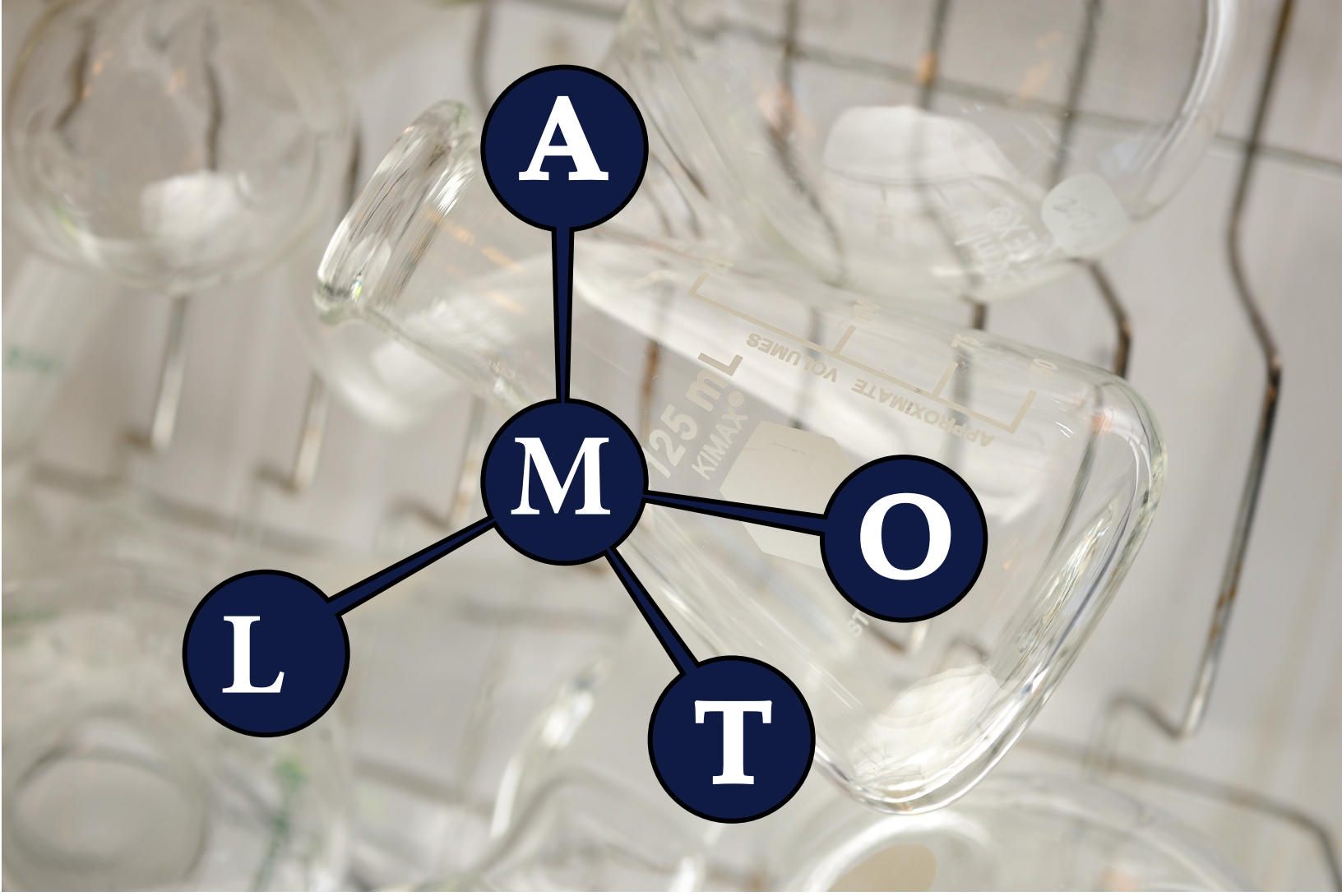

42nd Annual

Medicinal Chemistry & Pharmacognosy Meeting-in-Miniature

May 17-19, 2015

THE UNIVERSITY of MISSISSIPPI
DEPARTMENT OF
BIOMOLECULAR SCIENCES

MALTO 2015
University of Mississippi
Contents

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The participants of the 42nd Annual MALTO Medicinal Chemistry-Pharmacognosy Meeting-in-Miniature gratefully acknowledge the following contributors whose support has ensured continuation of the MALTO Scientific Forums:

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General Program

Sunday, May 17, 2015

6:00-8:30 PM **Registration and Mixer**
Bryant Hall, (The Circle) University of Mississippi
Food provided by Party Waitin' to Happen--Cash Bar

Monday, May 18, 2015

Breakfast for registrants: you are on your own—The Inn at OleMiss provides complimentary breakfast.

All podium sessions held at The Thad Cochran Research Center (TCRC) Natural Products Center-Centennial Auditorium – Room 1000
All poster sessions and lunches held at TCRC atrium (outside room 1000)

Coffee, soft drinks, water, and snacks will be provided in TCRC-1000 atrium each morning and throughout the day for both Monday and Tuesday sessions.

7:45 AM **Welcoming Remarks**

***John M. Rimoldi**, Professor of Medicinal Chemistry and President of MALTO, Inc., School of Pharmacy, University of Mississippi*

***David D. Allen,** Dean and Professor of Pharmacology & Executive Director of the Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi*

8:00-9:20 AM **Podium Session 1**

9:20–11:00 AM **Graduate Student Poster Session 1 & Break**

11:00-12:15 PM **A. Nelson Voldeng Memorial Lecture**

Alan P. Kozikowski
Professor, Drug Discovery Program, College of Pharmacy, University of Illinois at Chicago.
"Chemistry, the Brain, and Cancer – Ups and Downs on the Road to HDAC6i Drugs"

12:15-1:30 PM **Lunch (TCRC atrium)**
Provided by Party Waitin' to Happen

1:40-3:00 PM **Podium Session 2**

3:00-4:40 PM **Postdoctoral Poster Session 2 and Break**

4:40-5:00 PM **Dr. James McChesney,** *Arbor Therapeutics, LLC*

6:00-8:30 PM **Dinner**
Boure, upper room, 110 Courthouse Square
Cash Bar

Tuesday, May 19, 2015

8:00 – 9:20 AM **Podium Session 3**

9:20-9:40 AM **Break**

9:40-11:00 AM **Podium Session 4**

11:00 –12:00 PM **MALTO Business Meeting**
TCRC 1044

12:00-1:00 PM **Lunch provided by Newk's (TCRC atrium)**

Award Presentations
2015 Robert A. Magarian Podium Presentation Award
2015 Thomas L. Lemke Poster Presentation Award
2015 Ronald F. Borne Postdoctoral Poster Presentation Award

1:00 PM **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 included 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 (University of. Louisiana at Monroe, 1995-2004), and E. Kim Fifer (Arkansas, 2004 – 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. Subsequently, similar awards were established in 2003 for the outstanding student poster in honor of Dr. Thomas L. Lemke and in 2015 for the outstanding postdoctoral poster presentation in honor of Dr. Ronald F. Borne.

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 plaque 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, *University of Kansas*
2014 Richard E. Lee, *St. Jude Children's Research Hospital*

28th Annual A. Nelson Voldeng Memorial Lecture

Dr. Alan Kozikowski is Professor Emeritus of Medicinal Chemistry and Pharmacognosy, and Director of the Drug Discovery Program at The University of Illinois at Chicago. Alan received his B.S. in Chemistry from the University of Michigan in 1970, his Ph.D. in Organic Chemistry from the University of California at Berkeley in 1974 under the direction of Professor W. G. Dauben, and served as an NIH Postdoctoral Fellow at Harvard University with Professor E. J. Corey from 1974-1976. He began his academic career in the Department of Chemistry at The University of Pittsburgh in 1976, and rose to the rank of Professor in 1983. In 1990 Alan joined the Mayo Clinic as Professor and Director of Chemistry Research, and in 1995, moved to Georgetown University as Professor and Director of the Drug Discovery Program in the Department of Neurology. He served as an Adjunct Professor at Johns Hopkins University School of Medicine and as Professor of Medicinal Chemistry at UIC from 2003 to 2013.

Dr. Kozikowski is an internationally renowned medicinal chemist, having published over 500 papers in peer-reviewed journals, awarded over 100 patents, and presented nearly 150 invited symposia and university lectures. Alan's awards are numerous and include: Sloan Foundation Fellow (1978-1980), Camille and Henry Dreyfus Teaching Scholar (1982-1987); Ciba-Geigy Award (1982); Japan Society for the Promotion of Science Fellow (1984); Akron ACS Awardee (1989); Johnson & Johnson Focused Giving Grant Awardee (1988). He served as VP of Medicinal Chemistry at Trophix Pharmaceuticals (1993-1994) and was the Founder of Acenta Discovery.

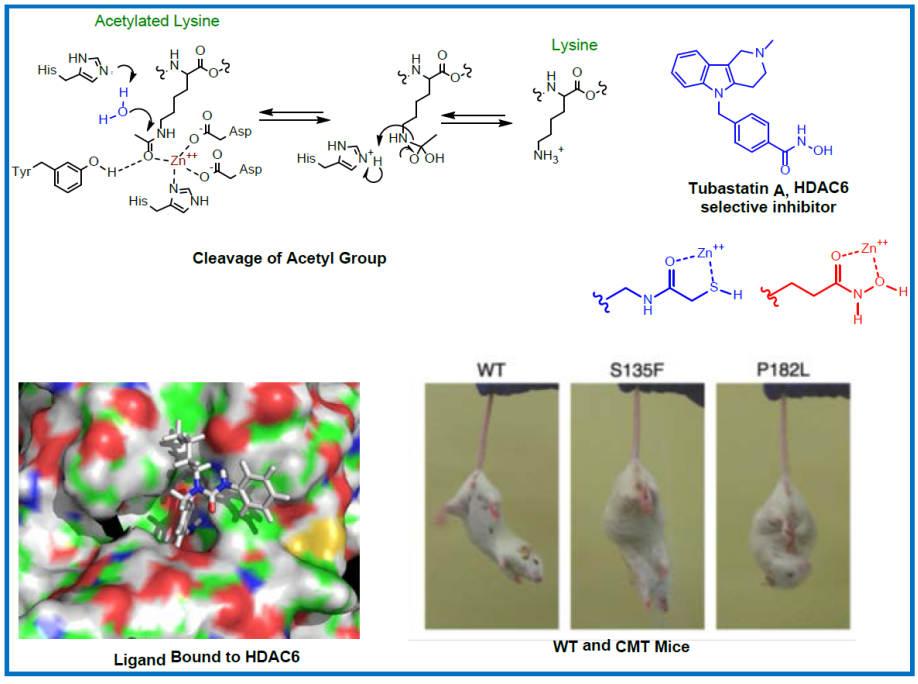
Dr. Kozikowski's group was the first to synthesize Huperzine A, an alkaloid which was in phase II clinical trials for Alzheimer's disease, and now under study as an antidote against nerve gas toxins. He has also developed a potential medication for use in cocaine abuse (Nocaine) and other novel transporter ligands [triple reuptake inhibitors] for use in the therapy of mood disorders. Based upon a natural product lead, his group has generated novel GSK-3b inhibitors for use in bipolar disorder and for the treatment of spinal muscular atrophy, in collaboration with the SMA Foundation in NY. He founded Apotheca Therapeutics, a company committed to advancing GSK-3 inhibitors to the clinic for use in brain cancers. He has discovered a unique inhibitor of the NAAG peptidase, which is in Phase II clinical trials for prostate cancer imaging. His work in the nicotinic field has led to a recent patent filing and the identification of novel antidepressants being developed in partnership with PsychoGenics. His group also has designed drug leads for use in tuberculosis and toxoplasmosis. Lastly, his interest in epigenetics has led to the discovery of highly selective (>1000-fold), nM potency HDAC6 inhibitors that are being studied in cancer, colitis, transplant medicine, Rett syndrome, CMT, and others. Plans to move these agents to the clinic are underway.

28th Annual A. Nelson Voldeng Memorial Lecture

Alan P. Kozikowski, Ph.D. *Professor, Drug Discovery Program, University of Illinois at Chicago*

"Chemistry, the Brain, and Cancer – Ups and Downs on the Road to HDAC6i Drugs"

Histone deacetylases or HDACs are associated with the removal of acetyl groups from histones and a host of other proteins. Class I, II and IV HDACs require Zn2+ as a cofactor for their deacetylating activity and these are often referred to as the conventional HDACs. The sirtuins 1-7 are dependent on nicotinamide adenine dinucleotide for their activity and form class III of the HDACs. HDAC6 has garnished significant attention due to its unique structure and activity, and to the finding that HDAC6 knockout animals remain viable. While HDAC6 does not work on nuclear histones, it is involved in the acetylation status of proteins such as cortactin, HSF-1, HSP90, and tubulin. In particular, HDAC6 controls the acetylation status of the microtubule protein α-tubulin, and microtubule-dependent transport rates are more efficient along acetylated α-tubulin than deacetylated α-tubulin. This effect stems from the increased association of the motor proteins kinesin-1 and dynein with acetyl-tubulin, and therefore, affects both anterograde and retrograde transport activities. Thus, in addition to facilitating anterograde transport of new cargo to synaptic zones, acetyl-tubulin also increases the ability of damaged organelles or misfolded proteins to leave synaptic zones. This may be very important for Rett Syndrome as well as other disease conditions, as damaged mitochondria and elevated levels of improperly spliced mRNA transcripts have been noted in MeCP2-deficient neurons. In this lecture I will present information on the design, synthesis, and testing of ligands that are highly selective for HDAC6 inhibition and show how such compounds may find use as potential therapies in diseases such as Rett syndrome, Alzheimer's disease, cancer, stroke, and CMT.



Robert A. Magarian Outstanding Podium Presentation Award

Dr. Robert A. Magarian is professor emeritus of pharmacy and medicinal chemistry, College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK, and Past-President of MALTO (1972-2013). 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) and received many awards one of which was the Taylor Medal, the highest honor awarded to a student by the University of Mississippi. He practiced as a pharmacist in Illinois from January 1960 to August 1961.

Dr. Magarian's research was multidisciplinary, 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. 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, 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” (Infinity Publishing). He is currently working on his third novel, a mystery titled, “You’ll Never See Me Again,” which will be published in the of summer 2015. For additional information please visit his web site: www.robertamagarian.com.”

[MALTO Medicinal Chemistry, OK Inc., became a not-for-profit organization in 1972 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: 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: 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: Mitchell A. Avery

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

2003 *Lindsay Odom*, "Alkylation and Cyclization Reactions of Diazoketones: Synthesis of Substituted Azetidines," University of Mississippi, Advisor, 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, Richard E. Lee.

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

2006 *Tarek Mahfouz*, "Computer-aided Inhibitor Discovery of the Botulinum Neurotoxin Serotype A," University of Houston, Advisor, 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, Richard E. Lee.

2008 *Yatan Shukla*, "Novel Pregnane Glycosides from *Hoodia gordonii*," University of Mississippi, Advisor, 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, Mark T. Hamann.

2010 *Sarah Chajkowski,* "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 at Monroe, Advisor, Khalid El Sayed.

2013 *Min Xiao*, "Discovery of 4-Aryl-2-benzoyl-imidazoles as Tubulin Polymerization Inhibitors with Potent Antiproliferative Properties," University of Tennessee Health Sciences Center, Advisor, Wei Li.

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

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 spent 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.

Thomas L. Lemke Outstanding Student Poster Presentation Award Past Recipients:

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

2005 *Wayun Sheng*, "3D High-resolution NMR Characterization of Recombinant CB2 Membrane Protein Fragment," University of Houston, Advisor, Xiang-Quinn (Sean) Xie.

2006 *Lukasz Kutrzeba*, "In-vitro Studies on Metabolism of Salvinorin A," University of Mississippi, Advisor, 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, Robert J Doerksen.

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

2009 *Lacey D. Gamblin*, "Synthesis of Thiourea Analogues as Potential Somatostatin Receptor Subtype 4 Agonists" Southern Illinois University, Edwardsville, Advisor, 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," 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*," Advisor, Mark Hamann.

2013 *Chalada Suebsuwong*, "An Approach to Identifying Potent and Selectifve DXG-out RIP1 Kinase Inhibitors," Advisor, Gregory D. Cuny.

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

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, 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 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. 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.

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). 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 will be published by the University Press of Mississippi in June 2015 and his history book, *1936 – A Pivotal Year in American and World History: The Confluence of Sports and Politics*, is currently being reviewed by Nautilus Publishing Company.

Meeting Schedule

7:45 AM **Welcoming Remarks (TCRC 1000)**

8:00-9:20 AM **Podium Session 1:** ***Mr. Eric Bow, Presiding***

8:00 O1 **COMPUTATION-NMR COMBINED APPROACHES TO ADDRESS CONFIGURATIONAL ISSUES OF SYNTHETIC/NATURAL PRODUCTS**

Joonseok Oh, Amanda L. Waters, Mark T. Hamann

Department of BioMolecular Sciences, Division of Pharmacognosy and Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA

8:20 O2 **FINDING LEAD COMPOUNDS FOR THE NEXT GENERATION OF ANTI-INFLAMMATORY DRUGS USING AN INNOVATIVE ENZYME-CHAIN REACTION**

Hironari Akasaka, Nanhong Tang, Vanessa Cervantes and Ke-He Ruan

Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX 77204-5037

8:40 O3 **DESIGN, SYNTHESIS, BIOLOGICAL EVALUATION, AND METABOLIC STABILITY ENHANCEMENT OF THE DUAL SIGMA RECEPTOR ANTAGONIST DAT INHIBITOR AGENTS AS POTENTIAL TREATMENT FOR STIMULANT ABUSE**

Walid Alsharif[1], Theresa Kopajtic[2], Murugesh Kandasamy[1], Bonnie A. Avery[1], Takato Hiranita[2], Jonathan L. Katz[2] and Christopher R. McCurdy[1]

[1]University of Mississippi School of Pharmacy; [2]NIDA Intramural Research Program.

9:00 O4 **IDENTIFICATION AND EVALUATION OF POTENT INHIBITOR OF HUMAN MONOAMINE OXIDASE B FROM *CALEA URTICIFOLIA***

Vedanjali Gogineni[1], Narayan D Chaurasiya[2], Francisco Leon[1], Marvin J Nuñez[3], Larry A Walker[1,2], Babu L Tekwani[1,2] and Stephen J. Cutler[1]

[1]Department of BioMolecular Sciences and [2]National Center for Natural Products Research, (RIPS) School of Pharmacy, The University of Mississippi, University, MS 38677, USA and [3]Laboratorio de Investigacion en Productos Naturales, Facultad de Quimica y Farmacia, Av. Heroes y Martires del 30 de Julio, San Salvador, El Salvador.

