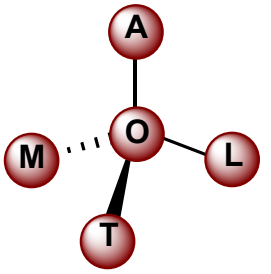
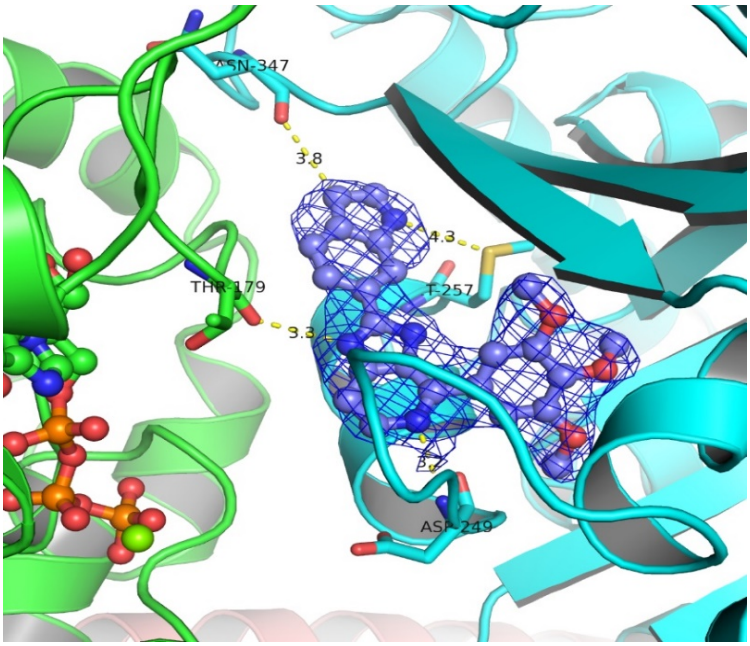
Forty-Sixth Annual
MALTO
Medicinal Chemistry & Pharmacognosy
Meeting-in-Miniature

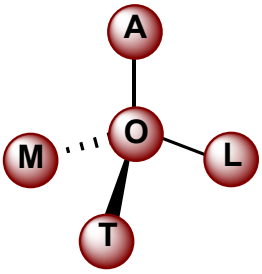
May 20th – 22nd, 2019

Hosted by

The Department of Pharmaceutical Sciences
College of Pharmacy
University of Tennessee Health Science Center, Memphis, TN







2019 MALTO Meeting

At the University of Tennessee Health Science Center College of Pharmacy

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MALTO Contributors and Sponsors

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The 46th Annual MALTO Medicinal Chemistry and Pharmacognosy Meeting-in-Miniature

May 20th -22nd, 2019

GENERAL PROGRAM

Monday PM - May 20th, 2019

5:00 – 6:30	**Registration** UTHSC College of Pharmacy (COP), 881 Madison Avenue, Memphis, TN
6:30 – 8:30	**Faculty & Student Mixer** UTHSC College of Pharmacy (COP), 881 Madison Avenue, Memphis, TN

NOTE: All events on Tuesday 21th, 2019 and Wednesday, May 22nd, 2019 will be held on the first floor of the College of Pharmacy (COP) building located at 881 Madison Avenue, Memphis, TN.

Tuesday AM - May 21st, 2019

7:30 – 8:25	**Poster Setup (COP Lobby)**
8:30 – 8:40	**Welcoming Remarks (COP Room 102)** Dr. Marie A. Chisholm-Burns, Dean College of Pharmacy Introduction by Dr. Georgi Petkov, Chair, Department of Pharmaceutical Sciences, UTHSC College of Pharmacy
8:45 – 10:25	**Podium Session 1 - Dr. Jesse A. Jones Presiding (COP Room 102)** Abstracts O1-O5
10:25 – 10:45	**Coffee Break (COP Room 118-119)** *Posters are available for viewing only (COP Lobby)*
10:45 – 12:00	**32nd Annual A. Nelson Voldeng Memorial Lecture** *Keynote Presenter: Jeff Aubé, Ph.D. Fred Eshelman Distinguished Professor of Chemistry, The University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC*

Tuesday PM - May 21st, 2019

12:00 – 2:30	**Concurrent Lunch (COP Room 118-119) & Poster Session (COP Lobby)**
2:30 – 4:50	**Podium Session 2 – Mr. Hanxuan Li presiding (COP Room 102)** Abstracts O6-O12
4:50 – 5:10	**Coffee Break (COP Room 118-119)**
5:10 – 6:30	**Podium Session 3 – Ms. Sahar Algamdi presiding (COP Room 102)** Abstracts O13-O16
6:30	**Dinner**

Wednesday - May 22nd, 2019

8:00 – 9:20	**Podium Session 4 – Ms. Najah Albadari presiding (COP Room102)** Abstracts O17-O20
9:20 – 9:40	**Coffee Break (COP Room 118-119)**
9:40 – 11:00	**Podium Session 5 – Ms. Shanshan Deng presiding (COP Room 102,** Abstracts O21-O24
11:00 – 12:00	**MALTO Business Meeting (COP Room 102)**
12:00 – 1:30	**Lunch (COP Room 118-119)** **MALTO Awards Presentation (Dr. John Rimoldi)** • *Robert A. Magarian Podium Presentation Award* • *Thomas L. Lemke Poster Presentation Award* • *Ronald F. Borne Postdoctoral Poster Presentation Award* **Closing Remarks (Dr. Wei Li)**

ADJOURN

MALTO Medicinal Chemistry and Pharmacognosy

A Brief History

MALTO began with the concept of a miniature medicinal chemistry meeting at which students could have the opportunity to present their research to their peers and mentors. This concept was first put into practice in the early 1960's under the leadership of Drs. Portoghese, Cannon, Smissman, and Bauer at the Universities of Minnesota, Iowa, Kansas, and Illinois, respectively (MIKI). Credit for the concept and the inspiration for our own miniature medicinal chemistry meeting must be given to this group of individuals. For several of us who experienced the excitement and value of such an experience it was only natural to attempt to bring this same opportunity to our region of the country.

In the spring of 1974, Tom Lemke (University of Houston) called his KU classmate Nelson Voldeng (Nels) at the University of Arkansas to ask what he thought of the idea. Not only did Nels think that the idea would work in our region of the country, but he indicated that he had another transplanted Kansan at Arkansas, Danny Lattin. When the conversation got around to who else might be interested in helping to develop a MIKI clone, Danny suggested Bob Magarian at Oklahoma who had also experienced MIKI while a post-doc at KU. Thus, a regional medicinal chemistry meeting in the South Central region of the U.S. was born. By the time of the first meeting (October 2-4, 1974) two other schools had signed on under the leadership of Jay Nematollahi at the University of Texas and Ray Saenz at Northeast Louisiana University.

The first meeting, titled "First Annual Medicinal Chemistry Meeting-in-Miniature", was sponsored by the University of Houston, The Upjohn Company, E.R. Squibb & Sons, Roche Laboratories, and Alcon Eye Research Foundation. Dr. Joe Buckley, Dean at the University of Houston, welcomed the attendees who listened to 17 student and faculty presentations plus invited presentations from Dr. E. Wenkert of Rice University and Dr. S. Welch from the Chemistry Department at the University of Houston. Dr. Lin Cates suggested a shorter name for the organization and the members voted to call the organization ALTO (Arkansas, Louisiana, Texas and Oklahoma).

Since football was "king" in Arkansas, Texas and Oklahoma the decision was made to move the meeting to the spring, rather than risk a scheduling conflict, and Bob Magarian volunteered to host the second meeting in Oklahoma.

The second annual ALTO meeting took place in Norman, Oklahoma and was preceded by a mixer with 32 attendees. The largest contingent at the 2nd meeting came from Texas Southern University (8). The meeting saw 13 student and faculty presentations and three invited presentations from faculty at Oklahoma including Drs. Pushkar Kaul, Alfred Weinheimer and Francis Schmitz. The highlight of the meeting was a cookout prepared by master chef Magarian and an evening of excitement in downtown Norman. It should be mentioned that ALTO'S expenses for 1975 amounted to $131.64, leaving a balance of $395.00 in the ALTO account.

The 3rd ALTO Medicinal Chemistry & Pharmacognosy Meeting in Miniature took place on May 19-21, 1976 in Monroe, Louisiana and besides attendance by the four founding schools, representatives and presentations came from Texas Southern University, the University of

Mississippi, and Southwestern Oklahoma State Colleges. A total of 24 presentations were given plus an invited lecture by Dr. W.K. Taylor from Northeast Louisiana University.

The 4th annual meeting returned to Houston hosted by Texas Southern University. Again the meeting had participation from Southwestern Oklahoma University and the University of Mississippi. Following the meeting Mississippi was asked to join ALTO and they were accepted. Beginning with the 5th annual meeting at Little Rock the organization took on its present name of MALTO.

MALTO completed its cycle of host institutions following the 6th and 7th annual meetings, which were hosted by the University of Mississippi in 1979, and the University of Texas in 1980. In 1982 MALTO became an IRS 501(c) 3 not for profit Oklahoma Corporation (Tax exempt) with Bob Magarian, President; Ron Borne, Vice President; Tom Lemke, Secretary; and Danny Lattin, Board Member.

Other milestone events in the history of MALTO consisted of the participation and hosting of a meeting by Xavier University in 1986 in New Orleans (13th meeting). In 1988 the organization began the first A. Nelson Voldeng Memorial Lecture. This began at the 15th MALTO meeting and Dr. Wendel Nelson gave the lecture. Auburn University hosted this meeting. Eighty-two registrants attended the meeting and it marked the first meeting attended by faculty from the University of Georgia. In 1991 Tom Lemke resigned as secretary/treasurer (1974 - 1991). He has been followed in this office by Bob Sindelar (Mississippi, 1991 - 1995), Michael Crider (Louisiana, Monroe, 1995-2004), E. Kim Fifer (Arkansas, 2004 – 2017), and Dai Lu (Texas A&M, 2018 - present).

The 19th Annual MALTO Meeting hosted by the University of Arkansas was the first meeting at which attendance exceeded 100 registrants.

At the 1993 meeting (20th MALTO) the University of Tennessee participated for the first time. In 1994, Peter Ruenitz, University of Georgia began attending the meetings. At the 25th Annual MALTO Meeting (1998) poster sessions were used for the first time. Posters became necessary when the number of papers submitted exceeded the time available for podium sessions. (8 posters and 22 presentations). In 1999, an award for the outstanding student podium presentation was established in the name of Robert A Magarian. Similar awards were established in 2003 and 2015 for the outstanding student poster in honor of Dr. Thomas L. Lemke and the outstanding postdoctoral poster in honor of Dr. Ronald F. Borne, respectively.

A. Nelson Voldeng Memorial Lecture

A. Nelson Voldeng was Professor of Medicinal Chemistry at the University of Arkansas, College of Pharmacy from 1964 until lingering illness forced his retirement in 1986. Nelson was born and raised in the south-central Kansas town of Wellington. He earned both his B.S. in Pharmacy (1960) and his Ph.D. in Medicinal Chemistry (1964) at the University of Kansas. His dissertation advisor was the late Dr. Edward E. Smissman. Nelson was well known for his efforts to encourage promising undergraduate pharmacy students to continue their education in graduate studies in the pharmaceutical sciences. Numerous pharmacy students worked with him in his research laboratory and many of these students made presentation at MALTO meetings. Nelson's research interest included the synthesis of novel, broad-spectrum penicillin derivatives and the synthesis of long-acting opiate analgesics derived from pentapeptides.

Nelson was one of the founding organizers of our MALTO organization. Since 1973, when MALTO held its first meeting, Nelson provided energetic leadership, and worked tirelessly to help bring the idea of an annual regional medicinal chemistry and pharmacognosy meeting to fruition. Until his death in 1987, Nelson continued to contribute his energies to ensure the successful growth of MALTO.

The MALTO faculty voted unanimously in 1987 to name the annual lecture by a visiting scientist the "A. Nelson Voldeng Memorial Lecture" in recognition of Nelson's invaluable contributions to MALTO. The first A. Nelson Voldeng Memorial Lecture was presented on June 13, 1988, during the 15th Annual MALTO Meeting held at Auburn University. Dr. Wendel L. Nelson, Professor of Medicinal Chemistry at the University Of Washington School Of Pharmacy, who had been a fellow graduate student of Voldeng and a personal friend of long standing, presented this inaugural lecture.

The MALTO faculty designed a special plague commemorating the A. Nelson Voldeng Memorial Lecture. This plaque and an honorarium are presented annually to the visiting scientist lecturer. A copy of the first plaque was presented by MALTO to Nelson's wife, Mrs. Diana Voldeng of Little Rock, Arkansas.

A. Nelson Voldeng Memorial Lecturers:

1988 Wendel L. Nelson, University of Washington
1989 Peter Gund, Merck, Sharpe and Dohme Laboratories
1990 Walter Korfmacher, National Center for Toxicological Research
1991 Duane D. Miller, Ohio State University
1992 Corwin Hansch, Pamona College
1993 William H. Pirkle, University of Illinois
1994 J. Andrew McCammon, University of Houston
1995 Robert P. Hanzlik, University of Kansas
1996 James A. Bristol, Parke-Davis Pharmaceuticals
1997 Yvonne Martin, Abbott Laboratories
1998 Gunda Georg, University of Kansas
1999 Michael F. Rafferty, Parke-Davis Pharmaceuticals
2000 Robert C. Anderson, Sphinx Pharmaceuticals, a Division of Eli Lilly & Company

2001 Phillip Crews, University of California at Santa Cruz
2002 David H. Coy, Tulane Medical College
2003 Dennis M. Zimmerman, Eli Lilly and Company
2004 Mitchell S. Steiner, MD, FACS, GTx, Inc.
2005 F. Ivy Carroll, RTI International
2006 Michael Eissenstat, Sequoia Pharmaceuticals
2007 Peter A. Crooks, University of Kentucky
2008 Kenner C. Rice, National Institute on Drug Abuse
2009 Thomas R. Webb, St. Jude Children's Research Hospital
2010 Derek Lowe, Vertex Pharmaceuticals
2011 Harold Kohn, University of North Carolina
2012 James D. McChesney, Arbor Therapeutics, LLC, Ironstone Separations, Inc., Cypress Creek Pharma, Inc.
2013 Thomas E. Prisinzano, Department of Medicinal Chemistry, University of Kansas
2014 Richard E. Lee, St Jude Children's Research Hospital
2015 Alan Kozikowski, University of Illinois at Chicago
2016 Richard A.F. Dickson, Texas Heart Institute
2017 Maria Alvim-Gaston, Eli Lilly and Company
2018 Carol Fierke, Texas A&M University

32nd Annual A. Nelson Voldeng Memorial Lecture

The University of Tennessee Health Science Center
College of Pharmacy, Memphis, TN

2019 Presenter

Jeff Aubé, Ph.D.
Fred Eshelman Distinguished Professor of Chemistry,
The University of North Carolina Eshelman School of Pharmacy
Chapel Hill, NC

Biographical Information

Dr. Jeffrey Aubé joined the UNC Eshelman School of Pharmacy faculty as a Professor in the Division of Chemical Biology and Medicinal Chemistry in the summer of 2015. In addition to holding a joint appointment in the Department of Chemistry, Dr. Aubé is a member of the Center for Integrative Chemical Biology and Drug Discovery.

Before joining the School, Dr. Aubé was a professor at the University of Kansas where he served as the director of their Chemical Methodologies and Library Development Center and their Specialized Chemistry Center. Prior to that, he served as interim chair of KU's Department of Medicinal Chemistry from 2003 until 2005.

Dr. Aubé has authored more than 220 publications, received more than twenty research and teaching awards, and has been invited to give more than 300 lectures.

32nd Annual A. Nelson Voldeng Memorial Lecture

Tuesday May 21st, 2019 10:45 – 12:00 am

STEROIDS: FROM BIOLOGY BACK TO CHEMISTRY

Jeffrey Aubé
UNC Eshelman School of Pharmacy
University of North Carolina at Chapel Hill

Medicinal chemistry, by definition, entails the discovery of novel chemical entities for use in treating patients. As such, this field and the basic science of organic synthesis have had a relationship of mutual dependence since their creation many decades ago. In this talk, I will describe a recent experience in our laboratory in which a medicinal chemistry based project inspired us to re-investigate an organic synthesis problem of many years standing.

The treatment of advanced prostate cancer often involves the use of abiraterone, a clinically used, first-in-class, inhibitor of cytochrome P450 17A1 (CYP17A1), the ultimate purpose of which is to diminish growth of tumors by depriving them androgens such as testosterone and dihydrotestosterone. Unfortunately, abiraterone also inhibits the biosynthesis of glucocorticoids and mineralcorticoids, which share aspects of biosynthesis with androgens. The identification of two different biochemical determinants of selectivity, along with preliminary efforts to use structure-based design toward more selective abiraterone derivatives, will be described. This project is a collaborative venture with the laboratory of Emily Scott at the University of Michigan and her colleagues Elyse Petrunak and Rahul Yadav; work in our laboratory was begun by Charlie Fehl and continued by Caleb Vogt.

Work in the above project led us to think broadly about the problem of steroid analog synthesis, including those containing rings in which an additional nitrogen group had been added through a nitrogen insertion reaction. This, in turn, led us to re-consider a long-standing problem in this type of ring-expansion chemistry: regioselectivity. Typical ring expansion sequences, including the Schmidt reaction and the Baeyer-Villiger reactions, only permit the selective conversion of a very specific type of substrate (one containing a single substituent adjacent to a reactive carbonyl group) to one of two possible products. The alternative product that might be desired from this reaction is not easily made and other substrates types generally proceed without any useful level of selectivity. Approaches to the solution of these issues will be presented. The work in this project was performed by former graduate student Manwika Charaschanya.

The Robert A. Magarian Outstanding Podium Presentation Award

Dr. Robert A. Magarian, professor emeritus of medicinal chemistry and vice chair of the Department of Medicinal Chemistry and Pharmaceutics, College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK, retired on June 30, 1996 after 26 years. He had been professor of medicinal chemistry at the University of Oklahoma since 1978, having served as associate professor from 1970. Prior to joining the faculty at Oklahoma, he was assistant professor of medicinal chemistry at the St. Louis College of Pharmacy from 1967 to 1970. He was a National Institutes of Health Postdoctoral Fellow under Dr. Edward Smissman in the Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas from 1966 to 1967.

Dr. Magarian attended the University of Mississippi where he earned a B.A. degree in Chemistry and Biology (1956); B.S. in Pharmacy (with highest honors; January, 1960); and a Ph.D. in Medicinal Chemistry (August, 1966). While an undergraduate in the University of Mississippi School of Pharmacy, he was initiated as a member of the Rho Chi National Honor Society (1959); was the recipient of the Rexall Trophy Award (1959); and in 1960 he received three awards: The Merck Award, the Lehn and Fink Gold Medal Award, and Taylor Medal---the highest honor awarded by the University of Mississippi. He practiced as a pharmacist in Illinois from January 1960 to August 1961.

Dr. Magarian's research was directed at finding pure (nonestrogen) estrogen antagonists, which were effective in treating different breast cancers (hormonal and non-hormonal dependent tumors) in both pre- and postmenopausal females. His approach to investigating pure antiestrogens was multidisciplinary, involving: (1) the design and synthesis of new organic compounds; (2) the pharmacological testing of each compound; (3) testing the compounds in tissue culture assays involving breast cancer cells; (4) the use of single crystal x-ray analysis of each molecule to study its structure; and (5) molecular modeling to assist in the design of new agents.

During his career, Dr. Magarian published many articles, abstracts, review articles, and book chapters in the breast cancer area. He has ten U.S. patents on antiestrogenic and antitumor agents (di- and triarylcyclopropyl analogs) synthesized and tested in his laboratory by graduate students and postdoctoral fellows. Some of his key publications involve: "Synthesis and Biological Evaluation of a series of Pure Cyclopropyl Antiestrogens," *J. Med. Chem*.; "Influence of Novel Tirarylcyclopropyl Analogues on Human Breast Cancer Cells in Culture," *Anti-Cancer Drugs*; *Anticancer research*; *Breast Cancer & Treatment*; "Synthesis and Enantiomeric Separation of an Antitumor Agent," *Anti-Cancer Drug Design*; *Bioorganic Chemistry*; *Bioorganic and Medicinal Chemistry*; "Molecular Structures and Conformational Studies of Triarlycyclopropyl and related Non-Steroidal Antiestrogens," *Acta. Cryst*; *J. Med. Chem*.; "The Medicinal Chemistry of Nonsteroidal Antiestrogens: A Review," *Current Medicinal Chemistry*.

Dr. Magarian is listed in Who's Who in America; Who's Who in the Southwest; American Men and Women of Science, Chemistry; The International Who's Who of Intellectuals (Cambridge, England); and Men of Achievement (Cambridge, England). He was an Associate Editor of the international journal, *Current Medicinal Chemistry*. His research was supported by Mead Johnson, National Science Foundation, National Institutes of Health (National Cancer Institute), and the Presbyterian Health Foundation. During his teaching career, Dr. Magarian received numerous teaching awards: the Baldwin Study-Travel Award in 1978 from the University of

Oklahoma for teaching excellence, which allowed him to travel to England where he presented two papers at an international chemistry meeting held at Oxford University; the Associated Distinguished Lectureship Award from the University of Oklahoma in 1988; in 1985 the Rho Chi Society's Excellence in Teaching and Research Award; and in 1996, the Rho Chi Society Recognition Award for "Promoting Scholastic Excellence and Imparting Knowledge in Creative and Helpful Ways."

Dr. Magarian is a member of the American Chemical Society, American Association of College of Pharmacy, Sigma Xi, Phi Kappa Phi, Golden Key National Honor Society, and the Kappa Psi Pharmaceutical Fraternity. Dr. Magarian became the Executive Director of The Kappa Psi Pharmaceutical Fraternity, Inc. in January, 1980, occupying that position in The Kappa Psi Central Office, College of Pharmacy, University of Oklahoma HSC until June 30, 2000.

