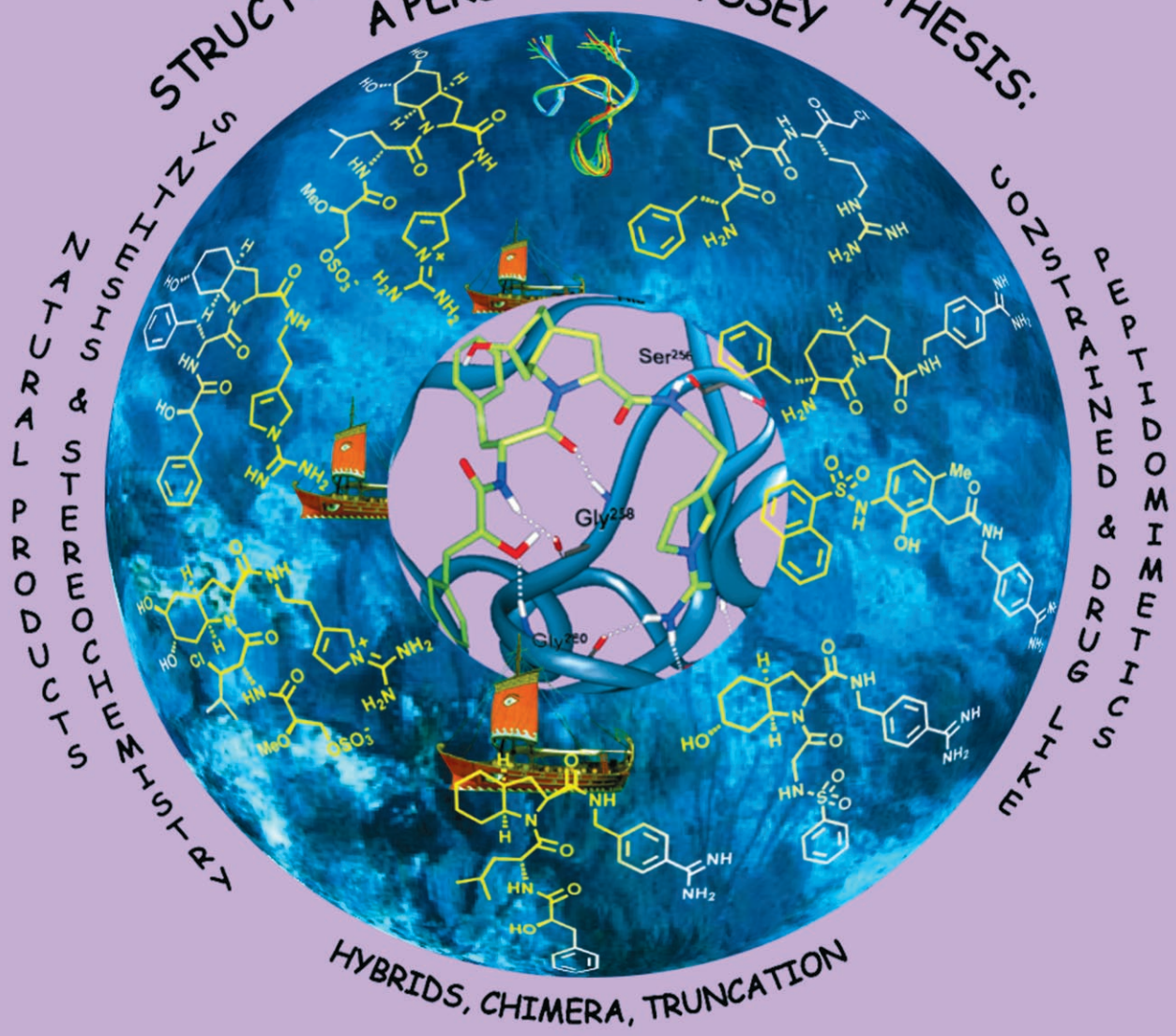

This image symbolizes the structure-based organic synthesis paradigm in the context of natural and synthetic compounds as inhibitors of thrombin, the last proteolytic enzyme in the complex blood-coagulation cascade leading to platelet aggregation and blood clots. Shown at the north end of an ocean backdrop is a ribbon diagram of the 65-amino acid hirudin, isolated from the saliva of leeches, and recognized early on as a potent inhibitor of thrombin. Moving westward in a counterclockwise fashion are three new members of the aeruginosin family of serine protease inhibitors: dysinosin A (thrombin IC_{50}=46 nM), oscillarin (IC_{50}=28 nM), and chlorodysinosin A (IC_{50}=5.7 nM). Total synthesis has also established structure and absolute stereochemistry. The inner circle depicts an X-ray co-crystal structure of oscillarin in complex with thrombin, showing the catalytic serine residue and the antiparallel H-bond arrangement with Gly 258. Using a mixture of natural and unnatural fragments generates bioactive hybrids, chimeras, and truncated analogues, as shown in the southern end. Moving eastward from hirudin is PPACK, the first synthetic peptidomimetic chloromethyl ketone analogue of D-Phe-Pro-Arg in this series, followed by a constrained indolizidinone (IC_{50}=4 nM), and a "drug-like" achiral analogue (IC_{50}=17 nM), all conceived on the basis of molecular modeling, then validated through synthesis and X-ray crystallography in complex with the enzyme. The three ships symbolize the personal Ulyssean odyssey in our quest to reach the Ithaca of drug prototypes relying on structure-based organic synthesis.

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Structure-Based Organic Synthesis of Drug Prototypes: A Personal Odyssey**

Stephen Hanessian*[a]

1. Introduction: the *How* and *Why* of Organic Synthesis

The practice of organic synthesis over the past century has witnessed periods of monumental achievements, due in major part to the creativity and ingenuity of the practitioners of this discipline. With the advent of sophisticated physical separation techniques, powerful instrumental methods, and enabling methodologies, the gap between such "golden periods" has narrowed to a point of quasi-constant euphoria. Indeed, the frequency with which complex chemical structures are synthesized, often concurrently in different research laboratories worldwide, is astounding and is a testament to the creative output of the modern-day synthetic chemist.[1]

Nature has been a constant provider of fascinating chemical substances, many of which are endowed with important if not life-saving properties. Therefore, it comes as no surprise that such molecules have been the targets of chemical synthesis over the years. Traditionally, the focus of attention, even when spectroscopic and methodology tools were not as sophisticated, was the conquest of natural products by total synthesis.[2] A great deal of fundamental science was developed as a result of these studies, providing the synthetic chemist with mechanistic insight and a constantly replenished arsenal of newer and powerful methodologies in all aspects of bond-forming reactions.[3] Today, stereocontrolled synthesis of enantiopure complex natural products is the expected norm, and the level of sophistication in design and execution is a yardstick by which ingenuity and elegance are measured. Given adequate resources and time, the synthesis of natural products with high levels of complex architectures can now be contemplated with optimism. Being relatively comfortable with the *how* of total synthesis of today and optimistic about the prospects for the near future, one is compelled to ask about the *why*. The answer, at least in part, may lie in the exciting prospects of interfacing organic synthesis with the biology of life processes, and ultimately the well-being of humankind. Natural products[4] and synthetic "small molecules"[5] have been the foundation of the pharmaceutical industry in the Western world for decades. In the interim, the molecular basis of drug action has evolved by leaps and bounds, often overshadowing significant achievements in organic synthesis. Indeed, deciphering the genetic code, and the far-reaching implications of such groundbreaking discoveries in developing better drugs may be the way of the future.[6] Nevertheless, organic synthesis still remains as the focal point of drug discovery and will continue to be practiced for the foreseeable future. With a strong biological basis for a given disease etiology and additional structural information from proteins involved in a given pathway, organic synthesis has been the basic platform and the modus operandi toward the development of potential therapeutic agents. Within the pharmaceutical industry, powerful techniques such as high-throughput screening of large numbers small organic molecules are the first steps toward chemical hits that may evolve into druggable leads. Further optimization in conjunction with de novo design and the screening of various biological parameters may culminate with a drug candidate.[7]

Answering the *why* of synthesis from the vantage point of an academic researcher may be less evident.[8] In academia, the primordial task is to teach co-workers how to think, and to apply that thought process toward solving problems (a.k.a. "basic research"). Academic "freedom" also gives us the privilege to chose our own projects, and to "have fun" working on them. For a purely target-oriented synthetic chemist, this more than often translates into natural product synthesis. With sufficient funding and a talented team of co-workers, total synthesis can be an exhilarating activity (in spite of its occasional setbacks).[9] In the process, new methods are frequently discovered that give lasting value to the effort long after the euphoric conquest of the natural product itself is forgotten with the passing of time. Despite the arduous climb to the summit, there is a great deal of personal pride and satisfaction in completing a total synthesis. Most multistep syntheses involve at least one or two key steps which may have the signature of the researcher as he or she showcases chemistry developed "in-house". This author has commented on the individualistic aspect of total synthesis, which varies from the "Nike approach" (just do it), to the "Sinatra approach" (I did it my way), to the "Kekulé approach" (it came to me in a dream), and finally to the "Archimides approach" (eureka, eureka).[10] As a logic-based and reagent- and reaction-driven enterprise in the laboratory, organic synthesis will continue to be an ideal forum for

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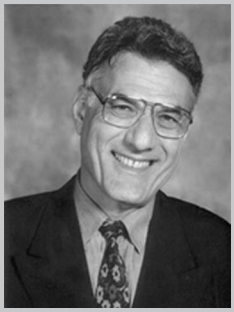
[**] *On the occasion of receiving a doctorate honoris causa from the University of Urbino, July 3, 2006*

co-worker training. Each target molecule presents its challenges, and the height of the synthetic complexity bar can be raised at will depending on the structure and stereochemical intricacies of the molecule. As newer and more powerful methods are developed, the expectations for efficiency and creative design associated with a given target molecule will also be heightened. More and more, the reasons proffered for the synthesis of a given molecule will be subject to scrutiny and justification, especially by funding agencies. Although complex natural product synthesis can be exciting for the challenge it presents and the rigorous co-worker training it offers, it is also an opportune time for academic researchers to consider other equally rewarding synthetic targets at the interface of chemistry and biology. Thus, the concept of synthesis can be applied, in part, to molecules invented or created on the computer screen in conjunction with the three-dimensional structural characteristics of active sites of pharmacologically relevant proteins, particularly those of known X-ray crystallographic coordinates.[11]

2. A "Reorientation" of Organic Synthesis

In spite of the great and continuing advances made in organic synthetic methodology, particularly with catalytic processes,[12] the objective of total synthesis has remained constant over the years, focusing mostly on the attainment of the target molecule while highlighting one or more chemical reactions used in critical sequences. Frequently, reaching this goal is the final chapter of the synthesis odyssey before another journey is begun with the next target molecule. As mentioned above, many heroic efforts have advanced the subdiscipline of organic synthesis, especially with the invention of newer and more efficient synthetic methods. Furthermore, researchers are also making great strides in combining biological relevance with synthetic chemistry—a good mix for potential funding. In the process, hundreds of well-trained co-workers have gone onward to pursue independent and highly successful research careers in industry or academia.

A survey of the architecturally complex molecules synthesized over the last decade reveals the prowess of the synthetic chemist.[1] However, when it comes to potentially useful therapeutic properties in humans, many of these, although exhibiting potent in vitro or in vivo activities, may not be suitable as drugs due to undesirable pharmacokinetic properties.[13] Cognizant of these shortcomings, a "reorientation" of our creative thought process may be in order, so that the role of the traditional approach to natural product synthesis in drug discovery may be expanded. The following brief survey of established strategies are worthy of comment.



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2.1. Target-oriented synthesis (TOS)

This time-honored traditional strategy starts by choosing a given structure, which is then subjected to a retrosynthetic analysis, eventually identifying one or more simple starting materials. Appropriate reactions are then conceived and executed in the "forward" sense, culminating with the assembly of the intended target structure. These principles of antithetic thinking were advanced by the pioneering work of E. J. Corey over four decades ago.[14] Together with the visual aspect of the analysis[10,15] comes an element of realistic planning, which necessitates an understanding of the fundamental principles of bond formation and chemical reactivity.

2.2. Diversity-oriented synthesis (DOS)

Conceptually, this strategy, which has been recently popularized by Schreiber,[16] is diametrically opposed to target-oriented synthesis. The small-molecule starting material, which is defined at the outset, is subjected to reactions that culminate with the synthesis of more than one molecule. The strategy relies heavily on a preconceived notion of functional diversity and the choice of substrates that are amenable to such diversification using well-known reactions. Generation of rings by sequential, cascade, or tandem cyclizations is a common practice in DOS, often simulating biosynthetic processes for natural products.[17] The final molecules may not bear any resemblance to a natural product, or they may be hybrid-type structures in which an important pharmacophore is present. By deploying diverse functionality on a core structure (which is often concealed), such synthetic molecules may find application in the hit-generation process against one or more therapeutic protein targets. Molecules emerging from a DOS strategy tend to have molecular weights higher than those generated by traditional combinatorial methods.[18]

Although not labeled as such, the lead-optimization stage in pharmaceutical research has relied on a form of diversity-oriented synthesis over the years, albeit after an initial active structure was identified. In recent times, the same industry has become "numbers conscious", opting to screen thousands of compounds from libraries by high-throughput techniques rather than to adopt a "lego"-type approach to introduce elements of diversity, albeit from fewer well-decorated scaffolds. Unfortunately, the rush to synthesize (or acquire) large sets of chemical compounds and to put them through the various stages of pharmaceutical development has fallen short of the projected expectations in terms of new drug entities.[19]

2.3. Function-oriented synthesis (FOS)

In this relatively new entry into the arena of strategic syntheses, natural products with demonstrated biological activities are analyzed for the relevance of their subunits with regard to interactions with their biological targets. Such subunits are subsequently synthesized, or appended to simpler structures to simulate the entire motif. Biological data including toxicity, pharmacokinetics, and physical data is then used to guide the synthesis of analogues.

One of the bottlenecks in the further development of interesting leads from natural products is their availability in only limited quantities from their respective sources. By identifying functionally relevant subunits and incorporating them in appropriate synthetic counterparts of the original structure, the supply problem can be circumvented, provided that activity is maintained. Elegant examples of this strategy have been demonstrated by Wender and co-workers[20] for new analogues of bryostatin, and by Nicolaou,[21] Danishefsky,[22] and their respective research groups, particularly in the case of second-generation epothilones. Efforts within the pharmaceutical industry[23a] have also greatly advanced the chemistry and biology of the epothilones through analogue design and synthesis, either independently or in collaboration with academic groups.[23b]

2.4. Structure-based organic synthesis (SOS)

A relatively well-known strategy that is extensively used in the pharmaceutical industry relies on so-called structure-based ligand design.[24] A small-molecule ligand to a therapeutically relevant protein is subjected to an iterative chemical-modification approach until optimal binding is achieved. Knowledge of the three-dimensional structure of the protein by X-ray crystallography or by high-resolution NMR is followed by solving the structure of a protein–ligand complex. This structural information has led to newer insights relying on fragment-based lead discovery[25] and fragment-based drug discovery,[26] NMR-based approaches,[27,28] high-throughput crystallography,[29,30] and mass spectrometry,[31] leading to the de novo design of drug-like molecules.[32] The Protein Data Bank (PDB) contains thousands of co-crystal structures with registered crystallographic coordinates and many in the presence of complexed organic molecule ligands. From a heuristic standpoint, nothing could be more exciting than to literally "see" a synthetic inhibitor molecule nestled in the active site of the enzyme with its appendages clinging to their complementary binding sites by H bonding, charge, and hydrophobic interactions. However, this can also give a false sense of empowerment to the practitioner, for if drug discovery were as simple a process, then there would be many more billion-dollar drugs.

The road from bench to market is a treacherous one, in spite of the medicinal chemist's ingenuity. Nature always seems to have the last word. Nevertheless, the fruits of organic synthesis in the pharmaceutical industry are in perpetual harvest with scores of marketed life-saving drugs and many more in the making. In this regard, the heroic efforts of process chemists in streamlining often complex synthetic operations and rendering the practically impossible possible while being cost-effective is another testament to creativity and dedication to the cause.[33]

Our approach to structure-based organic synthesis (SOS) has relied on exploiting the structural basis of protein targets in relation to bioactive natural products, or to existing drugs with the intention of designing new prototypes and related entities for initial testing as a proof of principle. Thus, in this approach, the process of total synthesis undergoes a paradigm shift, as it is intentionally oriented toward synthetic unnatural molecules intended as potential novel inhibitors, agonists, or antagonists with well-designed three-dimensional structures for optimal binding to proteins and other macromolecules.[34] This academic "targeted" approach to the synthesis of bioactive molecules for pharmaceutical and agrochemical applications also serves to provide much needed information for validating (or invalidating) certain hypotheses pertaining to interactions at the molecular level. Frequently, these are inspired by biological activities initially observed with natural products (Figure 1).

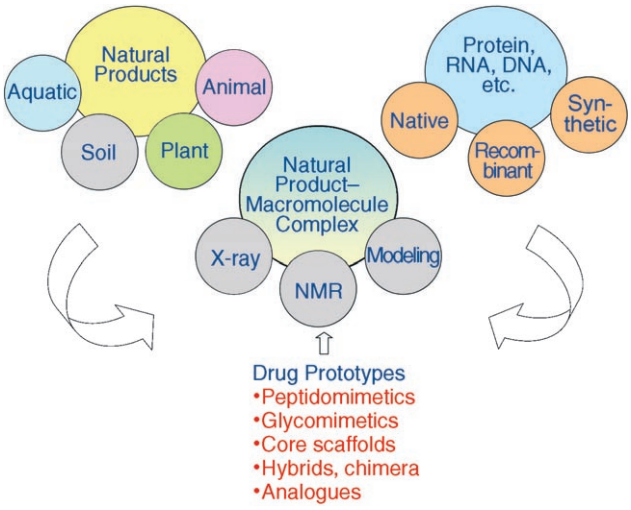


Figure 1. Natural products at the crossroad of academic and pharmaceutical research.