9:20–11:00 AM **Graduate Student Poster Session 1 & Break**

11:00-12:15 PM **A. Nelson Voldeng Memorial Lecture**

Alan P. Kozikowski
Professor, Drug Discovery Program, College of Pharmacy, University of Illinois at Chicago.
"Chemistry, the Brain, and Cancer – Ups and Downs on the Road to HDAC6i Drugs"

12:15-1:30 PM **Lunch (TCRC atrium)** *Provided by Party Waitin' to Happen*

1:40-3:00 PM **Podium Session 2:** ***Mr. Michael Cunningham, Presiding***

O5 1:40 **SMALL-MOLECULE ANALOGS OF A POTENT SMAC-MIMETIC THAT TARGETS SURVIVIN AND INDUCES APOPTOSIS *IN VITRO***
Kinsie Arnst, Qinghui Wang, Wei Li*
Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, Tennessee 38163

O6 2:00 **IDENTIFICATION AND CHARACTERIZATION OF ALLOSTERIC SITE(S) FOR CB2 NEGATIVE ALLOSTERIC MODULATORS (NAMS)**
Pankaj Pandey, Kuldeep K. Roy, and Robert J. Doerksen*
Division of Medicinal Chemistry, Department of BioMolecular Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA

O7 2:20 **SELECTIVE STABILIZATION OF THE KRAS G-QUADRUPLEX: A NOVEL THERAPEUTIC TARGET**
Rhianna K. Morgan[1], Khondaker Miraz Rahman[2], and Tracy A. Brooks[1,*]
[1]Department of BioMolecular Sciences, Division of Pharmacology, School of Pharmacy, University of Mississippi, University, MS 38677; [2]Institute of Pharmaceutical Sciences, King's College, London, England, United Kingdom

O8 2:40 **SYNTHETIC STUDIES OF 7-OXYGENATED APORPHINE ALKALOIDS AND STRUCTURAL REVISION OF (–)-ARTABONATINE A**
Angela F. Ku[1] and Gregory D. Cuny[2]*
[1]Department of Chemistry, [2]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, 77204

3:00-4:40 PM **Postdoctoral Poster Session and Break**

4:40-5:00 PM **James McChesney,** *Arbor Therapeutics, LLC*

6:00-8:30 PM **Dinner** *Boure, upper room, 110 Courthouse Square - Cash Bar*

Tuesday May 19, 2015

8:00 – 9:20 AM **Podium Session 3:** ***Mr. Mohamed Jihan, Presiding***

O9 8:00 **OLEANOLIC ACID ACRYLATE ELICITS ANTIDEPRESSANT-LIKE EFFECT MEDIATED BY 5-HT_{1A} RECEPTOR**

Fajemiroye O. James[1,2], Prabhakar R. Polepally[2], Jordan K. Zjawiony[2], Costa E. Alves[1]

[1]Department of Pharmacology, Federal University of Goias, Brazil, [2]Department of BioMolecular Sciences, Division of Pharmacognosy, School of Pharmacy, University of Mississippi, 38677, USA

O10 8:20 **CD2 PROTEIN DERIVED MINI-PROTEINS (CYCLOTIDES) FOR MODULATION OF CD2-CD58 PROTEIN-PROTEIN INTERACTION: IMPLICATIONS IN AN AUTOIMMUNE DISEASE**

Rushikesh Sable[1], Thomas Durek[2], David Craik[2] and Seetharama Jois[1]

[1]Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of Louisiana at Monroe LA 71201. [2]Institute for Molecular Bioscience, The University of Queensland, St. Lucia, Australia

O11 8:40 **THE PRODUCTION OF NOVEL DRUG COMPOUNDS THROUGH THE SYMBIOSIS BETWEEN ENDANGERED PLANTS AND ENDOPHYTES**

Jordanne Fletcher, Mark T. Hamann*

Department of Biomolecular Sciences, Division of Pharmacognosy University of Mississippi, 38677

O12 9:00 **SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 20(S),24(S AND R)-DIHYDROXYVITAMIN D3 ISOMERS**

Zongtao Lin[1], Srinivasa Reddy Marepally[1], Dejian Ma[1], Linda K. Myers[1], Arnie E. Postlethwaite[2,3], Robert C. Tuckey[4], Duane D. Miller[1], Wei Li[1]*

[1]Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN 38163, United States .[2]Department of Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, United States. [3]Department of Veterans Affairs Medical Center, Memphis TN 38104, United States. [4]School of Chemistry and Biochemistry, University of Western Australia, Crawley, Perth, WA 6009, Australia.

9:20-9:40 AM **Break**

9:40-11:00 AM **Podium Session 4:** ***Miss Kelsey Leucke presiding***

O13 9:40 IDENTIFICATION OF NOVEL INHIBITORS OF BOTULINUM NEUROTOXIN A

Chinni Yalamanchili[1,2], Vamshi K. Manda[1], Amar G. Chittiboyina[1], William A. Harrell Jr[3], Robert P. Webb[3], and Ikhlas A. Khan[1,2,4*]

[1]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, The University of Mississippi, University, MS 38677, USA. [2]Divison of Pharmacognosy, Department of BioMolecular Sciences, The University of Mississippi, University, MS 38677, USA. [3]US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21702-5011, USA. [4]Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

O14 10:00 DISCOVERY OF NOVEL SURVIVIN INHIBITORS WITH POTENT ANTIPROLIFERATIVE PROPERTIES

Min Xiao, Jin Wang, Yan Lu, Duane. D. Miller, and Wei Li

Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, Tennessee, 38163

O15 10:20 STRUCTURE-BASED DESIGN OF POTENT AND SELECTIVE DLG-OUT RIPK1 INHIBITORS

Chalada Suebsuwong[1], Malek Najjar[2], Soumya S. Ray[3], Roshan J. Thapa[4], Jenny L. Maki[5], Shoko Nogusa[4], Saumil Shah[5], Danish Saleh[5], Peter J. Gough[6], John Bertin[6], Junying Yuan[7], Siddharth Balachandran[4], Gregory D. Cuny[8], Alexei Degterev[2,5]

[1]Department of Chemistry, University of Houston, 77204 [2]Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 02111 [3]Department of Neurology, Brigham & Women's Hospital and Harvard Medical School, 02139 [4]Immune Cell Development and Host Defense Program, Fox Chase Cancer Center, 19111 [5]Department of Developmental, Molecular & Chemical Biology, Tufts University School of Medicine, 02111 [6]Pattern Recognition Receptor Discovery Performance Unit, Immuno-Inflammation Therapeutic Area, GlaxoSmithKline, 19426 [7]Department of Cell Biology, Harvard Medical School, 02115 [8]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, 77204

O16 10:40 PROGRESS TOWARD THE TOTAL SYNTHESIS OF A DISCORHABDIN RELATED NATURAL PRODUCT FOR THE CONTROL OF PANCREATIC CANCER

Xiaojuan Wang and Mark T. Hamann

Department of Biomolecular Sciences, University of Mississippi, University, MS 38677, USA.

11:00 –12:00 PM **MALTO Business Meeting**
TCRC 1044

12:00-1:00 PM **Lunch provided by Newk's (TCRC atrium)**

Award Presentations
2015 Robert A. Magarian Podium Presentation Award 2015
Thomas L. Lemke Poster Presentation Award
2015 Ronald F. Borne Postdoctoral Poster Presentation Award

1:00 PM **Adjourn**

Podium Presentation Abstracts

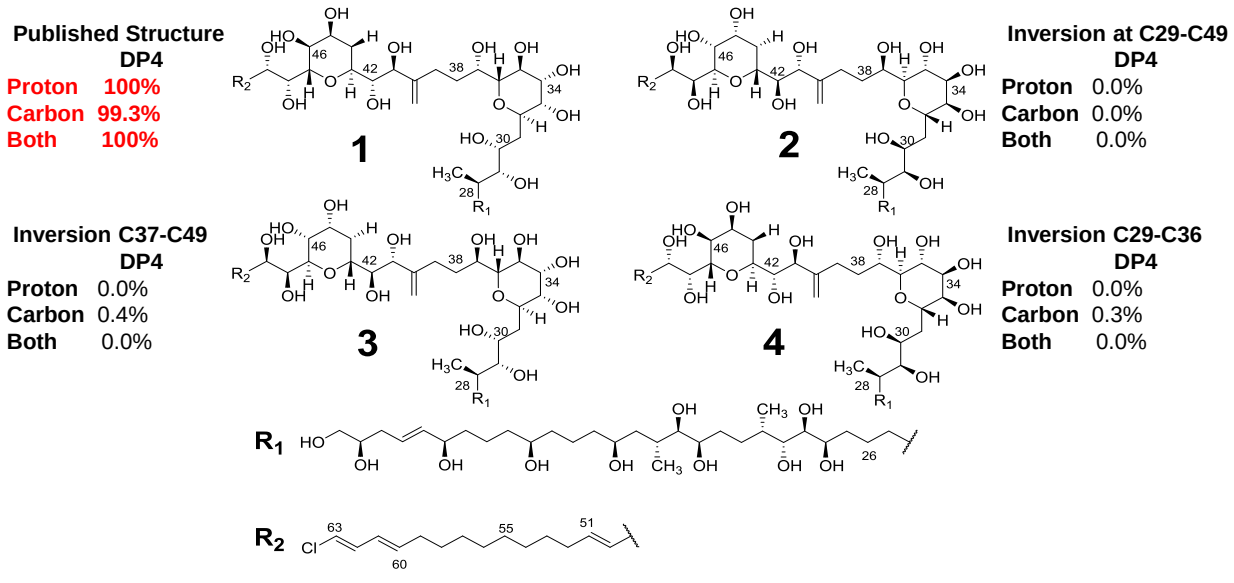
O1 – Graduate Student, Podium

COMPUTATION-NMR COMBINED APPROACHES TO ADDRESS CONFIGURATIONAL ISSUES OF SYNTHETIC/NATURAL PRODUCTS

Joonseok Oh, Amanda L. Waters, Mark T. Hamann

Department of BioMolecular Sciences, Division of Pharmacognosy and Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA

Even though NMR analysis is recognized as a pertinent tool for 3D structural determination of synthetic/natural products, the approach is often ineffective in cases of compounds possessing conformationally flexible chains and/or their quantities being limited. Quantum mechanical (QM) calculations coupled with conventional NMR applications have emerge as a useful alternative to address stereochemical details of complex and flexible compounds and successfully employed to implement 3D structural assignments or revisions. It is particularly interesting to establish stereostructures based on the comparison of NMR chemical shift values, coupling constants and ECD calculations with their experimental data. Furthermore, these approaches can be enhanced upon application of advanced statistical tools (CP3 and DP4 analyses). Herein, we are demonstrating details regarding the recent successful applications of QM-NMR coupled analyses with a structural confirmation process of complex and flexible polyketide karlotoxin 2.



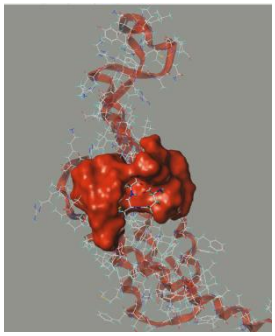
O2– Graduate Student, Podium

FINDING LEAD COMPOUNDS FOR THE NEXT GENERATION OF ANTI-INFLAMMATORY DRUGS USING AN INNOVATIVE ENZYME-CHAIN REACTION

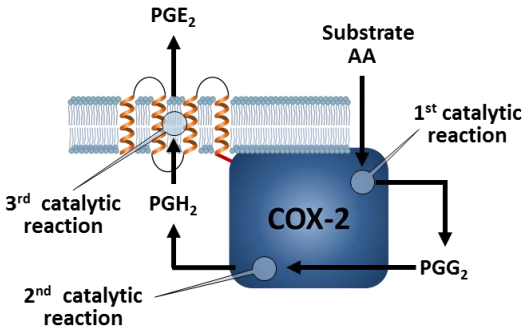
Hironari Akasaka, Nanhong Tang, Vanessa Cervantes and Ke-He Ruan

Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX 77204-5037

The major obstacles in identification of reliable lead compounds targeting an inducible and inflammatory microsomal prostaglandin E2 (PGE_2) synthases-1 (mPGES-1) in cell-based screening are i) instability of the enzyme substrate, prostaglandin H2 (PGH_2), ii) interference of non-inducible cytosolic PGE_2 synthase (cPGES) and mPGES-2 in cells to produce a large amount of PGE_2, and iii) huge assay numbers of the random-compounds library. In this study, a reliable and specific cell-based screening assay was developed using a stable cell line specifically expressing an engineered hybrid enzyme, COX-2-10aa-mPGES-1. The hybrid enzyme has three catalytic functions continually converting a stable and low cost substrate, arachidonic acid (AA), to PGG_2, PGH_2 and then PGE_2 within a single enzyme molecule. This eliminated the interferences of cPGES and mPGES-2 that share COX-2-produced PGH_2. To increase the screening specificity we integrated a virtual screening and cell-based assays. Virtual screening of 380,000 drug-like compounds containing benzene ring(s) against the mPGES-1 3D model yielded 19-"seed-compounds" within high binding scores. A selected chemical compound library (1596 compounds) was created based on the structural similarities of the 19 seed compounds for HTS. Using a stable cell line expressing COX-2-10aa-mPGES-1 and the stable substrate, AA, we obtained the 15 lead compounds with high hit rate (6%) inhibiting PGE_2 produced by COX-2-10aa-mPGES-1 cell. All lead compounds were subjected to more specific AA-metabolite profile analysis using ^{14}C-labeled AA. The specific inhibition of the mPGES-1 in producing PGE_2 was observed. The lead compounds significantly inhibited PC-3 migration as comparted to control cells. The study has demonstrated that the use of the hybrid enzyme, COX-2-10aa-mPGES-1, has allowed a more reliable and specific screening assay for finding lead compounds targeting mPGES-1. It will have a great impact on the discovery of more specific NSAIDs targeting inflammatory mPGES-1 to fundamentally overcome the side effects of COX-2 inhibitors.



A protomol of mPGES-1



COX-2-10aa-mPGES-1

O3– Graduate Student, Podium

DESIGN, SYNTHESIS, BIOLOGICAL EVALUATION, AND METABOLIC STABILITY ENHANCEMENT OF THE DUAL SIGMA RECEPTOR ANTAGONIST DAT INHIBITOR AGENTS AS POTENTIAL TREATMENT FOR STIMULANT ABUSE

Walid Alsharif[1], Theresa Kopajtic[2], Murugesh Kandasamy[1], Bonnie A. Avery[1], Takato Hiranita[2], Jonathan L. Katz[2] and Christopher R. McCurdy[1]

[1]University of Mississippi School of Pharmacy; [2]NIDA Intramural Research Program.

Cocaine addiction and abuse are one of the most complex public health issues and concerns that cause significant morbidity and mortality worldwide. Cocaine abuse and addiction are associated with a serious health problems and complications such as heart diseases, neurological, and psychological disorders. Furthermore, cocaine abuse and addiction have been associated with an increase in the risk of HIV, hepatitis B and C, and socials problems, such as violence and crimes. Cocaine is a stimulant that causes an increase in dopaminergic neurotransmission accumulation in the brain, particularly in the ventral portion of striatum by its ability to bind with high affinity to the dopamine transporters (DAT). Cocaine also binds to sigma-1 receptors, and several studies have suggested interactions between sigma-1 receptors and dopamine systems in which cocaine appears to act predominantly to produce its behavioral effects. To date, there are no effective therapies available to treat cocaine abuse and addiction and there are no approved medications for treatment such illness. Therefore, development an effective treatment for cocaine abuse and addiction is necessary to reduce the associated morbidity and mortality, and most importantly, to reduce the impact of these disorders on the individual and society. In the search for an effective drug for the treatment of cocaine abuse and addiction, and based on our previous work on CM699 that showed high affinity for sigma-1 and DAT, and its ability to attenuate the cocaine self-administration. We have found that stimulant self-administration (cocaine or methamphetamine) was blocked by dual inhibition of the DAT and σRs. Furthermore, immunoprecipitattion studies indicated that CM699 blocked the (+)- pentazocine induced dissociation of σRs from BiP, and indication of antagonist effects. However, CM699 had a short half lives in Human and Rat liver microsomes assays (*in vitro*), 12.7 and 4.4 min respectively, and about 4.4 hr in rat *in vivo* assay. Although CM699 had a half-life of 4.4 hr in rat, a compound with utility as a treatment for stimulant abuse will need a longer half-life, achieved either by structural change or by formulation. In this regard, we have decided to make more analogs of CM699 in order to enhance blockade of cocaine self-administration and metabolic stability. The CM699 derivatives were synthesized and their affinities toward sigma receptors and dopamine transporter measured using radioligand binding assays. Among the tested compounds, WA378 had affinities of 5.70, 0.967, and 203 nM at σ1Rs, σ2Rs and DAT, respectively, while CM699 had affinities of 14.0, 2.30 and 318 nM at the same respective sites. These compounds were also screened for their stability in liver microsome assays. All analogs showed superior metabolic stability to CM699. These results suggest that WA378 may be useful as a pharmacological tool in developing new treatments for stimulant abuse (cocaine or methamphetamine), and this novel approach could be a turning point in the development of medications to treat drug addiction.

O4– Graduate Student, Podium

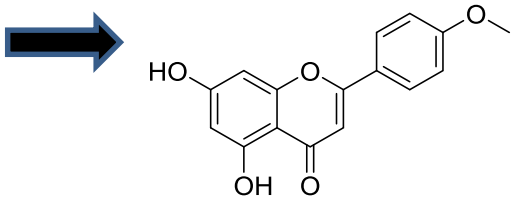
IDENTIFICATION AND EVALUATION OF POTENT INHIBITOR OF HUMAN MONOAMINE OXIDASE B FROM *CALEA URTICIFOLIA*

Vedanjali Gogineni[1], Narayan D Chaurasiya[2], Francisco Leon[1], Marvin J Nuñez[3], Larry A Walker[1,2], Babu L Tekwani[1,2] and Stephen J. Cutler[1]

[1]Department of BioMolecular Sciences and [2]National Center for Natural Products Research, (RIPS) School of Pharmacy, The University of Mississippi, University, MS 38677, USA and [3]Laboratorio de Investigacion en Productos Naturales, Facultad de Quimica y Farmacia, Av. Heroes y Martires del 30 de Julio, San Salvador, El Salvador.

Calea urticifolia, commonly known as "juanislama", belongs to the family Compositae and has long been used in folk medicine for the treatment of gastric ulcers as well as a tropical bacteriocide in El Salvador. *C. urticifolia* is known to contain sesquiterpene lactones, principally germacranolides and flavonoids, isoeugenol and phloroglucinol derivatives. The germacranolides are known to possess antibacterial, antitumorogenic, antifungal and cytotoxic properties.[1] Based on the monoamine oxidase (MAO-A and -B) inhibitory assay results, we found that the chloroform extract of *C. urticifolia* showed inhibition of human MAO-A and MAO-B with IC_{50}'s of 2.491 and 1.857 µg/mL for MAO-A and MAO-B, respectively. Further fractionation of *C. urticifolia* showed that the 3:2 ethyl acetate : hexane fraction showed the highest inhibitory activity against MAO-A and –B followed by bioassay-guided fractionation that resulted in the isolation of the flavonoid, acacetin (**1**), which showed inhibition of MAO-A and -B with IC_{50}'s of 0.121 and 0.049 µM, respectively, using phenelzine as a positive control. The docking calculation was conducted to explore the binding mode of the compound with MAO-A and B.

C. urticifolia



(**1**)

Acknowledgement: This work was supported by NIH - National Institute of General Medical Sciences P20GM104932 (COBRE-In Vitro Research Core).

References. [1] Yamada, M.; Matsuura, N.; Suzuki, H.; Kurosaka, C.; Hasegawa, N.; Ubukata, M.; Tanaka, T.; Iinuma, M., Germacranolides from *Calea urticifolia*. *Phytochemistry* **2004,** *65* (23), 3107-3111.

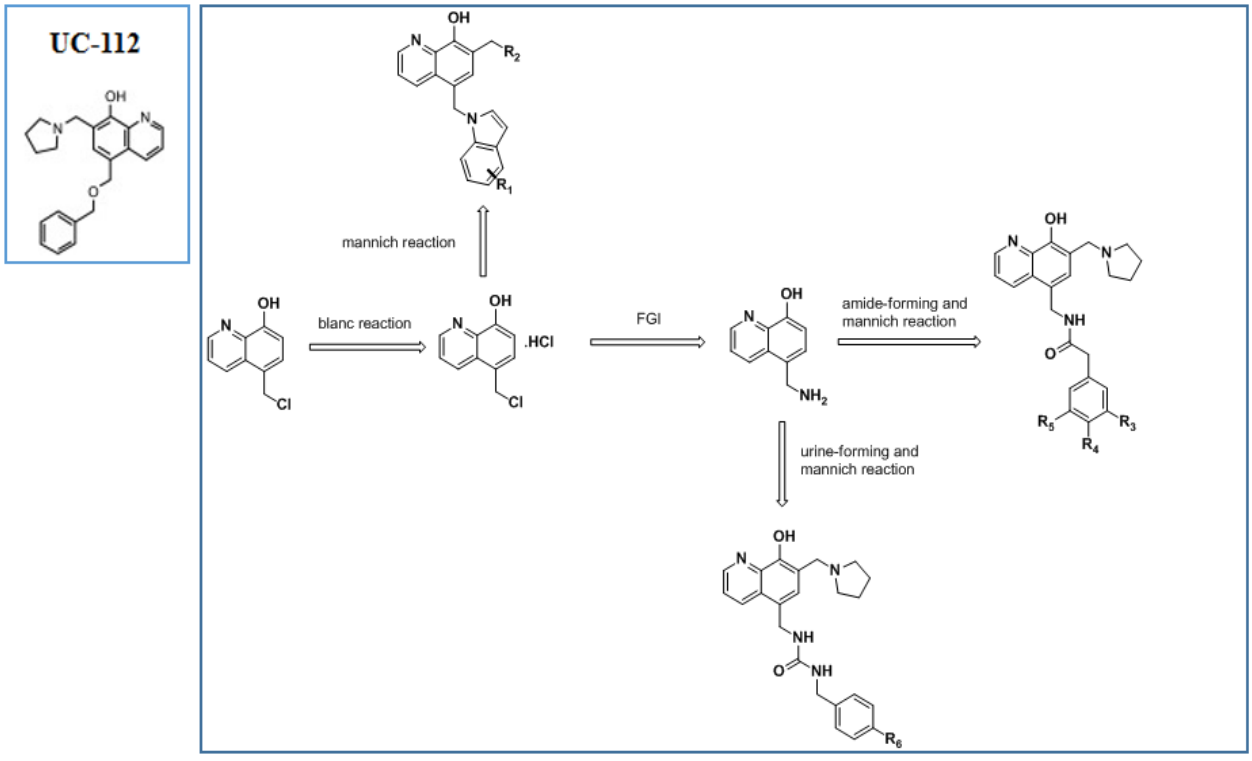
O5– Graduate Student, Podium

SMALL-MOLECULE ANALOGS OF A POTENT SMAC-MIMETIC THAT TARGETS SURVIVIN AND INDUCES APOPTOSIS *IN VITRO*

Kinsie Arnst, Qinghui Wang, Wei Li*

Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, Tennessee 38163

Survivin is an inhibitor of apoptosis (IAP) protein that is up-regulated in many tumor types and undetectable in most adult differentiated cells, making it an attractive target for anticancer therapy. Our laboratory has previously performed a shape-based virtual screening against a drug-like compound library and identified a novel hit compound, UC-112, that mimics the IAP-binding motif of SMAC, an endogenous apoptotic protein. Furthermore, it demonstrated potent apoptotic activation, down-regulation of survivin, and tumor inhibition. From this scaffold, we have synthesized a series of compounds to selectively target survivin and restore apoptosis *in vitro*. Herein, we report the schematic synthesis of UC-112 analogs as well as the biological data validating the potency and cytotoxicity against several metastatic cancer cell lines. Additionally, we confirm the down-regulation of survivin as a result of drug treatment.



