PS-1  **Chemical Biology of Non-replicating *Mycobacterium tuberculosis***

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Chemical biology has a major role to play in helping society recover from its failure to maintain a sufficient pipeline of agents to treat infectious diseases that are long neglected, newly emergent, or evolving to drug-resistant states. How we develop anti-infectives is shaped by our view of infectious disease. In the 19th century, human infectious disease was seen as microbes growing in a human test tube. We now know that microbial adaptation to the host environment can make different genes essential in vivo than are required for growth in vitro. For example, hypoxic, oxidative, nitrosative, acidic, carbohydrate-poor micro-environments encountered by *Mycobacterium tuberculosis* (Mtb) in vivo are strikingly different from standard culture conditions in which anti-Mtb agents are traditionally screened. Such conditions in the host force Mtb subpopulations into non-replicative persistence accompanied by phenotypic tolerance (that is, non-genetic resistance to conventional antimicrobials).

Therefore, this lab has used synthetic compounds, natural products and known drugs in high-throughput screens against isolated Mtb enzymes or whole mycobacteria with a focus on the following targets. Each is non-essential in standard culture but is essential for Mtb in an infected host: the E2 and E3 components of pyruvate dehydrogenase, which double as components of peroxynitrite reductase; the pathways that control intra-mycobacterial pH homeostasis, including a serine protease encoded by Rv3671c; the nucleotide excision repair pathway; and the proteasome.

This talk will focus on a novel class of proteasome inhibitors that are the first to display marked selectivity for the proteasomes of a pathogen over that of its host. The compounds act as suicide substrate inhibitors for the Mtb proteasome but as simple substrates for the human proteasome. The distinction may be attributable to non-conserved residues outside the active site that control the movement of a loop when the inhibitor binds. If pathogen-selective proteasome inhibitors can be used to treat infectious disease, they would add inhibition of protein degradation to the short list of processes targeted by current antimicrobial agents, almost all of which inhibit synthesis.

The work on proteasome inhibitors was a collaboration between Gang Lin in this laboratory with Dongyang Li and Huilin Li at Brookhaven National Labs, Haiteng Deng at Rockefeller University and L. P. Sorio de Carvalho, J. D. Warren, H. Tao and others at Weill Cornell.

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PS-2  **Substrate Activity Screening: A New Fragment-Based Method for Inhibitor Discovery**

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Substrate Activity Screening (SAS) is a fragment-based method for the rapid development of novel, drug-like enzyme inhibitors. The method consists of three
steps: (1) a diverse library of low molecular weight substrates is screened against an enzyme target to identify lead fragments, (2) the identified fragments are rapidly optimized by subsequent rounds of analogue synthesis and evaluation, and (3) the optimized substrates are converted to inhibitors by direct incorporation of mechanism-based inhibitor pharmacophores. Because the assay requires productive substrate binding and turnover, false positives often seen in traditional high-throughput inhibitor screens are eliminated. Additionally, catalytic substrate turnover results in signal amplification enabling the identification of very weakly active lead fragments. The successful application of the SAS approach to the rapid identification of novel, potent and selective small molecule inhibitors to therapeutically relevant proteases and phosphatases will be presented.

References:

PS-3 Allosteric inhibitors and activators of caspases

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Caspases are a class of intracellular cysteine proteases specific for aspartate substrates that effect fate determining decisions including innate inflammatory response and cell death, among others. As such there has been considerable interest both in academic and pharmaceutical sectors to develop tools to control caspase activity. Unfortunately, the strong dependence for a P1 aspartate acid has made it challenging to find specific small molecule inhibitors. We and others have shown the caspases are highly dynamic proteases that exist in on- and off-states. We have exploited this dynamics to discover specific small molecule allosteric inhibitors and activators. These studies have been complemented by antibodies and engineered enzyme constructs that can mimic these effects both in vitro and in cells. This presentation
will present these studies and their implications in understanding apoptosis and innate inflammation.

**IL-01 Methods of structure assessment in “OBSC” Split/Mix libraries**

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One of the most limiting factors in the application of the powerful techniques of Split/Mix libraries of the “One Bead One Compound” or the “One Bead Some Compounds” (OBSC) type is that of accessing the structures of the active hits. Structure elucidations by MS-MS techniques are only successful in some types of libraries limited to simple molecules and small peptide structures. Often molecules are not readily ionized or fragmented in the MS-MS instrument or they appear as triple or quadruple charged species for which the fragment spectra are essentially impossible to deconvolute using conventional techniques.

We have developed a range of dedicated methods and software that gives the opportunity for almost complete success in the entire range of molecules one could wish to subject to split mix libraries. These include direct “from bead” injection combined with predictive deconvolution software for the entire library and fitting procedures to identify the optimal match between spectra and prediction. This method was used for the complete deconvolution of cell-adhesion hits from a 55,000 compound library. The fitting procedure ensures extremely accurate structure determination.

We also developed the Point Matrix Encoding of beaded resins for complete decoding of more focused libraries of 5,000 - 30,000 compounds. The implementation involved production of macro-beads containing polymer embedded immobilized fluorescent microspheres, construction of an equipment for recording of 3-D structure of the microsphere matrix at a rate of at least 3 beads / s and Split/Mix synthesis of compound libraries with recording of the codes for all beads in each synthesis step as well as for biologically active hits. The technique is very reliable and is constantly improved. Examples of affinity ligands and sulfated peptides as heparin mimetics will be presented.

**IL-02 Dynamic Ligation Screening, a powerful method for the fragment-based development of protein ligands**

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Fragment-based methods in drug discovery have become popular during recent years as they can provide protein ligands with significantly increased ligand efficiency. [1] Classical methods of fragment-based drug discovery such as NMR and X-ray crystallography face two major challenges: The detection of low-affinity fragments binding to specific protein sites can be problematic and the optimal linkages of two hit fragments are difficult to find.
Dynamic Ligation Screening (DLS) provides a powerful solution to both challenges and has been demonstrated successfully for the discovery and development of small molecule fragments binding to defined protein sites. [2, 3] DLS enables the rapid and site-directed identification of low-affinity binders by exploiting template-assisted fragment assembly. In DLS the effects of single fragments on a ligation reaction are recorded via a biochemical assay employing one fragment per microtiter plate well. So far, Dynamic Ligation Screening was conducted with libraries of 200-6000 fragments consuming only minor catalytic amounts of enzyme. Enzymatic assays as well as protein binding assays can be adapted to the DLS method and peptide electrophiles of bis-electrophiles have been employed as active-site-specific probes. [2, 3] In protease assays decreased initial rates of product formation from a fluorogenic enzyme substrate indicated the inhibitory activity of the reversibly formed ligation product. Selected hits were modified synthetically in order to verify the binding site. Via an iterative scanning of different binding sites on the protein surface, moderately active peptidic inhibitors could be transformed into potent, entirely non-peptidic inhibitors. Thermodynamics of protein-assisted fragment ligations were studied for caspase-3, the cellular switch for apoptosis. Experimental results were fitted to a model simulating the additivity or cooperativity of binding contributions of reversibly ligated fragments. The free energy and equilibrium of the ligation reaction were derived thereof. The method has been further extended to other protein targets such as phosphatases [4] and to protein-protein interactions. Beyond reversible reactions, irreversible ligation reactions have been developed and are discussed with respect to DLS. [6]

References:

IL-03 Colorful Chemical Genetics using DOFLA (Diversity Oriented Fluorescence Library Approach)

Young-Tae Chang

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With the successful result of Human Genome Project, we are facing the problem of handling numerous target genes whose functions remain to be studied. In chemical genetics, instead of using gene knock-out or overexpression as in conventional genetics, a small molecule library is used to disclose a novel phenotype, eventually for the study of gene function. While a successful chemical genetics work will identify a novel gene product (target protein) and its on/off switch, the small molecule complement, and thus chemical genetics promises an efficient “two birds with one stone” approach, the most serious bottleneck of modern chemical genetics is the step of target identification. The currently popular affinity matrix technique is
challenging because the transformation of the lead compound into an efficient affinity molecule without losing the biological activity is not easy, requiring intensive SAR studies. To surrogate the well known problem, our group has developed a linker tagged library and has successfully identified multiple target proteins so far. While successful, the affinity matrix technique requires a breakdown of the biological system to pool the proteins into one extract, which inherently introduce a lot of artifacts, such as dilution and abolishing the biological environment, etc. As the next generation of tagged library, we are currently developing fluorescence tagged libraries for in situ target identification and a visualization of the biological events using Diversity Oriented Fluorescence Library Approach (DOFLA). The basic hypothesis is DOFLA of the same fluorescence scaffold, but with various diversity elements directly attached around the core, may selectively respond to a broader range of target proteins in intact biological system and facilitate the mechanism elucidation and target identification. The high throughput strategy using colorful chemical genetics will open the efficient road to chemical genomics and in vivo bioimaging probe development.

References:

IL-04 From Combinatorial Chemistry to Nanoparticles to Cancer Targeting

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Using one-bead-one-compound (OBOC) combinatorial library methods, we have developed several peptidic and peptidomimetic ligands against specific cell surface receptors of a number of different cancer cell types. These ligands include LLP2A, LXY3 and LXW7 that target the α4β1, α3β1, and αvβ3 integrins, respectively. These ligands can be used as efficient targeting agents to deliver therapeutic radionuclides, drugs or toxins to the tumor site. We have recently developed a number of amphiphilic polymers, comprised of a cluster of cholic acids (4 to 10) linked by a series of lysines and attached to one end of a linear polyethylene glycol chain (PEG, 2000-5000 Dalton). Under aqueous condition, such telodendrimers can self-assemble to form highly stable micelles. The sizes of these micelles (20-150nm) are tunable. This nanoplatform is multifunctional and highly versatile. We can readily load hydrophobic drugs, radionuclides, and fluorochromes, as well as quantum dots, and iron nanoparticles into the hydrophobic core of these micelles. We can also conjugate cancer-targeting ligands to the distal end of the telodendrimer such that these ligands will be displayed on the surface of the drug-loaded nanoparticles. In vivo near infra-red optical imaging studies with hydrophobic fluorescent dye demonstrated that xenograft uptake of the nanoparticles was greatly enhanced by the cancer targeting peptide. Confocal microscopy revealed that the targeted nanoparticles, unlike the naked nanoparticles, were distributed throughout the entire tumor mass and not just in the perivascular space. In addition to paclitaxel, we have also successfully loaded SN-38 and etoposide into these nanocarriers. This novel nanoplatform, in conjunction with cancer targeting ligands, shows great promise in
future cancer therapy and imaging. In addition, it could also be exploited as a highly efficient intracellular delivery tool for basic research.

**IL-05 Synthesis of natural products and their derivatives based on combinatorial chemistry and laboautomation**

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Biologically active natural products have served as effective biochemical probes for discovery of not only new drug targets but also new biomarkers. The synthesis of small molecules based upon the structure of biologically active natural products would be an effective and promising way for identification of new biochemical probes. We have recently focused on new synthetic technologies such as combinatorial chemistry and laboautomation technology, which allow one to improve efficiency of the chemical synthesis of natural products and their derivatives. Herein we present the synthesis of natural products and their derivatives based on combiantorial chemistry and laboautomation.

References:
IL-06  Natural Products as Leads for Combinatorial Drug Discovery

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Natural products account for a significant proportion of small molecule drugs on the market. However, nature has evolutionarily selected them for biological activity rather than use as a human therapeutic. This suggests that their druglike properties can be further improved by generating and evaluating libraries of natural product analogues. In the talk, I will give examples from our work with an emphasis on natural products that inhibit enzymes involved in the epigenetic post-translational modification of histones.

References:

IL-07  Sequester Copper to Generate Multifunctional Agents for Protecting Neurons from Amyloid-β Peptide Toxicity

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A toxic 39-43 residues polypeptide, amyloid-β (Aβ) peptide exerts the toxic effects on neurons by its abnormal accumulation and interaction with excessive metals in
brain. The decelerated degradation of Aβ evokes an imbalance between Aβ production and degradation, which may be the prime reason for Alzheimer’s disease (AD) [1]. By binding and reducing redox metal ions such as copper (Cu (Ⅱ)), Aβ can generates free radicals which are toxic to neurons [2-4]. So Aβ aggregation blockers [5], copper chelators [6] or Aβ degradation substances may have benefits for AD therapy. We synthesized compounds that contain both an Aβ-recognizing moiety and a cleaving domain following ‘Recognizing-Cleaving’ strategy. Here we show the small multifunctional compounds that can sequester copper from the Aβ-copper complex, then the resulted complexes can be lytically activated and interfere with the Aβ aggregation process as well as degrade Aβ into fragments. Our results also suggest that either monomeric and oligomeric Aβ or both are cleaved. The combined effects of compounds are sufficient to protect neurons from toxicity induced by Aβ. This ‘Recognition-Cleaving’ approach yields a potent and selective strategy for the clearance of Aβ and can be applied to other protein aggregates which are induced or decorated by copper.

References:

**IL-08 Application of Diversity Oriented Synthesis (DOS) to Identification of Biologically Active Molecules**

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Diversity-oriented synthesis (DOS) can be used to synthesize diversified molecules on a large scale. As with all large-scale experiments, this process requires a major investment in equipment, consumables and time. Therefore, careful careful design is critical. As the complexity of the libraries to be generated increases, additional considerations become important. What are the issues that should be considered when planning DOS project? Which features in the design strategy are critical to consider ensuring that all of the potential products will be synthesized? How are the reaction selected to optimize product synthesis and yield? Over the last several years, through an experimental process, we have successfully developed an optimized our synthetic strategy. Our approach incorporates multi-component reactions into a tightly controlled process that generates molecules with maximal structural complexity.

In this presentation, we would like to our DOS approach to generate structural diverse of drug-like molecules, and in conjunction with zebrafish based phenotypic screening, we have identified a number of scaffolds with superb biological activity for several biological important targets.
IL–09  Focused Library Protocol in Preparation of Bioactive Small-Molecule Probes and Their Applications in Cell Imaging Study

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Development of bioactive natural products into the molecular probes is a helpful method in current chemical biology studies. In order to introduce the report groups to the targeted small molecules, identification of a proper position is usually the most challenging task. In our recent works, the focused library strategy by parallel synthesis has been found a convenient protocol in these efforts. In this presentation, we wish to report our recent progress in making the suitable biological probes by assistance of parallel synthesis, as well as their applications in the cell imaging and bioactivity mechanism studies.

Figure 1. Representative bioactive small molecule derivatives used as the fluorescent probes in cell imaging studies.
IL-10 Supported reagents and catalysts on polymer beads: How fast & clean they can afford in organic reactions?

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Nowadays, developing Green process in chemical industry has drawn much attention from scientists. Heavy metals should be avoided or recovered completely from the API intermediate. VOCs should be minimized in developing a new chemical process. Recently, we reported several new polymer supported IBX reagents which showed excellent oxidative properties1. They were readily prepared in two steps; coupling of 2-iodobenzoic acid moiety to polystyrene (PS) resins, followed by subsequent oxidation. We proved that the polymer supported IBX reagents were mild and efficient oxidants in conversion of alcohols to the corresponding aldehydes or ketones. Especially, macroporous PS-supported IBX amide (PMS-IBX) resin can oxidize effectively a variety of alcohols even in polar solvents. In addition, we have found that a gel type of polymer supported IBX reagent is a mild and operationally simple brominating agent for aromatic compounds 2.

Polymer supported N-heterocyclic carbene (NHC) palladium catalysts3 for C-C bond formation was also reported. These polymer supported NHC-palladium catalysts exhibited excellent catalytic activity for Heck, Suzuki and Sonogashira cross-coupling reactions under mild conditions. In particular, the polymer-supported PEG-NHC-Pd catalysts were effective in C-C coupling even in aqueous system. In addition, all catalysts were recovered quantitatively from the reaction mixture by simple filtration, and were able to be reused for a number of cycles with consistent activity. Silica-supported NHC-Pd catalyst4 also exhibited excellent performance in Suzuki reaction under mild condition (rt and short reaction time).

References

Acknowledgments: This work has been supported by BK 21 & WCU program.
IL-11  Synthesis of new probes for chemical glycobiology: application to PET and fluorescent imaging of glycoproteins, glycoclusters, and living cells

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It has been becoming clear that cell-surface glycans are involved in a variety of important physiological events, such as cell-cell recognition, adhesion, signal transduction, quality control, and circulatory residence of proteins. However, their physiological roles in whole body systems have not been well understood. Positron emission tomography (PET), which can visualize the locations of radiotracers with high sensitivity, should be a powerful tool in order to examine the in vivo dynamics of glycans such as glycoproteins and glycoclusters. We therefore developed a new DOTA-labeling probe 1 [1,2]. The high reactivity of 1 enabled the labeling of lysine residues in peptides and proteins at low concentration (~10^-8 M) within a short reaction time (10~30 min) to result in selective labeling of the more accessible lysine residues. MicroPET of the glycoproteins, [68Ga]DOTA-orosomucoid and asialoorosomucoid, labeled by the present method, successfully visualized the differences in the circulatory residence of glycoproteins in rabbit, in the presence or absence of the sialic acids [1].

We then developed an efficient method for the preparation of large glycoclusters based on our new method for click reaction. PET and fluorescence imaging of the synthetic glycoclusters as well as living cells will also be discussed in the conference.

References:

IL-12  Diversity Oriented Synthesis of Novel Pyrimidine Fused Heterocyclces

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Pyrimidine fused heterocycles exhibit multiple biological activities and may be considered privileged structures in medicinal chemistry. We have designed and synthesized a variety of novel scaffolds containing pyrimidine as the core structure. This presentation will focus on our design strategy and the methodological development.

**IL-13 High-throughput Synthesis of Small Molecules Mimicking Proteins: Glial-cell Derived Neurotrophic Factor and Insulin**

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The ADME properties of proteins present a significant hurdle to their use as therapeutic agents, but the unique activity of specific proteins like insulin has prompted the development of appropriate protocols and processes. Yet, they still offer many challenges compared to small molecules. Recombinant DNA methods typically used to obtain bioactive proteins also makes them expensive to manufacture and limits their broader use in science and technology.

