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# Reflections on a 40-year career in drug design and discovery

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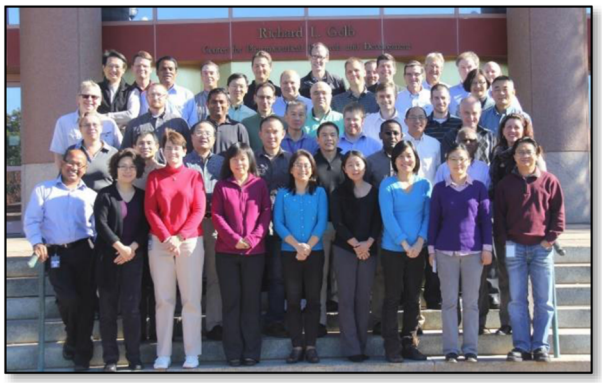
## Abstract

In this article, I reflect on a 40-year career in drug discovery at Bristol Myers Squibb that encompassed the cardiovascular, central nervous system and antiviral therapeutic areas. I share scientific observations made in the design and optimization of cAMP phosphodiesterase inhibitors, prostacyclin partial agonists, maxi-K ion channel openers, influenza and respiratory syncytial virus inhibitors, hepatitis C virus NS3/4A proteas, NS5A replication complex and NS5B polymerase inhibitors and inhibitors of HIV-1 attachment and maturation.



Zhongyu Wang, Brain Venables, B. Naidu Narasimhulu, Kevin Gillman, Eric Mull, Timothy Connolly, Louis Chupak, John Kadow, Kyle Eastman, Scott Martin, Jacob Swidorski, Manoj Patel, X. Alan Wang, Paul Scola, Kevin Peese, Omar Lopez, Jeff Romine, Kyle Parcella, John Bender, Rich Hartz, Michael Bowsher, Gan Wang, Xiaofan Zheng, Alicia Regueiro-Ren, Yong Tu, Zhiwei Yin, Zhong Yang, Van Nguyen, Sing-Yuen Sit, Eric Gillis, Makonen Belema, Li-Qiang Sun, Nick Meanwell, Piyasena Hewawasam, Catherine Hathaway, Ny Sin, Yan Chen, Kathy Grant-Young, Ning-Ning Xu, Min Ding, Qian Zhao, Barbara Zheng, Zheng Liu, Tao Wang. Missing are Zhongxing Tim Zhang and Jie Chen.

The virology chemistry team at Bristol Myers Squibb October 19th, 2015.

**Keywords** Phosphodiesterase 3 inhibitors · Prostacyclin agonists · Maxi-K openers · RSV inhibitors · HCV NS3/4A, NS5A & NS5B inhibitors · HIV-1 attachment & maturation inhibitors

**Abbreviations**

| | |
|---|---|
| ACAT | acyl-CoA:cholesterol acyltransferase |
| AI | attachment inhibitor |
| AUC | area under the curve |
| BID | bis-in-die (twice daily) |
| BMS | Bristol Myers Squibb |
| BPA | blood platelet aggregation |
| BVDV | bovine viral diarrhea virus |

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| | |
|---|---|
| CADD | computer-aided drug design |
| cAMP | cyclic adenosine monophosphate |
| CFTR | cystic fibrosis transmembrane conductance regulator |
| CNS | central nervous system |
| CSD | Cambridge Structural Database |
| CV | cardiovascular |
| FDA | U.S. Food and Drug Administration |
| GI | gastrointestinal |
| GT | genotype |
| HA | hemagglutinin |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV-1 | human immunodeficiency virus 1 |
| HTS | high-throughput screening |
| IND | investigational new drug |
| IV | intravenous |
| MMP | matched molecular pair |
| MOA | mechanism of action |
| NHV | normal healthy volunteer |
| NMR | nuclear magnetic resonance |
| NSAID | non-steroidal anti-inflammatory drug |
| PDE | phosphodiesterase |
| $PGI_2$ | prostacyclin |
| POC | proof-of-concept |
| PK | pharmacokinetic |
| RNA | ribonucleic acid |
| RSV | respiratory syncytial virus |
| SAR | structure-activity relationship |
| SLFN12 | Schlafen 12 |
| SNRT | sinoatrial node recovery time |
| U.S. | United States |
| USAN | United States Adopted Names |
| WT | wild-type |

## Introduction

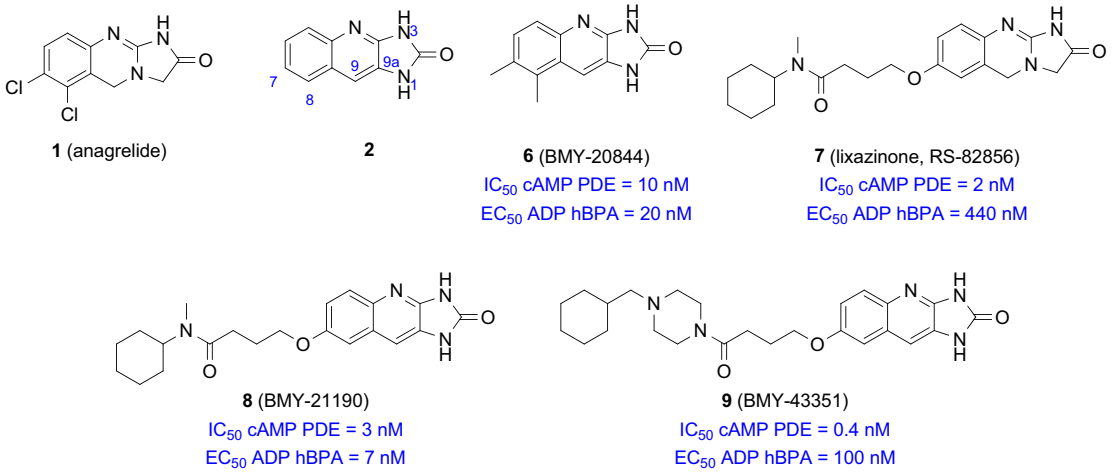
My family had no background in studying chemistry or, more specifically, organic chemistry, but I developed an affinity for this branch of science during high school where I focused my last 2 years of study on passing qualifying exams that would enable me to enter university. I was the first in my extended family to attend university and was followed 5 years later by my youngest brother, Neil J. Meanwell, who completed his Ph.D. in inorganic chemistry and who is currently a Professor of Chemistry at Camosun College, Vancouver Island, Canada. Neil's eldest son, Michael W. Meanwell, has recently started his independent career as an organic chemist at the University of Alberta where he is the Manley and Marian Johnston Professor in Chemistry. I completed my Ph.D. studies at the University of Sheffield in 1979 where I developed synthetic approaches to prostanoids and jasmone under the supervision of Dr. D. Neville Jones, a creative chemist who was also an inspiring mentor [1]. In early October of 1979, I began a post-doctoral fellowship at Wayne State University in Detroit, Michigan in the laboratories of Professor Carl R. Johnson where I developed aspects of sulfoximine chemistry, including the first preparation and reactions of sulfonimidoyl fluorides, and synthetic approaches to natural products like β-panasinsene and hop ether that, in part, sought to take advantage of sulfoximine chemistry [2, 3]. The Johnson laboratory was vibrant with a cadre of bright and capable graduate students that included Jim Zeller, who went on to direct the process group at Parke-Davis in Holland, Michigan, Mike Barbachyn, who would go on to discover linezolid, Tom Penning, who went on to be the lead inventor of celecoxib, John Kadow who was the lead chemist in the discovery of fostemsavir and beclabuvir, and Bob Elliott, who founded J-KEM Scientific. The experiences in these two laboratory settings were both complementary and rewarding, with the challenges encountered providing me with an important foundation for a career in drug design and discovery. I had been attracted to the pharmaceutical industry as a potential career after the compounds that I had prepared during my Ph.D. work were screened by Allen and Hanburys, the respiratory arm of Glaxo Laboratories. However, while this had piqued my interest in pursuing a career in drug discovery, I had only a very limited understanding of the principles of bioactive compound design. Nevertheless, I was able to fulfill that ambition in August of 1982 when I reported to work at the Mead Johnson site of Bristol Myers in Evansville, Indiana where I was to be part of the cardiovascular (CV) drug discovery group reporting to Dr. John E. Lawson. As a drug discovery venue, the Evansville site had originated in 1955 as the "Mead Johnson Research Center" established by the then newly-appointed corporate president D. Mead Johnson. Despite the small size of the enterprise, this site had developed a significant reputation in drug discovery and development by producing several drugs and drug candidates, including the β-adrenergic blocking agents sotalol and bucindolol, the antiarrhythmic agent encainide and the azapirone anxiolytic buspirone. An early and notable contribution to drug design emerged as a consequence of studies by Aubrey (Ole) Larsen who devised the methanesulfonamide moiety as a phenol bioisostere that is a hallmark of the structure of sotalol. My arrival in Evansville coincided with the harmonization of research at Bristol Myers into the "Pharmaceutical Research and Development Division" under the leadership of Dr. Giulio Vita and the retirement of Larsen.

The first project that I was assigned to was to explore analogues of anagrelide (**1**), an inhibitor of blood platelet aggregation (BPA) discovered by phenotypic screening that

had been advanced into clinical study where it was found to be far more potent in a Phase 1 trial than had been anticipated; unfortunately, the compound caused thrombocytopenia on repeat dosing that extended beyond 4 days and which led to a redirection of the clinical program toward the treatment of polycythemia vera and related orphan diseases [4]. However, my initial encounter with **1** ended abruptly when Dr. Vita declared a distinct lack of interest in the molecule at the annual program review meeting held 2 weeks after I had started work, a rather blunt introduction to pharmaceutical management decision making that, to a neophyte, seemed to reflect a somewhat mercurial nature that I had not anticipated. I was promptly reassigned before I had even been able to run my first chemical reaction and over the course of the next 12 months, I cycled through three programs in rapid succession, providing for a very frustrating first year, although one that was not without its useful lessons. Two pieces of sage advice that my colleague the late Graham S. Poindexter, an excellent mentor to all who knew him, shared with me during that time was to always conduct reactions on a reasonable scale such that even in the face of a poor yield, there would be sufficient material to complete several rounds of biological screening, of importance in an era where much testing was conducted in animal models of disease. That did not present a problem since that was my natural tendency; however, the second piece of advice, which was to always work with heterocycles, was a little more challenging given that up to that point in my career, my experience of heterocycles had largely been limited to THF and pyridine. Nevertheless, I embraced the philosophy and began to develop knowledge of heterocycle synthesis, properties and function, all of which I came to appreciate far more deeply with the fullness of time and experience.

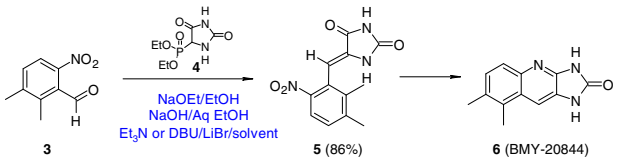
Michael J. Antonaccio had been recruited to lead the CV discovery group in early 1983 and in the summer of that year, he hired J.J. Kim Wright as head of CV chemistry to whom I was destined to report directly and indirectly for almost the next 20 years. They resurrected interest in **1** and late in the summer of 1983, I was asked to investigate the potential to identify molecules based on an alternate heterocyclic scaffold that would preserve the anti-platelet effects of the compound, which by then had been determined to be a function of inhibition of platelet cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE), but divorce from the thrombocytopenia. The latter was a seemingly formidable challenge since there was no preclinical model of the side effect, despite a survey of more than a dozen species, and no predictive in vitro assay; consequently, the approach pursued was one of identifying a novel chemotype that would be tested in humans based on the belief that an alternate heterocycle might mitigate the toxicity. Working initially as a lone chemist and under the threat of being moved to yet another project if I did not produce a lead within 6 months, we targeted a series of molecules that were to be prepared as ungarnished prototypes. These would then be equated with the modest but detectable potency of the parent 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one (i.e. **1** lacking the two chlorine substituents), a useful strategy that I continue to consider an effective approach and advocate for where appropriate. The parent 1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one **2**, a molecule with low prevalence in the literature that was restricted to just two published articles, both of which were >30 years old and which merely described synthetic approaches, emerged as the lead chemotype. The initial sample of **2** exhibited poor solubility properties, not unlike the tetrahydroimidazo[2,1-*b*]quinazolin-2-one series, and frustrated with trying to isolate pure material from the partially saturated 9,9a-dihydro precursor, I handed J. Stuart Fleming a sample of the mixture and asked him to test the compound prior to submitting it through the formal channels. He called me a few days later to inform me that the compound was an inhibitor of ADP- and collagen induced rabbit BPA with potency comparable to the anagrelide prototype [5]. Not surprisingly, this provided an impetus to rapidly develop a process to access the fully oxidized compound which reproduced the platelet inhibitory profile. We embarked on a broad synthesis campaign with assistance from a team that began to grow as the program evolved and BMY-20844 (**6**), the 7,8-dimethyl derivative, was identified as a compound suitable for advancement into clinical study. However, synthetic access to these molecules was long and laborious until we devised the Wadsworth-Emmons reagent **4**, a compound obtained straightforwardly by bromination of hydantoin followed by an Arbuzov reaction with triethyl phosphite, a process that was exothermic in nature. The phosphonate **4** proved to be a highly effective, reliable and practically convenient reagent for the preparation of C-5 substituted hydantoin derivatives, as depicted in Scheme 1 [6]. Phosphonate **4** would be my first marketed product since it was commercialized by Lancaster Synthesis after we had published the reactivity profile of the compound. The reaction of **4** with the activated but sterically encumbered aldehyde **3** provided **5** in 86% yield as a single isomer *via* a procedure that was both rapid and preparatively straightforward, with the product precipitating in essentially pure form after diluting the reaction mixture with water. The identity of the product was confirmed by measuring the long range $^{1}H$-$^{13}C$ coupling constant between the vinyl proton and the C-4 carbonyl carbon atom in the fully coupled $^{13}C$ nuclear magnetic resonance (NMR) spectrum with the *J* value larger for the *trans* relationship than the *cis* [6]. The subsequent hydrogenation of **5**, cyclization of the aniline onto the hydantoin C-4 carbonyl and oxidation to afford **6** was uneventful, benefiting from all of the optimization work that we had done up to that point. This preparative procedure was adopted by the process group to make the material needed for

investigational new drug (IND) toxicological and clinical studies [5]. The development of this synthetic methodology advanced the program significantly, providing rapid, convenient and reliable access to a wide variety of analogues with differing functionalities whilst also offering an important lesson in program prosecution. Another important lesson that I learned in this year of study was that the identification of a proprietary chemotype provided for the ready adoption of emerging and precisely how this observation relates to the thrombocytopenic effects of **1** remains to be determined. Interestingly, the recent developments that uncovered this biochemical pharmacological effect was the result of phenotypic screening, providing a compelling example of this approach to drug discovery whilst reflecting an interesting symmetry given that **1** was also discovered by a phenotypic screen [4].




