



**Trip Report:
30th National Medicinal Chemistry Symposium
Seattle, Washington
June 25- 29, 2006**

**Charles R. Heap, Ph.D.; Anthony D. Pechulis, Ph.D.;
Margarita Kirova-Snover, Ph.D. and Zhicai Yang, Ph.D.**

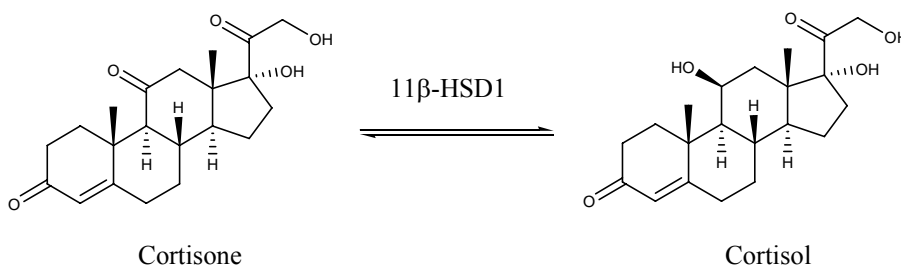
Medicinal Chemistry Department
Albany Molecular Research, Inc.
21 Corporate Circle
Albany, NY 12212

Abstract: The 30th National Medicinal Chemistry Symposium was held in Seattle, Washington from June 25-29, 2006. This report highlights selected material presented at this conference.

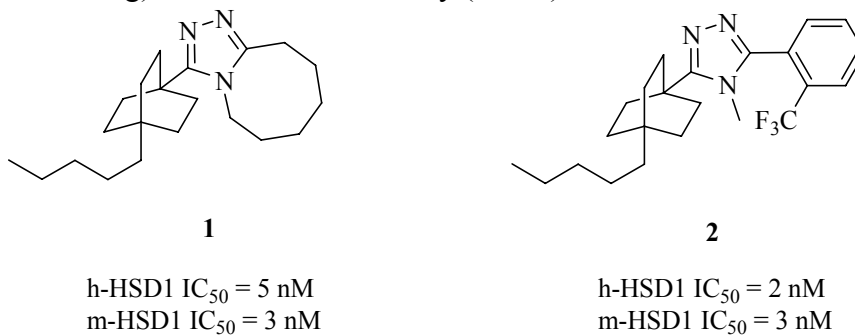
“11 β -HSD1 Inhibitors and Cognition: A Novel Approach to Memory Disorders,”*Xin Gu (Merck & Co.), NJ.*

In this talk, the speaker from Merck described studies on pharmacological inhibition of 11 β -HSD1 prolonged retention of implicit memory.

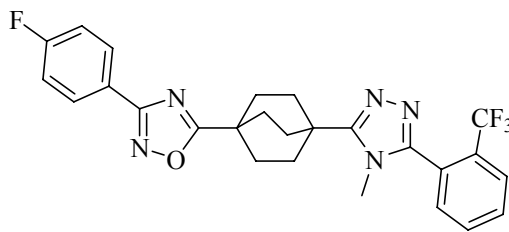
The enzyme 11 β -HSD1 plays a central role in regulating intracellular concentrations of glucocorticoids by converting inactive cortisone to the metabolically active hormone cortisol. It has been hypothesized that inhibition of 11 β -HSD1 would lower intracellular cortisol concentrations and thereby treat metabolic syndrome.



Scientists at Merck have discovered that bicycle[2,2,2]octyltriazoles are potent inhibitors of human 11 β -HSD1. Compound **1** has demonstrated high potency against both human and mouse 11 β -HSD1 enzymes (h-HSD and m-HSD1, respectively). Optimization of the right side of the molecule led to a more potent and selective compound **2**, which inhibits cortisone to cortisol conversion almost completely 4 h after dosing. However, compound **2** still suffers from high clearance (273 mL/min/kg) and low bioavailability (21%F) in mouse.



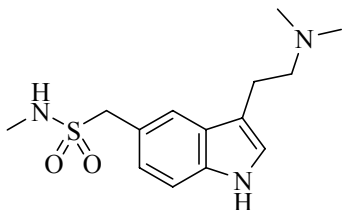
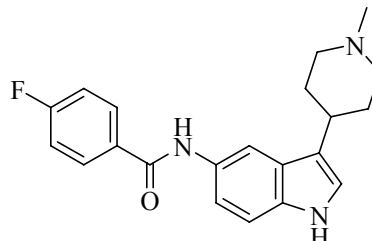
In further studies, incorporation of oxadiazole in the left side of the molecule led to the identification of a very interesting compound **3**, which is very potent (IC₅₀ = 2.2 nM against h-HSD1, IC₅₀ = 1.9 nM against m-HSD1) and very selective (1800-fold over HSD2). In addition, compound **3** has excellent PK profile with low clearance (mouse: 5.88 mL/min/kg; rat: 5.39 mL/min/kg; dog: 3.51 mL/min/kg), long half life (mouse: 17.7 h; rat: 5.1 h; dog: 9.8 h), and high oral bioavailability (mouse: 58%; rat: 83%, dog: 100%).

**3**h-HSD1 IC₅₀ = 2.2 nMm-HSD1 IC₅₀ = 1.9 nM

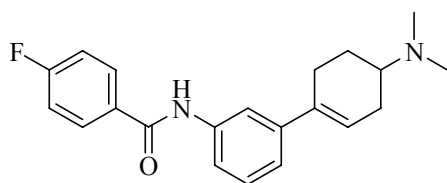
“Discovery of *N*-[3-(4-Dimethylaminocyclohex-1-enyl)-aryl]-benzamides as Novel Selective 5-HT_{1F} Receptor Agonists,”*Deyi Zhang (Eli Lilly and Company), Indianapolis, IN.*

A new class of selective 5-HT_{1F} receptor agonists was reported.

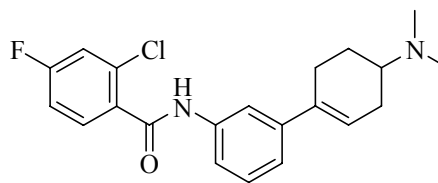
Sumatriptan (**4**), a potent 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor agonist, is the first 5-HT₁ receptor agonist clinically used for migraine treatment. By modification of both side chains of compound **4**, a close analogue, LY334370 (**5**), has been identified as a potent and selective 5-HT_{1F} receptor agonist (K_i = 2.1 nM). Compound **5** has been efficacious against migraine attacks in clinical studies.

**4****5**

Replacement of the indole core with a simple phenyl ring led to the discovery of very potent analogues **6** and **7** as 5-HT_{1F} receptor agonists (K_i = 2.6 nM and 0.75 nM, respectively). Both compounds **6** and **7** demonstrated good selectivity over 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}.

