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Treating a Global Health Crisis with a Dose of Synthetic Chemistry

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The SARS-CoV-2 pandemic has prompted scientists from many disciplines to work collaboratively toward an effective response. As academic synthetic chemists, we examine how best to contribute to this ongoing effort. The current pandemic draws comparisons to past global health crises where synthetic chemists have made significant translational contributions through fundamental research. In the context of manufacturing compounds like remdesivir, several research areas are outlined herein which require further development and creativity from chemists in order to drive advances in antiviral research during this time of need. As a community, driving future innovations in synthetic chemistry will be imperative if we are to tackle global health threats such as COVID-19.

1. INTRODUCTION

The ongoing COVID-19 crisis has changed the landscape of the world; for chemists, the mandated self-isolation and social distancing directives have significantly disrupted the status quo of research efforts. In the United States alone, the novel coronavirus (SARS-CoV-2) has infected over 2.1 million people with 116,000 fatalities as of June 16, 2020,[1] and has brought life as we know it to an indefinite standstill.

Scientists from every field have been organizing efforts to develop COVID-19 therapeutics. Across 65 countries, 172 treatments are being investigated in 308 active or recruiting clinical trials for the treatment of COVID-19 as of May 10, 2020.[2] The urgency of the current crisis has galvanized chemists to assay vast compound libraries in search of new antiviral therapies.[3] At an impressive pace,[4,5] scientists are attacking the problem from all sides: repurposing existing therapeutics,[6] piloting virtual screening campaigns,[7] and investigating the structural basis for viral entry into host cells.[8]

With all these efforts underway, what should we as synthetic chemists in academia prioritize to contribute to this pandemic response? In the absence of a vaccine, the first line of defense will likely be an antiviral therapeutic. Among the many therapies currently being explored, existing synthetic small molecule drugs may be the best opportunity for bringing a medicine to the market to meet rising global demand.

With all these efforts underway, what should we as synthetic chemists in academia prioritize to contribute to this pandemic response?

The sheer scale of the current pandemic naturally draws comparisons to past global health crises. In the century since the tragic 1918 Spanish Flu pandemic, which infected up to one-third of the world's population,[9] synthetic chemistry has been instrumental in meeting the challenge of infectious disease on a global scale; examples abound. Following the discovery of natural penicillin in 1929,[10] the development novel antibiotic medications such as penicillin V (**1**, Figure 1) in the ensuing decades revolutionized infectious disease medicine. These innovations were realized in the postwar era through a combination of total synthesis, semisynthesis, and large-scale fermentation processes.[11] The synthesis of quinine (**2**) in 1944[12] inspired countless chemists and other scientists to focus on treating malaria on a worldwide scale. These efforts led to the eventual development of medicines like chloroquine (**3**) and artemisinin (**4**), along with a host of other compounds,[13] which changed the way we think about treating parasitic diseases.[14] Toward the end of the twentieth century, the HIV/AIDS crisis mobilized the chemistry community to develop a suite of compounds (e.g., **5**, **6**) useful for the mitigation of infection as the retrovirus spread

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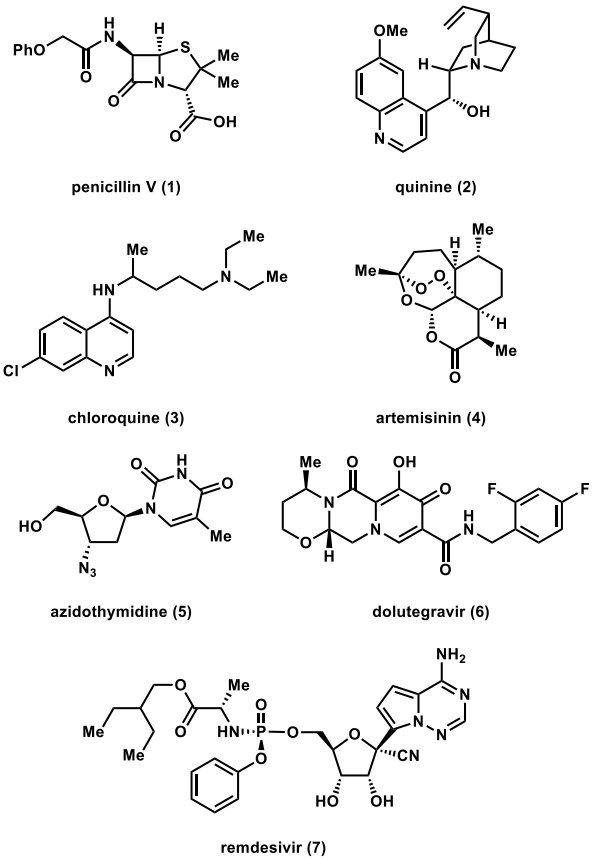

Figure 1. Globally impactful active pharmaceutical ingredients (APIs).

across the globe.[15] In each of these cases, synthetic chemists—both in academic and industrial laboratories—played pivotal roles in addressing serious human health crises on a global scale. Taking a small molecule therapeutic from initial discovery to large-scale manufacturing is no small feat, and the degree to which the scientific community has been successful in meeting the challenge of treating infectious diseases is intimately tied to the global-scale synthesis and distribution of such medicines.

The first hurdle to surmount in tackling the COVID-19 crisis is identifying and validating a particular treatment through clinical trials. Regardless of the therapeutic compound that is identified by the collaborative efforts of clinicians, medicinal chemists, biologists, and others, we anticipate a pressing need to quickly access large quantities of an effective active pharmaceutical ingredient (API). Consider Gilead's lead candidate remdesivir (**7**), which was recently granted emergency approval by the Food and Drug Administration (FDA) in the US.[16] Compounds such as **7** have typically undergone a protracted process development campaign to identify an "ideal" route for manufacture on scale. Estimates of how many people will be infected by SARS-CoV-2 and require small molecule pharmaceutical intervention vary widely; however, even in the best case scenario, one can envision the supply line will be strained in its current form.[17−19] This shortcoming will necessitate the development of an optimal route, which has already begun.[20] Furthermore, the availability of multiple potential routes for consideration increases the possibility of identifying a practical, efficient synthesis of the target compound starting from unique feedstock chemicals.[21] In addition to issues of preparing a potentially massive quantity of API, we are also faced with the necessity of a low-cost treatment. Experts anticipate the continued spread of the virus in developing countries, thus necessitating cost-effective manufacturing of those therapies that are identified.[22] Navigating these manufacturing concerns will be pivotal for quelling this disease worldwide. This will be a challenge for synthetic chemists—are we equipped to handle it?