Work in our laboratory over the past decade has focused on small molecules that can mimic the action of proteins. The natural product demethylasterriquinone B1 is an insulin mimic with oral activity in mouse diabetes models, and the synthetic compound CUR-162590 is a partial mimic of glial-cell derived neurotrophic factor (GDNF) in promoting the survival of cultured rat dopaminergic neurons.[1] The generation of modest libraries based on these two lead structures has exploited well-known methods such as supported reagents. The in-cell evaluation of the biological properties of the resulting libraries, intrinsically low-throughput methods, have still enabled promising new agents to be identified. These include molecules with oral glucose lowering activity[2] and molecules with the ability to promote the differentiation of human embryonic stem cells to dopaminergic neurons. Key features of the active molecules discovered could not have been inferred from past structure-activity relationships, endorsing the empirical approach to active agent discovery that is intrinsic to combinatorial science.

References:

Acknowledgments: Financial support by the California Institute for Regenerative Medicine (RS1-00289-1) is appreciated.
Diversity-orientated synthesis of clausena alkaloids and their analogs from intramolecular cyclizations of oxirane-containing enamides

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Rutaceae Clausena lansium (Lour.) Skeels is a fruit tree widely distributed in southern China. In folk medicine, its leaves and fruits are used to treat asthma, influenza, gastrointestinal disorders, viral hepatitis and dermatological diseases.1 Due to the pioneering work of Huang and her co-workers1 in the mid to later 1980s, a number of clausena alkaloids including clausenamide 1, neoclausenamide 2 (a diastereoisomer of clausenamide 1), homoclausenamide 3, ζ-clausenamide 4 and cycloclausenamide 5 (Scheme 1) were isolated from the hot-water extract of the leaves. Later, lansimide-3 6, a hydrated form of homoclausenamide was reported.2 In 1996, Milner and coworkers3 isolated the optically active (+)-N-methyl-N-[(Z)-styryl]-3-phenyloxirane-2-carboxamide, SB-204900 (+)-7 (Scheme 1), from a hexane extract of Clausena lansium leaves.

Despite the important pharmacological activity and interesting molecular structures, the synthesis and the biosynthetic pathways of clausena alkaloids have remained largely unexplored. In this talk, I will present our study of diversity-orientated synthesis of Clausena alkaloids and their analogs from intramolecular cyclizations of oxirane-containing enamides.4-6

References:

Acknowledgments: We thank National Natural Science Foundation of China for financial support.
Generation of the Various Drug-like 5-Membered Heterocyclic Libraries using CS2 with Merrifield Resin based on Combinatorial Chemistry

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Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs. This is especially true for five-member ring heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities. In this respect, the potential of the pyrazole, triazole, isoxazole, and thiazole scaffolds to serve as a privileged structure for the generation of drug-like libraries in drug-discovery programs has been amply demonstrated. The recent success of a pyrazole COX-II (cyclooxygenase) inhibitor, thiadiazole GPCR and various protein kinase inhibitors have further highlighted the importance of these heterocycles in medicinal chemistry. In our research program for the generation of novel drug-like hit compounds to discover anti-inflammatory and anti-cancer agents based on combinatorial chemistry, we needed to develop a synthetic strategy and chemistry applicable in a combinatorial approach for the preparation of various drug-like 5-membered derivatives. On this SCS09, I will talk about my recent research results which are solid and solution-phase synthesis of the various 5-membered ring construction methodologies as well as their biological activities for new drug discovery.

**IL-16  A Diversity-Oriented Approach to Sultam Libraries**

**Paul R. Hanson**

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Diversity-oriented-synthesis (DOS) has emerged as a powerful strategy in the generation of structurally complex and skeletally diverse heterocyclic small molecules. Collections of such small molecules can possess a wide range of both physical and biological properties and as such are ideal for probing chemical space to identify novel lead compounds. In this regard, sulfonamides and their analogs are known to possess broad-spectrum bioactivity. Sultams, the cyclic analogs of sulfonamides, represent an intriguing subclass of relatively unexplored “molecular real estate” due to their wide biological profile. This potency, when coupled with their unique chemical properties, elevates sultams as promising candidates for drug discovery. Herein are reported efforts towards the generation of diverse libraries of sultams utilizing a variety of strategies including functional group pairing utilizing sulfonamide linchpins, one-pot multi-component protocols, metathesis cascade reactions and utilization of ROMP strategies. The libraries synthesized comprise individual sub-libraries in sufficient quantities (10-20 mg) and high purity (>90%) for HTS on numerous screening platforms within the NIH-MLSCN and other biological collaborators.

**References:**


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**IL-17  MCRs: Bench to Bedside with ‘Iterative Efficiency’**

**Christopher Hulme**, Shashi Chappeta, Srikanth Reddy and Justin Dietrich
This presentation will discuss new and old approaches to enhance the rate of molecular probe discovery and close the growing knowledge gap between chemical and biological space, created by recent advances in systems biology. As such, multi-component reactions are advocated as tools to build proprietary compound collections, founded on the central tenets of efficiency in medicinal chemistry: i) the potential for increased ‘iterative speed’ around the ‘hypothesis–synthesis–screening’ loop and ii) reduced numbers of required iterations for expedited value chain progression. Combination of these two tenets defines the concept of ‘Iterative Efficiency’. Front loading collections in this respect, has afforded several successful 'bench to bedside' studies with no required intermediate ‘scaffold hopping’. Such examples may be viewed as the original ‘holy grail’ of combinatorial chemistry, now enabled by the exponentially increasing MCR-derived ‘chemical diversity space’ made accessible in recent years.

Iterative Efficiency = f (Iterative Speed, accessible chemical diversity)

References:

Acknowledgements: The Abbott Laboratories Scaffold Oriented Synthesis Group is thanked for a New Faculty Award to CH.

IL-18 Combinatorial biosynthesis of novel antibiotics of nocathiacin I

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1
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Natural products, especially the large families synthesized by polyketides (PKS), non-ribosomal peptide synthetases (NRPS) and the hybridization of PKS/NRPS, have been valuable sources for bioactive compounds due to their structural diversity and a wide range of biological activities. Although the structures of these compounds are typically diverse and complex, they have similar mechanism of generation in
biological systems, in which the compounds are produced by dedicated biosynthetic pathways consisting of a series of enzymes with exquisite catalytic activities. Combinatorial biosynthesis provides a feasible opportunity for producing novel “unnatural” natural products.

Nocathiacin I is a cyclic pyridine-polythiazolyl peptide with excellent in vitro activity against multiple resistant strains of Gram-positive bacteria, such as *Staphylococcus aureus* (MASA), multi-drug resistant *Enterococcus faecium* (MREF), vancomycin-resistant *Enterococci* (VRE) and fully penicillin-resistant *Streptococcus pneumoniae* (PRSP), with MICs at the level of ng/ml, but the low aqueous solubility has limited its therapeutic utility. According to the proposed biosynthetic pathway of nocathiacin I, we have genetically manipulated the NRPS in order to obtain novel derivatives with higher aqueous solubility and intrinsic activity. The biosynthesis of the dehydroalanine side chain has been our main target for initial modifications. Swapping and deletion of modular from the particular pathway and replacement and modification of the tailoring enzymes, such as methyltransferases, oxidase and glycosyltransferase, have resulted in generation of structurally new derivatives of nocathiacin I, which exhibited higher aqueous solubility and activity.

Based on in-depth understanding of various biosynthetic pathways for potent natural products, combinatorial biosynthesis is being proven as a unique and promising strategy on generating novel bioactive compounds by genetic manipulations, which may expedite the process of drug discovery.

![Nocathiacin I](image_url)

**IL-19** Solid-phase total synthesis of apratoxin A and its derivatives and their biological evaluation

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Apratoxin A (1), isolated from the marine cyanobacterium *Lyngbya majuscula*, a 25-membered cyclic depsipeptide and exhibits potent cytotoxic activity.[1] Three methylated amino acid (N-Me-Ile, N-Me-Ala, O-Me-Tyr) residues joined a proline ester and a thiazoline moiety to an aliphatic moiety containing four asymmetric
centers. The aliphatic moiety 2 was prepared by proline-catalyzed asymmetric aldol reaction, Ru-catalyzed asymmetric hydrogenation, and Paterson’s anti-aldol reaction as key steps. Coupling with a modified cysteine 3, followed by thiazoline formation provided 4. Solid-phase peptide formation of 8 was performed using chlorotrityl lantern with methylated amino acids, 5, 6, and 7. After coupling of 4 and 8, the linear cyclization precursor was cleaved from the polymer-support and underwent macrolactamization leading to apratoxin A (1). Based on this method, several derivatives were synthesized. Details and their biological evaluation will be presented.

References:

**IL-20**  Aromatic Heterocycles: Versatile Starting Materials for Diversity Oriented Synthesis using Asymmetric Catalysis as Key Technology

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Selected examples from our laboratory for the transformation of inexpensive furans, pyrroles and pyridines towards natural product like scaffolds using asymmetric catalysis as key technology will be discussed.
References:
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IL-21 Amino acid promoted Ullmann-type coupling reactions and their applications in the assembly of pharmaceutically important heterocycles

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Ullmann-type coupling reactions between aryl halides and N-containing reagents, phenols and other related nucleophilic agents are a traditional method for preparing corresponding aromatic compounds that are important in pharmaceutical science. However, a significant drawback of these reactions is the requirement of a high reaction temperature, which greatly limited its scope of application. This shortcoming stimulated considerable efforts to develop relatively mild coupling conditions in recent years.1 The successive examples are highly dependent on the use of special ligands such as $N,N$- or $N,O$-bidentate compounds. In this report we will summarize our efforts on the development of new reaction conditions for Ullmann-type coupling using amino acids as promoters,2 describe that there is an accelerating effect caused by an ortho-amide group.3 The applications of these coupling reactions in the synthesis of heterocycles like substituted indoles, 1,2-disubstituted benzimidazoles, N-substituted 1,3-dihydrobenzimidazol-2-ones, substituted benzothiazoles, 3-acyl oxindoles and 2,3-disubstituted benzofurans, are also reported.4
IL-22 Design, synthesis and screening of a library of peptidyl-oligo(boroxole) receptors for complex oligosaccharides in physiological conditions

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In the past decade, boronic acids have emerged as an important class of boron compounds that demonstrate excellent stability to air and aqueous media. The ability of boronic acids to bind reversibly to simple carbohydrates in neutral water can be exploited in the design of sensors and receptors for biologically relevant, cell-surface oligosaccharides. Because of the inherent structure of sugar molecules, oligosaccharide recognition under physiological conditions poses a formidable challenge to organic chemists. The potential applications of small oligosaccharide-binding molecules are numerous, and include therapeutic uses such as diagnosis and selective drug delivery, use as biological probes or analytical biosensors, and supports for affinity purification. This presentation will describe the discovery of a unique class of boronic acids capable of binding hexopyranosides in water. These hemiboronate units, named benzoboroxoles, were essential to the design of a small library of well-defined peptidyl-diboroxole receptors for complex oligosaccharides.
The library was synthesized using a combinatorial solid-phase approach with the Irori® technology, and it was screened in a biochemical assay for the selective recognition of the T-antigen disaccharide, a cancer-associated cell-surface marker. A few high-affinity receptors of low micromolar IC50 were identified, and their binding behavior in neutral water was characterized using competition experiments and systematic evaluation of analogues. These results suggest that low molecular weight receptors for biologically relevant glycoconjugates could be made to rival the efficiency of Nature’s carbohydrate-binding proteins.

References

IL-23 Development of Fluorescent Glucose Bioprobes and their Application toward Discovery of Novel Anti-diabetic Agents

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The development of novel fluorescence bioprobes can serve an important role in the discovery of new therapeutic agents and study in Chemical Biology. In this presentation, the full-color tunable new fluorescent core skeleton will be introduced and their photochemical properties with our demonstration of their applicability in the development of new biosensors. We have developed a full-color-tunable fluorescent core skeleton, 1, 2-dihydropyrrolo [3.4-β] indolizin-3-one, by complexity-generating one-pot reactions. This core skeleton can accommodate various wavelengths of the emission maxima simply by changing the substituents, having different electronic properties, which is also supported by computational studies. These novel fluorophores have excellent photophysical and photochemical properties, moderate to excellent absolute quantum yields, resistance to photobleaching, pH-independent fluorescence, large Stokes shifts, drug-like lipophilicity for membrane permeability, etc. Further, we have successfully demonstrated the bioapplication of our fluorophore B5 in the immunofluorescence for visualizing EGFR on HeLa cells with cetuximab—an EGFR-targeting chimeric monoclonal antibody. In addition, glucose bioprobes were developed for monitoring the cellular uptake of glucose in physiological condition. In our previous research, we reported that Cy3-Glc-α is a novel bioprobe for bioimaging and screening for new anti-cancer agents through the efficient in vitro monitoring of glucose trafficking. As
an extension of our study, we pursued the design and synthesis of a series of novel fluorescent glucose bioprobes with the variation of linker regions and fluorescent dyes, because we observed undesired aggregations of Cy3-Glc-α bioprobe at the cell surface, especially in adipose cells. This new array of fluorescent glucose bioprobes was successfully applied in the flow cytometry to monitor the global event of cellular glucose uptake. The development of novel fluorescent glucose bioprobes can provide the unique research tool for high-content screening or bioimaging which is applicable for the identification of new therapeutic agents, which regulate the glucose uptake, as a novel treatment of obesity and diabetes. Actually we discovered a small molecule AMPK activator, confirmed by western-blot analysis using phosphoAMPK antibody (T172). This compound demonstrated the actual glucose uptake in cellular system monitored by our fluorescent glucose bioprobe, which has almost identical enhancement of glucose cellular uptake by insulin.

References:

IL-24 Integrating Technologies in Drug Discovery: Successful Case Studies

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The modern paradigm for the discovery of novel drug candidates is an iterative process of hypothesis, synthesis and biological testing which typically requires hundreds of cycles to arrive at the NCE. To expedite the discovery process, this cycle time must be minimized to achieve the desired objective in a timely manner. The pragmatic use of technologies derived from the advent of combinatorial chemistry, such as parallel synthesis and automated LCMS purification, microwave synthesis, and electronic lab notebooks, have proven highly effective in this regard. Several medicinal chemistry case studies will be presented that demonstrate the application of these technologies at Incyte to the discovery of potent inhibitors of strategic biological targets.

IL-25 Combinatorial approaches applied to the identification and optimization of tumor inhibitors

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To improve the chances of finding agents that are active against biological targets of interest, technologies such as combinatorial chemistry and ultra-high-throughput
screening (HTS) have considerably expanded the numbers of compounds that can be evaluated for their biological activity. In a context of intense commercial pressure to increase discovery productivity the demand for new technologies persists, and better integration and coordination of known technologies is essential in building up flexible capabilities to accelerate the development of small-molecule agents against relevant therapeutic targets.

The chemistry driven technologies implemented at Nerviano Medical Sciences, and their combined application in discovery, will be illustrated with examples from oncology projects.

On one hand we describe how our combinatorial chemistry effort contributed to the optimization of PLK-1 inhibitors in a project that progressed all the way to the identification of a clinical candidate. Furthermore, in an entirely different and complementary approach, we succeeded in gradually building up an inhibitor of Hsp-90, a molecular chaperone protein, by assembling it from small fragments in a structure guided way.

Our Oncology unit has developed a methodological platform to discover small molecule kinase inhibitors, which we refer to as the ‘Kinase Platform’. A panel of over 50 cloned and expressed kinases is set up for weekly selectivity screens. Hundreds of crystal structures are available for the rational planning of hit expansions by parallel synthesis. Multiple HTS campaigns are run in a year in order to jump start new kinase inhibition projects by testing a.o. some 60,000 compounds from our ‘Kinase Targeted Libraries’ prepared over the years. As an example we retrace the discovery of NMS-P937, a powerful and selective, orally available PLK-1 inhibitor ready for clinical trials.

In recent years we have developed and patented a number of NMR screening techniques in order to facilitate fragment-based approaches (FBA) and their full integration in the company’s research workflow. Fragment-based drug design is based on screening selected smaller populations of compounds (typically just around one thousand) in a search for low-affinity fragments. Thanks to their low molecular weight, the fragments have a high binding efficiency even if they are high micromolar to millimolar ligands, i.e. in spite of possessing an affinity which would be considered unattractive for larger molecules (>300 Da). Experimental structure determination of the binding mode often enables to overcome an initial weakness by the design of rational growth towards drug-like molecules with excellent binding efficiency, as will be shown here for an ATPase target, the molecular chaperone Hsp90. The path from a common molecular fragment to a drug-like compound with favorable ADME-PK properties and efficacy in an in vivo human ovarian cancer xenograft model will be described. The discovery mode of this project, taking full advantage of NMR screening and Fragment Based Approaches, will be explained.

IL-26  Design and synthesis of a new small-molecule compound class of pan- and isoform-selective PI3-Kinase inhibitors: SFP6 series

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A new small-molecule compound class was designed to selectively target phosphoinositide 3-kinase (PI3K). Using the crystallographic coordinates of publicly available PI3K-gamma co-crystallized with LY294002, and annotating PI3K-gamma/LY294002 interactions, a set of new chemotypes were designed leading to the development of the SFP6 compound series. The core structure of SFP6 was constructed via solution-phase synthesis and its derivatization was carried out under microwave irradiation conditions for quick compound and SAR generation. With an average synthetic pathway of 4 steps, a broad range of molecular diversity was generated using a robust and validated tool set of reliable reaction transformations and conditions. The screening of the designed compounds in enzymatic assays validated the computational models affording potent pan- and isoform-selective PI3K inhibitors. Three proof-of-concept compounds were used as probes in both in vitro and in vivo assays. Comparison of these 3 new compounds (SF2503, SF2506 and SF2523) against the PI3K- multikinase inhibitor LY294002 shows these new small molecules (MW < 400 Daltons) are up to 24 times more selective against specific PI3K isoforms while also potently inhibiting several other desirable cancer-relevant targets (e.g., mTOR, PIM-1, DNA-PK).