emerging discoveries from others who had begun to explore the anagrelide chemotype, with several patent applications appearing in the second year of our effort. The advantage offered by the introduction of the amide-containing side chain observed with lixazinone (**7**) transferred to the imidazo[4,5-*b*]quinolin-2-one chemotype **2**, with **8** offering enhanced potency while **9** provided a homologue with enhanced aqueous solubility, an enduring challenge for both series [7, 8]. This highlighted the value of a proprietary chemotype to allow for the rapid interpretation and implementation of competitive developments and was a compelling strategic insight that has endured. Unfortunately, in a Phase 1 dose escalation clinical study, **6** failed to impart a significant effect on ex vivo BPA inhibition, presumably a function of absorption and pharmacokinetic (PK) issues that were not fully elucidated. It is also not clear that **6** would have resolved the thrombocytopenia side effect associated with **1**, the mechanism of which is only now beginning to come into focus 50 years after the compound's discovery [4]. Anagrelide (**1**) interferes with megakaryocyte differentiation and proplatelet formation and has been shown to stabilize a complex between a dimer of cAMP PDE3A and a dimer of the RNase Schlafen 12 (SLFN12), acting as a molecular glue that enhances the half-life of SLFN12 in cells whilst favoring the active, dephosphorylated form of the enzyme. The role and function of the Schlafen proteins, of which there are six expressed in humans, in physiology and disease is still

As the chemistry lead for what I viewed to be a developing anti-thrombotic franchise and with a drive to be successful in providing drug candidates, I engaged in developing a deeper understanding of the mechanisms of platelet function and the broader field of thrombosis whilst enhancing my awareness of competitive activity. Consequently, I began to prepare select compounds appearing in the literature that were claimed to be broad-spectrum inhibitors of BPA, the attribute that distinguished **1** and the imidazo[4,5-*b*]quinolin-2-ones **6**, **8** and **9** from the majority of the most prominent anti-platelet agents at the time, which were generally active against a narrower range of stimuli. The value of this approach was further enhanced by its potential to identify an alternate chemotype or mechanism of action that would fulfill our target profile should the imidazo[4,5-*b*]quinolin-2-one series fail to deliver on objectives, a concern that I subsequently learned would be a constant companion. This was another important and enduring insight that I developed and one that would subtend strategic decisions in many subsequent projects where either




**Scheme 1** Synthesis of BMY-20844 (**6**)

an alternate scaffold or mechanism of action (MOA) offered the potential for the rapid relief in the face of an unanticipated challenge. While almost all of the literature compounds that I prepared failed to meet expectations, one that did was the acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor octimibate (**10**), which I prepared in the summer of 1987 [9]. Octimibate (**10**) exhibited potency comparable to the parent imidazo[4,5-*b*]quinolin-2-one **2** and, interestingly, human platelets were 10-fold more sensitive to inhibition induced by ADP than rabbit platelets [10]. Preliminary studies by my biochemical pharmacology collaborator, the late Steve Seiler, indicated that **10** was enhancing cAMP levels in platelets, providing an explanation for the broad spectrum of inhibitory action [10]. Despite the absence of a defined mechanism of action and with the tacit approval of Kim Wright, I began to develop a plan to explore **10** in more detail. In a search for inspiration for design concepts, I sat down one Saturday afternoon in early October of 1987 and perused every molecule in the United States Adopted Names (USAN) dictionary seeking ideas for structural motifs that had some overlap with **10** and which might be gainfully explored. Whilst this exercise provided me with an excellent opportunity to review the existing pharmacopeia and assimilate the general complexion of drug molecules, a more important facet for me was that I would be reviewing and selecting chemotypes and functionalities from a body of molecules that had some form of validation as a drug or drug candidate. In effect, I was unwittingly following the wisdom and advice of Sir James Black who said "The most fruitful basis for the discovery of a new drug is to start with an old one", a comment that I encountered only much later, although I have been unable to precisely pinpoint its origin [11]. One molecule that I found intriguing and appealing based on its relative simplicity was the non-steroidal anti-inflammatory drug (NSAID) oxaprozin (**11**) which incorporated a 4,5-diphenyloxazole ring, a heterocycle that I had not previously encountered, and a propionic acid side chain. After perusing the literature associated with oxazoles, which was more of a burden then in the absence of digital literature searching, and learning how they were constructed, I began the campaign by synthesizing the nonanoic acid homologue of **11** which inhibited human BPA with $EC_{50}$ values of 1.4–2.5 μg/ml, about 10-fold less potently than **10** [12]. With the view that we may need an azole heterocycle with 4 vectors that would more effectively mimic those of **10**, we adopted pyrazole as a workhorse heterocyclic chemotype with which to explore structure-activity relationships (SARs), a decision that was instrumental in deducing fundamental aspects of the molecular topology of the pharmacophore [13]. A few months into the campaign, Steve Seiler called me one morning to inform me that he and his team had elucidated that **10** was functioning as a partial agonist at the prostacyclin ($PGI_2$) receptor, which explained the observation of elevated cAMP in platelets while enhancing the appeal of the chemotype since it would act synergistically with cAMP PDE inhibitors [10]. Interestingly, I had not seen Steve face-to-face for about a week, an unusual occurrence that, in this case, had coincided with me experiencing a reaction to being exposed to some of these compounds. I had experienced a form of facial flushing and swelling, with a reddening of the skin but with no discomfort and no other symptoms that might be attributed to $PGI_2$ agonism. When Steve called me, the effect had begun to wane and my skin had taken on a sort of waxy pallor whilst my new associate, Michael Rosenfeld, was beginning to experience some skin sensitivity with the appearance of reddened blotches. The synthetic accessibility of these early compounds was such that, at this point in the effort, we were typically preparing five or more final compounds a week on gram scale and the $PGI_2$ agonism provided a potential explanation for the symptoms. While the effect may have been related to the specific compounds being made at that time, we exercised greater caution and a heightened awareness of the properties of the compounds more broadly, with the result that, for us, there was no significant reoccurrence. Although we explored a wide range of azoles, an exercise that provided us with practical insight into their synthesis, attributes and physicochemical properties, we adopted the 4,5-diphenyloxazole as the main vehicle for drug design based on its properties and synthetic accessibility. By installing aromatic rings in the side chain of the nonanoic acid lead, we hoped to constrain conformational mobility as a means of pre-organizing the molecule for optimal receptor recognition, a strategy that ultimately led to the design of BMY-45778 (**12**) as the most potent and defining compound of the series, which was prepared by Jeff Romine [14, 15]. Interestingly, the single crystal X-ray structure of **12** revealed that the phenoxy ring, both oxazole heterocycles and one of the phenyl rings attached to the terminal oxazole adopted a planar topography, with just a $10^{o}$ variation from planarity (Fig. 1), a topography also found to be present in solution based on $^{1}$H-NMR analyses that were enabled once we had a developed the necessary cadre of molecules to study [14]. This was an important element in

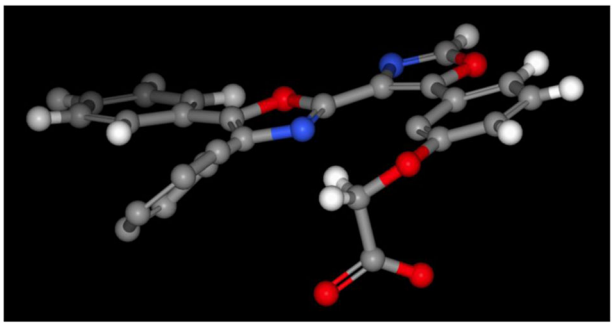
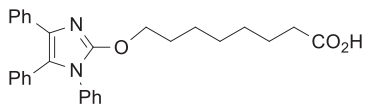
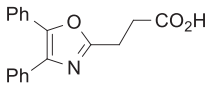


**Fig. 1** Single crystal X-ray structure of **12** depicting the planar topography (Cambridge Structural Database (CSD): PIDWII, 1233161)

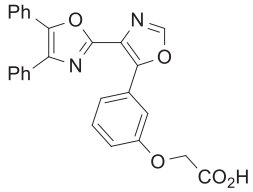
molecular recognition since analogues not able to access a planar topographical arrangement were much less potent, indicative that the binding pockets of some targets demand planarity in their ligands. This is an interesting insight in an era when escaping from the flatlands has been persistently advocated and to which I am fully sympathetic [16]. Interestingly and, somewhat surprisingly given the partial agonist nature of these compounds, we were not able to identify a $PGI_2$ antagonist from the large and diverse collection of molecules that we had synthesized throughout the program.



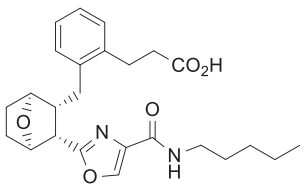
**10** (octimibate)



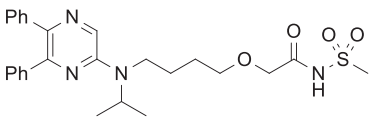
**11** (oxaprozin)



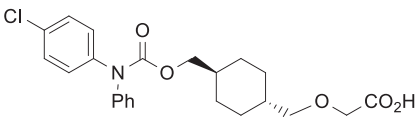
**12** (BMY-45778)



**13** (ifetroban)



**14** (selexipag)



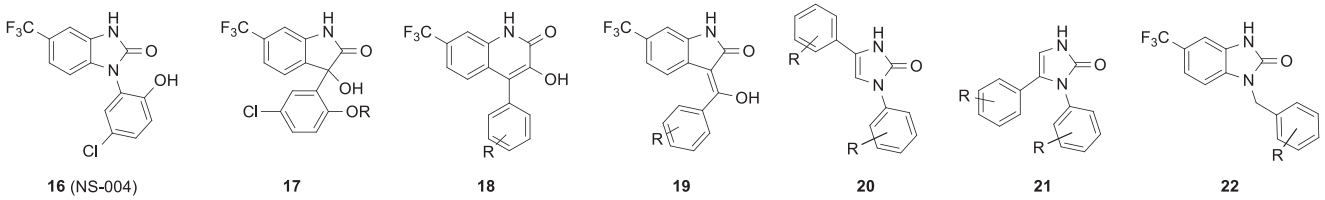
**15** (ralinepag)

My anti-thrombotic era came to an end in late 1991 following the final consolidation of research under the new Bristol Myers Squibb (BMS) organization where the priorities of the cardiovascular group were directed toward thromboxane receptor antagonists, as exemplified by ifetroban (**13**). The 1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one program ended with a failure to identify compounds with targeted metabolic stability while the non-prostanoid $PGI_2$ agonist project ended with studies conducted in cynomolgus monkeys who were found to be poorly tolerant of orally administered **12**. However, the non-prostanoid $PGI_2$ agonist chemotype was of interest to other companies and the pharmacophore that we had painstakingly mapped out is represented in selexipag (**14**), a prodrug discovered by Nippon Shinyaku and developed clinically by Actelion for the treatment of pulmonary arterial hypertension (PAH) [17]. This compound was part of the $30 billion dollar acquisition of Actelion by Johnson and Johnson in 2017 and is currently marketed as Uptravi®, with the value of the drug for those suffering from PAH reflected in worldwide sales that reached $1.322 billion in 2022. In addition, United Therapeutics is currently evaluating ralinepag (**15**) in Phase 3 clinical trials, also for a PAH indication [18].

With the consolidation of research at the new Bristol Myers Squibb organization, which meant that the CV group would be based in Lawrenceville, New Jersey, I availed myself of the opportunity to move into the central nervous system (CNS) arena where I hoped to expand my therapeutic area experience and further advance my medicinal chemistry knowledge and skills. There I began collaborating with Val Gribkoff, a scientifically rigorous electrophysiologist who was advocating for studying openers of the large conductance, $Ca^{2+}$-dependent potassium channel known as maxi-K as an approach to enhancing cellular hyperpolarization that would protect neurons against the excitotoxic cell death that follows a stroke and contributes to the development of the ischemic penumbra [19]. The benizimidazol-2-one derivative NS-004 (**16**) was a prototype maxi-K opener that was adopted as a lead molecule after confirming its activity in electrophysiology assays and we began to develop a plan to explore and understand the channel opening pharmacophore inherent to the compound. In contemplating **16** as a design template and in the complete absence of any SAR information, we initially assumed that the secondary amide, the phenol moiety and the $CF_3$ substituent were important contributory elements to the pharmacophore and these were preserved in the concepts that we developed, which were designed to provide additional opportunities for structural elaboration. The initial design concepts focused on exploring the relationship between the phenolic hydroxy substituent and the heterocyclic core which, by virtue of the single rotatable bond in the molecule, suggested the potential for either an orthogonal arrangement, represented by 3-hydroxy oxindoles **17**, or a coplanar arrangement where we designed templates that projected the phenol and C=O moieties in proximity, as represented by **18** and **19**. In addition, we contemplated the two topologically complementary deannelative arrangements captured in **20** and **21** and the effect of altering the functional group relationships in the stretched analogue **22**.

These concepts provided ample opportunity to explore the substitution pattern of the phenol and heterocyclic rings while success with one of the concepts would allow introduction into the others, although with some interpretation dependent on the structural background. However, the ability to explore many of these concepts required the development of synthetic methodology to access key building blocks that, at that time, were not available commercially. A particularly important intermediate was 6-trifluoromethyl isatin (**25**), a precursor to **17**–**19** that could not be accessed by the classic Sandmeyer synthesis because formation of the heterocycle ring element relied upon a ring closure reaction that was dependent on the nucleophilicity of the aromatic ring. This problem was solved by combining *ortho*-directed metalation of *tert*-butyl (3-(trifluoromethyl)phenyl)carbamate (**23**) to generate the lithium anion which was reacted with diethyl oxalate to afford **24** which, in turn, was cyclized to give **25** under aqueous acidic but not anhydrous acidic conditions, as summarized in Scheme 2 [20–22]. A new synthetic approach to the selective functionalization of benzimidazole-2-one that provided access to analogues of **22** was also developed as part of this campaign [23].