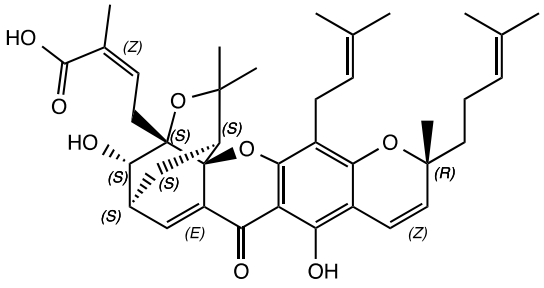
O6– Graduate Student, Podium

IDENTIFICATION AND CHARACTERIZATION OF ALLOSTERIC SITE(S) FOR CB2 NEGATIVE ALLOSTERIC MODULATORS (NAMS)

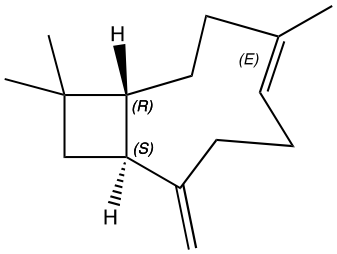
Pankaj Pandey, Kuldeep K. Roy, and Robert J. Doerksen*

Division of Medicinal Chemistry, Department of BioMolecular Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA

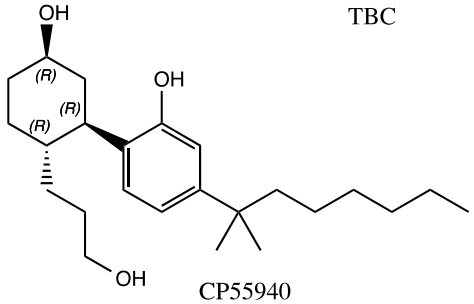
The cannabinoid receptor type 2 (CB2) is a class-A G-protein coupled receptor. Selective CB2 agonism (relative to CB1) is a preferred therapeutic approach to avoid CB1-mediated psychoactive adverse-effects. Allosteric modulators (AMs) exhibit distinct therapeutic advantages over orthosteric modulators in terms of enhanced target specificity and reduced or null off-target side-effects. To date, only a few AMs of the CB2 receptor have been identified with micromolar activity, and there is not sufficient knowledge of the allosteric site(s) within the CB2 receptor to allow efficient targeting and aid the search for new potent AMs. Therefore, our aim is to identify and characterize the allosteric binding site(s) of known negative AMs (NAMs) of CB2, Dihydrogambogic acid (DHGA) and trans-β-caryophyllene (TBC), and to characterize their potential modes of interaction with the CB2 receptor. We used a computational molecular modeling approach first to map allosteric sites using a CB2 receptor model complexed with the well-known orthosteric ligand CP55940 within the orthosteric site. Then, we performed Glide docking of multiple conformers of DHGA and TBC into the five predicted binding sites within the CB2 receptor. Each of the two top-ranked protein-ligand complexes, CB2–DHGA–CP55940 and CB2–TBC–CP55940, were then separately embedded into a hydrated lipid bilayer system and subjected to 100 ns molecular dynamics simulation using the NAMD program. Key results and insights will be presented, which could further be used to guide the design and synthesis of novel high affinity and selective NAMs of the CB2 receptor.



DHGA (S-isomer)



TBC



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O7– Graduate Student, Podium

SELECTIVE STABILIZATION OF THE KRAS G-QUADRUPLEX: A NOVEL THERAPEUTIC TARGET

Rhianna K. Morgan[1], Khondaker Miraz Rahman[2], and Tracy A. Brooks[1]

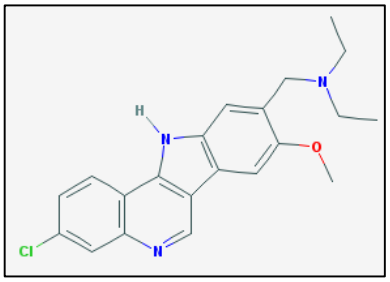
[1]Department of BioMolecular Sciences, Division of Pharmacology, School of Pharmacy, University of Mississippi, University, MS 38677; [2]Institute of Pharmaceutical Sciences, King's College, London, England, United Kingdom

Pancreatic cancer rates have increased over the past decade. Over 60% of pancreatic cancers harbor mutations in the kRAS oncogene. Mutant kRAS results in constitutive activity, enabling continuous cell proliferation to occur, which is a fundamental hallmark of cancer. Targeting kRAS activity or expression are a validated therapeutic approaches in mutant kRAS expressing tumors; transcriptional silencing would cause selective apoptosis in kRAS-addicted cells.

This study focuses on the formation of secondary DNA structures within the promoter region of this oncogene and the search to identify selective stabilizing agents. The kRAS promoter has three distinct guanine-rich regions (near, mid, and far) capable of forming higher order G-quadruplexes (G4s). These important structures, and particular that within the mid-region, have transcriptional silencing potential that is strengthened in the presence of selective G4-stabilizing small molecules.

Over 1,600 compounds have been screened from our collaborator and the NCI Diversity Set II by the Förster Resonance Energy Transfer (FRET) melt assay and confirmed by electronic circular dichroism (ECD) for their stabilization potential. All validated pharmacophores that selectively stabilize the mid-G4 were then tested for kRAS promoter activity via the Dual-Reporter Luciferase assay. From the NCI Diversity Set II, compound NSC 317605 increased thermodynamic stability of the mid-G4 by approximately 18 degrees and significantly down-regulated kRAS promoter activity. From the KN-series of compounds, several showed high thermodynamic stability with a corresponding suppression of promoter activity.

The search for selective stabilizing molecules of the mid-G4 resulted in five agents that strengthen structure stability and suppress kRAS transcription. Future studies will include qPCR to examine kRAS gene fold expression, and eventually these compounds can be examined in vivo by looking at kRAS mutated pancreatic cancer in Zebrafish. This work emphasizes the potential of the G4 within the kRAS promoter as a novel therapeutic target for pancreatic cancer.



NSC-317605

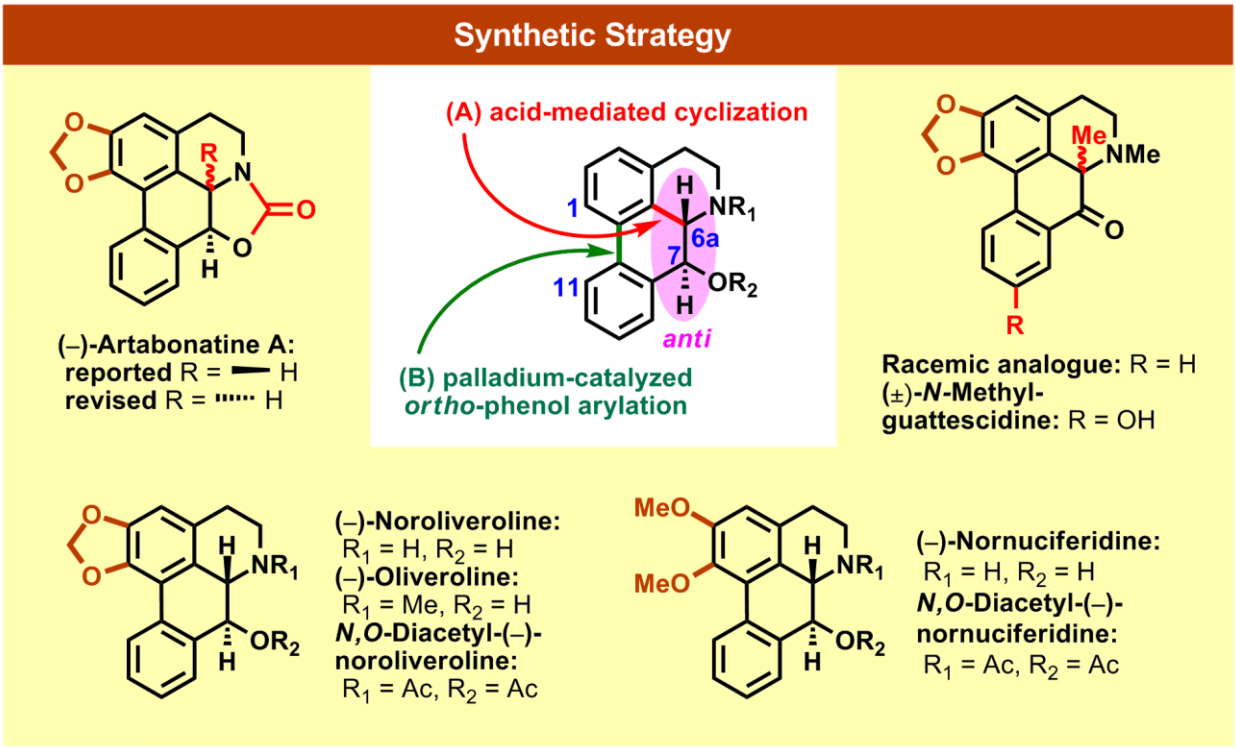
O8– Graduate Student, Podium

SYNTHETIC STUDIES OF 7-OXYGENATED APORPHINE ALKALOIDS AND STRUCTURAL REVISION OF (–)-ARTABONATINE A

Angela F. Ku[1] and Gregory D. Cuny[2]*

[1]*Department of Chemistry and*[2]*Department of Pharmacological and Pharmaceutical Sciences, University of Houston, 77204*

Aporphine alkaloids are a privileged scaffold as GPCRs and monoamine transporter ligands. A series of 7-oxygenated aporphine alkaloids possessing *anti*-configuration between protons 6a and 7 have been identified in nature, but their pharmacology has not been extensively studied. In order to explore their bioactivities, a synthesis was established by utilizing a diastereoselective one-pot reductive acid-mediated cyclization followed by palladium-catalyzed *ortho*-arylations. Moderate catalyst loading (10 mol %) and short reaction times (30 min) were sufficient for the XPhos precatalyst to mediate the arylations in excellent yields. Five alkaloids in the families of noroliveroline and nornuciferidine were successfully prepared. However, the configuration of the natural product (–)-artabonatine A was revised from *anti* to *syn* based on comparison of NMR spectral data and specific rotations. In addition, (±)-artabonatine A and *anti*-(±)-artabonatine A demonstrated different *in vitro* pharmacological activities highlighting the benefit of preparing natural products and non-natural isomers.



O9– Graduate Student, Podium

OLEANOLIC ACID ACRYLATE ELICITS ANTIDEPRESSANT-LIKE EFFECT MEDIATED BY 5-HT$_{1A}$ RECEPTOR

Fajemiroye O. James[1,2], Prabhakar R. Polepally[2], Jordan K. Zjawiony[2], Costa E. Alves[1]

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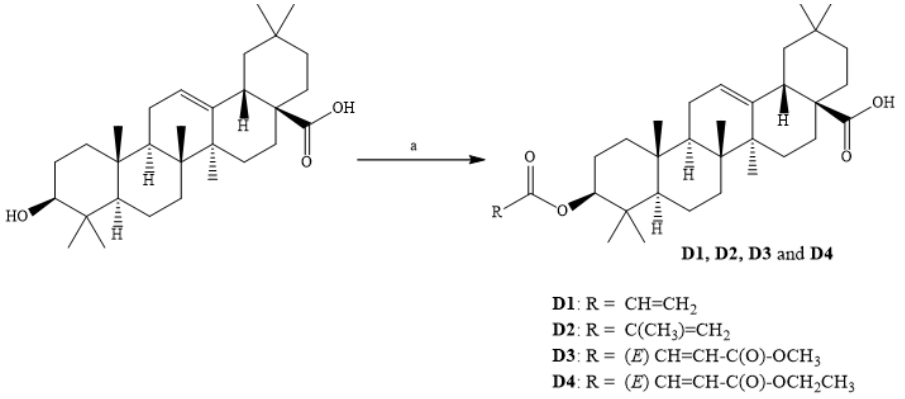
As the search for new drugs for the treatment of depression continues gaining attention, this study evaluates antidepressant-like effect and neural mechanisms of four oleanolic acid derivatives i.e. acrylate (D1), methacrylate (D2), methyl fumarate (D3) and ethyl fumarate (D4).



Scheme: Reagents and conditions (a) appropriate acyl chloride Et_3N, dry DCM N_2, rt, 4 h

All derivatives were obtained by simple one-step esterification of oleanolic acid prior to pharmacological screening in the forced swimming (FS) and open field (OF) tests. Pharmacological tools like α-methyl-*p*-tyrosine (AMPT, catecholamine depletor), *p*-chlorophenylalanine (serotonin depletor), prazosin (PRAZ, selective α1-receptor antagonist), WAY-100635 (selective serotonin 5-HT1A receptor antagonist) as well as monoamine oxidase (MAO) and functional binding assays were conducted to investigate possible neural mechanisms. In the FS test, D1 showed the most promising antidepressant-like effect without eliciting locomotor incoordination. Unlike group of mice pretreated with AMPT 100 mg/kg, PCPA 100 mg/kg or PRAZ 1 mg/kg, the effect of D1 was attenuated by WAY-100635 0.3 mg/kg pretreatment. D1 demonstrated moderate inhibition of MAO-A (IC_{50} = 48.848 ± 1.935 μM), potency (pEC_{50} = 6.1 ± 0.1) and intrinsic activity (E_{max} = 26 ± 2.0 %) on 5-HT$_{1A}$ receptor. In conclusion, our findings showed antidepressant-like effect of D1 and possible involvement of 5-HT$_{1A}$ receptor.

O10– Graduate Student, Podium

CD2 PROTEIN DERIVED MINI-PROTEINS (CYCLOTIDES) FOR MODULATION OF CD2-CD58 PROTEIN-PROTEIN INTERACTION: IMPLICATIONS IN AN AUTOIMMUNE DISEASE

Rushikesh Sable[1], Thomas Durek[2], David Craik[2] and Seetharama Jois[1]

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Modulation in CD2-CD58 protein-protein interaction can be helpful to prevent progression of Rheumatoid Arthritic condition. The goal of this project is to design and characterize stable, small CD2 protein derived peptide molecules that are grafted onto cyclotide molecules. Previously established cyclic peptide sequences were used here to design the grafted sequences. Cyclotide grafting strategy imparts exceptional thermal and enzymatic stability to the peptides. Five different grafted sequences designed using YASARA molecular modeling software. The specific aims of the project were: a) to design peptides by grafting onto the cyclotide molecules b) to evaluate the cell adhesion interaction inhibition activity of cyclotides and c) to elucidate the stability profile of a grafted cyclotide molecule.

A lymphocyte-epithelial cell adhesion assay was used to evaluate protein-protein interaction inhibition activity. For the determination of serum stability of designed molecules was incubated in human serum for 72 hours and for thermal stability assessment the change in ellipticity (Circular Dichroism) data used after gradual increase in cyclotide temperature from 25 to 85 °C. Flow cytometry and SPR techniques were used to confirm the binding specificity of designed molecules to CD58 protein. Virtual binding of these designed molecules to the CD58 and CD48 (protein present in rodents having 60% homology to CD58) protein structures were studied by docking with the use of AutoDock software.

Among five different grafted cyclotides, SFTI 1-1 showed promising cell adhesion inhibitory activity (IC_{50} ~ 100 nM). Binding specificity of SFTI1-1 was also reflected in the results of flow cytometry and SPR assays. It also demonstrated good serum and thermal stability. Results of docking showed SFTI1-1 binding to the CD58 and CD48 proteins with relatively low docking energy.

O11– Graduate Student, Podium

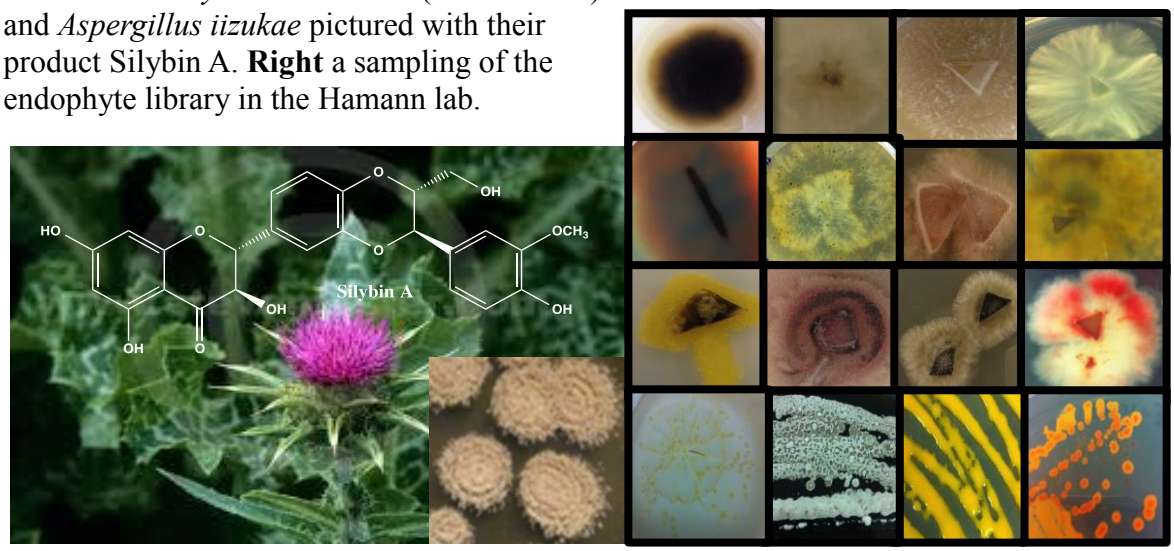
THE PRODUCTION OF NOVEL DRUG COMPOUNDS THROUGH THE SYMBIOSIS BETWEEN ENDANGERED PLANTS AND ENDOPHYTES

Jordanne Fletcher, Mark T. Hamann

Department of Biomolecular Sciences, Division of Pharmacognosy University of Mississippi, 38677

Endophytes are microbes that coexist within an organism in a symbiotically. The host offers a suitable habitat and in return many endophytes will produce unique secondary metabolites that act to support or defend the host in a fashion similar to the immune system including the well-known examples of taxol and podophyllotoxin among numerous additional compounds. Studies have increasingly shown many secondary metabolites of interest are produced by an interaction of the biosynthetic pathways of the endophyte coupled to the biosynthetic pathways of the host, such as silyban A and maytansine. While many sources of endophytes have been examined to date, rare and endangered plant species and their endophytes are currently an untapped resource for potentially interesting and innovative compounds.

Below is the *Silybum marianum* (Milk Thistle) and *Aspergillus iizukae* pictured with their product Silybin A. **Right** a sampling of the endophyte library in the Hamann lab.



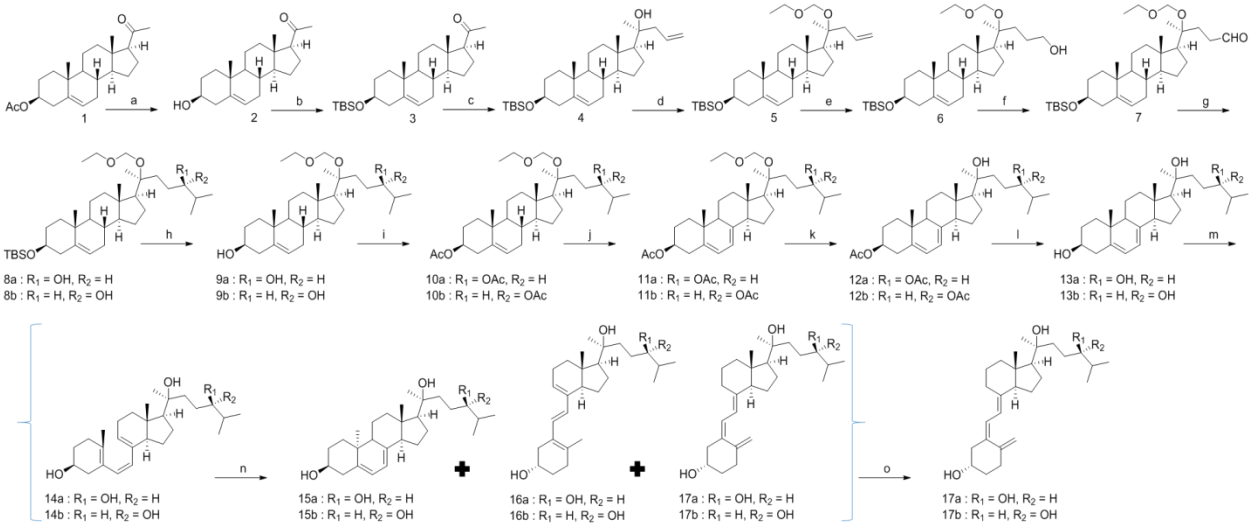
O12– Graduate Student, Podium

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 20(S),24(S AND R)-DIHYDROXYVITAMIN D3 ISOMERS

Zongtao Lin[1], Srinivasa Reddy Marepally[1], Dejian Ma[1], Linda K. Myers[1], Arnie E. Postlethwaite[2,3], Robert C. Tuckey[4], Duane D. Miller[1], Wei Li[1]*

[1]Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN 38163, United States .[2]Department of Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, United States. [3]Department of Veterans Affairs Medical Center, Memphis TN 38104, United States. [4]School of Chemistry and Biochemistry, University of Western Australia, Crawley, Perth, WA 6009, Australia.