IL-27 Synthesis and Evaluation of Sphingosine Analogs as Inhibitors of Sphingosine Kinase

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Sphingolipid-metabolizing enzymes control the critical balance of the cellular levels of sphingolipids, including the apoptotic inducing ceramide (Cer) and the proliferative inducing sphingosine-1-phosphate (S1P). Many evidences indicate that sphingosine kinase (SPHK) plays a critical role in regulating cellular processes but pharmacological inhibition of SPHK has been somehow an untested field due to lack of research into development of inhibitors of SPHK. Presence of two isoforms of SPHK also complicated the development process as current inhibitors of SPHKs are non-specific. Besides being able to inhibit both SPHK isoforms, the inhibitors also target protein kinase C (PKC) and other sphingosine dependant kinases. In this lecture, we will describe our efforts in developing inhibitors to either of the SPHK isoforms. A novel and stereoselective method of synthesizing theses inhibitors has been developed. A number of novel and specific inhibitors of human recombinant SPHKs were identified and these compounds demonstrated inhibition of SPHKs at micromolar concentrations, making them more potent than dimethylsphingosine (DMS), a well-known inhibitor of SPHKs. In particular, one of the inhibitors was found to be selective toward a particular isoform of SPHK and does not inhibit PKC.
IL-28  Library Approach to Non-Psychotropic Biaryl Cannabinoid Receptor Agonists

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NSAIDS and narcotics are used to treat postoperative pain. These drugs are associated with a number of unwanted side effects – gastrointestinal bleeding, constipation and respiratory depression. In search of new analgesic therapies without such side effects, a drug discovery program was initiated to identify peripherally-acting cannabinoid receptor agonists. There are two cannabinoid receptors: CB1 and CB2. Both receptors are believed to play a role in pain. Mixed CB1/2 receptor agonists, e.g. WIN 55,212-2, produce potent antinociception with equivalent efficacy to morphine in animal models of acute pain, persistent inflammatory pain and neuropathic pain. Psychotropic activity is observed with WIN 55,212-2 because of the stimulation of CB1 receptors in the brain. Retaining the desired analgesic action of CB receptor agonists without their CNS liability may be accomplished by limiting CNS bioavailability. A solid phase library approach was used to peripheralize a biaryl cannabinomimetic by incorporating a unique combination of polar substituents. The new agonists (Ki CB1/2 < 10 nM) demonstrate antinociception free of CNS side effects as determined by the catalepsy ring test. Examples will illustrate that certain physiochemical properties were required to arrive at peripheral CB receptor agonists.

IL-29  High pressure, high temperature reactions in continuous flow: merging discovery and process chemistry

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The application of flow reactors to increase the parameter space of organic chemistry reactions in current laboratory practice is outlined with help of examples such as Diels-Alder reactions, Knorr reactions, Heck chemistry, different aromatic nucleophilic substitutions and other reactions. The lecture demonstrates the advantages of flow reactors operating in a parameter space up to 350°C (662°F) and 200 bar (2900 psi), sometimes under supercritical conditions, in some cases in a few hundred milliseconds. The flow reactors described in the lecture offer for the first time an alternative solution to the microwave batch scale up.

IL-30  Combinatorial Deuteration of Pharmaceuticals

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The deuteration of ligands must change their binding affinities for receptors, based on First Principles. This has remained non-obvious to drug researchers since the first forays into drug deuteration in 1969. We believe that the effect of deuteration at any given position in a molecule is not predictable, but can be established using empirical methods—most importantly, combinatorial synthesis followed by screening for activity. In this talk, I will summarize Deuteria Pharmaceuticals' research and provide results obtained to date.

IL-31  Fragment-based and Structure-guided Design of Allosteric Kinase Inhibitors

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The majority of marketed and late stage development protein kinase inhibitors are ATP-competitive. As a result, they often display non-specific activities due to
undesirable off-target interactions with other protein kinases.[1] Combinatorial chemistry and high-throughput screening (HTS) have played important roles for the discovery of novel “hits” and facilitated the hit-to-lead and lead optimization. Recently, a more rational and complementary approach, fragment-based drug discovery was recognized as useful tool in identification of high-quality “hits”, hit-to-lead and lead optimization[2] since the first description in the literature more than a decade ago.[3,4] This new approach has become practical only in recent years due to significant advances in technology such as X-ray crystallography, NMR, Surface Plasmon Resonance (BiaCore), Mass Spectrometry and Isothermal Calorimetry.[5]

In this talk, fragment-based and structure-guided design of allosteric kinase inhibitors using protein X-ray crystallography, high throughput medicinal chemistry and cell biology will be presented.

References:

IL-32 Cross-Coupling Catalyses with PS-PEG Resin-Supported Palladium Complexes

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Allylic and aromatic substitution reactions via a variety of carbon-carbon and carbon-nitrogen bond forming coupling catalyses (e.g. Tsuji-Trost reaction, Suzuki-Miyaura coupling, Hartwig-Buchwald reaction, etc.) were performed in water with amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium complexes to realize green, safe, and high-throughput organic synthesis.[1] Highly stereoselective allylic substitution (up to 99% ee) and biaryl coupling (up to 94% ee) were achieved also in water under heterogeneous conditions with PS-PEG resin-supported chiral phosphin-palladium complexes.[2] The immobilized complexes were readily removed (recovered) by simple filtration without leaching of palladium species, and reused several times without any loss of their catalytic as well as stereoselective ability.
IL-33  Combinatorial Green Techniques for Organic and Medicinal Chemistry Applications

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This talk presents an overview on the fluorous-based green techniques for organic and medicinal chemistry applications. The unique phase separation and broad combinatorial capability of fluorous technologies have led to the development of chromatography-free separations, chemical recycling techniques, atom economic reactions, energy-focused microwave reactions, metal-free organocatalysis, aqueous media reactions, and modified reagents. The utility of these fluorous tools have been demonstrated in discovery and medicinal chemistry labs in industrial, as well as organic labs for academic research. Issues associated with the fluorous chemicals will be discussed.1-8

References:


IL-34 Discovering highly potent small molecule inhibitors of cyclophilin A using computational drug design approach

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The discovery of cyclophilin A (CypA) inhibitor is now of a special interest in the treatment of immunological disorders. So far, few potent small molecule CypA inhibitors have been reported, and their activities are not so promising. By using a strategy integrating focused combinatorial library design, virtual screening, de novo design, chemical synthesis and bioassay, we have discovered a series of novel small molecular CypA inhibitors [1-3], among which the activities of the most active inhibitors are at the level of nanomole. This result demonstrated the efficiency of our drug design strategy.

References

IL-35 Small-molecule peptides inhibit human Zα1-antitrypsin polymerization

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The Z variant of α₁-antitrypsin polymerizes within the liver and gives rise to liver cirrhosis and the associated plasma deficiency leads to emphysema. In this work, a combinatorial approach based on the inhibitory mechanism of α₁-antitrypsin was developed to arrest its pathogenic polymerization. One peptide emerged as the most tight-binding ligand for Z α₁-antitrypsin. Characterization of this tetrapeptide by gel electrophoresis and biosensor analysis revealed its markedly improved binding specificity and affinity compared with all previously reported peptide inhibitors. In addition, the peptide is not cytotoxic to lung cell lines. A model of the peptide-protein complex suggests that the peptide interacts with nearby residues by hydrogen bonds, hydrophobic interactions, and cavity-filling stabilization. The combinatorially selected peptide not only effectively blocks the polymerization but also promotes dissociation of the oligomerized α₁-antitrypsin. These results are a significant step towards the potential treatment of Z α₁-antitrypsin related diseases.

References:

IL-36 Automated Oligosaccharide Synthesis and Synthetic Vaccines

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The importance of cell surface oligosaccharides and glycosaminoglycans in signal transduction processes of biomedical significance is now well established. Described is the development of a fully integrated platform based on automated oligosaccharide synthesis and carbohydrate arrays to address biological problems. Particular emphasis in this lecture will be placed on the new automated synthesis platform that will be made available to laboratories around the world. Based on the automated synthesis platform, carbohydrate arrays can be accessed for use in screening of proteins and blood sera. Described will be the development of carbohydrate-based vaccines against a series of diseases. Recent examples that will be discussed include vaccine candidates against malaria, Leishmaniasis, and anthrax. The malaria vaccine candidate is now in preclinical development.

Finally, the use of microreaction systems constructed from etched silicon for rapid reaction optimization will be described. This new reaction system should find wide application in academic and industrial research laboratories from discovery to process chemistry and production.

Understanding and controlling the protein-nanomaterial interaction is crucial to design functional nanomedical devices. Indeed proteins from blood, serum or any other biological fluid immediately coat any surface the fluid comes in contact with and it is through this adsorbed layer that the surface interacts with other proteins or cells. The study of protein-surface interaction is a very complicated problem because of the high heterogeneity of proteins and because of the lack of reliable techniques to characterize the interaction process.

Here we present a Protein-Surface Interaction Microarray (PSIM): an innovative high-throughput technique to quantitatively characterize the protein-nanostructured surface interaction. PSIM exploits the high-throughput power of protein microarray technology in order to obtain, in one single experiment, protein-surface binding isotherms of a panel of proteins on a panel of different nanomaterials. This technique has been applied to characterize different metal-oxide nanostructured thin films produced by supersonic cluster beam deposition [1]. Since these films have a nanoscale roughness that can be tailored and regulated from 1 nm up to 30 nm, they are very promising as substrates for different applications in cell-based assays, biosensors and microfabricated devices [2,3] and they are particularly suitable for investigating the role of the nanoscale roughness in the process of protein-surface interaction [4]. We have employed PSIM to compare substrates with different surface roughness and with different post deposition treatments using a panel of proteins such as BSA, Streptavidin, Fibrinogen.

Results demonstrated that PSIM is a powerful technique for the characterization of nanostructured materials thanks to the possibility to study quantitatively, with a fluorescence-based assay and in high-content the interaction of surfaces with a wide panel of proteins as a function of nanostructure production parameters.

References

IL-38  Nano-Combinatorial Libraries to Regulating Biological Activities of Nanomaterials

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Nanomaterials are being investigated for their applications in medicine in addition to their wide potential use in industry and our daily life. However, due to their small size and large surface areas, nanoparticles bind biomolecules, enter cells, and induce toxicity in cells and in animals. Due to their large surface areas, chemistry modification of their surface may have a major impact on their bioactivity. To test this hypothesis, we designed and synthesized carbon nanotube and gold nanoparticle libraries and screened their protein binding and cellular activities. The actual synthesis posed challenges on reaction monitoring and product characterization on nanoparticle’s surface. We developed a series of analytical techniques and methods to assist the synthesis of nanoparticle libraries. Biological screening results showed that surface chemistry diversity can modulate nanoparticle’s interactions with proteins, and control their cellular activities. Biocompatible or enzyme-specific nanoparticles were selected and surface structure-activity relationship can be elucidated. The rapid generation of molecular diversity on nanoparticle’s surface and discovery of leading candidates and the associated structure-activity relationships demonstrated the general utility of the nano-combinatorial library approach in nanomedicine and nanotoxicity research.

References

IL-39  Computational design of synthetic receptors

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One of the most important areas of research in modern material science is predictive modelling and rational design of synthetic receptors. For the past ten years Cranfield developed a unique tool in rational design of molecularly imprinted polymers (MIPs) using a computational approach. The concept is to simulate a complex formation between selected monomers and template in a monomer mixture using SYBYL 6.9™ (Tripos Inc., St.Louis, US) as the industry standard molecular modelling software. Molecular modelling is used to screen a virtual library of functional monomers against target compounds in conditions mimicking the polymerisation mixture. The result of this screening permits selection of monomers, which are able to form a strong complex with the template. This software can be used also to predict the stoichiometric ratio of monomers to template in a self-assembled complex existing in a given solvent and at a particular temperature. The results obtained recently and those previously published show clear correlations between the modelling data and
the polymer properties (affinity and selectivity) for most of the polymer systems studied.

Examples on some of the synthetic receptors developed in Cranfield using this approach are: triazine herbicides (atrazine, desmetryn), chlorophenols, lindane, DDT, algal and fungal toxins (domoic acid, microcystin-LR, aflatoxin B1, ochratoxin A), drugs such as tylosin, salbutamol, ephedrine, epinephrine, isoproterenol, fluticasone, drugs of abuse (cocaine, methamphetamine, methadone).

The creative use of this approach permitted us to develop MIPs with:

- **High affinity:** (MIP for atrazine with \( K_d = 1.5 \text{ nM} \); microcystin-LR with \( K_d = 0.3 \text{ nM} \); polymers for proteins with \( K_d = 30-100 \text{ nM} \)
- **Stability:** MIPs work for 6-36 months with no variations in affinity
- **Specificity:** MIPs have equal or better selectivity than natural receptors
- **High binding capacity:** best MIPs have saturation capacity 80-100 mg/g

**IL-40 High-Throughput Technologies in the Search for New Selective Heterogeneous Catalysts**

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Combinatorial chemistry (CC) together with high-throughput technologies (HTT) [1] are combined in our labs to an iterative HT workflow, which is high-throughput based throughout the complete cycle, i.e. synthesis, characterization and data mining. Objectives of our search strategies are the discovery and optimization of new heterogeneous catalysts and materials for various applications including fuel cell electrocatalysts, photocatalysts, reforming and combustion catalysts, sensor materials, piezoelectric as well as thermoelectric materials.

Our approach often uses the method of “directed evolution”, i.e. hit-selection and optimization for the exploration of parameter space. Starting libraries consist of diverse collections of binary mixed oxides as well as reference catalysts. Their performance is recorded under reaction conditions with ecIRT, GC or MS. The
compositions of the most active/selective materials are optimized by composition spread libraries. Subsequently the best compositions are doped (3% and 10%) with up to 60 different elements M. In iterative steps best polynary oxides are selected and their compositions optimized. This process is continued until there is not any improvement in the objective function.

In the present contribution examples for this proceeding will be given: catalysts for the selective hydrogenation of CO in the presence of large excess of CO₂ have been developed, for the dry reforming of methane, or the combustion of soot in the presence of hydrocarbons and nitric oxide.

References:

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IL-41 Design of selective semiconductor gas sensors using combinatorial solution deposition

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The oxide semiconductors such as SnO₂, ZnO, In₂O₃, and WO₃ provide a facile and cost-effective sensing of trace concentration of toxic or explosive gases. However, the simple sensing mechanism based on the oxidative or reductive interactions between target gas and negatively charged surface oxygen hinders the selective detection of a specific gas. Various methods have been explored to accomplish selective gas detection using oxide semiconductors. These include the modulation of sensing temperature, the addition of a noble metal or oxide catalyst, the deposition of a coating layer for the selective filtering of a gas, the design of multi-compositional sensing materials, surface modification, manipulation of the nano-structure, and the use of a neural network algorithm. With the exception of the manipulation of the sensing temperature and nano-structure, almost all approaches can be best optimized when one employs combinatorial routes. And the design of a multi-compositional gas sensing material is very important not only for achieving the selective gas detection of a single chemical quantity but also in establishing a sensor materials library for the pattern recognition of smells containing multiple chemical quantities, both which can be realized conveniently, effectively, and rapidly using combinatorial approaches.

In the present contribution, the combinatorial approaches to fabricate oxide semiconductor gas sensors is reviewed, and the design of selective gas sensing materials is demonstrated through the combinatorial solution deposition of SnO₂, ZnO, and WO₃ sols. From the gas response to C₂H₅OH, CH₃COCH₃, CO, C₃H₈, H₂, and NO₂, it was found that the selective detection of C₂H₅OH could be attained in the SnO₂-ZnO composite sensor at 300°C and ZnO-WO₃ composite sensor at 400°C. And WO₃ sensors could detect CH₃COCH₃ in the presence of C₂H₅OH. The discrimination between C₂H₅OH and CH₃COCH₃ was discussed in the viewpoints of electronegativity, heterostructure effect, and sensing temperatures.
Fig.1 The ratio between the sensitivities to C$_2$H$_5$OH 200 ppm and CH$_3$COCH$_3$ 200 ppm (Log($S_{ac}/S_{ac}$)) (a) at 300 and (b) 400°C.

References:

IL-42 Identification of the Pseudo-cubic phase in PbTiO$_3$ - CoFe2O4 composite through combinatorial approach

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Anomalous increase in dielectric constant, nonlinear dielectric constant and magnetoelectric coefficient was found in epitaxial 80PbTiO$_3$-20CoFe$_2$O$_4$ composite film by using combinatorial method. Subsequently, the composition-structure relationship in the combinatorial PbTiO$_3$-CoFe$_2$O$_4$ materials library was thoroughly analyzed using the synchrotron radiation high-resolution micro-diffraction technique combined with first-principle calculation.
A pseudo-cubic phase caused by the epitaxial stress was identified around 80% PbTiO$_3$. It was this metastable phase and the orientations of the crystallites that resulted in the property abnormality in the composition range.

**IL-43 High-throughput experimentation under microwave conditions: rapid reaction scouting, reaction optimization and library synthesis in silicon carbide microtiter plates**

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High-speed microwave synthesis has attracted a considerable amount of attention in recent years [1]. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid reaction optimization, for the efficient synthesis of new chemical entities, or for discovering and probing new chemical reactivity.

Reaction optimization and the generation of compound libraries using microwave technology is generally performed in automated sequential format using single-mode cavities and appropriate robotics. The use of standard deep well microtiter plate systems in conjunction with microwave heating is troublesome due to (i) the thermal instability of the plates under comparatively high-temperature microwave conditions, and (ii) the formation of significant temperature gradients between individual wells, leading to a non-uniform temperature distribution across the typically microwave transparent plates. Another significant limitation is the fact that currently available commercial microtiter plates for use in multimode microwave reactors does not allow processing under sealed vessel conditions.
Herein we describe a 20 deep-well (5 x 4) microtiter plate that allows the use of standard GC/HPLC vials for performing sealed vessel microwave synthesis. This format is particularly valuable for direct reaction screening and reaction optimization allowing synthesis and analysis to be performed in the same reaction vessel. Several examples that will highlight the usefulness of this strategy for organic synthesis will be given [2].