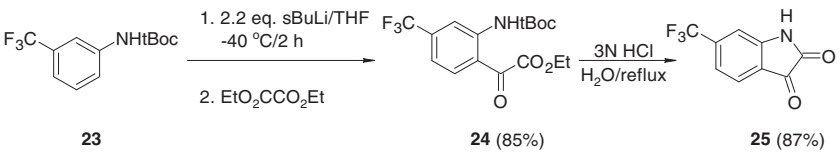
found ourselves in a position to screen prototypical representatives of each chemotype and select the optimal leads for further study. There was thus an absence of the pressure to pursue the first positive lead molecule that came along, a circumstance that allowed for the removal of the kind of bias that had the potential to shape the overall trajectory of the program. We were able to comprehensively survey the various chemotypes with, remarkably, channel-opening activity observed in almost all of them. While the stretched chemotype **22** provided active maxi-K openers and delineated fundamental SARs which revealed a requirement for an electron withdrawing substituent on the phenyl ring of the heterocycle, the oxindole chemotype **17** offered improved efficacy at higher concentrations and was pursued more vigorously [24–27]. The 3-hydroxy-oxindole derivatives were active and also required an electron withdrawing substituent on the heterocycle for expression of channel opening activity, while the 3-fluoro homologues demonstrated improved CNS penetration. Flindokalner (**26**), devised and synthesized by Piyasena Hewawasam, was ultimately selected for clinical study and subsequently advanced into a Phase 3 clinical trial for evaluation as an intravenously



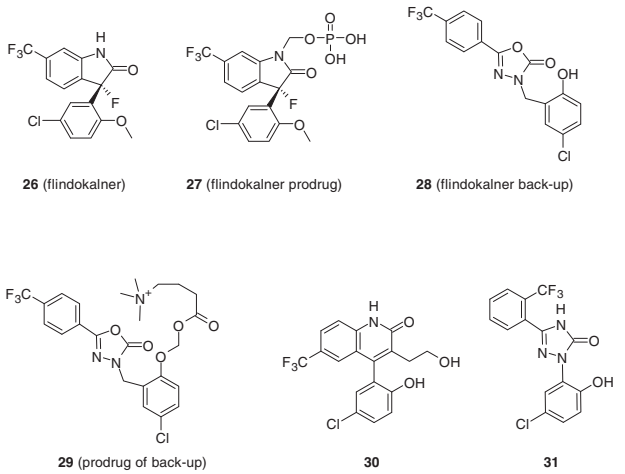

In the first year of the maxi-K program, compound screening proved to be laborious because of a reliance on testing compound effects on native maxi-K channels in patches isolated from neuronal cell membranes where these channels were not sufficiently abundant to allow routine evaluation. Although a possible source of frustration, we took advantage of this opportunity to explore all of the design concepts that had been conceived which we were able to complete in relatively short order. With the obtention of a clone of the maxi-K channel RNA from mouse (*mSlo*) and, subsequently, human (*hSlo*) that expressed the channel proteins in *Xenopus oocytes*, we

(IV)-administered treatment for the improvement of symptoms following a stroke [19, 25–27]. However, it was shortly after the discovery of **26** that I was recruited by Kim Wright to lead virology chemistry and John Starrett assumed responsibility for the maxi-K chemistry team, collaborating with Val Gribkoff to complete the preclinical profiling of **26**. John subsequently addressed the limited aqueous solubility of **26** with the phosphonooxymethyl prodrug **27** and identifying the 1,3,4-oxadiazol-2(3*H*)-one **28** and its prodrug **29** as back-up compounds [28–30]. The discovery working group also advanced the quinoline-2-one **30** into clinical study for the

**Scheme 2** Synthetic approach developed to access 6-trifluoromethyl isatin (**25**)



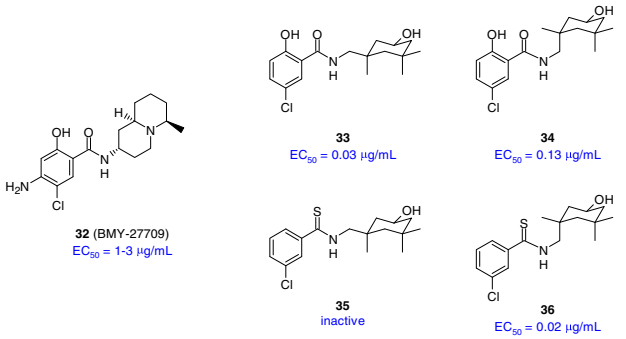
treatment of erectile dysfunction and the triazolone **31** for the treatment of urinary incontinence [31, 32]. Unfortunately, **26** failed to demonstrate a significant activity in ameliorating the effects of an ischemic stroke, adding yet another mechanism to the broad palette of failure for this devastating disease, whilst **30** and **31** ultimately failed to advance to late-stage clinical studies [33].



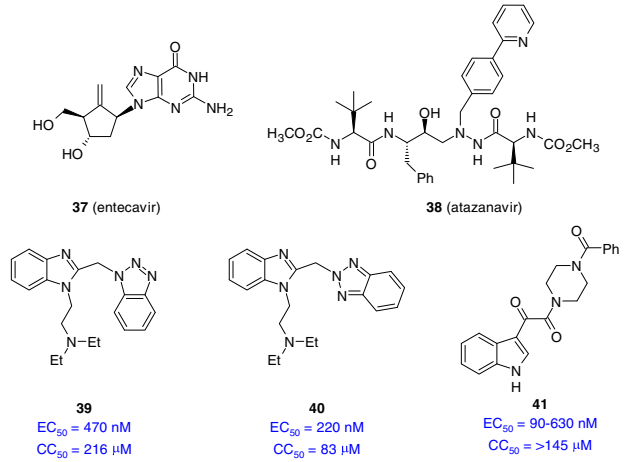

One interesting opportunity that emerged from this program was when Val Gribkoff examined the effects of **16** on the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-dependent small conductance chloride channel that had first been cloned in 1989 [34]. In *Xenopus* oocytes expressing wild-type (WT) CFTR, concentrations of **16** ranging from 10–30 µM rapidly and reversibly enhanced current to 30–60% of the maximal effect of cAMP. The effect of **16** was muted when tested against the ΔF508 mutant channel with <20% increase in current compared to WT but co-application with cAMP produced an enhanced effect. In a collaborative effort conducted in Michel Lazdunski's laboratory near Nice, France, the effects of **16** on WT and ΔF508 CFTR were reproduced and extended to Vero cells expressing the chloride channels, with the data suggesting that the drug targeted the phosphorylated form of the channel [34]. Although this study presented an interesting opportunity for drug discovery that would ultimately be addressed more than a decade later with the development of clinically effective channel potentiators (channel openers) and channel trafficking correctors, after careful deliberation the company chose not to pursue therapeutics directed toward cystic fibrosis, a disease management area that fell outside of the existing portfolio and focus [35].

The structural diversity of the clinical compounds to emerge from the maxi-K program reflects the benefit of developing the broad range of scaffolds that were explored in the first year of the campaign and provided an excellent foundation for the considerable success the team enjoyed in identifying clinical candidates that targeted both the CNS and periphery. In contrast, my life in virology during this period was considerably bleaker as we sought to continue to develop mechanistically novel human immunodeficiency virus-1 (HIV-1) inhibitors and to build a preclinical and clinical franchise around inhibitors of both hepatitis C virus (HCV), which had just been characterized molecularly, and respiratory viruses. Using a phenotypic screening approach, Mark Krystal and his team had discovered and characterized the influenza virus fusion inhibitor **32** and Milind Deshpande, who was leading the burgeoning library synthesis group, devised and constructed a small library of 175 compounds in which the amine moiety was varied. This initiative identified the cyclohexanol **33** as a compound with enhanced antiviral potency compared to the prototype, with the axial isomer **34** 4-fold weaker. This result provided an excellent lesson in bias in drug design since I had assumed that the amine in **32** was likely to be pharmacophoric. However, the library prepared by Milind and his team demonstrated the potential of focused combinatorial chemistry to rapidly explore a pharmacophore in an unbiased fashion. The amine discovered with **33** and **34** was then used to interrogate potential salicylic acid replacements which identified a thioamide derivative that, interestingly, was the result of reaction at an alternative site of the substrate to that anticipated. In this chemotype, the axially-disposed isomer **36** was considerably more potent than the equatorial isomer **35**, the reverse of the SAR associated with **33** and **34** [36–39]. Unfortunately, the lead molecule **32** exhibited antiviral activity toward only the H1 and H2 hemagglutinin (HA) subtypes and despite an extensive study around the chemotype that was expansive in nature, we were never able to achieve significant inhibition of the H3 virus subtype. A detailed scientific examination that was able to combine resistance mutation data with labeling by an azide-based photoaffinity probe that generated a reactive nitrene intermediate on irradiation, provided an understanding of the observed profile. The photoaffinity labeling experiments presented a challenge but the broad-based SAR survey that had been conducted along with experiments that had identified inhibitors of the HA inhibitors indicated that under the acidic conditions of the assay, the compounds were trapped in the HA protein and could not readily be displaced. This suggested conducting the photolabelling experiments at low pH, an experimental design that more effectively captured the active site residues with the nitrene probe. This allowed us to propose that the salicylamide moiety functioned as a carboxylic acid bioisostere by engaging with the side chain guanidine of an arginine residue that was present in H1 and H2 HA but not in H3 HA, where the residue was a histidine, much less

basic and lacking the two H-bond donors that would complement **32**–**34**. With the inability to identify a viable chemotype with broad spectrum influenza inhibition, we abandoned this program after 18 months. However, while were unsuccessful in identifying broad spectrum influenza inhibitors, the scientific discoveries and insights that were gleaned were interesting and proved to be informative for later programs, particularly in HCV.

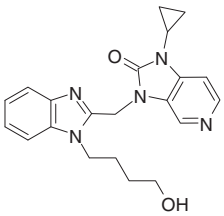



The virology biology and chemistry groups spent the next few years devising and implementing a range of screening assays for several viruses of interest and exploring medicinal chemistry approaches to biochemical targets. However, we had little to show for our effort although under Rich Colonno's leadership of virology, entecavir (**37**) was discovered to be a potent hepatitis B virus (HBV) inhibitor and the HIV-1 protease inhibitor atazanavir (**38**) was licensed in, both of which went on to be highly successful drugs [40, 41]. Persistence is an important trait, although it can be abused and, despite the limited library of compounds available for screening at that time, our proclivity toward phenotypic screening ultimately proved to be fruitful. Mark Krystal and his team discovery the respiratory syncytial virus (RSV) fusion inhibitors **39** and **40** while a screen devised by Pin-fang Lin and Wade Blair identified the prototype HIV-1 attachment inhibitor **41**, both of which acted on viral coat proteins, although with quite different and novel MOAs [42–45]. The RSV inhibitors **39** and **40** had been in the compound collection for over 30 years and had experienced many screening campaigns without producing a positive effect, thus largely being viewed as dark matter prior to our discovery. The glyoxamide **41** was a member of a commercial library of amides and sulfonamides that had developed some notoriety within BMS for its low fidelity of purity, with several samples still containing acid chloride substrates that would often be active in a screen but of no redeeming value as lead molecules. Fortunately, we were able to reproduce the inhibitory activity of **41** with freshly synthesized material and this molecule proved to be a bona fide lead that we would spend more than 6 years investigating and developing.

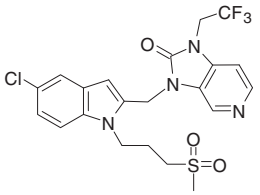



Careful profiling of these leads confirmed their validity and both spawned full phase optimization campaigns, with the RSV inhibitor program ultimately identifying BMS-433771 (**42**) as a clinical candidate although not after some travail [46]. To demonstrate proof-of-concept for antiviral effect in the cotton rat model of infection, we had to resort to a topical delivery mode in which the animals were exposed to an aerosol of the drug for 22 h a day. This required 20 gram quantities of inhibitor with a water solubilizing element, which the pharmacophore fortunately tolerated. Kuo-Long Yu and the team provided these materials with seemingly apparent ease, with synthetic accessibility to the benzimidazol-2-one derivatives that had become the workhorse chemotype benefitting from the earlier methodology development [23]. MOA studies with this chemotype relied upon the characterization of viruses grown to be resistant to **42** and were complemented by the development of a diazirine-based a photoaffinity probe that was designed to generate a reactive carbene to label the virus target protein. These studies initially identified the fusion (F) protein as the target, while labeling studies conducted with elements of the purified F protein suggested that the molecule interfered with 6-helix bundle formation, a critical step that occurs during the later stages of the membrane fusion process [47]. Interestingly, subsequent crystallographic studies conducted by others pursuing RSV fusion inhibitors based on this chemotype and others suggested that they bound to the core of the intact fusion protein trimer, stabilizing it toward the conformational changes essential for triggering membrane fusion and a productive infection [48]. Unfortunately, a change in strategic direction at BMS led to **42** being abandoned just 1 month before the IND application was anticipated to be filed. While this was a disappointment for a team that had overcome several significant challenges, the chemotype and MOA attracted the attention of others and both

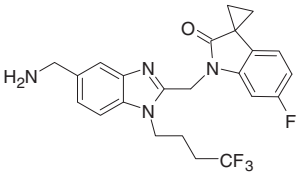
riletamovir (**43**) and sisunatovir (**44**) have demonstrated clinical efficacy in experimental infections in normal healthy volunteers (NHVs) [48–52]. While **43** was advanced into Phase 3 clinical studies, it appears to have been abandoned by its sponsor in 2022. The FDA granted Fast Track designation to **44** in 2020 and in 2022 the compound was acquired by Pfizer as part of a transaction with a value of up to $525 million [53].




**42** (BMS-433771)




**43** (riletamovir)

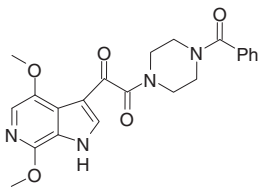



**44** (sisunatovir)

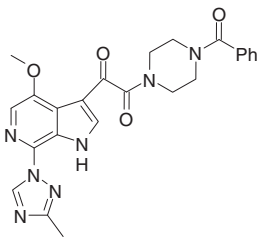
The HIV-1 AI program presented unique challenges associated with the gp120 target, with variability in the sensitivity of a number of viruses despite the good sequence conservation in the putative binding site pocket. HIV-1 gp120 is a protein that exploits conformational mobility as one element in avoiding immune surveillance, with glycation (the glycan shield) and the ability to generate resistance mutations being the other two methods. Surveying the SARs associated with the lead HIV-1 AI **41** using the pseudovirus assay that had identified the hit molecule moved quickly initially based on the relative ease of exploring variations to the benzoyl moiety; however, molecular edits at this site were poorly tolerated and this motif was maintained throughout much of the program. Considerably greater success was achieved by substituting the core indole from which the 4-fluoro and 4-methoxy analogues were 50- and 300-fold more potent than **41**, respectively. The C-5 and C-6 positions of the indole heterocycles were poorly tolerant of substitution but C-7 was not, and the C-4, C-7-dimethoxy indole derivative exhibited an $EC_{50}$ of 250 pM in the pseudovirus assay. However, the intrinsically poor aqueous solubility of the chemotype was a persistent challenge that was addressed, in part, by exploring azaindole derivatives that ultimately focused on the 6-aza chemotype since that allowed substitution at both C-4 and C-7 [54]. Prosecution of the program required the development and/or optimization of a number of synthetic methodologies in order to access the full panoply of target molecules as we wrestled with the challenges presented by potency variation and the inherent pharmaceutical properties [55]. BMS-488043 (**45**) emerged as a clinical candidate that provided proof-of-concept (POC) for the HIV-1 AI mechanism in a Phase 2a clinical study where there was a dose-related reduction in viral load, although concomitant administration of the drug with a high fat meal was required in order to drive plasma exposure, a function of solubility- or dissolution-limited absorption problems with the molecule. While **45** was advancing in the clinic, optimization continued and under John Kadow's leadership we found that a heterocycle substituent installed at C-7 was optimal, with those azoles and azines that were capable of adopting a coplanar arrangement with the azaindole core the most potent. This finding built upon observations made by Kap-Sun Yeung with the indole chemotype with C-7 carboxamides in which the dimethyl-amide was substantially less active than the mono-methyl or primary amide, interpreted as a need for coplanarity between the core and the substituent. This was another example of pharmacophore favoring planarity and since *N*-linked azoles offered an advantage in PK profiling assays, temsavir (**46**) was selected as a clinical candidate and advanced into Phase 1 study. However, the need for a high fat meal to drive the plasma exposure of **45** precipitated a campaign to identify a solubility-enhancing prodrug, with a phosphonooxymethyl moiety fulfilling the needs of the program, demonstrating excellent dose escalation in preclinical studies and abrogating the food effect. Phosphonooxymethyl prodrugs of both **45** and **46** were prepared as well as an additional analogue of the latter compound, with salt selection important for compound isolation and chemical stability. The application of this kind of prodrug is best suited to BCS class II compounds that exhibit high membrane permeability but low aqueous solubility and requires a delicate balance of drug properties and release, which occurs presystemically and is mediated by alkaline phosphatase at the brush border membrane in the gastrointestinal (GI) tract, to ensure that drug is absorbed before precipitating in the gut. Fostemsavir (**47**) was accepted as a clinical candidate along with two other AI prodrugs, with one falling out in IND toxicology studies when the parent drug precipitated in tissues, a function of its intrinsically low aqueous solubility combined with the ability of the phosphonooxymethyl prodrug technology to very effectively deliver drug to plasma and tissues. The success of this phosphonooxymethyl-based prodrug approach, for which precedent had largely been restricted to IV drugs, led to the formation of a team at the Biocon-Bristol Myers Squibb Research Center in Bangalore, India dedicated to

developing expertise in prodrug design and exploration to provide solutions to a broad range of developability challenges across the portfolio. In addition, in order to further enhance the awareness of prodrug technology within BMS, I partnered with my colleague Dinesh (Dolatrai) Vyas from oncology, who had been intimately involved in the discovery of etoposide phosphate and other anticancer prodrugs, to publish an internal quarterly newsletter that captured emerging developments. Collaborating with Dinesh on this initiative was immensely rewarding at many levels since he is an excellent scientist who brought new dimensions to my knowledge and understanding of medicinal chemistry. Moreover, I not only benefited directly from his mentorship on this enterprise, but I was an indirect recipient of his mentoring skills through the several members of my team that he had nurtured through the early phases of their careers.