Dr. Magarian has been writing fiction since his retirement and has published two medical thrillers: *The Watchman* and *72 Hours,* and a detective thriller titled, *You'll Never See Me Again, A Crime to Remember*. He is working on his fourth novel, a detective thriller in which he is bringing back his lead detective, Noah McGraw, and his partner, Holly Roark. For additional information please visit his web site: www.robertamagarian.com.

* * *

MALTO Medicinal Chemistry, OK Inc., became a not-for-profit organization in 1982 with Dr. Magarian as its president.

Past Recipients of The Robert A. Magarian Outstanding Student Podium Presentation Award

1999: Robert H. Cichewicz, "Dimerization of Resveratrol by the Grapevine Pathogen Botrytis cinerea," University of Louisiana at Monroe, Monroe, LA. **Advisor: Dr. Samir A. Kouzi.**

2000: Valeria N. Rubin, "Preparation and Selective Estrogen-Like Bone Protective and Cholesterol-Lowering Effect of Hydroxytriarylethylenes Bearing Acidic Side Chains," University of Georgia. **Advisor: Dr. Peter C. Ruenitz**

2001: Theresa L. Johnson, "Inhibition of Lactate Dehydrogenase C: The Design Synthesis, and Testing of Ligands as an Approach to Male Contraception," University of Mississippi, **Advisor: Dr. Mitchell A. Avery**

2002: Kris Virga, "Structure-Based Design and Synthesis of Pantothenate Kinase Inhibitors," University of Tennessee, **Advisor: Dr. Richard E. Lee**

2003: Lindsay Odom, "Alkylation and Cyclization Reactions of Diazoketones: Synthesis of Substituted Azetidines," University of Mississippi, **Advisor: Dr. John M. Rimoldi**

2004: Kerim Babaolu, "Crystal Structure of Dihydropteroate Synthase from Bacillus anthracis: Studies into Mechanism and Starting Point for Novel Inhibitor Design," University of Tennessee Health Science Center, **Advisor: Dr. Richard E. Lee**.

2005: Nakul Telang, "Design, Synthesis and Biological Evaluation of Isoflavones as Antigiardial Agents," University of Mississippi, **Advisor: Dr. Mitchell Avery.**

2006: Tarek Mahfouz, "Computer-aided Inhibitor Discovery of the Botulinum Neurotoxin Serotype A," University of Houston, **Advisor: Dr. James M. Briggs**.

2007: Kirk Hevener, "Structure-Guided Virtual Screening Against Dihydropteroate Synthase Utilizing Pharmacophore Filtering and Fragment-based Constraints," University of Tennessee Health Science Center, **Advisor: Dr. Richard E. Lee.**

2008: Yatan Shukla, "Novel Pregnane Glycosides from *Hoodia gordonii*," University of Mississippi, **Advisor: Dr. Ikhlas A. Khan.**

2009: Amir E. Wahba, "Zinc Mediated Reductive *N*-Alkylation and Amidation of Nitro Arenes with an Application to natural Products," University of Mississippi, **Advisor: Dr. Mark T. Hamann.**

2010: Sarah Chijkowski, "The Reaction of the Sesquiterpene Lactone Repin with Various Amine Nucleophiles," University of Mississippi, **Advisor: John M. Rimoldi.**

2011: Amanda Waters, "Methodologies for the Structural Assignment of Karlotoxin Polyketides in High-Throughput using Overlaid 2D NMR Techniques," University of Mississippi, **Advisor: Mark T. Hamann.**

2012: Fathy Behery, "Tocotrienol Elecrophilic Substitution Products as Breast Cancer Proliferation and Migratio Inhibitory Leads," University of Louisiana, Monroe, **Advisor, Khalid El Sayed.**

2103: Min Xiao, "Discovery of 4-Aryl-2-benzoyl-imidazoles as Tubulin Polymerization Inhibitor with Potent Antiproliferative Properties," University of Tennessee, **Advisor: Wei Li.**

2014: Eric Bow, "Novel Benzofuran and Benzopyran Scaffolds Targeting the Cannabinoid Receptors," University of Mississippi, University of Mississippi, **Advisor: John M. Rimoldi.**

2015: Chalada Suebsuwong, "Structure-Based Design of Potent and Selective DLG-OUT RIPK1 Inhibitors," University of Houston, **Advisor: Greg Cuny.**

2016: Quinghui Wang, "Structural Optimization of ABI-231 Targeting the Colchicine Site in Tubulin for Advanced Melanoma," University of Tennessee, **Advisor: Wei Li.**

2017: Songtao Lin, "Investigation of 20S(OH)D3 Analogs as Potent VDR Agonists and Anti-Inflammatory Agents," University of Tennessee, **Advisor: Wei Li**.

2**018: Kinsie Arnst**, "Targets the Colchicine Binding Site on Tubulin and Overcomes Taxane Resistance" University of Tennessee Health Science Center, **Advisor: Wei Li**.

The Thomas L. Lemke Outstanding Poster Presentation Award

Thomas L. Lemke is Professor of Medicinal Chemistry and Associate Dean at the College of Pharmacy at the University of Houston. He received his B.S. in Pharmacy from the University of Wisconsin (1962) and went on to complete his Ph.D. in Medicinal Chemistry under Dr. Edward E. Smissman in 1966. Dr. Lemke went on to work as a Research Scientist for Upjohn from 1966 to 1970 at which time he joined the faculty at the University of Houston as Assistant Professor of Medicinal Chemistry, was promoted through the ranks receiving tenure in 1975, then Full Professor in 1984. In 1984 he was honored to spend two years as Visiting Professor at the Institut De Chimie, Universite Louis Pasteur, De Strasbourg, in Strasbourg, France where he worked in the Laboratory of Jean-Marie Lehn, who went on to receive the Nobel Prize in Chemistry.

Dr. Lemke is also a noted author of several well-known books, one being "Review of Organic Functional Groups, Introduction to Medicinal Chemistry," and he is one of the editors of the textbook "Foye's Principles of Medicinal Chemistry."

Most noteworthy of Dr. Lemke's contributions is the fact that he was one of the founding organizers of our MALTO organization. He, along with Nelson Voldeng, who we also honor every year with the Nelson Voldeng Memorial Lecture, had the vision and, with a lot of hard work, made it happen.

It is therefore very fitting that we, the MALTO community of scholars (faculty and students), show our great appreciation to Dr. Thomas Lemke for a job well done by naming this award in his honor.

Past Recipients of The Thomas L. Lemke Outstanding Student Poster Presentation Award

2003: Srinivasan P. Venkatachalan, "Effect of Urethane on the $5HT3_A$ and $5HT3_{AB}$ Receptor," University of Lousiana, Monroe, **Advisor: Dr. Marvin K Schulte.**

2005: Wayun Sheng, "3D High-resolution NMR Characterizatin of Recombiant CB2 Membrane Protein Fragment," University of Houston, **Advisor: Dr. Xiang-Qun (Sean) Xie.**

2006: Lukasz Kutrzeba, "In-vitro Studies on Metabolism of Salvinorin A," University of Mississippi, **Advisor: Dr. Jordan K. Zjawiony**.

2007: Prasanna Sivaprakasam, "Computational Insights into PfDHFR-TS: Application of 2D,3D-QSAR and Docking Studies to Cycloguanil Derivatives," University of Mississippi, **Advisor: Dr. Robert J Doerksen**.

2008: Sanju Narayanan, "Discovery of Highly Selective σ_2 Antagonist as Anti-cocaine Agent," **Advisor: Dr. Christopher R. McCurdy.**

2009: Lacey D. Gamblin, "Synthesis of Thiourea Analogues as Potential Somatostatin Receptor Subtype 4 Agonists" Southern Illinois University, Edwardsville, **Advisor: Dr. A. Michael Crider.**

2010: Swapnil Kulkarni, "Studies Towards Total Synthesis of Pseudolaric Acid B," University of Mississippi, **Advisor: Mitchel A. Avery.**

2011: Horrick Sharma, "Synthesis, Docking and Biological Studies of Phenanthrene β-Diketo Acids as Novel HIV-1 Integrase Inhibitors," University of Tennessee, **Advisor: John K. Buolamwini.**

2012: Amanda L. Waters, "Isolation and Structure Determination of Antifungal Lactone Lipids and Other Secondary Metabolites From Sooty Mold, *Scorias Spongiosa*," University of Mississippi, **Advisor: Mark Hamann.**

2013: "An Approach to identifying Potent and Selective DXG-OUT RIP1 Kinase Inhibitors," University of Houston, **Advisor: Gregory D. Cuny**

2014: Manal A. Nael, "Targeting Protein Kinase RNA-like Endoplasmic Reticulum Kinase to Manage Alzheimer's Disease," University of Mississippi, **Advisor: Robert J. Doerksen.**

2015: Jai Shankar K. Yadlapalli, "Pharmacology, Pharmacokinetics, and Therapeutic Implications of Morphine-6-*O*-Sulfate sodium in Diabetic Neuropathy," University of Arkansas, **Advisor: Peter A. Crooks.**

2016: Abu Bakar Siddique, "Extra-Virgin Olive Oil Based Oleocanthal: A Promising Lead for the Control of C-MET-Dependent Brest Malignancies," Univesity of Louisiana, **Advisor: Khalid El Sayed.**

2017: Sri Sujana Immadi, "Application of Hemetsberger-Knittel Reaction in the Synthesis of Indole/Azaindole-2-carboxamides for Development of Allosteric Modulators of Cannabinoid CB1 Receptor, Texas A & M University, **Advisor: Dai Lu.**

2018: Vikas Mishra, "Selective CB2 Receptor Agonists as Dual Suppressors for Pain and Cancer Growth" Texas A&M University, **Advisor: Dai Lu**.

The Ronald F. Borne Outstanding Postdoctoral Poster Presentation Award

Dr. Ronald F. Borne, professor emeritus of medicinal chemistry at the University of Mississippi, School of Pharmacy, retired on June 30, 2006 after 38 years of service to the University. A native of New Orleans, LA, he earned the B.S. degree in chemistry from Loyola University of the South, the M.S. degree in organic chemistry from Tulane University, and the Ph.D. in medicinal chemistry from the University of Kansas (under the tutelage of Professor Matt Mertes). Early in his career, he was employed as chemist at the Ochsner Research Medical Foundation and as a research chemist at the C. J. Patterson Co. in Kansas City, KS. After earning his doctorate degree he joined Mallinckrodt Chemical Works in St. Louis, MO as a research chemist.

In 1968 he joined the faculty at the University of Mississippi as an assistant professor of medicinal chemistry and began a career of teaching, research and administration. He was promoted to the rank of associate professor in 1970 and to full professor in 1973. He received the Outstanding Teaching Award for the University in 1972 and the School of Pharmacy Outstanding Teacher Award on six occasions (1982, 1983, 1989, 1993, 1997 and 1988). He was named the State of Mississippi Professor of the Year in 1992 by the National Council for the Advancement and Support of Education. In 1994 Dr. Borne received the Burlington Northern Faculty Achievement Award from the University of Mississippi and the National Rho Chi
Lecture Award. In 1996 he received the Distinguished Pharmacy Educator Award from the American Association of Colleges of Pharmacy.

Dr. Borne's research career and interests primarily involved efforts to elucidate the importance of conformational factors in the actions of agents affecting the central and peripheral nervous systems. In particular: analgetics, anti-arthritics, dopaminergics, cholinergics and adrenergics received considerable attention. Other recent interests included synthesis of novel pharmacotherapeutic agents for the treatment of dependence on cocaine and other substances of abuse as well as the synthesis of new antimalarial agents. In 1988-89 he was awarded an N.I.H. Senior International Fellowship to conduct research in the Department of Pharmacology at the University of Edinburgh Medical School in Edinburgh, Scotland. His research involved the synthesis of radioligands selective for serotonin 5-HTlA receptors as diagnostic tools for Alzheimer's disease, and the synthesis of analogues of the excitatory amino acids, glutamate and aspartate, to study the etiology of senile dementia disorders. Because of the interdisciplinary nature of his research program, Dr. Borne established collaborative relationships with other researchers and has published with a faculty or staff member in every other department or division in the School of Pharmacy (pharmacology, pharmacognosy, pharmaceutics, pharmacy administration, clinical pharmacy, RIPS, NCNPR, continuing education), including the Pharmacy Library. He has received federal research funding from NIH, NSF, the Department of Education, NASA, the Department of Commerce, CDC and the Department of Defense as well as several industrial research companies. Dr. Borne has published approximately 100 research, drug abuse education and professional publications and book chapters covering a span of six decades and was granted four U.S. patents.

Dr. Borne held several administrative positions in the School of Pharmacy and the University. He served as Chairman of the Department of Medicinal Chemistry (1979-88), Associate Vice Chancellor for Research and Dean of the Graduate School (1985-86), and as Associate Vice Chancellor for Research (1998-2001). In the latter position he was responsible for coordinating all research activities on campus with numerous state and national agencies and coordinated all university-related research activities with the Mississippi Congressional delegations. During this period, extramural funding (external grants and contracts) on the Oxford campus increased from $18.6 million in FY96-97 to $73.6 million in FY00-01. He also established the Laboratory for Applied Drug Design and Synthesis (LADDS) in the Department of Medicinal Chemistry. When he returned to full time teaching and research in 2001 the University established an endowment to establish the Ronald F. Borne Endowed Chair of Medicinal Chemistry. Dr. Borne was also heavily committed to community service through his appointment as Chairman of the City of Oxford Park Commission Board. During this period (1978-1980) the city experienced its greatest growth in park and recreational facilities as exemplified by the construction of a $275,000 Community Activity Center and a $300,000 public swimming pool, the city's first community pool. He was subsequently appointed to serve on the School Board for the City of Oxford Public School System (being the first member of the University Community to be appointed to that Board) and served as member and as Vice-Chair from 1980-1983. He is a medicinal chemist by education and a writer by avocation. He has written poetry, a play, and has several non-scientific articles and short stories published in the *Ole Miss Review*, *Mississippi Magazine*, and the *Ole Miss Spirit*. He has also written or edited several books including *The Great College Coaches Cookbook,* (Stanley-Clark Publishing Co., 1988) and *Beginnings and Ends*, (Nautilus Publishing Co., 2012). His biography of Mississippian Hugh Clegg, *TROUTMOUTH: The two careers of Hugh Clegg*, was published by the University Press of Mississippi in 2015. Dr. Borne passed away unexpectedly on October 18, 2016, while working on a history book, *1936 – A Pivotal Year in American and World History: The Confluence of Sports and Politics*. His insight and contributions to MALTO will be sorely missed.

Past Recipients of The Ronald F. Borne Outstanding Postdoctoral Poster Presentation Award

2015: Pallavi Rajaputra, "Far Red Light-Activatable Prodrugs of a Photosensitizer and Anti-Cancer Drug for Effective Tumor Ablation Using Photodynamic Therapy", University of Oklahoma, **Advisor: Youngjae You.**

2016: Staya Prakash Shukla, "Homo- and Hetero-Multimerizations of Peptoids to Target Cancer," University of Houston, **Advisor: Gomika Udugamasooriya.**

2017: Moses Bio, "Targeted Far-Red Light Activatable Prodrugs: Folate Receptor-Targeting, Optical Imaging, and a Combination of Photodynamic Therapy and Site-Specific Chemotherapy", University of Oklahoma, **Advisor: Youngjae You.**

2018: Pankaj Pandey, "Identification of Potent Natural Product Chemotypes as Cannabinoid Receptor 1 Inverse Agonists Using Protein Structure-Based Virtual Screening". University of Mississippi, **Advisor: Robert J. Doerksen**.

Meeting Schedule

Monday PM - May 20th, 2019

5:00 – 6:30 **Registration**
UTHSC College of Pharmacy, 881 Madison Avenue, Memphis, TN

6:30 – 8:30 **Faculty & Student Mixer**
UTHSC College of Pharmacy, 881 Madison Avenue, Memphis, TN

NOTE: All events on Tuesday 21th, 2019 and Wednesday, May 22nd, 2019 will be held on the first floor of the College of Pharmacy (COP) building located at 881 Madison Avenue, Memphis, TN.

Tuesday AM - May 21st, 2019

7:00 – 8:30 **Poster Setup (COP Lobby)**

8:30 – 8:40 **Welcoming Remarks (COP Room 102)**
Dr. Marie A. Chisholm-Burns, Dean College of Pharmacy
Introduction by Dr. Georgi Petkov, Chair, Department of Pharmaceutical Sciences, UTHSC College of Pharmacy

PODIUM SESSION 1 – Dr. Jesse A. Jones presiding (8:45 – 10:25 am)

8:45 **O-1** **A CATALYST-FREE SYNTHESIS OF B-FLUORO-A,B-UNSATURATED CARBONYL COMPOUNDS**
Amna T. Adam and David A. Colby*
Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, Oxford, MS.

9:05 **O-2** **MULTICYCLIC STABLE GRAFTED PEPTIDE FOR IMMUNOMODULATION**
Pravin Parajuli, Rushikesh Sable, and Seetharama Jois*.
Department of Basic Pharmaceutical and Toxicological Sciences, College of Pharmacy, University of Louisiana at Monroe, LA 71201

9:25 **O-3** **AN ORALLY AVAILABLE TUBULIN INHIBITOR, VERU-111, SUPPRESSES TRIPLE-NEGATIVEBREAST CANCER TUMOR GROWTH AND METASTASIS**
Shanshan Deng [‡, 1], Raisa I Krutilina [‡, 2], Qinghui Wang [1], Zongtao Lin [1], Deanna N. Parke [2], Hilaire C. Barch [2], Hao Chen [1], Duane D. Miller [1], Tiffany N. Seagroves [2, *] and Wei Li [1, *]

[1] Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN38163, United States, [2] Department of Pathology, University of Tennessee Health Science Center, Memphis, TN38103, United States.

9:45 **O-4** **SYNTHESIS OF A GYMNOTHESPIROLIGNAN MODEL SUBSTRATE**
Ghada Ali,[1] Gregory Cuny.*[1, 2]
[1]Department of Chemistry, [2]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, Texas, 77204.

10:05 **O-5** **OPTIMIZED SYNTHESIS OF RACEMIC ZCZ011, A POSITIVE ALLOSTERIC MODULATOR OF CB_1 RECEPTOR, RESOLUTION AND CHARACTERIZATION OF ITS ENANTIOMERS**
Sri Sujana Immadi[1], Zhixing Wu[1], Rachel Dopart[2], Debra A. Kendall[2], Kristen R. Trexler[3], Steven G. Kinsey[3], and Dai Lu[1*]
[1]Rangel College of Pharmacy, Health Science Center, Texas A&M University, Kingsville, TX, 78363, USA; [2]Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT 06269, USA; [3]Department of Psychology, West Virginia University, Morgantown WV 26506, USA

10:25 – 10:45 **Coffee Break (COP Room 118-119)**

10:45 – 12:00 **32nd A. NELSON VOLDENG MEMORIAL LECTURE**
Keynote Presenter: Jeff Aubé, Ph.D. Fred Eshelman Distinguished Professor of Chemistry, The University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC

Tuesday PM - May 21st, 2019

12:00 – 2:30 **CONCURRENT LUNCH (*COP Room 118-119*) & POSTER SESSION (*COP Lobby*).**

Graduate Student Poster (GSP) & Postdoc Poster (PDP)

GSP-1 **IDENTIFICATION OF A NEW CALCIUM-DEPENDENT PROTEIN KINASE 1 INHIBITOR CHEMOTYPE WITH POTENT CRYPTOSPORIDIUM PARVUM INHIBITORY ACTIVITY**
Elise Waldron-Young[1], Grant Whitman[2], Mathew Hulverson[2], and Wes Van Voorhis[2], and Greg Cuny[1*]
[1] Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, Texas, 77204. [2]Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington 98109, United States.

GSP-2 **PROGRESS TOWARD THE SYNTHESIS OF FLUORINATED 3-METHOXYFLAVONES AS POTENTIAL ANTIOXIDANTS**

Reem Alkhodier and David A. Colby*
Department of BioMolecular Sciences, College of Pharmacy, the University of Mississippi, Oxford, MS

GSP-3 **CHARACTERIZATION OF HER-2 TARGETED MODIFIED PEPTIDOMIMETIC**

Achyut Dahal, Leeza Shrestha, Seetharama D. Jois*
School of Basic Pharmaceutical and Toxicological Sciences, College of Pharmacy, University of Louisiana at Monroe, Monroe, LA.

GSP-4 **Computer Aided Design of NADH:quinone Oxidoreductase as an antimicrobrial target in *H. pylori***

Nicole Vita[1], Alex Mugengana[1], Michael LaFleur[2], and Richard Lee[1]*
1. St. Jude Children's Research Hospital department of Chemical Biology and Therapeutics, 262 Danny Thomas Pl., Memphis, TN, 38105; 2. Arietis Pharma, 650 Albany St #130, Boston, MA 02118

GSP-5 **THE DISCOVERY AND DEVELOPMENT OF THIENOPYRIMIDINES AS INHIBITORS OF HELICOBACTER PYLORI THROUGH THE RESPIRATORY COMPLEX**

Alex K. Mugengana[1,2], Kevin Moran[3], Autumn B. Gandt[3], Nicole Vita[1,2], Lalit K. Sharma[2], Elizabeth C. Griffith[2], Lei Yang[2], Ekaterina Gavrish[3], Michael D. Lafleur[3], Richard E. Lee[2*]
[1]Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN. [2]Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, TN. [3]Arietis Pharma, Boston, MA

PDP-1 **Brain Uptake Studies of Morphine-6-O-sulfate (M6S) in Rats**

Zaineb A. F. Albayati[a], Jai Shankar K. Yadlapalli[a], Narsimha R. Penthala[a], Philip J. Breen[a], Maxim Dobretsov[b], Howard P. Hendrickson[c], and Peter A. Crooks[a*]
[a]Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205; [b]Present address: Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg, Russia. [c]Samford University McWhorter School of Pharmacy, Birmingham, Alabama 35229

PDP-2 ***In Vivo* Evaluation of Vancomycin and BT-2-minipeg-2-vancomycin in Rat Plasma and Bone Tissue after i.p. administration**

Zaineb. AF Albayati[1], Manjula Shanker[2], Andrew J Morris[2], Philip J Breen[1] and Peter A Crooks[1]
[1]College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR; [2]College of Pharmacy, University of Kentucky, Lexington, KY

PDP-3 **USE OF α-FLUORONITROALKENES AS A SYNTHETIC EQUIVALENT FOR FLUORO ALKYNES IN CYCLOADDITION REACTION WITH ORGANIC AZIDES**

Sampad Jana[1], Sweta Adhikari[1], Micheal R. Cox[1], Sudeshna Roy*[1]
[1]Department of Biomolecular Sciences, School of Pharmacy, University of Mississippi, MS 38655.

