



**Trip Report:
High-Throughput Chemistry
SanDiego, California
March 16 – 18, 2005**

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***Abstract:** “High Throughput Chemistry” Conference was held in San Diego, California, March 16-18, 2005. This conference was organized by the IBC Life Sciences as part of the Drug Discovery Series. The conference included a total of 24 lectures and a poster session.*

“Convergent Library Synthesis of Complex Molecules through Domain Shuffling”

Scott E. Schaus, Ph.D., Assistant Professor, Chemistry and Pharmacology Boston University.

Diversity oriented synthesis has provided a new paradigm for the chemical synthesis of small molecules. New methodologies are driven by the desire to synthesize compound libraries with expanded diversity possessing stereochemical features, novel ring systems, and diverse presentations of functional groups. Convergent synthesis employs two complex fragments from independent synthesis and joins the two fragments in a chemical ligation step. The successful implementation of this approach in library construction providing access to structurally diverse molecules was presented.

“Volatilizable Solid and Liquid Supports and Linkers for High Throughput Organic Synthesis”

Richard A. Houghten, Ph.D., President and Director, Torrey Pines Institute for Molecular Studies.

A practical new concept involving solid and liquid supports was presented. This entails the use of any solid or liquid support/linker combination that can be completely transformed to volatile materials. This enables the desired synthetic compound to remain as the sole product in the final reaction vessel. A range of specific synthetic examples was presented including low molecular weight acyclic and heterocyclic compounds, peptidomimetics and both free and protected peptides.

“Application of Supercritical Fluid Chromatography to High Throughput Chemistry”

Larry Truesdale, Ph.D., Senior Director, Pfizer Research & Development.

This talk covered the use of supercritical fluid chromatography to support high throughput chemistry as applied to drug discovery. Its use in large library characterization and purification and the application of chiral SFC in hit follow-up was emphasized.

“High Throughput Approaches Applied to the Construction of Libraries”

Armen M. Boldi, Ph.D., Group Leader, Discovery Chemistry Division, Discovery Partners, Inc.

Various compound libraries, constructed using robust and high throughput synthetic transformations, highlight a range of chemistries, methods, and techniques. Purification strategies including resin scavenging, supported liquid extraction, reagent modification and scavenging, and reverse-phase purification were utilized. The high throughput synthesis and high throughput purification of a range of libraries was described.

“Acceleration of Multi-Component Reactions”

Michael Pirrung, Ph.D., Professor, Chemistry, Duke University.

Multi-component reactions can be significantly accelerated, up to 300-fold compared to reactions in organic solvent, by conducting them in water. This rate acceleration permits building blocks that usually react poorly, such as sterically hindered compounds, to participate in efficient Ugi and Passerini reactions. The rate acceleration is related to the high cohesive energy density of water. Reactions in water provide an alternative to high-pressure reactions that is much more practical, and the rate accelerations observed suggest that multi-component reactions have negative activation volumes. The reaction products are often insoluble in water, permitting ready purification by filtration to provide unpurified material of adequate purity for initial biological testing.

“Synthesis and Structure Activity Relationship of DF508-CFTR Modulators”

Sabine Hadida, Ph.D., Group Leader, Vertex Pharmaceuticals Incorporated.

Cystic Fibrosis (CF) is a fatal genetic disease caused by decreased anion transport across respiratory epithelia due to mutations in the PKA-gated anion channel, CFTR. Approximately 70% of CF patients are homozygous for a single mutation that causes the deletion of phenylalanine at position 508 (DF508-CFTR) resulting in improper folding of the protein, decreasing both channel surface density and gating. Parallel synthesis has led to promising DF508-CFTR modulators that increase chloride transport in DF508-human bronchial epithelial cells. Three types of modulators have been described:

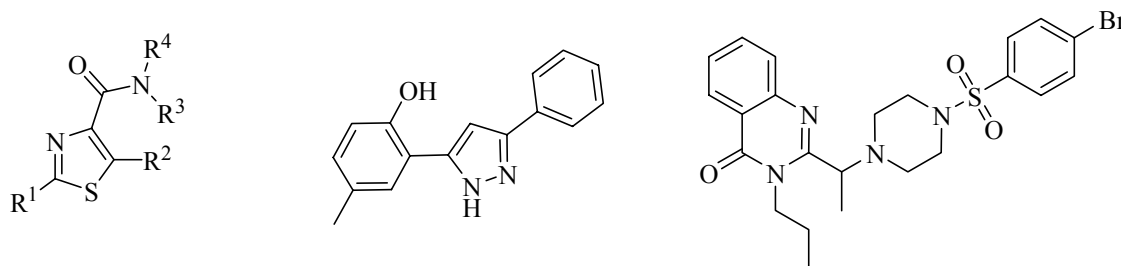
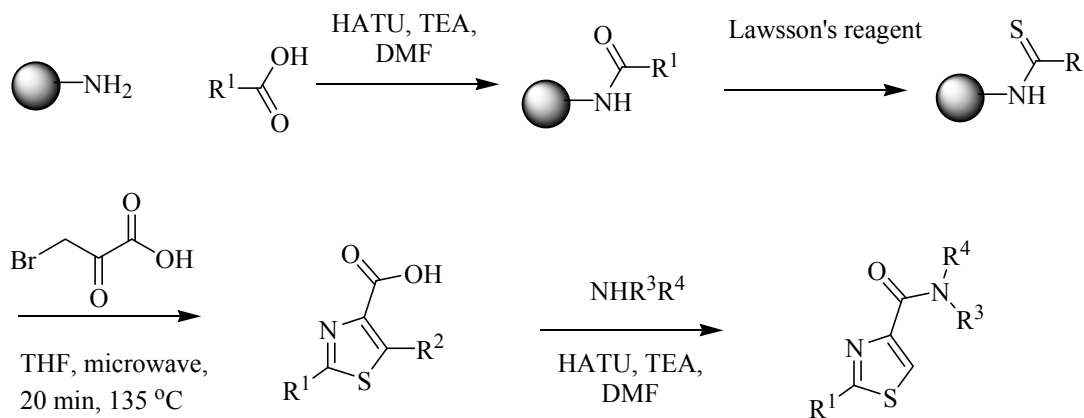