Vitamin D3 can be metabolized by CYP11A1 (P450scc) to produce 20S-hydroxyvitamin D3 [20S(OH)D3] as a major product, which can be further hydroxylated into 20S,24-dihydroxyvitamin D3 isomers by CYP24A1 in our previous studies. However, the limited amount of both enzymatic isomers hindered the determination of their absolute configurations at C24, and further impeded investigations of their biological activities. In this study, 20(S),24(S)-dihydroxyvitamin D3 [20S,24S(OH)2D3] and 20(S),24(R)-dihydroxyvitamin D3 [20S,24R(OH)2D3] were both chemically synthesized, separated by preparative HPLC, characterized by NMR, and confirmed to be identical to enzymatically generated counterparts. A biological comparison of them together with their 1α-OH derivatives displayed that they possess different behaviors in vitamin D receptor (VDR) activation and anti-inflammation activity, as well as metabolism kinetics against CYP27B1.



[a]Reagents and conditions: (a) aq. KOH, MeOH, r.t., 2 h. 95%. (b) TBSCl, imidazole, DMF, r.t., overnight. 90%. (c) Allylmagnesium bromide, THF, 0 ºC - r.t., overnight. 82%. (d) EOMCl, DIPEA, CH_2Cl_2, r.t., overnight. 89%. (e) 9-BBN, THF, 0 ºC - r.t., 24 h; H_2O, r.t., 0.5 h; NaOH, H_2O_2, -20 ºC - r.t., overnight. 76%. (f) PDC, CH_2Cl_2, r.t., 24 h. 94%. (g) Isopropylmagnesium bromide, THF, 0 ºC - r.t., 6 h. 85%. (h) TBAF, THF, r.t., 12 h. 100%. (i) Ac_2O, pyridine, DMAP, 6 h. 91%. (j) Dibromantin, AIBN, Benzene: Hexane (1:1), reflux 20 min; TBAB, THF, r.t., 75 min, then TBAF, r.t., 50 min. 44%. (k) CSA, MeOH:DCM (1:1), 0 ºC - r.t., 12 h. 30% (61% recovered). (l) aq. KOH, MeOH, 2 h. 90%. (m) UVB, Et_2O, 15 min. (n) Ethanol, reflux, 3 h. (o) HPLC, ACN:H_2O. 13% (steps m, n and o). Overall yield 1.6%.

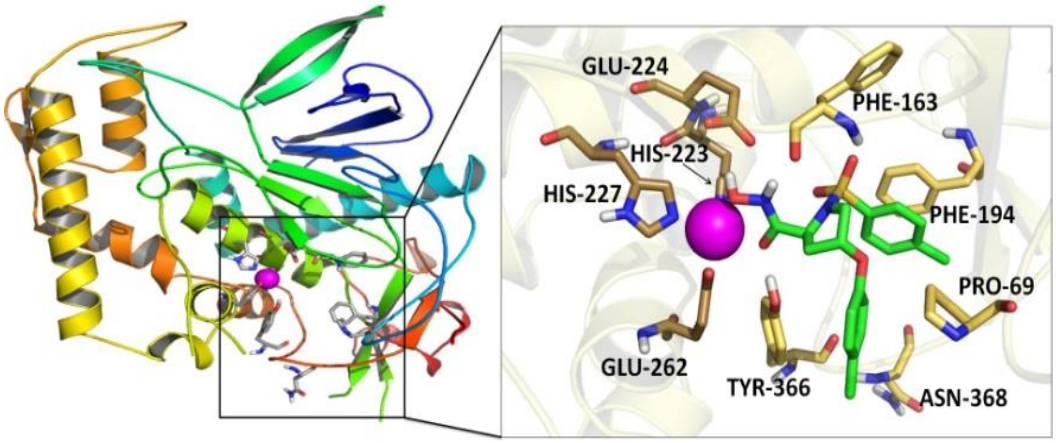
O13– Graduate Student, Podium

IDENTIFICATION OF NOVEL INHIBITORS OF BOTULINUM NEUROTOXIN A

Chinni Yalamanchili[1,2], Vamshi K. Manda[1], Amar G. Chittiboyina[1], William A. Harrell Jr[3], Robert P. Webb[3], and Ikhlas A. Khan[1,2,4*]

[1]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, The University of Mississippi, University, MS 38677, USA. [2]Divison of Pharmacognosy, Department of BioMolecular Sciences, The University of Mississippi, University, MS 38677, USA. [3]US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21702-5011, USA. [4]Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Botulinum neurotoxins (BoNTs), classified as class A bioterror agents are the most potent known toxins and are the causative agents of botulism. Current, post-exposure treatment using antitoxins is ineffective to treat the already neuron internalized toxin. Our aim is to find novel small-molecule 'phytochemical' inhibitors of BoNT serotype A (BONT A). Our approach comprises of three stages: selection of plants, *in silico* screening, and testing using bioassays. Fifteen plants were selected from 'traditional medicine' based on symptoms similar to botulism. Around 850 phytochemicals from these fifteen plants were virtually screened *in silico* in the reported BoNT A-inhibitor crystal structures. From the *in silico* output, top 50 compounds were selected based on their docking scores, visual inspection and structural diversity. These compounds were screened *in vitro* by HPLC-based BoNT A Light Chain protease bioassay. Based on the *in vitro* results, seven compounds were further screened using the mouse phrenic nerve-hemidiaphragm *ex vivo* assay (MPNHDA). At 20 μM, NPC-ACA-3 showed marginal protection by inhibiting the loss of twitch tension in the mouse hemidiaphragm in the presence of BoNT A. The details of the workflow along with the *in vitro* and *ex vivo* data will be presented.



O14– Graduate Student, Podium

DISCOVERY OF NOVEL SURVIVIN INHIBITORS WITH POTENT ANTIPROLIFERATIVE PROPERTIES

Min Xiao, Jin Wang, Yan Lu, Duane. D. Miller, and Wei Li

Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, Tennessee, 38163

The anti-apoptotic protein survivin is highly expressed in most human cancer cells, but has very low expression in normal differentiated cells. Survivin promotes cell proliferation, inhibits apoptosis, facilitates angiogenesis in tumors, and its expression has been shown to strongly correlate with multiple mechanisms of drug resistance. Thus survivin is considered as an attractive cancer drug target. A series of novel survivin inhibitors based on the oxyquinoline scaffold from our recently identified hit compound UC-112 were designed and synthesized. These new analogs were tested against a panel of cancer cell lines including one with multidrug-resistant phenotype. Several new UC-112 analogs showed IC_{50} values in the nanomolar range in anti-proliferative assays. The best three compounds among them along with UC-112 were submitted for NCI-60 cancer cell line screening. The results indicated that structural modification from UC-112 to our best compound **4g** has improved activity by four folds (2.2 μM for UC-112 vs. 0.5 μM for **4g**, average GI_{50} values over all cancer cell lines in the NCI-60 panel). Mechanism of action studies using western blot analyses and drug affinity responsive target stability assay validated survivin as the target of our new compounds. This novel scaffold is promising for the development of selective survivin inhibitors as potential anticancer agents.

O15– Graduate Student, Podium

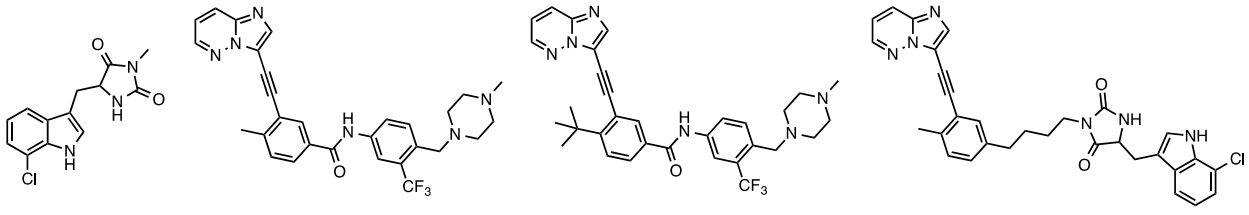
STRUCTURE-BASED DESIGN OF POTENT AND SELECTIVE DLG-OUT RIPK1 INHIBITORS

Chalada Suebsuwong[1], Malek Najjar[2], Soumya S. Ray[3], Roshan J. Thapa[4], Jenny L. Maki[5], Shoko Nogusa[4], Saumil Shah[5], Danish Saleh[5], Peter J. Gough[6], John Bertin[6], Junying Yuan[7], Siddharth Balachandran[4], Gregory D. Cuny[8], and Alexei Degterev[2,5]

[1]Department of Chemistry, University of Houston, 77204 [2]Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 02111 [3]Department of Neurology, Brigham & Women's Hospital and Harvard Medical School, 02139 [4]Immune Cell Development and Host Defense Program, Fox Chase Cancer Center, 19111 [5]Department of Developmental, Molecular & Chemical Biology, Tufts University School of Medicine, 02111 [6]Pattern Recognition Receptor Discovery Performance Unit, Immuno-Inflammation Therapeutic Area, GlaxoSmithKline, 19426 [7]Department of Cell Biology, Harvard Medical School, 02115 [8]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, 77204

Receptor Interacting Protein Kinases (RIPKs) are a group of serine (Ser)/threonine (Thr) kinase which play important roles in inflammation, immune responses and death-inducing processes. RIPK1 has been shown to be a key mediator for regulated necrosis (e.g. necroptosis), which is involved in many pathological conditions including cerebral and retinal ischemia, myocardial infarction, and other ischemic-reperfusion injuries. Previously reported RIPK1 inhibitors, e.g. necrostatin-1 (Nec-1), are known to be type III kinase inhibitors that bind to an allosteric pocket stabilizing a DLG-out/Glu-out conformation that results in excellent kinase selectivity. However, the optimized Nec-1 analog, 7-Cl-O-Nec-1, has only moderate cellular potency (IC_{50} = 210 nM for blocking TNF-α induced cell death in FADD-deficient Jurkat cells).

Type II kinase inhibitors have additional interactions with the hinge binding region of the protein kinase resulting in increased potency relative to type III inhibitors. Ponatinib, a type II kinase inhibitor previously developed to block Abl kinase, was also identified to be a potent RIPK1 inhibitor (cellular IC_{50} = 34 nM). A new class of RIPK1 inhibitors has been designed based on the ponatinib scaffold by utilizing structural differences around the gatekeeper residue of Abl (Thr315) and RIPK1 (Met92), and interaction between Lys and Glu residues (RIPK1: Lys45-Glu63, Abl: Lys271-Glu286) in the αC-Glu-out conformation. In this study, we discovered selective RIPK1 inhibitor analogs of ponatinib (e.g. CS6, *in vitro* IC_{50} = 26 nM) versus Abl (CS6, *in vitro* IC_{50} = 34000 nM). In addition, a necrostatin-ponatinib hybrid (e.g. PN10) shows better RIPK1 cellular activity (IC_{50} = 10 nM) than either 7-Cl-O-Nec-1 (~20-fold) or ponatinib (~3-fold).



O16– Graduate Student, Podium

PROGRESS TOWARD THE TOTAL SYNTHESIS OF A DISCORHABDIN RELATED NATURAL PRODUCT FOR THE CONTROL OF PANCREATIC CANCER

Xiaojuan Wang and Mark T. Hamann

Department of Biomolecular Sciences, University of Mississippi, University, MS 38677, USA.

Pancreatic cancer arises when cells in the pancreas, begin to multiply out of control and form a mass. In 2014, an estimated 46,000 people in the US are expected to be diagnosed with pancreatic cancer and 40,000 to die of it. Pancreatic cancer the fourth highest cause of death from cancer worldwide. Deaths from pancreatic cancer have changed little over time. The available drugs for the control of pancreatic cancer include four first-line drugs approved for the treatment of pancreatic cancer: fluorouracil, erlotinib hydrochloride, gemcitabine hydrochloride, and mitomycin C. While all of these drugs are being used alone and in combination, no one drug or combination of therapies has been shown to drastically increase the median survival rate. Most therapies show only a modest increase in survival measured in weeks or months at best. The outstanding potency and selective inhibition of pancreatic cancer cells *in vitro* makes this class of new discorhabdin related molecules highly promising leads. Here we will present the progress toward the total synthesis and medicinal chemistry studies of this class. The goal is generating a gram of this new class for further bioactivity and toxicity studies.

Poster Presentation Abstracts

P1 – Graduate Student, Poster

SYNTHESIS AND IDENTIFICATION OF SELECTIVE IRREVERSIBLE LIGANDS FOR SIGMA-2 RECEPTORS

Walid Alsharif[a], Anthony Comeau[b], Christophe Mesangeau[a], Wayne D. Bowen[b], and Christopher R. McCurdy*.[a]

[a]*Department of BioMolecular Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677,* [b]*Department of Molecular Pharmacology, Physiology and Biotechnology, Brown University, Providence RI, 02912*

Sigma receptors represent a unique class of receptors. There are two sigma subtypes; sigma-1 and sigma-2 receptors. The sigma-1 receptor is well known because of the receptor sequence information and availability of selective sigma-1 ligands; however, not much is known about sigma-2 receptor due to the unavailability of truly selective sigma-2 ligands. It has been observed that sigma-2 receptors have a 10-fold higher density in proliferating tumor cells than in quiescent tumor cells, and that sigma-2 receptor agonists are capable of killing tumor cells via apoptotic and non-apoptotic mechanisms. This gives sigma-2 ligands possible application as effective agents for the treatment of cancer, and most importantly, finding selective sigma-2 receptor ligands will help in isolation and characterization of this receptor. Selective-irreversible binding of ligands to a protein is one of the most useful approaches to characterize and understand functions associated to that protein. In this regard, we have incorporated an isothiocyanate moiety on our previous selective sigma-2 compounds. The resulting ligands contain an electrophilic center that can bind covalently to a nucleophilic site in the sigma-2 receptor. Among the tested compounds, WA350 and WA352 produced selective irreversible inhibition of sigma-2 binding over sigma-1 binding. Nevertheless, WA350 showed higher potency and selectivity for sigma-2 over sigma-1 than the other compounds irreversibly. Interestingly, WA349 showed an excellent binding affinity toward sigma-2 over sigma-1, and we are currently awaiting the completion of this compounds irreversible binding assays and will include them in publication

P2 – Graduate Student, Poster

THE EFFECT OF MAZ ON KRAS TRANSCRIPTION: A ROLE FOR THE G-QUADRUPLEX

Harshul Batra[1] and Tracy A Brooks[1]

[1]*Department of Biomolecular Sciences, Division of Pharmacology, School of Pharmacy, University of Mississippi, University, MS 38677*

kRAS is a proto-oncogene that is mutated in >30% of all cancers, particularly in 60-90% of pancreatic cancers. It is a GTPase protein affecting normal cell proliferation, division, and apoptosis. Mutated kRAS leads to continuous activity and uncontrolled proliferation. To date there have been no successful clinical agents targeting mutant kRAS activity. Modulating kRAS expression has shown anti-proliferative promise as an approach in pancreatic cancer models, but is not a main avenue of pursuit for clinical development due to lack of a molecular target. Our lab is focused on the regulation of kRAS transcription through a variety of G-rich regions of DNA in the promoter capable of forming non-B-DNA structures termed G-quadruplexes (G4s). In the current study, we sought to determine the effect of the transcription factor MYC-Associated Zinc finger protein (MAZ) on the regulation of kRAS, with a particular focus on the three putative G4-forming regions (herein termed near, mid, and far in reference to their relative proximity to the transcriptional start site). In a study of the kRAS promoter using a series of luciferase plasmids, MAZ expression led to a concentration-dependent decrease in promoter activity. This action was localized to interactions with the mid-G4-forming region. In the context of a more multifaceted intracellular mileau as found in the pancreatic cancer cell lines MiaPaCa-2, Panc-1, BxPc3, and Capan-1 the MAZ overexpression does not alter kRAS transcription until 2000 ng of plasmid is transfected. Further investigation will determine the kRAS promoter region and structural conformation of DNA (single-stranded, double-stranded, or G4-DNA) to which MAZ is binding. Ultimately, an understanding of the regulation of this G-rich region of DNA, by MAZ or any other transcription factors such as Sp1 or p53, is an important part of the larger puzzle leading to a targeted drug discovery program focused on G4-regulation. Ultimately, G4-stabilization-mediated down-regulation of kRAS has high potential for anti-cancer efficacy in pancreatic cancers, where there is a dire need for novel therapeutic development.

P3 – PharmD/Graduate Student, Poster

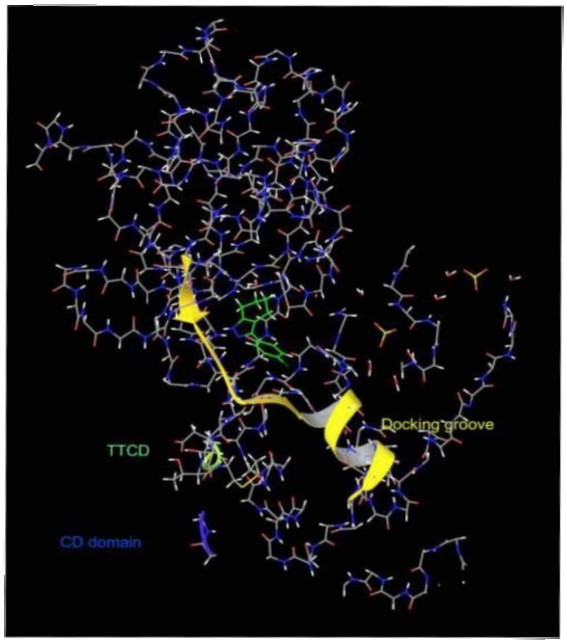
3D ANALYSIS AND SELECTIVE TARGETING OF ERK2/CASPASE-9 INTERACTION FOR THE DEVELOPMENT OF PROBES TO SUPPRESS CASPASE-9 ACTIVATION

Veena Gadepalli, Manal Nael, and Robert J. Doerksen*

Department of BioMolecular Sciences, University of Mississippi School of Pharmacy, University, MS 38677

Caspases are cysteine-dependent, aspartate-specific proteases that, when activated, initiate a pathway that destroys cellular components. Caspase-9, involved in the intrinsic pathway, belongs to the peptidase C14 family and has three major domains: a prodomain containing the caspase activation and recruitment domain (CARD), a large subunit catalytic domain (LSCD), and a small subunit catalytic domain (SSCD). Release of cytochrome c from the mitochondria triggers caspase activation. The MAPK pathway directly controls caspase-9 activation by phosphorylating its Thr125 residue, which inhibits caspase-9 activation, thereby terminating the apoptosis process either reversibly or irreversibly.

The major docking site in caspase-9, called the D domain, that regulates the binding and phosphorylation of caspase-9 at Thr125 by ERK2, is located in the N-terminal prodomain of the caspase, with Arg10 being especially significant. Arg10, Arg11, and other basic residues are exposed on the surface of this domain in caspase-9 and form a highly positively charged path that is available for interaction with other proteins. Also a direct interaction between the D domain of caspase-9 and the TTCD motif in ERK2 (as seen in the Figure, which shows the PDB structure 4G6N of ERK2) has been demonstrated.



We expect that through the development of a small molecule probe that will specifically target the ERK2/caspase-9 interaction, we can circumvent the consequences of ERK2-driven caspase-9 activation while maintaining the general function of both proteins in their independent pathways. Towards this goal, we report on a detailed analysis of the 3D-interaction of ERK2 and the D domain of caspase-9.

Acknowledgement: Financial support for this research was provided by National Science Foundation EPS-0556308, EPS-0903787 and EPS-1006883. This investigation was conducted in a facility constructed with support from research facilities improvement program C06RR14503 from the NIH National Center for Research Resources.