PDP-4 **CELLULOSE SURFACE UTILITY AS AN ARTIFICIAL EXTRACELLULAR MATRIX FOR NEURAL DIFFERENTIATION**

Soma Shekar Dachavaram [1], Chetan Pandanaboina [2], Krishna Deo Sharma [3] Thomas Risch [2], Jennifer Y. Xie [3], and Peter A. Crooks*[1]
[1]Department of Pharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, AR. [2]Neuroscience Laboratory, Arkansas Biosciences Institute (ABI), Arkansas State University, Jonesboro, AR. [3]Arkansas State University, College of Sciences & Mathematics, Arkansas State University, AR.

PDP-5 **Synthesis and evaluation of Azaindole Quinuclidinones as Novel Cannabinoid Ligands**

Narsimha R. Penthala,[a] Amal M. Shoeib,[b] Soma Shekar Dachavaram,[a] Allen Snider,[a] Paul L. Prather,[b] Peter A. Crooks[a]*
[a]Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA
[b]Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

PDP-6 **IMIDAZOLE AND BENZIMIDAZOLE CARBAMATES OF MELAMPOMAGNOLIDE B AS POTENT, ORALLY BIOAVAILABLE ANALOGS FOR TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA**

Venumadhav Janganati, [a] Zaineb A. F. Albayati,[a] Zheng Chen,[a] Earl J. Morris,[a] Jessica Ponder,[c] Philip J. Breen,[a] Craig T. Jordan[b] and Peter A. Crooks[a]*
[a] Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA; [b] Division of Hematology, University of Colorado, Aurora, CO 80045, USA; [c] Department of Toxicology, University of Colorado, Aurora, CO 80045, USA

PDP-7 **IDENTIFICATION OF USP1 INHIBITORS BY UBIQUITIN-RHODAMINE ASSAY**

Sandipan Roy Chowdhury, Patrick Chuong, Amit Gupta, and Alexander Statsyuk
Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX

PDP-8 **SMALL MOLECULE POTENTIATORS FOR OXACILLIN AGAINST METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS**

Suresh Dharuman[1], John Elmore[1], Carl Thompson[1], Michael E. Johnson[2], Robert M. Daum[3], and Richard E. Lee*[1]

[1]Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, Tennessee. [2]Center for Pharmaceutical Biotechnology, University of Illinois at Chicago. [3]Department of Pediatrics, University of Chicago, Illinois.

PDP-9 **BT2-MINIPEG-2 CIPROFLOXACIN CONJUGATE: A POTENTIAL BONE TARGETIN-G ANTI-BACTERIAL AGENT**

Shobanbabu Bommagani[1], Zaineb AF Albayati[1], Mark S Smeltzer[2] and Peter A Crooks[*1]

Department of Pharmaceutical Sciences, College of Pharmacy[1], Department of Microbiology & Immunology, College of Medicine[2], University of Arkansas for Medical Sciences, Little Rock, AR 72205

PDP-10 **RELEASING STUDIES OF THE SIGNALING MOLECULE, HYDROGEN SULFIDE, BY NOVEL ANTILEUKEMIC 1,2,4-THIADIAZOLIDINE-3,5-DIONE (TDZD) DERIVATIVES IN THE PRESENCE OF THIOLS IN VITRO, AND THEIR ANTILEUKEMIC ACTIVITIES**

Suresh K. Bowroju,[a] Narsimha R. Penthala,[a] Eloisi C. Lopes,[c] Karl D. Straub,[b] Monica L. Guzman,[c] Peter A. Crooks[a*]

[a]Department of Pharmaceutical Sciences, College of Pharmacy, [b]Department of Biochemistry & Molecular Biology, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, AR-72205 and [c]Division of Hematology/Oncology, Department of Medicine, Weill Cornell Medical College, New York, NY 10065

PDP-11 **STRUCTURE-BASED VIRTUAL SCREENING APPROACH TO IDENTIFY NOVEL MraY INHIBITORS FOR TUBERCULOSIS CHEMOTHERAPHY**

Shamba Chatterjee[1], Pankaj Pandey[1], Robert J. Doerksen[1], Timothy D. H. Bugg[2], Christina L. Stallings[3], Sudeshna Roy[1]*

[1]Department of Biomolecular Sciences, University of Mississippi, University, MS 38677, USA. [2]Department of Chemistry, University of Warwick, Gibbet Hill, Coventry, CV4 7AL. [3]Department of Molecular Microbiology, Washington University in St. Louis School of Medicine, St. Louis, MO 63110, USA.

PDP-12 **INVESTIGATION OF DETRIFLUOROACETYLATIVE CARBON–CARBON BOND CLEAVAGE OF α-ARYL PENTAFLUORO GEM-DIOLS TO PREPARE DIFLUOROMETHYLARENES**

Hari R. Khatri,[†] Changho Han,[‡] and David A. Colby[*,†]

[†] Department of BioMolecular Sciences, University of Mississippi, University, Mississippi 38677, United States

[‡] Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, Indiana 47907, United States

PODIUM SESSION 2 – Mr. Hanxuan Li presiding (2:30 – 4:50 pm)

2:30 **O-6** **A STRAIGHT FORWARD REGIOSELECTIVE ROUTE TO 4-FLUORO-1,2,3-TRIAZOLES**

Sweta Adhikari,[1] Sampad Jana,[1] Micheal R. Cox,[1] Sudeshna Roy*[1]
[1]Department of Biomolecular Sciences, School of Pharmacy, University of Mississippi, MS 38655

2:50 **O-7** **Amides of mycophenolic acid as molecular pharmacology probes for elucidating *Cryptosporidium parvum* and Human IMPDH inhibitor selectivity**

SeungHeon Lee[1], Angela Ku[1], Mohan Rao Vippila [1], Minjia Zhang[2], Xingyou Wang[2], Liz Hedstrom[2,3], Gregory D. Cuny[1]
[1]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, TX 77204 [2]Department of Biology and [3]Chemistry, Brandeis University, Waltham, MA 02454

3:10 **O-8** **SMALL-MOLECULE INHIBITION OF THE *C. DIFFICILE* FAS-II ENZYME, FABK, BY PHENYLIMIDAZOLE ANALOGUES RESULTS IN SELECTIVE ACTIVITY**

Jesse A. Jones[1], Allan M. Prior[2], Ravi K.R. Marreddy[3], Rebecca D. Wahrmund[1], Julian G. Hurdle[3], Dianqing Sun[2], and Kirk E. Hevener[1#]
[1]Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN. [2]Department of Pharmaceutical Sciences, The Daniel K. Inouye College of Pharmacy, University of Hawaii, Hilo, Hawaii. [3]Center for Infectious and Inflammatory Diseases, Institute of Biosciences and Technology, Texas A&M Health Science Center, Houston, Texas,

3:30 **O-9** **Potential Antitumor and Antioxidant Activities of Vincetoxicum Arnottianum against Breast Cancer**

Zartash Zahra[a,b], Muhammad Majid[b,c], Sonia Maryam[a], Saima Ali[a], Muhammad Rashid Khan[a], Hamed I. Ali[b,*]
[a]Departmentof Biochemistry, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan, [b]Department of Pharmaceutical sciences, Irma Lerma Rangel College of pharmacy, Texas A&M University, Kingsville, TX, USA [c]Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan

3:50 **O-10** **COMPUTER-AIDED DESIGN OF PERIPHERALLY-RESTRICTED ANTAGONISTS OF THE CANNABINOID RECEPTOR 1 (CB1)**

AyoOluwa O. Aderibigbe[1], Pankaj Pandey[1], Robert J. Doerksen[1,2,*]
[1]Division of Medicinal Chemistry, Department of BioMolecular Sciences; and [2]Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677, USA

4:10 **O-11 DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF MX-106 ANALOGS AS POTENT AND SELECTIVE SURVIVIN INHIBITORS**

Najah Albadari, Shanshan Deng, Hao Chen, Sicheng Zhang, Zhongzhi Wu, Duane D. Miller*, and Wei Li*
Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN.

4:30 **O-12 DESIGN AND SYNTHESIS OF NOVEL HETERO-MULTIVALENT LIGANDS TARGETING KINASES**

Samanthreddy Kedika[1] and D. Gomika Udugamasooriya*[,1]
[1]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, TX-77204

4:50 – 5:10 **Coffee Break (COP Room 118-119)**

PODIUM SESSION 3 – Ms. Sahar Algamdi presiding (5:10 – 6:30 pm)

5:10 **O-13 In silico screening of Bulbine genus reveals potential PXR activators**

Alhusban M.[1], Ali Z.[2], Khan S.[2] Chittiboyina AG.[2], & Khan IA[1,2]
[1]Department of Biomolecular Sciences, Division of Pharmacognosy, School of Pharmacy, The University of Mississippi, MS 38677, USA. [2]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences

5:30 **O-14 TARGETING THE POLYCYSTINS/TAZ COMPLEX FOR THE TREATMENT OF OSTEOPOROSIS**

Hanxuan Li[1], Zhousheng Xiao[2], Hao Chen[1], Micholas D Smith[3], Jeremy C Smith[3], Darryl Quarles[2] and Wei Li*[1]
[1.]Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN [2.]Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN [3.]UT/ORNL Center for Molecular Biophysics, Oak Ridge National Laboratory, Oak Ridge, TN

5:50 **O-15 DESIGN AND DISCOVERY OF SMURF1 INHIBITORS VIA UBFLUOR ASSAY**

Patrick Chuong[1], Sandipan Roy Chowdhury[1], Steven Kennedy[1], Amit Gupta[1], Alexander Statsyuk*[1]
[1]Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX.

6:10 **O-16 MOLECULAR DYNAMICS SIMULATION FOR BINDING OF ALCOHOL TO THE C1 DOMAIN OF PRESYNAPTIC MUNC13-1**

Youngki You and Joydip Das*
Department of Pharmacological & Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX 77204, U.S.A.

6:30 **Dinner Location: 331 Madison Ave #2, Memphis, TN 38103.**

Wednesday AM - May 22nd, 2019

PODIUM SESSION 4 – Ms. Najah Albadari Presiding (8:00 – 9:20 am)

8:00 **O-17** **A novel Single-chain Enzyme Complex with chain-reaction properties Rapidly Producing Thromboxane A_2 and Exhibiting Powerful Anti-Bleeding Functions**

Yan Li [a], Qun-Ying Li [a, b], Qing-Lan Ling [a], Shui-Ping So [a] and Ke-He Ruan [a, *]
[a] The Center for Experimental Therapeutics and Pharmacoinformatics, Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, Texas 77204, U.S.A.
[b] Visiting Scholar from Department of Ultrasound, Second Affiliated Hospital, Zhejiang University College of Medicine, Hangzhou City, Zhejiang Province 310009, China.

8:20 **O-18** **ANTI-INFLAMMATORY EFFECT OF SELECTIVE CB2 INVERSE AGONISTS IN MURINE AND HUMAN MICROGLIAL CELLS**

Sahar S. Alghamdi, Kirk E. Hevener, Bob M. Moore II*.
Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN.

8:40 **O-19** **MYXOBACTERIAL PERCEPTION, DEGRADATION, AND TRANSFORMATION OF EXOGENOUS ENVIRONMENTAL QUORUM SIGNALS**

Barbara I. Adaikpoh[1], D. Cole Stevens*[1]
[1]Pharmacognosy Division, Department of BioMolecular Sciences, University of Mississippi

9:00 **O-20** **VALIDATION OF VIMENTIN AS NON-SMALL CELL LUNG CANCER STEM CELL BIOMARKER**

Haowen Zhang,[1] Satya Prakash Shukla[1], and D. Gomika Udugamasooriya*[,1,2]
[1]Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX
[2] Department of Cancer System Image, MD Anderson Cancer Center, Houston, TX

9:20 – 9:40 **Coffee Break (COP Room 118-119)**

PODIUM SESSION 5 – Ms. Shanshan Deng (9:40 – 11:00 am)

9:40 **O-21** **SYNTHESIS OF FLUOROFLAVONES AS POTENTIAL NEUROPROTECTIVE AGENTS**

Maali D. Alshammari, and David A. Colby*
Department of BioMolecular Sciences, University of Mississippi, University, Mississippi, 38677, USA

10:00 **O-22** **PHYTOCHEMICAL INVESTIGATION OF T. CRISPA AND T. SINENSIS TO DEVELOP A VALIDATED METHOD TO ANALYSE HERBAL DIETARY SUPPLEMENTS OF CLOSELY RELATED TINOSPORA SPECIES**

Abidah Parveen[1,3], Omer Fantoukh[1], Zulfiqar Ali*[2], Yan Hong Wang*[2], Vijayasankar Raman[2], Ikhlas A. Khan*[1,2]

[1]Department of Biomolecular Sciences, Division of Pharmacognosy, [2]National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, University, MS, 38677, USA, [3]Abbottabad University of Science & Technology, Havelian, Abbottabad District, KPK, Pakistan.

10:20 **O-23** **Validating the folklore use of *Ipomoea batatas* L. Lam. as hepatoprotective agent against hepatomas and liver injuries using *in vitro* and *in vivo* modeling in male Sprague Dawley rats.**

Muhammad Majid[a,b], Zartash Zahra[a,b], Muhammad Waleed Baig[b], Fatima Ijaz[b], Muhammad Rashid Khan[b], Hamed I. Ali[a], Ihsan-ul-Haq[b*]

[a] Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Kingsville, Texas, 78363, USA

[b]Department of Pharmacy & Biochemistry, Faculty of Biological Sciences, Quaid-i-Azam University (45320), Islamabad, Pakistan.

10:40 – 12:00 **MALTO Business Meeting (COP Room 102)**

12:00 – 1:30 **Lunch (COP Room 118-119)**

MALTO Awards Presentation (Dr. John Rimoldi)

- *Robert A. Magarian Podium Presentation Award*
- *Thomas L. Lemke Poster Presentation Award*
- *Ronald F. Borne Postdoctoral Poster Presentation Award*

Closing Remarks (Dr. Wei Li)

ADJOURN

ABSTRACTS OF PODIUM PRESENTATIONS

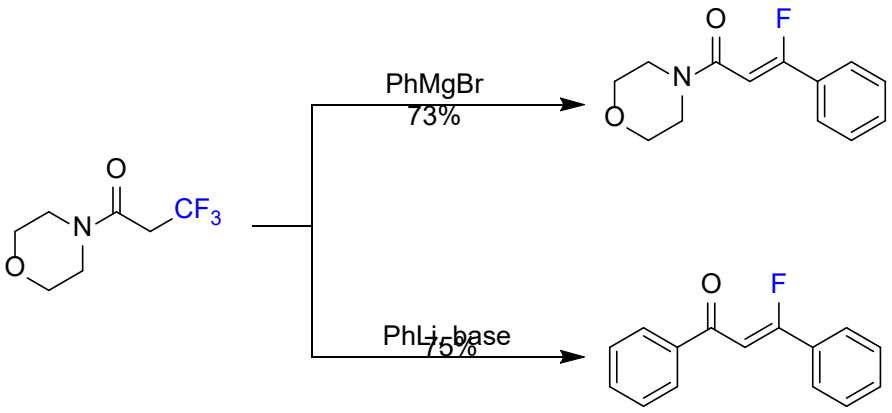
Podium Abstract O-1

A CATALYST-FREE SYNTHESIS OF *B*-FLUORO-A,*B*-UNSATURATED CARBONYL COMPOUNDS

Amna T. Adam and David A. Colby*

Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, Oxford, MS.

The incorporation of fluorine on organic molecules can produce unique properties such as increasing lipophilicity, bioavailability, and membrane permeability as well as decreasing drug metabolism. Another specific example of fluorinated structures is that fluoroalkenes can serve as bioisosteres of peptide bonds. Although amide bonds in many peptides are easily hydrolyzed by enzymes *in vivo,* the framework of fluoroalkenes has hydrolytic stability and is resistant to this process. Currently, there are numerous methods to synthesize *α*-fluoro-*α,β*-alkenes; however, the synthesis of *β*-fluoro-*α,β*-alkenes are more challenging. In fact, there are three approaches available to synthesize *β*-fluoro-*α,β*-unsaturated alkenes, and two of the methods are limited to alkynes as substrates. The third uses chromium (II)-mediated reductive coupling to access *β*-fluor-*α,β*-alkenes as reported by Ishihara and colleagues. Our design builds upon Ishihara's observation that reacting N-(3,3,3-trifluropropanoyl)oxazolidinone in the presence of $SnCl_4$ gave rise to 3,3-difluoropropenoic imide. Our approach exploits a less stable 3,3-difluoropropenoic morpholine imide as a substrate for nucleophilic addition of Grignard reagent. This simple approach is free of metal catalysis and generates the *β*-fluoro-*α,β*-alkenes in a one-pot reaction using Grignard as both a base and nucleophile. Using this method, we have generated *β*-fluoro-*α,β*-unsaturated alkenes with alkyl and aryl Grignard reagents. This method provides direct access to an important class of bioisosteres of peptide bonds.



Podium Abstract O-2

MULTICYCLIC STABLE GRAFTED PEPTIDE FOR IMMUNOMODULATION

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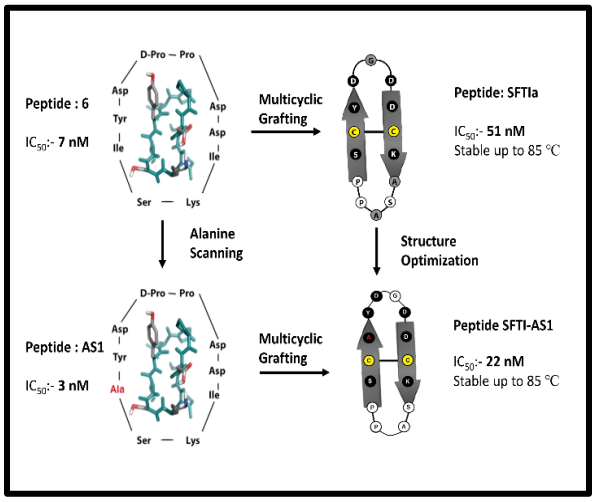
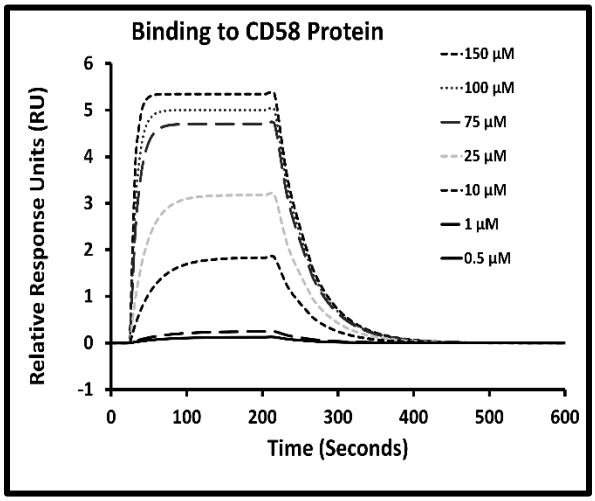
Activation, proliferation and cytokine production is an initial step of T cells for immune response generation during progression of an autoimmune diseases. CD58 is a co-stimulatory molecule found in antigen presenting cells (APC). CD58 is found to be increased in autoimmune diseases and inflammation. Inhibition of CD2-CD58 protein-protein interaction (PPI) between APC and T cells is known to hinder activation of T-cells. This inhibition is found to have promising role in slowing the progression of autoimmune diseases such as rheumatoid arthritis and psoriasis. From the alanine scanning studies of previously designed peptides, we obtained a potent CD2-CD58 PPI inhibitor peptide, AS1, having IC_{50} of 3 nM in lymphocyte-epithelial cell adhesion assay. In this study, we are grafting the peptide AS1 in multicyclic SFTI framework and evaluating the potency and stability of the grafted peptide (SFTI-AS1). SFTI-AS1 was synthesized, purified and characterized using HPLC, Mass Spectrometry, NMR and Circular Dichroism studies. SFTI-AS1 inhibited adhesion between OVCAR-3:T-cells and HFLS-RA:T-cells with IC_{50} of 23.34 ±4.62 nM and 37.23 ±1.02 nM respectively. Flow cytometry and surface plasmon resonance data reveled that SFTI-AS1 binds to CD58 protein in CD2 binding region. SFTI-AS1 also inhibited activation of T-cell as suggested by calcium flux assay and western blot analysis. SFTI-AS1 also exhibited exceptional thermal, chemical and enzymatic stability. In summary, muticyclic grafted peptides can be used as therapeutic agents to modulate autoimmune diseases.