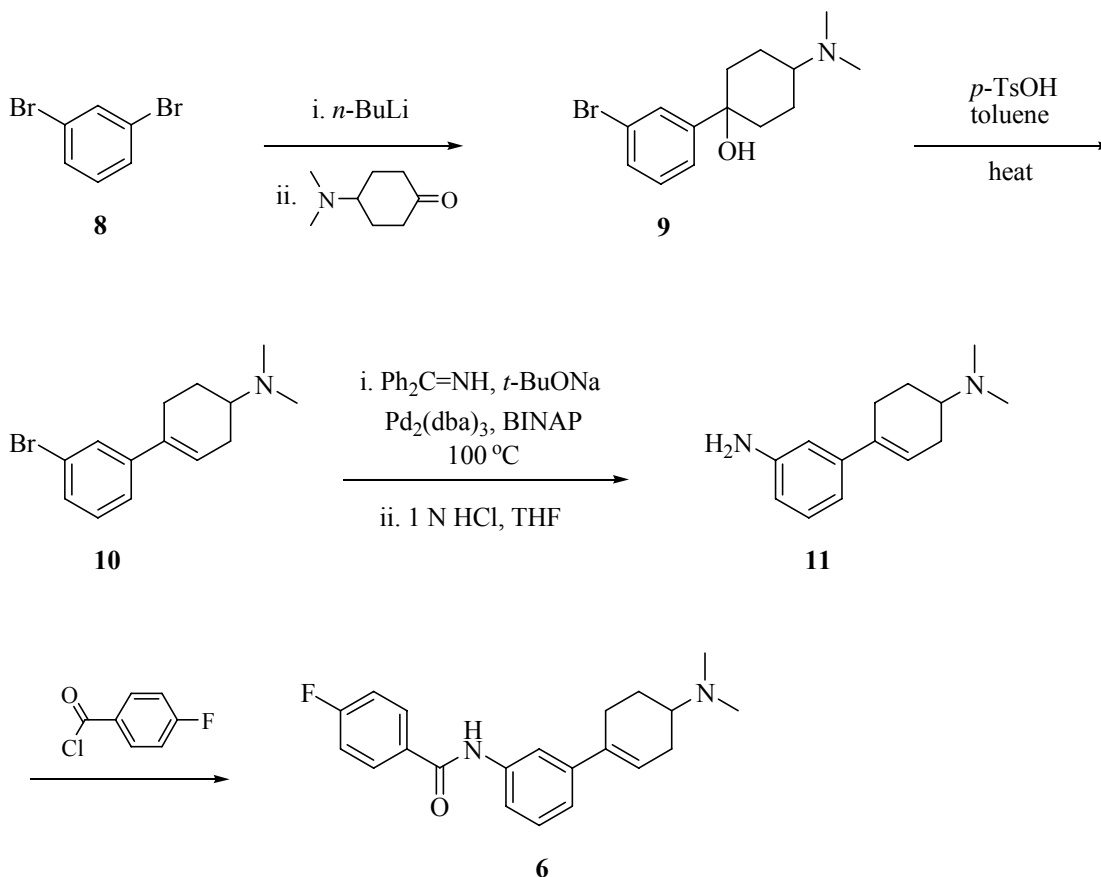
**6**

5-HT_{1F} Ki = 2.6 nM
 Selectivity Ratio:
 5-HT_{1A}/5-HT_{1F}: 120
 5-HT_{1B}/5-HT_{1F}: ND
 5-HT_{1D}/5-HT_{1F}: 1000

**7**

5-HT_{1F} Ki = 0.75 nM
 Selectivity Ratio:
 5-HT_{1A}/5-HT_{1F}: 240
 5-HT_{1B}/5-HT_{1F}: 700
 5-HT_{1D}/5-HT_{1F}: 440

Synthesis of compound **6** was outlined in Scheme 1. Mono-lithium-bromo exchange of the commercially available dibromobenzene (**8**), followed by treatment of 4-dimethylaminocyclohexanone provided alcohol **9** smoothly. Dehydration of compound **9** under acidic conditions afforded olefin **10** in good yield. Buchwald reaction of compound **10** with benzophenone imine followed by hydrolysis generated the corresponding amine **11**. Treatment of amine **11** with 4-fluorobenzoyl chloride yielded the desired **6**.

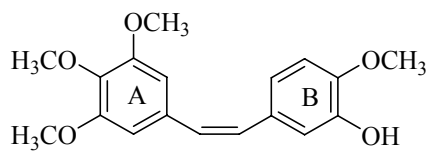
Scheme 1

“New Class of Heterocombretastatins: Synthesis and Antitumor Activity,”

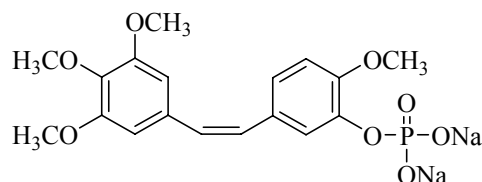
Giuseppe Giannini (Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.), Italy.

A scientist from Italy presented a new series of combretastatin analogues as antitumor agents.

Combretastatin A-4 (CA-4, 12), a natural stilbenoid isolated from *Combretum caffrum*, is a new vascular targeting agent known for its antitumor activity. The corresponding phosphate prodrug 13 is water-soluble and currently in Phase I clinical trials for human cancer.

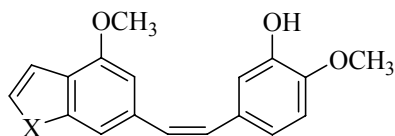


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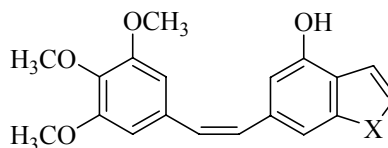


13

Modification of both A-ring and B-ring of the molecule led to identification of novel combretastatin analogues 14a-b and 15a-c, respectively. As shown in Table 1, these compounds (14a-b and 15a-c) possess significant antitumor activity against BMEC and H-460 cell lines.



14a, X = O
14b, X = S



15a, X = O
15b, X = S
15c, X = NH

Table 1: Antitumor activity of Compounds 14 and 15

Compound	IC ₅₀ (nM)	
	BMEC	H-460
14a	35	5.3
14b	17	-
15a	49	53
15b	87	74
15c	28	-

“Flow Technology for Drug Discovery,”

Stephanie Y.F. Wong-Hawkes et al (GlaxoSmithKline R & D), Harlow, UK.

The GSK researchers described an automated synthesis instrument which takes advantage of the unique advantages of microfluidics. The instrument was dubbed “ALOE” for automated lead optimization equipment. The reagents are combined within an extremely narrow tube which allows for faster mass transfer and the exposure of the reactants and products to heating times which are much shorter than required for reactions carried out in bulk solution. During the discovery/lead optimization stage, the instrument can be interfaced directly to a micro flow assay

system or conventional plate-based assay system so that new compounds are made and analyzed in a single operation, allowing very rapid SAR to be developed.

Scale-up can be accomplished by utilizing a multi-chambered reaction cell which compromises some of the advantages of microfluidics for sake of scale. The reaction parameters can be optimized on a real-time basis and production rates of up to 1 mg/minute have been realized.

“Applications of Nanotechnology in Drug Discovery,”

John F. Ryan et al (Bionanotechnology IRC, University of Oxford), Oxford, UK.

