



**Trip Report:
Drug Discovery Chemistry
La Jolla, California
April 22 -24, 2006**

Jinhai Yang, Ph.D. and Larry Yet, Ph.D.

Medicinal Chemistry Department
Albany Molecular Research, Inc.
21 Corporate Circle
Albany, NY 12212

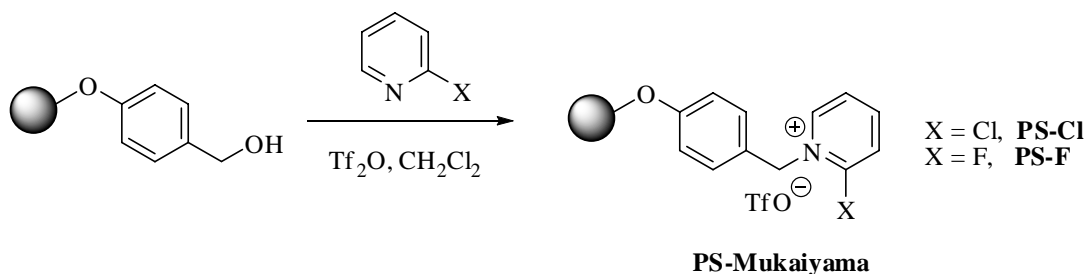
***Abstract:** Cambridge Healthtech Institute's "Drug Discovery Chemistry" was held at the Hilton Torrey Pines in La Jolla, California, on April 22-24, 2006. About 220 attendees from biotech and pharmaceutical companies as well as academic institutions attended this conference. This symposium featured four different tracks: Track 1: Compound Library Design and Synthesis; Track 2: Natural Products Chemistry; Track 3: Fragment-Based Drug Discovery; and Track 4: G-Protein Coupled Receptor Drug Discovery. This report highlights selected material from information presented in seminars from each track.*

“The Scope of Polymer-Supported Mukaiyama Reagent for the Preparation of Solution-Phase Libraries”

Stefano Crosignani, Geneva, Switzerland.

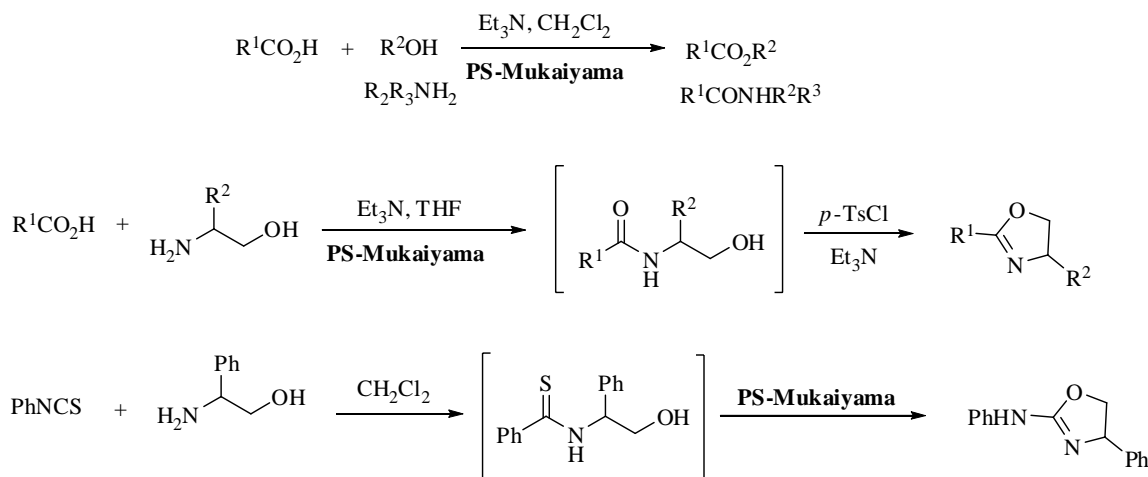
Dr. Crosignani gave a presentation on the synthesis of a polymer-supported Mukaiyama reagent and on the synthetic utility of this reagent for the preparation of solution-phase libraries. Polymer-supported N-alkyl-2-chloro pyridinium triflate was synthesized in one step from the Wang resin with 2-chloro- or 2-fluoropyridine in the presence of trifluoromethanesulfonic anhydride (Scheme 1).

Scheme 1



Typical examples of the use of this PS-Mukaiyama reagent included the synthesis of (1) esters from Serono's proprietary acids and alcohols, (2) amides from Serono's proprietary acids and amines, (3) 2-oxazolines from acids and amino alcohols, and (4) 2-aminooxazolines from isocyanides and amino alcohols (Scheme 2). The work-up involved only filtration of the resin onto an amino-functionalized SPE column and concentration of the filtrate yielded the compounds in good yields and >90% purity.

Scheme 2



“Chemically Conditioned Extracts of Ginger Oil: Leadlike “Alkaloidal” Compounds Derived from Natural Extracts via Reductive Amination”

Hiromi Arai, Kristin Beierie, Cody Fullenwider, Zoya Kai, and Gilbert M. Rishton (California State University).*

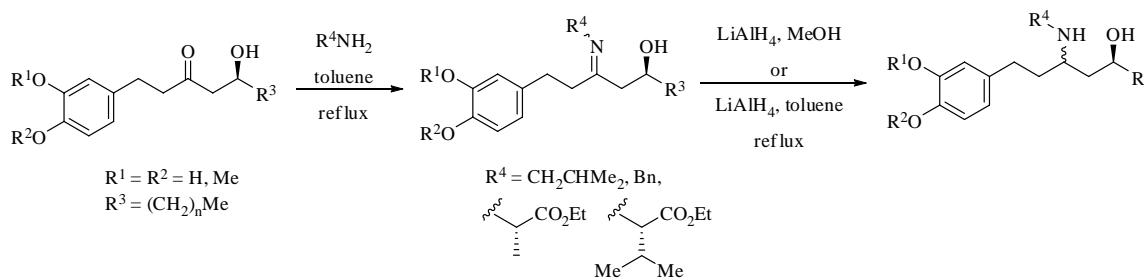
Dr. Rishton presented both a poster and speaker presentations on the concept of “chemically conditioned extracts”. “Chemical conditioning” of natural extracts coupled with pre-fractionation for the chemically conditioned extracts is to facilitate successful biochemical screening of extracts by destroying the reactive natural compounds that generate false positive results in biochemical assays.

Natural ginger oil, chosen as an example, contains hundreds of small molecules including the well-characterized gingerol series of aryl ketones, 1,3-diketones and α,β -unsaturated ketones, which are reactive electrophiles in the extract. The “conditioned extracts” contain both natural compounds and novel unnatural nitrogen-containing alkaloidal amine products that are particularly leadlike and druglike. Thus reductive amination/reduction of these extracts with various amines enabled the development of many different and structurally diverse leadlike and druglike mixtures from the same natural extract (Scheme 3). At the same time, the reductive amination/reduction procedure destroyed many of the reactive electrophiles in the natural extract such as the ketones, converting them to chemically stable compounds such as amines.

These conditioned extracts were fractionated by flash column chromatography and are characterized by LC-MS and ^1H NMR spectroscopic methods. These compounds were submitted to the α -secretase inhibition assays for an Alzheimer’s disease program. Some compounds showed >50% inhibition by a single point data @ 10 μM .

This proof of principle should be generally applicable to the any and all natural extracts.

Scheme 3



“Heterocyclic Synthesis Utilizing Microwaves and Supported Reagents in High-Throughput Medicinal Chemistry”

Daryl R. Sauer, Abbott Laboratories.

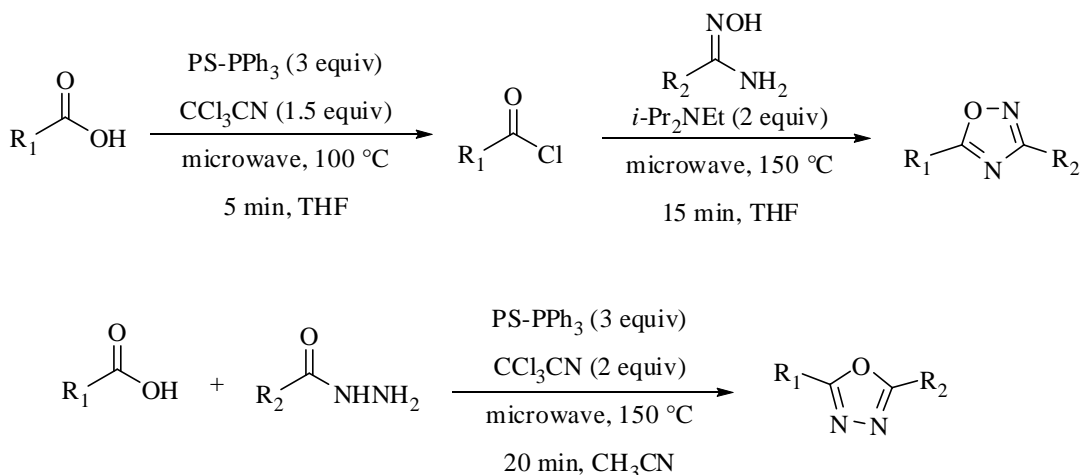
Dr. Sauer described the role of the High Throughput Organic Synthesis (HTOS) Facility at Abbott Laboratories. This centralized, highly automated, state of the art, parallel synthesis facility allowed the discovery of more highly optimized biological tools and drug candidates with particular emphasis on preparing libraries of analogs designed to rapidly generate structure activity relationship (SAR) and to accelerate lead development and optimization. This facility

concentrated on preparing analogs for medicinal chemistry programs and allowed the project chemists to focus on targets not amenable to parallel synthesis.

A description of the work flow from the parallel library synthesis techniques using polymer supported and scavenging reagents, microwave techniques and purification methods to compound registration in Abbott's internal databases was outlined.