Herein, I have selected examples from several research projects performed in our research group over the past 25 years, with emphasis on rationales, design elements, and potential applications. This richly rewarding experience also serves to showcase the value of collaborative research between an academic group and the biotech or pharmaceutical industries. In the process, new generations of synthetic chemists have received excellent training and exposure to the rigors of drug-discovery research. Coming short of reaching the intended objectives of an exciting research program for an academic group, while clearly disappointing, does not diminish the intellectual and practical elements of co-worker training. Our industrial partners, in turn, have benefited from the fruits as well as the trials and tribulations of such research programs, which otherwise may have not been realized entirely within their re-

spective organizations given the high risks associated with such projects.

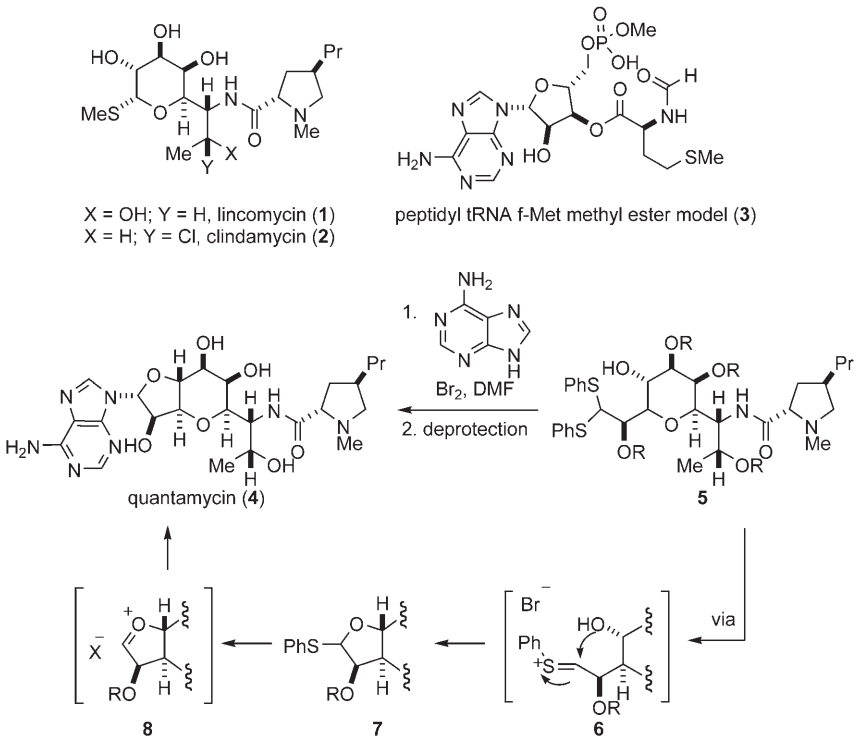
3. Antibacterial Agents

3.1. RNA-binding ligands

The field of RNA structure and function[35] has blossomed in recent years, especially as a result of the elegant X-ray structural work by various groups.[36] Many antibiotics exert their action as inhibitors of bacterial protein biosynthesis at the ribosomal level.[37] Elegant co-crystal structures of macrolides, other antibiotics,[38] and aminoglycosides[39,40] have been published with fascinating revelations with regard to their mode of binding. RNA has been the target for binding studies with small molecules.[41] We describe three projects focusing on the design and synthesis of potential antibiotics as RNA drug prototypes.

3.1.1. "Quantamycin"

The antibiotic lincomycin (**1**) has been in clinical use for over two decades for the treatment of certain Gram-positive infections[42] (Scheme 1). Extensive chemical modification has also led to clindamycin (**2**), a 7-*epi*-chloro lincomycin with an improved antibacterial profile (Scheme 1).[43] This unique class of 8-carbon amino sugars has not been encountered again as a natural product since its initial discovery. Even in the absence of crystallographic structural data in the early 1980s, it was known that protein biosynthesis at the ribosomal level was driven by codon–anticodon recognition at the mRNA level. In collaboration with ex-UpJohn scientists in Kalamazoo, Michigan, we hypothesized that modification of lincomycin to an analogue capable of mimicking the first adenine nucleotide in an aminoacyl tRNA could act as an inhibitor of the process. Such a modification was carried out by using the peptidyl tRNA formylmethionine (fMet, compound **3**). Quantum mechanical calculations involving the juxtaposition of potential high-electron-density (HOMO) sites of the model tRNA nucleotide with lincomycin suggested a hybrid structure we called "quantamycin" (**4**).[44] The energy difference between the calculated and proposed bound conformations was found to be minimal, which augured well for the validation of the hypothesis through synthesis. The key steps in the assembly of the novel *trans*-fused perhydrofuropyran motif was an anomeric C-vinylation, which was elaborated to the dithioacetal **5**, followed by intramolecular etherification via the thionium intermediate **6**, and the direct formation of a 9-adenyl nucleoside from the corresponding phenylthioglycoside **7**, presumably via the anomeric oxocarbenium ion **8**. Inhibition studies in an *E. coli* cell-free system showed that quantamycin was able to displace labeled lincomycin to the extent of 15–20%. This "honorable" result based on a theoretical premise featuring a fictitious synthetic molecule was greeted with enthusiasm in 1984, long before any crystallographic information was available on RNA components.[39,40] With the extensive structural information presently available regarding the site of binding of clindamycin to the 23S rRNA within the 50S ribosomal unit in the vicinity of the peptide exit tunnel,[38] new chemically modified lincomycins can no doubt be envisaged as sequels to quantamycin.[45] Interestingly, other bicyclic perhydrofuropyran nucleosides[46] have been isolated[47] and synthesized[48] since then.



Scheme 1. Key steps in the synthesis of quantamycin (**4**).

*3.1.2. A hybrid amino sugar between lincomycin and erythromycin: 3-*N,N*-dimethylaminolincomycin*

Although the combination of functional groups or substructures of different bioactive molecules into a hybrid molecule is intuitively evident, few if any drugs have been successfully developed by this adopting strategy.[49] Macrolides and lincomycin-type amino sugar antibiotics inhibit protein biosynthesis by stimulating the dissociation of peptidyl tRNA from the bacterial ribosome during the translocation process.[37] Elegant X-ray crystallographic studies of complexes of erythromy-

cin (**9**) and clindamycin (**4**) have shown that they each bind at the peptide exit tunnel region[38] (Figure 2). ^{1}H NMR and ^{13}C NMR studies have also been reported in conjunction with

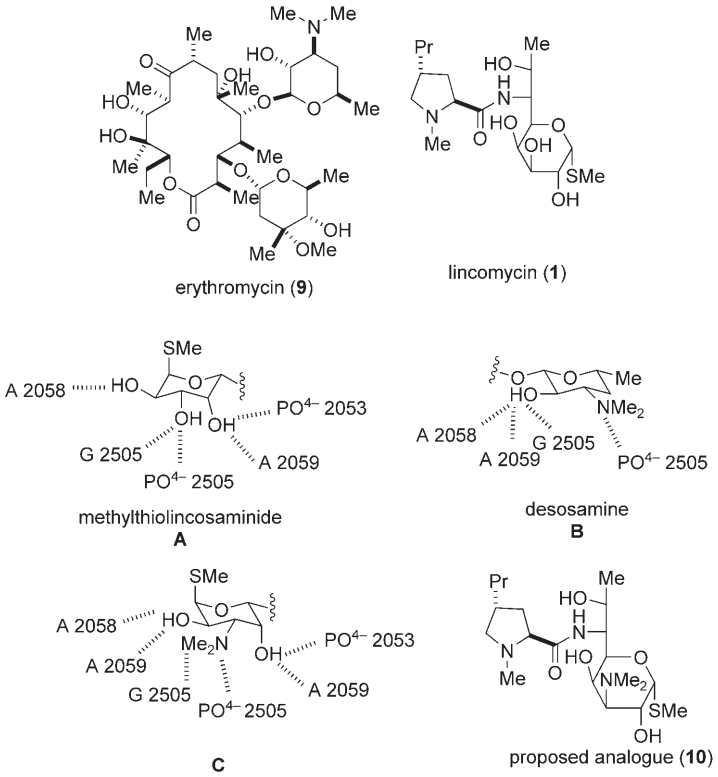


Figure 2. Proposed hybrid 3-dimethylaminolincomycin (**10**) and expected interactions with RNA residues.

ribosome-bound conformations.[45b] Coincidentally, clindamycin binds very proximally to erythromycin with a virtual overlap of the methylthiolincosaminide portion of the former on the desosamine sugar of the latter. The interactions of hydroxy groups in clindamycin with A 2058, G 2505, PO^4 2505, and PO^4 2503 are matched with analogous interactions in desosamine. We therefore hypothesized that the replacement of the C3 OH group in lincomycin by a dimethylamino group as in **10** would result in a stronger charge interaction with PO^4 2505, hopefully leading to a more potent antibiotic.[50]

Much to our surprise, the synthetic 3-dimethylaminolincomycin hybrid structure **10** was found to display no inhibition of the growth of *E. coli* or *S. aureus* at concentrations of 10 μM. However, against the same organisms, lincomycin (**1**) showed MIC values of >10 μM and 3–5 μg mL^{-1}, respectively. The hybrid analogue **10** may be intrinsically inactive due to inefficient cell penetration, efflux, or it is simply not recognized at the ribosomal level. The development of cross-resistance in the macrolide–lincosamine–streptogramine B (MLS_B)[51] area warrants further studies to discover new active entities. Previous attempts have been made to synthesize hybrids of lincomycin with chloramphenicol, for example, but the biological results were not encouraging.[52]

3.1.3. Aminoglycoside antibiotics: a new paradigm in analogue design

The well-known class of bactericidal aminoglycosides have been used as life-saving therapeutic agents for decades.[53] However, their widespread use has been somewhat limited due to their nephro- and ototoxicity.[54] They are also substrates for enzymatic inactivation by bacteria that have acquired resistance.[53] Aminoglycosides inhibit protein biosynthesis by disrupting the fidelity of the tRNA selection step during the binding process to the A-site of the bacterial ribosome 16S RNA subunit.[37,55] Specifically, codon misreading affects recognition of the mRNA sequence, leading to aberrant translation. The crystal structures of aminoglycoside–A-site complexes have been solved with excellent resolution.[39,40] Insightful NMR[56] and mass spectrometric studies[57] have also been reported. These elegant studies rekindled our long-standing interest in the chemical modification of readily available aminoglycosides.[58] Many relevant contributions have also been reported by other groups in the chemical modification of aminoglycosides.[59] Paromomycin (**11**), a 4,5-disubstituted branched analogue of 2-deoxystreptamine which exhibits strong binding to the A-site of the 16S RNA, was a suitable antibiotic to study (Figure 3). Crystallographic studies[40] have revealed a unique bioactive L-shaped conformation of paromomycin and the virtual coincidence of rings I and II with those of tobramycin (**12**), a 4,6-disubstituted aminoglycoside antibiotic. Inspired by the X-ray structural information, we surmised that the introduction of aminoalkyl ethers at C2″ of paromomycin could provide hybrid analogues in which a portion of the ring III in the tobramycin (**12**) landscape might also be reached through these basic tethers. Initial efforts focused on the synthesis of extended 2″-aminoalkyl ethers, which were found to have similar inhibitory activity to paromomycin.[60] We then extended the study to include a variety of aryl, heteroaryl, and other diverse motifs as end-group aminoalkyl ethers attached to C2″. The ω-aryl and ω-heteroaryl aminoethyl ethers were found to exhibit superior antibacterial activity against sensitive strains of *S. aureus* as a test organism.[60] Intrigued by these results, we obtained X-ray co-crystal structures of several such analogues (Figure 3). Surprisingly, the anticipated projection of the C2″-appended ether chains toward the empty site normally occupied by ring III of tobramycin was not observed. Instead, rings III and IV of the 2″-(3-pyridyl)methylaminoethyl ether analogue **13**[60] were oriented differently in the A-site with respect to the parent antibiotic.[40] The β-D-ribofuranosyl ring was turned by 40° together with a change to a C3″-*endo* instead of a C2″-*endo* pucker. This also resulted in a 90° change in the orientation of ring IV in this and other 2″-ether analogues of paromomycin. Furthermore, a network of H bonds leads to new interactions and to compactly folded structures with unique binding sites. Thus, the deployment of hydrophobic ether-type appendages created a new paradigm

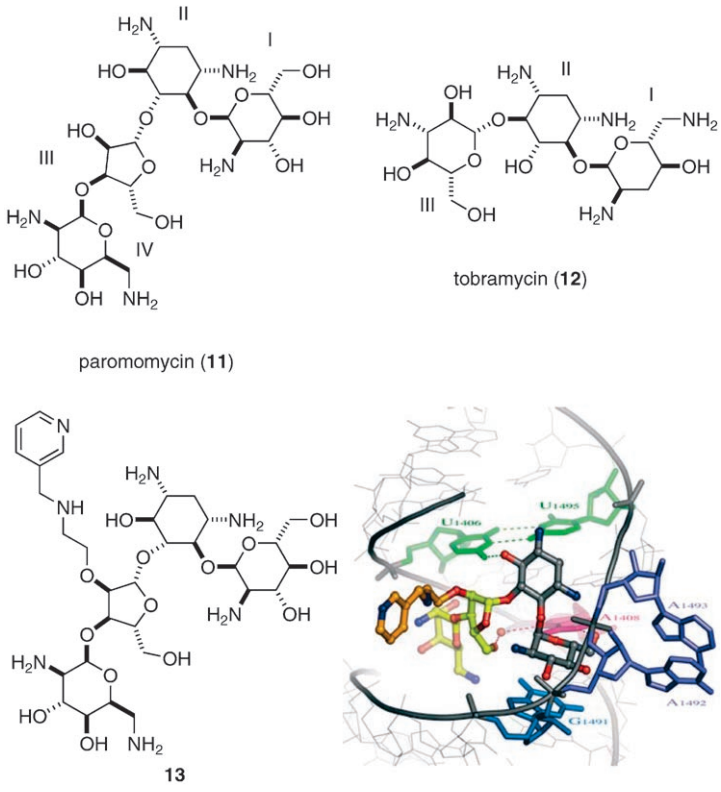


Figure 3. Structures of paromomycin (**11**), tobramycin (**12**), and branched analogue **13**. Also shown is the top view of the complex between **13** and the A-site RNA oligonucleotide. Adenine residues A 1492 and A 1493 are dark blue, G 1491 is paler blue, A 1408 is pink, and the U 1406–U 1495 base pair is green. The bridging water molecule between the hydroxy group at C5′′ of ring III and N7 of A 1408 is also shown in pink. Note the U–U pair with standard H bonds and the pseudopair of ring I and A 1408.

with regard to improving potency that can be further exploited toward the development of novel aminoglycoside analogues with diminished toxicities.

Incorporation of an L-2-hydroxy-4-amino amide appendage in conjunction with a hydrophobic tether further improved the potency against *S. aureus*.[61] Modifying the sites of enzymatic phosphorylation at C3′ of ring A eventually led to paromomycin analogues with much improved antibacterial profiles.

This successful chemical modification program on paromomycin serves as a good example of the novelty that can be achieved by deviating from the norm. Thus, rather than introducing aliphatic basic groups as appendages to seek additional interactions with the phosphate group in the RNA,[58b,62] a paradigm shift considers the effect of introducing hydrophobic groups[63] in these highly polar molecules. In addition to changing the binding mode by conformational adjustments at the A-site, such derivatives may also possess altered pharmacokinetics compared with the parent aminoglycosides, as well as a different mode of interaction with inactivating enzymes.[53]

3.2. Bacterial cell-wall inhibitors

A major time-tested contributor to the antibacterial market is the class of β-lactam antibiotics.[64] These highly effective antibiotics have been the focus of attention and constant evolution since the serendipitous discovery of penicillin by Sir Alexander Fleming.[65] β-Lactam antibiotics exert their action by inhibiting the biosynthesis of the bacterial cell wall, interfering mainly with processes involving penicillin-binding proteins.[66] Their potency and therapeutic potential continues to improve with the design of analogues that possess better pharmacokinetics and especially by devising combination drug variants to combat resistance.[65]

3.2.1. Analogue design to probe the Tipper–Strominger hypothesis

The pioneering efforts of J. L. Strominger[67] and J.-M. Ghuysen,[68] among others, have laid a strong foundation to the understanding of the principles of bacterial cell-wall biosynthesis. Briefly, the peptidoglycan composed of muramyl peptides terminating with a D-Ala-D-Ala dipeptide residue (compound **14**), is cross-linked by pentaglycyl bridges mediated by discrete enzymatic processes to produce the basic component of the bacterial cell wall. In 1965, Strominger and Tipper[69] advanced the hypothesis that 6-phenylacetyl-6-aminopenicillanic acid (penicillin G, **15**) exerted its antibacterial action by mimicking the D-Ala-D-Ala terminal dipeptide in muramyl peptide **14** (Figure 4). A study of the topology and absolute configuration of penicillin G and D-Ala-D-Ala showed that such juxtaposition may not be too far-fetched, even though a *C*-methyl substituent in one of the D-Ala units was in fact missing in the natural product.

Intrigued by the Tipper–Strominger hypothesis, we reasoned that the synthesis of a muramyl peptide in which the terminal D-Ala-D-Ala residue was replaced by a 6-aminopenicillanic acid (6-APA) as in **16** would be an interesting probe as a potential mimic (Figure 4). Consequently, we synthesized a number of analogues (compounds **16**–**18**) in which the muramyl peptide and/or 6-APA were incorporated as key components.[70] Not surprisingly, no inhibition of bacterial growth was observed with these highly polar analogues. It then occurred to us that we had overlooked the importance of the aromatic moiety that was lacking in the composite muramyl peptide–6-APA constructs. Accordingly, we synthesized the two epimeric 4-*C*-aminobutyl penicillin G analogues (**19** and **20**) and their oxa counterparts (**21** and **22**) which incorporate a terminal aminoalkyl group to simulate the L-lysine residue in **14**. Testing these hybrid structures against penicillin-binding proteins in *E. coli* and *S. aureus* revealed a preference for the *S* isomer (compound **20**).