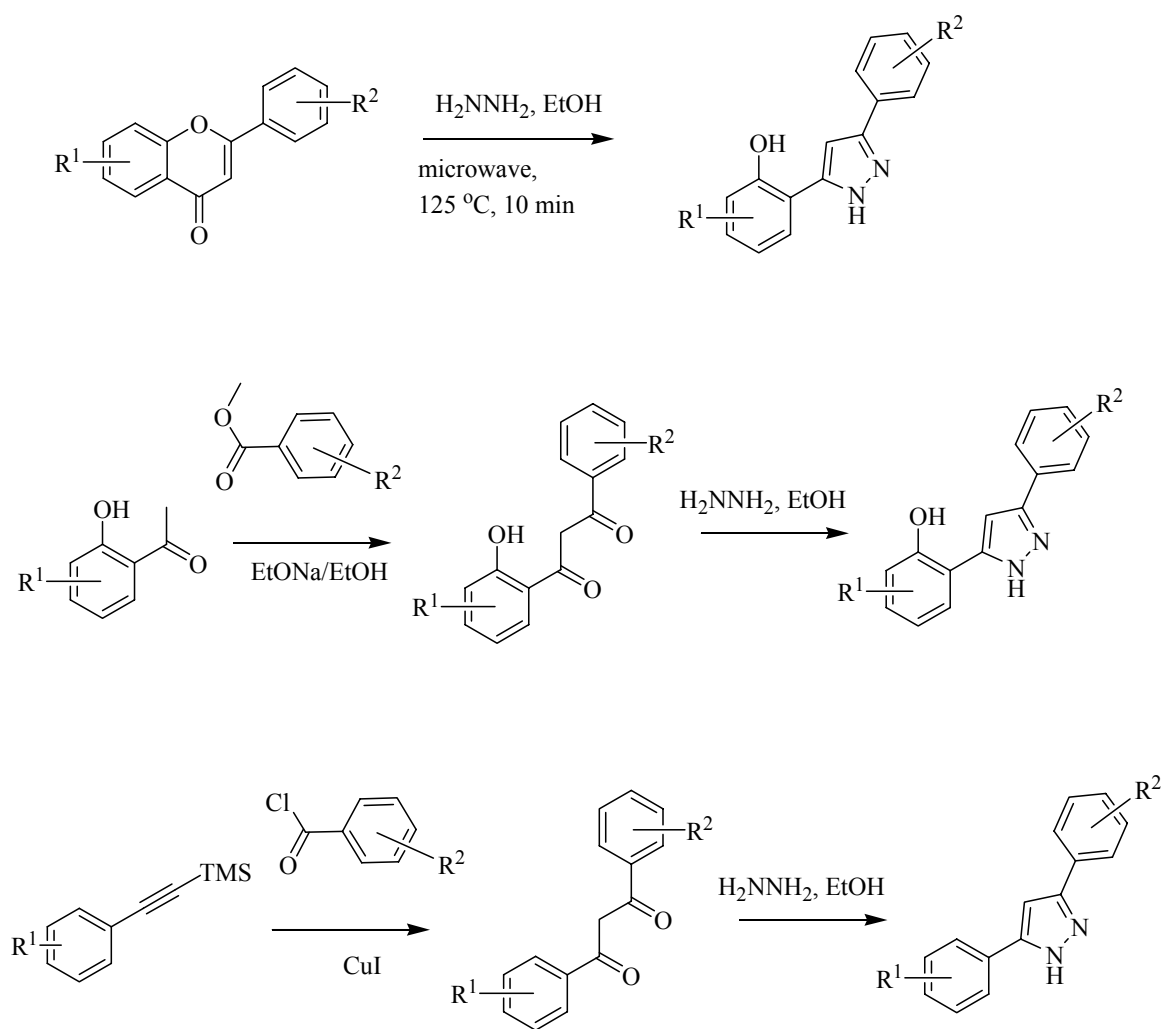
Figure 1

Carboxythiazoles were prepared using combination of solution and solid-phase synthesis, which facilitated purification.