References:

IL-44 Making Molecules on the Fly: Microwave-Assisted, Continuous Flow Organic Synthesis

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A process has been developed for the deposition of metal films onto the inner surface of micro-capillaries and these films have been examined by Scanning Electron Microscopy (SEM) and Energy Dispersive X-ray (EDX) analysis to confirm their structure and elemental composition. These films have been shown to be highly active in metal-catalyzed transformations including the Suzuki-Miyama and Heck couplings where the reactions are flowed through these capillaries while being microwaved where conversion times are in the order of minutes to seconds. Similar results have been found for other metal-catalyzed procedures, including metathesis, hydrosilylation, and ‘click’ reactions. Further, the role of metal films in transformations that are not specifically metal catalyzed (e.g., pericyclic reactions) has also been investigated. Here once again dramatic rate enhancements have been observed. Efforts have also been expended into differentiating ‘catalytic’ effects from simple ‘heating’ effects for the metal film. Further, aspects pertaining to ‘on-the-fly’ in-line analysis, reaction optimization and scaling up chemical reactions will be discussed.¹

Transformations investigated:
- Suzuki-Miyama coupling
- Heck reaction
- aryl amination
- hydrometallations
- multi-component coupling

Figure 1.
References

IL-45 Generation of a phosphine library and heterocyclic scaffold diversity accelerated by microwave chemistry

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In recent years, we have developed several concepts for microwave-assisted solution and solid-phase organic synthesis. These include the design of a cat-linker (possessing a metal-catching polyamide segment)[1] for facilitating Cu(II)-mediated hydroamidation of the resin-bound 2-alkynylanilides, the establishment of a self-assisted molecular editing (SAME) protocol[2] for one-pot synthesis and screening of aromatic amide-derived phosphines (Aphos), and the generation of heterocyclic scaffold diversity via sequential annulation reactions starting from the Ugi four-component reaction (U-4CR) products.[3] Our Aphos–Pd system enables room-temperature Suzuki–Miyaura cross-coupling reaction of unactivated aryl chlorides and it has been used in the total synthesis of amphidinolide Y.[4] As illustrated in the following figure, the acyclic U-4CR products are successively transformed into the fused rings, the C–N bond linked conjugates, and finally the spirocyclic compounds. Although molecular rigidity increases from the acyclic to the spirocyclic structures, these unfavorable entropy-reducing processes can be facilitated at high temperature under controlled microwave heating. We have taken conformational preference of the substrates into consideration in formulating the order of these annulations. Our results demonstrate that the integration of microwave-assisted U-4CR and post-Ugi annulations is a powerful approach for building molecular shape diversity based on novel heterocyclic scaffolds. These concepts will be presented with detail examples and the scope and potential of applications will be discussed.

References:
IL-46  A Potpourri of Recent Microwave-Assisted 2(1H)-Pyrazinone Chemistry

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In the last three decades 3,5-dichloro-2(1H)-pyrazinones have emerged as useful starting materials for the elaboration of different types of skeletons of biologically interesting compounds [1]. The 2(1H)-pyrazinone scaffold allows the easy introduction of a wide range of pharmacologically active groups with the ability to address the diverse set of biological targets. We will comment on our latest results regarding the application of focussed microwave irradiation for the decoration and conversion of this useful scaffold. Our recent results about the first palladium-catalyzed desulfitative Sonogashira-type cross-coupling [2] reaction as well as concerning a desulfitative Hiyama-type cross-coupling [3] will be presented. We will also comment on the development of a novel and versatile entry to asymmetrically substituted pyrazines [4], including a microwave-assisted Liebeskind-Srogl protocol, as well as on the elaboration of an unprecedented route for the synthesis of dihydropyrazine-2,3-diones applying aqueous (“green”) conditions [5]. A highly efficient method for the diversity oriented synthesis of tri- and tetrasubstituted furo[2, 3-b]pyrazines has been developed comprising a Ag⁺- or iodine-mediated intramolecular heteroannulation reaction [6].

The 2(1H)-pyrazinone scaffold

References:
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A novel ionic liquid supported, green synthetic protocol has been developed for the synthesis of tetrahydro-β-carboline tethered oxo and thio hydantoins by focused microwave irradiation. Ionic liquid bound tryptophan underwent Pictet-Spengler reaction with various carbonyl compounds to generate the immobilized tetrahydro-β-carbolines in environmentally benign green media. Subsequent reaction of substituted tetrahydro-β-carboline derivatives with various isocyanates and isothiocyanate in water/isopropanol to bring the target compounds in traceless fashion with high purities and excellent yields. This methodology offers numerous advantages over existing pathways to attain the pharmaceutically interesting compounds.

IL-48  Highly Diastereoselective Microwave-assisted Synthesis of 6-Spirosubstituted Pyrido[2,3-d]pyrimidine Derivatives via Chemoselective Multicomponent Reactions

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Selectivity is a key issue to be controlled in organic synthesis. In particular, chemoselectivity is synthetically useful because it gives one of several products selectively from the same substrate without the need to separate the product(s) from the product mixture. It continues to be developed as organic synthesis strives for ever-increasing levels of efficiency. As a result, many studies have focused on the chemoselectivity of reactions. In addition, multicomponent reactions offer convenient procedures for the introduction of many points of structural diversity into heterocyclic compounds prepared in a straightforward manner in a single synthetic step. Combining these features with the extremely fast microwave-assisted organic synthesis provides new methods for the rapid and efficient synthesis of heterocyclic libraries. Therefore, the development of highly microwave-assisted chemoselective multicomponent reactions remains a challenge. However, the utilization of diastereoselective multicomponent reaction to build spirosubstituted pyrido[2,3-d]pyrimidine skeleton was seldom investigated. There is only limited number of studies on related spirocyclic system. Quiroga et al synthesized
pyridopyrimidine–spirocyclohexanetriones by treatment of 6-aminopyrimidin-4-ones with dimedone and formaldehyde, but the reactions are not diastereoselective.[3] Wang et al. reported the reaction of N-(arylidene)naphthalen-2-amine with arylaldehyde and 1,3-dimethylbarbituric acid to give spiro-benzoquinolines with the disadvantage of poor diastereoselectivity and limited reaction scope.[4] Herein we have successfully developed a new multicomponent reaction system to furnish spirosubstituted pyrido[2,3-d]pyrimidines with high diastereoselectivity.

![Chemical structure](image)

References:

Acknowledgments:
We are grateful for financial support from the National Science Foundation of China (No. 20672090)

IL-49 A “CHEMICAL REVERSE APPROACH” TO DETECT LIBRARIES OF BIOMARKERS OF AUTOIMMUNE DISEASES

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Among the many outputs of the ‘omics’ revolution, the identification of specific biomarkers is a relevant target for disease diagnosis and for the set up of personalized treatments. Autoimmune diseases affecting an increasing number of individuals throughout the world, represent a large and diverse group of disorders categorized by tissue injury or pathology. Thus, reliable diagnostic/prognostic tools are necessary not only for an early diagnosis but also for monitoring disease activity. While the practical value of autoantibodies has been realized in some clinical conditions, it remains underutilized in the majority of diseases. In fact, sera from patients suffering from autoimmune disorders often contain multiple types of autoantibodies. Some autoantibodies can be exclusive of a disease and thus used as biomarkers for diagnosis; others fluctuate with disease exacerbations or remissions and are
extremely valuable in the follow up of patients. In this scenario, identification of autoantibodies, as disease biomarkers, should be achieved using native antigens in simple biological assays. However, growing evidences indicate that post-translational modifications (i.e., acetylation, lipiddation, citrullination, glycosylation), either native or aberrant, may play a fundamental role for specific autoantibody recognition in autoimmune diseases [1]. In this context, we have recently developed CSF114(Glc), a structure based designed glucosylated peptide, characterized by a β-turn structure [2], as the first Multiple Sclerosis (MS) Antigenic Probe accurately measuring high affinity autoantibodies (biomarkers of disease activity) by ELISA [3] on sera of a statistically significant patients’ population [4]. The selection of the glycopeptide CSF114 (Glc) was possible because of an innovative “chemical reverse approach” [5] optimizing the glycopeptide sequence able to detect the most specific and high affinity autoantibody titre in sera [6]. Aberrant glucosylation of myelin proteins (induced by a bacterial and/or viral infection?) is possibly triggering autoimmunity in Multiple Sclerosis. To demonstrate our hypothesis, we focused our efforts on the identification of the native antigens, targets of anti-CSF114 (Glc) autoantibodies involved in demyelination process. Therefore, we undertook a homology alignment study based on the primary sequence, on the conformation, and on the post-translational modifications (PTMs) of proteins localized in CNS.

Our “chemical reverse approach” was extended to other autoimmune conditions, proposing CSF114 as an “Universal Peptide Scaffold” to be modified for specific recognition of biomarkers [7]. Therefore, we are demonstrating that modification of the CSF114 β-turn structure with different aberrant PTMs, each one specific for antibody-mediated forms of different immune-mediated diseases (i.e. coeliac disease, primary biliary cyrrhosis, rheumatoid arthritis, etc.), is leading to a library of Antigenic Probes to be used in multiple diagnostic/prognostic immunoassays with a “theragnostic” aim.

References

IL-50 Chemical Microarrays - From Polymers to Small Molecules

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I will demonstrate a variety of approaches aimed at the preparation and high-content screening of polymer-library based microarray platforms and their application in a number of cell based screens. Fabrication methods, including both contact and inkjet printing of pre-formed polymers, inkjet blending of pre-formed polymers as well as direct inkjet based polymer synthesis and analysis with fixed and live cells on over 2000 features will be described. Using this technology I will show how polymers
have been developed for a myriad of applications, including control of stem cells fate, corneal bandages, bacterial capture and thermally responsive surfaces.

A second micorarray approach using 10,000 member Peptide Nucleic Acid (PNA)-encoded peptide libraries will also be described, illustrating the power of this technology in the analysis of proteases, kinases, as a tool of the identification of novel cell-specific ligands and new cellular delivery peptides.

**OP-01 Combinatorial Library Design based on Privileged Structure**

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It is a huge challenge to quickly find effective lead compounds for both biologists and medicinal chemists. Although there are many ways to search for biologically active lead compounds, few of them are fast and show high success rate. Many studies proved that there are two effective methods until now. One is to design a high efficient synthetic route to modify the existing synthetic process, which is based on biologically active natural products or clinical medicine including old drugs. Another effective way to discover new active compounds is to design, synthesize and screen chemical library based on privileged structures. Because these privileged structures have a unique three-dimensional structure and show good activity and selectivity to various protein receptors, it provides a shortcut to the research and discovery of new proteins and drugs. Therefore, we are trying to create libraries with truly diversified compounds based on privileged structures, including diversified functional groups or substituents, and molecular scaffolds. Our goal is to develop efficient, environmentally friendly, atom economic modern synthetic methods, in combination with medicinal chemistry and biological technology, to synthesize biologically active compounds and quickly provide samples for biological testing.

As a part of our continuing effort to assemble C–N and C–C bonds, we develop rapid, efficient and convenient protocols for the construction of diverse heterocyclic libraries1-5. Such as 2,6,9-substituted purines, 2,4(1H,3H)-quinazolinediones, 1,3-dihydrobenzimidazol-2-ones, and 2H-1,4-benzoxazin-3-(4H)-ones, which are important scaffolds embedded in a variety of alkaloids and responsible for a variety of biological responses.

References:

OP-02 Solid-Phase Synthesis of 2, 3-Disubstituted Benzo[b]thiophenes and Benzo[b]selenophenes

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The benzothiophene ring system has long been recognized as an excellent scaffold for development of many bioactive compounds for research and pharmaceutical purposes. We have recently developed a convenient and efficient solid-phase synthesis, based on a combination of palladium-mediated coupling and iodo cyclisation protocols, for the efficient synthesis of a library of 2,3-disubstituted benzothiophenes.1 This solid-phase synthetic strategy was successfully extended, via triazene chemistry, to synthesize other heterocyclic ring systems such as benzoselenophenes, cinnolines and phenanthrenes (Fig 1)

![Triazene on solid support](image)

Fig 1: Uniformed pathway for solid-phase synthesis of benzothiophenes, benzoselenophenes, cinnolines and phenanthrenes (R1= anchoring point to solid supports, R2 and R3 are alkyl or aryl substituents).

Reference:
2) C. T. Bui and B. L. Flynn. Solid-Phase Synthesis of Thienopyrimidines and other heterocyclic compounds for drug discovery research. In preparation

OP-03 A COMBINATORIAL APPROACH TO CHIRAL IMIDATES: A NEW CLASS OF NITROGEN-BASED CHIRAL LIGANDS

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Nitrogen-containing ligands are known as cheap, readily accessible and stable
alternatives for phosphane ligands, which are often very sensitive to air and require a multistep synthesis. We wish to present a combinatorial approach to a novel type of nitrogen-based mono- and bidentate ligands. These ligands are characterized by their modular structure, allowing an easy one-step synthesis by simply combining two readily variable precursors which are either commercially available, or can be reached in only a few steps: a cyclic imidate and a (chiral) amine, respectively diamine. These ligands show promising results in e.g. the Cu(I)-catalyzed asymmetric aziridination of methyl cinnamate, in asymmetric diethylzinc additions to benzaldehydes, and in the Pd(0)-catalyzed asymmetric allylic alkylation. Further exploration of this new ligand family is in progress.

References:

OP-04 Dynamic covalent chemistry of disulfide: a novel one-pot synthetic method for diverse sulfides and sulfur heterocycles

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Thio-disulfide interchange reactions have been recently applied to the study of catalysis, peptide assembly, molecular recognition, and formation of a molecular capsule and polyrotaxane. This study attempted to use thio-disulfide exchange reactions as a synthetic strategy to synthesize sulfides and sulfur heterocycles. We were pleased to find that sulfides could be achieved instantaneously in high yield after the addition of the alkyl halide or Michael acceptors in the dynamic equilibrium solution under the basic condition. Sulfides could be further converted to diverse sulfur heterocycles in one-pot such as 2H-benzo[b][1,4]thiazin-3(4H)-one and 2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one.

Scheme 1 The mechanism and process of the synthetic method for sulfides and sulfur heterocycles through thio-disulfide exchange reactions

This is the first successful example for the use of thio-disulfide exchange reactions to prepare the sulfides and the sulfur heterocycles with several advantages. First, sulfides are able to be obtained rapidly in high yield at room temperature under organic basic condition. Second, the reaction eliminates the need of costly metal catalysts, anhydrous and anoxybiotic conditions. Third, the reaction is highly chemoselective, so that only thiol-disulfide interchange occurs in the presence of other functional groups, then only the acquired aromatic mercapto group reacts with the alkyl halide or Michael acceptors to give the diverse sulfides and sulfur heterocycles.

References:

OP-05 The further study of Unique Spirocyclopiperazinium as Analgesics

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The discovery of high efficient analgesics without the side effects of drug dependency is highly desirable in pain treatment. During the course of developing analgesic drugs with new structure and mechanism, we have found several kinds of piperazinium compounds with high analgesic activity, \(^1\)-\(^7\) and preliminary structure-activity research hints that the structure of spirocyclopiperazinium is important. Encouraged by the information described above, we chose compound 1 as the lead compound since it had moderate analgesic activity while quite low effective dosage (0.2mg/kg sc, analgesic activity 70.4%) , then a series of spirocyclopiperazinium derivatives 2 were designed and prepared to improve the analgesic activity and decrease the toxicity. Pharmacology tests displayed that some of them exhibited similar analgesic activity to the precursor compound 1 but lower toxicity. The further investigation is in progress.

References:

Acknowledgments:
This research was supported by the fund of National Science Foundation of China (NSFC 20772009).

OP-06 Synthetic application of 1,2-diketones: versatile and practical synthesis of imidazol and indolo[3,2-a]carbazoles derivative in metanol under mild conditions

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Operationally simple, atom economical, and scalable synthesis of imidazoles from 1,2-diketones, aldehydes and amines and indolo[3,2-a]carbazoles from 1,2-diketones and indoles is shown to proceed readily in methanol with high yield. The scope of the reaction is quite broad; a variety of aromatic and aliphatic, activated and unactivated aldehydes as well as amines and indoles have all been shown to be viable substrates for this reaction.

**Acknowledgments:**
Financial support of this work by Chemistry and Chemical Research Center of Iran is gratefully appreciated.

**OP-07** Highly efficient synthesis of DOS (Diversity-Orientated-Synthesis) molecules on SynPhase Lanterns for an oncology program

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Mimotopes’ SynPhase Lanterns have been widely used in both academic research and pharmaceutical industry for generating new leads and for performing lead optimization in drug discovery programs during the last decade [1]. As the community of drug discovery research has shifted its focus from generating a larger number of compounds with limited diversity to delivering more drug-like DOS molecules, SynPhase Lanterns’ advantage of superior reaction kinetics, hassle free handling coupled with the established spit-mix sorting system makes SynPhase Lanterns an ideal platform for DOS chemistry. A number of highly complex DOS libraries (some scaffolds shown below) designed for an oncology program were successfully synthesized using SynPhase technology. Based on the screening
results of these libraries, some prominent candidates were selected for multiple cancer indications, which have led to significant commercial interest.

References:

OP-08 A New Strategy for the Synthesis of C-1 Quaternary Tetrahydrossoquinolin-1-formaldehydes Using FeCl₃·6H₂O as the Promoter

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A skeleton-rearrangement of 1-arylbenzazepines was developed with the assistance of 2 equiv. of FeCl₃·6H₂O. The N-substituents played a dramatic influence on the structures of the products. In the case of N-alkylbenzazepines, 1-aryl-tetrahydrossoquinolines (THIQs) were obtained, whereas N-acyl-benzazepine substrates yielded a series of novel 1-aryl-1-formyl-tetrahydrossoquinolines (THIQs). The N-acyl-1-aryl-1-formyl-THIQs can serve as the intermediates to prepare corresponding N-alkyl-1-aryl-1-formyl-THIQs. These findings not only added an additional example of organic transformations aided by iron reagent, but also paved a novel avenue to access THIQs, especially those with a fully functionalized quarternary C-1 carbon centre. The unique structural features of 1-formyl-1-aryl-THIQs represent a series of novel compounds worthy for biological screening, and the 1-formyl group also provides a valuable functionality warranting for further functional transformations and for the synthesis studies on 1,2-conjugated natural products. (supported by grants from the Chinese National Science Foundation (30772625), Shanghai Commission of Science and Technology (07pj14104))

Reference:
OP-09  Salvianolic Borneol Ester --- A New Combinatorial Compound from classical Herbs Formulations for Potential Therapeutic Agent of Alzheimer’s Disease

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A common way to search a new leading compound in botanical medicine is to isolate active ingredients from one single herb. Usually it is also difficult to zero in on the active ingredient from numerous ingredients of a targeted herb. In present study, we offer a navel strategy to develop a new leading compound and keep the bio-effect of a classical herbal combination from a classical herbal formulation based upon historical practice.

