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Fluoroaromatic fragments on 1,3-disubstituted ureas enhance soluble epoxide hydrolase inhibition

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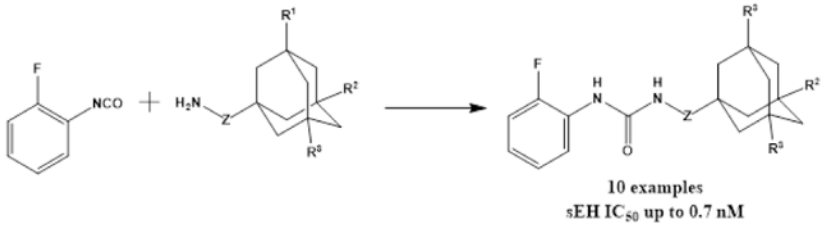
Abstract

A series of soluble epoxide hydrolase (sEH) inhibitors containing 2-fluorophenyl fragment was developed. Inhibition potency of the described compounds ranges from 0.7 to 630.9 nM. 1-(Adamantan-1-ylmethyl)-3-(2-fluorophenyl) urea (**3b**, IC_{50} = 0.7 nM) and 1-(adamantan-2-yl)-3-(2-fluorophenyl) urea (**3i**, IC_{50} =1.0 nM) were found to be the most potent sEH inhibitors within the described series. Crystal results suggest that potency is probably enhanced by extra hydrogen bond between the fluorine atom and catalytic tyrosine residues.

Graphical Abstract



Keywords

fluoroaromatics; soluble epoxide hydrolase; inhibitor; adamantane; urea

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1. Introduction

The mammalian soluble epoxide hydrolase (sEH) is an enzyme involved in the metabolism of epoxides of arachidonic acid and other natural epoxy-fatty acids,[1] which have numerous biological activities.[2] Through the addition of a water molecule, sEH converts epoxides into corresponding vicinal diols thus affecting inflammatory processes, pain and other disease states.[2] Thereby inhibition of sEH could be beneficial in treatment of many renal and cardiovascular diseases.[3,4] Although thousands of various sEH inhibitors were synthesized over the last few decades[5-7], they have limited bioavailability, especially toward the CNS where sEH is emerging as a potential target for neurological diseases.[8] Inhibitors of sEH containing fluorine atoms are among the most promising to go through the blood-brain-barrier.[9] Another structure fragment which is widely used in the design of sEH inhibitors is adamantane.[10,11] Herein, we decided to combine both adamantyl and fluoroaromatic fragments in a single molecule and test them as soluble epoxide hydrolase inhibitors, with physical properties that could allow to target sEH in the CNS.

2. Results and discussion

As a starting material we used 2-fluorophenyl isocyanate (**1**, Scheme 1) and various adamantyl amines **2a-j**. Starting amines **1a-h** have 1 to 3 methyl substituents in the bridgehead positions of adamantane or hydrocarbon spacers between adamantane and the amino group. In addition, the reactive amino groups of amines **2i** and **2j** are at the bridge position of adamantane.

Structures of the obtained chemicals were assessed by NMR, while purity was assessed by GC-MS, LC-MS and elemental analysis (see Supplemental materials for details). ^{19}F NMR spectra (δ −131.60±0.03, see experimental for details) show that structural changes in the adamantyl part of urea has no detectable effect on the electron structure of the fluorine substituted aromatic ring. Physical and chemical properties of the synthesized compounds (Table 1) show that introduction of hydrocarbon spacers between the adamantane fragment and the urea group leads to a decrease in melting points. Methyl substituents in bridgehead positions of adamantane also decrease melting points except of compound **3h** with methyl in each (3, 5 and 7) vacant bridgehead positions.

Calculated LogP for most of the synthesized compounds lays within the Lipinsky rule's borders.[13] Experimental LogP values for compounds **3b-d, 3i** and **3j** are very close to the calculated and in most cases are lesser. Thus the selected method can be used to predict logP for this type of compounds. Solubilities in water (sodium phosphate buffer) of ureas **3a-j** (Table 1) lie in a narrow interval of 50-90 μM and shows slight dependence on the structure of adamantane part of the molecule.