This study was not intended to develop new penicillins. Instead, we were interested to probe an intriguing hypothesis that could be validated through synthesis. It is possible that further modification of the hybrid structures would provide more effective compounds.[71]

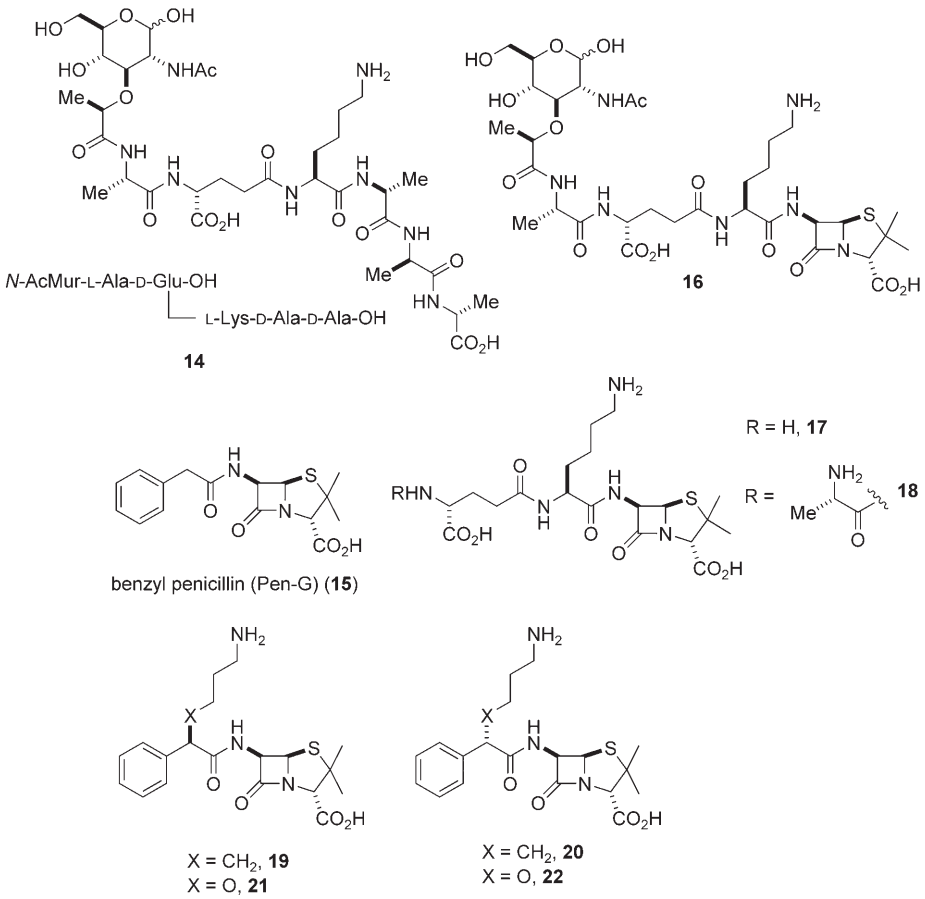


Figure 4. Hybrid muramyl peptide–penicillin G structures and aminoalkyl penicillins.

3.2.2. "Trinems", penems, and penams: unnatural β-lactams

After many years of pioneering "penem" and "cephem" chemistry,[64,65] the area of β-lactam antibiotics was rewarded with the discovery of the carbapenems.[72] These naturally occurring novel structures launched a new era in β-lactam chemistry and biology with significant benefits for the treatment of bacterial infections. While maintaining the exquisite architecture of the β-lactam unit, carbon analogues of the penems found a new arena for drug development and clever design, particularly that the molecular basis of cell-wall biosynthesis had been thoroughly studied.[66] Intriguingly, the novel (*R*)-hydroxyethyl side chain in thienamycin (**23**) attached to C6 had the opposite absolute configuration relative to the penams (Figure 5).

Tricyclic carbapenems (trinems)[73] were designed as constrained variants of the 1-methyl carbapenems. Eventually, the preclinical candidate sanfetrinem (**24**) was the subject of numerous synthetic approaches.[74] Our interest in **24** was instigated by the need to develop a stereocontrolled synthesis that could potentially be amenable to scale-up. An important challenge was to devise practical methods for the incorporation of the C4 methoxy group in **24**. We developed a key stereocontrolled protonation reaction of a zinc-chelated enolate intermediate which led to a carbocyclic product having the desired *S* configuration at the carbon atom bearing the methoxy group.[75] In order to probe the importance of the position of the methoxy group, we also synthesized the epimeric 5-methoxy analogues **25** and **26**[76] as well as an extended α-hydroxyethyl analogue **27** and its methyl ether.[77] There was only a 5–10-fold lower antibacterial activity with compounds **25**–**27** against a number of sensitive strains, which was surprising. The 5-α-hydroxyethyl analogue **27** proved to be more effective than **25**, **26**, and **28**. Based on the well-known serine-mediated enzymatic cleavage of the β-lactam ring in cephalosporins,[78] it was anticipated that a similar mechanism might prevail with **24**, where the α-methoxy-oriented group would be an eventual leaving group (Figure 5). These speculations warrant further studies to substantiate the existence of such pathways. Our synthetic studies in the area of carbapenems and cephams also led to hybrid structures such as **28**[79a] in addition to tricyclic analogues **29**[79b,c] and **30.**[80,81]

3.3. Inhibitors of DNA gyrase and antibiotic action

A unique mode of antibacterial activity relies on the inhibition of DNA gyrase, the enzyme responsible for the supercoiling of DNA.[82] Since the discovery of nalidixic acid, many other quinolones have been developed and marketed with widespread clinical use. Much insight has been gained from biochemical and genetic studies regarding the mode of action as well as the development of acquired resistance to quinolone antibiotics.[83] Several quinolones are marketed today, and the quest for more potent variants is an ongoing activity in a number of pharmaceutical and biotech companies.

3.3.1. Quinolone antibiotics: probing the Shen–Mitscher model for DNA gyrase inhibition

In 1989 Shen, Mitscher, and co-workers[84] proposed an intriguing hypothesis for the mode of action of quinolones involving three essential recognition sites (Figure 6A). Extensive chemical modification studies have provided credence to the hypothesis that head-to-tail alignment of quinolones in tetrameric structures offered optimal interactions with the enzyme and DNA regions of the gyrase.[85]

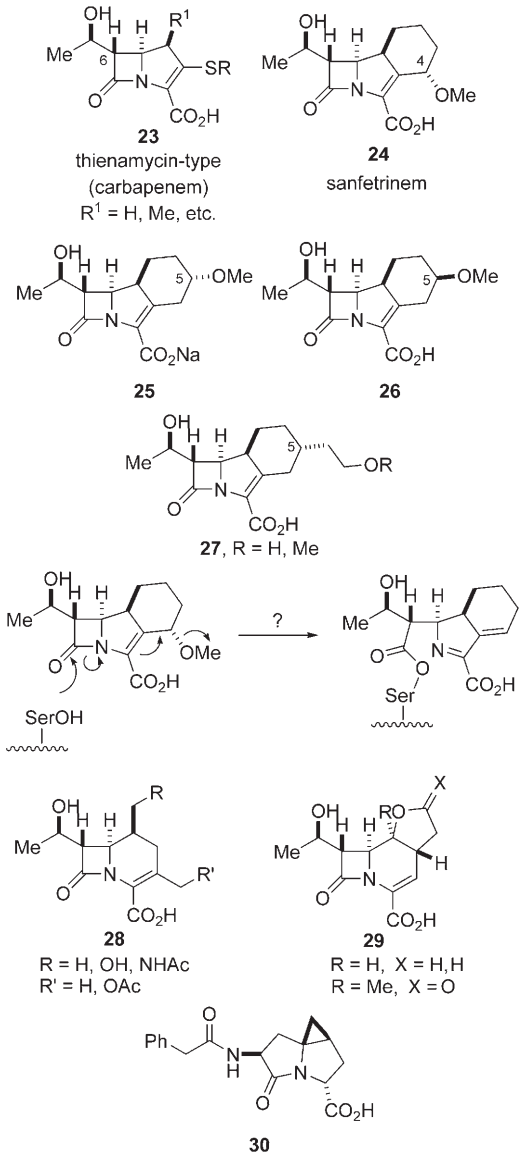


Figure 5. Natural and synthetic bicyclic and tricyclic carbapenems.

Based on the Shen–Mitscher hypothesis, we synthesized prototypical quinolones with pendant alkyl chains of defined length and terminating with representative purine and pyrimidine nucleobases in order to simulate the proposed interaction.[86] We hypothesized that the pendant nucleobases would engage in base-pair interactions with complimentary units in the DNA (Figure 6B). Unfortunately, the analogues consisting of four-carbon linkers to thymine, adenine, cytosine, and guanine showed no antibacterial activity, and the notion of hybrid quinolone-nucleobase motifs was abandoned. As with a myriad of other exploratory compounds, many factors may have contributed to the lack of activity including inefficient cellular penetration, efflux, and lack of recognition by the gyrase. Nevertheless, the model allowed the design of new chemical entities and to test its validity.

4. Antiviral Agents

Among the many viral infections known, none is more prevalent than the influenza virus, which causes major health concerns affecting large segments of the population worldwide.[87] Although it is usually associated with some discomfort commonly manifested as the "flu" or the common cold, the potential for mortality, especially among the elderly, is significant. Therapeutic options consist of vaccines[88] and two closely related drugs, amantadine and rimantadine.[89] The widespread use of vaccines is viewed with caution, except in the face of a pandemic, mainly due to mutations in the antigenic components of the viral surface proteins. On the other hand, the rapid emergence of resistance to amantadine and rimantadine, and the lack of efficacy against influenza B virus has curtailed their extensive use.

4.1. Neuraminidase inhibitors

Among the important cell-surface components of the influenza RNA virus are two glycoproteins that are essential for its viability.[90] A complex process in the infective cycle of the virus starts with its binding to the receptor of the host cell followed by endocytosis, replication, and the release of the virus into the host bloodstream. This release is mediated by the action of the enzyme neuraminidase,[91] which cleaves terminal *N*-acetylneuraminic acid (NANA, **31**) residues from the cell-surface glycoconjugate (Figure 7). By this ingenious process the virus avoids entrapment in the epithelial cells by aggregation, and it is propagated in a virulent form after its release. The crystal structure of neuraminidase[92] has revealed important insight into the design of inhibitors. This led to deoxyneuraminic acid

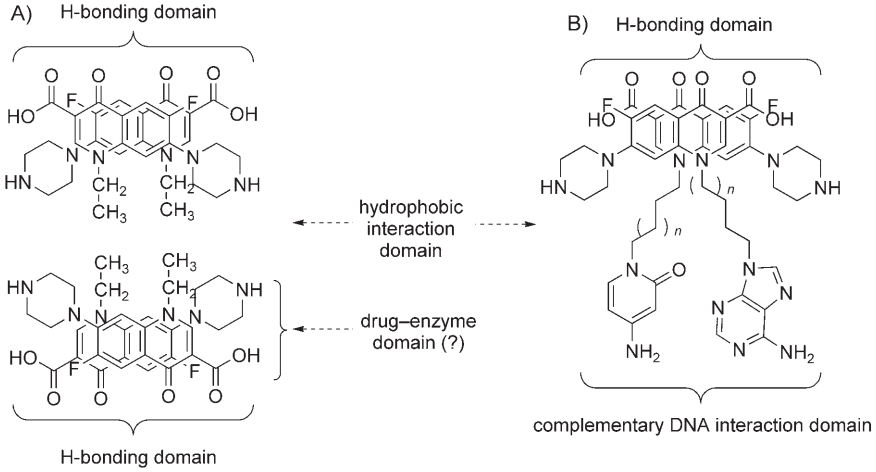


Figure 6. A) Shen–Mitscher model for quinolone binding and B) proposed nucleobase-appended hybrids.

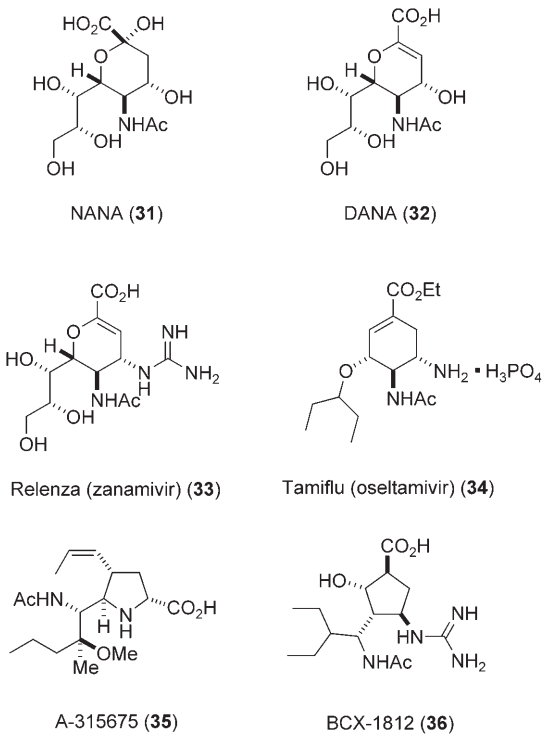


Figure 7. Structures of *N*-acetylneuraminic acid (NANA, **31**) and synthetic inhibitors of neuraminidase.

(DANA, **32**),[93] zanamivir (Relenza, **33**), a 4-deoxy-4-guanidino-unsaturated analogue of *N*-acetylneuraminic acid,[94] and oseltamivir (Tamiflu, **34**), which is a carbocyclic ester analogue that is highly active against influenza A and B viruses.[95,96] A-315075[97] (**35**) is a second-generation synthetic inhibitor of neuraminidase that was discovered as a result of extensive structure-based design in conjunction with X-ray crystallographic analysis of complexes with the enzyme. In spite of its apparent structural difference from the marketed drugs and to synthetic analogues such as **36**,[98] binding to the catalytic site of the enzyme was quasi-identical. Characteristic interactions of the carboxylic acid group, the *N*-acetyl group, and a hydrophobic interaction of the *cis*-propenyl group are hallmarks of this class of second-generation inhibitors. A striking difference was that the basic groups present in **33** and **34** were now replaced by a hydrophobic *cis*-propenyl group in **35**. This was rationalized based on a productive hydrophobic contact with the aliphatic chain in the Glu residue of the active site.[99] In this regard, it is of interest that the synthetic carbocyclic analogue **37**, in which the amino group was replaced by a vinyl group, was still an active inhibitor of the enzyme.[99] A co-crystal structure with neuraminidase revealed virtual juxtaposition of the core structure and the peripheral substituents on the analogous structure with **34** (as its carboxylic acid derivative **38**, Figure 8). However, the vinyl group now occupies the hydrophobic space between Glu and Asp residues. This constitutes a new paradigm and emphasizes the importance of hydrophobic groups in drug design.[63] The total synthesis of A-315675 (**35**) was undertaken with the prospect of devising a strategy that would be amenable to scale-up.[100] The retrosynthetic analysis shown in Figure 9 proceeds through the lactam **39**, which is derived from a stereocontrolled addition of ethyl propiolate to the nitrone **40**, followed by reduction to the *cis*-ester and cyclization. Aldehyde **41** was synthesized from D-serine (**42**) by exploiting the resident chirality of the amino acid through 1,2-induction. The two nitrogen atoms in **35** originate from D-serine and *p*-methoxybenzyl hydroxylamine. A particular attribute of this efficient total synthesis of an unnatural product (which could have easily passed for a natural one) was the highly crystalline state of several intermediates. The synthesis of **35**, which comprised 22 steps from D-serine in an overall yield of ~12% in an academic setting, is a glowing example of targeted collaborations with much mutual benefit. Scientists at Abbott Laboratories also reported their synthesis of **35** independently.[101]

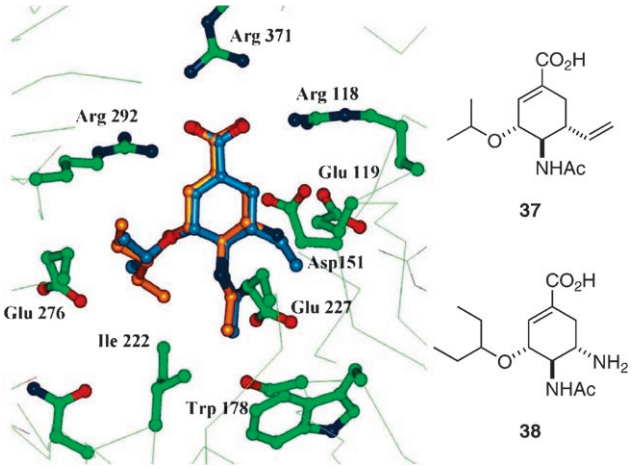


Figure 8. Crystal structures of compound **37** (blue) in neuraminidase enzyme (green) overlaid with GS-4071 (**38**, orange).

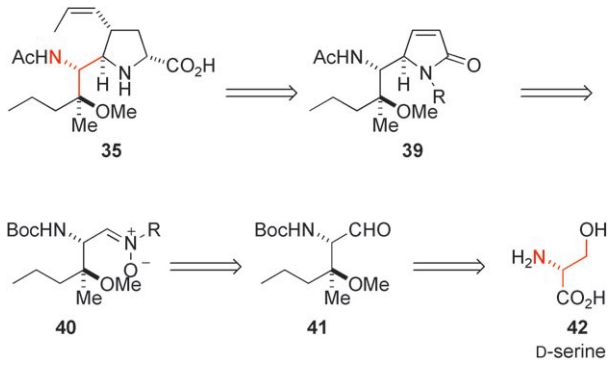


Figure 9. Retrosynthetic analysis of A-315675 (**35**). Boc = *tert*-butoxycarbonyl.

5. Anticancer Agents

In spite of great strides made in the field of drug discovery in relation to various diseases, cancer remains the most maligned and feared human affliction. The advent of potent antitumor agents with newly uncovered modes of action reflects exciting developments, although much remains to be done in our un-

derstanding of the molecular basis of tumorigenesis, metathesis, and prevention. In recent years, matrix metalloproteases[102] were identified as possible targets for intervention in relation to several pathological conditions including cancer.