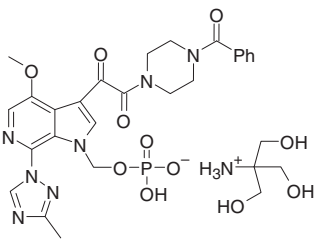
Fostemsavir (**47**) was approved by the United States (U.S.) Food and Drug Administration (FDA) on July 2nd, 2020 after being designated as "Breakthrough Therapy" and accorded "Fast Track" and "Priority Review" status to expedite review [57]. Approval in the European Union followed in February of 2021 and the drug is marketed as Rukobia® for highly treatment-experienced adults with multidrug-resistant HIV-1 who are failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. Fostemsavir (**47**) was the first HIV-1 drug with a new MOA to be introduced in the 15 year period from 2007 to mid-2022 and the interesting clinical profile of this molecule continues to be developed and understood [57–59]. The HIV-1 AIs have also been shown to be effective microbicides in non-human primates, particularly when used in combination with other virus entry inhibiting drugs, and



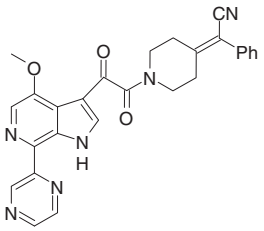
**45** (BMS-488043)



**46** (temsavir)



**47** (fostemsavir)

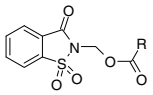


**48** (BMS-599793, DS003)

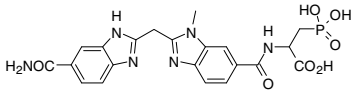
The capacity of **47** to deliver **46** in vivo in preclinical study was largely recapitulated in Phase 1 clinical trials, with the prodrug allowing dose escalation to targeted plasma levels that had been set after evaluation of **46** against viruses available from clinical studies with the protease inhibitor **38**. Targeted plasma levels were set at a concentration that would inhibit 90% of the circulating viral isolates by 90% ($EC_{90}$). However, the improved delivery of **46** from **47** unmasked PK deficiencies that had not been observed in preclinical studies, and it was clear that **46** exhibited a short plasma half-life in humans. This profile had been masked by flip-flop kinetics when administering **46** directly, a function of slow absorption due to the intrinsically poor aqueous solubility that had prolonged the absorption phase. At this point, Peter Timmins and Jonathan Brown at the BMS site in Moreton, England stepped in to develop an innovative slow-release formulation that relied upon the combination of a specialized site-of-absorption study and a novel in silico modeling approach to build an understanding of the drug release and absorption characteristics required to reliably deliver the drug on a bis-in-die (BID) dosing schedule [56]. This initiative was successful and provided a path forward for the Phase 3 BRIGHTE clinical study which was completed by ViiV Healthcare who had acquired **47** in 2016 [55, 56]. BMS-599793 (DS003, **48**) was licensed to the "International Partnership on Microbicides" who are studying the molecule for its potential to act as a topically-applied microbicide to prevent HIV-1 infection [60].

HCV was an important disease target from my very early days in virology but the absence of cell-based replication assays severely blunted inhibitor identification and characterization. We anticipated from the outset that combination therapy would be required to prevent the emergence of resistance since HCV was comprised of an RNA genome and there already existed considerable virus diversity with, at the time, 6 known genotypes (GTs) and multiple subtypes. GT1a was most prevalent virus in the U.S. and Europe while GT1b dominated in Asia. The development of in vitro biochemical assays had focused on the HCV NS3/4A protease and the NS5B RNA-dependent, RNA-polymerase (RdRp), antiviral targets with appeal based on prior experience with HIV-1 therapeutics, that were eventually enabled by X-ray crystal structure data. These assays were, by definition, approximations of the natural state in cells but were nevertheless useful for identifying lead inhibitors. The HCV NS3/4A protease was almost sloth-like in its processing activity compared to mammalian serine proteases and proved to be a challenging target, with an active site described as featureless or, as Carl

Decicco, my supervisor after the DuPont acquisition, liked to say, dimples on a golf ball. We explored saccharin and related activated carbonyl derivatives that were known mechanism-based serine protease inhibitor chemotypes that led to the discovery of the potent and selective inhibitors of mast cell tryptase **49** and **50** but not of HCV NS3/4A protease [61]. We subsequently engaged in a collaboration with Axys Pharmaceuticals designed to take advantage of their intriguing delta technology in which serine protease inhibitors that bound to the active site presented functionality with a geometry that, in conjunction with the catalytic serine oxygen and histidine nitrogen atoms, created a coordination site for $Zn^{2+}$ that would stabilize the complex. However, this identified only intractable inhibitors like **51** while the several series of peptide-based approaches that we explored were unsuccessful [62].

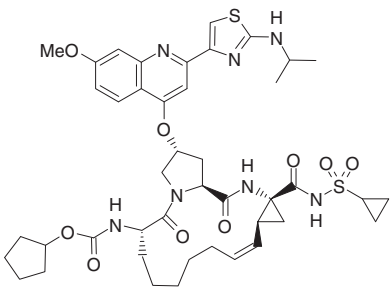


**49**: R = $(CH_2)_4NHCbz$
tryptase $IC_{50}$ = 110 nM
**50**: R = $C_6H_4$-4-NHCbz
tryptase $IC_{50}$ = 6.8 nM



**51** (APC-6336)

However, our prospects began to change in January of 2000 with the publication of a series of patent applications from Boehringer-Ingelheim that disclosed tripeptide-based inhibitors of HCV NS3/4A protease. These molecules were distinguished by the presence of a large $P_2$* substituent attached to the $P_2$ proline residue while the $P_1$ moiety was a substituted cyclopropylglycine and the C-terminus was a carboxylic acid moiety. These molecules were the result of a classic and painstaking medicinal chemistry optimization campaign that capitalized on the observation of product inhibition and provided an important foundation for HCV NS3/4A inhibitor design as well as the first clinical candidate based on this chemotype, BILN-2061 (**52**) [63]. This chemotype provided us with a suitable vehicle to explore the concept of exploiting the small but well-defined $S_1$' pocket of the enzyme, an idea that had been conceived several months earlier as we were winding down the collaboration with Axys Pharmaceuticals.

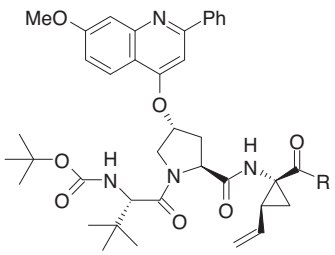


**52** (BILN2061)

The concept that had been envisioned was to access the $S_1$' site by exploiting an acylsulfonamide moiety that would preserve the acidic element that engaged the catalytic residues while providing for the read-through topology to project a substituent into the $S_1$' pocket. After having broken our pick twice on HCV NS3/4A protease as a biochemical target, we had been reluctant to propose exploring the concept in the context of the hexapeptide derivatives replete with several carboxylic acid moieties that were the most effective inhibitors at the time. We prepared the prototype acid **53** (Table 1) from the patent applications and were able to reproduce the claimed potency, with the simplest iteration of the design concept, the methanesulfonamide **54**, fully preserving the inhibitory activity of the progenitor [64]. However, guided by computer-aided drug design (CADD), the cyclopropyl homologue **56** offered significantly enhanced potency both in the biochemical enzymatic assay and, most particularly, in the GT-1b replicon assay that had just been developed by my colleague Min Gao and his team. X-Ray cocrystal structure data revealed that both of the sulfonamide oxygen atoms were involved in drug target interactions while the cyclopropyl ring optimally filled the $S_1$' pocket [65]. The *iso*-propyl homologue **55**, which results from the addition of just two hydrogen atoms to **56**, was 20-fold less potent in both assays, reflecting the importance of correctly occupying the $S_1$' pocket, while the cyclobutyl (**57**) and cyclopentyl (**58**) homologues were progressively weaker inhibitors than **56**.

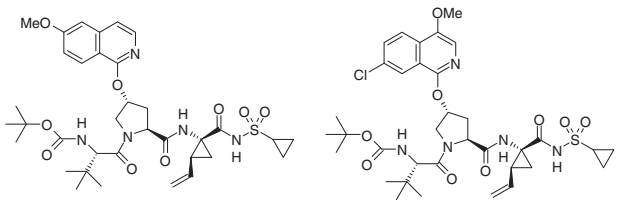
BMS-605339 (**59**) was the first candidate advanced into clinical study and demonstrated dose-dependent efficacy at reducing viral load following oral administration to

**Table 1** SARs associated with tripeptide-based inhibitors of HCV NS3/4A protease



| | R | $IC_{50}$ (nM) | $IC_{50}$ (nM) GT-1b replicon |
|---|---|---|---|
| **53** | OH | 54 | 660 |
| **54** | $NHSO_2CH_3$ | 37 | 1000 |
| **55** | $NHSO_2iPr$ | 19 | 97 |
| **56** | $NHSO_2cPr$ | 1 | 4 |
| **57** | $NHSO_2cBu$ | 4 | 29 |
| **58** | $NHSO_2cPentyl$ | 71 | 70 |

HCV-infected patients [64]. However, the compound was associated with mild bradycardia, PR interval prolongation and junctional rhythm disturbance, cardiac side effects that, although asymptomatic in nature, gave rise to significant safety concerns that, after considerable debate, was sufficient to terminate the clinical development of **59** [64, 66]. Humans were >50-fold more sensitive than preclinical species to the CV effects of **59** which could be recapitulated in a Langendorff isolated rabbit heart assay where heart rate decline and sinoatrial node recovery time (SNRT) prolongation were monitored, with test compounds assessed at a concentration of 10 µM. Despite the low throughput nature of this assay, Paul Scola and his team were able to identify BMS-650032 (**60**) within less than 20 structure-function iterations and concomitant with the decision to terminate **59**, a remarkable example of a combination of careful medicinal chemistry analysis, inspired drug design and intuitive interpretation of structure-function relationships. The structural differences between **59** and **60** are subtle in nature, with just a single chlorine atom added to the molecular formula and an alteration of the substitution pattern of the isoquinoline ring, but profound with respect to the cardiac liability profile. BMS-650032 (**60**) would become asunaprevir, named after its inventor Li-Qiang Sun.



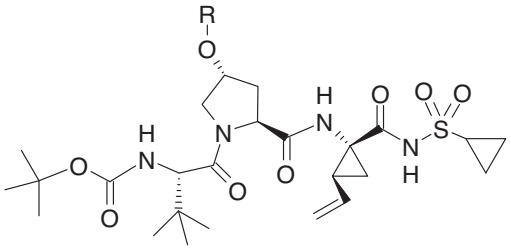
**59** (BMS-605339)

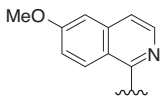
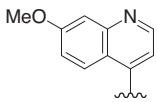
**60** (BMS-650032)
asunaprevir

In our studies, the isoquinoline $P_2$* moiety had offered improved PK properties, most effectively illustrated by the comparison between the data compiled in Table 2 for **61** and **62** [66, 67] The plasma area under the curve (AUC) in rats for the isoquinoline **61** measured over 4 h post-dose was almost 700-fold higher than that for the matched quinoline **62** whilst the liver levels of **61** were 100-fold higher. This is a remarkable effect for a seemingly subtle structural change in a molecule with a molecular weight of ~750 Da and which is not reflected in the antiviral profiles. A second example in a matched molecular pair (MMP) analysis of $P_1$-$P_3$ macrocycles amplified the difference to a 28,000-fold effect on the plasma area AUC and 1524 fold in liver exposure.