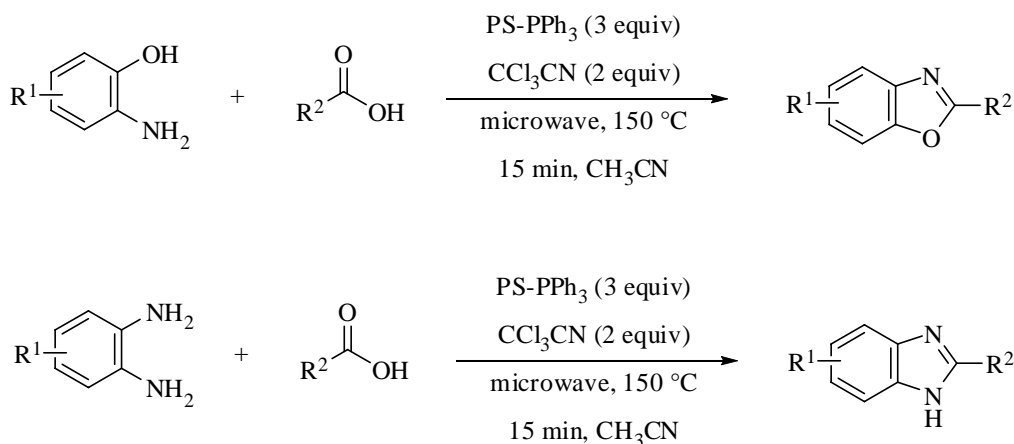
Most of the presentation focused on the use of several types of Suzuki reactions using polymer-supported palladium catalysts and the silica-carbonate resin for scavenging the excess boronic acids. Several key heterocyclic libraries dominated the rest of the talk. 1,2,4-Oxadiazoles and 1,3,4-oxadiazoles are bioisoteres of amides and acids as well as dipeptide mimetics and they both represent important structural motifs in drug discovery with a wide range of pharmaceutical and biological activities. A one-pot two step general synthesis of 1,2,4-oxadiazoles from carboxylic acids to their acid chlorides followed by reaction with aldoximes under microwave irradiation was presented (Scheme 4). Similarly, the reactions of carboxylic acids with acid hydrazides with polymer-bound triphenylphosphine in the presence of 2,2,2-trichloroacetonitrile under microwave irradiation afforded 1,3,4-oxadiazoles.

Scheme 4



This polymer-bound triphenylphosphine/2,2,2-trichloroacetonitrile combination was also useful in the parallel library syntheses of benzoxazoles and benzimidazoles from *ortho*-aminophenols and 1,2-phenylenediamines, respectively with carboxylic acids (Scheme 5).

Scheme 5

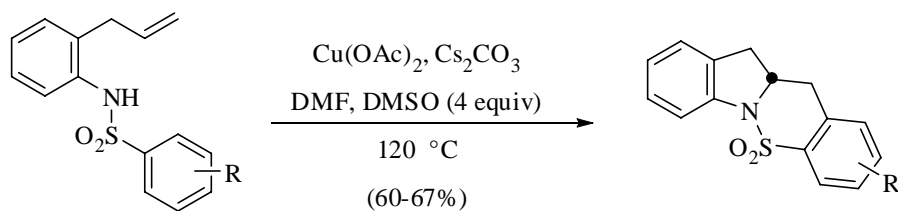


“Novel Synthesis of Cyclic Sulfamides and Sulfonamides: Access to Pharmacophores”

Sherry Chemler, University of Buffalo, State University of New York.

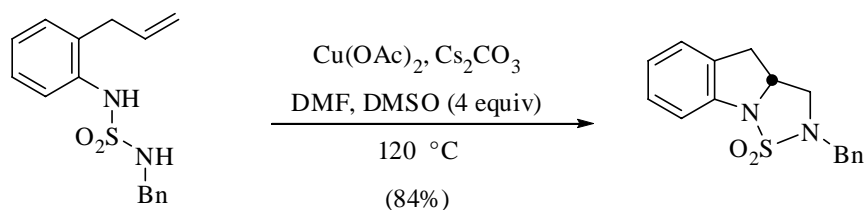
Professor Chemler described new synthetic methodology towards cyclic sulfamides and sulfonamides, which are promising pharmacophores for a variety of leads for various therapeutic areas in medicinal chemistry programs. Allyl benzenesulfonamides readily underwent copper carboxylate carboamination to yield various cyclic sulfonamides (Scheme 6). Where the R group was in the meta position, a regioselectivity of ~2.0-2.5:1 was observed in favor of the R group opposite of the sulfonamide. This chemistry also worked well where the sulfonyl group was replaced by a methylene (amino) or carbonyl (amide) group.

Scheme 6



Intramolecular diamination reaction also proceeded well under the same reaction conditions (Scheme 7). The scope of substrates, diastereoselectivity and other reaction conditions were also examined for this type of reaction.

Scheme 7



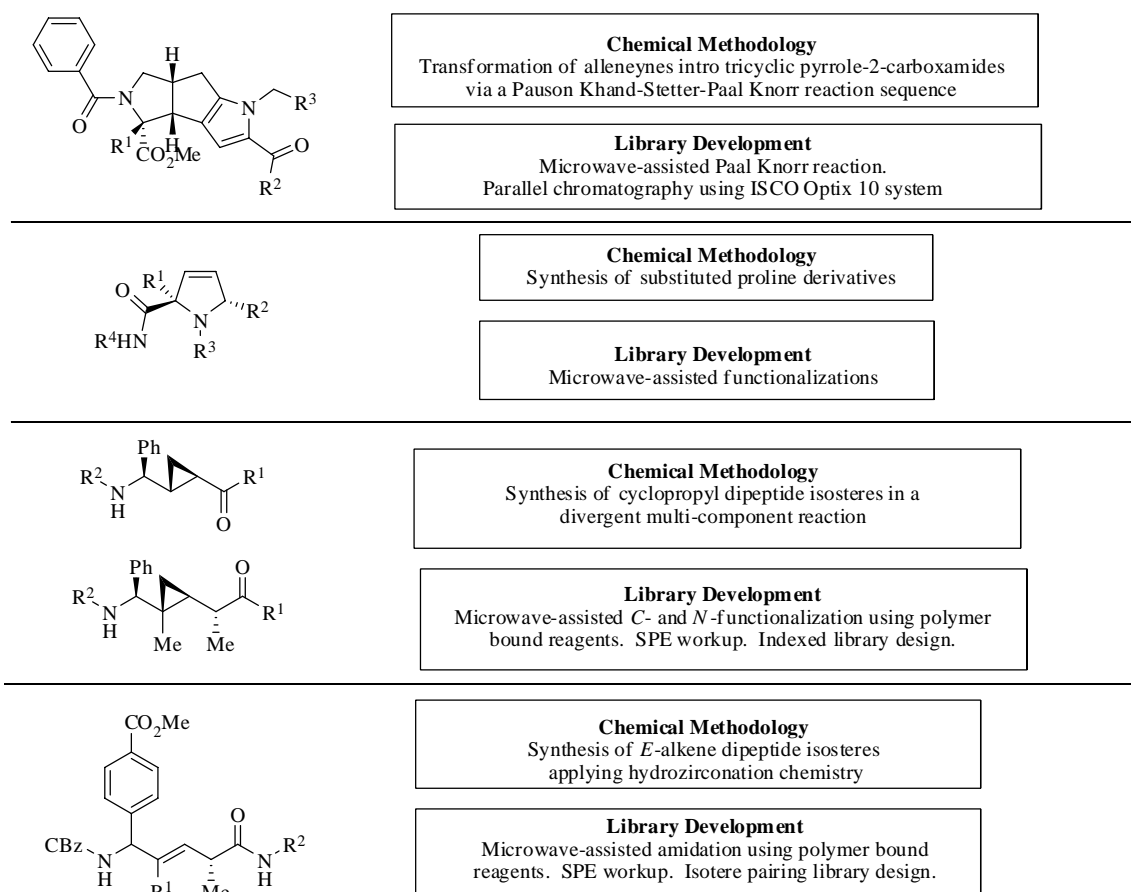
“Synthesis of Small Molecules with Functional and Structural Diversity”

Stefan Werner, University of Pittsburgh.

Dr. Werner provided a preview of The University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD) on how it applied methodologies that were developed in their department for compound library synthesis. He described all the current tools of microwave-assisted parallel synthesis, purification using silica bound reagents and SPE scavenging techniques, and database entries of these compound libraries.

Dr. Werner then presented four compound libraries showing unique chemical methodologies to each one and the methods for each library development. The libraries included tricyclic pyrrole-2-carboxamides, 3-pyrrolines, cyclopropyl dipeptide isosteres, and *E*-alkene dipeptide isosteres (Scheme 8).

Scheme 8

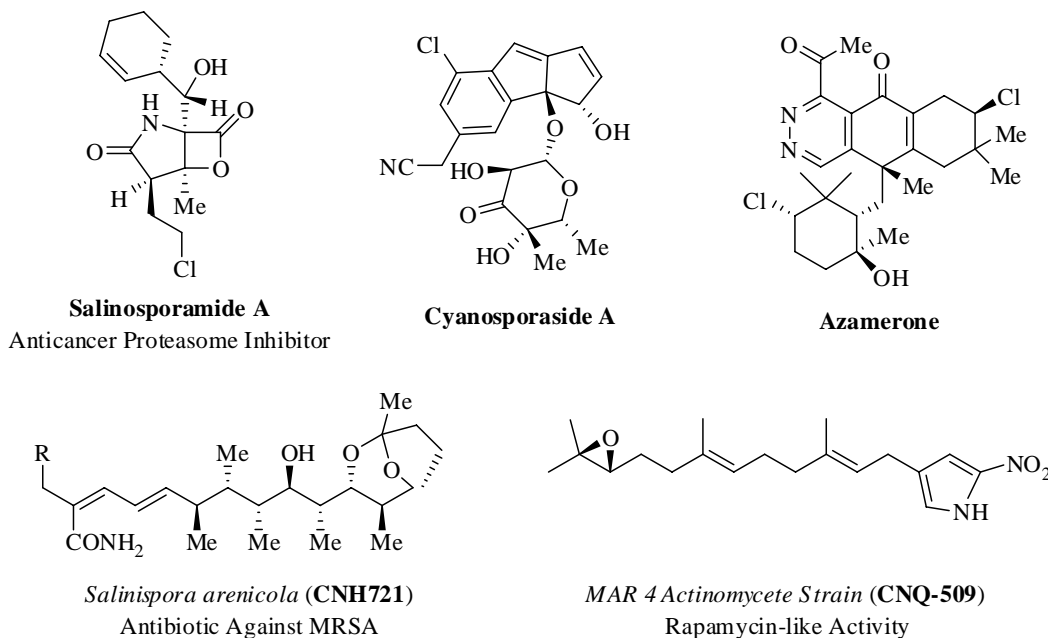


“Deep Sea Microorganisms, A New Resource for Drug Discovery”

William Fenical, Scripps Institution of Oceanography.