Since the deposition of amyloid-β protein (Aβ) is the main pathological change of Alzheimer’s disease (AD) and the destabilization of preformed Aβ aggregates is one of therapeutic strategies for treatment of AD. We investigated effects of mixed extract of Salvia Miltiorrhiza(SM) and related single compounds on the destabilization of Aβ₁₋₄₀ aggregates by using the thioflavin T quick assay in vitro. A significant effect was found in the extract of SM, cryptotanshinone and salvianolic borneol ester (SBE). Especially, SBE, a new single compound inspired from classical SM formulations, intensively destabilized Aβ aggregates in a concentration-dependent and a time-dependent manner. The effect of destabilization was confirmed by transmission electron microscope (TEM) and time-of-flight mass spectrometry (TOF-MS). Our results suggest that SBE might be a novel template for potential therapeutic agent of AD.

Acknowledgments:
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OP-10 Structure guided lead discovery for next-generation streptogramins that are less susceptible to antibiotic resistance

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Synercid\textsuperscript{\textregistered} is used to treat infections caused by vancomycin resistant Enterococcus faecium, methicillin resistant Staphylococcus species and some Streptococcus species. This drug belongs to the class of antimicrobials, known as streptogramins, and is composed of a Group A (dalfopristin) and a Group B (quinupristin) antibiotic. Independently, these compounds are bacteriostatic against Gram-positive bacteria, however, in combination they exhibit synergistic bactericidal effects due to permanent inhibition of the 50S ribosomal subunit. Resistance to the Group B streptogramins is conferred enzymatically by streptogramin B lyase (Vgb), which cleaves the ring structure of these peptide drugs. Vgb is encoded on chromosomal DNA and on bacterial plasmids allowing for potential dissemination of resistance. We have determined crystal structures of Vgb from \textit{S. aureus} in the apoenzyme form and in complex with quinupristin at 1.65 and 2.8\textgreek{A} resolution. The three-dimensional structure of Vgb consists of seven highly twisted beta-sheets that form blades arranged in a circular array, with a central water channel that is closed off at the top face of the protein. The top face possesses a large depression where quinupristin was bound predominantly through van der Waals interactions. We have elucidated the novel reaction mechanism employed by Vgb, where the initial abstraction of a proton is facilitated by a Mg$^{2+}$-linked conjugated system. Contrasting quinupristin binding to Vgb and the natural target, the 50S ribosomal subunit, revealed positions on Group B streptogramin that can be exploited for modification. We have shown that one such alteration decreases Group B streptogramin susceptibility to Vgb-mediated resistance, while having no impact on its antibiotic properties.

References:

Acknowledgments:
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OP-11 Applications of Solid-Phase Organic Synthesis (SPOS) in Lead Identification and Optimization

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Over the past decade, solid-phase organic synthesis (SPOS) has been widely used in drug discovery to 1) accelerate lead optimization by either preparation of single compounds or small arrays, and 2) prepare large prospective arrays for high throughput screening (HTS) for future hit and lead identification. The latter approach has been enabled by the implementation of automated compound synthesis and processing tools.

This presentation will highlight the use of SPOS for rapidly optimizing two series of inhibitors of human glycogen phosphorylase \( \alpha \) for treatment of Type 2 diabetes. This presentation will also describe the design and solid-phase synthesis of several large libraries (5000 compounds) used for hit identification in HTS.

Glycogen phosphorylase \( \alpha \) inhibitors

Thiazole libraries for GSK compound collection enhancement

**OP-12 Identification of human IgG Fc-fragment binding ligands for use in affinity purification of human IgG**

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The usefulness of encoded combinatorial library synthesis and screening\(^1\), in combination with multivariate design of experiments, for rapid lead discovery of IgG Fc-fragment binding ligands for use in affinity purification of monoclonal antibodies will be presented. A virtual combinatorial library containing more than 200,000 compounds, each resulting from the combination of three building blocks, was generated. Subsequently, VolSurf 2 descriptors in combination with principal component analysis (PCA) and design of experiments (DOE), were employed to...
select a subset spanning the largest possible part of the available chemical space. The selected compounds were analyzed for their building block frequency, and overrepresented building blocks were tested for chemical reactivity.

![Figure 1. Observed frequencies of the three types of building blocks in the hit structures.](image)

Building blocks exhibiting limited reactivity were excluded, while the building blocks that were found to be sufficiently reactive were used to synthesize a combinatorial library containing of 770 compounds. Using a fluorescence based read-out, protein binding was quantified for 679 (88%) of the library members. Strong correlations in the building blocks comprising the hit structures were observed (fig 1).

Selected hits were synthesized in larger scale, immobilized on a suitable chromatographic resin and tested for their ability to purify human IgG from a crude cell culture. One of the tested leads was able capture IgG from the crude cell culture with a purity of 84% and a column capacity of 3.81 mg/ml.

References:

**OP-13 The Use of Combinatorial/High-Throughput Methods for the Rapid Development of Novel Surface Coatings**

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A combinatorial workflow has been developed for surface coating research and development. The workflow is comprised of high throughput methods for all aspects of coating research such as experimental design, polymer precursor synthesis and characterization, coating formulation, coating deposition, curing, testing, and data analysis. Currently, the workflow is being extensively utilized for the development of novel marine coatings, antimicrobial coatings for biomedical applications, and coatings for preventing metal corrosion. The workflow will be described in detail and some representative results obtained using the workflow will be presented.
OP-14  Towards a fully synthetic “phage-display like” system for high-throughput screening

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Phage display random peptide libraries represents the unique available tool for in vivo high throughput screening[1]. The selection and identification of peptide sequences on phages associated with a tumor or other tissue after i.v. administration of a phage library, permits the identification of novel tumor/tissue targeted peptide sequences. This technology opened new gates towards tissue/cell specific targeting and allowed new strategies for drug targeting and diagnostics. However, this approach is intrinsically limited to the identification of peptides. Here, we introduce a fully synthetic “phage display like” system aimed at overcoming this intrinsic limitation of phage display libraries. As a first proof of concept, we have synthesized mono-dispersed cross-linked microspheres bearing different intensity-levels of FITC suitable for flow-cytometry analysis as mixtures. The synthetic system possesses also a magnetic arm that can be eventually used for tracing (using MRI) and isolating microspheres from tissues. Model peptides and combinatorial biased positional libraries of 12x2 peptides were directly synthesized on the microspheres and were screened for binding to prostate cancer model cells PC-3 and DU-145 using flow-cytometry. Deconvolution of one library resulted in a peptide with high affinity for PC-3 cells as compared to model peptide DUP-1 known to bind to these cells as shown using fluorescent microscopy. Similarly, a small molecule library generated by the known Ugi-reaction was covalently bound to the same kind of microspheres and analysed on the same cell-based bioassay. This experiment allowed us to identify one compound having high affinity for PC-3 cells in a competitive manner with DUP-1 peptide.

Two products were validated using an independent FACS based affinity assay. A peptide derivative has been submitted to microscopy analysis showing large internalization into PC-3 cells.

Overall, this work demonstrates that synthetic “phage-like” systems can be developed on the base of nano/microspheres including direct synthesis on them. These "phage like" systems can be used in the future for high throughput in vitro/in vivo screening. The advantage of such system is that non-peptide molecules might also be synthesized and screened in contrast to phage display strategy that identifies only peptides.

References:

OP-15  A Combinatorial Approach for Studying Shape-Control of Silver Nanoparticles

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The advantage of such system is that non-peptide molecules might also be synthesized and screened in contrast to phage display strategy that identifies only peptides.
Silver nanoparticles have been extensively studied for more than three decades because of their attractively physical and chemical properties due to different shape. In our laboratory, we developed a high-throughput UV-vis spectra measurement system and applied to silver nanoparticles. In addition, a workflow of a combinatorial approach was built for developing silver nanoprisms, including experiment design (DOE), parallel synthesis process and high throughput screening. A Chemspeed Synthesizer was used for parallel synthesis of silver nanoparticles library, which was designed using commercial software. For high throughput screening, a custom-designed high-throughput UV-Visible spectra measurement system was established using a linear CCD array detector (HR4000, Ocean Optics). Sixteen samples were measured sequentially and automatically with errors less than 5%. The response surface methodology was used to explore the relationships between synthesis variables and nanoparticle size as well as yield. This combinatorial approach was tested by control of silver nanoparticle shape and yield with reactant concentrations. The results of TEM images and UV-vis absorption spectra revealed a variety of properties which were provided for surface response analysis. A cross-analysis method with a figure of merit was developed for high throughput screening the coupling effects of nanoprism size and yield. Preliminary results showed the cross-analysis method was able to efficiently explore the relationships between synthesis variables and nanoprism size as well as yield. The limitation of this method will be discussed. Similar approach could be use for developing various nanoparticles with different shape and size.

OP-16 Combinatorial Discovery of Visible-Light Driven Photocatalysts Based on the ABO₃-type (A=Y, La, Nd, Sm, Eu, Gd, Dy, Yb, B=Al and In) Binary Oxides

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The visible photocatalytic activities of different kinds of ABO₃-type (A=Y, La, Nd, Sm, Eu, Gd, Dy, Yb, B=Al and In) binary oxides were studied by a combinatorial method. The materials library was synthesized by a parallel solution combustion synthesis technique. Through the degradation reaction of Methylene Blue under sunlight, two novel photocatalysts: cubic YInO₃ and perovskite YAlO₃ were identified rapidly. Scale-up experiments confirmed that the two photocatalysts, especially the YInO₃, have excellent visible photocatalytic activity for toluene oxidation and water splitting.
OP-17  Advances in Microwave Technology

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Microwave chemistry has made significant strides over the past two decades. Once considered a method best suited for high temperature and high pressure reactions quickly and efficiently, microwave chemistry has evolved into a technique that can be used across the entire range of organic transformations. The use of microwave energy is not limited to high temperature / high-pressure reactions. It is a highly efficient energy source capable of performing otherwise challenging reactions in a very short period of time. This presentation will focus on the recent developments surrounding microwave chemistry, including the use of gaseous reagents, the ability to perform reactions at both high temperatures and low temperatures (T < 35°C) and other advanced microwave synthesis techniques.

PP-01  Probing Chemical Space with Pilot-Scale Libraries: Strategies towards Diverse Sultams as Potential Small Molecule Therapeutic Agents

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Diversity-oriented-synthesis (DOS) has emerged as a powerful strategy in the generation of structurally complex and skeletally diverse small molecules. In this regard a number of efficient strategies have emerged employing skeletal rearrangement utilizing both functional-group-pairing (FGP) strategies and tandem metathesis (TM) strategies. To this effect, a number of strategies have been developed where-by skeletally diverse sultams could be generated using a variety of Click-Click-Cyclize protocols which include, domino ring-opening metathesis/ring-closing metathesis/cross metathesis (ROM-RCM-CM) strategies, microwave assisted epoxide ring opening/ ring-closing SNAr protocols, oxa- and aza-Michael cyclizations and transition metal mediated cyclizations. Combined with ROMP-derived soluble oligomeric reagents and scavengers, pilot scale libraries of skeletally diverse have been synthesized and are currently undergoing HTS on numerous screening platforms within the NIH-MLSCN and other biological collaborators.

PP-02  A New Approach Towards Microwave-Assisted Method Development and Optimization

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New equipment for sophisticated microwave-assisted method development and optimization is introduced allowing efficient handling of small-scale applications as well as first grade laboratory scale-up at elevated pressure and enhanced temperature. Precise reaction control, extended operation limits and effective application of low-absorbing solvents allow for developing new and unusual reaction pathways in microwave synthesis, thus broadening the scope of chemical research. The concept of a modular equipment family is outlined, which enables applying optimized protocols on any applicable scale in the instrument without reoptimization. This increases the efficiency of microwave-mediated synthesis even further, speeding up the entire process of academic and industrial research.

PP-03 Identification of human IgG Fc-fragment binding ligands for use in affinity purification of human IgG

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The usefulness of encoded combinatorial library synthesis and screening1, in combination with multivariate design of experiments, for rapid lead discovery of IgG Fc-fragment binding ligands for use in affinity purification of monoclonal antibodies will be presented. A virtual combinatorial library containing more than 200,000 compounds, each resulting from the combination of three building blocks, was generated. Subsequently, VolSurf2 descriptors in combination with principal component analysis (PCA) and design of experiments (DOE), were employed to select a subset spanning the largest possible part of the available chemical space. The selected compounds were analyzed for their building block frequency, and over represented building blocks were tested for chemical reactivity.

Building blocks exhibiting limited reactivity were excluded, while the building blocks that were found to be sufficiently reactive were used to synthesize a combinatorial library containing of 770 compounds. Using a fluorescence based read-out, protein binding was, quantified for 679 (88%) of the library members. Strong correlations in the building blocks comprising the hit structures were observed (fig 1).

Selected hits were synthesized in larger scale, immobilized on a suitable chromatographic resin and tested for their ability to purify human IgG from a crude cell culture. One of the tested leads was able capture IgG from the crude cell culture with a purity of 84% and a column capacity of 3.81 mg/ml.
**PP-04** Environmental friendly and economical synthesis of β-aminoester under solvent free condition

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The rapid growth in energy production, industrialization and urbanization and a significant increase in agricultural production in the world have caused a remarkable increase in pollutant emissions during the past several decades. The consequences of these growing emissions have been closely connected with enforced pollution loading on human and ecosystems health, which results in actual and potential risk for many sensitive individuals and receptors.

On the other hands, development of strategically important processes which are environmentally clean, more efficient, and lead to greater structural variation, with very simple work up procedure and high purity that minimize the formation of waste, and high yields are currently receiving considerable attention. In this context, herein we reported a very mild, easy, and catalytic process for Michael addition of aromatic and aliphatic amines to α,β-unsaturated olefins in the presence of catalytic amount of silicone tetrachloride.

\[ \text{R} = \text{Ar, alkyl} \quad \text{X} = \text{CN, COOR, COR} \]

\[ \text{RNH}_2 + \text{SiCl}_4 \quad (2 \text{ mol} \% \text{ SiCl}_4) \quad 60^\circ \text{C}, 3 \text{ h} \quad \rightarrow \text{RHN} \quad \text{X} \quad \text{70-97\%} \]

**References:**

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**PP-05** Fluorous chemistry aided solid-phase synthesis of O-linked glycopeptides

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Glycoproteins play important roles in various biological events such as cell adhesion, differentiation, and proliferation, as well as in numerous pathological processes ranging from viral and bacterial infections to cancer metastasis. However, lack of convenient access to glycopeptides with specific structure has hindered...
understanding of the glycobiology. The need to develop a novel and efficient chemical synthetic methodology for the synthesis of glycopeptides is urgent. [2]

Here we for the first time combined the solid-phase glycosylation and fluorous chemistry for facile synthesis and purification of glycopeptides (Scheme 1). Tentagel S NH2 resin with the aryl hydrazide ‘safety-catch’ linker was used as the solid phase support. A pentapeptide with a disaccharide was successfully synthesized and purified by a simple F-SPE with light-fluorous tag on glycosyl donor. This method integrates the advantages of the solid phase synthesis with the superiority of fluorous chemistry. Simple filtration during solid-phase synthesis simplifies the purification of intermediates. The tagged target glycopeptide is obtained through fluorous separation that greatly promotes the synthesis of glycopeptides.

Scheme 1 Fluorous chemistry aided solid-phase synthesis of O-linked glycopeptides

Reference:

PP-06 Diversity-Oriented Synthesis of Angular Bis(benzimidazole) Derivatives

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Diversity-oriented synthesis of angular bis (benzimidazole) analogues with three appendages was successfully achieved on soluble support by the assistance of microwave irradiation with satisfied purities and yields. All the progresses of reactions on polyethylene glycol were precisely monitored by 1H NMR spectroscopy. Originally, the synthetic route was designed through the coupling of conjugated diamine 1 and 3-chloro-2-nitro benzoic acid 9. A serendipitous product 13 was obtained after subsequently S_NAr reaction and cleavage step. These versatile
angular bis(benzimidazole) analogues 8 are investigated by the VEGF-R3 kinase inhibition assay and compound 8m exhibited the best VEGF-R3 inhibition. It indicated that the -hydroxy functional group contributes to the inhibiting effect of the VEGF-R3 kinase.

![UK-1, AJI9561, UK-1 derivative](image)

References:

PP-07 Systematization of 1,2-dihydropyrrolo[3,4-β] indolizin-3-one: Theoretical investigation, design, synthesis, and photophysical properties

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Recently, We developed a novel fluorescent core skeleton, 1,2-dihydropyrrolo[3,4-β] indolizin-3-one, by complexity-generating one-pot reactions through 1,3-dipolar cyclization followed by oxidative aromatization. This fluorescent core skeleton can accommodate various wavelengths of emission maxima by changing the electronic properties of substituents, which was postulated by computational studies. [1] To systematize the developed fluorescent system, first we design the various fluorescent compounds supported with the computational simulation. Based on that study, many types of variations such as extension of conjugation length between fluorescent core skeleton and substituent, position of substituent, annulations of benzene ring to fluorescent core skeleton, direction of annulations and extended substituent pattern of donor acceptor pair, were given to fluorescent core skeleton to manipulate the photophysical properties of the fluorescent core skeleton. Not only photophysical properties-structure relationship, but also photophysical properties-computational simulation relationship in our fluorescent core skeleton system will be discussed.

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PP-08 The C–C, C–N and C–S bonds formation and the construction of diverse heterocyclic libraries

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Cross-coupling reactions are presently considered the cornerstones in the field of organic synthesis. Reactions leading to C–C, C–N and C–S bonds formation, which are often the key steps involved in a wide range of organic processes, have been widely applied in the synthesis of the organically and medicinally interesting building blocks throughout pharmaceuticals, agrochemicals, natural products, and materials. Microwave-assisted organic reactions have been applied to a wide range of reaction types, including aromatic nucleophilic substitution, cycloaddition, and organometallic reactions, and it accelerates a variety of synthetic transformations via time- and energy-saving protocols. Recently, we have developed highly efficient and practical protocols for the Sonogashira Coupling, Suzuki coupling, Buchwald-Hartwig amination as well as the Heck coupling that were catalyzed by the inexpensive and environmentally benign Fe/Cu or prompted by microwave assistant [1-6]. The short reaction times, simple reaction conditions, and coupling with a broad substrate scope render these methods particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

As a part of our continuing effort to assemble C–C, C–N and C–S bonds, we aimed to develop rapid, efficient and convenient protocols for the construction of diverse heterocyclic libraries [7-10]. Such as 2,6,9-substituted purines, 2,4 (1H,3H) -quinazolinediones, 1,3-dihydrobenzimidazol-2-ones, and 2H-1,4-benzoxazin-3-(4H) -ones, which are important scaffolds embedded in a variety of alkaloids and responsible for a variety of biological responses. The versatility of these methodologies is suitable for library synthesis in drug discovery efforts.