With the advent of the HCV replicon assay, which in its initial iteration was a GT-1b variant, the virology team engaged in a screening campaign that assessed the effects of ~200,000 compounds against HCV and a bovine viral diarrhea virus (BVDV) replicon as a phylogenetically closely-related *Flavivirus* that functioned as a stringent

**Table 2** Antiviral and PK profiling of matched isoquinoline and quinoline-based HCV NS3/4A protease inhibitors

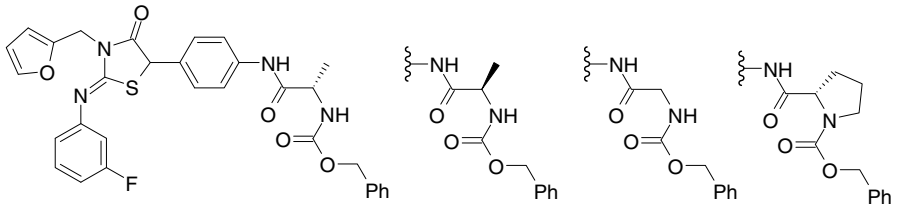


| R | **61**  | **62**  |
|---|---|---|
| $IC_{50}$ (nM) | 2.6 | 5 |
| $EC_{50}$ (nM) | 5.0 | 26 |
| AUC (µM. h) | 10.4 | 0.015 |
| Liver (ng/g) | 64710 | 620 |

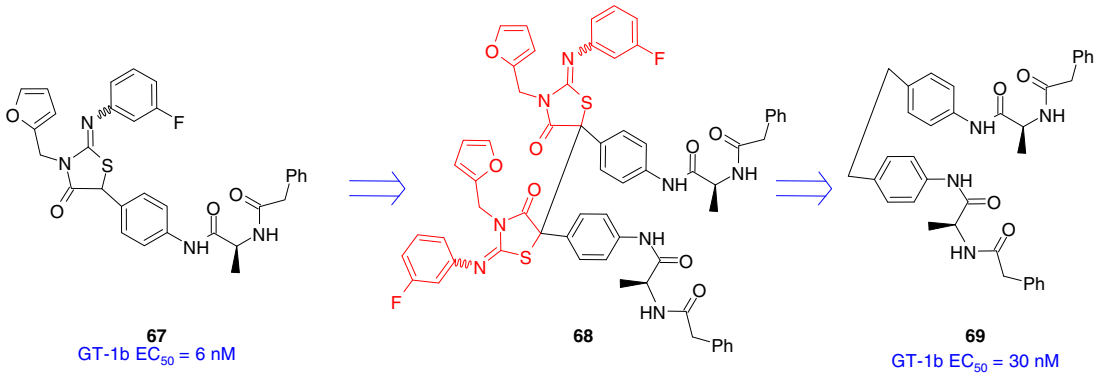
PK data are from rats dosed at 15 mpk ID in PEG/Tween 90:1 monitored from 0–4 h post dosing

counterscreen with which to triage hits [68]. The thiazolidinone **63** was identified as the only lead inhibitor, with its uniqueness emphasized by the absence of additional effective replicon inhibitors following screening of another 800,000 compounds [69]. Thiazolidinone **63** was a member of a purely prospective library synthesized in-house that differed significantly from literature compounds which were typically benzylidene derivatives prepared by a Knoevenagel condensation reaction between an aldehyde and the core heterocycle. Resistance studies with **63** mapped to NS5A, a protein with no known enzymatic activity that, even after 20 years of study, remains enigmatic in nature [70, 71]. While studies around the furan and fluorophenyl moieties gave a good dynamic range of potency, the SARs were less than precise and somewhat nebulous in nature in contrast to that associated with the alanine moiety, where there was high sensitivity to small molecular edits [68, 72]. Thus, the D-Ala isomer **64** was 200-fold less potent than **63** while glycine (**65**) and proline (**66**) were the only other active representatives of naturally occurring amino acids, with D-proline also considerably less potent than the natural L-isomer **66** [72]. However, as our familiarity with this chemotype grew, we became aware that some of them were inherently unstable. Concern about precisely what we were working with was heightened when incubation of the **67**, a close but more considerably more potent analogue of **63**, in replicon media for several days, during which time the compound was completely degraded, remarkably did not diminish its antiviral potency. Larry Snyder's determination

to understand this phenomenon was well-placed and he engaged the help of John Leet, the last vestige of the BMS natural products isolation group. John conducted a biogram analysis of the media that had been incubated with **67**, which identified two very minor degradants that demonstrated antiviral activity in addition to the more prominent inactive compounds that we had already characterized. The experiment was repeated on a larger scale with the compound incubated at a concentration of 100 µM in 2 liters of media, which allowed isolation of 1.1 mg of each of the active degradants which were characterized as dimers **68**, with one converting to the more thermodynamically stable isomer when heated in DMSO at 50 °C in an NMR tube. We had determined that degradation of **67** in DMSO was the result of oxidation at C-5 of the thiazolidinone heterocycle to generate a radical intermediate, with products presumably formed by a reaction with molecular oxygen, a diradical in its ground state. The presence of small amounts of the dimers **68** suggested that the C-5 radical, which is stabilized in a captodative fashion by the C=O, sulfur and phenyl substituents, was sufficiently long-lived to be able to find another molecule in the cell culture media, no doubt facilitated by some aggregative association. Given the SAR observations, we postulated that the pharmacophore might be represented by the bibenzyl **69**, a compound readily accessible from the stilbene **70** which, in turn, was prepared from the commercially-available embedded stilbene diamine. This hypothesis turned out to be correct, with the bibenzyl derivative **69** a potent antiviral agent in the GT-1b replicon while the olefin **70** was even more active, with a remarkable 350-fold potency advantage over **69** [71–73]. As a consequence of this development, the crystal structure of the amino terminal domain of NS5A, which revealed a dimeric species, that was published almost exactly 3 years after our discovery held no surprises, although it did create many questions and ideas about the MOA of our compounds [74].



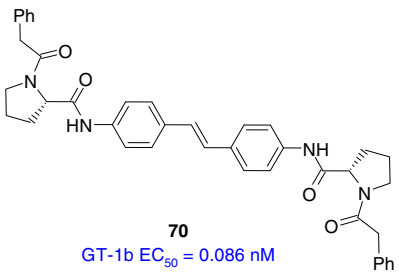
| | **63** | **64** | **65** | **66** |
|---|---|---|---|---|
| GT1b $EC_{50}$ | 0.57 µM | 96 µM | 5 µM | 0.11 µM |



**67**
GT-1b $EC_{50}$ = 6 nM

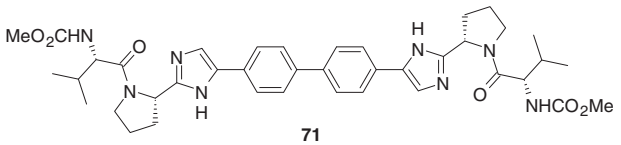
**68**

**69**
GT-1b $EC_{50}$ = 30 nM



**70**
GT-1b $EC_{50}$ = 0.086 nM
GT-1a $EC_{50}$ = >10,000 nM

Whilst the discovery of **70** held promise, the olefin was subject to light-induced isomerization and concern was expressed about the two embedded aniline moieties that, given the peptide-like nature of the terminal elements, had the potential to be released in vivo; however, the more significant challenge came with the discovery that **70** was inactive toward a newly developed GT-1a replicon [71]. While this gave a clear focus to the subsequent optimization campaign, building in GT-1a inhibition proved to be an arduous enterprise, with management patience wearing thin at least twice over the almost 4-year period of study. However, each threat to terminate the program within a few weeks of giving notice coincided with developments in SARs that preserved the program. While management seemed to believe in a cause/effect relationship, the reality was that the chemists were toiling diligently, with the breakthroughs the result of the kind of commitment and attention to detail that we were accustomed to contributing. Daclatasvir (**71**) was conceived of and synthesized by Makonen Belema and Van Nguyen and ultimately became the first HCV NS5A replication complex inhibitor to enter clinical trials, which occurred in November of 2007 [69, 71]. The Phase 1b clinical data with **71** were quite remarkable, with a dose of 1 mg associated with a 1.8 $\log_{10}$ reduction viral load measured at 24 h post-dose while a single 100 mg dose exhibited higher efficacy, with a 3.6 $\log_{10}$ reduction in plasma viremia measured at 48 h that persisted for 6 days [69]. There are some days that you never forget and seeing the initial efficacy associated with the 1 mg dose of **71** certainly qualifies, since it fully confirmed the translation of our preclinical discoveries to the clinical environment. That, and the subsequent development of the fuller graph presented in the article published in *Nature* in 2010 that describes the discovery of **71**, remain as indelible memories [69].

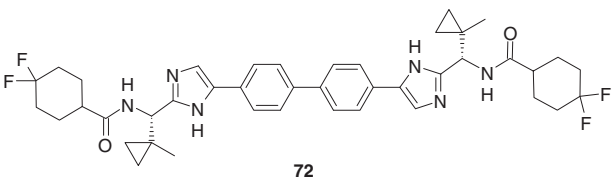



**71**

The NS3/4A inhibitor **60** and the NS5A inhibitor **71** were advanced into clinical trials within 2 months of each other which set the stage the for what would be described as a ground-breaking clinical trial in which a cohort of 11 non-responders to existing therapy were administered a combination of the two drugs for 24 weeks [75]. Two of the 11 patients were infected with GT-1b virus while the remaining nine were infected with the GT-1a subtype. A control group of 10 non-responders received the two small molecule drugs along with PEG-IFNα and ribavirin, the extant standard of care, for 24 weeks. In the dual combination cohort, four patients (the two GT-1b infected subjects and two who were infected with GT1a) remained virus free 12 weeks after the end of therapy, while all of the quadruple therapy group remained virus free at the same 12 week time point. This result demonstrated for the first time that an HCV infection could be cured by small molecule drugs in the absence of immune stimulation, an outcome described by Raymond T. Chung in the accompanying editorial as "A watershed moment in the treatment of hepatitis C" [76]. This result set the stage for the successful development of combinations of direct-acting antiviral agents (DAAs) that are curative after just 12 weeks of well tolerated therapy [77]. Indeed, just 2 years later the curing of chronic HCV infection was described as "the arc of a medical triumph" but since DAAs are all small molecule inhibitors, the accomplishment is perhaps better described as "the arc of a medicinal chemistry triumph" [78]. The impact of curative HCV therapeutics has manifested clinically as a significant reduction in the incidence of liver transplants attributable to the virus, with improvements in liver health and function and a reduction in mortality in those cured of the infection, a remarkably different circumstance to what had been predicted in the years before the advent of DAAs [79–83].

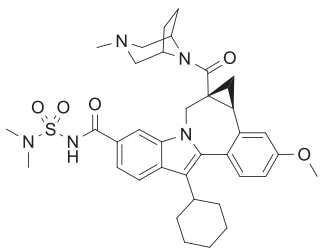
The success of the dual combination of **60** and **71** in curing the two GT-1b-infected patients in this clinical study led to the development of the two drugs being directed toward Japan where GT-1b was dominant, with marketing approval occurring on July 4th, 2014 [84].

An interesting aspect of the biochemical pharmacology of **71** is that of target vulnerability, defined as the fractional target occupancy required to produce a pharmacodynamic effect [85]. It was calculated that in GT-1b replicons, the ratio of HCV NS5A protein to **71** is of the order of 47,000:1 which equates to 23,500:1 based on the dimeric nature of the protein that is believed to be the drug target [86]. NS5A is and RNA binding protein that is believed to function in an oligomeric form in which a single molecule of **71** can disrupt the function of the higher order protein in the replication complex and during the packaging of RNA into the developing virion. The role of NS5A in RNA packaging was not captured in our replicon experiments but was shown in subsequent studies to contribute to the exceptionally rapid fall in plasma RNA observed in the clinical trials with **71**. In addition to highlighting the vulnerability of oligomeric viral proteins to therapeutic intervention, an examination of this mechanistic hypothesis led to the identification of molecules like **72** that were able to resensitize HCV that had developed resistance to **71** by binding to an allosteric site [86].




**72**

The final molecule in the HCV franchise was beclabuvir (**73**) which encountered some development challenges but was eventually approved in Japan on December 20th, 2016 as part of a fixed-dose triple combination with **60** and **70** referred to as DCV-TRIO and marketed under the trade-name Xymency™ [87, 88]. Interestingly, after presenting the discovery of **73** at the first-time disclosures session at the Spring meeting of the "American Chemical Society" held in San Diego in March 2012, where I stepped in for John Kadow who was not able to travel, the next day we found ourselves the subject of commentary by Derek Lowe in his blog [89, 90]. The title of the blog entry was "What's the ugliest drug? Or the ugliest drug candidate?" and **73** was specifically highlighted along with additional comments on **71** (see Box 1). The discovery and development of HCV inhibitors advanced acceptable drug properties beyond the rule of 5 guidelines whilst adding to an evolving complexity of drug candidates and the discovery of **73** had been particularly challenging. Nevertheless, the clinical success of HCV inhibitors has helped to set the stage for the contemporary era in which the pursuit of a wider range of modalities, including macrocyclic peptide drug candidates and targeted protein degraders, are further pushing the boundaries of drug design practices [91–94].



**73** (BMS-791325, beclabuvir)

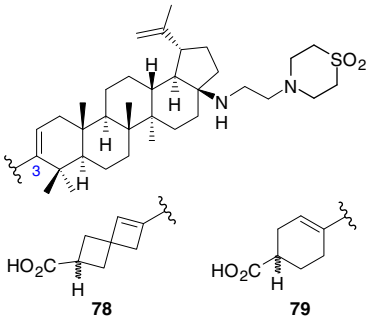
The final drug discovery vignette that I will share is focused on inhibitors of HIV-1 maturation. As we were winding down the HCV inhibitor programs, we reassessed the field of HIV-1 drug discovery and development where drugs had continued to be added to the pharmacopeia during the decade between 1998 and 2008 [95]. The landscape analysis concluded that there remained unmet medical need for new HIV-1 drugs acting by unique mechanisms that would reset the resistance clock. In addition, the field was beginning to consider approaches to enabling elite control over replication, where developments in immuno-oncology by our colleagues were germane, and cure of the disease, both of which remain significant challenges [96, 97]. We had been monitoring the fate of the HIV-1 maturation inhibitor bevirimat (**74**), a mechanistically interesting acylated derivative of betulinic acid, for some time following an earlier interest in the molecule as a potential licensing candidate [98, 99]. In Phase 2 clinical trials, **74** had demonstrated dichotomous

**Box 1.** Narrative on the ACS presentation on the invention of beclabuvir (**76**) by Derek Lowe in his blog

**What's the Ugliest Drug? Or The Ugliest Drug Candidate?**
"What's still making its way through the clinic can be even stranger-looking. Some of the odder candidates I've seen recently have been for the hepatitis C proteins NS5A and NS5B. Bristol Myers Squibb has disclosed some eye-openers, such as BMS-790052. (To be fair, that target seems to really like chemical matter like this, and the compound, last I heard, was moving along through the clinic.)
And yesterday, as Carmen Drahl reported from the ACS meeting in San Diego, the company disclosed the structure of BMS-791325, a compound targeting NS5B. That's a pretty big one, too - the series it came from started out reasonably, then became not particularly small, and now seems to have really bulked up, and for the usual reasons - potency and selectivity. But overall, it's a clear example of the sort of "compound bloat" that overtakes projects as they move on."
Derek Lowe "*In the Pipeline*" blog, March 26th, 2012

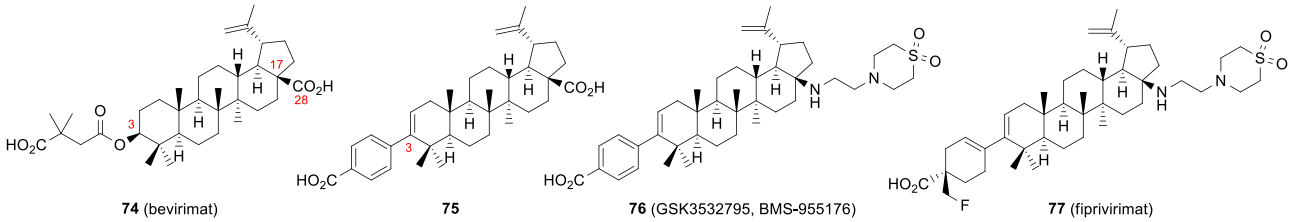
efficacy, with a 50% response rate that was shown to be due to the presence of pre-existing mutations in the virus Gag protein, an analysis that was published coincident with our rekindled interest [100]. These observations allowed for the development of a relatively straightforward screening tier to assess virus susceptibility but, a priori, we had no understanding of whether or not this was a solvable problem and our experience with enhancing the spectrum of action of antiviral activity of small molecule drugs had been mixed [101]. Bevirimat (**74**) had been discovered using a phenotypic screen and although a potent antiviral agent in cell culture, suffered from a 100-fold serum effect and exhibited sub-optimal solubility problems that had plagued its development. The clinical challenges encountered by **74** presumably contributed to its attracting only limited attention by the pharmaceutical industry but we felt that there was ample opportunity for a more detailed SAR study beyond the existing work which, at that time, we considered to be rudimentary in nature. Our initial focus was on understanding the relationship between the carboxylate moiety appended to the C-3 OH of **74** and the triterpenoid core. In a remarkable turn of events, the very first compound that Alicia Regueiro-Ren and her team prepared was the C-3-benzoic acid derivative **75** which exhibited in vitro potency and in vivo PK properties in the rat that were comparable to **74** [101]. Adding to the luster of **75**, the effect of added human serum albumin on the antiviral potency was 10-fold lower than that experienced by **74**. With this motif in hand, modification at the C-20 acid moiety, the only other convenient handle in the molecule, was pursued. A broad SAR survey was conducted at this site which revealed that mildly basic amines in this region of the pharmacophore conferred the targeted antiviral profile, including encompassing clinically-relevant and challenging polymorphic

viruses, whilst the presence of carboxylic acid moieties was associated with enhanced oral exposure. Guided by these principles, a thiomorpholine dioxide was identified as a mildly basic amine in which the sulfone element was interpreted as mimicking the oxygen atoms of a carboxylic acid moiety but without the burden of charge; thus, this ring system was viewed as a bioisostere of glycine or β-alanine [101]. The final molecular edit was to conduct a Curtius rearrangement on the C-20 acid which installed an amine attachment element attached directly to the core where the basicity was shielded, taking a cue from SAR observations where this concept led to an enhanced PK profile. This resulted in the identification of BMS-955176 (**76**), which was subsequently labeled as GSK3532795 following its acquisition by ViiV Healthcare, as a molecule meeting targeted antiviral and PK criteria that was advanced into clinical study in May, 2012 [101].