Professor Fenical described his research group’s work on the collection, isolation and characterization of actinomycetes from marine sediment samples with the goals of developing their potential as a source of new marine-derived pharmaceuticals and understanding their biological diversity in the oceans. His research group has examined this tropical marine environment and has undertaken a systematic approach to cultivate and identify “marine actinomycetes”, those uniquely adapted to growth in the sea. At least 13 diverse groups have been isolated. In culture, they have observed the production of a diversity of bioactive secondary metabolites, which possess unprecedented carbon skeletons and functionalities. Figure 1 shows the range of compounds isolated from the cultures with some interesting biological profiles.

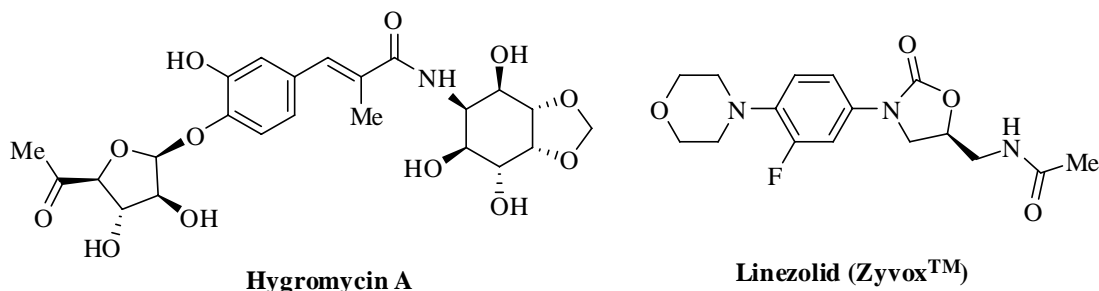
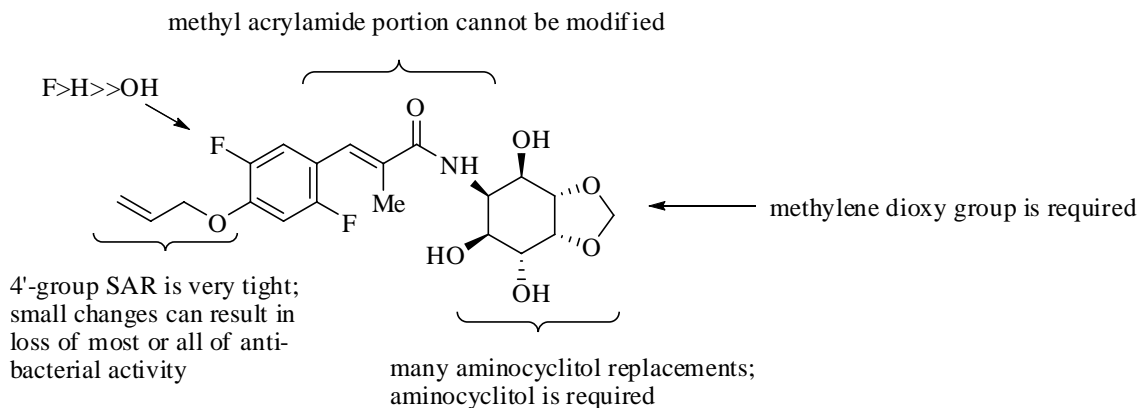
Figure 1



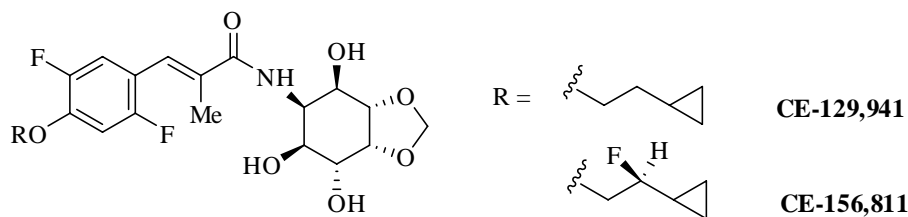
“Natural Product Redux: Potent Antibacterial Agents Derived from Hygromycin A”

Steven J. Brickner, Pfizer, Inc.

Dr. Brickner showed that an analysis of known antibacterial natural products in the literature as leads for a medicinal chemistry program led them to extensively re-examine Hygromycin A, isolated from *Streptomyces hygroscopicus*, as a lead (Figure 2). Unfortunately, hygromycin A had a limited spectrum of activity with a weak to moderate potency against MDR gram-positive pathogens of interest to human health. All new antibacterials were compared to the oxazolidinone Linezolid (Zyvox™) as a benchmark for comparison. Pfizer then spent many years performing SAR on the “truncated hygromycin A derivatives” to identify a lead compound for further development. Much of the early series focused on the series without the 2’-deoxyfuranose ring (Figure 3).

Figure 2**Figure 3****Truncated Hygromycin A Derivatives**

After much investigation, **CE-129,941** and **CE-156,811** represented a new class of antibacterial agents with oxazolidinone-like activity, with substantially improved pharmacokinetic properties and with excellent oral efficiency over the hygromycin A natural product.

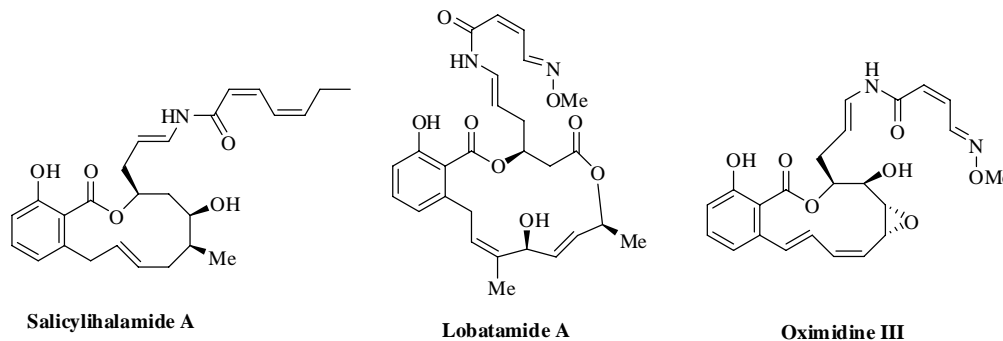
Figure 4**“Development of V-ATPase Inhibitors as Anticancer Agents”**

John A. Beutler, National Cancer Institute.

The salicylhalamides, lobatamides, and oximidines are marine and/or microbial natural products that potently inhibit cancer cell growth due to inhibition of the mammalian vacuolar ATPase. These structures all have in common a medium-sized salicylate lactone core with a unique Z-enamide double bond (Figure 5). The testing of salicylhalamide A, lobatamide A, and oximidine III in the NCI 60-cell tumor screening profile showed that the melanoma or osteosarcoma cell lines

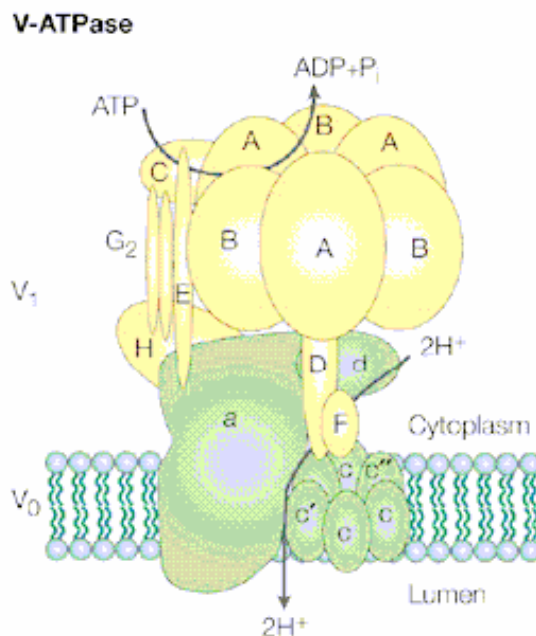
have the greatest sensitivity as a whole. From these screens, it has been suggested that these three compounds may act by a novel mechanism of action since their activity profile did not match compounds whose mechanisms of action are known.

Figure 5



Thus, a question was posed whether this ubiquitous enzyme complex was a valid target for cancer therapy. V-ATPases are ubiquitous proton-translocating pumps of eukaryotic cells, which reside within many intracellular compartments, such as endosomes, lysosomes, and secretory vesicles, which serve as crucial transporters responsible for the regulation of pH. The pumps are oriented such that protons are pumped out of the cytoplasm into the organelle or the extracellular space, where the hydrolysis of adenosine triphosphate (ATP) generates an electrochemical potential across the membrane that drives the transport of ions and solutes (Figure 6). V-ATPases have diverse functional roles such as receptor-mediated endocytosis, intracellular targeting of lysosomal enzymes, protein processing and degradation, and transport of small molecules. V-ATPases can also be found in the plasma membrane of certain cells such as renal intercalated cells for acid secretion, osteoclasts for bone degradation, and macrophages for control of cytoplasmic pH.

Figure 6



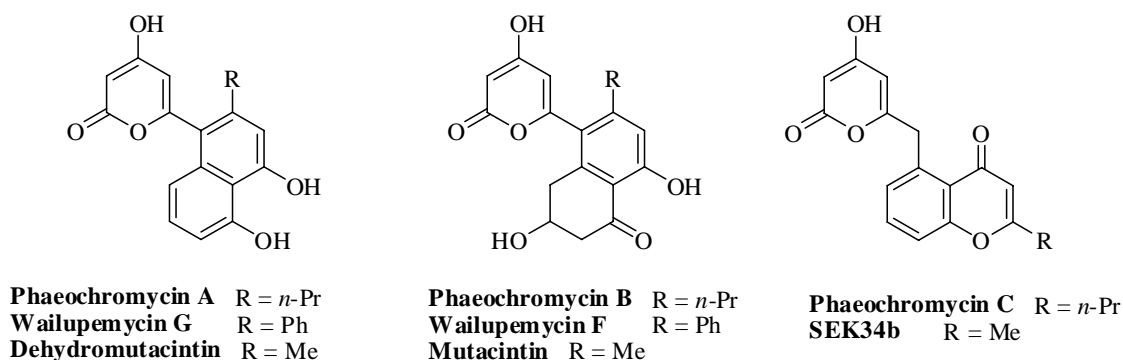
Further work on the structural biology of this V-ATPase system as well as the use of these unique compound inhibitors in anticancer therapy continues to be an active area of research.