5.1. Inhibitors of matrix metalloproteases (MMPs)

Collagenases and gelatinases belong to a family of zinc-containing proteolytic enzymes that play a key role in the degradation and remodeling of the extracellular matrix. Normal tissue regeneration relies on the controlled action of metalloproteases. However, under certain pathological conditions, overexpression of MMPs can result in the destruction of connective tissue and to metabolic alterations leading to malignant tumors. Thus, MMPs have been regarded as promising drug targets for the treatment of cancer.[102]

Initial encouraging results with MMP inhibitors such as marimastat (**43**) and CGS-27023 (**44**), especially with information provided by X-ray co-crystal structures[103] and NMR studies[104] instigated intensive efforts in the design and synthesis of different inhibitors. Based on these lead compounds, acyclic sulfonamides represented by **45** and which deploy requisite functionality at the P_1 (and other sites) were synthesized by routine methods in our laboratory (Figure 10).[105] Although these were structurally similar to **44**, their potent inhibitory activity against several MMPs revealed valuable information regarding the nature of the S_1, S_1', and S_2' subsites, which were systematically probed by chemical modification. The inclusion of a hydroxamic acid group was crucial for the excellent inhibitory activities observed against several MMPs.

We next considered oxacyclic- and azacyclic-constrained analogues[106] of our acyclic inhibitors, as exemplified by pyrrolidine scaffolds **46**–**49** (Figure 10). Modeling studies in the active site of MMP3 revealed a new interaction of the H-bonding type with a side chain hydroxy group favoring an *R* configuration in compound **49**.[107a] Several other constrained analogues were also synthesized in the context of this project. Unfortunately, the initial promise of MMP inhibitors as anticancer agents was not fulfilled due to adverse biological effects in clinical trials, possibly associated with the hydroxamic acid moiety and lack of selectivity.[108]

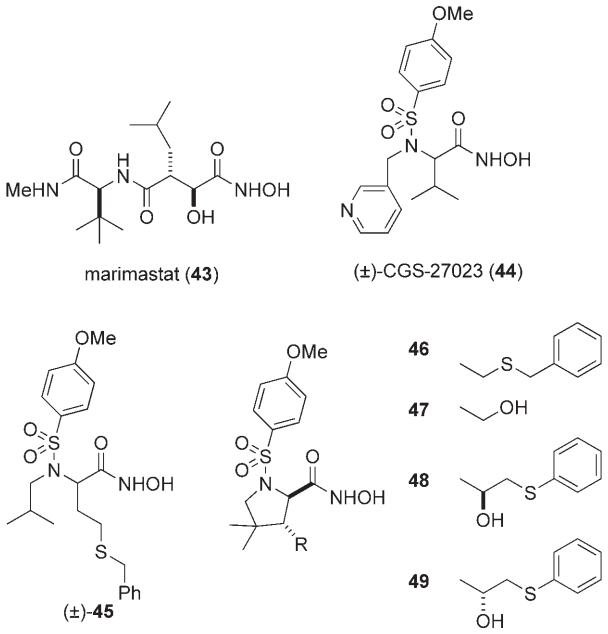


Figure 10. Structures of marimastat (**43**) and other synthetic MMP inhibitors.

5.2. Inhibition of histone deacetylases (HDAC)

HDACs are nuclear zinc-dependent enzymes that play a major role in regulating gene expression.[109] They catalyze the deacetylation of *N*-acetyl residues, leading to gene silencing. This process is counterbalanced by histone acetyltransferases (HATs) in conjunction with the remodeling of chromatin. Pathological conditions that perturb the balance between these two enzymes can lead to cancer.[110] Much effort exists in the development of HDAC inhibitors,[111] focusing mostly on synthetic inhibitors based on hydroxamic acid groups as zinc chelators. Trichostatin A (TSA, **50**)[111] is a natural product inhibitor, the structure of which has instigated the exploration of simpler surrogates such as suberoyl anilide hydroxamic acid (SAHA, **51**)[112,113] (Figure 11). X-ray co-crystal complexes have revealed the geometric and topological requirements of the aliphatic chain spanning the hydroxamic acid group and the aromatic moiety.[114]

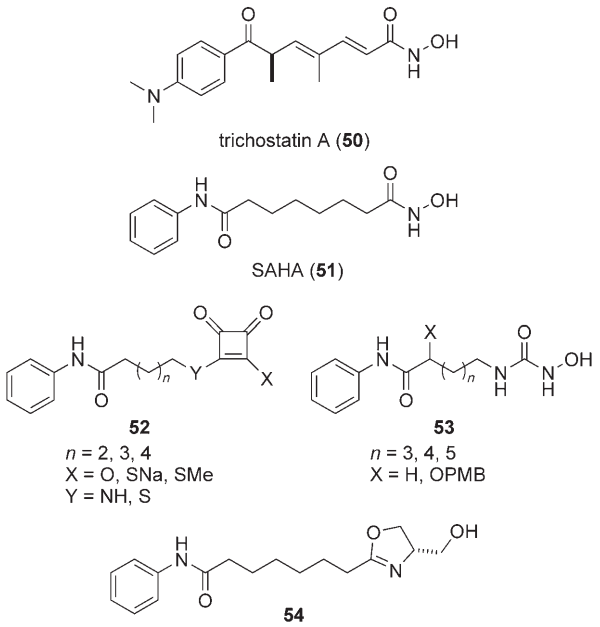


Figure 11. Structures of natural (compound **50**) and synthetic (compound **51**) HDAC inhibitors; proposed new zinc-binding motifs **52**–**54**. PMB = *para*-methoxybenzyl.

Our search for as yet unexplored zinc-binding motifs in this area led us to propose various analogues of squaric acid (compounds **52**), *N*-hydroxy ureas (compounds **53**), and hydroxy-

methyl oxazolines such as **54** as terminal entities on a SAHA-type skeleton with varying lengths of the hydrocarbon chain.[115] Unfortunately, these analogues did not inhibit HDAC at concentrations below 20 μM.

5.3. Inhibitors of human glioblastoma

Glioblastomas are brain tumors that proliferate at a high rate.[116] Although they rarely metastasize outside the brain, they have a high migratory potential in the nervous system. Brain tumors have a very poor prognosis, and excluding drastic surgical intervention, antitumor therapy is not effective.[117] Glioblastomas represent an unmet medical need even if the incidence is not as high as other types of cancer.

Seeking to mimic the region of a Y^PVNV tetrapeptide known to interact with a segment of the Grb2-SH2 domain,[118] we conceived of a hexopyranosidic scaffold **55**, which was to be "decorated" with appropriate functionality (Figure 12). Preliminary testing of some prototypes as inhibitors of Grb2-SH2 was disappointing, showing only 25–30% inhibition at 100 μM for the same analogues.[119] However, an opportunity arose to test these aryl glycosides against human glioblastoma and melanoma tumor cell lines. Inhibition of growth was observed with aryl β-D-glycopyranosides containing ether, ester, and sulfonamide groups.[119,120] Although the exact mechanism of antiproliferative activity is not clear, it was established that these "glycomers" were inducers of apoptosis in glioblastoma cells. Furthermore, it was encouraging to realize that these compounds were capable of penetrating the cells in the lines tested.

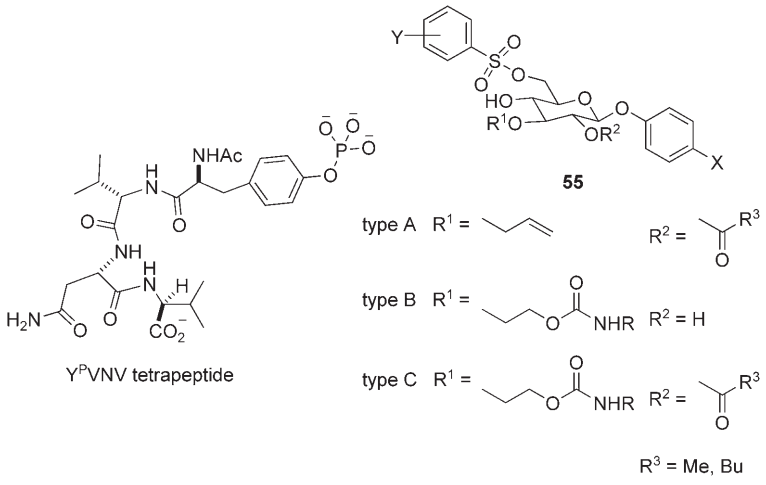


Figure 12. Structure of a natural Y^PVNV tetrapeptide and proposed carbohydrate-derived scaffolds (glycomers).

6. Herbicides and Fungicides

The agricultural industry is a multibillion-dollar business which in many indirect ways has an impact on our quality of life.[121] Crop protection, animal health, and genetically engineered products are but a few of this giant industry's activities. Contrary to some opinions, agrochemical research can be as sophisticated as drug discovery, relying on structure-based design for lead compounds. Practically, however, an agrochemical product addresses different criteria such as high-volume production and cost effectiveness as limiting factors. As in drug design, natural products have played an important role in agrochemistry, as highlighted by two case studies in our research group.

6.1. Hydantocidin and hadacidin: from natural herbicides to hybrids

The spirohydantoin nucleoside hydantocidin (**56**)[122] is a proherbicide by virtue of an in vivo phosphorylation to the corresponding 5′-phosphate HMP (**57**). It is a substrate for the enzyme adenylosuccinate synthetase (AdSS),[123] which converts adenosine monophosphate to the corresponding N6-aspartylated analogue en route to the final product, inosine monophosphate (Figure 13). It is assumed that hydantocidin phosphate is a mimic of IMP or AMP.[124]

Hadacidin, *N*-hydroxy-*N*-formylglycine (**58**),[125] is a weak inhibitor of AdSS, acting as a mimic of aspartic acid. Most welcome structural information became available when a co-crystal structure of **57** and **58** with AdSS was reported.[126] Inspired by Michelangelo's "Creation of Adam", in which the extended arm of Adam vies to touch the powerful hand of God,[127] we thought to bridge the gap between the imide nitrogen atom of **56** and the C2 achiral carbon atom of **58** to "create" a hybrid structure. Molecular modeling suggested a three-carbon linker with an *S* configuration of the newly created stereogenic carbon atom. Accordingly, both *R*- and *S*-hybrid structures were synthesized by using novel asymmetric reactions aimed at *N*-hydroxy-*N*-formyl amino acids.[128] We were pleased to find that the *S*-hybrid structure **59** showed an inhibitory activity against *E. coli* AdSS of $IC_{50} = 43$ nM, compared with $IC_{50} = 665$ nM for the *R* isomer **60**. Even more gratifying was the improved inhibitory activity relative to **56** and hadacidin individually ($IC_{50} = 167$ nM and 3.5 μM, respectively). Furthermore, simple alkyl chain extension of **58** or N1 of **56** resulted in much diminished activity. Co-crystal X-ray structures of **59** and **60** with AdSS revealed only minor differences in the conformation of the *n*-propyl linker[128] (Figure 13). Presumably, in the case of the less active *R* isomer, the enzyme undergoes some conformational change to accommodate the substrate. The conceptual approach to designing a bisubstrate inhibitor such as **59** took full advantage of the available X-ray structural information. There are very few examples of successfully linking two weak natural product inhibitors to achieve a hybrid structure with significantly improved activity over either one.[49,129] Although the case in hand remains unprecedented in the herbicide field, the potential to use strategies such as SAR by NMR[27–28] or SAR by X-ray crystallography,[28–31] as well as fragment-based design[25,26] are evident.

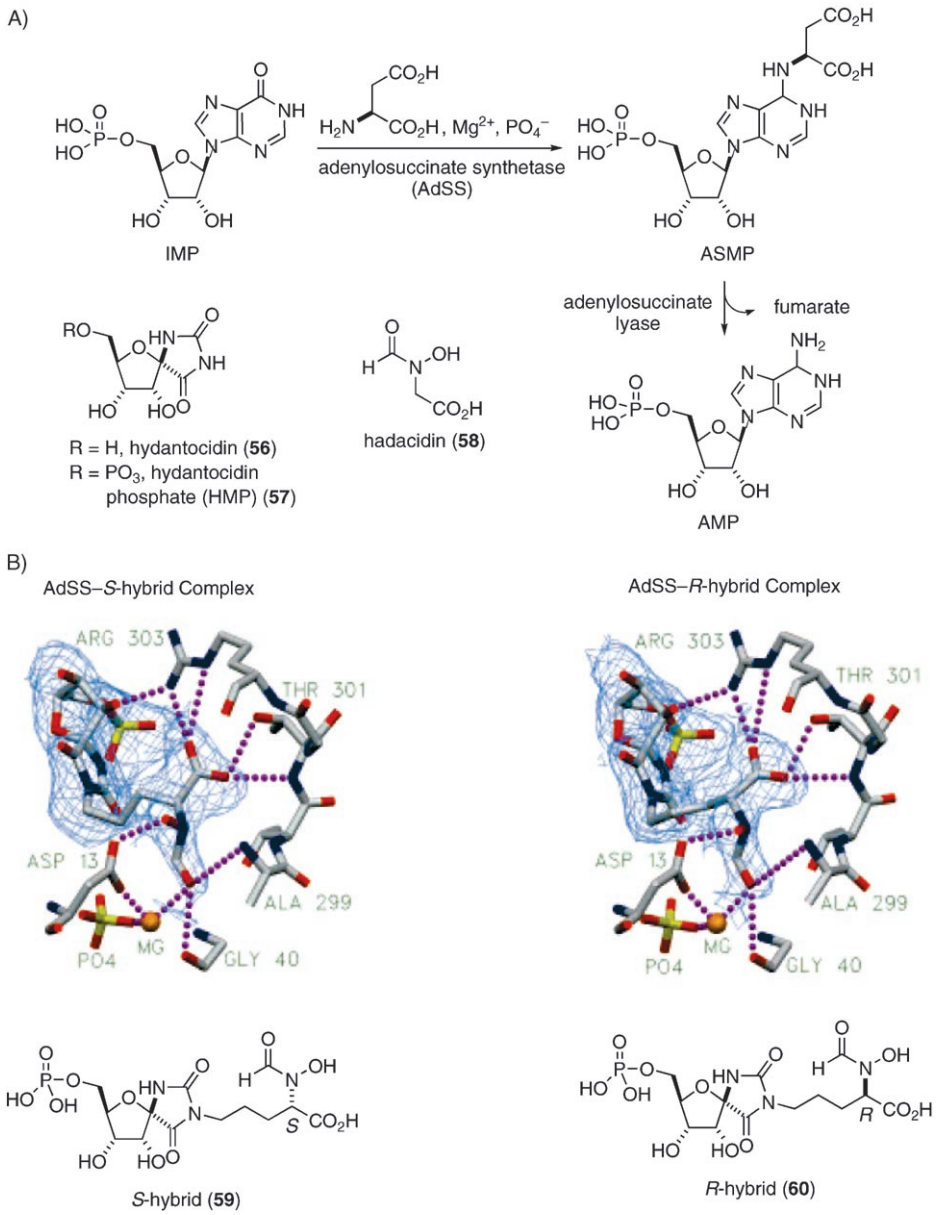


Figure 13. A) structures of herbicidal natural products **56**–**58** and their target enzyme adenylosuccinate synthetase (AdSS); B) diastereomeric herbicidal hybrid structures **59** and **60** and their X-ray co-crystal structure complexes with AdSS.

The stereocontrolled synthesis of 1,2-*trans*-*N*-nucleosides from thioglycosides[46b,48c,f] was a key step in the synthesis of various pyrimidine and purine analogues of *N*-malayamycin. Interestingly, fungicidal activity was highly dependent on the nature and stereochemistry of substituents as well as the heterocyclic anomeric unit. An efficient short synthesis of β-pseudouridine was also developed as an intermediate to malayamycin A.[131] The single-crystal X-ray structure of malayamycin A showed an unexpected orthogonal deployment of the urea group, bisecting the tetrahydropyran ring. Based on this structural information and independent modeling studies, a tricyclic analogue, **64**, which permanently orients the urea group in this preferred position was also synthesized. Unfortunately, this rigidified analogue was devoid of fungicidal activity.

The malayamycin synthesis story is all the more relevant when one considers that the natural product itself was isolated over a decade ago,[47d] and it remained in the proprietary domain until the opportunity arose for structural confirmation through synthesis.[48e,130] The potential for biological activity for natural and unnatural analogues of compounds relating to malaymycin A with applications for human use remains to be explored.

6.2. Malayamycin A: from a natural fungicide to an unnatural analogue

The fungicidal *C*-nucleoside malayamycin A (**61**) was isolated from the soil organism *Streptomyces malaysiensis* by scientists at the Syngenta Crop Protection Unit in Jeallott's Hill, UK[47d] (Figure 14). A structure was proposed based on NMR studies, although its confirmation including absolute stereochemistry had to await a total synthesis.[48d,130] In an effort to determine the role of functional groups in **61**, especially the bicyclic β-pseudouridine component, several *N*-nucleosides such as **62** were synthesized. As a result, it was found that the *N*-cytidinyl analogue **63** was at least as active as malayamycin A itself.[48f]

7. Cardiovascular Agents

The largest incidence of morbidity and mortality in the western world is the result of cardiovascular disease.[132] Hypertension, hypercholesterolemia, and stroke are among the leading medical conditions related to heart and brain function. Blockbuster drugs are sold worldwide for the control of high blood pressure and elevated levels of cholesterol and lipids. These drugs have been developed following years of intensive research on several fronts, including structure-based design.[133] They are among the true success stories of the pharmaceutical industry.