**78** **79**

HIV-1 maturation inhibitors bind to the viral capsid-SP1 protein and interfere with protease-mediated cleavage to release the SP1 peptide, the final and rate-determining step in maturation [106]. The capsid protein comprises of 215–250 hexamers interspersed with precisely 12 pentamers that confer the unique cone shape to the assembled capsid. As an oligomeric structure, inhibition of capsid protein processing has been shown to exert a dominant negative effect on capsid uncoating, which is a carefully choreographed event, such that the incorporation of <5% of defective proteins is sufficient to exert an antiviral effect [107–109]. Thus, interfering with HIV-1 capsid maturation also represents a target of high vulnerability [85].




**74** (bevirimat) **75** **76** (GSK3532795, BMS-955176) **77** (fipravirimat)

As monotherapy administered over 10 days to HIV-1 infected patients, **76** was effective at reducing viral load and fully suppressed the polymorphic viruses that had complicated the development of **74**. However, clinical development of **76** had to be abandoned following a Phase 2b study in which it was administered in combination with the nucleoside analogues tenofovir and emtricitabine, as a consequence of gut intolerability and the emergence of resistant virus that was often a complex complexion involving multiple mutations [102]. At the time that **76** was advanced, the back-up program had focused on further enhancement of the antiviral profile, which we considered a reasonable objective in the absence of a known liability. This proved to be prescient and by the time the clinical data with **76** had become clear, we were well advanced on the path to identifying fipravirimat (**77**) [103]. The approach adopted was to screen molecules with C-3 variants against the key emerging clinical mutations which identified two series with promising activity, one that used the bicyclobutane found in **78** as an interesting phenyl bioisostere and a second that was based on a cyclohexene chemotype and exemplified by **79** [103] The latter offered the better antiviral profile toward a broader range of clinical mutants and was optimized to **77** which is currently in Phase 2 clinical trials where it has demonstrated dose-related reductions in viral load in HIV-1-infected subjects following oral administration on a once daily dosing regimen [103–105].

## Epilogue

In a 40-year career in drug discovery and development, I have witnessed tremendous change, the vast majority of which has been for the good and has significantly enhanced the process of candidate identification and in vitro and in vivo profiling. In the early days of my career, we did not enjoy the kind of preclinical PK support or liability profiling that is commonplace today and which is critical to the identification of quality clinical compounds. The changes implemented over the last four decades have subtended the discovery of many innovative transformational medicines and small molecule drugs continue to exert a significant impact on human health and longevity, although in a way that is not always fully appreciated by the public at large

[81,110–113]. The effects of small molecule drugs on mortality associated with an HIV-1 infection has been substantial whilst the curing of HCV is a significant achievement, although the handful of successfully marketed HCV therapies reflect a rather dismal success rate of just 2% [81, 112, 114].

I joined the pharmaceutical industry during the ascent of CADD and experienced the advent of combinatorial chemistry in response to the emergence of high-throughput screening (HTS) both of which debuted with expectations that would prove to be somewhat unrealistic. However, both have found important roles in the drug discovery process and their historical evolution may provide guidance for the implementation and expectations of artificial intelligence. Nevertheless, synthetic organic chemistry remains a core competency in drug discovery and development, although in some respects this appears to have evolved into somewhat of a commodity item with the expansion of outsourcing and the commercial availability of a wide range of building blocks and capping agents that can facilitate rapid and convenient target compound assembly [115–117]. I believe that we fully embraced belief in the importance of synthetic acumen, viewing each synthetic challenge in the pursuit of answering biochemical pharmacological questions as a stimulus to invent new reagents and methodologies [6, 22, 23, 55]. Physical organic chemistry is an inextricably critical component in understanding physicochemical properties and molecular recognition and, by extension, the principles of drug design [118–120]. This is an important principle which we pursued with vigor, with a number of the observations and discoveries forming the basis of Perspective and review articles that had the dual purpose of embellishing our knowledge whilst sharing our thoughts and insights with the broader medicinal chemistry community at large [121–133]. Indeed, although these endeavors were time-consuming, I encouraged my team to engage in communicating their scientific discoveries and we found this to be an immensely rewarding act of self-education and enlightenment that further enhanced our medicinal chemistry skills while garnering recognition from the broader medicinal chemistry community and burnishing the reputation of BMS. Notably, we were to learn that we were embracing words of wisdom from Bill Greenlee and other medicinal chemistry luminaries that we admire [134–136]. Several of these publications had a remarkable but unintended effect on my visibility within the medicinal chemistry community, most notably a synopsis on applications of bioisosteres in drug design [127]. I had a assembled a slide deck on this topic for an *ACS Prospectives* meeting held in Philadelphia in 2009 where Paul S. Anderson, the retired Senior Vice President of Chemical and Physical Sciences at DuPont Pharmaceuticals and the 2008 Priestley Medalist, was our plenary speaker. Paul had taken the book of slides home and e-mailed me a couple of weeks later to encourage me to synthesize the bioisostere material into a Perspective article for the *Journal of Medicinal Chemistry*. I had not contemplated that path but a query to Bill Greenlee was met with enthusiasm and the article was published in early 2011 [133, 136]. The publication of this Perspective appeared to restore my standing with Derek Lowe, who commented on the article in his blog on March 22nd, 2011 (see Box 2), whilst also leading to invitations to present lectures on the topic at the annual "Drew Residential School on Medicinal Chemistry and Biology in Drug Discovery" and the biennial "Swiss Course on Medicinal Chemistry" [136]. These have been enjoyable experiences where I have been able to contribute to helping the next generation of medicinal chemists learn about what for me has been an enjoyable and rewarding career choice. These events have also created the opportunity to meet some wonderful scientists from all over the world who have become good friends and acquaintances.

I have had the good fortune to report to excellent supervisors, (in chronological order) Dr. John E. Lawson, J.J. Kim Wright, Graham Johnson, Carl P. Decicco, Joel C. Barrish, Percy H. Carter and Gregory D. Vite, who provided the kind of guidance and mentorship that allowed us ample opportunity to pursue our ideas although all were sources of good scientific suggestion that advanced our studies. They also acted as important sounding boards for discussion on a range of topics and I thank all of them for their support and collegiality. In prosecuting the individual programs, I was also fortunate to be able to collaborate with very many remarkable scientists, all of whom were creative and

**Box 2.** Narrative by Derek Lowe in his blog on the Perspective article "Synopsis of some recent tactical application of bioisosteres in drug design." Published in the *Journal of Medicinal Chemistry* in 2011 [133, 136]

A 200-Proof Shot of Medicinal Chemistry

For the chemists out there in the crowd: have you been looking for a paper to read that's filled, beginning to end, with good, solid, old-fashioned medicinal chemistry? Look no further than this one, on recent reports of isosteres. This sort of thing is still the heat of med-chem as it's practiced in the real world—messing around with the structure of an active molecule to see what you can improve and what you can get away with.

If you're not a medicinal chemist, the idea of a bioisostere is some chemical group that can substitute for another one. Classic examples are things like swapping in a tetrazole ring for a carboxylic acid or an oxadiazole for an ester. Here are some examples—even if your organic chemistry is shaky, you can see the similarities across these structures. If it works, you can change the other properties of your molecule (solubility, stability, selectivity) for the better while still keeping the key features that made the original group valuable for activity. It's not something that just automatically comes through every time—sometimes there just is no substitute - but it works enough of the time to be one of the essential techniques.

committed, with almost all of them co-authors on the publications that describe the many scientific discoveries that we made together and shared with the broader drug discovery community. We pursued many first-in-class targets with a strong communal belief that we would be successful and I particularly want to express my gratitude to them for their collaborative spirit, creativity and commitment which made the challenges associated with each discovery campaign more enjoyable and the achievements all the more rewarding. This was particularly the case in virology where we relied extensively on phenotypic screening which delivered antiviral leads with novel MOAs that we could not have anticipated and many of which would be very difficult to reduce to a biochemical screen. The HCV NS5A inhibitor campaign elegantly exemplifies that discovery principle, with this viral protein function still unapproachable using a biochemical assay. I believe that you discover what you screen for, so screen design is of paramount importance and the high content nature of a phenotypic screen maximizes the chance of success whilst also identifying novel MOAs that can be challenging to anticipate.

Every drug needs a champion and individual bias can influence a discovery and development portfolio. Fortunately, Carl Decicco, my supervisor through much of the successful HCV inhibitor campaigns, believed both in what we were pursuing and in our ability to deliver drug candidates. These programs were not always viewed favorably in the many corners of BMS although, not surprisingly, the Phase 2a clinical efficacy data changed views considerably. Carl and Rich Colonno were strong advocates for the preclinical HCV work, no doubt a reflection of their own direct experiences with the challenge of discovering effective and potent antiviral agents. This is the kind of intimate experience that can give a manager a stronger sense and understanding of the challenges faced by those designing and synthesizing molecules in the pursuit of a meaningful drug candidate. However, the effect extends beyond the manifestation of empathy and support and I've learned several times that selecting a target and pursuing it with a strong sense of conviction in its potential can be of paramount importance to success. However, decision making in drug discovery and development is a delicate balancing act, inherently flawed based on an absence of predictive accuracy, and knowing when to conclude a discovery program with grace is also an important trait. During my career, several substantial opportunities were missed that were subsequently exploited by others, notably $PGI_2$ partial agonists, CFTR modulators and RSV fusion inhibitors. However, the science that we conducted and the molecules and pharmacophores that we defined have been of benefit to mankind, which is ultimately a source of satisfaction.

The effects of small molecules can be remarkable, illustrated most effectively by **71** which addresses a target that would be deemed undruggable in a world where reductionist screening has become a key focus. I believe that the future of small molecule drugs has never been brighter, with proximity-induced protein and RNA modulation emerging technologies that have immense potential, and the rising appreciation of innovative screen design. While these technologies will have their successes, for some there will be setbacks along the way. However, that is the hallmark of drug discovery and development, an arduously challenging enterprise that does reward those with fortitude and which translates into the transformative medicines that society needs for many challenging diseases.

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## Compliance with ethical standards

**Conflict of interest** The author declares no competing interests.



## References

1. Brown PJ, Jones DN, Khan MA, Meanwell NA, Richards PJ. Conjugate additions to α,β-unsaturated sulphoxides: syntheses of cyclopentenones and 9-deoxyprostanoids. J Chem Soc Perkin Trans I. 1984:2049–60. https://doi.org/10.1039/P19840002049.
2. Johnson CR, Meanwell NA. Ketone methylenation with optical resolution. Total synthesis of the ginseng sesquiterpene (-)-β-panasinsene and its enantiomer. J Am Chem Soc. 1981;103:7667–9. https://doi.org/10.1021/ja00415a052.
3. Johnson CR, Bis KG, Cantillo JH, Meanwell NA, Reinhard MFD, Zeller JR, et al. Preparation and reactions of sulfonimidoyl fluorides. J Org Chem. 1983;48:1–3. https://doi.org/10.1021/jo00149a001.
4. Meanwell NA. Anagrelide—a clinically effective cAMP phosphodiesterase 3A inhibitor with molecular glue properties. ACS Med Chem Lett. 2023;14:350–61. https://doi.org/10.1021/acsmedchemlett.3c00092.
5. Meanwell NA, Roth HR, Smith Edward CR, Wedding DL, Wright JJK, Fleming JS, et al. 1,3-Dihydro-2*H*-imidazo[4,5-*b*] quinolin-2-ones—inhibitors of blood platelet cAMP phosphodiesterase and induced aggregation. J Med Chem. 1991;34:2906–16. https://doi.org/10.1021/jm00113a034.
6. Meanwell NA, Roth HR, Smith ECR, Wedding DL, Wright JJK. Diethyl 2,4-dioxoimidazolidine-5-phosphonates: Horner-Wadsworth-Emmons reagents for the mild and efficient