“Natural Product Lead Discovery: Isolation and Precursor Directed Synthesis of Hits for Target-Based Screening”

Edmund I. Graziani, Wyeth Research.

Dr. Graziani gave a presentation based on the premise that natural products are currently an active area of research at Wyeth for the discovery of lead compounds for medicinal chemistry programs in all therapeutic areas. For example, he described the isolation of the phaeochromycins and related compounds as inhibitors of MAPKAPK-2 (MK2) for rheumatoid arthritis (Figure 7). This initial hit was then taken onto a MK2 medicinal chemistry program. Dr. Graziani also discussed the preparation of novel sulfur-containing analogs of rapamycin by precursor-directed biosynthesis.

Figure 7



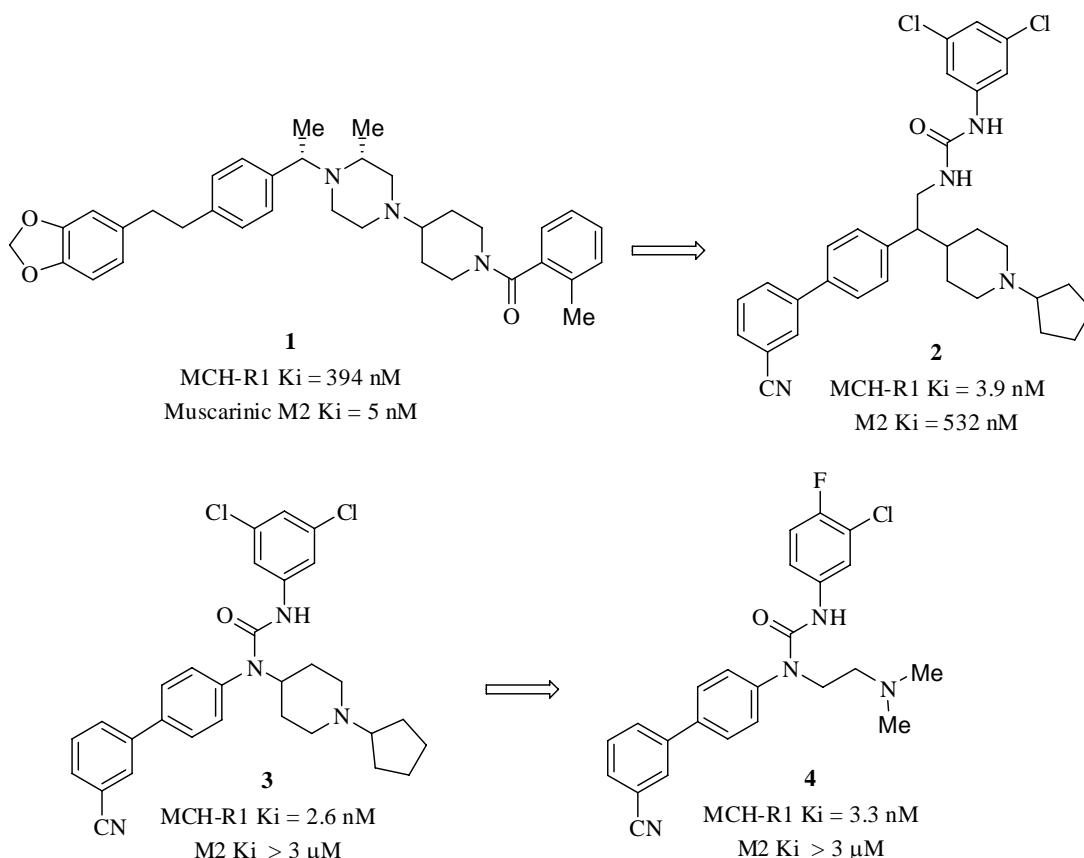
“Design and Synthesis of Orally Efficacious Melanin Concentrating Hormone (MCH) Receptor Antagonists as Antiobesity Therapeutics”

Anand Palani, Schering-Plough Research Institute.

Melanin concentrating hormone (MCH) is a 19 residue peptide found in the central nervous system. It regulates feeding and energy homeostasis by interacting with the central melanocortin system. MCH-R1 is a G-protein coupled receptor expressed in the central nervous system. It has been observed that MCH-R1 null mice exhibit hypermetabolic phenotype and are resistant to diet induced obesity (DIO). Therefore, it is expected that small molecule antagonists of MCH-R1 may have antiobesity therapeutic effects. The role of MCH-R2 is currently unknown.

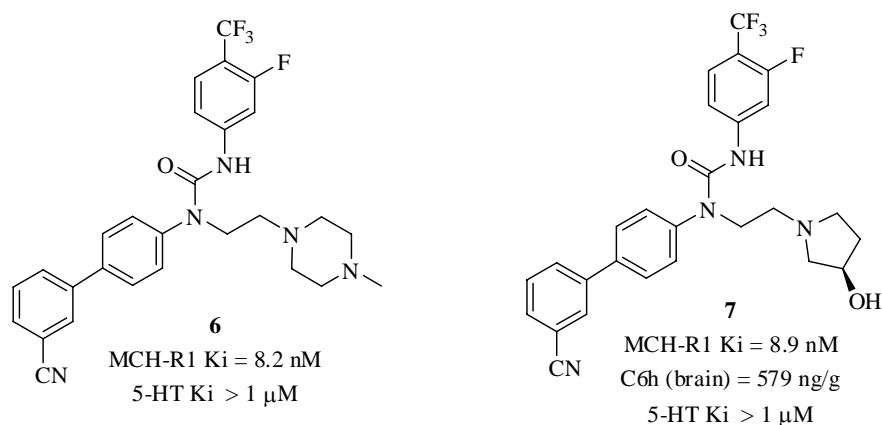
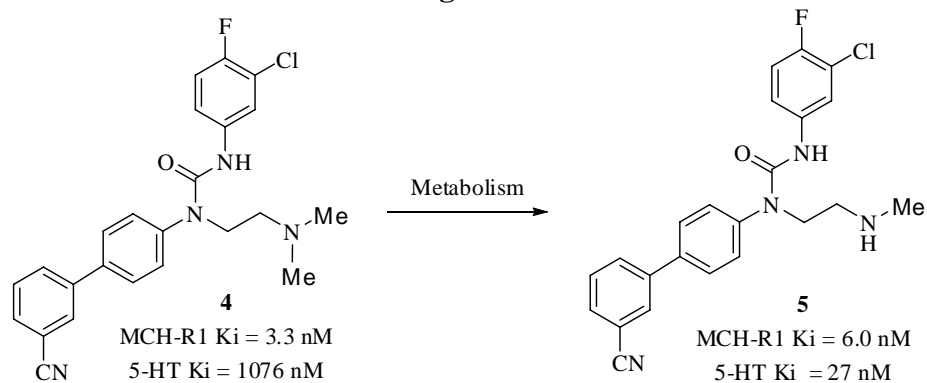
Early lead compounds 1-4 (Figure 8) were discovered during an in-house screening campaign. It was found that 5 (Figure 9), a metabolite of compound 4, showed undesirable strong inhibition of 5-HT reuptake transporter. Replacement of the dimethylamino group with cyclic amines led to analogues 6 and 7 with greatly improved selectivity versus the 5-HT reuptake transporter (Figure 9).

Figure 8



The general synthesis of biaryl aminoethylureas is shown in Scheme 9. From this round of SAR studies, compound **7** emerged with promising MCH-R1 antagonist activity, and dose dependently decreased food intake and body weight in mice studies. However, the biaryl aniline was considered as a possible liability because the 3'-cyanobiaryl aniline was highly positive in the Ames assay and posed an unacceptable risk to certain target patient population. Therefore, variation of aniline core led to analogues **8-13** (Figure 10). As demonstrated by the activity of compound **13**, the bicyclo[4.1.0]heptane effectively mimics the aryl moiety. The general synthesis of this class of analogues is shown in Scheme 10. It should be noted that reductive amination reactions gave a mixture of *trans/cis* isomers in greater than 9:1 ratio.