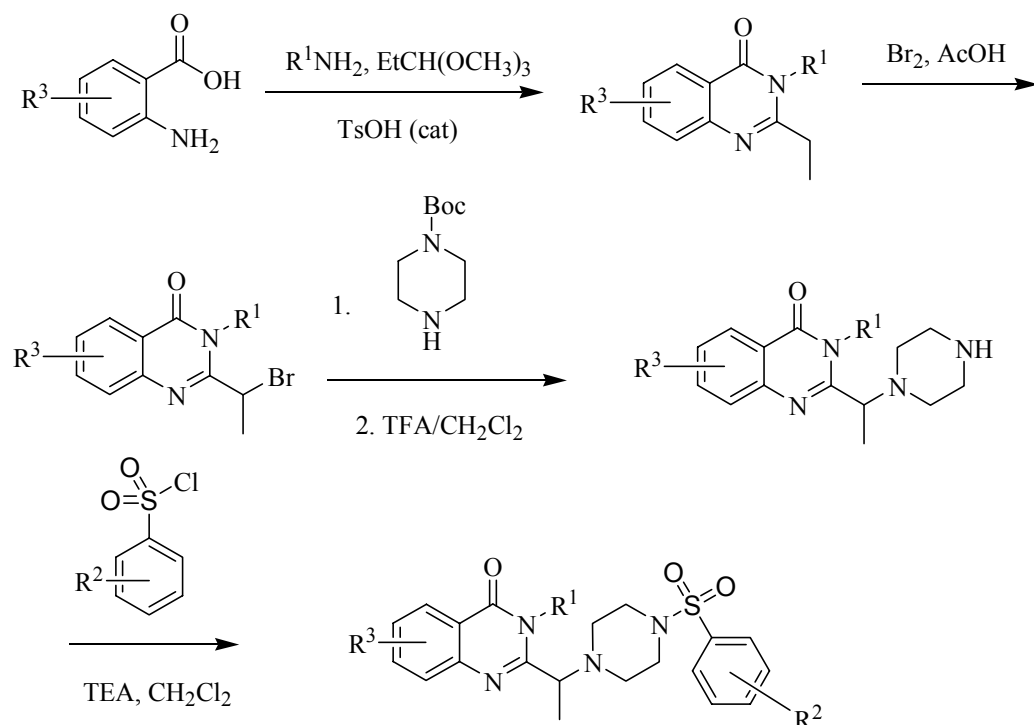
Scheme 1

3,5-Diarylpyrazoles were prepared using three synthetic routes:



Scheme 2

Third class of potent compounds, quinozalines, was prepared according to Scheme 3:



Scheme 3

“Biological Perspectives on Lead Generation Libraries”

Deborah S. Hartman, Ph.D., Director, Lead Discovery Department, AstraZeneca Pharmaceuticals LP.

Emerging paradigms in lead generation depend on increasing the quality & accessibility of compound libraries for both random and directed high throughput screening. Characteristics of a high quality compound library, what constitutes a lead-like compound in the early phases of drug discovery, and approaches to biological profiling of compound collections was discussed.

“Nucapalooza: The High Throughput 5-Minute Microwave Synthesis of Nucleosides”

Brett Bookser, Ph.D., Manager, Parallel Chemistry, Metabasis Therapeutics, Inc.

Nucleosides and nucleotides have a long history of efficacy as antiviral and anticancer agents, and are also well-recognized inhibitors and activators of myriad metabolic pathways and therapeutic targets. Prior parallel synthesis of nucleoside analogues required derivatization of preformed nucleosides. A microwave version of the Vorbruggen glycosylation reaction was developed which allows high throughput synthesis of nucleoside libraries from coupling of diverse base and carbohydrate building blocks.

“Focused Libraries of Heterocycles”

Peter Madrid, Ph.D. Student, University of California at San Francisco. (Presenting for R. Kip Guy, Ph.D., Assistant Professor)

Many initial lead compounds contain heterocyclic systems derived from convergent synthetic routes with two or more intact ring systems as precursors. In lead optimization, a common need is to balance attempts to gain affinity or selectivity by varying these ring systems with "drug like" character of the resulting products as predicted by computational methods. A coupled design/synthesis approach was discussed that allows for rapid optimization of both properties.

“Privileged Structures: Applications in High Speed Analog Chemistry to Accelerate Kinase Drug Discovery”

Scott Mitchell, Ph.D., Principal Scientist, Cellular Genomics Inc.

This presentation explored a proprietary set of privileged structures, which have been functionalized in High Speed Analog Chemistry (HSAC) to create a highly active signal transduction inhibitor library. Scaffolds form the foundation of a tightly integrated platform for kinase drug discovery; which encompasses medicinal chemistry, high speed analog chemistry, computational chemistry, chemoinformatics and high throughput screening. Data demonstrating how this approach is accelerating internal drug discovery programs was presented, including examples of potent, drug-like kinase inhibitors in angiogenesis/oncology and autoimmune/inflammatory disease. 7:30

“The Molecular Libraries Roadmap: Complementing Industry by Empowering Academics”

John M. Schwab, Ph.D., Program Director, Division of Pharmacology, Physiology, and Biological Chemistry, National Institute of Health.

