Contents
29th National Medicinal Chemistry Symposium
University of Wisconsin – Madison
June 27 – July 1, 2004

Sponsored by
The University of Wisconsin-Madison, Department of Chemistry and the
School of Pharmacy, and the American Chemical Society, Division of Medicinal
Chemistry

Organizing Committee .......................................................................................................................... ii
Welcome to Madison ............................................................................................................................ iii
Honorary Chair - Ralph F. Hirschmann ............................................................................................ v
2004 Medicinal Chemistry Award .................................................................................................... vii
ACS Division of Medicinal Chemistry Executive Committee 2004 .................................................... ix
Symposium Corporate Sponsors ........................................................................................................ x
History of the Division of Medicinal Chemistry ................................................................................ xiv
Summary of Past Meeting Sites ......................................................................................................... xvii
ACS Division of Medicinal Chemistry Past Officers - Chairs ............................................................ xix
ACS Division of Medicinal Chemistry Past Officers ........................................................................ xx
Program for the 29th National Medicinal Chemistry Symposium Detailed Events ................................xxi
Speaker Abstract Listings ................................................................................................................. xxv
Poster Abstract Listings .................................................................................................................... xxvii
Speaker Abstracts
Poster Abstracts
Author Index ........................................................................................................................................ xxxv
Campus Map ..................................................................................................................................... xli
Memorial Union Floor Plan ................................................................................................................ xlii
Organizing Committees
29th National Medicinal Chemistry Symposium
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Honorary Chair
Dr. Ralph F. Hirschmann

General Chair
Daniel H. Rich
University of Wisconsin-Madison
Madison, Wisconsin

Program Chair
James R. McCarthy, Eli Lilly Corporation

Program Committee
Jerry Adams, GlaxoSmithKline Collegeville
Dean Brown, AstraZeneca, Inc.
Ron Griffith, Genelabs Technologies, Inc.
George D. Hartman, Merck & Company, Inc. West Point
Mark E. Duggan, Merck & Company, Inc. West Point
Alan Naylor, GlaxoSmithKline Harlow
Ben Shen, University of Wisconsin-Madison
Jon Thorison, University of Wisconsin-Madison
Lihu Yang, Merck & Company, Inc.
Welcome to the 29th National Medicinal Chemistry Symposium!

We are delighted you are able to attend and hope that the meeting will be rewarding, both intellectually and socially. Because the Madison campus is so accessible during the summer, we have organized the meeting as informally as possible. We continue the long tradition of single sessions interspersed with frequent breaks of open time, so that you will be able to discuss the science reported. The posters will be up for three days and we have scheduled two formal sessions for viewing posters to allow both presenters and other participants’ ample time to see each other’s results.

We are especially grateful to the many organizations that supported this meeting through financial donations and other material assistance. We wish to thank AstraZeneca for sponsoring the opening reception, Pfizer for sponsoring the poster session receptions, and Amgen for sponsoring the banquet reception. I especially want to thank Dr. James McCarthy for his work to organize the program for this meeting and all the program committee members who contributed their time and ideas to make this meeting a success.

Tuesday afternoon is open for you to enjoy as you wish. There are a number of tours available that might appeal to you, or you can certainly stay on campus and just enjoy the ambiance of the Union Terrace on the shores of Lake Mendota. University of Wisconsin-Madison faculty and students will be wearing "host" ribbons; ask them for their advice if you like. The banquet Wednesday evening will be held at the Monona Terrace, which is located on Lake Monona. The convention center was built according to designs proposed by Frank Lloyd Wright and provides citizens and visitors alike the opportunity to experience Madison's other lake. Have a great time in Madison.

Sincerely,

Daniel H. Rich, General Chair.

Welcome to UW-Madison

UW-Madison is renown for its educational quality, outstanding faculty, and superb research achievement. Founded in 1848, UW-Madison has ranked among the top ten universities in every study of scholarly reputation since 1910. The departments of Chemistry, Biochemistry, Chemical Engineering, and Pharmacy are all ranked within the top 10 in their respective fields by both U.S. News & World Report (2002) and the NRC (1995). In 2002, UW-Madison ranked second nationally in total R&D expenditures. In 1998, UW-Madison conferred the most doctorate degrees in science and engineering in the nation. With 2,200 faculty and 42,000 students (including 10,000 graduate students), the strength and breadth of research and training at UW-Madison is truly impressive. There are more than 113 departments in 13 major schools and colleges offering nearly 4,300 courses.