Figure 9



Scheme 9

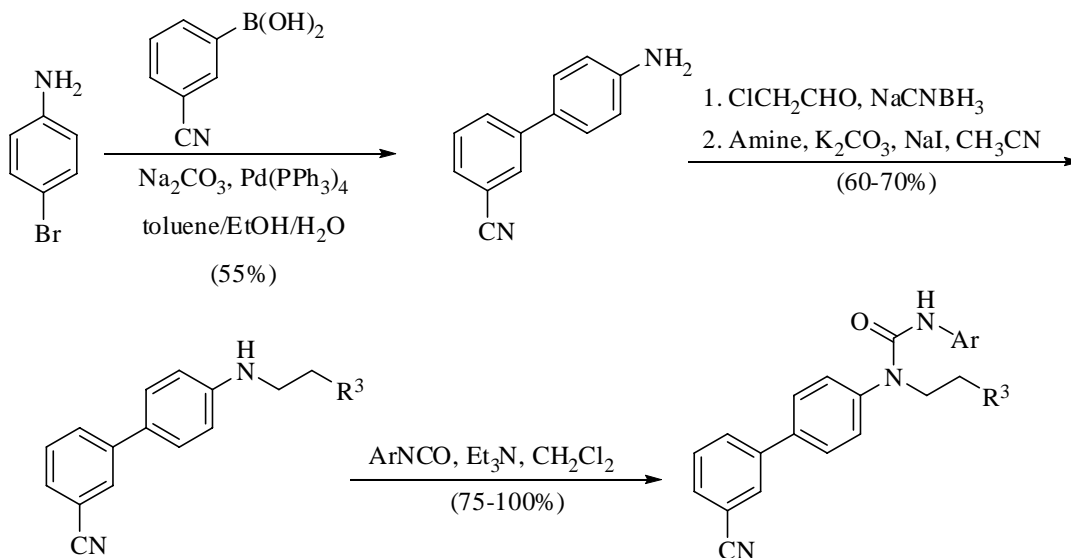
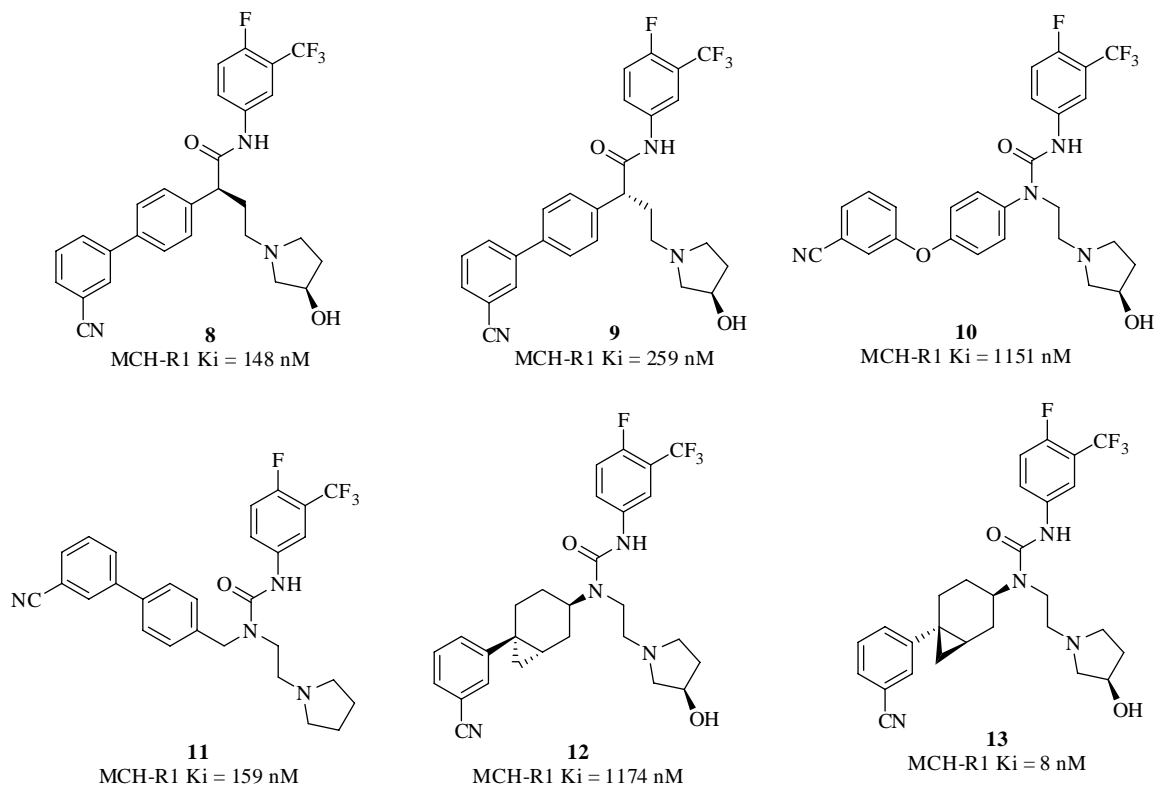
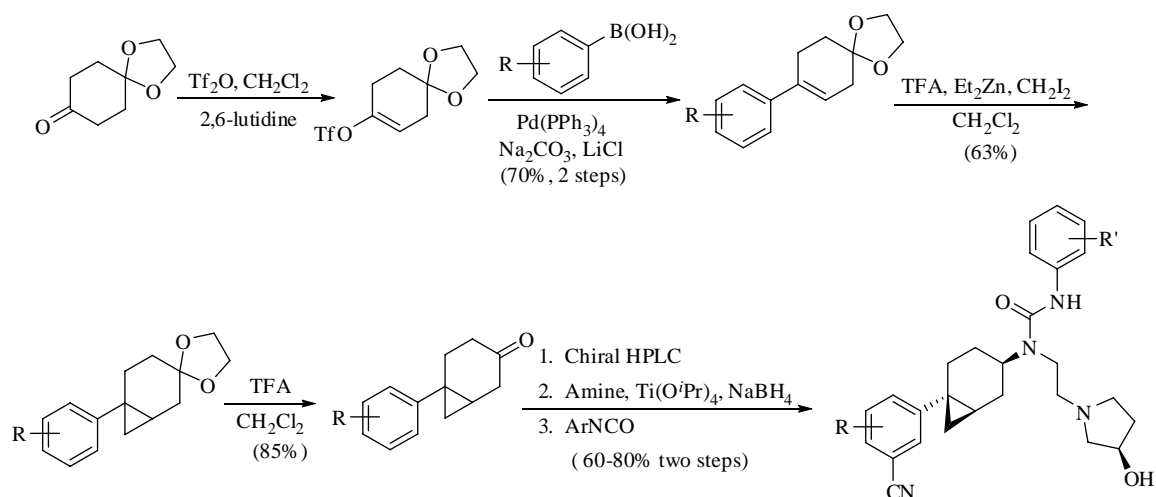


Figure 10



Scheme 10



In order to further improve the pharmacokinetic properties, the bicyclo[4.1.0]heptane core was replaced with bicyclo[3.1.0]hexane (Figure 11). The general synthesis is shown in Scheme 11. Attempted direct cyclopropanation from the cyclopentenone intermediate was unsuccessful.

Figure 12

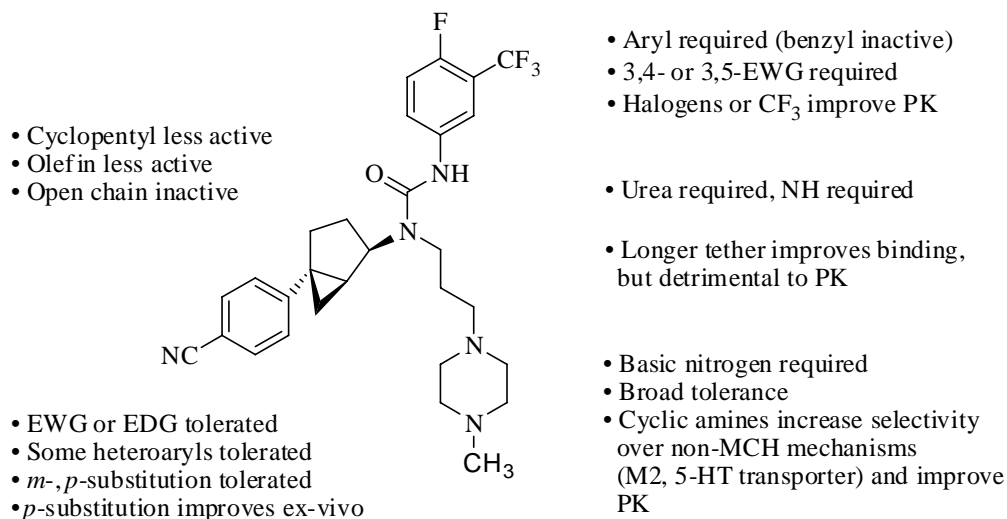
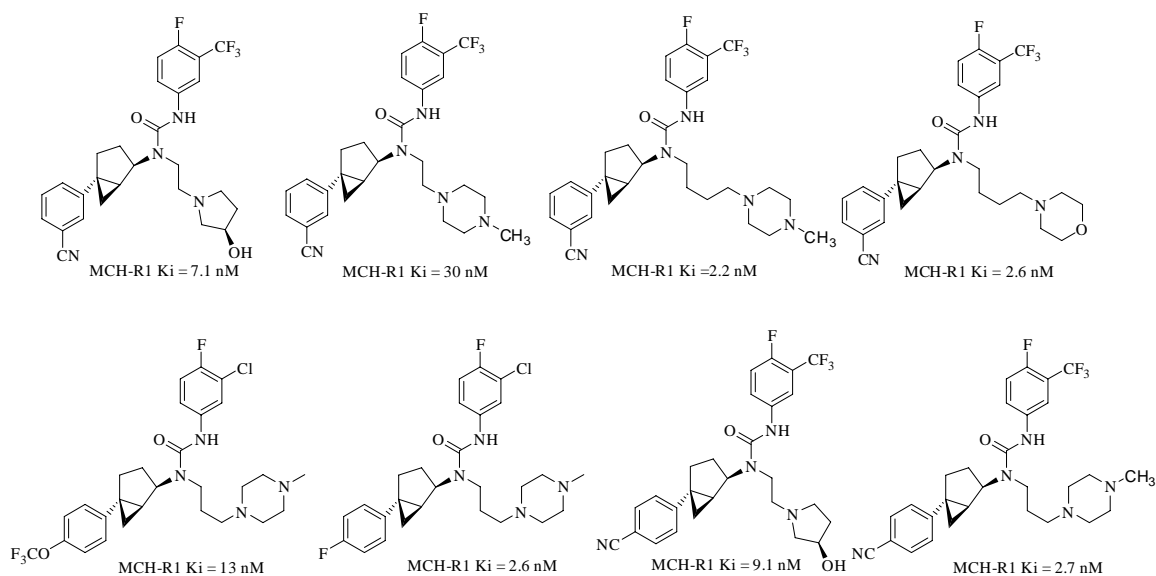


Figure 13



In summary, a series of potent and selective MCH-R1 antagonists have been discovered with selectivity over M2, MCH-R2 and 5-HT transporter receptors. The issue of biaryl aniline substructure with Ames liabilities has been addressed. Several compounds show *in vivo* efficacy in a DIO mouse study.

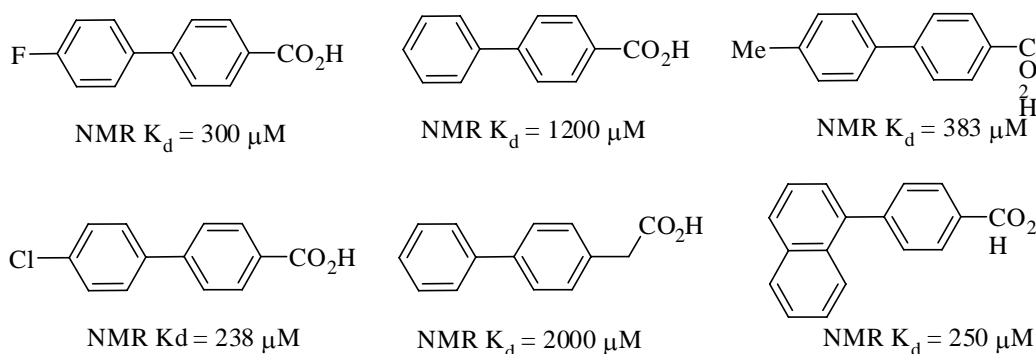
“Fragment-based Discovery of a Potent Inhibitor of the Antiapoptotic Protein Bcl-XL”

Andrew M. Petros, Abbott Laboratories.