References:
[8] Zhaoguang Li, He Huang, Hongbin Sun, Hualiing Jiang, Hong Liu,* J. Comb. Chem. 2008, 10, 484.

PP-09 High-throughput Drug Screen Based on a Tumor Gene Target PDCD10

Hui Zhang², Hui Huang¹, Na Li¹, Taiping Shi¹
Apoptosis is a programmed cell death and plays an essential role in embryonic development, intracellular homeostasis and organism defense damage from in and out of the cells. Disorder of apoptosis has been validated to involve in many human conditions including neurodegenerative disease, ischemic damage, autoimmune disorders and many types of cancers. It’s meaning for studying on the factors associated with apoptosis, and some drugs designed on those targets have been applied in treatments of some tumors. Previous researches have suggested that PDCD10 (programmed cell death 10) can function as an antiapoptotic gene interacting with MST4, a member of Ste20-related kinases family, and promote cell proliferation and transformation via modulation of the extracellular signal-regulated kinase (ERK) pathway. Moreover, knockdown the expression of PDCD10 or MST4 significantly attenuated cell growth and anchorage-independent growth. And more importantly, either overexpressing or endogenous PDCD10 can increase the MST4 kinase activity in vitro.

We successfully expressed and purified recombinant protein PDCD10 and MST4 in E.coli BL21(DE3). ELISA assay revealed that recombinant MST4 might phosphorylate substrate to a certain extent, and recombinant PDCD10 might promote the phosphorylation. We then established compounds screening platform based on this ELISA assay. To find out inhibitors of PDCD10, we have screened about thousands of compounds from a compound library cooperated with Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, and found one compound could inhibit the activity of PDCD10 and MST4. Western blot analysis and flow cytometry assay would be used to validated the specific effect of the positive compound on PDCD10. We would optimize the lead compounds and evaluate the pharmacology effects for further application.

PP-10 Polymer-supported ionic liquids for conversion of fructose into 5-hydroxymethylfurfural

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Utilizing renewable carbon sources, such as biomass, is becoming increasingly important part of strategy to lower the total emissions of CO2. Abundant biomass resources can be transformed into sustainable supply of valuable intermediates for the production of plastics, fine chemicals, and fuels.1 Among many possible biomass derived chemicals, 5-hydroxymethylfurfural (5-HMF) has already been considered as one of the key platform chemical intermediates which can be converted to various chemicals such as 2,5-furandicarboxylic acid, 2,5-dimethylfuran, 2,5-bis (hydroxymethyl) tetrahydrofuran and 2,5-dihydroxymethyl furan. Fig.1 shows a general type of the
reaction. \[2\]

Fig. 1 Dehydration of Fructose to 5-HMF

Recently, ionic liquids (ILs) have attracted considerable attention because they have been considered as a new and environment-friendly reaction medium. Ionic liquid immobilized polymer supports also brings many advantages such as stability, reusability and easier separation. Here, we prepared various types of ionic liquid immobilized polymer beads from chloromethyl polystyrene (CM-PS) resin and proved that they were efficient heterogeneous catalysts for the dehydration processes of fructose, separation and recycling. The influence of a substituted group of imidazolium salts and anions on their catalytic activity for this conversion was summarized.

References:

Acknowledgments:
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PP-11 Antioxidant activity of hydroxycinnamoyl-dipeptide library

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Antioxidants have been intensively studied for disease treatment and prevention. They are also industrially utilized as food additives to inhibit food deterioration and as cosmetic ingredients to delay skin-aging\[^{[1]}\]. Hydroxycinnamic acid exist broadly in nature and exhibit antioxidative activities\[^{[2]}\]. In our previous study, we conjugated hydroxycinnamic acid with the well-known antioxidative peptides and demonstrated their synergistic effect by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging test and lipid peroxidation test \[^{[3]}\]. Hydroxycinnamic acid conjugated with carnosine (β-alanyl-histidine) showed enhance antioxidative activities, which seemed to be originated from the radical scavenging activity of histidine.

Herein, we synthesized hydroxycinnamic acids conjugated with histidine dipeptide libraries by solid phase peptide synthesis (SPPS) method and measured their antioxidant activities. As expected, when histidine-containing dipeptides were conjugated to hydroxycinnamic acid, they showed much enhanced antioxidative activities in both of the assay systems. We selected several active
compounds and further optimized their antioxidant activities by changing their concentrations, functional groups and the position of histidine. The compounds have shown great potential to be used as an active and safe antioxidant in pharmaceutical and cosmetic industries.

References:

Acknowledgments:
This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A050432).

PP-12 Preparation of Ladder Type Peptide Library with Multiple Capping Reagent and Its Application to Screening of Serine/Threonine Kinase Peptide Substrate Specificity

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Since the One-Bead One-Compound (OBOC) peptide library method was first presented in 1991, it was widely used for finding the peptide ligands/substrates of proteins [1]. The OBOC peptide library can be also synthesized in ladder-type by using capping reagents during each coupling steps and, as a result, a full peptide substrate for bio assay and its fractions for sequencing are synthesized on the same resin beads. The peptides fractions reveal several peaks in MALDI-TOF MS analysis due to their mass difference, and the sequence of the target peptides were easily identified by matching each of the mass differences with the corresponding amino acids. By applying these techniques on photo labile linker (PLL) coupled HiCore resin [2][3] , the peptide substrate specificities of tyrosine kinases, such as p60\(^{\text{tyr}}\), ZAP-70, and Brk were successfully screened [4][5]. But there is one short coming in applying this method for the identification of peptide substrates in full-fledged way. For example, a pair of leucine and isoleucine, and glutamine and lysine cannot be distinguished from each other directly because they have same molecular weight. To overcome this problem, we used multiple capping reagents, when necessary after coupling steps. By using different capping reagents, we could identify and distinguish isobaric amino acids directly from OBOC peptide library. After preparation of OBOC peptide library and using multiple capping reagents, we applied this for the screening of peptide substrate specificity of several serine/threonine kinases successfully.

References:
In this study, the practical construction of pilot library with benzopyranylpyrazole—a novel core skeleton through the recombination of privileged structures, benzopyran and pyrazole—was successfully conducted through the efficient utilization of solution-phase parallel synthesis using solid-phase reagents and solid-phase parallel synthesis. We also developed a novel procedure for the synthesis of benzopyranylpyrazoles via regioselective condensation of substituted hydrazines with \( \beta \)-keto aldehyde. The diversity of this core skeleton was expanded by the regioselective introduction of alkyl- and aryl-substituent at the \( R_1 \) diversity point on pyrazole moiety and by the introduction of piperazine on benzopyran substructure, which provide the \( R_2 \) diversity point. Lastly, the introduction of nitro group on benzopyran moiety can accelerate the nucleophilic aromatic substitution of piperazine and provide the \( R_3 \) diversity point at the aniline moiety through the reduction of nitro group. In this pilot library, we only focused the diversification at \( R_1 \) position with either \( R_2 \) or \( R_3 \) position, which was maximized its diversity through the rational selection of building blocks using chemoinformatics. Overall, 192-membered benzopyranylpyrazole pilot library was constructed with pending potentials for further diversification, and the average purity of the library is 87%.

References:

PP-14  
Polymer-Supported \( N \)-Heterocyclic Carbene-Copper(I) Catalyst for “Click Chemistry”
Recently, “click chemistry” has drawn great interest as one of the most powerful ligation methods that can simply and quickly generate almost unlimited libraries of compounds. The “click” reaction, especially Cu(I) catalyzed version of the Huisgen [3+2] cycloaddition between organic azides and terminal alkynes yielding 1,4-disubstituted 1,2,3-triazoles has numerous applications in biology, material science, and organic synthesis. Since Cu(I) was known to be an effective catalytic species in 2001,[2] many types of Cu(I) catalyst have been developed.[3] However, most of them were homogeneous type and brought about significant problems such as difficulties in separation and recovery of the expensive, toxic catalysts. To avoid these drawbacks, several heterogeneous catalyst systems were also reported.[4] Nevertheless, there is still a need for developing new heterogeneous Cu(I) catalyst system that is stable in air and moisture and highly active for “click” reaction. Herein, we describe the polymer-supported NHC-Cu (I) catalyst as a simple, convenient and efficient heterogeneous catalyst for the “click” reaction of various azides and terminal alkynes. In the presence of the catalyst, the “click” reaction proceeded smoothly with high yields.

References:

Acknowledgments:
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PP-15 Preparation of Macroporous Poly(methacrylic acid-co-methyl methacrylate) (PMAA-co-PMMA) Bead with Uniform Sized Pore and Its Bio Application

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Many researchers have made strong effort to develop macroporous polymer beads which can be used as solid supports in solid-phase organic synthesis and as adsorbents in column chromatography.[1] However, despite of a quite number of endeavor, it is still hard to control the porosity and the pore size distributions within the polymer beads by previously reported methods.
In this study, we prepared silica nanoparticles (NPs) embedded poly (methyl methacrylate) (PMMA) beads by polymerization of methyl methacrylate monomer with mono dispersed silica NPs. Then, the silica NPs embedded PMMA beads were hydrolyzed with sodium hydroxide for obtaining macroporous structure by removing the embedded silica NPs. At the same time, part of methyl methacrylate turned to methacrylic acid, which led PMMA beads to macroporous poly (methacrylic acid-co-methyl methacrylate) (PMAA-co-PMMA) beads. For bio application, trypsin was immobilized to the macroporous PMAA-co-PMMA beads. The immobilized trypsin revealed full enzyme activity and reusability for peptide bond cleavage. We expect that the macroporous PMAA-co-PMMA beads are applicable in various bio applications.

References:

Acknowledgments:
This work has been supported by the Intelligent Micro System Center, which is sponsored by the Korea Ministry of Commerce, Industry & Energy.

PP-16 Microwave-Assisted Fluorous Synthesis of 1,4-benzodiazepine-2,5-diones Libraries

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Compounds with a 1,4-benzodiazepine-2,5-diones core exhibit a wide range of pharmacological properties. A library of 1,4-benzodiazepine-2,5-diones was synthesized in this project using microwave-assisted fluorous chemistry method. A perfluorooctanesulfonyl tag was used to protect 4-hydroxy benzaldehydes in Ugi four-component reactions to facilitate the separation of intermediates. The introduction of fluorous tag had no negative impact on the reactivity of the reactants and improved the yield of Ugi four-component reactions. The perfluorooctanesulfonyl tag was readily removed by microwave-assisted and palladium-catalyzed Suzuki coupling reactions to introduce diverse aryl components to benzodiazepine rings. All the intermediates and final 1,4-benzodiazepine-2,5-diones were characterized by HPLC/MS. Final products were also characterized by 1H NMR, HRMS and 13C NMR. In this work, two diverse 4-hydroxy benzaldehydes, four diverse anthranilic acids, five diverse amino acid esters and one isocyanide were applied in four-component reactions and eight diverse boronic acids were used in the Suzuki coupling reaction. A larger library of 1,4-benzodiazepine-2,5-diones can potentially be generated in our future research.
PP-17  Discovery of novel small molecule inhibitors against protein tyrosine phosphatase 1B by high-throughput screening

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Protein tyrosine phosphatase 1B (PTP1B) plays a critical role in many physiological and pathological processes and regarded as a promising target for the treatment of diabetes and cancer [1, 2]. Great efforts have been devoted to the development of potent and selective PTP1B inhibitors. They are mainly active site-directed pTyr mimetics or targeted at the secondary binding pockets around the conserved active site. However, selectivity between PTP1B and other highly homologic PTPs and low bioavailability remains as two obstacles to seek for anti-PTP1B drugs. Herein, several small molecules have been identified as potent PTP1B inhibitors by in vitro screening our in-home chemical library based on privileged structures.

The inhibitory activity of the most potent hit is calculated as IC₅₀=2µM using both endpoint and kinetics methods. Selectivity study showed the hits possessed more than 2-folds selectivity between PTP1B and src homology phosphatase-2 (SHP2), and 5-folds between PTP1B and another non-receptor type PTP (haematopoietic protein tyrosine phosphatase, HePTP). Primary structure-activity relationship analysis showed the large lipophilic groups may increase the activity, meanwhile reducing the solubility. Compared with the known PTP1B inhibitors, the hits are more drug-like and showed considerable potency without negatively charged groups. Modification on the diverse points is undergoing to improve the inhibitory activity and selectivity between PTPs.

References:

PP-18  Parallel synthesis and antitumor evaluation of 1,2,3-triazoles libraries

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Akt (protein kinase B, PKB) is a serine/threonine kinase that promotes cellular proliferation, growth, survival. Akt activation plays a critical role in tumorigenesis.
Consequently, Akt inhibitors could be powerful anticancer agents. Many kinds of Akt inhibitors have been developed during the past few years. Among them, H-89 is an important lead compound with sulfonamide and ethylenediamine groups as pharmacophores.\(^1\)\(^,\)\(^2\) Besides, 1,2,3-triazoles have been well-recognized for their broad range of pharmacological properties, such as antiviral, antifungal activities, especially their antitumor activity.\(^3\) Thus, we focused on parallel synthesis of 1,2,3-triazoles with sulfonamide and ethylenediamine groups via a Cu(I)-catalyzed 1,3-dipolar alkyne-azide coupling reaction. Herein, the focused triazoles library was synthesized and tested for antiproliferative activities in vitro against different tumor cell lines. Most of the compounds showed good antiproliferative activities against HL-60 cell line. Compound OLL039 exhibited high potency with an IC\(_{50}\) value of 1.45 µM, while only few compounds showed good antiproliferative activities against HepG2 cell line, except compound OLL038 with an IC\(_{50}\) value of 3.34 µM. Further structure modification and biological assays are underway.

References:

Acknowledgments:
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PP-19 The discovery and optimization of novel small molecules inhibiting the interaction of CKLF1 and CCR4

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A number of investigations have been linked to respiratory viral infections and chemokines. Chemokine-like factor1 (CKLF1) is a new chemokine that has a broad spectrum of chemotactic activity on lymphocytes.\(^{[1]}\) In addition, CKLF1 can promote proliferation of mouse muscle cells and human bone progenitor cells, and thus has a significant function in asthma. CKLF1 has been identified as one of the ligands of CCR4.\(^{[2]}\)
Using a competitive ligand-receptor binding assay targeting CKLF1 and CCR4 interaction, we found a hit (IMMLG190) through screening our privileged structure libraries. Moreover, a set of novel compounds were designed to modify IMMLG190. The synthesis and preliminary structure-activity relationship will be presented. Through structure modification and optimization, we discovered three more potent compounds.

References:

PP-20  Synthesis and immunological activities evaluation of a new muramyl dipeptide derivative (MDP-11)

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Muramyl dipeptide and its derivatives have widely biological activities such as adjuvant activity, stimulation of nonspecific resistance against bacterial, viral, and parasitic infections and against tumors ect. However, their applications were limited in clinic due to some side effects and quick elimination. Therefore, we have deeply concerned with the synthesis and immunological studies of its derivatives in order to avoid the side effects with improved and more defined pharmarcological profiles. Our group recently found a new MDP derivative named MDP-11, which structure is composed of three building blocks, however, without sugar fragment. They are D-Gln, as the necessary pharmacophore, L-Phe and benzoic acid derivative. Advantageous solid-phase peptide synthesis method and basically satisfied immunological activity of MDP-11 revealed that the compound could be a novel and nonspecific immunostimulator.

PP-21  Chemical Library and Structure–Activity Study of Analogues of (+)Calanolide A as Anti-HIV-1 Agents

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(+)-Calanolide A, one of naturally occurring coumarin derivatives, isolated from a tropical rainforest plant of the species Calophyllum lanigerum, has been reported to be active against HIV-1 and Mycobacterium tuberculosis. Its impressive biological activity, coupled with the striking structure featuring a densely functionalized benzene core adorned with three contiguous benzopyran subunits, prompted us to undertake the synthetic and biological studies of novel analogues of (+)-Calanolide A.
Our initial investigation resulted that racemic 11-demethyl-12-oxo calanolide A, which had two fewer chiral carbon centers at the C-11 and C-12 positions than (+)-calanolide A, had a comparably inhibitory activity and better therapeutic index (EC$_{50}$=0.11 μM, TI=818) against HIV-1 in vitro. A library based on this structural core was then designed and synthesized with introduction as the most diversity points as possible (Figure 1). The systematic evaluations of anti-HIV-1 activity in vitro concluded their structure–activity relationships (SARs). Finally, some promising compounds showing potent anti-HIV-1 activity, i.e. 10-bromomethyl-11-demethyl-12-oxo calanolide A (EC$_{50}$ =2.85 nM, TI > 10,526) [1], were obtained. Continuous studies focusing on the synthetic methodology and biological activity of novel 10-substituted-11-demethyl-12-oxo calanolide A analogs will be discussed.

![Chemical Structures](image)

Figure 1 Design of analogues of (+)-Calanolide A

References:

PP-22 A Convenient, Protection-free protocol for synthesis of compound libraries from amino alcohol scaffolds

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An adapted method for the convenient synthesis of compound libraries from amino alcohols is presented. Operating on one of two possible sites with similar reactivity requires careful control of conditions and usually results in formation of side products. Orthogonal protection of one site allows operation on the alternate site but is usually followed by an additional deprotection step. Additional steps usually add to the complexity of the reaction sequence and decrease yields. Herein, we report a simple protocol to operate on the amine functionality of an amino alcohol without protecting the hydroxyl. The protocol employs potassium carbonate as a heterogeneous base in a 9:1 mixture of dichloromethane with methanol as solvent for carrying out N-acylations of amino alcohols. The advantage of the method is that the base is removed by a simple filtration at the end of the reaction whereas the methanol acts as an internal quench reagent converting the excess acyl halide to the corresponding methyl ester. This gives clean reaction profiles with no aqueous
workup and a simple chromatographic purification (if any) to get pure compounds in high yields and purities. This methodology for the synthesis of compound libraries allows quicker throughput, lowered cost per compound and cleaner reactions using off-the-shelf reagents, without compromising on quality or quantity of final product.

