 (dd, *J*=12.6

Hz, 7.8 Hz, 1H), 3.56 (dd, *J*=12.8 Hz, 8.4 Hz, 1H), 1.80 (t, *J*=6.6 Hz, 1H), 1.76 (t, *J*=6.3 Hz, 1H), 1.44 (quin, *J*=6.9 Hz, 2H), 1.35 (m, 4H), 0.93 (t, *J*=7.1 Hz, 3H). HRMS (EI^+) *m/z* for $C_{26}H_{32}NO_2$ $[M + H]^+$: calcd, 390.2433; found, 390.2428.

2-(2-(Isopropoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-80). Refer to general procedure for *t*-Boc deprotection: yellowish solid, 42 mg, 95% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.33-7.37 (m, 4H), 7.29 (dd, *J*=8.7 Hz, 7.5 Hz, 2H), 7.28 (m, 1H), 7.04 (tt, *J*=7.4 Hz, 7.3 Hz, 1.1 Hz, 1H), 6.99 (d, *J*=4.0 Hz, 1H), 6.97 (d, *J*=2.0 Hz, 1H), 6.86-6.92 (m, 3H), 4.65 (t, *J*=8.1 Hz, 1H), 4.61 (sep, *J*=6.0 Hz, 1H), 3.61 (dd, *J*=12.6 Hz, 7.6 Hz, 1H), 3.56 (dd, *J*=12.6 Hz, 8.6 Hz, 1H), 1.32 (d, *J*=6.1 Hz, 3H), 1.20 (d, *J*=6.1 Hz, 3H). HRMS (EI^+) *m/z* for $C_{23}H_{26}NO_2$ $[M + H]^+$: calcd, 348.1964; found, 348.1960.

2-(2-(Isobutoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-81). Refer to general procedure for *t*-Boc deprotection: white foam, 37 mg, 92% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.33-7.37 (m, 4H), 7.29 (dd, *J*=8.7 Hz, 7.5 Hz, 2H), 7.27 (m, 1H), 7.04 (tt, *J*=7.6 Hz, 7.3 Hz, 1.0 Hz, 1H), 7.01 (d, *J*=3.0 Hz, 1H), 6.97 (d, *J*=8.8 Hz, 1H), 6.88-6.92 (m, 3H), 4.70 (t, *J*=8.1 Hz, 1H), 3.74 (dd, *J*=6.4 Hz, 2.4 Hz, 2H), 3.62 (dd, *J*=12.9 Hz, 7.6 Hz, 1H), 3.56 (dd, *J*=12.9 Hz, 8.6 Hz, 1H), 2.09 (sep, *J*=6.6 Hz, 1H), 1.04 (d, *J*=4.6 Hz, 3H), 1.02 (d, *J*=4.3 Hz, 3H). HRMS (EI^+) *m/z* for $C_{24}H_{28}NO_2$ $[M + H]^+$: calcd, 362.2120; found, 362.2122.

2-(2-(Allyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-82). Refer to general procedure for *t*-Boc deprotection: yellow oil, 42 mg, 95% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.33-7.36 (m, 4H), 7.29 (dd, *J*=8.7 Hz, 7.5 Hz, 2H), 7.28 (m, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 6.99 (d, *J*=8.8 Hz, 1H), 6.99 (d, *J*=3.0 Hz, 1H), 6.89

(dd, *J*=8.8 Hz, 1.0 Hz, 2H), 6.88 (dd, *J*=8.8 Hz, 2.5 Hz, 1H), 6.05 (m, 1H), 5.38 (dq, *J*=17.3 Hz, 1.6 Hz, 1H), 5.27 (dq, *J*=10.6 Hz, 1.4 Hz, 1H), 4.72 (t, *J*=8.1 Hz, 1H), 4.56 (m, 2H), 3.61 (m, 2H). HRMS (EI^+) *m/z* for $C_{23}H_{24}NO_2$ $[M + H]^+$: calcd, 346.1807; found, 346.1802.

2-(2-(Propargyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-83). Refer to general procedure for *t*-Boc deprotection: yellowish solid, 45 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.35 (d, *J*=4.3 Hz, 4H), 7.29 (dd, *J*=8.7 Hz, 7.4 Hz, 2H), 7.28 (m, 1H), 7.11 (d, *J*=8.8 Hz, 1H), 7.05 (t, *J*=7.5 Hz, 1H), 6.95 (d, *J*=2.8 Hz, 1H), 6.87-6.90 (m, 3H), 4.78 (d, *J*=2.3 Hz, 2H), 4.71 (t, *J*=8.0 Hz, 1H), 3.61 (d, *J*=7.8 Hz, 2H), 3.03 (t, *J*=2.4 Hz, 1H). HRMS (EI^+) *m/z* for $C_{23}H_{22}NO_2$ $[M + H]^+$: calcd, 344.1651; found, 344.1646.

2-(2-(Cyclopropylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-95). Refer to general procedure for *t*-Boc deprotection: white foam, 0.14 g, 98% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.33-7.39 (m, 4H), 7.28 (dd, *J*=8.6 Hz, 7.6 Hz, 2H), 7.27 (m, 1H), 7.03 (t, *J*=7.5 Hz, 1H), 6.98 (d, *J*=2.8 Hz, 1H), 6.94 (d, *J*=8.8 Hz, 1H), 6.88 (dd, *J*=8.8 Hz, 1.0 Hz, 2H), 6.87 (dd, *J*=8.8 Hz, 3.0 Hz, 1H), 4.70 (t, *J*=8.1 Hz, 1H), 3.85 (dd, *J*=10.1 Hz, 7.1 Hz, 1H), 3.78 (dd, *J*=10.1 Hz, 7.1 Hz, 1H), 3.68 (dd, *J*=12.8 Hz, 7.7 Hz, 1H), 3.60 (dd, *J*=12.8 Hz, 8.5 Hz, 1H), 1.28 (m, 1H), 0.64 (m, 2H), 0.33 (m, 2H). HRMS (EI^+) *m/z* for $C_{24}H_{26}NO_2$ $[M + H]^+$: calcd, 360.1964; found, 360.1960.

2-(2-(Cyclohexylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-96). Refer to general procedure for *t*-Boc deprotection: white solid, 83 mg, 99% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.30-7.37 (m, 4H), 7.29 (dd,

J=8.9 Hz, 7.3 Hz, 2H), 7.27 (m, 1H), 7.04 (tt, *J*=7.6 Hz, 7.3 Hz, 1.0 Hz, 1H), 7.01 (d, *J*=2.8 Hz, 1H), 6.96 (d, *J*=8.8 Hz, 1H), 6.90 (dd, *J*=8.8 Hz, 1.0 Hz, 2H), 6.89 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.67 (t, *J*=8.0 Hz, 1H), 3.76 (dd, *J*=6.1 Hz, 1.8 Hz, 2H), 3.61 (dd, *J*=12.8 Hz, 7.7 Hz, 1H), 3.56 (dd, *J*=12.6 Hz, 8.6 Hz, 1H), 1.72-1.85 (m, 6H), 1.30 (m, 3H), 1.08 (q, *J*=11.5 Hz, 2H). HRMS (EI^+) *m/z* for $C_{27}H_{32}NO_2$ $[M + H]^+$: calcd, 402.2433; found, 402.2430.

2-(2-(3-Cyanopropoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-97). Refer to general procedure for *t*-Boc deprotection: white foam, 0.14 g, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.31-7.39 (m, 4H), 7.30 (dd, *J*=8.5 Hz, 7.4 Hz, 2H), 7.28 (m, 1H), 7.05 (tt, *J*=7.8 hz, 7.3 Hz, 1.0 Hz, 1H), 7.02 (d, *J*=2.3 Hz, 1H), 6.98 (d, *J*=9.9 Hz, 1H), 6.91 (dd, *J*=8.6 Hz, 1.0 Hz, 2H), 6.88 (m, 1H), 4.72 (t, *J*=8.0 Hz, 1H), 4.05 (m, 2H), 3.59 (m, 2H), 2.51 (dt, *J*=7.2 Hz, 1.3 Hz, 1H), 2.40 (m, 1H), 2.09 (m, 2H). HRMS (EI^+) *m/z* for $C_{24}H_{25}N_2O_2$ $[M + H]^+$: calcd, 373.1916; found, 373.1919.

2-(2-(4-Cyanobutyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-98). Refer to general procedure for *t*-Boc deprotection: white solid, 0.12 g, 84% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.25-7.38 (m, 7H), 7.05 (t, *J*=7.5 Hz, 1H), 7.04 (d, *J*=2.8 Hz, 1H), 6.99 (d, *J*=8.8 Hz, 1H), 6.91 (dd, *J*=8.7 Hz, 1.1 Hz, 2H), 6.90 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.67 (t, *J*=8.1 Hz, 1H), 3.99 (m, 2H), 3.62 (dd, *J*=12.9 Hz, 7.8 Hz, 1H), 3.56 (dd, *J*=12.7 Hz, 8.5 Hz, 1H), 2.48 (t, *J*=7.1 Hz, 2H), 1.91 (m, 2H), 1.72 (m, 2H). HRMS (EI^+) *m/z* for $C_{25}H_{27}N_2O_2$ $[M + H]^+$: calcd, 387.2073; found, 387.2068.

Scheme 5-5. Synthesis of **ET-84–ET-86** and **ET-99–ET-101**

N-t-Boc-2-(2-(acetoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.87). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.87** as a colorless oil (50 mg, 91% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33 (t, *J*=8.1 Hz, 2H), 7.28 (d, *J*=7.7 Hz, 2H), 7.31 (m, 1H), 7.21 (t, *J*=7.3 Hz, 1H), 7.17 (d, *J*=7.5 Hz, 2H), 7.10 (t, *J*=7.3 Hz, 1H), 6.99 (d, *J*=8.6 Hz, 2H), 6.98 (m, 1H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.56 (br s, 1H), 4.29 (t, *J*=7.2 Hz, 1H), 3.68 (t, *J*=6.7 Hz, 2H), 2.21 (s, 3H), 1.41 (s, 9H).

N-t-Boc-2-(2-(acryloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.88). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%)) to give **5.88** as a colorless oil (49 mg, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (dd, *J*=8.6 Hz, 7.5 Hz, 2H), 7.26 (m, 1H), 7.26 (d, *J*=7.5 Hz, 2H), 7.20 (tt, *J*=8.3 Hz, 7.3 Hz, 1.4 Hz, 1H), 7.15 (d, *J*=7.1 Hz, 2H), 7.11 (tt, *J*=7.7 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.03 (d, *J*=8.8 Hz, 1H), 7.01 (d, *J*=9.2 Hz, 2H), 6.86 (dd, *J*=8.8 Hz, 2.9 Hz, 1H), 6.53 (dd, *J*=17.4 Hz, 1.3 Hz, 1H), 6.27 (dd, *J*=17.4 Hz, 10.4 Hz, 1H), 5.99 (dd, *J*=10.4 Hz, 1.3 Hz, 1H), 4.55 (br s, 1H), 4.25 (t, *J*=7.7 Hz, 1H), 3.68 (dt, *J*=13.3 Hz, 6.0 Hz, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(chloroacetoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.89). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%)) to give **5.89** as a white solid (29 mg, 48% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29-7.36 (m, 4H), 7.23 (t, *J*=7.4 Hz, 1H), 7.18 (d, *J*=7.3 Hz, 2H),7.12 (t, *J*=7.5 Hz, 1H),

7.04 (d, *J*=8.8 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 2H), 6.93 (s, 1H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.56 (br s, 1H), 4.33 (t, *J*=8.5 Hz, 1H), 4.24 (s, 2H), 3.66 (m, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(isobutyryloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.90). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%)) to give **5.90** as a colorless oil (54 mg, 91% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (t, *J*=8.1 Hz, 2H), 7.27 (d, *J*=7.9 Hz, 2H), 7.26 (m, 1H), 7.21 (m, 1H), 7.17 (d, *J*=7.5 Hz, 2H), 7.10 (t, *J*=7.2 Hz, 1H), 6.98 (d, *J*=8.2 Hz, 2H), 6.97 (d, *J*=9.0 Hz, 1H), 6.85 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.57 (br s, 1H), 4.28 (t, *J*=7.4 Hz, 1H), 3.68 (m, 2H), 2.76 (quin, *J*=6.9 Hz, 1H), 1.41 (s, 9H), 1.29 (d, *J*=7.0 Hz, 3H), 1.25 (d, *J*=7.0 Hz, 3H).

N-t-Boc-2-(2-(3-methylbutanoyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.91). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (10%/90%)) to give **5.91** as a colorless oil (64 mg, ~100% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (dd, *J*=8.5 Hz, 7.6 Hz, 2H), 7.26 (d, *J*=7.7 Hz, 2H), 7.28 (m, 1H), 7.21 (tt, *J*=8.2 Hz, 7.3 Hz, 1.3 Hz, 1H), 7.17 (d, *J*=7.3 Hz, 2H), 7.10 (t, *J*=7.4 Hz, 1H), 6.99 (d, *J*=8.8 Hz, 1H), 6.98 (d, *J*=8.1 Hz, 2H), 6.85 (dd, *J*=8.8 Hz, 2.9 Hz, 1H), 4.57 (t, *J*=6.0 Hz, 1H), 4.28 (t, *J*=7.5 Hz, 1H), 3.66 (dd, *J*=12.8 Hz, 5.7 Hz, 2H), 2.38 (dd, *J*=6.7 Hz, 4.3 Hz, 1H), 2.23 (d, *J*=7.0 Hz, 1H), 2.14 (m, 1H), 1.41 (s, 9H), 1.01 (t, *J*=6.5 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H).

N-t-Boc-2-(2-(acetoxyacetoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.92). Refer to general procedure for reaction of a phenol with an acid chloride. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to

(20%/80%)) to give **5.92** as a colorless oil (47 mg, 75% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (t, *J*=8.1 Hz, 2H), 7.30 (m, 1H), 7.29 (d, *J*=7.5 Hz, 2H), 7.22 (tt, *J*=8.4 Hz, 7.3 Hz, 1.3 Hz, 1H), 7.19 (d, *J*=7.7 Hz, 2H), 7.10 (t, *J*=7.4 Hz, 1H), 7.02 (d, *J*=8.8 Hz, 1H), 6.98 (d, *J*=7.9 Hz, 2H), 6.83 (dd, *J*=8.8 Hz, 2.7 Hz, 1H), 4.79 (d, *J*=5.5 Hz, 2H), 4.61 (br s, 1H), 4.29 (t, *J*=7.6 Hz, 1H), 3.66 (t, *J*=6.4 Hz, 2H), 2.18 (s, 3H), 1.39 (s, 9H).

2-(2-(Chloromethylacetoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-84). Refer to general procedure for *t*-Boc deprotection: white solid, 43 mg, 94% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.34-7.39 (m, 4H), 7.30 (d, *J*=7.6 Hz, 2H), 7.29 (m, 1H), 7.14 (d, *J*=3.0 Hz, 1H), 7.13 (m, 1H), 7.11 (d, *J*=8.8 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.1 Hz, 2H), 6.90 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.46 (t, *J*=8.1 Hz, 1H), 3.87 (t, *J*=6.3 Hz, 2H), 3.60 (dd, *J*=12.9 Hz, 8.1 Hz, 1H), 3.56 (dd, *J*=13.1 Hz, 7.8 Hz, 1H), 3.13 (t, *J*=6.6 Hz, 2H). HRMS (EI$^+$) *m/z* for $C_{23}H_{23}NO_3Cl$ $[M + H]^+$: calcd, 396.1366; found, 396.1370.

2-(2-(Isobutyryloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-85). Refer to general procedure for *t*-Boc deprotection: white foam, 46 mg, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.36 (dd, *J*=8.6 Hz, 7.6 Hz, 2H), 7.35 (m, 2H), 7.28 (m, 1H), 7.27 (d, *J*=8.1 Hz, 2H), 7.18 (d, *J*=2.8 Hz, 1H), 7.13 (tt, *J*=7.6 Hz, 7.5 Hz, 1.0 Hz, 1H), 7.05 (d, *J*=8.8 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.1 Hz, 2H), 6.90 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.43 (t, *J*=8.1 Hz, 1H), 3.58 (d, *J*=8.1 Hz, 2H), 2.86 (sep, *J*=7.1 Hz, 1H), 1.31 (d, *J*=6.8 Hz, 3H), 1.27 (d, *J*=6.8 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{24}H_{26}NO_3$ $[M + H]^+$: calcd, 376.1913; found, 376.1912.

2-(2-(3-Methylbutanoyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-86). Refer to general procedure for *t*-Boc deprotection: colorless oil/white solid, 48 mg, 86% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.37 (d, *J*=7.6 Hz, 2H), 7.35 (d, *J*=7.3 Hz, 2H), 7.26-7.30 (m, 3H), 7.16 (d, *J*=2.8 Hz, 1H), 7.13 (tt, *J*=7.6 Hz, 7.3 Hz, 1.1 Hz, 1H), 7.06 (d, *J*=8.9 Hz, 1H), 7.00 (dd, *J*=8.7 Hz, 1.1 Hz, 2H), 6.90 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.44 (t, *J*=8.0 Hz, 1H), 3.60 (dd, *J*=12.9 Hz, 8.1 Hz, 1H), 3.55 (dd, *J*=12.9 Hz, 8.1 Hz, 1H), 2.49 (dd, *J*=7.0 Hz, 2.4 Hz, 2H), 2.15 (sep, *J*=6.8 Hz, 1H), 1.04 (d, *J*=4.3 Hz, 3H), 1.03 (d, *J*=4.6 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{25}H_{28}NO_3$ $[M + H]^+$: calcd, 390.2069; found, 390.2064.

N-t-Boc-2-(2-(4-pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.104). Refer to general procedure for Mitsunobu reaction. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (50%/50%)) to give **5.104** as a colorless oil (0.13 g, 70% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.56 (dd, *J*=6.1 Hz, 3.0 Hz, 2H), 7.31 (dd, *J*=8.3 Hz, 7.6 Hz, 2H), 7.28 (d, *J*=7.3 Hz, 2H), 7.22 (m, 3H), 7.16 (d, *J*=5.6 Hz, 2H), 7.06 (t, *J*=7.5 Hz, 1H), 7.01 (d, *J*=2.0 Hz, 1H), 6.94 (d, *J*=8.6 Hz, 2H), 6.84 (dd, *J*=8.9 Hz, 2.9 Hz, 1H), 6.78 (d, *J*=8.9 Hz, 1H), 5.02 (d, *J*=13.4 Hz, 1H), 4.96 (d, *J*=13.1 Hz, 1H), 4.61 (t, *J*=7.7 Hz, 1H), 4.56 (br s, 1H), 3.73 (m, 2H), 1.40 (s, 9H).

N-t-Boc-2-(2-(3-pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.105). Refer to general procedure for Mitsunobu reaction. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (75%/25%)) to give **5.105** as a colorless oil (0.17 g, 92% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.58 (d, *J*=4.6 Hz, 1H), 8.53 (s, 1H), 7.54 (d, *J*=8.1 Hz, 1H), 7.31 (m, 2H), 7.29 (m, 1H),

7.26 (d, *J*=7.6 Hz, 2H), 7.21 (tt, *J*=8.6 Hz, 7.3 Hz, 1.0 Hz, 1H), 7.16 (d, *J*=6.8 Hz, 2H), 7.06 (t, *J*=7.5 Hz, 1H), 7.02 (s, 1H), 6.94 (d, *J*=8.3 Hz, 2H), 6.86 (d, *J*=1.5 Hz, 2H), 4.94 (d, *J*=11.6 Hz, 1H), 4.91 (d, *J*=11.6 Hz, 1H), 4.53 (t, *J*=7.8 Hz, 1H), 3.70 (m, 2H), 1.39 (s, 9H).

N-t-Boc-2-(2-(2-pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.106). Refer to general procedure for Mitsunobu reaction. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (50%/50%)) to give **5.106** as a colorless oil (0.15 g, 75% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.87 (d, *J*=5.8 Hz, 1H), 8.61 (dt, *J*=8.0 Hz, 1.3 Hz, 1H), 8.07 (t, *J*=6.9 Hz, 1H), 7.99 (d, *J*=8.1 Hz, 1H), 7.18-7.34 (m, 7H), 7.08 (m, 2H), 6.89-6.96 (m, 3H), 6.87 (dd, *J*=8.7 Hz, 2.8 Hz, 1H), 5.47 (d, *J*=15.2 Hz, 1H), 5.37 (d, *J*=14.9 Hz, 1H), 4.74 (t, *J*=7.8 Hz, 1H), 3.80 (dd, *J*=13.7 Hz, 7.2 Hz, 1H), 3.64 (m, 1H), 3.49 (dd, *J*=13.7 Hz, 8.9 Hz, 1H), 1.38 (s, 9H).

N-t-Boc-2-(2-(furfuryloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.107). Refer to general procedure for Mitsunobu reaction. The crude product was purified via Biotage® purification system (DCM/Hexanes (75%/25%) to (100%/0%)) to give **5.107** as a yellow oil (61 mg, 61% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.45 (d, *J*=0.9 Hz, 1H), 7.18-7.32 (m, 8H), 7.05 (t, *J*=7.4 Hz, 1H), 6.94 (d, *J*=3.0 Hz, 2H), 6.92 (d, *J*=8.7 Hz, 2H), 6.83 (dd, *J*=8.8 Hz, 2.7 Hz, 1H), 6.36 (m, 2H), 4.91 (d, *J*=3.6 Hz, 2H), 4.52 (t, *J*=7.8 Hz, 1H), 3.70 (t, *J*=6.5 Hz, 2H), 1.38 (s, 9H).

N-t-Boc-2-(2-(3-furanylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.108). Refer to general procedure for Mitsunobu reaction. The crude product was purified via flash SiO_2 chromatography (DCM/Hexanes (25%/75%) to (100%/0%)) to

give **5.108** as a colorless oil (0.16 g, 89% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41 (t, *J*=1.6 Hz, 1H), 7.40 (s, 1H), 7.30 (dd, *J*=8.5 Hz, 7.5 Hz, 2H), 7.26 (m, 2H), 7.20 (m, 3H), 7.05 (t, *J*=7.3 Hz, 1H), 6.96 (d, *J*=1.5 Hz, 1H), 6.92 (d, *J*=8.1 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 1H), 6.84 (dd, *J*=8.8 Hz, 2.5 Hz, 1H), 6.36 (d, *J*=0.8 Hz, 1H), 4.86 (dd, *J*=20.0 Hz, 11.6 Hz, 2H), 4.53 (t, *J*=7.8 Hz, 1H), 3.71 (m, 2H), 1.39 (s, 9H).

N-t-Boc-2-(2-(2-thiopheneylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.109). Refer to general procedure for Mitsunobu reaction. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (2%/98%)) to give **5.109** as a colorless oil (0.11 g, 59% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33 (dd, *J*=4.8 Hz, 1.5 Hz, 1H), 7.30 (dd, *J*=8.3 Hz, 7.6 Hz, 2H), 7.20-7.27 (m, 3H), 7.19 (m, 1H), 7.06 (d, *J*=7.3 Hz, 1H), 6.99-7.03 (m, 3H), 6.97 (d, *J*=2.8 Hz, 1H), 6.93 (s, 1H), 6.90 (d, *J*=8.8 Hz, 2H), 6.84 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 5.14 (dd, *J*=19.1 Hz, 11.7 Hz, 2H), 4.55 (t, *J*=7.8 Hz, 1H), 4.51 (br s, 1H), 3.71 (t, *J*=6.7 Hz, 2H), 1.38 (s, 9H).

N-t-Boc-2-(2-(3-thiopheneylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.110). Refer to general procedure for Mitsunobu reaction. The crude product was purified via flash SiO_2 chromatography (DCM/Hexanes (10%/90%) to (65%/35%)) to give **5.110** as a colorless oil (97 mg, 52% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31 (m, 1H), 7.30 (dd, *J*=8.5 Hz, 7.5 Hz, 2H), 7.26 (d, *J*=6.8 Hz, 2H), 7.18-7.21 (m, 4H), 7.05 (t, *J*=7.3 Hz, 1H), 7.00 (dd, *J*=5.1 hz, 1.3 Hz, 1H), 6.96 (d, *J*=1.8 Hz, 1H), 6.93 (d, *J*=7.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 1H), 6.83 (dd, *J*=8.8 Hz, 2.5 Hz, 1H), 4.99 (dd, *J*=19.2 Hz, 11.6 Hz, 2H), 4.66 (t, *J*=7.8 Hz, 1H), 4.53 (br s, 1H), 3.71 (m, 2H), 1.39 (s, 9H).

N-t-Boc-2-(2-(2-(4-morpholinyl)ethoxy)-5-phenoxyphenyl)-2-phenylethylamine (5.111). Refer to general procedure for Mitsunobu reaction. The

crude product was purified via Biotage® purification system (EtOAc/DCM (40%/60%) to (80%/20%)) to give **5.111** as a brownish white solid (0.15 g, 76% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.31 (m, 6H), 7.19 (m, 1H), 7.04 (t, *J*=7.2 Hz, 1H), 6.90-6.94 (m, 3H), 6.85 (dd, *J*=9.0 Hz, 2.7 Hz, 1H), 6.80 (d, *J*=8.8 Hz, 1H), 4.98 (t, *J*=5.7 Hz, 1H), 4.56 (t, *J*=8.0 Hz, 1H), 4.05 (sext, *J*=3.9 Hz, 2H), 3.62-3.79 (m, 2H), 3.70 (t, *J*=4.7 Hz, 4H), 2.74 (q, *J*=4.7 Hz, 2H), 2.52 (t, *J*=4.0 Hz, 4H), 1.38 (s, 9H).

2-(2-(4-Pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-99). Refer to general procedure for *t*-Boc deprotection: yellowish foam, 0.13 g, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.82 (d, *J*=6.6 Hz, 2H), 7.96 (d, *J*=6.8 Hz, 2H), 7.36-7.39 (m, 4H), 7.33 (dd, *J*=8.7 Hz, 7.5 Hz, 2H), 7.29 (m, 1H), 7.18 (d, *J*=2.3 Hz, 1H), 7.08 (tt, *J*=7.6 Hz, 7.5 Hz, 1.0 Hz, 1H), 7.03 (d, *J*=9.1 Hz, 1H), 6.94 (m, 2H), 6.90 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 5.47 (d, *J*=16.2 Hz, 1H), 5.41 (d, *J*=15.9 Hz, 1H), 4.91 (t, *J*=8.3 Hz, 1H), 3.69 (dd, *J*=12.8 Hz, 8.0 Hz, 1H), 3.63 (dd, *J*=13.0 Hz, 8.5 Hz, 1H). HRMS (EI$^+$) *m/z* for $C_{26}H_{25}N_2O_2$ $[M + H]^+$: calcd, 397.1916; found, 397.1920.

2-(2-(3-Pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-100). Refer to general procedure for *t*-Boc deprotection: white foam, 0.17 g, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.84 (d, *J*=5.6 Hz, 1H), 8.81 (s, 1H), 8.48 (d, *J*=8.1 Hz, 1H), 8.08 (dd, *J*=8.1 Hz, 5.8 Hz, 1H), 7.27-7.37 (m, 7H), 7.15 (d, *J*=3.0 Hz, 1H), 7.11 (d, *J*=9.1 Hz, 1H), 7.08 (tt, *J*=7.6 Hz, 7.3 Hz, 1.0 Hz, 1H), 6.94 (dd, *J*=8.8 Hz, 1.01 Hz, 2H), 6.92 (dd, *J*=9.1 Hz, 3.0 Hz, 1H), 5.33 (dd, *J*=22.2 Hz, 13.1 Hz, 2H), 4.82 (t, *J*=8.0 Hz, 1H), 3.65 (dd, *J*=12.8 Hz, 8.0 Hz, 1H), 3.59 (dd, *J*=12.8

Hz, 8.5 Hz, 1H). HRMS (EI^+) *m/z* for $C_{26}H_{25}N_2O_2$ $[M + H]^+$: calcd, 397.1916; found, 397.1915.

2-(2-(2-Pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-101). Refer to general procedure for *t*-Boc deprotection: white foam, 0.13 g, 95% yield. ^1H NMR (400 MHz, methanol-d_4) δ 8.88 (d, *J*=5.1 Hz, 1H), 8.55 (dt, *J*=8.0 Hz, 1.4 Hz, 1H), 8.01 (t, *J*=6.4 Hz, 1H), 7.92 (d, *J*=8.1 Hz, 1H), 7.33 (dd, *J*=8.7 Hz, 7.5 Hz, 2H), 7.24-7.31 (m, 5H), 7.13 (d, *J*=2.8 Hz, 1H), 7.10 (d, *J*=9.3 Hz, 1H), 7.09 (t, *J*=7.3 Hz, 1H), 6.94 (dd, *J*=7.7 Hz, 1.1 Hz, 2H), 6.92 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 5.47 (d, *J*=14.4 Hz, 1H), 5.38 (d, *J*=14.2 Hz, 1H), 4.91 (m, 1H), 3.66 (dd, *J*=12.8 Hz, 7.7 Hz, 1H), 3.60 (dd, *J*=12.8 Hz, 8.5 Hz, 1H). HRMS (EI^+) *m/z* for $C_{26}H_{25}N_2O_2$ $[M + H]^+$: calcd, 397.1916; found, 397.1914.

Scheme 5-6. Synthesis of **ET-87** and **ET-88**

2-(2-Benzyloxy-5-hydroxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-87). Refer to general procedure for *t*-Boc deprotection: white solid, 49 mg, ~100% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.31-7.38 (m, 7H), 7.27 (d, *J*=7.1 Hz, 2H), 7.26 (m, 1H), 6.92 (d, *J*=8.8 Hz, 1H), 6.71 (d, *J*=2.8 Hz, 1H), 6.67 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 5.01 (d, *J*=11.6 Hz, 1H), 4.96 (d, *J*=11.4 Hz, 1H), 4.65 (t, *J*=8.1 Hz, 1H), 3.58 (dd, *J*=12.8 Hz, 8.0 Hz, 1H), 3.52 (dd, *J*=12.8 Hz, 8.5 Hz, 1H). HRMS (EI^+) *m/z* for $C_{21}H_{22}NO_2$ $[M + H]^+$: calcd, 320.1651; found, 320.1652.

N-*t*-Boc-2-(2-benzyloxy-5-(*tert*-butyldimethylsiloxy)phenyl)-2-(phenyl)ethylamine (5.117). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl protection. The crude product was purified via flash SiO_2

chromatography (EtOAc/Hexanes (10%/90%)) to give **5.117** as a colorless oil (1.11 g, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.30-7.35 (m, 3H), 7.24-7.27 (m, 4H), 7.19 (d, *J*=6.6 Hz, 2H), 7.18 (m, 1H), 6.77 (d, *J*=8.8 Hz, 1H), 6.69 (d, *J*=2.8 Hz, 1H), 6.65 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 4.93 (dd, *J*=19.5 Hz, 11.6 Hz, 2H), 4.53 (t, *J*=7.7 Hz, 1H), 4.22 (m, 1H), 3.72 (m, 2H), 1.39 (s, 9H), 0.95 (s, 9H), 0.10 (d, *J*=24.3 Hz, 6H).

N-*t*-Boc-2-(2-hydroxy-5-(*tert*-butyldimethylsiloxy)phenyl)-2-(phenyl)ethylamine (5.118). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. The crude product was obtained as a colorless oil/foam (0.90 g, 98% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (t, *J*=7.5 Hz, 2H), 7.24-7.28 (m, 3H), 6.71 (d, *J*=8.6 Hz, 1H), 6.59 (dd, *J*=8.6 Hz, 3.0 Hz, 1H), 6.38 (br s, 1H), 6.21 (br s, 1H), 4.77 (br s, 1H), 4.42 (dd, *J*=8.5 Hz, 6.2 Hz, 1H), 3.67 (m, 2H), 1.42 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H).

N-*t*-Boc-2-(2-hexyloxy-5-(*tert*-butyldimethylsiloxy)phenyl)-2-(phenyl)ethylamine (5.119). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (20%/80%)) to give **5.119** as a colorless oil (0.38 g, 35% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.28 (m, 4H), 7.18 (t, *J*=7.0 Hz, 1H), 6.65-6.69 (m, 2H), 6.64 (dd, *J*=8.3 Hz, 2.8 Hz, 1H), 4.57 (br s, 1H), 4.48 (t, *J*=7.8 Hz, 1H), 3.69-3.87 (m, 4H), 1.70 (quin, *J*=6.6 Hz, 2H), 1.40 (s, 9H), 1.40 (m, 2H), 1.31 (m, 4H), 0.94 (s, 9H), 0.90 (t, *J*=6.8 Hz, 3H), 0.12 (s, 6H).

N-*t*-Boc-2-(2-hexyloxy-5-hydroxyphenyl)-2-(phenyl)ethylamine (5.120). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to

(20%/80%)) to give **5.120** as a colorless oil (0.22 g, 76% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.28 (m, 4H), 7.18 (tt, *J*=7.6 Hz, 7.0 Hz, 1.6 Hz, 1H), 6.71 (d, *J*=8.6 Hz, 1H), 6.68 (d, *J*=2.8 Hz, 1H), 6.65 (dd, *J*=8.6 Hz, 3.0 Hz, 1H), 5.01 (s, 1H), 4.64 (br s, 1H), 4.51 (t, *J*=8.0 Hz, 1H), 3.82 (m, 2H), 3.71 (m, 2H), 1.71 (quin, *J*=6.5 Hz, 2H), 1.40 (m, 2H), 1.39 (s, 9H), 1.31 (m, 4H), 0.90 (t, *J*=6.9 Hz, 3H).

2-(2-Hexyloxy-5-hydroxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-88). Refer to general procedure for *t*-Boc deprotection: colorless oil/white foam, 0.19 g, 99% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.30-7.36 (m, 4H), 7.26 (m, 1H), 6.82 (d, *J*=8.6 Hz, 1H), 6.69 (d, *J*=3.0 Hz, 1H), 6.67 (dd, *J*=8.5 Hz, 2.9 Hz, 1H), 4.63 (t, *J*=8.1 Hz, 1H), 3.87 (m, 2H), 3.60 (dd, *J*=12.8 Hz, 8.0 Hz, 1H), 3.54 (dd, *J*=12.8 Hz, 8.2 Hz, 1H), 1.75 (t, *J*=6.7 Hz, 1H), 1.72 (t, *J*=6.3 Hz, 1H), 1.42 (m, 2H), 1.33 (m, 4H), 0.92 (t, *J*=7.0 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{20}H_{28}NO_2$ $[M + H]^+$: calcd, 314.2120; found, 314.2119.

Scheme 5-7. Synthesis of **ET-89**

2-(Isoindolinyl-1,3-dione)(1-(2-benzyloxy-5-(triisopropylsiloxy)phenyl))-ethene (5.121). To a solution of **2.67** (5.05 g, 10.06 mmol) in THF (32 mL) at 0^{o}C was added KHMDS (20.12 mL, 10.06 mmol, 0.5M in toluene) over 5 min. After stirring at 0^{o}C for 10 min, a solution of **5.44** (1.61 g, 4.19 mmol) in THF (10 mL) was added and the reaction was warmed to room temperature. After 24 h, the reaction was quenched with water and diluted with EtOAc. The organic layer was washed with brine and saturated NH_4Cl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via Biotage® purification system (EtOAc/Hexanes

(0%/100%) to (25%/75%)) to give **5.121** as a yellow oil/yellow solid (1.69 g, 77% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.89 (q, *J*=2.8 Hz, 2H), 7.87 (d, *J*=15.5 Hz, 1H), 7.75 (q, *J*=2.8 Hz, 2H), 7.50 (dd, *J*=8.2 Hz, 1.4 Hz, 2H), 7.43 (d, *J*=15.2 Hz, 1H), 7.41 (t, *J*=7.8 Hz, 2H), 7.32 (tt, *J*=8.1 Hz, 7.3 Hz, 1.3 Hz, 1H), 7.01 (d, *J*=3.0 Hz, 1H), 6.81 (d, *J*=8.9 Hz, 1H), 6.72 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 5.10 (s, 2H), 1.26 (m, 3H), 1.11 (d, *J*=6.8 Hz, 18H).

N-*t*-Boc-2-(2-hydroxy-5-(triisopropylsiloxy)phenyl)ethylamine (5.122). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. Compound **5.121** was hydrogenated as a solution in EtOAc. The crude hydrogenated product was obtained as a yellowish solid (0.38 g, 21% yield). The phthalimide group was then exchanged for a Boc group by following the general procedure for phthalimide deprotection and subsequent *t*-Boc protection. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (50%/50%)) to give **5.122** as a colorless oil (0.16 g, 44% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.69 (d, *J*=8.6 Hz, 1H), 6.63 (dd, *J*=8.6 Hz, 2.8 Hz, 1H), 6.59 (d, *J*=2.8 Hz, 1H), 6.41 (br s, 1H), 4.85 (br s, 1H), 3.28 (t, *J*=6.4 Hz, 1H), 3.26 (t, *J*=6.1 Hz, 1H), 2.76 (t, *J*=7.2 Hz, 2H), 1.45 (s, 9H), 1.22 (m, 3H), 1.08 (d, *J*=7.1 Hz, 18H).

N-*t*-Boc-2-(2-hexyloxy-5-(triisopropylsiloxy)phenyl)ethylamine (5.123). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (10%/90%)) to give **5.123** as a colorless oil (0.19 g, 81% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.67 (m, 3H), 4.73 (br s, 1H), 3.89 (t, *J*=6.6 Hz, 2H), 3.34 (q, *J*=6.1 Hz, 2H), 2.74 (t,

J=6.3 Hz, 2H), 1.77 (dt, *J*=15.2 Hz, 6.6 Hz, 2H), 1.45 (m, 2H), 1.42 (s, 9H), 1.33 (m, 4H), 1.22 (m, 3H), 1.09 (d, *J*=7.1 Hz, 18H), 0.91 (t, *J*=7.1 Hz, 3H).

N-*t*-Boc-2-(2-hexyloxy-5-hydroxyphenyl)ethylamine (5.124). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (20%/80%)) to give **5.124** as a colorless oil/white solid (0.11 g, 87% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.72 (d, *J*=9.4 Hz, 1H), 6.64-6.67 (m, 2H), 4.80 (br s, 1H), 4.69 (s, 1H), 3.89 (t, *J*=6.4 Hz, 2H), 3.35 (q, *J*=5.6 Hz, 2H), 2.76 (t, *J*=6.4 Hz, 2H), 1.77 (dt, *J*=14.8 Hz, 6.6 Hz, 2H), 1.45 (m, 2H), 1.43 (s, 9H), 1.34 (m, 4H), 0.91 (t, *J*=7.1 Hz, 3H).

N-*t*-Boc-2-(2-hexyloxy-5-phenoxyphenyl)ethylamine (5.125). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **5.125** as a white solid (0.11 g, 80% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.29 (dd, *J*=8.8 Hz, 7.4 Hz, 2H), 7.04 (tt, *J*=7.5 Hz, 7.4 Hz, 1.1 Hz, 1H), 6.94 (dd, *J*=8.6 Hz, 1.0 Hz, 2H), 6.78-6.89 (m, 3H), 4.74 (br s, 1H), 3.95 (t, *J*=6.5 Hz, 2H), 3.35 (q, *J*=6.2 Hz, 2H), 2.78 (t, *J*=6.5 Hz, 2H), 1.81 (quin, *J*=6.5 Hz, 2H), 1.48 (m, 2H), 1.41 (s, 9H), 1.36 (m, 4H), 0.92 (t, *J*=7.0 Hz, 3H).

2-(2-Hexyloxy-5-phenoxyphenyl)ethylamine Hydrochloride (ET-89). Refer to general procedure for *t*-Boc deprotection: white solid, 91 mg, 99% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.30 (dd, *J*=8.7 Hz, 7.4 Hz, 2H), 7.04 (t, *J*=7.3 Hz, 1H), 6.98 (dd, *J*=6.6 Hz, 3.0 Hz, 1H), 6.89-6.93 (m, 4H), 4.03 (t, *J*=6.6 Hz, 2H), 3.15 (t, *J*=7.6 Hz, 2H), 2.94 (t, *J*=7.5 Hz, 2H), 1.83 (quin, *J*=6.6 Hz, 2H), 1.51 (quin, *J*=7.3 Hz, 2H), 1.38 (m, 4H), 0.94 (t, *J*=7.1 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{20}H_{28}NO_2$ $[M + H]^+$: calcd, 314.2120; found, 314.2115.

Scheme 5-8. Synthesis of **ET-90**

N-*t*-Boc-N-methyl-2-(2-(hexyloxy)-5-phenoxyphenyl)-2-phenylethylamine (5.126). Refer to general procedure for N-methylation of a *t*-Boc protected amine. The crude product was purified via flash SiO_2 chromatography (EtOAc/hexanes (10%/90%)) to give **5.126** as a colorless oil (0.19 g, 79% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.23-7.31 (m, 6H), 7.17 (t, *J*=6.4 Hz, 1H), 7.04 (m, 2H), 6.93 (d, *J*=8.3 Hz, 1H), 6.91 (m, 1H), 6.82 (dd, *J*=8.7 Hz, 3.0 Hz, 1H), 6.76 (d, *J*=8.6 Hz, 1H), 4.73 (t, *J*=7.5 Hz, 1H), 3.82-3.92 (m, 3H), 3.74 (dd, *J*=13.6 Hz, 7.3 Hz, 1H), 2.76; 2.65 (s, 3H), 1.73 (quin, *J*=6.9 Hz, 2H), 1.41 (quin, *J*=6.7 Hz, 2H), 1.35 (s, 9H), 1.32 (m, 4H), 0.91 (t, *J*=6.8 Hz, 3H).

N-Methyl-2-(2-(hexyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-90). Refer to general procedure for *t*-Boc deprotection: colorless oil/white solid, 0.17 g, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.31-7.37 (m, 4H), 7.29 (dd, *J*=8.6 Hz, 7.3 Hz, 2H), 7.27 (m, 1H), 7.05 (d, *J*=3.0 Hz, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 6.98 (d, *J*=8.8 Hz, 1H), 6.88-6.91 (m, 3H), 4.75 (t, *J*=8.1 Hz, 1H), 3.97 (m, 2H), 3.70 (d, *J*=8.1 Hz, 2H), 2.70 (s, 3H), 1.81 (t, *J*=6.4 Hz, 1H), 1.77 (t, *J*=6.6 Hz, 1H), 1.45 (quin, *J*=6.9 Hz, 2H), 1.35 (m, 4H), 0.93 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, methanol-d_4) δ 159.7, 154.1, 151.6, 140.8, 130.8, 130.7, 130.0, 129.2, 128.6, 123.7, 120.7, 120.5, 118.7, 114.2, 69.8, 53.4, 43.3, 34.4, 32.8, 30.4, 27.0, 23.7, 14.4. HRMS (EI$^+$) *m/z* for $C_{27}H_{34}NO_2$ $[M + H]^+$: calcd, 404.2590; found, 404.2585.

Scheme 5-9. Synthesis of **ET-91–ET-94**

N-*t*-Boc-2-(2-benzyloxy-5-((4-triisopropylsiloxy)phenoxy)phenyl)-2-(phenyl)ethylamine (5.133). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%)) to give **5.133** as a colorless oil (0.44 g, 69% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31-7.37 (m, 3H), 7.24-7.28 (m, 4H), 7.18-7.21 (m, 3H), 6.92 (d, *J*=2.8 Hz, 1H), 6.82 (d, *J*=8.6 Hz, 1H), 6.82 (s, 4H), 6.74 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 4.96 (dd, *J*=19.3 Hz, 6.8 Hz, 2H), 4.57 (t, *J*=8.0 Hz, 1H), 4.54 (br s, 1H), 3.71 (t, *J*=6.6 Hz, 2H), 1.39 (s, 9H), 1.25 (m, 3H), 1.10 (d, *J*=7.1 Hz, 18H).

N-*t*-Boc-2-(2-benzyloxy-5-((3-triisopropylsiloxy)phenoxy)phenyl)-2-(phenyl)ethylamine (5.134). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (10%/90%)) to give **5.134** as a colorless oil (0.49 g, 78% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (m, 1H), 7.33 (t, *J*=7.6 Hz, 2H), 7.24-7.28 (m, 4H), 7.18-7.21 (m, 3H), 7.11 (t, *J*=8.1 Hz, 1H), 6.97 (d, *J*=2.5 Hz, 1H), 6.85 (d, *J*=8.9 Hz, 1H), 6.81 (dd, *J*=8.7 Hz, 2.7 Hz, 1H), 6.58 (dd, *J*=7.7 Hz, 1.9 Hz, 1H), 6.48 (d, *J*=9.1 Hz, 2H), 4.98 (dd, *J*=19.7 Hz, 11.9 Hz, 2H), 4.58 (t, *J*=8.0 Hz, 1H), 4.54 (br s, 1H), 3.72 (t, *J*=7.8 Hz, 2H), 1.39 (s, 9H), 1.23 (m, 3H), 1.07 (d, *J*=7.3 Hz, 18H).

N-*t*-Boc-2-(2-benzyloxy-5-(4-fluorophenoxy)phenyl)-2-(phenyl)ethylamine (5.135). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (20%/80%)) to give **5.135** as a colorless oil/yellowish solid (0.41 g, 85% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32-7.38 (m, 3H), 7.25-7.29 (m, 4H), 7.18-7.22 (m, 3H), 6.99 (dd, *J*=9.0 Hz, 8.2 Hz, 2H), 6.94 (d, *J*=2.8 Hz, 1H), 6.88 (dd, *J*=9.2 Hz, 4.2 Hz, 2H), 6.85 (d, *J*=8.8

Hz, 1H), 6.78 (dd, *J*=9.0 Hz, 1H), 4.98 (dd, *J*=18.8 Hz, 11.7 Hz, 2H), 4.58 (t, *J*=8.0 Hz, 1H), 4.53 (br s, 1H), 3.72 (sep, *J*=6.3 Hz, 2H), 1.39 (s, 9H).

N-*t*-Boc-2-(2-benzyloxy-5-(3-fluorophenoxy)phenyl)-2-(phenyl)ethylamine (5.136). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (20%/80%)) to give **5.136** as a colorless oil/white solid (0.38 g, 77% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.36 (d, *J*=7.1 Hz, 2H), 7.35 (m, 1H), 7.25-7.29 (m, 4H), 7.22 (m, 2H), 7.20 (dd, *J*=8.1 Hz, 6.1 Hz, 2H), 6.98 (d, *J*=2.5 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 1H), 6.86 (dd, *J*=9.0 Hz, 2.4 Hz, 1H), 6.73 (dt, *J*=8.3 Hz, 2.2 Hz, 1H), 6.69 (dd, *J*=8.6 Hz, 2.3 Hz, 1H), 6.61 (d, *J*=10.6 Hz, 1H), 5.00 (dd, *J*=18.6 Hz, 11.5 Hz, 2H), 4.59 (t, *J*=8.0 Hz, 1H), 4.53 (br s, 1H), 3.72 (m, 2H), 1.38 (s, 9H).

N-*t*-Boc-2-(2-benzyloxy-5-(3-cyanophenoxy)phenyl)-2-(phenyl)ethylamine (5.137). Refer to general procedure for formation of a biaryl ether. The crude product was purified via Biotage® purification system (DCM/Hexanes (0%/100%) to (100%/0%)) to give **5.137** as a colorless oil (0.25 g, 51% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34-7.40 (m, 4H), 7.27-7.32 (m, 5H), 7.13-7.24 (m, 5H), 6.96 (d, *J*=2.8 Hz, 1H), 6.91 (d, *J*=8.8 Hz, 1H), 6.85 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 5.02 (dd, *J*=18.3 Hz, 11.5 Hz, 2H), 4.59 (t, *J*=8.0 Hz, 1H), 4.53 (br s, 1H), 3.79 (quin, *J*=6.7 Hz, 1H), 3.67 (quin, *J*=6.6 Hz, 1H), 1.38 (s, 9H).

N-*t*-Boc-2-(2-benzyloxy-5-(thiophen-3-yloxy)phenyl)-2-(phenyl)ethylamine (5.138). Refer to general procedure for formation of a biaryl ether. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (10%/90%)) to give **5.138** as a yellowish oil (0.16 g, 33% yield). ^{1}H NMR (400 MHz, chloroform-*d*)

δ 7.18-7.36 (m, 11H), 7.01 (d, *J*=2.3 Hz, 1H), 6.81-6.90 (m, 3H), 6.42 (s, 1H), 4.98 (dd, *J*=15.9 Hz, 11.8 Hz, 2H), 4.58 (t, *J*=7.9 Hz, 1H), 4.54 (br s, 1H), 3.72 (q, *J*=5.8 Hz, 2H), 1.39 (s, 9H).

N-*t*-Boc-2-(2-hydroxy-5-((4-triisopropylsiloxy)phenoxy)phenyl)-2-(phenyl)ethylamine (5.139). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (15%/85%)) to give **5.139** as a colorless oil/white foam (0.36 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34 (t, *J*=7.3 Hz, 2H), 7.24-7.28 (m, 2H), 6.81 (d, *J*=8.3 Hz, 2H), 6.77 (s, 4H), 6.69 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 6.58 (s, 1H), 4.83 (br s, 1H), 4.46 (dd, *J*=8.8 Hz, 4.8 Hz, 1H), 3.70; 3.59 (m, 2H), 1.43 (s, 9H), 1.24 (m, 3H), 1.09 (d, *J*=7.1 Hz, 18H).

N-*t*-Boc-2-(2-hydroxy-5-((3-triisopropylsiloxy)phenoxy)phenyl)-2-(phenyl)ethylamine (5.140). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (5%/95%) to (20%/80%)) to give **5.140** as a colorless oil/white foam (0.40 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35 (t, *J*=7.3 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 2H), 7.08 (d, *J*=8.1 Hz, 1H), 7.05 (s, 1H), 6.85 (d, *J*=8.6 Hz, 1H), 6.76 (dd, *J*=8.6 Hz, 2.8 Hz, 1H), 6.60 (s, 1H), 6.54 (dd, *J*=8.1 Hz, 2.0 Hz, 1H), 6.44 (dd, *J*=8.2 Hz, 1.6 Hz, 1H), 6.39 (s, 1H), 4.85 (br s, 1H), 4.47 (dd, *J*=9.0 hz, 4.9 Hz, 1H), 3.71; 3.58 (m, 2H), 1.44 (s, 9H), 1.20 (m, 3H), 1.06 (d, *J*=7.1 Hz, 18H).

N-*t*-Boc-2-(2-hydroxy-5-(4-fluorophenoxy)phenyl)-2-(phenyl)ethylamine (5.141). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was obtained as a yellowish foam (0.33 g, 96% yield). ^{1}H NMR (400

MHz, chloroform-*d*) δ 7.35 (t, *J*=7.5 Hz, 2H), 7.28 (d, *J*=7.1 Hz, 2H), 7.12 (s, 1H), 6.94 (t, *J*=8.6 Hz, 2H), 6.81-6.86 (m, 3H), 6.71 (dd, *J*=8.6 Hz, 2.8 Hz, 1H), 6.58 (s, 1H), 4.84 (br s, 1H), 4.48 (dd, *J*=8.7 Hz, 4.9 Hz, 1H), 3.74; 3.58 (m, 2H), 1.43 (s, 9H).

N-*t*-Boc-2-(2-hydroxy-5-(3-fluorophenoxy)phenyl)-2-(phenyl)ethylamine (5.142). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was obtained as a colorless oil/white foam (0.30 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35 (t, *J*=7.6 Hz, 2H), 7.28 (d, *J*=7.3 Hz, 2H), 7.18 (dd, *J*=15.0 Hz, 8.2 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 1H), 6.79 (dd, *J*=8.6 Hz, 2.8 Hz, 1H), 6.69 (dt, *J*=8.3 Hz, 2.4 Hz, 1H), 6.65 (dd, *J*=8.5 Hz, 1.9 Hz, 1H), 6.60 (s, 1H), 6.55 (d, *J*=10.4 Hz, 1H), 4.86 (t, *J*=5.8 Hz, 1H), 4.50 (dd, *J*=8.7 Hz, 4.9 Hz, 2H), 3.75; 3.59 (m, 2H), 1.44 (s, 9H).

N-*t*-Boc-2-(2-hydroxy-5-(3-cyanophenoxy)phenyl)-2-(phenyl)ethylamine (5.143). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%)) to give **5.143** as a colorless oil/white foam (0.17 g, 82% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.56 (br s, 1H), 7.25-7.39 (m, 7H), 7.08 (m, 1H), 7.06 (s, 1H), 6.92 (d, *J*=8.8 Hz, 1H), 6.78 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 6.55 (s, 1H), 4.89 (t, *J*=5.9 Hz, 1H), 4.52 (dd, *J*=9.0 Hz, 4.4 Hz, 1H), 3.77; 3.58 (m, 2H), 1.44 (s, 9H).

N-*t*-Boc-2-(2-hexyloxy-5-((4-triisopropylsiloxy)phenoxy)phenyl)-2-(phenyl)ethylamine (5.144). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (10%/90%)) to give **5.144** as a colorless oil (0.13 g, 43% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.28 (m, 4H), 7.18 (t, *J*=6.9 Hz, 1H),

6.89 (s, 1H), 6.81 (s, 4H), 6.74 (d, *J*=1.3 Hz, 2H), 4.56 (br s, 1H), 4.52 (t, *J*=7.8 Hz, 1H), 3.85 (m, 2H), 3.70 (t, *J*=6.6 Hz, 2H), 1.72 (dt, *J*=14.7 Hz, 6.4 Hz, 2H), 1.41 (m, 2H), 1.40 (m, 9H), 1.32 (m, 4H), 1.24 (m, 3H), 1.10 (d, *J*=7.1 Hz, 18H), 0.90 (t, *J*=7.0 Hz, 3H).

N-*t*-Boc-2-(2-hexyloxy-5-((3-triisopropylsiloxy)phenoxy)phenyl)-2-(phenyl)ethylamine (5.145). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via Biotage® purification system (EtOAc/Hexanes (0%/100%) to (10%/90%)) to give **5.145** as a colorless oil (62 mg, 21% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.29 (m, 4H), 7.18 (tt, *J*=7.5 Hz, 6.9 Hz, 1.7 Hz, 1H), 7.10 (t, *J*=8.1 Hz, 1H), 6.93 (d, *J*=2.5 Hz, 1H), 6.83 (dd, *J*=8.9 Hz, 2.8 Hz, 1H), 6.77 (d, *J*=8.9 Hz, 1H), 6.57 (dq, *J*=8.1 Hz, 2.3 Hz, 0.8 Hz, 1H), 6.49 (t, *J*=2.3 Hz, 1H), 6.46 (d, *J*=7.8 Hz, 1H), 4.56 (br s, 1H), 4.52 (t, *J*=7.8 Hz, 1H), 3.86 (m, 2H), 3.70 (t, *J*=6.7 Hz, 2H), 1.73 (m, 2H), 1.41 (m, 2H), 1.40 (s, 9H), 1.32 (m, 4H), 1.23 (m, 3H), 1.08 (d, *J*=7.1 Hz, 18H), 0.90 (t, *J*=7.1 Hz, 3H).

N-*t*-Boc-2-(2-hexyloxy-5-(4-fluorophenoxy)phenyl)-2-(phenyl)ethylamine (5.146). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.146** as a colorless oil (0.26 g, 94% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.27 (t, *J*=7.7 Hz, 2H), 7.22 (d, *J*=7.1 Hz, 2H), 7.19 (t, *J*=7.1 Hz, 1H), 6.98 (t, *J*=8.6 Hz, 2H), 6.91 (d, *J*=1.3 Hz, 1H), 6.87 (dd, *J*=9.0 Hz, 4.4 Hz, 2H), 6.78 (d, *J*=2.5 Hz, 2H), 4.55 (br s, 1H), 4.52 (t, *J*=7.8 Hz, 1H), 3.87 (m, 2H), 3.71 (q, *J*=6.8 Hz, 2H), 1.73 (dt, *J*=14.8 Hz, 6.4 Hz, 2H), 1.41 (m, 2H), 1.39 (s, 9H), 1.32 (m,4H), 0.91 (t, *J*=7.0 Hz, 3H).

N-*t*-Boc-2-(2-hexyloxy-5-(3-fluorophenoxy)phenyl)-2-(phenyl)ethylamine (5.147). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude

product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%)) to give **5.147** as a colorless oil (0.21 g, 89% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.30 (m, 5H), 7.19 (t, *J*=6.8 Hz, 1H), 6.94 (d, *J*=2.3 Hz, 1H), 6.86 (dd, *J*=8.7 Hz, 2.9 Hz, 1H), 6.80 (d, *J*=8.8 Hz, 1H), 6.72 (dt, *J*=8.3 Hz, 2.3 Hz, 1H), 6.68 (dd, *J*=8.1 Hz, 2.0 Hz, 1H), 6.60 (dd, *J*=10.5 Hz, 1.9 Hz, 1H), 4.56 (br s, 1H), 4.53 (t, *J*=7.8 Hz, 1H), 3.88 (m, 2H), 3.71 (m, 2H), 1.74 (quin, *J*=6.7 Hz, 2H), 1.41 (m, 2H), 1.39 (s, 9H), 1.33 (m, 4H), 0.91 (t, *J*=6.8 Hz, 3H).

N-*t*-Boc-2-(2-hexyloxy-5-(3-cyanophenoxy)phenyl)-2-(phenyl)ethylamine (5.148). Refer to general procedure for alkylation of a phenol with K_2CO_3. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **5.148** as a colorless oil (0.18 g, 90% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.37 (t, *J*=7.8 Hz, 1H), 7.29 (t, *J*=7.6 Hz, 3H), 7.19-7.23 (m, 3H), 7.14 (d, *J*=1.8 Hz, 1H), 7.12 (s, 1H), 6.92 (d, *J*=2.5 Hz, 1H), 6.86 (dd, *J*=8.7 Hz, 2.4 Hz, 1H), 6.82 (d, *J*=8.8 Hz, 1H), 4.55 (t, *J*=7.8 Hz, 1H), 4.55 (br s, 1H), 3.91 (m, 2H), 3.76; 3.67 (m, 2H), 1.76 (quin, *J*=6.6 Hz, 2H), 1.42 (m, 2H), 1.38 (s, 9H), 1.33 (m, 4H), 0.91 (t, *J*=6.8 Hz, 3H).

N-*t*-Boc-2-(2-hexyloxy-5-(4-hydroxyphenoxy)phenyl)-2-(phenyl)ethylamine (5.149). Refer to general procedure for *t*-butyldimethylsilyl or triisopropylsilyl deprotection. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **5.149** as a colorless oil/white solid (82 mg, 80% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21-7.29 (m, 4H), 7.18 (t, *J*=7.1 Hz, 1H), 6.89 (s, 1H), 6.83 (d, *J*=8.8 Hz, 2H), 6.77 (d, *J*=9.1 Hz, 2H), 6.74 (d, *J*=1.3 Hz, 2H), 4.91 (br s, 1H), 4.58 (br s, 1H), 4.51 (t, *J*=7.8 Hz, 1H), 3.84 (m, 2H), 3.70

(t, *J*=6.4 Hz, 2H), 1.72 (dt, *J*=14.7 Hz, 6.6 Hz, 2H), 1.42 (m, 2H), 1.40 (s, 9H), 1.31 (m, 4H), 0.90 (t, *J*=7.0 Hz, 3H).

2-(2-Hexyloxy-5-(4-hydroxyphenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-91). Refer to general procedure for *t*-Boc deprotection: colorless oil/white foam, 71 mg, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.29-7.36 (m, 4H), 7.26 (tt, *J*=7.5 Hz, 7.0 Hz, 1.8 Hz, 1H), 6.90-6.93 (m, 2H), 6.79 (dd, *J*=6.6 Hz, 2.5 Hz, 2H), 6.76 (m, 1H), 6.73 (dd, *J*=6.7 Hz, 2.4 Hz, 2H), 4.64 (t, *J*=8.1 Hz, 1H), 3.92 (m, 2H), 3.61 (dd, *J*=12.9 Hz, 7.8 Hz, 1H), 3.54 (dd, *J*=12.9 Hz, 8.3 Hz, 1H), 1.76 (dt, *J*=14.9 Hz, 6.6 Hz, 2H), 1.43 (quin, *J*=7.1 Hz, 2H), 1.34 (m, 4H), 0.93 (t, *J*=7.0 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{26}H_{32}NO_3$ $[M + H]^+$: calcd, 406.2382; found, 406.2381.

2-(2-Hexyloxy-5-(4-fluorophenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-92). Refer to general procedure for *t*-Boc deprotection: white solid, 0.22 g, 95% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.30-7.37 (m, 4H), 7.27 (m, 1H), 7.04 (dd, *J*=9.2 Hz, 8.2 Hz, 2H), 6.99 (t, *J*=3.0 Hz, 1H), 6.95 (d, *J*=6.3 Hz, 1H), 6.91 (t, *J*=4.4 Hz, 1H), 6.91 (dd, *J*=9.3 Hz, 4.6 Hz, 1H), 6.86 (dd, *J*=9.0 Hz, 2.9 Hz, 1H), 4.66 (t, *J*=8.1 Hz, 1H), 3.95 (m, 2H), 3.62 (dd, *J*=12.9 Hz, 7.8 Hz, 1H), 3.56 (dd, *J*=12.8 Hz, 8.5 Hz, 1H), 1.77 (dt, *J*=14.9 Hz, 6.6 Hz, 2H), 1.44 (quin, *J*=7.2 Hz, 2H), 1.35 (m, 4H), 0.93 (t, *J*=7.1 Hz, 3H). HRMS (EI$^+$) *m/z* for $C_{26}H_{31}NO_2F$ $[M + H]^+$: calcd, 408.2339; found, 408.2350.

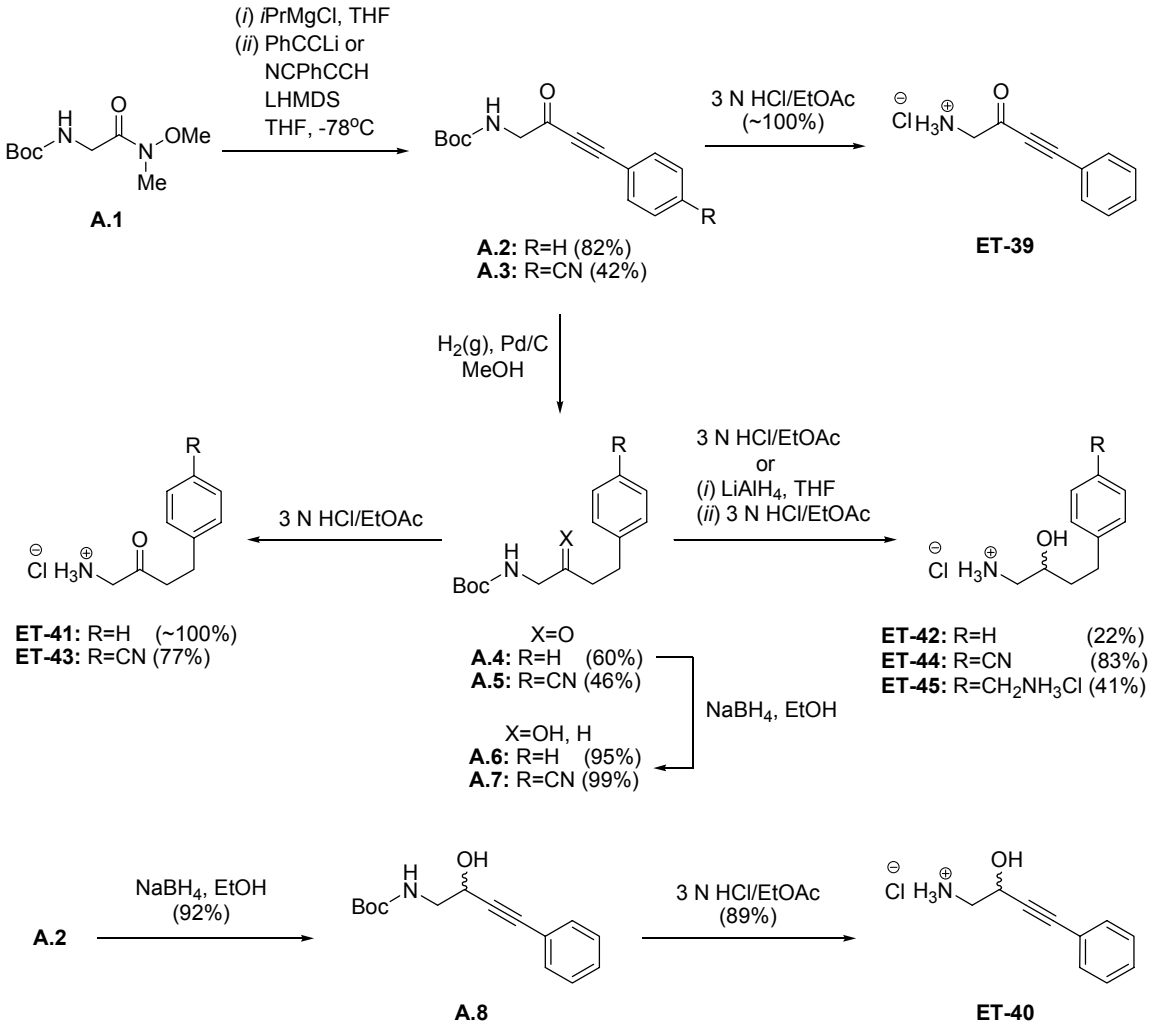
2-(2-Hexyloxy-5-(3-fluorophenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-93). Refer to general procedure for *t*-Boc deprotection: white solid, 0.19 g, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.25-7.37 (m, 6H), 7.04 (d, *J*=2.8 Hz, 1H), 7.01 (d, *J*=8.8 Hz, 1H), 6.95 (dd, *J*=8.9 Hz, 2.8 Hz, 1H), 6.77 (dt, *J*=8.3

Hz, 2.5 Hz, 1H), 6.71 (dd, *J*=8.3 Hz, 2.3 Hz, 1H), 6.62 (dt, *J*=10.6 Hz, 2.4 Hz, 1H), 4.68 (t, *J*=8.1 Hz, 1H), 3.98 (m, 2H), 3.64 (dd, *J*=12.8 Hz, 7.7 Hz, 1H), 3.58 (dd, *J*=12.9 Hz, 8.3 Hz, 1H), 1.79 (dt, *J*=14.8 Hz, 6.6 Hz, 2H), 1.45 (quin, *J*=7.2 Hz, 2H), 1.35 (m, 4H), 0.93 (t, *J*=6.9 Hz, 3H). HRMS (EI^+) *m/z* for $C_{26}H_{31}NO_2F$ $[M + H]^+$: calcd, 408.2339; found, 408.2333.

2-(2-Hexyloxy-5-(3-cyanophenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-94). Refer to general procedure for *t*-Boc deprotection: white solid, 97 mg, 61% yield. ^1H NMR (400 MHz, methanol-d_4) δ 7.48 (t, *J*=8.0 Hz, 1H), 7.39 (dt, *J*=7.6 Hz, 1.3 Hz, 1H), 7.31-7.38 (m, 4H), 7.27 (m, 1H), 7.22 (dq, *J*=8.3 Hz, 2.5 Hz, 1.0 Hz, 1H), 7.18 (dd, *J*=2.2 Hz, 1.4 Hz, 1H), 7.06 (d, *J*=2.8 Hz, 1H), 7.04 (d, *J*=8.9 Hz, 1H), 6.97 (dd, *J*=8.8 Hz, 2.8 Hz, 1H), 4.70 (t, *J*=8.1 Hz, 1H), 3.99 (m, 2H), 3.65 (dd, *J*=12.9 Hz, 7.8 Hz, 1H), 3.59 (dd, *J*=12.8 Hz, 8.5 Hz, 1H), 1.80 (dt, *J*=15.1 Hz, 6.5 Hz, 2H), 1.46 (quin, *J*=7.2 Hz, 2H), 1.36 (m, 4H), 0.94 (t, *J*=7.1 Hz, 3H). HRMS (EI^+) *m/z* for $C_{27}H_{31}N_2O_2$ $[M + H]^+$: calcd, 415.2386; found, 415.2391.

A.1.3.4 Appendix A Compounds

Scheme A-1. Synthesis of **ET-39**–**ET-45**



N-*t*-Boc-1-amino-4-phenylbut-3-yn-2-one (A.2). To a solution of **A.1** (1.02 g, 4.69 mmol) in THF (10 mL) at -15 to -10°C (ice methanol bath) was added dropwise *i*PrMgCl (2.34 mL, 4.69 mmol, 2M in THF) keeping the reaction temperature between -15 to -5°C. Lithium phenylacetylide (5.86 mL, 5.86 mmol, 1M in THF) was added dropwise keeping the reaction temperature below -15°C. After stirring at room temperature for 7 h, the reaction was cooled to <-20°C, quenched with 1N HCl (10.79

mL), and diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (35%/85%)) to give **A.2** as a yellowish white solid (0.99 g, 82% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.59 (d, *J*=7.2 Hz, 2H), 7.48 (t, *J*=7.4 Hz, 1H), 7.40 (t, *J*=7.4 Hz, 2H), 5.21 (br s, 1H), 4.25 (d, *J*=5.5 Hz, 2H), 1.46 (s, 9H).

N-*t*-Boc-1-amino-4-(4-cyanophenyl)but-3-yn-2-one (A.3). To a solution of 4-ethynylbenzonitrile (0.30 g, 2.39 mmol) in THF (5 mL) at -78^{o}C was added LHMDS (2.87 mL, 2.87 mmol, 1M in THF). In a separate round bottom flask, *i*PrMgCl (1.09 mL, 2.17 mmol, 2M in THF) was added dropwise to a solution of **A.1** (0.47 g, 2.17 mmol) in THF (5 mL) at -15^{o}C to -10^{o}C (ice/methanol bath) maintaining the temperature <-5^{o}C during the addition. The temperature was decreased to <-15^{o}C before transferring the lithium phenylacetylide solution at -78^{o}C via cannula over to the **A.1** reaction mixture. After stirring at room temperature for 20 h, the reaction was cooled to <-20^{o}C and quenched with 1 N HCl and diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (20%/80%) to (30%/70%)) to give **A.3** as a yellow green solid (0.26 g, 42% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.68 (d, *J*=4.8 Hz, 4H), 5.17 (br s, 1H), 4.24 (d, *J*=5.5 Hz, 2H), 1.46 (s, 9H).

1-Amino-4-phenylbut-3-yn-2-one Hydrochloride (ET-39). Refer to general procedure for *t*-Boc deprotection: brownish white solid, 0.38 g, ~100% yield. ^{1}H NMR

(400 MHz, methanol-d_4) δ 7.67 (dd, J=8.2 Hz, 1.4 Hz, 2H), 7.58 (tt, J=8.2 Hz, 7.6 Hz, 1.4 Hz, 1H), 7.49 (dd, J=7.7 Hz, 1.7 Hz, 2H), 4.23 (s, 2H).

N-*t*-Boc-1-amino-4-phenylbutan-2-one (A.4). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (10%/90%) to (15%/85%)) to give **A.4** as a colorless oil (0.22 g, 60% yield). ^{1}H NMR (400 MHz, chloroform-d) δ 7.28 (t, J=7.3 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 7.17 (dd, J=8.2 Hz, 1.4 Hz, 2H), 5.19 (br s, 1H), 3.97 (d, J=4.6 Hz, 2H), 2.94 (t, J=7.6 Hz, 2H), 2.75 (t, J=7.6 Hz, 2H), 1.44 (s, 9H).

N-*t*-Boc-1-amino-4-(4-cyanophenyl)butan-2-one (A.5). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2/C$. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (20%/80%) to (30%/70%)) to give **A.5** as a yellowish oil (97 mg, 46% yield). ^{1}H NMR (400 MHz, chloroform-d) δ 7.58 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 5.15 (br s, 1H), 3.97 (d, J=5.0 Hz, 2H), 3.00 (t, J=7.3 Hz, 2H), 2.78 (t, J=7.3 Hz, 2H), 1.44 (s, 9H).

1-Amino-4-phenylbutan-2-one Hydrochloride (ET-41). Refer to general procedure for *t*-Boc deprotection: white solid, 49 mg, ~100% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.26 (t, J=7.5 Hz, 2H), 7.22 (d, J=6.6 Hz, 2H), 7.17 (tt, J=7.0 Hz, 1.9 Hz, 1H), 3.92 (s, 2H), 2.94 (m, 2H), 2.88 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 203.4, 141.8, 129.6, 129.4, 127.3, 48.2, 42.2, 30.0.

1-Amino-4-(4-cyanophenyl)butan-2-one Hydrochloride (ET-43). Refer to general procedure for *t*-Boc deprotection: white solid, 64 mg, 77% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.64 (d, J=8.6 Hz, 2H), 7.42 (d, J=8.6 Hz, 2H), 3.94 (s, 2H), 3.02 (t, J=6.7 Hz, 2H), 2.93 (t, J=8.0 Hz, 2H).