Professor Ryan described the potential for atomic force microscopy (AFM) in drug discovery. This technique allows the measurement of molecular interactions at the level of single molecules which could offer new insights into drug discovery. AFM allows for the real-time measurement (~10 millisecond resolution) in a physiological state with a resolution of 0.4 nM. Variations of the salt concentration allow the study of protein-folding interactions. The tip of the AFM can be used to pry apart folded proteins, for example by using a gold tip which selectively bind the cysteine residues. Utilizing AFM, the researchers were able to capture real-time images of the opening of the IP₃R ion channel. Future directions for ARM could include the study of drug binding and interaction, protein function, and protein-protein interactions.

“Point use of Microfluidic Synthesis of multiple PET Biomarkers,”

Joseph Matteo et al (NanoTek), Walland, TN.

Positron Emission Tomography (PET) is a powerful yet complicated nuclear medicine imaging tool which produces a 3-D image of processes in the body. In drug discovery, PET could be utilized to measure drug uptake and clearance and as a non-invasive method to monitor the progression in disease. In a clinical setting, PET could be used as a diagnostic for cancer and in neurology to measure neuron activity.

The major complication of PET stems from the required use of a radioactive isotope, such as ¹⁸F which has a half-life of 2 hours and which requires a cyclotron for its manufacture. Currently, only FDG (¹⁸F-labeled glucose) is commercially available at a cost of \$300 per dose and it often takes more than 8 hours to transfer the FDG from its manufacture point to the patient, requiring very high levels of radio-labeling to account for the 4 half-life losses.

NanoTek is pursuing the goal of creating an automated synthesizer utilizing microfluidics which could produce the radio-labeled compounds at their point of use, for a much lower cost (~\$50/dose), and which could be administered to a patient within 30 minutes of their synthesis. This approach would enable a wide range of compounds to be labeled and their effects studied. The company was founded in October 2004 and their first “Minuteman” system became commercially available in June 2006. The device utilizes microfluidics to keep the reaction times short and to minimize the use of reagents, thereby decreasing the amount of shielding necessary. The reactor volume is 16 microliters and can produce enough compound in ~75 seconds for up to 4 patients. Future goals include partnering with Advanced Biomarker Technologies to develop a relatively small cyclotron (the size of a dining room table as opposed to current cyclotrons which

are the size of a small house) which could be interfaced with the Minuteman synthesizer unit to produce the radioisotopes on site and directly incorporate them into a compound to be dosed.

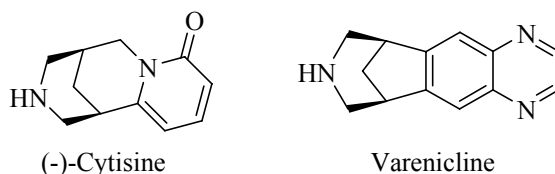
“Varenicline, a novel $\alpha 4\beta 2$ nAChR Partial Agonist: Discovery, Pharmacology, and Clinical Results in Smoking Cessation Trials,”

Jotham W. Coe (Pfizer), Groton, CT.

Smoking is recognized as a major health threat with 25% of the world population smoking and over 47 million people in the US alone. Of the regular smokers, 70% want to quit and are looking for help in breaking the habit. Smoking, as with all addictive drugs, leads to dopamine release which is the cause of the addiction.

Treatments such as the nicotine patch or chewing gum seek to break the addiction to cigarettes by providing a low, steady dose of nicotine which in theory would alleviate the craving to smoke. In practice, however, if someone wearing a patch also smokes, they get an increased dopamine release for a longer time, thereby giving a longer and stronger “high” and increasing the addiction.

Beginning in 1993, researchers at Pfizer sought to develop a partial agonist which would diminish the consequences of both nicotine presence and absence of nicotine in the body.¹ The initial lead compound was (-) Cytisine which was reported in a Russian study in the 1970's to have some effects on smoking cessation but with very few details provided. The first round of SAR work around cytisine gave compounds which were active and selective against $\alpha 4\beta 2$ nAChR but showed undesired antagonist activity².



A second round of SAR was able to achieve the goal of partial agonists with Varenicline being the most promising candidate.³ Varenicline displayed 34% activity towards dopamine and blocked the action of nicotine. The very rigid structure proved to be very selective and had a brain/plasma ratio of 3.3. In the clinic, Phase I b.i.d. dosing of varenicline at 1 mg for 2 weeks showed a drop in the average number of cigarettes smoked from 20 to 5 per day.⁴ In phase IIA, three times as many patients (roughly 50%) quit with varenicline than with either a placebo or Zyban. Phase III trials were conducted with 3600 patients and completed in September 2005: 44% of patients stopped smoking for at least 4 weeks after 9 weeks of treatment and 22% continued not to smoke for a year compared to 18% and 8% for the placebo group and 30% and 16% for Zyban.

Varenicline is currently undergoing priority FDA review with Pfizer planning to market the drug as Champix beginning August 2006.

¹ J. W. Coe et al. *Bioorganic Med. Chem. Lett.* **2005**, *15*, 4889.

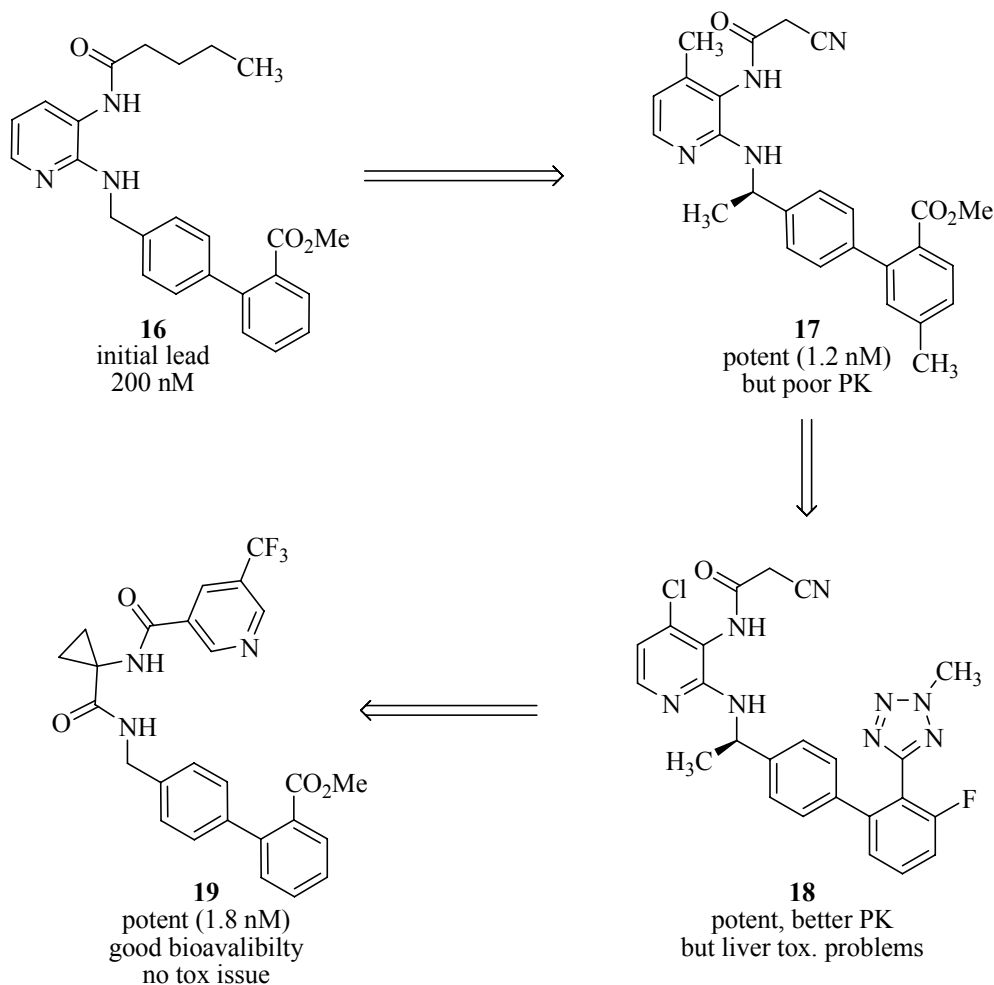
² *Bioorganic Med. Chem. Lett.* **2005**, *15*, 2974.