preparation of C-5 unsaturated hydantoin derivatives. J Org Chem. 1991;56:6897–904. https://doi.org/10.1021/jo00024a036.
7. Meanwell NA, Pearce BC, Roth HR, Smith ECR, Wedding DL, Wright JJK, et al. Inhibitors of blood platelet cAMP phosphodiesterase. 2. Structure-activity relationships associated with 1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-ones substituted with functionalized side chains. J Med Chem. 1992;35:2672–87.
8. Meanwell NA, Dennis RD, Roth HR, Rosenfeld MJ, Smith ECR, Wright JJK, et al. Inhibitors of blood platelet cAMP phosphodiesterase. 3. 1,3-Dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one derivatives with enhanced aqueous solubility. J Med Chem. 1992;35:2688–96.
9. Lautenschlager HH, Prop G, Niemann R. Octimibate sodium. Drugs Future. 1986;11:26–7.
10. Seiler S, Brassard CL, Arnold AJ, Meanwell NA, Fleming JS, Keely SL Jr. Octimibate inhibition of platelet aggregation: stimulation of adenylate cyclase through prostacyclin receptor activation. J Pharm Exp Ther. 1990;255:1021–6. http://jpet.aspetjournals.org/content/255/3/1021.
11. Raju TN. The Nobel chronicles. 1988: James Whyte Black, (b 1924), Gertrude Elion (1918-99), and George H Hitchings (1905-98). Lancet. 2000;355:1022. https://doi.org/10.1016/S0140-6736(05)74775-9.
12. Meanwell NA, Rosenfeld MJ, Trehan AK, Wright JJK, Brassard CL, Buchanan JO, et al. Nonprostanoid prostacyclin mimetics. 2. 4,5-diphenyloxazole derivatives. J Med Chem. 1992;35:3483–97. https://doi.org/10.1021/jm00097a006.
13. Meanwell NA, Rosenfeld MJ, Wright JJK, Brassard CL, Buchanan JO, Federici ME, et al. Structure-activity relationships associated with 3,4,5-triphenyl-1*H*-pyrazole-1-nonanoic acid, a nonprostanoid prostacyclin mimetic. J Med Chem. 1992;35:389–97. https://doi.org/10.1021/jm00080a028.
14. Meanwell NA, Romine JL, Rosenfeld MJ, Martin SW, Trehan AK, Wright JJK, et al. Nonprostanoid prostacyclin mimetics. 5. Structure-activity relationships associated with [3-[4-(4,5-diphenyl-2-oxazolyl)-5-oxazolyl]phenoxy]acetic acid. J Med Chem. 1993;36:3884–903. https://doi.org/10.1021/jm00076a018.
15. Meanwell NA, Romine JL, Seiler SM. Non-prostanoid prostacyclin mimetics. Drugs Future. 1994;19:361–85.
16. Lovering F, Bikker J, Humblet C. Escape from flatland: increasing saturation as an approach to improving clinical success. J Med Chem. 2009;52:6752–6. https://doi.org/10.1021/jm901241e.
17. Nakamura A, Yamada T, Asaki T. Synthesis and evaluation of N-acylsulfonamide and N-acylsulfonylurea prodrugs of a prostacyclin receptor agonist. Bioorg Med Chem. 2007;15:7720–5. https://doi.org/10.1016/j.bmc.2007.08.052.
18. Tran T-A, Kramer B, Shin Y-J, Vallar P, Boatman PD, Zou N, et al. Discovery of 2-(((1*R*,4*R*)-4-(((4-chlorophenyl)(phenyl)carbamoyl)oxy)methyl)cyclohexyl)methoxy)acetate (ralinepag): an orally active prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. J Med Chem. 2017;60:913–27. https://doi.org/10.1021/acs.jmedchem.6b00871.
19. Gribkoff VK, Starrett JE Jr, Dworetzky SI, Hewawasam P, Boissard CG, Cook DA, et al. Targeting acute ischemic stroke with a calcium-sensitive opener of maxi-K potassium channels. Nat Med. 2001;7:471–7. https://doi.org/10.1038/86546.
20. Macdonald JE, Poindexter GS. An anomalous metalation of a trimethylsilyl group. Tetrahedron Lett. 1987;28:1851–2. https://doi.org/10.1016/S0040-4039(00)95991-4.
21. Creary X. Reaction of organometallic reagents with ethyl trifluoroacetate and diethyl oxalate. Formation of trifluoromethyl ketones and α-keto esters via stable tetrahedral adducts. J Org Chem. 1987;52:5026–30. https://doi.org/10.1021/jo00231a036.
22. Hewawasam P, Meanwell N. A general method for the synthesis of isatins: preparation of regiospecifically functionalized isatins from anilines. Tetrahedron Lett. 1994;35:7303–6. https://doi.org/10.1016/0040-4039(94)85299-5.
23. Meanwell NA, Sit S-Y, Gao J, Wong HS, Gao Q, St. Laurent DR, et al. Regiospecific functionalization of 1,3-dihydro-2*H*-benzimidazol-2-one and structurally related cyclic urea derivatives. J Org Chem. 1995;60:1565–82. https://doi.org/10.1021/jo00111a014.
24. Meanwell NA, Sit S-Y, Gao J, Boissard CG, Lum-Ragan J, Dworetzky SI, et al. N-Benzylated benzimidazol-2-one derivatives: activators of large-conductance $Ca2^{+}$-dependent $K^{+}$ channels. Bioorg Med Chem Lett. 1996;6:1641–6. https://doi.org/10.1016/0960-894X(96)00296-X.
25. Hewawasam P, Meanwell NA, Gribkoff VK, Dworetzky SI, Boissard CG. Discovery of a novel class of BK channel openers: enantiospecific synthesis and BK channel opening activity of 3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2*H*-indol-2-ones. Bioorg Med Chem Lett. 1997;7:1255–60. https://doi.org/10.1016/S0960-894X(97)00202-3.
26. Hewawasam P, Erway M, Moon SL, Knipe J, Weiner H, Boissard CG, et al. Synthesis and structure-activity relationships of 3-aryloxindoles: a new class of calcium-dependent, large conductance potassium (maxi-K) channel openers with neuroprotective properties. J Med Chem. 2002;45:1487–99. https://doi.org/10.1021/jm0101850.
27. Hewawasam P, Gribkoff VK, Pendri Y, Dworetzky SI, Meanwell NA, Martinez E, et al. The synthesis and characterization of BMS-204352 (MaxiPost) and related 3-fluorooxindoles as openers of maxi-K potassium channels. Bioorg Med Chem Lett. 2002;12:1023–26. https://doi.org/10.1016/S0960-894X(02)00101-4.
28. Gillman KW, Hewawasam P, Schmitz WD, Lopez OD, Starrett JE, Provencal DP. Preparation of phosphate prodrugs of fluorooxindoles. World Patent Appl. WO2003/080047 A1. 2003.
29. Romine JL, Martin SW, Meanwell NA, Gribkoff VK, Boissard CG, Dworetzky SI, et al. 3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, BMS-191011: opener of large-conductance $Ca^{2+}$-activated potassium (maxi-K) channels, identification, solubility, and SAR. J Med Chem. 2007;50:528–42.
30. Hewawasam P, Ding M, Chen N, King D, Knipe J, Pajor L, et al. Synthesis of water-soluble prodrugs of BMS-191011: a maxi-K channel opener targeted for post-stroke neuroprotection. Bioorg Med Chem Lett. 2003;13:1695–8.
31. Hewawasam P, Erway M, Thalody G, Weiner H, Boissard CG, Gribkoff VK, et al. The synthesis and structure-activity relationships of 1,3-diaryl 1,2,4-(4*H*)-triazol-5-ones: a new class of calcium-dependent, large conductance, potassium (maxi-K) channel opener targeted for urge urinary incontinence. Bioorg Med Chem Lett. 2002;12:1117–20.
32. Vrudhula VM, Dasgupta B, Qian-Cutrone J, Kozlowski ES, Boissard CG, Dworetzky SI, et al. Atropisomeric 3-(β-hydroxyethyl)-4-arylquinolin-2-ones as maxi-K potassium channel openers. J Med Chem. 2007;50:1050–7.
33. Chen X, Wang K. The fate of medications evaluated for ischemic stroke pharmacotherapy over the period 1995-2015. Acta Pharm Sin B. 2016;6:522–30. https://doi.org/10.1016/j.apsb.2016.06.013.
34. Gribkoff VK, Champigny G, Barbry P, Dworetzky SI, Meanwell NA, Lazdunski M. The substituted benzimidazolone NS004 is an opener of the cystic fibrosis chloride channel. J Biol Chem. 1994;269:10983–6.
35. Bardin E, Pastor A, Semeraro M, Golec A, Hayes K, Chevalier B, et al. Modulators of CFTR. Updates on clinical development and future directions. Eur J Med Chem. 2021;213:113195.
36. Luo G, Torri A, Harte WE, Danetz S, Cianci C, Tiley L, et al. Molecular mechanism underlying the action of a novel fusion inhibitor of influenza A virus. J Virol. 1997;71:4062–70.
37. Yu K-L, Ruediger E, Luo G, Cianci C, Danetz S, Tiley L, et al. Novel quinolizidine salicylamide influenza fusion inhibitors. Bioorg Med Chem Lett. 1999;9:2177–80.

38. Deshpande MS, Wei J, Luo G, Cianci C, Danetz S, Torri A, et al. An approach to the identification of potent inhibitors of influenza virus fusion using parallel synthesis methodology. Bioorg Med Chem Lett. 2001;11:2393–6.
39. Yu K-L, Torri AF, Luo G, Cianci C, Grant-Young K, Danetz S, et al. Structure-activity relationships for a series of thiobenzamide influenza fusion inhibitors derived from 1,3,3-trimethyl-5-hydroxy-cyclohexylmethylamine. Bioorg Med Chem Lett. 2002;12:3379–82.
40. Wilber R, Kreter B, Bifano M, Danetz S, Lehman-McKeeman L, Tenney DJ, et al. Discovery and development of entecavir. In: Kazmierski WM, editor. Antiviral drugs. Hoboken, New Jersey: John Wiley & Sons; 2011. p. 401–16.
41. Bold G, Fässler A, Capraro H-G, Cozens R, Klimkait T, Lazdins J, et al. New aza-dipeptide analogs as potent and orally absorbed HIV-1 protease inhibitors: candidates for clinical development. J Med Chem. 1998;41:3387–401. https://doi.org/10.1021/jm970873c.
42. Yu K-L, Zhang Y, Civiello RL, Kadow KF, Cianci C, Krystal M, et al. Fundamental structure-activity relationships associated with a new structural class of respiratory syncytial virus inhibitor. Bioorg Med Chem Lett. 2003;13:2141–4.
43. Cianci C, Langley DR, Dischino DD, Sun Y, Yu K-L, Stanley A, et al. Targeting a binding pocket within the trimer-of-hairpins: small-molecule inhibition of viral fusion. Proc Natl Acad Sci USA. 2004;101:15046–51.
44. Wang T, Zhang Z, Wallace OB, Deshpande M, Fang H, Yang Z, et al. Discovery of 4-benzoyl-1-[(4-methoxy-1*H*-pyrrolo[2,3-b]pyridin-3-yl)oxoacetyl]-2-(*R*)-methylpiperazine (BMS-378806): a novel HIV-1 attachment inhibitor that interferes with CD4-gp120 interactions. J Med Chem. 2003;46:4236–9.
45. Lin P-F, Blair W, Wang T, Spicer T, Guo Q, Zhou N, et al. A small molecule HIV-1 inhibitor that targets the HIV-1 envelope and inhibits CD4 receptor binding. Proc Natl Acad Sci USA. 2003;100:11013–8.
46. Cianci C, Genovesi EV, Lamb L, Medina I, Yang Z, Zadjura L, et al. Oral efficacy of a respiratory syncytial virus inhibitor in rodent models of infection. Antimicrob Agents Chemother. 2004;48:2448–54.
47. Cianci C, Langley DR, Dischino DD, Sun Y, Yu K-L, Stanley A, et al. Targeting a binding pocket within the trimer-of-hairpins: small-molecule inhibition of viral fusion. Proc Natl Acad Sci USA. 2004;101:15046–51.
48. Vendeville S, Tahri A, Hu L, Demin S, Cooymans L, Vos A, et al. Discovery of 3-({5-chloro-1-[3-(methylsulfonyl)propyl]-1*H*-indol-2-yl}methyl)-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one (JNJ-53718678), a potent and orally bioavailable fusion inhibitor of respiratory syncytial virus. J Med Chem. 2020;63:8046–58.
49. Stevens M, Rusch S, DeVincenzo J, Kim Y-I, Harrison L, Meals EA, et al. Antiviral activity of oral JNJ-53718678 in healthy adult volunteers challenged with respiratory syncytial virus: a placebo-controlled study. J Infect Dis. 2018;218:748–56.
50. Martinon-Torres F, Rusch S, Huntjens D, Remmerie B, Vingerhoets J, McFadyen K, et al. Pharmacokinetics, safety, and antiviral effects of multiple doses of the respiratory syncytial virus (RSV) fusion protein inhibitor, JNJ-53718678, in infants hospitalized with RSV infection: a randomized phase 1b study. Clin Infect Dis. 2020;71:e594–603.
51. Cockerill GS, Angell RM, Bedernjak A, Chuckowree I, Fraser I, Gascon-Simorte J, et al. Discovery of sisunatovir (RV521), an inhibitor of respiratory syncytial virus fusion. J Med Chem. 2021;64:3658–76.
52. DeVincenzo J, Tait D, Efthimiou J, Mori J, Kim Y-I, Thomas E, et al. A randomized, placebo-controlled, respiratory syncytial virus human challenge study of the antiviral efficacy, safety, and pharmacokinetics of RV521, an inhibitor of the RSV-F protein. Antimicrob Agents Chemother. 2020;64:e01884.
53. Pfizer Press Release. Pfizer completes acquisition of ReViral. 2022. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-completes-acquisition-reviral.
54. Meanwell NA, Krystal MR, Nowicka-Sans B, Langley DR, Conlon DA, Eastgate MD, et al. Inhibitors of HIV-1 attachment: the discovery and development of temsavir and its prodrug fostemsavir. J Med Chem. 2018;61:62–80.
55. Wang T, Kadow JF, Meanwell NA. Innovation in the discovery of the HIV-1 attachment inhibitor temsavir and its phosphonooxymethyl prodrug fostemsavir. Med Chem Res. 2021;30:1955–80.
56. Timmins P, Brown J, Meanwell NA, Hanna GJ, Zhu L, Kadow JF. Enabled clinical use of an HIV-1 attachment inhibitor through drug delivery. Drug Discov Today. 2014;19:1288–93.
57. Kozal M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina J-M,and The BRIGHTE Trial Team, et al. Fostemsavir in adults with multidrug-resistant HIV-1 infection. N Engl J Med. 2020;382:1232–43.
58. Gartland M, Cahn P, DeJesus E, Diaz RS, Grossberg R, Kozal M, et al. Week 96 genotypic and phenotypic results of the fostemsavir phase 3 BRIGHTE study in heavily treatment-experienced adults living with multidrug-resistant HIV-1. Antimicrob Agents Chemother. 2022;66. https://doi.org/10.1128/aac.01751-21.
59. Markham A. Fostemsavir: first approval. Drugs. 2020;80:1485–90.
60. Herrera C, Harman S, Aldon Y, Rogers P, Armanasco N, Ziprin P, et al. The entry inhibitor DS003 (BMS-599793): a BMS-806 analogue, provides superior activity as a pre-exposure prophylaxis candidate. AIDS. 2021;35:1907–17.
61. Combrink KD, Gülgeze HB, Meanwell NA, Pearce BC, Zulan P, Bisacchi GS, et al. 1,2-Benzisothiazol-3-one 1,1-dioxide inhibitors of human mast cell tryptase. J Med Chem. 1998;41:4854–60.
62. Yeung K-S, Meanwell NA, Qiu Z, Hernandez D, Zhang S, McPhee F, et al. Structure-activity relationship studies of a bis-benzimidazole-based, $Zn^{2+}$-dependent inhibitor of HCV NS3 serine protease. Bioorg Med Chem Lett. 2001;11:2355–9.
63. Lamarre D, Anderson PC, Bailey M, Beaulieu P, Bolger G, Bonneau P, et al. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. Nature. 2003;426:186–90.
64. Scola PM, Wang A, Good AC, Sun L-Q, Combrink KD, Campbell JA, et al. Discovery and early clinical evaluation of BMS-605339, a potent and orally efficacious tripeptidic acylsulfonamide NS3 protease inhibitor for the treatment of hepatitis C virus infection. J Med Chem. 2014;57:1730–55.
65. Mecozzi S, Rebek J Jr. The 55% solution: a formula for molecular recognition in the liquid state. Chem Eur J. 1998;4:1016–22.
66. Scola PM, Sun L-Q, Wang AX, Chen J, Sin N, Venables BL, et al. The discovery of asunaprevir (BMS-650032), an orally efficacious NS3 protease inhibitor for the treatment of hepatitis C virus infection. J Med Chem. 2014;57:1730–52.
67. McPhee F, Sheaffer AK, Friborg J, Hernandez D, Falk P, Zhai G, et al. Preclinical profile and characterization of the hepatitis C virus NS3 protease inhibitor asunaprevir (BMS-650032). Antimicrob Agents Chemother. 2012;56:5387–96.
68. Lemm JA, O'Boyle DR II, Liu M, Nower PT, Colonno R, Deshpande MS, et al. Identification of hepatitis C virus NS5A inhibitors. J Virol. 2010;84:482–91.
69. Gao M, Nettles RE, Belema M, Snyder LB, Nguyen VN, Fridell RA, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. Nature. 2010;465:96–100.
70. Ross-Thriepland D, Harris M. Hepatitis C virus 1 NS5A: enigmatic but still promiscuous 10 years on! J Gen Virol. 2015;96:727–38.
71. Meanwell NA, Belema M. The discovery and development of daclatasvir: an inhibitor of the hepatitis C virus NS5A replication complex. Top Med Chem. 2019;32:27–55.