P4 – Graduate Student, Poster

DEVELOPING LINKED NUCLEIC ACID CLAMPS AS NOVEL ANTI-CANCER THERAPEUTICS BY TARGETING G-QUADRUPLEX IN THE PROMOTER OF C-MYC PROTO-ONCOGENE

Taisen Hao[1] and Tracy A. Brooks[1*]

[1*]*Department of Biomolecular Sciences, Division of Pharmacology, School of Pharmacy, The University of Mississippi, University, MS 38677*

The deregulation of c-Myc proto-oncogene is one of the major cancer hallmarks, and its overexpression is spotted in more than 80% of solid tumors. It is essential to silence c-Myc expression in order to regulate the growth of these tumor types. Among all the silencing strategies, targeting and stabilizing G4 structures formed in the guanine-rich nuclease hypersensitivity element III_1 (NHE III_1) region of the promoter, which serves as an on-off switch for c-Myc transcription, has been shown to be a promising strategy. Our central hypothesis is that G4 structure formation within the NHE III_1 region of the c-Myc promoter could be initiated and stabilized through our novel LiNA clamp approach which harbors the potential for both diagnostics and therapeutics. Our purpose is to develop a linked nucleic acid (LiNA) clamp that is able to specifically identify as well stabilizing the predominant G-quadruplex (G4) conformation within the c-Myc promoter. Three clamps (clamp a, clamp b, and clamp c) were designed against unique c-Myc promoter G4 formations. These clamps are less than 25 nucleotides complementing the flanking region of different G4 isoforms connected by a locked linker element. Binding properties and specificity of the clamps, c-myc promoter regulating ability as well as cytotoxicity against MCF-7 breast cancer cells line are confirmed at the moment. With this novel approach, we found the predominant G4 isoform from the possible equilibrating structures, and demonstrated that clamp A specifically detects and stabilizes this transcriptionally silencing G4 structure. These results highlight a non-small molecule mediated approach for the specific binding and stabilizing of the predominant G4 within the c-Myc promoter. Demonstration of our LiNA theory is the basis for developing clamp A as a selective non-small molecule mediated cancer therapy for lymphoma and other c-myc responsible cancers, as well as a diagnostic companion for c-Myc G4 targeted therapeutics of any kind. *Brooks Lab startup funds, University of Mississippi School of Pharmacy.*

P5 – Graduate Student, Poster

INVESTIGATING THE MECHANISM OF PRIMAQUINE-INDUCED HEMOLYTIC TOXICITY WITH NATURAL PRODUCT INHIBITORS OF NRH:QUINONE REDUCTASE 2 (NQO2)

Jagrati Jain[1, 2,] Narayan D Chaurasiya[1], NP Dhammika Nanayakkara[1], James D McChesney[3], Larry A Walker[1, 2] and Babu L Tekwani[1,2]
[1]National Center for Natural Products Research and [2]Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, University MS 38677; [3]Ironstone Separations Inc. Eta, MS

8-Aminoquinolines (8-AQs), including primaquine (PQ), are important class of anti-protozoal drugs, but the utility of this drug class is limited due to hemolytic toxicity in Glucose 6-phosphate dehydrogenase deficient (G6PDd) populations. Metabolites generated through cytochrome P_{450}-dependent pathways appear to be responsible for hemolytic effects of PQ. 5-hydroxy PQ (5-HPQ) is a reactive PQ metabolite and spontaneously converted to 5, 6-orthoquinone (5, 6-OQPQ) and quinone-imine. NRH:Quinone Reductase 2 (NQO2), catalyzes mandatory two-electron reduction of quinones to hydroquinones without accumulating semiquinones and free radicals. Thus, NQO2 seems to be a detoxification enzyme for toxic PQ metabolites. 5, 6-OQPQ produced concentration-dependent methemoglobin accumulation, oxidative stress generation and GSH depletion in normal and G6PDd human erythrocyte. Melatonin (Mel), resveratrol (Res) and quercetin (Quer), selective and potent NQO2 inhibitors were used to investigate mechanism of hemotoxic response of 5, 6-OQPQ. Mel and Quer significantly induced the hemotoxic action of 5, 6-OQPQ as observed with a synergistic increase in methemoglobin accumulation, oxidative stress generation and depletion of reduced glutathione. However, res though produced synergistic increase in methemoglobin accumulation and GSH depletion, but decreased the 5,6-OQPQ induced-oxidative stress, presumably due to its strong antioxidant function. The results indicate a protective role of NQO2 in hemolytic toxicity of PQ. Further studies on interactions of PQ metabolites with NQO2 should help in understanding the mechanism of PQ-induced hemolytic toxicity and development of safer antimalarial 8-AQ analogs.

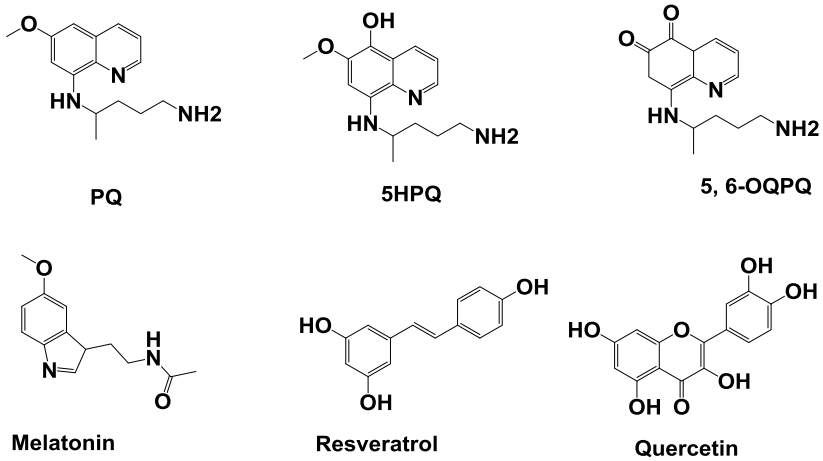


Figure 1: Primaquine (PQ), 5-hydroxyprimaquine (5HPQ), 5, 6-orthoquinone primaquine (5, 6-OQPQ) and natural product inhibitors of NRH:Quinone Reductase 2

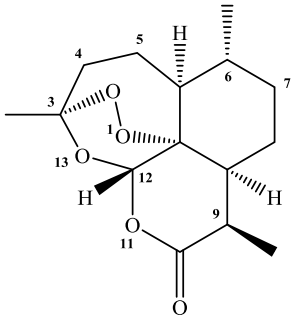
P6 – Graduate Student, Poster

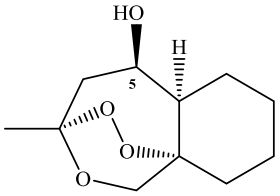
SIMPLIFIED ANALOGUES OF ARTEMISININ (QINGHAOSU)

Mohamed Jihan[1*]; Francisco Leon[1] ; Frank R Fronczek[2] ; John Rimoldi[1] and Mitchell Avery[1]

[1]Department of BioMolecular Science, Division of Medicinal Chemistry, School of Pharmacy, The University of Mississippi, University, MS 38677, and [2]Department of Chemistry, College of Science, Louisiana State University, Baton Rouge, LA 70803

Malaria in humans is a tropical and subtropical disease caused by up to five plasmodial species of parasites that are transmitted by infected anopheles mosquitos. Artemisinin **1** and many of its derivatives are highly effective against the most lethal drug-resistant strain of *Plasmodium falciparum* malaria *in vitro*. *In vivo* activity does not always follow *in vitro* structure-activity relationships (SAR) and it is an important issue in antimalarial drug design. Over the past forty years, SAR of artemisinin and many abbreviated derivatives has encompassed modification at positions 3,6,7,9,10,11 and 13 but notably, the C-4 and C-5 positions have remained synthetically elusive. A synthesis of 5β-hydroxy-D-seco-6- desmethylartemisinin **2** appears to offer an opportunity to explore SAR about the C-5 position. In the work proposed, we set out synthesis of **2** and conduct derivatization chemistry at C-5. In addition, access to C-4 via a C-5 carbonyl is in principle possible. Because the mechanism of action (MOA) appears to be related to a C-4 radical, by Fe(II)-mediated O-1-O-2/C-3-C-4 ring cleavages, logical modifications at C-5 is expected to test the proposed MOA and to provide additional structure activity relationship (SAR) to complement known modifications elsewhere in the backbone of the natural product.

1, Artemisinin 

 **2**

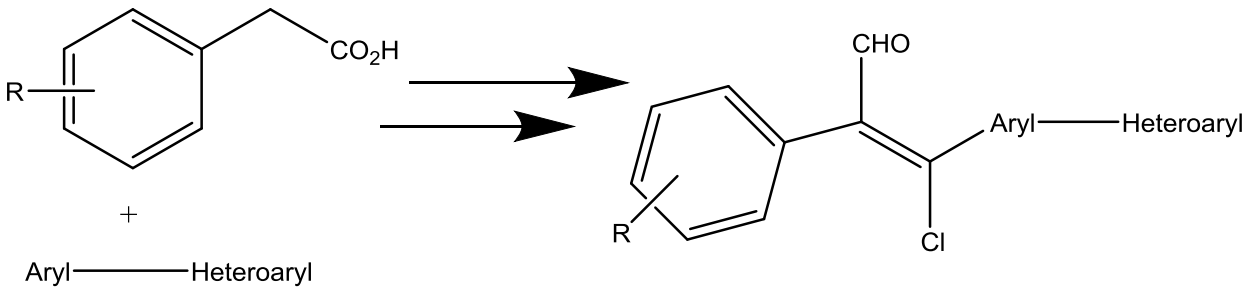
P7 – Undergraduate Student, Poster

SYNTHETIC APPROACHES TOWARDS SELECTED ANALOGUES; ANTI-HIV ACTIVITY IN 2,3-BIS-ARYL-3-CHLOROPROPENALS

Rochelle Joseph[†], Lynsey Carrier[†], Tony L. Perry[†]*

[†] *Department of Chemistry, Grambling State University, Grambling, LA 71245*

Bis-aryls represent a structural motif in both natural products and biologically active compounds. Hetero-aromatic-aromatic analogues of antiviral 2,3-bis-(aryl)-3-chloropropenals have been prepared via coupling of aryl carboxylic acids with hetero-aromatic-aromatic.



P8 – Graduate Student, Poster

DESIGN OF PERIPHERALLY RESTRICTED OPIOID AGONISTS: UTILITY OF METABOLICALLY LABILE STRUCTURES

Adam W. Keasling[1], Lisa L. Wilson[1], Prabhakar R.Polepally[1], Ikhlas A. Khan[3], Jakub Fichna[2], Jordan K. Zjawiony[1]

[1]Department of Biomolecular Sciences, Division of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677, [2] Department of Biochemistry, Faculty of Medicine, Medical University of Lodz, Poland, [3]National Center for Natural Products Research, University of Mississippi, University, MS 38677

Salvinorin A is a potent and selective kappa opioid receptor (KOR) agonist isolated from the leaves of the perceptiotropic mint *Salvia divinorum*. Salvinorin A represents the first known non-nitrogenous kappa opioid receptor agonist. Recent research has shown that incorporating aromatic moieties at the 22-position will induce mu opioid receptor (MOR) affinity while retaining KOR affinity. By utilizing metabolically labile linkages between the 2-position, which is essential for bioactivity, and the 22-position there is the potential to create compounds that peripherally restrict the compounds and limit CNS involvement. Herein, we report representative compounds and discuss a series of *in vivo* assays examining their utility towards models of gastrointestinal hypermotility and abdominal pain (peripheral activities) and lack of significant activity in CNS-mediated behavioral models.

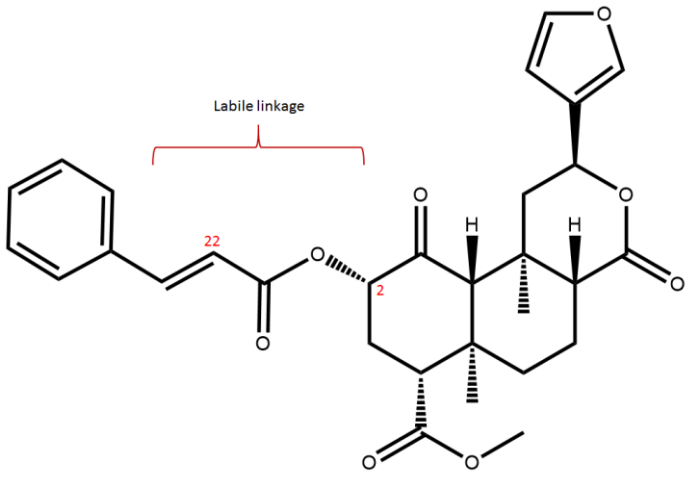


Figure 1. 2-*O*-cinnamoylsalvinorin B, representative example of labile structure.

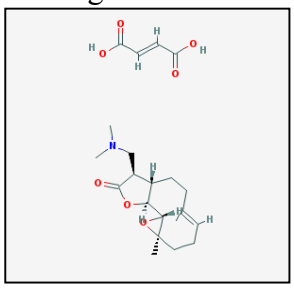
P9 – Graduate Student, Poster

THE STUDY OF INHIBITORY EFFECTS OF DIMETHYLAMINOPARTHENOLIDE AND ACTINOMYCIN-D ON PANC-1 PANCREATIC CANCER CELLS

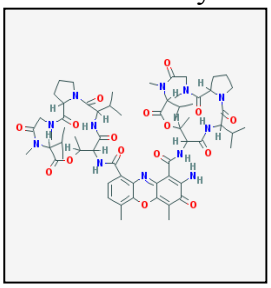
Gauri Lamture[a], Michael J. Borrelli[a,b], Peter A. Crooks[a]*

[a]*Department of Pharmaceutical Sciences* •[b]*Department of Radiology, University of Arkansas for Medical Sciences*

Background and significance:
Pancreatic cancer is the fourth leading cause of death in the US, and has one of the poorest 5 year survival rates of 5%. Its late diagnosis and the stromal barrier which develops around the tumor are reasons for the difficulty in treatment.
A novel anti-cancer drug, Dimethylaminoparthenolide (DMAPT), is the water soluble analogue of Parthenolide. It acts by inhibiting the NFκB pathway and by depleting the amount of glutathione and thus increasing ROS (reactive oxygen species), causing the cells to be more susceptible to oxidative stress induced cell death.
Actinomycin D (ActD) is a polypeptide antibiotic binds to DNA and inhibits RNA and protein synthesis, by inhibiting RNA polymerase II. The JNK pathway is involved in apoptotic cell death and is involved in increasing the expression of pro-apoptotic genes, like TNF. TNF requires ActD for apoptosis and activation of the JNK pathway. ActD is a very potent drug against pancreatic cancer; however, it failed in the clinical trials due to toxicity issues.
Goal and hypothesis:
New methods of drug delivery or new drug molecules, used alone or in combination are needed. We hypothesize that DMAPT and Actinomycin D, in combination, will behave in a synergistic manner and inhibit further cell growth. We know that DMPAT inhibits the NFκB pathway. ActD is known to induce apoptosis via the JNK pathway, which can be inhibited by high levels of NFκB. Thus by blocking NFκB with DMAPT, we avoid the inhibition of JNK of ActD and expect synergism.
Conclusion:
Actinomycin D and DMAPT are both effective anti-cancer agents, against Panc-1 cell growth. The combination shows a higher percentage of cell death than the individual agents with the Live-Dead, Caspase and Colony formation assays. However, the CompuSyn data indicates that there is synergism but with very low levels of inhibition. Also, the JNK pathway assay did not provide positive results suggesting it is not the primary mechanism of synergism. Further investigation of this combination may not be done due to the unfavorable CompuSyn data.



DMAPT



Actinomycin D

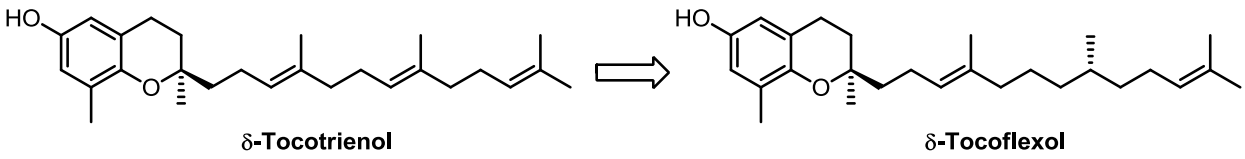
P10 – Graduate Student, Poster

SYNTHESIS OF δ-TOCOFLEXOL, A δ-TOCOTRIENOL ANALOGUE DESIGNED TO HAVE IMPROVED PHARMACOKINETIC PROFILE

Xingui Liu, Lijian Shao, Satheesh Gujarathi, Cesar Compadre, Martin Hauer-Jensen, Peter Crooks, Daohong Zhou, Guangrong Zheng*

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

Two vitamin E constituents, γ-Tocotrienol (GT3) and δ-tocotrienol (DT3), have shown promise as anticancer, neuroprotective, cardioprotective, and radioprotective agents. However, the limited bioavailability and short plasma elimination half-lives of these compounds diminish their potential therapeutic use. One of the reasons for their poor drug-like properties is believed to be their weak binding affinity to α-tocopherol transfer protein (ATTP). ATTP is the protein responsible for transferring the vitamin E compounds out of the liver, where they are subject to metabolism, into the systemic circulation. Thus, through computational modeling, we designed a new class of T3 analogues, named tocoflexols, with potentially increased binding affinity for ATTP. Herein, we report an efficient route for the synthesis of δ-tocoflexol starting from the corresponding DT3, which was obtained from annatto oil.



δ-Tocotrienol **δ-Tocoflexol**

P11 – Graduate Student, Poster

TARGETING PROTEIN KINASE C EPSILON (PKC-E) TO MANAGE ALZHEIMER'S DISEASE

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[1]*Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, MS, USA*

[2]*Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, MS, USA*

In Alzheimer's disease (AD), inhibition of protein kinase C epsilon (PKC-ε) translocation and activation is the result of direct binding of elevated levels of Amyloid Beta (Aβ) peptide to the PKC-ε substrate domain. Decreased PKC-ε activation leads to the following: (1) deactivation of HuD, an mRNA binding protein important in the stability and genetic expression of various mRNAs that play a role in neuronal plasticity of the CNS; (2) decreased mRNA stability of NEP (the major physiological Aβ peptide-degrading enzyme in the brain), allowing Aβ accumulation and disease progression. It was observed in AD transgenic mice that activation of PKC-ε could prevent synaptotoxic Aβ-oligomer elevation, synaptic loss, cognitive deficits, and amyloid plaque formation. Additionally, the treatment of AD mice and an aged rat model with bryostatin 1, a selective PKC-ε activator, which binds to the PKC-ε C1B domain (Figure 1), can dramatically reduce levels of Aβ, regenerate neurotrophic activity and synapses, and improve cognitive function. Furthermore, a severe AD patient who was confirmed to have a known genetic variant of PSEN1 (presenilin 1, a putative genetic marker for AD), showed promising benefits with bryostatin 1 treatment, whereas no other treatment had shown any benefits. Bryostatin's clinical improvements included for word vocalization, directed attentional focus and restoration of swallowing.

This study is aimed to identify new PKC-ε activators through a combined ligand and structure based approaches. We built the 3D model of the PKC-ε C1B domain based on the C1B domain of the human PKC-θ. Then, we defined the possible ligand binding pockets in PKC-ε C1B domain using a geometry-based cavity detection algorithm (fpocket). Two pockets were identified with druggability scores of 0.59 and 0.47 (Figure 1). The FRED exhaustive search docking algorithm was used to explore the binding mode of bryostatin 1, which showed good fitting into both pockets with comparable ChemGauss4 scores (–8.1 and –7.9). We generated drug-like databases of natural products and synthetic compounds to be used in the virtual screening step. We plan to select the best scoring compounds for biological screening.

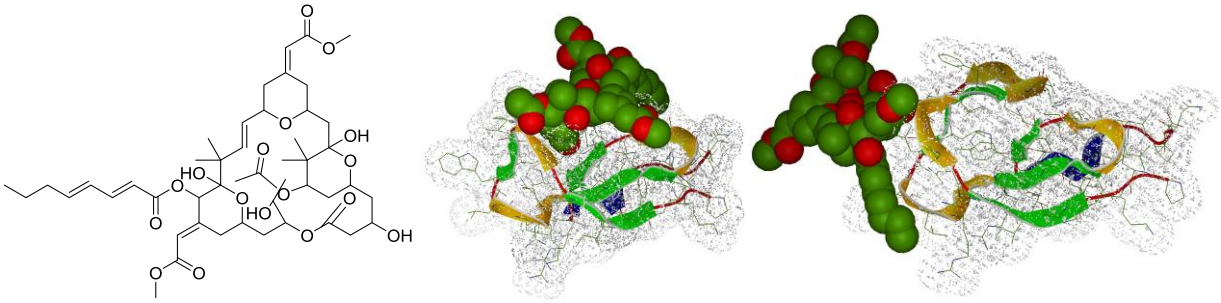


Figure 1. Left, the structure of bryostatin 1. Middle and right, the binding mode of bryostatin 1 (shown as spheres) in the two pockets.