The potency of the compounds was then measured against the human sEH. Data (Table 2) confirm that introduction of a single methylene spacer between adamantane substituent and the urea group is one of the most activity-enhancing structural change.[14] Further enlargement of such spacer leads to dramatic drop of activity, 15-fold when **3c** with ethylene spacer compared to spacerless **3a** and 170-fold for **3d** with butylene spacer compared to **3a**.

Surprisingly compound **3e** with 1,4-phenylene spacer show relatively moderate activity (94.2 nM) while previously tested diureas[15] and thioureas[16] bearing this fragment possessed low inhibitory activity of 0.7-57 μM. Moreover, the 2-fluoro substituted urea **3a** is 4-fold more active if compared to unsubstituted 1-(adamantan-1-yl)-3-phenyl urea and 37-fold more active than 2-hydroxy substituted analog (Table 2). This is quite unexpected, and reflect the particular properties of the C-F bond, and the interaction of the fluorine atom with its environment. Recently, thioureas containing fluorophenyl fragment were found to inhibit the human sEH. Interestingly the ureas described herein with similar structure of the reported thioureas are more potent, confirming previous findings.[16]

Introduction of one methyl substituent into bridgehead position of adamantane leads to 2.5-fold increase of activity (1.5 nM for compound **3f** compared to 3.7 nM of **3a**, Table 2). However, the addition of a second methyl group sets the activity back to the value of unsubstituted analog. Activity of compound **3h** with three methyl substituents in each available bridgehead position of adamantane is 25-fold less than activity of **3a.** Such decrease of activity could be explained by the lack of space for the bulky 3,5,7-trimethyladamantane in the most appropriate conformation available for these compounds.

An interesting result was obtained when adamantyl fragment was linked to the urea group by its bridge position. The activity of compound **3i** is 3.7-fold better than activity of **3a** and the only difference between them is the type of carbon atom in adamantane linked with urea nitrogen. To understand the origins of this activity difference between 1- and 2-adamantyl containing ureas the X-ray analysis of a single crystal was made (Figure 1). The asymmetric unit of the **3i** contains three molecules. The molecules are connected via six strong classical intermolecular hydrogen bonds, N2A–H2A···O1C, N3A–H3A···O1C, N2B–H2B···01A, N3B–H3B···01A, N2C–H2C···O1B, N3C–H3C···O1B. The H···A distances are 2.09, 2.20, 2.12, 2.10, 2.42 and 2.06 Å respectively and the angles are 157.8, 152.5, 150.3, 154.9, 132.9 and 148.0° respectively. There are also three unusual intramolecular hydrogen bonds, C36A–H36A···01A, C36B–H36B···O1B, C22C–H22C···O1C with H···A distances 2.27, 2.37 and 2.53 Å respectively and the angles of 120.2, 113.5 and 117.9° respectively. Symmetry codes: (i) –x, 1/2 + y, 1/2 – z. The crystallographic data for the investigated compound have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1543475.

The 2-fluorophenyl ring is twisted in position in which fluorine atom positioned closely to oxygen atom of the urea group. Such orientation of fluorine allows it to form hydrogen bonds with Tyr383 or Tyr466 at the sEH active site and does not interfere the formation of hydrogen bonds between the NH’s and Asp335. Such unpredicted orientation of fluorine atom gives very good explanation for the high activity of compound **3i**.

3. Conclusions

A series of soluble epoxide hydrolase (sEH) inhibitors containing a 2-fluorophenyl fragment was developed. Inhibition potency of the described compounds ranges from 0.7 to 630.9 nM. 1-(Adamantan-1-ylmethyl)-3-(2-fluorophenyl) urea(**3b**, IC_{50} = 0.7 nM) and 1-(adamantan-2-

yl)-3-(2-fluorophenyl) urea (**3i**, IC_{50} =1.0 nM) were found to be the most potent sEH inhibitors within the described series.