Keywords: Sunflower Trypsin Inhibitor, Multicyclic Grafted Peptide, Protein-Protein Interaction





Podium Abstract O-3

AN ORALLY AVAILABLE TUBULIN INHIBITOR, VERU-111, SUPPRESSES TRIPLE-NEGATIVE BREAST CANCER TUMOR GROWTH AND METASTASIS

Shanshan Deng [‡, 1], Raisa I Krutilina [‡, 2], Qinghui Wang [1], Zongtao Lin [1], Deanna N. Parke [2], Hilaire C. Barch [2], Hao Chen [1], Duane D. Miller [1], Tiffany N. Seagroves [2, *] and Wei Li [1, *]

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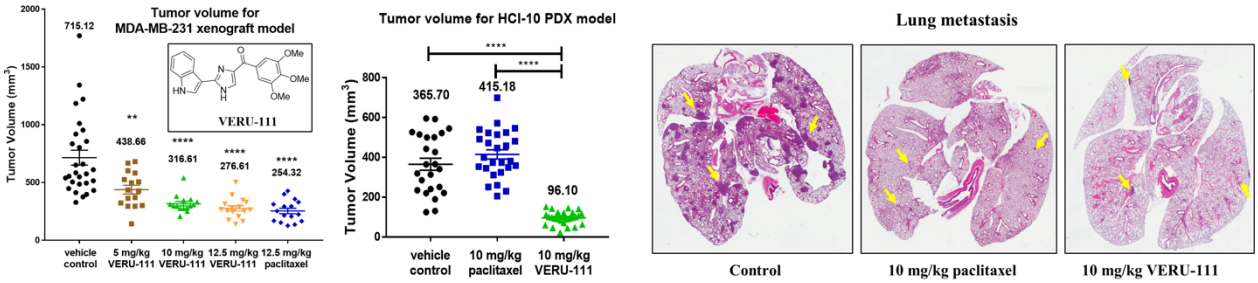
Triple-negative breast cancer (TNBC) accounts for ~15% of all breast cancers in the United States. TNBC has poorer overall prognosis relative to other molecular subtypes, due to the rapid development of drug resistance to conventional chemotherapies and the increased risk of visceral metastasis. A standard treatment regimen for TNBC is a taxane-based chemotherapy, such as paclitaxel, which stabilizes microtubules. However, drug resistance and neurotoxicities often limit taxane clinical efficacy, thus, there is an urgent need to develop new effective therapies to overcome resistance. We evaluated the pre-clinical efficacy of a novel, potent and orally bioavailable tubulin inhibitor, VERU-111, in TNBC models. VERU-111 showed remarkable cytotoxicity against TNBC cell lines. It also efficiently inhibited colony formation, cell migration and invasion. VERU-111 therapy also induced apoptosis and cell cycle arrest *in vitro* in a dose-dependent manner. Orally administered VERU-111 also inhibited the growth of MDA-MB-231 xenografts in a dose-dependent manner, with similar efficacies to paclitaxel, but without acute toxicity. Furthermore, orally administered VERU-111 significantly reduced metastasis from the mammary fat pad and in an experimental metastasis model. Finally, relative to paclitaxel, VERU-111 effectively killed a known taxane-resistant patient-derived xenograft (PDX) TNBC line (HCI-10) with similar efficacy to a treatment-naïve TNBC PDX line (HCI-2), and it suppressed the growth of TNBC PDX xenografts significantly *in vivo*. Collectively, these studies strongly suggest that VERU-111 is a potent inhibitor of TNBC aggressive phenotypes *in vitro* and *in vivo*. Thus, VERU-111 is a promising new generation of tubulin inhibitor for the treatment of TNBC.



Keywords: TNBC, anti-mitotic agents, microtubules, proliferation, metastasis

Podium Abstract O-4

SYNTHESIS OF A GYMNOTHESPIROLIGNAN MODEL SUBSTRATE

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Gymnothespirolignan A (**1**) and B (**2**) belong to a family of novel polycyclic spiro lignan natural products (Figure 1). They were isolated in 2014 from *Gymnotheca involucrate* and showed modest antiviral activities against respiratory syncytial virus (RSV) with an IC_{50} = 31.87 and 17.51 µM, respectively. Our interest in these compounds arose from their conformational restricted structure that provides fixed spatial orientation of functional groups that may be exploited for efficient and defined binding modes with biomolecular targets.

As an initial study, compound **6** (Figure 2) was utilized as a model substrate. In this presentation a successful synthesis of **6** will be illustrated using four key transformations: 1) Suzuki coupling for the construction of the biaryl bond in **3**; 2) Friedel-Crafts acylation for the fluorenone **4** synthesis; 3) Grignard reaction to generate diol **5**; 4) Acidic cyclization to form the spiro cyclic ether and furnish our model substrate **6**. This approach is now being applied to the synthesis of natural products **1** and **2**.

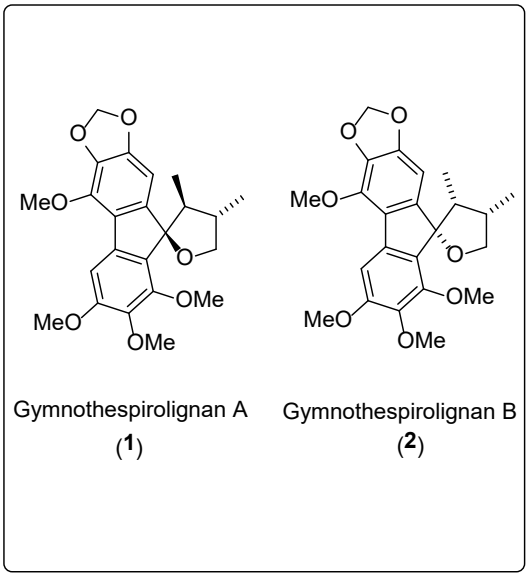

Figure 1. Structures of polycyclic spiro lignans **1** and **2**.

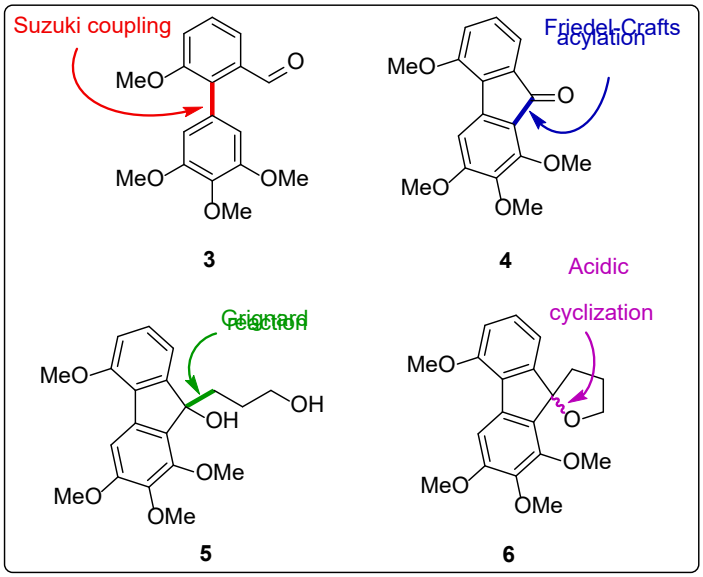

Figure 2. Key synthetic transformations used in the synthesis of **6**.

Key words: Lignan, Suzuki, Grignard, synthesis.

Podium Abstract O5

OPTIMIZED SYNTHESIS OF RACEMIC ZCZ011, A POSITIVE ALLOSTERIC MODULATOR OF CB_1 RECEPTOR, RESOLUTION AND CHARACTERIZATION OF ITS ENANTIOMERS

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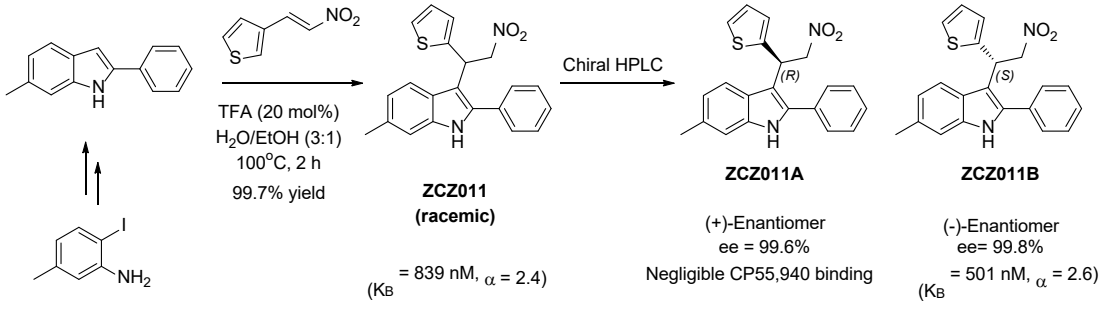
In pre-clinical studies with mice, it has been found that positive allosteric modulators (PAMs) of the cannabinoid CB1 receptor enhances the effect of pain-relief endogenous chemicals that the body produced in response to stress or injury. ZCZ011 is a positive allosteric modulator of the CB_1 receptor. It exhibits CB_1-dependent antinociceptive effects in murine models of pathological pain. The compound is a racemate carrying one chiral center. Investigation of GAT211, a close analog of ZCZ011, revealed that the (*R*)-enantiomer of GAT211 functions as an allosteric partial agonist of the CB_1 receptor and its (*S*)-enantiomer acts as a pure CB_1 positive allosteric modulator (PAM). This warrants the isolation and study of the ZCZ011 enantiomers. To this end, we first optimized the synthesis of ZCZ011 through various Lewis acid-catalyzed Michael addition reactions, and found that the reaction catalyzed by trifluoroacetic acid provided ZCZ011 in nearly quantitative yield (99.7%). Resolution of its enantiomers was achieved by chiral HPLC. The two enantiomers, ZCZ011A and ZCZ011B, were obtained with enantiomeric excess (ee) values greater than 99.5%. Recrystallization of the enantiomers individually in the mixture of MeOH/Acetone/Water (15:4:1) generated suitable crystals for structure determination by X-ray crystallography. X-ray crystallography analysis showed that the (+)-isomer of ZCZ011 has a (*R*)-configuration, and its (-)-isomer has a (*S*)-configuration. Preliminary in vitro and in vivo pharmacology data in characterization of those enantiomers will also be discussed.



Acknowledgment: This work was funded by NIH Grant DA039942.

Key Words: ZCZ011, Positive allosteric modulator, PAM, CB_1 receptor, enantiomers, optimization, cannabinoid receptor

Podium Abstract O-6

A STRAIGHT FORWARD REGIOSELECTIVE ROUTE TO 4-FLUORO-1,2,3-TRIAZOLES

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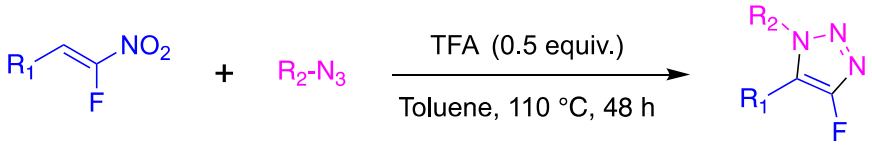
Triazoles are important heteroaromatic scaffolds with a wide range of biological activities such as antiviral, analgesic, anti-inflammatory, anti-convulsant, antimicrobial, antiproliferative and anticancer effects.[1] Despite the broad applications of 1,2,3-triazoles in medicinal to material chemistry,[2] reports for preparation of fluorotriazoles are scarce. It is now well established that incorporation of a fluorine atom in heterocyclic moieties can intensely impact the reactivity, pharmacokinetic, and stereoelectronic properties of these compounds.[3] The general method to access 1,2,3-triazoles utilizes either Huisgen or the copper(I)-catalyzed alkyne-azide cycloaddition reactios.[4] Fluoroalkynes being highly unstable species poses a limitation in directly accessing the fluorotriazoles using the standard cycloaddition conditions. We identified 2-fluoro-2-nitroalkenes as a synthetic equivalent of fluoroalkyne that could undergo 1,3-dipolar cycloaddition reactions to provide direct access to fluorotriazoles.[5] Here, we discuss the development of a synthetic method for the cycloaddition of 2-fluoro-2-nitroalkenes with organic azides in presence of trifluoroacetic (TFA) acid to generate 1,5-fluorotriazoles regioselectively.



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Podium Abstract O-7

Amides of mycophenolic acid as molecular pharmacology probes for elucidating *Cryptosporidium parvum* and Human IMPDH inhibitor selectivity

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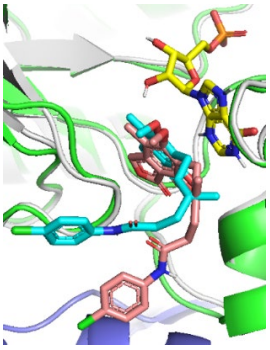
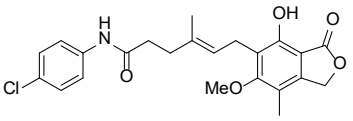
Inosine-5'-monophosphate dehydrogenase (IMPDH) is an enzyme that catalyzes oxidation of inosine 5'-monophosphate (IMP) to xanthosine 5'-monophosphate (XMP) as the rate-limiting step in the purine biosynthesis of guanine nucleotides. Since IMPDH regulates intracellular guanine nucleotide pools, it has been postulated to be critical for cell proliferation of eukaryotes and prokaryotes. Human IMPDH2 (*h*IMPDH2) is a tetrameric enzyme highly expressed during cell proliferation. Mycophenolic acid (MPA) is the prototypic *h*IMPDH inhibitor (*h*IMPDH2 IC_{50} = 7 nM) and is used clinically as an ester prodrug (e.g. mycophenolate mofetil) for immunosuppression preventing rejection following organ transplantation.

Cryptosporidium parvum (Cp) is an intracellular protozoan parasite that invades epithelial cells of the small intestine causing gastrointestinal illness and it is particularly problematic in children and immune-compromised adults. *Cp* appears to have obtained its IMPDH from bacteria by lateral gene transfer, which likely accounts for its distinct structure compared to the human isozymes. Furthermore, MPA does not inhibit *Cp*IMPDH (IC_{50} >> 10μM). However, six structurally unique classes of *Cp*IMPDH inhibitors have been reported with selectivity (>> 100-fold) verses *h*IMPDH2.

We have now generated hybrids of MPA with molecular fragments common to *Cp*IMPDH inhibitors and found derivatives that retain activity against both enzymes. Molecular docking studies revealed that the hybrid inhibitors likely bind to the two isozymes in diverse ways providing new insights into the design of selective inhibitors of *Cp*IMPDH and similar isozymes found in several pathogenic bacteria IMPDHs, such as *Mtb*, *S. aureus* and *Enterococcus* sp.

Keywords: IMPDH, *Cryptosporidium parvum*, mycophenolic acid





SH-19

*Cp*IMPDH (IC_{50} = 42 ± 20 nM)

*h*IMPDH2 (IC_{50} = 131 ± 60 nM)

Figure. Differential docking binding modes of **SH-19** in *Cp* and hamster IMPDH isozymes

Podium Abstract O-8

SMALL-MOLECULE INHIBITION OF THE *C. DIFFICILE* FAS-II ENZYME, FABK, BY PHENYLIMIDAZOLE ANALOGUES RESULTS IN SELECTIVE ACTIVITY

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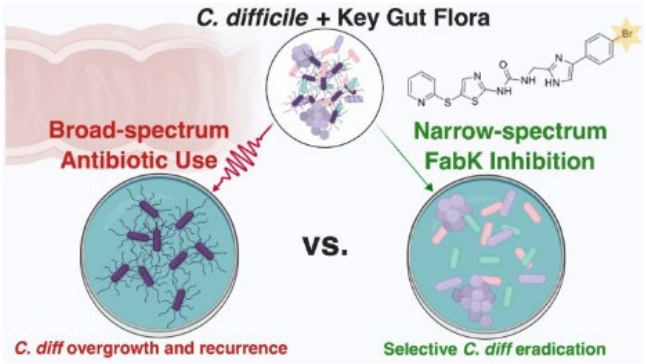
[1]Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN. [2]Department of Pharmaceutical Sciences, The Daniel K. Inouye College of Pharmacy, University of Hawaii, Hilo, Hawaii. [3]Center for Infectious and Inflammatory Diseases, Institute of Biosciences and Technology, Texas A&M Health Science Center, Houston, Texas,

Clostridioides difficile infection (CDI) is a leading cause of significant morbidity, mortality, and healthcare-related costs in the United States. After standard therapy, recurrence rates remain high with multiple recurrences not uncommon. Causes include use of broad-spectrum antibiotics that disrupt the normal host microbiota and treatment-resistant spore formation by *C. difficile*. Thus, novel druggable anti-*C. difficile* targets that promote narrow-spectrum eradication and inhibition of sporulation are of urgent need. As a critical rate-limiting step within the FAS-II bacterial fatty acid synthesis pathway, which supplies precursory component phospholipids found in bacterial cytoplasmic and spore-mediated membranes, enoyl-acyl carrier protein (ACP) reductase II (FabK) represents such a needed target. FabK is essential in *C. difficile* and is structurally and mechanistically distinct from other isozymes found in gut microbiota species, making CdFabK an attractive narrow-spectrum target. We report here the biochemical activity of a series of phenylimidazole analogues, the kinetic evaluation of CdFabK, and microbiological data suggesting these compounds' selective antibacterial activity against *C. difficile* over several other prominent gut organisms. The compounds display promising selective, low micromolar CdFabK inhibitory activity without significantly affecting the growth of other gut organisms, and the series prototype (1b) is shown to be competitive for the CdFabK cofactor and uncompetitive for the substrate. A series analogue (1g) shows maintained inhibitory activity while also possessing increased solubility. These findings represent the basis for future drug discovery efforts by characterizing the CdFabK enzyme while demonstrating its druggability and potential role as a narrow-spectrum anti-difficile target.



Keywords: Antibacterial, *Clostridioides difficile*, FabK, phenylimidazole, narrow-spectrum

Podium Abstract O-9

Potential Antitumor and Antioxidant Activities of Vincetoxicum Arnottianum against Breast Cancer

Zartash Zahra[a,b], Muhammad Majid[b,c], Sonia Maryam[a], Saima Ali[a], Muhammad Rashid Khan[a], Hamed I. Ali[b,*]

[a]*Departmentof Biochemistry, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan*
[b]*Department of Pharmaceutical sciences, Irma Lerma Rangel College of pharmacy, Texas A&M University, Kingsville, TX, USA*
[c]*Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan*

Vincetoxicum arnottianum (Wight) is a member of genera *Vincetoxicum*, family Apocynaceae, rich in anticancer alkaloids. Current study is conducted to appraise the antioxidant and anticancer potential of *Vincetoxicum arnottianum* (VA) against MCF-7 human breast cancer cell line. The aerial parts of VA was extracted with methanol (VAM) and ethyl acetate (VAE), Qualitative and quantitative phytochemical investigations for the total phenolic (TPC), flavonoid contents (TFC), and alkaloids were conducted. Qualitative analysis of VAM and its derived fractions indicated the existence of considerable quantities of phenols, tannins, and flavonoids. Flavonoids (6.4±0.14 % and 5.5±0.08 %), alkaloids (9.5±0.17% and 16.5±0.5%), and of β-carotene (0.676±0.01µg/mg and 0.195±0.02 µg/mg) were estimated in the VAM and VAE respectively. VAE also displayed TFC (382.50±1.67µg, compared to GAE/mg dry extract) and TPC (291.17±0.82µg; compared to RE/mg dry extract). Multimode antioxidant assays including DPPH, hydroxyl radical, nitric oxide, and iron chelation power were performed using VAM and VAE extract. VAE extract revealed the highest scavenging activities (IC_{50}: 141.56±3.67, 299.66±4.67, 75.92±1.89, 330.46±6.23). A significant correlation was observed between free radical scavenging activity of DPPH with TPC ($R^2 = 0.8780^{**}$) and with TFC ($R^2 = 0.8066^{**}$), in hydroxyl radical ($R^2 = 0.8220^{**}$) TPC and with TFC ($R^2 = 0.7592^{*}$), nitric oxide scavenging effect exhibited significant correlation with TPC ($R^2 = 0.8513^{**}$) and with TFC ($R^2 = 0.7812^{*}$), TPC ($R^2 = 0.8243^{**}$) and TFC ($R^2 = 0.8131^{**}$). The VAM and VAE constituents were analysed by HPLC. HPLC analysis of VAM indicated the high amount of ferulic and vanillic acid was detected of 2.2433 and 2.1249 µg/mg DW, respectively. VAE exhibited maximum caffeic acid (16.029±0.19 µg/mg) and rutin (11.917±0.12 µg/mg). Three pure compounds were isolated from VAM extract. The flash column chromatography was conducted for isolation of the potentially active constituents. The structures of the isolated compounds (V1, V2 and V3) were elucidated (**Chart 1)** by different spectrometric methods including ^{1}HNMR, ^{13}CNMR, DEPT, and IR spectra. The MTT assay using MCF-7 cell line was applied to investigate the antiproliferative activity of the extracts and the isolated compounds. Potential potent IC50 was revealed by VAM extract of 5.98 µg/ml and by VAE extract of 23.98 µg/ml at 72h. These extracts have the highest antiproliferative activities. Further assays including cell cycle analysis, Annexin V/PI staining, migration/invasion assay, and western blotting are conducted. The results of this study suggested that the antioxidant and antitumor activities of *Vincetoxicum arnottianum* are mainly attributed to the presence of phenolic acid (*e.g.* vanillic acid), alkaloids, and flavonoids (*e.g.* quercetin) in VAM and VAE.

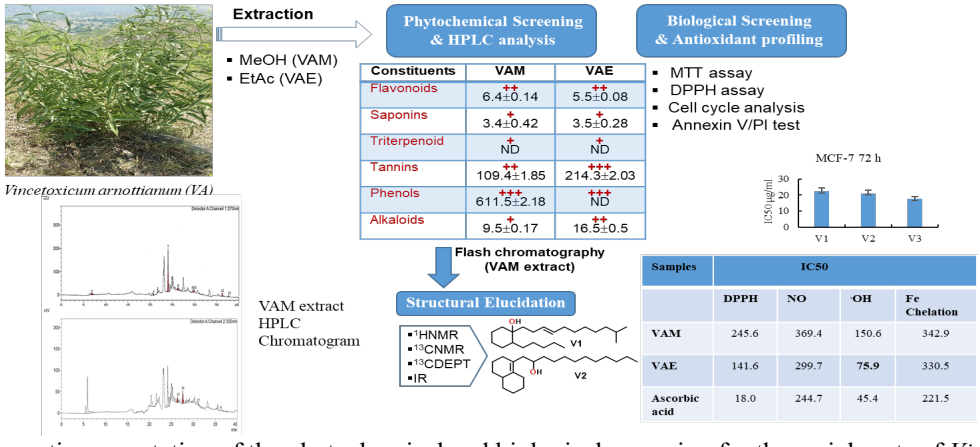


Chart 1. Schematic presentation of the phytochemical and biological screening for the aerial parts of *Vincetoxicum arnottianum* (VA; Wight).