This talk was focused on major NIH research funding initiatives designed to promote the use of small molecules to interrogate biology. The Molecular Libraries initiative is a major component of the NIH Roadmap for Medical Research, with the goal of discovering unique small-molecule probes for biology. The Centers of Excellence in Chemical Methodologies and Library Development (CMLD centers) feature team-based approaches to the development of new methodologies related to chemical diversity.

“Practical Tactics Addressing Examples of Challenging Flash Chromatography Purification Situations”

Mikael Mahler, Ph.D., Senior Applications Scientist, Teledyne Isco, Chang-Hsing Liang Optimizer Pharmaceuticals, Inc.

High pKa compounds, polar compounds and natural products are classes of compounds known for their difficult purification step. Their convenient purification exploiting automated flash chromatography instruments and RediSep(TM) columns was described.

“Microfluidic Systems for High Throughput and Combinatorial Chemistry”

Andrew J. de Mello, Ph.D., Professor, Chemical Nanosciences, Imperial College of London, United Kingdom.

The development of synthetic chemistry utilizing microfluidic reactors was of increasing interest in recent years. Miniaturization of reaction systems offers several advantages over the macroscale. These include improved mixing efficiencies and increased thermal transfer, leading to improved

reaction selectivity, low sample consumption and higher sample throughput per unit volume. This presentation provided an overview of studies that demonstrate how careful control of experimental variables, high mass and thermal transfer rates and intelligent detection protocols can be used to perform rapid and high-efficiency molecular synthesis in continuous flow systems.

“Automated Medicinal Chemistry”

Andreas Steinmeyer, Ph.D., Head, Medicinal Chemistry III, Schering AG, Germany.

In order to meet the requirements of the modern drug discovery process an efficient platform for high throughput synthesis, analytics, purification and reformatting of high quality compound libraries was established by taking advantage of laboratory automation. This presentation demonstrated how these systems offer a high degree of flexibility and allow the generation of a wide variety of structural series for different target families.

“Recent Developments in Mass-Directed LC/MS and SFC/MS Purification for the Medicinal Chemistry Laboratory”

Daniel B. Kassel, Ph.D., Senior Director, Analytical and Discovery Technologies, Syrrx, Inc.

In this session, we heard about developed and incorporated high throughput technologies that span the continuum of drug discovery, from "gene-to-structure" and from "structure-to-drug." Extending across both of these areas, analytical chemistry and more specifically, liquid chromatography/mass spectrometry (LC/MS), has emerged as an important, key technology. In this presentation, some of the advances that have been made at Syrrx in the area of high throughput small molecule analysis was highlighted.

“Developing Extensive Solid-Phase CombiChem for Use in Distributed Drug Discovery”

William L. Scott, Ph.D., Research Professor, Chemistry, Indiana University Purdue University Indianapolis, Indiana.

There is strong precedent for important drugs arising from the peptidomimetic class of molecules. There is also an abundance of published solid-phase combinatorial chemistry to peptidomimetic libraries and related structures, utilizing resin bound amino acids as starting materials. This talk described the solid-phase chemistry process we have developed to synthesize a much larger "basis" set of resin bound amino acid-like starting materials, thereby greatly expanding the numbers and variety of drug lead molecules accessible through published chemistry. It also described our recent solid-phase work to lactam and other scaffold-based peptidomimetics. All this chemistry is a foundation for the potential libraries at the core of the distributed drug discovery approach.

“Very Large Chemical Spaces of Multicomponent Reactions”

Alexander Doemling, Ph.D., Vice President, Chemistry, Priaton GmbH, Germany.

Convergent multicomponent reactions (MCRs) span the largest chemical space in organic chemistry accessible in a one-pot manner. It is assumed that with the more than 600 MCRs described so far a chemical space comprising >1020 drug-like small molecule is opened up. A database of several hundred MCRs is now available to discover novel leads and hits by means of computationally screening and/or synthesis and biological screening. The concept of the MCR database and its exploitation in drug discovery is presented. Novel MCRs are introduced >1020 means ten to the power of TWENTY.

“Fluorous Synthesis for Solution-Phase Libraries”

Wei Zhang, Ph.D., Director, Discovery Chemistry, Fluorous Technologies, Inc.

Fluorous synthesis is a "beadless" high throughput technology that employs perfluoroalkyl chains instead of resins to facilitate the separation process. Traditional solution-phase reaction conditions and phase-tag separations are successfully integrated into fluorous synthesis. This presentation describes the recent efforts on the development of fluorous compounds including reagents, scavengers, protecting groups, and their applications in the synthesis of drug-like library scaffolds. The combination of fluorous synthesis with microwave technology and multi-component reactions was also highlighted.

“Enabling Technologies for Lead Discovery”

Bruce Clapham, Ph.D., Assistant Professor, The Scripps Research Institute.