4. Experimental

4.1 General methods

The mass spectra were obtained on a Thermo Scientific Incos 50 mass spectrometer and on an Agilent 7820/5975 GC/MS system (HP-5MS quartz capillary column, 30 m; carrier gas helium; oven temperature programming from 80 to 280°C; injector temperature 250°C). The 1H NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500.13 MHz using DMSO- d6 as solvent and tetramethylsilane as reference. The elemental compositions were determined on a Perkin Elmer 2400 Series II analyzer. 2-Fluorophenyl isocyanate was commercial product (Sigma Aldrich). Initial adamantyl amines were synthesized according to the known procedures.[8] The solvents were dried according to standard procedures.

4.2 General procedure for the synthesis of ureas 3a-j.

To 1 equiv. of corresponding amine **2a-j** in 40 equiv. of DMF was added 1 equiv. of 2-fluorophenyl isocyanate and 1 equiv. of Et3N (2 equiv. when amine used in form of hydrochloride) at 0 °C. The reaction mixture was stirred at room temperature overnight. After adding 1N HC1 and water, the resulting white precipitates were collected by suction filtration.

4.2.1. 1-(Adamantan-1-yl)-3-(2-fluorophenyl) urea (3a)—White solid, mp 199-200 °C. ^{19}F NMR: δ −131.57 (s, 1F). ^{1}H NMR: δ 8.12 (t, 1H, 6-Ph, *J* 8.3), 8.10 (s, 1H, NH), 7.14 (q, 1H, 3-Ph, *J* 8.2), 7.04 (t, 1H, 5-Ph, *J* 8.2), 6.90-6.85 (m, 1H, 4-Ph), 6.45 (s, 1H, NH), 2.02 (s, 3H, Ad), 1.93 (d, 6H, Ad, *J* 2.8), 1.63 (t, 6H, Ad, *J* 2.8). MS (EI) m/z: 288 (3.5%, $[M]^+$), 135 (14.4%, $[Ad]^+$), 111 (100%, $[F\text{-}Ph\text{-}NH2]^+$), 93 (11.0%), 79 (12.5%). Elemental analysis: calcd. for $C_{17}H_{21}FN_2O$ C70.81%, H7.34%, F6.59%, N9.71%; found C70.82%, H7.35%, F6.60%, N9.69%.

4.2.2. 1-[(Adamantan-1-yl)methyl]-3-(2-fluorophenyl) urea (3b)—White solid, mp 191-192 °C. ^{19}F NMR: δ −131.62 (s, 1F). ^{1}H NMR: δ 8.29 (s, 1H, NH), 8.16 (t, 1H, 6-Ph, *J* 8.3), 7.16 (q, 1H, 3-Ph, *J* 8.1), 7.05 (t, 1H, 5-Ph, *J* 8.2), 6.92-6.87 (m, 1H, 4-Ph), 6.60 (t, 1H, NH, *J* 5.9), 2.81 (d, 2H, CH_2-NH, *J* 6.0), 1.94 (s, 3H, Ad), 1.64 (q, 6H, Ad, *J* 12.0), 1.46 (d, 6H, Ad, *J* 2.5).^{13}C NMR: δ 155.07 (s, 1C, C=O), 151.36 (d, 1C, C-F, J_{CF} 240.2), 128.61 (d, 1C, 4-Ph, J_{CF} 10.0), 124.37 (d, 1C, 5-Ph, J_{CF} 3.8), 121.10 (d, 1C, 6-Ph, J_{CF} 7.5), 119.71 (s, 1C, 1-Ph), 114.69 (d, 1C, 3-Ph, J_{CF} 18.8), 50.84 (s, 1C, CH_2-NH), 39.72 (s, 3C, Ad), 36.60 (s, 3C, Ad), 33.40 (s, 1C, Ad quart), 27.72 (s, 3C, Ad). MS (EI) m/z: 302 (3.0%, $[M]^+$), 135 (12.2%, $[Ad]^+$), 111 (100%, $[F\text{-}Ph\text{-}NH2]^+$), 93 (10.0%), 79 (13.5%). Elemental analysis: calcd. for $C_{18}H_{23}FN_2O$ C71.50%, H7.67%, F6.28%, N9.26%; found C71.58%, H7.65%, F6.31%, N9.22%.