Welcome to Madison

Madison is Wisconsin's beautiful capital city. Its topography is a vestige of the glacial age. Madison is renowned for its scenic lakes, trees, and surrounding farmland. Madison is the only—state capital
on an isthmus—built on the ridge between Lake Mendota and Lake Monona. The city's centerpiece is the majestic State Capitol. Set on the highest point between the two lakes, the Capitol dominates the skyline for miles. Visitors to the city of 200,000 can enjoy abundant cultural, social, and recreational activities: the Farmer's Market on Saturday mornings, hundreds of miles of bike trails, myriad ethnic and Midwestern cuisine restaurants and pubs, dozens of live music venues, and countless water sports, among others.

Madison, Wisconsin, consistently ranks as a top community in which to live, work, play, and raise a family. A favorite midwestern getaway, Madison is also a premier meeting and convention destination. The following is just a sampling of the accolades our city has recently received!

- **#1 Best Places for Business, Madison, WI.** *Forbes Magazine*, May 24, 2004
- **One of 12 Best Walking Cities**, *Prevention*, April, 2004
- **#2 Medium Metro Area For Doing Business in America**, *Inc. Magazine*, March, 2004
- **One of the Best Designer Cities in the Country**, *HOW Design*, December, 2003
- **Healthiest City for Men**, *Men's Health Magazine*, November, 2003
- **Best Midsize City in the Midwest for Entrepreneurs**, *Entrepreneur Magazine*, October, 2003
- **Madison Ranks #1 Best College Sports Towns**, *Sports Illustrated On Campus*, September, 2003
- **Friendliest City in the Midwest**, *Midwest Living Magazine*, June, 2003

Take a walk along Lake Mendota shore if you have time on Tuesday. There is a nice path from the Union to the end of Picnic point, a walk about 3 miles round trip. Or walk down State Street to the capitol square. The Wisconsin State Capitol features the only granite dome in the United States and is the fourth largest dome by volume in the world. As you walk along State Street, see the new Overture Center for the performing arts, which just opened this summer. Or walk south from the Capitol to the roof of Monona Terrace and admire the view on Lake Mendota. Straight south of the campus you will find Henry Vilas Zoo on the shores of Lake Wingra. Across this jewel of a lake you can see the University Arboretum, a popular spot for joggers and walkers alike. Closer to the Union, stop in the Elvehjem Art Museum, named after the former president of the University. Elvehjem, a biochemist, was a major contributor to vitamin A biochemistry.

We hope you will have time to absorb some of the ambiance of Madison. You soon will begin to understand why Madison is considered such a nice place to live.
Ralph Hirschmann, the Rao Makineni Professor of Bioorganic Chemistry at the University of Pennsylvania, has made seminal contributions to organic, medicinal, and bioorganic chemistry for over fifty years. A naturalized American citizen, born in Bavaria, Germany, Ralph Hirschmann came to the US in his teens and earned a B.A. degree from Oberlin College in 1943. Following three years of military service during World War II, he entered graduate school at the University of Wisconsin (Madison), where he received a Ph.D. degree under the mentorship of Professor William S. Johnson in 1950. That year he joined the Merck Research Laboratories as a process research chemist and retired in 1987, having served as Senior Vice President of Chemistry and of Basic Research. During his tenure in the latter capacity, his team discovered and/or developed several major drugs including Vasotec, Lisinopril, Primaxin, Ivomec, Mevacor, and Proscar. Early in his career (1952), he discovered the steroidal C-nor-D-homo rearrangement. He explained this reaction by introducing the term “stereoelectronic control,” now an integral concept of organic chemistry. During the 1960s, with Robert G. Denkewalter, he directed the first solution total synthesis of an enzyme, ribonuclease A (RNase A), and in 1969 announced jointly the total synthesis of ribonuclease A achieved by Merrifield on solid support. Prior to these announcements, it was questioned by many whether any synthetic protein of this size would fold correctly without a template.

Hirschmann thrived in the interdisciplinary environment of the pharmaceutical industry. Research carried out in Rahway in the 1950s and published in the early 1960s made a significant contribution to medicinal chemistry by demonstrating that one can improve the therapeutic index of an anti-inflammatory steroid via a biochemistry-based prodrug design. Knowing that the level of N-acetyl glucosaminidase in a joint is elevated in direct relation to the severity of the disease, he generated the 21- N-acetyl glucosaminide, a biologically inactive prodrug that is selectively activated in the inflamed joint (drug latentiation). The underlying concept is widely employed now-a-days.
Prior to his promotion to Vice-President for Basic Research in 1976, with responsibility in Rahway, West Point, Montreal, and Terlings Park (UK), he served as Merck’s Executive Director of Medicinal Chemistry in West Point, Pennsylvania. Merck agreed to let the peptide group join him at West Point. There, he initiated research on the peptide hormone somatostatin that had just been isolated and characterized chemically and biologically at the Salk Institute. Diabetes-induced retinopathy was the therapeutic target. This research, directed with Daniel F. Veber, led to the elucidation of the hormone’s bioactive conformation, which has served as the basis for all subsequent chemical endeavors in the somatostatin field ever since. This research and the prior synthesis of RNase did much to stimulate peptide research in the pharmaceutical industry. Somatostatin remains one of Ralph’s principal research interests to this day.