P12 – Graduate Student, Poster

DESIGN OF A DUAL PEPTIDOMIMETIC INHIBITOR THAT INHIBITS EGFR HETERODIMERIZATION

Himgauri Naik, Sandeep Pallerla, Seetharama Jois.

Department of Basic Pharmaceutical Sciences, School of Pharmacy, University of Louisiana at Monroe LA 71201

Deregulation of the signaling pathway via HER2 is known to occur in some tumor cells. The extracellular domain of EGFR consists of four domains, of which domain II and domain IV are known to be involved in the dimerization process. Overexpression of these receptors or upon binding of ligand to these receptors leads to homo-and hetero-dimerization of these receptors. We have designed several peptidomimetic molecules to inhibit the EGFR heterodimerization interaction that have shown antiproliferative activity and specificity for HER2 positive cancer cell lines. One particular peptidomimetic exhibited antiproliferative activity in the lower nanomolar range concentration in HER2 overexpressing lung cancer cell line. To improve the stability of this peptidomimetic we have designed D-amino acid based peptidomimetics and evaluated their antiproliferative activity. To further modify the peptidomimetic, we plan to attach a lipid stearic acid. Using docking studies (AUTODOCK) we have defined the possible binding sites of these peptidomimetics on domain IV of HER2. Results suggested that compounds designed bind to HER2 protein, in particular to domain IV of HER2. Our computational and experimental studies suggest that the designed molecules inhibit HER2:HER3 interaction and can be therapeutically useful for HER2 positive breast and lung cancer. Funding for this research was provided by NIGMS/NIH grant 8P20GM103424.

P13 – Graduate Student, Poster

DESIGN AND SYNTHETIC STUDIES OF SELECTIVE RIP2 KINASE INHIBITORS

Sameer Nikhar,[1] Alexei Degterev[2] and Gregory D. Cuny[1]

[1]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, TX 77204 [2]Department of Developmental, Molecular & Chemical Biology, School of Medicine, Tufts University, Boston, MA 02111

Receptor interacting protein kinase 2 (RIP2), a dual Ser/Thr and Tyr kinase has been shown to play an important role in inflammatory bowel diseases (IBDs), such as Crohn's disease. It is an adaptor protein that undergoes autophosphorylation and subsequent activation after its interaction with NOD2 through its CARD domain. Once activated, it undergoes non-degradative polyubiquitination and subsequent induction of IKK mediated NF-kB activation and results in production of inflammatory cytokines. Earlier studies of RIP2 were based on ATP competitive inhibitors that bind to the ATP binding site of the enzyme. But the recent co-crystal structure of RIP2 in complex with ponatinib showed the presence of allosteric Asp-Phe-Gly (DFG) out binding pocket that is similar to the DLG out form of RIP1.

RIP1 is an isozyme of RIP2 that has been shown to be inhibited by both type II (e.g. ponatinib) and type III inhibitors (e.g. Nec-1). Moreover, a hybrid molecule made by combining Nec-1 and ponatinib showed excellent selectivity and potency against RIP1 as observed from biochemical and cell-based assays. Here, we are going to use a similar strategy for making a library of compounds as potential inhibitors of RIP2 through modification of the R_1 and R_2 positions (Fig 1).

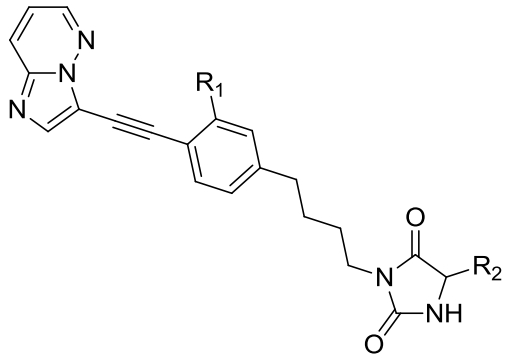


Figure 1: Proposed RIP2 inhibitors.

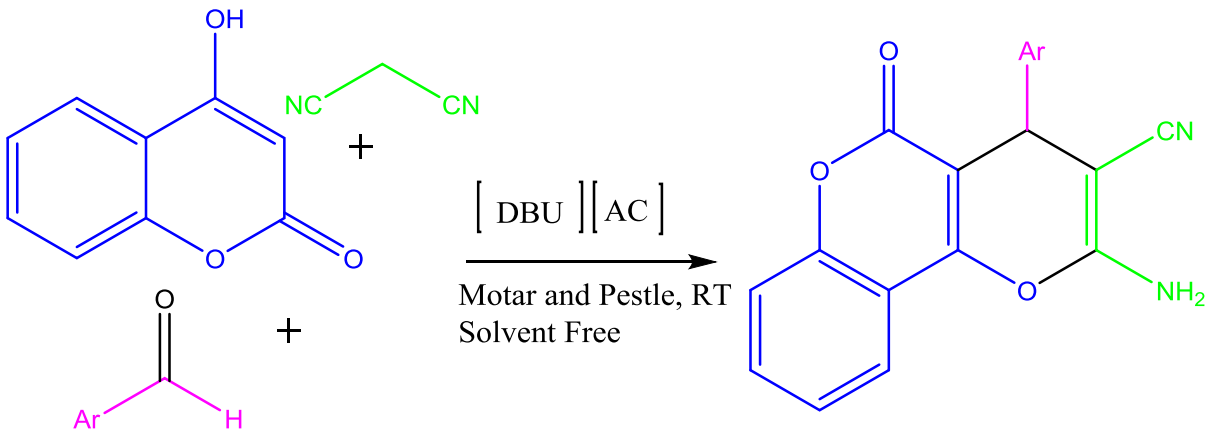
P14 – Graduate Student, Poster

A SOLVENT-FREE APPROACH TO ARYL AND HETEROARYL 3,4-DIHYDROPYRANO[C]CHRPMENES

Gabriel Ouma[†], Alexander Trochez[†], A' Miracle Wesley[†], Tony L. Perry[†]*

[†] *Department of Chemistry, Grambling State University, Grambling, LA 71245*

Using a one-pot three component reaction of heteroaromatic aromatic aldehydes, malononitrile, and 4-hydroxycoumarin is described. An ionic liquid at room temperature utilizing a mortar and pestle allowed for a versatile approach to functionalize 3,4-dihydropyrano[c]chromenes. This method features decreased reaction times, atom efficiency, product selectivity, operational simplicity, and environmentally benign processes.



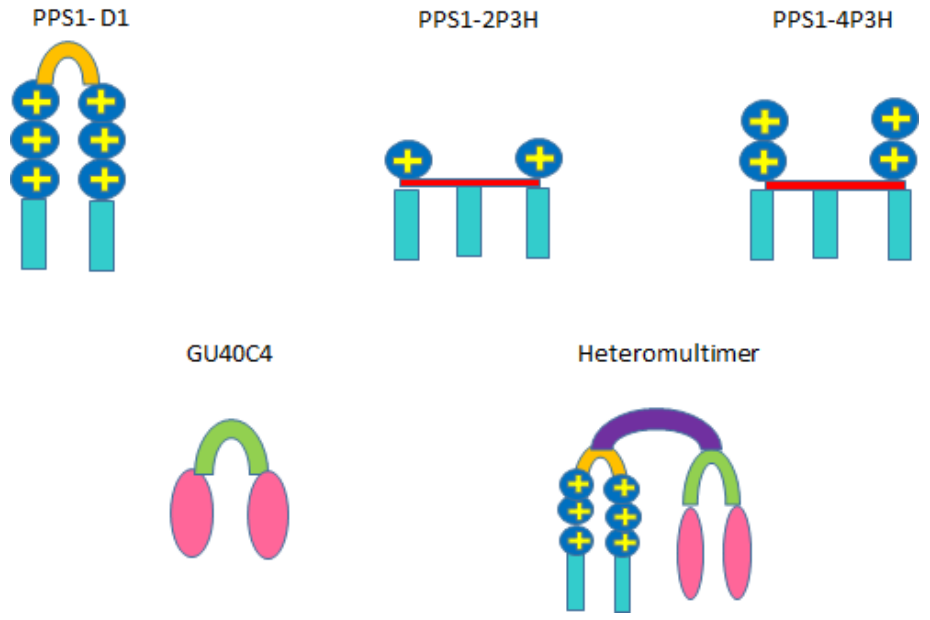
P15 – Graduate Student, Poster

VALIDATING CANCER SPECIFIC HOMO- AND HETERO-MULTIMERIC PEPTIDOMIMETICS

Suchi Raghunathan[1], Satya Prakash Shukla[1] and Gomika Udugamasooriya[1*].

[1]*Dept. of Pharmacological & Pharmaceutical Sciences, University of Houston, 77204.*

Our laboratory designs and develops combinatorial libraries of peptidomimetics, and already identified several biologically active peptoids. Lipid-phosphatidylserine (PS) targeted PPS1D1 and VEGFR2 targeted GU40C4 are two of the therapeutically active peptoids among them. PPS1D1 displayed cytotoxic effect on HCC 4017 lung- cancer cell lines. Here, we explored its activity on wide range of multiple lung cancer cell lines and found that PPS1D1 exhibited similar efficacy on all these lung cancer cell lines tested. Further, we developed unique multimeric derivatives of PPS1, PPS1-2P3H and PPS1-4P3H. We found that these derivatives also displayed similar activity as PPS1D1 but did not lead to any significant improvement in the cytotoxicity. Previously we have shown that VEGFR2 targeted GU40C4 has antagonistic activity on VEGFR2 receptor which promotes angiogenesis and tumor growth. We hypothesized that generating a heteromultimer by linking PPS1D1 to GU40C4 could target VEGFR2 and lipid-PS as a single molecule to enhance the cytotoxic effect, as both these bio-molecules are strongly co-expressed on tumor endothelial cells. Developed heteromultimers provided better cytotoxic effect over individual and synergistic effect of both peptoids.



P16 – Graduate Student, Poster

IMMUNOHISTOCHEMICAL AND BIOCHEMICAL ANALYSIS OF CANNABINOID RECEPTORS IN JAPANESE MEDAKA (*Oryzias latipes*)

Santu K. Singha[1] , Ikhlas A. Khan[2,3] , Asok K. Dasmahapatra [1,3]

[1]Department of BioMolecular Sciences, Division of Pharmacology, [2]Division of Pharmacognosy, [3]National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, MS

Japanese medaka (*Oryzias latipes*) genome consists of three cannabinoid receptor paralogs; two of them (*cnr1a* and *cnr1b*) showed structural identity with human CB1 receptor (*CNR1*) and the other (*cnr2*) with human CB2 receptor (*CNR2*). The present study was aimed to find out whether these CB receptors were expressed in Japanese medaka and what is the significance of the presence of two *cnr1* paralogs in medaka genome. Eight reproductively active fish, four male and four female, were used for collections of brain, eye, gill, heart, kidney, liver, spleen and gonad (testis/ovary) tissues and processed for quantitative real-time PCR (qPCR) analysis using gene-specific primers. For immunohistochemical analysis of cb1 receptor expressions on male tissues, human polyclonal antibodies were used. Our qPCR analysis indicates that *cnr1a* and *cnr1b* mRNAs were expressed in all tissues except liver and ovary both in male and female fish. However, maximum expression was found in brain. Expression of *cnr2* was observed in all organs used, while most expressions were noticed in gill and kidney. Further, immunohistochemical studies of cb1 receptor expressions indicate that cb1 immunoreactivity was found in forebrain (diencephalon), midbrain (optic tectum) and in hindbrain (cerebellum). Moreover, cb1 immunoreactive cells were also found in kidney tubules and gill filaments. No immunoreactivity was observed in hepatocytes. Our data indicate that both *cnr1* and *cnr2* receptors are operative in Japanese medaka. Although due to lack of specific antibody we were unable to differentiate the expression of cnr1a and cnr1b protein in these tissues. From our qPCR data, we expect that the expression of cb1 is mostly cnr1a rather than cnr1b. Moreover, cb1 immunoreactivity in kidney and gill tissues indicates that cb1 receptor also plays significant role in osmoregulation/osmotic balance in fish.

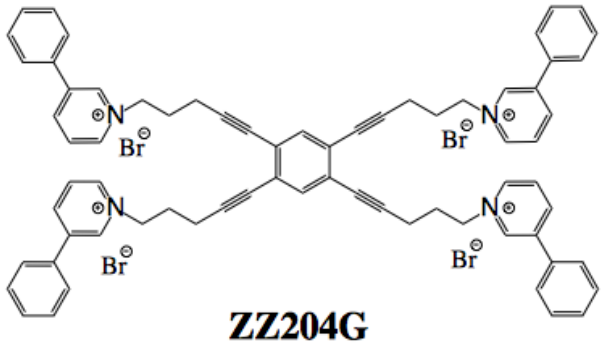
P17 – Graduate Student, Poster

AN *IN VIVO* STUDY OF A NOVEL ANALGESIC AGENT ZZ204G

Wan, Anqi[1], Yadlapalli, Jai Shankar K[1], Dobretsov, Maxim[2], Fifer, E. Kim[1] and Crooks, Peter A[1]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR USA; [2]Department of Anesthesiology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR USA.

Pain is a global public health priority, and more than 20% of adults worldwide suffer from pain. Although there are many analgesics on the market (opioids, NSAIDs, etc.), treatment of pain remains a vexing problem. Recent studies have led to the discovery of small molecule antagonists of α9α10 nicotinic acetylcholine receptors (nAChRs) as a novel class of safe and powerful analgesic compounds. However more research is needed to determine the mechanism of action and the types of pain that is responsive to these compounds. Toward this goal, in this study, a small non-peptide molecule, ZZ204G (a *tetrakis*-quaternary ammonium analog), was selected and synthesized. The antinociceptive efficacy of ZZ204G was tested in rats using hot water tail flick latency (TFL), hind limb paw withdrawal hot plate threshold (HPT), paw pressure threshold (PPT) and pinprick sensitivity threshold (PST) tests. Results showed that ZZ204G has a long lasting analgesic effect with a quick onset in tests for superficial burning (HPT and TFL) and mechanical pricking pain (PST). Compared to morphine (an opioid), ZZ204G showed higher potency and longer duration of action in TFL, HPT and PST tests. The effect of ZZ204G was dose-dependent in three assays (TFL, HPT and PST), with ED_{50} values of 190.5 ± 18.8 μg/kg (TFL), 25.5 ± 9.1 μg/kg (HPT) and 167.8 ± 79.9 μg/kg (PST), respectively. However, only weak analgesic activity was observed in the PPT test, which demonstrated that ZZ204G is less effective for deep tissue (muscle and ligaments) pain. Based on these results and other literature data, the effect of ZZ204G can tentatively be attributed to its ability to modulate the activity of the skin keratinocyte acetylcholinergic system that works in particular to set and maintain excitability thresholds of epidermal nociceptors. Hence ZZ204G is a promising new antinociceptive agent for superficial/burning pain.



ZZ204G

P18 – Graduate Student, Poster

PHARMACOLOGY, PHARMACOKINETICS AND THERAPEUTIC IMPLICATIONS OF MORPHINE-6-*O*-SULFATE SODIUM IN DIABETIC NEUROPATHY

Jai Shankar K.Yadlapalli[a], Zaineb Albayati[a], Benjamin Ford[c] , Anqi Wan[a] ,Narasimha Reddy Penthala[a] , Paul L Prather[c], William E Fantegrossi[c], Maxim Dobretsov[b], Peter A. Crooks[a]

[a] *Department of Pharmaceutical Sciences,* [b] *Department of Anesthesiology,* [c] *Department of Pharmacology and Toxicology , University of Arkansas for Medical Sciences, Little Rock, AR, USA*

This study evaluated the analgesic potency and tolerance profile of morphine and its ester derivative, morphine-6-*O*-sulfate (M6S), in a rat model of diabetic neuropathy and the discriminatory stimulus effects of M6S in normal rats. Diabetes was induced in male Sprague-Dawley rats with streptozotocin, 65mg/kg (i.p.). Hot water tail-flick latency, paw pressure, pinprick sensitivity and hot plate withdrawal thresholds (HTL, PPT, PST and HPT) were measured during acute and chronic treatment for both drugs. cAMP, GTPγS assays were performed in human μ and δ opioid receptors (OR). HPLC-DAD stability studies on M6S were performed *in vitro* in various pH buffers and biological fluids. Pharmacokinetic parameters for M6S were studied via i.v. (2mg/kg) and i.p. (5.6, 10 mg/kg) administration. Drug discrimination studies were conducted to assess morphine like interoceptive effects of M6S. In diabetic animals, M6S was 3-20 fold more potent over morphine depending on pain modality tested. In addition, M6S was 2-4 fold more efficacious over morphine on HPT and PST tests. Furthermore, no tolerance was seen to M6S during 9 days chronic daily dosing as opposed to morphine. M6S did not exhibit cross tolerance to morphine. In cAMP & GTPγ assays, M6S is 5-fold more potent than morphine at δ OR and the δ antagonist naltrindole blocked M6S analgesia by 50% *in vivo*. HPLC-DAD analysis and pharmacokinetic studies showed no evidence for hydrolysis of M6S to morphine. In drug discrimination studies, M6S only partly substituted (50% drug appropriate response) for morphine even at the highest therapeutic dose. Collectively our data suggest that the superior potency, efficacy and tolerance profile of M6S over morphine in diabetic neuropathy is attributed to its ability to act as a mixed mu/delta opioid agonist and also hints at potential clinical utility of M6S as a less abused opioid alternative over morphine at analgesic dose range.

P19 – Postdoctoral Fellow, Poster

DETECTION AND DETERMINATION OF PARTHENOLIDE (PTL) IN PLASMA AND BONE SAMPLES FROM MSV-PTL-TREATED AML-PDX MICE

Zaineb A F Albayati[1], Hongliang Zong[2], Siddhartha Sen[2], Guodong Zhang[3], David G. Gorenstein[4], Xuewu Liu, Mauro Ferrari, Peter A. Crooks[1], Gail J. Roboz[2], Haifa Shen[3,6], and Monica L. Guzman[2]

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This work was aimed to determine the concentration of PTL (Fig.1) in plasma and femur bone samples obtained from PDX- mice after a single i.v. injection of MSV-PTL nanoparticles at a dose of 2.5 mg/kg of PTL. The MSV-PTL delivery system was designed as a temporary drug delivery system in which the end goal was to achieve PTL release in the bone marrow niche. Plasma and femur bones from MSV-PTL treated AML-PDX mice obtained 1 h after administration of PTL were removed from the animal and stored at -80 ^{o}C. Prior to analysis, bones were pulverized and homogenized in a mixture of hexane:acetonitrile (1:1), vortex-mixed, sonicated for 1 min and centrifuged. The supernatant was evaporated to dryness under nitrogen gas at 37 °C. The residue was reconstituted in 30 µL of acetonitrile/methanol (1:1), and 5 µL of this solution injected onto an LC/MS/MS spectrometer. To detect PTL in plasma samples, 50 µL of control or MSV-PTL-treated plasma samples were extracted with 600 µL of acetonitrile/methanol (1:1). The mixture was vortexed for 30s, sonicated for 1 min and centrifuged. The supernatant was then evaporated to dryness at 37 °C under nitrogen gas, the residue reconstituted with 50 µL of acetonitrile/methanol (1:1) and 5 µL was injected onto the LC/MS/MS spectrometer. Following i.v. dosing of the MSV-PTL nanoparticle system, PTL was detected in bone samples within 1h with an average concentration of 375.0 ± 14.7 nM. However, no PTL was detected in the plasma at the 1 h time point indicating that there was likely no degradation of the MSV-PTL nanoparticles to release PTL in plasma. Thus, the data are consistent with selective targeting of the bone and *in vivo* release of PTL from the MSV-PTL nanoparticles in bone tissue, since measurable levels of PTL were observed in the femur bones of mice 1 h after a single i.v. injection of MSV-PTL nanoparticles.