Historically, global health crises akin to the coronavirus pandemic have spurred synthetic chemists, as essential innovators and inventors, to contribute to the collective response. While the role of the academic synthetic chemist is traditionally viewed as focused on answering largely *fundamental* questions, *translational* research, sparked by public health crises, can lead to widely applicable *fundamental* knowledge. Specifically, careful consideration of the supply chain scalability or reimagining the synthesis of COVID-19 therapeutics is not outside of the responsibility of the academic synthetic chemist, despite not historically being a primary focus of most research groups. In light of the global scale of the current pandemic and the intense cost-pressures for synthetic manufacturing processes, the challenges ahead are immense. *However, the synthetic chemistry community is better positioned than ever before to respond to the current crisis with new synthetic strategies and innovative technologies.*

2. SYNTHETIC CHEMISTRY IN PAST GLOBAL HEALTH CRISES

The general populace—even those well-versed in science—might take for granted the synthetic innovation required to develop medicines for crises past. Indeed, bacterial infections, HIV/AIDS, and malaria are largely considered to be treatable diseases in the modern developed world. However, mitigation of these diseases was not trivial. Without fundamental innovation from chemists working with other scientific experts, the global threat of these diseases would be much more severe today. Therefore, in this critical moment in history, chemists' response to the threat of COVID-19 is of paramount importance. As seen through a series of case studies addressing infectious diseases, chemists have the ability to contribute effective solutions for combatting global health crises.

As seen through a series of case studies addressing infectious diseases, chemists have the ability to contribute effective solutions for combatting global health crises.

2.1. Interplay of Synthetic Methodology and Total Synthesis in the Development of Antibiotics. The development of antibiotics was one of the most important scientific innovations of the twentieth century, as it drastically reduced the threat of bacterial infections.[23,24] Though the early antibiotics era was characterized by fully synthetic compounds (e.g., sulfonamides and organoarsenicals) and was largely pioneered by industrial chemists, the modern era of natural product-based antibiotics witnessed significant contributions from academia.[25−27] Penicillin V (**1**) and vancomycin (**12**) provide two examples where synthetic chemists have made impactful, translational contributions by pursuing fundamental research interests (Figure 2).

The discovery of penicillin G (**8**, Figure 2A) in 1929 ushered in the modern antibiotic era and changed the way bacterial

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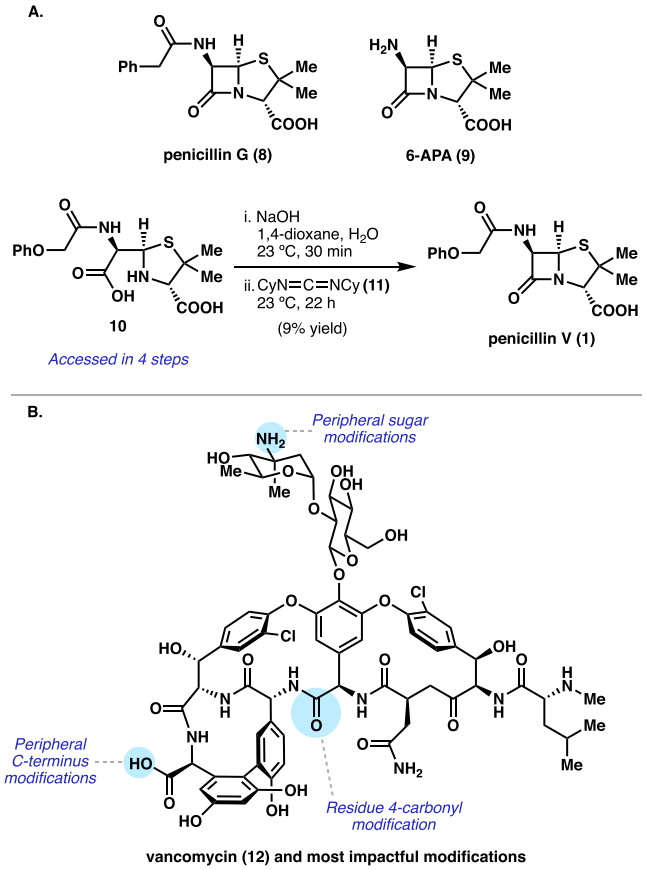

Figure 2. Advances in antibiotic synthesis.

infections are treated.[10] Despite its widespread success, this new antibiotic still had its imperfections. Penicillin G displayed a relatively narrow spectrum of bioactivity and poor pharmacokinetic properties. It was postulated that structural changes to the penicillin scaffold could result in improved medicinal properties, thus prompting the quest for novel unnatural penicillin analogues.[25,28] Toward this goal, John Sheehan pursued the total synthesis of penicillin V (**1**) while at the Massachusetts Institute of Technology.[29] These studies provided a number of important conceptual advances, including the identification and synthesis of a simplified penicillin core, 6-aminopenicillanic acid (6-APA, **9**), which could serve as a viable precursor to a suite of penicillin analogues through acylation.[30,31] A subsequent discovery of a scalable fermentation route to **9** accelerated the development of many useful penicillin derivatives through this key intermediate.[32,33] In addition, Sheehan's research efforts also afforded practical synthetic innovations, which continue to be robust synthetic tools in modern organic chemistry. Efforts toward penicillin V (**1**) resulted in the discovery of a neutral peptide coupling reagent (carbodiimide **11**),[34] capable of enabling the transformation of **10** → **1**,[29] which was the key step in accessing the strained β-lactam ring in the penicillin core. These amide coupling reagents were critical to the development of solid-phase peptide synthesis due to their reliable efficiencies.[35] Sheehan's work additionally introduced several widely used protecting groups (such as phthalimide and *t*-butyl esters).[29] Overall, the pioneering translational studies advanced by Sheehan provided valuable strategic insight into accessing novel penicillins and a wealth of fundamental knowledge regarding the manipulation of strained ring systems and amide couplings.