He started a second career at the University of Pennsylvania in 1987, where he initiated collaborative research in the field of peptidomimetics with Professors Amos B. Smith, III, and K. C. Nicolaou, now Professor of Chemistry at the Scripps Research Institute in La Jolla, CA. He also held the position of University Professor of the Medical University of South Carolina. The peptidomimetic research at Penn proved to be seminal. It showed that the peptide backbone is not required for receptor binding, but that the B-D-glucose scaffold, to which diverse substituents can be attached, can mimic B-turns; this lead ultimately to the concept of radial symmetry to explain the privileged nature of the scaffold. Secondly, the collaborations established that in the design of inhibitors of proteolytic enzymes, where H-bond interactions are required, the pyrrolinone backbone offers improved transport properties over peptide bonds because of reduced solvation. It also revealed that polypyrrolinones are versatile building blocks that can generate novel helices and turns in addition to B-strands.

Hirschmann has been recognized with three honorary degrees and three endowed lectureships; three chairs are linked to his name. He has received recognition through many awards including the Merck & Co. Inc. Board of Directors Scientific Award and the National Academy of Sciences Award for the Industrial Application of Science. He also received the Romanes Lectureship Award in Pharmacy (Edinburgh), the Agnes Borrowman Special Lectureship in Pharmacy (London University), the Nichols Medal (New York Section, ACS), Chemical Pioneer Award (American Institute of Chemists), the Microbial Chemistry Medal (Kitasato University, Tokyo), the Gold Medal of the Max Bergmann Kreis (Munich), the first Gensia Lecturer, Frontiers in Chemistry Lecture Series [Scripps Clinic and Research Foundation (now The Scripps Research Institute)], the Alfred Burger Award (ACS), the Dr. Josef Rudinger Award of The European Peptide Society, the Edward E. Smissman Bristol Myers Squibb Award (ACS), the Arthur C. Cope Medal in 2000, the presidential National Medal of Science awarded by President Clinton, and in 2002 the Willard Gibbs Medal (Chicago Section, ACS). He is a member of the National Academy of Sciences, a Senior Fellow of the Institutes of Medicine of the National Academies, and a Fellow of the American Academy of Arts and Sciences.
2004 Medicinal Chemistry Award

Dr. Chris Lipinski, recently retired from the Pfizer Global Research and Development Groton Laboratories, has been selected as the recipient of the 2004 Division of Medicinal Chemistry Award of the ACS Division of Medicinal Chemistry. The award will be presented at the 2004 National Medicinal Chemistry Symposium to be held June 30, 2004. The award is given biennially in even-numbered years to a scientist whose research has directly or indirectly had a significant effect on Medicinal Chemistry.

Dr. Lipinski is well-known for his research into the relationship between physiochemical properties of drugs and their gastrointestinal absorption and his development of simple rules for the prediction of oral absorption. Known broadly as Lipinski’s Rule of Five, this important technique allows medicinal chemists to predict the likelihood of good oral absorption for a drug candidate based on its molecular weight, number of hydrogen bond donors and acceptors, and clogP. While certain exceptions exist (e.g. macrolide antibiotics, cardiac glycosides), the Rule of Five has gained broad acceptance and has strongly influenced the way medicinal chemistry is practiced. Rule of Five parameters are now carefully considered throughout the pharmaceutical industry in selecting lead structures for optimization and in the design and synthesis of compound libraries for screening.

Dr. Lipinski received a B.Sc. degree in chemistry from San Francisco State College in 1965 and a Ph.D. in 1968 in physical organic chemistry from the University of California, Berkeley. He joined Pfizer in 1970 following a National Institutes of General Medical Sciences Postdoctoral Fellowship at the California Institute of Technology. At Pfizer, Dr. Lipinski supervised the medicinal chemistry drug discovery laboratories for 20 years, discovering multiple gastrointestinal and diabetic clinical candidates. During this time, he became interested in the design of bioisosteres and in physical chemical properties of drugs and their quantitative structure activity relationships, especially as they relate to problems of oral activity.
In 1990 Dr. Lipinski established a highly automated laboratory combining computations and experimental physical property measurements and provided experimental solubility measurements on medicinal compounds synthesized at the Pfizer Groton site. Computationally he champions a very pragmatic, end user-oriented approach to the optimization of oral activity, as exemplified by his Rule of Five. Dr. Lipinski retired in June 2002, after 32 years at Pfizer, having been promoted to Senior Research Fellow, Pfizer’s highest scientific position.