Podium Abstract O-10

COMPUTER-AIDED DESIGN OF PERIPHERALLY-RESTRICTED ANTAGONISTS OF THE CANNABINOID RECEPTOR 1 (CB1)

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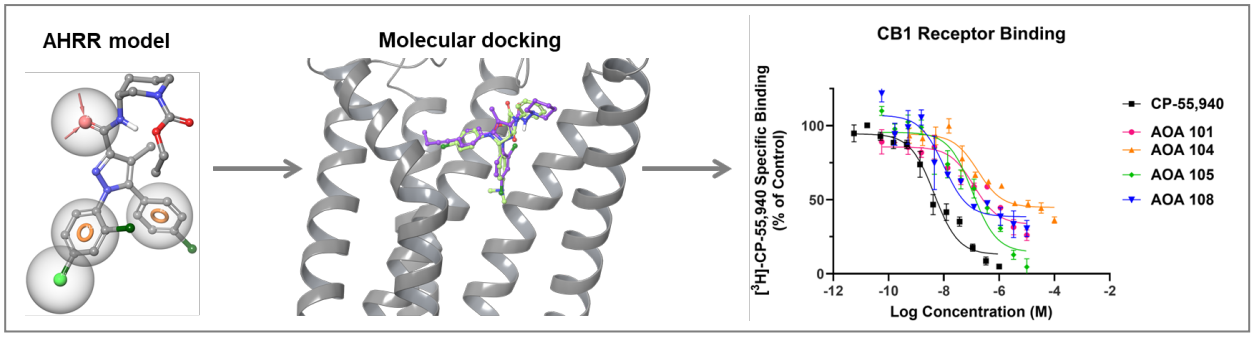
[1]Division of Medicinal Chemistry, Department of BioMolecular Sciences; and [2]Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677, USA

In obesity management, molecules that act through different pharmacological mechanisms are sought as anti-obesity agents due to the limited number and contraindications of the current FDA-approved pharmacotherapeutic options. There is great potential for molecules that block cannabinoid receptor 1 (CB1) to serve as drugs for obesity management but the early reported CB1 blockers suffered from CNS-mediated adverse effects. However, peripherally-restricted CB1 blockers, which do not accumulate in the CNS in sufficient amounts to elicit these neuropsychiatric adverse effects, are highly promising in obesity management.

In this study, from an extensive literature search we created a database of CB1-over-CB2 selective molecules for which there is reliable experimental evidence of their being peripherally restricted obtained. Using the molecules in the database, we generated and validated pharmacophore models using Phase, Schrödinger software. We also developed 3D-QSAR models based on the best-ranking four-point pharmacophore model which had a BEDROC score of 0.99. We applied the top-ranking 3D-QSAR model and molecular docking as virtual screening tools to evaluate public databases. Following the virtual screening, 21 molecules were purchased and evaluated for cannabinoid activity. Radioligand displacement assays revealed that 10 molecules have binding affinities (Ki) < 100 nM for the CB1 receptor. In conclusion, hit molecules obtained from the computational design serve as excellent starting points for the development of CB1antagonists as anti-obesity agents.



Keywords: Cannabinoid receptor 1; Peripheral restriction; Virtual screening

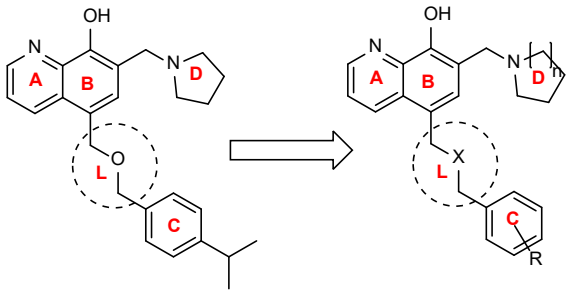
Podium Abstract O-11

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF MX-106 ANALOGS AS POTENT AND SELECTIVE SURVIVIN INHIBITORS

Najah Albadari, Shanshan Deng, Hao Chen, Sicheng Zhang, Zhongzhi Wu, Duane D. Miller*, and Wei Li*

Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN.

Apoptosis is an essential process for tissue development and homeostasis of all metazoans. However, cancer cells have evolved a variety of processes to compromise apoptosis or programmed cell death via mutation, selection, and overgrowth and thus generate cells that are highly adapted to survival and growth. Survivin (BIRC5) as the smallest member of the inhibitor of apoptosis protein (IAP) family plays a substantial role in the inhibition of cancer cell apoptosis and as a cell division regulator. Survivin is selectively highly expressed in tumor cells, whereas its expression is very low in healthy adult tissues. The overexpression of survivin in various cancer types is correlated with chemotherapy resistance, metastasis, and poor patient outcomes. Therefore, survivin is considered as a cancer-specific biomarker and serves as a potential cancer-specific target. Significant efforts have been made to develop small molecules that can regulate the function of survivin and restore the apoptotic function. Herein we report the design and syntheses of a series of novel survivin-targeting agents based on the hydroxyquinoline scaffold from our lead compound MX-106, a novel small molecule that showed high potency in promoting survivin degradation. Compounds NA-1-89 and NA-1-94 with a triazole linker have an average IC_{50} value of 2 μM in melanoma and breast cancer cell lines. Western blot studies demonstrated that both NA-1-89 and NA-1-94 downregulate survivin at a concentration as low as 5 μM. Further mechanistic and *in vivo* studies are ongoing to confirm their efficacy and to determine their safety.



MX-106 **NA-X**

Podium Abstract O-12

DESIGN AND SYNTHESIS OF NOVEL HETERO-MULTIVALENT LIGANDS TARGETING KINASES

Samanthreddy Kedika[1] and D. Gomika Udugamasooriya*,[1]

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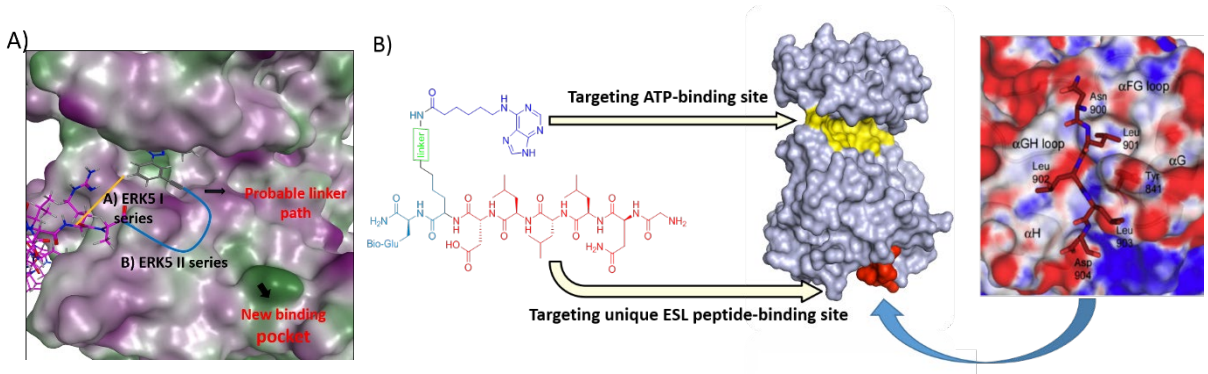
Multivalent ligands consist of multiple copies of monomers that are connected through a linker. These ligands show improved affinity and specificity towards their target through avidity effect. However, the linker regions of these multimers have not been used to find additional binding sites on protein surface. These binding sites can improve ligand's specificity towards protein by providing target specific interactions. We apply this concept in kinases because most of the ligands targeting kinases are non-specific. They target the conserved ATP binding pocket. Specificity can be achieved by identifying unique interactions outside ATP binding pocket. We will achieve this by i) developing hetero-bivalent ligands by joining ATP binding site and secondary binding site targeted compounds using a linker. Then ii) use the linker to find additional binding 'hot spots' by a combination of molecular modeling and combinatorial chemistry approaches. We apply this concept in two different kinase systems: i) Extracellular Regulated Kinase5 (ERK5) where we explore shorter linker region to identify allosteric pockets. So far, we identified a heterobivalent ligand and a binding pocket on kinase surface using molecular modeling (Fig. A). ii) EphrinA3 (EphA3) kinase where we explore longer linker region (Fig. B) to find allosteric pockets. So far, we identified potent heterobivalent ligand EPHB2.3 (Kd~250 nM) using ELISA like assay. Additional binding moieties will be incorporated onto both these linkers, improving overall binding, activity and specificity of resultant hetero-multivalent ligands.



Podium Abstract O-13

In silico screening of Bulbine genus reveals potential PXR activators

Alhusban M.[1], Ali Z.[2], Khan S.[2] Chittiboyina AG.[2], & Khan IA[1,2]

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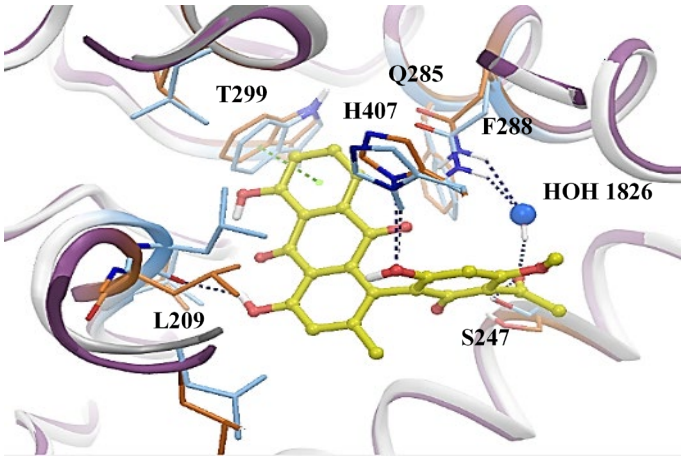
The witnessed upsurge of herbal medicines in the Western healthcare has outpaced adequate scientific understanding of the products efficacy and safety, opening the door for potential adverse effects. The genus *Bulbine* (Asphodelaceae), which consists of 80 species found in Australia and Africa, is widely used in herbal medicines. Lately, *B. natalensis* is marketed as a dietary supplement to boost testosterone and sexual health. On the contrary, the chronic use of *B. natalensis* supplement is reported to cause liver injury. Due to the safety concerns and structural similarities with known modulators of drug metabolizing enzymes and transporters, 45 known phytochemicals originated from genus *Bulbine* were evaluated with docking simulations against the pregnane X factor (PXR), the master regulator of the drug metabolizing enzymes. These compounds were probed against PXR ligand binding domain (LBD) as well as at the site of the coregulator. Our findings suggest 11 compounds (20-29 and 40-41) to have potential binding affinity toward the LBD of PXR as compared to hyperforin (43) the positive control. These compounds showed vital interactions with recognized residues (H407, S247, Q289 and W299) indispensable for the PXR induction. Further *in vitro* investigation will be conducted for verification.

B22



PDB: 1NRL and 1M13

Podium Abstract O-14

TARGETING THE POLYCYSTINS/TAZ COMPLEX FOR THE TREATMENT OF OSTEOPOROSIS

Hanxuan Li[1], Zhousheng Xiao[2], Hao Chen[1], Micholas D Smith[3], Jeremy C Smith[3], Darryl Quarles[2] and Wei Li*[1]

[1.]Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN [2.]Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN [3.]UT/ORNL Center for Molecular Biophysics, Oak Ridge National Laboratory, Oak Ridge, TN

Osteoporosis (OP) is a severe disease in the US that leads to fractures in about half of postmenopausal white women and one third of older white men. It represents an imbalance in bone remodeling such that osteoclast-mediated bone resorption exceeds osteoblast (Ob)-mediated bone formation (Ob-BF), resulting in bone loss, fragility, and fractures. Recently, a new molecular target for developing osteo-anabolics is suggested by the observation that decreased Ob-BF is often accompanied by increased marrow adipose tissue (MAT) in OP. This inverse association indicates that transition between Obs and adipocytes may have pathogenic importance in some types of OP. An explanation will be the cells committed to the Ob lineage are converted to adipocytes. This hypothesis is supported by the fact that this process does exist when β-catenin is disrupted in Obs. We also found that the loss of Pkd1 in cells committed to the Ob lineage causes osteopenia due to decreased Ob-BF and increased MAT, and TAZ, a transcription factor that is regulated by extracellular matrix stiffness, interacts with the Pkd1 C-terminal tail (Pkd1-CTT) to differentially stimulate Runx2-mediated osteoblasgenesis and inhibit PPARγ-mediated adipogenesis. Through virtual high-throughput screening efforts in collaboration with the Oak Ridge National Laboratory (ORNL), we identified a candidate, Zinc01442821 (MS), that targeting the Pkd1-CTT/TAZ complex in silico. Subsequent in vitro test showed that MS was able to enhance TAZ nuclear translocation, dose-dependently stimulated the expression of Runx2 and its downstream gene Osteocalcin, and attenuated the expression of PPARγ and its downstream gene aP2. Based on the structure of MS, we further synthesized several derivatives which showed improved potency and metabolic stability. Preliminary structure-activity relationship (SAR) studies provide hints on structural requirements for these MS derivatives and facilitate our efforts in further modifications of this scaffold.

Podium Abstract O-15

DESIGN AND DISCOVERY OF SMURF1 INHIBITORS VIA UBFLUOR ASSAY

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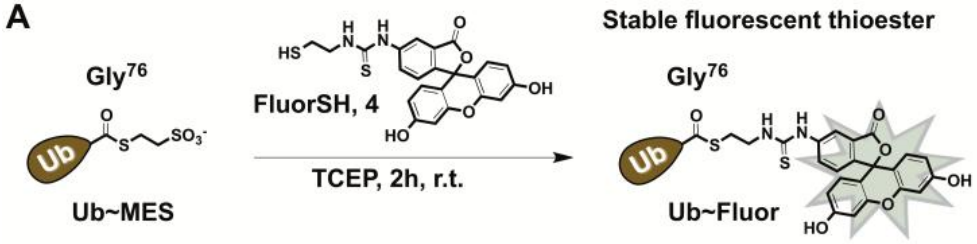
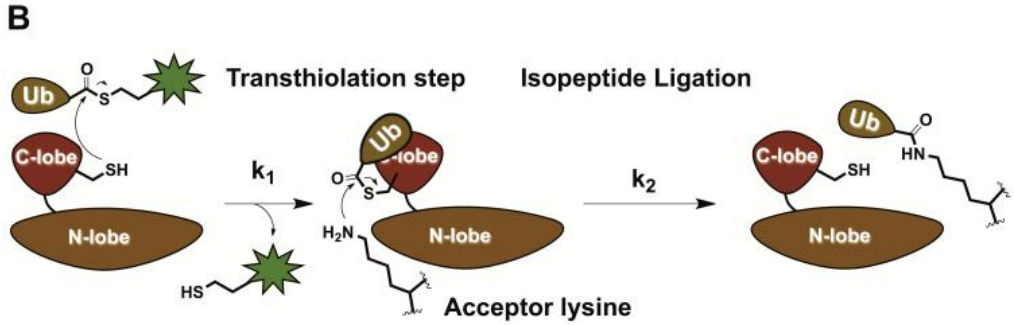
Pulmonary Arterial Hypertension (PAH) is a rare and incurable disease that affects around 10,000 people a year in the United States. Current treatments only focus on temporarily alleviating symptoms; however, little efforts have been made on finding a permanent curative option. It has been shown that PAH is associated with the dysregulation of bone morphogenetic protein receptors (BMPR) which in turn is regulated by SMAD (Mothers Against Decapentaplegic Homolog) proteins. Smurf1 is a E3 ubiquitin ligase in the ubiquitin proteasome system that signals for the degradation of SMAD proteins, thus inhibition of Smurf1 may be critical for drug discovery against PAH.

The status quo for Smurf1 inhibitor screening is to test synthetic compounds in cellular assays or animal models which are severely limited by time and resource constraints. Our lab has previously developed a fluorescent tagged ubiquitin screening method (UbFluor) for another family of E3 ubiquitin ligases. The UbFluor assay represents a novel fast and inexpensive screening method to expedite the discovery of Smurf1 inhibitors. In our studies, we have identified a few lead compounds against Smurf1 and demonstrated IC_{50} values in the μM range. This prompted us to further investigate the structure activity relationship and create analogs based on these modifications. Our findings offer proof that our UbFluor assay can quickly and cost-effectively screen against Smurf1 inhibitors, which will aid the process of designing and evaluating novel selective Smurf1 inhibitors.





Podium Abstract O-16

MOLECULAR DYNAMICS SIMULATION FOR BINDING OF ALCOHOL TO THE C1 DOMAIN OF PRESYNAPTIC MUNC13-1

Youngki You and Joydip Das*

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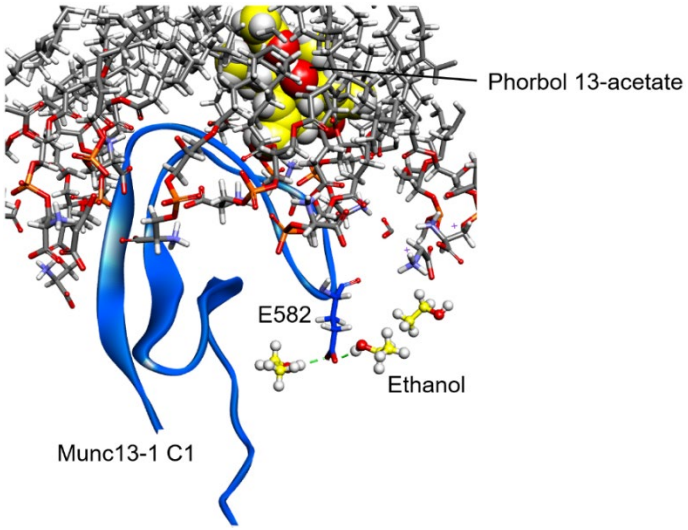
Munc13-1 is an essential presynaptic protein involved in the priming of synaptic vesicle and releasing of neurotransmitter in the brain. It is activated by secondary messengers, such as diacylglycerols (DAG) and phorbol ester. Munc13-1 contains a C1 domain where DAG/Phorbol ester bind. The C1 domain has a crucial role for Munc13-1 translocation to the plasma membrane. Ethanol has a significant effect on pre-synaptic function and our earlier studies identified Glu-582 of C1 domain as the alcohol-binding residue. In this study, we describe a 250 ns molecular dynamics (MD) simulation study on the interaction of ethanol and the activator-bound C1 domain in the presence of varying percentages of phosphatidylserine. Our results suggest that the C1 domain forms fewer number of the hydrogen bond with phorbol 13-acetate in the presence of ethanol than in water. C1 domain shows higher stability in ethanol than in water. Ethanol does not change the protein structure significantly. Ethanol molecules form hydrogen bonds with the Glu-582 and they retain their positions in vicinity (4Å) of Glu-582 for 88 ns during MD simulation. When Glu-582 was mutated to alanine, the retention time of ethanol molecules was reduced about 19%. This study is important in providing structural basis of ethanol's action in presynaptic proteins for developing effective therapeutics for Alcohol Use Disorder (AUD).

Keywords: Munc13-1 C1 domain, alcohol interaction, protein dynamics



Podium Abstract O-17

A novel Single-chain Enzyme Complex with chain-reaction properties Rapidly Producing Thromboxane A_2 and Exhibiting Powerful Anti-Bleeding Functions

Yan Li [a], Qun-Ying Li [a, b], Qing-Lan Ling [a], Shui-Ping So [a] and Ke-He Ruan [a, *]

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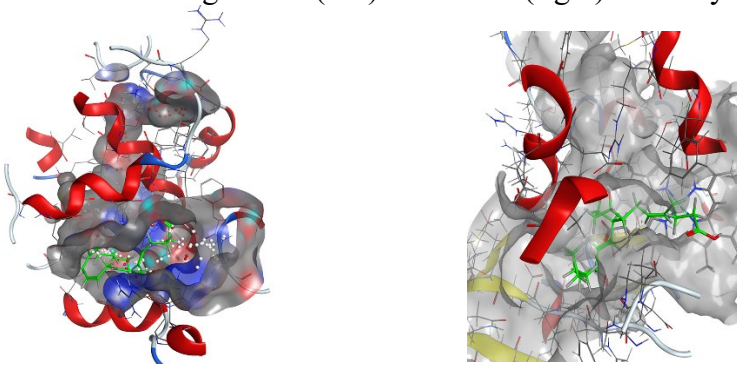
[b] Visiting Scholar from Department of Ultrasound, Second Affiliated Hospital, Zhejiang University College of Medicine, Hangzhou City, Zhejiang Province 310009, China.

Uncontrollable bleeding is still a worldwide killer. In this study, we aimed to investigate a novel approach, which exhibited effective hemostatic properties and saved life in various bleeding emergencies. According to the structure-based enzymatic design, we have engineered a novel single-chain hybrid enzyme complex (SCHEC), COX-1-10aa-TXAS. We linked the C-terminus of cycloocygenase-1 (COX-1) to the N-terminus of the thromboxane A_2 (TXA_2) synthase (TXAS) through a 10-amino acid residues linker. This recombinant COX-1-10aa-TXAS could effectively pass COX-1-derived intermediate prostaglandin (PG) H_2 (PGH_2) to the active site of TXAS, resulting in an effective chain-reaction property to produce the hemostatic prostanoid, TXA_2 rapidly. Meanwhile, COX-1-10aa-TXAS constrained the production of other pro-bleeding prostanoids, such as prostacyclin (PGI_2) and prostaglandin E_2 (PGE_2), through reducing the common substrate, PGH_2 being passed to those synthases. Therefore, based on these multiple properties, this novel COX-1-10aa-TXAS indicated a powerful anti-bleeding ability to treat a variety of bleeding situations, and even useful for bleeding prone situations, including nonsteroidal anti-inflammatory drugs (NSAIDs)-resulted TXA_2-deficient and PGI_2-mediated bleeding disorders. This novel SCHEC has a great potential to be developed into a biological hemostatic agent to treat severe hemorrhage emergencies, which will prevent the complications of blood loss and save life.