N-*t*-Boc-1-amino-4-phenylbutan-2-ol (A.6). To a solution of **A.4** (0.16 g, 0.60 mmol) in EtOH (3 mL) at 0°C was added $NaBH_4$ (0.02 g, 0.60 mmol) After stirring at room temperature for 1 h, the reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (30%/70%)) to give **A.6** as a colorless oil (0.15 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28 (t, *J*=7.5 Hz, 2H), 7.20 (d, *J*=7.5 Hz, 2H), 7.19 (t, *J*=7.9 Hz, 1H), 4.89 (br s, 1H), 3.72 (br s, 1H), 3.31 (dq, *J*=12.7 Hz, 3.1 Hz, 1H), 3.07 (quin, *J*=6.6 Hz, 1H), 2.80 (quin, *J*=7.3 Hz, 1H), 2.69 (dt, *J*=13.9 Hz, 8.1 Hz, 1H), 2.42 (br s, 1H), 1.76 (dt, *J*=8.0 Hz, 6.2 Hz, 2H), 1.44 (s, 9H).

N-*t*-Boc-1-amino-4-(4-cyanophenyl)butan-2-ol (A.7). To a solution of **A.5** (0.02 g, 0.08 mmol) in EtOH (2 mL) at 0°C was added $NaBH_4$ (0.03 g, 0.08 mmol) After stirring at room temperature for 1 h, the reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was obtained as a colorless oil (22 mg, 99% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.57 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 4.88 (br s, 1H), 3.70 (br m, 1H), 3.28 (dq, *J*=14.5 Hz, 3.5 Hz, 1H), 3.10 (q, *J*=7.6 Hz, 1H), 2.84-2.91 (m, 1H), 2.76 (dt, *J*=14.1 Hz, 8.2 Hz, 1H), 1.75 (m, 2H), 1.45 (s, 9H).

1-Amino-4-phenylbutan-2-ol Hydrochloride (ET-42). Refer to general procedure for *t*-Boc deprotection. The deprotected product was found to contain impurities by ^{1}H NMR. The free amine was formed by treating the product with a solution 1M K_2CO_3 and extracting with DCM. The organic layer was dried over $MgSO_4$,

filtered, and concentrated under reduced pressure. The crude product was purified via flash prep TLC (MeOH/DCM (10%/90%)) and treated with 3N anhydrous HCl solution in EtOAc to give **ET-42** as a yellowish solid (26 mg, 22% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.27 (t, J=7.2 Hz, 2H), 7.22 (d, J=6.6 Hz, 2H), 7.16 (tt, J=7.1 Hz, 1.6 Hz, 1H), 3.75 (m, 1H), 3.01 (dd, J=12.7 Hz, 3.2 Hz, 1H), 2.78 (dd, J=12.8 Hz, 9.3 Hz, 1H), 2.81 (m, 1H), 2.68 (m, 1H), 1.79 (t, J=12.2 Hz, 1H), 1.76 (dd, J=8.7 Hz, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 142.8, 129.5, 127.0, 112.4, 68.1, 46.1, 37.8, 32.5.

1-Amino-4-(4-cyanophenyl)butan-2-ol Hydrochloride (ET-44). Refer to general procedure for *t*-Boc deprotection: yellowish solid, 15 mg, 83% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.65 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 3.77 (sep, J=4.4 Hz, 1H), 3.04 (dd, J=12.6 Hz, 3.1 Hz, 1H), 2.91 (m, 1H), 2.81 (dd, J=12.8 Hz, 9.3 Hz, 1H), 2.78 (m, 1H), 1.80 (m, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 149.1, 133.4, 130.7, 119.9, 110.8, 68.0, 46.0, 37.2, 32.6.

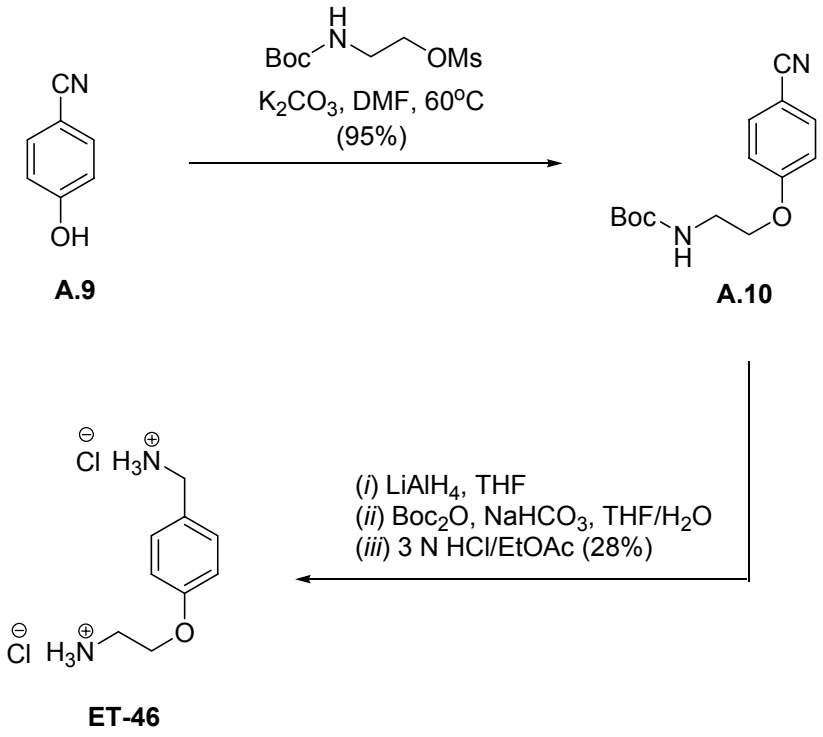
1-Amino-4-(4-aminomethylphenyl)butan-2-ol Dihydrochloride (ET-45). To a suspension of lithium aluminum hydride (0.01 g, 0.34 mmol) in THF (2 mL) at 0^{o}C, was added a solution of **A.5** (0.02 g, 0.08 mmol) in THF (1 mL). After stirring at room temperature overnight, the reaction was quenched with water (0.013 mL), 10% aqueous NaOH (0.026 mL) and water (0.039 mL). The reaction was filtered to remove the precipitated aluminum salts. The filtrate was washed with water and brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash prep TLC (MeOH/DCM (10%/90%)). The purified amine was then dissolved in MeOH (0.5 mL) and treated with 3N anhydrous HCl solution in EtOAc (0.5 mL) for 1.5 h. After concentrating under

reduced pressure, the reaction was exposed to Et_2O to precipitate the dihydrochloride salts: white solid, 8 mg, 41% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.38 (d, J=8.1 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 4.07 (s, 2H), 3.78 (sep, J=4.2 Hz, 1H), 3.03 (dd, J=12.5 hz, 3.2 Hz, 1H), 2.79 (dd, J=12.6 Hz, 9.2 Hz, 1H), 2.85 (m, 1H), 2.70 (m, 1H), 1.77 (m, 2H).

N-t-Boc-1-amino-4-phenylbut-3-yn-2-ol (A.8). To a solution of **A.2** (0.15 g, 0.56 mmol) in EtOH (3 mL) at 0^{o}C was added $NaBH_4$ (0.02 g, 0.56 mmol) After stirring at room temperature for 1 h, the reaction was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (15%/85%)) to give **A.8** as a yellow oil (0.14 g, 92% yield). ^{1}H NMR (400 MHz, chloroform-d) δ 7.43 (dd, J=5.0 Hz, 1.7 Hz, 2H), 7.32 (d, J=1.7 Hz, 2H), 7.31 (m, 1H), 5.03 (br s, 1H), 4.69 (br s, 1H), 3.57 (br d, J=15.4 Hz, 1H), 3.38 (dt, J=14.1 Hz, 5.7 Hz, 1H), 2.82 (br s, 1H), 1.46 (s, 9H),

1-Amino-4-phenylbut-3-yn-2-ol Hydrochloride (ET-40). Refer to general procedure for *t*-Boc deprotection: yellowish solid, 91 mg, 89% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.46 (dd, J=7.8 Hz, 1.9 Hz, 2H), 7.36 (d, J=1.7 Hz, 2H), 7.35 (m, 1H), 4.81 (dd, J=8.1 Hz, 3.9 Hz, 1H), 3.25 (dd, J=12.8 Hz, 3.9 Hz, 1H), 3.14 (dd, J=12.8 Hz, 8.1 Hz, 1H).

Scheme A-2. Synthesis of **ET-46**

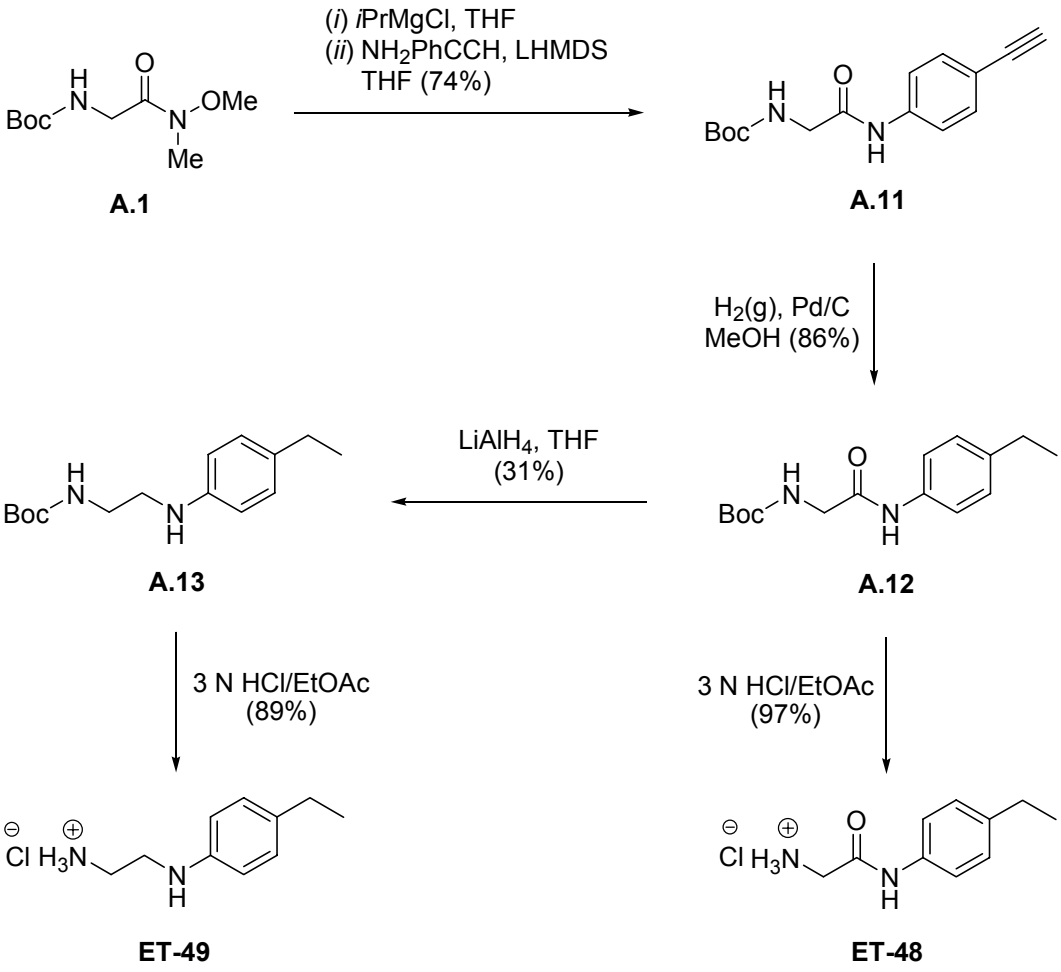


4-(2-(*t*-Boc-amino)ethoxy)benzonitrile (A.10). To a solution of 4-cyanophenol (0.20 g, 1.68 mmol) in DMF (15 mL) was added K_2CO_3 (0.46 g, 3.36 mmol) and N-*t*-Boc-2-aminoethyl mesylate (0.44 g, 1.85 mmol). After stirring at 60°C for 48 h, the reaction was diluted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%)) to give **A.10** as a white solid (0.42 g, 95% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.59 (d, *J*=8.8 Hz, 2H), 6.95 (d, *J*=9.0 Hz, 2H), 4.95 (br s, 1H), 4.07 (t, *J*=5.1 Hz, 2H), 3.55 (q, *J*=5.5 Hz, 2H), 1.45 (s, 9H).

4-(2-Aminoethoxy)benzylamine Dihydrochloride (ET-46). To a suspension of lithium aluminum hydride (77 mg, 2.04 mmol) in THF (6 mL) at 0°C, was added a

solution of **A.10** (0.21 g, 00.81 mmol) in THF (2 mL). After stirring at room temperature for 42 h, the reaction was quenched with water (0.077 mL), 10% aqueous NaOH (0.154 mL) and water (0.232 mL). The reaction was filtered to remove the precipitated aluminum salts. The filtrate was washed with water and brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. When the crude product was treated with a 3N anhydrous HCl solution in EtOAc, the precipitated hydrochloride salts were found to contain impurities by ^{1}H NMR. The amine hydrochloride was then *t*-Boc protected following the general procedure for *t*-Boc protection of an amine hydrochloride or hydrobromide salts. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (20%/80%)). The *t*-Boc protected amine was subsequently deprotected following the general procedure for *t*-Boc deprotection: white solid, 55 mg, 28% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.45 (d, J=8.6 Hz, 2H), 7.09 (d, J=8.8 Hz, 2H), 4.27 (t, J=5.0 Hz, 2H), 4.07 (s, 2H), 3.39 (t, J=4.8 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 160.1, 131.8, 127.5, 116.2, 65.4, 43.8, 40.3.

Scheme A-3. Synthesis of **ET-48** and **ET-49**



(2-*t*-Boc-amino)-N-(4-ethynylphenyl)acetamide (A.11). To a solution of 4-ethynylaniline (0.17 g, 1.43 mmol) in THF (3.5 mL) at -78°C was added LHMDS (1.95 mL, 1.95 mmol, 1M in THF). In a separate round bottom flask, *i*PrMgCl (0.58 mL, 1.15 mmol, 2M in THF) was added dropwise to a solution of **A.1** (0.25 g, 1.15 mmol) in THF (3.5 mL) at -15°C to -10°C (ice/methanol bath) maintaining the temperature <-5°C during the addition. The temperature was decreased to <-15°C before transferring the lithium phenylacetylide solution at -78°C via cannula over to the **A.1** reaction mixture. After stirring at room temperature for 20 h, the reaction was cooled to <-20°C and quenched

with 1 N HCl and diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%) to (30%/70%)) to give **A.11** as a tan solid (0.23 g, 74% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.26 (br s, 1H), 7.49 (d, *J*=8.8 Hz, 2H), 7.45 (d, *J*=9.0 Hz, 2H), 5.20 (br s, 1H), 3.92 (d, *J*=6.0 Hz, 2H), 3.04 (s, 1H), 1.48 (s, 9H).

(2-t-Boc-amino)-N-(4-ethylphenyl)acetamide (A.12). Refer to general procedure for catalytic hydrogenation with Pd/C or $Pd(OH)_2$/C. The crude product was purified via flash SiO_2 chromatography (EtOAc/Hexanes (25%/75%)) to give **A.12** as a white solid (0.12 g, 86% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.96 (br s, 1H), 7.41 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.2 Hz, 2H), 5.19 (br s, 1H), 3.91 (d, *J*=6.2 Hz, 2H), 2.61 (q, *J*=7.6 Hz, 2H), 1.48 (s, 9H), 1.21 (t, *J*=7.6 Hz, 3H).

N-(2-(*t*-Boc)-aminoethyl)-4-ethylbenzenamine (A.13). To a suspension of lithium aluminum hydride (19 mg, 0.37 mmol) in THF (2 mL) at 0^{o}C, was added a solution of **A.11** (25 mg, 0.09 mmol) in THF (1 mL). After stirring at room temperature overnight, the reaction was cooled to 0^{o}C and slowly quenched with water. After adding a solution of 1N HCl dropwise until the solution became clear, the reaction was diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash prep TLC (EtOAc/Hexanes (25%/75%)) to give **A.13** as a brownish solid (7 mg, 31% yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.02 (d, *J*=8.6 Hz, 2H), 6.59 (d, *J*=8.4 Hz, 2H), 4.80 (br s, 1H), 3.36 (t, *J*=6.0 Hz, 2H), 3.25 (t, *J*=5.7 Hz, 2H), 2.54 (q, *J*=7.5 Hz, 2H), 1.45 (s, 9H), 1.19 (t, *J*=7.5 Hz, 3H).

2-Amino-N-(4-ethylphenyl)acetamide Hydrochloride (ET-48). Refer to general procedure for *t*-Boc deprotection: white solid, 37 mg, 97% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.47 (d, J=8.6 Hz, 2H), 7.17 (d, J=8.8 Hz, 2H), 3.82 (s, 2H), 2.61 (q, J=7.6 Hz, 2H), 1.21 (t, J=7.6 Hz, 3H).

N-(2-Aminoethyl)-4-ethylbenzenamine Hydrochloride (ET-49). Refer to general procedure for *t*-Boc deprotection: brownish oil, 5 mg, 89% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.32 (d, J=7.5 Hz, 2H), 7.26 (d, J=8.2 Hz, 2H), 3.61 (t, J=7.0 Hz, 2H), 3.29 (t, J=7.0 Hz, 2H), 2.66 (q, J=7.6 Hz, 2H), 1.22 (t, J=7.6 Hz, 3H).

A.2 $TAAR_1$ *in vitro* cAMP functional assay

A.2.1 Agonist activity assay

After incubating in fresh medium for at least 2 h, HEK293 cells stably transfected with rat or mouse $TAAR_1$ were harvested in Krebs-Ringer-HEPES buffer (KRH) and preincubated with 200 µM 3-isobutyl-1-methylxanthine (IBMX) for 20-30 minutes. Cells were incubated in KRH with 133 µM IBMX and 3µL of the test compound, forskolin (10 µM), or vehicle (dimethyl sulfoxide, DMSO) for 1 h at 37 °C (300 µL total volume). The cells were boiled for 20 min after addition of 100 µL 0.5 mM sodium acetate buffer. The cell lysate was centrifuged to remove cellular debris, and an aliquot (30 µL) was transferred to an opaque, flat bottom 96-well plate (Corning #3917).

The cAMP content of the aliquot was measured by use of the Hithunter^{TM} cAMP XS kit (DiscoveRX, Fremont, CA). The plate was shaken on a titer plate shaker for 2 min after addition of 20 µL of cAMP XS antibody/lysis mix. After incubation in the dark for 1h, 20 µL of cAMP XS ED reagent was added and the plate was shaken for 2 min.

After another hour of incubation in the dark, 40 µL of cAMP XS EA/CL substrate mix was added and the plate was shaken for 2 min. The plate was sealed with an acetate plate sealer (Thermo Scientific #3501) and allowed to incubate in the dark for 15-18 h before luminescence was measured (3 readings/well at 0.33 s/reading) on an Analyst^{TM} AD Assay Detection System (LJL Biosystems) or a Packard Fusion Microplate Reader. Data were reported relative to **T_1AM** and expressed as %T_1AM. The activity of **T_1AM** at 10µM was set as 100 %T_1AM. Concentration-response curves were plotted and EC_{50} values were calculated with Prism software (GraphPad, San Diego, CA). Standard error of the mean was calculated from the EC_{50} and E_{max} values of each independent triplicate experiment by use of Prism Software (GraphPad, San Diego, CA).

A.2.2 Antagonist activity assay

Same as the agonist activity assay procedure described above with the following changes: cells that were harvested in KRH buffer and preincubated with IBMX for 20-30 minutes were incubated in KRH with 133 µM IBMX and 3µL of the putative antagonist, or vehicle (DMSO) for 30 min at 37 °C (300 µL total volume). 3µL of the competing agonist (T_1AM, EC_{50} concentration (33 nM) as the final concentration), **T_1AM** (10 µM), forskolin (10 µM) or vehicle (DMSO) was then added to the reactions before incubating for 1h at 37^{o}C. The cells were then processed as described in the agonist activity assay. Concentration-response curves were plotted and IC_{50} values were calculated by use of Prism software (GraphPad, San Diego, CA).

A.2.23 Cytotoxicity Assay

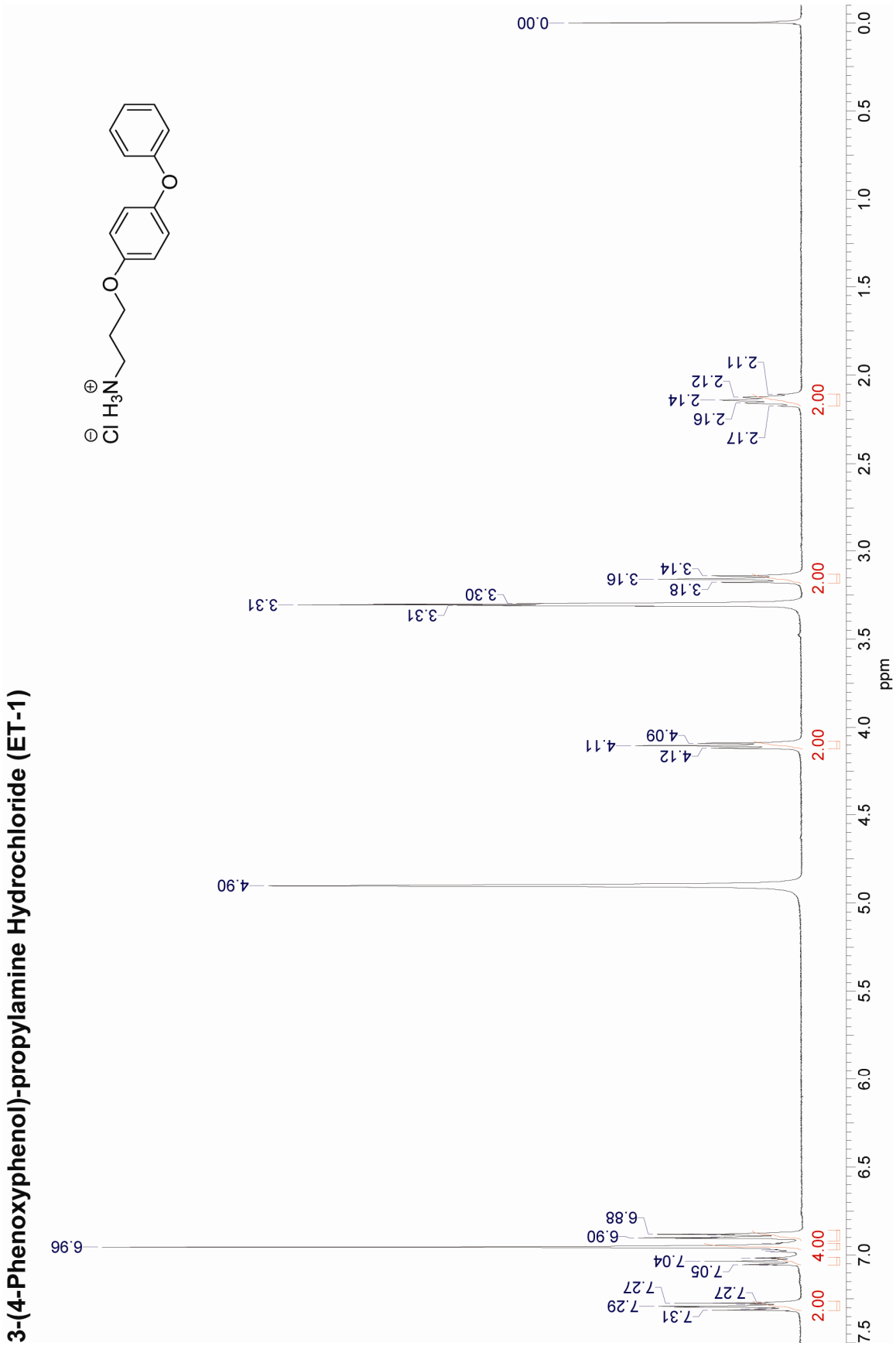
After incubating in fresh medium for at least 2 h, HEK293 cells stably transfected with rat or mouse $TAAR_1$ were harvested in Krebs-Ringer-HEPES buffer (KRH) and

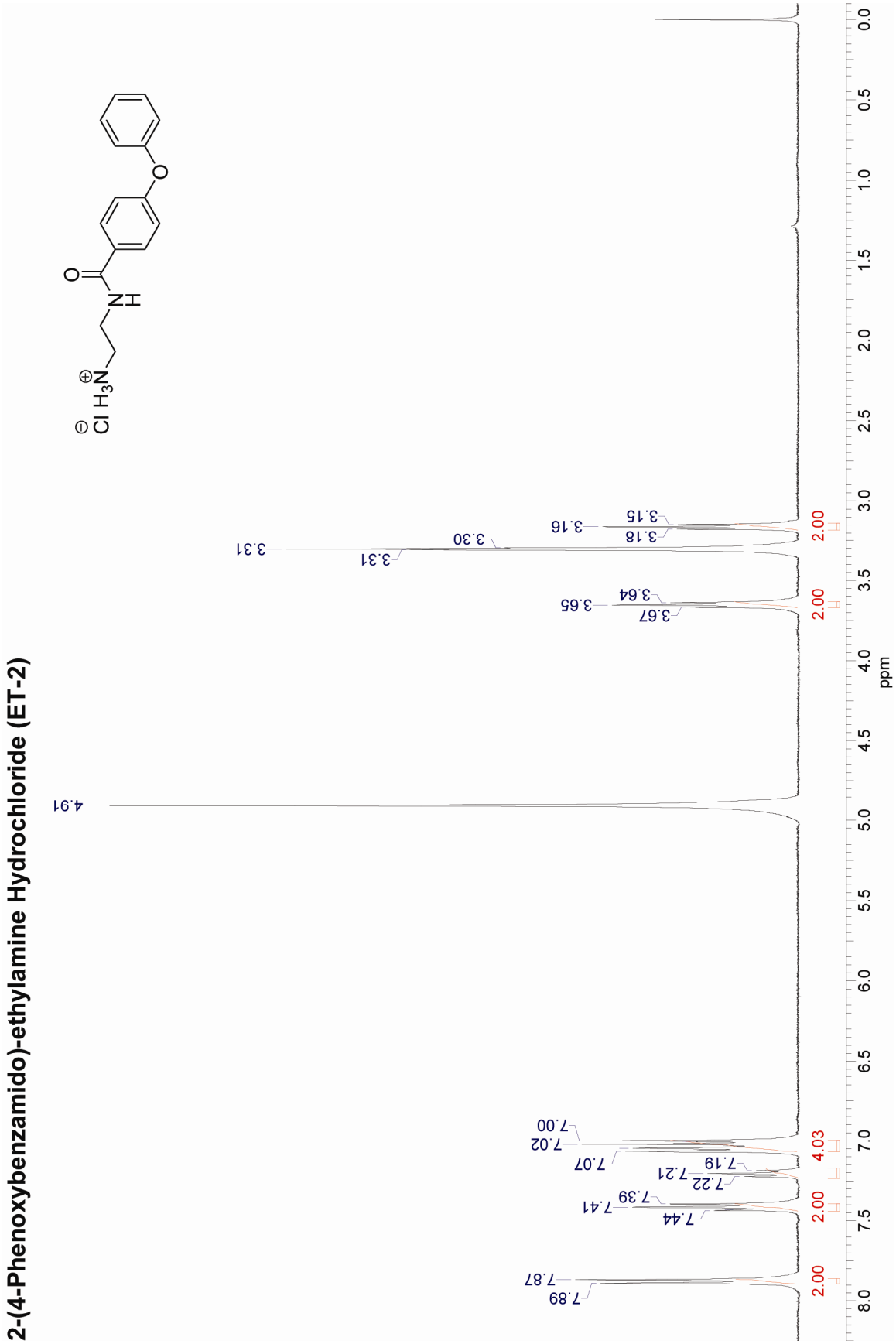
preincubated with 200 μM 3-isobutyl-1-methylxanthine (IBMX) for 20-30 minutes. Cells were incubated in KRH with 133 μM IBMX and 3μL of the test compound, forskolin (10 μM), or vehicle (dimethyl sulfoxide, DMSO) for 1.5-2 h at 37 °C (300 μL total volume). A 100 μL aliquot of the cell solution was transferred to an opaque, flat bottom 96-well plate (Corning #3917) after adding 500 μL 0.5 mM sodium acetate buffer at pH=6.2. Cell viability was measured employing the CellTiter-Glo Luminescent Cell Viability Assay (cat# G7571) from Promega. Following the addition of 100 μL of CellTiter Glo® Reagent, the plate was shaken for 2 min. After incubating at room temperature for 10 min, luminescence was measured (3 readings/well at 0.33 s/reading) on an Analyst^{TM} AD Assay Detection System (LJL Biosystems) or a Packard Fusion Microplate Reader.

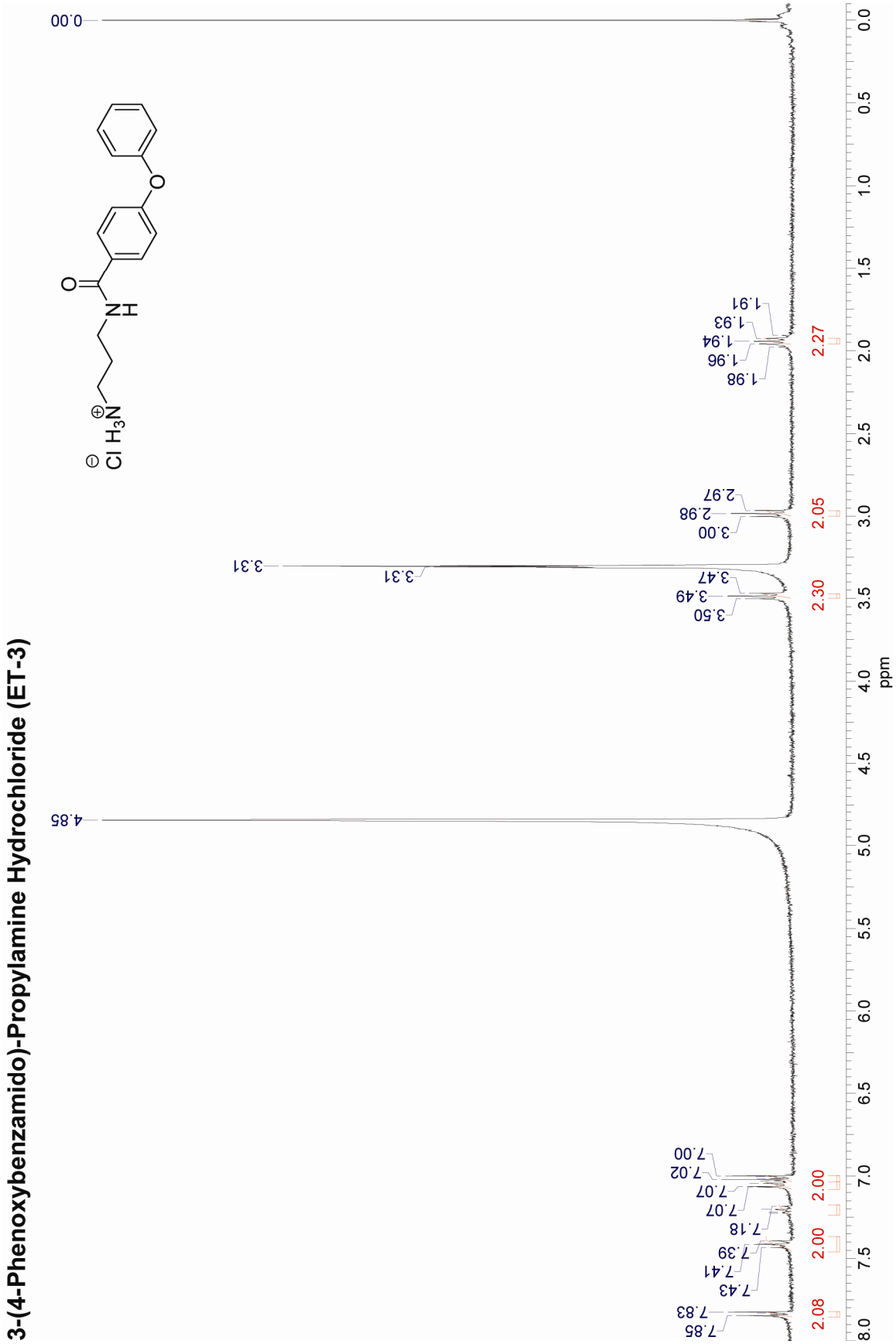
Appendix B

^{1}H and ^{13}C NMR Spectra

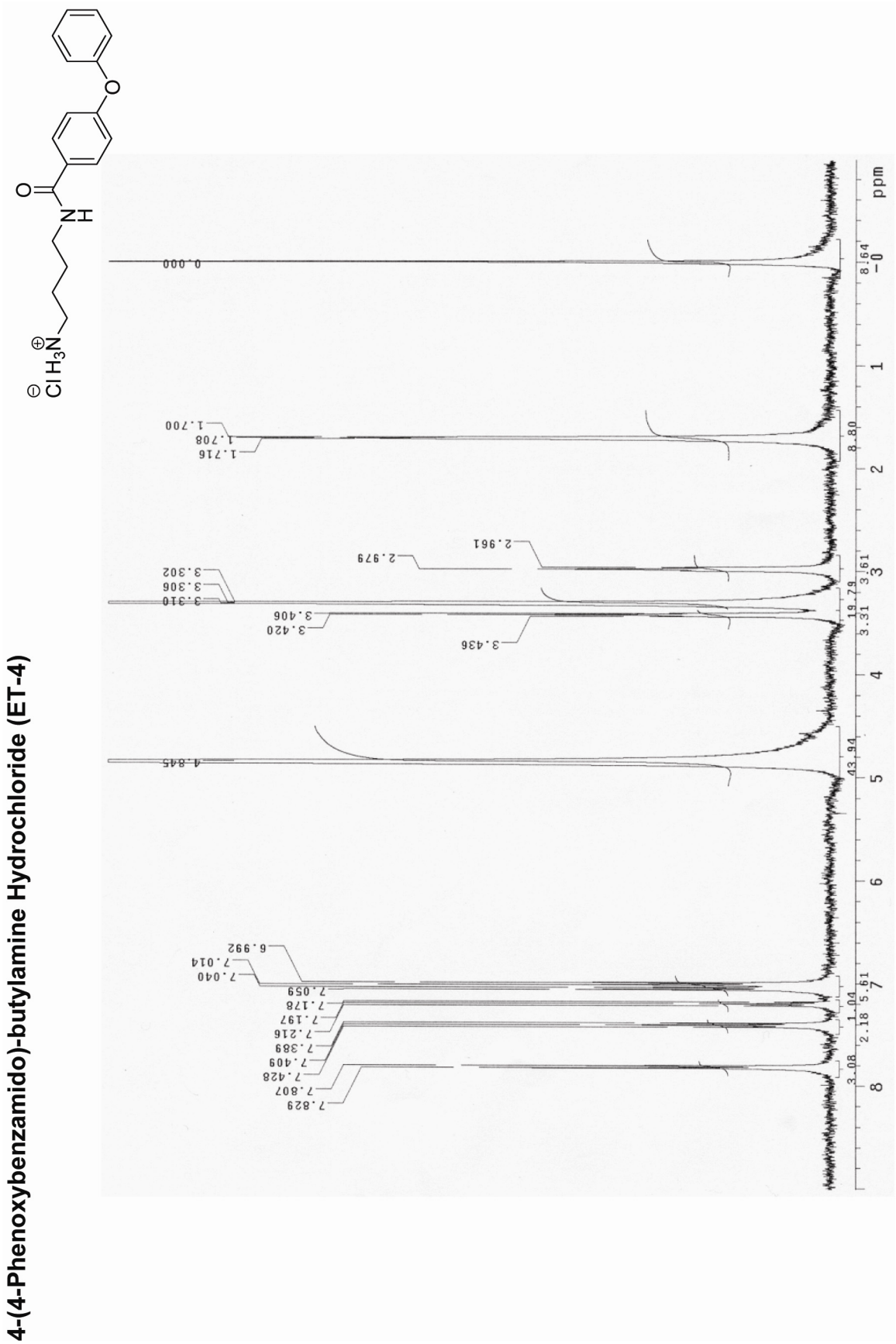
of Final Compounds


3-(4-Phenoxyphenol)-propylamine Hydrochloride (ET-1)
Cl H3N
0.00
2.11
2.12
2.14
2.16
2.17
3.14
3.16
3.18
3.30
3.31
3.31
4.09
4.11
4.12
4.90
6.88
6.90
6.96
7.04
7.05
7.27
7.27
7.29
7.31
2.00
2.00
2.00
4.00
2.00
ppm

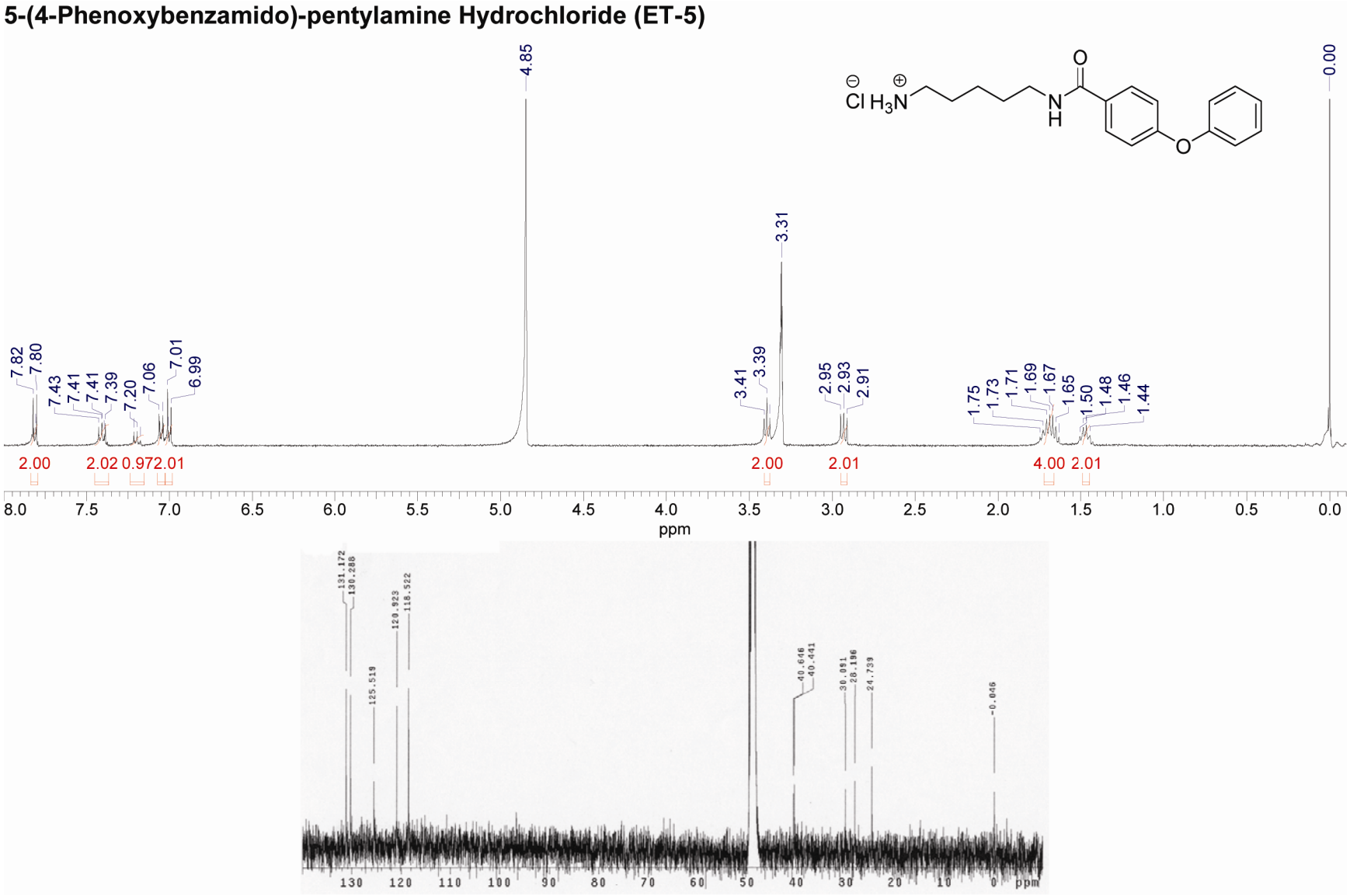

2-(4-Phenoxybenzamido)-ethylamine Hydrochloride (ET-2)
O
NH
H3N
Cl
7.89
7.87
7.44
7.41
7.39
7.22
7.21
7.19
7.07
7.02
7.00
4.91
3.67
3.65
3.64
3.31
3.31
3.30
3.18
3.16
3.15
2.00
2.00
4.03
2.00
ppm

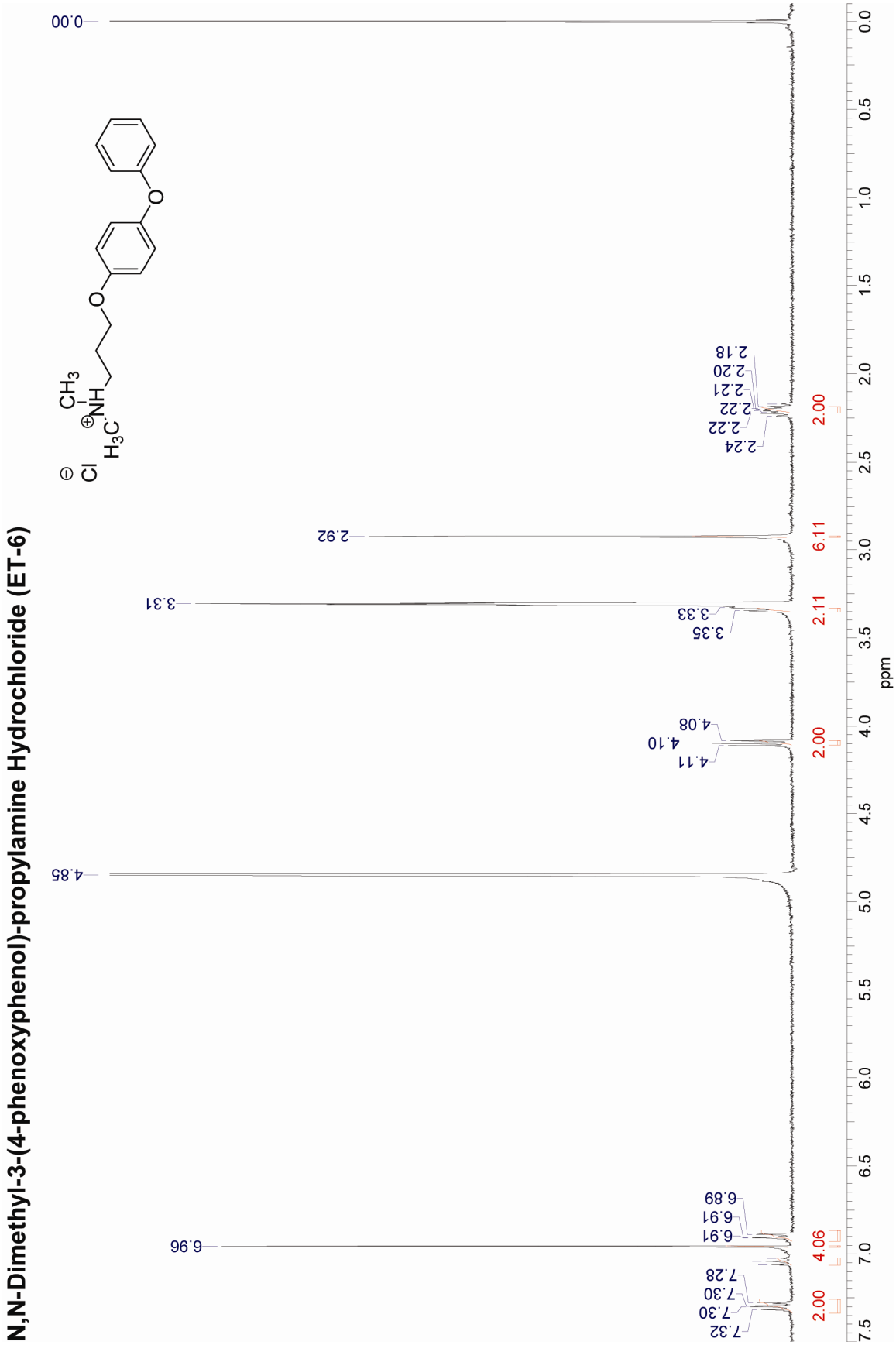

3-(4-Phenoxybenzamido)-Propylamine Hydrochloride (ET-3)
0.00
4.85
3.31
3.31
7.85
7.83
7.43
7.41
7.39
7.18
7.07
7.07
7.02
7.00
3.50
3.49
3.47
3.00
2.98
2.97
1.98
1.96
1.94
1.93
1.91
2.08
2.00
2.00
2.30
2.05
2.27
ppm

4-(4-Phenoxybenzamido)-butylamine Hydrochloride (ET-4)

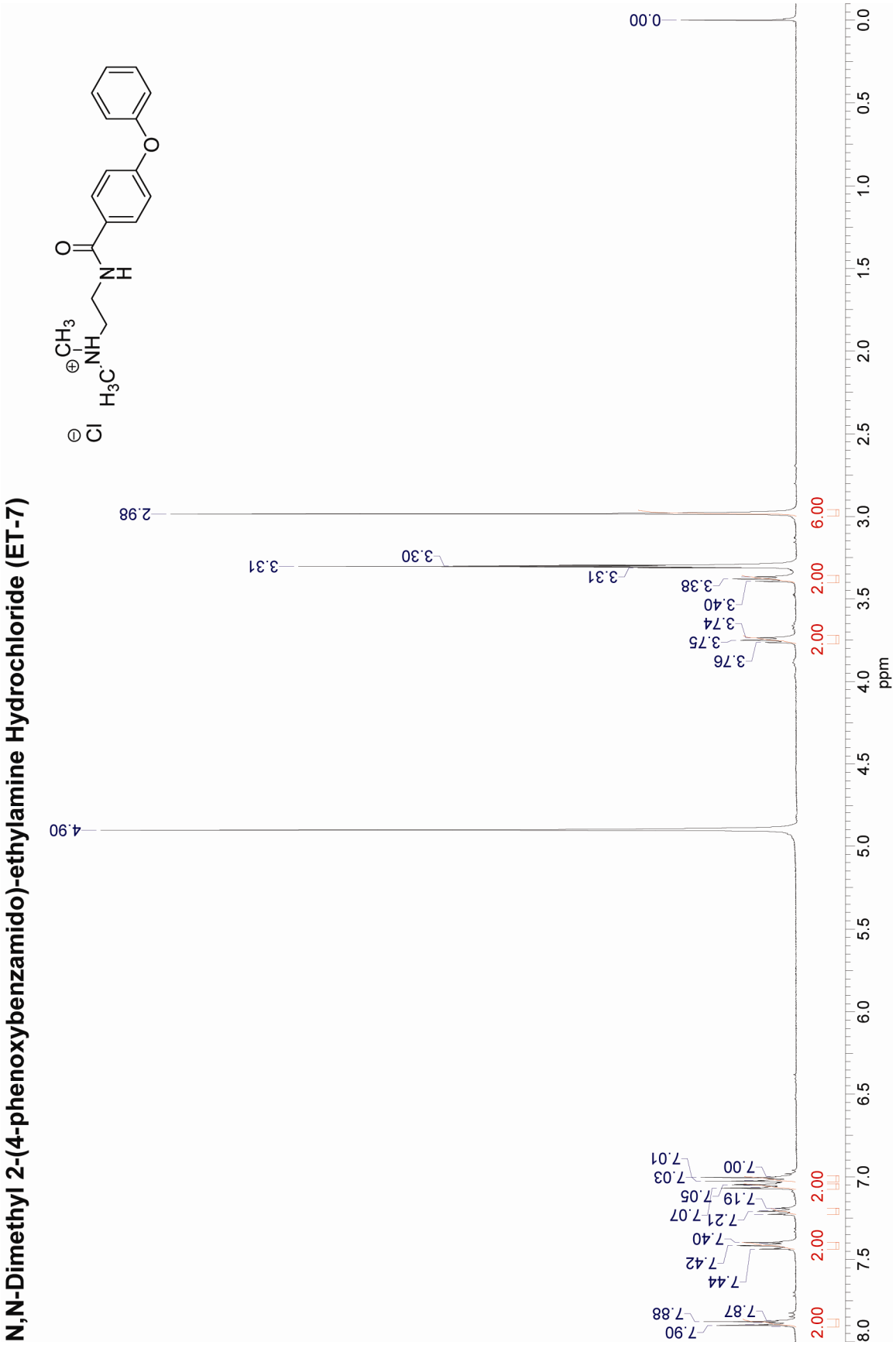


5-(4-Phenoxybenzamido)-pentylamine Hydrochloride (ET-5)

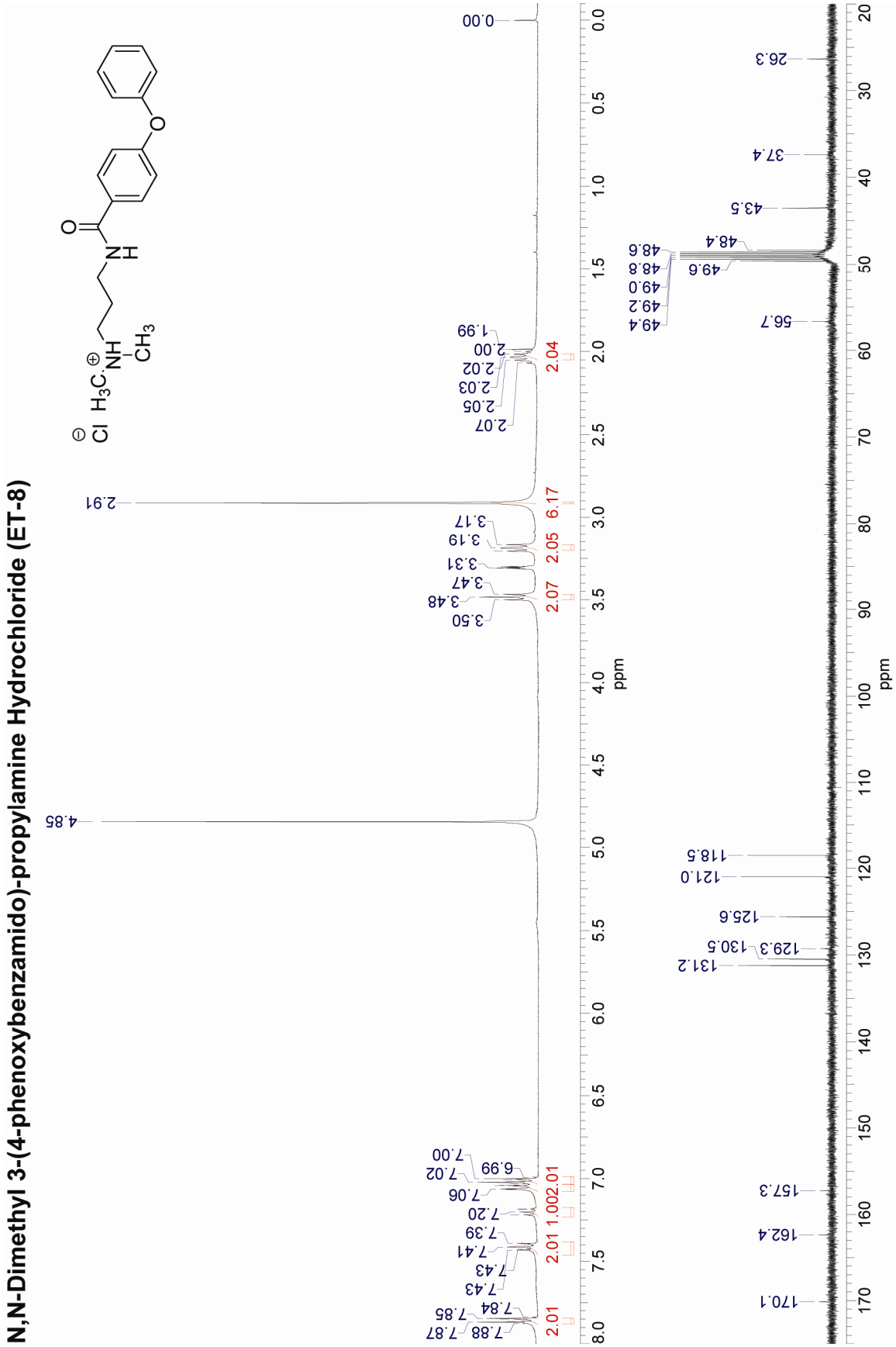



N,N-Dimethyl-3-(4-phenoxyphenol)-propylamine Hydrochloride (ET-6)
0.00
2.18
2.20
2.21
2.22
2.22
2.24
2.92
3.31
3.33
3.35
4.08
4.10
4.11
4.85
6.89
6.91
6.91
6.96
7.28
7.30
7.30
7.32
2.00
4.06
2.00
2.11
6.11
2.00
ppm

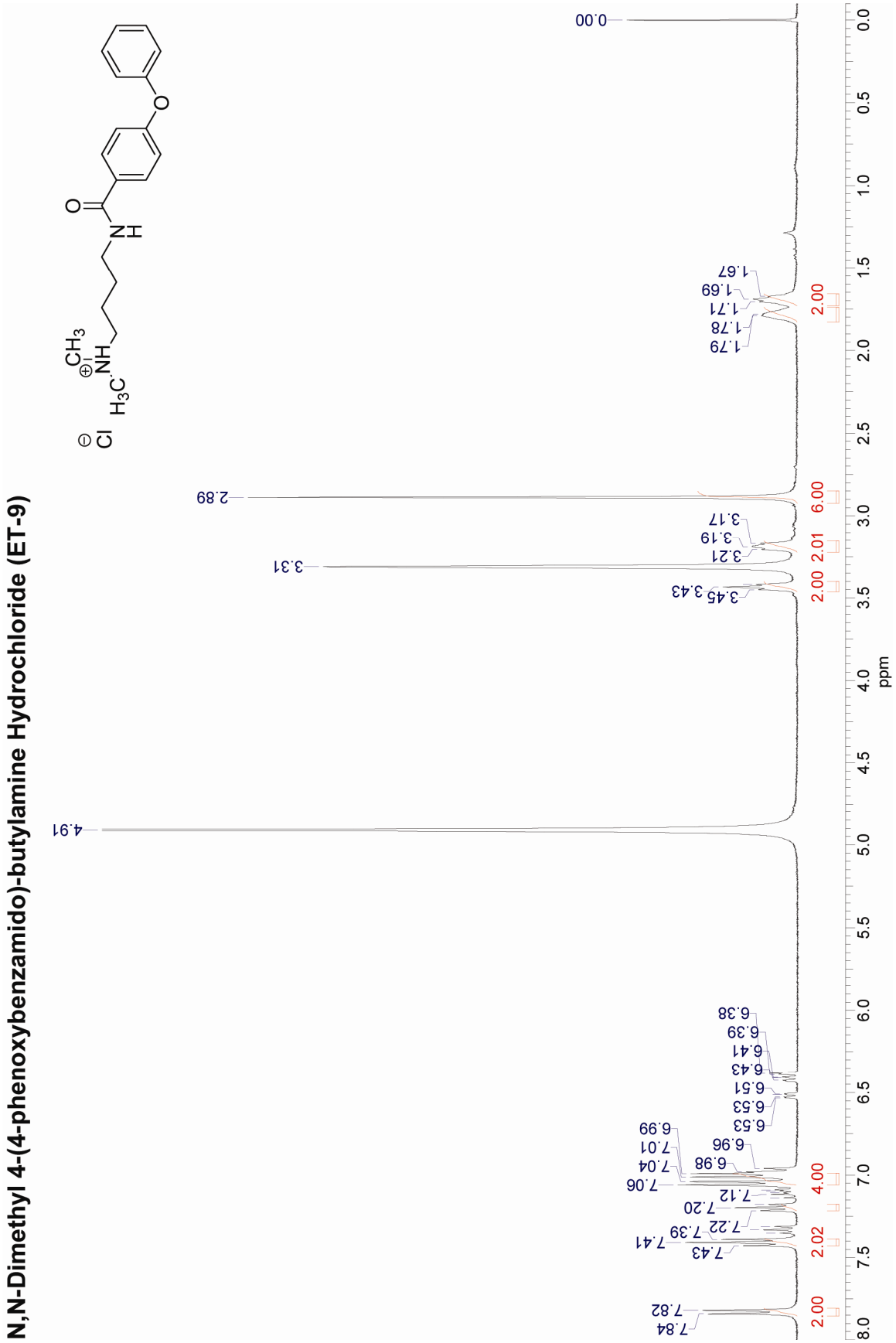
N,N-Dimethyl 2-(4-phenoxybenzamido)-ethylamine Hydrochloride (ET-7)



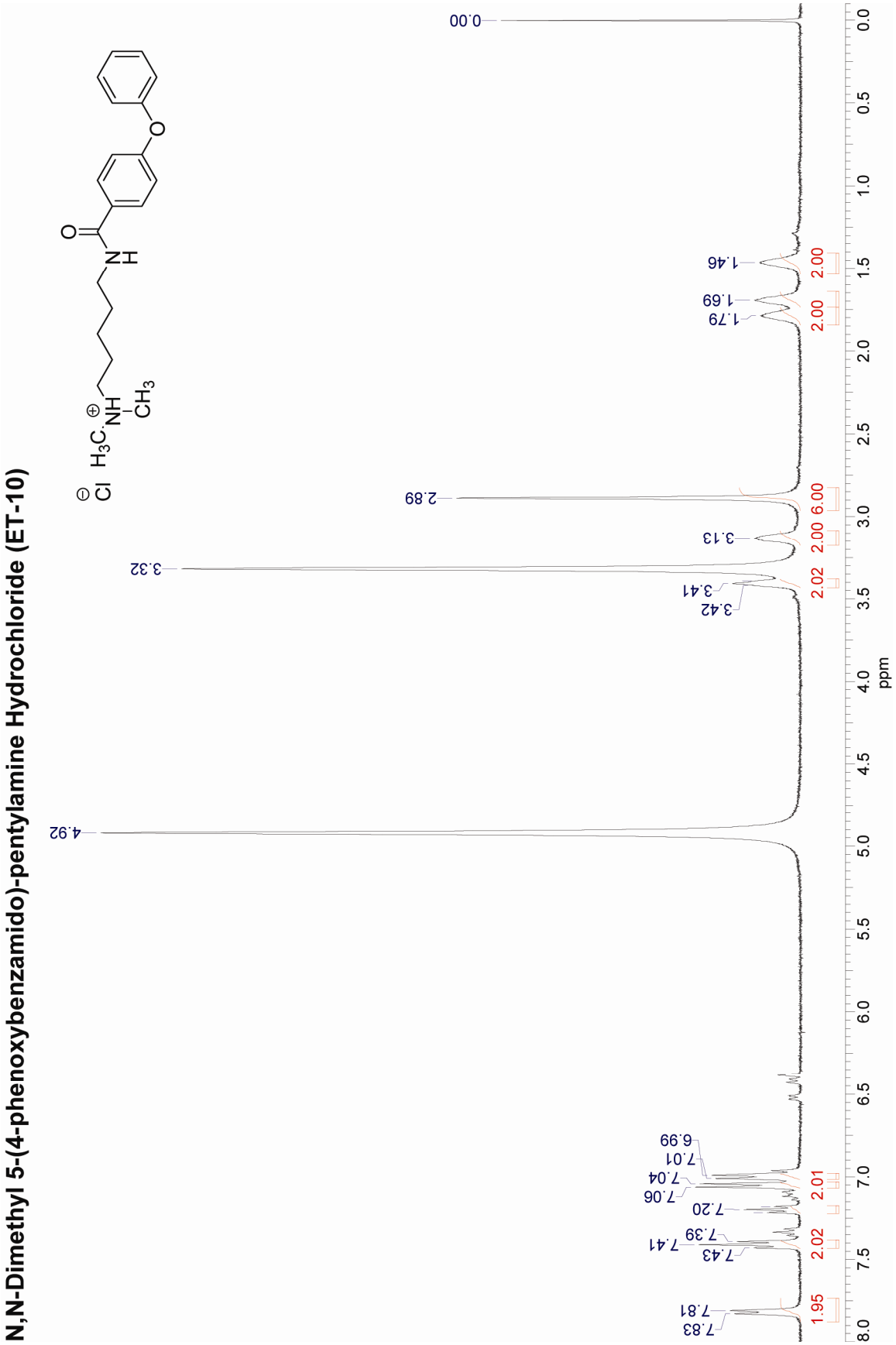
N,N-Dimethyl 3-(4-phenoxybenzamido)-propylamine Hydrochloride (ET-8)



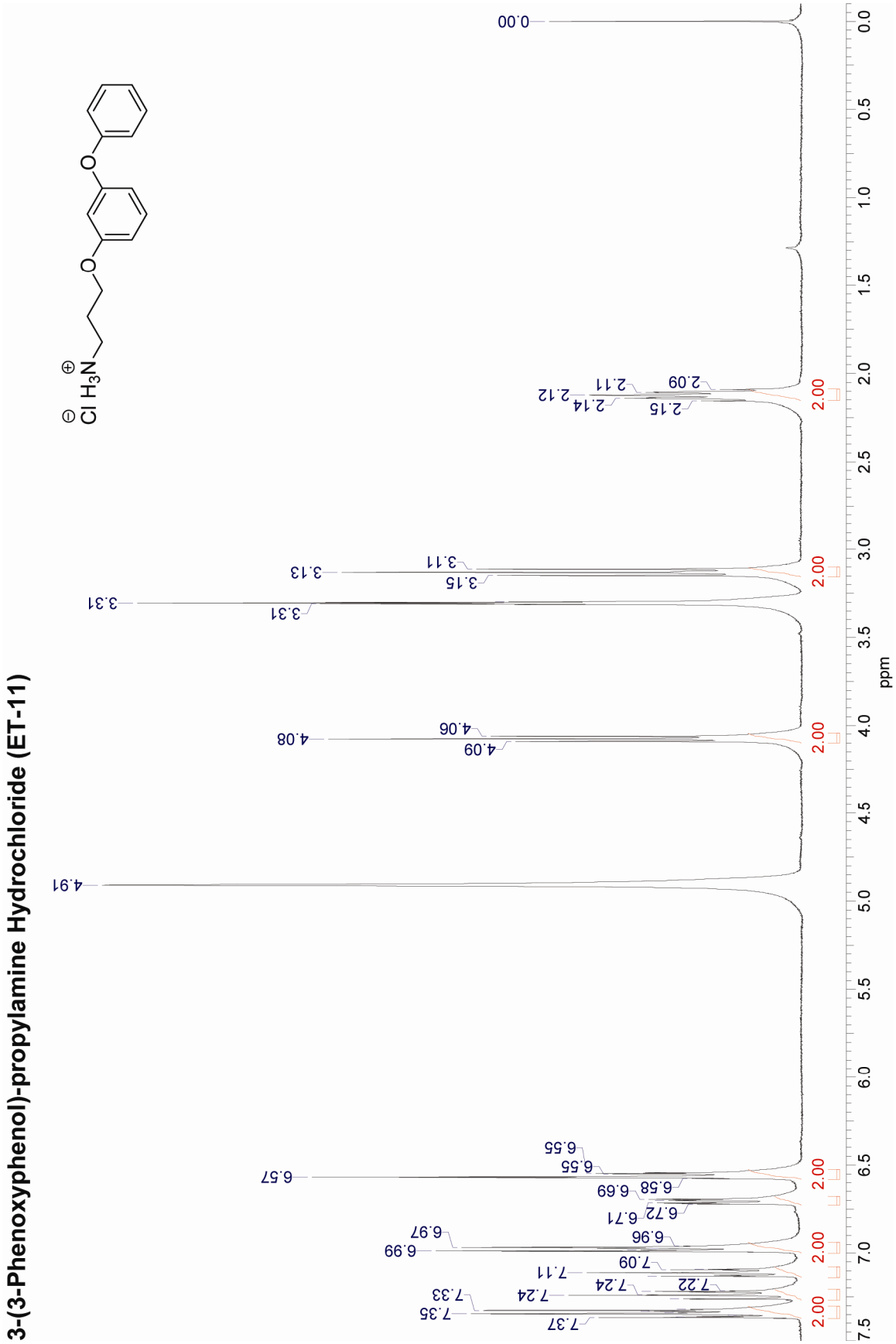
N,N-Dimethyl 4-(4-phenoxybenzamido)-butylamine Hydrochloride (ET-9)

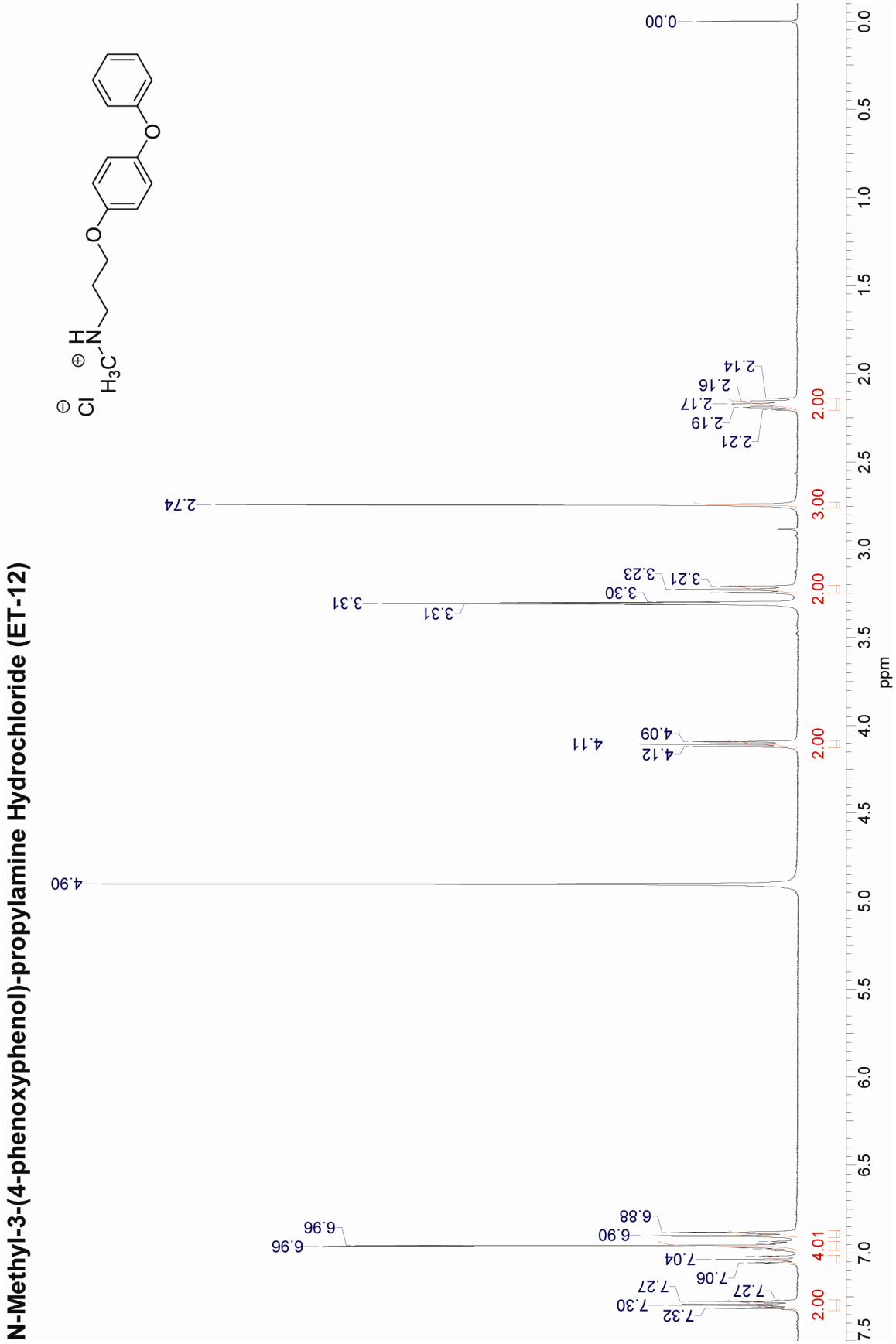


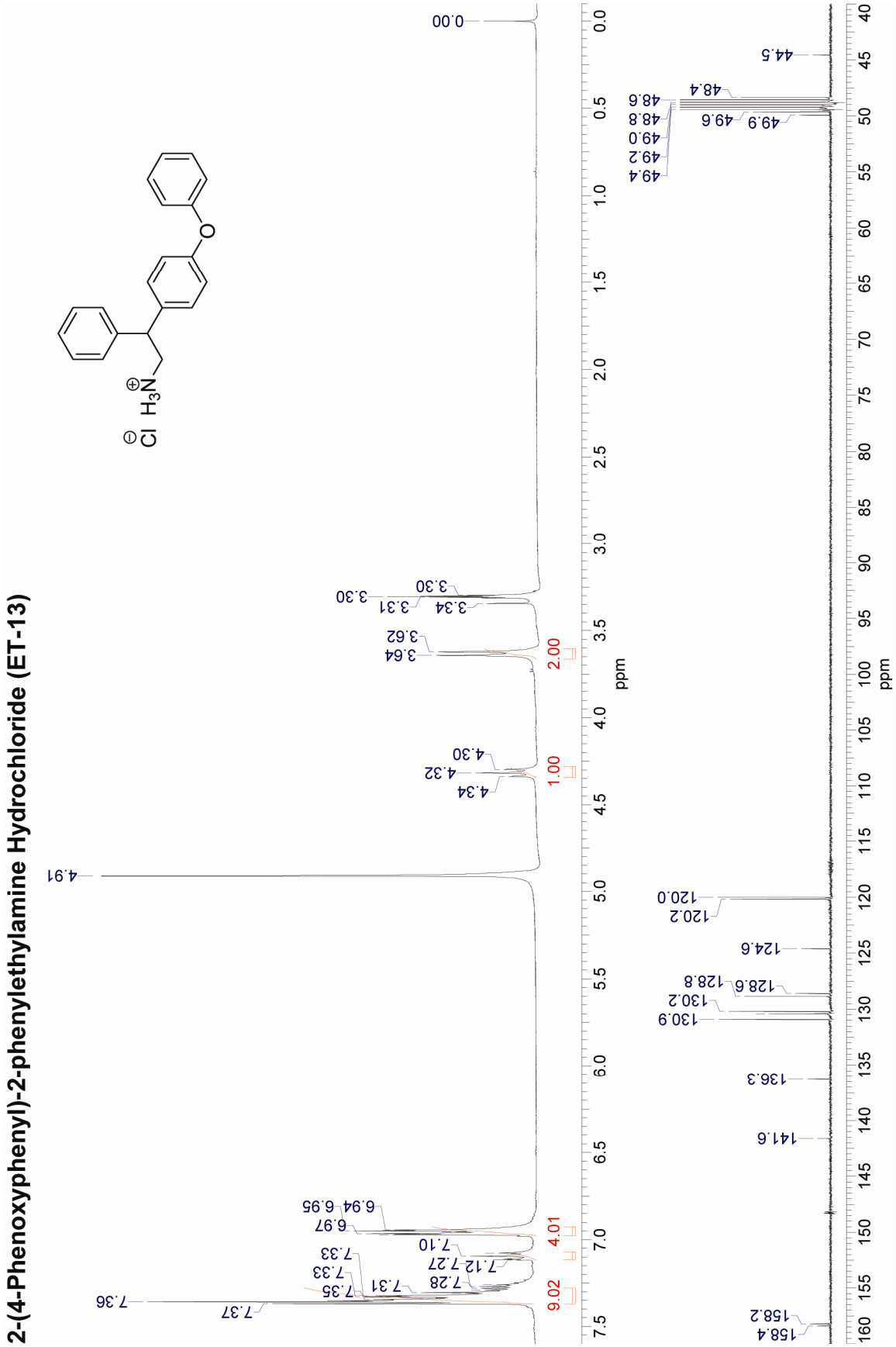
N,N-Dimethyl 5-(4-phenoxybenzamido)-pentylamine Hydrochloride (ET-10)