Dr. Lipinski is an active contributor to the medicinal chemistry community. He is a member of the Medicinal Chemistry Division of the American Chemical Society, the American Association of Pharmaceutical Sciences, the Society for Biomolecular Screening, and the European Federation of Pharmaceutical Sciences. He is a frequent invited speaker at national and international conferences on medicinal and pharmaceutical chemistry. He is a member of the Editorial Board of the Journal of Pharmaceutical Science, the Highlights Advisory Board of Nature Reviews Drug Discovery, and the advisory boards of several other journals. Since 1984, he has been an adjunct faculty member at Connecticut College in New London, CT. He serves on scientific advisory boards for the Global Alliance for TB Drug Development, ASDI II, Advanced Chemistry Development Labs and the Matrical company and is a consultant for Symyx and the Hereditary Disease Foundation. Dr. Lipinski has over 180 publications and invited presentations and 17 issued U.S. patents.
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In the early years of the American Chemical Society, a special interest subgroup—the Pharmaceutical Section—was established. At the 40th national meeting of the society, held in June 1909 at the Central High School Building in Detroit, the Pharmaceutical Section petitioned the ACS Council for a change of status and a change of name—to the Division of Pharmaceutical Chemistry. Alviso Burdett Stevens (University of Michigan), chair of the Pharmaceutical Section, and Benjamin L. Murray (Merck & Company), secretary of the Pharmaceutical Section, were elected to their offices in the new division by the 36 members present. A subsequent mail vote of the Council of the ACS, in October 1909, unanimously approved the new division. (Listed as entertainment highlights for the 320 members and guests at this 1909 ACS meeting were a boat ride on the Detroit River and a visit to Hiram Walker & Sons.)

When the Division of Pharmaceutical Chemistry was established, many of its members were pharmacists, either in academia or in industry. Early national meeting programs largely reflected interests in drug assay methods and formulation improvements. However, the membership profile was slowly changing. In 1920 the Division became the Division of Chemistry of Medicinal Products. Within a relatively few more years, the Division's membership was composed chiefly of individuals with degrees and professional careers in chemistry, and the members' interests began to center on the chemical structure of drugs.

In 1928 a final name change was made to the Division of Medicinal Chemistry. The primary stated goal was the stimulation of progress in medicinal chemistry research. The term "medicinal chemistry" replaced the less precise one "pharmaceutical chemistry," and medicinal chemists were recognized by the scientific community as practitioners of a unique type of chemistry (sometimes related to but nevertheless separate and distinct from organic chemistry, biochemistry, and pharmacy).

In addition to conducting oral presentations of research findings at national ACS meetings, the Division has been aggressive in initiating and promoting a variety of scholarly activities to benefit medicinal chemists. The first national Medicinal Chemistry Symposium I (sponsored by the Division) was held in 1948 at the University of Michigan, with F.P. Blicke as general chair and Glenn E. Ullyot as program chair. Symposia have subsequently been held regularly in alternate even-numbered years, always on a university campus. In 1968 the symposium assumed an international flavor, meeting at Laval University in Quebec under joint sponsorship with the newly formed Medicinal Chemistry Division of the Chemical Institute of Canada. Another joint symposium with this group was held at the University of Toronto in 1982.

From the early days of the Division, it was recognized that an English language journal dedicated exclusively to medicinal chemistry research would be highly desirable. However, for years it was questionable whether a large enough constituency existed to support such a publication. Many medicinal chemists had been publishing their work in the Journal of Organic Chemistry and in other "pure" chemistry journals, but editors of these serials became increasingly resistant to including results of pharmacological testing or discussions of structure-activity relationships.

Some editors viewed medicinal chemistry research as "applied" rather than "basic" or "fundamental" chemistry. In the middle and late 1950s, there was increased discussion of division sponsorship of a medicinal chemistry research journal—a serial that would be on a scientific level with
the pre-eminent journals in other specialized fields of chemistry. The Scientific Edition of the Journal of the American Pharmaceutical Association had for many years accepted medicinal chemistry papers, but only as a part of its coverage of all aspects of pharmacy-related research.