Despite widespread success in treating infections with antibiotics, a persistent increase in the number of drug-resistant bacterial strains has been observed since their 1929 discovery.[36] This resistance arms race has spurred the need to develop novel antibiotic compounds. An important medicine in treating antibiotic-resistant infections is vancomycin (**12**, Figure 2B), a complex glycopeptide antibiotic.[37] First isolated in the 1950s, **12** has inspired many synthetic approaches and impressive total syntheses by a number of academic groups.[38,39] In an illustrative approach, Boger's research laboratory at The Scripps Research Institute focused on the preparation of analogues which could be used in treating infections caused by strains of antibiotic-resistant bacteria.[40] The approach consisted of two stages: first, accomplishing a convergent total synthesis of vancomycin (**12**), and then leveraging key intermediates in the synthesis to access a wide range of structural analogues. These efforts laid the groundwork for a series of structure−activity relationship (SAR) studies that ultimately afforded rationally designed antimicrobial agents with improved activities. In particular, vancomycin-resistant bacteria contain a modification of the D-Ala−D-Ala sequence of lipid II, a bacterial cell wall precursor, to a D-Ala−D-Lac sequence for which vancomycin displayed significantly lower activity.[38,40c] Building from this precedent, Boger's studies started with modifications of the residue 4-carbonyl, involved in the recognition via hydrogen bonding, which ultimately led to a series of peripheral modifications that had a significant effect on the antibiotic activity against both vancomycin-resistant and vancomycin-sensitive bacteria.[41] Although discrete mechanisms of action are still under investigation for many of these analogues, these efforts by Boger and co-workers underscore how academic synthetic programs targeting major healthcare challenges simultaneously achieve concrete solutions and provide invaluable fundamental insight.

2.2. Evolution of HIV/AIDS Therapeutics through Collaborations between Academia and Industry. The response to the HIV/AIDS epidemic is a powerful example of the synergistic roles academic and industrial chemists can play in addressing novel diseases through the development of new medicines (Figure 3A). In the early 1980s, the Centers for Disease Control and Prevention reported the emergence of a new epidemic in which the first clusters of patients exhibited rare conditions typically observed in immunocompromised individuals. The initially reported cases shared common immunodeficiencies. Moreover, the identification in the mid-1980s of a retrovirus termed human immunodeficiency virus (HIV) as the causative agent for acquired immunodeficiency syndrome (AIDS) suggested that an antiviral small molecule drug may effectively treat the disease.[15,42] A highly collaborative group of research scientists and medical professionals at the National Cancer Institute, academic institutions, and Burroughs Wellcome Co. discovered that the nucleoside analogue zidovudine (azidothymidine (AZT), **5**), a failed cancer therapeutic, inhibited replication of the virus in cells and decreased mortality and opportunistic infections in AIDS patients.[43−45] These time-sensitive efforts ultimately led to the approval of this nucleoside reverse transcriptase inhibitor by the FDA in March 1987.[46] Despite the significance of AZT (**5**) as the first approved HIV therapeutic, this compound suffered from dose-limiting toxicity and emergence of resistance, prompting chemists to develop new therapeutics to mitigate the crisis.[47] Massive efforts in the context of this crisis, notably by Roche,[48] Abbott,[49] and Merck,[50] led to the rapid FDA approval of a number of first generation HIV protease inhibitors as effective treatments.[51]

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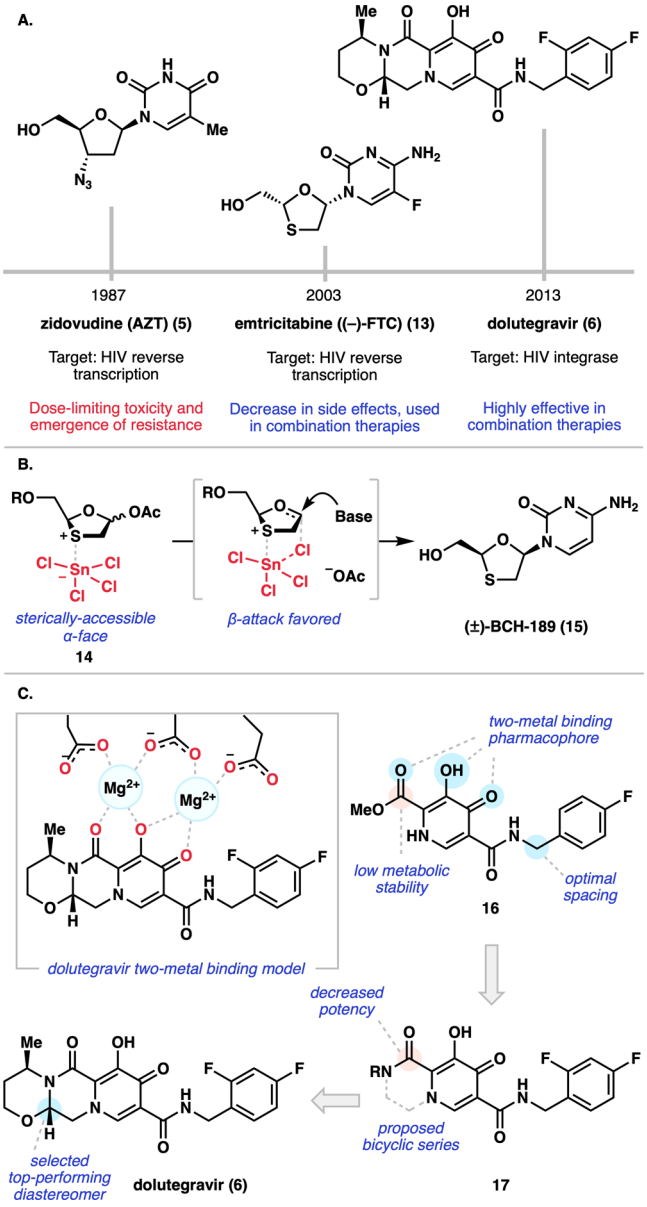

Figure 3. Evolution of HIV/AIDS therapeutics.

In this ongoing crisis, further developments continue to yield improved, next-generation HIV therapeutics. In particular, this section highlights the contributions of academic synthetic chemists and the capabilities of rational drug design in the development of emtricitabine (**13**) and dolutegravir (**5**), respectively.