4.2.3. 1-[1-(Adamantan-1-yl)ethyl]-3-(2-fluorophenyl) urea (3c)—White solid, mp 172-173 °C. ^{19}F NMR: δ −131.60 (s, 1F). ^{1}H NMR: δ 8.25 (s, 1H, NH), 8.18 т (1H, 6-Ph, *J* 8.3), 7.16 (q, 1H, 3-Ph, *J* 8.1), 7.05 (t, 1H, 5-Ph, J 8.1), 6.92-6.87 (m, 1H, 4-Ph), 6.49 (d, 1H,

NH, *J* 9.2), 2.52 (t, 1H, CH(CH_3)-NH, *J* 1.7), 1.96 (s, 3H, Ad), 1.70-1.45 (m, 12H, Ad), 0.96 (d, 3H, CH_3, *J* 6.8). MS (EI) m/z: 316 (2.0%, $[M]^+$), 135 (14.0%, $[Ad]^+$), 111 (100%, [F-Ph-NH2]$^+$), 107 (5.0%), 93 (11.0%), 79 (14.0%). Elemental analysis: calcd. for $C_{19}H_{25}FN_2O$ C72.12%, H7.96%, F6.00%, N8.85%; found C72.10%, H7.95%, F5.98%, N8.87%.

4.2.4. 1-[1-(Adamantan-1-yl)butane-2-yl]-3-(2-fluorophenyl) urea (3d)—White solid, mp 154-155 °C. ^{19}F NMR: δ −131.58 (s, 1F). ^{1}H NMR: δ 8.17 (t, 1H, 6-Ph, *J* 8.3), 8.11 (s, 1H, NH), 7.15 (q, 1H, 3-Ph, *J* 8.1), 7.05 (t, 1H, 5-Ph, *J* 7.8), 6.92-6.86 (m, 1H, 4-Ph), 6.41 (d, 1H, NH, *J* 8.6), 3.68 (q, 1H, CH(C_2H_5)-NH, *J* 6.1), 1.90 (s, 3H, Ad), 1.67-1.45 (m, 12H, Ad), 1.41-1.30 (m, 2H, CH_3-CH_2-CH), 1.15 (d, 2H, C-CH_2-CH, *J* 8.7), 0.82 (t, 3H, CH_3, *J* 7.3) MS (EI) m/z: 344 (1.0%, $[M]^+$), 315 (2.0%, $[M\text{-}C_2H_5]^+$), 135 (22.0%, $[Ad]^+$), 111 (100%, [F-Ph-NH2]$^+$), 93 (10.0%), 79 (12.0%). Elemental analysis: calcd. for $C_{21}H_{29}FN_2O$ C73.22%, H8.49%, F5.52%, N8.13%; found C72.25%, H8.45%, F5.55%, N8.16%.

4.2.5. 1-[4-(Adamantan-1-yl)phenyl]-3-(2-fluorophenyl) urea (3e)—White solid, mp 183-184 °C. ^{19}F NMR: δ −131.63 (s, 1F). ^{1}H NMR: δ 8.99 (s, 1H, NH), 8.50 (s, 1H, NH), 8.16 (t, 1H, 6-Ph, *J* 8.1), 7.32 (dd, 4H, Ph, *J* 8.6, *J* 51), 7.22 (q, 1H, 3-Ph, *J* 8.1), 7.13 (t, 1H 5-Ph, *J* 7.7), 7.01-6.96 (m, 1H, 4-Ph), 2.05 (s, 3H, Ad), 1.84 (s, 6H, Ad), 1.76-1.70 (m, 6H, Ad). MS (EI) m/z: 364 (17.9%, $[M]^+$), 227 (10.4%, $[Ad\text{-}Ph\text{-}NH_2]^+$), 196 (5.1%), 170 (24.3%), 133 (5.3%, $[Ad]^+$), 111 (100%, [F-Ph-NH2]$^+$), 106 (7.3%), 93 (8.5%), 79 (10.6%). Elemental analysis: calcd. for $C_{23}H_{25}FN_2O$ C75.80%, H6.91%, F5.21%, N7.69%; found C75.88%, H6.94%, F5.25%, N7.66%.