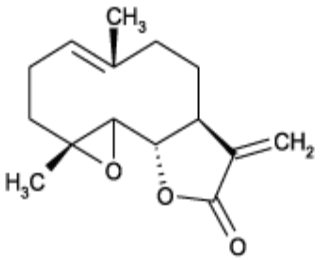

Fig. 1. Structure of parthenolide, Molecular Formula: $C_{15}H_{20}O_3$, Molecular weight: 248.32

P20 – Postdoctoral Fellow, Poster

DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF NOVEL 5*H*-CHROMENOPYRIDINES AS POTENTIAL ANTI-CANCER AGENTS

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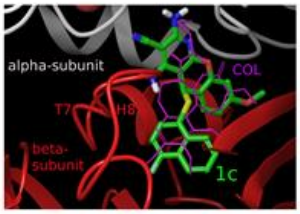
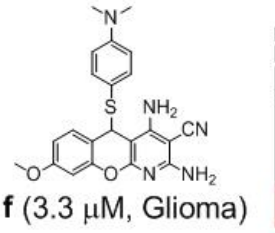
A novel series of 5*H*-chromenopyridines was identified as anticancer agents in our continuing effort to discover and develop new small molecule anti proliferative agents. Based on our initial lead **SP-6-27 compound**, we designed and synthesized novel tricyclic 5*H*-thiochromenopyridine and *5H*-chromenopyridine analogs to evaluate the impact of an additional ring as well as conformational flexibility on cytotoxic activity against human melanoma and glioma cell lines. All of the *5H*-thiochromenopyridines have been achieved in good yield (89% to 93%) using a single step three component cyclization without need of purification. The *5H*-chromenopyridine analog of the potent *5H*-thiochromenopyride was obtained in good yield upon purification. All newly prepared *5H*-thiochromenopyridines showed moderate cytotoxicity against three melanoma and two glioma cell lines (3 – 15 μM). However, the *5H*-chromenopyridine analogues lost cytotoxic activity. We explored the potential interactions of all prepared compounds with the colchicine binding site in tubulin utilizing Schrodinger Molecular Modeling Suite. Interestingly, most *5H*-substituted-thiochromenopyridines showed decent glide scores ranging from -8.8 to -8.0. The moderate cytotoxic activity of *5H*-thiochromenopyridines shows the promise of developing chromenopyridines as potential anticancer agents.

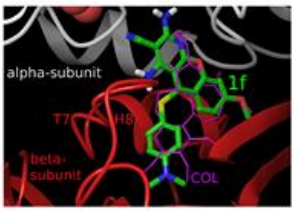
Key Words: Glioma, Melanoma, Chromene, Chromenopyridine, anti-proliferative activity.

1c (3.6 μM, Melanoma)





1f (3.3 μM, Glioma)



P21 – Postdoctoral Fellow, Poster

A STEPWISE STRATEGY FOR OPTICAL IMAGE-COUPLED PHOTODYNAMIC THERAPY USING CLICK REACTION

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Image–guided treatment has become a widely accepted approach for personalised treatment of cancer. One of such approaches in the field of photodynamic therapy is fluorescence image-guided photodynamic therapy for superficial tumors. However, fluorescence emission and generation of singlet oxygen are two competing processes and thus it is difficult to achieve two functions with current photosensitizers. To overcome this challenge, we have developed a stepwise strategy for fluorescence-guided photodynamic therapy using a bioorthogonal click reaction. A donor rhodamine azide (Rh-N_3) acts as an effective fluorescence agent. After fluorescence imaging, an acceptor phthalocyanine-dibenzocyclooctyne (Pc-(DIBAC) was added to form a FRET dyad Rho-(DIBAC)-Pc. This FRET dyad effectively generated singlet oxygen by a short wavelength light (531 nm). In our preliminary study, no dark toxicity was observed to human bladder cancer cells (T-24) for Rh-N_3 plus equimolar Pc-(DIBAC) up to 5 □M. When the wells of bladder cancer cells with these click reaction components were illuminated (531 nm diode laser, 5.6 mW/cm^2 for 30 min), most of the cells were dead (< 10 % survival) even at 0.05 □M. There was no significant phototoxicity with each individual component (either Rh-N_3 or Pc-DIBAC) at the same concentration range. The high cells dead is attributed to the generation of singlet oxygen through FRET following the dyad formation in the cells. This strategy provides a new tool for efficient fluorescence imaging and PDT with short wavelength excitation (causing minimum damage to muscle layers), which would be useful for detecting and treating superficial tumors.

P22 – Postdoctoral Fellow, Poster

SYNTHESIS OF MELAMPOMAGNOLIDE B ESTERS AS ANTICANCER AGENTS

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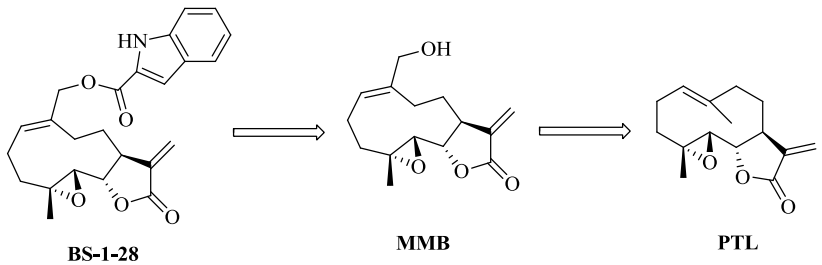
Recent years have seen a surge of interest in the isolation and synthesis of novel sesquiterpene lactones (SLs) and studies to determine their anti-cancer properties. Parthenolide (PTL) is a sesquiterpene lactone with specific toxicity towards acute myelogenous leukemia (AML) stem cells compared with normal hematopoietic stem cells. PTL was isolated from the plant *Tanacetum parthenium* (commonly referred as feverfew), and is a naturally occurring SL containing an α-methylene-γ-lactone ring and an epoxide moiety in its structure. It is believed that the α-methylene-γ-lactone moiety interacts covalently with nucleophilic sites on biological macromolecules via Michael addition chemistry. Recent studies have shown that PTL is capable of inducing robust apoptosis in primary AML cells, proving to be equally effective among all subpopulations within primary AML specimens, including leukemia stem cells (LSCs). A key water-soluble amino-adduct of parthenolide, dimethylaminoparthenolide (DMAPT), has advanced into clinical studies in humans. Likewise Melampomagnolide B (MMB), which is a naturally-occuring SL structurally related PTL and isolated from *Magnolia glandiflora*, selectively targets AML stem cells. MMB was synthesized from PTL using selenium dioxide/*tert*. butylhydrogen peroxide reagents (Scheme 1). Unlike PTL, MMB has a primary hydroxyl moiety, which facilitates the structural diversification of the molecule and allows the development of novel analogues with improved water-soluble, bioavailable and drug-like properties. Accordingly we have design and synthesized a series of MMB esters of a variety of substituted 2- and 3-indole carboxylic acids. All the synthesized analogues were screened for anticancer activity against a panel of 60 human tumor cell lines and also screened against M9ENL AML and primary AML cell lines; they were generally much more potent as anticancer agents than either PTL or MMB. Among these compounds, analogue BS-1-28 was found to be the most potent anticancer agent with GI_{50} values <10 nM against BT-549 and T-467 D breast cancer cell lines. A second analogue, compound BS-2-04, was found to be a potent anti-leukemic agent with an EC_{50} value of 720 nM against M9ENL cells in culture.

Scheme 1



BS-1-28 **MMB** **PTL**

P23 – Postdoctoral Fellow, Poster

A VIRTUAL SCREENING PROTOCOL TO IDENTIFY POTENTIAL SMALL MOLECULE INHIBITORS OF PKNG

Andrew Castleman[1], Devipriya Mohan[1], Neil Hunter[1] E. Blake Watkins[1] and Ashok Philip[1]

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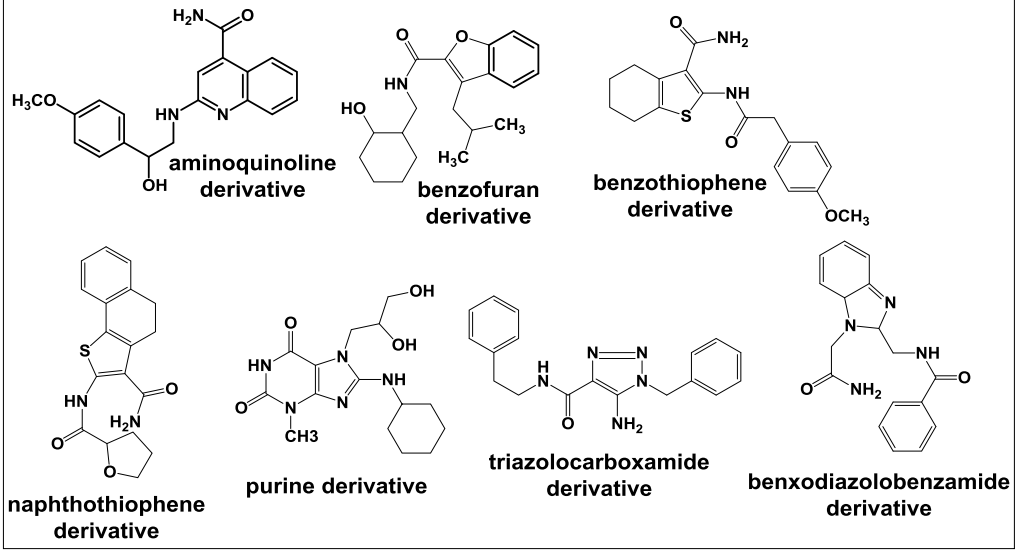
Our research goal is to identify chemically diverse, selective, small molecules with the potential to inhibit PknG, a molecular target for treatment of multidrug resistant *latent* tuberculosis (TB). In this abstract we present a robust virtual screening protocol that identified 7 chemically diverse classes of small molecules (**Figure 1**). 3D crystal structure of PknG was analyzed for binding site requirements followed by Ligand-Based Virtual Screening employing AX20017 as the virtual lead. Virtual screening was performed using UNITY module of SYBYL X 2.1.1. Query "hits" then docked employing SURFLEX-DOCK suite in SYBYL and ranked based on SURFLEX-DOCK scores. Overall, 892 ligands were identified from a 2D database (*Zinc*) of 5 million ligands. 892 ligands were then docked into PknG using Surflex-Dock module which generated multiple poses for each compound and assigned a total score for each pose based on similarity, polarity and other scoring parameters. The candidate ligands were categorized based on their chemical diversity. Ligands with desired hydrogen bonding interactions, high docking score and those bound in the pocket with minimal steric interactions were selected for commercial purchase and chemical synthesis. Current TB treatment options are rendered either ineffective or fail due to prolonged duration of treatment, cost of treatment, ineffective intracellular penetration of drugs, and the ability of Mtb to remain latent and be reactivated in immunocompromised patients. In this setting, our goal to inhibit PknG, a critical enzyme involved in Mtb survival, with chemically diverse small molecules makes a significant contribution to drug discovery efforts aimed at treating the *latent* form of TB.

Figure 1: Representative Classes



P24 – Postdoctoral Fellow, Poster

VARYING THE TAIL LENGTH OF TOCOTRIENOL: SYNTHESIS AND PRELIMINARY ANTIOXIDANT ACTIVITY STUDY

Satheesh Gujarathi, Lijian Shao, Xingui Liu, Wei Feng, Daohong Zhou, Guangrong Zheng*

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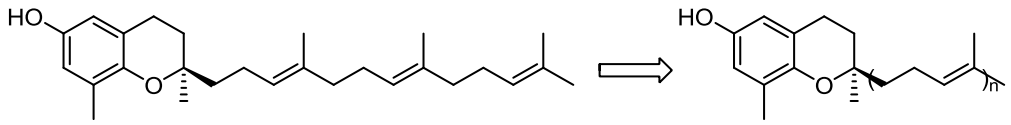
γ-Tocotrienol (γ-T3) and δ-tocotrienol (δ-T3), two vitamin E homologues, are some of the most effective and low-toxic radioprotective agents identified to date. Ionizing radiation (IR)-triggered overproduction of reactive oxygen species (ROS) with concordant induction of DNA damage and cell death is one of the major mechanisms of normal tissue injury during radiotherapy. Because of the strong antioxidant action of T3s, they can protect against direct cell damage by scavenging IR-induced ROS and chain-terminating free radical lipid peroxidation (LPO). Due to their high lipophilicity, T3s likely exert their antioxidant activity within the cell membranes. Recently studies have indicated that the anti-ROS and anti-LPO actions of vitamin E compounds occur specifically at cell membrane's hydrophobic-water interface; and the mobility of the molecules in the cell membrane is also important for the antioxidant potency. We hypothesize that the location and mobility of T3s in cell membrane are correlated to the length of their tail unit. To test this hypothesis, we synthesized a series of δ-T3 analogues with varying isoprenyl units (from one to four) to explore relationship between the tail length and antioxidant activity. Preliminary antioxidant data of these compounds will be reported.



δ-Tocotrienol **n = 1, 2, 4**

P25 – Postdoctoral Fellow, Poster

SYNTHESIS OF CARBAMATE AND CARBONATE DERIVATIVES OF MELAMPOMAGNOLIDE B AND THEIR EVALUATION AS POTENT ANTI-CANCER AGENTS

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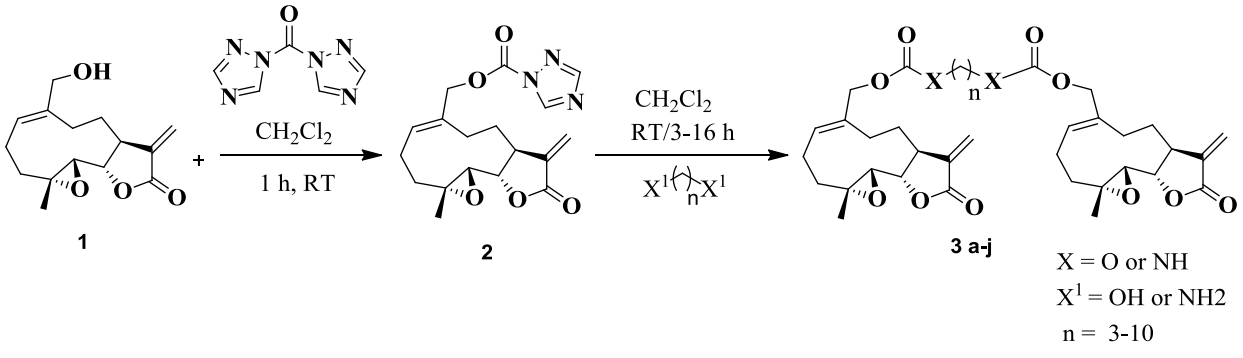
Melampomagnolide B (MMB) (**1**) is a natural sesquiterpene lactone structurally related to parthenolide (PTL) that exhibits anti-leukemic properties similar to PTL. Unlike PTL, the presence of a primary hydroxyl group in the MMB molecule allows the opportunity for examining the biological activity of a variety of conjugated analogs of MMB. In the present study, a series of carbamate and carbonate dimers of melampomagnolide B (**3a-j**) were generated by reaction of a key triazole carbamate of MMB (**2**) with various diaminoalkane and dihydroxyalkane reactants. The triazole carbamate derivative of MMB was obtained from the reaction of MMB with carbonylditriazole. The dimeric analogues of MMB were screened for anti-leukemic activity against AML and ENL M9 cell lines. Most of the dimers exhibited promising anti-leukemic activity (EC_{50}: 0.54-7.3 μM). Interestingly, the compounds exhibited significantly reduced cytotoxic effects (EC_{50} = 10-30 μM) against normal bone marrow cells (CD34+45d). Moreover, these compounds were also evaluated for anti-cancer activity against a panel of 60 human cancer cell lines. From preliminary studies 3 compounds (4, 5, 8 carbon chain length carbamate dimers of MMB) were selected for 5 dose testing, which indicated that these compounds showed potent growth inhibition against both hematological and solid human tumor cell lines, with GI_{50} values in the range 250-780 nM against the majority of cell lines in the leukemia sub-panel, and GI_{50} values in the nanomolar to low micromolar range against a significant number of human solid tumor cell lines in the 60 cell panel. The 8-carbon chain length carbamate dimer exhibited the most promising anti-cancer activity and was considered a promising lead compound for further development.



P26 – Postdoctoral Fellow, Poster

DESIGN AND SYNTHESIS OF LOBELANE ANOLOGUES AS TREATMENTS FOR METHAMPHETAMINE ABUSE

S. R. Joolakanti[a], J. R. Nickell[b], L. P. Dwoskin[b], G. Zheng[a] and P. A. Crooks[a,*]

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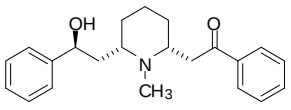
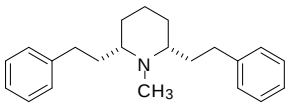
Methamphetamine (METH) abuse is a serious concern in the United States with approximately 100,000 new METH users every year. METH promotes dopamine (DA) release in the CNS by reversing the DA transporter, inhibiting monoamine oxidase and interacting with the vesicular monoamine transporter-2 (VMAT-2). The end result of these biochemical events is a heightened reward/pleasure sensation that become addictive and results in chronic METH abuse in order to sustain this pleasurable sensation. Currently there are no FDA approved medications to treat METH addiction. Lobeline, the major alkaloid in *Lobelia inflata*, inhibits dopamine uptake into synaptic vesicles *via* an interaction with the tetrabenzene (TBZ) binding site on VMAT2, and also inhibits METH reward in rat behavioral studies, but lacks good drug-like properties. Structural modification of lobeline afforded lobelane, which is 10–15-fold more potent than lobeline in inhibiting vesicular DA uptake by VMAT2 and METH evoked DA release.

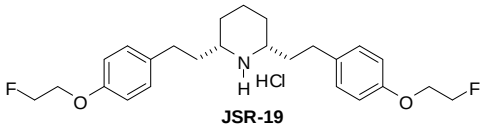
In the present study, we focused on structural modifications of lobelane that would lead not only to increased water-solubility and drug likeness, but also utility as candidates for positron emission tomography (PET) studies to better understand their VMAT2 binding efficacy *in vivo* as well as their bio-distribution in the body. We designed and synthesized several fluorinated and non-fluorinated lobelane analogues and evaluated their neurochemical activity to determining their inhibition of [^{3}H]DA uptake into rat striatal synaptic vesicles. Interestingly these compounds were very potent and selective vesicular [^{3}H]DA uptake inhibitors.



Lobeline



Lobelane



JSR-19

The ethylflouro derivative of lobelane, **JSR-19**, was synthesized and evaluated for neurochemical activity. Interestingly this compound was a very potent (Ki = 0.040 ± 0.0015 μM) vesicular [^{3}H]DA uptake inhibitor and had significantly less potency at dopamine (DAT) (1.67 ± 0.296) and serotonin (SERT) (0.640 ± 0.0337) transporters. These results prompted us to focus on the synthesis and evaluation of a small library of **JSR-19** analogs and to evaluate them for their ability to selectively inhibit vesicular [^{3}H]DA uptake into rat striatal synaptic vesicles.

P27 – Postdoctoral Fellow, Poster

IMPORTANCE OF C1 DOMAIN OF PKC IN ITS REGULATION BY CURCUMIN

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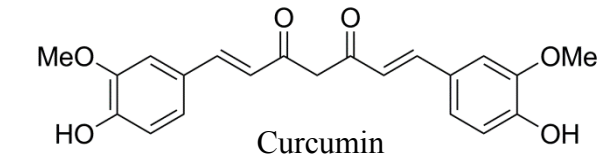
The mechanism of the regulation of protein kinase C (PKC) by curcumin is poorly understood. PKC is a family of serine/threonine kinases implicated in many diseases including cancer. The PKC family has been divided into three main groups: conventional (α, β and γ); novel (δ, ε, η, θ and μ) and atypical (ζ, ι and λ). PKCs have four domains, termed C1 through C4 that play distinct roles in their function. Here, we have examined the effect of curcumin on PKCα and PKCε activity by measuring their translocation from cytosol to membrane using *Western blot and confocal microscopy. Curcumin inhibited the TPA* (12-*O*-Tetradecanoylphorbol-13-acetate)- induced membrane translocation of PKCα, but not *PKCε. To understand the role of regulatory C1 and C2 domains in PKC regulation by curcumin, four mutants were constructed, where C1 and C2 domain of* PKCα and PKCε *were swapped. Curcumin significantly inhibited membrane translocation of PKCε mutant, in which εC1domain was replaced with αC1 domain. On the other hand, PKCα mutants with εC1 or εC2 and the PKCε mutant with αC2 were inactive. This study shows that C1 domain of PKCα is important for the inhibition activity by curcumin. This study has implication in design isoforms-specific PKC modulators.*



P28 – Research Instructor, Poster

SYNTHESIS AND ANTI-CANCER ACTIVITY OF INDOLE-3-YL-2-OXOACETATE DERIVATIVES OF THE SESQUITERPENE LACTONE MMB

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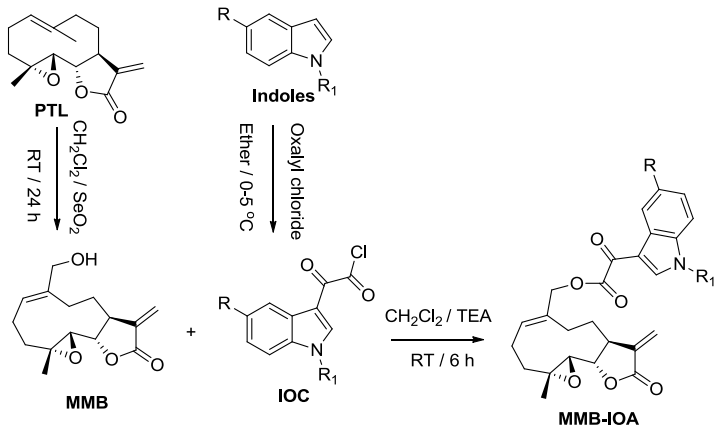
Recently, parthenolide (**PTL**) and its structurally related sesquiterpene lactone analogs were extensively investigated as anti-inflammatory, antimicrobial, antiviral and potent anti-cancer agents. The guaianolide, pseudoguaianolide, germacrolide, melampolide, heliangolide, and 4,5-dihydrogerma-cranolide series of natural products are the various known sesquiterpene lactones. Among these, currently only three sesquiterpene lactones: thapsigargin, artemisinin, and the dimethylamino adduct of parthenolide (DMAPT), are in clinical trials. Recently, our research group has reported on the synthesis and anti-leukemic activity of a melampolide sesquiterpene lactone, melampomagnolide B (**MMB**) and its analogs. In the present work we describe the synthesis and evaluation of anti-cancer activity of novel indole-3-yl-2-oxoacetate derivatives of MMB (**MMB-IOA**). These novel natural product derivatives have been screened for their effects in leukemia M9ENL AML cell lines and against a panel of 60 human cancer cell lines. Potent compounds emerging from these studies were also evaluated for their toxicity against cord blood normal cell lines.