Inspired by the 1989 disclosure of the potent anti-HIV activity and low cytotoxicity of the oxathiolane nucleoside analogue 3′-thia-2′,3′-dideoxycytidine (BCH-189, **15**, Figure 3B), an academic team at Emory University, led by Dennis Liotta, pursued the optimized synthesis and evaluation of this compound and several analogues.[52] A major challenge that emerged in the development of an efficient synthesis of BCH-189 was the nonselective glycosylation of the oxathiolane core, which resulted in mixtures of α-(*trans*) and β-(*cis*) diastereomers. Liotta postulated that the thiaphilic Lewis acid $SnCl_4$ would preferentially associate on the sterically accessible α-face of the oxathiolane as in **14** and, thus, could direct the nucleobase approach to the desired β-face to diastereoselectively give **15**.[52] Further development of an enzymatic resolution of the corresponding butyrate esters provided robust access to discrete enantiomers of BCH-189. Unexpectedly, the "unnatural" L-nucleoside ((−)-BCH-189 (**15**), lamivudine, 3TC, Figure 3B) proved to be nearly 100 times more potent than the corresponding D-nucleoside ((+)-**15**).[53] These initial studies also led to the development of fluorinated analogue (−)-FTC (**13**) which proved similarly efficacious. The strong academia−industry partnership between Emory and Burroughs Wellcome, as well as manufacturing efforts by GlaxoSmithKline,[54] facilitated the development of (−)-FTC (emtricitabine, **13**) as a potential clinical candidate. After receiving FDA approval in 2003, emtricitabine (**13**) is currently a component of nine fixed-dose combination therapies,[55] two of which are on the World Health Organization Model List of Essential Medicines as some of the "most efficacious, safe and cost-effective medicines for priority conditions."[56]

Since the identification of the first line of HIV medicines, continued research into the HIV life cycle has revealed a deeper mechanistic understanding of viral pathogenesis and ultimately led to the invention of new drugs with unique targets.[57] One such drug is dolutegravir (**6**), an HIV integrase inhibitor developed by Shionogi Pharmaceuticals and GlaxoSmithKline. HIV integrase is an attractive target due to its unique role in the retroviral life cycle and thus is often targeted in combination therapies. This enzyme contains a conserved active site consisting of two divalent metal ions (Mg^{2+}).[58,59] Initial rational drug design efforts centered around developing a two-metal-binding pharmacophore along with an adjacent hydrophobic aryl portion (Figure 3C). After it had been determined that the spacing of a hydrophobic difluoroarene was key to the compound's potency, additional studies further revealed that amides exhibited superior metabolic stability compared to esters in this series, as in **16**. While crucial for stability, the installation of the conformationally planar amide, as in **17**, decreased the potency of the molecule due to suboptimal coordination of both Mg^{2+} ions. Following the development of another series of improved bicyclic analogues that productively locked the amide conformation,[60] additional SAR studies demonstrated that a pendant hydroxy group on the piperazinone increased potency and could be tethered to the proposed bicyclic scaffold to increase stability, as depicted in **17**.[59] Lastly, systematic examination of each diastereomer in this series led to the identification of dolutegravir (**6**) as the most effective.[61] This frontline HIV integrase inhibitor is a powerful example of how over 30 years of research encompassing biology, biochemistry, synthetic chemistry, etc., has provided to chemists the tools to design a better drug.

2.3. Recent Response to Flu Pandemics: Preparing for a Tamiflu Shortage. (−)-Oseltamivir phosphate (Tamiflu, **19**) is a neuraminidase inhibitor that sprang into the public eye in response to both the 2005 H5N1 Avian Flu epidemic and the 2009 H1N1 Swine Flu pandemic (Figure 4). Development of this therapeutic began at Gilead in the late 1990s as a part of a rational design campaign aimed at developing inhibitors for neuraminidase,[62] an enzyme which cleaves the terminal sialic acid residues of cellular glycans in order to aid the escape of newly created viruses from host cells.[63] Neuraminidase is present in both influenza A and B viruses, making it an appealing target for therapies which could be useful against a wide variety of influenza strains. Fundamental research efforts into the neuraminidase-mediated mechanism of glycan cleavage identified sialic-acid-derived oxocarbenium ion **18** as a key intermediate.[63] Cyclohexenyl scaffolds were found to be appropriate transition state mimics of **18**, resulting in the development of

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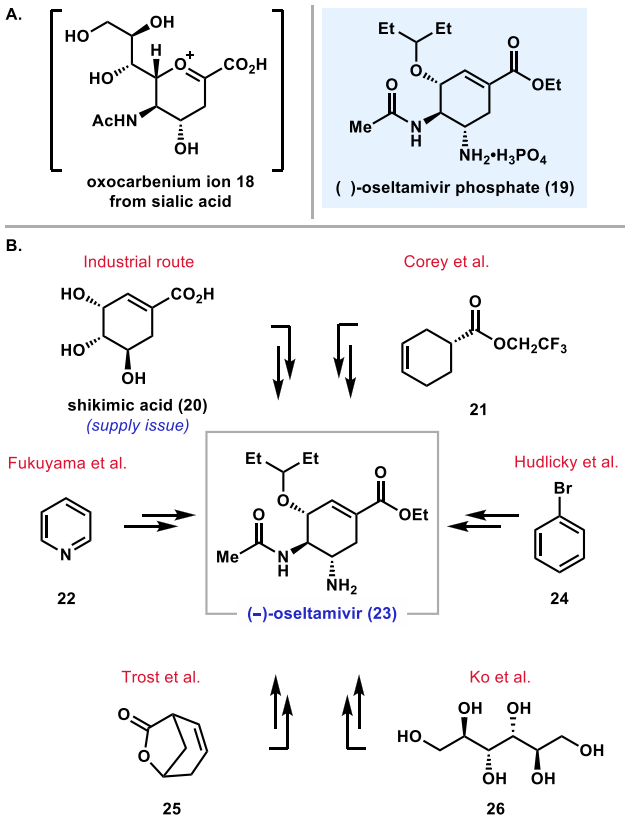

Figure 4. Synthesis of oseltamivir phosphate.

several series of inhibitors, eventually leading to the production of **19**. Concerted efforts were made to optimize the drug candidate's properties for oral availability and storage stability.[62] Ultimately these properties led to intense governmental interest as a treatment and efforts to stockpile the medicine in preparation for a flu pandemic.[64] The development of (−)-oseltamivir phosphate (**19**) and its discovery by rational design is a testament to the invaluable ability of organic chemists to understand reaction mechanisms and execute target-oriented syntheses in the development of important therapies.