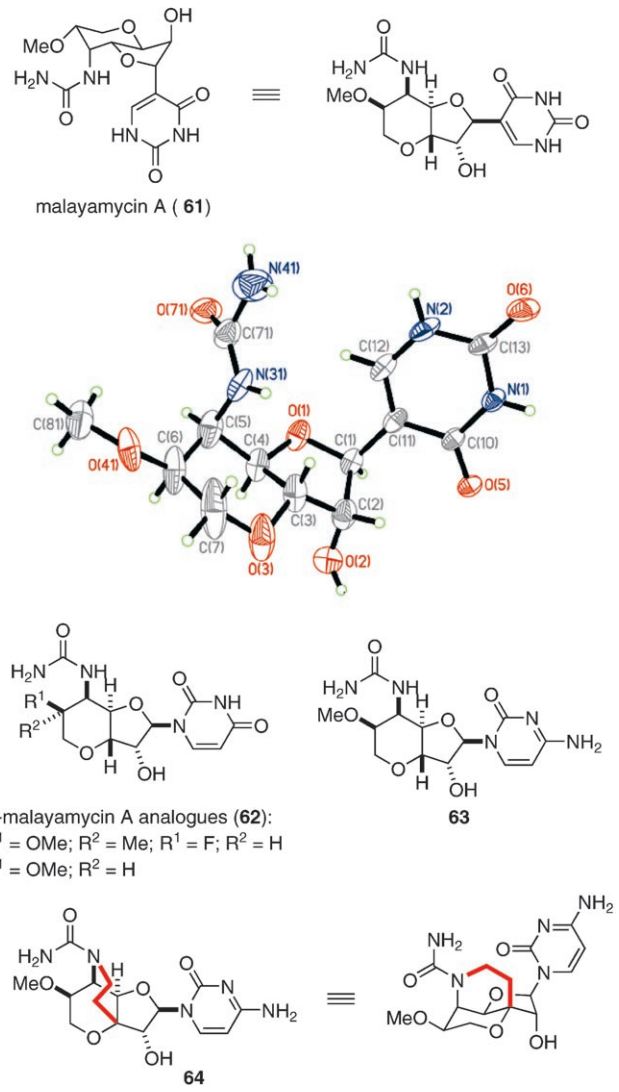


Figure 14. Malayamycin A (**61**) with X-ray structure shown and synthetic bicyclic *N*-nucleosides **62**–**64**.

7.1. Inhibition of angiotensin-converting enzyme (ACE)

Inhibitors of ACE are among the earliest mechanism-based marketed drugs for hypertension.[134] A hallmark example of drug discovery by structure-based design is captopril (**65**)[135] (Figure 15). This rather simple proline analogue was found to bind to the zinc metalloenzyme ACE, mimicking a natural substrate. Today, there are several drugs that have evolved from this historical example, such as ramipril (**66**). In the course of our studies of unnatural analogues of proline, we developed methods for the synthesis *cis*- and *trans*-4,5-methano-L-prolines.[136] As the spatial requirements of bicyclic cyclohexane captopril analogues favored only one stereoisomer as exemplified by **66**, we were curious to see if the spatially smaller methano analogues were also subject to stereochemical discrimination by ACE. To our surprise, both *cis*- and *trans*-4,5-methano captoprils **67** and **68**, and the homologated pipecolic acid analogues were found to be equally active in tests against the enzyme.[137] In an unrelated case, *cis*- and *trans*-4,5-methano-L-

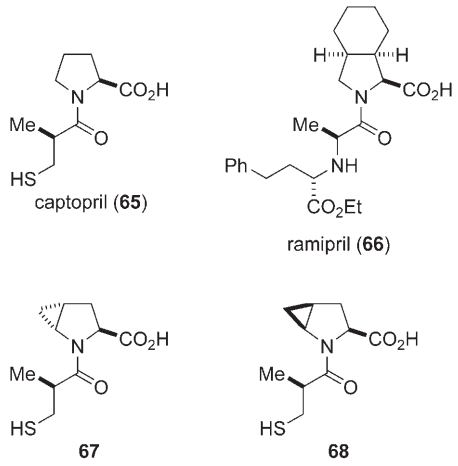


Figure 15. Structures of established ACE inhibitors **65** and **66**, and synthetic constrained analogues **67** and **68**.

proline nitriles were found to be preferred inhibitors of dipeptidyl peptidase IV.[138] This class of constrained cyclic amino acids[139] warrants further study as replacements of proline residues in peptide sequences, particularly as conformational and stereoelectronic factors seem to outweigh sterics.

7.2. Inhibition of renin

The enzyme renin is an aspartyl protease known to cleave angiotensinogen at the Leu-Val site to release angiotensin I, which is further cleaved in the enzymatic cascade that produces vasoconstricting peptides.[140] The known mode of action of renin instigated intensive efforts in the pharmaceutical industry in search of inhibitors as a means to control hypertension. Highly active entities were indeed discovered through structure-based design.[141] However, problems with bioavailability, and the complex nature of some of the designed inhibitors caused a regression of these intensive efforts a decade ago. The fruits of structure-based design were nevertheless revealed in the discovery of a structurally simple analogue of 8-aryl octanoic acid as a potential inhibitor at the ex-Ciba–Geigy pharmaceutical laboratories in Basel, Switzerland. Indeed, extensive optimization culminated with the discovery of CGP 60536 (**69**, aliskiren, Figure 16). With the identification **69** as a potential antihypertension agent, there arose a need to devise a practical synthesis that could be adaptable to scale-up. This somewhat daunting objective carried with it a number of provisos, namely to avoid the use of chiral auxiliaries for cost issues, toxic reagents based on heavy metals, and azide as a source of nitrogen. Our design strategy toward meeting these conditions was influenced by the power of visual imagery in the retrosynthetic analysis shown in Figure 16.[142] Drawing the extended structure of the target molecule in a "curled up" depiction as **69a** unveiled a bond disconnection strategy that generated a bicyclic lactam **70** as an advanced intermediate. The cleavage of a lactam by acid, and the benzylic amine bond by hydrogenolysis would in fact reveal the intended target. Disconnections from **70** would lead to the ketone **71**, itself to be made via an intramolecular Dieckmann condensa-

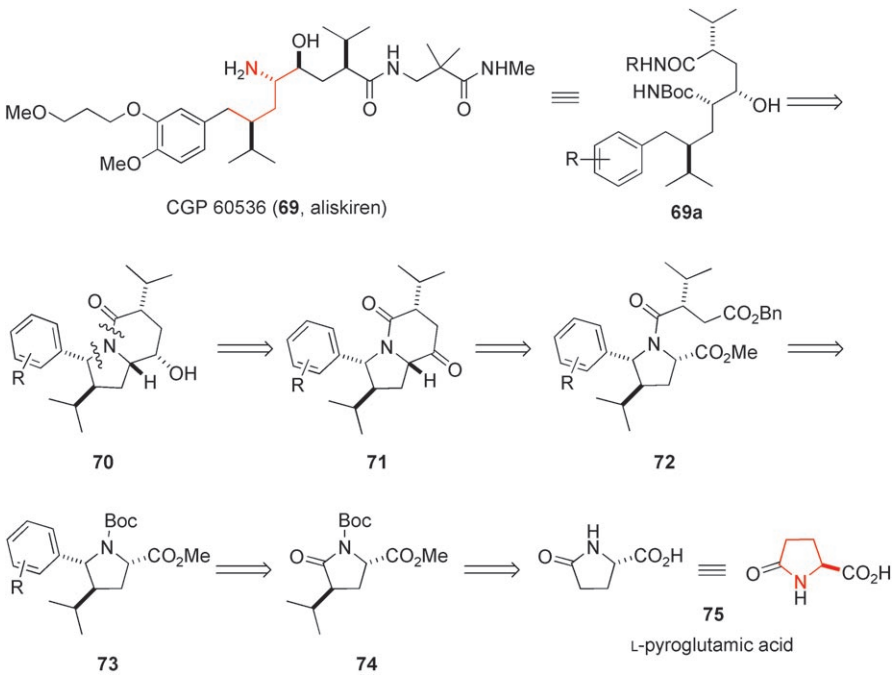


Figure 16. Structure of aliskiren (**69**) and an initial retrosynthetic analysis involving an intramolecular Dieckmann condensation. Bn = benzyl.

tion of **72**. The substituted L-prolines **73** and **74** would arise from the readily available L-pyroglutamic acid **75** via expedient enolate alkylation and iminium ion chemistry.

Using the *p*-methoxyphenyl analogue of **69** as a target, our plan worked true to its origins, except for an incorrect orientation of the second isopropyl group in **71**. An X-ray crystal structure of an intermediate revealed an equatorial disposition for the isopropyl group which we were unable to epimerize! However, taking a minor detour from **76** by switching to phosphonate anion chemistry as a chain-extension strategy led to intermediates **77**–**80** en route to the prototype inhibitor

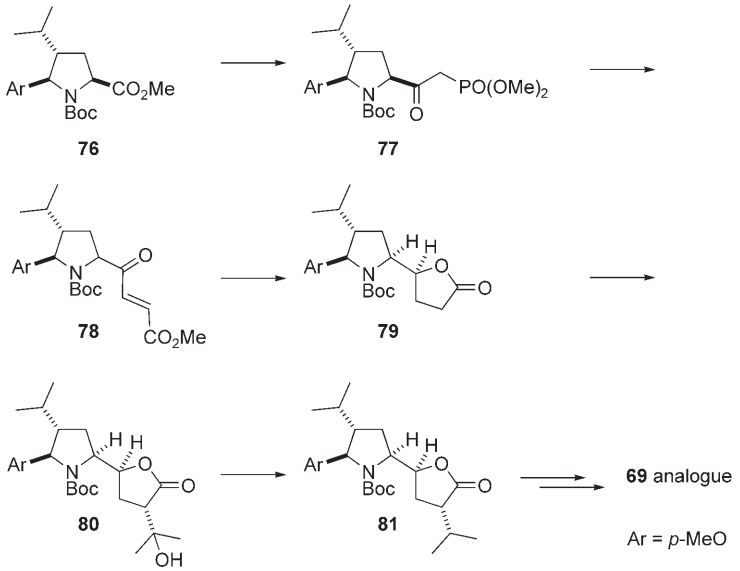


Figure 17. β-Ketophosphonate route to **69** analogue.

(Figure 17). The heuristic feature of this synthesis emphasizes the importance of seeing with the mind's eye, much like the symbolism and perspective-based paintings by Salvador Dali. Had the acyclic form of the target molecule not been represented as a topological variant **69a** (Figure 16), the connection to a bicyclic lactam precursor may have been overlooked. In this regard, it is worth mentioning that such visual connections can be easily accomplished by existing software.[10] Other groups have reported different approaches toward the synthesis of **69**, including extensive use of chiral auxiliaries.[143]

7.3. Inhibition of endothelin-converting enzyme (ECE)

The endothelins are a family of potent vasoconstricting peptides that act on smooth-muscle tissue and the central nervous system.[144] Through a complex process mediated by endopeptidases, pro-endothelin is converted into Big ET-1, which is cleaved by endothelin converting enzyme (ECE) into the 21-amino-acid ET-1 at the Trp-Val site. ET-1 is the most powerful local vasoconstrictor known.[145] It binds to its receptor on a G-coupled protein resulting in the activation of several enzymes, which increase the concentration of intracellular Ca^{2+}, eventually causing contraction of blood vessels. Thus, like ACE and renin, inhibition of ECE has been a relevant strategy to control hypertension[134] and other serious vascular disorders.

ECE is a zinc metalloprotease which has not yet been crystallized. Nevertheless, intensive efforts have led to the synthesis of many inhibitors.[146,147] Our objective was to gain insight into the functional and topological requirements of potential pharmacophores present in acyclic inhibitor acids **82** and **83**[147] (Figure 18). We considered azacyclic-constrained variants onto which isobutyl and aryl alkyl chains could be tethered. This would result in several diastereomers in each series which would be used to probe the topology of the scaffolds and the preferred spatial orientation of the appendages in the enzyme active site. Extensive synthetic studies led to a series of enantiopure pyrrolidine and piperidine α-phosphonic acids exemplified by **84** and **85**, respectively (Figure 18).[148] Whereas testing for ECE inhibition did not reveal a distinct SAR among the various diastereomers, analogues **84** and **85** showed promising activity (respectively 91 and 98% inhibition at 10^{-5} M). The prospects of developing dual or triple

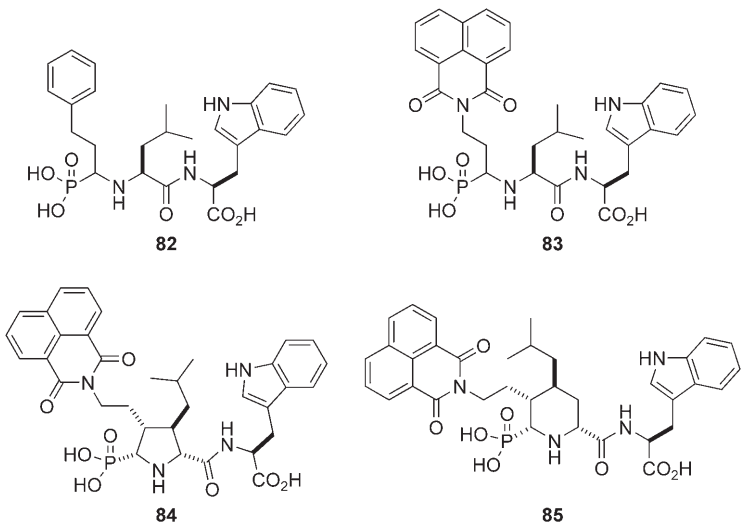


Figure 18. Structures of synthetic ECE inhibitors **82** and **83**; proposed constrained azacyclic analogues **84** and **85**.

inhibitors of enzymes such as ECE, ACE, and NEP (neutral endopeptidase) remains a challenge in this field.

7.4. Inhibition of thrombin: lessons from natural products

Thrombin (Factor IIa) is the last enzyme in the complex intrinsic cascade process that cleaves fibrinogen to fibrin.[149] Thrombin is a serine protease that holds a central position in the blood-coagulation cascade, which culminates with platelet aggregation and the formation of blood clots that can ultimately lead to stroke. This unmet medical need is the subject of intensive efforts to find safe and effective antithrombotic agents. A 65-amino-acid polypeptide called hirudin, isolated from the saliva of leeches, was found to have inhibitory properties toward thrombin.[150] Early X-ray crystallographic studies of D-Phe-L-Pro-L-Arg analogues as tripeptidic mimics of the thrombin-sensitive sequence in fibrinogen, in complex with thrombin, revealed the crucial S_1, S_2, and S_3 pockets as well as the site of the catalytic triad involving a serine residue.[151] Since then, a plethora of synthetic inhibitors have been reported based on information gleaned from X-ray crystallography.[152,153] Ximelagatran (Exanta, **87**), a totally synthetic compound based on X-ray structural data of thrombin, was initially approved for limited post-surgical use as an antithrombotic (Figure 19).[133] However, its use was recently discontinued owing to some toxicity.[154]

Extensive modeling studies in collaboration with scientists at AstraZeneca (Mölndal, Sweden) led to the design and synthesis of constrained analogues of D-Phe-L-Pro-L-Arg, exemplified by the indolizidinone **88** ($IC_{50} = 18$ nM against thrombin),[155] shown in Figure 19. A co-crystal structure with thrombin showed the expected interactions. It was also clear that the amino group of the D-Phe residue could be replaced by a hydroxy group with the correct configuration. Compared with the crystal structure of the original linear tripeptide, it appeared that some amino acid residues had shifted their positions, although modeling of the docked inhibitor prior to its synthesis showed nearly ideal superposition (Figure 19). Further synthetic efforts led to the aminoindolizidinone **89**, which showed an inhibition value of $IC_{50} = 4.7$ nM.[156] The epimeric amine **90** was 500-fold less active, while other analogues designed based on modeling of X-ray data were of variable activity.[157] Key steps in the synthesis of these indolizidinones were the stereocontrolled introduction of hydroxy and amino groups at tertiary carbon atoms via lactam enolate chemistry.[155–158] Synthetic approaches to indolizidinones and related bicyclic lactam carboxylic acids have been reported by us and various other research groups.[159]

7.4.1. Phenol P_2/P_3 core motifs as thrombin inhibitors

The power of modeling based on X-ray structural information was manifested in the design of achiral thrombin inhibitors with a phenolic core motif.[160] The replacement of a core entity such as an indolizidinone with simple heterocyclic, heteroaromatic, or aromatic units has clear practical advantages from an industrial point of view. A series of P_1 and P_3 substituents with diverse functionality was designed, synthesized, and tested as thrombin inhibitors. Excellent inhibition was shown by a series of P_3 sulfonamides with good selectivity against trypsin. A co-crystal structure of a naphthylsulfonamide **91** ($IC_{50} = 17$ nM against thrombin) bound to thrombin showed the expected interactions of essential H bonds and side chains (Figure 20). Related phenolic core structures have been reported in the patent literature.[161] Inhibitors with relatively simple structures that are also devoid of chirality but which harbor a set of orthogonally modified functionality are clearly attractive. They are also more versatile in terms of diversification of the rigid scaffold and the pharmacophoric appendages relative to those derived from natural products.[19b]

7.4.2. Marine and freshwater natural product thrombin inhibitors

The aeruginosins[162] are a relatively new class of linear peptidic secondary metabolites isolated from aquatic sources.[162] They exhibit inhibitory activity against serine proteases such as thrombin and trypsin. The aeruginosins share a common 1-aza-[4.3.0]bicyclic 2-carboxylic acid core unit that may contain one or two hydroxy groups. No less than 21 members of the aeruginosin family have been isolated from cyanobacteria inhabiting freshwater algae and marine salt-water sponges.[163] Of these, six have been synthesized and their structures confirmed or revised.[164,165] X-ray crystallographic studies of complexes have shown productive interactions at three sites.[166] Thus, the P_1 (substrate) group, consisting of a guanidine end group acts as an arginine mimetic and makes a charge contact with an Asp residue at the S_1 site of the enzyme. The P_2 and P_3 sites are associated with backbone and hydrophobic interac-