Keywords: Hemostasis, Prostanoids, Thromboxane A_2, Enzyme Engineering.

Computational modeling of AA (left) and PGH_2 (right) to the hybrid enzyme



Podium Abstract O-18

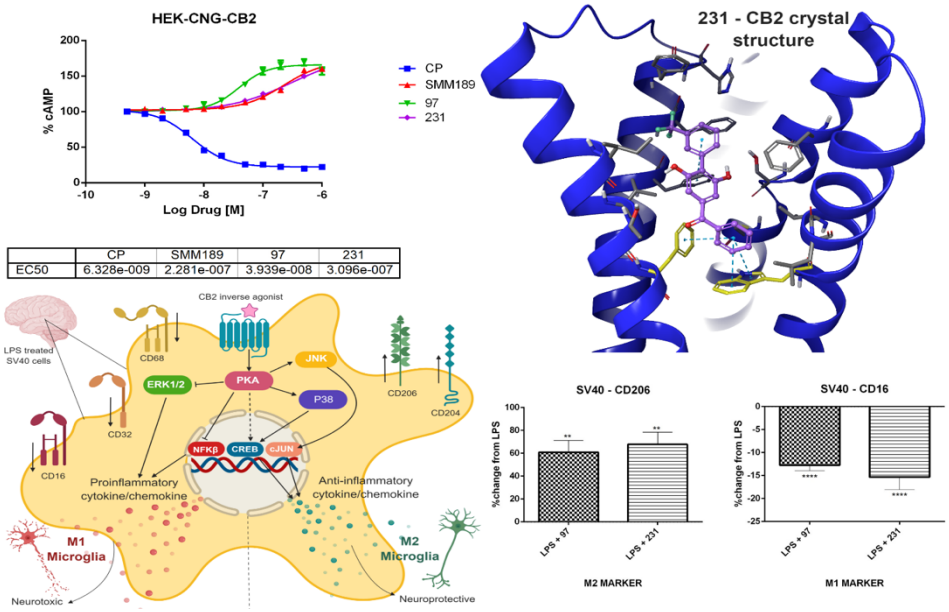
ANTI-INFLAMMATORY EFFECT OF SELECTIVE CB2 INVERSE AGONISTS IN MURINE AND HUMAN MICROGLIAL CELLS

Sahar S. Alghamdi, Kirk E. Hevener, Bob M. Moore II*.

Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN.

Purpose: In the last 10 years, CB2 receptor has been emerged as a promising therapeutic target for treating multiple neurodegenerative disease (NDD) conditions such as Alzheimer's (AD), Parkinson's (PD), HIV and multiple sclerosis. CB2 receptors are predominantly expressed in the immune cells such as microglia, natural killer cells, B cells and macrophages with low or no detectible level in neurons in the central nervous system. During neuroinflammation, CB2 receptor expression is upregulated in microglial cells thus modulating the activated microglia can be a potential therapeutic approach for treating neurodegenerative diseases. When microglia cells are activated, the phenotype is changed from surveillance (M0) phenotype to an activated pro-inflammatory phenotype (M1) which contributes to increased inflammation and progression of neurodegenerative diseases. Selective CB2 inverse agonists can serve as novel anti-inflammatory therapeutics by switching the microglial cell neurotoxic M1 phenotype to an M2 pro-healing neuroprotective effect phenotype which is the key step in modulating the neuroinflammatory process.

Results/Discussion: Compounds 231 and 97 triggered a shift in murine and human microglia polarization from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype after 24 hours. The M1 markers were significantly decreased and M2 markers significantly increased compared to LPS after drug treatment. In addition, 97 and 231 increased JNK, c-JUN, CREB and p38 levels and decreased ERK1/2 and NFκB representing a unique anti-inflammatory mechanism of CB2 inverse agonists in microglia. These data suggest that CB2 inverse agonists can serve as novel class of compounds for treating neuroinflammation in central nervous system diseases.



	CP	SMM189	97	231
EC50	6.328e-009	2.281e-007	3.939e-008	3.096e-007

Podium Abstract O-19

MYXOBACTERIAL PERCEPTION, DEGRADATION, AND TRANSFORMATION OF EXOGENOUS ENVIRONMENTAL QUORUM SIGNALS

Barbara I. Adaikpoh[1], D. Cole Stevens*[1]

[1]*Pharmacognosy Division, Department of BioMolecular Sciences, University of Mississippi*

The challenging access to Myxobacterial species that are cultivable in axenic conditions continues to demonstrate the potential for discovery of new chemical entities (NCEs). Supported by taxonomic distribution analysis of this taxa which highlights genera-specific metabolic profiles, genomics-guided approaches coupled with innovative techniques to activate "silent" biosynthetic pathways can provide a view of undiscovered specialized metabolites with structural novelty from Myxobacteria. Recent efforts to probe the predatory activities of Myxobacteria revealed their ability to eavesdrop and modify chemical signals, including their prey's acylhomoserine lactones (AHLs), in their native environment hence suggesting their role as ecological regulators of micro-fauna.

We hypothesize that Myxobacteria cultivation conditions through supplementation with quorum sensing molecules (QSMs) will result in production of specialized metabolites not produced under typical cultivation.

MS/MS datasets were obtained from extracts of *Archangium* sp. strain Cb G35 exposed to a set of QSMs from bacterial, fungal and plant origin. Using the Global Natural Products Social Molecular Networking (GNPS) platform to provide a visual representation of the QSM-induced change in metabolic space, we observed the generation of new specialized metabolites with molecular weights ranging from 200-1000 Da, belonging to various molecular families and an interesting disappearance of certain native metabolites depicting a switch on/off in biosynthesis. Furthermore, these new specialized metabolites were produced as characteristic responses to each QSMs providing a basis for comparison and the identification of these metabolites would reveal compounds and enzymatic reactions never reported from this genus of Myxobacteria.

Keywords: Myxobacterial metabolites, Novel compounds, Chemical signals

Podium Abstract O-20

VALIDATION OF VIMENTIN AS NON-SMALL CELL LUNG CANCER STEM CELL BIOMARKER

Haowen Zhang,[1] Satya Prakash Shukla[1], and D. Gomika Udugamasooriya*[,1,2]

[1]Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX
[2] Department of Cancer System Image, MD Anderson Cancer Center, Houston, TX

Cancer stem cells (CSCs) are believed to be responsible for driving metastasis and relapse by giving rise to new tumors. Identification and targeting of reliable CSC biomarkers can tremendously improve the survival of patients by developing better detection and therapeutic strategies. It has been well established that intermediate filament protein -vimentin is a crucial component in epithelial to mescenchymal transition (EMT). We hypothesized that vimentin plays an important role in CSCs. Recently, we used our unique "unbiased" on-bead two-color(OBTC) peptoid combinational cell screen technology to identify a vimentin specific compound called JM3A. We selected two non-small cell lung cancer cell lines: H1299 (high vimentin expression) and H2122 (low vimentin expression), that shows mesenchymal-like and epithelial-like traits respectively, as our model systems to study vimentin roles in CSCs. Through different conditions in magnetic-beads-based pull-down technique we confirmed JM3A can bind cell surface vimentin. qPCR and cloning techniques will be used to verify the results of pull-down. The ultimate goal of this project is to develop a unique compound that can specifically bind CSCs as well as provide a new perspective way for cancer treatment.

Keywords: Lung cancer, Cancer stem cell, Peptoids, Vimentin

Podium Abstract O-21

SYNTHESIS OF FLUOROFLAVONES AS POTENTIAL NEUROPROTECTIVE AGENTS

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Flavones are polyphenol natural products that are known to have neuroprotective effects against many diseases caused by the formation of reactive species. Flavonoids are subgroup of flavones and they are believed to function as antioxidants. Specifically, they target free radicals and eliminate their harmful effects by acting as radical scavengers. Introducing a fluorine atom into a biologically active molecule is known to produce a significant impact, for that reason, fluoroflavones were designed to improve the potency of the antioxidant activity and potentially be used as neuroprotective agents. A monofluorinated and trifluoromethylated flavone were synthesized by using commercially available fluorination reagents, *N*-fluorobenzenesulfonimide; and Togni's or Umemoto's respectively. After the synthesis of the desired flavones and their monofluorinated and trifluoromethylated derivatives, biological testing was conducted. First, antioxidant activity was evaluated by using DPPH antioxidant assay and displayed that the fluorinated flavones are more potent compared to their un-fluorinated derivatives. Second, neuroprotective assay showed that both fluorinated and un-fluorinated flavones have potential neuroprotective activity. In addition, ^{19}F NMR experiments were conducted on fluoroflavones to investigate the effect on the chemical shift of the fluorine atom during the radical exchange.

Podium Abstract O-22

PHYTOCHEMICAL INVESTIGATION OF *T. CRISPA* AND *T. SINENSIS* TO DEVELOP A VALIDATED METHOD TO ANALYSE HERBAL DIETARY SUPPLEMENTS OF CLOSELY RELATED *TINOSPORA* SPECIES

Abidah Parveen[1,3], Omer Fantoukh[1], Zulfiqar Ali*[2], Yan Hong Wang*[2], Vijayasankar Raman[2], Ikhlas A. Khan*[1,2]

[1]Department of Biomolecular Sciences, Division of Pharmacognosy, [2]National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, University, MS, 38677, USA, [3]Abbottabad University of Science & Technology, Havelian, Abbottabad District, KPK, Pakistan.

Tinospora crispa Miers ex Hook.f. & Thomson indigenous to south Asia, bears morphological similarity with closely related *Tinospora* species such as *T. sinensis* and *T. cordifolia*, which are distributed in south east Asia. These plants are twinning, woody climbers and the stems possess therapeutic properties, particularly anti-diabetic. *Tinospora sinensis* is usually substituted for *T. cordifolia*, but the likelihood of substitution of either species with *T. crispa* could render the unsuspecting consumer to adverse effects such as hepatotoxicity; since cases of hepatotoxicity from the use of *T. crispa* have been reported. Phytochemical investigation of *T. crispa* and *T. sinensis* was performed to elaborate chemical diversity of the secondary metabolites and hence help to resolve quality and safety issues. The study of the stems led to the isolation of nineteen compounds including one new from *T. crispa* and fifteen metabolites from *T. sinensis* including two new compounds. Chemical structures were elucidated by 1D and 2D NMR spectroscopy and confirmed by HRESIMS. A rapid, sensitive and reproducible method was established using ultra-high-performance liquid chromatography coupled with photodiode array and single quadrupole electrospray mass spectrometry detectors to achieve decisiveness in not only identifying but also differentiating *T. crispa* from *T. sinensis* and other closely related *Tinospora* species. A chemical fingerprint was developed with a flavonoid, two alkaloids, an amide and six diterpenoids. Thirty-four *Tinospora* plant samples and dietary supplements claiming *T. crispa*, *T. sinensis* and *T. cordifolia* were analyzed. The newly developed and validated method successfully resulted in the conclusive identification of two *Tinospora* herbal dietary supplements that were mislabeled or adulterated. To conclude, the phytochemical investigation of *T. crispa* and *T. sinensis* led to the isolation of thirty four compounds including specie specific compound/s that were instrumental in the development of an analytical method that was tested for its usefulness. The newly developed method resulted in the conclusive identification of *T. crispa* and also distinguishing closely related *Tinospora* species among plant samples and dietary supplements.

Keywords (*Tinospora crispa*, tinocrispide, chemical fingerprint)

Podium Abstract O-23

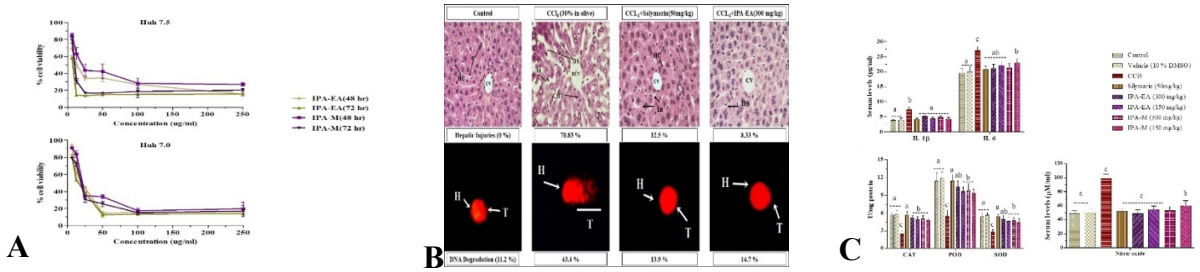
Validating the folklore use of *Ipomoea batatas* L. Lam. as hepatoprotective agent against hepatomas and liver injuries using *in vitro* and *in vivo* modeling in male Sprague Dawley rats.

Muhammad Majid[a,b], Zartash Zahra[a,b], Muhammad Waleed Baig[b], Fatima Ijaz[b], Muhammad Rashid Khan[b], Hamed I. Ali[a], Ihsan-ul-Haq[b*]

[a] *Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Kingsville, Texas,* 78363, *USA*
[b]*Department of Pharmacy & Biochemistry, Faculty of Biological Sciences, Quaid-i-Azam University (*45320*), Islamabad, Pakistan.*

Ipomoea batatas L. Lam. is traditionally used worldwide against hepatic carcinomas, inflammations and hepatitis. To validate this medicinal claim, an investigation against liver cancer and chronic hepatic injuries was conducted in male Sprague Dawley rats. Multi-mode phytochemical screening, antioxidant profiling, protein kinase inhibition and *in vitro* cytotoxicity against human hepatoma cells (Huh7.0 and Huh7.5) were assessed against *I. batatas* aerial (IPA-EA and IPA-M) extracts. Carbon tetrachloride (CCl_4) induced hepatotoxicity model was conducted in male Sprague Dawley rats. Protective effect of the extracts against oxidative damage and genotoxicity was evaluated from blood and homogenates of the excised liver after four weeks of treatment. Hematological parameters, biochemical investigations, enzymes expression, pro-inflammatory cytokines suppression and the comet assay-assisted genetic variations were assessed. *I. batatas* extracts showed significant protein kinase inhibitory activity against *Streptomyces* 85E strain with > 15mm bald phenotype and cytotoxicity against Huh 7.0 and Huh 7.5 (IPA-EA, IC_{50} = 14.17 and 21.67 µg/ml, respectively). Extracts revealed dose dependent hepatoprotective potential in rats. Damage to CCl_4 intoxicated liver (70.83%) was restored by IPA-EA (300 mg/kg) to 8.33% in comparison to Silymarin (12.5%) used as standard drug. IPA-EA comparatively regulated liver enzymes (ALT, AST and ALP) to (40.8±0.45, 29.7±0.6 and 121.2±2.8 U/L respectively) than CCl_4 (97.37±3.45, 105.9±2.1 and 347.1±7.2 U/L respectively). While DNA degradation was reduced from 43.4% to 14.7% in comparison to Silymarin (13.9%). Level of pro-inflammatory markers (IL-1β, IL-6 and NO) was recorded (5.09±0.30, 21.14±1.34 pg/ml and 49.02±5.56 µM/ml, respectively) in IPA-EA group and CCl_4 intoxicated rats (7.45±0.56, 27.16±1.22 pg/ml and 98.87±6.22 µM/ml, respectively) while endogenous antioxidant enzymes (CAT, SOD and POD) were considerably normalized. Polyphenols and anthocyanins within *I. batatas* are the key constituents for its hepatoprotective effect.

Key words: *Ipomoea*, CCl_4, Polyphenol, Hepatitis, hepatoma, Hepatotoxicity



ABSTRACTS OF POSTER PRESENTATIONS

Abstracts of Graduate Students Posters (GSP)

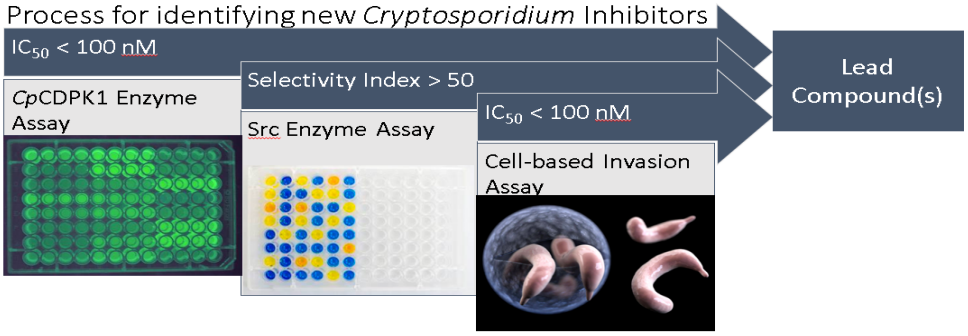
GSP-1

IDENTIFICATION OF A NEW CALCIUM-DEPENDENT PROTEIN KINASE 1 INHIBITOR CHEMOTYPE WITH POTENT CRYPTOSPORIDIUM PARVUM INHIBITORY ACTIVITY

Elise Waldron-Young[1], Grant Whitman[2], Mathew Hulverson[2], and Wes Van Voorhis[2], and Greg Cuny[1*]

[1] Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, Texas, 77204. [2]Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington 98109, United States.

Background: Nitazoxanide, the only FDA approved anti-cryptosporidiosis agent, often fails in immunocompromised patients. These individuals are at the highest risk of cryptosporidiosis complications and death. Thus, novel agents active against *Cryptosporidium* are urgently needed. We have identified a new lead compound against *Cryptosporidium* via inhibition of calcium-dependent protein kinase 1 (CDPK1).
Methods: A panel of type 1 ½ and type 2 kinase inhibitors were screened against Cryptosporidium parvum calcium-dependent protein kinase 1 (*Cp*CDPK1), which has emerged as a potential therapeutic target in the treatment of cryptosporidiosis. Compounds were also tested for selectivity against the human kinase Src. Finally, compounds were assessed in a cell-based invasion model.
Results: Interestingly, none of the type 2 kinase inhibitors blocked *Cp*CDPK1 with IC_{50}s < 200 nM, indicating this kinase does not readily adopt a DGF-out confirmation. However, the type 1½ inhibitors based on a pyrido-pyrimidinone scaffold demonstrated potent inhibition (*Cp*CDPK IC_{50} < 30 nM). Furthermore, a subset of derivatives provided encouraging selectivity verses Src (selectivity index (SI) = IC_{50} Src / IC_{50} *Cp*CDK1 > 50) with one analogue blocking *Cryptosporidium parvum* proliferation in the cell-based invasion model (EC_{50} = 140 nM).



Conclusions: Preliminary analysis has revealed derivatives that achieves selectivity over a human kinase, Src, and potent anti-cryptosporidiosis activity in a cell-based invasion model. Current efforts are underway to analyze the structure-activity relationship of this chemotype and to advance select derivatives into in vivo models of cryptosporidiosis.

Keywords: infectious disease, CDPK1, *Cryptosporidium*, kinase

GSP-2

PROGRESS TOWARD THE SYNTHESIS OF FLUORINATED 3-METHOXY-FLAVONES AS POTENTIAL ANTIOXIDANTS

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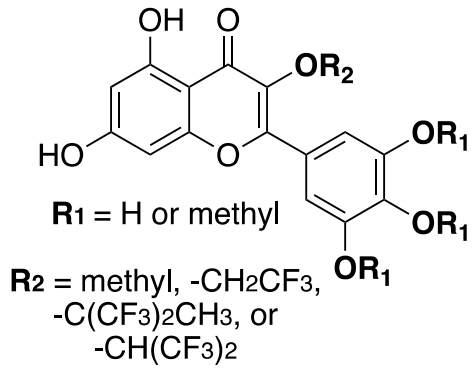
Department of BioMolecular Sciences, College of Pharmacy, the University of Mississippi, Oxford, MS

Our bodies produce free radicals that are required for regular physiological functions but are harmful when present in excess. There's compelling evidence on the link between these radicals and neurodegenerative diseases. Antioxidants can scavenge free radicals, and flavones from food have been heavily investigated for this role. In addition, fluorination of biologically active compounds is a strategy to improve chemical properties during drug development. Research continues to show that incorporating fluorine atoms can enhance potency and reduce metabolism. Herein, we propose a synthesis for polyhydroxylated 3-methoxyflavones and their fluorinated derivatives. The structures have been characterized using ^{1}H, ^{13}C NMR, and 2D NMR. The total synthesis of polyhydroxylated flavones was challenging, due to the presence of many phenolic groups. A Friedel-Crafts reaction was optimized to alkylate the polyphenolic starting material. Although these alkylated phenols could not be directly cyclized to the flavone scaffold, by using a silyl protecting group, the cyclization was successful. A three-step process was then developed to create the flavone and remove the silyl groups. Additional optimizations of the 3-methoxyflavones and their fluorinated counterparts is underway. Our synthetic route will be a valuable tool to synthesize additional fluorinated flavones for evaluation as potential antioxidants.

Keywords: Synthesis, Flavones, Antioxidants.