Gilead—and subsequently Roche, which licensed **19** from Gilead shortly following its development—have disclosed several reports on the industrial-scale synthesis of the drug which comprise a robust manufacturing route that has remained in place to the present day.[62,65−68] Nevertheless, global supply was strained in both the bird flu epidemic and the swine flu pandemic.[64] In 2005, it was estimated that the global supply would only treat 2% of the population.[69] In response, Roche pledged to increase output to 300 million treatments per year,[69] and bolstered its supply line by sublicensing portions of production to manufacturing partners.[70] Despite these efforts, supply was again strained in 2009. The cost of shikimic acid (**20**, Figure 4B), the natural product which serves as the starting material for the industrial synthesis, skyrocketed from $40 to $1,000 per kilogram.[71] Attempts to increase production of shikimic acid by large-scale fermentation have been explored but are still ongoing.[72] These high-profile supply issues also motivated new approaches to synthesize **19** among academics, and numerous research groups have published synthetic routes to the compound that do not rely on shikimic acid (**20**).

By developing new reaction paradigms, academics were able to leverage broadly available starting materials in this synthesis, which, in theory, could be deployed in the event of a pandemic-related supply crisis. Selected examples of syntheses demonstrate that a wide variety of starting materials could be leveraged to access oseltamivir (**23**), from feedstocks such as pyridine (**22**),[73] D-mannitol (**26**),[74] and bromobenzene (**24**)[75] to other known starting materials such as cyclohexene **21**[76] or lactone **25**.[77] While these academic routes (and many others)[78] demonstrated desirable properties such as a chromatography-free synthesis[73] or a short synthetic sequence,[77] it is worth noting that academic routes generally do not match the same standard of "greenness" as Roche's preferred manufacturing route.[79] While the overall impact of these syntheses on the large-scale production of (−)-oseltamivir (**23**) in the event of a shikimic acid shortfall remains to be determined, this timely academic response provided a rich platform for the development of novel chemistry and fundamental knowledge within the frame of a translational molecule of interest.

3. CHALLENGES IN THE SYNTHESIS OF REMDESIVIR

Everyone is looking hopefully toward pharmaceutical companies to identify, validate, and mass-produce a therapeutic that can temper the toll of COVID-19. To best accelerate this process, academic chemists should also engage manufacturing concerns through synergistic efforts, but how exactly can we contribute to improving the synthesis of an API on a global scale? As a thought experiment, we consider remdesivir (**7**), which has recently been approved for emergency use by the FDA and is currently undergoing numerous clinical trials.[16] A close look at the published and patented routes to **7** suggests that the manufacturing route may be costly. Steps toward rendering the synthesis more "ideal"[80] could help to meet the possible global demand. Even if remdesivir (**7**) does not emerge as the most effective small molecule therapeutic in the clinic, the core problem remains: supply chain limitations and bottlenecked manufacturing could significantly hinder the way we address this crisis. Therefore, developing efficient, scalable methods for constructing urgently needed molecules and creative ways to leverage abundant materials could prove indispensable in our efforts to deliver medicines to patients.

Therefore, developing efficient, scalable methods for constructing urgently needed molecules and creative ways to leverage abundant materials could prove indispensable in our efforts to deliver medicines to patients.

The retrosynthesis of **7** (Scheme 1A) highlights key disconnections that demonstrate many longstanding, interconnected challenges in nucleotide prodrug chemistry.[81] Remdesivir (**7**) arises from late-stage coupling of nucleoside **27** with phosphoramidate **35**. In turn, nucleoside **27** is constructed from α-cyanation and *C*-glycosylation of ribolactone **28**. In a forward sense, these disconnections represent a series of nontrivial transformations: efficient *C*-glycosylation, diastereoselective cyanation, and site- and stereoselective phosphoramidation of **27**. Furthermore, protecting group manipulations are necessary for overcoming many of these obstacles.

The synthesis begins with the in situ protection of the free amine of pyrrolotriazinamine **29** with TMSCl (Scheme 1B). The formation of the bis(trimethylsilyl)amine allows for the

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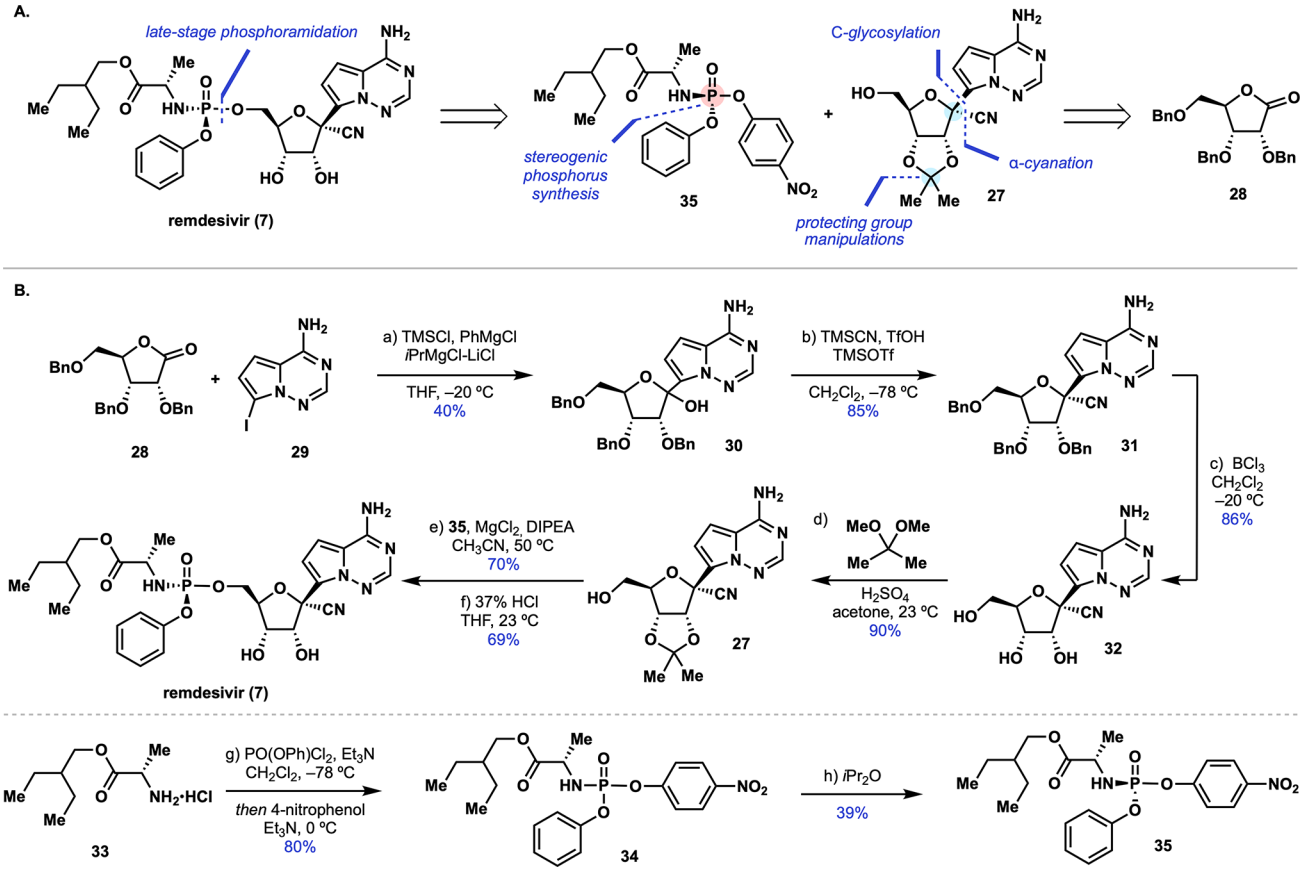
Scheme 1. Synthesis of Remdesivir