³ J. W. Coe et al. *Bioorganic Med. Chem. Lett.* **2005**, *15*, 4889.

⁴ *Drug Metabolism and Disposition.* **2006**, *34*, 121-134.

“Bradykinin B1 Receptor Antagonists as Novel Analgesics,”*Michael R. Wood et al (Merck Research Laboratories), West Point, PA.*

Bradykinin B1 receptors are G-protein coupled receptors which are believed to play a role in chronic pain and inflammation. Initial screening of the Merck compound library produced lead compound **16** with an hBK₁ Ki = 200 nM. Optimization around the 2,3-diaminopyridine core provided the very active **17** (hBK₁ Ki = 1.2 nM) but, which suffered from poor PK properties due to oxidation of the aryl methyl groups and saponification of the ester moiety. Replacement of the methyl groups with halogens and replacement of the ester gave **18** which retained activity while substantially increasing the bioavailability and half-life of the compound in vivo.⁵



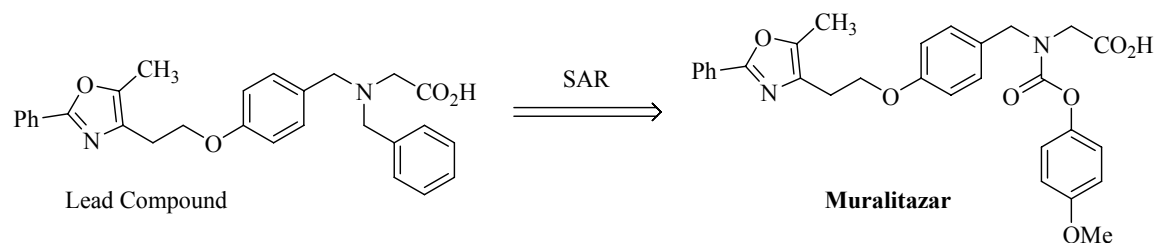
Further evaluation of these compounds, however, implicated the 2,3-diaminopyridine core in liver toxicity. The key pharmacophores were identified and the core was replaced by a cyclopropylamino acid, which may prove to be a general replacement for the diaminopyridine moiety. Compound **19** retains the original potency of **17** with a Ki of 1.8 nM and has good rat bioavailability.⁶

⁵ S. D. Kuduk et al. *J. Med. Chem.* **2004**, *47*, 6439.

⁶ M. R. Wood et al. *J. Med. Chem.* **2006**, *49*, 1231.

“Discovery and Structure-Activity Relationships of Novel PPAR α / γ Dual Activators,”*Peter W. Cheng et al (BMS), Princeton, NJ.*

Given the recent dramatic increase in the number of cases of Type II diabetes and the fact that the current drugs for this condition have a number of safety issues, the researchers at BMS sought to develop a dual PPAR α / γ activator. PPARs belong to a nuclear hormone receptor superfamily and act as transcription factors in the regulation of genes. Agonists of PPAR γ are known to increase insulin sensitivity while PPAR α agonists increase fatty acid oxidation, leading to a decrease in plasma triglyceride concentrations and modest increases in HDL cholesterol.



The lead compound for this project was generated from known PPAR ligands. SAR work was done through a combination of library and single compound synthesis, ultimately resulting in Muralitazar. This candidate displayed strong binding for PPAR α ($IC_{50} = 250$ nM) and γ ($IC_{50} = 190$ nM) and good selectivity against other nuclear hormone receptors.⁷

In the clinic, the ED_{50} for glucose lowering was 0.1 mg/kg/day and 0.2 mg/kg/day for triglyceride lowering. The compound displayed good PK properties and was advanced to Phase III clinical trials where substantial improvements were observed for 70% of patients. A 5 mg dose of Muralitazar resulted in a 27% reduction of triglyceride levels. The compound displayed excellent ADME/PK properties in vivo. However, during Phase III trials, a potential problem developed (a 2.2% increased rate in the incidence of myocardial infarction)⁸ which would have required further evaluation of the drug and BMS decided to drop the compound at this time.

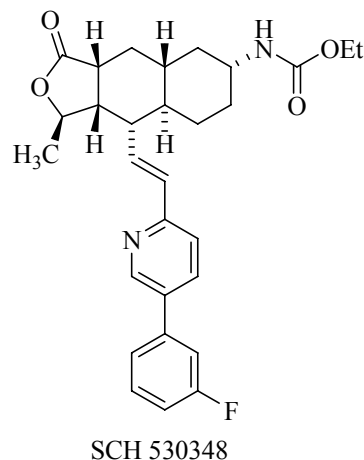
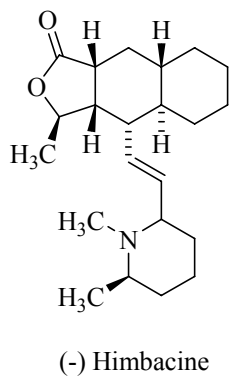
“Discovery of a Potent, Orally active Thrombin Receptor (Protease Activated Receptor-I) Antagonist as a Novel Antiplatelet Agent,”*Samuel Chackalamannil et al (Schering-Plough Research Inst.), Kenilworth, NJ.*

The development of a Thrombin Receptor (Protease Activated Receptor-I, PAR-I) antagonist is an attractive target for the treatment of acute coronary syndrome because it would prevent platelet aggregation while leaving the fibrin-generating pathway intact. This approach should alleviate the side effects of the currently available drugs such as Warfarin which can lead to excessive bleeding.⁹

⁷ P. Devasthale et al. *J. Med. Chem.* **1996**, 48, 2248.

⁸ (a) J. M Brophy. *J. American Medical Assoc.* **2005**, 294, 2539; (b) S.E. Nissen et al. *J. American Medical Assoc.* **2005**, 294, 2581.

⁹ S. Borman. *C & E News.* **2005**, 83, 40.



Schering's work on this project began as a spin-off on their work on the total synthesis of Himbacine and SAR around this compound. While Himbacine itself was not active on the PAR-I project, some of the related compounds provided the first lead structure. The researchers at Schering prepared over 2000 analogs to explore the SAR around the lead and had two early development candidates fail because of safety concerns (problems with CYP and clearance rates). The project eventually produced SCH 530348 which passed all of the safety and tox issues and was moved into the clinic. Phase I trials demonstrated that dosing at 10 mg completely suppressed platelet aggregation. SCH 530348 was granted FDA fast-track status and Phase II trials are currently ongoing.