4.2.6. 1-[3-methyl(Adamantan-1-yl)]-3-(2-fluorophenyl) urea (3f)—White solid, mp 149-150 °C. ^{19}F NMR: δ-131.60 (s, 1F). ^{1}H NMR: δ 8.12 (t, 1H, 6-Ph, *J* 8.3), 8.10 (s, 1H, NH), 7.14 (q, 1H, 3-Ph, *J* 8.1), 7.04 (t, 1H, 5-Ph, *J* 7.7), 6.90-6.85 (m, 1H, 4-Ph), 6.46 (s, 1H, NH), 2.07-1.37 (m, 14H, Ad), 0.81 (s, 3H, CH_3). MS (EI) m/z: 302 (1.9%, $[M]^+$), 149 (8.2%, $[CH_3\text{-}Ad]^+$), 111 (100%, [F-Ph-NH2]$^+$), 107 (12.2%), 93 (20.8%), 79 (11.9%). Elemental analysis: calcd. for $C_{18}H_{23}FN_2O$ C71.50%, H7.67%, F6.28%, N9.26%; found C71.56%, H7.65%, F6.28%, N9.19%.

4.2.7. 1-[3,5-dimethyl(Adamantan-1-yl)]-3-(2-fluorophenyl) urea (3g)—White solid, mp 181-182 °C. ^{19}F NMR: δ −131.60 (s, 1F). ^{1}H NMR: δ 8.11 (t, 1H, 6-Ph, *J* 8.3), 8.09 (s, 1H, NH), 7.14 (q, 1H, 3-Ph, *J* 8.1), 7.04 (t, 1H 5-Ph, *J* 7.7), 6.90-6.86 (m, 1H, 4-Ph), 6.47 (s, 1H, NH), 2.09-1.11 (m, 13H, Ad), 0.82 (s, 6H, $2CH_3$). MS (EI) m/z: 316 (1.8%, $[M]^+$), 111 (100%, [F-Ph-NH2]$^+$), 107 (13.1%), 93 (5.5%), 83 (11.2%). Elemental analysis: calcd. for $C_{19}H_{25}FN_2O$ C72.12%, H7.96%, F6.0%, N8.85%; found C72.16%, H7.90%, F6.08%, N8.83%.

4.2.8. 1-[3,5,7-trimethyl(Adamantan-1-yl)]-3-(2-fluorophenyl) urea (3h)—White solid, mp 212-213 °C. ^{19}F NMR: δ −131.60 (s, 1F). ^{1}H NMR: δ 8.11 (t, 1H, 6-Ph, *J* 8.3), 8.09 (s, 1H, NH), 7.14 (q, 1H, 3-Ph, *J* 8.1), 7.03 (t, 1H 5-Ph, *J* 7.7), 6.90-6.87 (m, 1H, 4-Ph), 6.48 (s, 1H, NH), 1.51-1.02 (m, 12H, Ad), 0.83 (s, 9H, $3CH_3$). MS (EI) m/z: 330 (0.7%, $[M]^+$), 121 (13.9%), 111 (100%, [F-Ph-NH2]$^+$), 107 (7.9%), 93 (5.5%), 79 (5.1%). Elemental

analysis: calcd. for $C_{20}H_{27}FN_2O$ C72.70%, H8.24%, F5.75%, N8.48%; found C72.74%, H8.29%, F5.77%, N8.39%.

4.2.9. 1-(Adamantan-2-yl)-3-(2-fluorophenyl) urea (3i)—White solid, mp 196-197 °C. ^{19}F NMR: δ −131.59 (s, 1F). ^{1}H NMR: δ 8.36 (s, 1H, NH), 8.18 (t, 1H, 6-Ph, *J* 8.3), 7.16 (q, 1H, 3-Ph, *J* 8.1), 7.06 (t, 1H 5-Ph, *J* 7.7), 6.95 (d, 1H, NH, *J* 8.0), 6.91-6.87 (m, 1H, 4-Ph), 3.78 (d, 1H, CH-NH, *J* 7.8), 1.89-1.55 (m, 14H, Ad). MS (EI) m/z: 288 (1.6%, $[M]^+$), 111 (100%, $[F\text{-}Ph\text{-}NH2]^+$), 91 (6.6%), 79 (8.9%). Elemental analysis: calcd. for $C_{17}H_{21}FN_2O$ C70.81%, H7.34%, F6.59%, N9.71%; found C70.84%, H7.28%, F6.61%, N9.77%.