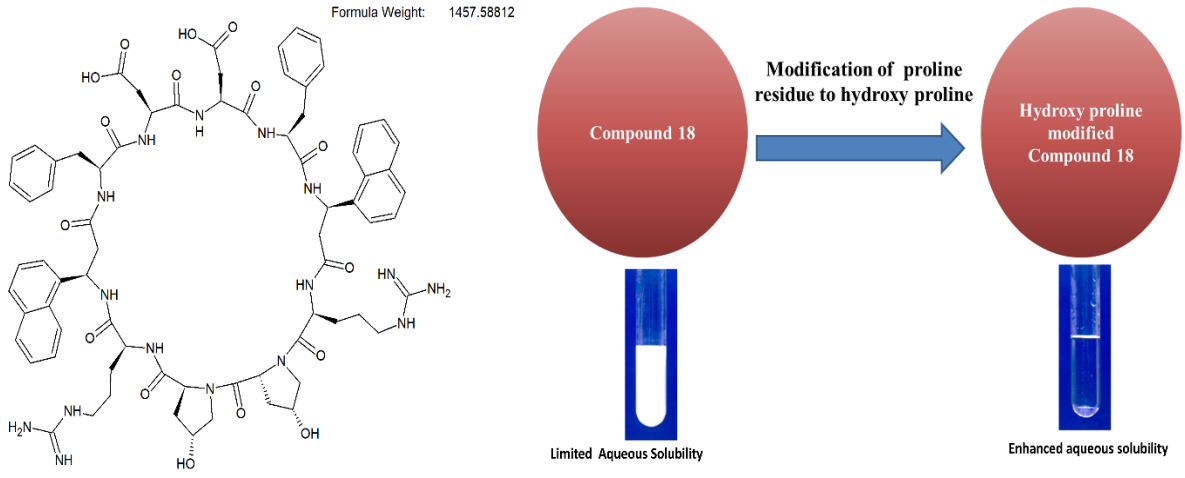
GSP-3

CHARACTERIZATION OF HER-2 TARGETED MODIFIED PEPTIDOMIMETIC

Achyut Dahal, Leeza Shrestha, Seetharama D. Jois*

School of Basic Pharmaceutical and Toxicological Sciences, College of Pharmacy, University of Louisiana at Monroe, Monroe, LA.

Overexpression of HER2 is mostly associated with development of more aggressive and poorer prognosis in breast cancer and non-small cell lung cancer. HER2 has become an important target for cancer treatment therapy. We have designed several peptidomimetics that targets domain IV of HER2 and inhibit HER2 mediated dimerization. Among them one of the peptidomimetics, Compound 18 that exhibited antiproliferative activity in nanomolar range in HER2 overexpressing cancer cell line and showed the in-vivo anti-tumor activity in mice. Compound 18 has limited aqueous solubility and to enhance the solubility of compound 18, hydroxy moiety was added to the compound at proline residue of peptide sequence. Compound 18 with hydroxy moiety exhibited significantly increased aqueous solubility compared to compound 18. Molecular docking was used to evaluate the binding of the hydroxy-compound 18 with the extracellular domain of HER2.Modified peptidomimetic retained the antiproliferative activity towards HER2 positive cancer cell line and IC_{50} in BT474 cell line and A549 cells line were found to be 54.19 ±1.0382 nM and 519 ±1.56 nM respectively. The thermal stability was evaluated using circular dichroism which showed that modified hydroxy compound 18 was stable at higher temperature. In summary, the modified hydroxy compound 18 showed better anti-proliferative activity on HER2 positive cancer cell line and increased water solubility compared to compound 18. The research reported in this presentation was supported by NCI of NIH under the grant number 1R15CA188225-01A1.



Modified Hydroxy-Proline Compound 18

GSP-4

Computer Aided Design of NADH:quinone Oxidoreductase as an antimicrobrial target in *H. pylori*

Nicole Vita[1], Alex Mugengana[1], Michael LaFleur[2], and Richard Lee[1]*

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Due to the increasing prevalence of antibiotic resistance in *Helicobacter pylori*, the development of treatments with a novel mode of action is necessary. The NADH:quinone oxidoreductase (Complex I) was identified as a potential *H. pylori* drug target through analysis of hits from a high-throughput screening campaign. Structure-based design was used to rationalize *the H. pylori* screening hits by building a homology model of the putative binding pocket using *Thermus thermophilus* as a template (PDB: 4HEA and 2FUG). The homology model of the active site was used to create an induced fit docking model that allowed the visualization of possible binding poses of experimentally active compounds found previously by a high-throughput screen and further supported by activity against resistant mutants. To aid the modeling of experimentally active compounds, known non-specific Complex I inhibitors and a quinone substrate were docked into the proposed binding pocket. The modeling of the active ligands show that this series of ligands may bind and interact at the interface between NuoD, NuoB, and NuoH inhibiting activity of the quinone substrate. It is believed that the inhibition of the natural substrate interferes with the electron transfer from the N2 iron-sulfur cluster to the quinone ultimately inhibiting the production of ATP, suggesting that Complex I could be a novel target for *H. pylori* antimicrobial agents. This model proposes that a combination of structure-based design and ligand-based design could be used to increase diversity and amount of Complex I inhibitors against eukaryotes and prokaryotes.

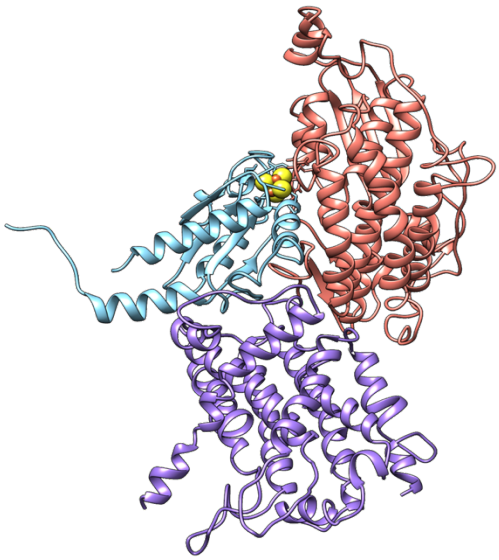

Figure 1. A homology model of the quinone binding pocket of NADH:quinone oxidoreductase, a putative target of Complex I inhibitors.

GSP-5

THE DISCOVERY AND DEVELOPMENT OF THIENOPYRIMIDINES AS INHIBITORS OF HELICOBACTER PYLORI THROUGH THE RESPIRATORY COMPLEX

Alex K. Mugengana[1,2], Kevin Moran[3], Autumn B. Gandt[3], Nicole Vita[1,2], Lalit K. Sharma[2], Elizabeth C. Griffith[2], Lei Yang[2], Ekaterina Gavrish[3], Michael D. Lafleur[3], Richard E. Lee[2*]

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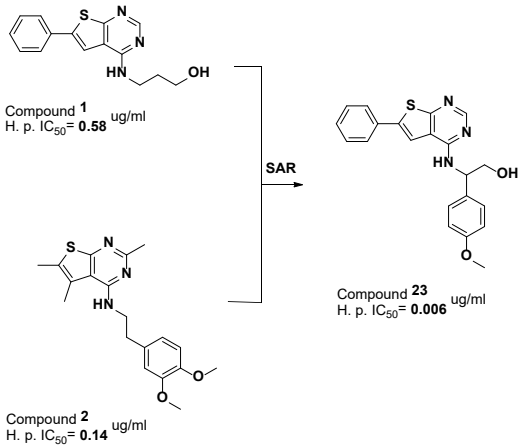
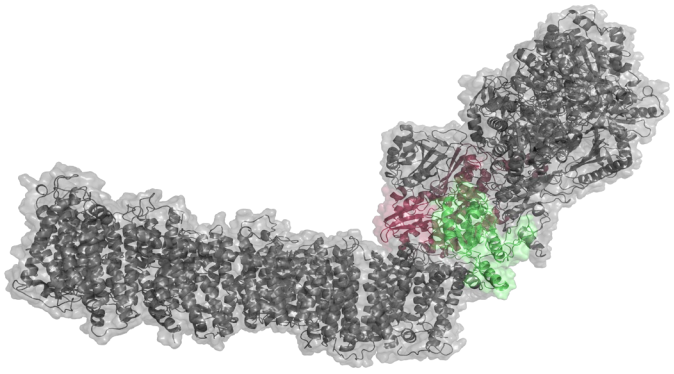
The rate of successful treatment for *Helicobacter pylori* infections, with the triple therapy regimen, is fast approaching 75%. The triple therapy, which consists of a proton pump inhibitor and two broad-spectrum antibiotics such as clarithromycin and amoxicillin, is rapidly becoming ineffective mainly due to the rise of resistance against these antibiotics. In the search for narrow spectrum drugs for the treatment of *H. pylori* infections, a high-throughput screen was performed to identify selective compounds against *H. pylori*. This screen revealed two structurally related thienopyrimidines. Structure-Activity Relationship of the thienopyrimidines against *H. pylori* was examined through the synthesis of 27 analogs, efforts that merged elements of the two scaffolds. The resulting leads demonstrated high potency with an acceptable cytotoxicity profile against the human FaDu cells. Mode of action studies were performed by the generation and sequencing of resistant mutants. These experiments identified *H. pylori*'s respiratory Complex I as the putative target of the series, with amino acid changes found in the D subunit of NADH:Quinone Oxidoreductase (NuoD). Lead compounds demonstrated potency in an *ex vivo* model but not in the *in vivo* efficacy studies in a *H. pylori* murine infection model, suggesting further optimization of the pharmacological properties is required for this series.





The homology model of *H. pylori*'s Complex I. NuoD is colored in red.

Postdoctoral Fellows Posters (PDP)

PDP-1

Brain Uptake Studies of Morphine-6-O-sulfate (M6S) in Rats

Zaineb A. F. Albayati[a], Jai Shankar K. Yadlapalli[a], Narsimha R. Penthala[a], Philip J. Breen[a], Maxim Dobretsov[b], Howard P. Hendrickson[c], and Peter A. Crooks[a*]

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M6S, a polar, zwitterionic sulfate ester of morphine (MOR, Fig. 1), is a powerful and safe analgesic in several rat models of pain. Results of *in vivo* experiments have indicated that M6S is not a prodrug, since M6S is not biotransformed into MOR after i.p. administration. However, it was not known if M6S could be hydrolyzed to MOR in brain (by brain sulfatases) after possible uptake of M6S from plasma to brain. This study was aimed at investigating the concentrations of M6S (and MOR if present) in brain and trunk plasma after an i.p. dose of 5.6 mg/kg of M6S (as the sodium salt) in male Sprague-Dawley rats. A sensitive and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method was developed for the simultaneous determination of M6S and MOR in trunk plasma and brain after M6S administration. Morphine-d_6 was used as an internal standard. Multiple reaction monitoring (MRM) was used for detection and quantitation of M6S, MOR and morphine-d_6 in the turbo ion spray positive mode. The chromatographic separation was carried out on an Alltech Altima C18 column. The calibration curves of both M6S in rat brain and trunk plasma showed excellent linearity between 10-1,000 ng/mL, with correlation coefficients (R^2) of 0.999 and 0.991, respectively. The calibration curve for MOR in brain showed a linearity between 50 and 1,000 ng/mL with an R^2 of 0.989. The results indicate that M6S appears to reach brain tissues in low, but significant, concentrations. Moreover, M6S is not biotransformed into MOR, as the latter was not detectable in brain. Supported by an Arkansas Research Alliance grant.

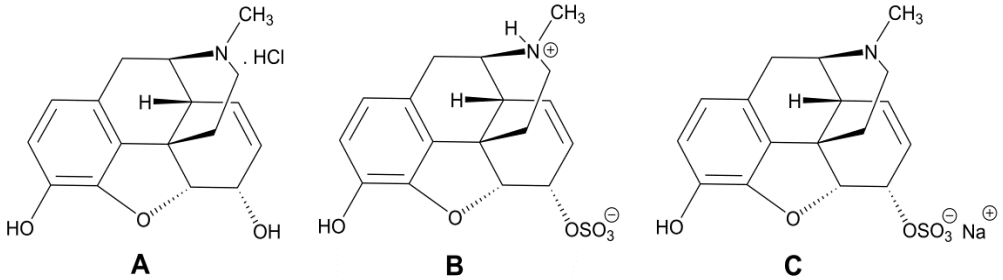


Figure 1 Chemical structures of morphine hydrochloride (**A**), morphine-6-*O*-sulfate (zwitterion, **B**) and morphine-6-*O*-sulfate sodium salt (**C**).

Key words: Brain uptake, morphine-6-O-sulfate, morphine, LC-MS/MS, rats

PDP-2

In Vivo Evaluation of Vancomycin and BT-2-minipeg-2-vancomycin in Rat Plasma and Bone Tissue after i.p. administration

Zaineb. AF Albayati[1], Manjula Shanker[2], Andrew J Morris[2], Philip J Breen[1] and Peter A Crooks[1]

[1]College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR
[2]College of Pharmacy, University of Kentucky, Lexington, KY

Vancomycin (vanco) is a glycopeptide antibiotic widely used in the treatment of bone infections. The objectives of the present study were to determine the plasma and bone content of vanco and BT-2-minipeg-2-vancomycin (BT2-vanco, Fig. 1) after a single i.v. bolus dose and 7 multiple i.p. doses of vanco or BT2-vanco in Albino Wistar male rats. The pharmacokinetic profiles (PKs) of vanco and BT2-vanco after a single i.v. dose were also determined. Thirty five rats weighing 250-300 g received a single i.v. injection of either vanco (50 mg/kg) or BT2-vanco (the molar equivalent of 50 mg/kg vanco). Five animals were sacrificed at 1, 6, 12, 24, 72 and 168 h after injection. To compare i.v. injection with i.p. injection, an additional 20 rats received 7 i.p. injections of vanco or BT2-vanco every 12 h. Five rats were euthanized at 1, 6 and 12 h after the seventh i.p. dose. Plasma and the left tibia bone were collected and processed. The results indicate that vanco and BT2-vanco peaked in plasma and bone 1 h after i.v. and i.p. injections with a concentration of 13.00 ± 4.40 µM and 1.04 ± 0.31 µM for vanco and 41.22 ± 19.52 µM and 4.89 ± 3.41µM for BT2-vanco in plasma and bone, respectively after i.v. injection. A concentration of 15.6 ± 4.4 µM and 7.3 ± 0.9 µM for vanco and 21.1 ± 4.7 µM and 56.6 ± 18.7 µM for BT2-vanco in plasma and bone, respectively were observed after i.p. injection. PK analysis estimated that vanco had a maximum concentration (C_{max}) of 12.63 ± 5.32 µM at a maximum time (T_{max}) of 1 h, a clearance (Cl_{tot}) of 0.65 ± 0.27 L/h/kg, a half-life ($t_{1/2}$) of 1.44 ± 0.19 h and an AUC of 58.71 ± 23.14 h*µM. The results indicate that BT2-vanco led to a change in biological fate of vanco characterized by a reduction in Cl (0.048 ± 0.013 L/h/kg), a longer $t_{1/2}$ of 21.14 ± 10.89 h, and an increase in AUC of 631.39 ± 213.10 h* µM, ensuring a greater duration and higher concentration of BT2-vanco in the plasma facilitating its penetration into the tibia bone. In conclusion, BT2-vanco provides a potential carrier system for vanco to be used in the treatment of bone infections.
Supported by grants from Pradama, Inc.

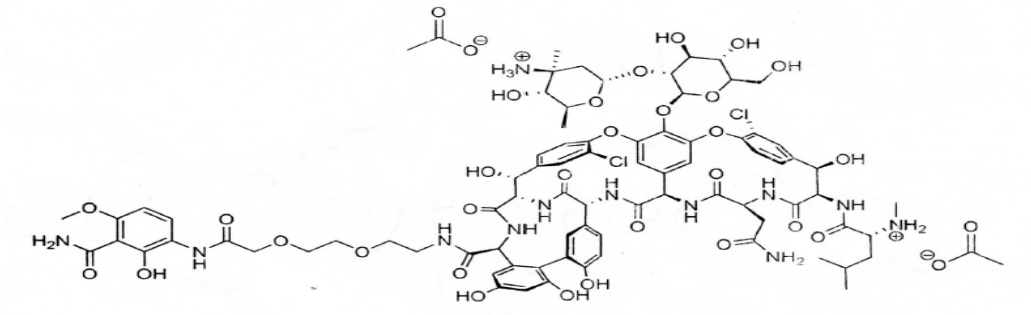


Figure 1. Structure of BT-2-minipeg-2-vancomycin.

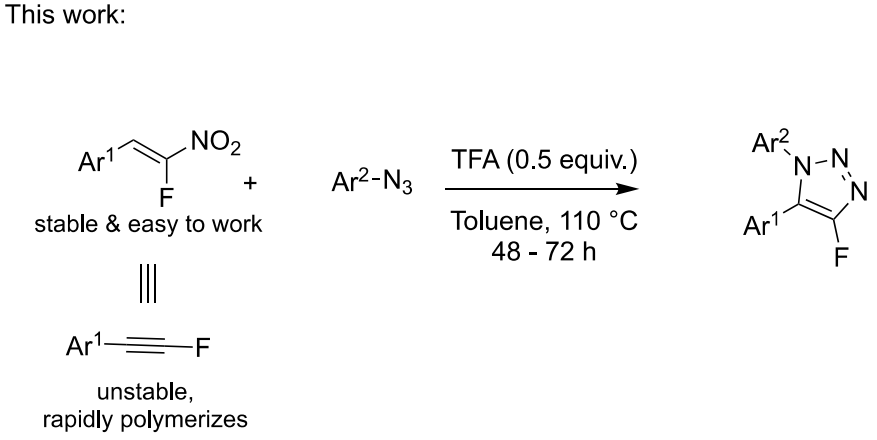
PDP-3

USE OF α-FLUORONITROALKENES AS A SYNTHETIC EQUIVALENT FOR FLUORO ALKYNES IN CYCLOADDITION REACTION WITH ORGANIC AZIDES

Sampad Jana[1], Sweta Adhikari[1], Micheal R. Cox[1], Sudeshna Roy*[1]

[1]Department of Biomolecular Sciences, School of Pharmacy, University of Mississippi, MS 38655

1,3-Dipolar cycloaddition reactions are notable for the synthesis of a great variety of heterocycle systems. In particular, the Cu(I)-catalyzed Huisgen-variant of azide-alkyne cycloaddition (CuAAC) reaction discovered by Sharpless, and Fokin has made 1,2,3-triazoles ubiquitous beyond pharmaceuticals in chemical biology and biomedical fields. The CuACC reaction transformed the classical Huisgen 1,3-dipolar cycloaddition that required harsh conditions and led to a mixture of 1,4- and 1,5-regioisomers into a regioselective reaction requiring mild conditions and short reaction time. Notably, 1,5-disubstituted 1,2,3 triazoles are scarce in pharmaceutical and chemotherapeutic agents since the regioisomeric 1,4-disubstituted 1,2,3 triazoles are more prevalent and readily accessed via CuAAC reaction. With the surge of fluorinated compounds in the past couple of decades in drugs, agrochemicals, and materials, regioselective access to fluorinated 1,5-disubstituted-1,2,3-triazoles is especially desirable. Owing to the volatility and instability of fluoroacetyenes, which rapidly oligomerizes to afford fluoro substituted benzene derivatives, restrict their use in CuAAC reactions. In this presentation, we showcase the use of α-fluoronitroalkenes as a synthetic equivalent of fluoroacetylenes in [3+2] cycloaddition reaction with organic azides to afford fluorinated 1,5-disubstituted-1,2,3-triazoles regioselectively. This method has a relatively broad substrate scope and the ensuing fluorinated 1,5-disubstituted-1,2,3-triazoles have drug-like properties that could be used as medicinal and pharmaceutical agents.



PDP-4

CELLULOSE SURFACE UTILITY AS AN ARTIFICIAL EXTRACELLULAR MATRIX FOR NEURAL DIFFERENTIATION

Soma Shekar Dachavaram [1], Chetan Pandanaboina [2], Krishna Deo Sharma [3] Thomas Risch [2], Jennifer Y. Xie [3], and Peter A. Crooks*[1]

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Key words: cellulose surface, neural differentiation, extra cellular matrix (ECM)

Development of the nervous system (NS) is a complex and highly organized process in which neural stem cells (NSCs) undergo a tightly regulated self-renewal, migration, and differentiation. Thus, the neural stem cells are able to populate the NS with neurons, astrocytes, and oligodendrocytes. In neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and traumatic brain injuries, the loss of neural cells causes permanent loss such as loss of sensory and motor functions. The available therapy to cure these neurodegenerative diseases is not sufficient. However, cell replacement therapy utilizing extra cellular matrices (ECM) offers a ray of hope to address this problem. The use of ECM during differentiation may increase the yield of differentiated neural cells. In this respect, the use of biodegradable cellulose may be a valuable alternative to using synthetic polymers. In the current study, micron cellulose and TEMPO cellulose Form-I (TCF-I) were utilized as an artificial matrix to differentiate neuronal stem cells (NSCs) into neurons and oligodendrocytes (ODCs). We differentiated E14 rat NSCs into neurons for one week. After a week of differentiation, we determined the percentage of cells positive for the neuronal marker βIII tubulin and the glial marker glial fibrillary acidic protein (GFAP) relative to the total cell count. The highest percentage of NSCs differentiated into neurons on micron cellulose (33% compared to 24% on poly-D-lysine (PDL), 24%). GFAP positive cells were 10% on cellulose and 15% on PDL. For ODC differentiation, NSCs propagated for 10 days using combinations of platelet-derived growth factor and basic fibroblast growth factor. The cells were collected and plated on MC and TCF-I, then differentiated for one week using oligodendrocyte differentiation medium containing triiodothyronine. Due to negative surface on TCF-I surface, the cell attachment efficiency is low when compared to MC. After seven days of differentiation, immunofluorescence data for both MC and TCF-I showed that about 70% of NSCs differentiated into receptor interacting protein positive ODCs and 30% NSCs differentiated into astrocytes identified by GFAP expression. Interestingly, almost all differentiated cells also expressed nestin protein, suggesting that MC and TCF-I surfaces could be useful ECMs for supporting neural regeneration.