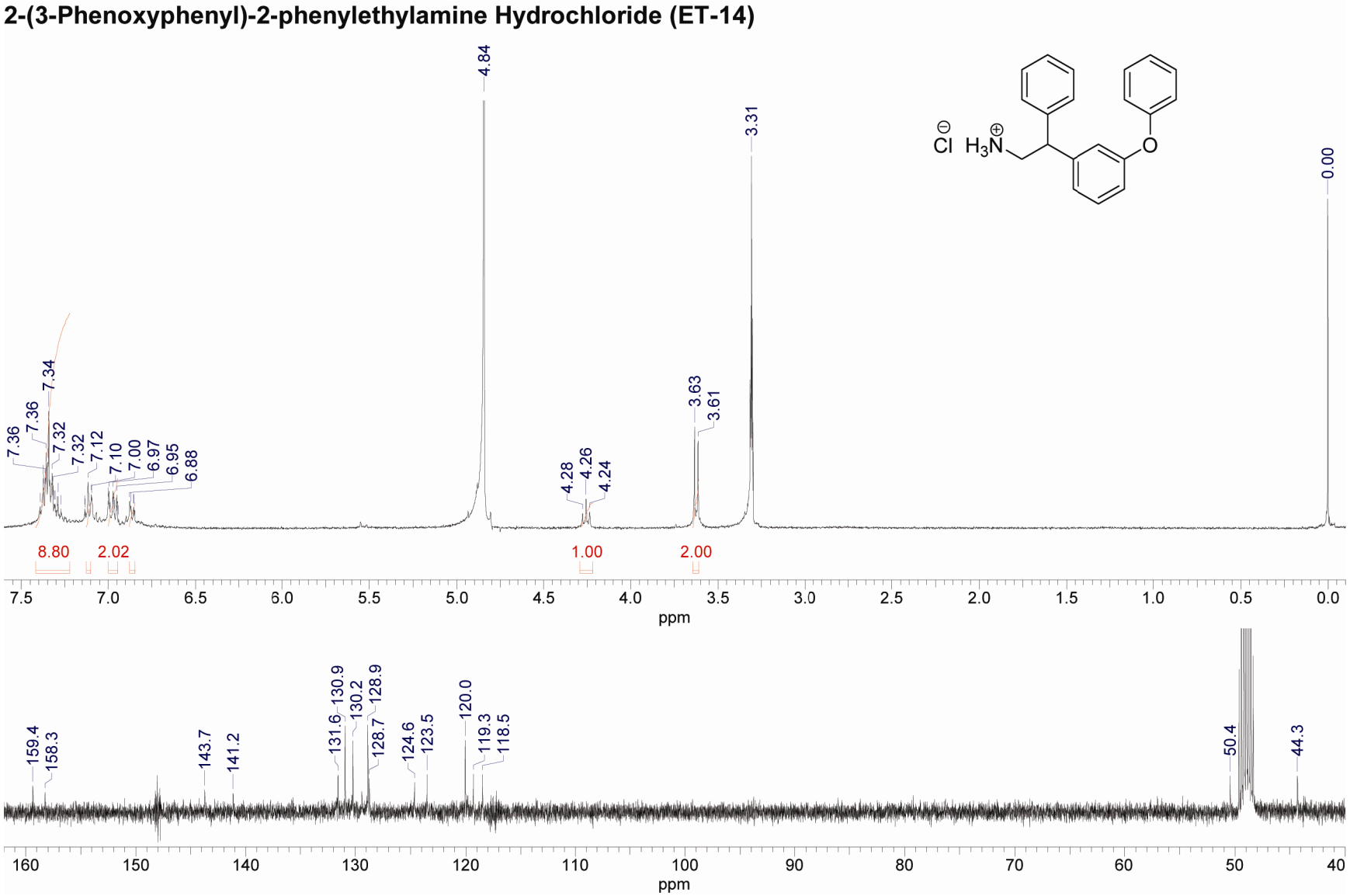
3-(3-Phenoxyphenol)-propylamine Hydrochloride (ET-11)

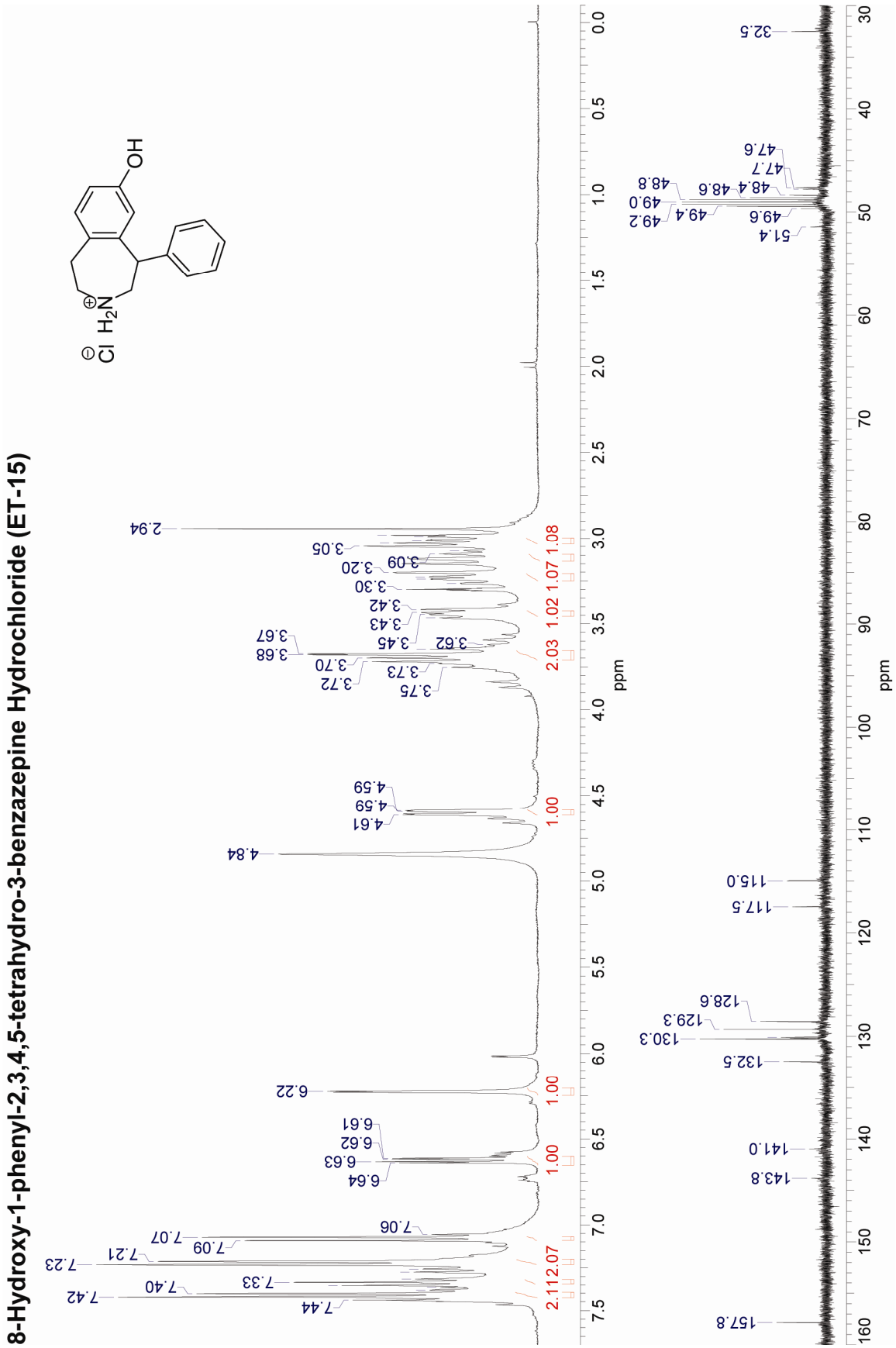



N-Methyl-3-(4-phenoxyphenol)-propylamine Hydrochloride (ET-12)
Cl
H3C
N
H
O
O
0.00
2.14
2.16
2.17
2.19
2.21
2.74
3.21
3.23
3.30
3.31
3.31
4.09
4.12
4.11
4.90
6.88
6.90
6.96
6.96
7.04
7.06
7.27
7.27
7.30
7.32
2.00
3.00
2.00
2.00
4.01
2.00
ppm

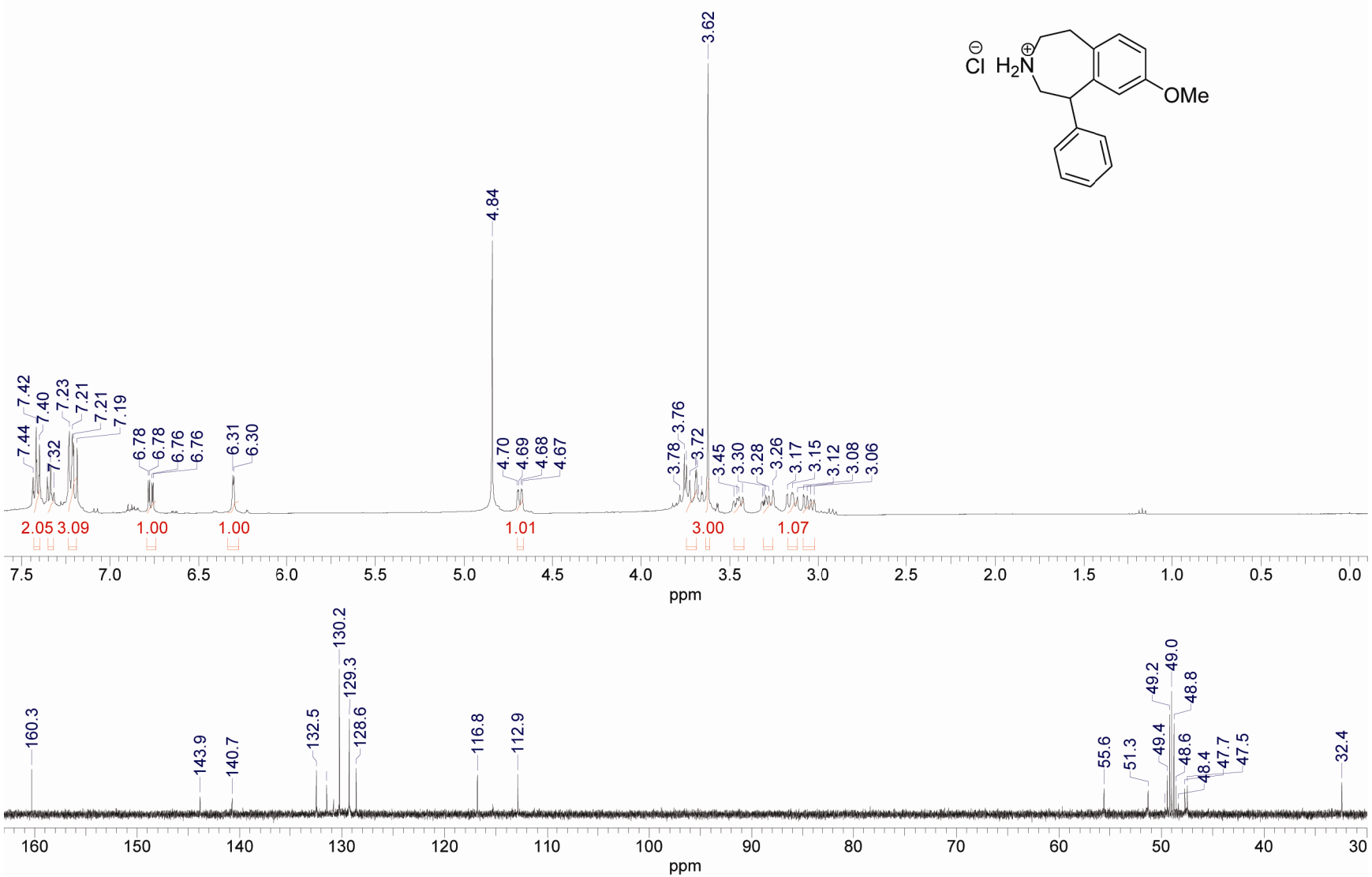

2-(4-Phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-13)
Cl⊖ H3N⊕
0.00
3.30
3.31
3.34
3.62
3.64
4.30
4.32
4.34
4.91
6.94
6.95
6.97
7.10
7.12
7.27
7.28
7.31
7.33
7.33
7.35
7.36
7.37
9.02
4.01
2.00
1.00
ppm
44.5
48.4
48.6
48.8
49.0
49.2
49.4
49.6
49.9
120.0
120.2
124.6
128.6
128.8
130.2
130.9
136.3
141.6
158.2
158.4
ppm

2-(3-Phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-14)

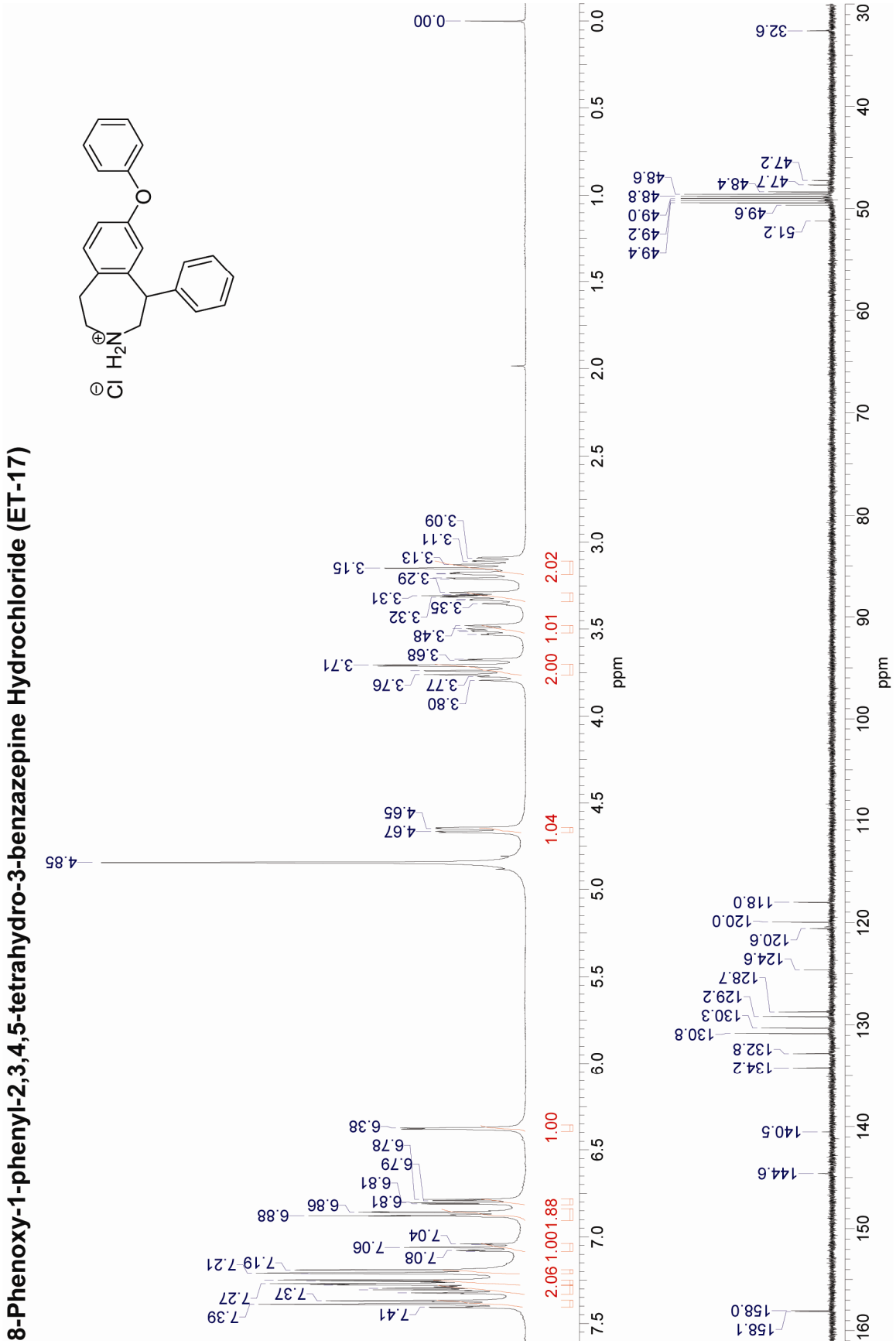



8-Hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-15)
OH
⊕ H2N
⊖ Cl
ppm
ppm

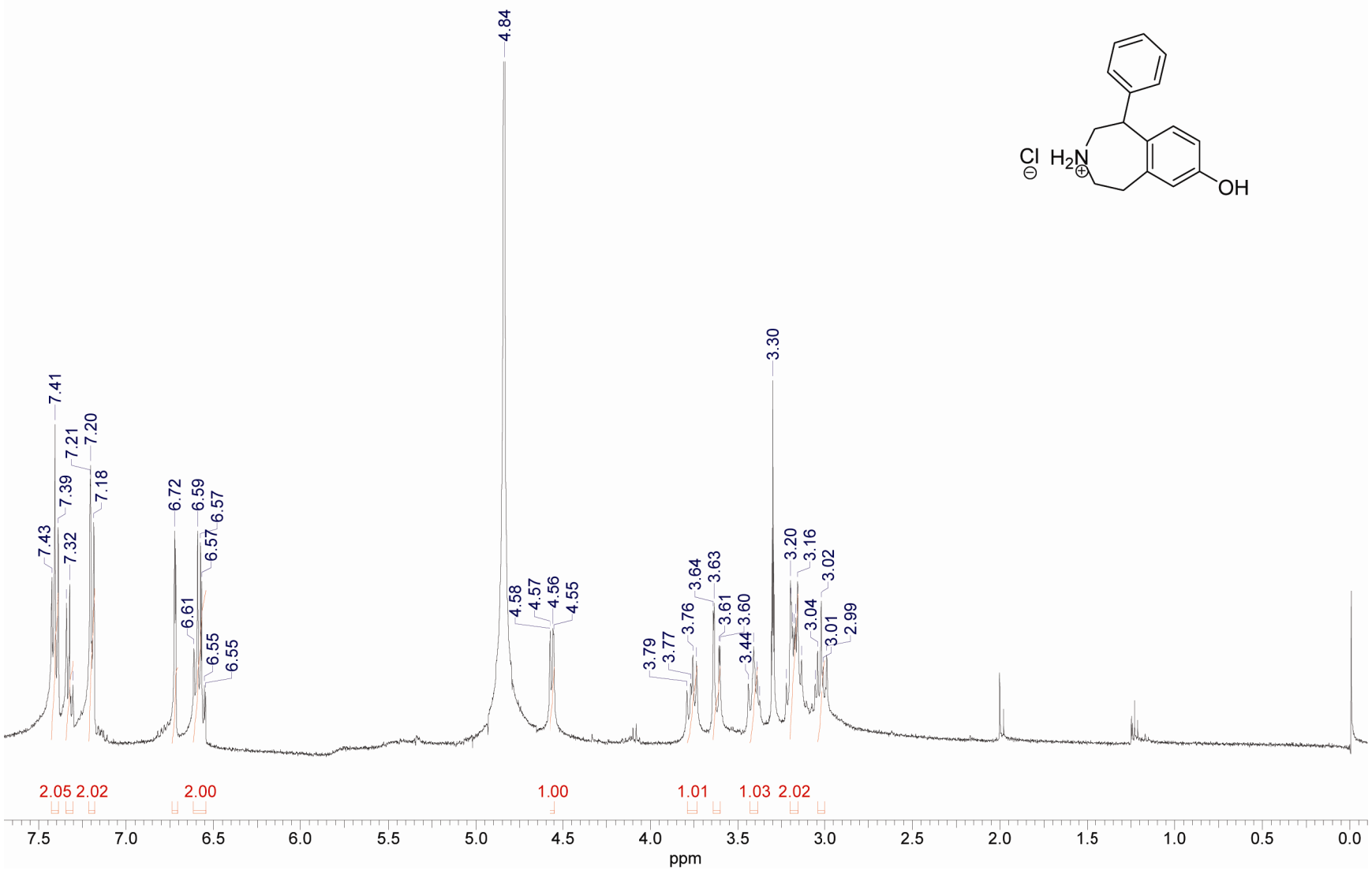
8-Methoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-16)



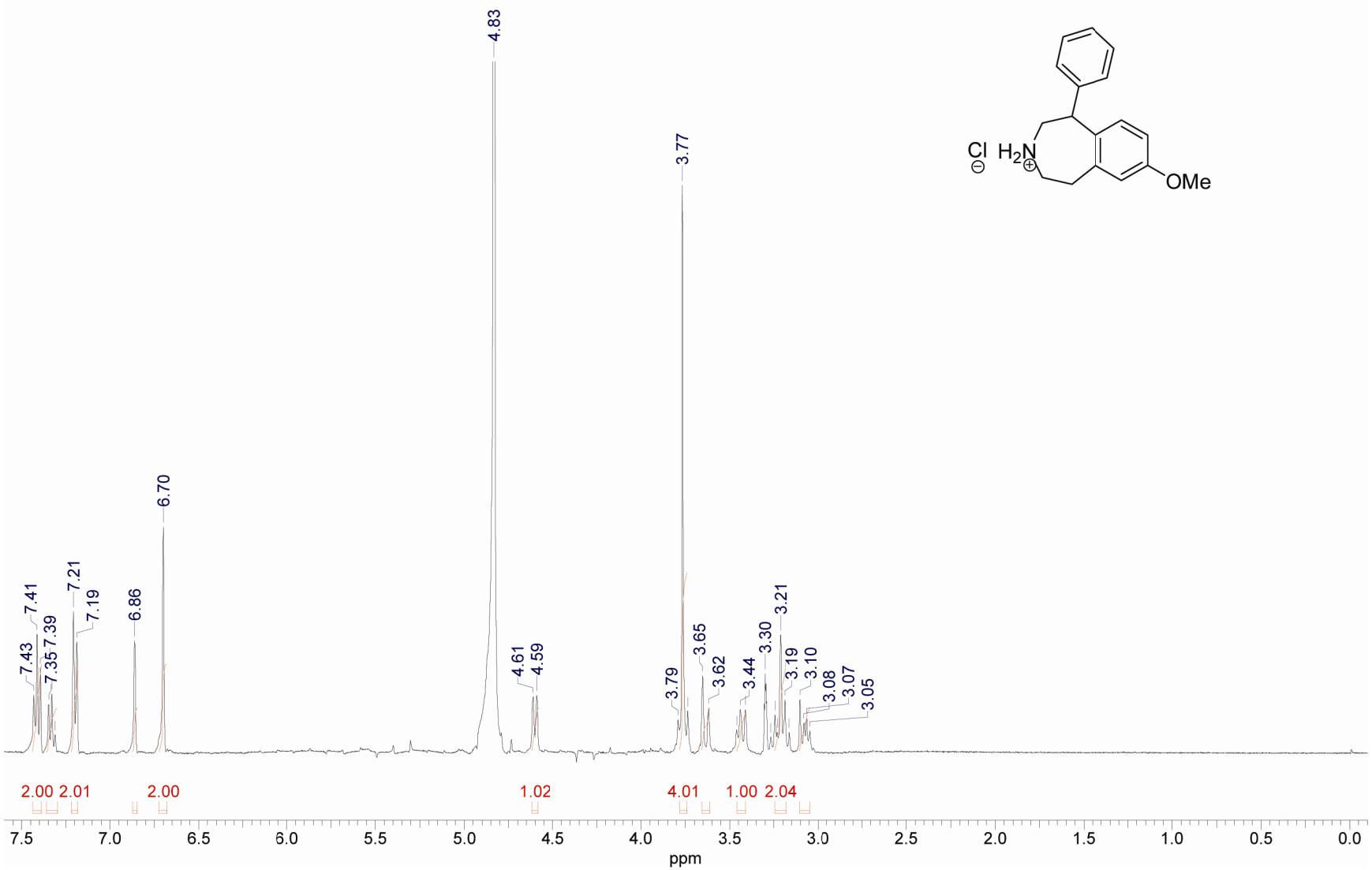
8-Phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-17)



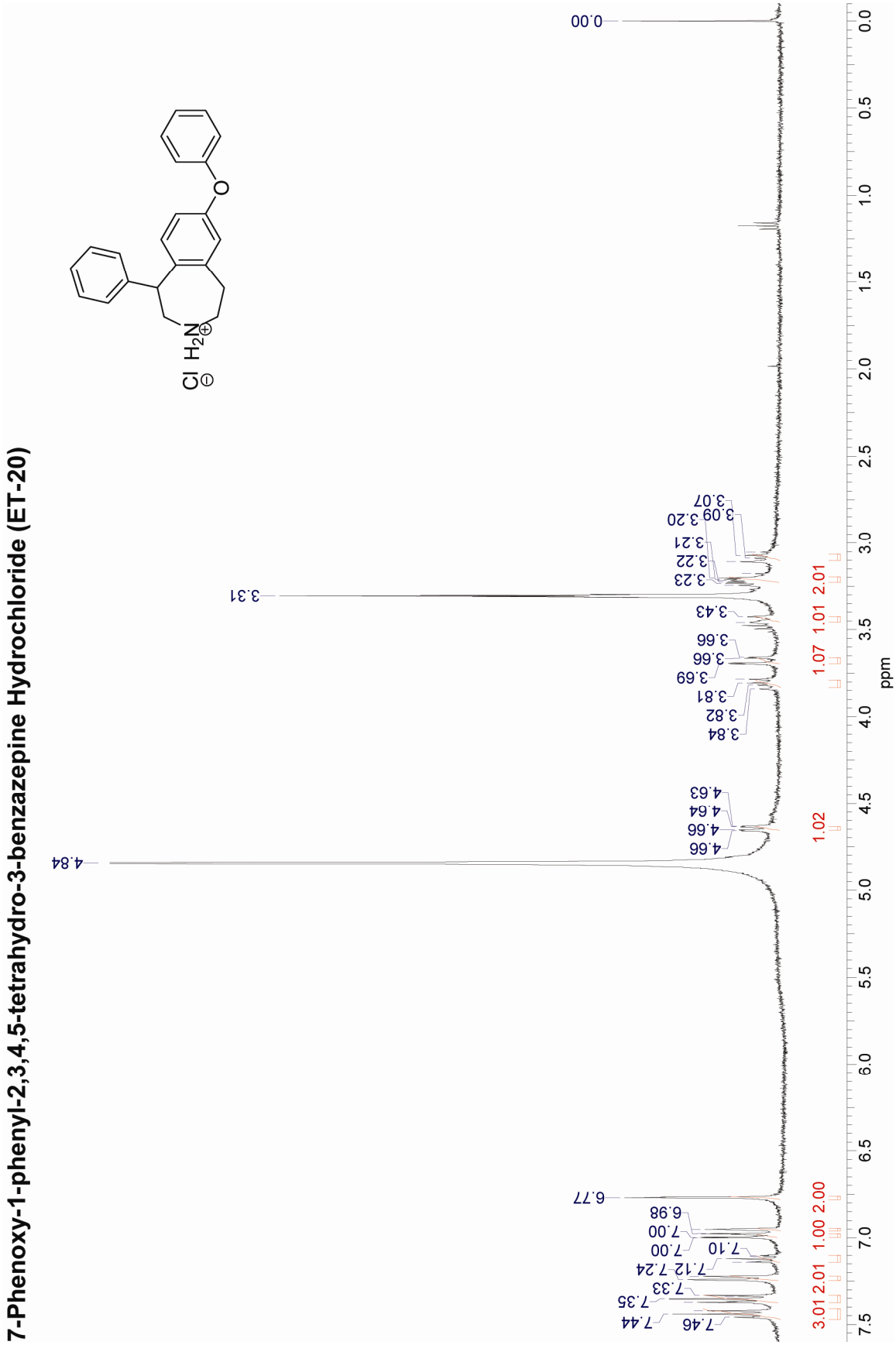
7-Hydroxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-18)



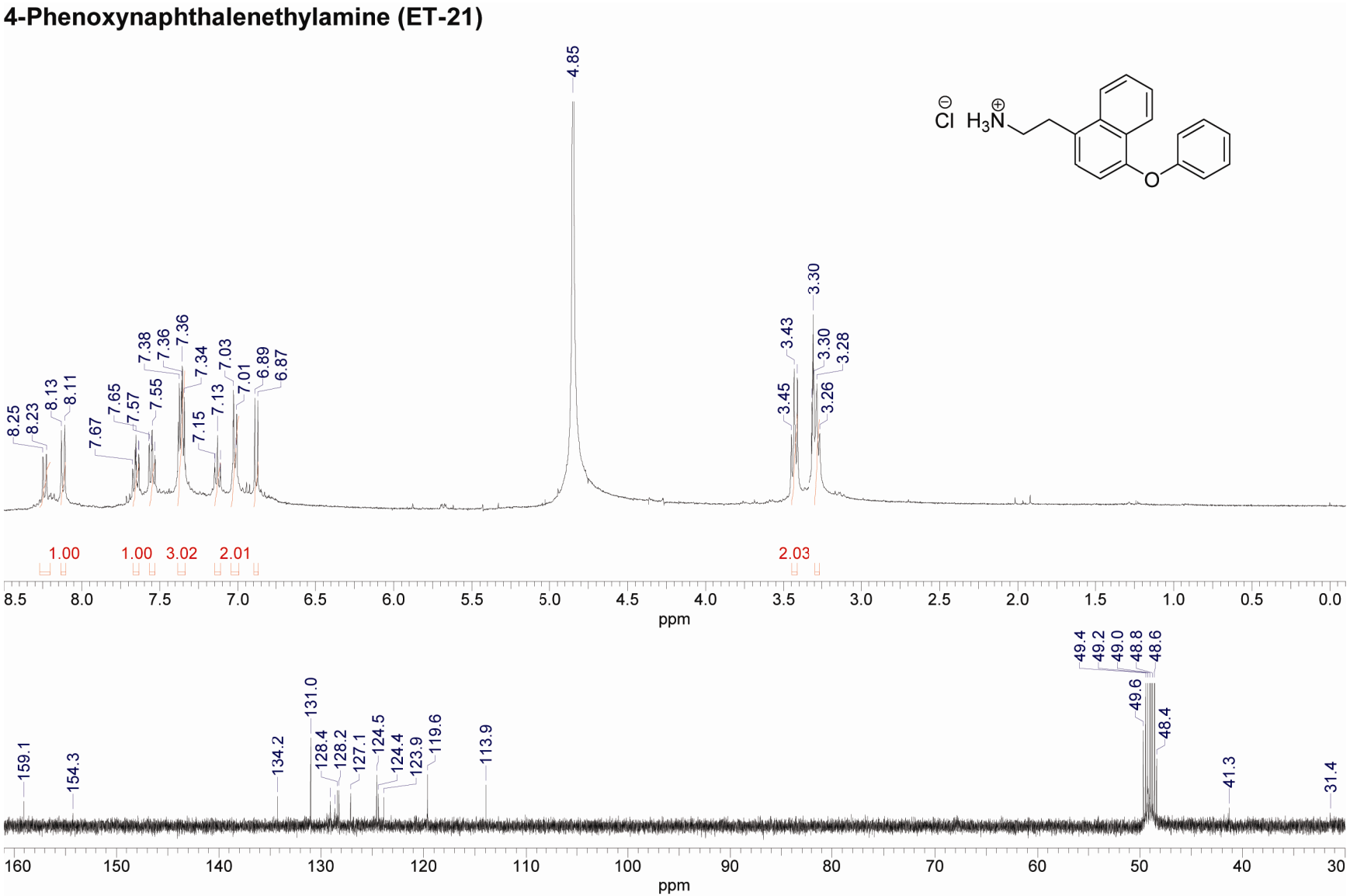
7-Methoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-19)



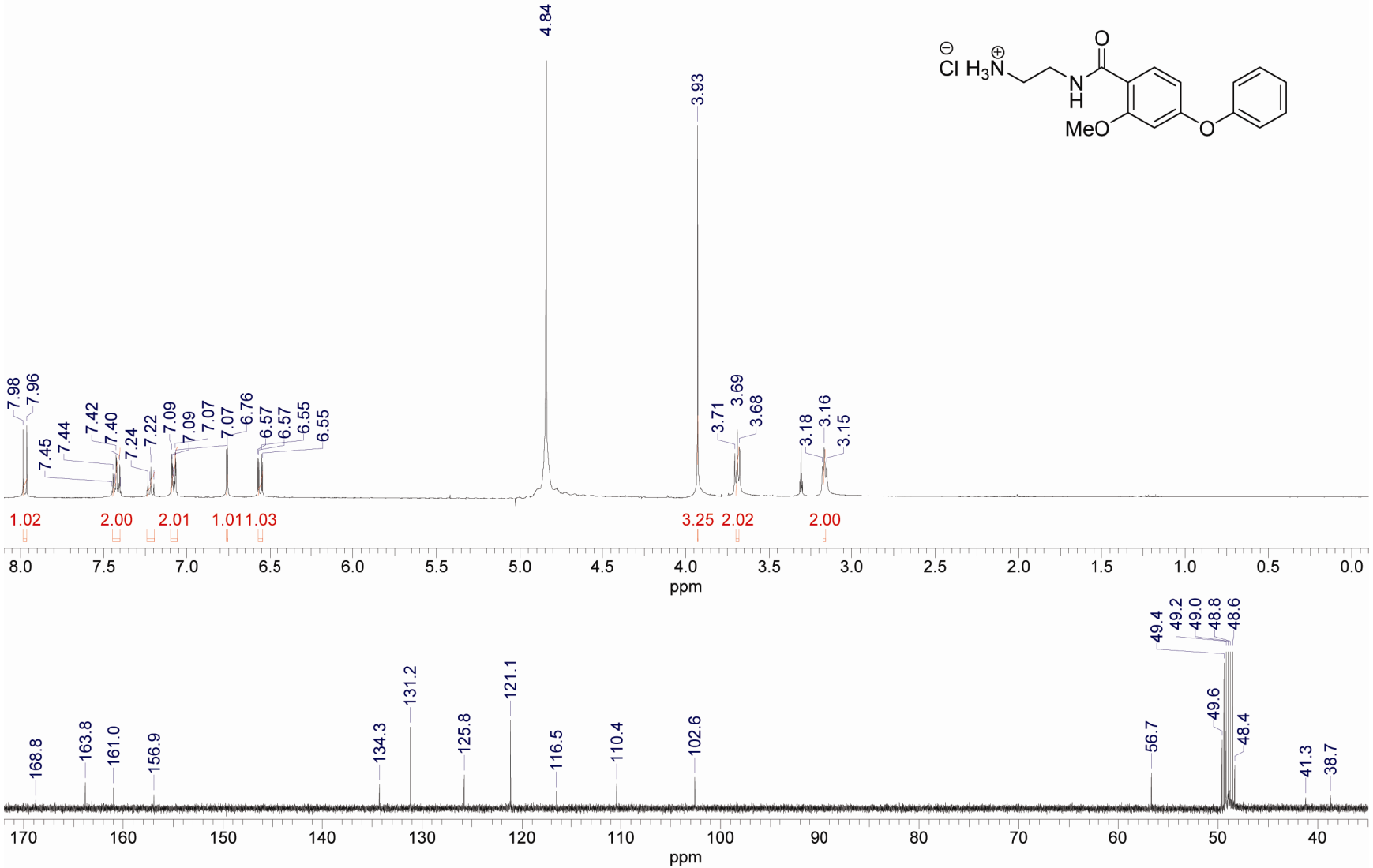
7-Phenoxy-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine Hydrochloride (ET-20)



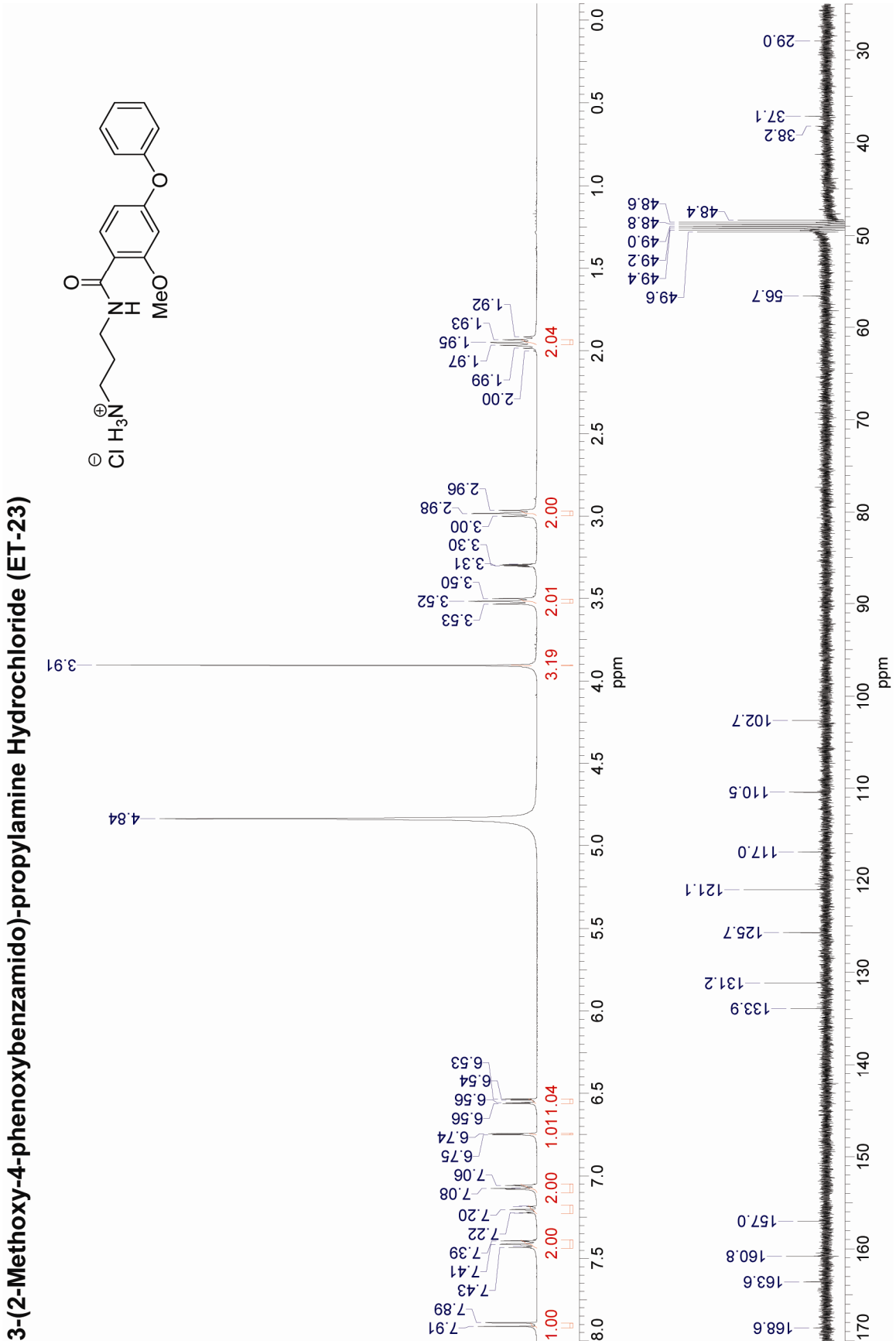
4-Phenoxynaphthalenethylamine (ET-21)



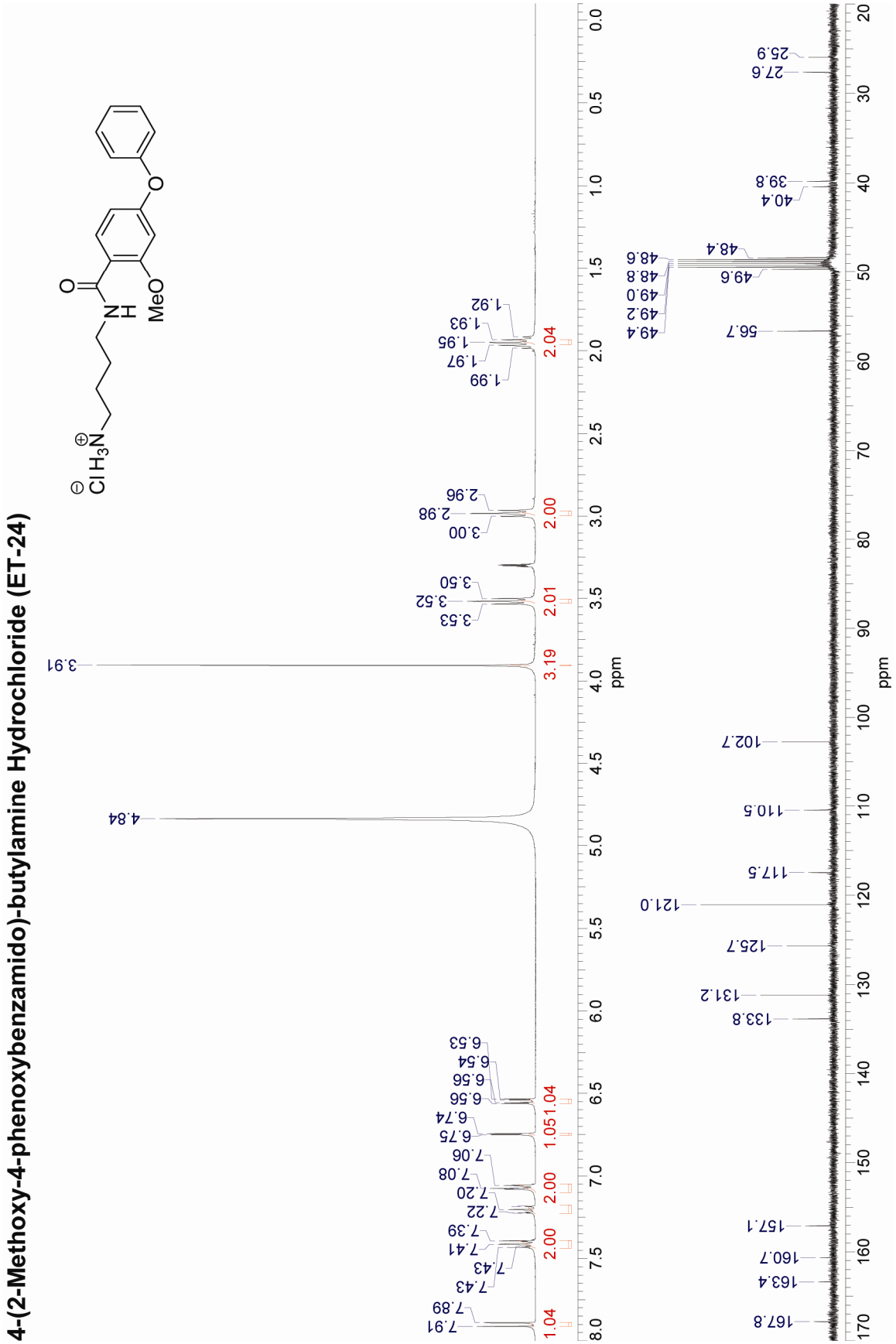
2-(2-Methoxy-4-phenoxybenzamido)-ethylamine Hydrochloride (ET-22)



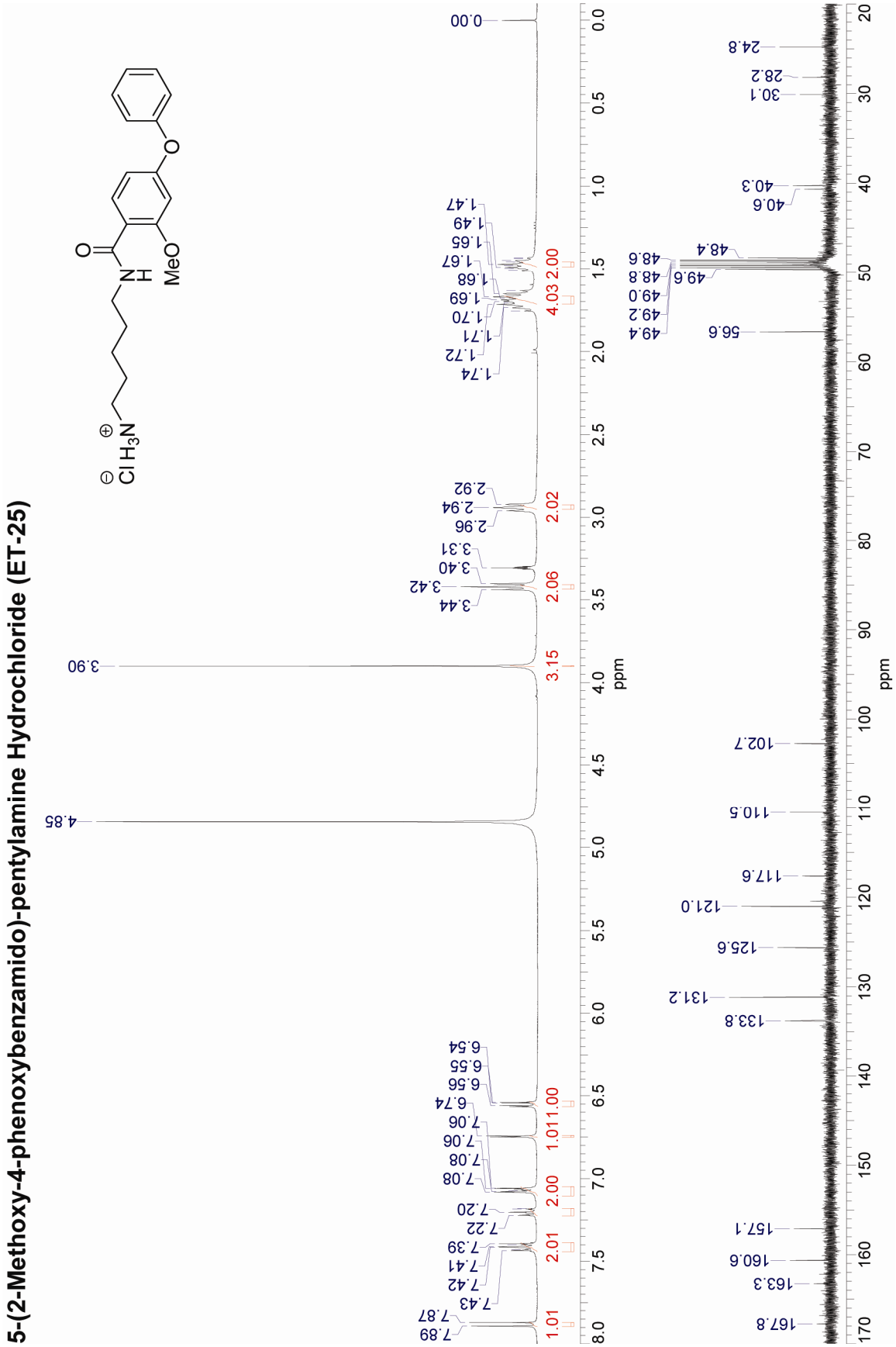
3-(2-Methoxy-4-phenoxybenzamido)-propylamine Hydrochloride (ET-23)



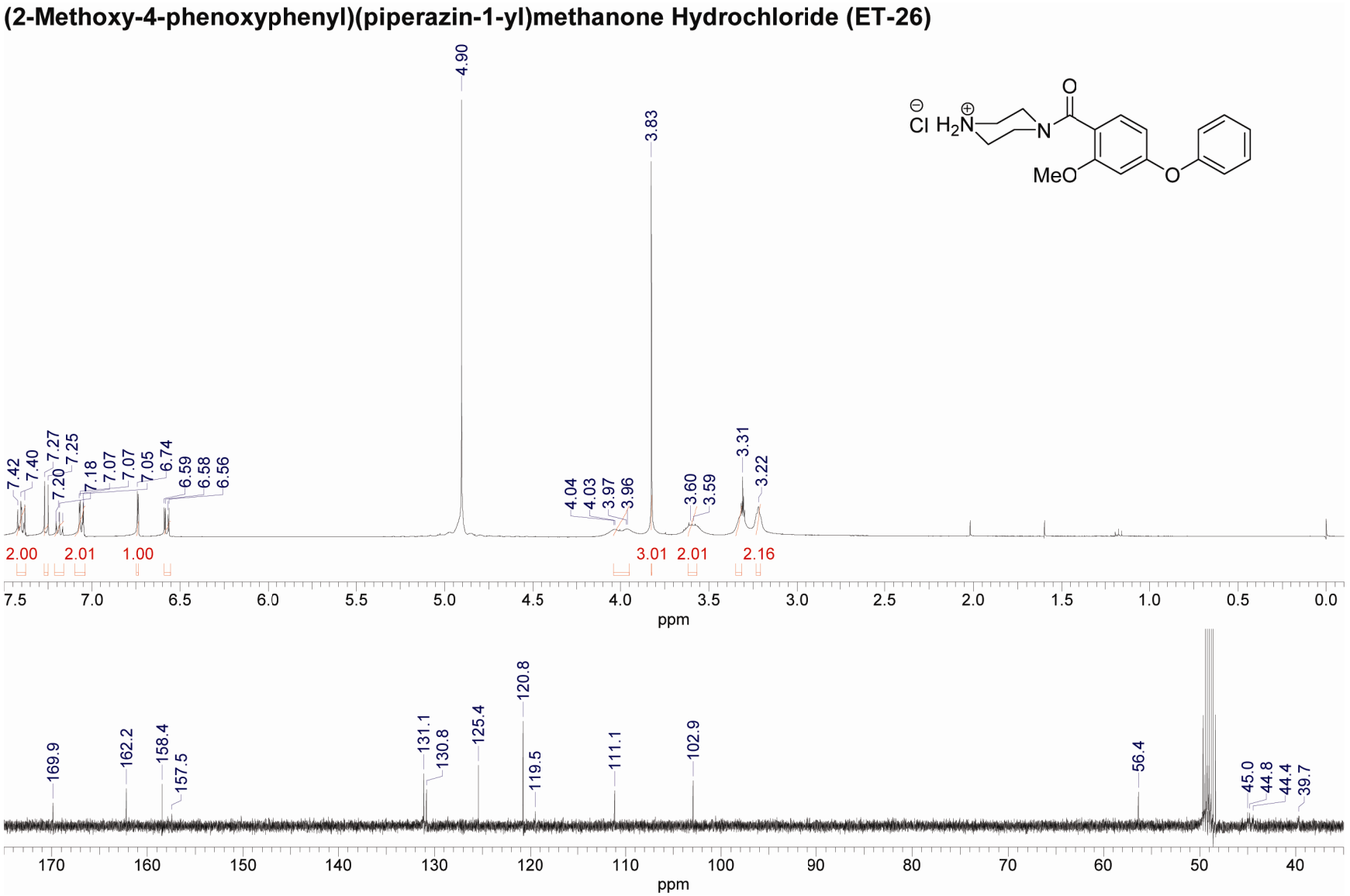
4-(2-Methoxy-4-phenoxybenzamido)-butylamine Hydrochloride (ET-24)



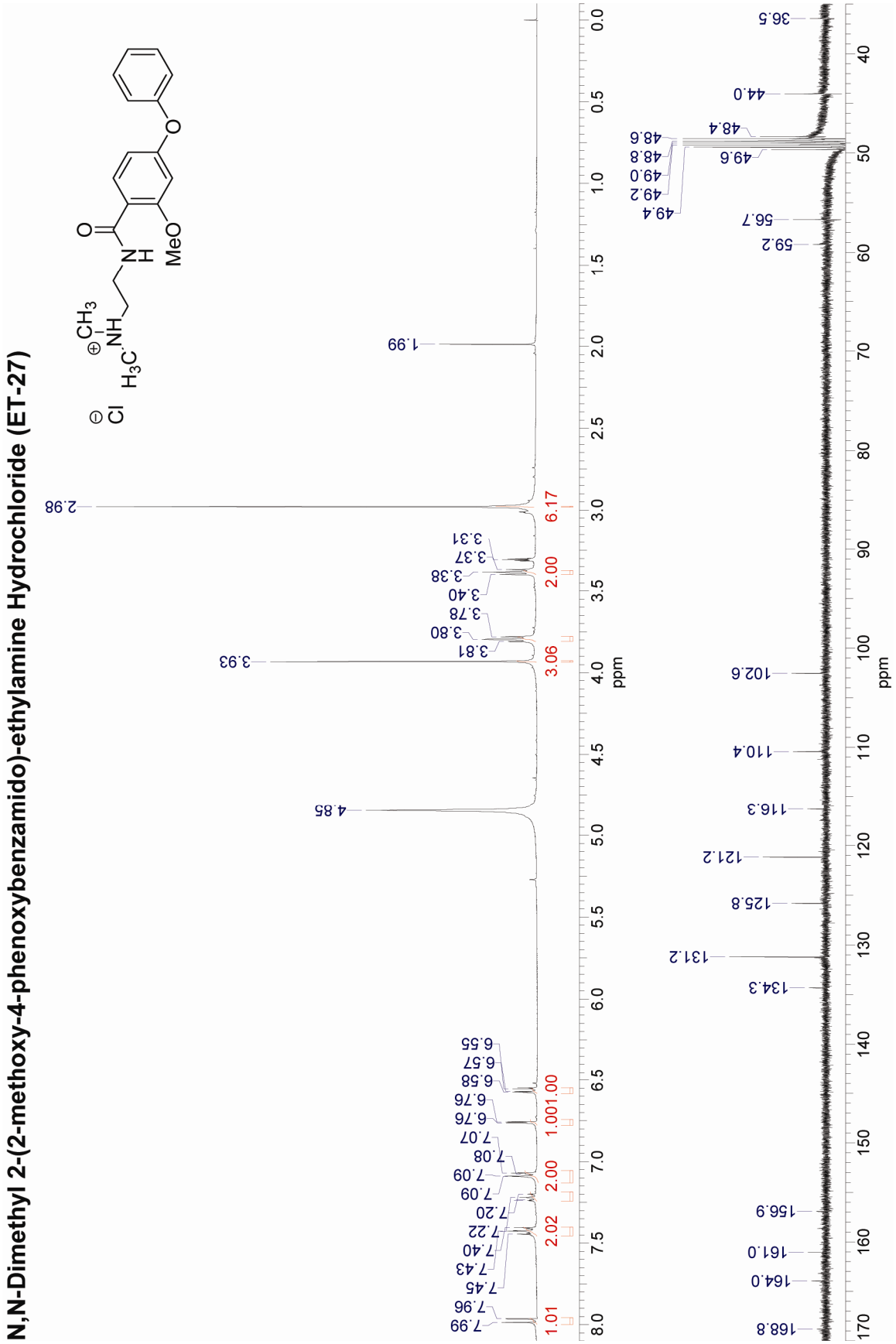
5-(2-Methoxy-4-phenoxybenzamido)-pentylamine Hydrochloride (ET-25)



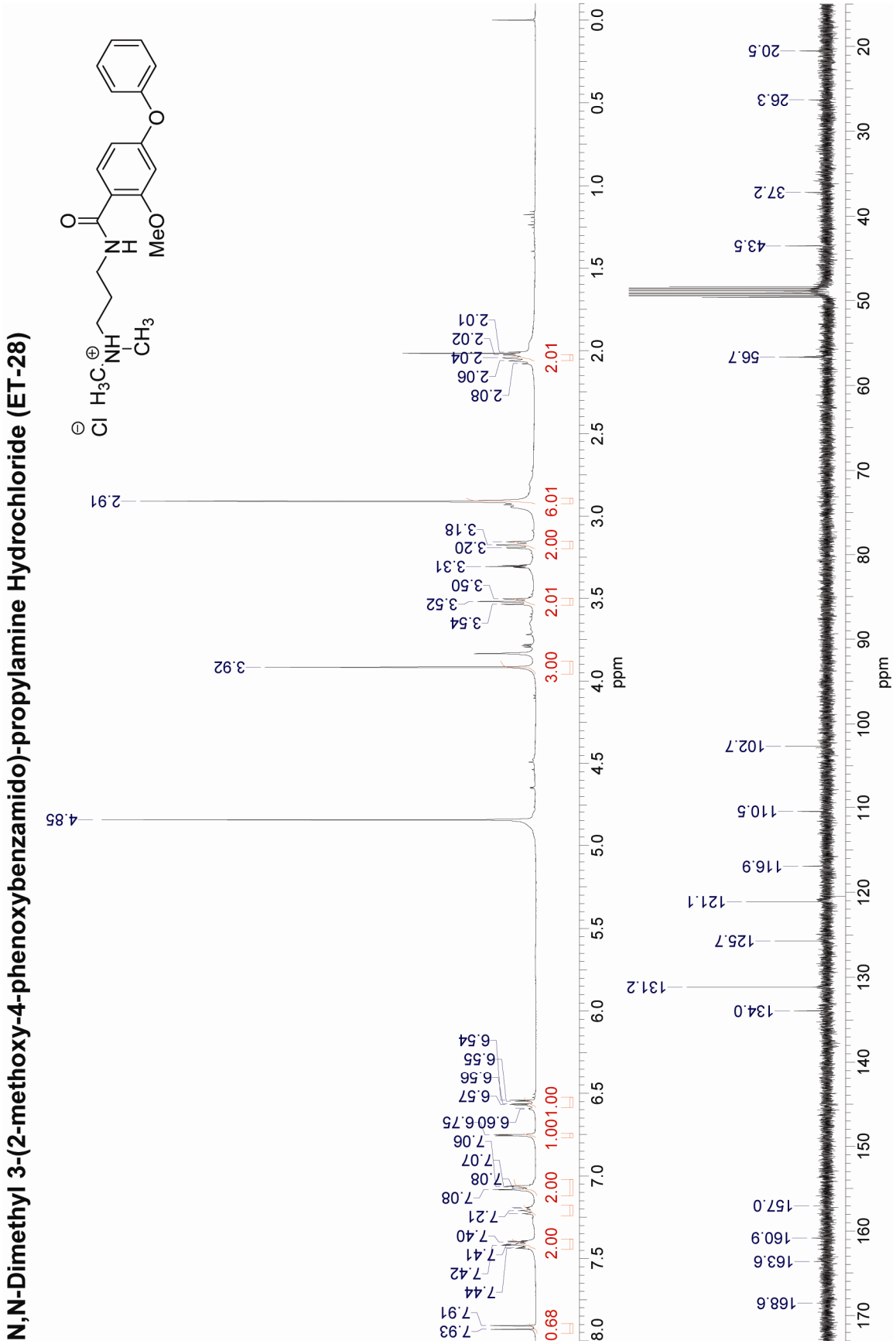
(2-Methoxy-4-phenoxyphenyl)(piperazin-1-yl)methanone Hydrochloride (ET-26)



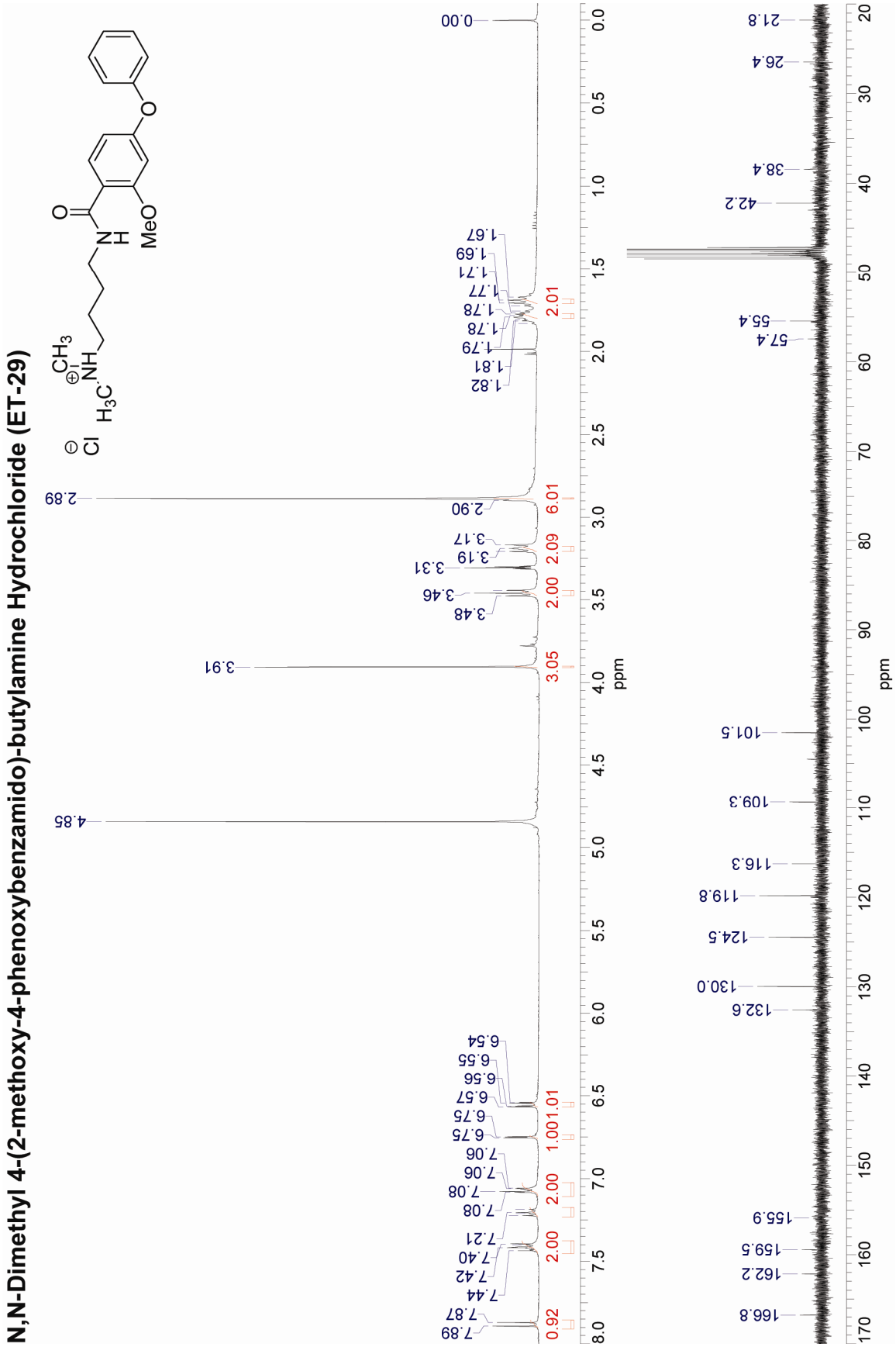
N,N-Dimethyl 2-(2-methoxy-4-phenoxybenzamido)-ethylamine Hydrochloride (ET-27)



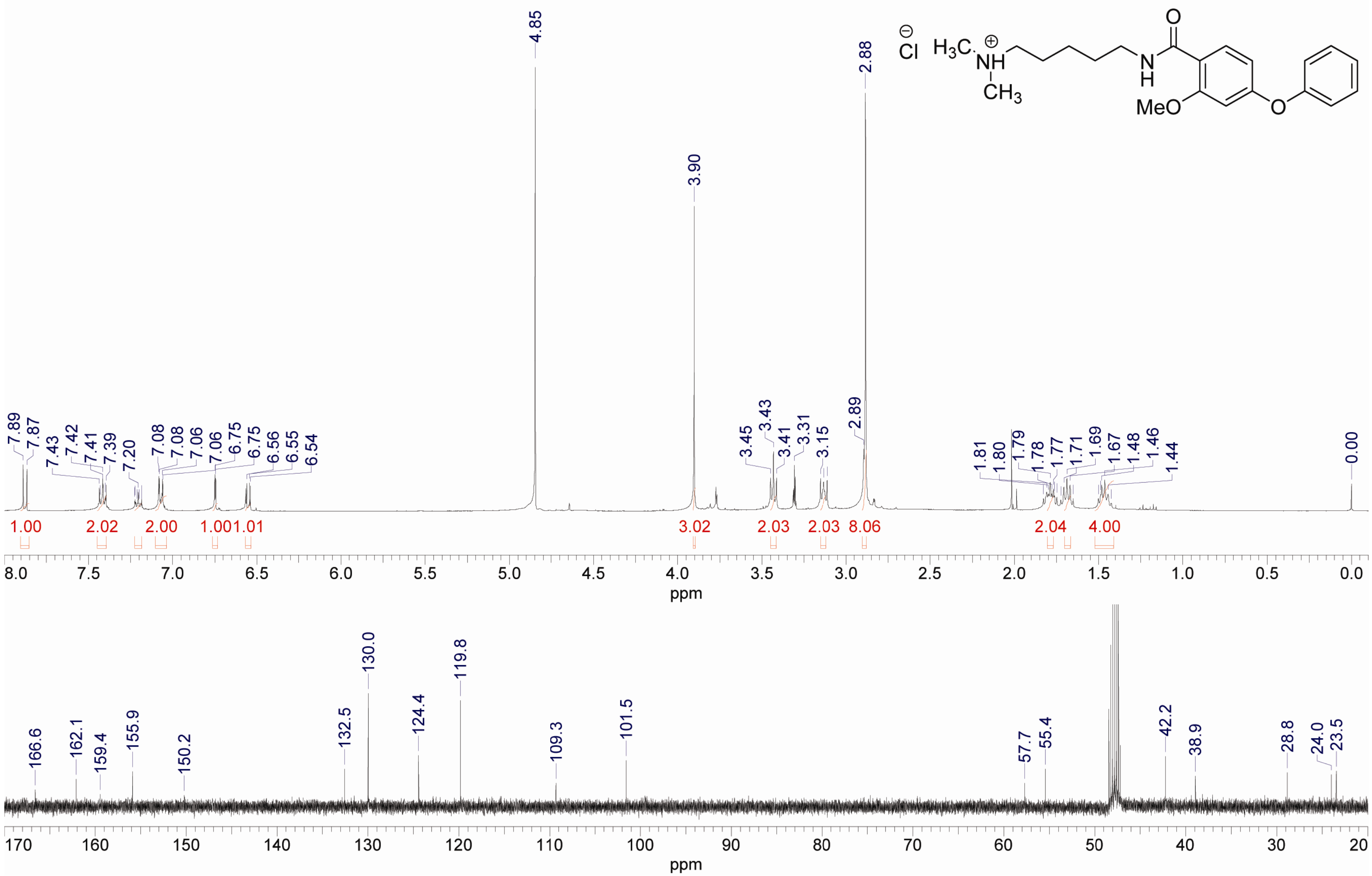
N,N-Dimethyl 3-(2-methoxy-4-phenoxybenzamido)-propylamine Hydrochloride (ET-28)

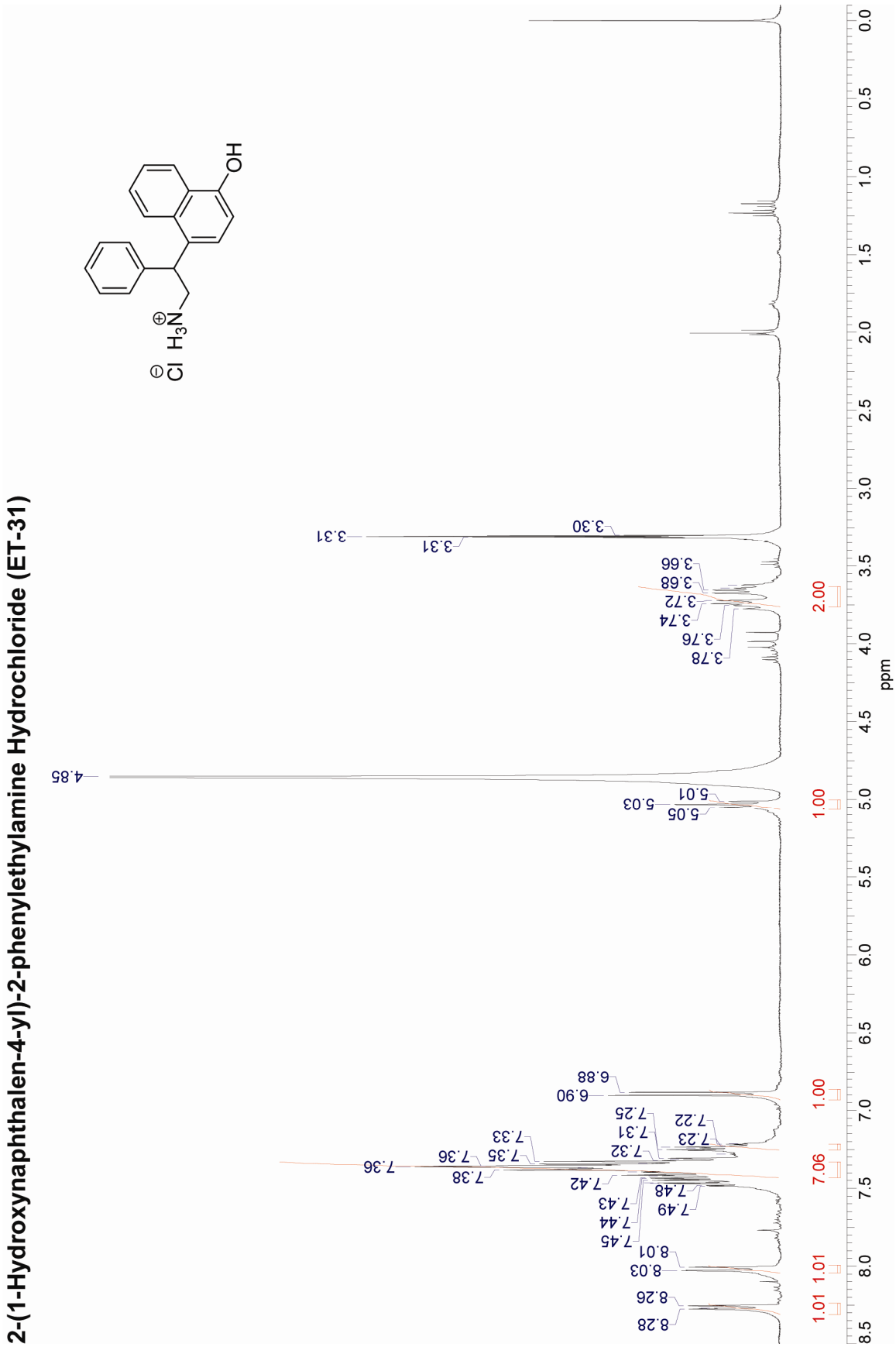


N,N-Dimethyl 4-(2-methoxy-4-phenoxybenzamido)-butylamine Hydrochloride (ET-29)

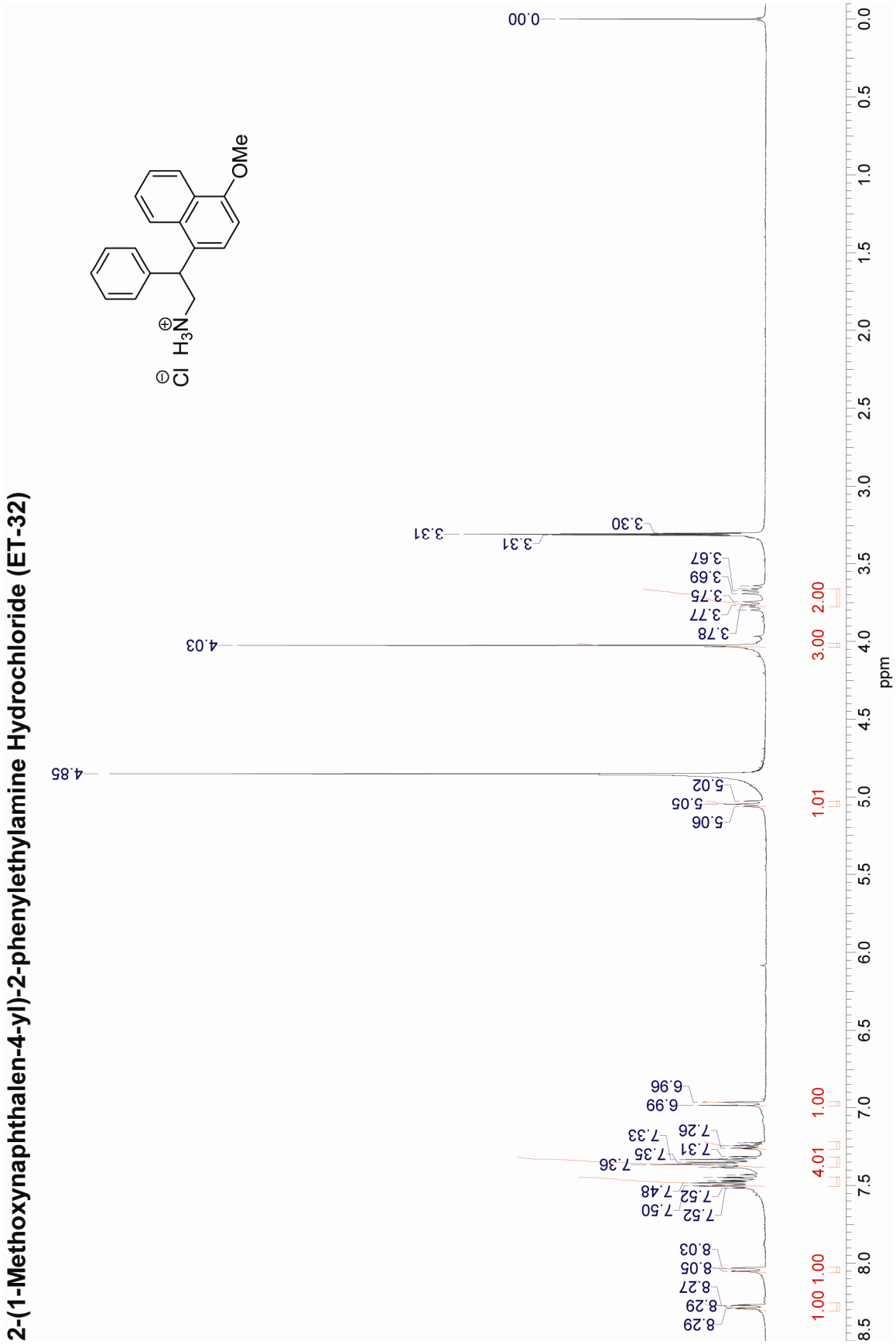


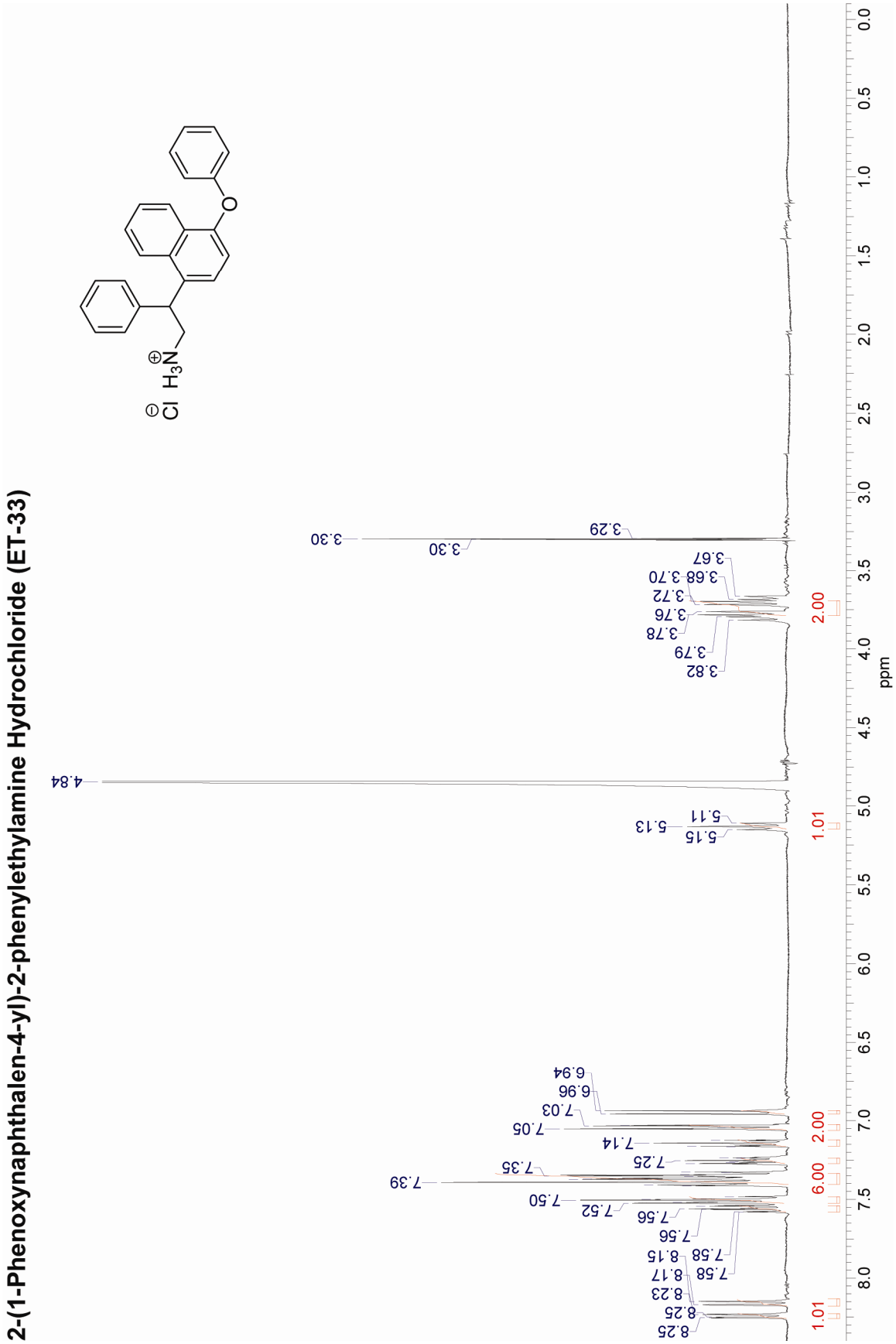
N,N-Dimethyl 5-(2-methoxy-4-phenoxybenzamido)-pentylamine Hydrochloride (ET-30)