Apoptosis, or programmed cell death, is the body’s normal way of disposing damaged or unwanted cells. It is important in embryonic development and for normal tissue homeostasis and disruption of this process has been implicated in diseases such as cancer. The Bcl family is the gatekeeper to the apoptotic pathway and over-expression of Bcl-XL protein has been observed in cancer cells. Bcl-XL protein has eight α -helix segments and is complexed to Bak peptide.

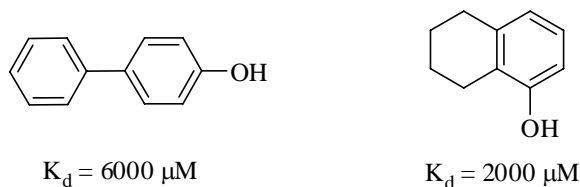
An ‘SAR by NMR’ approach was taken to screen for first-site binding fragment. A 10,000-compound library with molecular weight around 215 was monitored for binding with ^{15}N -HSQC spectrum and several biaryl carboxylic acids were identified as first-site binders (Figure 14).

Figure 14



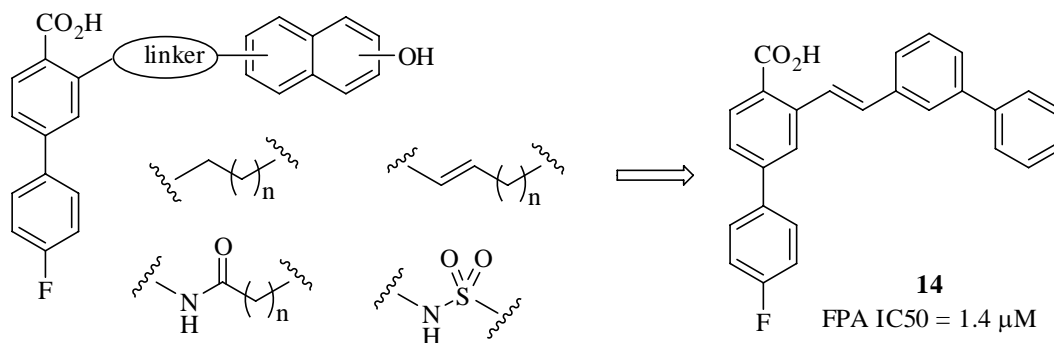
The NMR structure of bound fragments modeled by computational chemistry found that the biaryl acid bound to peptide hot spot with two key interactions maintained (Leu and Asp), and second site (Ile pocket of Bak peptide) was still accessible for extra binding. Therefore, a 3,500-compound library with $\text{MW} \sim 150$ was screened and two aryl phenols were identified (Figure 15).

Figure 15

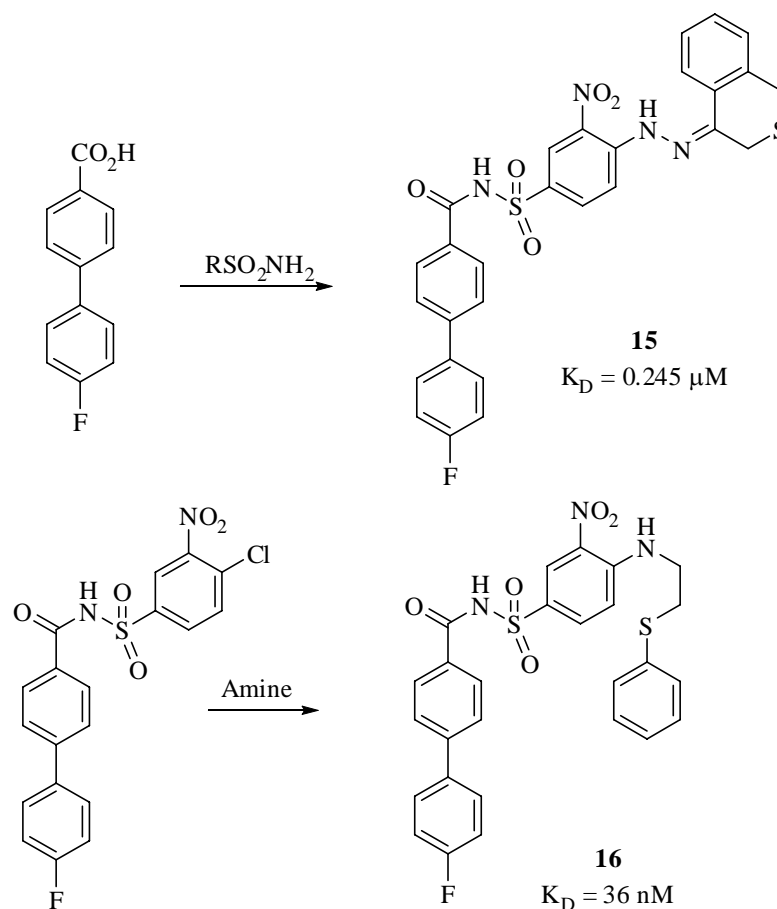


These two fragments were then combined into one molecule by a linker (Figure 16). Early lead compound **14** was then further diversified by reacting a carboxylic acid with 120 sulfonamides (Scheme 12). That effort led to compound **2** and then compound **3** with significantly improved binding efficiency.

Figure 16

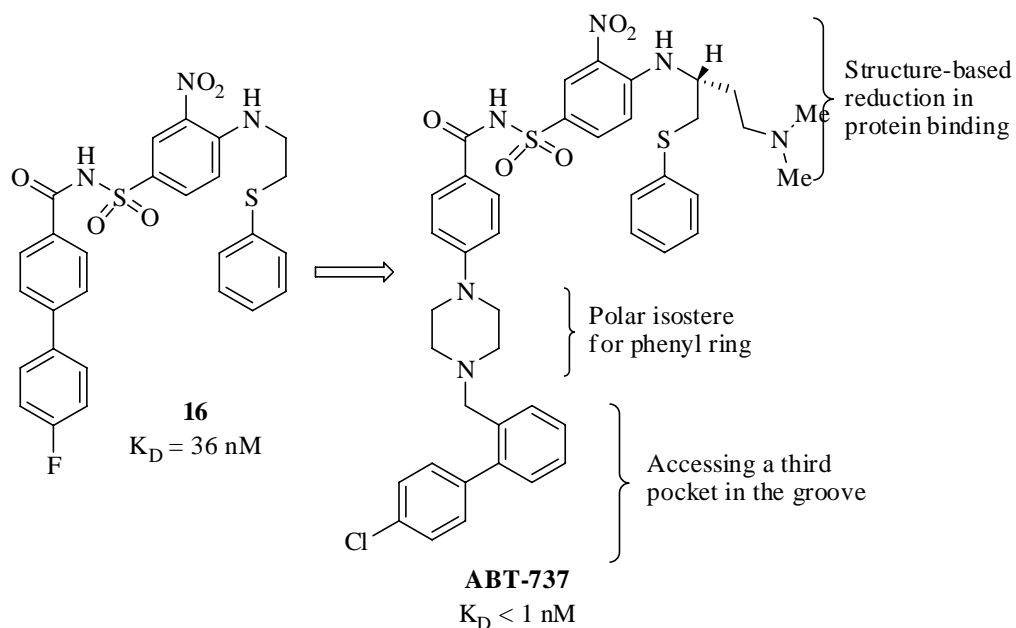


Scheme 12



Upon further structure-based activity optimization, **ABT-737** (Figure 17) was successfully identified as a potent Bcl-X_L inhibitor which resulted in complete tumor regression with no tumor re-growth in any CR tumors by end of the study. In addition, **ABT-737** showed efficacy equivalent or superior to paclitaxel and vincristine, and was superior in treating established tumors in comparison with known cytotoxic agents such as cisplatin, etoposide, carboplatin, and cyclophosphamide.

Figure 17



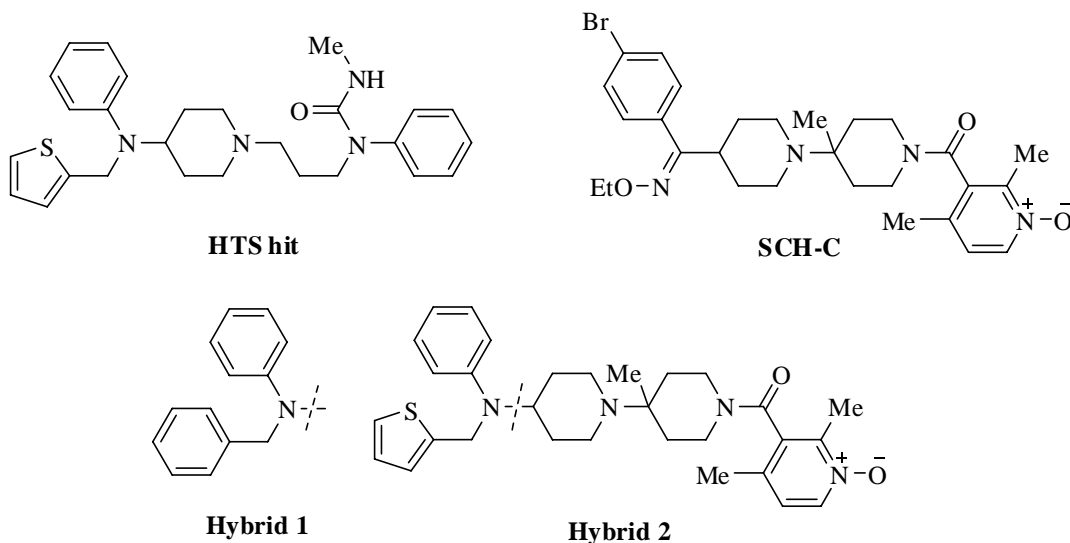
“A LMW CCR5 Antagonist in Combination with CsA Prolongs Graft Survival in Life Supporting Kidney TX Model in Cynomolgus Monkeys”

Gebhard Thoma, Novartis Institutes for BioMedical Research.