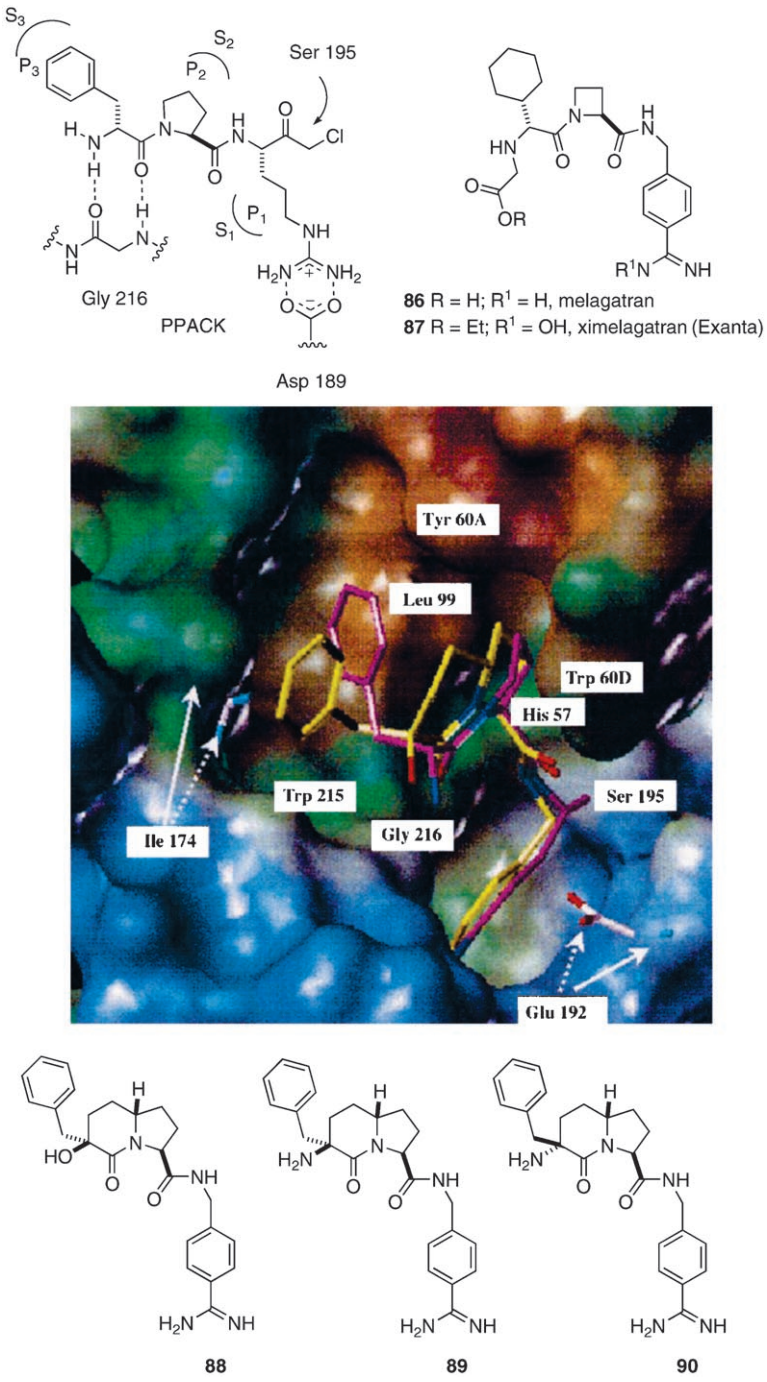


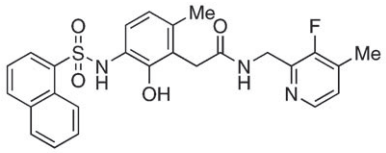
Figure 19. Structure of PPACK and constrained indolizidinone analogues **88**, **89**, and **90**; X-ray co-crystal structure of **88** overlaid with PPACK is shown in color.

tions, respectively. The D-Phe or D-Leu residues at the P_3 sites of the inhibitor bind in the hydrophobic S_3 pocket of the enzyme.

Within the aeruginosin group, the dysinosins represent a unique subset of dihydroxylated octahydroindole-2-carboxylic acid amides, isolated from the *Dysideidae* family of marine sponges[167] (Figure 21). The structure and configurational assignment of dysinosin A (**92**) was achieved through a total synthesis[168] following NMR and X-ray structure work with thrombin.[167] A novel 1-amidino-Δ-3,4-pyrroline subunit, hitherto unknown among natural products, was Nature's substitute for an arginine mimetic in dysinosin A. A complex of dysinosin A and thrombin delineated the anticipated P_1, P_2, and P_3 interactions at the active site, although the *trans*-diaxial diol unit present in the octahydroindole core made no discernible contacts. (Figure 20).[167]

Soon after the completion of our synthesis of dysinosin A,[168] we became aware of the existence of a novel aeruginosin isolated from freshwater algae and represented by a unique cyclic guanidine as an arginine mimetic end group.[169a] The total synthesis[170] of this presumed structure was met with utter disappointment when testing revealed the lack of any inhibition of thrombin. In the interim, a second patent appeared[169b] in which the exact same structure was proposed with the 1-amidino-Δ-3,4-pyrroline as the end group (rather than the incorrect isomeric cyclic guanidine). Our total synthesis of "the real" oscillarin (**93**) confirmed its structure and configurational identity.[170] Also rewarding was the inhibitory activity of our synthetic oscillarin against thrombin (IC_{50} = 28 nM), which was the highest recorded among the known aeruginosins. A co-crystal structure with thrombin revealed the characteristic L-shaped architecture of oscillarin in the active site with the expected P_1, P_2, and P_3 site interactions.

A 2003 patent by the ex-Pharmacia research group revealed yet another novel aeruginosin (Figure 20).[171] Although no stereochemical descriptions were given, the published structure was identical to that of dysinosin A, with the inclusion of a chlorine atom on the β position of the leucine residue. The patent also reported unprecedented activity against thrombin and related serine proteases involved in the thrombolytic cascade. We therefore undertook the total synthesis and structural confirmation of this "chlorodysinosin A" (**94**). The presence of a β-chloroleucine residue presented a number of challenges, not the least of which was its propensity to un-



91

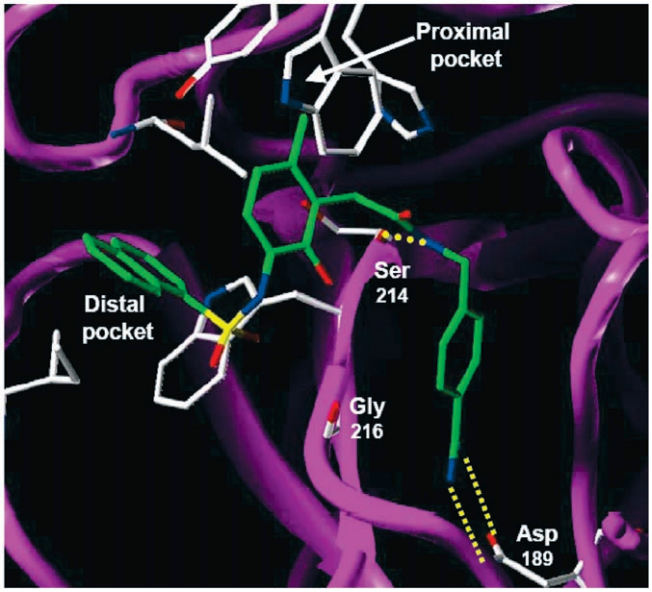


Figure 20. X-ray crystal structure of **91** bound in the thrombin active site. Essential H bonds to Asp 189, Ser 214, and to side chains of the proximal and distal pockets involved in lipophilic interactions are shown.

dergo β-elimination at any stage of the synthesis. Furthermore, while we could assume with reasonable certainty that the absolute configuration of chlorodysinosin would correspond to that of the known deschloro analogue **92**, we did not know which stereochemistry to assign to the chloroleucine. In defiance to Murphy's law, we developed a stereocontrolled synthesis of 3(*S*)-chloro-D-leucinol and used it to complete the total synthesis.[172] We were pleased that our "3(*R*)-chloro hunch" was correct, as all physical constants of the synthetic product matched the reported data. We had not yet appreciated the subtleties of replacing a pro-*R* methine hydrogen atom in dysinosin A with a chlorine atom, as in chlorodysinosin A, until the results of enzymatic analysis became available. In fact, chlorodysinosin A proved to be the most potent in vitro inhibitor of thrombin to date. Of further interest was its potent activity against Factor VII and Factor Xa compared with dysinosin A and oscillarin (IC_{50} values toward thrombin: 5.7 nM; trypsin: 37 nM; Factor VIIa: 3.9 nM; Factor XIa: 4 nM). It is remarkable that a single chlorine atom, placed in a crucial side chain involved in the P_2/S_3 hydrophobic interaction, would be so superior to its methylene counterpart. A co-crystal structure with thrombin confirmed the stereochemistry of the carbon bearing the chlorine atom (Figure 21). Other important interactions were also identified and compared with those made by dysinosin A lacking the chloro group. Preliminary modeling offered plausible reasons for the improved potency. Thus, favorable changes in charge distribution, better accommodation of the chlorine atom in the S_3 subsite with release of water (entropic gain), and stabilization of the χ^1 bond angle constraint may contribute to the enhanced binding.

Starting with the naturally occurring 65-amino-acid hirudin as an inhibitor of thrombin and information gleaned from the thrombin-sensitive sequence in fibrinogen, humans and Nature have worked in tandem to create new and better inhibitors of this critically important enzyme. In spite of its unfortunate demise as a marketable antithrombotic agent, Exanta[133,154] is the product of structure-based design and is a testimony for the inspiration provided by natural products in drug discovery.[173,174]

8. Central Nervous System Agents

CNS drugs have been omnipresent as far back as folk medicine and the coexistence of humans and the plant world. Quinine and morphine are among the most celebrated natural product ingredients discovered in serendipitous ways. Reference to "drugs that would quit all pain and strife and bring forgetfulness of every ill" was made by Helen of Troy offering wine laced with opium to Telemacchus (Homer in the Odyssey).[175] Today, drugs for the management of depression and schizophrenia, among others, are routinely prescribed by physicians and psychiatrists alike.[176] The complex receptor systems associated with the CNS presents a great challenge to achieve safe drugs with little or no side-effects. This black-box area of ancient and modern-day maladies is also the cause of a number of unmet medical needs such as dementia and Alzheimer's disease.[177]

8.1. Morphinomimetics: eye-teasing Dali-esque molecules

Morphine (**95**), a constituent of opium found in poppy seeds and used strictly in a regimented hospital environment, remains today the ultimate pain killer in extreme cases.[178] Ironically, the diacetyl derivative of morphine is heroin, a dangerously addictive substance, whereas the monomethyl ether, codeine, is an over-the-counter ingredient of cold medicines. During our studies of the [1,2]-Stevens rearrangement[179] of 13-substituted enantiopure dihydromethanodibenzoazocines derived from L-amino acids,[180] we uncovered a topological relationship between the isopavine-type products and morphine (Figure 22). When the 13-methyl "azocine" **96**, prepared from L-alanine was converted into the corresponding isopavine, its μ-receptor activity was disappointingly weak. Soon after, it was realized that this "stripped-down" morphinomimetic was, in fact, an analogue of *ent*-morphine, with an "inverted" orientation of the lone pair. Switching to D-alanine led to *ent*-**96** and *ent*-**97** with a morphine-like topology, including the correct orientation of the lone pair. Subsequent introduction of aromatic substituents on *ent*-**97** led to analogues exhibiting activity toward the μ-receptor in the low nanomolar range.[181]

Since the discovery of stereochemistry and its relevance to organic synthesis, it has been customary for synthetic chemists to build molecular models and to study their three-dimension-

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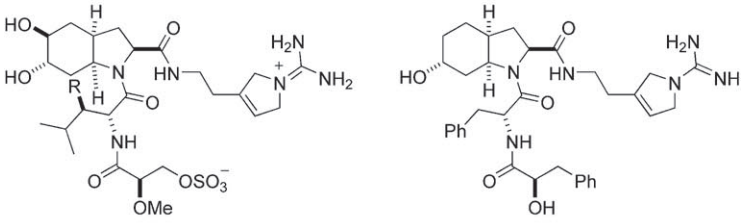

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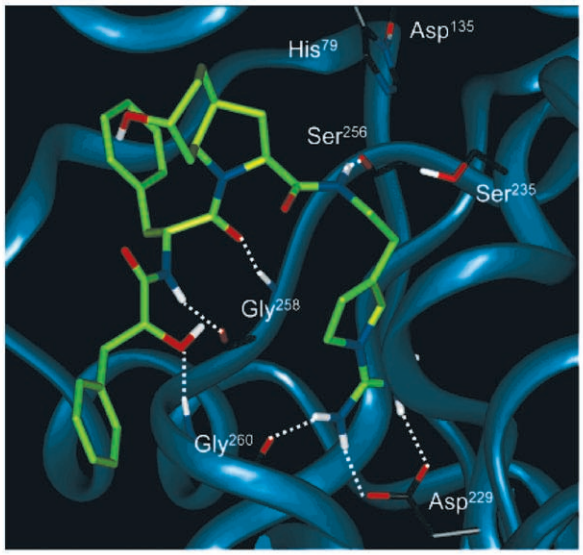

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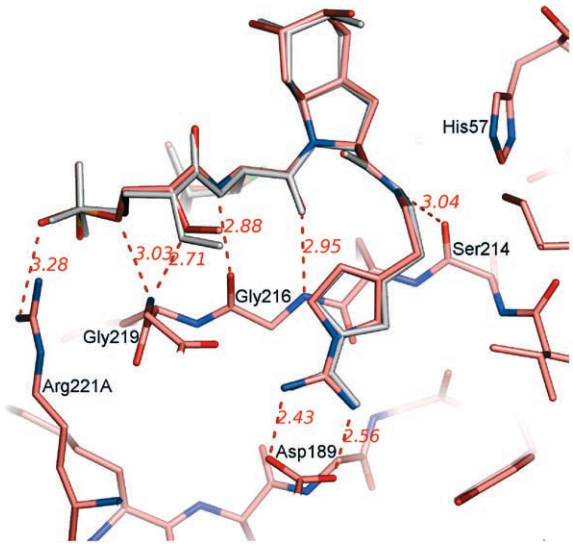


Figure 21. A) Structures of natural thrombin inhibitors **92**–**94**; B) X-ray co-crystal structures of oscillarin, and C) dysinosin (grey) and chlorodysinosin A (pink) in thrombin.

tably, organic chemistry is still taught, by and large, in a two-dimensional medium such as the classroom white- (or black)board. Even colorful PowerPoint presentations of didactic material can miss the exciting prospects of "seeing" the third dimension, if for nothing more than to appreciate steric and proximity effects.

8.2. Inhibitors of BACE: relevance to Alzheimer's disease

Alzheimer's disease and other forms of dementia are serious and debilitating medical conditions amongst the elderly population.[177] A hallmark event in the process leading to the disease is the deposition of plaques of β-amyloid (Aβ) protein in the brain.[182] This complex process is initiated by two important sequential enzymatic steps attributed to the membrane-bound aspartic protease BACE (β-secretase, memapsin 2) and γ-secretase.[183] Cleavage of β-amyloid precursor protein (APP) by BACE releases a large ectodomain and produces a membrane-bound C_{99} fragment, which in turn is a substrate for β-secretase, and the resultant release of Aβ. BACE is considered an ideal target enzyme to inhibit as a means of controlling plaque formation and the neurodegenerative consequences that it elicits.[184]

8.2.1. Carbocyclic and heterocyclic peptidomimetics

Tang, Ghosh, and co-workers[185] disclosed the first X-ray crystal structure of the extracellular domain of BACE complexed with a synthetic 1-nM heptapeptide inhibitor OM99-2 (**98**) (Figure 23). The unnatural hydroxyethylene spacer was intended as a transition-state mimic of a Leu-Ala subunit. Our studies were first aimed at a systematic chemical modification of OM99-2 and its isopropyl congener OM00-3,[185b] including the introduction of elements of constraint through carbocyclic and heterocyclic variants of the hydroxyethylene isostere (Figure 23). Relying on information provided in the X-ray structures[185] and our own efforts in molecular modeling in collaboration with Novartis scientists in Basel, Switzerland, we introduced a fused cyclopentane (CP) ring at the P_1' Ala position and proceeded to systematically truncate the P_1'–P_4' end of the molecule as exemplified in compounds **98**–**101**[186] (Figure 23). Although some inhibitory activity was sacrificed in the process, the des-Phe-Glu CP analogue **101**, harboring the P_2' Ala OH unit, revealed an unexpected level of selectivity vis-à-vis cathepsin D while maintaining good activity against BACE (IC_{50} = 6.0 μM for cathepsin D and 39 nM for BACE, respectively). An X-ray co-crystal structure revealed excellent superposition of the peptidic backbone with the original OM99-2 (Figure 23). The P_2' Ala OH showed two specific interactions with Tyr 198 and Arg 128. This phase of the study

ality in space. Although nowadays the same can be accomplished on the computer screen with the added numerical bonus of energy data, there is still a nostalgic if not pedagogically pleasing merit of actually touching and "playing" with ball-and-stick-type molecular models. Our Dali-esque discovery of isopavines as morphinomimetics attests to this fact. Regret-

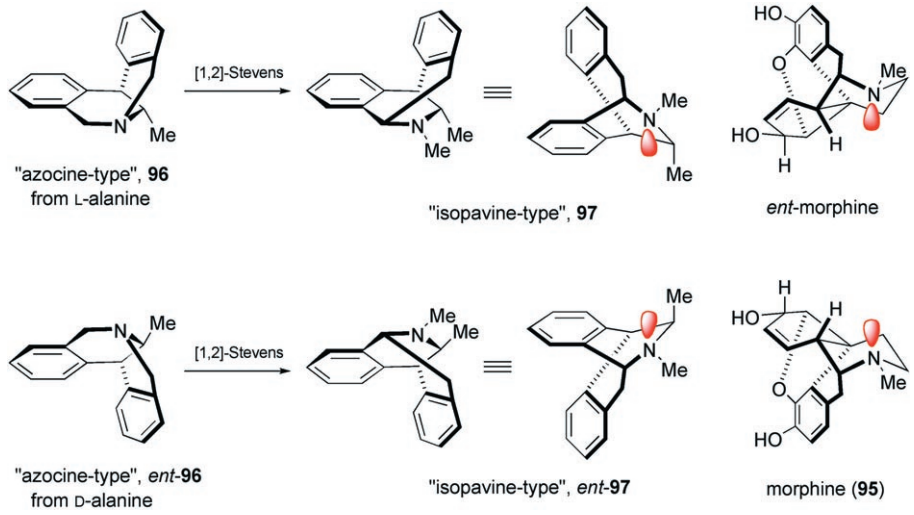


Figure 22. Structures of morphine **95**, *ent*-morphine, and *ent*-azocine **96**-isopavine types **97**, showing topological and lone-pair convergence.