4.2.10. 1-[2-(Adamantan-2-yl)pentane-1-yl]-3-(2-fluorophenyl) urea (3j)—White solid, mp 137-138 °C. ^{19}F NMR: δ −131.58 (s, 1F). ^{1}H NMR: δ 8.31 (s, 1H, NH), 8.17 (t, 1H, 6-Ph, *J* 8.1), 7.16 (q, 1H, 3-Ph, *J* 8.1), 7.06 (t, 1H, 5-Ph, *J* 7.8), 6.92-6.86 (m, 1H, 4-Ph), 6.48 (t, 1H, NH, *J* 5.5), 3.30-2.97 (m, 2H, CH_2-NH), 1.95-1.38 (m, 16H, Ad-CH), 1.35-1.28 (m, 2H, CH_3-CH_2), 1.25-1.11 (m, 2H, CH_3-CH_2-CH_2), 0.88 (t, 3H, CH_3, *J* 6.9). MS (EI) m/z: 358 (1.1%, $[M]^+$), 315 (1.8%, $[M\text{-}C_3H_7]^+$), 135 (11.5%, $[Ad]^+$), 111 (100%, $[F\text{-}Ph\text{-}NH2]^+$), 93 (9.0%), 79 (6.0%). Elemental analysis: calcd. for $C_{22}H_{31}FN_2O$ C73.71%, H8.72%, F5.30%, N7.81%; found C73.69%, H8.73%, F5.29%, N7.80%.

4.3 Determination of inhibitory potency (IC_{50}) by fluorescent assay[15].

Enzyme (~1 nM human sEH) was incubated at 30 °C with inhibitors ($[I]_{final}$ = 0.4 – 100,000 nM) for 5 min in 100 mM sodium phosphate buffer (200 μL, pH 7.4) containing 0.1 mg/mL of BSA and 1% of DMSO. The substrate (cyano(2-methoxynaphthalen-6-yl)methyl *trans*-(3-phenyloxyran-2-yl)methylcarbonate, CMNPC) was then added ($[S]_{final}$ = 5 μM). Activity was assessed by measuring the appearance of the fluorescent 6-methoxynaphthaldehyde product (λ_{em} = 330 nm, λ_{ex} = 465 nm) at 30 °C during a 10 min incubation (Spectramax M2; Molecular Device, Inc., Sunnyvale, CA). The IC_{50} values that are the concentrations of inhibitors that reduce activity by 50% were calculated from at least five different concentrations, each in triplicate, with at least 2 on either side of 50% activity mark.

Acknowledgments

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Highlights

- Ureas with adamantane and fluoroaromatic fragments were studied as sEH inhibitors.
- 10 new ureas with IC_{50} up to 0.7 nM were synthesized.
- Extra hydrogen bond between the fluorine atom and sEH discovered by X-Ray crystallography.
- Found no effect of changes in the adamantyl on the electron structure of the fluoroaromatic ring.