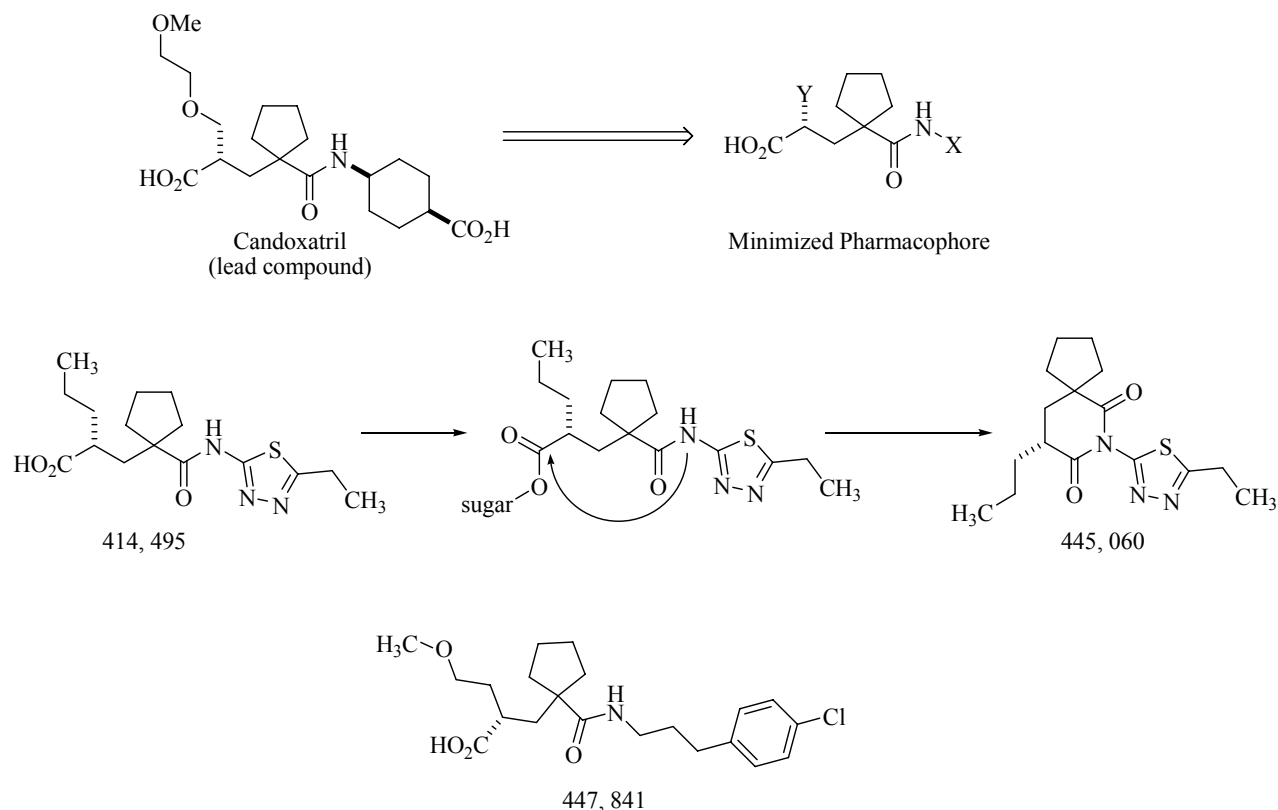
“Designing Small Molecular NEP Inhibitors for the Treatment of FSAD,”

Don Middleton (Pfizer), Sandwich, Kent, UK.

Female sexual arousal disorder (FSAD) is a condition which affects up to 40% of women (at least 25 million women in the US) and for which there is no approved therapy. The Pfizer team sought to develop potent and selective inhibitors of NEP (neural endopeptidase). The rationale for this target is that genital blood flow is regulated by vasoactive intestinal peptide (VIP) which is known to be degraded by NEP. Inhibition of NEP should lead to higher levels of VIP and thereby increase blood flow.¹⁰

Designing a drug to treat FSAD has several unique requirements: dosing is expected to be prn (on demand) which requires a rapid T_{max} ; a half-life of 5-10 hours to avoid accumulation; and a potent compound so that dosing is less than 100 mg. Middleton explained his belief that the choice of a lead compound is critical to a project and he therefore chose a lead which was as similar to approved drugs as possible and with the minimal pharmacore for activity to keep the molecular weight less than 400 if at all possible.

¹⁰ D. C. Pryde et al. *J. Med. Chem.* **2006**, *49*, 4409.



As a lead, the Pfizer team chose Candoxatril which had been developed by Pfizer in the 1990's as a treatment for chronic heart failure and was known to inhibit NEP. The minimal pharmacophore was explored by a combination of parallel and single compound synthesis and produced UK-414,495 as a development candidate. All of the data for UK-414,495 was looking good until the toxicology results showed emesis, mucosal, and intestinal damage in dogs but not in rat. The toxicity was not due to NEP effects because other potent compounds did not display these effects and was determined not to be the result of an oxidative metabolite. The culprit was determined to be glucuronidation which leads to degradation of the drug by cyclization to produce UK-445,060. The reason for the toxicology issue in UK-414,495 and not in related compounds was due to the pKa of the amide NH which is estimated at 9.6 versus 16.5 for a non-heterocyclic amide.

Returning to the library work and focusing on small changes to what they believed was a quality lead compound, the Pfizer team produced UK-447,841.¹¹ Compound 447,841 was potent (0.5 nM), had a Caco2 value of 33, and a bioavailability of 70% for a 25-100 mg dose. The acyl glucuronide of this compound displayed excellent stability and the cyclization to the cyclic imide was not observed after 50 hours. In the clinic, UK-447,841 had a half-life of 7-10 hours, a T_{max} of less than 1 hour, and a bioavailability of 90%.

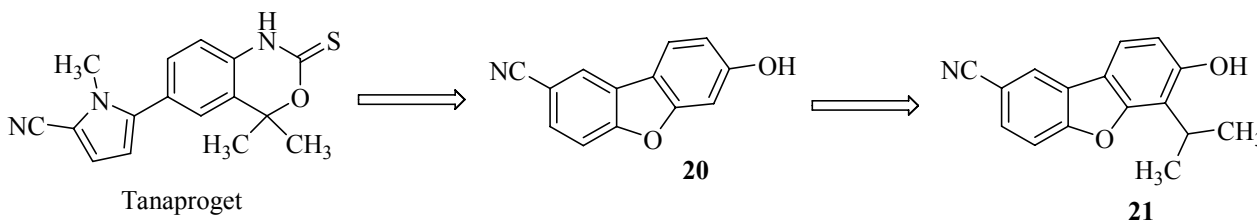
¹¹ R. Armer et al. *Drug News Perspect.* **2006**, *19*, 65.