This presentation covered 3 research topics from the group that can be used in High Throughput Chemistry applications. These included: 1) The preparation of ring-opening metathesis polymerization-solid phase resins for synthetic chemistry, 2) The application of diazocarbonyls for the creation of diverse heterocycle "lead-like" scaffolds, and 3). Lewis acid promoted C-N bond forming reactions to introduce pharmacophore functional groups into target molecules.

“High Throughput Genomic Methods for Discovery and Optimization of Novel Biological Products”

Mark J. Burk, Ph.D., Senior Vice President, BioScience Products R&D, Diversa Corporation.

Natural organisms produce a vast array of complex chemical entities via numerous enzyme-mediated reactions. A broad range of high throughput biological technologies that facilitate discovery and optimization of either individual enzymes or multi-enzyme pathways was developed. This presentation highlighted the benefits of combining discovery from natural diversity with powerful directed evolution techniques to develop a variety of novel biological products that display differentiated properties. During this presentation, several examples were discussed.

“Capillary-Based Instrument for Screening Metal-Based Catalysts for Slow Organic Reactions”

Stephen Weber, Ph.D., Professor, Chemistry, University of Pittsburgh .

Soluble metal-ligand complexes are useful as catalysts for many organic reactions. The large number of metals and ligands available suggests a combinatorial approach to catalyst discovery. Carrying out reactions in very small (microliter) volumes in capillaries has many advantages in this regard, including material conservation, isolation from the atmosphere, and ease of transport of species by using pressure induced flow. A capillary reactor was developed in which separate zones of catalyst and reactants are combined and react, and products are detected. Zones are loaded into the capillary reactor from an autosampler, they react in parallel in the capillary reactor (at elevated temperature), and are ejected serially and under computer control for analysis by online GC.

“Drug Discovery Based on the Technique of Molecular Imprinting”

Klaus Mosbach, Ph.D., Director, The Center of Molecular Imprinting, Lund University, Sweden.

The technique of molecular imprinting allows for the preparation of highly stable synthetic polymers with specific binding acting as artificial enzymes or receptors for target molecule. The principal of the technique was described first followed by exemplifying the technique for drug discovery (apart from other aspects e.g. as tailor-made purification material) developed in our laboratory.

“Dynamic Medicinal Chemistry in High Throughput Synthesis”

John Cashman, Ph.D., Director and Founder, Human Bio-Molecular Research Institute .

Utilization of drug-like materials in high throughput (HT) synthesis of pharmacologically active compounds is facilitated by judicious choice of template structure. Information-rich starting materials such as natural products have useful properties as starting points for HT synthesis. This talk showed the further use of drug metabolism and bioavailability concepts early on in the design phase of library construction for generation of pharmacologically active compounds. The following classes of compounds represent successful application of this concept including medications development to treat: pain, depression, smoking and drug addiction, attention deficit disorder, and Alzheimer's Disease.

“New Polymer Supports and Reagents for Organic Synthesis”

Yoon-Sik Lee, Ph.D., Professor, Chemical Engineering, Seoul National University, Korea.

Specially designed PS based resins; ionic group containing or core-shell type resins were developed and applied for various organic syntheses such as oxidations, difficult substitution reactions, transition metal catalyzed C-C bond formations, and peptide coupling reactions. If the shell structure is modified properly, they can be used as an ideal polymer support for chemical proteomics study.

“Discovery of Potent MCH1R Antagonists through ECLiPS and Parallel Synthesis”

Suresh Babu, Ph.D., Senior Research Scientist, Chemistry, Pharmacepia Drug Discovery, Inc.

ECLiPS (Encoded Combinatorial Libraries on Polymeric Support) is an efficient combinatorial technology utilized to synthesize chemical libraries for drug discovery in identifying lead compounds. The ECLiPS libraries are carefully designed to have drug-like properties and the optimization of the lead compounds from the libraries is very straightforward. This presentation described the discovery of potent MCH1R (Melanin Concentrating Hormone1 Receptor) antagonists through ECLiPS and parallel synthesis.

Obesity has reached epidemic proportions in the industrialized world. A recent CDC survey estimated that 64% of US adults are either overweight or obese, and that the US annual medical cost, directly attributed to obesity have reached \$75 billion.

MCH1R is widely recognized in the pharmaceutical industry as an important anti-obesity target. Small molecule MCH1R antagonists (Figure 2) have shown in vivo efficacy in several animal models of body weight regulation and feeding behavior.