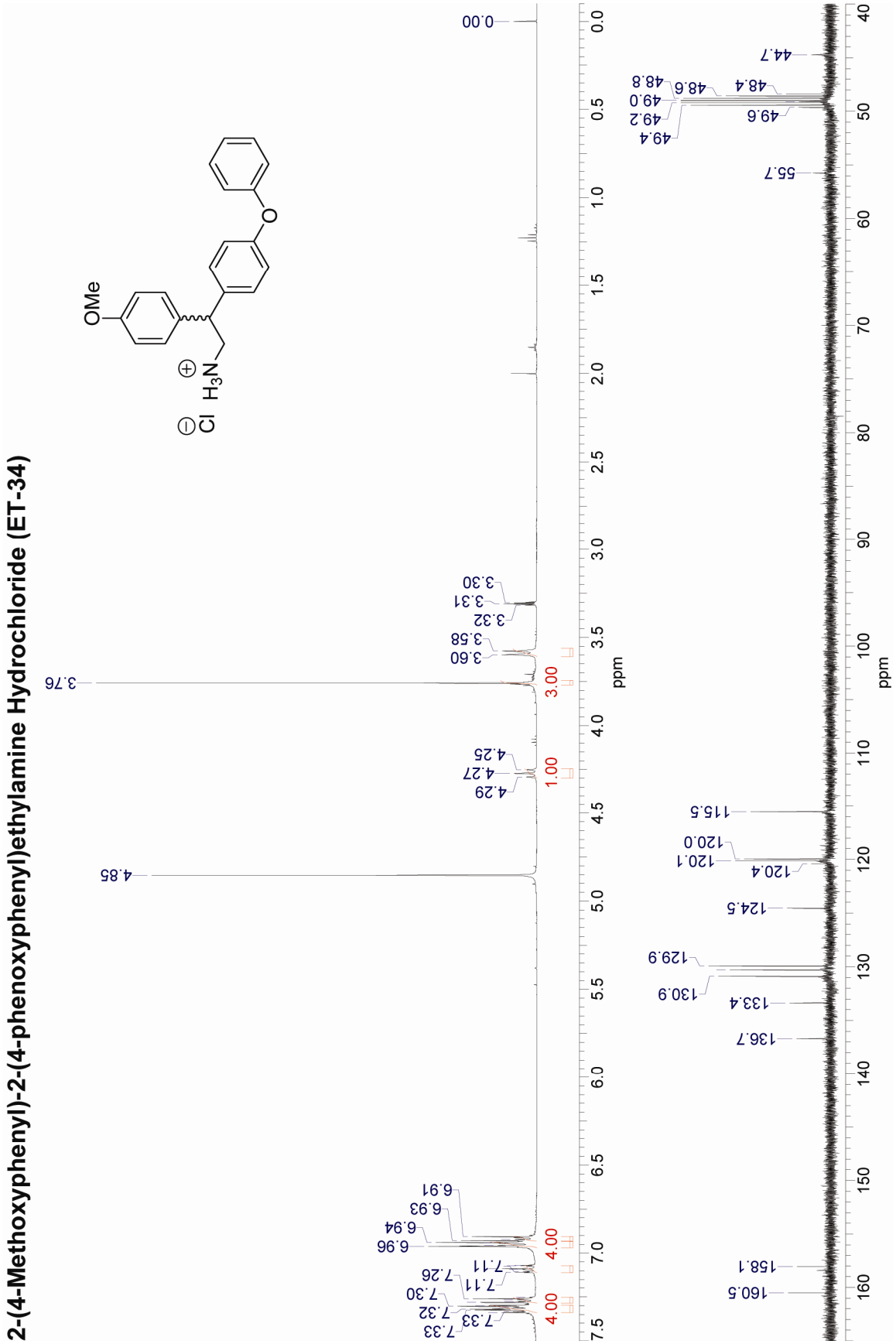

2-(1-Hydroxynaphthalen-4-yl)-2-phenylethylamine Hydrochloride (ET-31)
OH
$H_3N^{\oplus}$
$Cl^{\ominus}$
8.28
8.26
8.03
8.01
7.45
7.44
7.43
7.49
7.48
7.42
7.38
7.36
7.35
7.36
7.32
7.33
7.31
7.23
7.25
7.22
6.90
6.88
5.05
5.03
5.01
4.85
3.78
3.76
3.74
3.72
3.68
3.66
3.31
3.31
3.30
1.01
1.01
1.01
1.00
7.06
1.00
1.00
2.00
ppm

2-(1-Methoxynaphthalen-4-yl)-2-phenylethylamine Hydrochloride (ET-32)

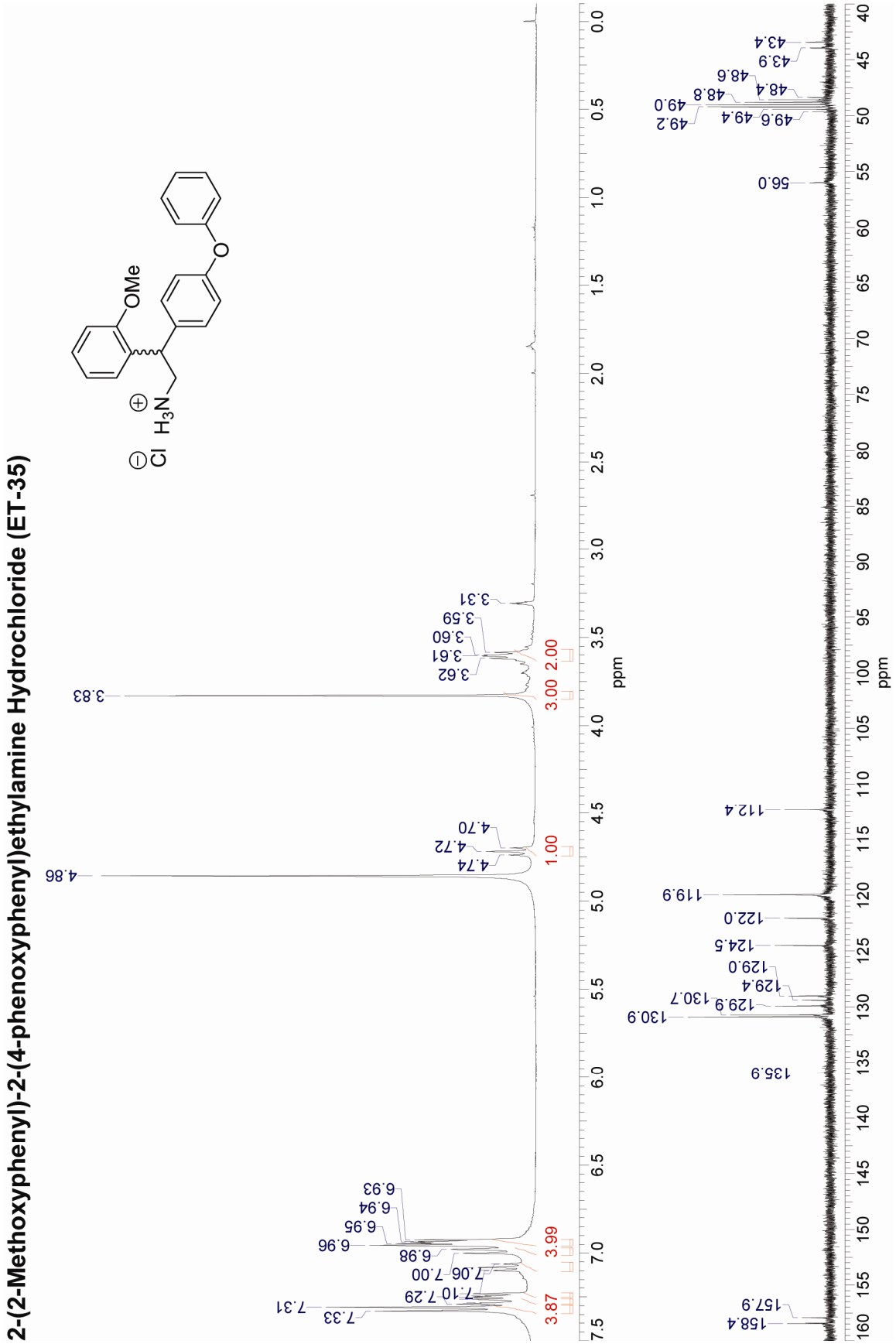


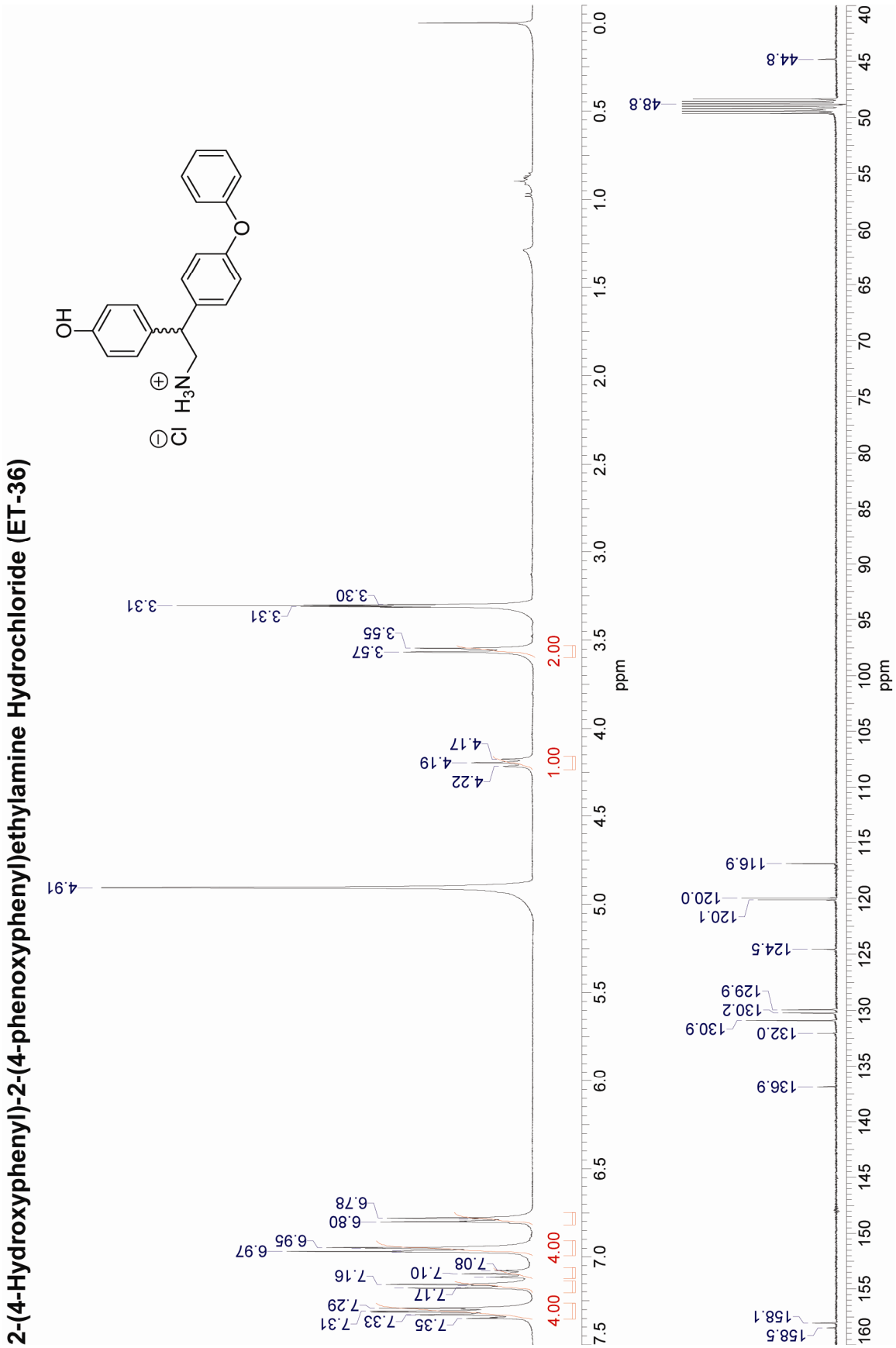

2-(1-Phenoxynaphthalen-4-yl)-2-phenylethylamine Hydrochloride (ET-33)
Cl
H3N
8.25
8.25
8.23
8.17
7.58
8.15
7.58
7.56
7.56
7.52
7.50
7.39
7.35
7.25
7.14
7.05
7.03
6.96
6.94
5.15
5.11
5.13
4.84
3.82
3.79
3.78
3.76
3.72
3.68
3.70
3.67
3.30
3.30
3.29
1.01
6.00
2.00
2.00
1.01
2.00
ppm

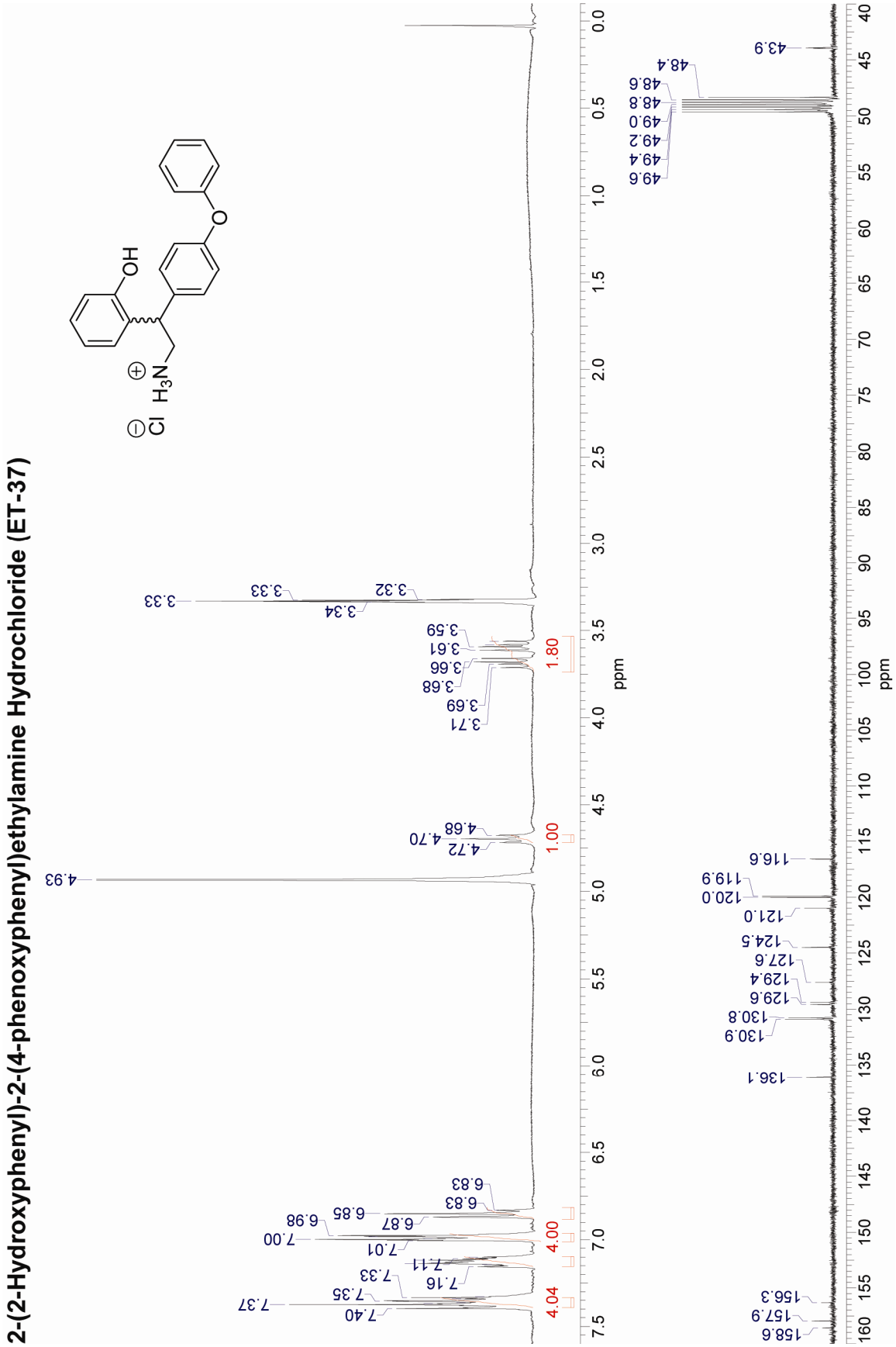
2-(4-Methoxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-34)

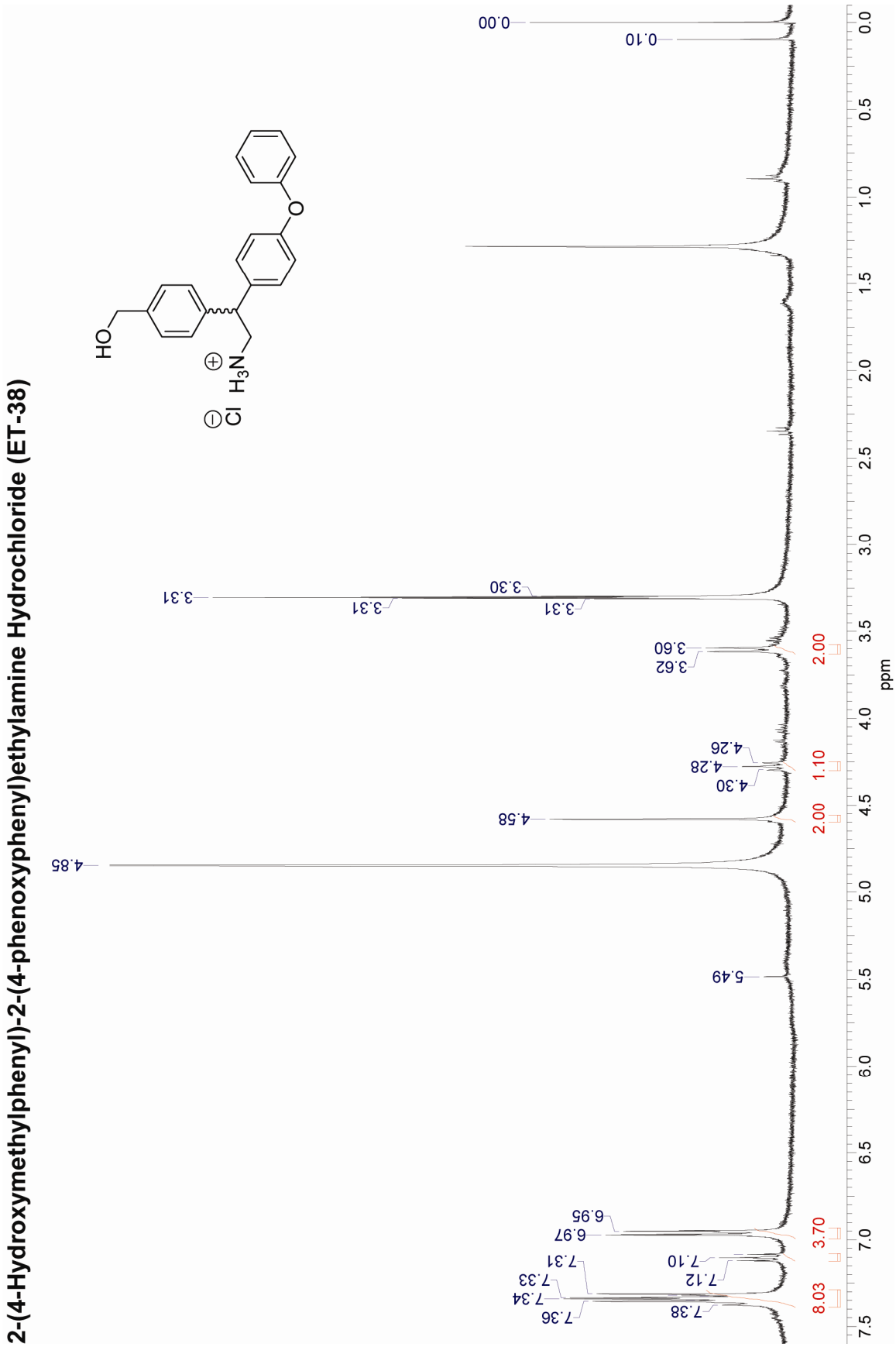


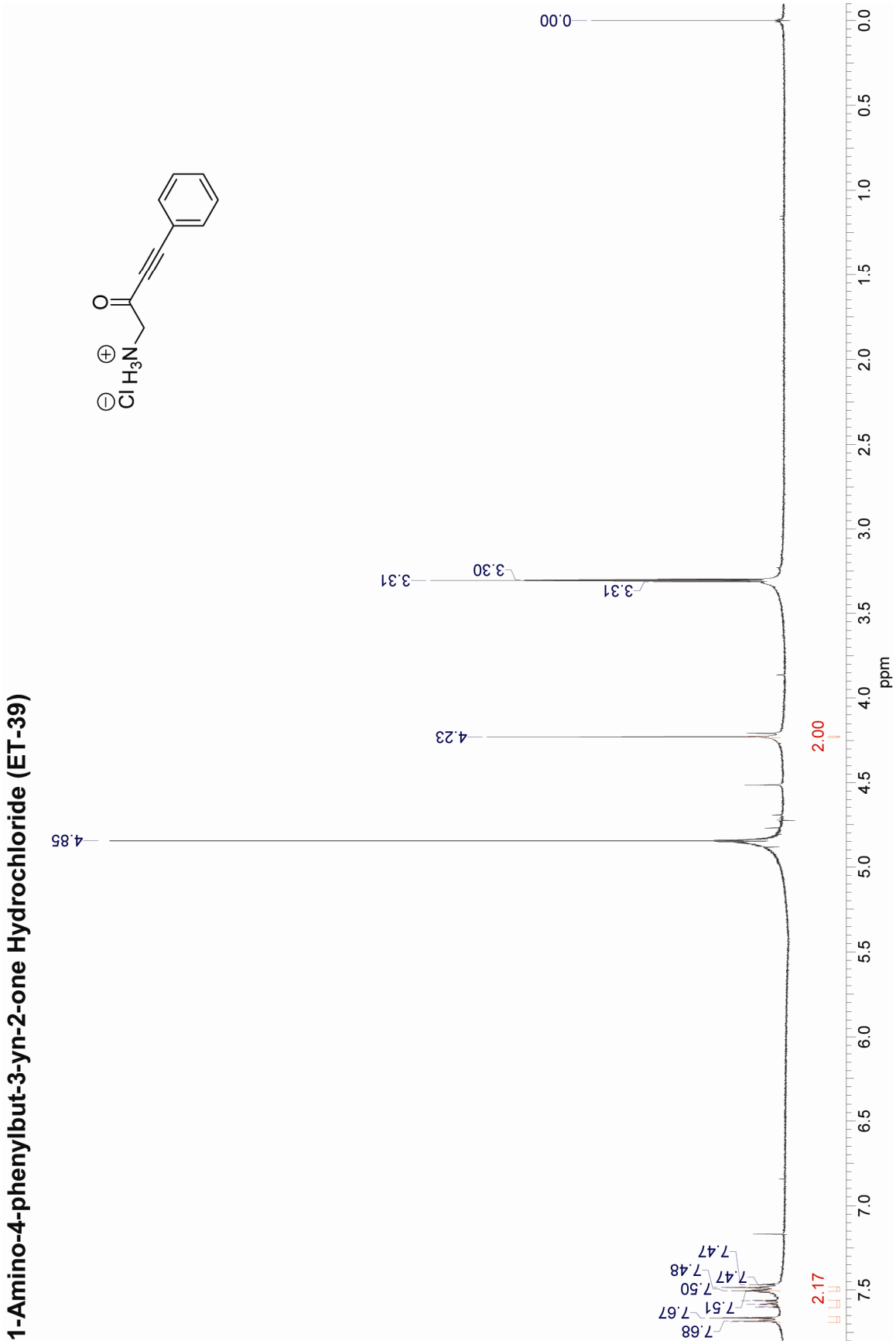
2-(2-Methoxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-35)

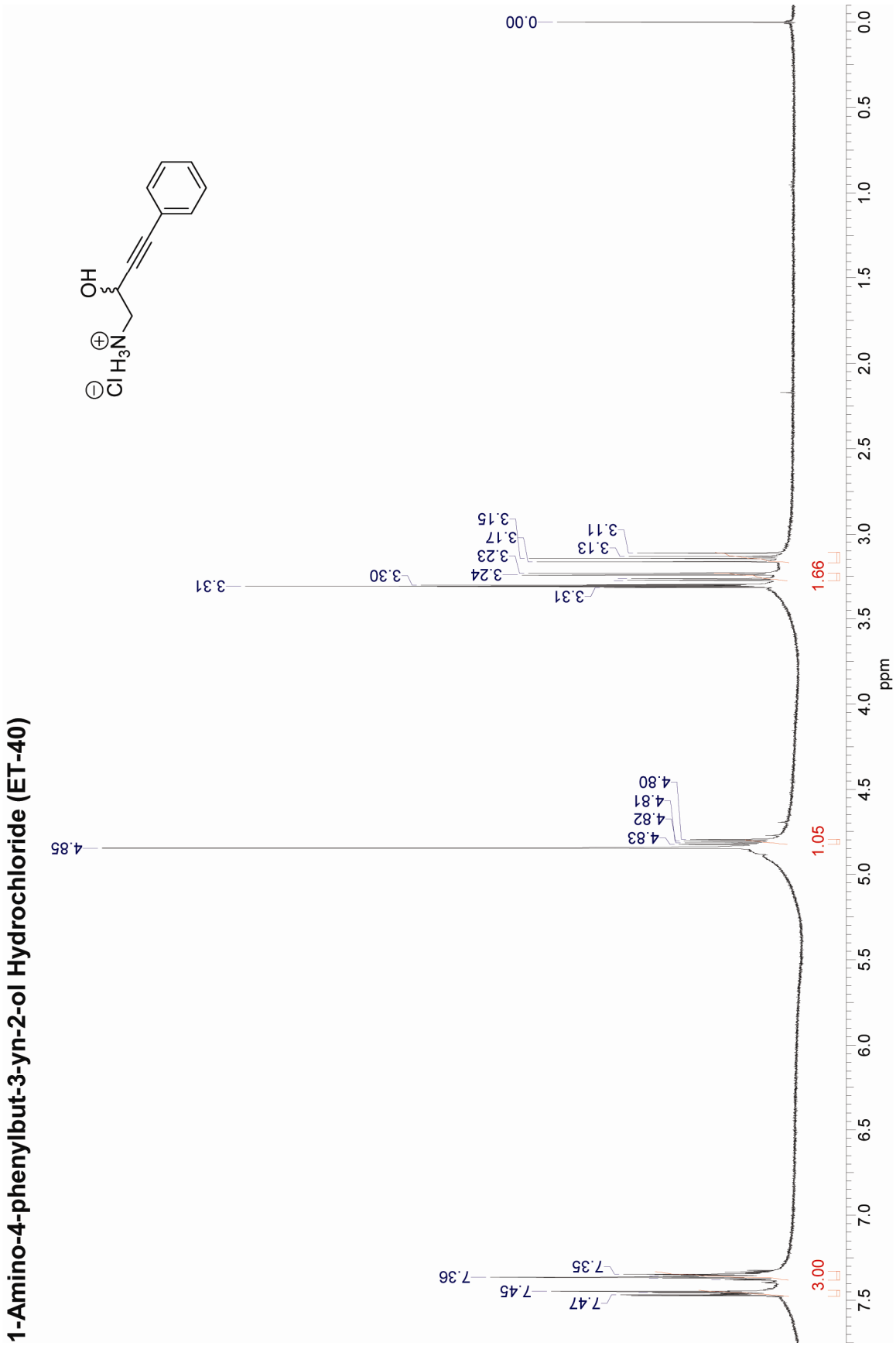


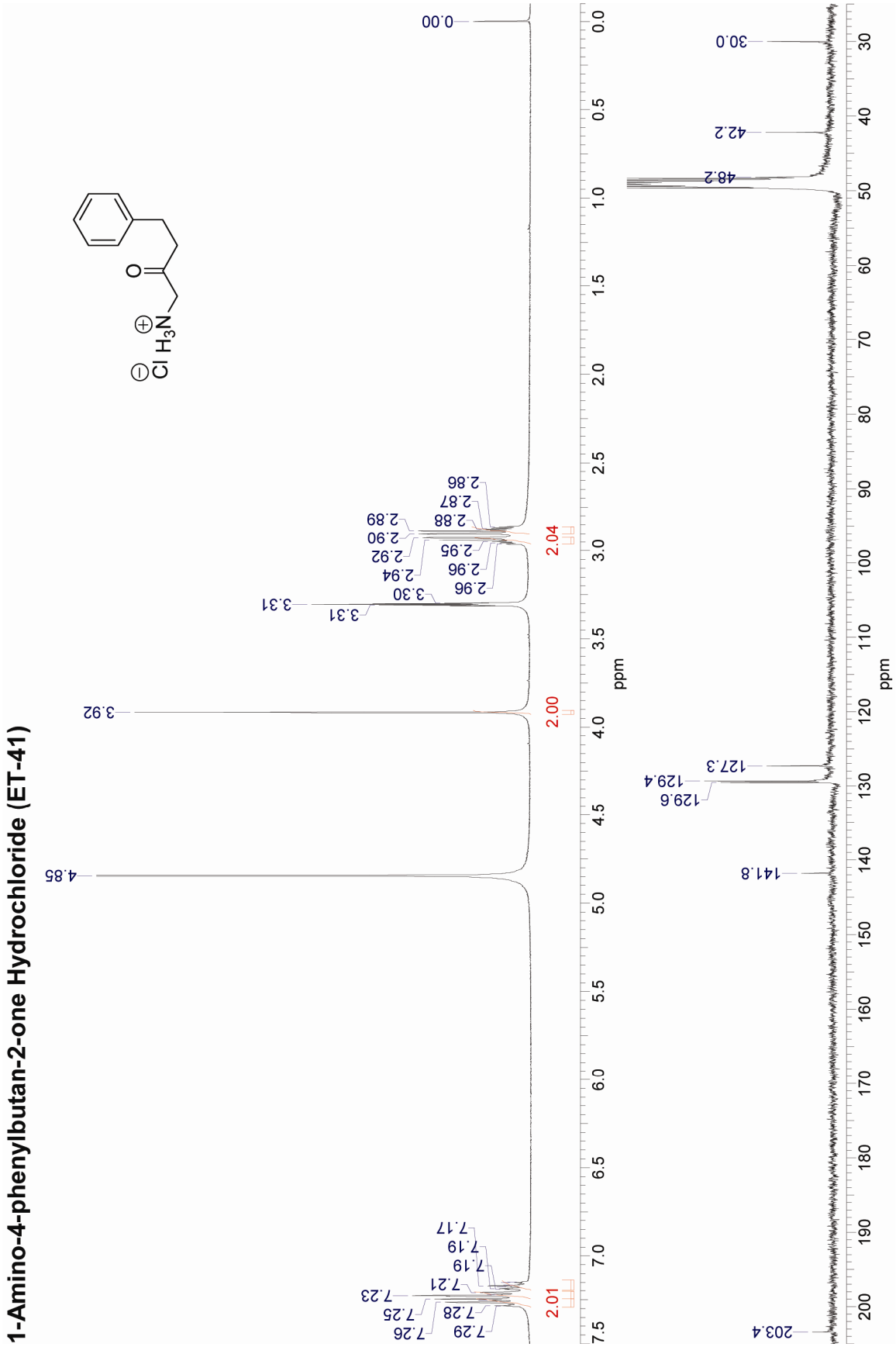

2-(4-Hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-36)
OH
O
H3N
Cl
4.91
4.22
4.19
4.17
3.57
3.55
3.31
3.30
7.35
7.33
7.31
7.29
7.17
7.16
7.10
7.08
6.97
6.95
6.80
6.78
4.00
4.00
1.00
2.00
ppm
158.5
158.1
136.9
132.0
130.9
130.2
129.9
124.5
120.1
120.0
116.9
48.8
44.8
ppm


2-(2-Hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-37)
OH
O
H3N
Cl
ppm
ppm

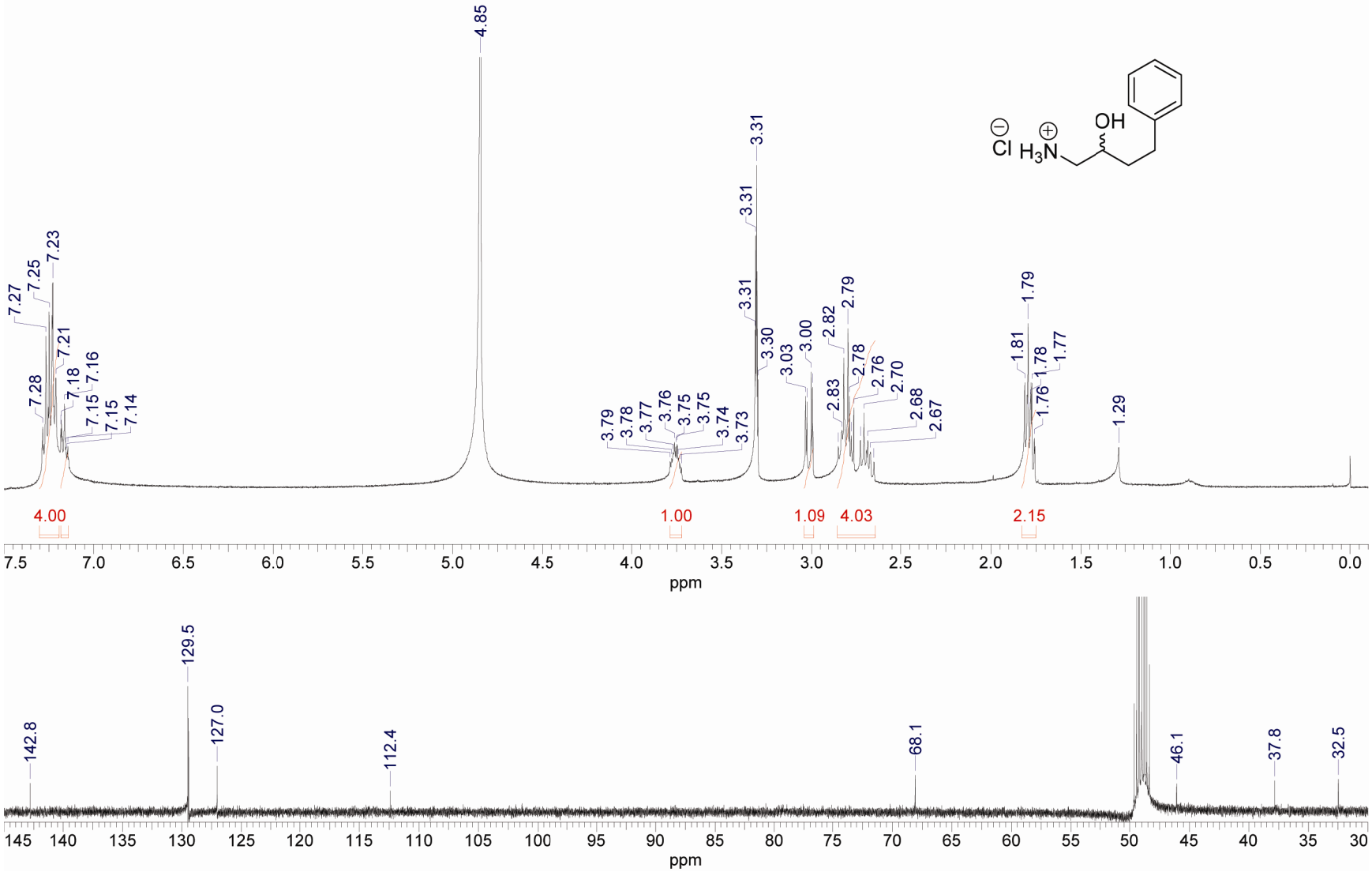

2-(4-Hydroxymethylphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-38)
HO
O
H3N
Cl
ppm
0.00
0.10
3.31
3.30
3.31
3.31
3.62
3.60
4.30
4.28
4.26
4.58
4.85
5.49
6.97
6.95
7.38
7.36
7.34
7.33
7.31
7.12
7.10
2.00
1.10
2.00
3.70
8.03

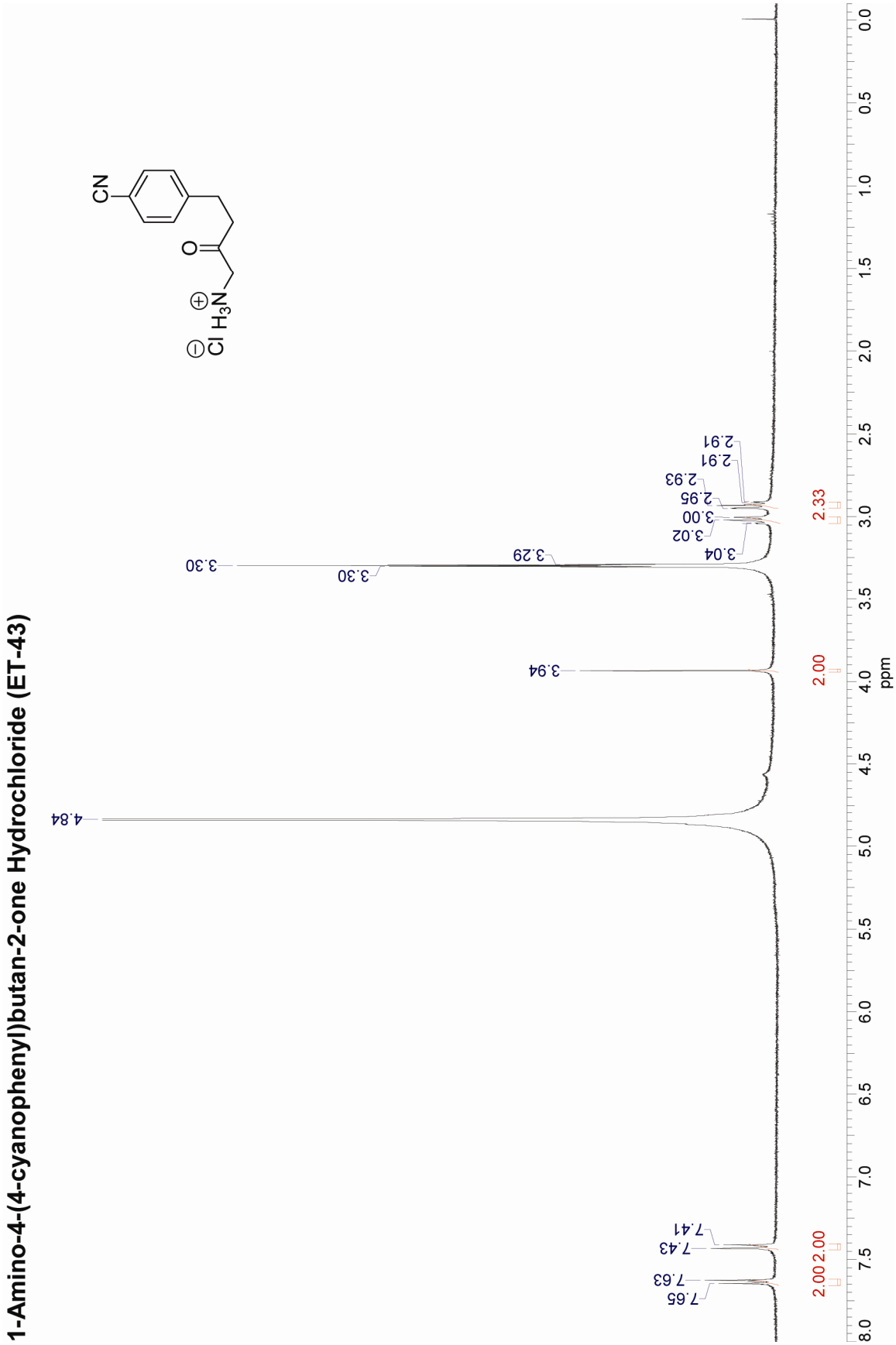

1-Amino-4-phenylbut-3-yn-2-one Hydrochloride (ET-39)
O
⊕
H3N
Cl
⊖
4.85
4.23
3.31
3.30
3.31
0.00
7.68
7.67
7.51
7.50
7.48
7.47
7.47
2.00
2.17
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5


1-Amino-4-phenylbut-3-yn-2-ol Hydrochloride (ET-40)
OH
⊕
H3N
⊖
Cl
0.00
3.11
3.13
3.15
3.17
3.23
3.24
3.30
3.31
3.31
4.80
4.81
4.82
4.83
4.85
7.35
7.36
7.45
7.47
3.00
1.05
1.66
ppm

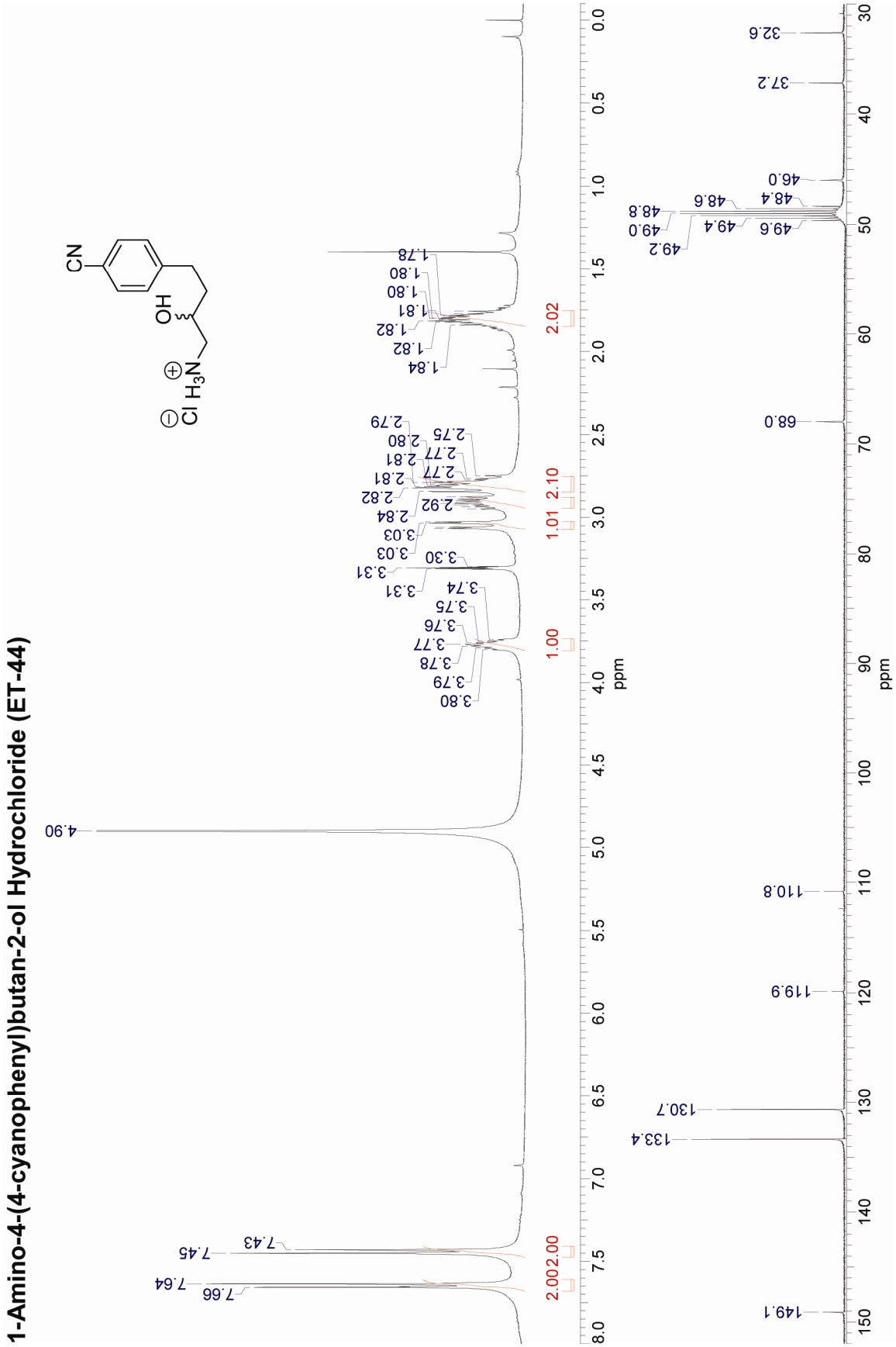

1-Amino-4-phenylbutan-2-one Hydrochloride (ET-41)
O
⊕
H3N
Cl
⊖
0.00
2.86
2.87
2.88
2.89
2.90
2.92
2.94
2.95
2.96
2.96
3.30
3.31
3.31
3.92
4.85
7.17
7.19
7.19
7.21
7.23
7.25
7.28
7.29
2.01
2.00
2.04
ppm
30.0
42.2
48.2
127.3
129.4
129.6
141.8
203.4
ppm

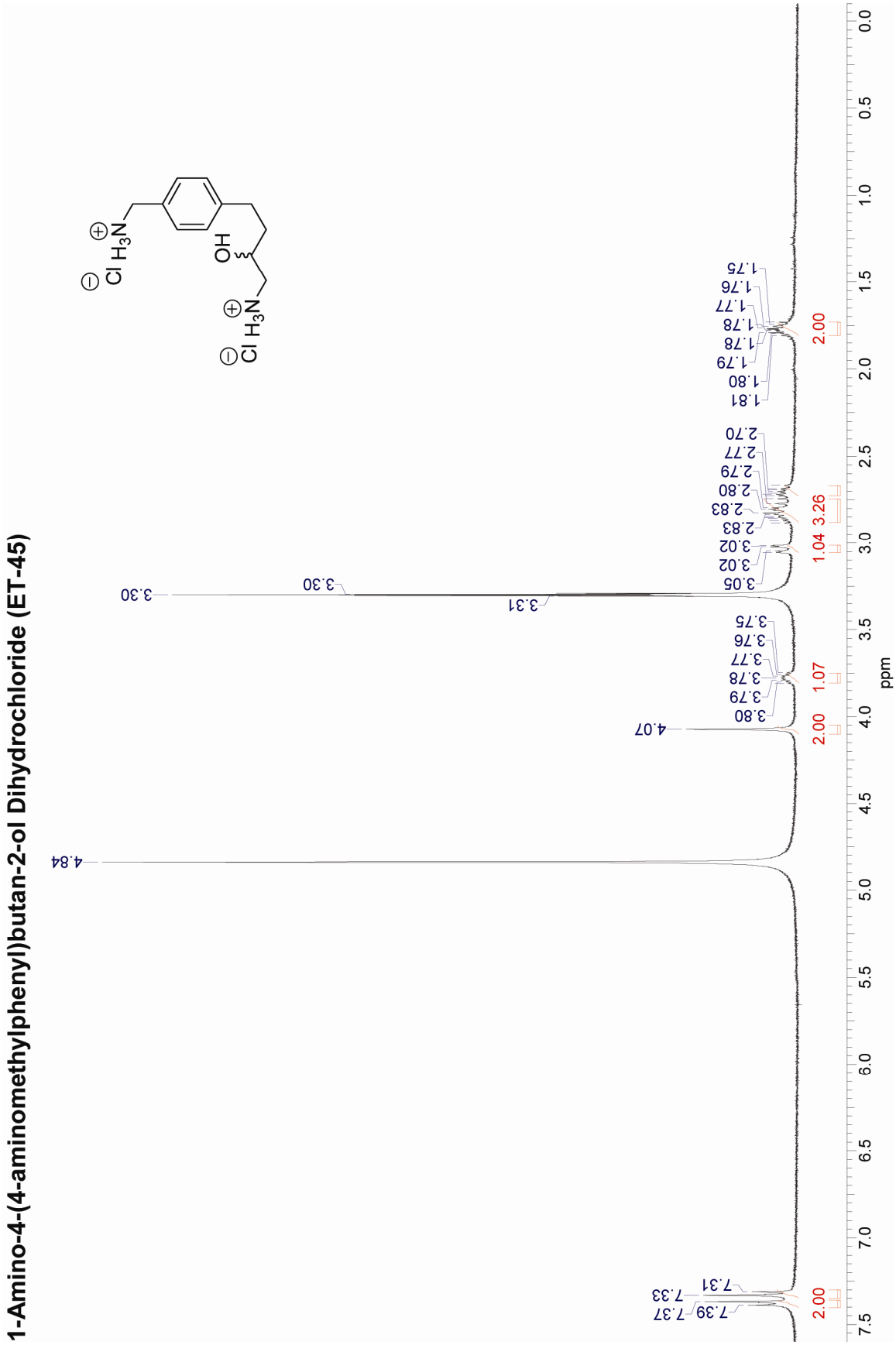
1-Amino-4-phenylbutan-2-ol Hydrochloride (ET-42)

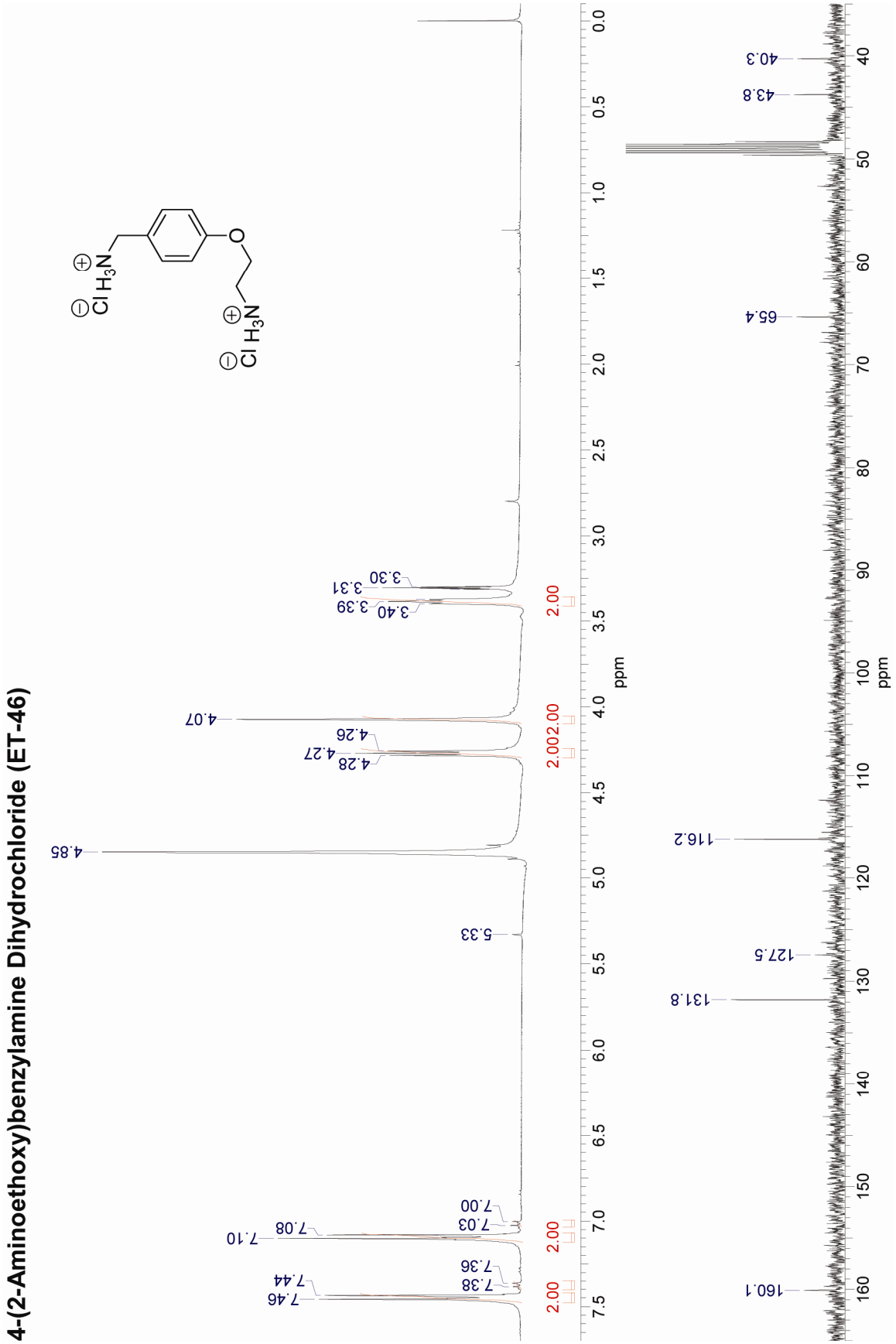



1-Amino-4-(4-cyanophenyl)butan-2-one Hydrochloride (ET-43)
CN
O
$\oplus$ H_3N
$\ominus$ Cl
4.84
3.94
3.30
3.30
3.29
3.04
3.02
3.00
2.95
2.93
2.91
2.91
7.65
7.63
7.43
7.41
2.00
2.00
2.00
2.33
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

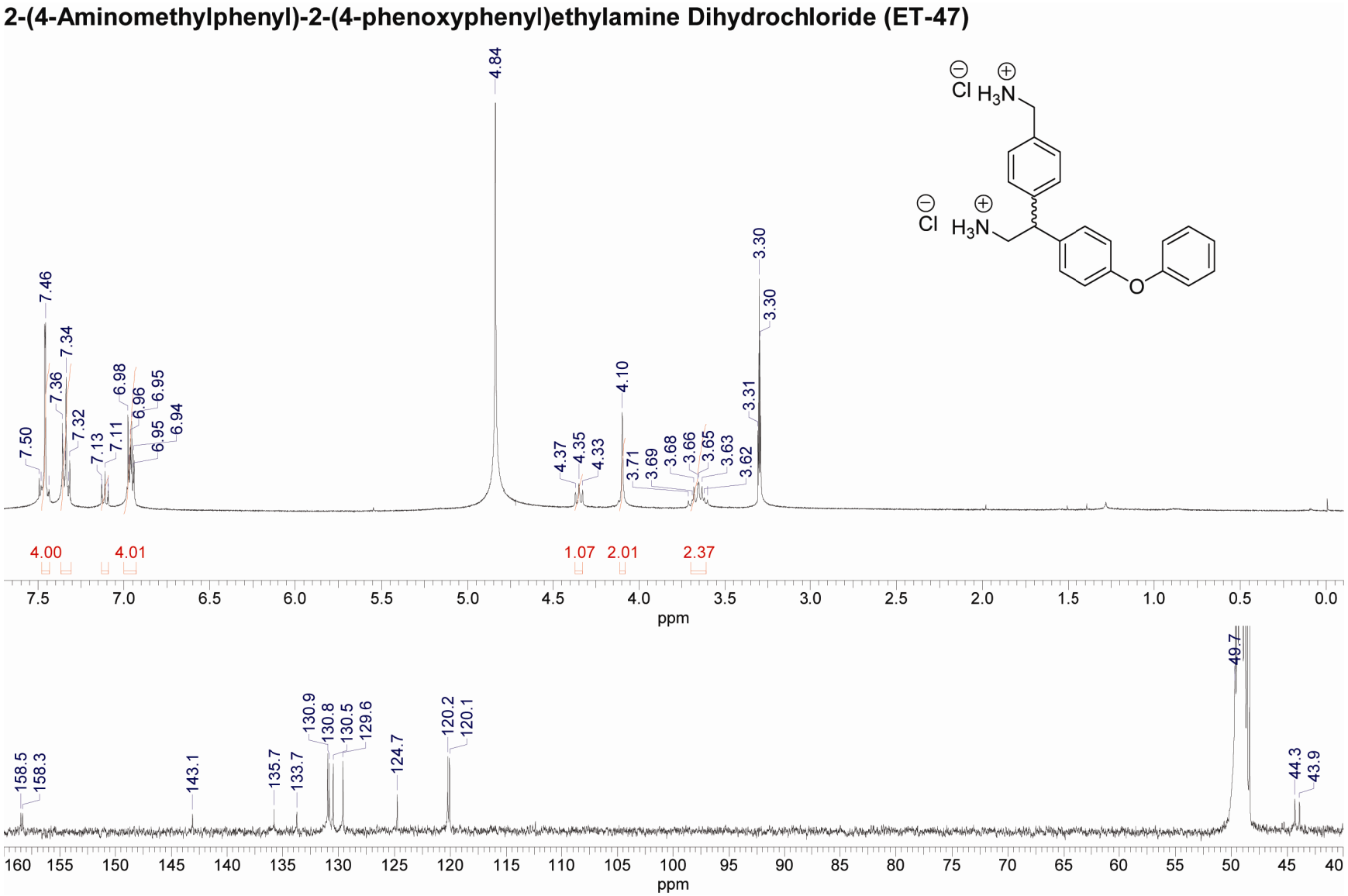
1-Amino-4-(4-cyanophenyl)butan-2-ol Hydrochloride (ET-44)



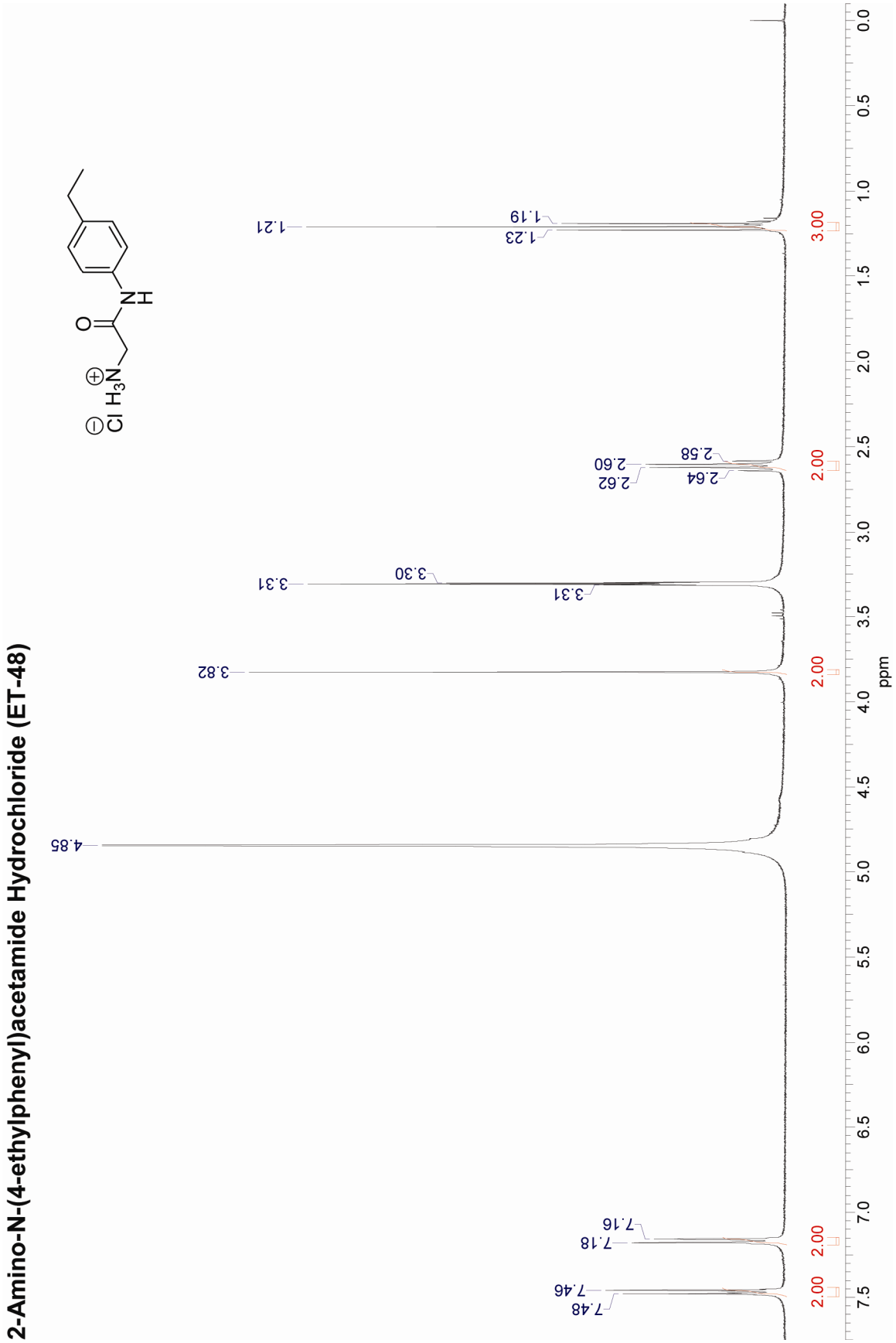

1-Amino-4-(4-aminomethylphenyl)butan-2-ol Dihydrochloride (ET-45)
OH
Cl H3N
Cl H3N
7.39
7.37
7.33
7.31
4.84
4.07
3.80
3.79
3.78
3.77
3.76
3.75
3.31
3.30
3.30
3.05
3.02
3.02
2.83
2.83
2.80
2.79
2.77
2.70
1.81
1.80
1.79
1.78
1.78
1.77
1.76
1.75
2.00
1.04
3.26
2.00
1.07
2.00
ppm


4-(2-Aminoethoxy)benzylamine Dihydrochloride (ET-46)
Cl H3N
Cl H3N
4.85
5.33
4.07
4.28
4.27
4.26
3.40
3.39
3.30
3.31
7.46
7.44
7.38
7.36
7.10
7.08
7.03
7.00
2.00
2.00
2.00
2.00
ppm
160.1
131.8
127.5
116.2
65.4
43.8
40.3
ppm

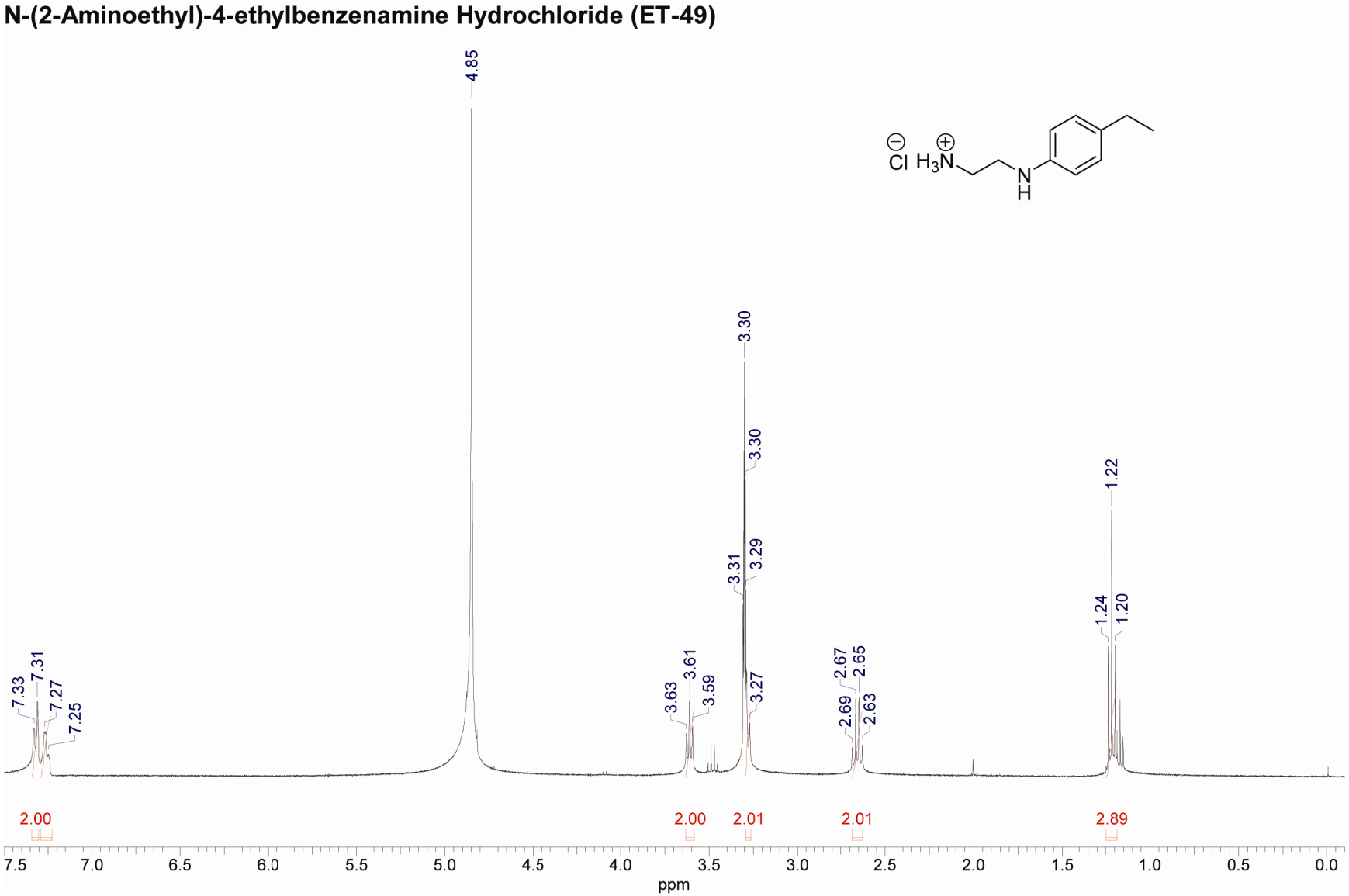
2-(4-Aminomethylphenyl)-2-(4-phenoxyphenyl)ethylamine Dihydrochloride (ET-47)



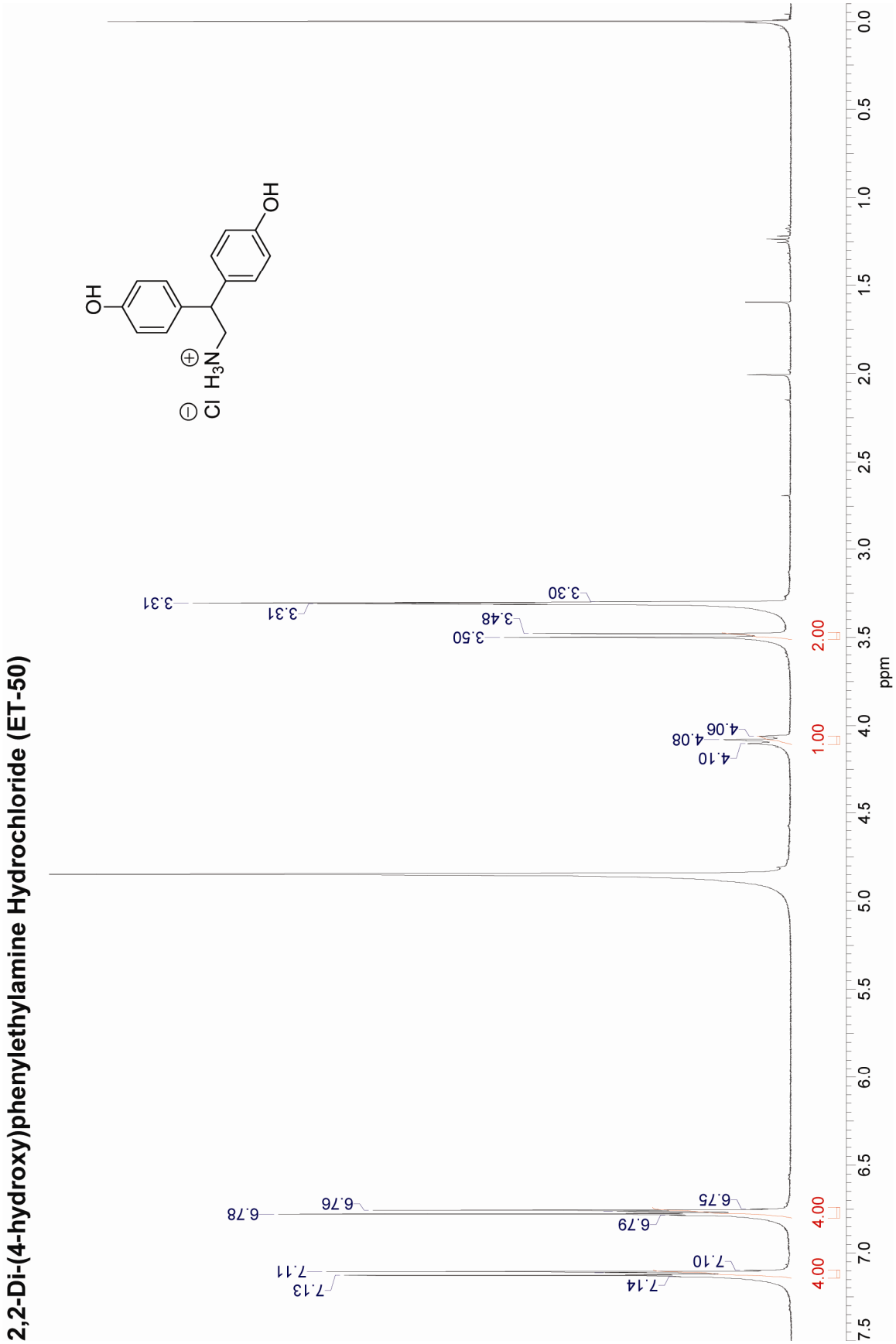
2-Amino-N-(4-ethylphenyl)acetamide Hydrochloride (ET-48)