“Novel Dibenzofurans as Progesterone Receptor Modulators,”*J.M. Diffendal et al (Wyeth Research), Collegeville, PA.*

Progesterone receptor modulators are common as oral contraceptives and in hormone replacement therapy, and in most cases are steroidal. This class of compounds displays some unwanted side-effects such as nausea, headache, and weight gain. This poster focuses on non-steroidal progesterone receptor modulators that may display fewer side-effects.

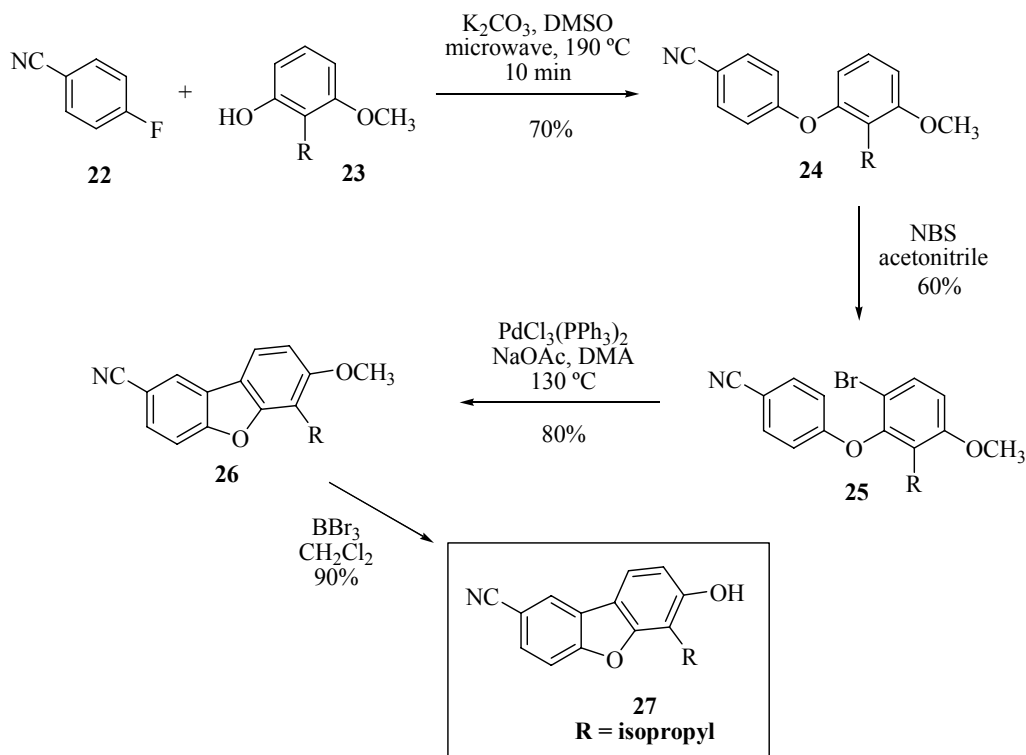
One such non-steroidal compound is Tanaproget, shown in Figure 1. Structure-aided drug design was used to analyze Tanaproget and generate ideas for novel structures. The crystal structure of Tanaproget in the binding pocket of the progesterone receptor was analyzed to determine the functionality that may be important. First, modification of the ring system of Tanaproget was considered, while the apparent pharmacophores (such as NH, cyano, and dimethyl) were held in the same approximate locations. It was also believed that the A ring system, containing the thioester could be eliminated, while maintaining some polarity by replacement of NH with OH. Finally, adding an additional ring would constrain the molecule.

The simplified hypothetical molecule (**20**) was then docked into the progesterone receptor binding site, *in silico*. It was found that the nitrile and the hydroxyl groups corresponded well to the approximate locations for the corresponding groups in Tanaproget. It was determined that a hydrophobic group, the isopropyl, would fit well into the region occupied by the gem-dimethyl in Tanaproget. This gave rise to a structure such as compound **21**.



Preparation of compounds such as **21** proceeded as shown in Scheme 2. Addition of resorcinol derivatives such as **23** to 4-fluorobenzonitrile, with potassium carbonate and microwave heating, provided diphenyl ether **24**, via S_NAr. Bromination with NBS was followed by palladium-catalyzed cyclization to give compound **26**. Treatment of **26** with BBr₃ cleaved the methyl group, to afford targets such as **27**.

Scheme 2



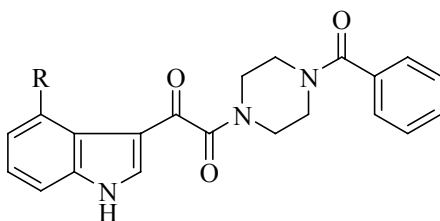
Analogues of **27** were screened in a T47D alkaline phosphatase assay and a number of active analogues of **27** were discovered. The most active were R = isopropyl ($\text{IC}_{50} = 28 \text{ nM}$), R = sec-butyl (single enantiomer) ($\text{IC}_{50} = 22 \text{ nM}$).

“Inhibitors of HIV Attachment,”

John Kadow (Bristol-Myers Squibb Pharmaceutical Research Institute), Wallingford, CT.

There are three steps that occur during fusion of a virus to a cell: attachment, fusion protein activation, and virus membrane/host membrane fusion. This project was focused on inhibiting HIV infection at the site of attachment of the virus to the cell. Specifically, the interaction of the host cell CD4 surface molecule with the HIV surface protein gp120 was targeted. Some of this information can be found in the following reference: T. Wang et al. *J. Med. Chem.* **2003**, *46*, 4236.

Compound **28** (BMS-216) was found to be selective against HIV-1. The compound possessed a good therapeutic index, and activity early in the viral life cycle. The inhibition of CD4 binding to gp120 was found to be competitive and reversible. BMS-216 was the first example of a small molecule with such a mode of action.

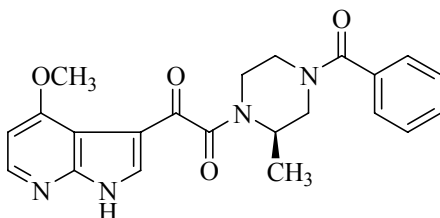


28: R = H; BMS-216

29: R = F; BMS-705

Derivative **29** (BMS-705) exhibited enhanced potency (10- to 1500-fold) and was bioavailable in rat, dog, and cynomolgus monkey when administered orally as a solution. Compound **29** was metabolized by multiple P450's and a high clearance was predicted. Solubility was a limiting factor for this compound; an aqueous suspension of compound **29** was poorly bioavailable.

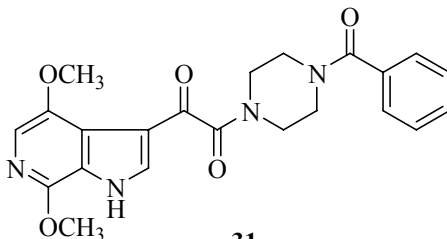
The next compound in the series (**30**, BMS-378806) was found to bind at a similar affinity, and displays good pharmacology such as low protein binding, good oral bioavailability, and good safety profile, compared to compound **29**. It was presumed that the additional nitrogen atom in the heterocycle, along with the methoxy group, provided the better solubility. However, minimal CNS penetration observed in various species, and exposure was low in the clinic.