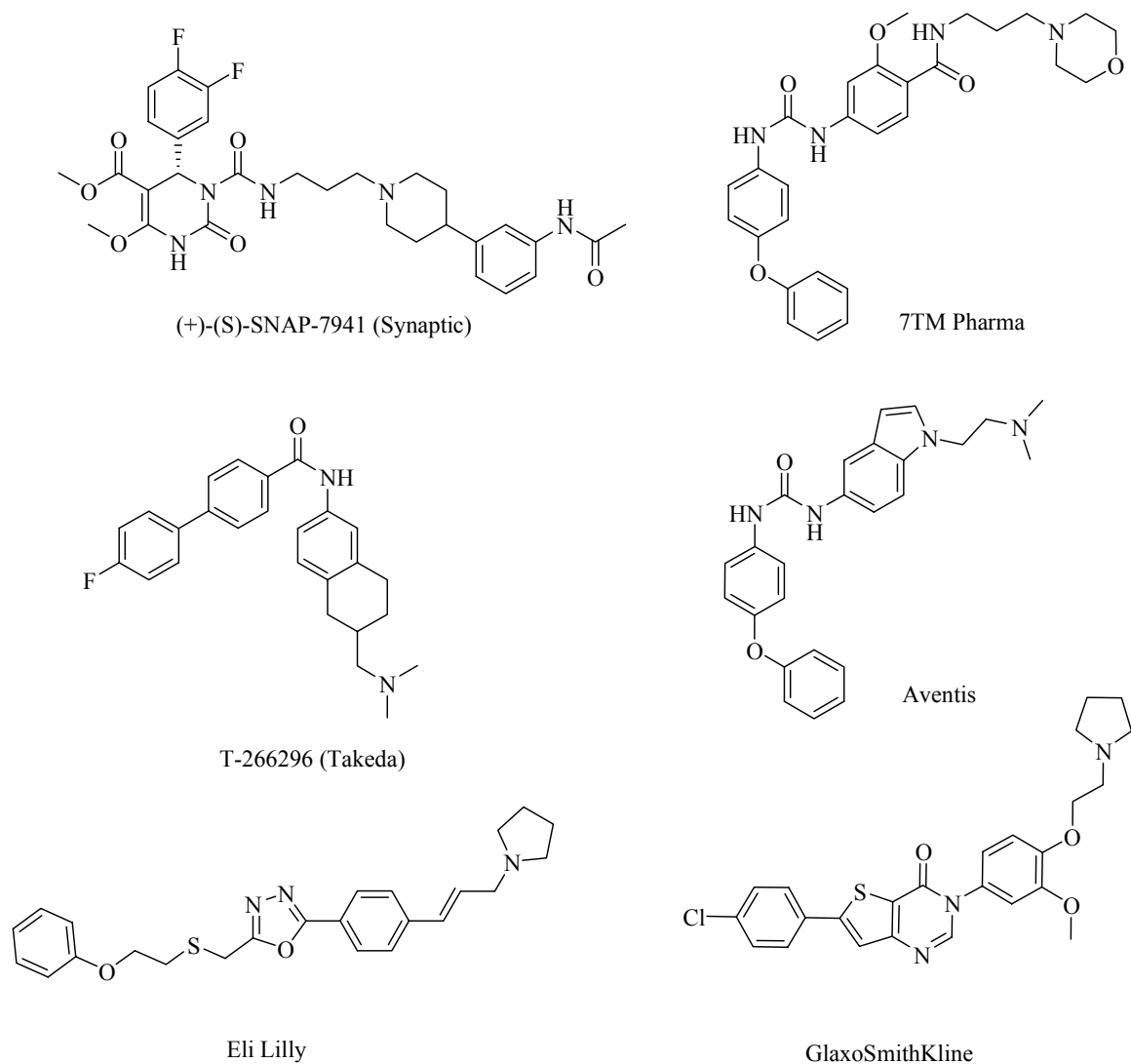
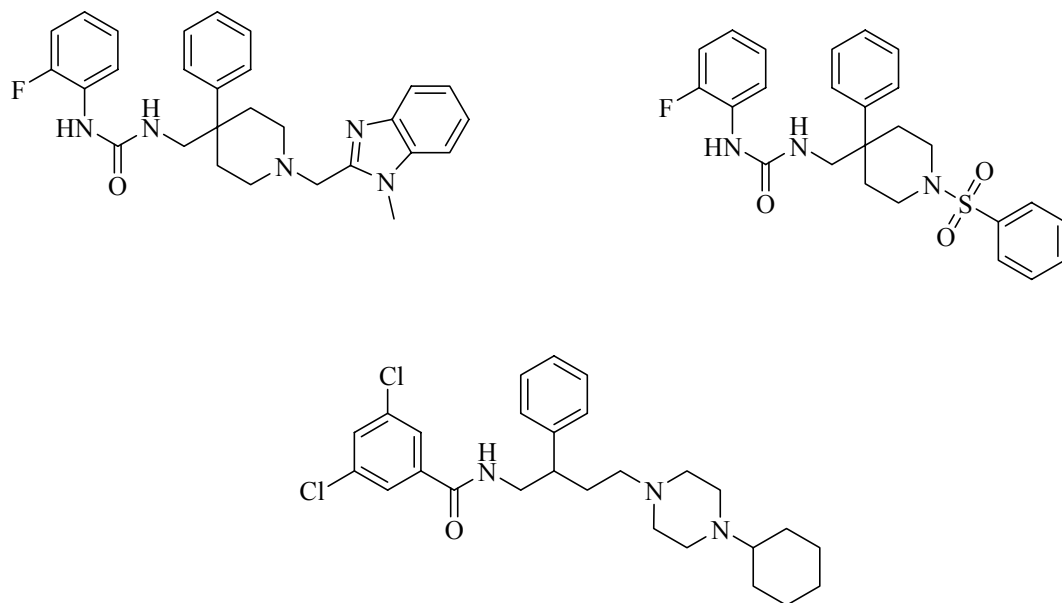