72. Romine JL, St. Laurent DR, Leet JE, Martin SW, Serrano-Wu MH, Yang F, et al. Inhibitors of HCV NS5A: from iminothiazolidinones to symmetrical stilbenes. ACS Med Chem Lett. 2011;2:224–9.
73. Lemm JA, Leet JE, O'Boyle DR II, Romine JL, Huang XS, Schroeder DR, et al. Discovery of potent hepatitis C virus NS5A inhibitors with dimeric structures. Antimicrob Agents Chemother. 2011;55:3795–802.
74. Tellinghuisen TL, Marcotrigiano J, Rice CM. Structure of the zinc-binding domain of an essential component of the hepatitis C virus replicase. Nature. 2005;435:374–9.
75. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012;366:216–24.
76. Chung RT. A watershed moment in the treatment of hepatitis C. N Engl J Med. 2012;366:273–5.
77. Chung RT, Baumert TF. Curing chronic hepatitis C—the arc of a medical triumph. N Engl J Med. 2014;370:1576–8.
78. Meanwell NA. 2015 Philip S. Portoghese medicinal chemistry lectureship. Curing hepatitis c virus infection with direct-acting antiviral agents: the arc of a medicinal chemistry triumph. J Med Chem. 2016;59:7311–51.
79. Manns MP, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. Nat Rev Gastroenterol Hepatol. 2022;19:533–50. https://doi.org/10.1038/s41575-022-00608-8
80. Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. Hepatology. 2017;65:804–12.
81. Meanwell NA, Ewing WR. In praise of remarkably powerful centamolecular therapeutic agents. ACS Med Chem Lett. 2019;10:1094–7.
82. Janjua NZ, Wong S, Abdia Y, Jeong D, Buller-Taylor T, Adu PA, et al. Impact of direct-acting antivirals for HCV on mortality in a large population-based cohort study. J Hepatol. 2021;75:1049–57. https://doi.org/10.1016/j.jhep.2021.05.028.
83. Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. Dig Liver Dis. 2011;43:66–72.
84. Poole RM. Daclatasvir + asunaprevir: first global approval. Drugs. 2014;74:1559–71.
85. Tonge PJ. Drug-target kinetics in drug discovery. ACS Chem Neurosci. 2018;9:29–39.
86. Sun J-H, O'Boyle DR II, Fridell RA, Langley DR, Wang C, Roberts SB, et al. Resensitizing daclatasvir-resistant hepatitis C variants by allosteric modulation of NS5A. Nature. 2015;527:245–8.
87. Gentles RG, Ding M, Bender JA, Bergstrom CP, Grant-Young K, Hewawasam P, et al. Discovery and preclinical characterization of the cyclopropylindolobenzazepine BMS-791325, A potent allosteric inhibitor of the hepatitis C virus NS5B polymerase. J Med Chem. 2014;57:1855–79. https://doi.org/10.1021/jm4016894.
88. Zappulo E, Scotto R, Buonomo AR, Maraolo AE, Pinchera B, Gentile I. Efficacy and safety of a fixed dose combination tablet of asunaprevir + beclabuvir + daclatasvir for the treatment of Hepatitis C. Expert Opin Pharmacother. 2020;21:261–73. https://doi.org/10.1080/14656566.2019.1697674.
89. Kadow JF, Gentles R, Ding M, Bender J, Bergstrom C, Grant-Young K, et al. Discovery of BMS-791325, an Allosteric NS5B Replicase Inhibitor for the Treatment of Hepatitis C. First time Disclosures Session at the 243rd National ACS Meeting and Exposition, San Diego CA, March 25–29th, MEDI 23, 2012.
90. Lowe D. What's the ugliest drug? Or the ugliest drug candidate? 2012. https://www.science.org/content/blog-post/what-s-ugliest-drug-or-ugliest-drug-candidate.
91. Meanwell NA. Improving drug design: an update on recent applications of efficiency metrics, strategies for replacing problematic elements, and compounds in nontraditional drug space. Chem Res Toxicol. 2016;29:564–616. https://doi.org/10.1021/acs.chemrestox.6b00043.
92. Li J, Eastgate MD. Current complexity: a tool for assessing the complexity of organic molecules. Org Biomol Chem. 2015;13:7164–76. https://doi.org/10.1039/C5OB00709G.
93. Eastgate M, Schmidt M, Fandrick K. On the design of complex drug candidate syntheses in the pharmaceutical industry. Nat Rev Chem. 2017;1:0016. https://doi.org/10.1038/s41570-017-0016.
94. Ermondi G, Jimenez DG, Sebastiano MR, Caron G. Rational control of molecular properties is mandatory to exploit the potential of PROTACs as oral drugs. ACS Med Chem Lett. 2021;12:1056–60. https://doi.org/10.1021/acsmedchemlett.1c00298.
95. Tseng A, Seet J, Phillips EJ. The evolution of three decades of antiretroviral therapy: challenges, triumphs and the promise of the future. Br J Clin Pharm. 2015;79:182–94. https://doi.org/10.1111/bcp.12403.
96. Li JZ, Blankson JN. How elite controllers and posttreatment controllers inform our search for an HIV-1 cure. J Clin Invest. 2021;131:e149414. https://doi.org/10.1172/JCI149414.
97. Deeks SG, Archin N, Cannon P, Collins S, Jones RB, de Jong MAWP, et al. Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021. Nat Med. 2021;27:2085–98. https://doi.org/10.1038/s41591-021-01590-5.
98. Kashiwada Y, Hashimoto F, Cosentino LM, Chen C, Garrett PE, Lee K-H. Betulinic acid and dihydrobetulinic acid derivatives as potent anti-HIV agents. J Med Chem. 1996;39:1016–7. https://doi.org/10.1021/jm950922q.
99. Martin DE, Salzwedel K, Allaway GP. Bevirimat: a novel maturation inhibitor for the treatment of HIV-1 infection. Antivir Chem Chemother. 2008;19:107–13.
100. Van Baelen K, Salzwedel K, Rondelez E, Van Eygen V, De Vos S, Verheyen A, et al. Susceptibility of human immunodeficiency virus type 1 to the maturation inhibitor bevirimat is modulated by baseline polymorphisms in Gag spacer peptide 1. Antimicrob Agents Chemother. 2009;53:2185–8.
101. Regueiro-Ren A, Swidorski JJ, Liu Z, Chen Y, Sin N, Sit S-Y, et al. Design, synthesis, and SAR of C-3 benzoic acid, C-17 triterpenoid derivatives. Identification of the HIV-1 maturation inhibitor 4-((1*R*,3a*S*,5a*R*,5b*R*,7a*R*,11a*S*,11b*R*,13a*R*,13b*R*)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1*H*-cyclopenta[*a*]chrysen-9-yl) benzoic acid (GSK3532795, BMS-955176). J Med Chem. 2018;61:7289–313.
102. Morales-Ramirez J, Bogner JR, Molina J-M, Lombaard J, Dicker IB, Stock DA, et al. Safety, efficacy, and dose response of the maturation inhibitor GSK3532795 (formerly known as BMS-955176) plus tenofovir/emtricitabine once daily in treatment-naïve HIV-1-infected adults: week 24 primary analysis from a randomized Phase IIb trial. PLoS ONE. 2018;13:e0205368.
103. Regueiro-Ren A, Sit S-Y, Chen Y, Chen J, Swidorski JJ, Liu Z, et al. The discovery of GSK3640254, a next generation inhibitor of HIV-1 maturation. J Med Chem. 2022;65:11927–48.
104. JoshI SR, Fernando D, Igwe S, McKenzie L, Krishnatry AS, Halliday F, et al. Phase I evaluation of the safety, tolerability, and pharmacokinetics of GSK3640254, a next-generation HIV-1 maturation inhibitor. Pharm Res Perspect. 2020;8:e00671. https://doi.org/10.1002/prp2.671.
105. Spinner CD, Felizarta F, Rizzardini G, Philibert P, Mitha E, Domingo P, et al. Phase IIa proof-of-concept evaluation of the antiviral efficacy, safety, tolerability, and pharmacokinetics of the next-generation maturation inhibitor GSK3640254. Clin Infect Dis. 2022;75:786–94. https://doi.org/10.1093/cid/ciab1065.

106. Regueiro-Ren A, Dicker IB, Hanumegowda U, Meanwell NA. Second generation inhibitors of HIV-1 maturation. ACS Med Chem Lett. 2019;10:287–94.
107. Müller B, Anders M, Akiyama H, Welsch S, Glass B, Nikovics K, et al. HIV-1 gag processing intermediates transdominantly interfere with HIV-1 infectivity. J Biol Chem. 2009;284:29692–703.
108. Lee S-K, Harris J, Swanstrom R. A strongly transdominant mutation in the human immunodeficiency virus type 1 gag gene defines an Achilles heel in the virus life cycle. J Virol. 2009;83:8536–43.
109. Checkley MA, Luttge BG, Soheilian F, Nagashima K, Freed EO. The capsid-spacer peptide 1 Gag processing intermediate is a dominant-negative inhibitor of HIV-1 maturation. Virology. 2010;400:137–44.
110. Lichtenberg FR. Sources of U.S. longevity increase, 1960-2001. Quart Rev Econ Financ. 2004;44:369–89. https://doi.org/10.1016/j.qref.2004.05.005.
111. Lichtenberg FR. The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries, 1982-2001. Int J Health Care Financ Econ. 2005;5:47–73. https://doi.org/10.1007/s10754-005-6601-7.
112. Lichtenberg FR. The effect of new drug approvals on HIV mortality in the US, 1987-1998. Econ Hum Biol. 2003;1:259–66. https://doi.org/10.1016/S1570-677X(02)00031-X.
113. Hostenkamp G, Lichtenberg FR. The impact of recent chemotherapy innovation on the longevity of myeloma patients: US and international evidence. Soc Sci Med. 2015;130:162–171. https://doi.org/10.1016/j.socscimed.2015.02.003.
114. Melnikova I. Hepatitis C therapies. Nat Rev Drug Discov. 2008;7:799–800. https://doi.org/10.1038/nrd2661.
115. Campos KR, Coleman PJ, Alvarez JC, Dreher SD, Garbaccio RM, Terrett NK, et al. The importance of synthetic chemistry in the pharmaceutical industry. Science. 2019:eaat0805. https://doi.org/10.1126/science.aat0805.
116. Blakemore DC, Castro L, Churcher I, Rees DC, Thomas AW, Wilson DM, et al. Organic synthesis provides opportunities to transform drug discovery. Nat Chem. 2018;10:383–94. https://doi.org/10.1038/s41557-018-0021-z.
117. Grygorenko OO, Volochnyuk DM, Ryabukhin SV, Judd DB. The symbiotic relationship between drug discovery and organic chemistry. Chem Eur J. 2020;26:1196–237. https://doi.org/10.1002/chem.201903232.
118. Persch E, Dumele O, Diederich F. Molecular recognition in chemical and biological systems. Angew Chem Int Ed. 2015;54:3290–327. https://doi.org/10.1002/anie.201408487.
119. Bissantz C, Kuhn B, Stahl M. A medicinal chemist's guide to molecular interactions. J Med Chem. 2010;53:5061–84. https://doi.org/10.1021/jm100112j.
120. Kuhn B, Gilberg E, Taylor R, Cole J, Korb O. How significant are unusual protein−ligand interactions? Insights from database mining. J Med Chem. 2019;62:10441–55. https://doi.org/10.1021/acs.jmedchem.9b01545.
121. Bender JA, Meanwell NA, Wang T. The mono-functionalization of symmetrical polyamines. Tetrahedron. 2002;58:3111–3128.
122. Meanwell NA. Improving drug candidates by design: a focus on physicochemical properties as a means of improving compound disposition and safety. Chem Res Toxicol. 2011;24:1420–56.
123. Yeung K-S, Meanwell NA. Inhibitors of hERG channel trafficking—a cryptic mechanism for QT prolongation. Annu Rep. Med Chem. 2013;48:335–52.
124. Gillis EP, Eastman KJ, Hill MD, Donnelly DJ, Meanwell NA. Applications of fluorine in medicinal chemistry. J Med Chem. 2015;58:8315–59.
125. Meanwell NA. Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design. J Med Chem. 2018;61:5822–80.
126. Johnson BM, Shu Y-Z, Zhuo X, Meanwell NA. Metabolic and pharmaceutical aspects of fluorinated compounds. J Med Chem. 2020;63:6315–86.
127. Subbaiah MAM, Meanwell NA. Bioisosteres of the phenyl ring: recent strategic applications in lead optimization and drug design. J Med Chem. 2021;64:14046–128.
128. Meanwell NA, Loiseleur O. Applications of isosteres of piperazine in the design of biologically active compounds. Part 1. J Agric Food Chem. 2022;70:10942–71.
129. Meanwell NA, Loiseleur O. Applications of isosteres of piperazine in the design of biologically active compounds. Part 2. J Agric Food Chem. 2022;70:10972–1004.
130. Beno BR, Yeung K-S, Bartberger MD, Pennington LD, Meanwell NA. A survey of the role of non-covalent sulfur interactions in drug design. J Med Chem. 2015;58:4383–438.
131. Wu Y-J, Meanwell NA. Geminal diheteroatomic motifs: some applications of acetals, ketals and their sulfur and nitrogen homologues in medicinal chemistry and drug design. J Med Chem. 2021;64:9786–874.
132. Greenlee WJ. Adventures in medicinal chemistry: a career in drug discovery. Annu Rep Med Chem. 2014;19:11–23.
133. Meanwell NA. Synopsis of some recent tactical application of bioisosteres in drug design. J Med Chem. 2011;54:2529–91.
134. Hatley RJD, Procopiou PA, McLachlan SP, Westendorf LE, Meanwell NA, Ewing WR, et al. Writing your next medicinal chemistry article: journal bibliometrics and guiding principles for industrial authors. J Med Chem. 2020;63:14336–56. https://doi.org/10.1021/acs.jmedchem.0c01159.
135. Murcko MA. What makes a great medicinal chemist? A personal perspective. J Med Chem. 2018;61:7419–24. https://doi.org/10.1021/acs.jmedchem.7b01445.
136. Lowe D. A 200-proof shot of medicinal chemistry. In the Pipeline. 2011. https://www.science.org/content/blog-post/200-proof-shot-medicinal-chemistry.