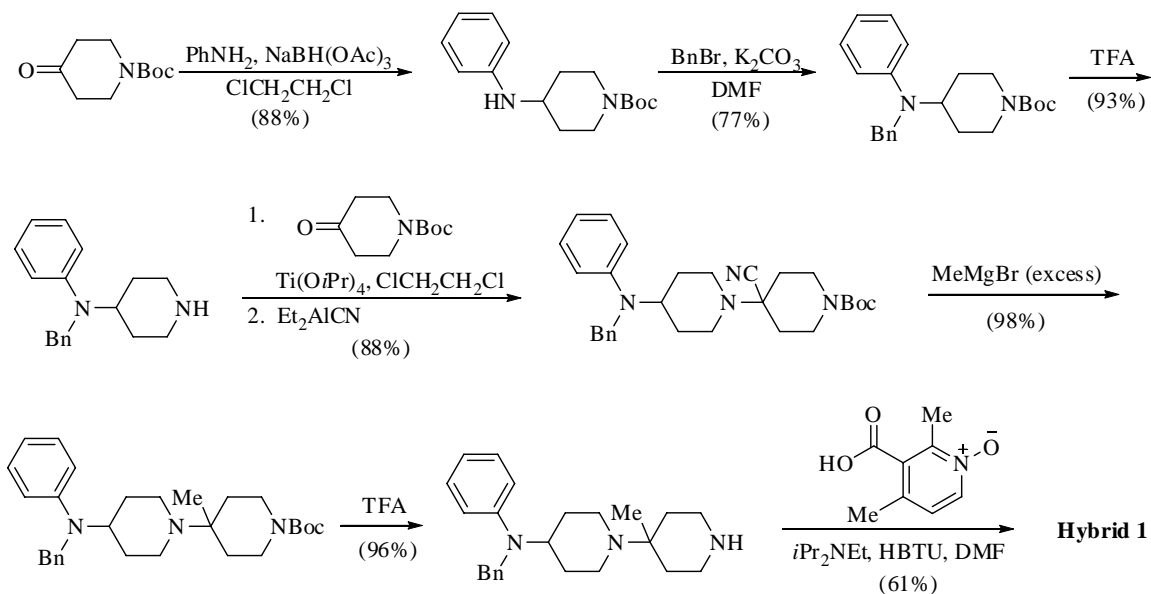
Chemokines are peptides of 8-12 kDa expressed either constitutively or upon cytokine stimulation. They bind to G-protein coupled receptors primarily on leukocytes and there are over 20 known chemokine receptors. CCR5 is an inflammatory chemokine receptor expressed in blood leukocytes and inflamed tissue. It is known that CCR5 is involved in localization of leukocytes in inflammatory lesions and potential indications for CCR5 antagonism include psoriasis, rheumatoid arthritis, and transplantation.

Initial hybrid compounds for CCR5 antagonism were generated from a HTS hit and a SCH-C compound (Figure 18). The synthesis for these hybrids is shown in Schemes 13 and 14.

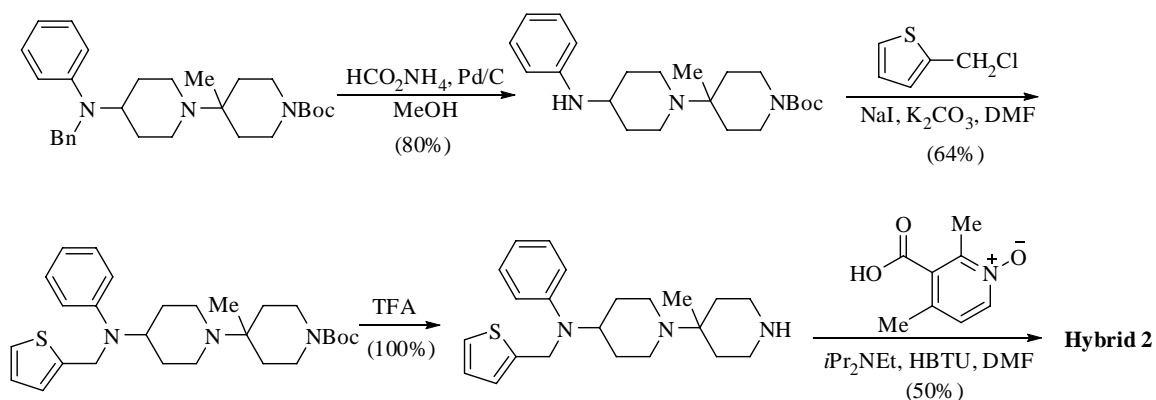
Figure 18



Scheme 13



Scheme 14



Two early hybrid compounds indicated cross-activity with cyno CCR5, but were inactive on rodent CCR5 (Table 1). Results of further SAR studies are shown in Table 2.

Table 1

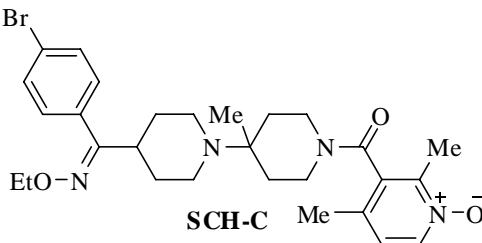
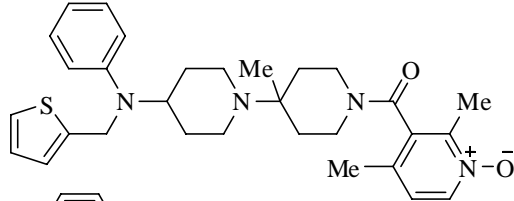
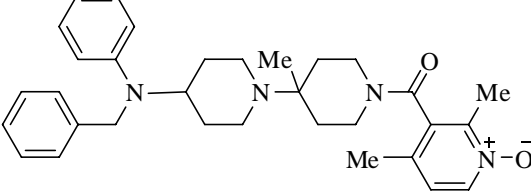
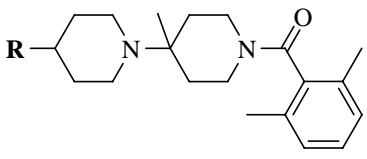
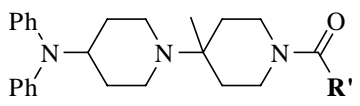
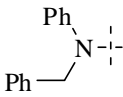
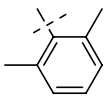
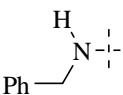



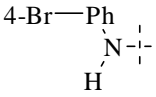

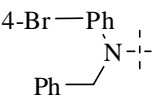
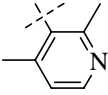
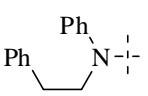
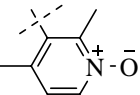

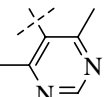
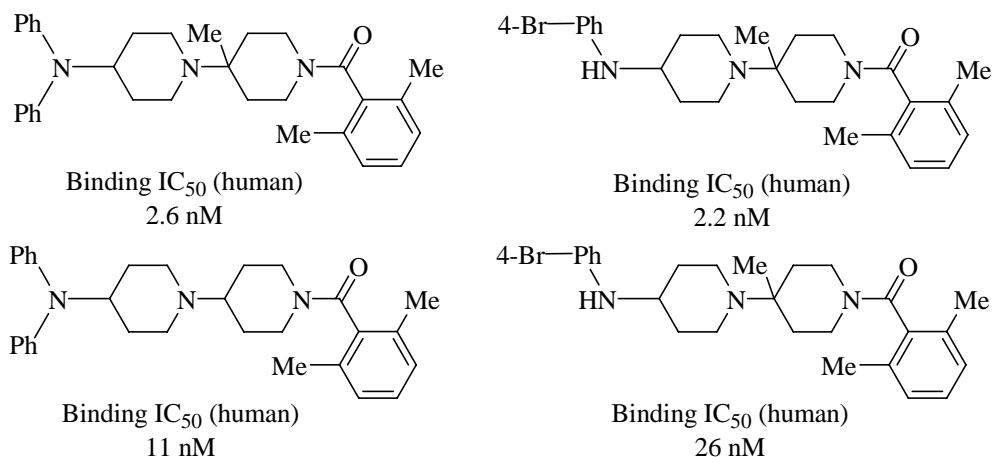
	Binding IC ₅₀ (nM)		Ca ²⁺ Mobilization IC ₅₀ (nM)	
	human	cyno	human	cyno
 <p>SCH-C</p>	4.8	130	26	2100
	0.7	0.6	6.9	6.7
	1.5	10	12	27

Table 2

			
R	Binding IC ₅₀ (nM) (human)	R'	Binding IC ₅₀ (nM) (human)
	1.4		2.6
	> 1000		7.8
	100		200
	2.2		408
	2.3		2.3
	38		3.3
	2.6		1.0

Compounds with methyl group in the core are generally more potent than the ones without methyl group (Figure 19).

Figure 19



A potent CCR5 antagonist NIBR-1282 (structure not shown) was selected for further efficacy studies of transplantation in cynomolgus monkey. No prolongation of graft survival was observed when it was administered alone. However, when combined with Neoral, significant prolongation was achieved. In addition, no undesired drug-drug interactions were observed.

“NMR Auxiliary Binding Screen for Lead Optimization: Design of Novel Renin Inhibitors that Access the S2 Pocket”

Don Emerson, Pfizer, Inc.

Renin inhibitors are potentially effective therapeutics for treating hypertension, a leading risk factor for cardiovascular diseases. Early lead compound 17 was a HTS hit with IC_{50} of 6 μ M (Figure 20). Another renin inhibitor 18 was found to bind to the S3 pocket. Combining selected features of these two compounds gave compound 19 with IC_{50} of 650 nM. Overlay of X-Ray structures of 18 with polyhydroxymonoamide 20 revealed an extra binding opportunity in S2 pocket. Therefore, an auxiliary NMR screen was initiated to identify fragments binding at S2 and link them to compound 19 in order to improve potency. Small molecule fragments were screened in pools of five at 400 μ M individual concentrations, with protein concentration at 1 μ M. Ligand-mode NMR method (STD) was used to identify binders. Among 580 small screened small molecules, 60 fragments were identified. Top 20 consensus hits are shown in Figure 21. Several hit fragments were selected for further study and the boxed hit emerged as the winner for S2 binding. Inter-ligand NOE's (Figure 22) suggested possible linking sites for the S2 binding fragment to compound 19, and gave directions for synthetic follow-up efforts.