PDP-5

Synthesis and evaluation of Azaindole Quinuclidinones as Novel Cannabinoid Ligands

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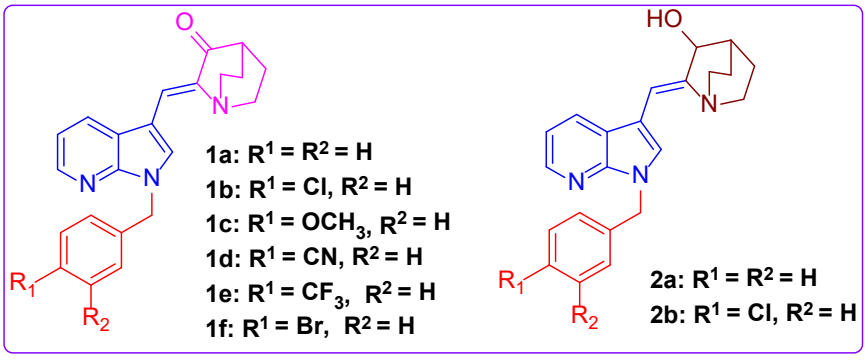
Previously, we have reported a novel class of cannabinoid receptor ligands possessing an indole nucleus as a key structural element, along with a quinuclidinone moiety (IQD's). The IQD ligands bind to both CB_1 and CB_2 cannabinoid receptors with high affinity in the nanomolar range. The azaindole nucleus is found to be another structural element which has been reported to play a key role in the affinity and activity of synthetic cannabinoids. In the present study a series of *N*-alkyl/*N*-benzyl 7-azaindolequinuclidinone (AIQD) analogs (**1a-1f**, **2a-2b**) have been synthesized and evaluated for their affinity toward CB_1 and CB_2 receptors and are identified as a novel class of cannabinoid receptor ligands. AIQD analogs are more drug like with improved pharmacokinetic properties compared to previously reported IQD analogs. Systematic structure activity relationship studies indicated that AIQD analogs are CB_1/CB_2 dual cannabinoid receptors ligands exhibiting good affinity at CB receptors, although they have generally lower affinity when compared to IQD's but are more selective towards CB2. Initial binding screens showed that AIQD analogs **1b**, **1d**, **1f** and **2b** (1 mM) produced more that 50% displacement of the CB_1/CB_2 non-selective agonist CP-55,940 (0.1 nM), which predicts that these compounds likely exhibit sub-micromolar affinity for both CB_1 and CB_2 receptors. Furthermore, *Ki* values determined from full competition binding curves showed that analogs **1a** and **1b** exhibit high affinity (110 and 115 nM) and selectivity (26.3 and 6.1-fold) for CB_2 relative to CB_1, respectively. Collectively, these initial studies suggest that further structure optimization of AIQD analogs may lead to the development of clinical useful AIQD cannabinoid agents.



Key words: Cannabinoid ligands, indole quinuclidinones, *N*-benzyl-7-azaindolequinuclidinone (AIQD), CB1/CB2 binding affinity, pharmacokinetic properties.

Acknowledgements: *We are grateful to the NIA/ NIH- P01AG012411-17A1 (PAC)*

PDP-6

IMIDAZOLE AND BENZIMIDAZOLE CARBAMATES OF MELAMPOMAGNOLIDE B AS POTENT, ORALLY BIOAVAILABLE ANALOGS FOR TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA

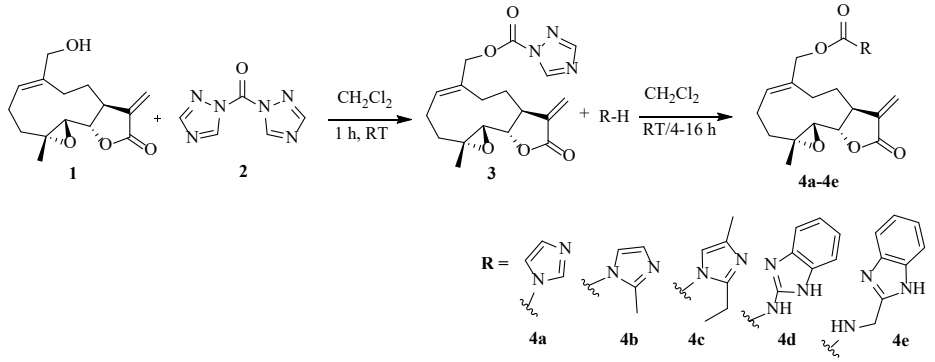
Venumadhav Janganati,[a] Zaineb A. F. Albayati,[a] Zheng Chen,[a] Earl J. Morris,[a] Jessica Ponder,[c] Philip J. Breen,[a] Craig T. Jordan[b] and Peter A. Crooks[a]*

[a] Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA; [b] Division of Hematology, University of Colorado, Aurora, CO 80045, USA; [c] Department of Toxicology, University of Colorado, Aurora, CO 80045, USA

Melampomagnolide-B (MMB) (1), a sesquiterpene lactone isolated from *Magnolia grandiflora* has anti-leukemic properties similar to parthenolide (PTL). Also, MMB can be synthesized from PTL utilizing selenium oxide oxidation of the C10 methyl group of PTL. Unlike PTL, the MMB molecule has a C-14 allylic hydroxyl functionality, which allows the synthesis of numerous derivatives of MMB by various chemical transformations and conjugations. Recently we designed and synthesized several conjugates of MMB, which exhibited potent anti-cancer activity against both hematological and solid tumor cell lines.

In the present study, we have designed and synthesized imidazole and benzimidazole carbamates of MMB (**4a-4e**) by reaction of MMB with 1,1′-carbonyl-di-(1,2,4-triazole) to afford MMB-triazole (**2**), which was reacted with various imidazole and benzimidazole amines in dichloromethane at ambient temperature for 4-16 h. The final compounds were purified by silica gel column chromatography, and their structures were confirmed by NMR and HRMS spectrometric analysis. These compounds were screened for anti-leukemic activity against M9 ENL1 cell line. Most of these compounds showed promising anti-leukemic activity (0.9-3.9 μM) compared to the parent compounds PTL (7.0 μM) and MMB (15.5 μM). Moreover, the comparative plasma PK profiles and oral bioavailabilities of MMB and the imidazole carbamate analog **4a** in BALB/c male mice indicated that **4a** has improved in vivo exposure after oral administration when compared to an equimolar dose of MMB, and had a 1.5-fold longer half-life than MMB. The significantly greater oral bioavailability of **4a** when compared to that of MMB, coupled with the 16-fold greater antileukemic potency of **4a** compared to MMB, predict a potential therapeutic advantage of **4a** over an equimolar dose of MMB.

Keywords: parthenolide; melampomagnolide B; carbamate derivatives; anticancer activity.



PDP-7

IDENTIFICATION OF USP1 INHIBITORS BY UBIQUITIN-RHODAMINE ASSAY

Sandipan Roy Chowdhury, Patrick Chuong, Amit Gupta, and Alexander Statsyuk

Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX

Breast cancer susceptibility type 1 gene *BRCA1* encode proteins which control genomic stability and are essential for DNA double strand break (DSB) repair by homologous recombination (HR) repair. These genes are often mutated or silenced in breast and ovarian cancers resulting in Poly (ADP-ribose)polymerase (PARP) inhibitor sensitivity. Thus, PARP inhibitors are the only FDA-approved drugs for *BRCA1*-mutant tumors. However, therapeutic resistance to PARP inhibitors has emerged, leading to a serious need for a new class of drugs.

The deubiquitinating enzyme ubiquitin-specific protease 1 (USP1) in association with ubiquitin-associated factor 1 (UAF1) is significantly upregulated in *BRCA1*-mutant tumors. USP1 associates with UAF1 to form a heterodimeric complex that is required for the deubiquitinase activity. Knockdown or inhibition of USP1 leads to destabilization of replication fork, which results in decreased viability of *BRCA1*-mutant tumor cells, indicating a synthetic lethal relationship. Although several USP1/UAF1 inhibitors have been reported in recent years, they've had issues with potency and selectivity. Recently, we have identified two lead compounds as USP1/UAF1 inhibitors based on Ubiquitin-Rhodamine assay. The compounds are structurally related and possess promising IC_{50} values against USP1/UAF1. A third compound with a similar structure was completely inactive. This prompted us to further investigate the structure activity relationship of known USP1/UAF1 inhibitors along with ours. This study will also help us to design and develop novel and USP1 selective USP1/UAF1 inhibitors.

PDP-8

SMALL MOLECULE POTENTIATORS FOR OXACILLIN AGAINST METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

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Staphylococcus aureus is a Gram-positive bacterium that causes infections in various parts of the body. Methicillin-resistant *Staphylococcus aureus* strains have become increasingly dangerous and life threatening to human health due to widespread resistance. They are responsible for a wide variety of infectious diseases such as skin infections, bloodstream infections, and surgical wound infections etc., The VraS/VraR two component regulatory system plays a crucial role in developing several resistance genes such as PBP2a encoded by mecA and thus develops resistance to □-lactam antibiotics including methicillin and oxacillin. The VraS is a membrane histidine kinase, that has ATP binding domain which is conserved with the ATPase domain of eukaryotic Hsp90 molecular chaperones. Therefore, small molecule mammalian protein kinases could be used to inhibit bacterial histidine kinases and thus potentiate antibiotic activity. Recently, Striker et al., reported that the pyrazolopyridazine GW779439X synergies oxacillin in methicillin-resistant Staphylococcus aureus (MRSA) through inhibition of the PASTA kinase Stk1. Herein, we have screened ATP competitive inhibitors from focus biomolecules highly selective kinase inhibitor library and selected Tofactinib which was found to bind VraS weakly by surface plasmon resonance. Using this scaffold, we synthesized fifty analogs and tested them against MRSA USA 300 strain in the presence of oxacillin using checkerboard assays. A clear structure activity relationship was developed with fifteen compounds showing strong synergy. The best compound 4223 exhibits a 16-fold decrease in oxacillin MIC at 3.12 □g/mL concentration. It is important to note that these small molecules did not show any antibiotic activity on their own, indicating that only lowering the MIC value for oxacillin by blocking the antibiotic stress response network.

PDP-9

BT2-MINIPEG-2 CIPROFLOXACIN CONJUGATE: A POTENTIAL BONE TARGETIN -G ANTI-BACTERIAL AGENT

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Osteomyelitis is a serious inflammatory condition of bone that is most often associated with infection by the bacterial pathogen *Staphylococcus aureus*. Treatment of these infections is extremely challenging owing in part to the increasing prevalence of *S. aureus* strains resistant to methicillin and other beta-lactam antibiotics. Previous studies have demonstrated that the bone targeting agent BT2-minipeg-2 conjugated to vancomycin and delivered systemically by intravenous (IV) or intraperitoneal (IP) injection has similar antibiotic activity as Vancomycin and accumulates in bone to a greater degree than vancomycin alone, but that this was associated with severe nephrotoxicity. Therefore, there is an urgent need for more effective systemic delivery of antimicrobial agents to bone. We have designed and synthesized several BT2-minipeg-2 conjugates of the quinolone antibiotics such as ciprofloxacin, sparfloxacin and moxifloxacin (**BS-6-21, BS-6-32, BS-6-35, BS-6-39, BS-6-49, BS-6-68,** and **BS-6-71**). These conjugates were initially tested for their antibacterial activity. Most of these conjugates were less potent (less than 50-fold activity) compared to the corresponding parent antibiotic. Interestingly, the BT2-minipeg-2 ciprofloxacin conjugate, **BS-6-68**, demonstrated significant antibacterial activity (25% activity of the parent compound). Pilot *in vivo* studies with the **BS-6-68** were carried out to select an appropriate dosing for IP Injection of **BS-6-68** and the parent compound ciprofloxacin. IP doses of 10 mg/kg ciprofloxacin or 22.2 mg/kg BT2-minipeg-2 ciprofloxacin (the molar eq. of 10 mg/kg ciprofloxacin) were investigated utilizing female C57BL/6 mice (20-25 g) per experiment. The levels of ciprofloxacin and BT2-minipeg-2 ciprofloxacin in plasma and bone tissues were determined by a new LC-MS/MS method. **BS-6-68** and ciprofloxacin were both detected in plasma and bone after IP administration of **BS-6-68**, indicating that some metabolic cleavage to ciprofloxacin had occurred; ratios (AUC) of **BS-6-68**:ciprofloxacin were 3.4 and 0.58 in bone and plasma, respectively. After IP administration of ciprofloxacin the drug was detected in both plasma (80%) and bone (20%). The molar ratio of ciprofloxacin in bone after IP ciprofloxacin administration and **BS-6-68**/ciprofloxacin in bone after IP **BS-6-68** administration was 0.8, indicating a 20% increase in molar concentration of **BS-6-68**/ciprofloxacin.

PDP-10

RELEASING STUDIES OF THE SIGNALING MOLECULE, HYDROGEN SULFIDE, BY NOVEL ANTILEUKEMIC 1,2,4-THIADIAZOLIDINE-3,5-DIONE (TDZD) DERIVATIVES IN THE PRESENCE OF THIOLS IN VITRO, AND THEIR ANTILEUKEMIC ACTIVITIES

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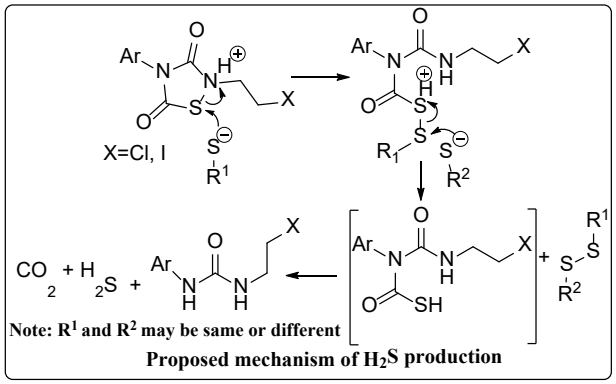
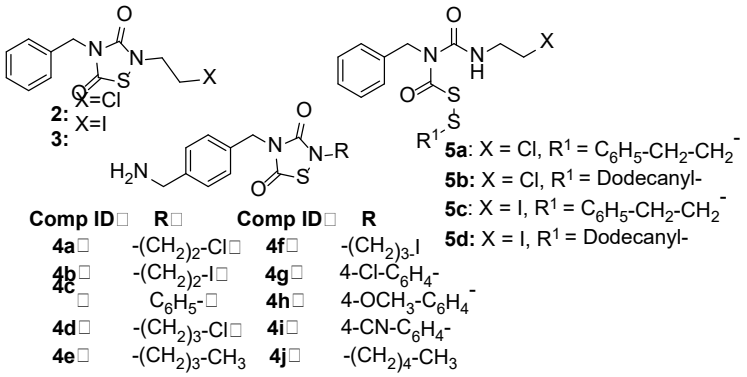
In the current research field one of the emerging areas is the development hydrogen sulfide (H_2S) releasing moieties that could be used as therapeutic agents, since H_2S is an endogenous modulator that plays significant physio-pathological roles in several biological systems. In our earlier work, we studied the antileukemic activity of TDZD-8 (**1**) analogs and also reported the unusual rapid cell death kinetics (typically< 2h) by TDZD analogs. We have now shown in-vitro that heterocycle ring opening of TDZD analogs through nucleophilic attack of thiols at the ring sulfur atom results in cleavage of the sulfur-nitrogen bond, leading to formation of an electrophilic disulfide adduct that can react with a second thiol molecule to form an intermediate that releases H_2S and generates a terminal disulfide product. We speculate that such a mechanism, if it involves reaction of an endogenous molecule containing a cysteine residue, may explain how these TDZD analogs exert their antileukemic activity at the cellular level. We have now synthesized several novel TDZD analogs whose H_2S releasing properties have been evaluated in-vitro after exposure to a variety of thiols. These analogs include simple TDZD analogues (**2-3**), amino-TDZD analogues (**4a-4j**) and TDZD-disulfide analogues **(5a-5d)** as H_2S-releasing compounds, and have evaluating these analogs against leukemia MV4-11 cells. TDZD analogs (**3** and **4f**), and ring-opened TDZD disulfide analog (**5c**) exhibited potent antileukemic activity against MV4-11 cells with LD_{50} values of 1.6 µM, 2.02 µM and 0.75 µM, respectively. Further development of these molecules as clinical candidates to treat leukemia are under investigation.





Comp ID	R	Comp ID	R
4a	-$(CH_2)_2$-Cl	4f	-$(CH_2)_3$-I
4b	-$(CH_2)_2$-I	4g	4-Cl-C_6H_4-
4c	C_6H_5-	4h	4-OCH_3-C_6H_4-
4d	-$(CH_2)_3$-Cl	4i	4-CN-C_6H_4-
4e	-$(CH_2)_3$-CH_3	4j	-$(CH_2)_4$-CH_3

Key words: Hydrogen sulfide releasing agents, anti-leukemic activity, TDZD

PDP-11

STRUCTURE-BASED VIRTUAL SCREENING APPROACH TO IDENTIFY NOVEL MraY INHIBITORS FOR TUBERCULOSIS CHEMOTHERAPHY

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Tuberculosis (TB) remains the leading cause of death worldwide from a single infectious agent, claiming 1.6 million lives in 2017 according to the World Health Organization. The emergence of extensive and multi-drug-resistant TB warrants development of new therapeutics to control this epidemic. MraY (phospho-N-acetylmuramoyl-pentapeptide-transferase) enzyme catalyzes an essential step in peptidoglycan biosynthesis of bacterial cell walls and is an unexploited target for chemotherapeutics development. Although several classes of nucleoside-based natural products target MraY but none have been developed for clinical use due to their poor in vivo efficacy and target promiscuity. We are seeking to identify new small molecule inhibitors of MraY of different scaffolds using a protein-structure-based virtual screening (VS) approach. Since there is no reported $MraY_{Mtb}$ crystal structure, homology models of $MraY_{Mtb}$ were constructed with Modeller based on the published crystal structure of MraY from *Aquifex aeolicus* in complex with muraymycin D2 (MD2). The best homology model was further validated through docking of known $MraY_{Mtb}$ inhibitors, yielding an enrichment factor of 16 with high ROC (0.99) and BEDROCK score (0.994). The model was further refined by performing molecular dynamics simulation (100 ns) with muramycin D2 (MD2) complex. No significant changes were observed in protein conformation (protein Cα RMSD < 1 Å) during the simulation. The ZINC15 database of ~12 million commercially available compounds were screened against the best $MraY_{Mtb}$ homology model using GOLD software. An energetically optimized E-pharmacophore model was constructed from MD2-$MraY_{Mtb}$ complex that was also used as a prefilter in VS. 40 hits were identified based on the ChemScore function, clustering, and visual inspection of ligand interactions with $MraY_{Mtb}$. 16 hits were purchased on the basis of cost and availability. In vitro testing of biochemical inhibition of MraY and Mtb inhibition are underway. Subsequent structure-activity-relationship studies will result in new non-nucleoside-based inhibitors of MraY. This work will establish a new therapeutic strategy for TB and other drug-resistant infections.

PDP-12

INVESTIGATION OF DETRIFLUOROACETYLATIVE CARBON–CARBON BOND CLEAVAGE OF α-ARYL PENTAFLUORO GEM-DIOLS TO PREPARE DIFLUOROMETHYLARENES

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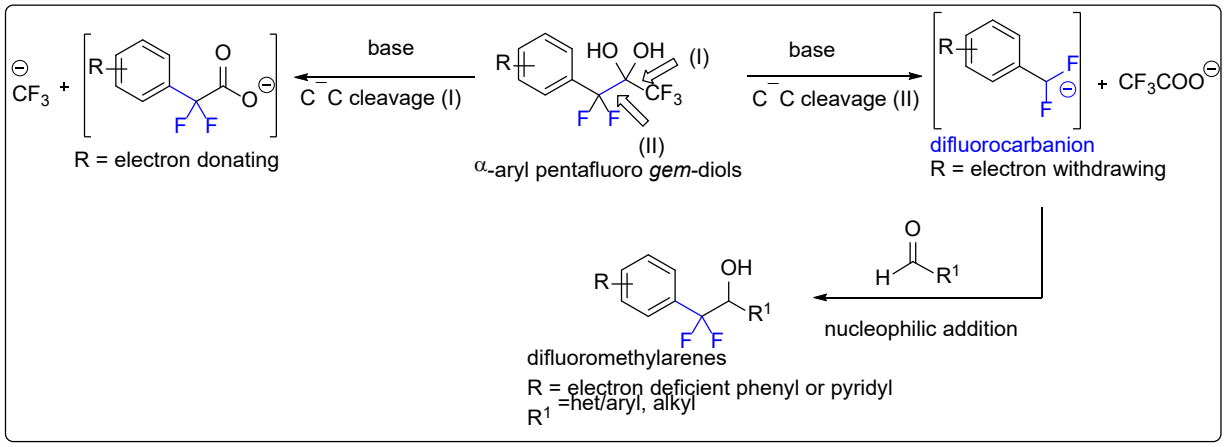
The selective cleavage of carbon–carbon bonds in organic synthesis presents a significant challenge, yet exploiting these processes can be a way to generate reactive intermediates such as difluorobenzyl carbanion ($ArCF_2^-$) intermediates, which could be valuable synthons to create aryldifluoromethyl derivatives (Ar-CF_2-R). Aryldifluoromethyl derivatives are important building blocks in many bioactive compounds, and elegant synthetic methods to access them are limited. We have conducted fragmentation study of α-aryl pentafluoro gem-diols, and discovered a mild detrifluoroacetylative approach to generate carbanion ($ArCF_2^-$) which upon reaction with aldehydes created difluoromethylarenes (Scheme 1). The efficiency generating carbanions is dependent on the nature and position of substituents on the aromatic and heteroaromatic rings, solvents and carbonate base (alkali metal carbonate M_2CO_3). Fluorinated *gem*-diols with electron deficient aromatic and heteroaromatic rings, under basic condition and polar non-protic solvents generate difluorobenzyl carbanions ($ArCF_2^-$) whereas the electron rich *gem*-diols produced carboxylate anions by release of fluoroform.



Scheme 1. Study of C–C bond cleavage and synthesis of difluoromethylarenes

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