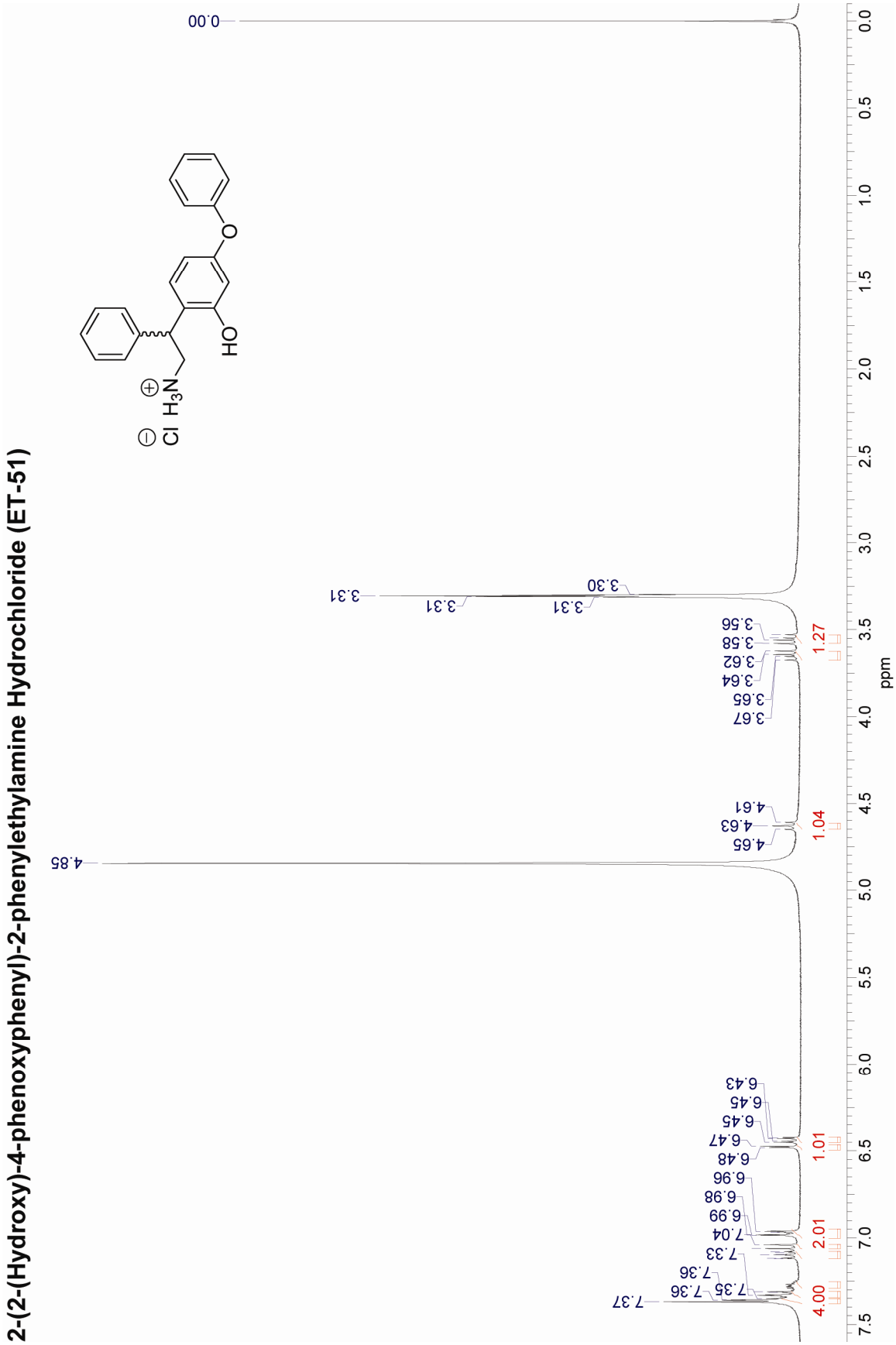


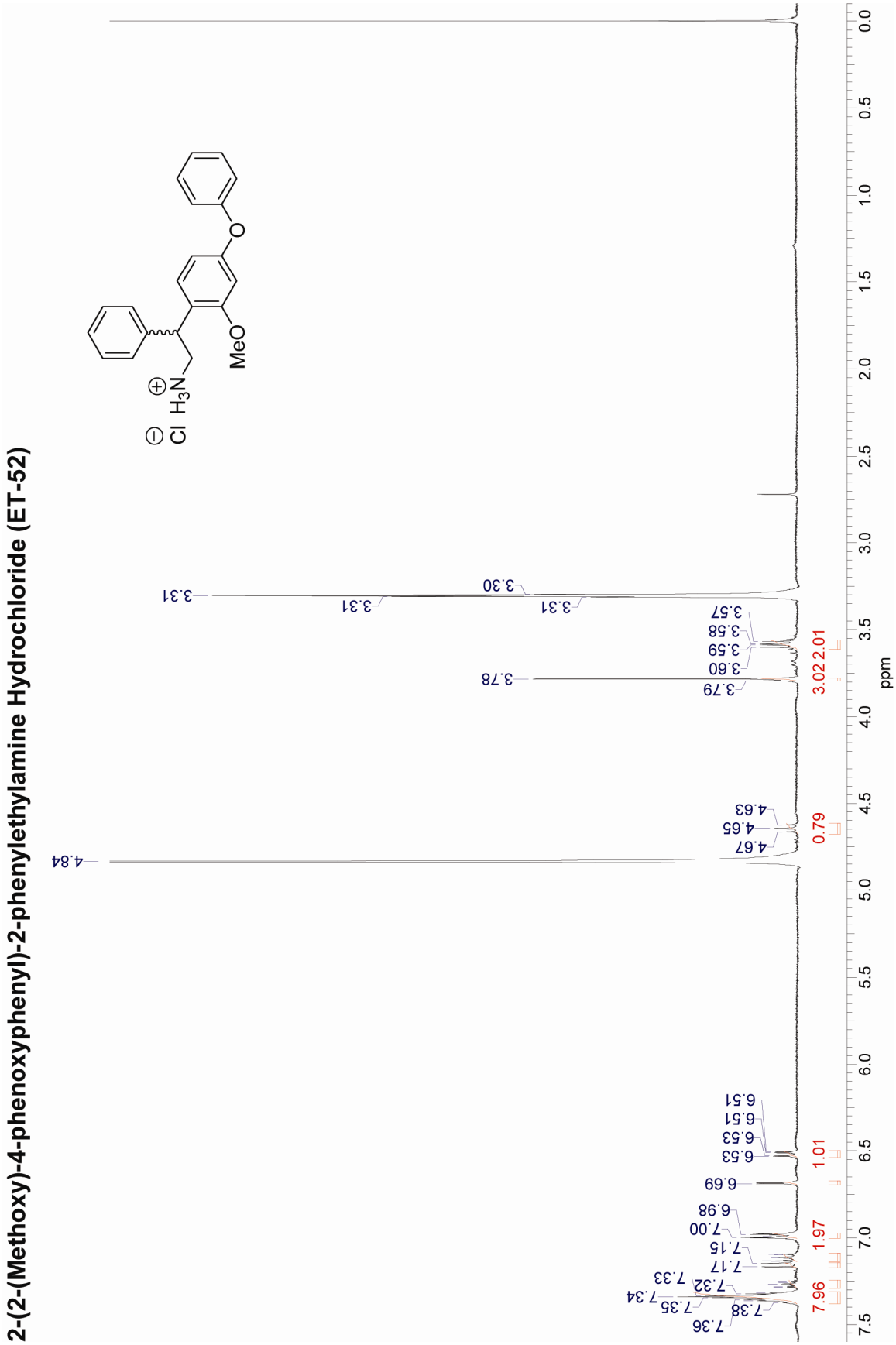
N-(2-Aminoethyl)-4-ethylbenzenamine Hydrochloride (ET-49)



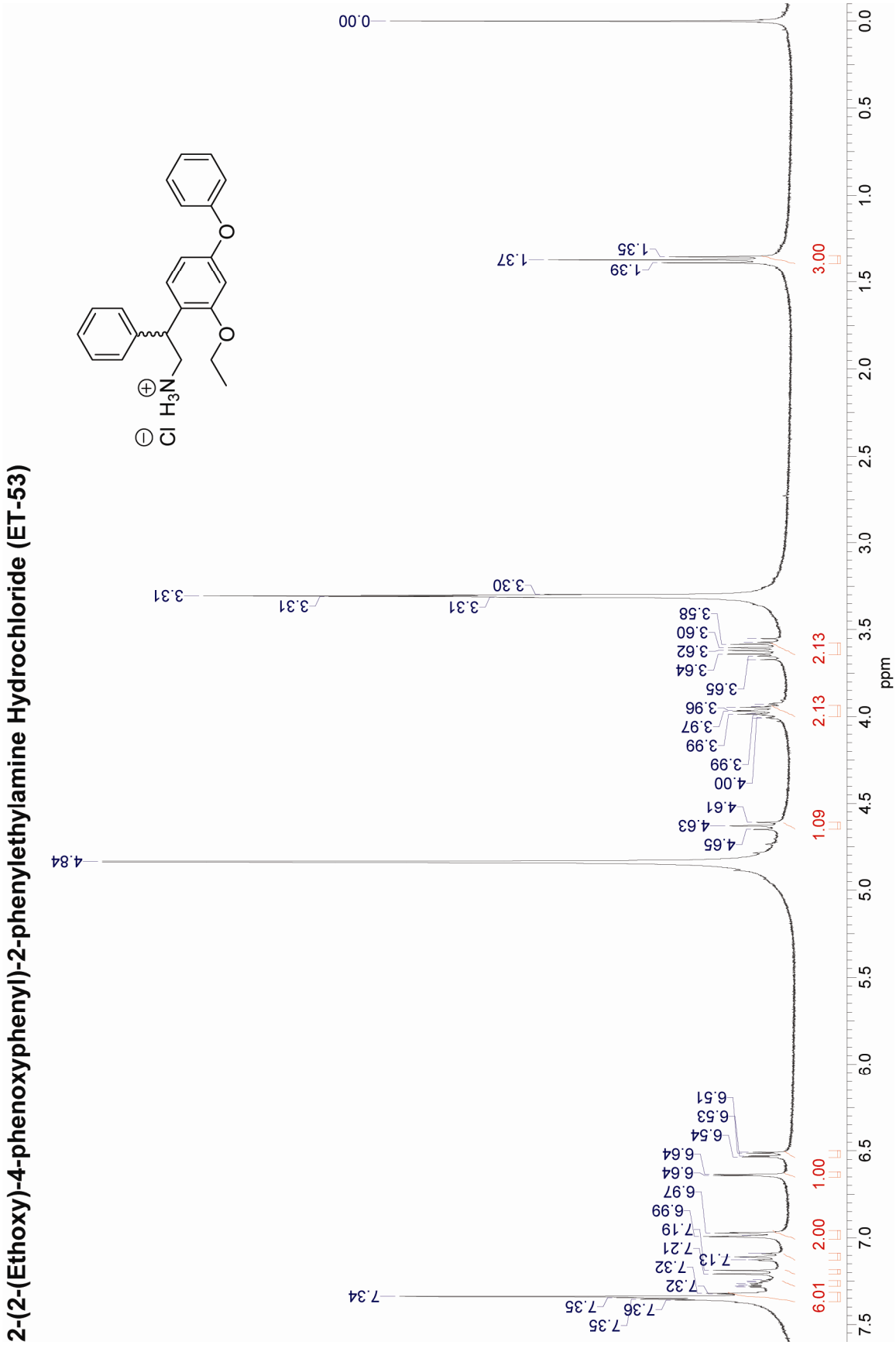
2,2-Di-(4-hydroxy)phenylethylamine Hydrochloride (ET-50)

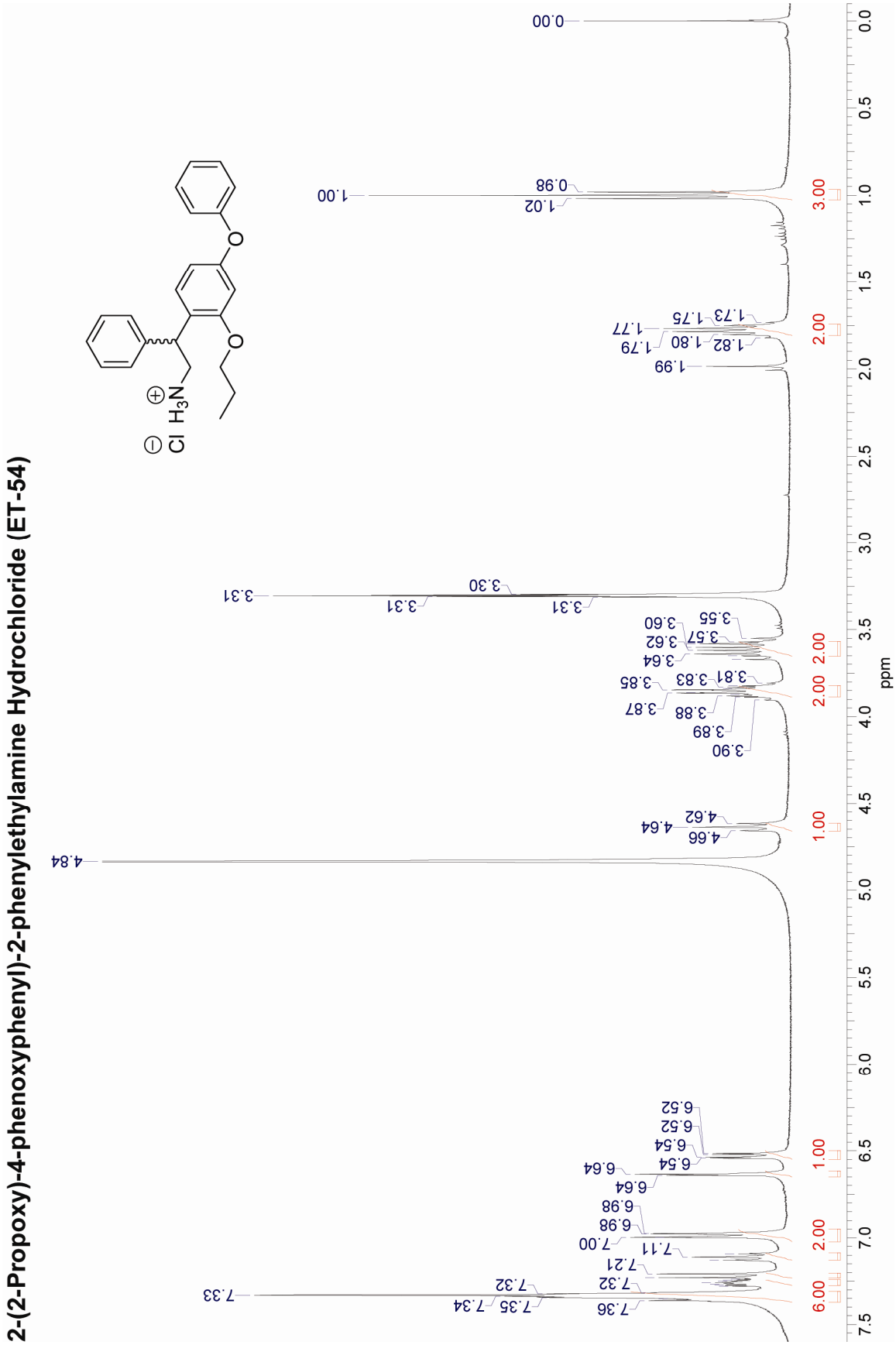



2-(2-(Hydroxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-51)
HO
O
⊕ H3N
⊖ Cl
0.00
3.30
3.31
3.31
3.56
3.58
3.62
3.64
3.65
3.67
4.61
4.63
4.65
4.85
6.43
6.45
6.45
6.47
6.48
6.96
6.98
6.99
7.04
7.33
7.36
7.36
7.37
4.00
2.01
1.01
1.04
1.27
ppm

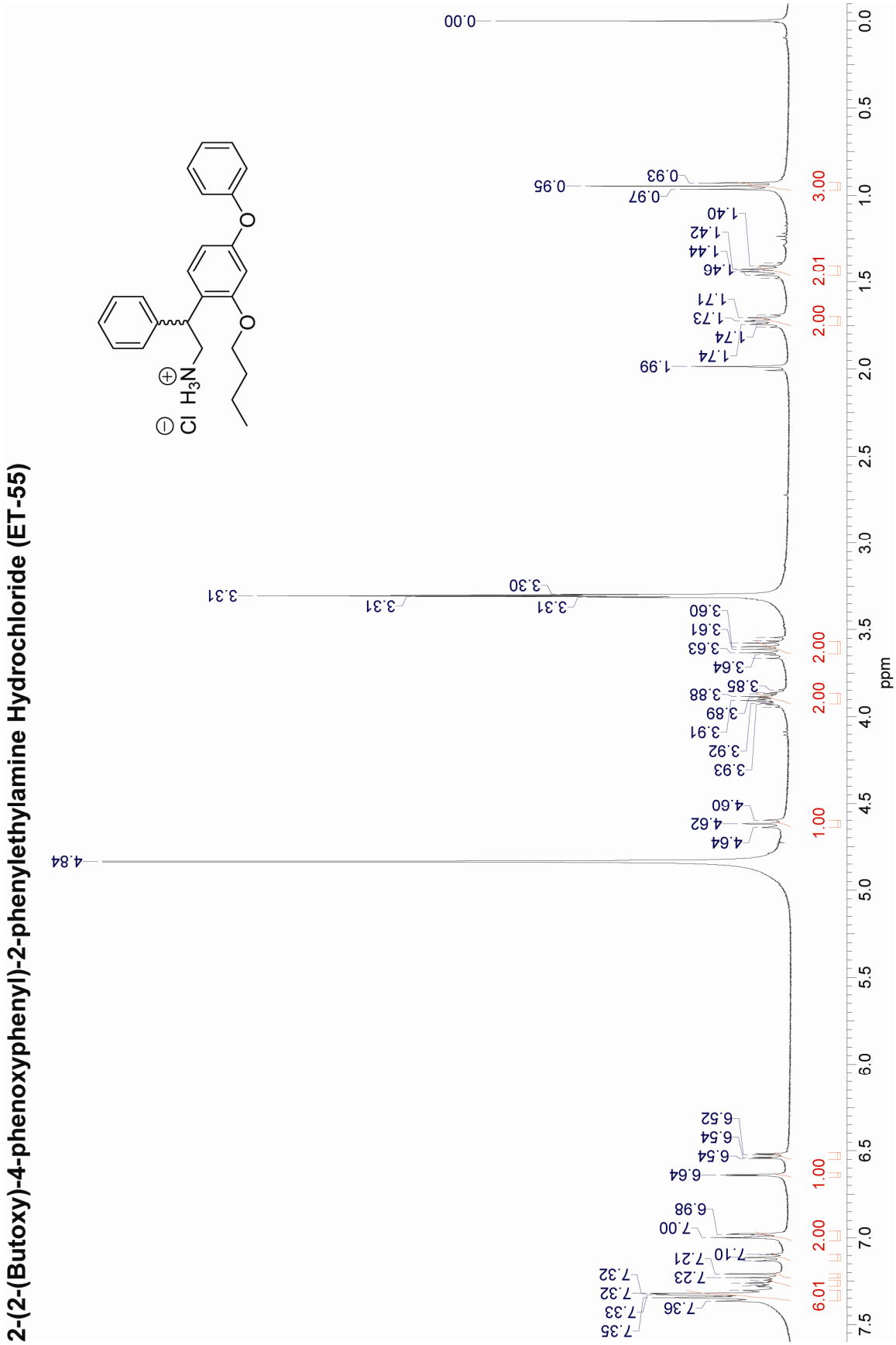

2-(2-(Methoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-52)
MeO
O
H3N
Cl
4.84
7.96
7.36
7.38
7.35
7.34
7.33
7.32
7.17
7.15
7.00
6.98
6.69
6.53
6.53
6.51
6.51
1.01
1.97
4.67
4.65
4.63
0.79
3.79
3.60
3.59
3.58
3.57
3.78
3.02
2.01
3.31
3.30
3.31
3.31
ppm

2-(2-(Ethoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-53)

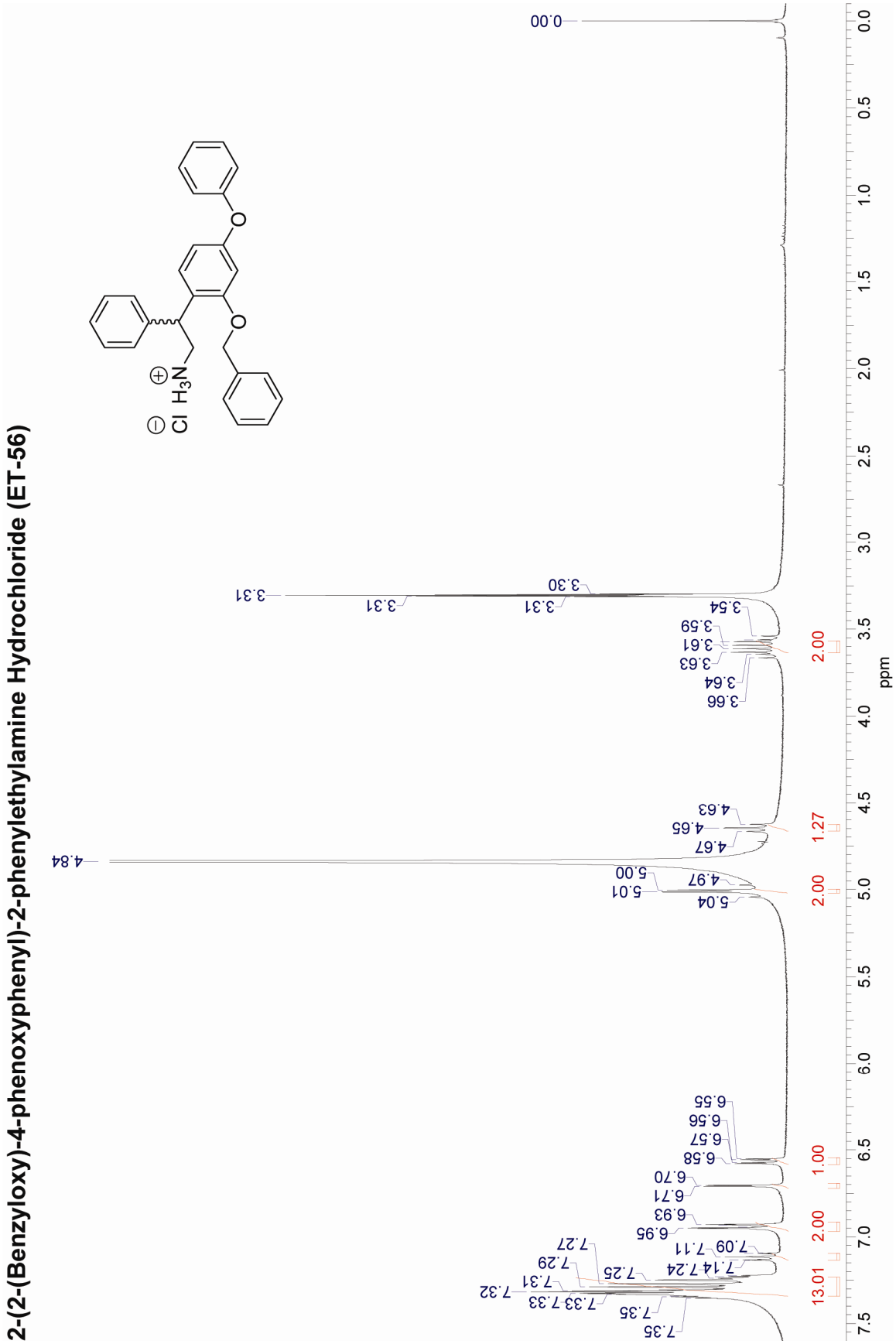


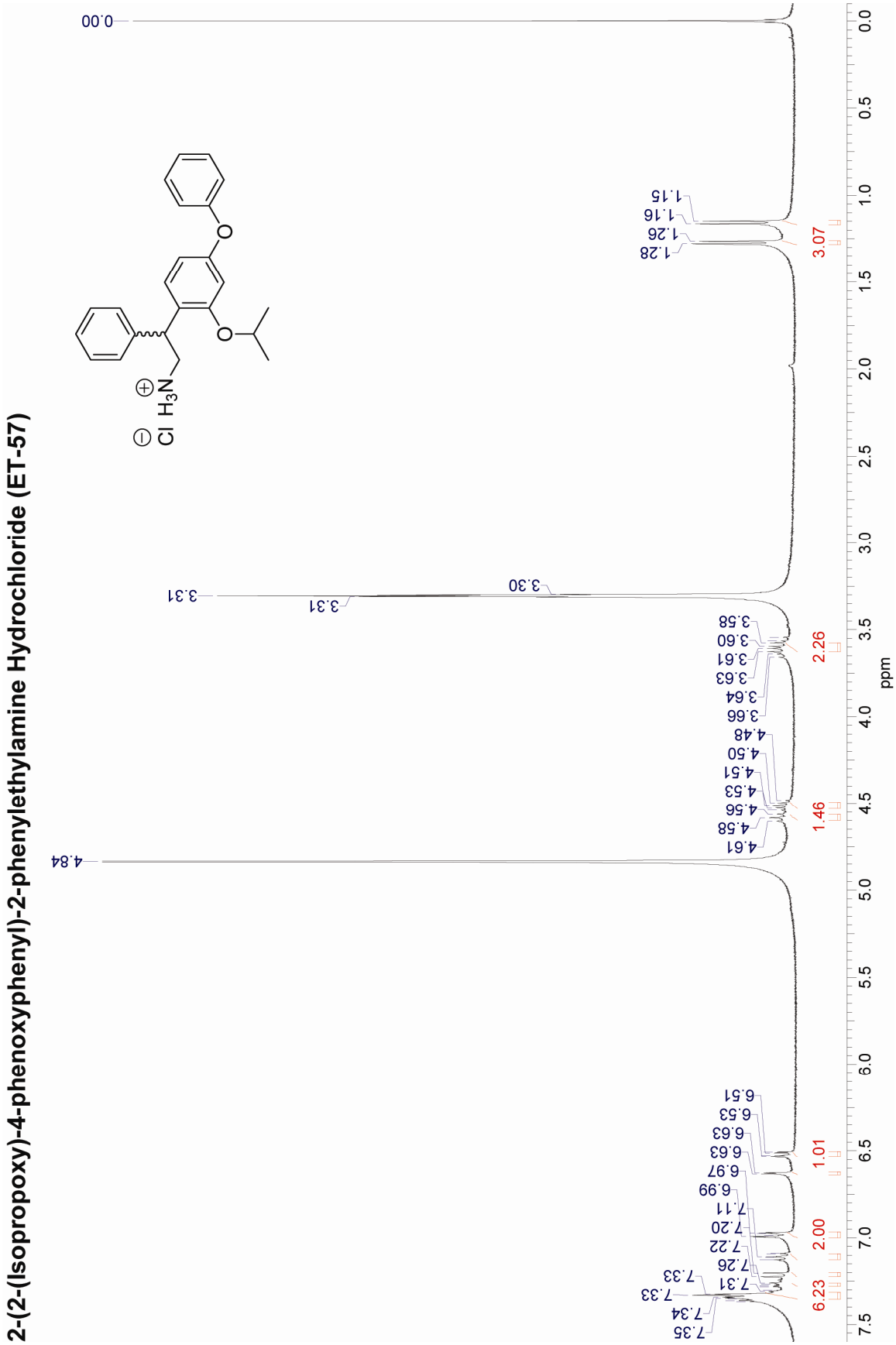

2-(2-Propoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-54)
ppm

2-(2-(Butoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-55)

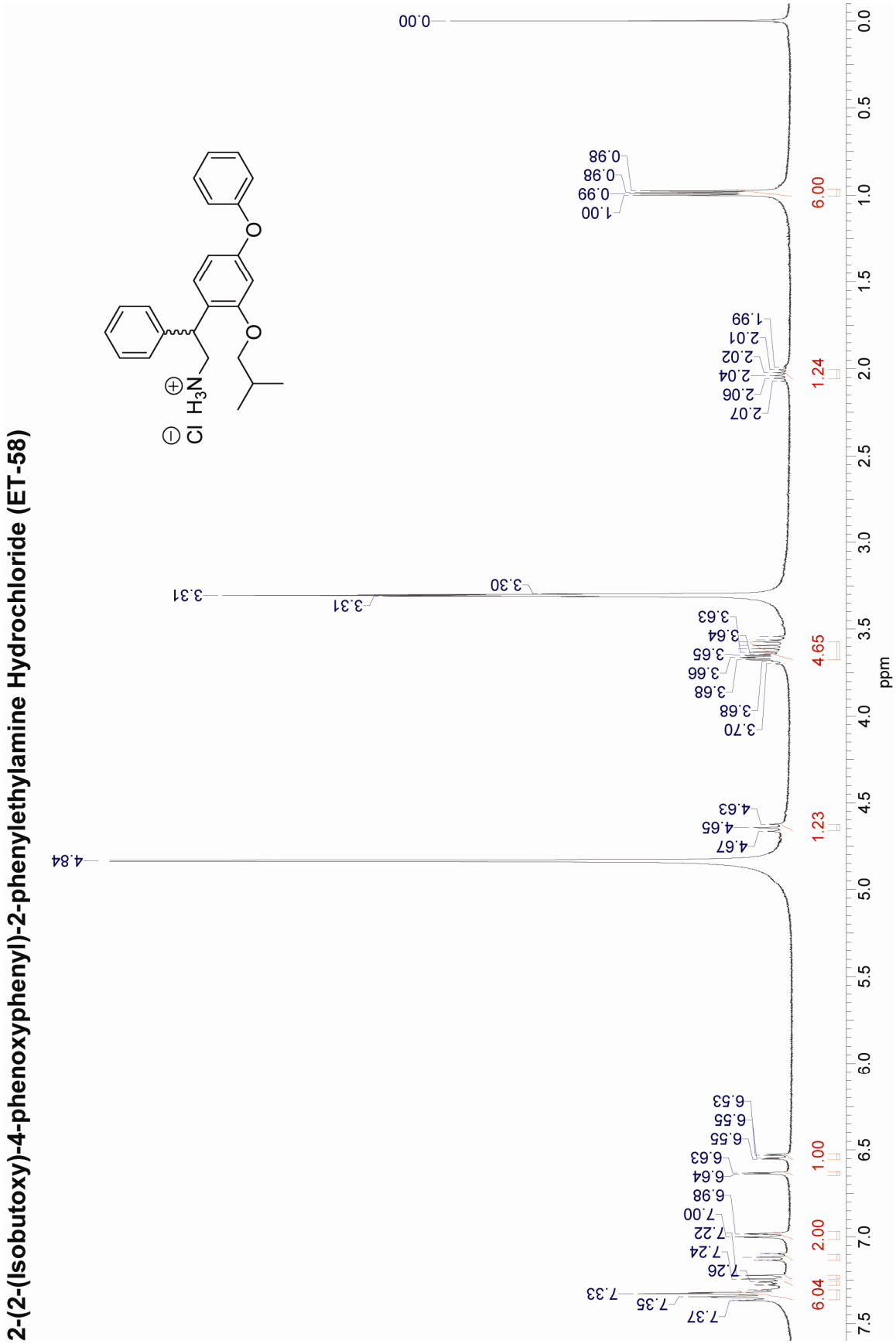


2-(2-(Benzyloxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-56)

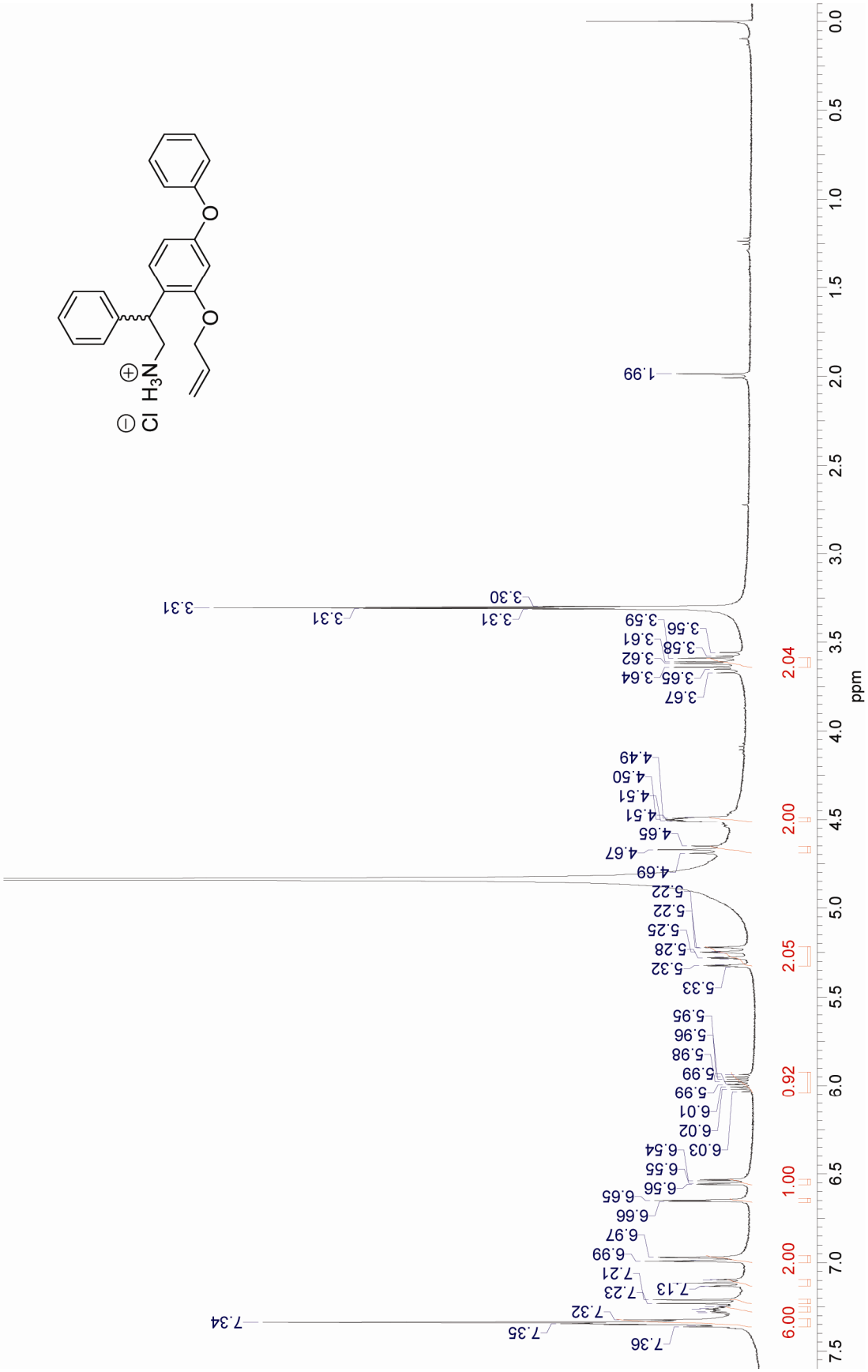



2-(2-(Isopropoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-57)
Cl H3N
0.00
1.15
1.16
1.26
1.28
3.07
3.30
3.31
3.31
2.26
3.58
3.60
3.61
3.63
3.64
3.66
4.48
4.50
4.51
4.53
4.56
4.58
4.61
1.46
4.84
1.01
6.51
6.53
6.63
6.63
6.97
6.99
7.11
2.00
7.20
7.22
7.26
7.31
7.33
6.23
7.33
7.34
7.35
ppm

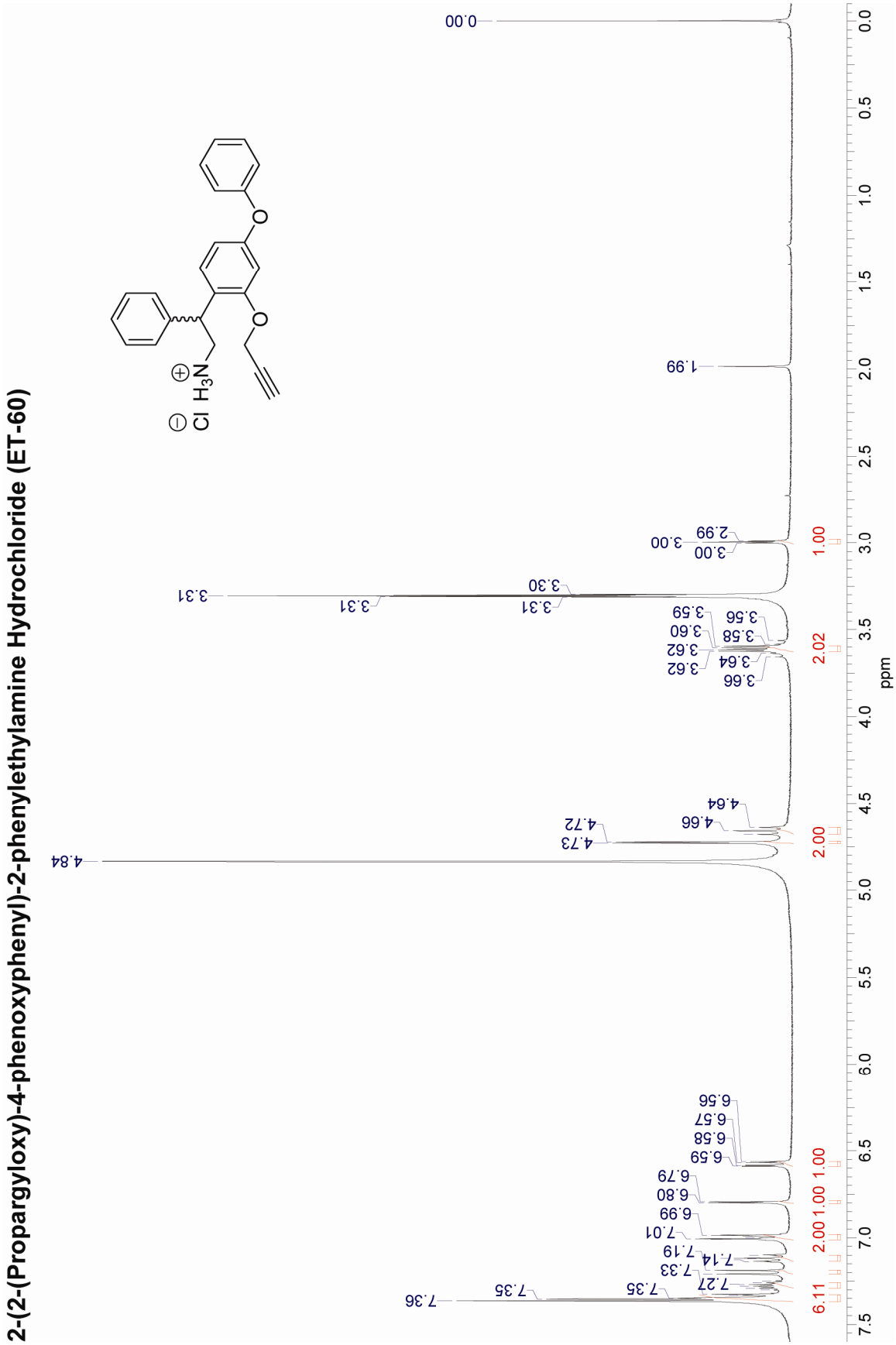
2-(2-(Isobutoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-58)



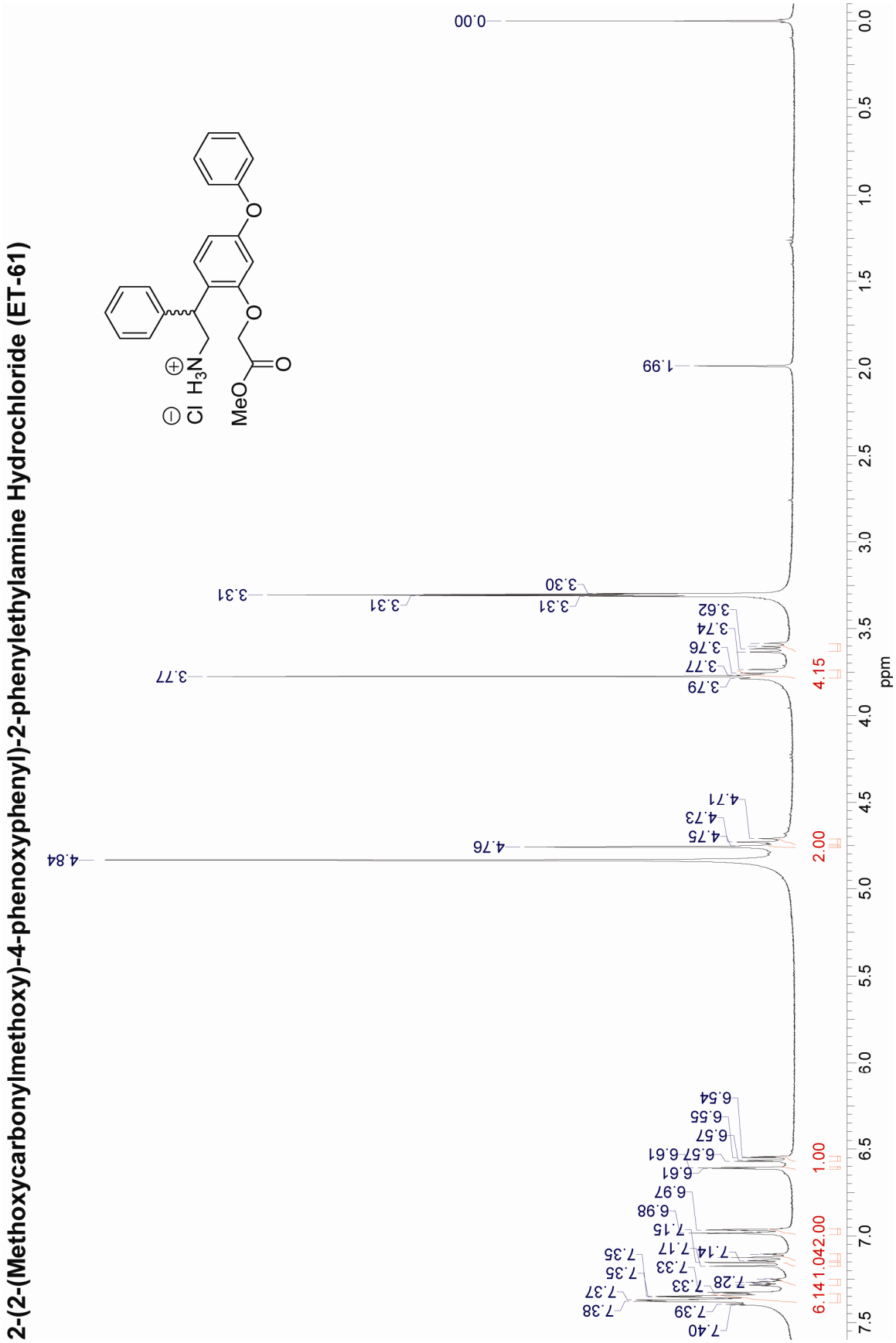
2-(2-(Allyloxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-59)



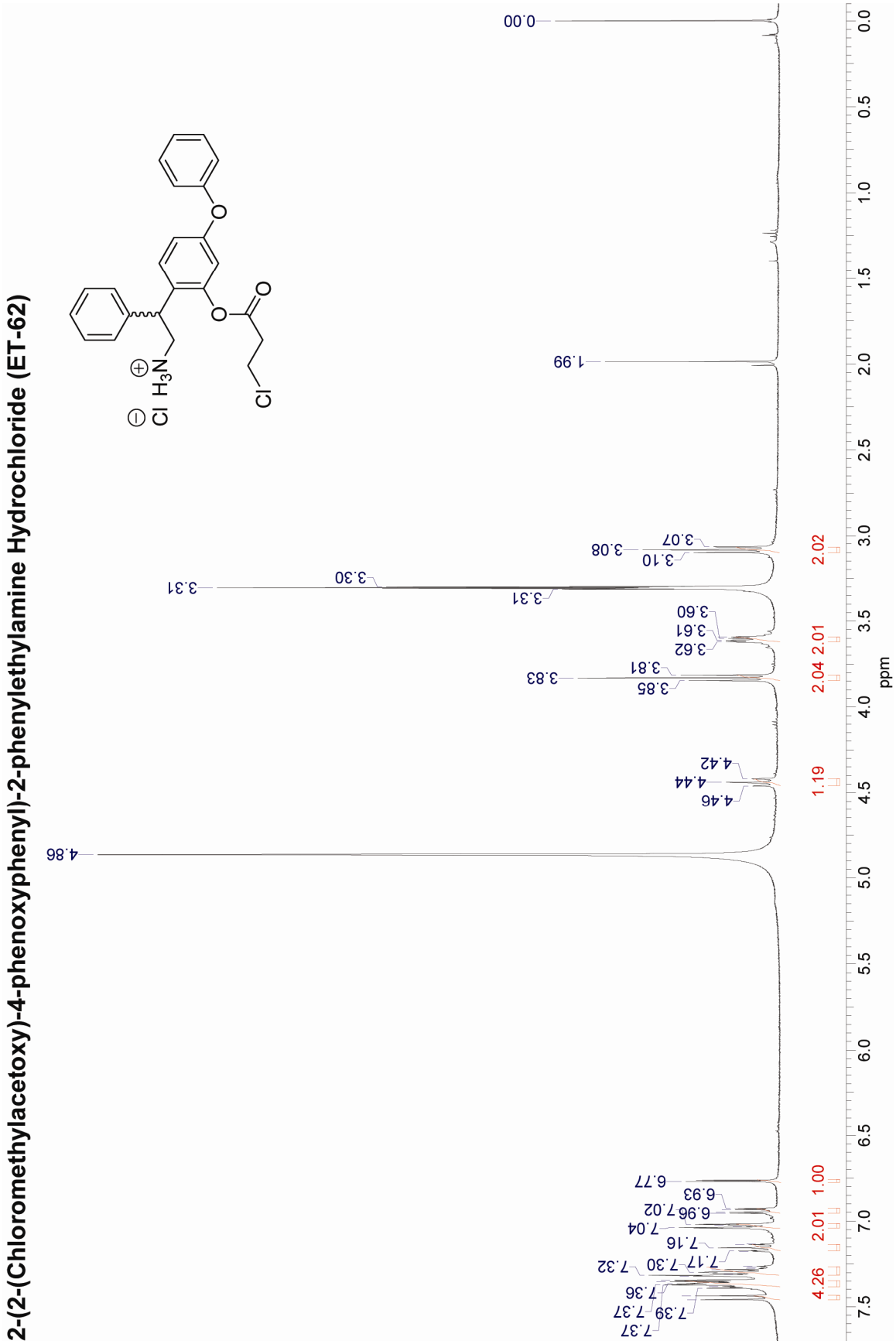
2-(2-(Propargyloxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-60)

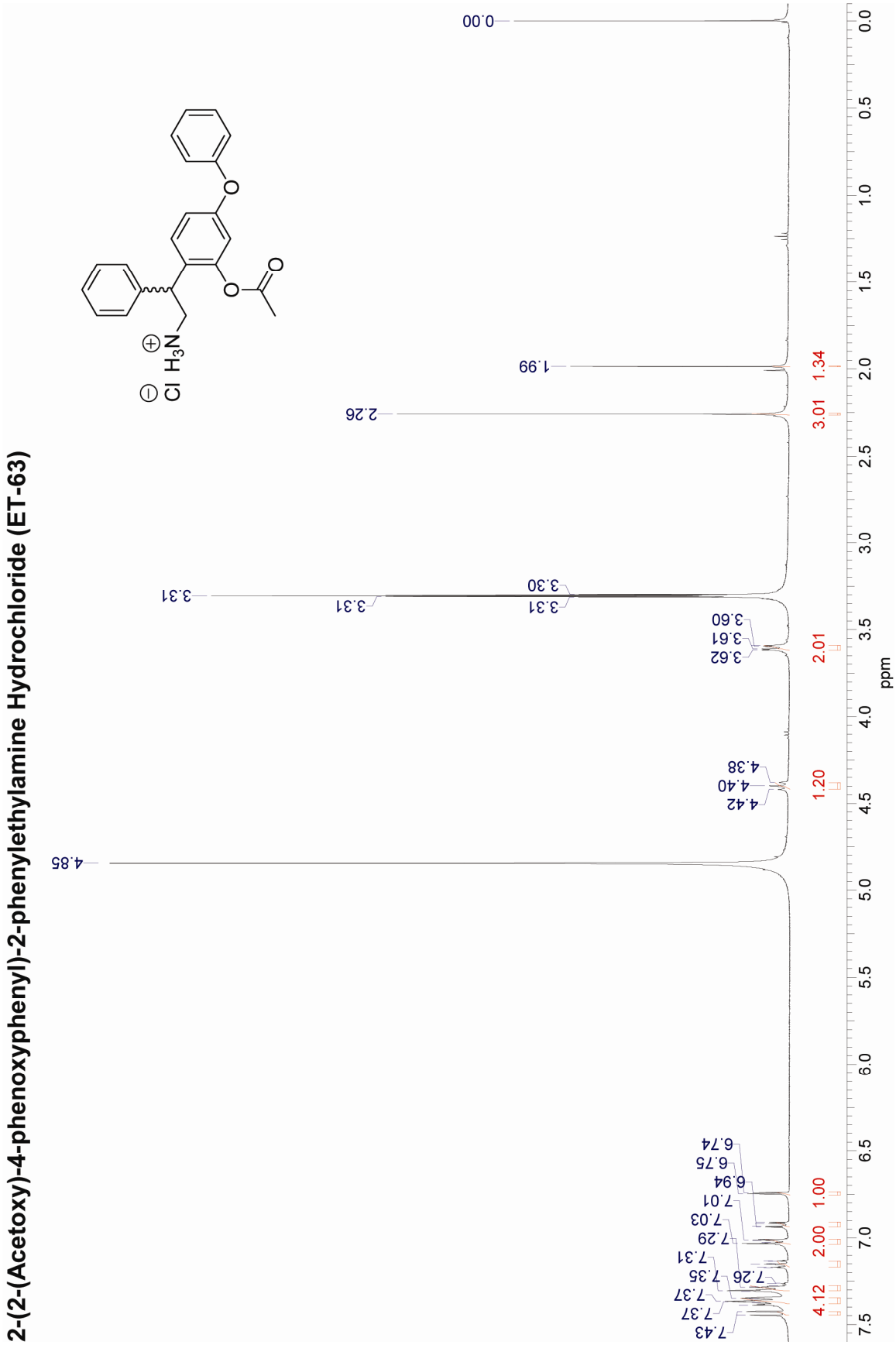


2-(2-(Methoxycarbonylmethoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-61)

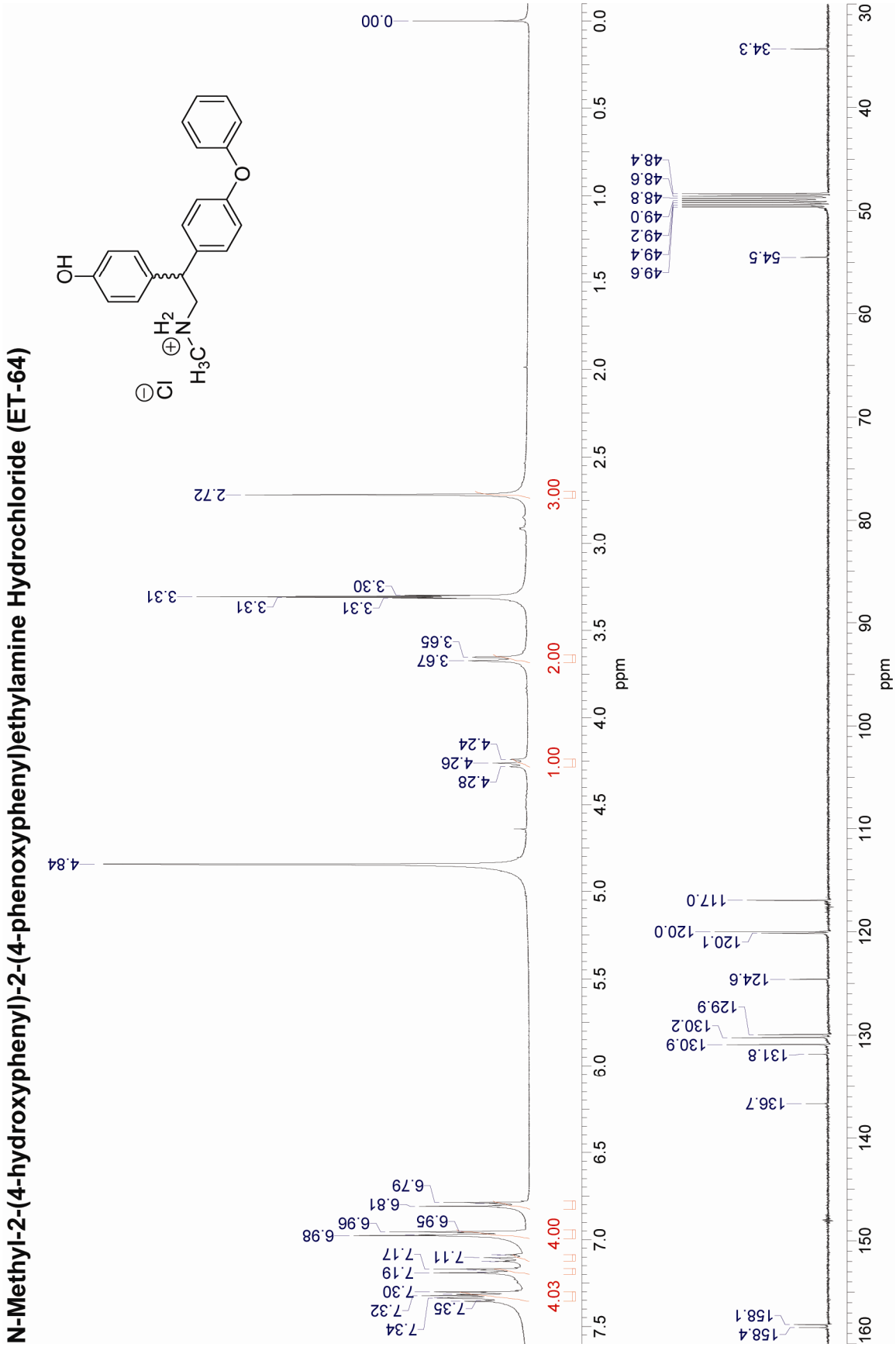


2-(2-(Chloromethylacetoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-62)

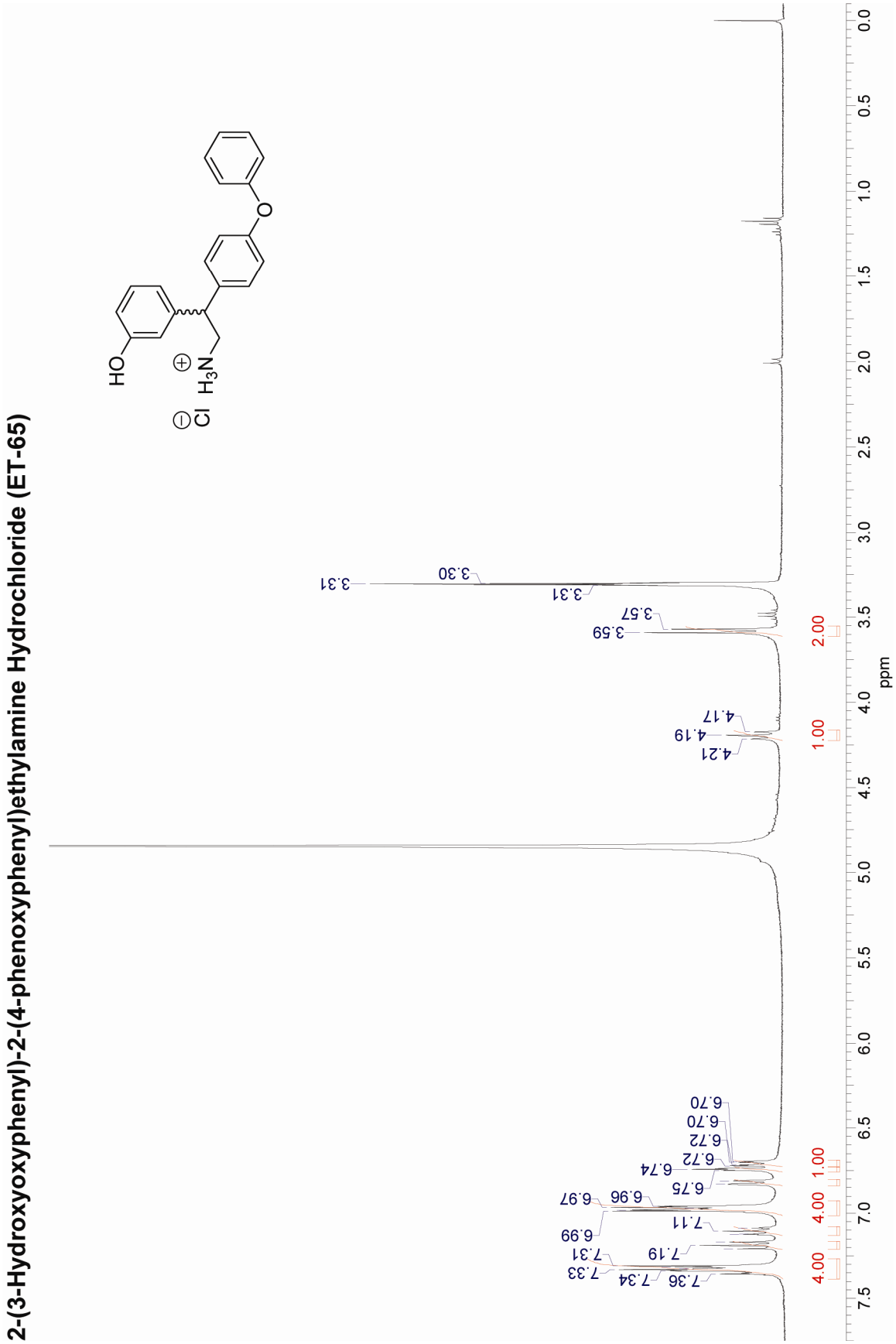



2-(2-(Acetoxy)-4-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-63)
ppm

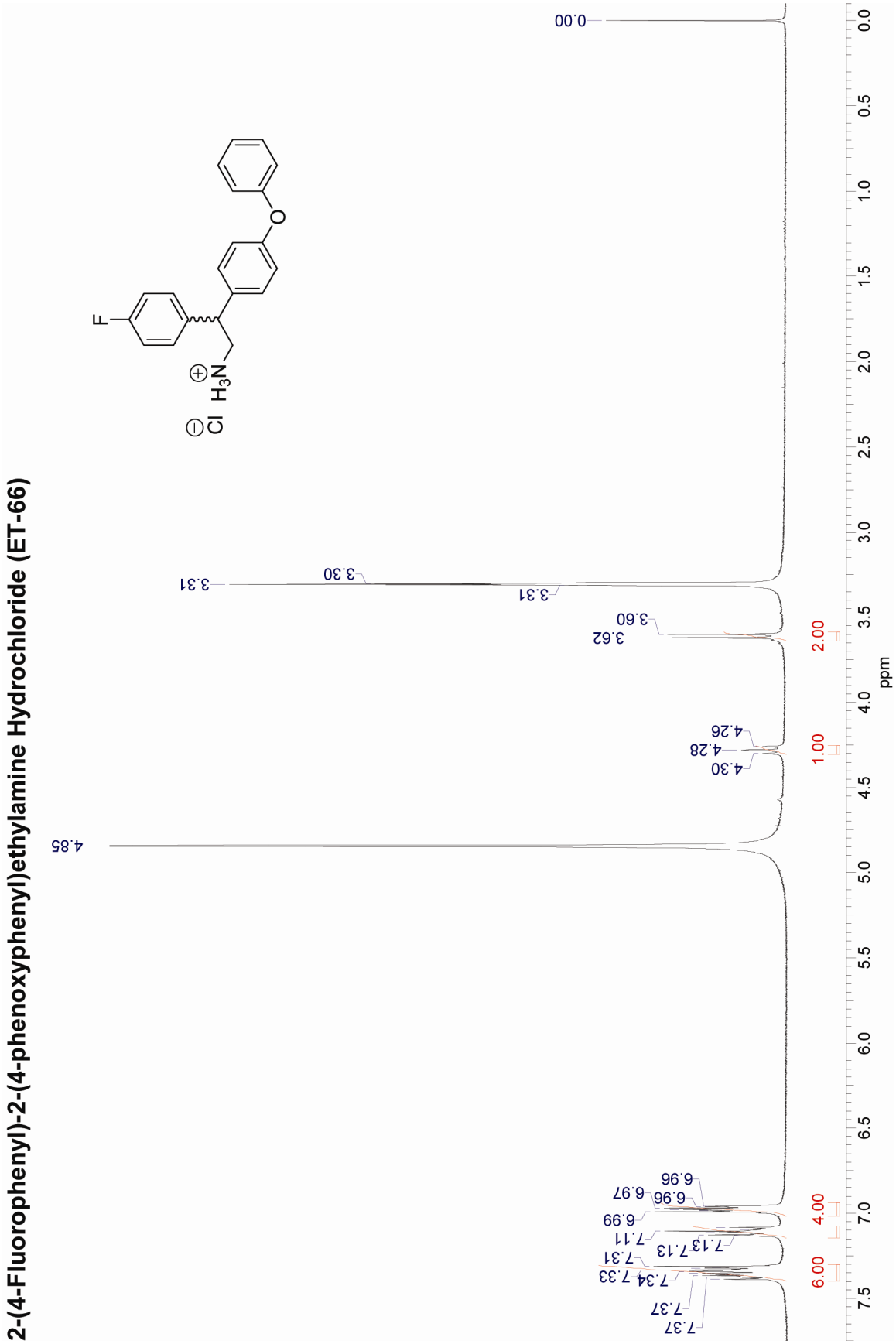
N-Methyl-2-(4-hydroxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-64)



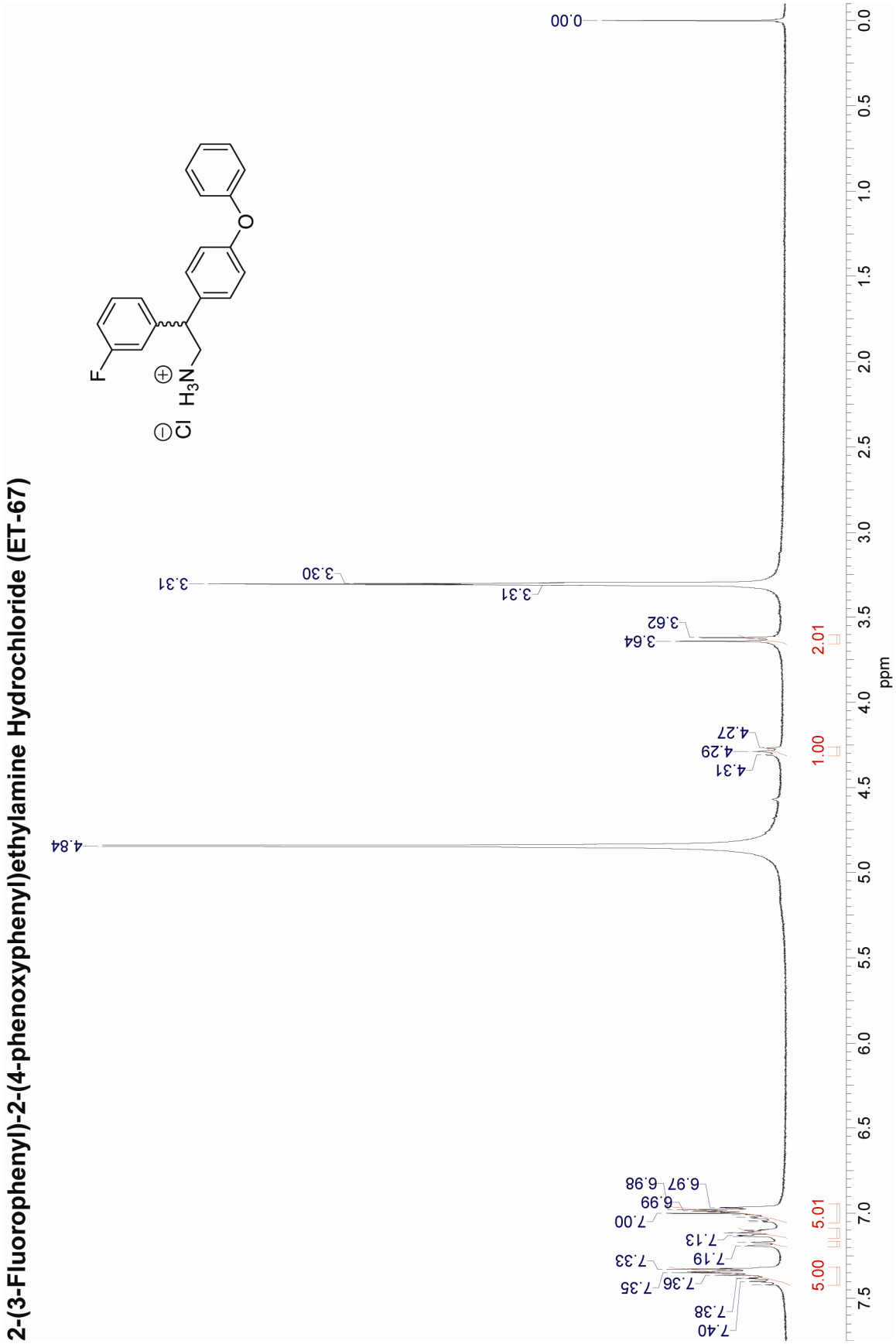
2-(3-Hydroxyoxyphenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-65)



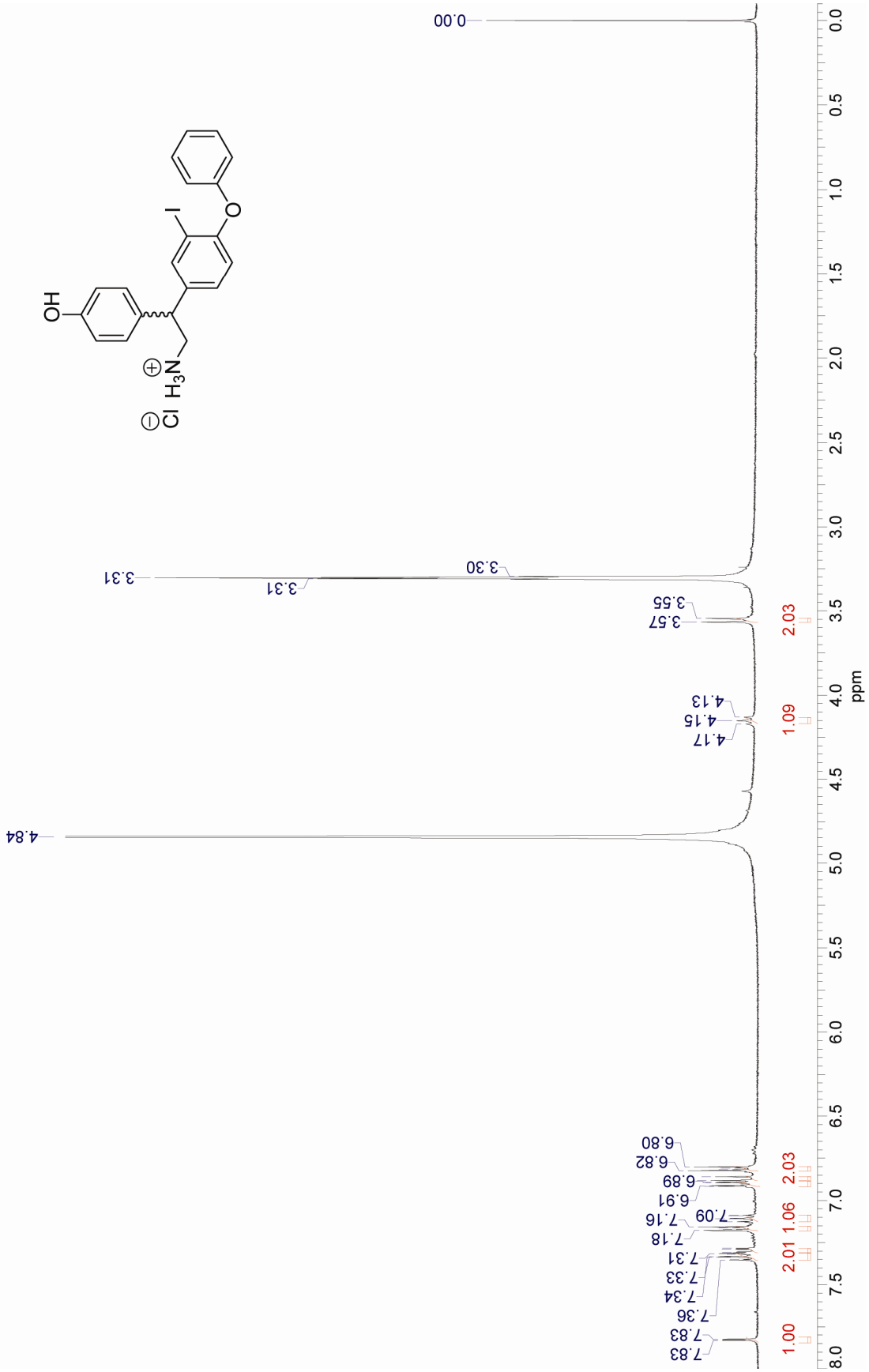
2-(4-Fluorophenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-66)



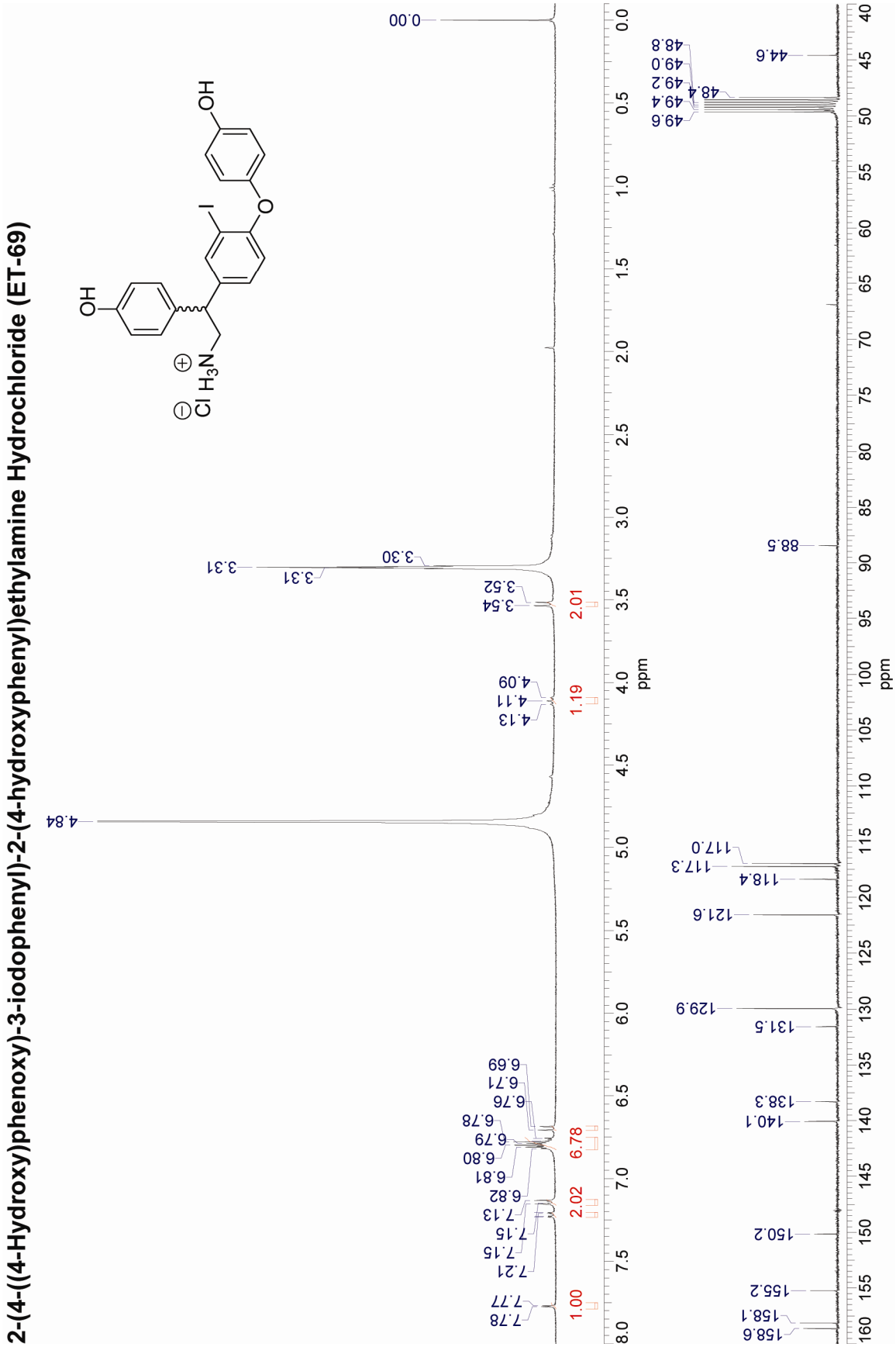
2-(3-Fluorophenyl)-2-(4-phenoxyphenyl)ethylamine Hydrochloride (ET-67)