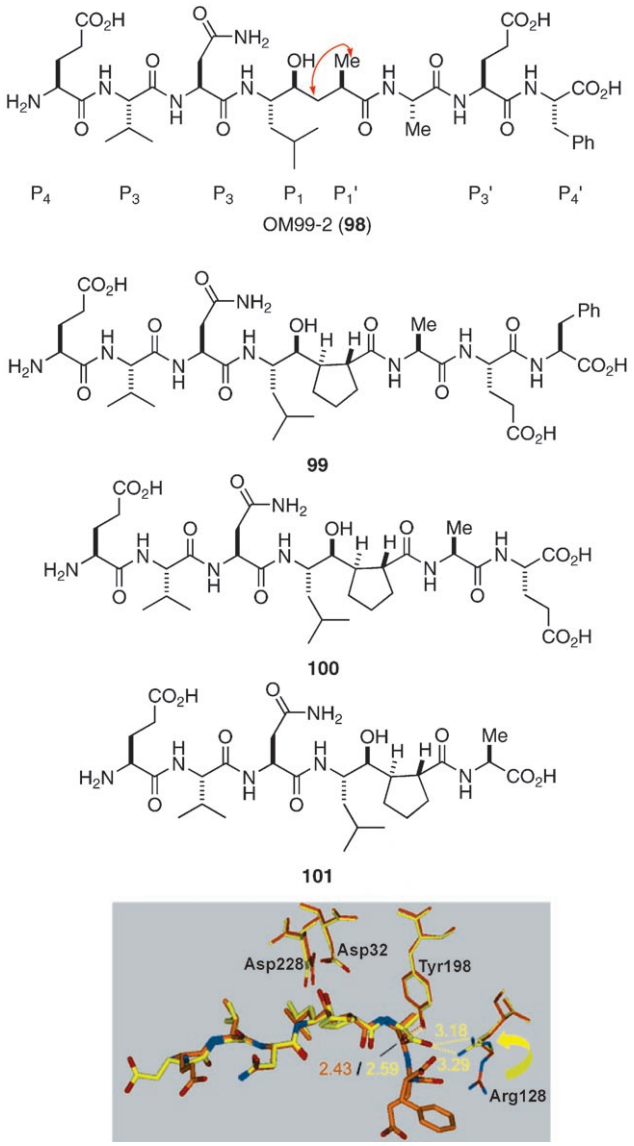


Figure 23. Structures of Ghosh–Tang inhibitor **98** and CP analogues **99**–**101**; X-ray co-crystal structure overlay of **101** (yellow) and **98** (orange) in BACE.

demonstrated the feasibility of introducing a carbocyclic CP unit in the hydroxyethylene isostere portion of OM99-2 without unduly affecting its bioactive conformation within the active site of the enzyme. Further observations led to the synthesis of a carbocyclic cyclopentanone **102** with truncated amino acids at either end, which also showed excellent superposition with OM99-2 in a co-crystal structure, and an IC_{50} value of 10 nM against BACE. However, activity against cathepsin D was also enhanced (IC_{50} = 56 nM, Figure 24). It is of interest that the carbonyl group

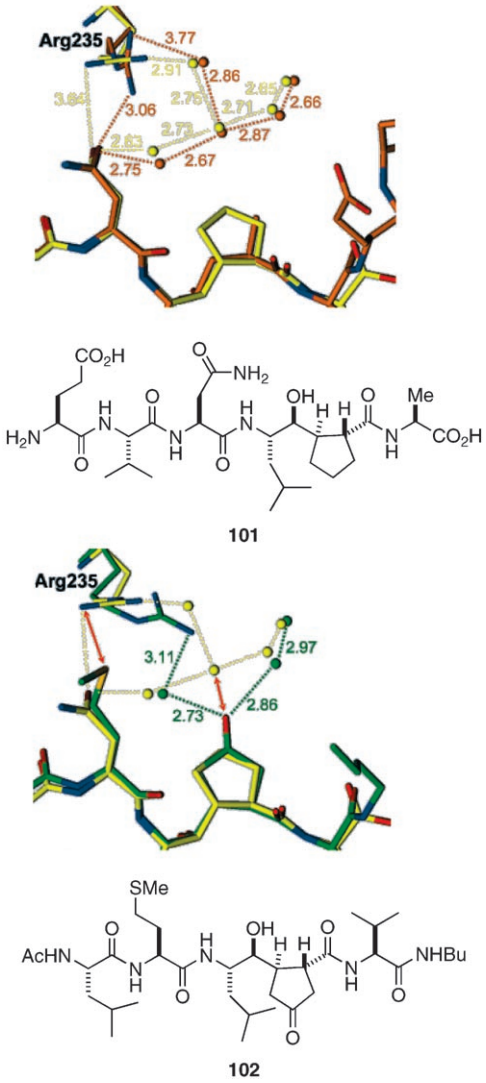


Figure 24. Binding interaction in the water-filled S_1 pocket (distances in Å) in BACE: A) comparison of **101** (yellow) and **98** (orange); B) comparison of **101** (yellow) and **102** (green). Water molecules are represented as orange, green, and yellow spheres.

in **102** causes the displacement of a water molecule in contrast to the complex with **101**.

Next, we synthesized the constrained oxacyclic hydroxyethylene isostere analogue **103** based on the promising results of the CP series[187] (Figure 25). Stereocontrolled syntheses of α-substituted butyrolactones were achieved by enolate and silylketene acetal chemistry. Further elaboration of the required diastereomer led to the intended analogues. Only weak inhibitory activity was observed with one analogue against BACE, while two others showed inhibition against cathepsin D. Thus, introduction of oxygen into the CP ring proved to be detrimental to the inhibition of BACE, possibly resulting from repulsive interactions of the ring oxygen atom with amide carbonyl groups in the active site, thus perturbing the preferred binding conformation.

To probe the P_1' site for possible productive H-bonding interactions, we also considered constrained azacyclic analogues (Figure 25). A variety of stereocontrolled methods were used to prepare the core hydroxyethylene isostere-constrained amino acids encompassing 3,4-disubstitituted pyrrolidine, 2-pyrrolidinone, and 5-pyrrolidinones **104**, **105**, and **106**, respectively.[188] These were then transformed into prototypical inhibitor structures patterned after the original CP lead. Molecular modeling suggested a good superposition by docking procedures on the co-crystal structure of the cyclopentanone analogue **102**. Indeed, only the lactam analogue **106**, the carbonyl group of which points in the same direction as the cyclopentanone carbonyl group of **102** in the enzyme, showed potent inhibitory activity at $IC_{50} <$ 10 nM (79% inhibition at 10 μM, Figure 25). Further modifications and truncations at different subsites of lead inhibitors have provided insight for the development of potent analogues with less peptidic character.

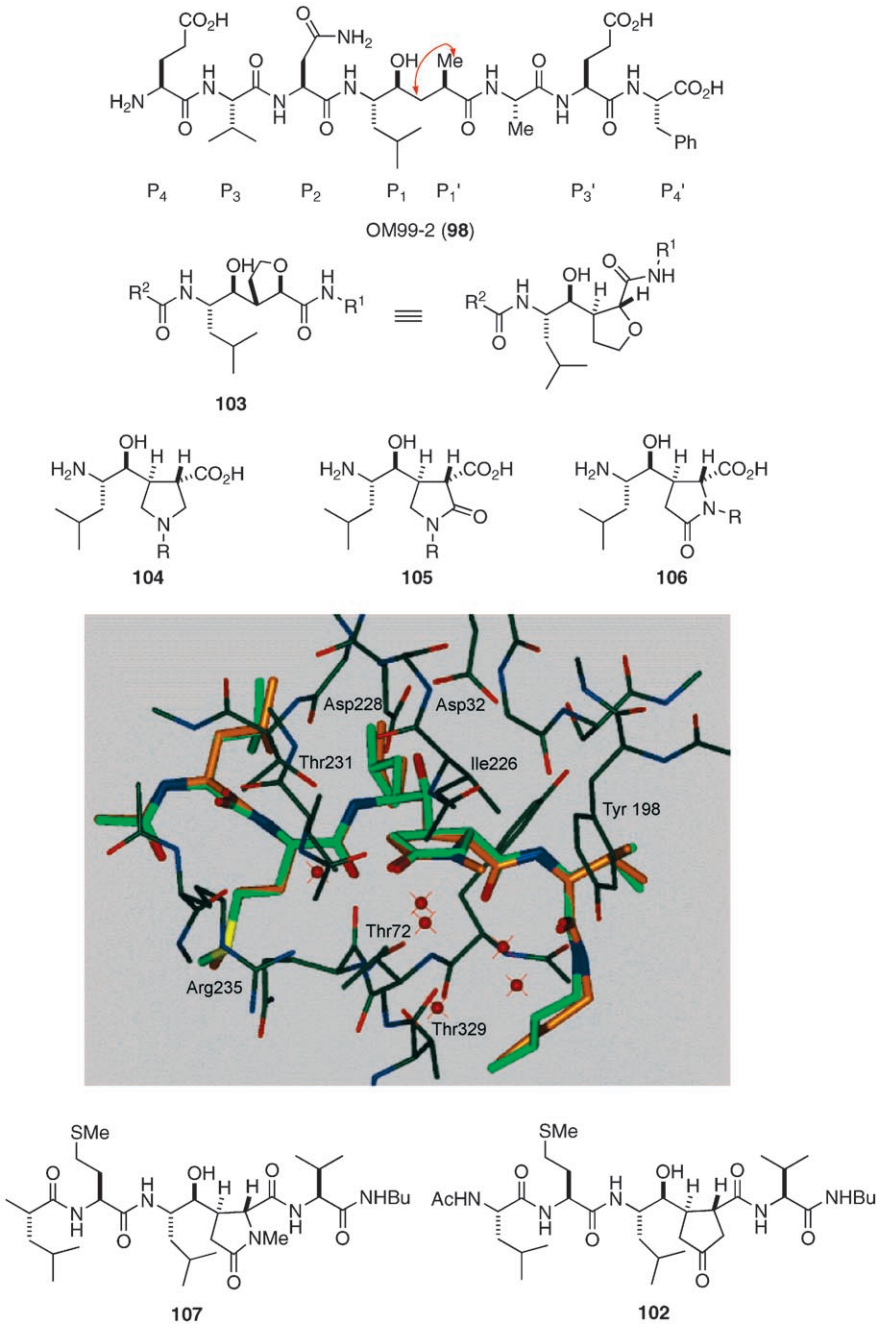


Figure 25. Structures of oxacyclic and azacyclic truncated analogues of the Ghosh–Tang inhibitor **98**. Modeled superposition of **107** on X-ray co-crystal structure of **102** in BACE. Water molecules are represented as red spheres.

8.2.2. Macroheterocyclic peptidomimetics

Based on the notion that substrates for proteases adopt an extended β-strand conformation[34c] in order to be recognized and cleaved, we designed macrocyclic variants of acyclic inhibitors of BACE (Figure 26). Macrocyclization is also a well-known strategy to preorganize the bioactive conformations of potential enzyme inhibitors.[189] This could lead to improved cell permeability, oral bioavailability, and proteolytic stability relative to open-chain analogues.[189] Accordingly, methods were developed for the synthesis of macroheterocyclic peptidomimetics in which the P_1 and P_3 subunits in the original OM00-3 (**108**) were tethered through thioether or ether bridges, and the extremities were truncated.[190]

Suitable subunits were constructed, and tethering was achieved through ring-closure metathesis[191] or through bis-al-

kylation with appropriate linkers. The *trans*-dithiamacrocycle **109** was found to inhibit BACE ($IC_{50} = 156$ nM) and pepsin ($IC_{50} < 10$ nM) (Figure 26). A co-crystal structure of **109** with BACE was solved to a resolution of 2.10 Å which supported our original hypothesis of maintaining a β-strand-like shape of the acyclic portion of **109** and nicely overlapping with the Tang–Ghosh inhibitor **108**. Remarkably, with the exception of a few structural changes, the designed macrocyclic compound maintained critical H-bonding interactions within the BACE active site. The electron density for the

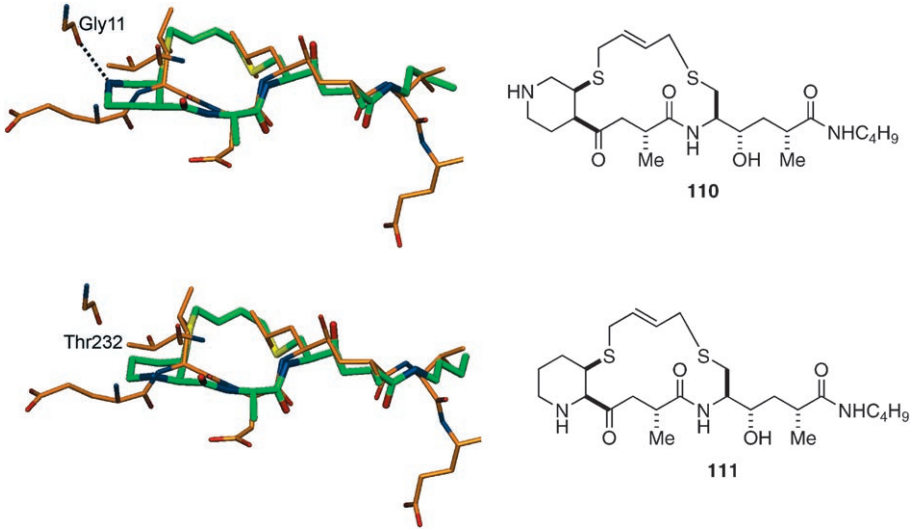


Figure 27. Overlay of OM00-3 (**108**) with models of bicyclic inhibitors **110** and **111** showing the intended interactions and the expected conformation.

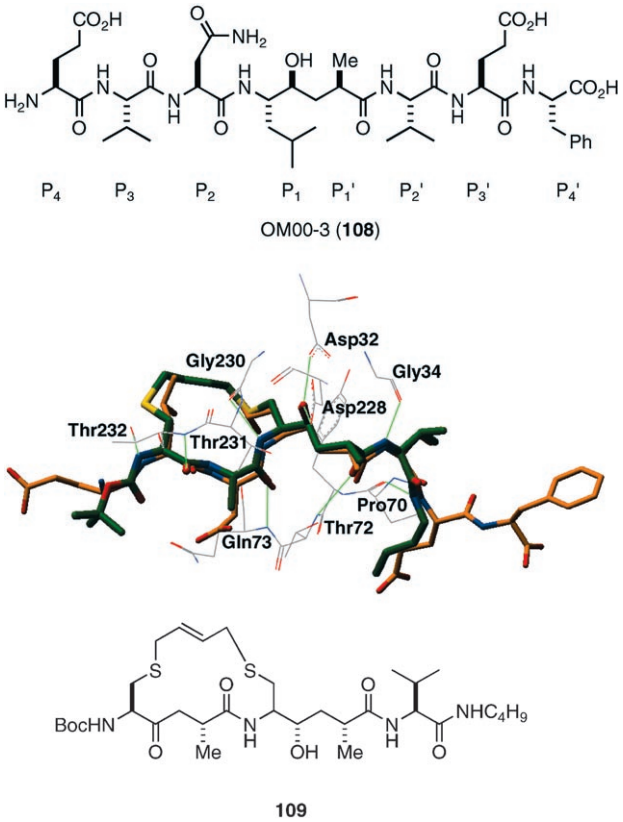


Figure 26. Overlay of the X-ray structures of BACE complexes with **109** (dark green) and **108** (OM00-3, orange).

spective diastereomers, which showed excellent congruence in the modeled superposition with **108** (Figure 27).[190] However, activity against BACE, cathepsin D, and pepsin was observed for only one of the 2,3-disubstituted diastereomers, **112** (Figure 28). In contrast, the modeled compounds **110** and **111**

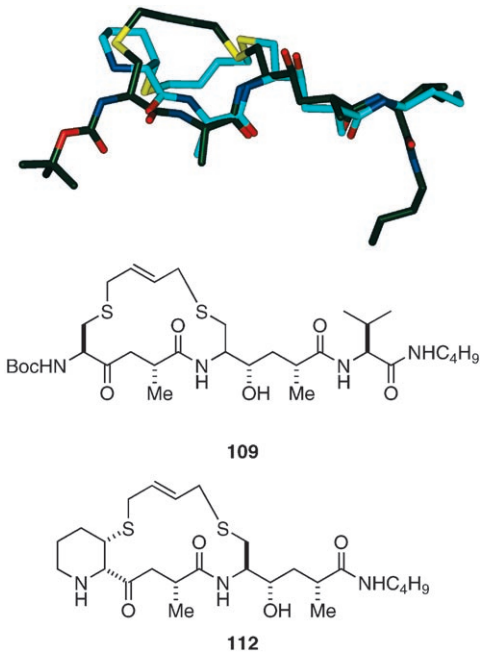
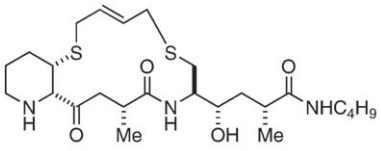


Figure 28. Overlay of the X-ray conformations of the BACE complexes with **109** (dark green) and **112** (cyan).

trans-butene linker in the co-crystal structure of the macrocycle **109** was weak, indicating conformational disorder. This may also explain the modest inhibitory activity due to relative flexibility of the macrocyclic structure. In order to improve interactions through additional H bonding and to introduce further rigidity, we developed stereocontrolled syntheses of regioisomeric bicyclic piperidine macrocycles **110**, **111**, and their re-

were not active against BACE. A co-crystal structure of **112** with BACE at 2.30 Å resolution revealed a good superposition of the backbone with the monocyclic macroheterocycle **109**, but the binding modes of the two differed substantially in several respects. Furthermore, the *trans*-dithia bridge of the bicyclic macroheterocycle **112** follows a completely different path in comparison with the monocyclic analogue **109**. As expect-



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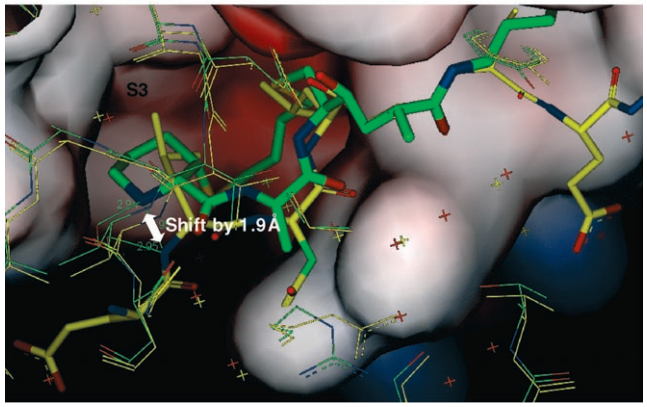


Figure 29. Overlay of the crystal structures of **112** (cyan) and **108** (OM00-3, orange) (partial surface to show S_3 pocket).

ed, an H bond with Thr 232 is observed, but the position of the nitrogen atom is shifted by 1.5–2.0 Å toward the S_3 pocket relative to OM00-3[185b] (Figure 29). Although our expectations for improved activity against BACE through conformational preorganization using macrocyclic variants of acyclic inhibitors was not fulfilled, a wealth of new methods were developed for disubstituted piperidine 2-carboxylic acids, and insightful information was gleaned from X-ray co-crystal structures.