desired *C*-glycosylation via 1,2-addition of an anion into benzylated ribolactone **28** to access nucleoside **30** in 40% yield. Cyanation of **30** occurs in high yield and diastereoselectivity to access cyano-nucleoside **31**. At this stage, cleavage of the benzyl groups on the nucleoside with boron trichloride cleanly affords triol **32** in 86% yield. Protection of the resulting vicinal C2′−C3′ diol of **32** as an acetonide furnishes substrate **27** for the phosphorylation reaction. The phosphoramidoyl chloridate partner is prepared from coupling of 2-ethylbutyl-L-alanine (**33**) and $PO(OPh)Cl_2$ under basic conditions. Following treatment with 4-nitrophenol, a mixture of diastereomers (**34**) is resolved through selective crystallization of the S_p isomer (**35**) in diisopropyl ether in 39% yield. The acetonide (**27**) is then coupled with **35** in the presence of $MgCl_2$. Subsequent cleavage of the acetonide under acidic conditions furnishes remdesivir (**7**) in a 6 step longest linear sequence from known ribolactone **28**.

We recognize that the current manufacturing route for remdesivir may have emerged from prior literature and patent disclosures by Gilead. Nonetheless, given the challenges associated with the synthesis of a complex nucleotide prodrug such as remdesivir (**7**), we have identified several areas of investigation which invite further development and creativity if chemists are to drive advances in antiviral research, especially in this time of need.

3.1. *C*-Glycosylation. The coupling of a nucleobase to a ribose through a C−C bond formation is a highly challenging step to effect. The development of new *C*-glycosylation techniques represents an important advance in the preparation of nucleic acid mimic compounds such as remdesivir (**7**).[82] The introduction of a C−C bond linkage instead of the usual C−N bond imparts hydrolytic stability to a nucleoside and can imbue the molecule with novel recognition motifs, impressively enabling a number of compounds with antiviral properties.[83] Most naturally occurring nucleosides exist in their *β*-anomeric form, requiring the stereoselective preparation of active drugs that mimic this motif to reflect this preferred diastereomer.[84] As was done in the synthesis of **7**, functionalization of a D-ribolactone is a common strategy to effect installation of the nucleobase in **30**. Organometallic species make competent nucleophiles for this purpose, but the resulting products are highly dependent on the substituents present at C2′, C3′, and C5′.[82] Further, the strongly basic nature of the nucleophile generated from the nucleobase requires in situ protection of the aniline moiety as the bis(trimethylsilyl)amine. The combination of the challenges in *β*-anomer selectivity, substituent effects, and in situ aniline protection results in a coupling step that proceeds in a reported yield of 40%. There remains an exciting opportunity for developing novel coupling methods not only to improve upon the existing approach of functionalizing the ribolactone but also for enlisting alternative, and possibly less expensive, feedstock chemicals.

3.2. Protecting Group Strategies. In the synthesis of nucleoside and nucleoside-containing natural products, protecting groups serve a critical dual purpose.[85] Masking sensitive functional groups is, at times, inevitable. However, protecting groups are often crucial for guiding the stereoselective functionalization of vicinal reactive centers on ribose cores. Early chemical glycosylations such as the Hilbert−Johnson reaction (and subsequently their silyl variants) have relied on anchimeric assistance of *O*-acetyl groups to achieve

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high β-selectivities.[86,87] In the context of *C*-nucleosides such as remdesivir, it has previously been observed that the α-selective functionalization with TMS-bearing nucleophiles, such as TMSCN, proceeds only in the presence of *O*-benzyl protecting groups which can stabilize the developing trimethylsilyl cation in the transition state.[88] However, while the benzyl protecting groups in **30** serve a key purpose in the stereoselective cyanation, the fact that the reported synthesis requires benzyl cleavage and subsequent installation of the acetonide over two steps highlights room for improvement in modern protecting group strategies. Indeed, we recognize that a general method for constructing tertiary stereocenters in nucleoside analogues without the need for protecting groups would be a powerful transformation in the context of antiviral research.