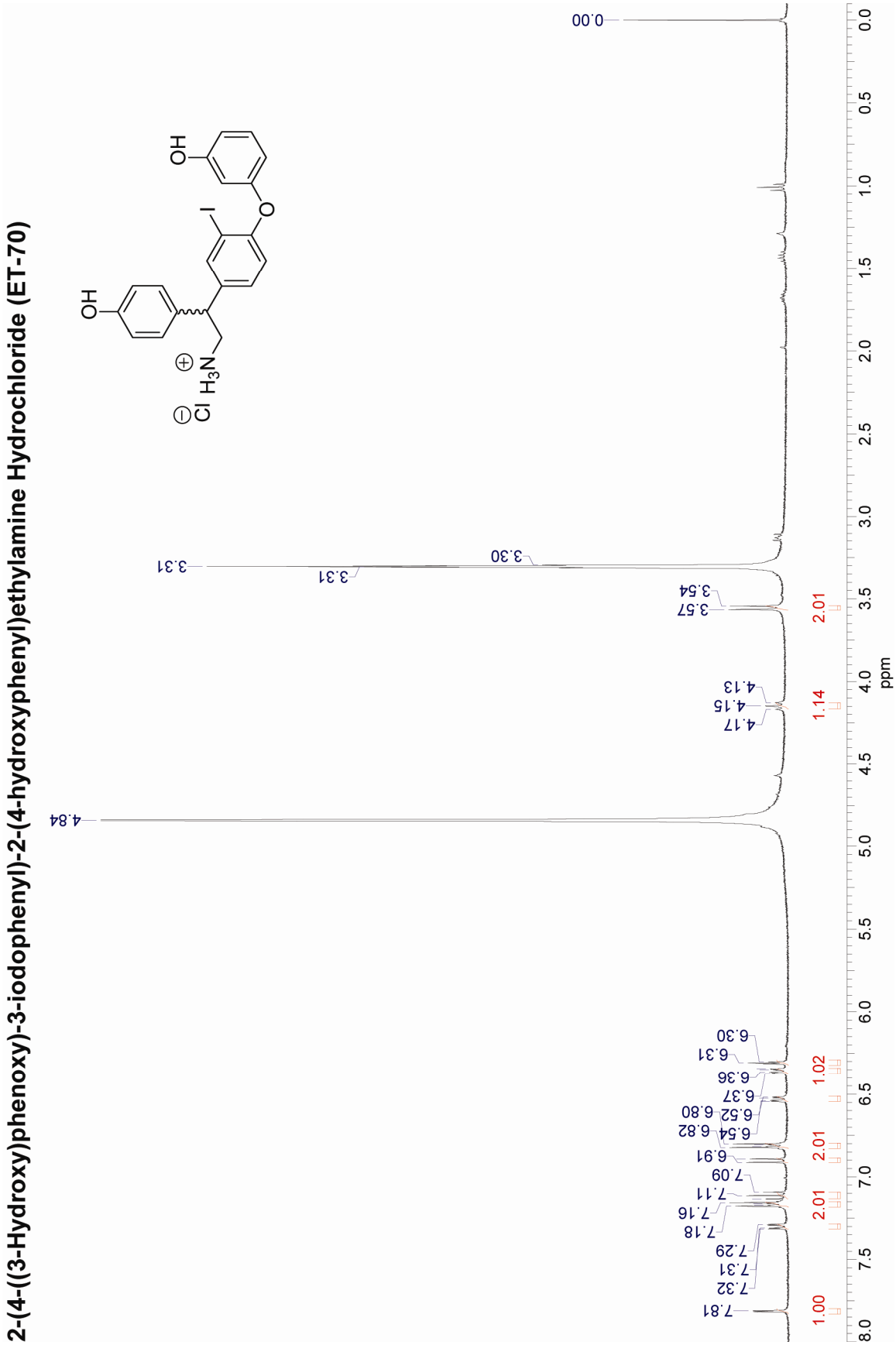
2-(4-Phenoxy-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine Hydrochloride (ET-68)



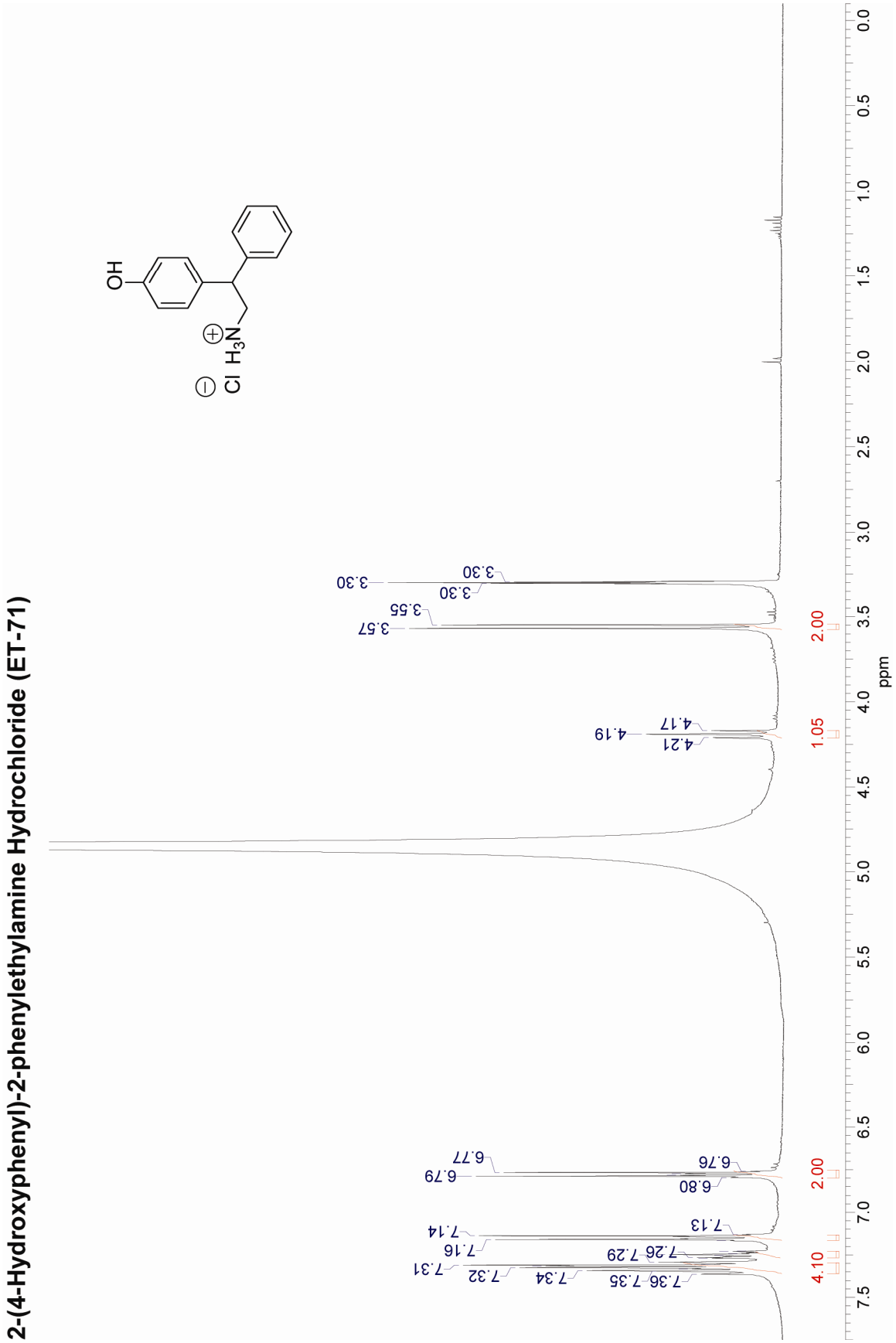
2-(4-((4-Hydroxy)phenoxy)-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine Hydrochloride (ET-69)



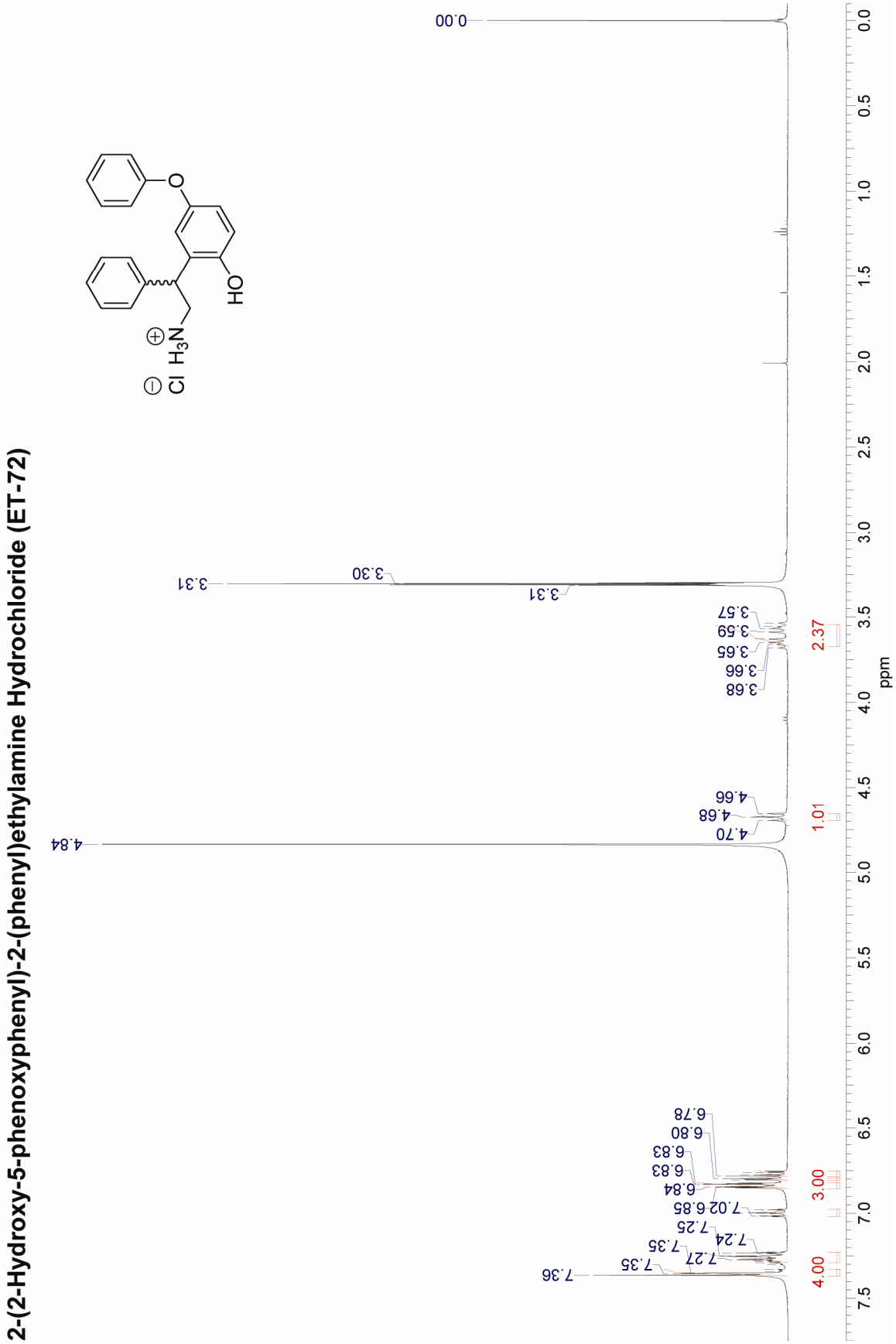
2-(4-((3-Hydroxy)phenoxy)-3-iodophenyl)-2-(4-hydroxyphenyl)ethylamine Hydrochloride (ET-70)



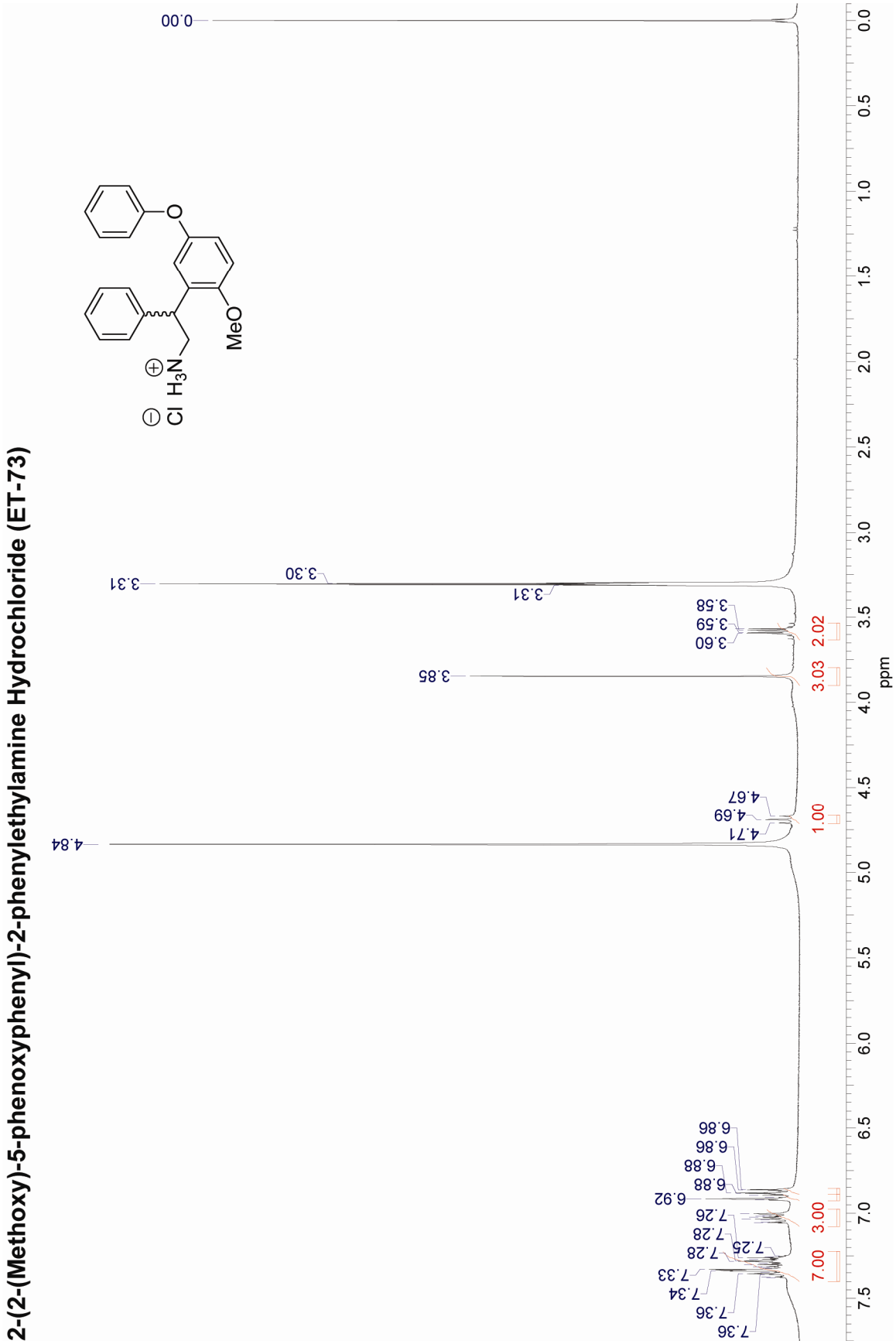
2-(4-Hydroxyphenyl)-2-phenylethylamine Hydrochloride (ET-71)



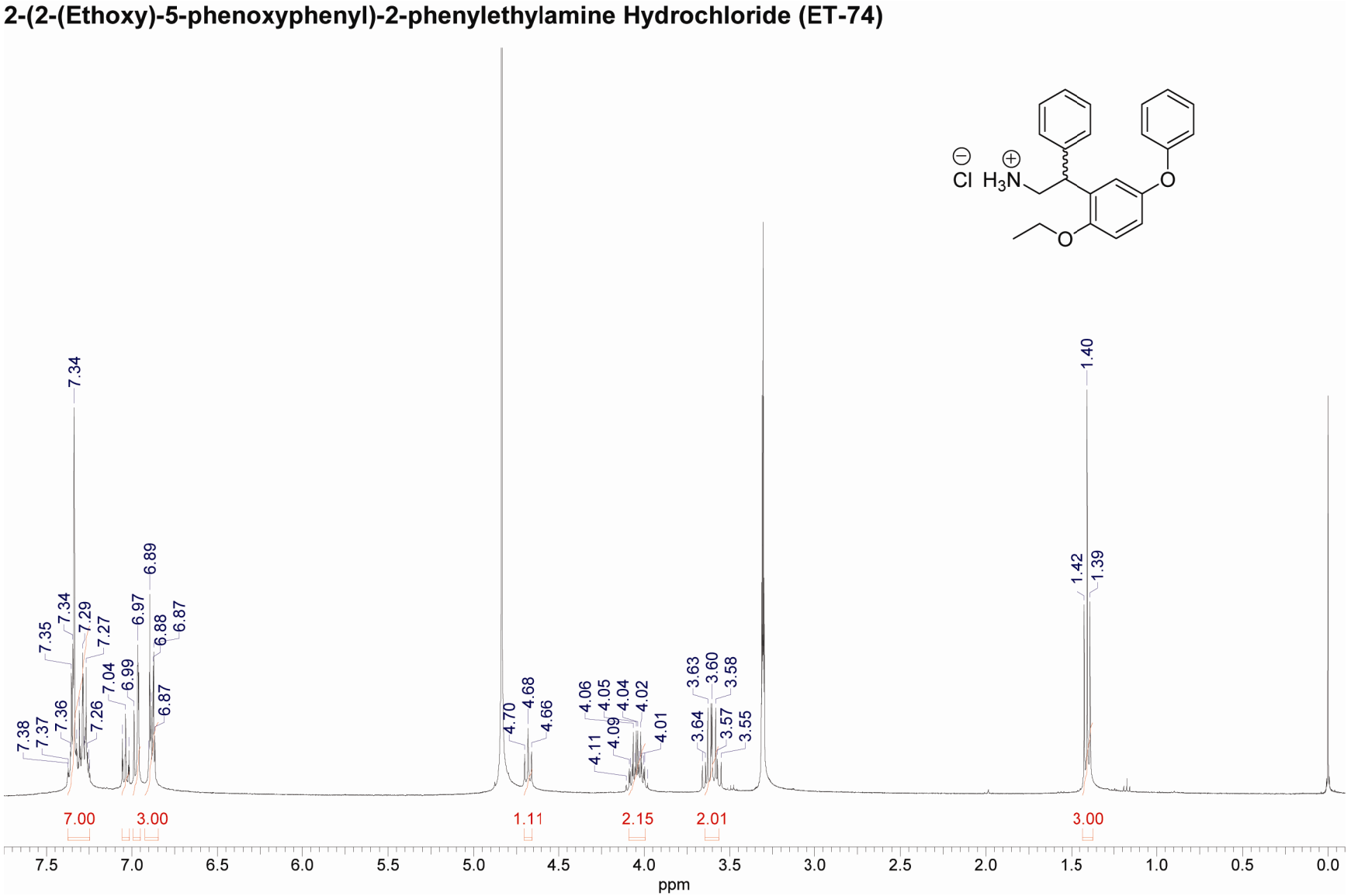
2-(2-Hydroxy-5-phenoxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-72)

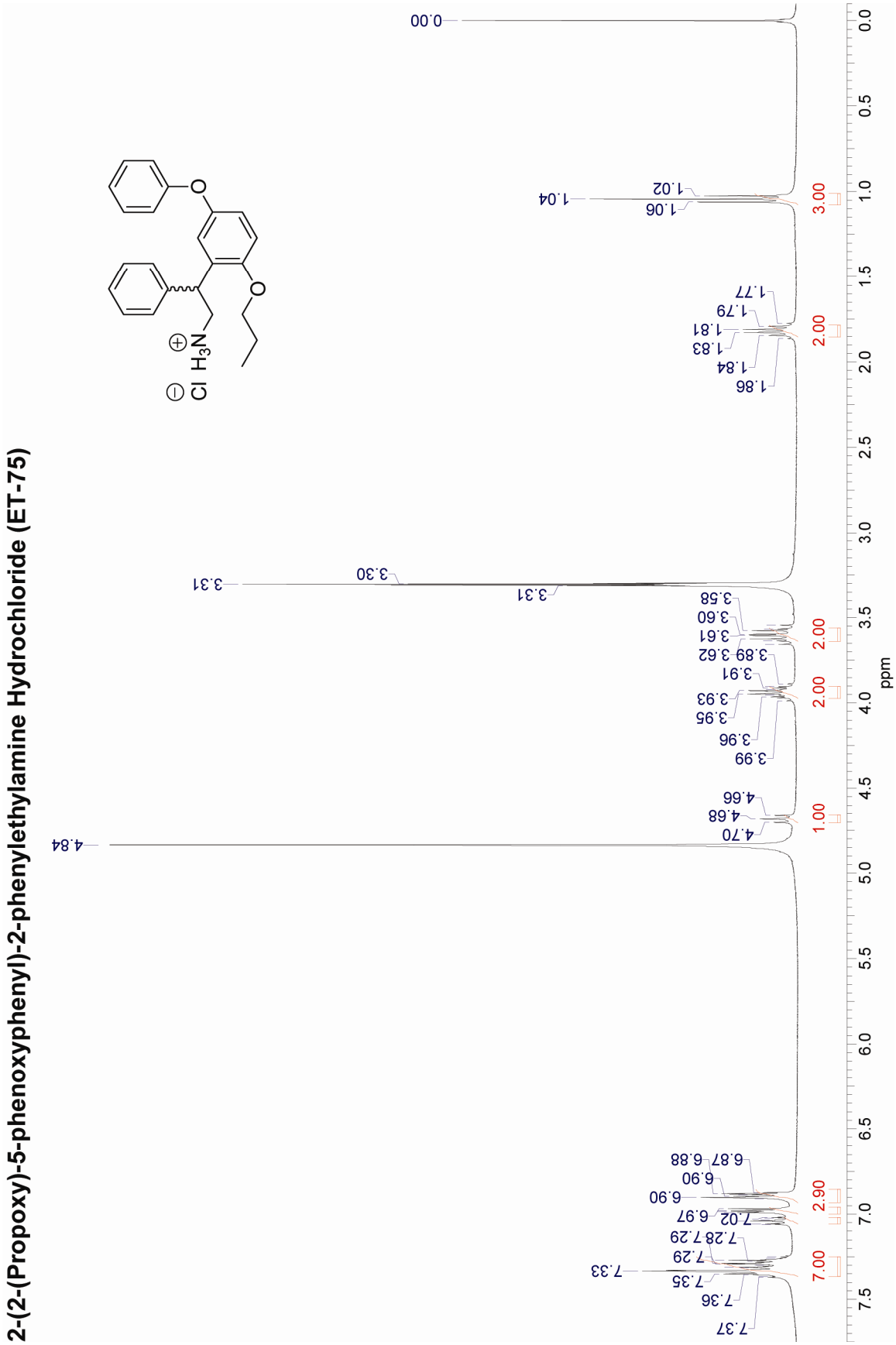


2-(2-(Methoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-73)

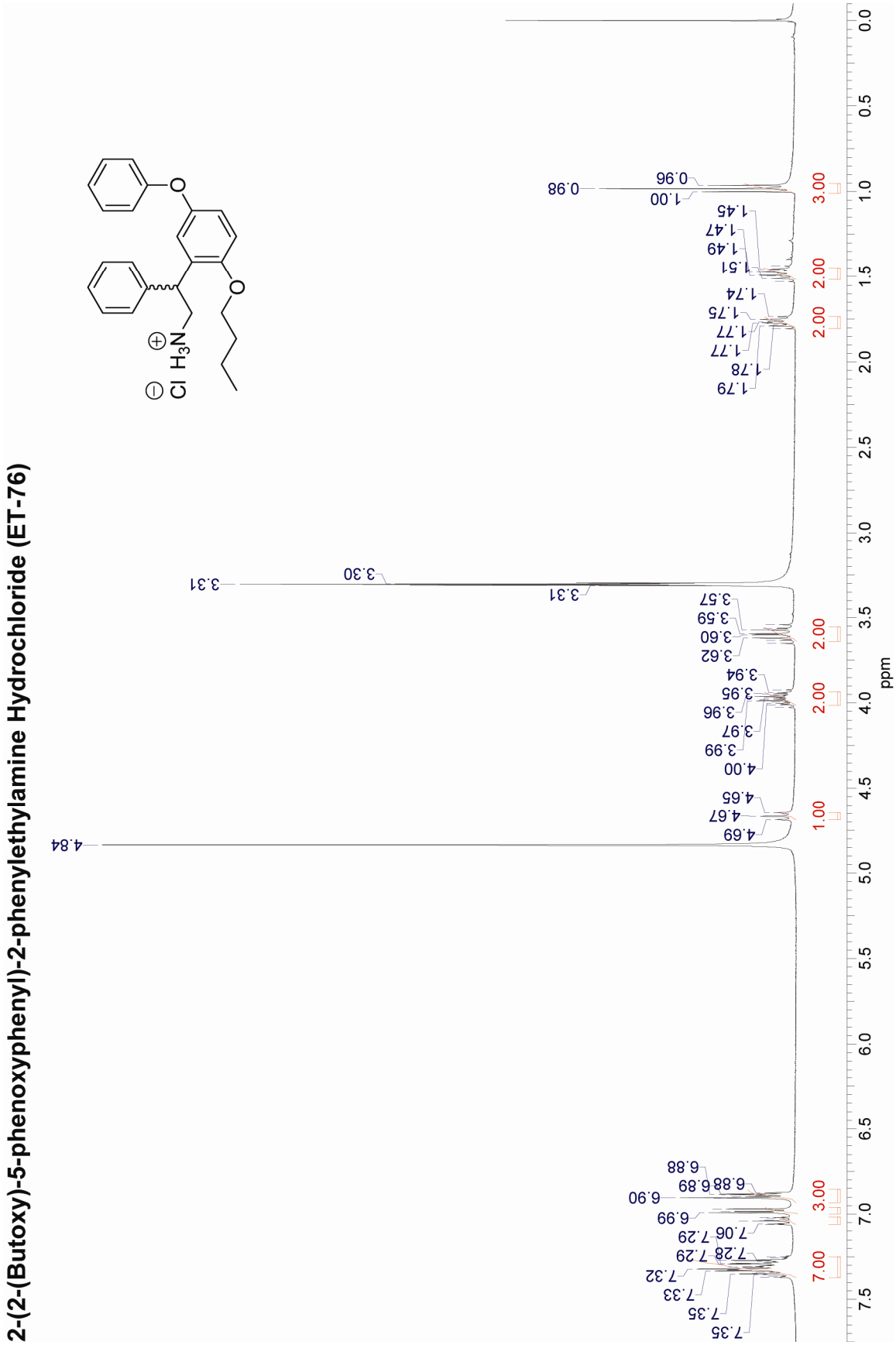


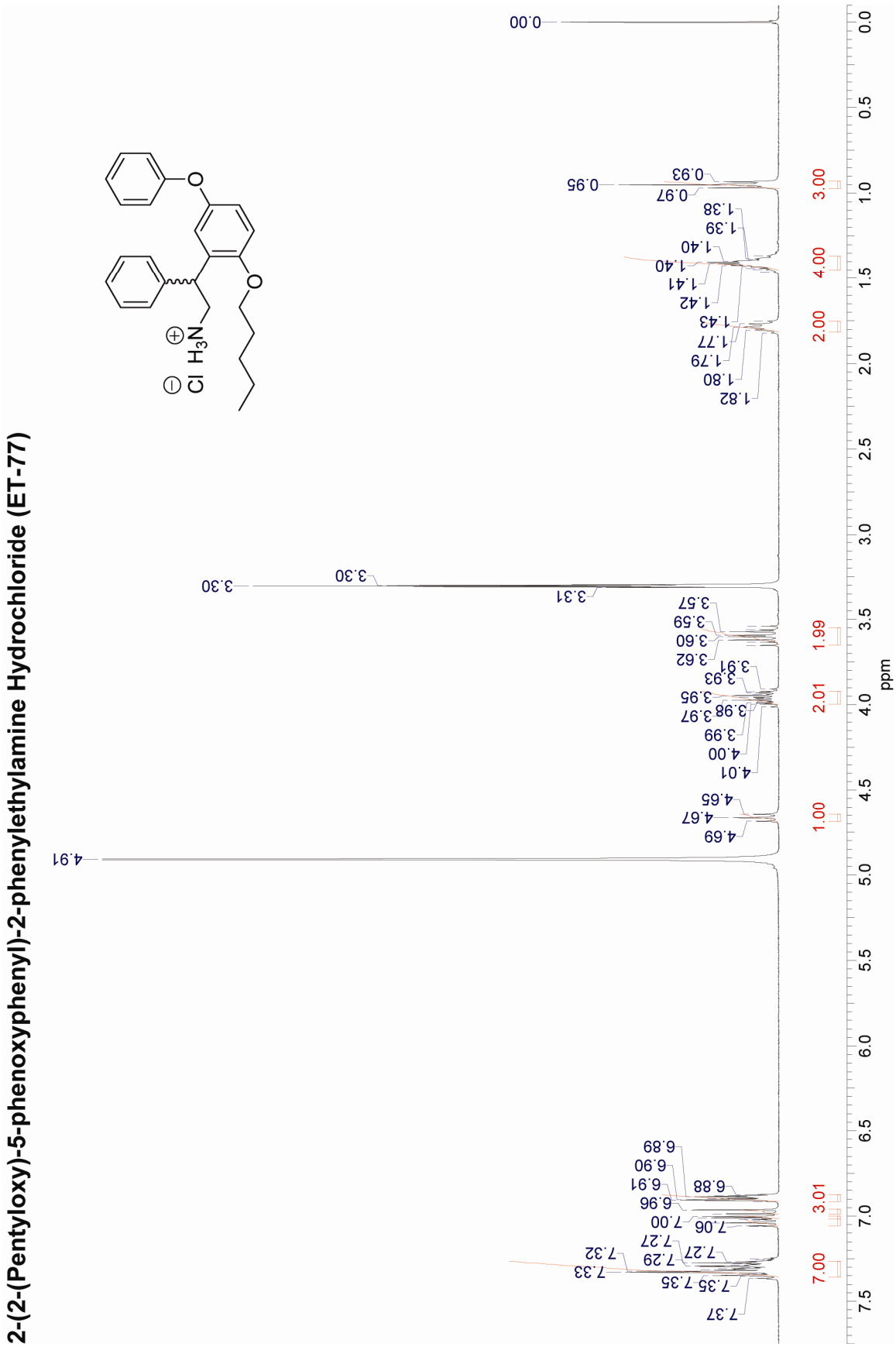
2-(2-(Ethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-74)



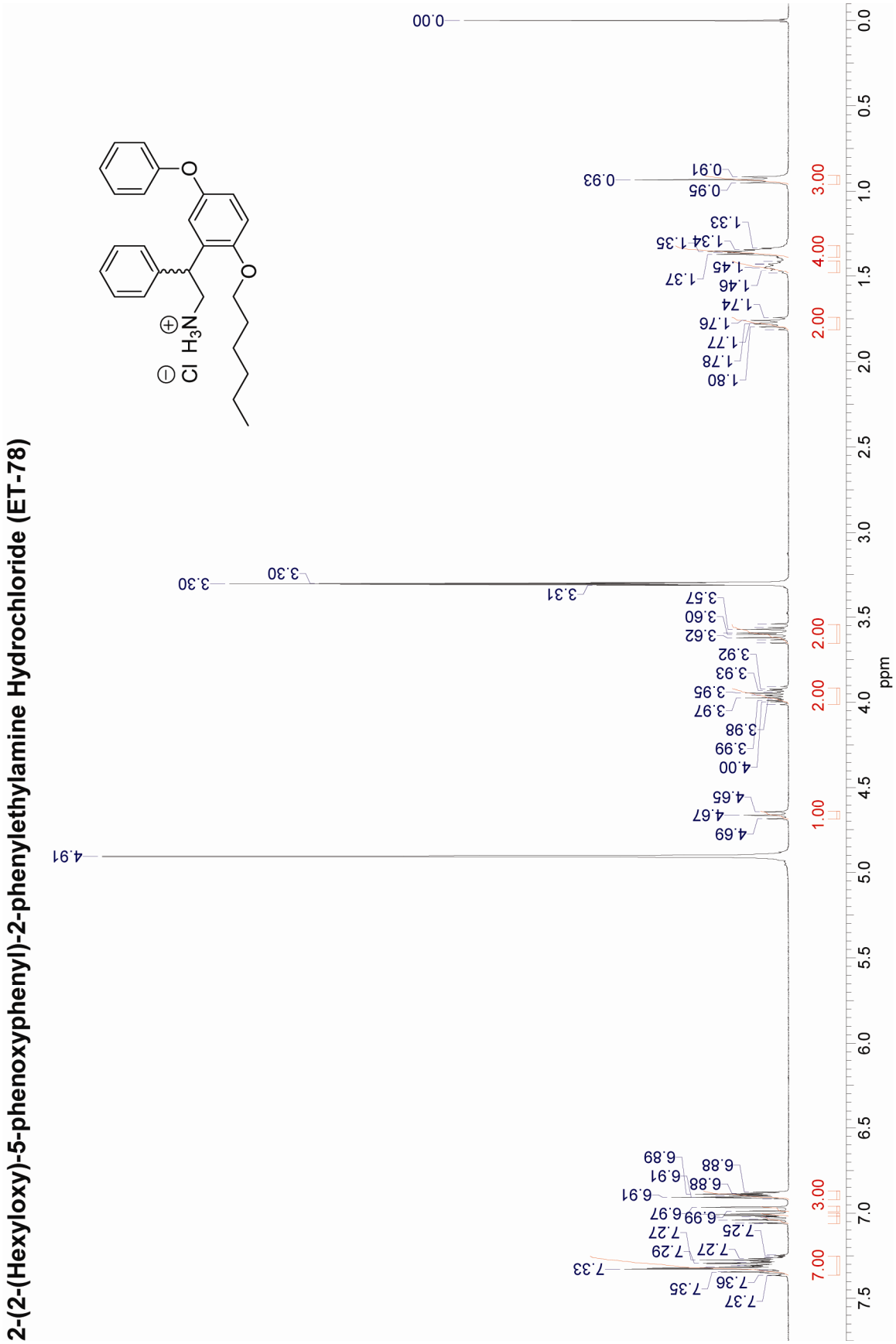

2-(2-(Propoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-75)
ppm

2-(2-(Butoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-76)

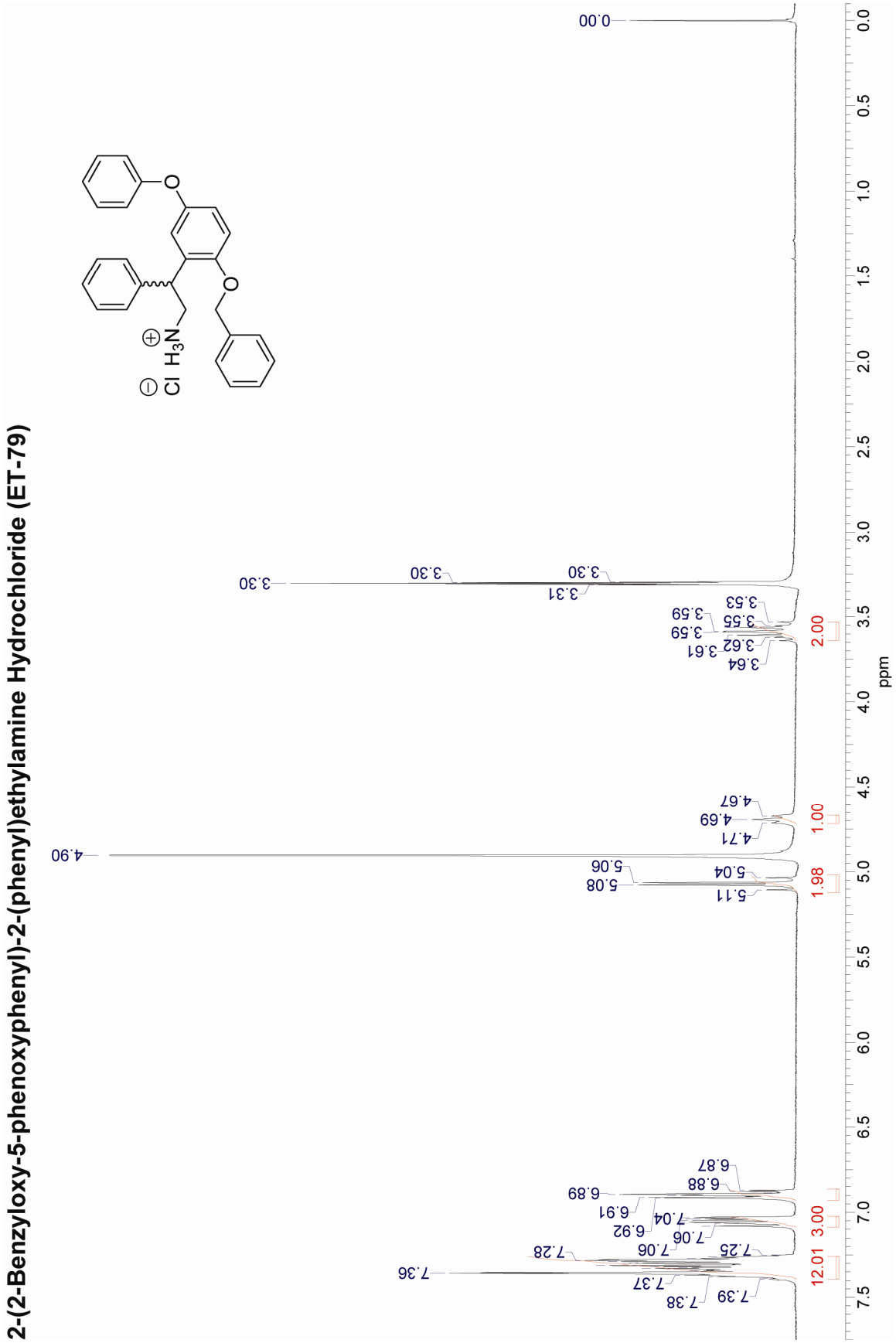



2-(2-(Pentyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-77)
ppm

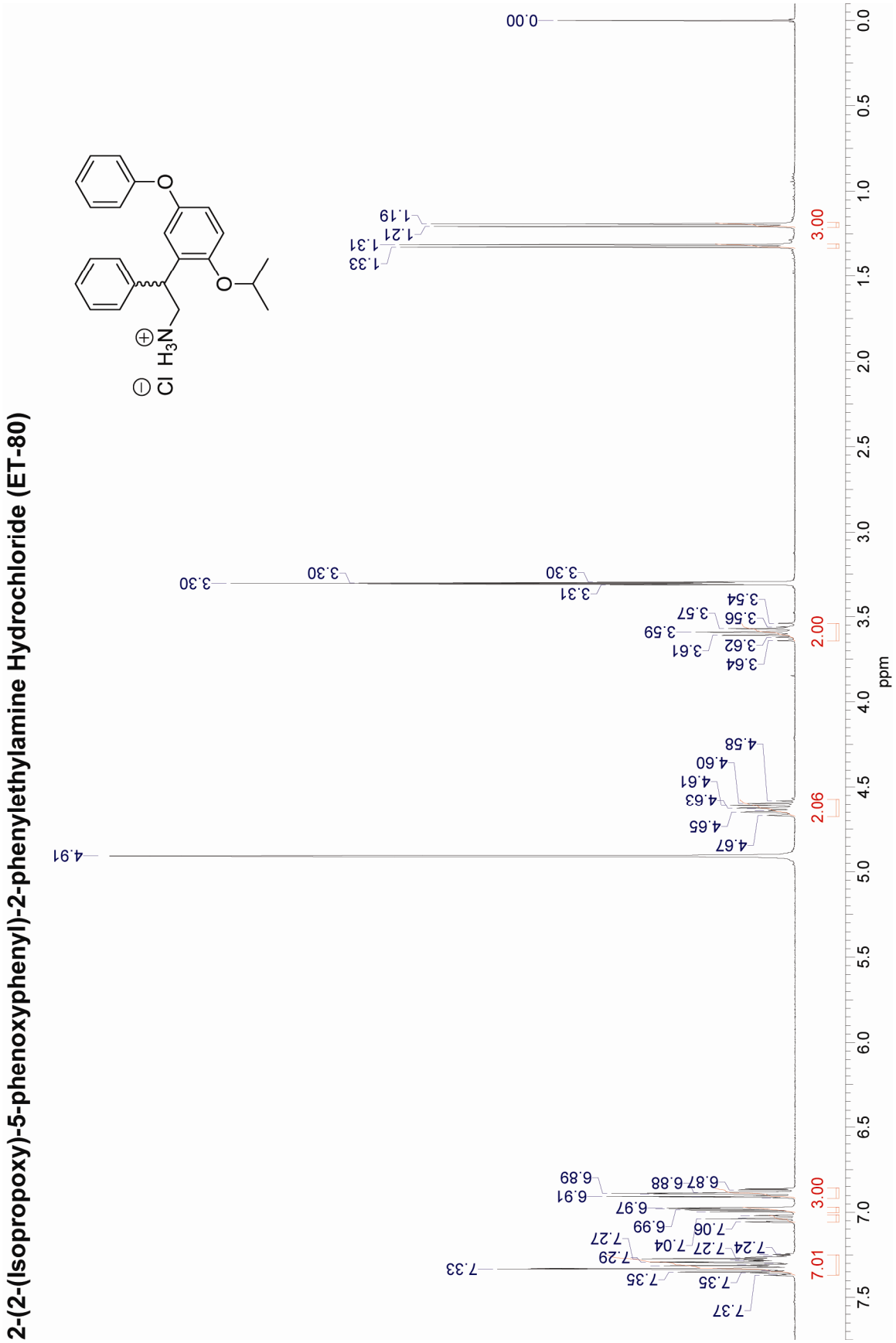
2-(2-(Hexyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-78)



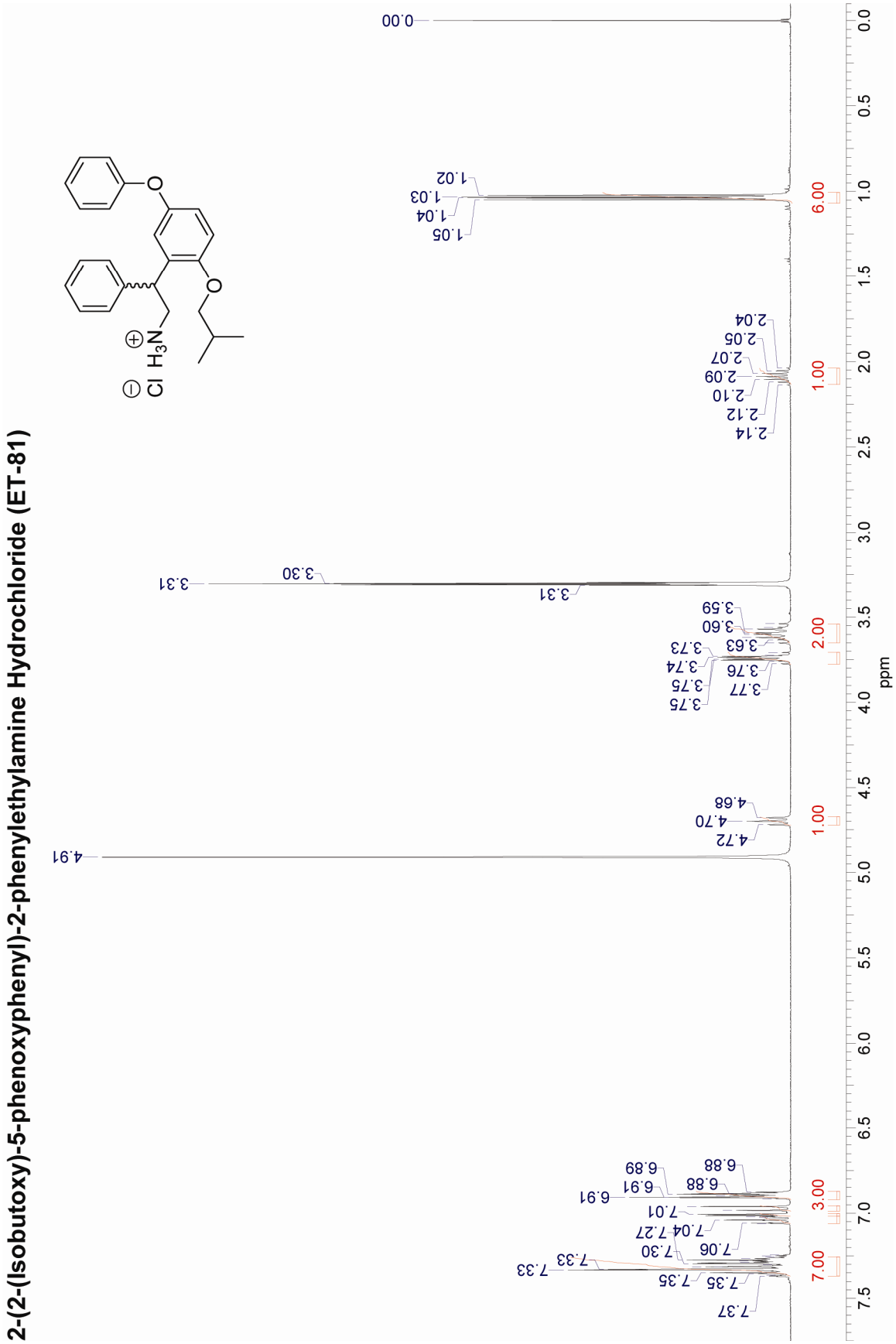
2-(2-Benzyloxy-5-phenoxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-79)



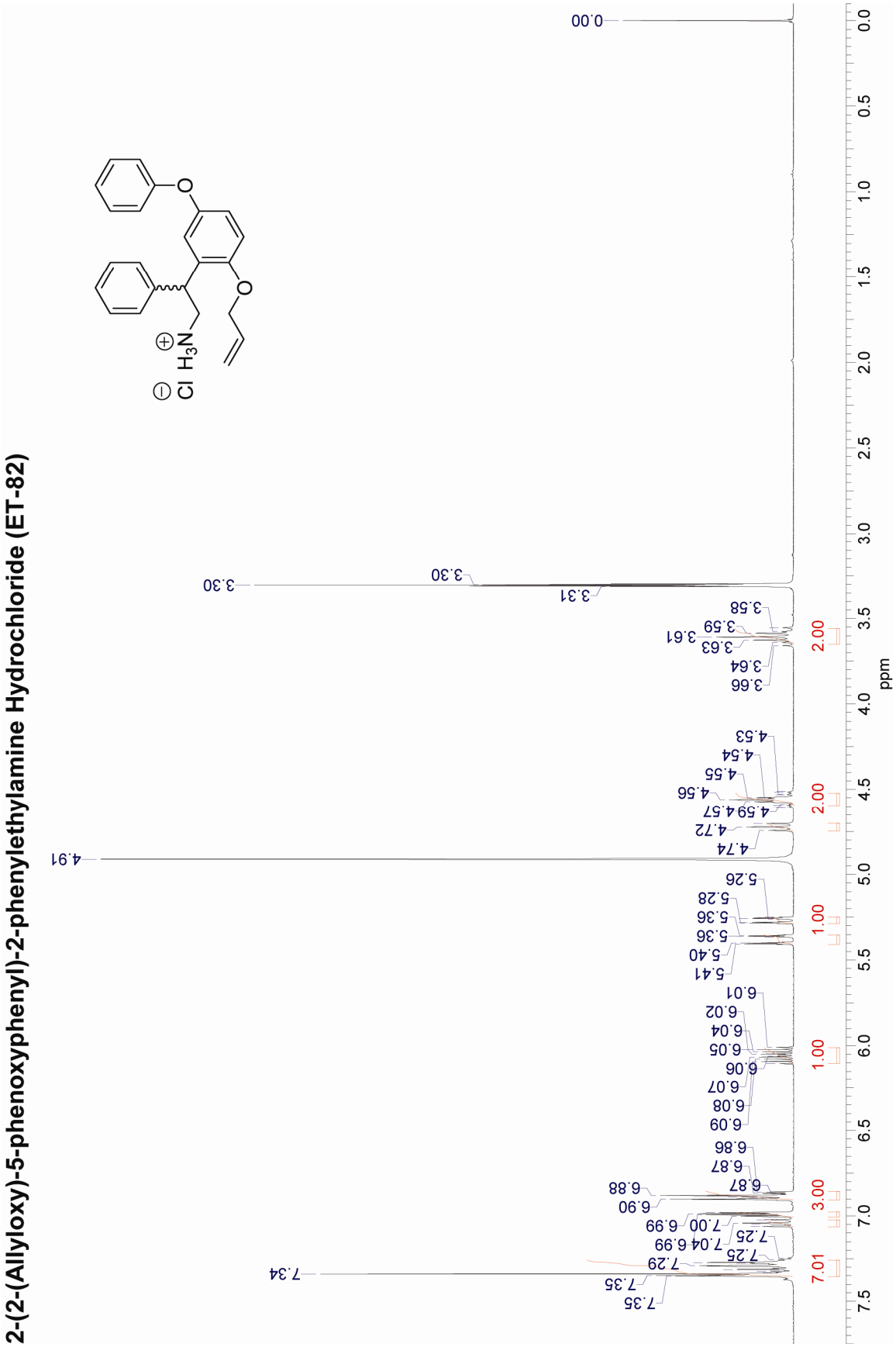
2-(2-(Isopropoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-80)

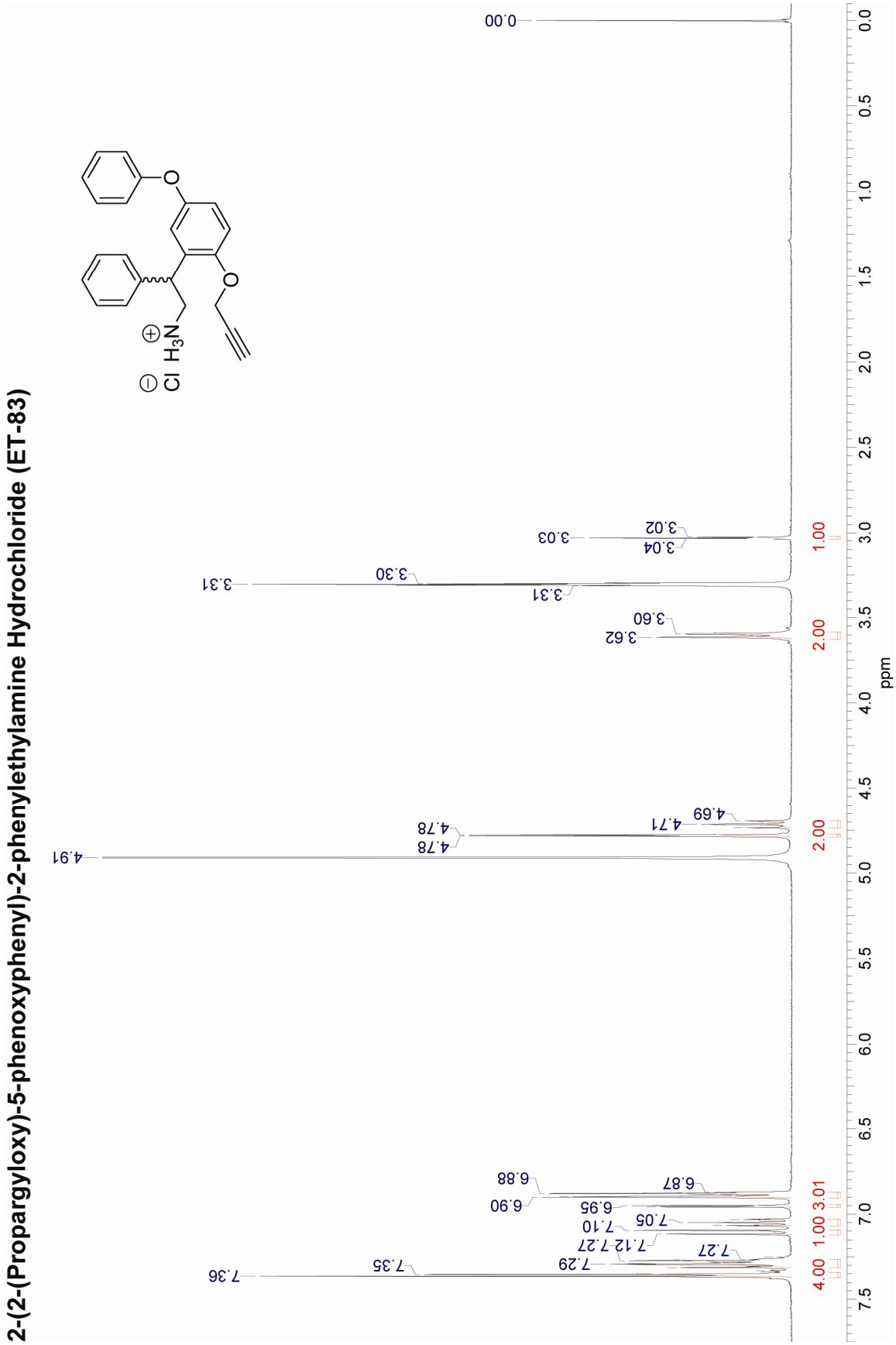


2-(2-(Isobutoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-81)

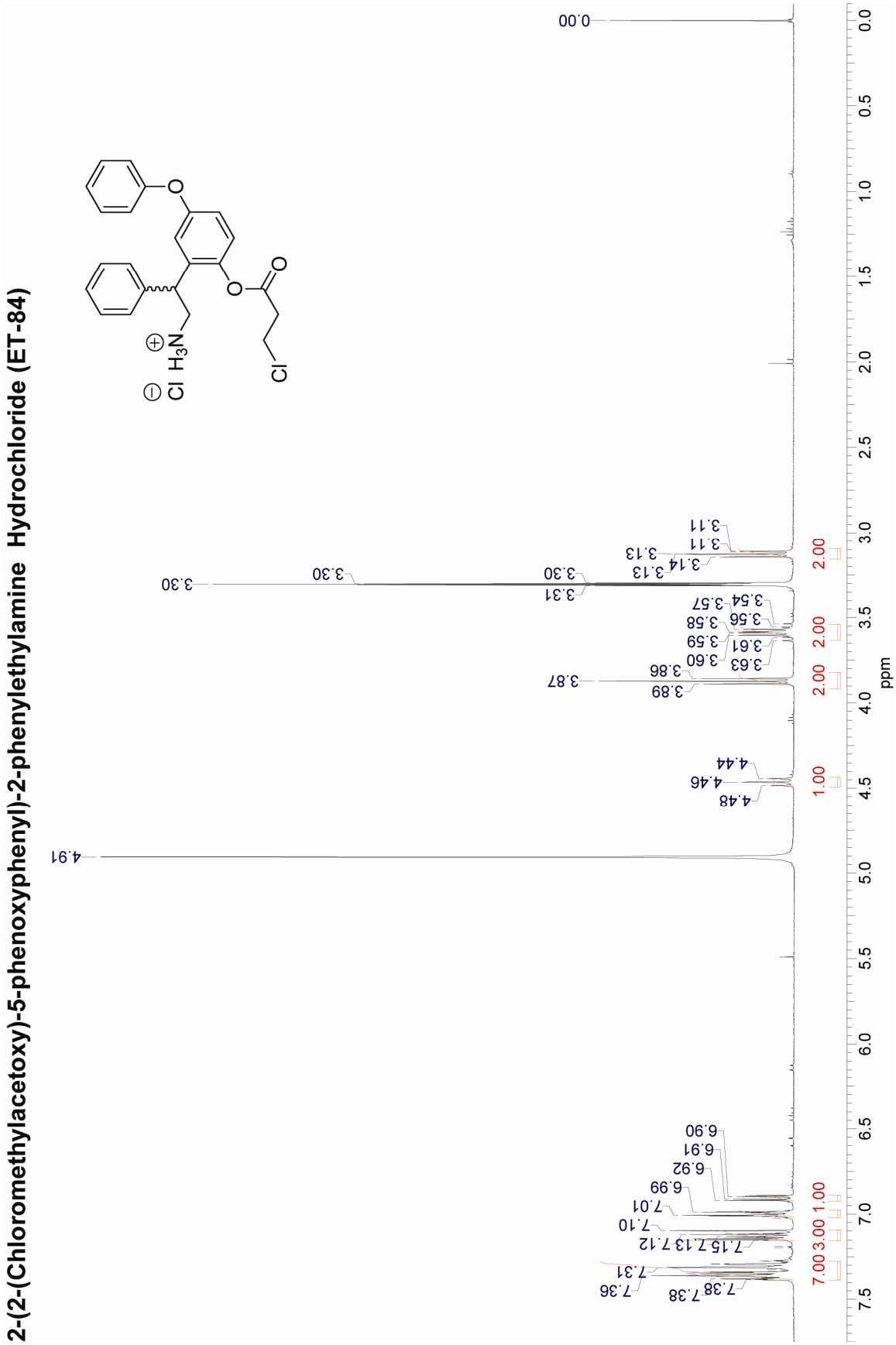


2-(2-(Allyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-82)

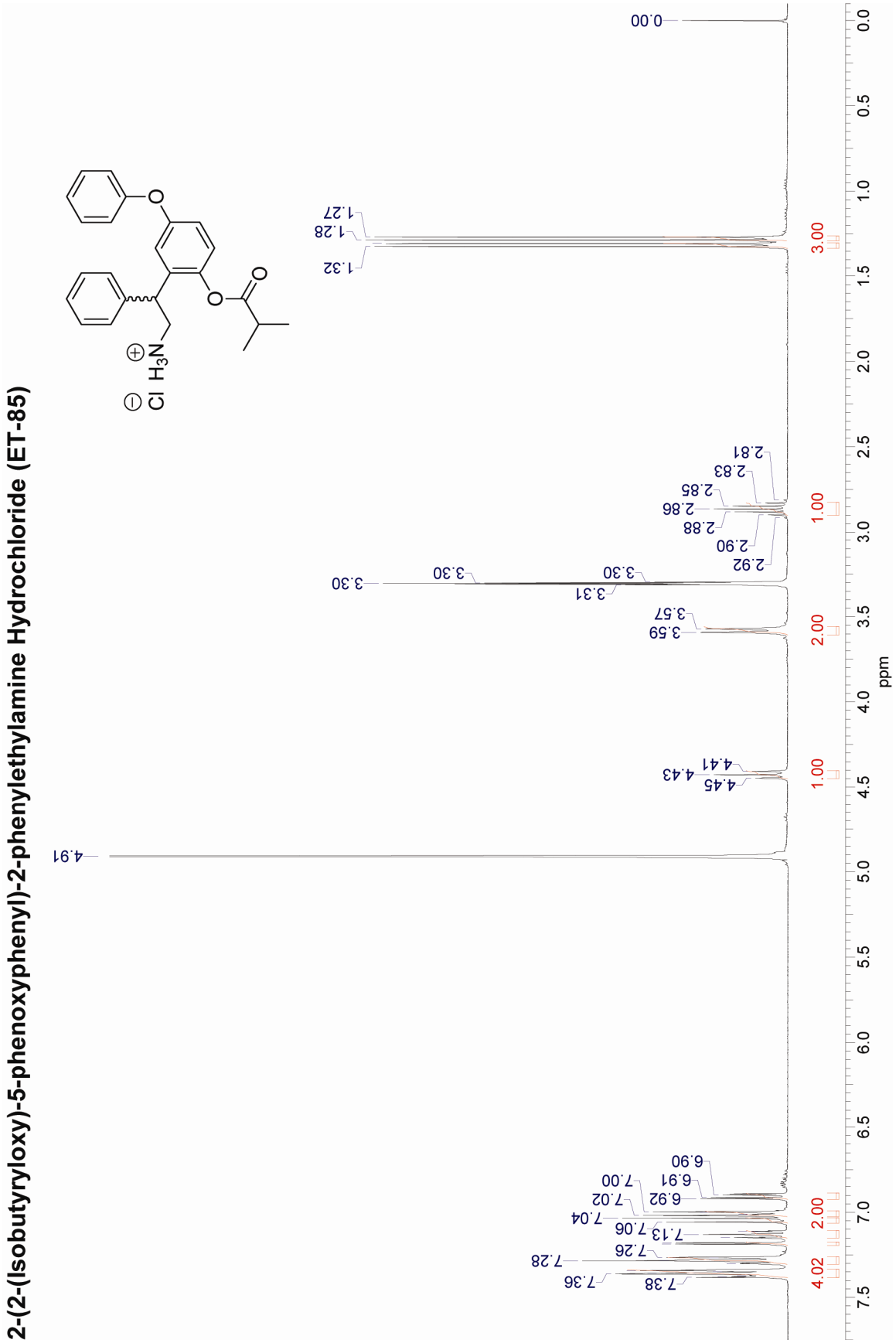


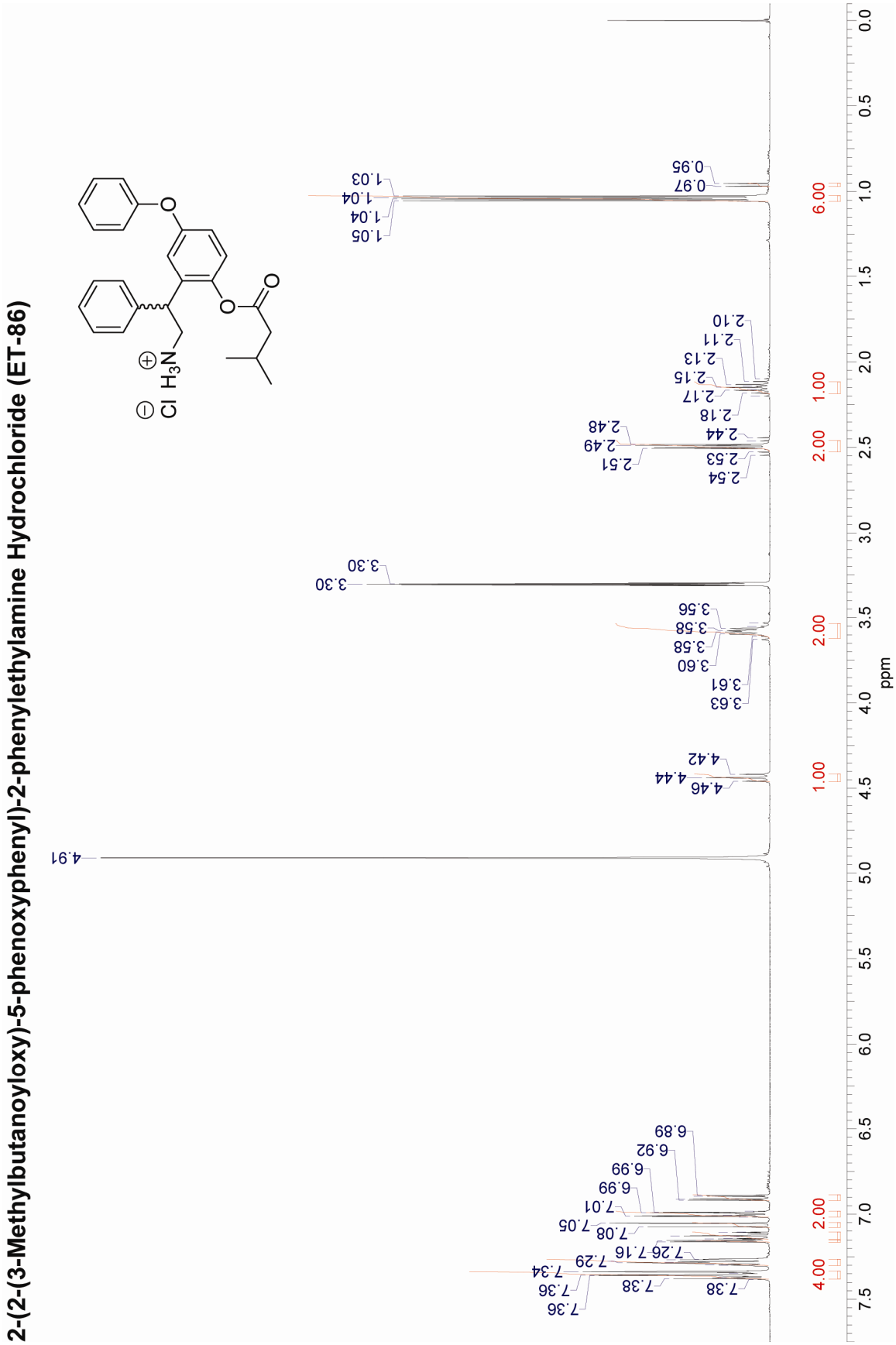

2-(2-(Propargyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-83)
0.00
3.04
3.02
3.03
3.31
3.30
3.31
3.62
3.60
4.69
4.71
4.78
4.78
4.91
6.87
6.88
6.90
6.95
7.05
7.10
7.12-7.27
7.27
7.29
7.35
7.36
4.00
1.00
3.01
2.00
2.00
1.00
ppm

2-(2-(Chloromethylacetoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-84)

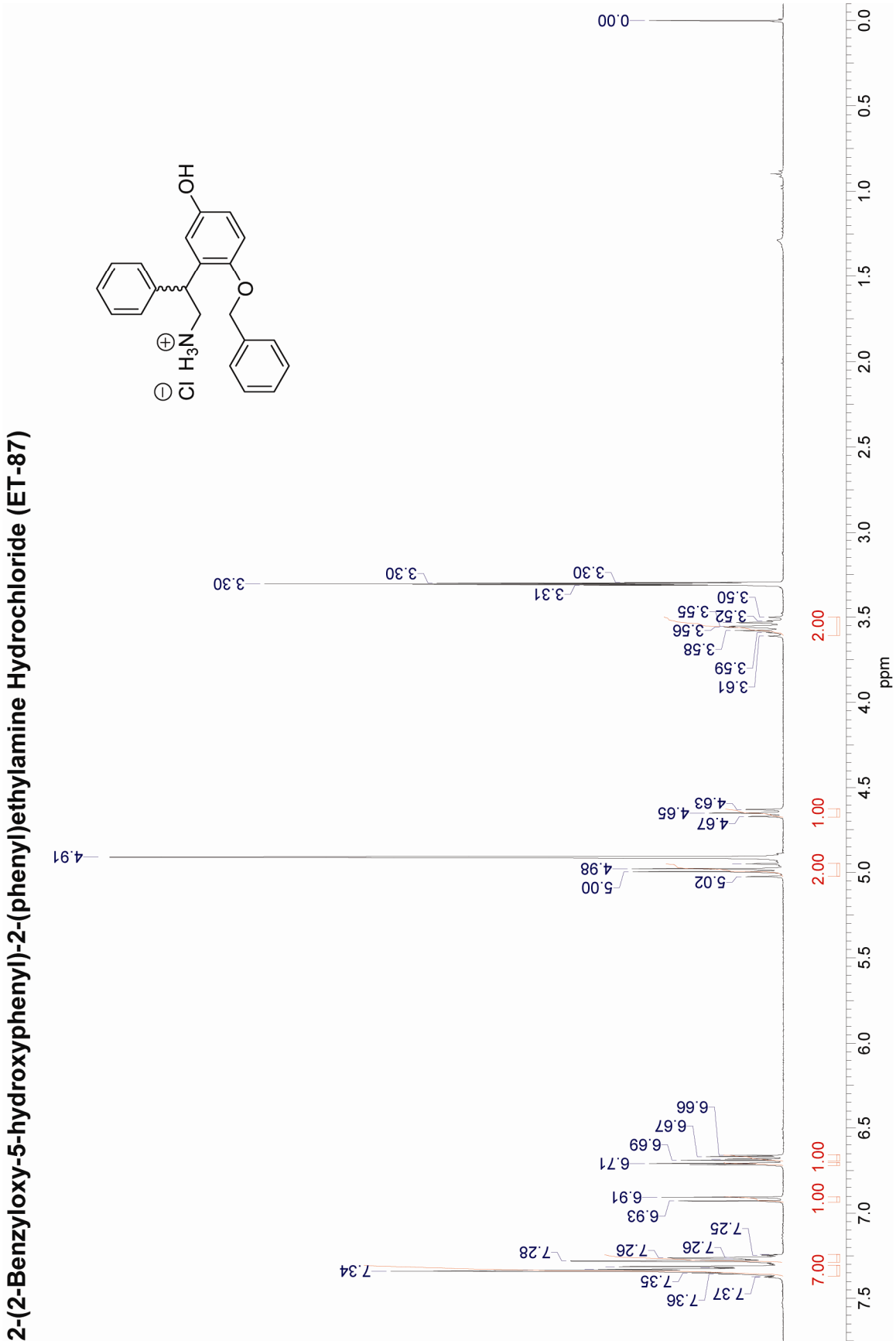


2-(2-(Isobutyryloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-85)

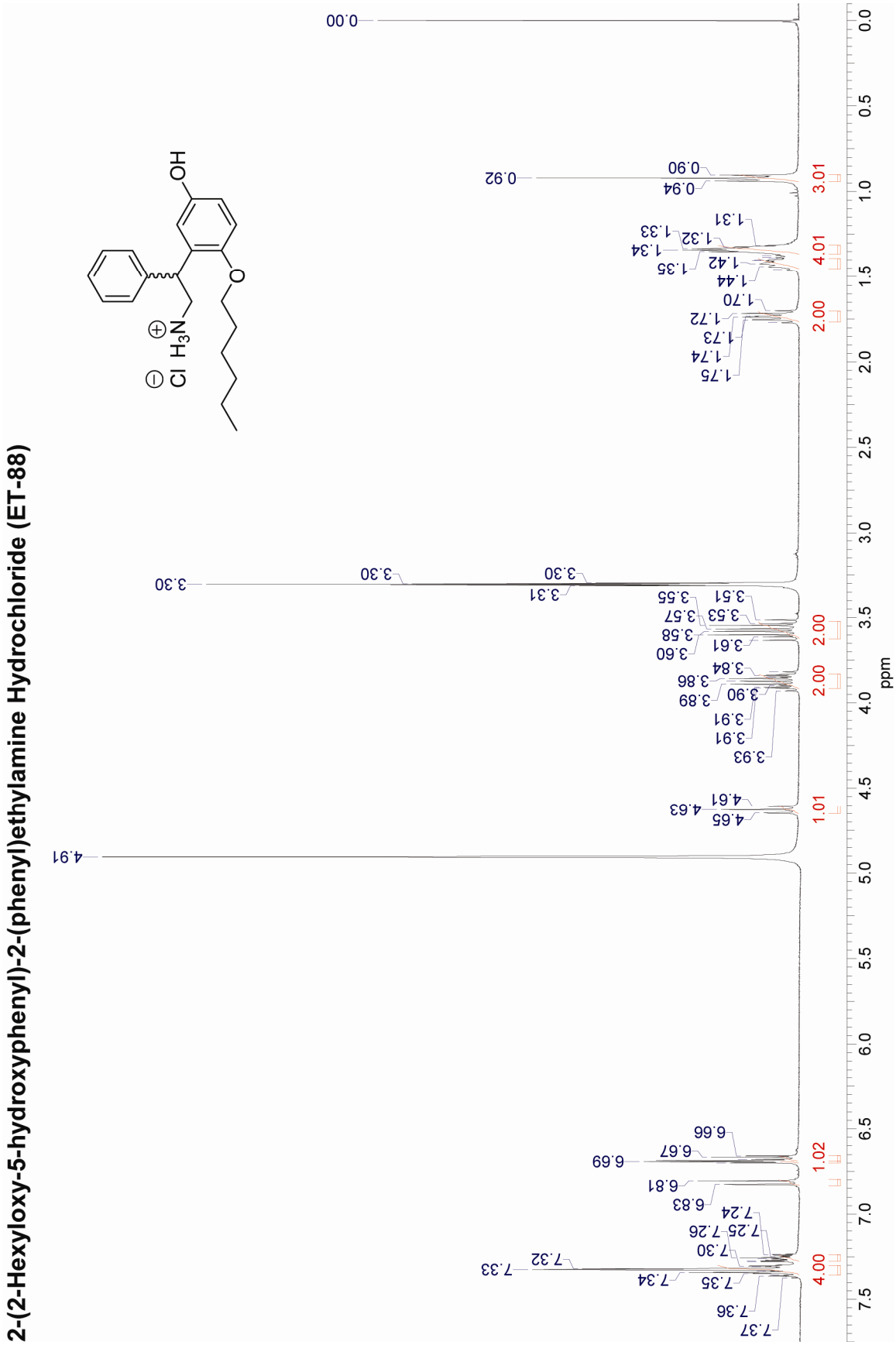



2-(2-(3-Methylbutanoyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-86)
Cl
H3N
ppm

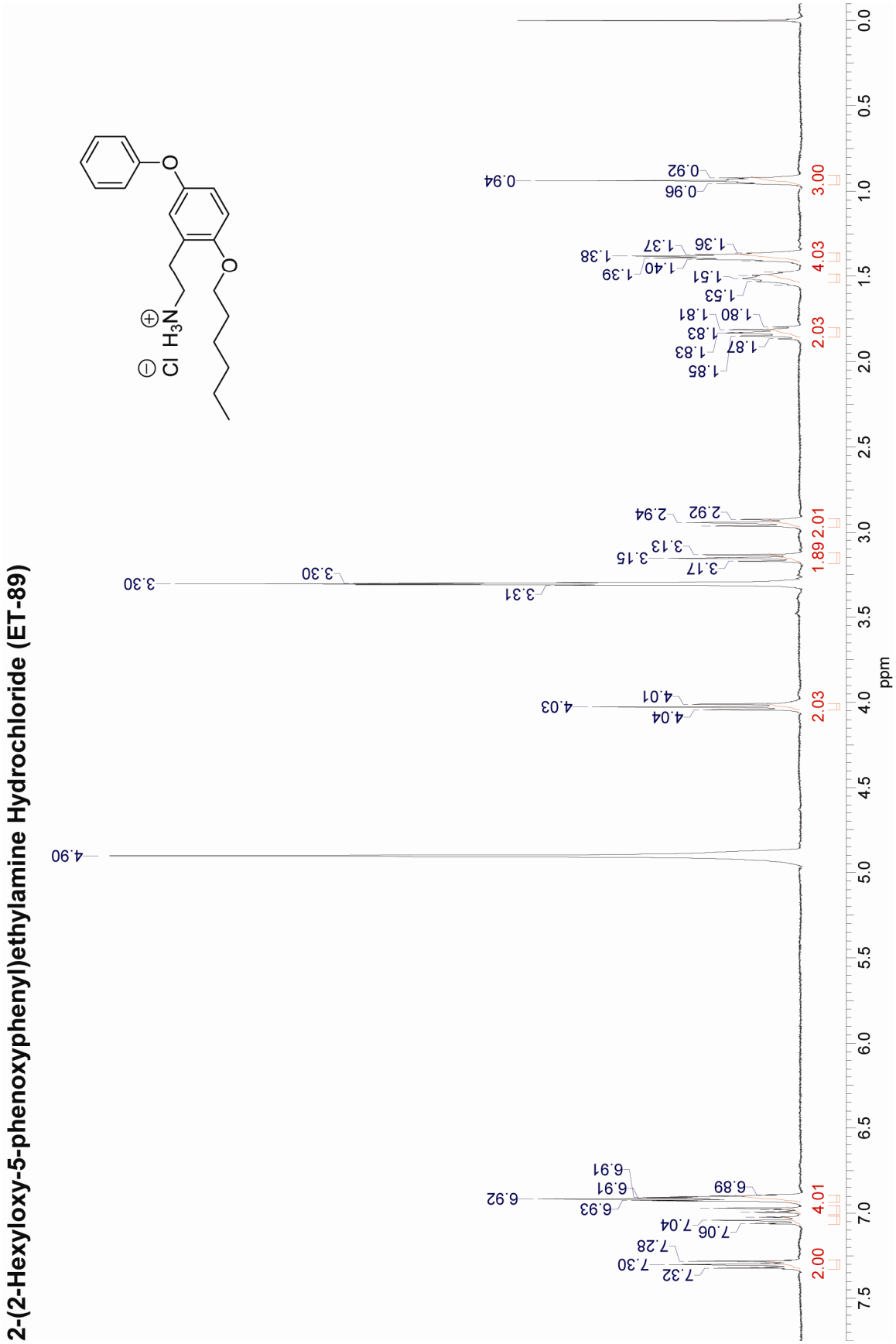
2-(2-Benzyloxy-5-hydroxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-87)