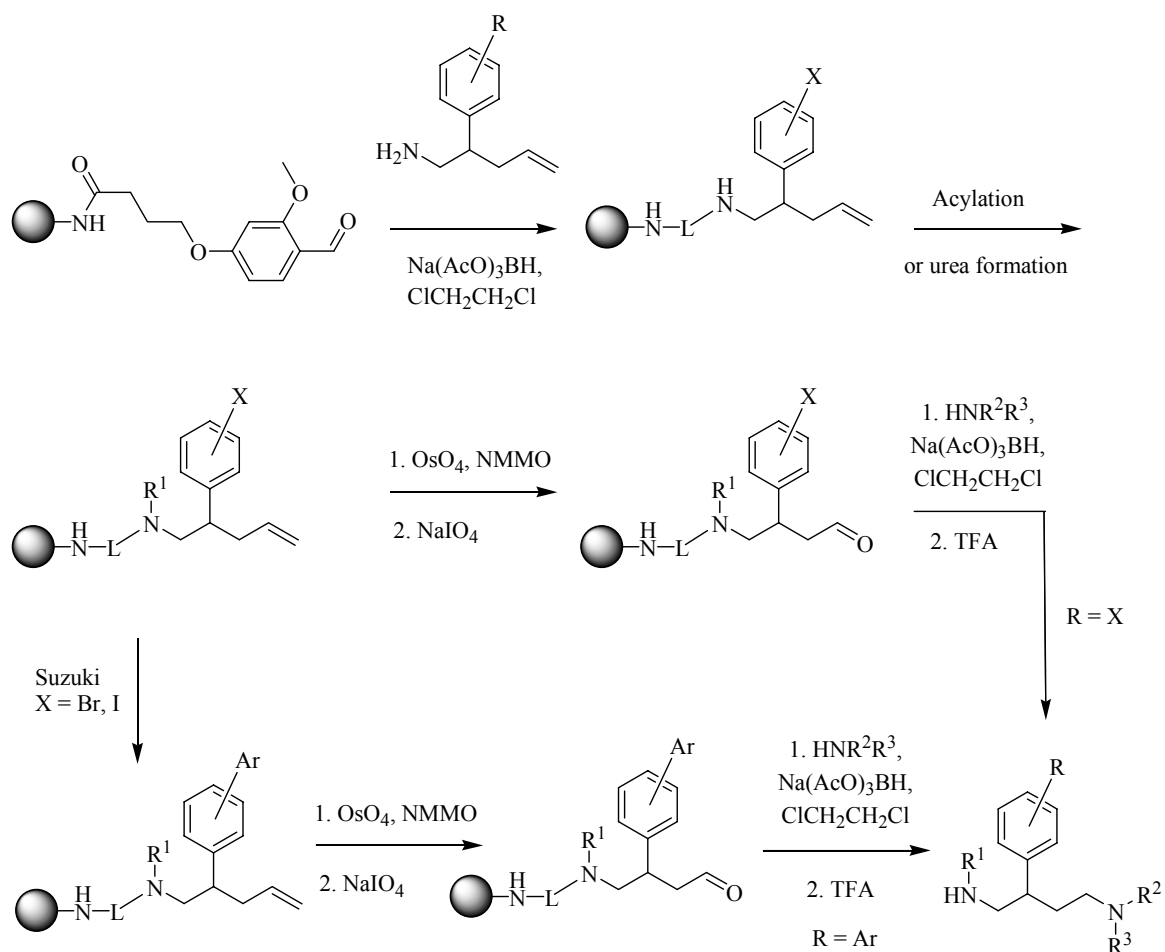