In 1958-59, Division representatives requested an informal, off-the-record meeting with the editor of the Scientific Edition, to discuss the feasibility of the Division's sponsorship and publication of the Journal of the American Pharmaceutical Association, Scientific Edition with expansion of its coverage of medicinal chemistry-related research, and the possibility of shortening or changing the journal's unwieldy name. The Division's request for such a meeting was rebuffed.

In 1959 there appeared the first issue of a commercially published serial, the Journal of Medicinal and Pharmaceutical Chemistry, edited by Arnold H. Beckett (the Chelsea College of Science and Technology, London) and Alfred Burger (the University of Virginia). This small-size journal appeared six times yearly. From its initial issue, it attracted high-quality research papers from prominent researchers in the international community (but chiefly from the United States and the United Kingdom). In 1960 the Division lobbied for ACS participation in the publication of this journal, and Division representatives took an active role in exploratory discussions between the ACS and the publisher.

In 1962 the Journal of Medicinal and Pharmaceutical Chemistry became an official publication of the American Chemical Society with Alfred Burger as sole editor. One year later the name was changed to the Journal of Medicinal Chemistry, and its physical dimensions were expanded to approximate those of other ACS serials. Editor Burger emphasized manuscript requirements of clear, concise, and grammatically correct writing and high-quality science. The established format for published papers was rigorously enforced.

Philip S. Portoghese succeeded Professor Burger as editor in 1972, and his title was changed to editor in chief in 1985. The administrative structure of the journal has evolved to include a group of senior editors, a perspectives editor, and a book review editor (all under the editor in chief), reflecting the increasingly diverse informational role of the journal and the massive increase in number, quality, and diversity of submitted manuscripts.

The number of yearly issues increased to 12 in 1971 and to 26 in 1992. The Journal of Medicinal Chemistry is universally recognized as the premier publication in medicinal chemistry research in the world. Professor Portoghese's 32-plus years in command must approach a longevity record for ACS publications, at least in contemporary times.

Annual Reports in Medicinal Chemistry first appeared as a Division publication in 1966. The series owes its existence, in large measure, to the efforts of the late C.K. ("Neil") Cain, who served as editor in chief for the first six years. Dr. Cain visualized an annual publication consisting of short chapters describing and referencing recent developments and advances in the broadest variety of areas of medicinal chemistry, to be written by investigators active in and cognizant with the subject of their chapter. Annual Reports was to be a paperback book and authors were to submit their manuscripts camera-ready, to minimize publication time and cost.

Every member of the Medicinal Chemistry Division receives a copy of Annual Reports as a prerequisite to membership. It was emphasized that section editors and authors (as well as the publisher) adhere rigorously to time deadlines to ensure that the volume will be in the hands of readers each year in mid to late September. Only once in 34 years has the distribution of Annual Reports in Medicinal Chemistry been delayed (to the great and extremely vocal consternation of readers). This review of research and discoveries in medicinal chemistry is recognized as the most significant of its kind.
Consistent with activities in other special interest divisions of the ACS, Division members favored formal recognition of outstanding contributions to medicinal chemistry. The Division established two awards honoring outstanding medicinal chemists, given in alternate years. The first Division of Medicinal Chemistry Award was presented in 1966 to Professor Bernard R. Baker at the Biennial Medicinal Chemistry Symposium at Indiana University. The roster of subsequent recipients of this award includes two Nobel laureates.

A second award, the Bristol Myers Squibb Award, was named in honor of the late Edward E. Smisson and was first presented in 1975 to Professor Corwin Hansch. With perhaps a single exception, this award also displays a roster of distinguished recipients.

A more recently established award, the Alfred Burger Award, also recognizes outstanding achievement by medicinal chemists. Its title honors a distinguished elder statesman of medicinal chemistry. The Burger Award is administered by the ACS.

In 1968 the Division established a Public Affairs Committee, with Dr. Glen Ullyot as its first chair. This Committee monitors federal and state government activities that affect medicinal chemistry, informing division members. The committee also recommends appropriate division and member responses. Division representatives have testified and supplied scientific expertise before committees of the Congress.

Illustrative of its concern for the future of medicinal chemistry, in 1990 the division (through the generosity of several industrial sponsors) initiated an on-going program of awarding of predoctoral graduate fellowships to a limited number of outstanding applicants. This successful program complements the student travel grant program, which enables graduate students to present results of their research at national ACS meetings or at the national symposium. Traditionally, these students are also guests at an awards luncheon hosted by Division officers and attended by recipients of other division research awards.