**PP-23**  
**Systematic structure-based design and synthesis of novel heterocyclic compound with potent anti-influenza activity**

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Influenza remains an important disease in human and animals. Three pandemics of influenza occurred in the last century, with an estimated death toll of million people. [1] The recent outbreak of highly pathogenic avian influenza virus H5N1 and 2009 H1N1 influenza (swine flu) highlight the urgent need for new classes of antiviral drugs. [2]

Basing on the high-throughput screening of our privileged structures library in stock, a series of compounds showed inhibitory activity on both Flu A and Flu B in collaboration with NIAID/NIH.

In this paper, one of the hited compounds consists of several critical components was optimized in medicinal chemistry to facilitate the understanding of respective contributions to inhibitory potency at the target virus. Sixty compounds were synthesized and tested for anti-influenza. Some of them exhibited the strongest activity both *in vitro* and *in vivo*. Basing on the structure-activity relationship (SAR), and optimization of the antiviral activity through systematic structure modification of the hitted compound, we wish to find a novel and effective small molecule inhibitors of influenza.

References:


**PP-24**  
**Synthesis of Pyrazolo[3,4-b]pyridinyl Hetero-biaryl compounds**

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Hetero-biaryl (HB) compounds are widely detected in numerous bioactive compounds, pharmacophore of drug-like molecule as well as potential drugs. A large number of coupling methods for obtaining HBs, such as Kumada, Negishi, Stille and Suzuki coupling, have been developed over the past years. Although these reactions provide a lot of advantages like wide reaction scope, functional group compatibility and relative good yield, they have several limitations. For example, low efficiency with bulky substrate, toxicity from dealing with transition metal, extra effort for screening proper catalyst or additive, expense and safety issue.
Therefore, we considered that another approach for obtain HBs in convenience should be meaningful. We develop a new synthetic method to afford pyrazolo[3,4-b]pyridinyl HBs from indole derivates as electrophile with aminopyrazole in one-step. Most of starting materials are commercially available or easily prepared by Vilsmeier-Haack reaction of indole substrates. Through optimized reaction condition, we can synthesize various pyrazolo[3,4-b]pyridinyl derivates in moderately yield. Our strategy shows broad reaction scope and can be applied the substrate with various functional groups. We can observe regioselectivity of pyridinyl structure due to possibility of attacking aminopyrazole. As well as, it provides highly bulky ortho-substituent biaryls, which usually regard as difficult to synthesize by widely used methods.

**PP-25 Solid Phase Parellel Synthesis of Diverse Libraries of Oleanolic Acid**

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Pentacyclic triterpenoids are known to exert their antitumor actions through different mechanisms, e.g., inducing apoptosis, inhibiting angiogenesis and tumor metastasis. However, most of pentacyclic triterpenoids showed only moderate activity, and only a few efforts to optimize their structures have been reported. Here we reported the design and solid phase parallel synthesis of diverse libraries of a pentacyclic triterpenoid, oleanic acid (1), and its A ring modified analogs 2a-d.

![Chemical Structures](image)

Modifications on A ring of 1 were first realized in liquid phase, leading to the 1-OH (2a), 2α-OH (2b), 3α-OH (2c), 23-OH (2d) analogs. Then we attempted to design and prepare diverse libraries with 1 and 2 as scaffolds. The principle is to attach diverse structures of substitutents to different positions on A ring of 1, in order to maximize the diversity of the derivatives in chemical space. With Lipinski’s rule of 5 as selection criteria, we selected a series of carboxylic acids from MDL ACDLab database, and then grouped the acids into 33 sets based on the difference of their hydrophobic, electrostatic and steric parameters. One representative acid was extracted from each set to form the whole set of building blocks for a diverse library. The library synthesis of 3β-OH esters of 1 were realized after its attachments to acid-labile resins and subsequent chemical transformations. We also tried to predict the reactivity for different acids with 3β-OH of 1 esters based on their hydrophobic, electrostatic and steric parameters, and monitor the ending point of the esterification.
reactions with different indicators. The reaction conditions, attachment and cleavage of the resins have also been optimized.

Cytotoxicity, inhibition of endothelial cell migration, and antiangiogenesis assays of oleanolic acid derivatives from the diverse libraries were performed, showing that some derivatives are better than 1 in one or more assays. These results demonstrated the potential of our diverse libraries as the reservoir for leading compounds with the antitumor activities. Further library preparation and biological evaluation are still undergoing in our lab.

References:

PP-26 Synthetic study of telomestatin derivatives by way of palladium-catalyzed coupling reaction of 5-bromooxazole

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Telomestatin[1] (1), isolated from Streptomyces anulatus 3533-SV4, is a potent specific telomerase inhibitor (IC50 = 5.0 nM) because it acts on a human telomere sequence to stabilize the specific DNA structure called G-quadruplex without affecting DNA polymerases or reverse transcriptases. The unique macrocyclic structure of telomestatin consists of the macrocyclic linkage of two methyloxazoles, five oxazoles, and one thiazoline ring. Because of the unique chemical structure along with its unusual and useful biological activity, telomestatin is an attractive synthetic target. It is also a candidate for the design and synthesis of analogues relevant to anti-cancer drug development. In 2006, we achieved a total synthesis of telomestatin [2]. Here, we wish to report the synthesis of telomestatin derivatives by diversification of the key intermediate containing 5-bromooxazole utilizing palladium-catalyzed coupling reactions.

We initially investigated the synthesis and functionalization of 5-bromooxazole 2. It was found that various functional groups were successfully introduced to the 5-position of the oxazole unit utilizing palladium-catalyzed cross coupling reaction and nucleophilic aromatic substitution reaction. Next, the cyclic compound 6
containing a 5-bromooxazole was synthesized from monooxazole 2, 3 and 4. Palladium-catalyzed cross coupling reaction of 6 with various boronic acids proceeded leading to the corresponding telomestatin derivatives.

References:

PP-27 An Integrated System for Preparation and Management of Diverse Compounds from Commercial, Synthetic, and Natural Sources

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The goal of our drug discovery research is to discover and develop novel chemical entities that increase understanding of the pathophysiology of or function as therapeutic leads for the treatment of catastrophic pediatric illnesses. One of our approaches is to utilize diverse chemical compounds for lead discovery. Our diverse screening compounds come from three sources: commercial vendors, internal high-throughput synthesis, and internal natural products separation. Our collection has more than 500,000 unique compounds and the expansion rate of this collection is nearly 10% a year. The complexity of the molecular diversity generation and the large numbers of operations require a highly integrated system to control, operate, and manage all the processes and compounds. We have developed an efficient system to integrate these three compound sources and multiple compound-related operations moving these compounds from crude compounds to high throughput screening to avoid the delays often experienced in the lead discovery stage. The process involves multiple custom-built protocols using Pipeline Pilot to receive, register, purify or separate, quantify, analyze, reformat, store and retrieve compounds. With this molecular diversity platform, biological exploration using chemical diversity can be efficiently and precisely carried out without human error.

Acknowledgements:
We appreciate collaborations from High Throughput Chemistry Center and High Throughput Screening Center at St. Jude Children’s Research Hospital, and National Center for Natural Products Research, University of Mississippi.

PP-28 Cancer Cell Inhibitory Activities of Diverse Pyrrolidine Dithiocarbamate Analogues

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Dithiocarbamates are a class of sulfur-based metal-chelating compounds with various applications in medicine. We reported previously that certain members of dithiocarbamates, such as pyrrolidine dithiocarbamate (PDTC), diethylthiocarbamate and disulfiram, were able to bind with tumor cellular copper,
inhibit proteasome, and induce apoptosis. Disulfiram has been used to treat alcohol
toxification by inhibiting aldehydes dehydrogenase (ALDH). Our goal is to optimize
dithiocarbamates for their proteasome inhibition, apoptosis induction, and cellular
inhibition activities without affecting ALDH. In the current study, we synthesized
diverse PDTC analogues with substitutions made to the pyrrolidine ring and studied
their cancer cell and ALDH inhibitory activities. Our data demonstrate that molecular
diversity is a powerful approach for exploring anti-cancer activity of small molecule
metal chelators.

PP-29 The further study of Unique Spirocyclopiperazinium as Analgesics

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The discovery of high efficient analgesics without the side effects of drug
dependency is highly desirable in pain treatment. During the course of developing
analgesic drugs with new structure and mechanism, we have found several kinds of
piperazinium compounds with high analgesic activity, 1-7 and preliminary
structure-activity research hints that the structure of spirocyclopiperazinium is
important. Encouraged by the information described above, we chose compound 1 as
the lead compound since it had moderate analgesic activity while quite low effective
dosage (0.2mg/kg sc, analgesic activity 70.4%) , then a series of
spirocyclopiperazinium derivatives 2 were designed and prepared to improve the
analgesic activity and decrease the toxicity. Pharmacology tests displayed that some
of them exhibited similar analgesic activity to the precursor compound 1 but lower
toxicity. The further investigation is in progress.

References:
2003, 13, 1535
2003, 13, 1729
Acknowledgments:
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**PP-30**  
Library synthesis of 3-hydroxyflavone derivatives and as fluorescent probes in biology systems

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3-Hydroxyflavones (3HFs) are dual-band fluorescent dyes due to an excited state intramolecular proton transfer (ESIPT) reaction. The dual emission of 3HF is highly sensitive to the properties of the environment, such as polarity, H-bond donor and acceptor ability, so that these dyes have been served as highly sensitive monitors of their microenvironments in biologically systems$^{[1]}$. It has been disclosed that the introduction of an electron donor group to the 4’-position of the 3HF increased the sensitivity of fluorescence, and the attached positively charged ammonium group at 6-position of the 3HF dramatically changed the relative intensities of the two emission bands$^{[2]}$.

In order to demonstrate the effect of aliphatic hydrocarbon chains, we synthesized two series 3HF derivatives with different lengths at 4’-and 6- position as shown in Scheme 1. The selected $R_1=$n-C$_2$H$_5$ and n-C$_4$H$_9$, the selected $R_2=$Me, n-C$_4$H$_9$, n-C$_6$H$_{13}$, n-C$_7$H$_{15}$, n-C$_8$H$_{17}$, n-C$_9$H$_{19}$, n-C$_{10}$H$_{21}$, n-C$_{10}$H$_{21}$, n-C$_{12}$H$_{25}$, including both even-numbered and odd-numbered carbon chain. The probes were synthesized from the starting material compound 2 by chloromethylation and Algar-Flynn-Oyamada reaction to get compound 5, then 6-ethoxymethylflavone derivatives were transformed into 6 by heating at 90°C in 40% HBr. The target probes were got from 6 with different tertiary amines. All 16 derivatives have been characterized by LC-MS and/or $^1$HNNMR. These fluorescent probes have been applied in biologically systems, including sonicated DOPC unilamellar vesicles (SUVs) and bovine serum albumin. Preliminary fluorescent study indicated the fluorescence intensity increased by addition of SUVs , but the increased intensity scales were depend on the length of carbon chain.

![Scheme 1](image-url)
**PP-31** Novel synthetic routes of 1,4-benzodiazepine derivatives via Ugi 4CR

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1,4-Benzodiazepine derivatives have shown various biological activities, such as anxiolytic, anticonvulsant, antihypnotic agents, selective cholecystokinin receptor subtype A or B antagonists, and so on. They are identified as an important type of privilege structures. Great attention has been drawn to the synthesis of this kind of heterocycles.\(^2\)

Multi-component reactions have become one of the most powerful methods for synthesis of small molecule libraries. The products are formed in a single step with simultaneous condensation reactions of several reagents. Simply varying components in MCR can greatly improve the molecular diversity required for combinatorial libraries. Ugi reaction is one of the most important 4-components reactions. It has been used to construct a large number of heterocycles library.\(^2,3\)

Here we reported several new synthetic routes to prepare the 1,4-benzodiazepin derivatives via Ugi 4CR, followed by other reactions such as reduction and cyclization. The Ugi reaction introduced great molecule diversities under the mild and easy to operate conditions. Some of the derivatives, e.g. 1,4-benzodiazepin-2-one, were synthesized through a one-pot reaction without purification of intermediates. A small library is under construction.

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**References:**


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**PP-32** A new synthetic method and biological evaluation of 1,4-Benzodiazepin-2,5(1H)-diones derivatives

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1,4-Benzodiazepin-2,5(1H)-diones core is well known as a “privileged structure” and possesses a broad spectrum of biological activities, including anticonvulsant, anxiolytic, anti-tumor properties and so on.\(^1\) Thus, to introduce the substituent diversity on 1,4-Benzodiazepin-2,5(1H)-diones core was greatly interesting by both medicinal chemists and organic chemists. Our recent efforts resulted in a practical and efficient parallel solution-phase method, in which a variety of compounds substituted at the 3-, 7-, and 8-positions of 1,4-Benzodiazepin-2,5(1H)-diones were synthesized.
The synthetic route to the multi-substituted 8-amino-1,4-benzodiazepin-2,5(1H)-diones derivatives is depicted in Scheme 1.

Scheme 1. Synthetic route to 8-Amino-1,4-benzodiazepin-2,5(1H)-diones derivatives.

(a) Phenols, 2h; secondary amines, 24h  
(b) SOCl₂, 2h  
(c) Methyl amino acid esters hydrochloride, 0°C, rt, 4h  
(d) Fe dust, 90°C, 4 h (e) ClCH₂COCl, rt, 1h (f) secondary amines, 40°C, 60h

A library based on the above structural core was designed and synthesized with introduction of three diversity points. Potent activity in vitro was observed in the NCI 60 human cancer cell line panel. Two novel compounds were identified to have GI₅₀ at 10⁻⁷ anti-tumor potency level. This finding provides an important clue that further optimization may conduct to obtain drug candidates with better anti-tumor activity.

References:

PP-33 A novel method for synthesis of analogues of benzimidazole-type proton pump inhibitors

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Benzimidazole-type proton pump inhibitors (PPIs) are a significant part of therapy for most acid-related diseases including gastroesophageal reflux disease, peptic ulcer diseases and acute gastrointestinal bleeding. [1] Over the past years, a number of advances have been archived for these type agents including the synthetic methods. Herein, a new synthetic route from 1,5-difluoro-2,4-dinitrobenzene (DFDNB) is reported to introduce more diversity points into the benzimidazole core to seek for novel proton pump inhibitors (Scheme 1).
To oversee the advantages, firstly, this method will help us to systematically investigate the structure-activity relationships (SARs) of benzimidazole ring, which did not previously pay enough attention. Secondly, two disparate intermediates were simultaneously gained (Route2-A and Route2-B) in the third reaction step, which enables us to generate the substituent diversities under the reliable reaction conditions.

References:

PP-34 Nano-Combinatorial Chemistry – A Novel Strategy for the Discovery of Biocompatible Nanotube through Combinatorial Nanotube Library Synthesis with Maximum Surface Chemistry Diversity

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A surface-modified multi-walled carbon nanotubes (MWCNTs) library containing 80 members was constructed through combinatorial synthesis. We discovered novel functionalized-MWCNTs with reduced protein binding, cytotoxicity, and immune responses using multiple biological screenings. In order to reveal the structure-activity relationship, magic angle spinning proton nuclear magnetic resonance spectroscopy (MAS 1H NMR), Fourier transform infrared spectroscopy (FTIR) and elemental analysis were applied to characterize MWCNTs’ surface molecules. Our approach is more effective in mapping chemical space governing
nanotube biocompatibility. In our subsequent studies, we investigated interactions between the f-MWCNT library and α-Chymotrypsin (ChT). We discovered four f-MWCNTs that site-specifically bound to ChT’s catalytic site and competitively inhibited ChT’s enzymatic function. Our results demonstrated the general utility of the nanocombinatorial library approach in nanomedicine and nanotoxicity research.

PP-35 Synthesis and biological screening of benzopyrano-Heterocyclic focused library for the Development of novel therapeutic agent of Osteoporosis

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Osteoporosis is a disease of bone that leads to an increased risk of fracture, which is a big threat to health among those aged people and cancer patients. Osteoclast, which acts together with osteoblast keeps the bone homeostasis in a process called bone remodeling and the incremental change of osteoclastogenesis is one of the major direct causes of osteoporosis. Biomedical scientific communities have focused on either the prevention or the medication of osteoporosis. Although there are several medicines, such as bisphosphates and hormones, available for the treatment and prevention of osteoporosis, new chemical entities as anti-osteoporosis agents are needed due to the significant side effects of existing therapeutic agents. To address these unmet demands, we aimed to discover new therapeutic agents for the treatment of osteoporosis using the molecular diversity and chemical biology.

The identification of RANKL initiated the fundamental understanding of osteoclastogenesis in osteoporosis, and the functional perturbation of RANKL-induced osteoclastogenesis can become an important readout in the format of cell-based screening with preosteoclast cells, Raw264.7. Through our mechanistic understanding of RANKL-induced osteoclastogenesis, we initiated the high throughput screening with the molecular diversity constructed with high throughput chemistry under the concept of diversity-oriented synthesis. After our extensive search of bioactive small molecule inhibitor toward the RANKL-induced osteoclastogenesis followed by the efficient construction of a focused library, we discovered novel bioactive small molecule inhibitor (IC₅₀: ~5µM) of RANKL-induced osteoclastogenesis in a dose-dependent manner with systematic structure-activity relationships. The development of this novel small molecule from molecular diversity and chemical biology can contribute the continuous effort for the development of new therapeutic agents for osteoporosis as well as new chemical small molecule perturbagens (research tools) for the fundamental understanding of molecular mechanism of RANKL-induced osteoclastogenesis.
PP-36 Selenium-Based Safety-Catch Linker: Solid-Phase Synthesis of Poly-substituted β-Lactam Derivatives

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The preparation of diverse libraries of organic compounds is an important facet of modern drug discovery programs [1]. One of the most commonly employed methods in library production is solid phase organic synthesis. Since substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents, the field of solid-phase heterocyclic chemistry has rapidly expanded for the preparation of pharmaceutically useful heterocyclic compounds [2].

Here we began from polystyrene-supported selenenyl acetic acid 1 [3], which was treated with Vilsmeier reagent [4] and various imines to give the corresponding resin 2 (Scheme 1). α-Alkylation of resin 2 was carried out to furnish polystyrene -supported lactam substituted selenium resin 3. Poly-substituted β-Lactam derivatives 4 were obtained through selenoxide syn-elimination of resin 3 with three diversities (R1, R2 and R3).