3.3. Phosphoramidate Coupling. Many ProTide drugs, such as remdesivir (**7**), require high diastereomeric purity at phosphorus for efficient in vivo conversion to the active triphosphate drug.[89] Compared to an abundance of methods for the construction of stereogenic carbons, the introduction of phosphorus stereocenters is also a fundamental challenge which remains underdeveloped.[90] While there have been several examples employing diastereomerically enriched phosphorylating reagents[91] (as in the case of **35**), there is a lack of general synthetic methods for the diastereoselective introduction of the phosphoramidate.[92] Innovation in this respect would represent a significant improvement as the synthesis of diastereomerically pure coupling precursors (such as **35**) is often achieved through a low yielding classical resolution. Also crucial to this step is the ability to select for coupling of the C5′ hydroxy group,[93] which invites further contributions, as this is classically accomplished through costly protecting group manipulations. Indeed, in the synthesis of remdesivir (**7**), protecting group manipulations of **32** were found to be vital for efficient coupling of the phosphoramidate; coupling of acetonide **27** in the presence of $MgCl_2$ proceeded in 70% yield compared to the analogous coupling of free triol **32** which proceeded in only 43% yield.[81] Recent advances in developing organocatalytic systems for concomitant activation of both the C5′ hydroxy nucleophile and the leaving group have allowed for selected diastereoselective synthesis of several ProTide analogues that partially address these shortcomings.[94] Despite this advance, more development is needed to extend these principles to a general method for diastereoselective phosphoramidate synthesis. Beyond this thought experiment, the construction of stereogenic phosphorus centers is central to the synthesis of many antiviral medicines, and there remain ample opportunities for improvement.

By focusing on the translational problem of remdesivir (**7**), one can see numerous opportunities for advancing new and fundamental methods that will be widely applicable. Indeed, many of the synthetic challenges present in a preparation of remdesivir still exist for numerous drugs that may be brought to market. In light of the current crisis, academic synthetic chemists should consider both how their ongoing fundamental research efforts can be applied to important therapeutics for the COVID-19 crisis. By performing translational research on molecules of interest like remdesivir, broadly impactful synthetic discoveries are certain to arise.

In light of the current crisis, academic synthetic chemists should consider both how their ongoing fundamental research efforts can be applied to important therapeutics for the COVID-19 crisis.

4. THE WAY FORWARD

In this In Focus paper, we have highlighted many of the challenges associated with the large-scale manufacturing of high-demand complex molecules like remdesivir. We now share our views on many of the future opportunities for how academic synthetic chemists can advance new synthetic strategies, invest in emerging transformative technologies, and rethink the way academic and industrial research efforts can work synergistically in response to this crisis. In the context of high-volume drug manufacturing, or the so-called "Age of Scalability",[95] we stress to an academic audience that optimal process routes should integrate cost-efficient methods for constructing the final API in a short synthetic sequence. Indeed, as others have noted,[96] chemical synthesis plays a central role in pharmaceutical drug discovery as a whole. Therefore, developing new chemistry and embracing transformational technologies in process development not only fundamentally advances the field, but also has a direct translational impact on delivering medicines to patients.

4.1. Repurposing Feedstock Chemicals. Chemists have often looked to the "chiral pool" as a renewable source of building blocks like ribose due to their utility for constructing complex natural products and drug compounds.[97] Similarly, in the face of a potential drug shortage amidst a global pandemic, feedstock chemicals—often the byproducts of the petroleum and agricultural industries—offer an attractive source of raw materials for drug synthesis.[98] While the use of feedstock chemicals toward the synthesis of complex molecules is a well-recognized opportunity in the field,[99] the need to rapidly manufacture hundreds of millions of doses of a given therapeutic both clarifies and challenges this broader aim. Indeed, the recent approval of remdesivir raises questions about whether the global supply of its raw starting materials can meet manufacturing demand, and therefore, repurposing alternative feedstock chemicals could be an excellent solution to this anticipated shortage.[100] The transformation of these commodity and feedstock chemicals into value-added materials for complex molecule synthesis is only made possible through transformational synthetic methodology.[101] We encourage the synthetic chemistry community to continue driving innovation in this area and develop new possibilities for repurposing feedstock chemicals into value-added material.

4.2. Robust Methods for sp^3-Functionalization. One of the inherent challenges in the synthesis of drugs such as remdesivir is the high degree to which they harbor stereochemical complexity. This level of complexity, however, is an outlier relative to many approved small molecule drugs. Indeed, the popularity and reliability of transition-metal-catalyzed cross-coupling reactions in industry have enriched the number of drug candidates that incorporate sp^2-rich arenes and heterocycles.[102] On the other hand, some have suggested that biologically active chemical space is, in fact, more biased toward sp^3-rich compounds due to their conformational rigidity, high three-dimensional shape complementarity, and excellent target specificity.[103] In the same way that development of powerful sp^2-coupling methods pushed the field to advance sp^2-rich drug candidates to the clinic, a similar resurgence in robust sp^3-functionalization

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methods is needed to facilitate broad access to this biologically active chemical space. Toward this end, C−H functionalization offers an attractive platform for decorating sp^3-rich molecular scaffolds with a variety of functional groups. Similarly, the advent of C−C functionalization methods has highlighted new strategies for carbon scaffold reorganizations to stereochemically complex intermediates.[104] Rendering these powerful synthetic strategies amenable to process-scale transformations, however, requires further investment in these research areas.

4.3. Principles of Green Chemistry. Principles of green chemistry[105] also carry significant weight in the development of sustainable manufacturing practices, and drug development is no exception. The use of large quantities of organic solvents and stoichiometric reagents generates a significant amount of waste, illustrating the need for more sustainable methods to produce essential medicines without unnecessarily damaging the environment. In light of these concerns, several areas of research have emerged as attractive solutions. The use of water as solvent, although traditionally neglected because of the low solubility and stability of many organic compounds in this medium, has challenged chemists to develop new methodology for adapting useful synthetic transformations to occur "on water" or under mild aqueous conditions.[106,107] In addition to enzymatic reactions, which are compatible with aqueous media and sustainable catalyst production,[108] transition metal catalysis employing earth-abundant base metals offers similar environmental and economic advantages.[109] Although nickel, iron, and cobalt catalysts have historically seen fewer pharmaceutical industry applications as compared to their precious metal counterparts, there has been recent progress in the development of first row metals for use in large-scale catalytic processes.[110] Photochemistry also represents a powerful tool for effecting complex transformations with minimal waste and byproduct formation. Indeed, a vast array of photochemical transformations that rely on minute catalyst loadings or solid-state, solvent-free reactivity have been reported, including use on manufacturing scale.[111] We encourage the continued exploration of these technologies and green chemistry tenets toward the manufacturing of essential medicines.