In the earlier years, Division membership and leadership was limited almost exclusively to men. After World War II, with more women pursuing careers in chemistry, Division membership began to include significant numbers of women, and women assumed leadership roles. In 1977 Dr. Barbara Roth was elected Division chair (the first woman to occupy this office). The Division now has a sizable number of women members, several serving or having served as Division officers and committee chairs. It is anticipated that the numbers of women chemists actively participating and leading in the affairs of the Division will continue to increase.

The Division of Medicinal Chemistry is now one of the largest special-interest divisions of the ACS, with a membership of well over 10,000, including a sizable number of chemists from foreign countries.

The author acknowledges with thanks the contribution of Cheryl A. Vockins of the ACS Records Office and Michele Gandy of the Office of Divisional Affairs, who were most helpful in supplying information on the early days of the Division.
### Past Meeting Sites

<table>
<thead>
<tr>
<th>No.</th>
<th>Date</th>
<th>Location</th>
<th>General Chair(s)</th>
<th>Program Chair(s)</th>
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<tbody>
<tr>
<td>1st</td>
<td>June 17-19, 1948</td>
<td>University of Michigan, Ann Arbor; Frederick F. Blicke, General Chair; Glenn E. Ullyot, Program Chair</td>
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<tr>
<td>2nd</td>
<td>June 15-17, 1950</td>
<td>Notre Dame University, Notre Dame, Indiana K. N. Campbell, General Chair; R. O. Roblin, Program Chair</td>
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<tr>
<td>3rd</td>
<td>June 12-14, 1952</td>
<td>University of Virginia, Charlottesville Alfred Burger, General Chair; F. Y. Wiselogle, Program Chair</td>
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<tr>
<td>4th</td>
<td>June 17-19, 1954</td>
<td>Syracuse University, Syracuse, New York; Amel R. Menotti, General Chair; Thomas P. Carney, Program Chair</td>
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<tr>
<td>5th</td>
<td>June 21-23, 1956</td>
<td>Michigan State University, East Lansing; Robert M. Herbst, General Chair; Loren M. Long, Program Chair</td>
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<td>6th</td>
<td>June 23-25, 1958</td>
<td>University of Wisconsin, Madison; Edward E. Smissman, General Chair; John H. Biel, Program Chair</td>
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<td>7th</td>
<td>June 20-22, 1960</td>
<td>University of Rhode Island, Kingston; John Defeo, General Chair; Richard V. Heinzelman, Program Chair</td>
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<tr>
<td>8th</td>
<td>June 18-20, 1962</td>
<td>University of Colorado, Boulder; Norman F. Wiu, General Chair; Nathan E. Sperber, Program Chair</td>
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<tr>
<td>9th</td>
<td>June 21-24, 1964</td>
<td>University of Minnesota, Minneapolis; Robert H. Miller, General Chair; Barry M. Bloom, Program Chair</td>
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<tr>
<td>10th</td>
<td>June 27-29, 1966</td>
<td>Indiana University, Bloomington; Ernest E. Campagne, General Chair; Arthur A. Patchett, Program Chair</td>
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<td>11th</td>
<td>June 23-26, 1968</td>
<td>Laval University, Quebec, Canada; Joint with Chemical Institute of Canada; Charles R. Engel and Louis Berlinguet Co-General Chairs; Scott J. Childress and Leslie G. Humber, Co-Program Chairs</td>
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<td>12th</td>
<td>June 22-25, 1970</td>
<td>University of Washington, Seattle; Walter C. McCarthy, General Chair; John R. Dice, Program Chair</td>
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<td>13th</td>
<td>June 18-22, 1972</td>
<td>University of Iowa, Iowa City; Joseph G. Cannon, General Chair; Irwin J. Pachter, Program Chair</td>
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<td>14th</td>
<td>June 16-20, 1974</td>
<td>University of New Hampshire, Durham; Robert E. Lyle, General Chair; John G. Topliss, Program Chair</td>
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<td>15th</td>
<td>June 20-24, 1976</td>
<td>University of Utah, Salt Lake City; Leroy B. Townsend, General Chair; Walter T. Moreland, Program Chair</td>
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<td>16th</td>
<td>June 18-22, 1978</td>
<td>Western Michigan University, Kalamazoo; Robert E. Harmon, General Chair; Daniel Lednicer, Program Chair</td>
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<td>17th</td>
<td>June 15-18, 1980</td>
<td>Rensselaer Polytechnic Institute, Rensselaer, New York; Sydney Archer, General Chair; Ralph F. Hirschmann, Program Chair</td>
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<td>18th</td>
<td>June 20-24, 1982</td>
<td>University of Toronto, Ontario, Canada; Leslie G. Humber, General Chair; Leslie G. Humber, Program Chair</td>
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# American Chemical Society, Division of Medicinal Chemistry