30

BMS-378806

The analogue BMS-488043 (compound **31**) was a backup for compound **30**. It was believed that compound **31** binds to the HIV-1 glycoprotein gp120, before CD4 does, and creates a new conformation. The safety profile on this compound was good, and it demonstrated dose-related antiviral activity. However, the compound needed to be administered along with a high-fat diet, in order to increase exposure levels.

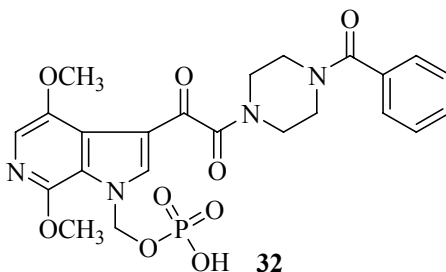


31

BMS-488043

In order to circumvent the necessity of administration with a high-fat diet, the compound could be formulated appropriately, or a prodrug analogue could be developed. Compound **32** was described as an attempt to develop such a prodrug. The phosphate would be cleaved in vivo, by alkaline

phosphatase. The exposure of the compound was found to be independent of food intake. The drawback is that formaldehyde is released as the phosphate degrades.



These inhibitors of HIV attachment were thought to be attractive alternatives to HAART (highly active anti-retroviral therapy), which is a combination cocktail of inhibitors of HIV reverse transcriptase and protease. Because of severe side effects, compliance with this method can be problematic. Resistant viruses have thus evolved and this has led to the search for new biological targets, such as these gp120-CD4 inhibitors.

A good review of recent approaches toward anti-HIV chemotherapy is: E. De Clercq. *J. Med. Chem.* **2005**, *48*, 1297.

“CCR5 Antagonists for HIV Therapy,”

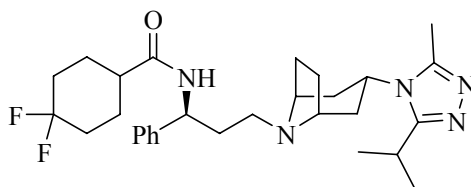
Chris Barber (Pfizer Global Research and Development), Sandwich, Kent, UK.

This project also explored the inhibition of HIV-1 entry into host cells. Specifically, the binding of HIV-1 gp120 with the chemokine coreceptor CCR5 was investigated. In nature, the ligands for CCR5 are the proinflammatory peptides called chemokines. CCR5 is the coreceptor used by the R5-tropic HIV-1 strains, which predominate during the early stages of HIV-1 infection.

The HIV co-receptor CCR5 was identified as a particularly attractive target for the discovery of viral entry inhibitors, as G-protein coupled receptors have traditionally proven tractable targets for the design of selective low-dose, orally bioavailable drugs.

UK-427,857 (Maraviroc TM) is the most advanced CCR5 antagonist for the treatment of HIV, entering phase III in November 2004.

Compound **33** was active across a wide range of HIV isolates and shows off-set kinetic from the receptor. The tropane appears to enhance antiviral activity. The compound is in phase III trials, but more analogues were desired in case resistance was observed.



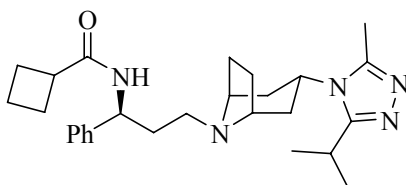
33

Maraviroc (UK-427857)

MIP-1 β IC₅₀ = 2 nM

antiviral activity mean IC₉₀ = 1 nM

Compound **34** is an analogue of **33** with similar activity. However, compound **34** did not possess a desirable safety profile with respect to QT prolongation.



34
MIP-1 β IC₅₀ = 7 nM
antiviral activity mean IC₉₀ = 8 nM

“Design and Synthesis of Selective GSK-3 Inhibitors,”

Robert Davies, Corni Forster, Dave Lauffer, Pan Li, Albert Pierce, Kirk Tanner, Ernst Ter Haar, Woods Wannamaker, Jinwang Xu (Vertex Pharmaceuticals Inc.), Cambridge, MA.

Glycogen synthase kinase 3 (GSK-3) is a serine/threonine kinase which functions in multiple biological pathways. It is a potential target for the development of novel drugs for treating a number of indications including neurodegenerative diseases, neuropsychiatric diseases, and type-2 diabetes.

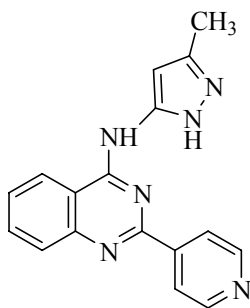
Using structure-based design, the Vertex researchers have successfully optimized a quinazoline series to obtain a selective inhibitor of GSK-3.

The Serine/Threonine protein kinase was discovered in 1980.¹² It exists in two isomeric forms (GSK-3 α and GSK-3 β) which are 97% identical in the catalytic domain. However, the sequences differ outside of the kinase domain. The activity of GSK-3 α is reduced by phosphorylation at Ser9, while the activity of GSK-3 β is reduced by phosphorylation at Ser21.

The potential therapeutic indications of GSK-3 are associated with:

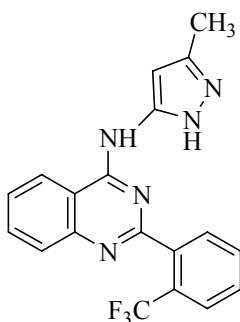
- neurodegeneration (stroke, Alzheimer’s disease, Parkinson’s disease)
- neuropsychiatric (schizophrenia and bipolar disorder)
- diabetes (type-2, NIDDM)

The Vertex Pharmaceuticals research team have screened over 50,000 compounds and followed up on 726 of the hits. Seventy-seven of these hits had IC₅₀<10 μ M. The best initial GSK-3 hit molecule **35** had the following structure:

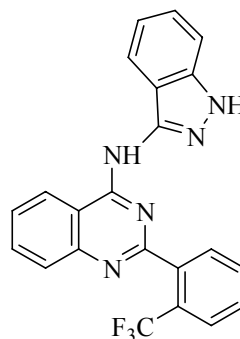
**35**

Ki against GSK-3: 60 nm (HTS IC₅₀=0.2 μM)
poor selectivity (Ki against Aur-2: 40 nm)

The Vertex Pharmaceuticals researchers used structural information to guide their design modifications and significantly improved the GSK-3 potency and selectivity over Aur-2. Their two current best lead molecules, **36** and **37**, have the following structures:

**36**

Ki against GSK-3: <2 nm
Ki against Aur-2: 60 nm

**37**

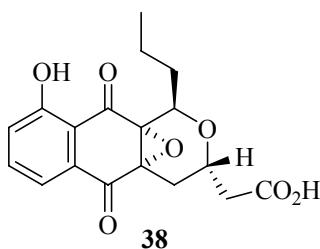
Ki against GSK-3: 9 nm
Ki against Aur-2: 3,600 nm

¹² R. S. Jope et al. *Trends in Biochemical Sciences*. **2004**, 29 (2), 95-102.