References:
It was noteworthy that polymer-supported selenium resins used here, not only facilitate the separation of the products, but also assist in the crucial reaction of $\alpha$-alkylation and selenoxide syn-elimination, which ensured the purity of the products.

References:

Acknowledgments:
We thank the National Natural Science Foundation of China (No. 20602029) for support.

PP-37  A New Strategy For The Construction Of C-1 Quaternary Tetrahydroisoquinolin-1-formaldehyde library By Using FeCl$_3$·6H$_2$O-Promoted Skeleton Rearrangement of 1-substituted Benzazepines

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A skeleton-rearrangement of 1-arylbenzazepines was developed with the assistance of 2 equiv. of FeCl$_3$·6H$_2$O. The N-substituents played a dramatic influence on the structures of the products. In the case of $N$-alkylbenzazepines, 1-aryl-tetrahydroisoquinolines (THIQs) were obtained, whereas $N$-acyl-benzazepine substrates yielded a series of novel 1-aryl-1-formyl-tetrahydroisoquinolines (THIQs). The $N$-acyl-1-aryl-1-formyl-THIQs can serve as the intermediates to prepare corresponding $N$-alkyl-1-aryl-1-formyl-THIQs. These findings not only added an additional example of organic transformations aided by iron reagent, but also paved a novel avenue to access THIQs, especially those with a fully functionalized quarternary C-1 carbon centre. The unique structural features of 1-formyl-1-aryl-THIQs represent a series of novel compounds worthy for biological screening, and the 1-formyl group also provides a valuable functionality warranting for further functional transformations and for the synthesis studies on 1,2-conjugated natural products. *(supported by grants from the Chinese National Science Foundation (30772625), Shanghai Commission of Science and Technology (07pj14104))
Diversity-oriented synthesis of N-heterocycles via tandem reactions

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Among the strategies used for preparation of small molecules, utilizing tandem reactions for design and synthesis of natural product-like compounds has attracted much attention, and the development of tandem reactions has been a fertile area in organic synthesis. Recently, we found that 2-alkynylbenzaldehyde was a versatile building block in tandem reactions for construction of heterocycles.
PP-39  Chemically Validated Combinatorial Approach to Large Libraries of Individual Drug Like Compounds

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Combination of 27,000 readily available synthetic building blocks followed by reactivity, synthetic feasibility, drug likeness and toxicity/stability filtering resulted in 11,377,102 highly feasible virtual structures obeying standard rules of drug-likeness (see Table 1). This combinatorial technology allows to synthesize up to 22,000 drug like compounds in 1 month using conventional parallel synthesis. 38 optimized reactions and 54 optimized chemical procedures result in screening compounds with 75 % feasibility (mean value calculated from the 6 years feasibility statistics).

Table 1. Calculated physical properties of feasible drug-like compounds.

<table>
<thead>
<tr>
<th>Physical property</th>
<th>Mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>398</td>
</tr>
<tr>
<td>ClogP</td>
<td>3.2</td>
</tr>
<tr>
<td>H-bond acceptors</td>
<td>6.9</td>
</tr>
<tr>
<td>H-bond donors</td>
<td>1</td>
</tr>
<tr>
<td>FISA*</td>
<td>67.36</td>
</tr>
<tr>
<td>Rotating bonds</td>
<td>6.19</td>
</tr>
<tr>
<td>LogS</td>
<td>-5.01</td>
</tr>
<tr>
<td>Heavy atoms count</td>
<td>27.5</td>
</tr>
</tbody>
</table>

*FISA - Hydrophilic solvent-accessible surface area.

PP-40  Combinatorial Chemistry of Carbonyl Compounds

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Readily available chlorotrimethylsilane was used as promoter and water scavenger in various condensation reactions. Simple synthetic and purification procedures have been developed that allow to synthesize structurally diverse drug like compounds.
References:

PP-41 Design, synthesis and antitumor activity of Novel 4′-O-Demethylepipodophyllotoxin Derivatives

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Podophyllotoxin is a bioactive lignan isolated from the roots of Podophyllum peltatum. Although the therapeutic application of podophyllotoxin is limited to topical use due to its high toxicity, its semisynthetic derivatives Etoposide and Teniposide have been widely used as important anticancer drugs in clinic. Extensive structure modifications have been carried out to improve pharmacological profile, particularly to enhance the inhibitory activity against drug-resistant tumor cell lines. Some newly developed derivatives, such as GL-331 and TOP-53, have displayed unique antitumor spectra and reached clinical trials. We present herein the
design, synthesis and antitumor activity of novel 4’-O-demethylepipodophyllotoxin derivatives.

It was reported that the linkage atom immediate to C$_4$ of podophyllotoxin derivatives would affect the antitumor spectra and drug-resistance profile significantly \[2\]. Accordingly, we designed five series of novel demethylepipodophyllotoxin derivatives with different linkage at C$_4$. Preliminary evaluation against several tumor cell lines, including sensitive cells and those with intrinsic or acquired drug-resistance, indicated that nine compounds are comparable or superior to the positive control GL-331. Further structural optimization and \textit{in vivo} evaluation are undergoing.

\[ \text{References:} \]


\textbf{PP-42} \textbf{Synthesis of Zwitterionic Salts of Pyridinium-Meldrum Acid and Barbiturate through Unique Four Component Reactions}

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Pyridinium salts derived from $\alpha$-halogenocarbonyl compounds are easily deprotonated to give pyridium ylide, which are prone to be high potential synthons and undergo versatile reactions. The most known reaction is Michael addition of active methylene groups in pyridinium salts onto suitable acceptor compounds to give polysubstituted pyridines and terpyridines, in which the pyridine is split off. The second widely used reaction is 1,3-dipolar cycloaddition of pyridinium salt with acetylene and activated alkenes to give indolizine derivatives, in which the pyridyl unit is remained. The third kind of reaction is reaction of pyridinium salts with alkenes bearing with electron-withdrawing groups to give the corresponding cyclopropanes and 2,3-dihydrofurans. we wish to report the formation of the unusual charge-separated pyridinium-Meldrum acid and $N,N$-dimethylbarbituric acid zwitterionic salts by a four component reaction which involves pyridine, $p$-nitrobenzyl bromide, or phenacyl bromide, aromatic aldehydes and Meldrum acid or barbituric acid with triethylamine as catalyst in acetonitrile.
Other types of the charge-separated pyridinium-Meldrum acid and \(N,N\)-dimethylbarbituric acid zwitterionic salts such as follows are also prepared in high yields in very convenient manner from the reaction of isoquinoline, \(N\)-methylimidazole. The stability, reactivity and the formation mechanism of this kind of zwitterionic salts are also investigated. On heating this kind of zwitterion salts could be converted to a mixture of cyclopropanes and 2,3-dihydrofurans in different ratio. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

**References:**


**PP-43 Tandem Reaction of 1,3-Thiazolidinedione, aldehyde, arylamine and ethyl cyanoacetate: A Facile Access to Polyfunctional Dihydrothiophenes**

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Multicomponent reactions (MCRs) involving tandem processes, with at least three different substrates reacting in a well-defined manner to form a single compound, have emerged as an effective tool for atom economic and benign organic synthesis. Recently we have reported a novel domino reaction of 1,3-thiazolidinedione, malononitrile, aromatic aldehydes and amines. The reaction is very unique because the ring-opening/recyclization or spirocyclization process unexpectedly occurs at the ring of 1,3-thiazolidinedione with different kind of amines. In order to obtain more information about mechanism of product formation in this multicomponent reaction and to examine the substrate scope and limitation of this novel domino reaction, in this text we wish to report the interesting results of using ethyl cyanoacetate, cyanoacetamide as two substrates in the multicomponent reactions. The tandem four-component reactions of ethyl cyanoacetate, 1,3-thiazolidinedione, aldehyde, and arylamine catalyzed by triethylamine gave the highly functionalized dihydrothiophenes in moderate yields (Scheme 1).
When cyanoacetamide was carried out in the reaction, several kinds of products were formed according to the different structure of amines and the reaction conditions. In the presence of triethylamine, the reaction of pyrrolidine, piperidine, morpholine gave the expected dihydrothiophenes as main products. When no triethylamine was added, diethylamine and piperidine gave S-S bond bridged pyridinedione derivatives (Scheme 2). Pyrrolidine and morpholine gave an dicyano substituted pyridinedione as main product.

References:
into two structure models: the derivatives of dipeptide (Arg-Pro) (type1) and diketopiperazine (type2).

Ten target compounds were synthesized and characterized by MS, $^1$H-NMR and $^{13}$C-NMR. The biological activity of these target molecules is under evaluation.

**PP-45 Searching ApoE/Aβ Binding Regions to Identify Compounds Blocking Their Interaction**

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The abnormal accumulation of cerebral amyloid β-peptide (Aβ) is a primary pathological hallmark in Alzheimer’s disease (AD) [1]. The E4 isoform of apolipoprotein E (ApoE) is considered as one of the most important risk factor for AD, and it becomes the research focus since 1993 [2]. Many studies demonstrate that Apolipoprotein E4 (ApoE4) inhibits Aβ clearance and stimulates Aβ deposition by binding Aβ directly [3-5]. So blocking the ApoE/Aβ interaction could be an effective pharmacological intervention for AD. We first used a systematic reductionist analysis and used peptide-array methodology to search the functional sequences within the ApoE/Aβ binding regions (ApoE244-272 and Aβ12-28), then evaluated their capacities of blocking ApoE/Aβ interaction by ELISA assay and Western Blotting assay. ApoE fragments ApoE249-256, its truncated form ApoE249-255, Aβ fragments Aβ17-21 and Aβ17-22 were proved to block the ApoE/Aβ interaction effectively. Interestingly, the peptides Aβ17-22 overlap with key areas involved in Aβ self-assembly into amyloid aggregates. Congo Red is an inhibitor of Aβ self-association and interacts with Aβ by binding to exactly the same region as ApoE. Our results showed that Congo Red is a more potent blocker of the ApoE/Aβ interaction than any of the peptides mentioned above, with a Kd of 400 nM. The compounds identified in our study or their analogues can be directly used as lead compounds in developing drugs that antagonize the ApoE/Aβ interaction.

**Reference**


**PP-46 Designed Hybrid Peptides Utilizing Solvent Effects Inhibit β-amyloid Oligomerization and Attenuate Cytotoxicity**

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One of the two major pathogenic characteristics is senile plaque in Alzheimer’s disease (AD), which is consisted of aggregated β-amyloid (Aβ) [1]. Now soluble oligomer are believed to correlates better with dementia than insoluble fibrillar deposits [2]. Consequently, attention has been focused on inhibiting Aβ oligomerization to alleviate Aβ cytotoxicity.

In our study, we designed hybrid peptides combining the Aβ recognition motif and the solvent disruptive sequences. All synthetic hybrid peptides can affect Aβ fibrillization and alter the morphology of Aβ aggregates variously in vitro. The solvent disruptive sequences can change the surface tension of solutions, while the recognition motif binding to Aβ. The effects of these peptides indicated that surface tension is important in the process of Aβ aggregation. Also compounds with the recognition motif can inhibit cytotoxicity of Aβ in cell culture probably by decreasing the amount of toxic Aβ oligomers. However, those peptides without the recognition motif did not show the same effects on Aβ aggregation and reducing cytotoxicity of Aβ. Hence, both recognition domain and solvent effect should be considered as important factors when designing molecules to target Aβ aggregation.

Reference

PP-47  Silica-Supported Sulfonic Acid-Functional Ionic Liquid as Scavengers for the Synthesis of Amides

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Silica-supported sulfonic acid-functional ionic liquid was synthesized by covalent attachment of functional ionic liquid on silica gel. As a part of our program to explore the potential application of functional ionic liquids in combinatorial chemistry, amino- and carboxyl-functional ionic liquids have been reported previously as scavengers in parallel synthesis of target compounds [1,2]. Herein we reported the use of silica-supported sulfonic acid-functional ionic liquid coated by a common ionic liquid as scavenger in the removal of excess amine in the synthesis of amides. Desired products were obtained with high purity with a sequestration time of less than 2 hours.
Compared with solid support without common ionic liquid, we have found that combination of a silica supported sulfonic acid-functional ionic liquid with common ionic liquid can create a homogeneous reaction media on the surface of silica in non polar solvent. The used scavenger can be regenerated and recycled several times without significant loss of activity. The scavenger allows the removal of excess amine by simple filtration. The scavenger immobilized in this way was air-stable and thermally stable to allow facile use and storage without any precautions.


Acknowledgements: Financial support for this work from Shanghai Commission of Science and Technology and Shanghai Leading Academic Discipline Project (Project Number: B507) are gratefully acknowledged.

PP-48 Removal of iodine catalyst by silica-supported functionalized ionic liquid

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Over the past decades, combinatorial chemistry has emerged as a powerful tool for drug discovery. The use of polymeric scavengers leads to efficient hybrid approaches which combine the purification advantages of solid-phase synthesis with the flexibility of solution-phase synthesis. 1 Although the principles of using polymeric reagents to scavenge unwanted by-products or excess starting materials at the end of a reaction were well established, less attention has been paid on the development of scavengers for the removal of catalysts after a synthetic step. 2 Moreover, currently reported examples were focused on the sequestration of metallic catalysts such as palladium, ruthenium and rhodium. On the other hand, iodine has been reported as a versatile catalyst in a range of organic transformations. 3 Herein we introduce a new method for the removal of iodine catalyst using supported ionic liquid as a heterogeneous scavenger.
Silica gel-supported carboxyl-functionalized ionic liquid was prepared by a simple impregnation method. To demonstrate the potential of this scavenger, aldehydes were reacted with indole in the presence of catalytic amount of iodine. Upon completion, the catalyst was removed through the formation of trihalide anion. In general, the sequestration processes accomplish within 15min and the purities of desired products are in 97-99%. This is the first example on the scavenging of a nonmetal catalyst.


Acknowledgments: Financial support for this work from the Shanghai Commission of Science and Technology and Shanghai Leading Academic Discipline Project (Project Number: B507) are gratefully acknowledged.

PP-49 Synthesis of Polysubstituted Pyridines under the Combined Microwave-Ultrasound Irradiation: K2CO3-Promoted Tandem Addition/Cyclization/Hydrogen Transfer Process

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The tandem reaction of chalcones, malononitrile and methanol for the synthesis of highly functionalized 2-methoxy-4,6-diarylnicotinonitrile derivatives have been developed. Taking the advantage of weak base K2CO3 instead of strong base\textsuperscript{1)}\textsuperscript{1)}, a variety of products can be prepared in good yields and purities under the combined microwave and ultrasound irradiation (MW-US). The reaction was proposed to undergo a tandem transformation of Michael addition, methylate addition to C≡N of the adduct, cyclization to 1,4-dihydropyridine and intermolecular hydrogen transfer between dihydropyridine and chalcones. The scaffolds of poly-substituted pyridines have been claimed to have several biological activities, and this useful method is suitable for scale up synthesis of the desired products, and providing a valuable synthetic tool for chemists.

\[ \text{R}_1\text{R}_2\text{O} + \text{CN} + \text{CH}_3\text{OH} \xrightarrow{\text{K}_2\text{CO}_3, \text{MW-US}} \text{R}_1\text{R}_2\text{CN} \]


Acknowledgements: Financial support for this work from Shanghai Commission of Science and Technology and Shanghai Leading Academic Discipline Project (Project Number: B507) are gratefully acknowledged.
PP-50  N-phenyl-2,2-dichloroacetamide Derivatives as Anticancer drug: Design, Synthesis, Biological Evaluation

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Sodium dichloroacetate (DCA), a well-known inhibitor of mitochondrial pyruvate dehydrogenase kinase (PDK) [1] is an activator of pyruvate dehydrogenase (PDH). Recent study shows that DCA can induce cancer cell apoptosis, decrease proliferation, and inhibit tumor growth, without apparent toxicity [2-3]. Nevertheless, the anti-cancer activity of DCA is very low (IC₅₀ =1011 μM for A₅₄₉), and therefore it is necessary to modify the DCA to enhance its activity.

\[ \text{DCA} \]

\[ \text{IC}_{50} = 1011 \mu M \]

As a metal salt, the low activity of DCA might due to its low liposolubility. Accordingly we designed, synthesized more than 120 DCA derivatives to enhance liposolubility. The derivatives include metal-salts, organic ammonium salts, esters and amides. Unexpectedly, most compounds didn’t show better activity, except N-phenyl-2,2-dichloroacetamide(1, IC₅₀ reduced nearly 10-fold). Therefore, optimization of the aniline ring was accomplished by systematically varying the substituents at the ortho, meta, and para positions. Result shows substitution at the ortho position compare to meta position and para position had a better potency (i.e., 2, IC₅₀=14.78 μM) and N-(3-iodophenyl)-2,2-dichloroacetamide’s(3) IC₅₀ is as low as 4.8 μM. Subsequently, we synthesized a series of disubstituted N-phenyl-2,2-dichloroacetamide, among them, N-(3,5-diiodophenyl)-2,2-dichloroacetamide (3) shows the highest activity, and it was selected to be an optimized lead compound. Very importantly, this kind of compounds showed very low toxicity, for example, the LD₅₀ of compound 2 and 3 are 4549 and 1117mg/kg for mice respectively.

References:

Acknowledgements. This work was supported by the National Natural Science Foundation of China (No. 20872078)

PP-51  Minimal Peptides with Anti-Bacterial and Anti-Cancer Activities

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According to the antimicrobial peptides we have cloned previously and the information from protein databases \cite{1,2}, 10 short peptides (5-10 amino acids) were designed to investigate the minimal functional peptide segments. The peptides were synthesized, purified by HPLC and characterized by Mass Spectrometer, named 1 to 10 respectively. The liquid growth-inhibition assay\cite{3}. showed four of these peptides have antimicrobial activities to several bacterial species, including Gram-positive *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative *Escherichia coli*, *Vibrio vulnificus*, at concentrations between 0.5 and 1μM. These peptides also inhibited the growth of non-small cell lung cancer cell line H460 or its paclitaxel-resistant variant H460_{taxR} at an IC50 between 1μM and 0.1mM while showing no effect on the growth of normal human fibroblasts at the same concentration. The results indicate that these short peptides can be used as anti-cancer agents.

References:
\cite{2} http://www.expasy.org/

Acknowledgments:
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