## Past Officers

### Secretary- Treasurer

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Program for the 29th National Medicinal Chemistry Symposium
June 27- July 1, 2004
Madison, Wisconsin

Sunday, June 27, 2004
10 AM – 8:00 PM  Registration  Main Lounge

1:00 PM  Opening remarks  Union Theater
Daniel H. Rich, Chair; James R. McCarthy, Program Chair; Charles Casey, ACS President; Jeanette Roberts, Dean of the School of Pharmacy; University of Wisconsin-Madison; Honorary Chair: Dr. Ralph F. Hirschmann

1:30 PM  Session 1: Inhibitors of Hepatitis C  Union Theater
Ron Griffith, Chair, Genelabs (650) 562-1580; rgriffith@genelabs.com
1. Pierre L. Beaulieu, Boehringer Ingelheim, “Allosteric Inhibitors of the Hepatitis C Virus NS5B Polymerase: Towards Novel Anti-HCV Therapies”; pbeaulieu@lav.boehringer-ingelheim.com
2. Kevin Duffy, GlaxoSmithKline “The Discovery of Potent, Non-Nucleoside Inhibitors of the Hepatitis C Virus RNA-Dependent RNA Polymerase”; Kevin.j.duffy@gsk.com
3. David B. Olsen, Merck Research Labs. “Mechanism of Action and SAR of 2’ Modified Nucleoside Inhibitors of Hepatitis C Virus RNA Replication”; david_olsen@merck.com
4. Youla Tsantrizos, Boehringer Ingelheim “The Design and Synthesis of BILN-2061, a Potent Inhibitor of the Hepatitis C Virus: From NMR Tube to the Clinic”; ytsantrizos@lav.boehringer-ingelheim.com

5:00 PM  Plenary Session Sponsored by Eli Lilly  Union Theater
Professor Samuel J. Danishefsky, Department of Chemistry, Columbia University and Laboratory of Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, “Archives on the Power of Chemical Synthesis”; (212) 639-5501
s-danishefsky@ski.mskcc.org

6:00-9:00 PM  Symposium Mixer Sponsored by AztraZeneca Corporation  Tripp Commons

Monday, June 28, 2004
8:00 AM  Session 2: SERMS and SARMS  Union Theater
Co-chairs: George D. Hartman, Merck West Point (215) 652-7279; George-hartman@merck.com and Mark E. Duggan (215) 652-6118; mark_duggan@merck.com

SERMS
1. John Katzenellenbogen, University of Illinois, “Nuclear Hormone Receptors: Structure, Function, Ligands and Imaging”; jkatzene@uiuc.edu
2. Jeff Dodge, Lilly Research laboratories, Discovery and Pharmacology of LY2066988: A Novel Highly Potent SERM for the Treatment of Uterine Fibroids”; dodge_jeffrey_a@lilly.com
3. Richard E. Mewshaw, Wyeth Research, “Exploiting New Scaffolds Toward the Discovery of ErB-Selective Ligands”; mewshar@wyeth.com
SARMS

4. Duane Miller, University of Tennessee, “Novel, Selective Androgen Receptor Modulators (SARMS) – Past, Present and Future”; dmiller@utmem.edu

5. Yuntae Kim, Merck and Co., “A Novel Benzimidazole Class of Androgen Receptor Modulators”; yuntae_kim@merck.com

6. Chongqing Sun, Bristol-Myers Squibb, “Highly Potent and Muscle Selective Bicyclic N-Aryl Hydantoin SARMs”; chongqing.sun@bms.com

12 Noon Lunch Tripp Commons

1:30 PM Session 3: Kinase Inhibitors Union Theater
Jerry Adams, Chair, GlaxoSmithKline, Collegeville (610) 270-5465; jerry.l.adams@gsk.com

1. Karen Lackey GlaxoSmithKline, RTP NC, “Systems Based Research in the Kinome”; Karen.e.lackey@gsk.com

2. Peter Traxler, Novartis Pharmaceuticals, Basel, “Recent Progress in the Design of Tyrosine Kinase Inhibitors”; peter.traxler@pharma.novartis.com

3. Mark Fraley, Merck & Co., Inc., “Optimization of the 1H-Indol-2-yl-Quinolin-2-one Class of KDR (VEGFR-2) Kinase Inhibitors: In Vitro and In Vivo Characterization of a Clinical Candidate”; mark_fraley@merck.com

4. Neil Moss, Boehringer Ingelheim “Evaluation of Compounds that Bind p38 MAP Kinase in a “Phe out” Conformation”; nmoss@rdg.boehringer-ingelheim.com