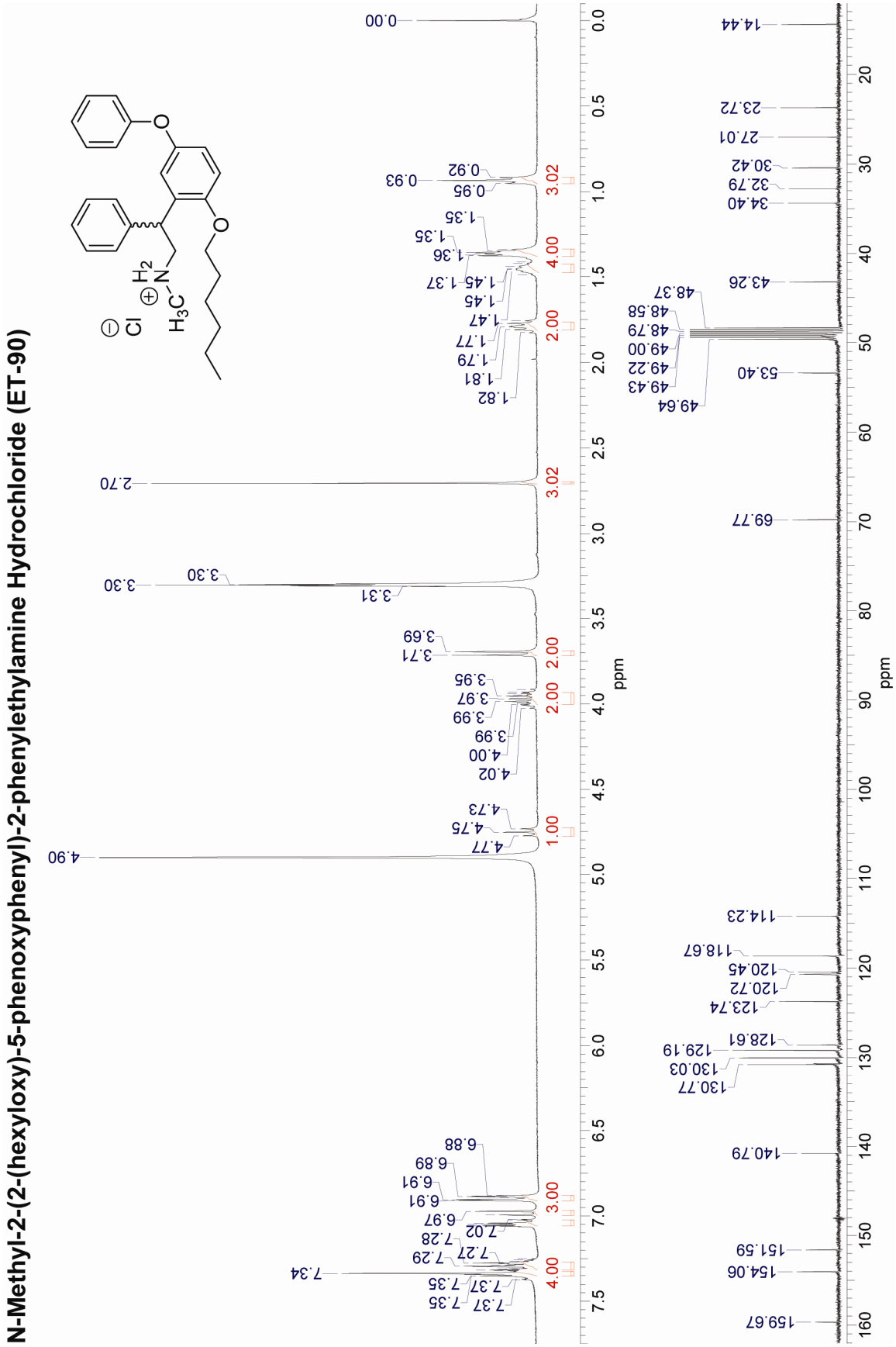
2-(2-Hexyloxy-5-hydroxyphenyl)-2-(phenyl)ethylamine Hydrochloride (ET-88)



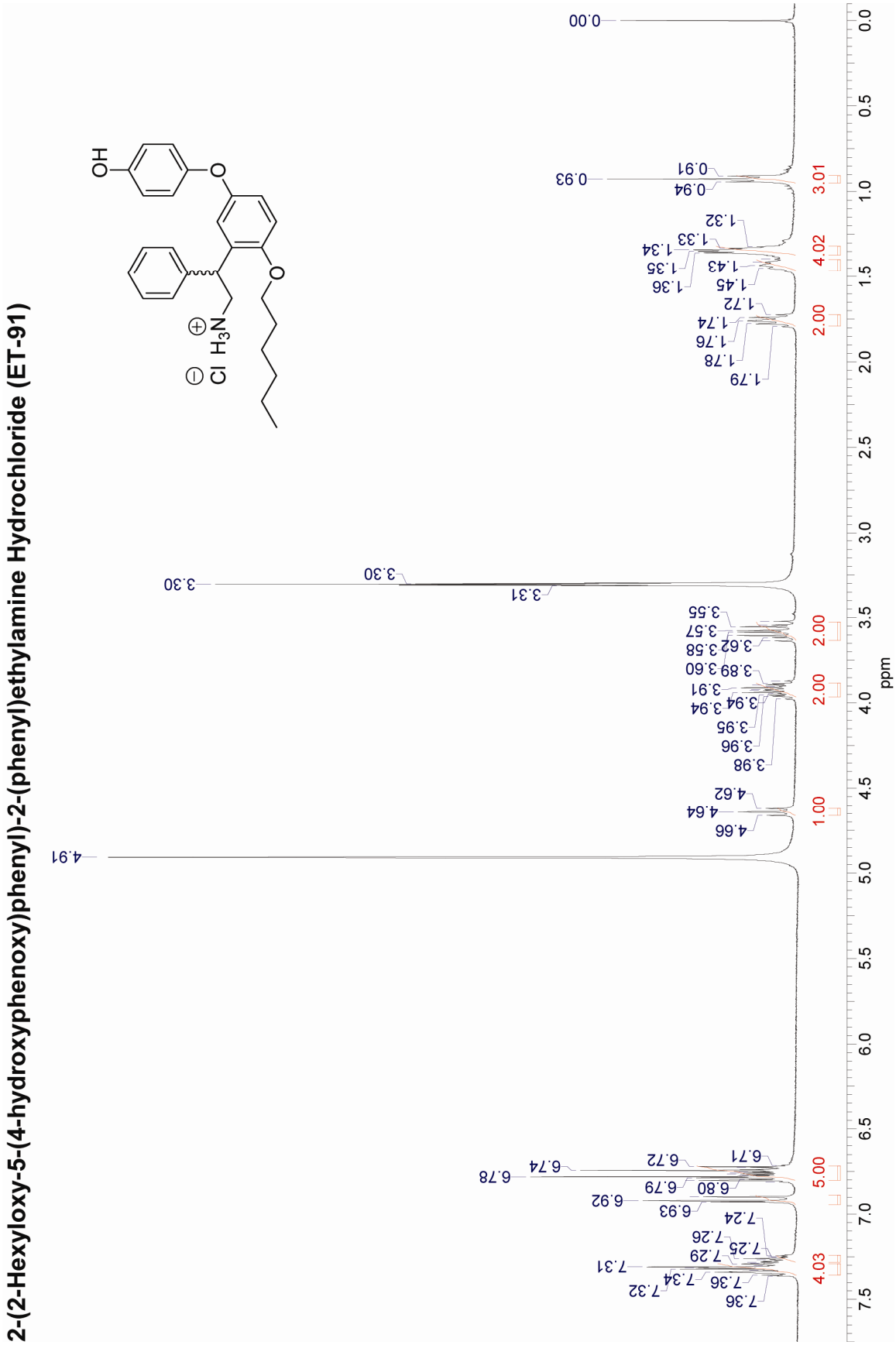
2-(2-Hexyloxy-5-phenoxyphenyl)ethylamine Hydrochloride (ET-89)



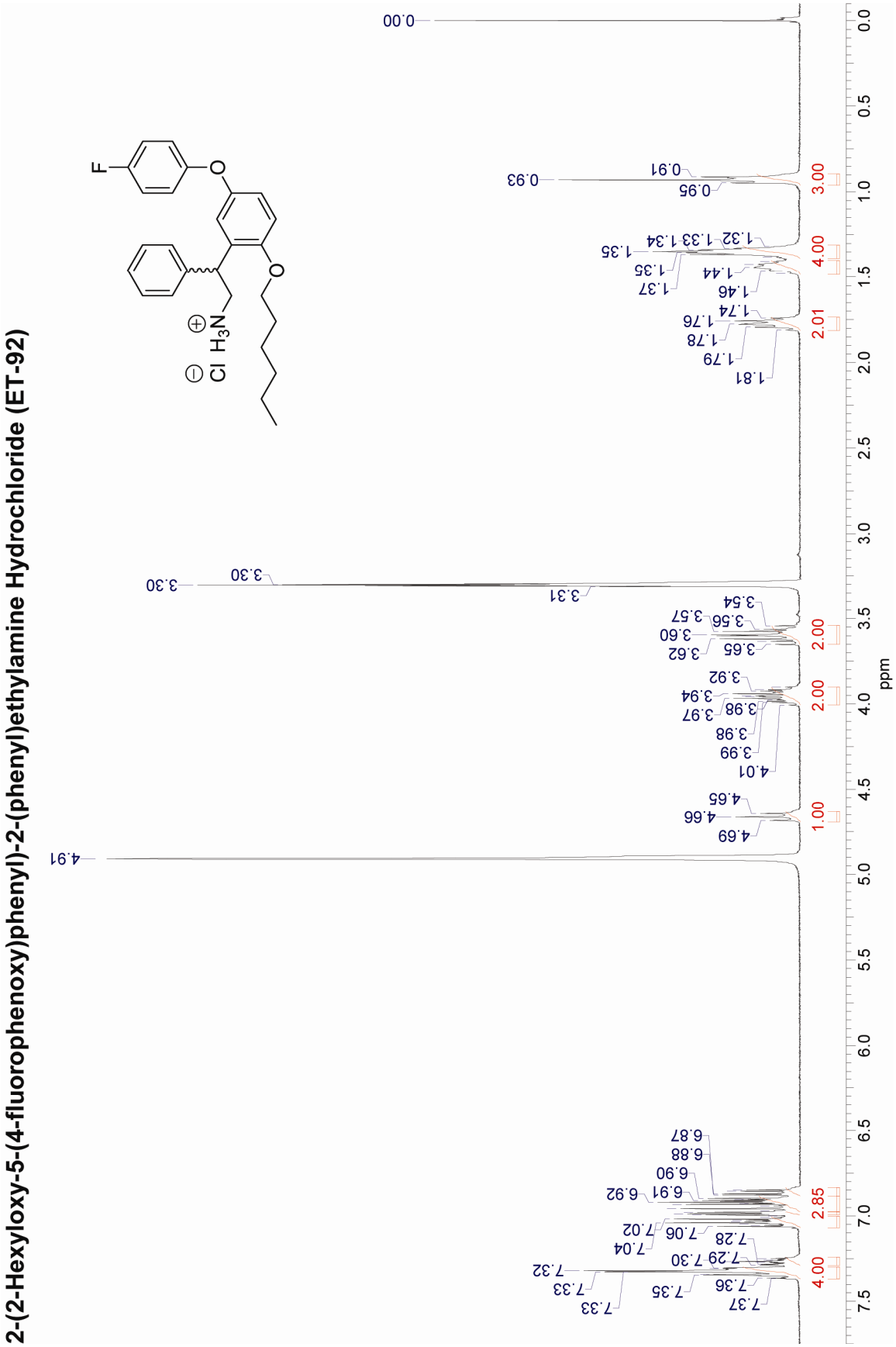
N-Methyl-2-(2-(hexyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-90)



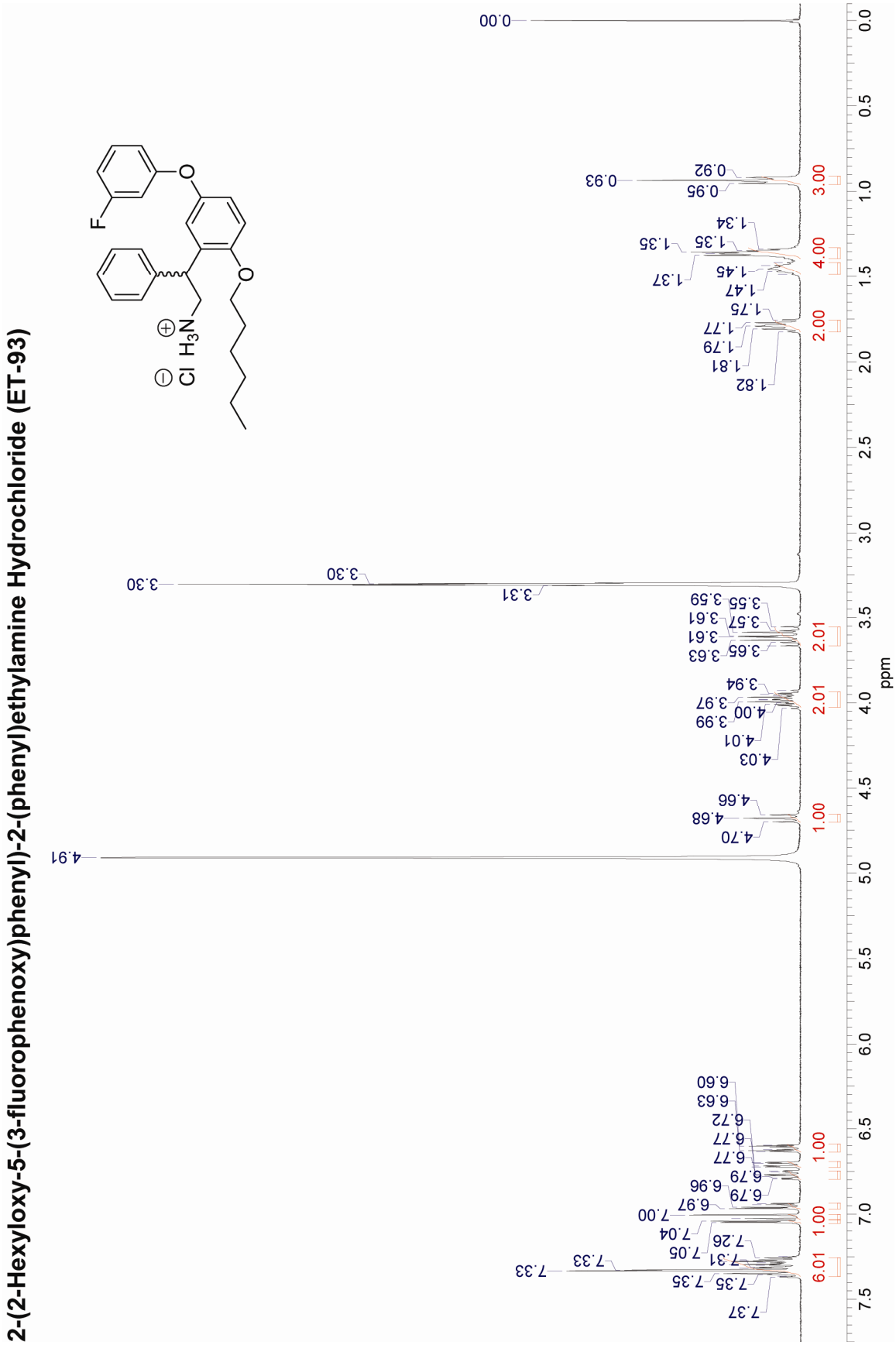
2-(2-Hexyloxy-5-(4-hydroxyphenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-91)



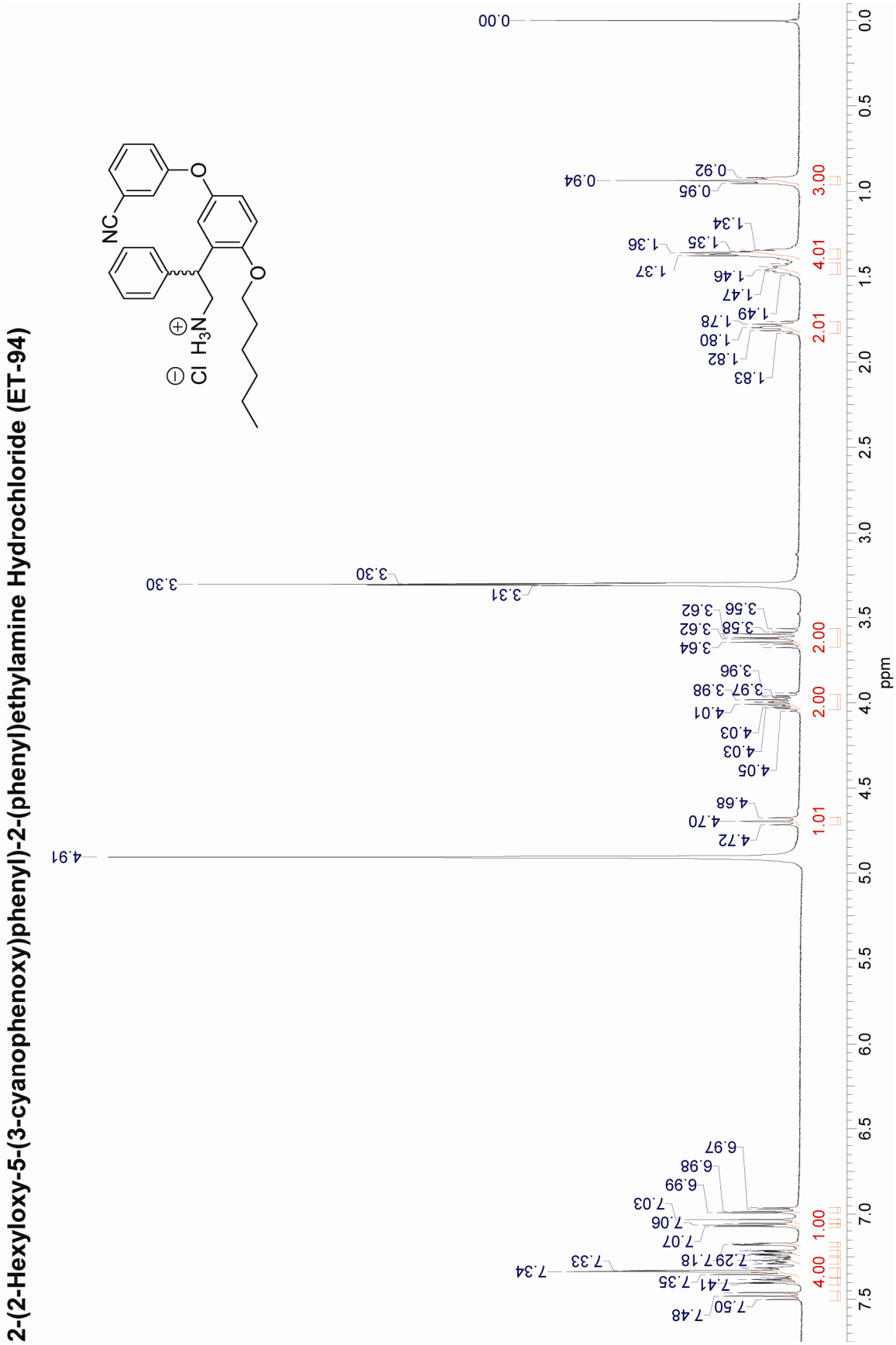
2-(2-Hexyloxy-5-(4-fluorophenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-92)



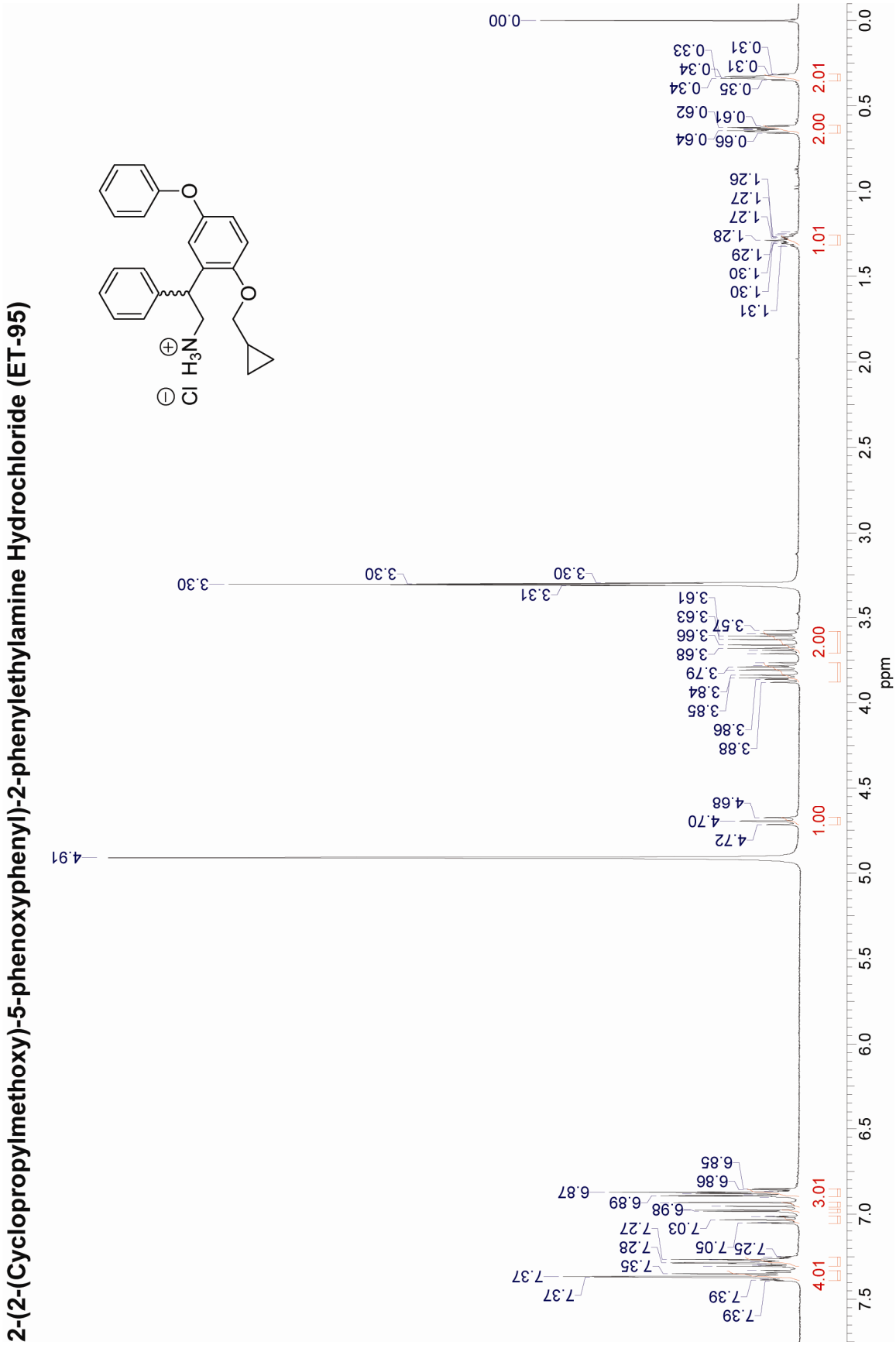
2-(2-Hexyloxy-5-(3-fluorophenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-93)



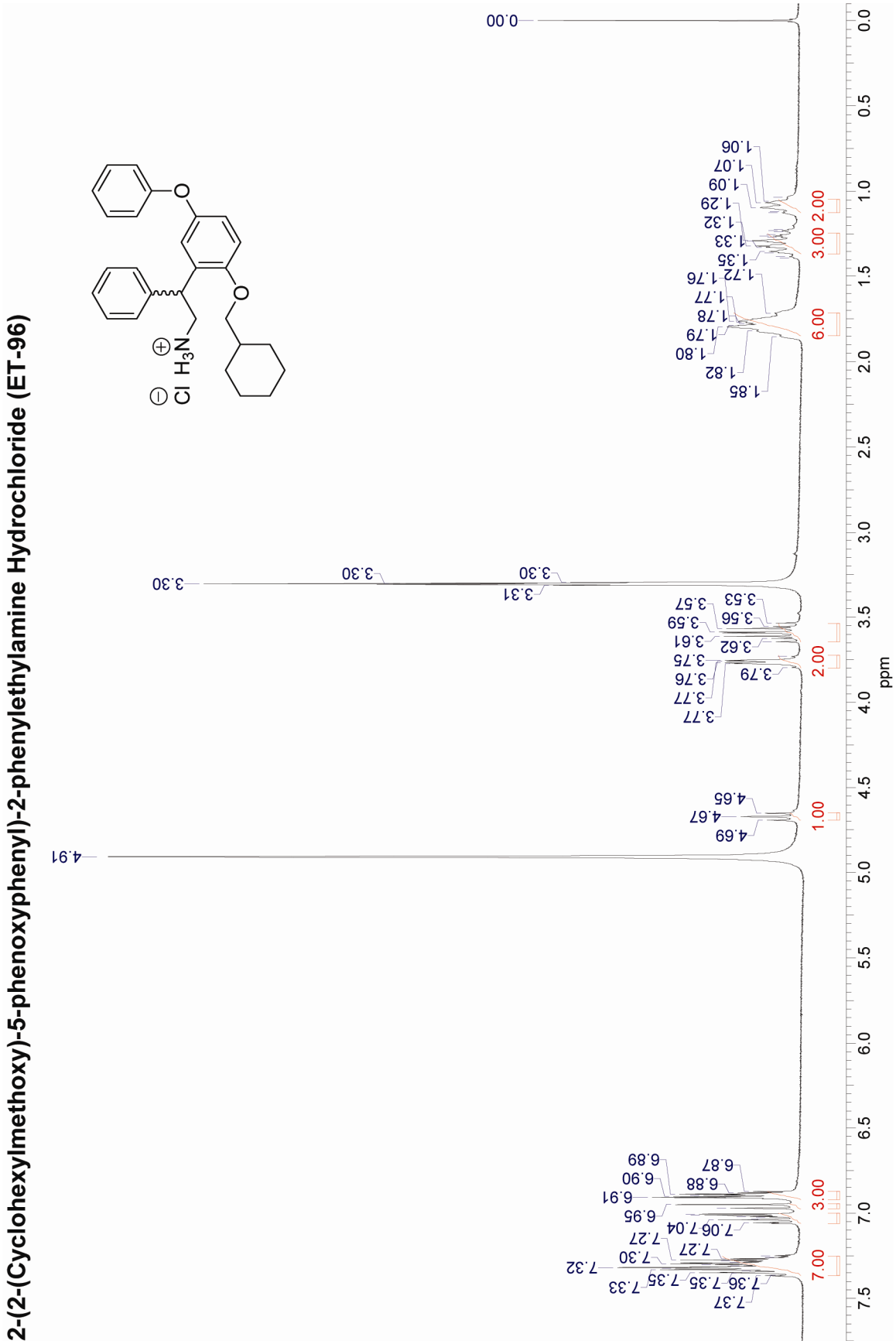
2-(2-Hexyloxy-5-(3-cyanophenoxy)phenyl)-2-(phenyl)ethylamine Hydrochloride (ET-94)



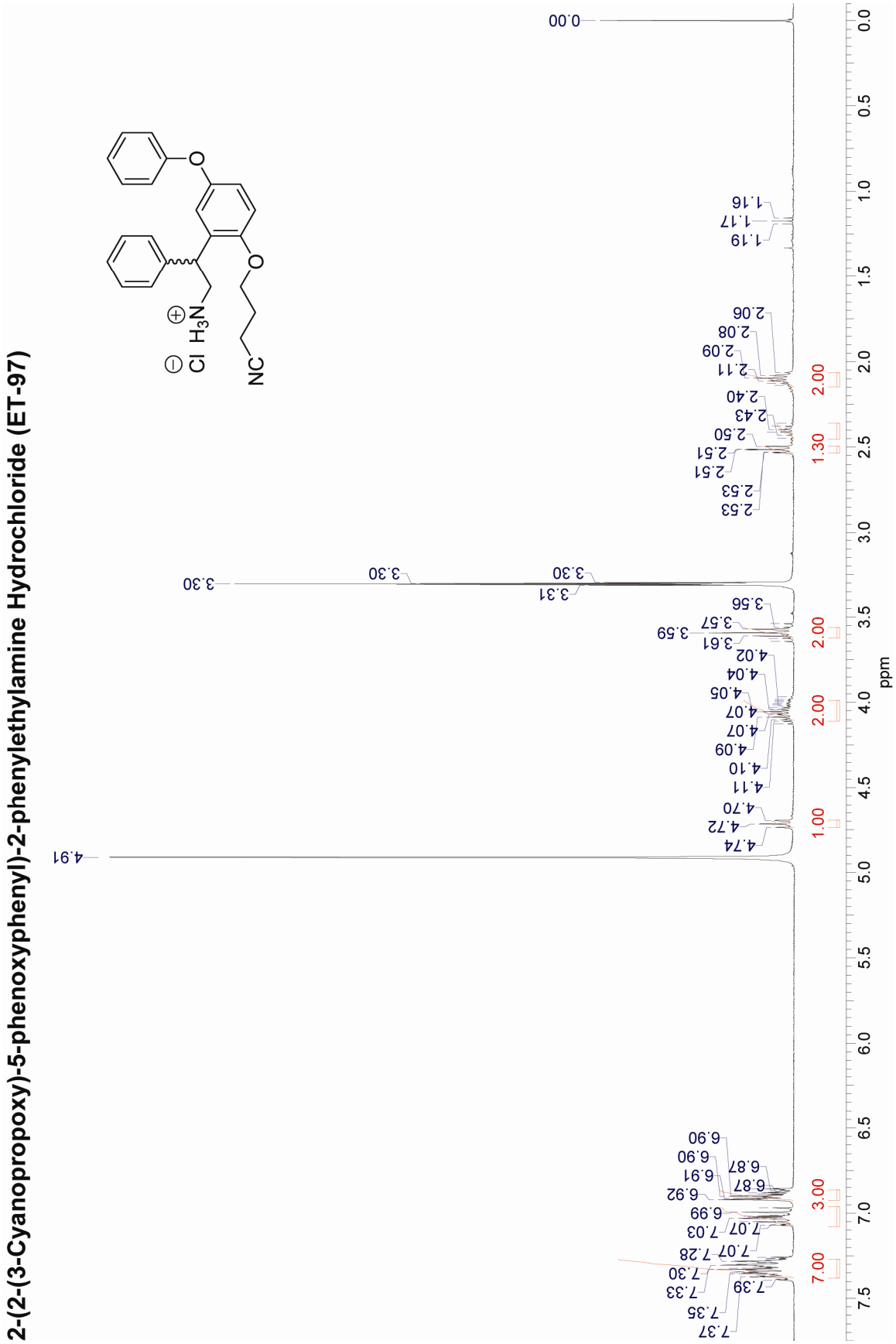
2-(2-(Cyclopropylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-95)



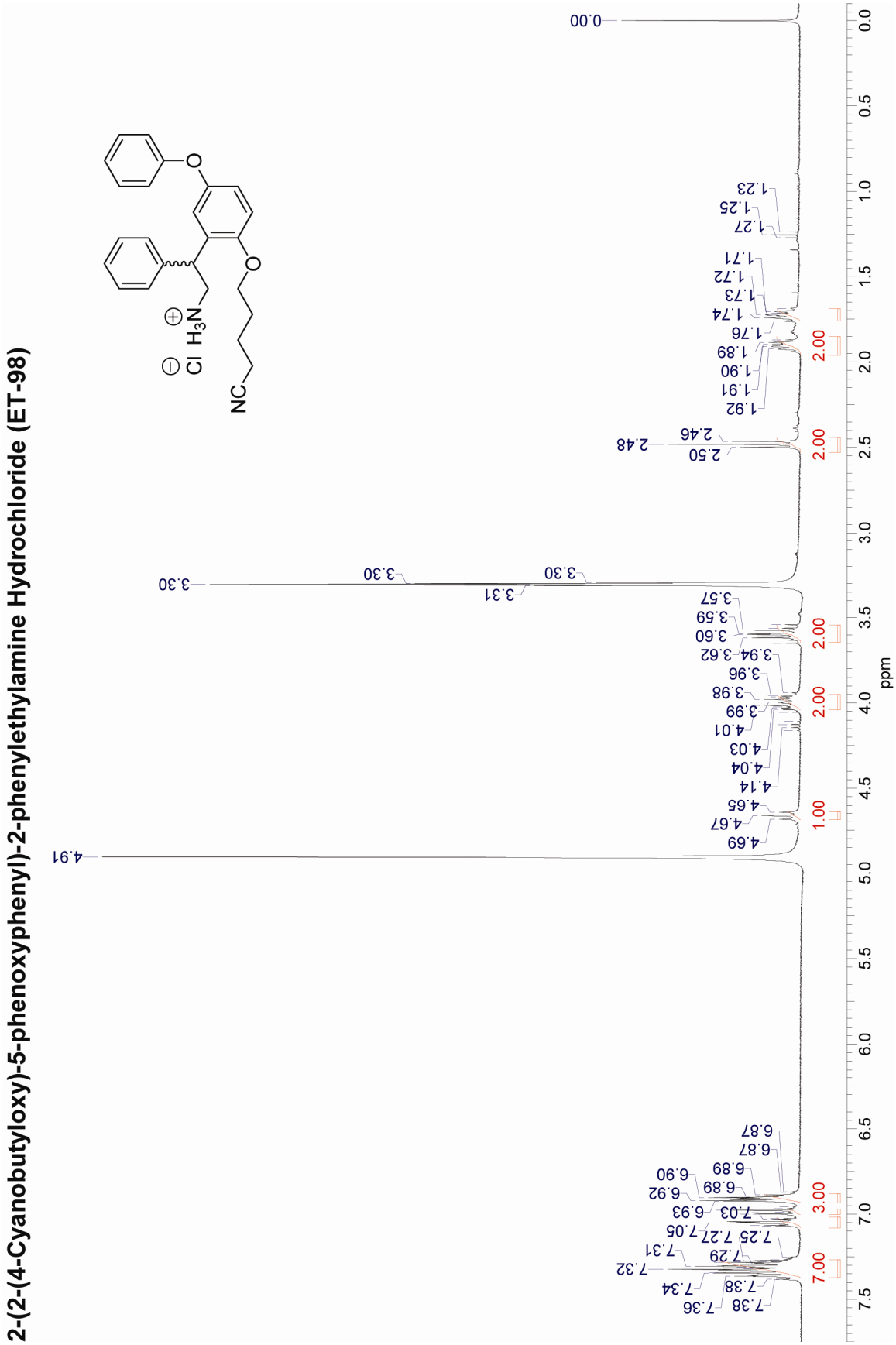
2-(2-(Cyclohexylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-96)

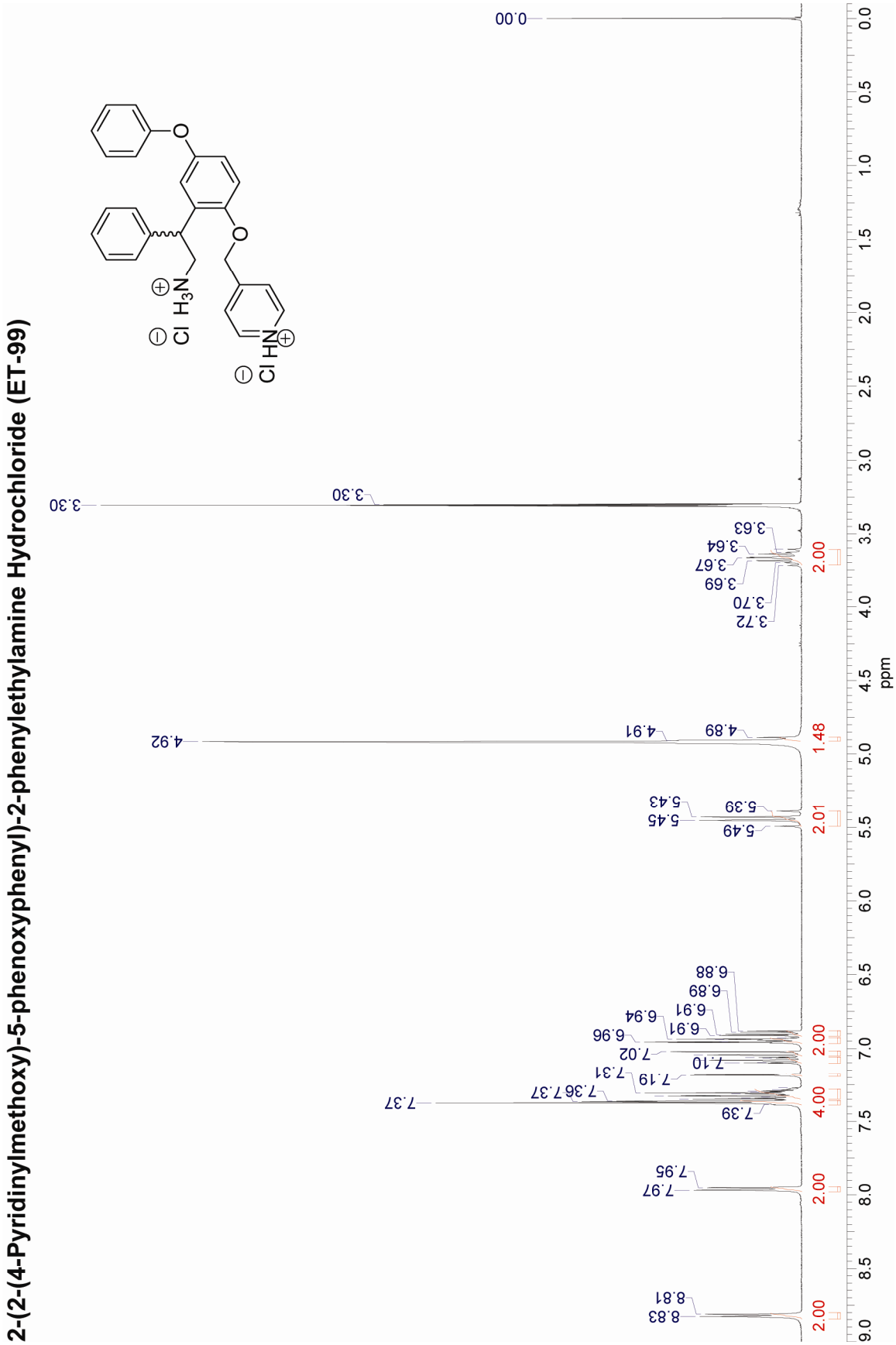


2-(2-(3-Cyanopropoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-97)

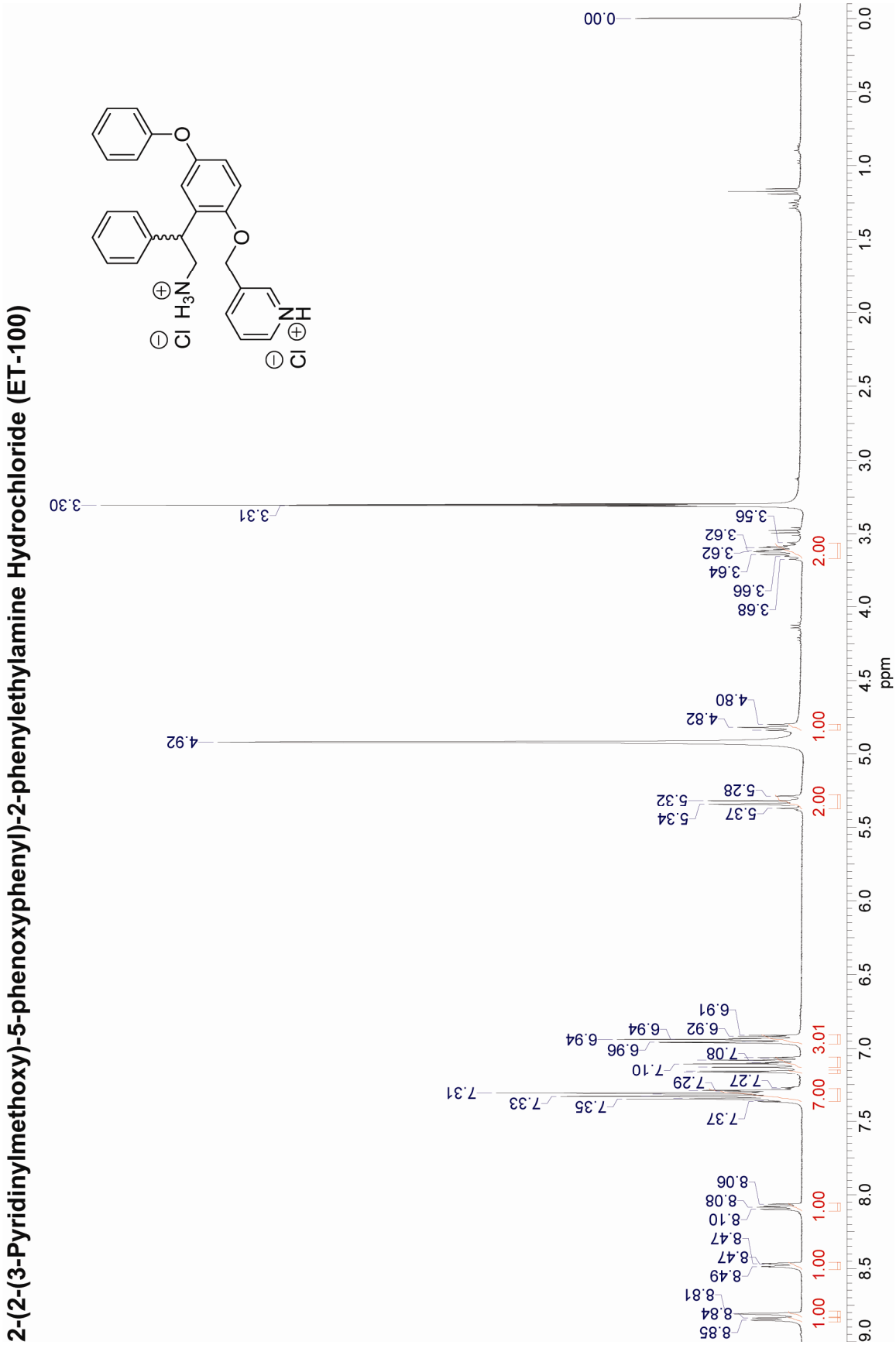


2-(2-(4-Cyanobutyloxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-98)

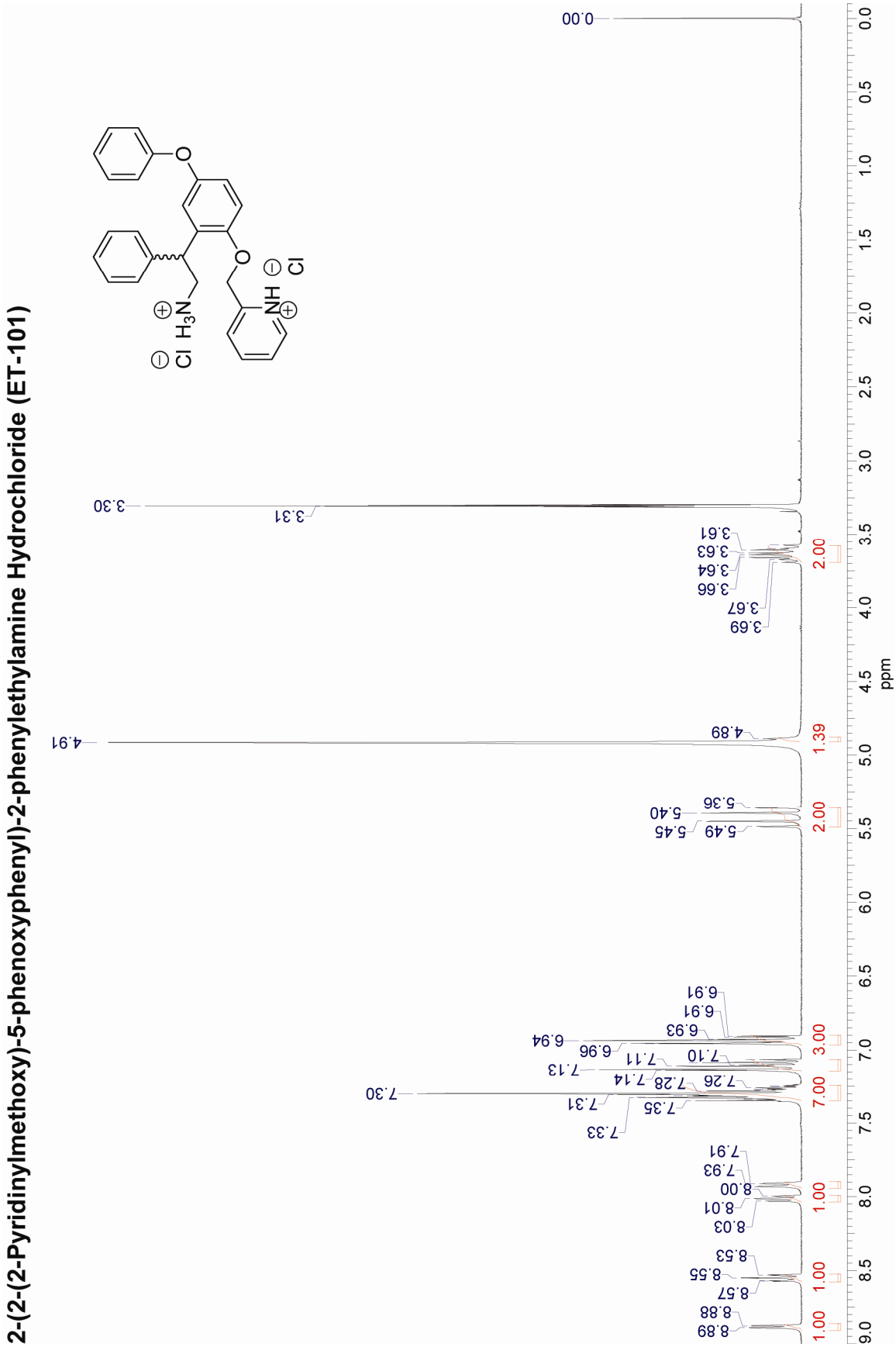


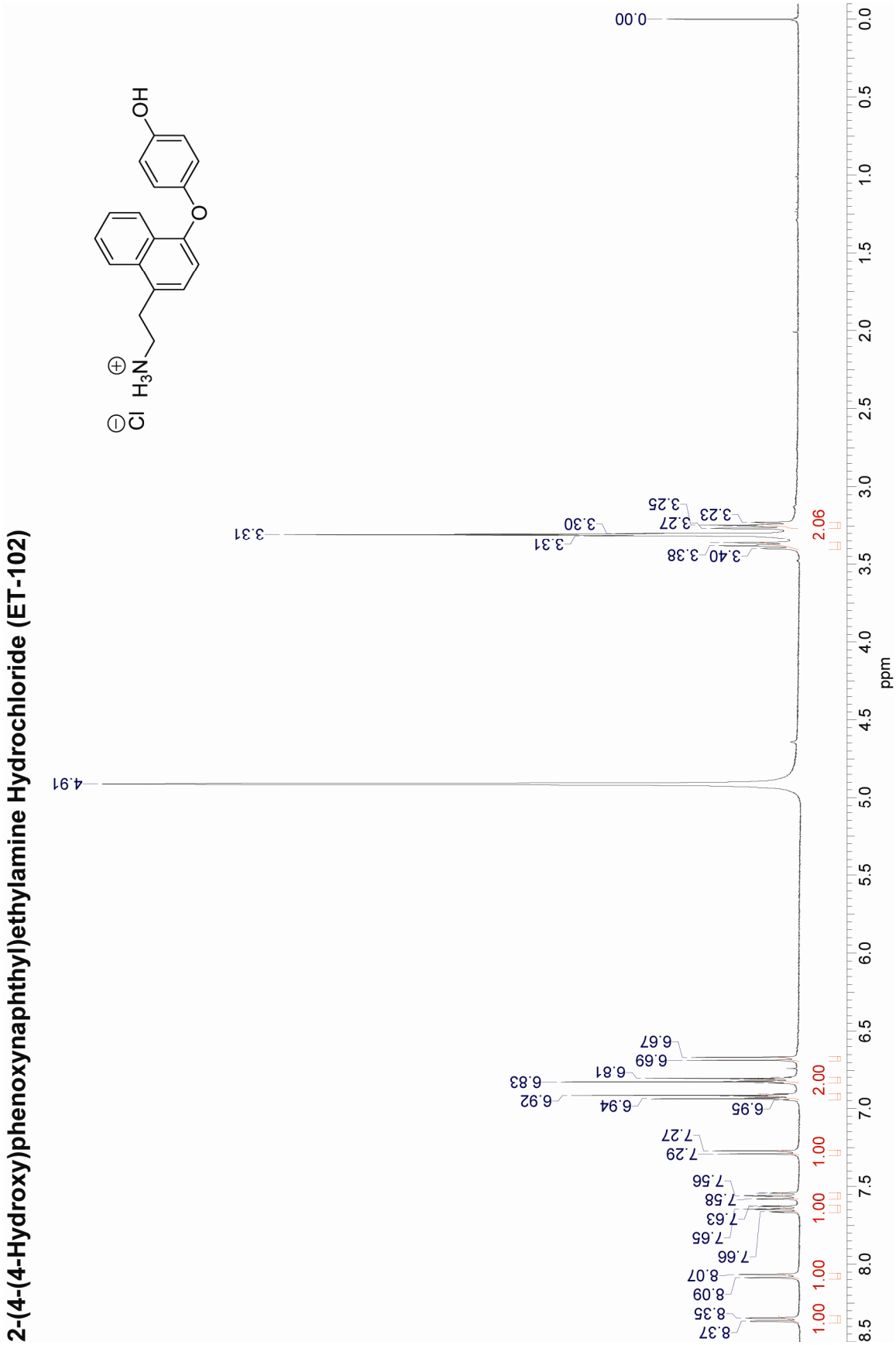

2-(2-(4-Pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-99)
0.00
3.30
3.63
3.64
3.67
3.69
3.70
3.72
4.89
4.91
4.92
5.39
5.43
5.45
5.49
6.88
6.89
6.91
6.91
6.94
6.96
7.02
7.10
7.19
7.31
7.36
7.37
7.37
7.39
7.95
7.97
8.81
8.83
2.00
2.00
4.00
2.00
2.01
1.48
2.00
ppm

2-(2-(3-Pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-100)

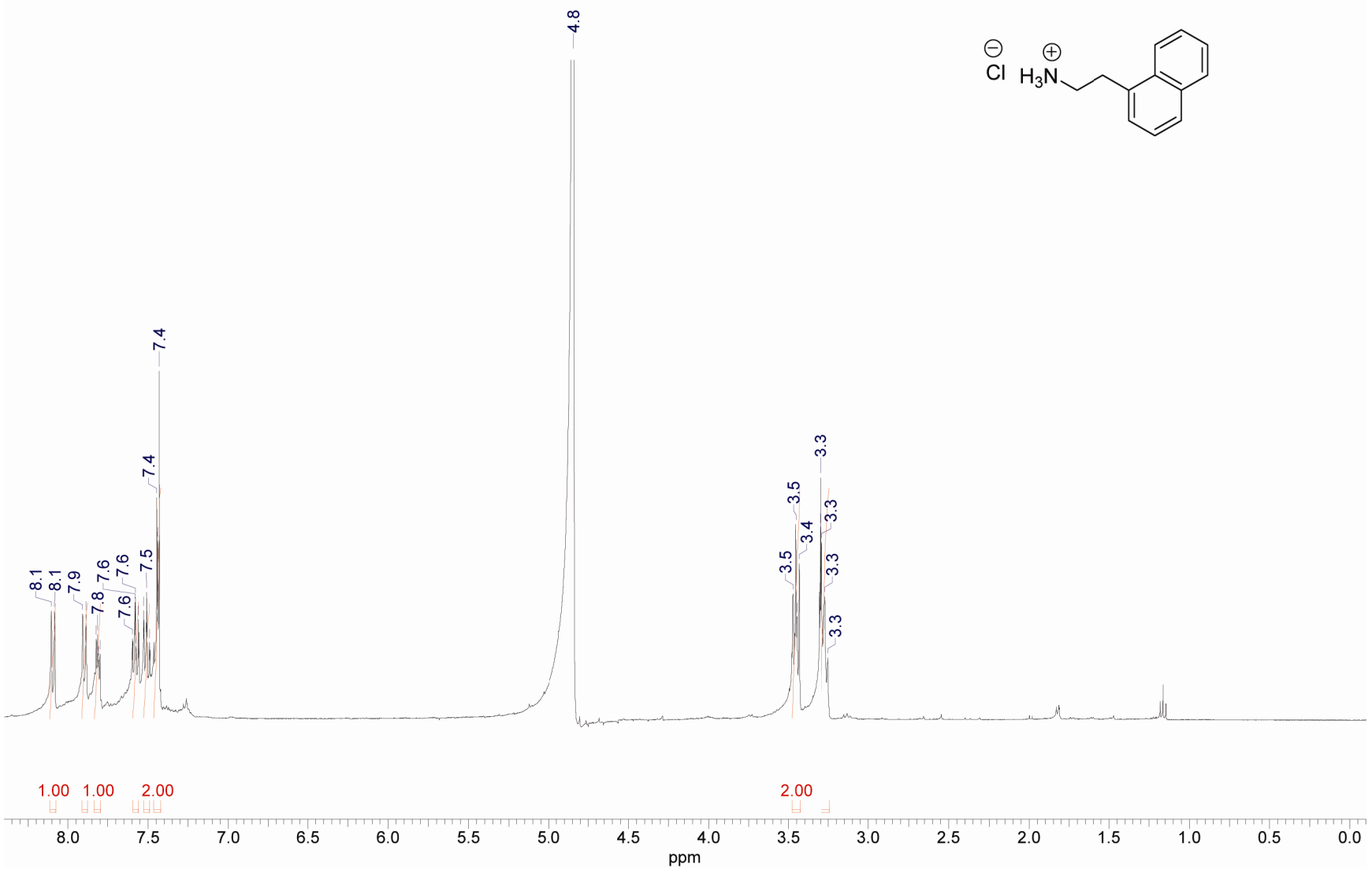


2-(2-(2-Pyridinylmethoxy)-5-phenoxyphenyl)-2-phenylethylamine Hydrochloride (ET-101)

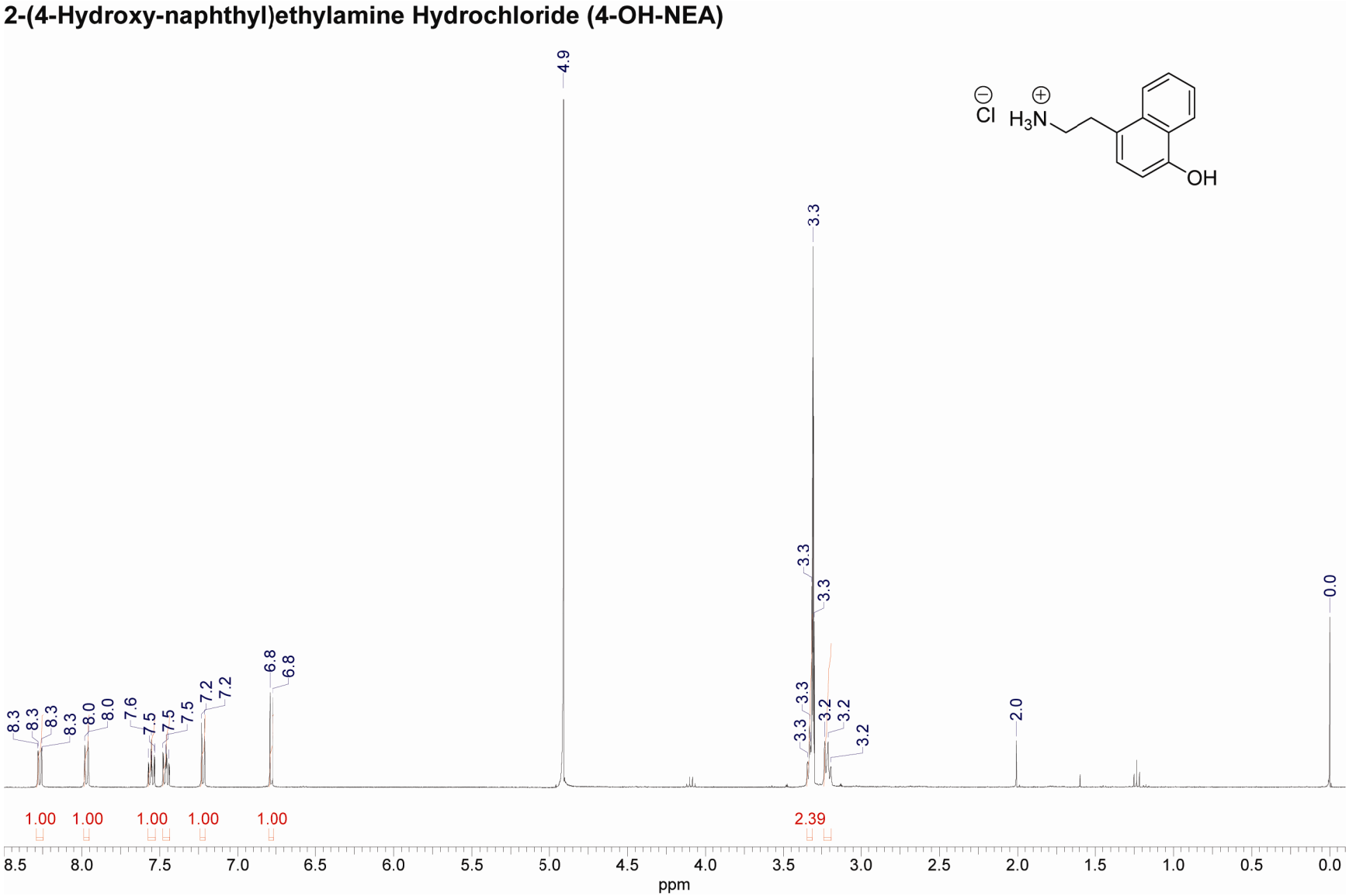



2-(4-(4-Hydroxy)phenoxynaphthyl)ethylamine Hydrochloride (ET-102)
OH
O
H3N
Cl
8.37
8.35
8.09
8.07
7.66
7.65
7.63
7.58
7.56
7.29
7.27
6.95
6.94
6.92
6.83
6.81
6.69
6.67
4.91
3.40
3.38
3.31
3.30
3.27
3.25
3.23
3.31
0.00
1.00
1.00
1.00
1.00
1.00
2.00
2.06
ppm

2-(Naphthyl)ethylamine Hydrochloride (1-NEA)



2-(4-Hydroxy-naphthyl)ethylamine Hydrochloride (4-OH-NEA)



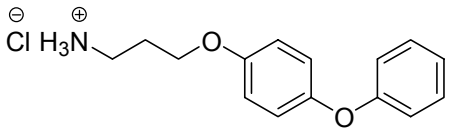
Appendix C

Final Compounds Inventory

And Summary of $TAAR_1$ Activity

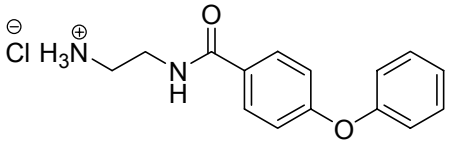
C.1 Final Compounds Inventory

ET-1



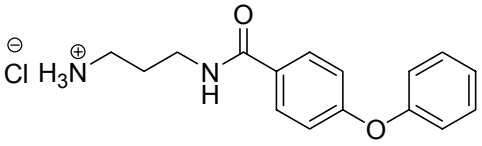
$C_{15}H_{18}ClNO_2$
Mol. Wt.: 279.7619

ET-2



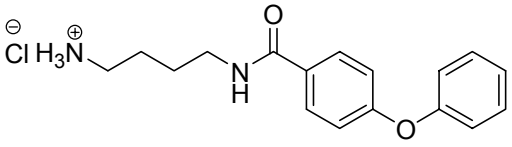
$C_{15}H_{17}ClN_2O_2$
Mol. Wt.: 292.7607

ET-3



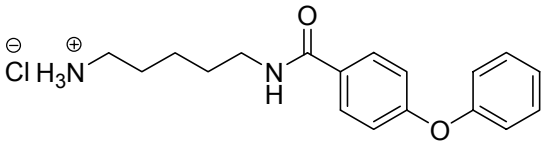
$C_{16}H_{19}ClN_2O_2$
Mol. Wt.: 306.7873

ET-4



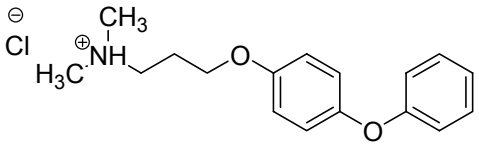
$C_{17}H_{21}ClN_2O_2$
Mol. Wt.: 320.8138

ET-5



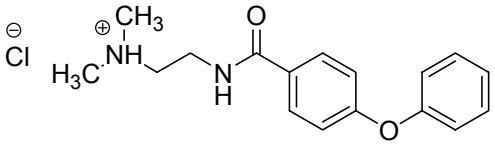
$C_{18}H_{23}ClN_2O_2$
Mol. Wt.: 334.8404

ET-6



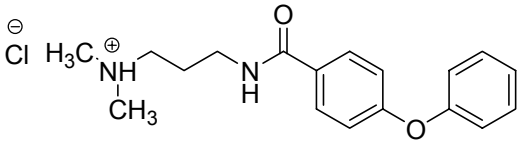
$C_{17}H_{22}ClNO_2$
Mol. Wt.: 307.8151

ET-7



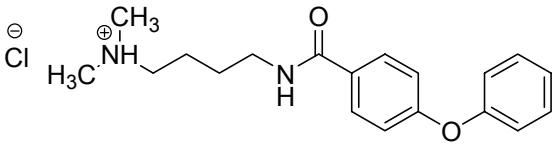
$C_{17}H_{21}ClN_2O_2$
Mol. Wt.: 320.8138

ET-8



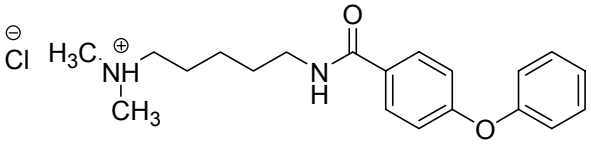
$C_{18}H_{23}ClN_2O_2$
Mol. Wt.: 334.8404

ET-9



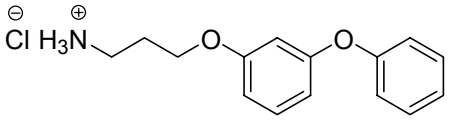
$C_{19}H_{25}ClN_2O_2$
Mol. Wt.: 348.867

ET-10



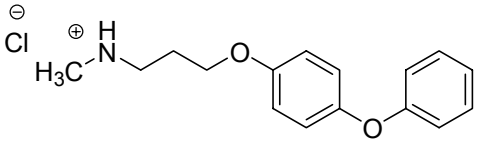
$C_{20}H_{27}ClN_2O_2$
Mol. Wt.: 362.8936

ET-11



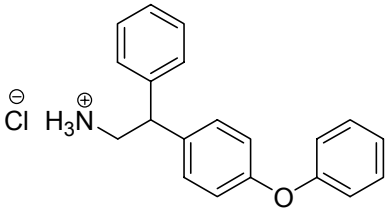
$C_{15}H_{18}ClNO_2$
Mol. Wt.: 279.7619

ET-12



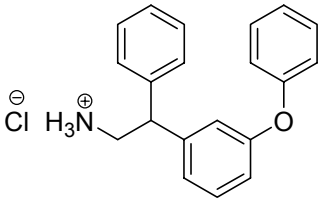
$C_{16}H_{19}ClNO_2$
Mol. Wt.: 292.7806

ET-13



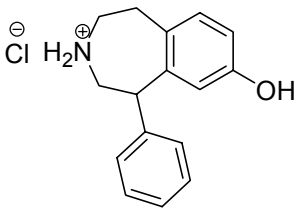
$C_{20}H_{20}ClNO$
Mol. Wt.: 325.8319

ET-14

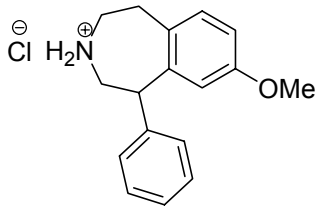
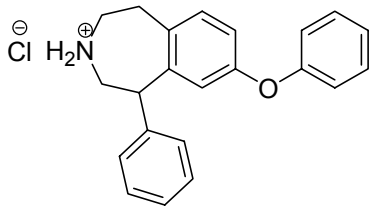
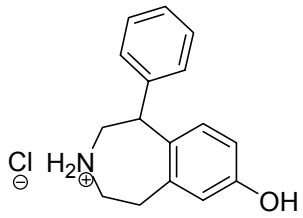
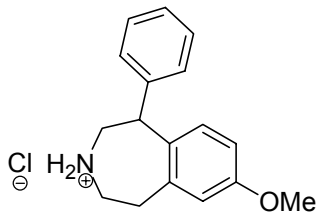
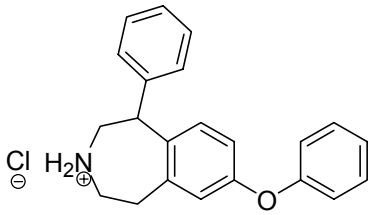
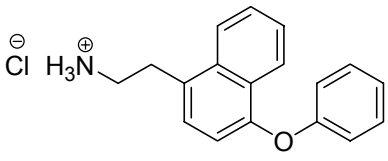


$C_{20}H_{20}ClNO$
Mol. Wt.: 325.8319

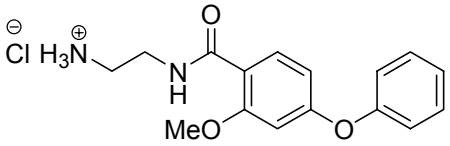
ET-15



$C_{16}H_{18}ClNO$
Mol. Wt.: 275.7732

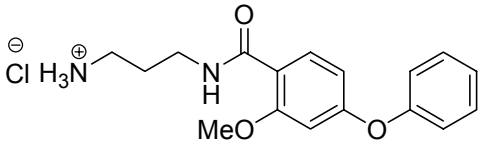
ET-16		$C_{17}H_{20}ClNO$ Mol. Wt.: 289.7998
ET-17		$C_{22}H_{22}ClNO$ Mol. Wt.: 351.8692
ET-18		$C_{16}H_{18}ClNO$ Mol. Wt.: 275.7732
ET-19		$C_{17}H_{20}ClNO$ Mol. Wt.: 289.7998
ET-20		$C_{22}H_{22}ClNO$ Mol. Wt.: 351.8692
ET-21		$C_{18}H_{18}ClNO$ Mol. Wt.: 299.7946

ET-22



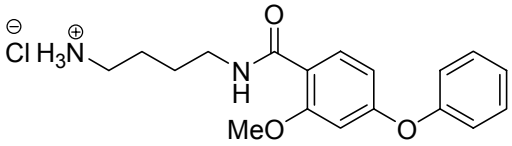
$C_{16}H_{19}ClN_2O_3$
Mol. Wt.: 322.7867

ET-23



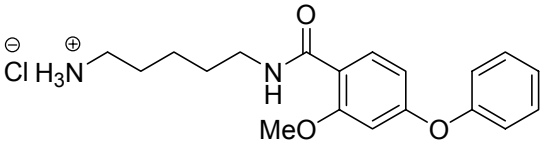
$C_{17}H_{21}ClN_2O_3$
Mol. Wt.: 336.8132

ET-24



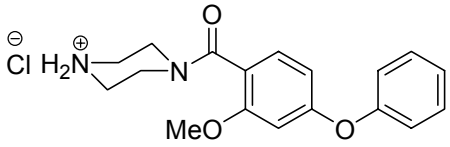
$C_{18}H_{23}ClN_2O_3$
Mol. Wt.: 350.8398

ET-25



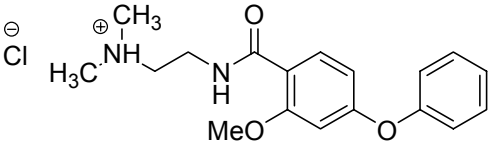
$C_{19}H_{25}ClN_2O_3$
Mol. Wt.: 364.8664

ET-26



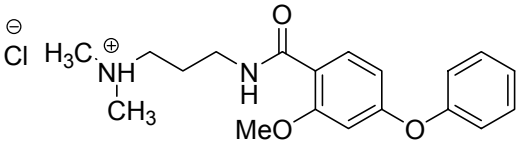
$C_{18}H_{21}ClN_2O_3$
Mol. Wt.: 348.8239

ET-27



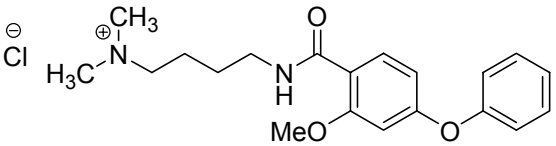
$C_{18}H_{23}ClN_2O_3$
Mol. Wt.: 350.8398

ET-28

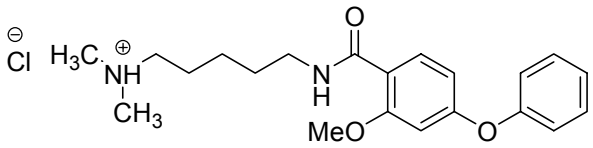
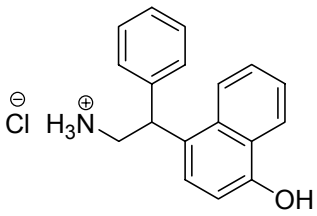
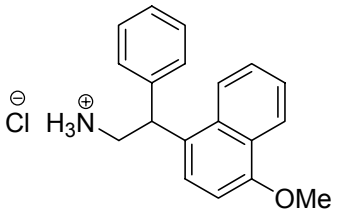
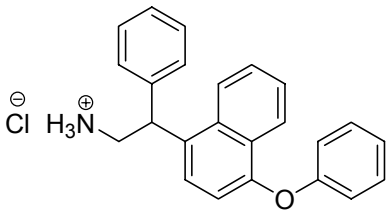
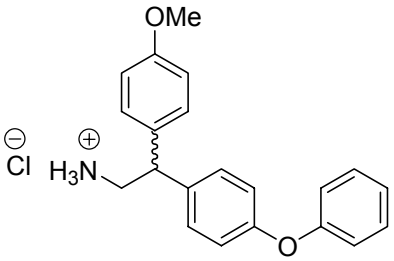
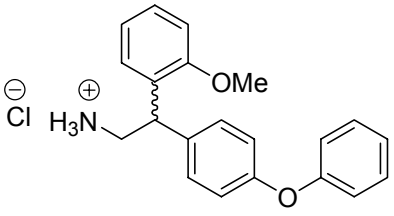