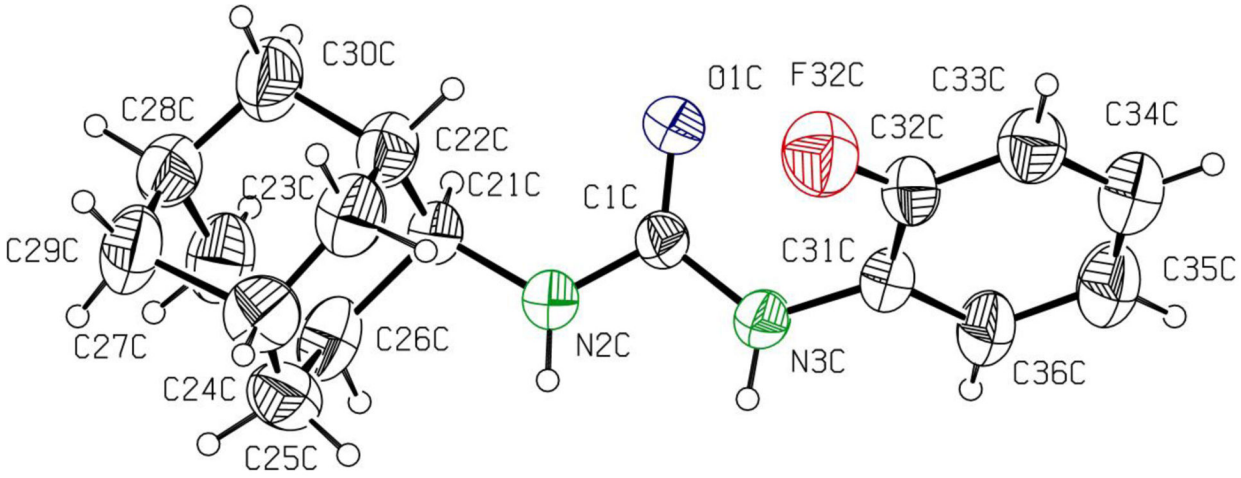
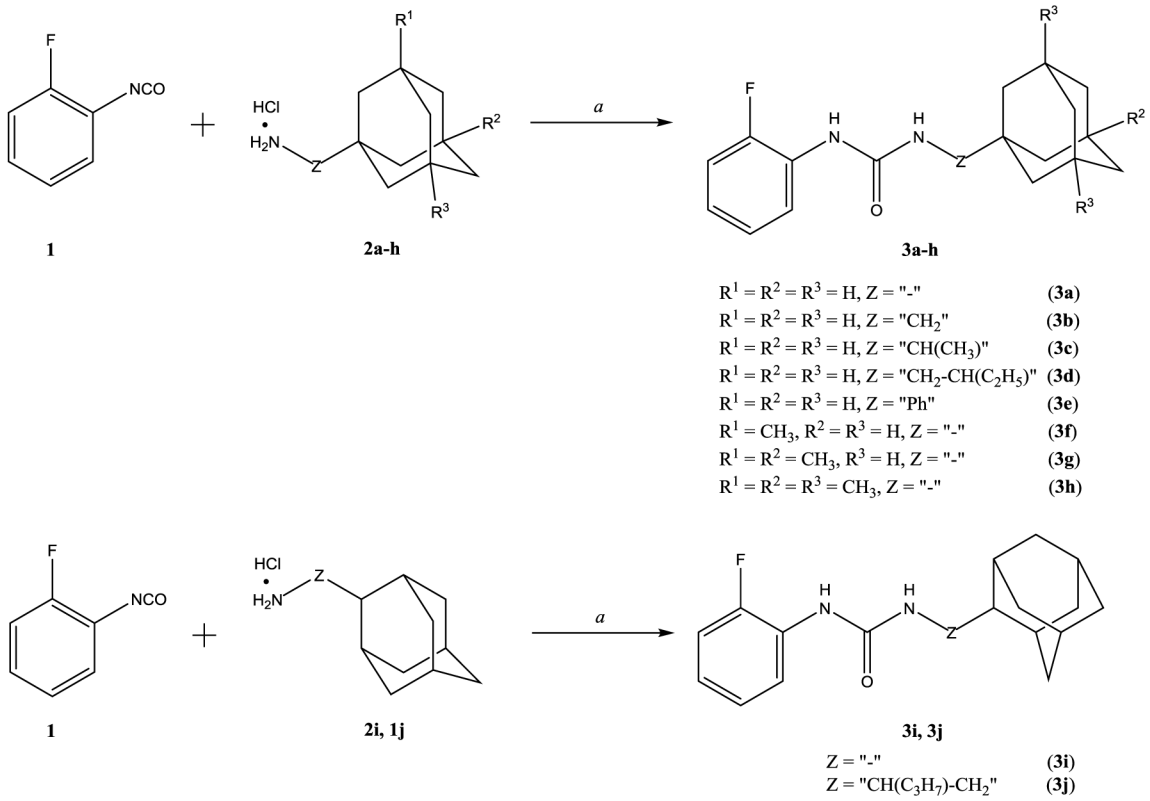


Fig. 1.

ORTEP diagram showing 50 % probability anisotropic displacement ellipsoids of non-hydrogen atoms for compound **3i** according to single crystal XRD data collected at 298(2) K.