9. Miscellanea

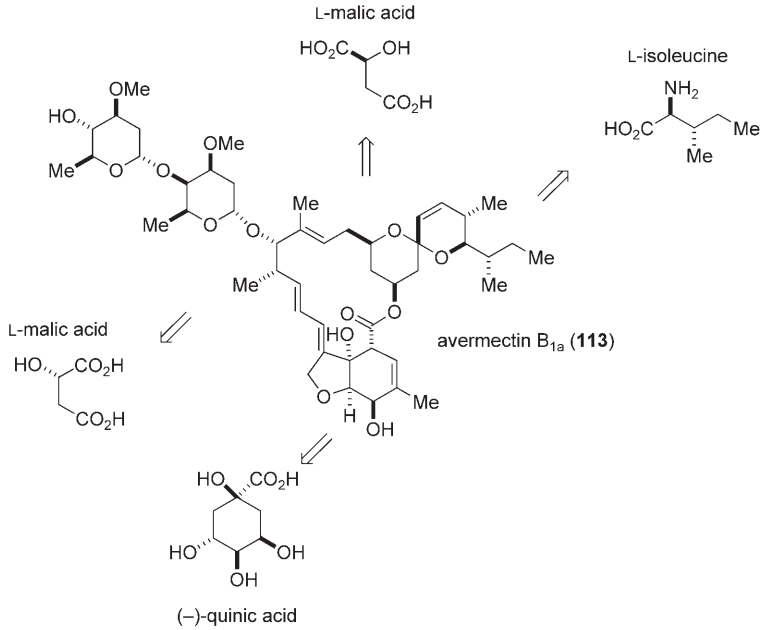
9.1. Tinkering with Nature's macrolides

9.1.1. Avermectin B_{1a}

The naturally occurring macrolide avermectin B_{1a} (**113**) is a member of the dioxaspiroacetal family of natural products possessing potent anthelmintic properties (Figure 30).[192] It commands a substantial share of the market in the animal-health industry. Having completed the first total synthesis of avermectin B_{1a},[193,194] we became aware that the penultimate step in the synthesis presented a challenging stereochemical problem, which resulted in the C2 epi analogue **114**.[195] The solution to this troublesome hurdle came from a conceptually simple idea reminiscent of an enzymatic relay mechanism. Partial deconjugation–epimerization took place in the presence of imidazole[193b] to provide the natural configuration. The successful implementation of a selective ozonolytic cleavage[196] of the dienic system in **113** led us to consider the semisynthesis of a homologated trienic analogue **115** of avermectin B_{1a}.[197] Unfortunately, this ring-expanded analogue was devoid of anthelmintic activity.

9.1.2. Bafilomycin A_1

The hygrolide group of macrolide antibiotics comprises the unusual 16-membered tetraenic macrolactone bafilomycin A_1 (**116**),[198,199] the structure and absolute stereochemistry of which was established by X-ray crystallographic analysis[200] and NMR spectroscopy.[198] A unique pattern of intramolecular H bonds confers an element of rigidity to the otherwise flexi-



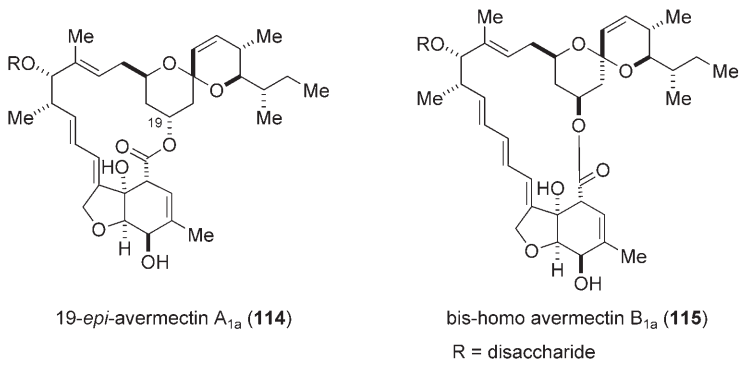
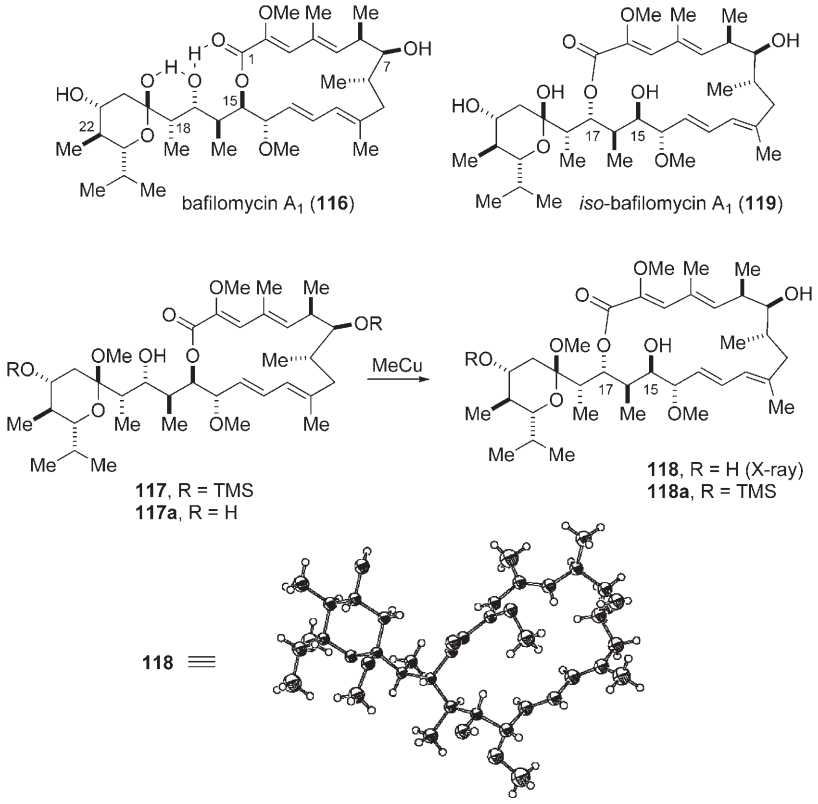


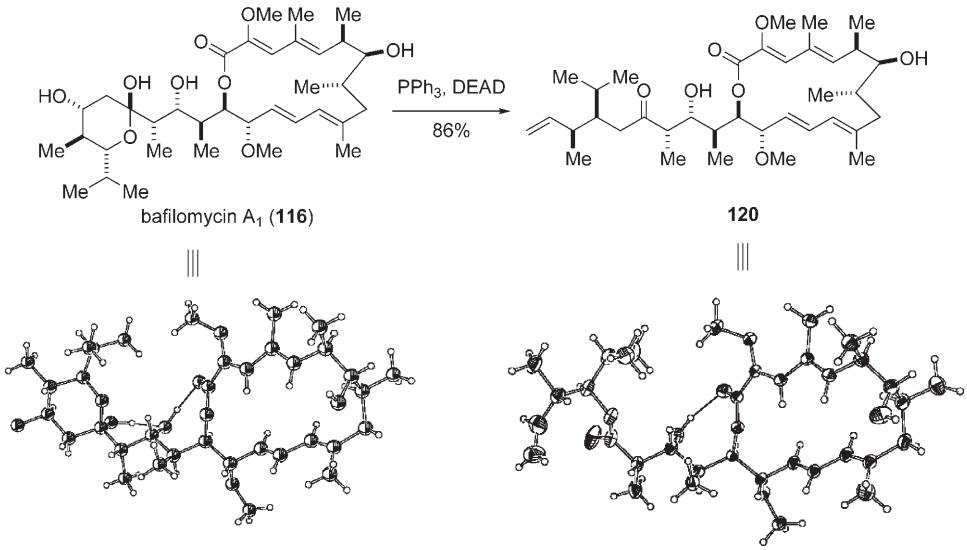
Figure 30. Retrosynthetic analysis of avermectin B_{1a} (**113**), and epi and bis-homo analogues **114** and **115**.

ble sugar-like appendage (Scheme 2). This subtle structural feature may play a role in the selective enzyme inhibitory activity of bafilomycin A_1 on V-type membrane ATPases.[201] Prior to our total synthesis of the natural product,[202] we were engaged in a chemical modification program seeking to maintain activity while eliminating undesirable toxicity. In one such experiment, we attempted to add an organocopper reagent to an analogue that was presumed to have a carbonyl group at C7. Instead, we effected an efficient ring-expansion reaction on a bis-*O*-TMS intermediate **117** to produce the crystalline 18-membered *iso*-bafilomycin A_1 glycoside **118** after desilylation in a dilute solution of THF. A single-crystal analysis confirmed the structure of **118**. (Scheme 2)[203] Treatment of the bis-*O*-TMS ether derivative **118a** with TBAF (0.2 M) resulted in ring contraction to the original 16-membered glycoside **117a**. These unique transformations can be rationalized based on proximity effects leading to orthoacid salt intermediates, which can undergo fragmentation to regenerate the original macrolactone or its homologated congener. Unfortunately, *iso*-bafilomycin A_1 (**119**) was found to be inactive, thus emphasizing the importance of the C17 hydroxy group and the overall shape of the macrolide ring.



Scheme 2. Structures of bafilomycin A1 (**116**), and ring-expanded analogue **119**; crystal structure of **118**. TMS = trimethylsilyl.

In another effort to introduce novel functionality in bafilomycin A_1, we attempted a Mitsunobu reaction at C21 of the pyranose ring (Scheme 3). Instead of the desired configurational inversion, a Grob-like fragmentation took place simply in the presence of triphenylphosphine and diethylazodicarboxylate to afford the macrolactone **120**.[204] The ring-opening reaction was also observed with *iso*-bafilomycin A_1 **117a** under the same conditions. Remarkably, the solid-state X-ray crystal structure of **120** was very reminiscent of the overall structure of bafilomycin A_1, including an intramolecular H bond of the C17 OH group with the lactone carbonyl and the proximity in space of the C2 methoxy group with the isopropyl group of the sugar-like ring (Scheme 3). Whereas bafilomycin A_1 is quite sensitive to acid and base, the ring-opened product **120** remained unchanged in 3 N HCl for several hours. It is also of interest that compound **120** maintained significant inhibitory activity on V-type ATPase relative to bafilomycin A_1 itself.



Scheme 3. Structures of bafilomycin A (**116**) and macrolactone fragmentation product **120**; crystal structures of **116** and **120**.

10. Synopsis and Future Outlook

10.1. From discovery and process research to the CROs

As the saying goes, "it was the best of times, it was the worst of times". So go the evolutionary cycles of the pharmaceutical industry, once revered as the maker of miracle drugs for the benefit of humankind. While this noble objective is still at the basis of pharmaceutical research, the industry itself has come under scrutiny, experienced controversy, and provoked criticism at times.[205]

Clearly, the past decade has seen a paradigm shift in the discovery and process research sectors of the pharmaceutical industry. The desire for accelerated hit finding by screening large libraries of compounds, either acquired from outside sources or from internal sample collections, has changed the role of the synthetic chemist in the industry. Unraveling of the genetic code, leading to novel protein targets, and powered by sophisticated high-throughput assay methods has necessitated the need to rapidly access and test larger and larger numbers of chemical compounds. Chemists, in turn, have risen to the challenge by "inventing" various ingenious technologies for the mass production of new chemical entities via combinatorial or parallel synthesis methods. Today, the main issue in discovery research is not to generate enough hit-to-lead compounds, but to ensure their quality as druggable entities. Even in the most favorable cases, the many hurdles that lie ahead en route to a seemingly promising pre-clinical candidate may eventually lead to disappointment.

Process chemists, on the other hand, face the daunting task of devising practical and economical routes to drug candidates.[33] As a group, they have been enormously successful in streamlining some of the most difficult synthetic operations in a timely and cost-effective fashion. However, rising costs and manpower issues have pervaded the hallowed grounds of pharmaceutical research and have changed the face of drug development. Today, outsourcing chemistry to small and large contract research organizations (CROs) has become the norm for large and small companies alike.[206] Most process groups will outsource intermediates to be produced up to kilogram quantities before repatriating them to assemble the drug substance in-house or at the manufacturing facility. This may be an economically viable strategy to accelerate the large-scale production process of drug substances for the time being. Eventually, the cost of offshore CRO activities will also escalate.

At the level of discovery, many key building blocks (scaffolds) are contracted out for the production of sets of libraries and then imported back to be tested in-house. Depending on the level of expertise (which is rapidly expanding), the CROs may in fact develop new synthetic methods on their own. Slowly the center of gravity for technical creativity may be in danger of shifting positions unless the spirit and incentive for innovation is restored with the industry again. For this to occur, the synthetic chemist must find ways to acquire knowledge rapidly, keep an open eye on serendipity, and manage time well, while being creatively productive.

10.2. From academic freedom to the rigors of drug discovery

As mentioned in the introductory section above, academic research is, in principle, an enviable scientific endeavor, giving its practitioners the freedom to choose exciting projects and an opportunity to contribute to fundamental science. Alas, this utopian view of university life is seldom shared by funding organizations nowadays due to the ever-diminishing budgets and changes in science policies.

The large majority of PhD- and MSc-level organic chemistry graduates seek positions in discovery or process research groups in the pharmaceutical or other high-impact industries. More often than not, there will also be a one- or two-year postdoctoral training period. These young scientists will have performed innovative research during their university years, contributing to natural product synthesis, methodology, or other exciting and equally valid areas. Even though they emerge highly trained in the skills of synthetic chemistry and problem solving, their exposure to the rigors of practical medicinal chemistry is minimal. Traditionally, the pharmaceutical industry has had a penchant to recruit bench chemists with honed synthetic skills, knowing that the rest will be acquired "on the job".

The trend to "fast-track" research in the pharmaceutical industry has compelled synthetic chemists to devise and pursue the shortest possible sequences for their reactions, preferably using well-established and low-risk transformations. If at all possible, chirality is generally avoided. Thus, there is an awakening of sorts for a young PhD recruit joining a medicinal chemistry group in a biotech or pharmaceutical research organization. Recent memories of synthesizing architecturally complex natural products containing several stereogenic centers will quickly fade away to be replaced by the mundane reality of aromatic and heterocyclic compounds in pursuit of kinase inhibitors or compounds that bind GPCRs, for example. Catalytic or other asymmetric processes to generate chirality in an important intermediate (usually containing other functionalities and protective groups), as frequently experienced in a PhD thesis research project, will be supplanted with the synthesis of a common heterocyclic scaffold that can be engaged in metal-catalyzed coupling reactions with aromatics and heteroaromatics to produce a "series" for SAR.

Thus, the landscape of many pharmaceutical target molecules "flatten out", although their bioactive conformations may adopt twists and turns around rotatable bonds. Fortunately, Nature is also as receptive to flat, heteroaromatic, aromatic, and related chemical entities as it is to complex multifunctional natural products. The latter however, may be less "druggable".[4]

Therein lies an opportunity to explore and exploit these magnificent molecular recognition events that have become "visual" in so many instances, thanks to protein crystallography. The same applies to RNA, DNA, and other macromolecules which are exciting, but more challenging drug targets. Academic research is in a unique position to address new ventures and challenges with ingenuity, vigor, and dedication. To do so

necessitates a renewed vision of the role of organic synthesis at the interface of chemistry, biology, and medicine. Introducing new courses in a graduate chemistry curriculum that cover the important continuum from synthesis to structural biology to pharmacology would provide a strong foundation for future research careers in the pharmaceutical industry. One of the most important contributions by academic synthetic chemists is the continual development of new and useful methodologies, which may someday be applied toward a life-saving drug substance. Oftentimes, technology transfer for practical applications can also lead to research funding, and even a patent for the invention. A more rewarding experience, however, is in the training of co-workers who may choose to pursue research careers in the pharmaceutical industry. They are ultimately the principal source of a continually replenished human talent that will contribute to the invention of new medicines for the benefit of humankind.

Drug discovery and development is a biology-based, chemistry-driven endeavor. It is labor-intensive, and it is difficult to predict its outcome, let alone ensure its success. Today, pharmaceutical companies are working diligently to fill their pipelines with new entities, in dealing with the prohibitive costs of research toward launching a drug, and in maintaining a competitive share of the market. In spite of adverse public opinion at times, we should not lose sight of the tremendous progress made over many decades in eradicating disease and improving the quality of life, thanks to pharmaceutical research. It is also gratifying to see that unmet medical needs such as Alzheimer's disease, stroke, diabetes, certain forms of cancer, and a host of autoimmune diseases are presently being addressed vigorously in the pharmaceutical industry.

Academics can also contribute to these important areas by seeking solutions to unanswered fundamental questions in the physical and biological sciences, providing deeper insight into the chemistry–biology interface through basic research. This can be achieved independently, funds permitting, or in collaboration, as outlined in the examples experienced in this personal odyssey. In a letter to his brother Theo, Vincent Van Gogh is known to have written these words (perhaps referring to his unique painting style?): "*For the great things are not done by impulse, but by a series of small things brought together*" (1888). Surely, the same applies to drug discovery.

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