Figure 20

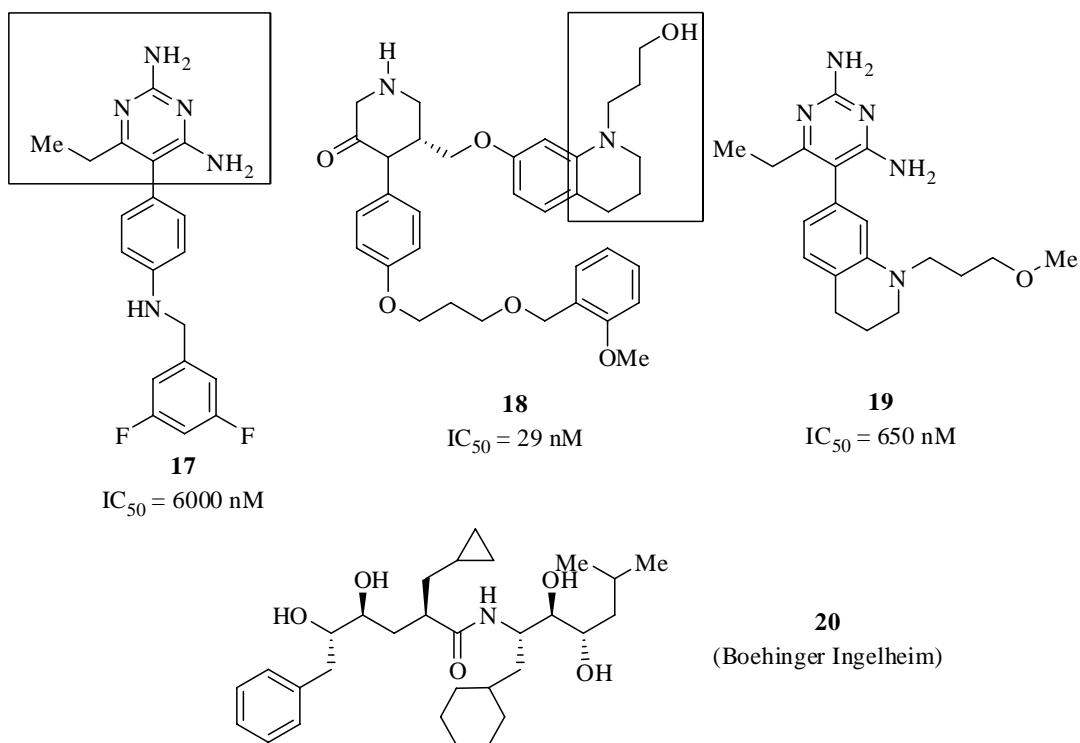


Figure 21

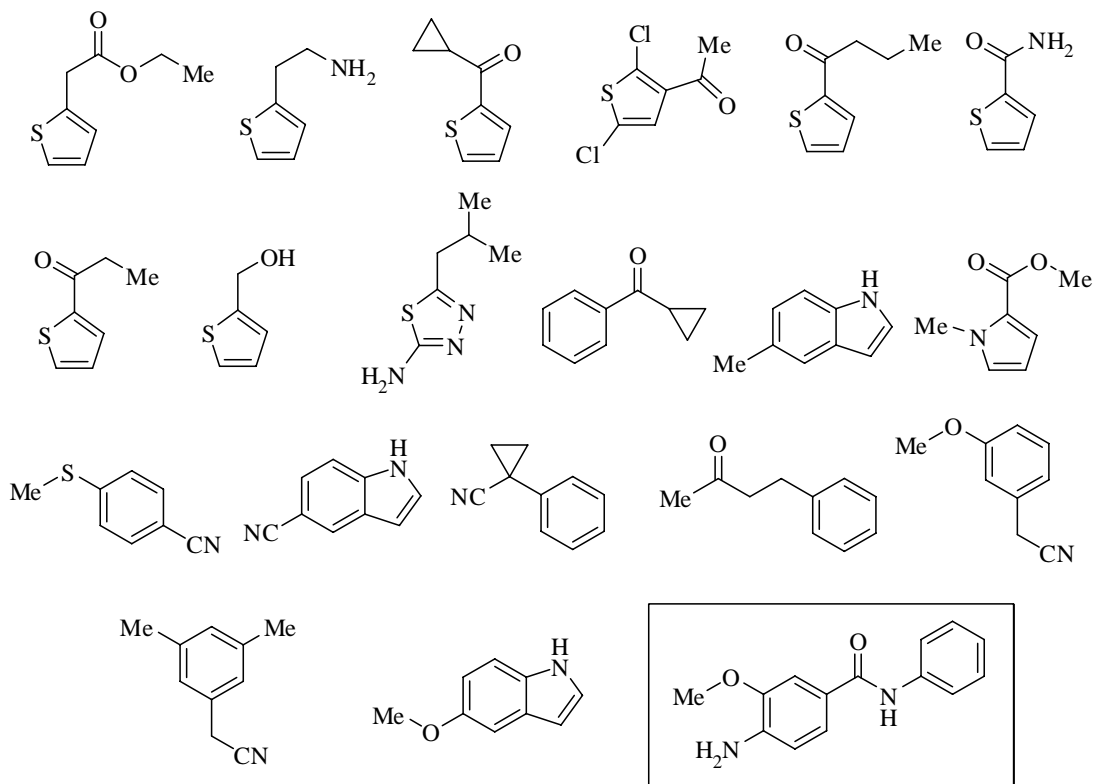
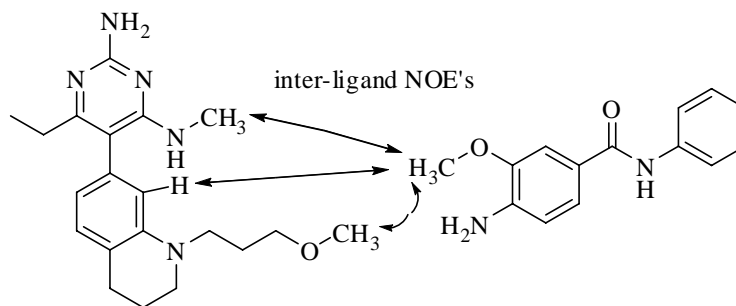


Figure 22



Combination of the auxiliary binder and lead compound **19** generated analogue **21** (Figure 23) and upon further structure based drug design, second and third generation compounds **22-25** were synthesized with improved and optimized S2 binding. Result of SAR studies in the S2 pocket is shown in Table 3. Rewardingly, compound **25** was discovered as a single-digit nanomolar inhibitor against renin.

Figure 23

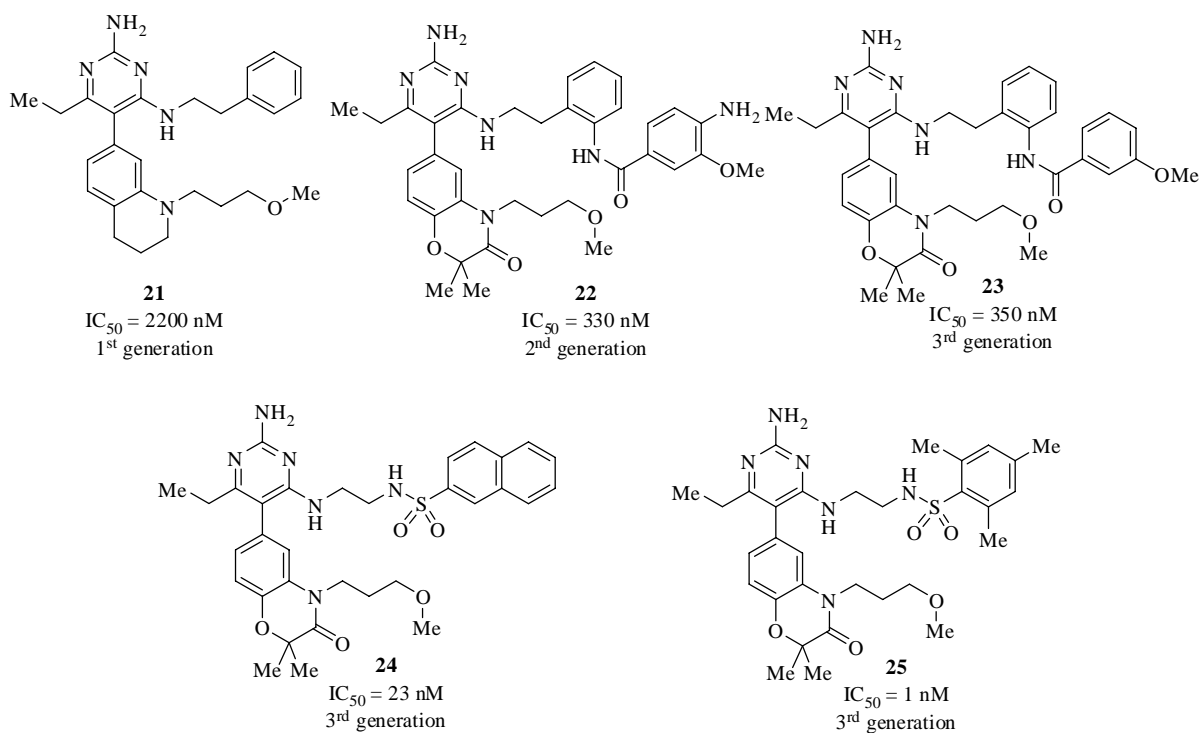
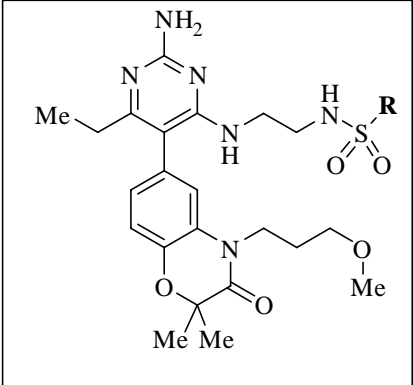
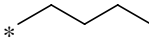
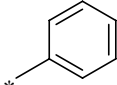
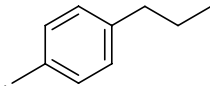
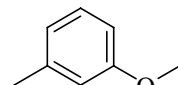
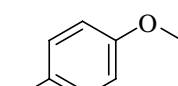
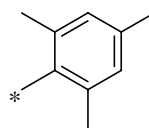


Table 3

	R	IC ₅₀ (nM)
		35
		29
		18
		14
		11
		1