4.4. Biocatalysis. Biocatalysis has emerged as a powerful paradigm for effecting stereoselective reactions in a sustainable and scalable fashion.[112] Indeed, the recent awarding of the Nobel Prize in Chemistry to Professor Frances Arnold[113] is further testament to the growing impact of this area of research. With directed evolution techniques, enzymes can be engineered to a remarkable degree of activity and selectivity, providing high-value intermediates from simple biochemical building blocks. Compared to many conventional organic methods, biocatalysis operates under more environmentally friendly aqueous conditions and sources enzyme catalysts from renewable fermentation, obviating the need for expensive transition metal catalysts which require careful purification protocols. In addition, because of the abundance of engineered enzymes which operate under similar reaction conditions with few side reactions, biocatalytic cascades have emerged as powerful demonstrations of how complex molecules can be prepared through multiple stereoselective transformations in a single reaction vessel.[114] Biocatalysis thus represents an attractive platform for developing scalable, efficient reactions and should see rapid advances in the context of manufacturing complex pharmaceuticals.

4.5. Electrochemistry. Over the last two centuries, electrochemistry has been used in industrial processes to prepare large quantities of commodity chemicals. More recently, there has been a resurgence in electrochemical methods which offer a direct means for achieving challenging oxidations in an industry setting.[115] Despite the relative paucity of electrochemical transformations in the fine chemicals and pharmaceutical industry, performing oxidations under "green" conditions with electric current instead of stoichiometric oxidants merits further attention.[116] From a safety perspective, process-scale oxidations with stoichiometric oxidants present unique challenges due to dangerous runaway exotherms and handling of sensitive reagents.[117] Electrocatalytic oxidations not only circumvent these concerns but also represent promising avenues for repurposing feedstock chemicals into value-added intermediates for drug manufacturing.

4.6. Computer-Assisted Synthesis. As one considers which tools to prioritize in the development of new syntheses, it is worth noting that the surge in the popularity of high-throughput experimentation and data analysis, faster physics-based calculations, and machine learning (ML) has brought computer-assisted synthesis into the forefront of many synthetic toolkits. To this end, the development and publication of well-designed data sets and development of new physics-based descriptors are fundamental to applying established ML techniques to synthetic chemistry in a meaningful way. These applications commonly take the form of synthesis planning,[118] selectivity predictions,[119] or reaction optimization.[120] In investigating a particular target, synthetic chemists often evaluate several routes in parallel to test a desired go/no-go step that may be the lynchpin of a particular route—by applying these computational tools, one can ideally predict a priori whether a step is feasible and thus inform better prioritization. Additionally, as many reactions require intensive optimization, the implementation of tools to automate or design better optimization strategies could significantly reduce the amount of resources spent improving a new method. While there has been significant progress in this regard since the advent of computer-assisted synthesis more than half a century ago,[121] there is still a need to continue refining these techniques. Indeed, these tools have already been applied to some facets of the COVID-19 crisis such as determining low-cost routes to hydroxychloroquine,[122] which is currently being investigated as a potential therapeutic.[2] We posit that the increased development and implementation of these newly developed toolkits will be vital to developing the best possible routes as they become standard in the field of synthetic chemistry.

4.7. Global Collaborations. In addition to advocating for the adoption of transformational technologies in modern drug manufacturing practices, we also encourage a reimagining of the evolving relationship between academic synthetic chemists and industry. During this period of high-intensity collaboration toward discovery of an antiviral treatment, global problems will require global solutions. Even companies cannot do this alone, and the intervention of outside philanthropic institutions can be beneficial to arrive at the best solutions. We need to internalize this lesson going forward. To make the most impact, academic laboratories will need to engage industrial collaborations as well as initiate multilab collaborations to tackle the problem from multiple fronts. Relationships with industry become particularly valuable for estimating manufacturing-scale costs of raw materials and chemical processes. These collaborations are the ideal combination of translational and fundamental research and will undoubtedly characterize the next era of synthetic chemistry to develop solutions to this crisis.

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5. CONCLUSION

Lessons learned from past efforts by synthetic chemists to address global health crises will effectively inform current and future efforts when a need of global proportions arises. Crises like these cause us to reconsider what we generally prioritize as impactful when conducting research in synthetic chemistry. While proof-of-concept advances are well incentivized in academia, we contend that the incremental advances from proof-of-concept to successful commercialization—and everything in between—are also important and should be recognized as such. In regards to methods development, there has already been a push to expand the scope to include polar functional groups and heteroatoms found in biologically active molecules;[123] however, in light of the current crisis, it becomes more important than ever to consider these translational aspects and to fully explore the limits of new methodologies to frame problem selection for future improvements. Ideally this should include reports of negative results, which are more likely to be omitted in publications and presentations. In addition to functional group tolerance, exploring the scope of a newly developed methodology should include the extension of the method to nonprivileged scaffolds.[124] Additionally, we caution that all of us in the chemistry community are very susceptible to the "overhype" of up-and-coming methods, and we urge students and scholars of chemistry not only to consider "attractive" problems that are more likely to lead to "high-impact" proof-of concept publications but also to recognize opportunities in more translational problems. These considerations can be specifically realized in the peer review process and more generally in the way that we evaluate the impact of fundamental and translational research. This change begins with the recognition that we, as academic synthetic chemists, have a role in addressing the "valley of death" between a fundamental discovery and bringing the technology to the market through small steps.

The synthetic chemist's legacy in addressing past crises is impressive, yet the effort is never complete. In light of unsolved problems, we require a steady stream of innovation to solve the challenges for the current COVID-19 pandemic and future crises; the opportunities for chemists are manifold. Having considered the past successes in historical crises, here we have offered a series of observations and recommendations for how chemists can address this current crisis. Attention to *translational* problems can lead to questions of interest in a *fundamental* or academic level. The way forward for synthetic chemists is to embrace disruptive technologies, engage in collaborations that effectively harness the expertise of academic and industrial synthetic chemists, and consider the most effective manner to conduct fundamental research in a way that encourages translational applications. *In these uncertain times, we must do everything we can to address the challenges ahead. It is time to react.*

The synthetic chemist's legacy in addressing past crises is impressive, yet the effort is never complete.

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