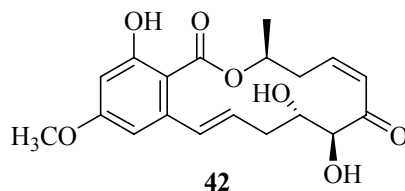
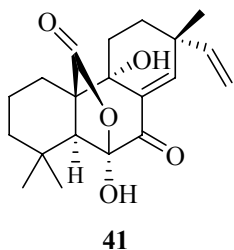
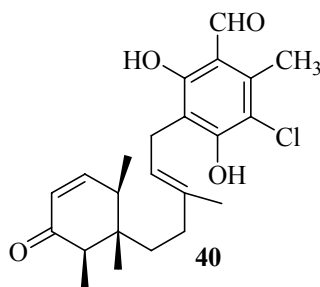
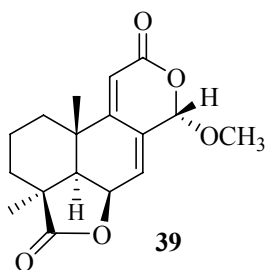
“Natural Products through Bioorganic Chemistry – What’s Next?”

George A. Ellestad (Columbia University).

George Ellestad’s talk reflected on his career in chemical and bioorganic studies of natural products at Lederle and Wyeth Laboratories. An overview of some of the more prominent projects was presented beginning with studies on the chemistry and structure activity relationships of some biologically active fungal metabolites. He described the efforts of his research team at Lederle Laboratories focused on the structure elucidation of Frenolicin (**38**)¹³, an antifungal and antitumor agent:

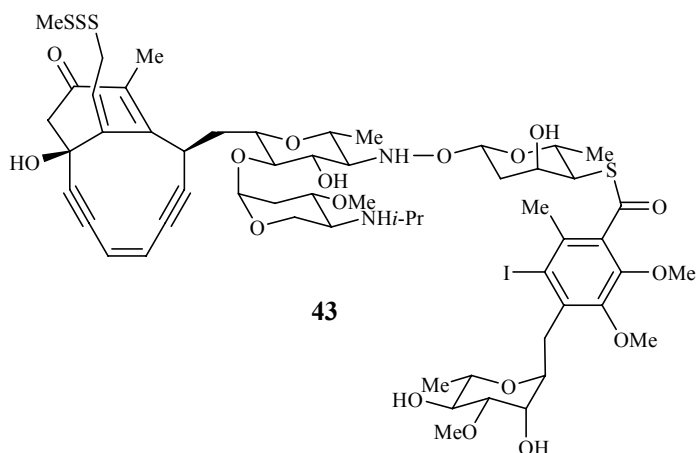


George Ellestad devoted significant portion of his talk to the efforts of his research teams in the search for antifungal and hypocholesteremic agents using the Protozoan *Tetrahymena Pyriformis* species. His research group at Lederle Laboratories was successful in elucidating the structures of LL-1271 (**39**)¹⁴, LL-1272 (**40**)¹⁵, LL-S491 (**41**)¹⁶ and LL-Z1640 (**42**)¹⁷. The isolation and structure elucidation of LL-1271 is notable in that it is the first example of a terpene with a C₁₆ carbon skeleton. The antibiotic LL-S491 displayed significant antibacterial activity against certain Gram-positive organisms and strong antiviral activity against *Herpes simplex*. All these compounds exhibited strong antiprotozoal activity against *Tetrahymena Pyriformis*.

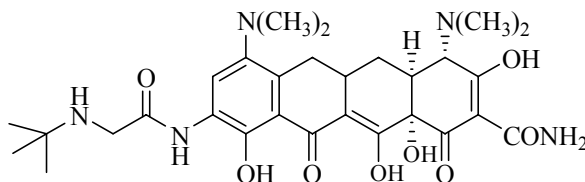


While working at Lederle Laboratories Ellestad and his coworkers also elucidated the structure of a new class of broad spectrum antibiotics, known as the glycocinnamoylspermidines, on the basis of hydrolytic experiments in conjunction with ¹H NMR, ¹³C NMR and x-ray crystallographic analysis.¹⁸ This class of novel antibiotics bind to bacterial DNA and inhibit the gyrase B enzyme.¹⁹

Ellestad and his team were the first to discover and elucidate the structure, absolute stereochemistry and bioorganic chemistry of Calicheamicin γ_1 (**43**), a novel ten-membered ring enediyne containing antibiotic and antitumor agent.^{20,21} This discovery led to the discovery of Mylotarg™ (gemtuzumab ozogamicin), a calicheamicin-antibody conjugate for the treatment of relapsed myeloid leukemia.



The next topic of Ellestad's lecture focused on the discovery of Tigecycline (**44**), a novel tetracycline antibiotic, which overcomes bacterial efflux pumps.²² He explained that there are two major resistance mechanisms to the tetracyclines among pathogens. The first mechanism involves ribosome protection, which is mediated by proteins that interact with the ribosome, allowing protein synthesis even in the presence of tetracyclines. This type of resistance mechanism is found in bacteria that cause many sexually transmitted diseases. The second resistance mechanism involves the expulsion of antibiotics by tetracycline efflux pumps. The efflux mechanism, first observed in Gram-negative organisms (*Escheria coli*), is an active transport mechanism based on a proton-motive force. Removal of the repressor protein allows transcription of efflux protein which then removes the tetracycline from the cytosol.²³ Tigecycline is a new generation tetracycline antibiotic with broad antimicrobial spectrum and potent activity against both Gram-positive and Gram-negative aerobic and anaerobic bacteria possessing tetracycline-resistant determinants. It effectively overcomes the tetracycline efflux pump mechanism of bacterial resistance.



George Ellestad concluded his talk with comments on the present and future directions of drug discovery which he summarized in the following trends:

- search for antimicrobial agents which target cellular functions other than protein, nucleic acid, peptidoglycan synthesis and topoisomerases;
- development of multidrug transporters that export hydrophobic antineoplastic agents and antibiotics from target cells;
- manipulation of biosynthetic genes of antimicrobial and antitumor agents from microbes;
- combination of genetic and chemical manipulations to come up with new entities;

- chemical synthesis;
- development of small molecule inhibitors of protein-protein interactions.

- ¹³ Ellestad et al. *J. Am. Chem. Soc.* **1968**, *90*, 1325.
- ¹⁴ Ellestad et al. *J. Am. Chem. Soc.* **1970**, *92*, 5483.
- ¹⁵ Ellestad et al. *Tetrahedron*. **1969**, *25*, 1323.
- ¹⁶ Ellestad et al. *J. Am. Chem. Soc.* **1972**, *94*, 6206.
- ¹⁷ Ellestad et al. *J. Org. Chem.* **1978**, *43*, 2339.
- ¹⁸ Ellestad et al. *J. Am. Chem. Soc.* **1978**, *100*, 2515.
- ¹⁹ Osburne et al. *Antimicrobial Agents and Chemotherapy*. **1990**, *34*, 1450.
- ²⁰ Ellestad et al. *J. Am. Chem. Soc.* **1987**, *109*, 3466.
- ²¹ Ellestad et al. *J. Am. Chem. Soc.* **1992**, *114*, 985.
- ²² Ellestad et al. *J. Med. Chem.* **1994**, *37*, 184.
- ²³ Hinrichs et al. *Science*. **1994**, *264*, 184.