Figure 2

Work on lead optimization was started from three hit compounds (Figure 3): two piperidine derivatives and one derivative of diaminobutane.

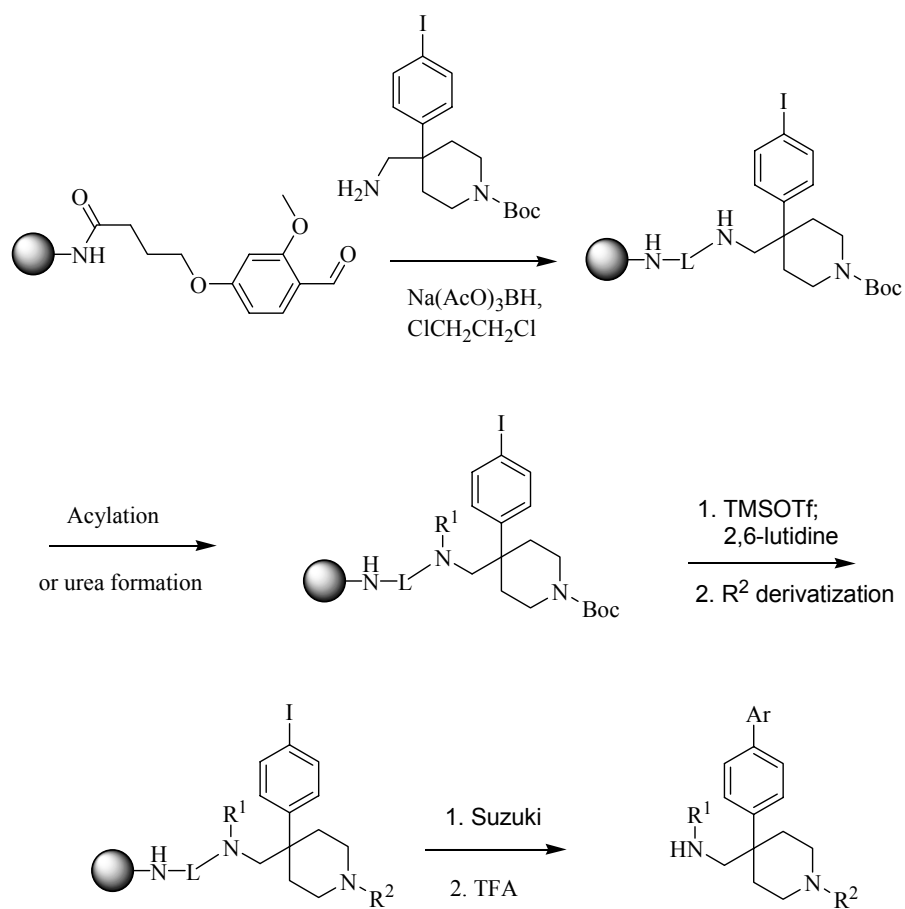
**Figure 3**

Parallel synthesis of diaminobutane derivatives was performed according to Scheme 4:



Scheme 4

Selected SAR data for diaminobutane series were presented.
 Synthesis of second lead optimization library was performed according to Scheme 5:

**Scheme 5**

Structure of optimized compounds and SAR summary for these two classes of compounds is presented in Figure 4.

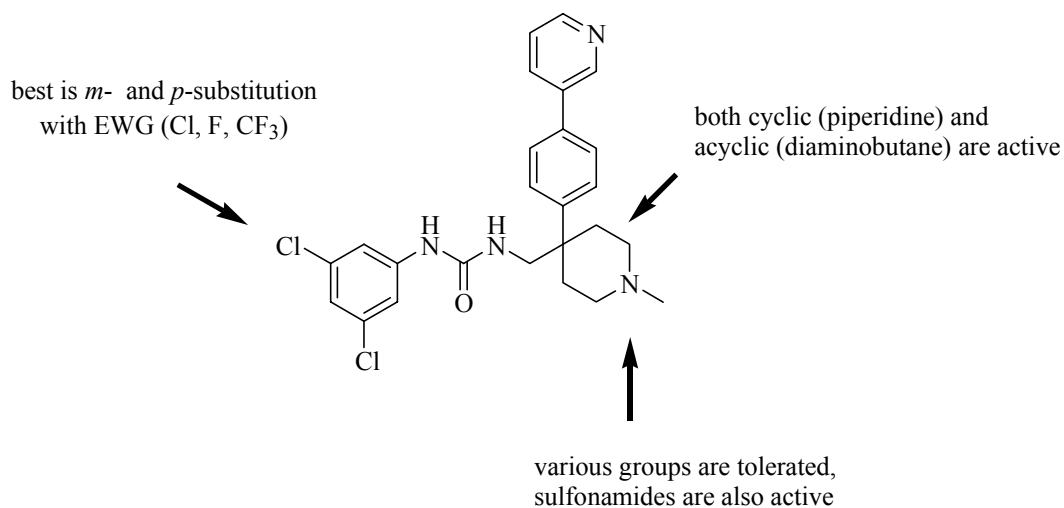


Figure 4

“Natural Product-like Skeletally Diverse Polycyclic Compounds”

Reni Joseph, Ph.D., Principal Research Scientist, MDS Inc.

This talk featured work on diversity-oriented synthesis in developing high throughput approaches to obtain natural product-like complex polycyclic compounds having stereochemically and 3-dimensional skeletally diverse architectures. Specific examples included the recent development of stereocontrolled solid phase synthesis methods and their utilization in library generation of indoline and tetrahydroquinoline-based alkaloid-like skeletally diverse polycyclic derivatives.

Enhancing Lead Generation and Optimization via High Throughput Synthesis Methods”

John M. Nuss, Ph.D., Vice President, Chemistry, Exelixis Inc.

As the scope and generality of high throughput synthesis and its attendant technologies advances, these methodologies have become an increasingly powerful tool for medicinal chemistry and more rapid lead discovery and optimization. This talk dealt with the development of a combinatorial chemistry program and its integration into a discovery program. Methods and technologies developed for the synthesis and characterization of large (> 3MM compound), diverse and dense compound libraries were discussed.