$C_{19}H_{25}ClN_2O_3$
Mol. Wt.: 364.8664

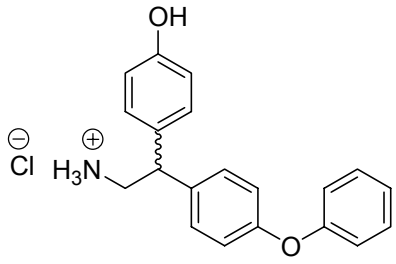
ET-29



$C_{20}H_{26}ClN_2O_3$
Mol. Wt.: 377.885

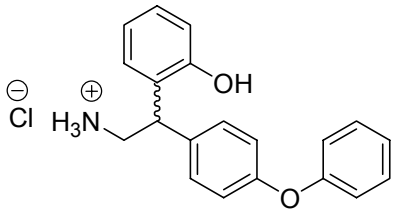
ET-30		$C_{21}H_{29}ClN_2O_3$ Mol. Wt.: 392.9196
ET-31		$C_{18}H_{18}ClNO$ Mol. Wt.: 299.7946
ET-32		$C_{19}H_{20}ClNO$ Mol. Wt.: 313.8212
ET-33		$C_{24}H_{22}ClNO$ Mol. Wt.: 375.8906
ET-34		$C_{21}H_{22}ClNO_2$ Mol. Wt.: 355.8579
ET-35		$C_{21}H_{22}ClNO_2$ Mol. Wt.: 355.8579

ET-36



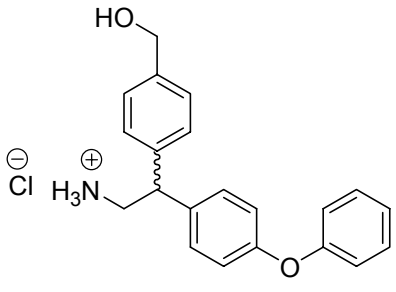
$C_{20}H_{20}ClNO_2$
Mol. Wt.: 341.8313

ET-37



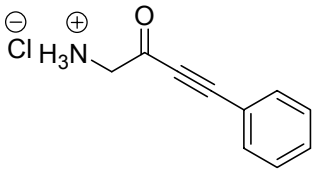
$C_{20}H_{20}ClNO_2$
Mol. Wt.: 341.8313

ET-38



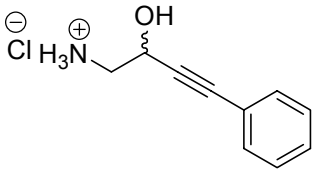
$C_{21}H_{22}ClNO_2$
Mol. Wt.: 355.8579

ET-39



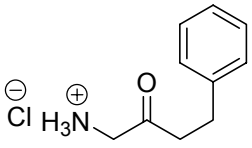
$C_{10}H_{10}ClNO$
Mol. Wt.: 195.6455

ET-40



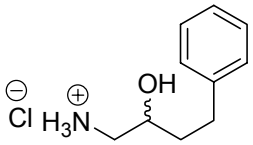
$C_{10}H_{12}ClNO$
Mol. Wt.: 197.6614

ET-41



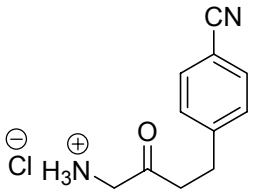
$C_{10}H_{14}ClNO$
Mol. Wt.: 199.6773

ET-42



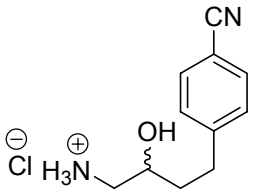
$C_{10}H_{16}ClNO$
Mol. Wt.: 201.6931

ET-43



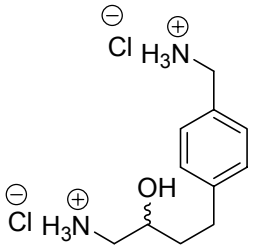
$C_{11}H_{13}ClN_2O$
Mol. Wt.: 224.6867

ET-44



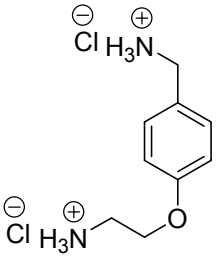
$C_{11}H_{15}ClN_2O$
Mol. Wt.: 226.7026

ET-45



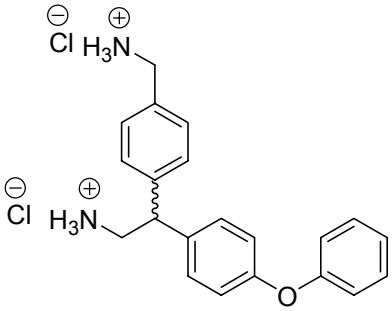
$C_{11}H_{20}Cl_2N_2O$
Mol. Wt.: 267.1953

ET-46

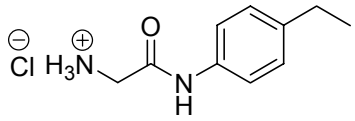
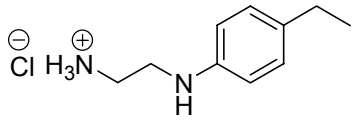
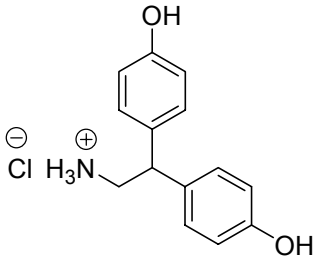
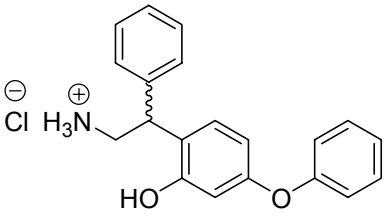
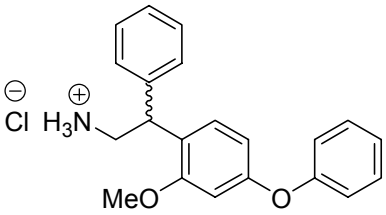
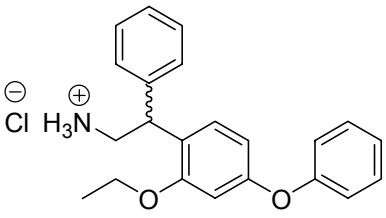


$C_9H_{16}Cl_2N_2O$
Mol. Wt.: 239.1421

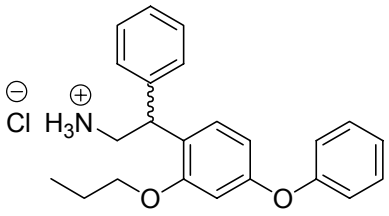
ET-47



$C_{21}H_{24}Cl_2N_2O$
Mol. Wt.: 391.3341

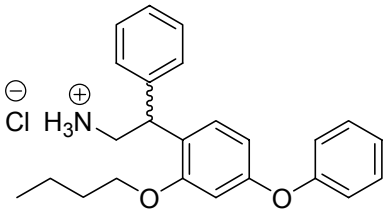
ET-48		$C_{10}H_{15}ClN_2O$ Mol. Wt.: 214.6919
ET-49		$C_{10}H_{17}ClN_2$ Mol. Wt.: 200.7084
ET-50		$C_{14}H_{16}ClNO_2$ Mol. Wt.: 265.7353
ET-51		$C_{20}H_{20}ClNO_2$ Mol. Wt.: 341.8313
ET-52		$C_{21}H_{22}ClNO_2$ Mol. Wt.: 355.8579
ET-53		$C_{22}H_{24}ClNO_2$ Mol. Wt.: 369.8845

ET-54



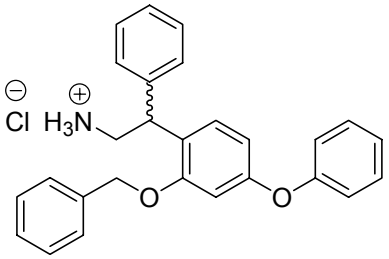
$C_{23}H_{26}ClNO_2$
Mol. Wt.: 383.911

ET-55



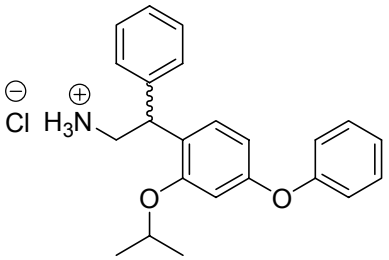
$C_{24}H_{28}ClNO_2$
Mol. Wt.: 397.9376

ET-56



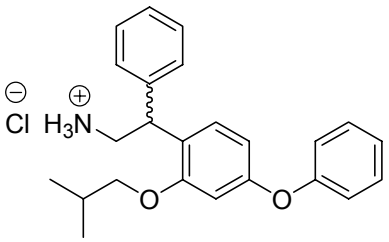
$C_{27}H_{26}ClNO_2$
Mol. Wt.: 431.9538

ET-57



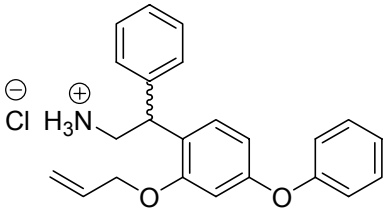
$C_{23}H_{26}ClNO_2$
Mol. Wt.: 383.911

ET-58



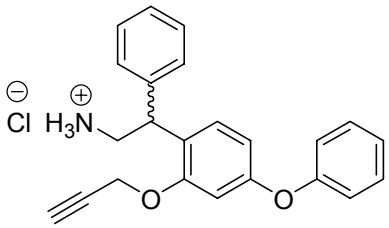
$C_{24}H_{28}ClNO_2$
Mol. Wt.: 397.9376

ET-59



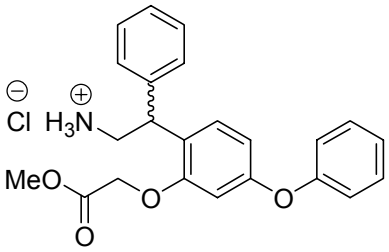
$C_{23}H_{24}ClNO_2$
Mol. Wt.: 381.8952

ET-60



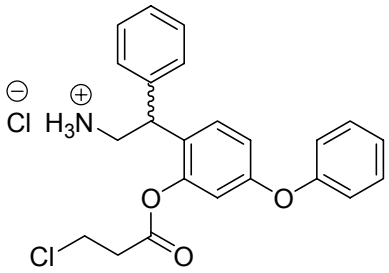
$C_{23}H_{22}ClNO_2$
Mol. Wt.: 379.8793

ET-61



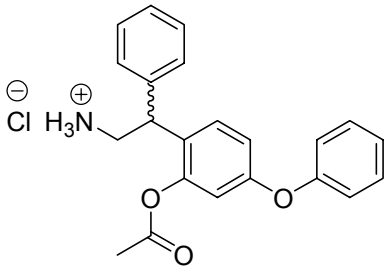
$C_{23}H_{24}ClNO_4$
Mol. Wt.: 413.894

ET-62



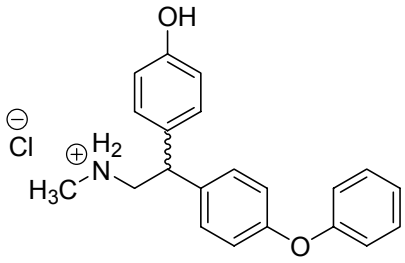
$C_{23}H_{23}Cl_2NO_3$
Mol. Wt.: 432.3396

ET-63



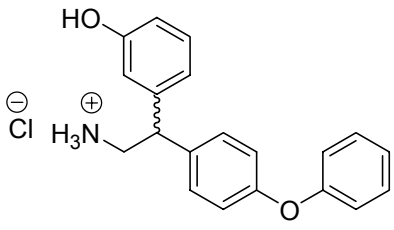
$C_{22}H_{22}ClNO_3$
Mol. Wt.: 383.868

ET-64



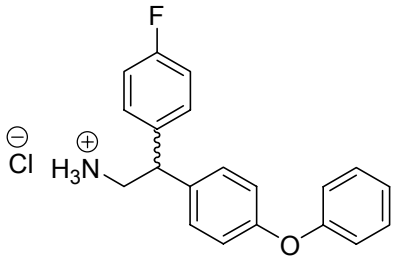
$C_{21}H_{22}ClNO_2$
Mol. Wt.: 355.8579

ET-65



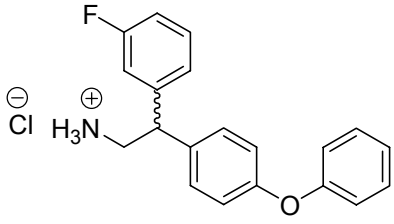
$C_{20}H_{20}ClNO_2$
Mol. Wt.: 341.8313

ET-66



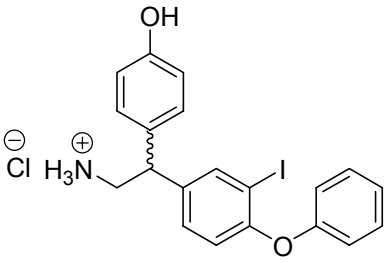
$C_{20}H_{19}ClFNO$
Mol. Wt.: 343.8224

ET-67



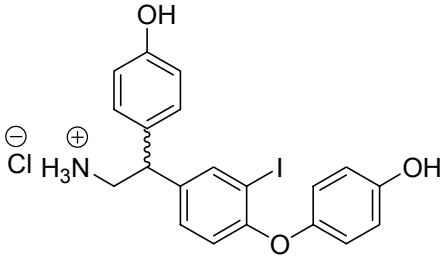
$C_{20}H_{19}ClFNO$
Mol. Wt.: 343.8224

ET-68



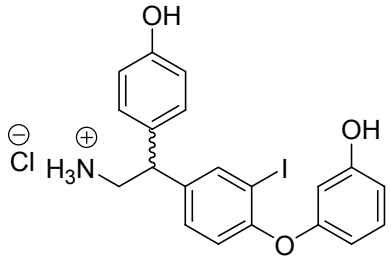
$C_{20}H_{19}ClINO_2$
Mol. Wt.: 467.7278

ET-69



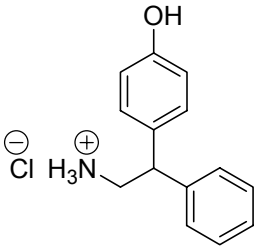
$C_{20}H_{19}ClINO_3$
Mol. Wt.: 483.7272

ET-70



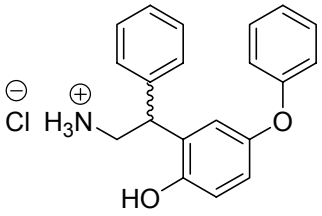
$C_{20}H_{19}ClINO_3$
Mol. Wt.: 483.7272

ET-71



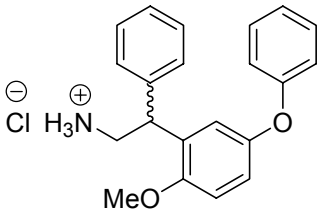
$C_{14}H_{16}ClNO$
Mol. Wt.: 249.7359

ET-72



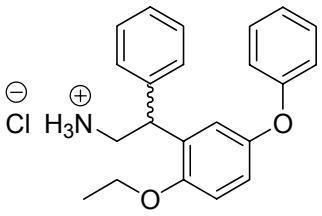
$C_{20}H_{20}ClNO_2$
Mol. Wt.: 341.8313

ET-73



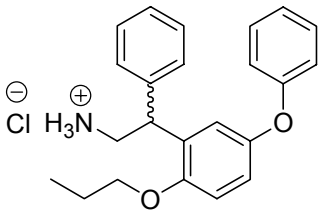
$C_{21}H_{22}ClNO_2$
Mol. Wt.: 355.8579

ET-74

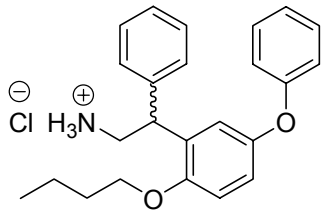
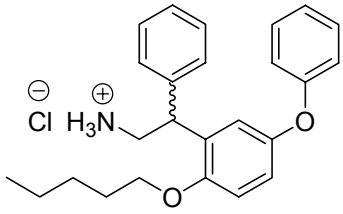
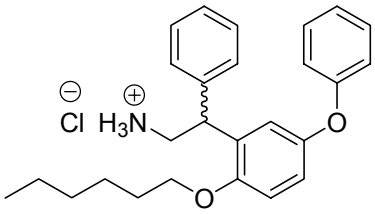
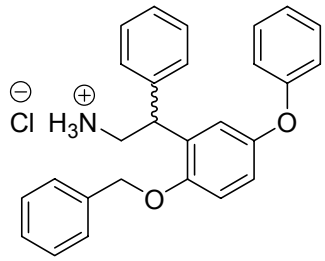
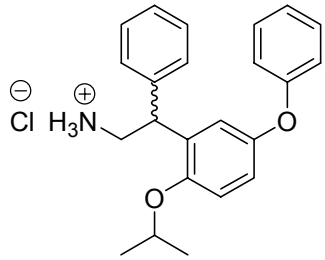
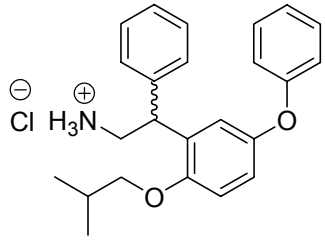


$C_{22}H_{24}ClNO_2$
Mol. Wt.: 369.8845

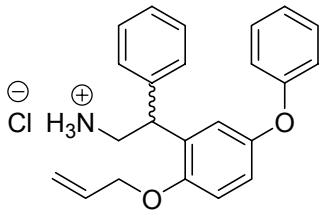
ET-75



$C_{23}H_{26}ClNO_2$
Mol. Wt.: 383.911

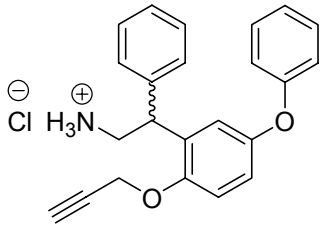
ET-76		$C_{24}H_{28}ClNO_2$ Mol. Wt.: 397.9376
ET-77		$C_{25}H_{30}ClNO_2$ Mol. Wt.: 411.9642
ET-78		$C_{26}H_{32}ClNO_2$ Mol. Wt.: 425.9908
ET-79		$C_{27}H_{26}ClNO_2$ Mol. Wt.: 431.9538
ET-80		$C_{23}H_{26}ClNO_2$ Mol. Wt.: 383.911
ET-81		$C_{24}H_{28}ClNO_2$ Mol. Wt.: 397.9376

ET-82



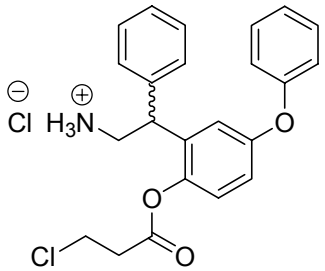
$C_{23}H_{24}ClNO_2$
Mol. Wt.: 381.8952

ET-83



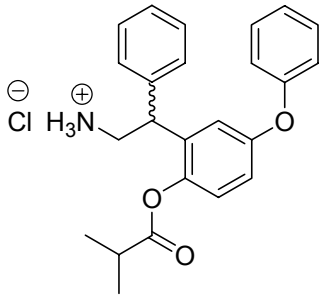
$C_{23}H_{22}ClNO_2$
Mol. Wt.: 379.8793

ET-84



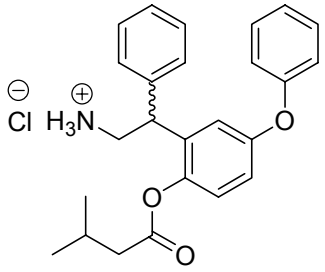
$C_{23}H_{23}Cl_2NO_3$
Mol. Wt.: 432.3396

ET-85

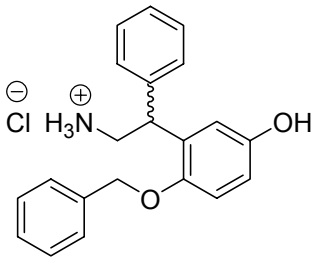
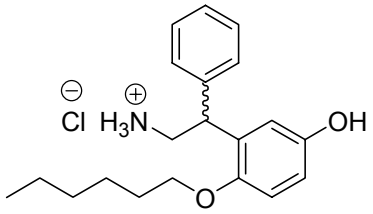
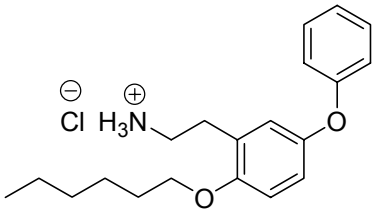
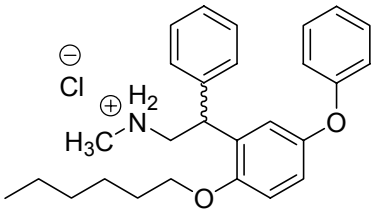
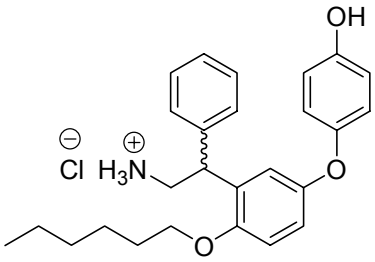
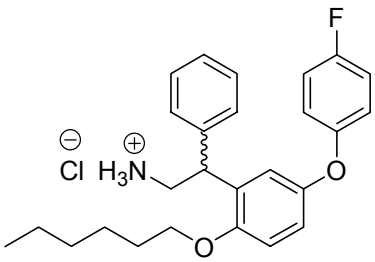


$C_{24}H_{26}ClNO_3$
Mol. Wt.: 411.9211

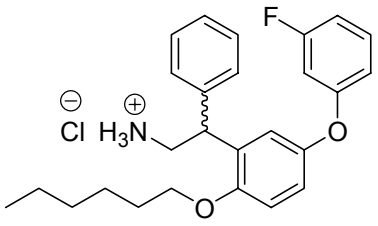
ET-86



$C_{25}H_{28}ClNO_3$
Mol. Wt.: 425.9477

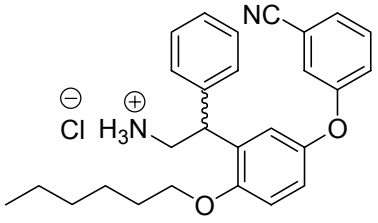
ET-87		$C_{21}H_{22}ClNO_2$ Mol. Wt.: 355.8579
ET-88		$C_{20}H_{28}ClNO_2$ Mol. Wt.: 349.8948
ET-89		$C_{20}H_{28}ClNO_2$ Mol. Wt.: 349.8948
ET-90		$C_{27}H_{34}ClNO_2$ Mol. Wt.: 440.0174
ET-91		$C_{26}H_{32}ClNO_3$ Mol. Wt.: 441.9902
ET-92		$C_{26}H_{31}ClFNO_2$ Mol. Wt.: 443.9812

ET-93



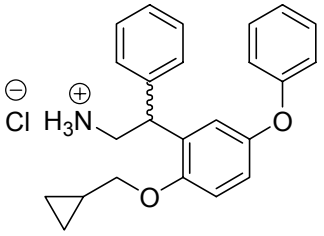
$C_{26}H_{31}ClFNO_2$
Mol. Wt.: 443.9812

ET-94



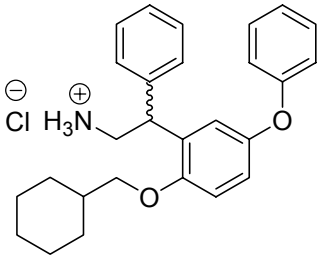
$C_{27}H_{31}ClN_2O_2$
Mol. Wt.: 451.0002

ET-95



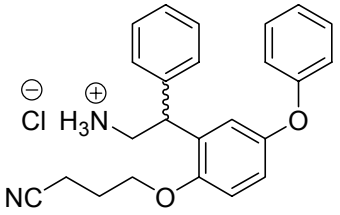
$C_{24}H_{26}ClNO_2$
Mol. Wt.: 395.9217

ET-96



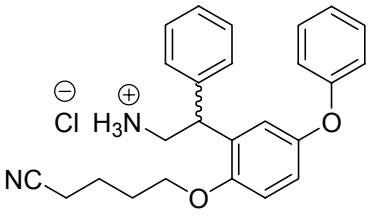
$C_{27}H_{32}ClNO_2$
Mol. Wt.: 438.0015

ET-97



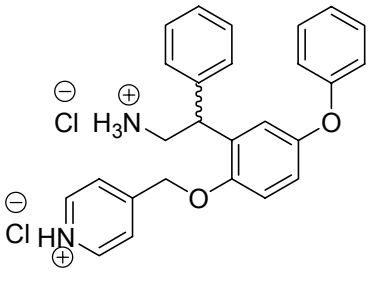
$C_{24}H_{25}ClN_2O_2$
Mol. Wt.: 408.9205

ET-98



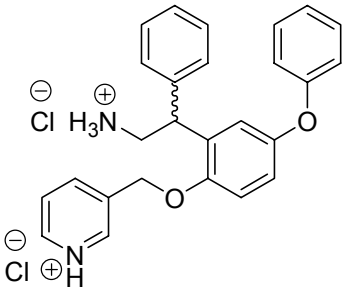
$C_{25}H_{27}ClN_2O_2$
Mol. Wt.: 422.9471

ET-99



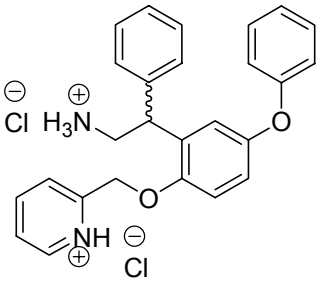
$C_{26}H_{26}Cl_2N_2O_2$
Mol. Wt.: 469.4028

ET-100



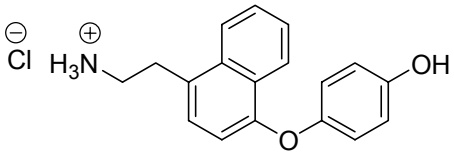
$C_{26}H_{26}Cl_2N_2O_2$
Mol. Wt.: 469.4028

ET-101



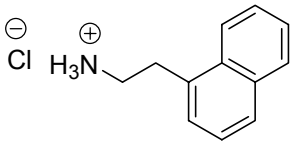
$C_{26}H_{26}Cl_2N_2O_2$
Mol. Wt.: 469.4028

ET-102



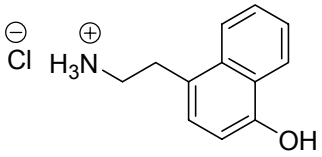
$C_{18}H_{18}ClNO_2$
Mol. Wt.: 315.794

1-NEA



$C_{12}H_{14}ClN$
Mol. Wt.: 207.6993

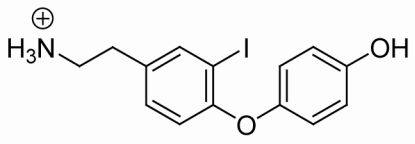
4-OH-NEA



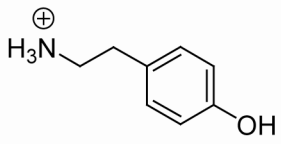
$C_{12}H_{14}ClNO$
Mol. Wt.: 223.6987

C.2 Summary of $TAAR_1$ Activity

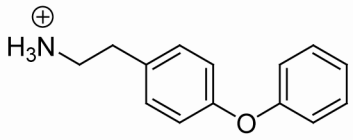
Table C1. Agonist activity of **T_1AM**, **PTA**, **Tyramine**, and **PEA** on $rTAAR_1$ and $mTAAR_1$



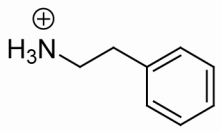
T_1AM



Tyramine



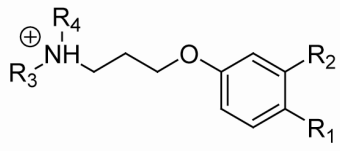
PTA



PEA

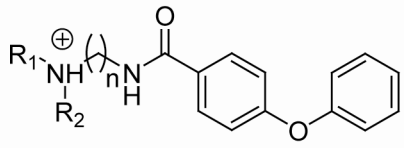
Compd	$rTAAR_1$			$mTAAR_1$		
	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
T_1AM	33 ± 3	100 ± 0	5	314 ± 43	100 ± 0	5
PTA	63 ± 7	93 ± 4	3	420 ± 66	85 ± 4	3
Tyramine	65 ± 1	119 ± 7	3	271 ± 52	110 ± 2	3
PEA	152 ± 13	121 ± 5	2	60	107	1

Table C2. Agonist activity of Aryloxypropanolamines on $rTAAR_1$ and $mTAAR_1$



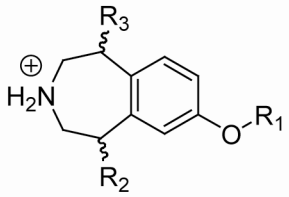
Compd	R_1	R_2	R_3	R_4	$rTAAR_1$			$mTAAR_1$		
					EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-1	OPh	H	H	H	758 ± 104	80 ± 3	2	433 ± 154	92 ± 2	2
ET-6	OPh	H	CH_3	CH_3	>1000	36 ± 6	2	463 ± 173	62 ± 2	2
ET-11	H	OPh	H	H	373 ± 9	90 ± 7	2	885 ± 549	78 ± 13	2
ET-12	OPh	H	CH_3	H	370 ± 70	46 ± 12	2	66 ± 12	113 ± 2	3

Table C3. Agonist activity of Benzamidoalkylamines on rTAAR$_1$ and mTAAR$_1$



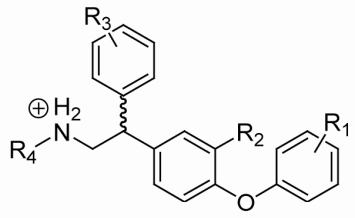
Compd	n	R_1	R_2	rTAAR$_1$			mTAAR$_1$		
				EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-2	2	H	H	>1000	4 ± 2	2	>1000	17 ± 5	2
ET-3	3	H	H	>1000	2 ± 1	2	>1000	2 ± 1	2
ET-4	4	H	H	>1000	31 ± 2	2	>1000	1 ± 1	2
ET-5	5	H	H	>1000	69 ± 7	2	905 ± 261	96 ± 5	2
ET-7	2	CH_3	CH_3	>1000	5 ± 4	2	>1000	7 ± 2	2
ET-8	3	CH_3	CH_3	>1000	2 ± 4	2	>1000	0 ± 2	2
ET-9	4	CH_3	CH_3	>1000	1 ± 4	2	>1000	3 ± 1	2
ET-10	5	CH_3	CH_3	>1000	44 ± 8	2	109 ± 6	82 ± 4	3

Table C4. Agonist activity of Tetrahydrobenzazepines on rTAAR$_1$ and mTAAR$_1$



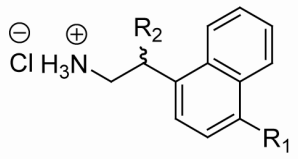
Compd	R_1	R_2	R_3	rTAAR$_1$			mTAAR$_1$		
				EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-15	OH	Ph	H	>1000	64 ± 7	2	>1000	51 ± 4	2
ET-16	OMe	Ph	H	561 ± 45	29 ± 9	2	>1000	79 ± 1	2
ET-17	OPh	Ph	H	>1000	32 ± 8	2	>1000	22 ± 3	2
ET-18	OH	H	Ph	>1000	24 ± 7	2	>1000	41 ± 2	2
ET-19	OMe	H	Ph	>1000	31 ± 4	2	>1000	31 ± 1	2
ET-20	OPh	H	Ph	>1000	86 ± 2	2	>1000	45 ± 5	2

Table C5. Agonist activity of β-Phenylphenoxyphenethylamines on rTAAR$_1$ and mTAAR$_1$



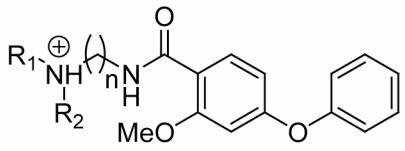
Compd	R_1	R_2	R_3	R_4	rTAAR$_1$			mTAAR$_1$		
					EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-13	H	H	H	H	28 ± 2	103 ± 4	3	>1000	35 ± 8	3
ET-34	H	H	*p*-OMe	H	142 ± 40	68 ± 8	3	>1000	31	1
ET-35	H	H	*o*-OMe	H	163 ± 18	84 ± 2	3	>1000	4	1
ET-36	H	H	*p*-OH	H	6 ± 1	114 ± 9	4	>1000	62 ± 6	3
ET-37	H	H	*o*-OH	H	467 ± 107	70 ± 6	3	>1000	2	1
ET-38	H	H	CH_2OH	H	728 ± 88	98 ± 2	3	>1000	1	1
ET-47	H	H	CH_2NH_3	H	>1000	25 ± 12	2	>1000	0	1
ET-64	H	H	*p*-OH	Me	5 ± 1	127 ± 2	4	>1000	42 ± 1	2
ET-65	H	H	*m*-OH	H	212 ± 39	106 ± 7	3	>1000	8	1
ET-66	H	H	*p*-F	H	28 ± 6	99 ± 9	3	>1000	29	1
ET-67	H	H	*m*-F	H	57 ± 6	110 ± 7	3	>1000	56	1
ET-68	H	I	*p*-OH	H	17 ± 2	107 ± 8	4	>1000	43	1
ET-69	*p*-OH	I	*p*-OH	H	4 ± 1	115 ± 2	6	>1000	34 ± 5	3
ET-70	*m*-OH	I	*p*-OH	H	22 ± 2	111 ± 9	4	>1000	6	1

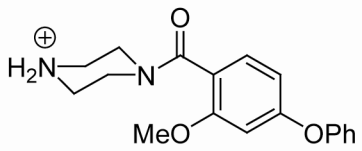
Table C6. Agonist activity of Naphethylamines on rTAAR$_1$ and mTAAR$_1$



Compd	R_1	R_2	rTAAR$_1$			mTAAR$_1$		
			EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-21	OPh	H	26 ± 1	113 ± 5	3	100 ± 22	104 ± 3	3
ET-31	OH	Ph	716 ± 269	89 ± 3	2	>1000	14 ± 4	2
ET-32	OMe	Ph	270 ± 66	71 ± 4	2	>1000	14 ± 4	2
ET-33	OPh	Ph	52 ± 4	100 ± 6	3	>1000	0 ± 2	2
ET-102	OPh-(*p*-OH)	H	19 ± 3	96 ± 2	3	171 ± 13	98 ± 1	2
1-NEA	H	H	65 ± 6	115 ± 2	2	82 ± 17	112 ± 3	2
4-OH-NEA	OH	H	46 ± 6	111 ± 5	3	649 ± 71	109 ± 2	2

Table C7. Agonist activity of Orthopramide-alkylamines on rTAAR$_1$ and mTAAR$_1$

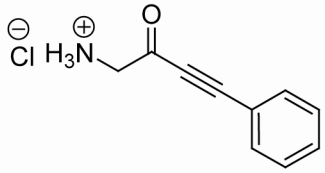




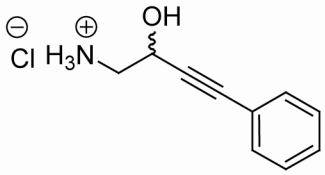
ET-26

Compd	n	R_1	R_2	rTAAR$_1$			mTAAR$_1$		
				EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-22	2	H	H	>1000	25 ± 4	2	>1000	36 ± 2	2
ET-23	3	H	H	>1000	5 ± 2	2	>1000	6 ± 1	2
ET-24	4	H	H	>1000	8 ± 2	2	>1000	2 ± 0	2
ET-25	5	H	H	>1000	12 ± 6	2	>1000	6 ± 1	2
ET-26	-	-	-	>1000	5 ± 8	2	>1000	0 ± 2	2
ET-27	2	CH_3	CH_3	>1000	4 ± 3	2	>1000	12 ± 4	2
ET-28	3	CH_3	CH_3	>1000	6 ± 7	2	>1000	0 ± 1	2
ET-29	4	CH_3	CH_3	>1000	0 ± 1	2	>1000	0 ± 1	2
ET-30	5	CH_3	CH_3	>1000	9 ± 2	2	>1000	43 ± 6	2

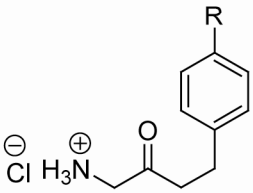
Table C8. Agonist activity of **ET-39-ET-46**, **ET-48** and **ET-49** on rTAAR$_1$ and mTAAR$_1$



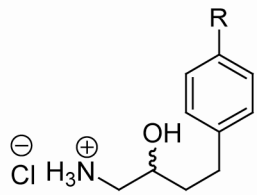
ET-39



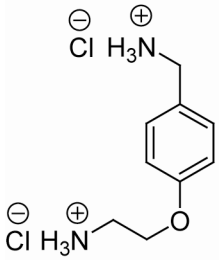
ET-40



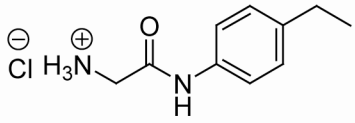
Compound	R
ET-41	H
ET-43	CN



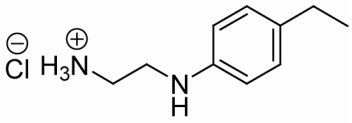
Compound	R
ET-42	H
ET-44	CN
ET-45	CH_2NH_3



ET-46



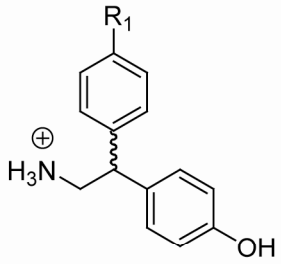
ET-48



ET-49

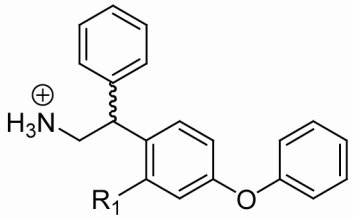
Compd	rTAAR$_1$			mTAAR$_1$		
	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-39	>1000	34 ± 12	2	>1000	10	1
ET-40	>1000	48 ± 13	2	>1000	20	1
ET-41	>1000	15	1	>1000	42	1
ET-42	>1000	70 ± 11	2	>1000	71	1
ET-43	>1000	3	1	>1000	0	1
ET-44	>1000	8	1	>1000	0	1
ET-45	>1000	7	1	>1000	0	1
ET-46	>1000	11	1	>1000	0	1
ET-48	>1000	15	1	>1000	0	1
ET-49	>1000	91	1	>1000	35	1

Table C9. Agonist activity of **ET-50** and **ET-71** on rTAAR$_1$ and mTAAR$_1$



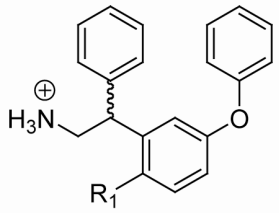
Compd	R_1	rTAAR$_1$			mTAAR$_1$		
		EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-50	OH	115 ± 12	105 ± 5	3	>1000	72	1
ET-71	H	78 ± 9	122 ± 16	3	>1000	49	1

Table C10. Agonist activity of **ET-13** position 2 analogs on rTAAR$_1$ and mTAAR$_1$



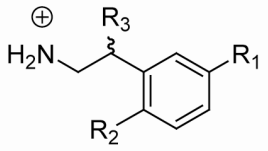
Compd	R_1	rTAAR$_1$			mTAAR$_1$		
		EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-51	OH	96 ± 10	108 ± 1	3	>1000	11	1
ET-52	OMe	35 ± 4	82 ± 8	3	>1000	1	1
ET-53	OEt	144 ± 31	95 ± 5	3	>1000	7	1
ET-54	OPr	>1000	69 ± 5	2	>1000	0	1
ET-55	OBu	>1000	31 ± 1	2	>1000	1	1
ET-56	OBn	>1000	58 ± 2	2	>1000	0	1
ET-57	O-*i*Pr	>1000	62 ± 2	2	>1000	3	1
ET-58	O-*i*Bu	>1000	15 ± 4	2	>1000	0	1
ET-59	OCH_2CHCH_2	169 ± 6	71 ± 4	2	>1000	2	1
ET-60	OCH_2CCH	138 ± 37	78 ± 1	2	>1000	11	1
ET-61	$OCH_2CO_2CH_3$	>1000	56 ± 0	2	>1000	5	1
ET-62	$O_2CCH_2CH_2Cl$	143 ± 4	57 ± 5	2	>1000	1	1
ET-63	O_2CCH_3	234 ± 43	74 ± 3	2	>1000	4	1

Table C11. Agonist activity of **ET-14** position 2 analogs on rTAAR$_1$ and mTAAR$_1$



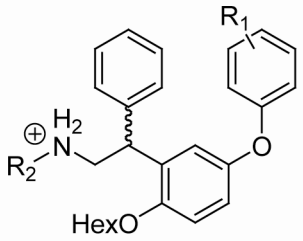
Compd	R_1	rTAAR$_1$			mTAAR$_1$		
		EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]	EC_{50}[a] ± SEM (nM)	E_{max}[b] ± SEM (%)	N[c]
ET-14	H	19 ± 2	131 ± 7	3	>1000	15 ± 4	3
ET-72	OH	232 ± 8	88 ± 9	2	>1000	1 ± 2	2
ET-73	OMe	102 ± 26	88 ± 1	3	>1000	2	1
ET-74	OEt	>1000	66 ± 3	2	>1000	0	1
ET-75	OPr	>1000	41 ± 0	2	>1000	0	1
ET-76	OBu	>1000	3 ± 0	2	>1000	0	1
ET-77	OPent	>1000	0 ± 3	2	>1000	0	1
ET-78	OHex	>1000	0 ± 1	2	>1000	0	1
ET-79	OBn	>1000	9 ± 1	2	>1000	0	1
ET-80	O-*i*Pr	>1000	40 ± 1	2	>1000	0	1
ET-81	O-*i*Bu	>1000	6 ± 1	2	>1000	0	1
ET-82	OCH_2CHCH_2	602 ± 10	79 ± 5	2	>1000	0	1
ET-83	OCH_2CCH	182 ± 46	103 ± 0	2	>1000	0	1
ET-84	$O_2CCH_2CH_2Cl$	>1000	50 ± 8	2	>1000	0	1
ET-85	$O_2CCH(CH_3)_2$	599 ± 165	53 ± 6	2	>1000	0	1
ET-86	$O_2CCH_2CH(CH_3)_2$	>1000	33 ± 7	2	>1000	0	1
ET-95	OCH_2-Cyclopropyl	>1000	26 ± 7	3	>1000	0	1
ET-96	OCH_2-Cyclohexyl	>1000	0 ± 3	2	>1000	0	1
ET-97	$OCH_2CH_2CH_2CN$	>1000	3 ± 4	2	>1000	1	1
ET-98	$OCH_2CH_2CH_2CH_2CN$	>1000	2 ± 2	2	>1000	0	1
ET-99	OCH_2-(4-Pyridinyl)	>1000	4 ± 2	2	>1000	0	1
ET-100	OCH_2-(3-Pyridinyl)	>1000	9 ± 0	2	>1000	0	1
ET-101	OCH_2-(2-Pyridinyl)	>1000	6 ± 1	2	>1000	0	1

Table C12. Agonist activity of β-phenyl and outer ring analogs of **ET-78** and **ET-79** on rTAAR$_1$ and mTAAR$_1$



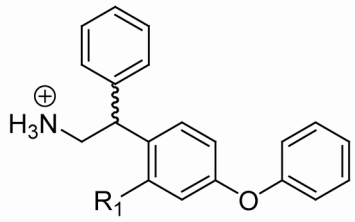
				rTAAR$_1$			mTAAR$_1$		
				EC_{50}[a]	E_{max}[b]		EC_{50}[a]	E_{max}[b]	
Compd	R_1	R_2	R_3	± SEM (nM)	± SEM (%)	N[c]	± SEM (nM)	± SEM (%)	N[c]
ET-87	OH	OBn	Ph	>1000	16 ± 3	2	>1000	0	1
ET-88	OH	OHex	Ph	>1000	37 ± 9	2	>1000	0	1
ET-89	OPh	OHex	H	201 ± 23	59 ± 6	2	>1000	0	1

Table C13. Agonist activity of **ET-78** analogs on rTAAR$_1$ and mTAAR$_1$



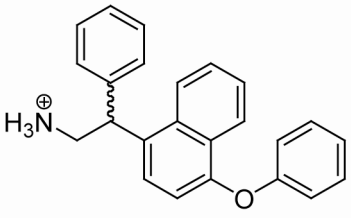
			rTAAR$_1$			mTAAR$_1$		
			EC_{50}[a]	E_{max}[b]		EC_{50}[a]	E_{max}[b]	
Compd	R_1	R_2	± SEM (nM)	± SEM (%)	N[c]	± SEM (nM)	± SEM (%)	N[c]
ET-90	H	CH_3	>1000	0 ± 3	2	>1000	0	1
ET-91	*p*-OH	H	>1000	16 ± 3	3	>1000	0	1
ET-92	*p*-F	H	>1000	0 ± 3	2	>1000	0	1
ET-93	*m*-F	H	>1000	0 ± 4	2	>1000	0	1
ET-94	*m*-CN	H	>1000	0 ± 4	2	>1000	0	1

Table C14. Antagonist activity of **ET-13** position 2 analogs on rTAAR$_1$ and mTAAR$_1$

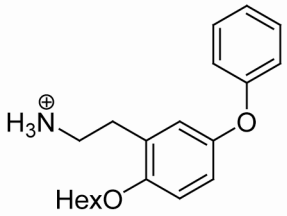


Compd	R_1	rTAAR$_1$			mTAAR$_1$			
		IC_{50}[d] ± SEM (μM)	I_{max}[e] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-53	OEt	-	-	-	>10	1	31	1
ET-54	OPr	-	-	-	>10	1	19	1
ET-56	OBn	-	-	-	>10	1	19 ± 2	2
ET-57	O-*i*Pr	-	-	-	>10	1	30	1
ET-58	O-*i*Bu	-	-	-	>10	1	18	1
ET-59	OCH_2CHCH_2	-	-	-	>10	1	17	1
ET-60	OCH_2CCH	-	-	-	>10	1	24	1
ET-62	$O_2CCH_2CH_2Cl$	-	-	-	>10	1	28	1

Table C15. Antagonist activity of **ET-33** and **ET-89** on rTAAR$_1$ and mTAAR$_1$



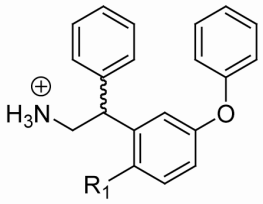
ET-33



ET-89

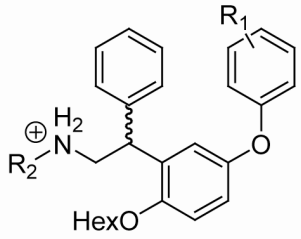
Compd	rTAAR$_1$			mTAAR$_1$			
	IC_{50}[d] ± SEM (μM)	I_{max}[e] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-33	-	-	-	7	1	26 ± 8	3
ET-89	-	-	-	8	1	23	2

Table C16. Antagonist activity of **ET-14** position 2 analogs on rTAAR$_1$ and mTAAR$_1$



Compd	R_1	rTAAR$_1$			mTAAR$_1$			
		IC_{50}[d] ± SEM (μM)	I_{max}[e] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-73	OMe	-	-	-	~10	1	12	1
ET-75	OPr	-	-	-	~10	1	14	1
ET-76	OBu	7 ± 1.9	12 ± 3	2	7	1	10 ± 5	2
ET-77	OPent	5 ± 0	6 ± 1	2	10	1	13 ± 11	2
ET-78	OHex	4 ± 0	3 ± 1	4	5 ± 0	2	7 ± 4	4
ET-79	OBn	5 ± 1	6 ± 3	2	8	1	14 ± 6	2
ET-80	O-*i*Pr	-	-	-	6	1	12 ± 7	2
ET-81	O-*i*Bu	>10	23 ± 6	2	8	1	11 ± 11	2
ET-82	OCH_2CHCH_2	-	-	-	3	1	7 ± 7	2
ET-83	OCH_2CCH	-	-	-	10	1	18 ± 10	2
ET-84	$O_2CCH_2CH_2Cl$	-	-	-	-	-	-	-
ET-85	$O_2CCH(CH_3)_2$	-	-	-	7	1	9 ± 9	2
ET-86	$O_2CCH_2CH(CH_3)_2$	-	-	-	4	1	3 ± 3	2
ET-95	OCH_2-Cyclopropyl	-	-	-	7	1	25 ± 3	2
ET-96	OCH_2-Cyclohexyl	5 ± 1	9 ± 1	3	6	1	18 ± 5	2
ET-97	$OCH_2CH_2CH_2CN$	>10	30 ± 2	3	>10	1	36 ± 5	2
ET-98	$OCH_2CH_2CH_2CH_2CN$	>10	23 ± 4	3	>10	1	29 ± 4	2
ET-99	OCH_2-(4-Pyridinyl)	7 ± 1	15 ± 2	3	>10	1	33 ± 4	2
ET-100	OCH_2-(3-Pyridinyl)	>10	33 ± 1	3	-	-	-	-
ET-101	OCH_2-(2-Pyridinyl)	7 ± 0	16 ± 2	3	8	1	21 ± 2	2

Table C17. Antagonist activity of **ET-78** analogs on rTAAR$_1$ and mTAAR$_1$



Compd	R_1	R_2	rTAAR$_1$			mTAAR$_1$			
			IC_{50}[d] ± SEM (μM)	I_{max}[e] ± SEM (%)	N[c]	IC_{50}[d] ± SEM (μM)	N[c]	I_{max}[e] ± SEM (%)	N[c]
ET-90	H	CH_3	5 ± 1	10 ± 4	3	6	1	24 ± 5	2
ET-92	*p*-F	H	3 ± 0	0 ± 3	3	7	1	8 ± 1	2
ET-93	*m*-F	H	3 ± 1	0 ± 5	3	6	1	9 ± 4	2
ET-94	*m*-CN	H	3 ± 1	2 ± 4	3	6	1	9 ± 3	2

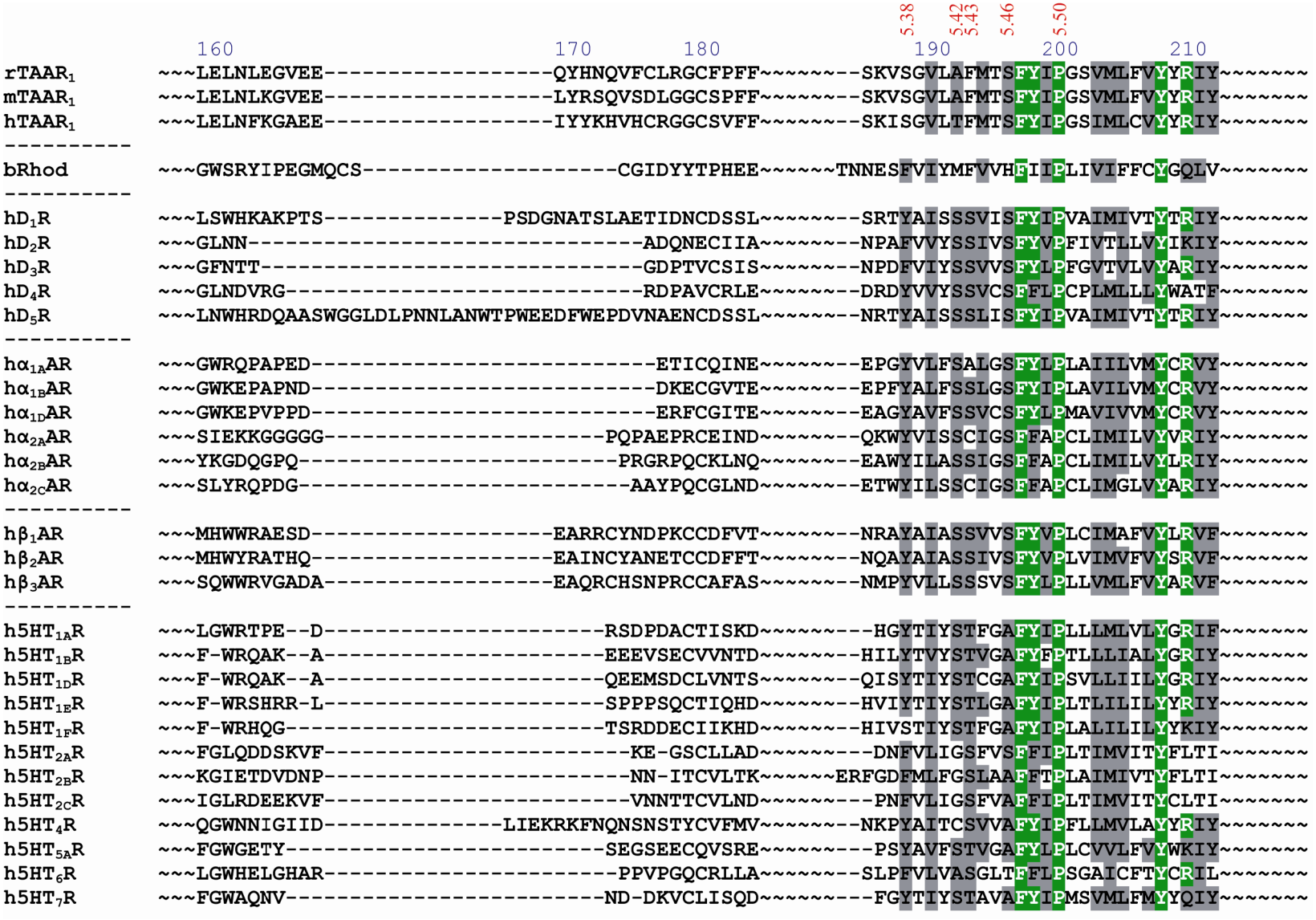
Appendix D

Sequence Alignment of Aminergic GPCRs

Sequence Alignment of Aminergic GPCRs

20
30
1.50
40
50
2.50
60
70
80
rTAAR1
mTAAR1
hTAAR1
bRhod
hD1R
hD2R
hD3R
hD4R
hD5R
hα1AAR
hα1BAR
hα1DAR
hα2AAR
hα2BAR
hα2CAR
hβ1AR
hβ2AR
hβ3AR
h5HT1AR
h5HT1BR
h5HT1DR
h5HT1ER
h5HT1FR
h5HT2AR
h5HT2BR
h5HT2CR
h5HT4R
h5HT5AR
h5HT6R
h5HT7R

rTAAR1
mTAAR1
hTAAR1
bRhod
hD1R
hD2R
hD3R
hD4R
hD5R
hα1AAR
hα1BAR
hα1DAR
hα2AAR
hα2BAR
hα2CAR
hβ1AR
hβ2AR
hβ3AR
h5HT1AR
h5HT1BR
h5HT1DR
h5HT1ER
h5HT1FR
h5HT2AR
h5HT2BR
h5HT2CR
h5HT4R
h5HT5AR
h5HT6R
h5HT7R
90
100
110
120
130
140
150
3.32
3.36
3.49
3.50
4.50
4.56


5.38
5.42
5.43
5.46
5.50
160
170
180
190
200
210
rTAAR1 ~~~LELNLEGVEE----------QYHNQVFCLRGCFPFF~~~~~~~~SKVSGVLAFMTSFYIPGSVMLFVYYRIY~~~~~~~~
mTAAR1 ~~~LELNLKGVEE----------LYRSQVSDLGGCSPFF~~~~~~~~SKVSGVLAFMTSFYIPGSVMLFVYYRIY~~~~~~~~
hTAAR1 ~~~LELNFKGAEE----------IYYKHVHCRGGCSVFF~~~~~~~~SKISGVLTFMTSFYIPGSIMLCVYYRIY~~~~~~~~
bRhod ~~~GWSRYIPEGMQCS----------CGIDYYTPHEE~~~~~~TNNESFVIYMFVVHFIIPLIVIFFCYGQLV~~~~~~~~
hD1R ~~~LSWHKAKPTS----------PSDGNATSLAETIDNCDSSL~~~~~~~~SRTYAISSSVISFYIPVAIMIVTYTRIY~~~~~~~~
hD2R ~~~GLNN----------ADQNECIIA~~~~~~~~NPAFVVYSSIVSFYVPFIVTLLVYIKIY~~~~~~~~
hD3R ~~~GFNTT----------GDPTVCSIS~~~~~~~~NPDFVIYSSVVSFYLPFGVTVLVYARIY~~~~~~~~
hD4R ~~~GLNDVRG----------RDPAVCRLE~~~~~~~~DRDYVVYSSVCSFFLPCPLMLLLYWATF~~~~~~~~
hD5R ~~~LNWHRDQAASWGGLDLPNNLANWTPWEEDFWEPDVNAENCDSSL~~~~~~~~NRTYAISSSLISFYIPVAIMIVTYTRIY~~~~~~~~
hα1AAR ~~~GWRQPAPED----------ETICQINE~~~~~~~~EPGYVLFSALGSFYLPLAIILVMYCRVY~~~~~~~~
hα1BAR ~~~GWKEPAPND----------DKECGVTE~~~~~~~~EPFYALFSSLGSFYIPLAVILVMYCRVY~~~~~~~~
hα1DAR ~~~GWKEPVPPD----------ERFCGITE~~~~~~~~EAGYAVFSSVCSFYLPMAVIVVMYCRVY~~~~~~~~
hα2AAR ~~~SIEKKGGGGG----------PQPAEPRCEIND~~~~~~~~QKWYVISSCIGSFFAPCLIMILVYVRIY~~~~~~~~
hα2BAR ~~~YKGDQGPQ----------PRGRPQCKLNQ~~~~~~~~EAWYILASSIGSFFAPCLIMILVYLRIY~~~~~~~~
hα2CAR ~~~SLYRQPDG----------AAYPQCGLND~~~~~~~~ETWYILSSCIGSFFAPCLIMGLVYARIY~~~~~~~~
hβ1AR ~~~MHWWRAESD----------EARRCYNDPKCCDFVT~~~~~~~~NRAYAIASSVVSFYVPLCIMAFVYLRVF~~~~~~~~
hβ2AR ~~~MHWYRATHQ----------EAINCYANETCCDFFT~~~~~~~~NQAYAIASSIVSFYVPLVIMVFVYSRVF~~~~~~~~
hβ3AR ~~~SQWWRVGADA----------EAQRCHSNPRCCAFAS~~~~~~~~NMPYVLLSSSVSFYLPLLVMLFVYARVF~~~~~~~~
h5HT1AR ~~~LGWRTPE--D----------RSDPDACTISKD~~~~~~~~HGYTIYSTFGAFYIPLLLMLVLYGRIF~~~~~~~~
h5HT1BR ~~~F-WRQAK--A----------EEEVSECVVNTD~~~~~~~~HILYTVYSTVGAFYFPTLLLIALYGRIY~~~~~~~~
h5HT1DR ~~~F-WRQAK--A----------QEEMSDCLVNTS~~~~~~~~QISYTIYSTCGAFYIPSVLLIILYGRIY~~~~~~~~
h5HT1ER ~~~F-WRSHRR-L----------SPPPSQCTIQHD~~~~~~~~HVIYTIYSTLGAFYIPLTLILILYYRIY~~~~~~~~
h5HT1FR ~~~F-WRHQG----------TSRDDECIIKHD~~~~~~~~HIVSTIYSTFGAFYIPLALILILYYKIY~~~~~~~~
h5HT2AR ~~~FGLQDDSKVF----------KE-GSCLLAD~~~~~~~~DNFVLIGSFVSFFIPLTIMVITYFLTI~~~~~~~~
h5HT2BR ~~~KGIETDVDNP----------NN-ITCVLTK~~~~~~ERFGDFMLFGSLAAFFTPLAIMIVTYFLTI~~~~~~~~
h5HT2CR ~~~IGLRDEEKVF----------VNNTTCVLND~~~~~~~~PNFVLIGSFVAFFIPLTIMVITYCLTI~~~~~~~~
h5HT4R ~~~QGWNNIGIID----------LIEKRKFNQNSNSTYCVFMV~~~~~~~~NKPYAITCSVVAFYIPFLLMVLAYYRIY~~~~~~~~
h5HT5AR ~~~FGWGETY----------SEGSEECQVSRE~~~~~~~~PSYAVFSTVGAFYLPLCVVLFVYWKIY~~~~~~~~
h5HT6R ~~~LGWHELGHAR----------PPVPGQCRLLA~~~~~~~~SLPFVLVASGLTFFLPSGAICFTYCRIL~~~~~~~~
h5HT7R ~~~FGWAQNV----------ND-DKVCLISQD~~~~~~~~FGYTIYSTAVAFYIPMSVMLFMYYQIY~~~~~~~~


220
rTAAR1 ~~FIAKGQARSINRA----------
mTAAR1 ~~FIAKGQARSINRT----------
hTAAR1 ~~LIAKEQARLISDA----------
bRhod ~~FTVKEAAAQQQES----------
hD1R ~~RIAQKQIRRIAAL----------
hD2R ~~IVLRRRRKRVNTKRSSRAFRAHLRAPLKGNCTH----------PEDMKLCTVIMKSNGSFPVNRRRVEAARRAQELEMEML
hD3R ~~VVLKQRRRKRILTRQNSQCNSVRPGFPQQTLSP----------
hD4R ~~RGLQRWEVARRAKLHGRAPRRPSGPGPPSPTPPAPRLPQDPCGPDCAPPAPGLPRGPCGPDCAPAAPGLPPDPCGPDCAPPAPGLPQD
hD5R ~~RIAQVQIRRISSLERAAEHAQSCRSSAACAPDT----------
hα1AAR ~~VVAKRESRGLKSGLKTDKSDSEQVTLRIHRKNA----------
hα1BAR ~~IVAKRTTKNLEAGVMKEMSNSKELTLRIHSKNF----------
hα1DAR ~~VVARSTTRSLEAGVKRERGKASEVVLRIHCRGA----------
hα2AAR ~~QIAKRRTRVPPSRRGPDAVAAPPGGTERRPNGLGPERSAGPGGAEAEPLPTQLNGAPGEPAPAGPRDTDALDLEESSSSDH-------
hα2BAR ~~LIAKRSNRRGPRAKGGPGQGESKQPRPDHGGALASAKLPALASVASAREVNGHSKSTGEKEEGETPEDTGTRALPPSWAAL---PNSG
hα2CAR ~~RVAKLRTRTLSEKRAPVGPDGASPTTENGLGAAAGAGENGHCAPPPADVEPDESSAAAERRRRRGALRRG----------
hβ1AR ~~REAQKQVKKIDSCERRFLGGPARPPSPSPSPVPAPAPPPGPPRP----------
hβ2AR ~~QEAKRQLQKIDKSEGRFHVQNLSQVEQ----------
hβ3AR ~~VVATRQLRLLRGELGRFPPEESPPAPS----------
h5HT1AR ~~RAARFRIRKTVKKVEKTGADTRHGASPAPQPKKSVN----------
h5HT1BR ~~VEARSRILKQTPNRTGKRLTRAQ----------
h5HT1DR ~~RAARNRILNPPSLYGKRFTTAH----------
h5HT1ER ~~HAAKSLYQKRGSSRHLSNRSTDSQ----------
h5HT1FR ~~RAAKTLYHKRQASRIAKEEVNGQ----------
h5HT2AR ~~KSLQKEATLCVSDLGTRAKLASFSFLP----------
h5HT2BR ~~HALQKKAYLVKNKPPQRLTWLTVSTVFQRDETPCSSPEKV----------
h5HT2CR ~~YVLRRQALMLLHGHTEEPPGLSLD--FLKCCKRNTAEE----------
h5HT4R ~~VTAKEHAHQIQMLQRAGASSESRPQS----------
h5HT5AR ~~KAAKFRVGSRKTN----------
h5HT6R ~~LAARKQAVQVASLTTGMASQASE----------
h5HT7R ~~KAARKSAAKHKFPGFPRVE----------


230
240
rTAAR1 ----------NLQVGLEGESRAPQS~~~~~~~
mTAAR1 ----------NVQVGLEGKSQAPQS~~~~~~~
hTAAR1 ----------NQKLQIGLEMKNGISQS~~~~~~~
bRhod ----------ATTQK~~~~~~~
hD1R ----------ERAAVHAKNCQTTTGNGKPVECSQPESSFKMSFK~~~~~~~
hD2R SSTSPPERTRYSPIPPSHHQLTLPDPSHHGLHSTPDSPAKPEKNGHAKDHPKIAKIFEIQTMPNGKTRTSLKTMSRR-KLSQQ~~~~~~~
hD3R ------DPAHLELKRYYSICQDTALGGPGFQERGGELKREEKTRNSLSPTIAPKLSLEVRKLSNGRLSTSLKLGPLQPRGVPL~~~~~~~
hD4R PCGPDCAPPAPGLPRGPCGPDCAPPAPGLPQDPCGPDCAPPAPGLPPDPCGSNCAPPDAVRAAALPPQTPPQTRRRRRAKITG~~~~~~~
hD5R ----------SLRASIK~~~~~~~
hα1AAR ----------PAGGSGMASAKTKTHFSVRLLKFS~~~~~~~
hα1BAR ----------HEDTLSSTKAKGHNPRSSIAVKLFKFS~~~~~~~
hα1DAR ----------ATGADGAHGMRSAKGHTFRSSLSVRLLKFS~~~~~~~
hα2AAR ----------AERPPGPRRPERGPRGKGKARASQVKPGDSLPRRGPGATGIGTPAAGPGEERVGAAKASRWRGRQN~~~~~~~
hα2BAR QGQKEGVCGASPEDEAEEEEEEEEEEECEPQAVPVSPASACSPPLQQPQGSRVLATLRGQVLLGRGVGAIGGQWWRRRAQLT~~~~~~~
hα2CAR ----------GRRRAGAEGGAGGADGQGAGPGAAESGALTASRSPGPGGRLSRASSRSVEFFLSRRRRARSSVCRRKVAQA~~~~~~~
hβ1AR ----------AAAAATAPLANGRAGKRRPSRLVAL~~~~~~~
hβ2AR ----------DGRTGHGLRRSSKFCL~~~~~~~
hβ3AR ----------RSLAPAPVGTCAPPEGVPACGRRPARLLPL~~~~~~~
h5HT1AR GESGSRNWRLGVESKAGGALCANGAVRQGDDGAALEVIEVHRVGNSKEHLPLPSEAGPTPCAPASFERKNERNAEAKRKMALA~~~~~~~
h5HT1BR ----------LITDSPGSTSSVTSINSRVPDVPSESGSPVYVNQVKVRVSDALLEKKKLMAA~~~~~~~
h5HT1DR ----------LITGSAGSSLCSLNSSLHEGHSHSAGSPLFFNHVKIKLADSALERKRISAA~~~~~~~
h5HT1ER ----------NSFASCKLTQTFCVSDFSTSDPTTEFEKFHASIRIPPFDNDLDHPGERQQISST~~~~~~~
h5HT1FR ----------VLLESGEKSTKSVSTSYVLEKSLSDPSTDFDKIHSTVRSLRSEFKHEKSWRRQKISGT~~~~~~~
h5HT2AR ----------QSSLSSEKLFQRSIHREPGSYTGRRTMQSIS~~~~~~~
h5HT2BR ----------AMLDGSRKDKALPNSGDETLMRRTSTIGKKSVQTIS~~~~~~~
h5HT2CR ----------ENSANPNQDQNARRRKKKERRPRGTMQAIN~~~~~~~
h5HT4R ----------ADQHSTHRMR~~~~~~~
h5HT5AR ----------SVSPISEAVEVKDSAKQPQMVFTVRHATVTFQPEGDTWREQ~~~~~~~
h5HT6R ----------TLQVPRTPRPGVE-SADSRRLATKHSR~~~~~~~
h5HT7R ----------PDSVIALNGIVKLQKEVEECANLSRLLKHERKNISIFK~~~~~~~

rTAAR1
mTAAR1
hTAAR1
bRhod
hD1R
hD2R
hD3R
hD4R
hD5R
hα1AAR
hα1BAR
hα1DAR
hα2AAR
hα2BAR
hα2CAR
hβ1AR
hβ2AR
hβ3AR
h5HT1AR
h5HT1BR
h5HT1DR
h5HT1ER
h5HT1FR
h5HT2AR
h5HT2BR
h5HT2CR
h5HT4R
h5HT5AR
h5HT6R
h5HT7R
250
260
270
280
290
300
310
6.30
6.48
6.50
6.52
6.55
6.58
7.35
7.39
7.39
7.39


320
330
rTAAR1 ~~~~~GKIFQKDSSRSKLFL----------
mTAAR1 ~~~~~GKIFQKDSSRSKLFL----------
hTAAR1 ~~~~~GKIFQKDSSRCKLFLELSS----------
bRhod ~~~~~CGKNPLGDDEASTTVSKTETSQVAPA----------
hD1R ~~~~~YRLCPATNNAIETVSINNNGAAMFSSHHEPRGSISKECNLVYLIPHAVGSSEDLKKEEAAGIARPLEKLSPALSVILDYDTDVSL
hD2R ~~~~~C----------
hD3R ~~~~~C----------
hD4R ~~~~~ACC----------
hD5R ~~~~~SHFCSRTPVETVNISNELISYNQDIVFHKEIAAAYIHMMPNAVTPGNREVDNDEEEGPFDRMFQIYQTSPDGDPVAESVWELDCE
hα1AAR ~~~~~IQCLCRKQSSKHALGYTLHPPSQAVEGQHKDMVRIPVGSRETFYRISKTDGVCEWKFFSSMPRGSARITVSKDQSSCTTARVRSK
hα1BAR ~~~~~CQCRGRRRRRRRRRRLGGCAYTYRPWTRGGSLERSQSRKDSLDDSGSCLSGSQRTLPSASPSPGYLGRGAPPPVELCAFPEWKAP
hα1DAR ~~~~~CQCRRRRRRRPLWRVYGHHWRASTSGLRQDCAPSSGDAPPGAPLALTALPDPDPEPPGTPEMQAPVASRRKPPSAFREWRLLGPF
hα2AAR ~~~~~RGDRKRIV----------
hα2BAR ~~~~~RPWTQTAW----------
hα2CAR ~~~~~RRRRRGFRQ----------
hβ1AR ~~~~~CARRAARRRHATHGDRPRASGCLARPGPPPSPGAASDDDDDDVVGATPPARLLEPWAGCNGGAAADSDSSLDEPCRPGFASESKV
hβ2AR ~~~~~LRRSSLKAYGNGYSSNGNTGEQSGYHVEQEKENKLLCEDLPGTEDFVGHQGTVPSDNIDSQGRNCSTNDSLL----------
hβ3AR ~~~~~RCGRRLPPEPCAAARPALFPSGVPAARSSPAQPRLCQRLDGASWGVS----------
h5HT1AR ~~~~~CKFCRQ----------
h5HT1BR ~~~~~FKCTS----------
h5HT1DR ~~~~~FRKAS----------
h5HT1ER ~~~~~CREHT----------
h5HT1FR ~~~~~CRC----------
h5HT2AR ~~~~~CQYKENKKPLQLILVNTIPALAYKSSQLQMGQKKNSKQDAKTTDNDCSMVALGKQHSEEASKDNSDGVNEKVSCV----------
h5HT2BR ~~~~~CNYRATKSVKTLRKRSSKIYFRNPMAENSKFFKKHGIRNGINPAMYQSPMRLRSSTIQSSSIILLDTLLLTENEGDKTEEQVSYV
h5HT2CR ~~~~~CNYKVEKKPPVRQIPRVAATALSGRELNVNIYRHTNEPVIEKASDNEPGIEMQVENLELPVNPSSVVSERISSV----------
h5HT4R ~~~~~CDDERYRRPSILGQTVPCSTTTINGSTHVLRDAVECGGQWESQCHPPATSPLVAAQPSDT----------
h5HT5AR ~~~~~RQH----------
h5HT6R ~~~~~CPRCPRERQASLASPSLRTSHSGPRPGLSLQQVLPLPLPPDSDSDSDAGSGGSSGLRLTAQLLLPGEATQDPPLPTRAAAAVNFF
h5HT7R ~~~~~CQYRNINRKLSAAGMHEALKLAERPERPEFVLRACTRRVLLRPEKRPPVSVWVLQSPDHHNWLADKMLTTVEKKVMIHD------

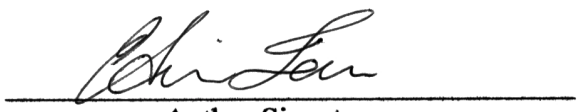

rTAAR1
mTAAR1
hTAAR1
bRhod
hD1R
EKIQPITQNGQHPT
hD2R
hD3R
hD4R
hD5R
GEISLDKITPFTPNGFH
hα1AAR
SFLQVCCCVGPSTPSLDKNHQVPTIKVHTISLSENGEEV
hα1BAR
GALLSLPAPEPPGRRGRHDSGPLFTFKLLTEPESPGTDGGASNGGCEAAADVANGQPGFKSNMPLAPGQF
hα1DAR
RRPTTQLRAKVSSLSHKIRAGGAQRAEAACAQRSEVEAVSLGVPHEVAEGATCQAYELADYSNLRETDI-
hα2AAR
hα2BAR
hα2CAR
hβ1AR
hβ2AR
hβ3AR
h5HT1AR
h5HT1BR
h5HT1DR
h5HT1ER
h5HT1FR
h5HT2AR
h5HT2BR
h5HT2CR
h5HT4R
h5HT5AR
h5HT6R
NIDPAEPELRPHPLGIPTN
h5HT7R

Publishing Agreement

It is the policy of the University to encourage the distribution of all theses and dissertations. Copies of all UCSF theses and dissertations will be routed to the library via the Graduate Division. The library will make all theses and dissertations accessible to the public and will preserve these to the best of their abilities, in perpetuity.

Please sign the following statement:

I hereby grant permission to the Graduate Division of the University of California, San Francisco to release copies of my thesis or dissertation to the Campus Library to provide access and preservation, in whole or in part, in perpetuity.



Author Signature

12-20-07

Date