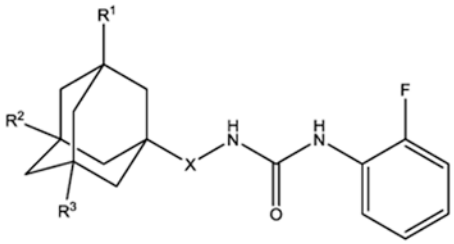


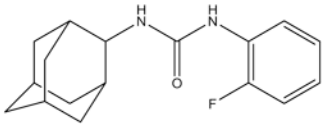
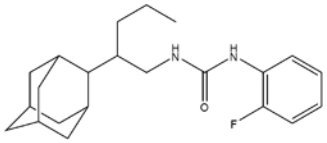
Scheme 1.

Reagents and conditions: a. DMF, Et_3N (2 equiv.), 8 h., rt

Table 1

Properties of compounds **3a-j**



#	R_1	R_2	R_3	X	LogP calc[a]	LogP exp[b]	mp °C)	Solubility (μM)[c]
3a	H	H	H	-	4.49	-	199-200	70-80
3b	H	H	H	CH_2	4.50	4.40	191-192	60-70
3c	H	H	H	$CH(CH_3)$	4.83	4.75	172-173	50-60
3d	H	H	H	$CH_2CH(Et)$	5.63	5.80	154-155	50-60
3e	H	H	H	Ph	6.17	-	183-184	80-90
3f	Me	H	H	-	4.55	-	149-150	50-60
3g	Me	Me	H	-	4.61	-	181-182	60-70
3h	Me	Me	Me	-	4.67	-	212-213	70-80
3i					4.33	4.20	196-197	80-90
3j					6.62	6.55	137-138	70-80

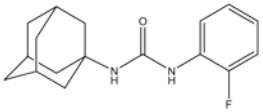
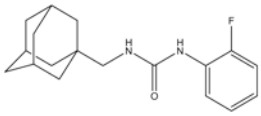
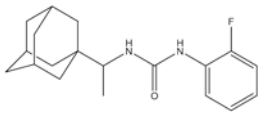
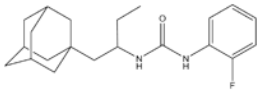
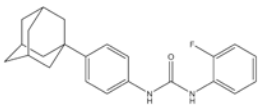
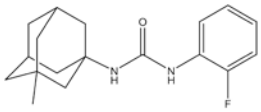
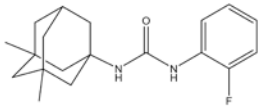
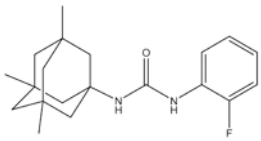
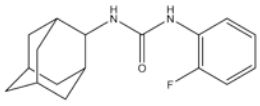
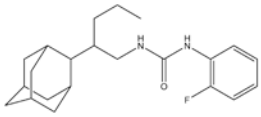
[a] Calculated using Molinspiration (http://www.molinspiration.com) © Molinspiration Cheminformatics.

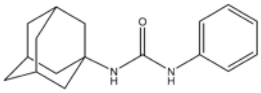
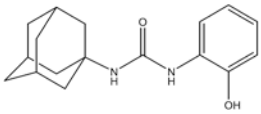
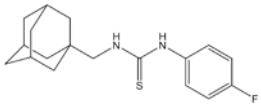
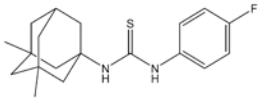
[b] Expeimental LogP were measured by HPLC-MS[12]

[c] Solubilities were measured in sodium phosphate buffer (pH 7.4, 0.1 M) containing 1% of DMSO.

Table 2

IC_{50} values for compounds **3a-j.**

#	Structure	IC_{50}(nM) [a]
3a		3.7
3b		0.7
3c		55.6
3d		630.9
3e		94.2
3f		1.5
3g		3.6
3h		94.3
3i		1.0
3j		106.2

#	Structure	IC_{50}(nM) [a]
		16.5
		138.5
		159.0 [b]
		551.0 [b]

[a] As determined via a kinetic fluorescent assay (Concentration of substrate 5 μM, concentration of human sEH 1 nM).[17] Results are means of three separate experiments.

[b] IC_{50} of thioureas[16] given for comparison.