The MMB indole-3-yl-2-oxoacetates were synthesized by the reaction MMB with different simple and substituted indol-3-yl-2-oxoacetyl chlorides (**IOC**) in the presence of triethylamine as base in dichloromethane at room temperature. From this library of compounds, MMB-IOA analogs containing an *N*-methyl-5-methoxyindole or an *N*-methyl-5-chlorindole moiety (PNR-9-05 and PNR-9-03, respectively) inhibited the growth of the cancer cell lines with GI_{50} value in the range 0.2 μM-4.12 μM and 0.19 -3.28 μM, respectively, against all 60 cancer cell lines in the panel. PNR-9-03 and PNR-9-05 also exhibited potent anti-leukemic activity against M9ENL AML cells with EC_{50} values of 1.2 μM and 0.97 μM, respectively. PNR-9-05 was found to no significant toxicity against cord blood normal cells.



P29 – Postdoctoral Fellow, Poster

FAR RED LIGHT-ACTIVATABLE PRODRUGS OF A PHOTOSENSITIZER AND ANTI-CANCER DRUG FOR EFFECTIVE TUMOR ABLATION USING PHOTODYNAMIC THERAPY

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Photodynamic therapy (PDT) is a process in which selective tumor ablation is achieved via controlled activation of a light sensitive drug to generate singlet oxygen (SO), which is a toxic species. How ever, PDT is limited due to short diffusion distance and short life span of SO. To overcome these limitations we designed a prodrug system. *(Med. Chem. 2014, 57, 3401-3409).* A cleavable prodrug (CPD) is made of a photosensitizer (PS) and an anticancer drug conjugated via a SO cleavable linker. Upon activation with light the singlet oxygen released from the PS will free the anticancer drug. This now diffuses to surrounding cancer cells and causes bystander killing. As a negative control, we used a non-cleavable prodrug system (NCPD), where the anti cancer drug cannot be released. The focus of this work is to demonstrate the effect of released anti-cancer drug Combretastatin A4 (CA4). A light diffusion distance dependent damage was observed in the NCPD where only PDT effect is possible. Whereas, the CPD treated cells were all dead due to released anti-cancer drug, which killed the surrounding cells. Cell cycle analysis showed cells accumulating in the G2 phase where microtubule inhibition occurs upon CPD treatment. Microtubule staining showed similar staining pattern of CPD to that of CA4. Overall we overcame the problems associated with PDT via a light controlled release of anticancer drug from the prodrug and achieved bystander effect and enhanced anti-tumor activity, which are two key subjects in effective tumor ablation. Details about in vivo results will be discussed.

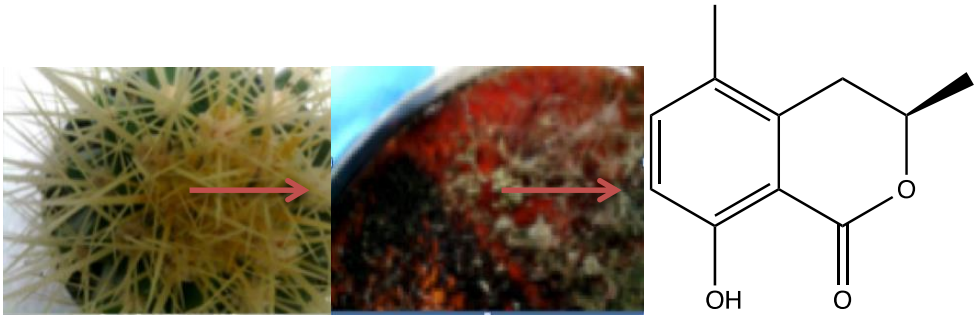
P30 – Postdoctoral Fellow, Poster

ANTIBACTERIAL ACTIVITY OF ISOCOUMARIN DERIVATIVES ISOLATED FROM CRITICALLY ENDANGERED CACTUS ENDOPHYTIC FUNGUS *FUSARIUM* SP.

Jnanendra Rath[1, 2], Xiaojuan Wang[1] and Mark T. Hamann[1]

[1] Department of Biomolecular Science, School of Pharmacy, University of Mississippi, Oxford, USA, [2] Department of Botany, Visva-Bharati University, Santiniketan, India

Endophytes have been proven to be a novel source of structurally diverse and biologically active compounds with great potential of new drug development. We have isolated an endophytic fungus *Fusarium* sp. from a critically endangered cactus *Echinocactus grusonii*. Colonies of *Fusarium* sp. often appears red in Malt extract medium due to production of pigments such as aurofusarin. Isocoumarin was isolated and purified from this fungus using series of purification methods including thin layer chromatography, column chromatography with Sephadex LH-20 and were analyzed using NMR for structural elucidation. Biological activity of this compound shows selective inhibition of pathogenic bacteria *Staphylococcus aureus* (100%) and 96 % inhibition of Methicillin resistant *Staphylococcus aureus*. The compound have an IC_{50} < 8 µg/ ml shows potential antibacterial properties against *Staphylococcus aureus*.



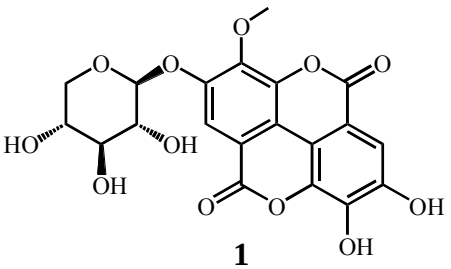
P31 – Visiting Scholar, Poster

HPLC-BASED ACTIVITY PROFILING FOR ANTITUMOR COMPOUNDS IN THE BARK OF *TERMINALIA ARJUNA*

Tao Wang, Shi Liu, Guangrong Zheng*

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205

The bark of *Terminalia arjuna* Wight & Arn. (*TA*) has been used for centuries in Ayurvedic medicine for various diseases including cancer. Several compounds, such as gallic acid and luteolin, which exhibit inhibitory effects on cancer cell growth, have been identified from this plant. Using HPLC-based activity profiling, multiple active fractions from aqueous extracts of *TA* bark were identified to have antitumor potential against MCF-7 human breast cancer cell line. Two ellagic acid derivatives, 3-O-methyl-ellagic acid 4-O-β-D-xylopyranoside (**1**) and 3-O-methyl-ellagic acid 3'-O-rhamnoside (**2**), were isolated from theses active fractions. The presentation will describe the isolation and cell growth inhibitory activity on MCF-7 cells.



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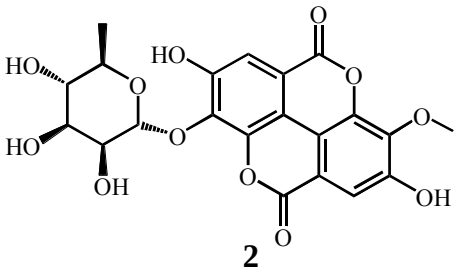


2

P32 – Postdoctoral Fellow, Poster

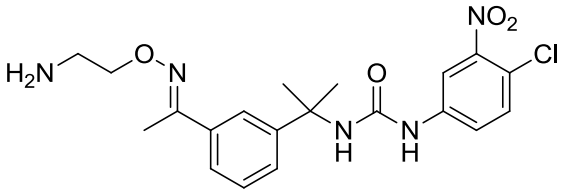
DESIGN OF *CRYPTOSPORIDIUM PARVUM* INOSINE 5'-MONOPHOSPHATE DEHYDROGENASE (IMPDH) INHIBITORS FOR ENTEROHEPATIC RECYCLING

Yong Wang[1], Deviprasad Gollapalli[2], Shufan Ge[1], Song Gao[1], Minjia Zhang[2], Lizbeth Hedstrom[2,3], Ming Hu[1] and Gregory D. Cuny[1]

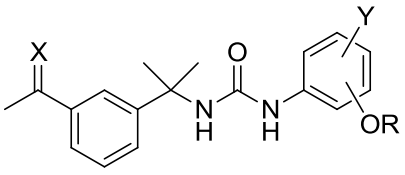
[1]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, TX 77204, [2]Department of Biology and [3]Chemistry, Brandeis University, Waltham, MA 02454

Cryptosporidium species, such as *C. parvum* and *C. hominis*, are gastrointestinal parasites that are a major cause of early childhood mortality, particularly in the developing world. *Cryptosporidium* infections cause diarrhea and malnutrition, and can be chronic and fatal in immunocompromised patients. Furthermore, *C. parvum* is a potential biowarfare agent, since oocysts can be easily introduced to water supplies and eradication is difficult.

C. parvum IMPDH is an attractive therapeutic molecular target since the parasite enzyme is structurally dissimilar from the human isozyme. Therefore, we have been developing selective and potent *C. parvum* IMPDH inhibitors in order to evaluate this strategy in pre-clinical disease models. To date, our most successful compound series has been urea-based compounds, with P131 demonstrating efficacy in a mouse model of cryptosporidiosis. However, high multidose oral administrations were required. One strategy to potential achieve better efficacy is through the design of *C. parvum* IMPDH inhibitors that can participate in enterohepatic recycling in order to maintain high gastrointestinal inhibitor concentrations with low systemic exposure. In this initial study, inhibitors have been prepared that incorporate a phenol into the urea-based series. Several of the compounds retained potent *C. parvum* IMPDH inhibitory activity and were efficient substrates for glucuronidation. Currently, these compounds are being evaluated in uptake and efflux studies using Caco-2 cells. Compounds that demonstrate efficient uptake and low efflux will then be evaluated in perfusion and pharmacokinetic studies to confirm enterohepatic recycling.



P131



X = CH_2, NOH
Y = Cl, CF_3
R = H, CH_3

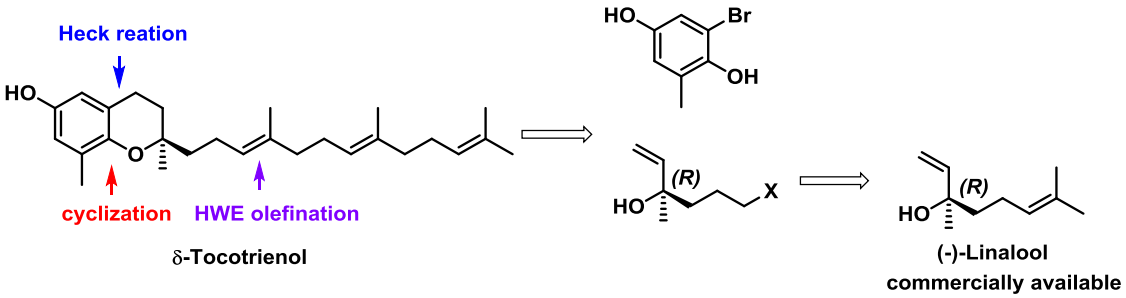
P33 – Postdoctoral Fellow, Poster

TOTAL SYNTHESIS OF δ-TOCOTRIENOL

Xuan Zhang and Guangrong Zheng*

Department of Pharmaceutical Sciences, College of Pharmaceutical, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, United States

Vitamin E is a group of lipid-soluble compounds including four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ). The tocotrienols have attracted increased attention recently as they have been shown to have some biological effects not seen with the tocopherols. However, it is very difficult and costly to isolate tocotrienols in pure forms from natural sources. Herein, we report an efficient and scalable synthetic route for δ-tocotrienol involving a Heck reaction between bromohydroquinone and a chiral synthon derived from (-)-linalool, followed by pyran ring formation and Horner–Wadsworth–Emmons olefination. This synthetic route is applicable to other three tocotrienols.



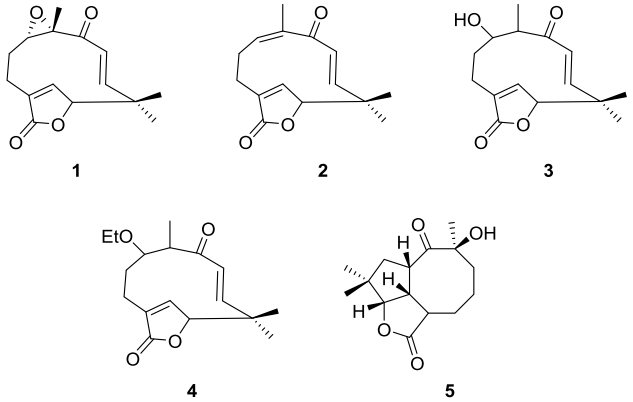
P34 – Postdoctoral Fellow, Poster

PHYTOCHEMISTRY AND ANTIPROLIFERATIVE ACTIVITY OF HUMULENES FROM *ASTERISCUS* SPECIES OF CANARIAN ISLANDS

Francisco León[1,3], Jorge Triana[2], José Luis Eiroa[2], Manuel Morales[2], Ignacio Brouard[3], José Quintana[4], Francisco Estévez[4]

[1]Department of BioMolecular Sciences, Division of Medicinal Chemistry, The University of Mississippi, University, MS 38677, USA; [2] Instituto de Productos Naturales y Agrobiología-Consejo Superior de Investigaciones Científicas (CSIC), Avda. Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain; [3] Departamento de Química, Unidad Asociada al CSIC, Universidad de Las Palmas de Gran Canaria, Campus de Tafira, 35017 Las Palmas de Gran Canaria, Canary Islands, Spain; [4] Departamento de Bioquímica. Universidad de Las Palmas de Gran Canaria, Plaza Dr. Pasteur s/n, 35016 Las Palmas de Gran Canaria, Canary Islands, Spain

Asteriscus Mill. is a genus belonging to the Inula-group of the family, Asteraceae, growing predominantly in the Mediterranean and North African regions. Around ten species are endemic to the Macaronesic region. *A. graveolens* subsp. *stenophyllus* (Link) Greuter (Synonym *Nauplius stenophyllus* (Link) Webb) collected in Gran Canaria and *Asteriscus schultzii* (Bolle) Pit & Proust (synonym *Nauplius schultzii*) collected in Lanzarote, Canary Island were studied. Their secondary metabolites were isolated by chromatographic methods and the structures were elucidated using spectroscopic and spectrometric methods and by comparison from literature. Four new humulen-type sesquiterpenoids were identified **1**-**4** and a new asteriscanolide **5** was isolated along with the known flavonoid, tricin, as well as four known sesquiterpenes **6**, asteriscunolido C **7**, asteriscunolides A **8**, asteriscanolide **9** from *A. graveolens* subs *stenophyllus*. Seven known compounds were identified from *A. schultzii*, that included, stigmasterol, scoporone, scopoletin, 5,6,7-trimethoxycoumarin, dehydroabietic acid, 7-oxodehydroabietic acid, 1α,4β,6β-trihydroxyeudesmane, and teuclatriol. Compounds **5**-**7** were assessed for cytotoxic activity against HL-60, U937 and U937/Bcl-2 cancer cell lines. Asteriscunolide C displayed cytotoxic properties at IC_{50} values of 14-19 μM. On the other hand, the absence of humulen-type sesquiterpene derivatives in *A. schultzii* suggested the deviation of this species from the genus *Asteriscus* and placed it under the close genus *Panellis*. Further phylogenetic studies should be perform.



A STANDARDIZED TOPICAL PREPARATION OF *SOLANUM LYCOCARPUM* FRUIT GLYCOALKALOIDS EFFECTIVELY HEALS CUTANEOUS LEISHMANIASIS.

CM Lezama-Dávila[1], JD McChesney[4], J Kenupp Bastos[3], M Abreu Miranda[3], R Fabiane Jorge Tiossi[3], J Carvalho da Costa[3], MV Lopes Badra Bentley[3], AP Isaac-Márquez[2]. [1] Department of Pathology, OSUMC, The Ohio State University, Columbus, OH, [2] Centro de Investigaciones Biomedicas, Universidad Autonoma de Campeche, Campeche, Mexico,[3] Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, S.P., Brazil.[4]Arbor Therapeutics, LLC, Etta, MS

Leishmaniasis continues to be a major worldwide health problem with an annual mortality of about 50,000 to 60,000 people. The growing resistance to currently used therapeutic drugs is a major challenge. Two glycoalkaloids, solamargine and solasonine, initially identified as major components of the Brazilian plant *Solanum lycocarpum* were tested for leishmanicidal activity. Both alkaloids killed intracellular and extracellular *L. mexicana* parasites more efficiently than the reference drug sodium stibogluconate. Ten μM of each individual alkaloid significantly reduced parasite counts in infected macrophages and dendritic cells. *In vivo* treatment of C57BL/6 mice with a topical preparation containing glycoalkaloid extract (45.1% solamargine and 44.4% solasonine) gave a significant reduction in lesion sizes and parasite counts recovered from lesions. The two alkaloids exert activity by different intracellular pathways in macrophages and dendritic cells. We conclude that this topical preparation made from a semi purified extract (a potential Botanical Drug) is effective and a potential new and inexpensive treatment for cutaneous leishmaniasis.

2015 MALTO Attendees

Grambling State University (3)
Joseph, Rochelle
Ouma, Gabriel
Perry, Tony

Union University (2)
Castleman, Andrew
Philip, Ashok

U. of Arkansas (17)
Albayati, Zaineb
Bommagani, Shoban
Crooks, Peter
Fifer, Kim
Gujarathi, Satheesh
Hussein, Hussein
Janganati, Venumadhav
Joolakanti, Shyamsunder
Lamture, Gauri
Liu, Xingui
Penthala, Narsimha
Shi, Peizhong
Wan, Aniq
Wang, Tao
Yadlapalli, Jai
Zhang, Xuan
Zheng, Guangrong

U. of Houston (14)
Akasaka, Hironari
Cuny, Gregory
Das, Joydip
Ku, Angela
Lemke, Pat
Lemke, Thomas
Nikhar, Sameer
Pany, Satyabrata
Raghunathan, Suchi
Ruan, Ke-He
Suebsuwong, Chalada
Udugamasooriya, Gomika
Wang, Yong
Williams, Louis

University of Louisiana at Monroe (4)
Jois, Seetharama
Naik, Himgauri
Pallerla, Sandeep
Sable, Rushikesh

U. of Mississippi (45)
Albadry, Mohamed
Alsharif, Walid
Batra, Harshul
Borne, Ron
Bow, Eric
Colby, David
Cunningham, Michael
Cutler, Steve
Doerksen, Robert
Fajemiroye, James
Fantoukh, Omer
Fletcher, Bailey
Gadepalli, Rama
Gadepalli, Veena
Galal, Kareem
Gogineni, Vedanjali
Haider, Saqlain
Hamann, Mark
Hao, Taisen
Hazlitt, Robert
Jain, Jagrati
Jain, Surendra
Jihan, Mohamed
Keasling, Adam
Khan, Ikhlas
Leon, Francisco
Leucke, Kelsey
McCurdy, Christopher
Morgan, Rhianna
Nael, Manal
Oh, Joonseok
Pandey, Pankaj
Parveen, Abidah
Rath, Jnanendra
Rimoldi, John
Roy, Kuldeep
Singha, Santu
Slater, Shuneize
Sowaileh, Munia
Tarawneh, Amer
Vasquez, Yelkaira
Wang, Xiaojuan
Wilson, Lisa
Yalamanchili, Chinni
Zjawiony, Jordan

U. of Oklahoma (5)
Bio, Moses
Magarian, Robert
Rajaputra, Pallavi
Thapa, Pritam
You, Youngjae

U. of Tennessee (8)
Arnst, Kinsie
Banerjee, Souvik
Donkor, Isaac
Li, Wei
Lin, Zongtao
Miller, Duane
Wu, Xiaoxin
Xiao, Min

Arbor Therapeutics, LLC
McChesney, James

University of Illinois at Chicago
Kozikowski, Alan