5. Haile Tecle, Pfizer Inc., “Non ATP Competitive MEK Inhibitors”; haile.tecle@pfizer.com

6:00-7:30 PM Poster Session Sponsored by Pfizer Inc. Great Hall
(Poster presenters with even numbers)
Dean Brown, Chair, AstraZeneca Corporation (302) 886-7535; dean.brown@astrazeneca.com

Tuesday, June 29, 2004

8:00 AM Session 4: Natural Products Biosynthesis Union Theater
Co-chaired by Ben Shen (608) 263-2673 bshen@pharmacy.wisc.edu and Jon Thorson (608) 262-3829 jsthorson@pharmacy.wisc.edu; University of Wisconsin-Madison

1. Chris Walsh, Harvard Medical School, “Glycosyltransferase Involved in Antibiotic Biosynthesis and Tailoring”; christopher_walsh@hms.harvard.edu

2. Jon Thorson, “Natural Product Glycorandomization”


4. C. Richard Hutchinson, Kosan Biosciences, “Medicinal Chemistry by Microbiology: The Kosan Story”; Hutchinson@kosan.com

12 Noon-1:30 PM Lunch Tripp Commons

1:30-5:30 PM Tours/Free time
Wednesday, June 30, 2004

8:00 AM  
**Session 5: NK1 Receptor Antagonists**  
*Union Theater*

*Alan Naylor, Chair, GlaxoSmithKline Harlow 011-44-1279-87-5220; alan.2.naylor@gsk.com*

1. Erik Hembre, Lilly Research Laboratories, “The Discovery and Optimization of Novel Triazole Based NK-1 Antagonists”; hembre_erik_j@lilly.com

2. John Humphrey Pfizer Inc., “Potent New NK1 Antagonists from a Modified Piperidine Template. Diastereoselective Synthesis of 2,3,6-Trisubstituted Piperidines”; john_m_humphrey@groton.pfizer.com

3. Paul Finke, Merck & Co., Inc., “Recent Progress in Orally Active NK-1 Antagonists”; paul_finke@merck.com

4. Patrick Schnider, Hoffman-La Roche Ltd., “Design and Synthesis of Potent and Selective Orally Active NK-1 Receptor Antagonists”; Patrick.schnider@roche.com

12 Noon  
Lunch  
*Tripp Commons*

1:30 PM  
**Session 6: Medicinal Chemistry Award Symposium, Sponsored by Pfizer Inc.**  
*Union Theater*

1. Nick Terrett, Pfizer Inc.; nick_terrett@cambridge.pfizer.com

2. Russell A. Lewthwaite, Pfizer Inc.; Russell_lewthwaite@sandwich.pfizer.com

3. Christopher A. Lipinski, Pfizer Inc.; Award Address - Christopher_a_lipinski@groton.pfizer.com

4:00-5:30 PM  
**Poster Session, Sponsored by AstraZeneca Corporation**  
*Great Hall*

(Poster presenters with odd numbers)

*Dean Brown, Chair, AstraZeneca (302) 886-7535; dean.brown@astrazeneca.com*

7:30 PM  
**Symposium Banquet, Reception sponsored by Amgen**  
*Monona Terrace*

Thursday, July 1, 2004

8:00 AM  
**Session 7: Late Breaking Session**  
*Union Theater*

*Lihu Yang, Chair, Merck & Co., (732) 594-4660; lihu_yang@merck.com*

1. Ann Weber (Merck): Discovery of MK-0431: A Potent, Selective Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes

2. P. K. Jadhav (Lilly): Discovery of Potent Non-Steroidal Mineralocorticoid Receptor Antagonists

3. Julio Medina (Tularik): Discovery and Development of the CXCR3 Antagonist T487 as Therapy for Th1-Mediated Immune Disorders

4. Marlon Cowart (Abbott): A New Mechanism with the Potential to Treat Erectile Dysfunction: the Medicinal Chemistry and Pharmacology of D4 agonists

5. Dave Donald (AstraZeneca): Novel Inhibitors of T cell proliferation

6. Arie Zask (Wyeth): Novel Antimicrotubule Agents for the Treatment of Cancer

7. Samit K. Bhattacharya (Pfizer): Discovery of CP-724714, a Potent and Selective ErbB2 Receptor Tyrosine Kinase Inhibitor

12 Noon – 1:30 Lunch  
*Tripp Commons*

Conference Adjourns  
xxiii
Notes
Abstract Listings

Speakers

Abstracts #1 - 34

1 ALLOSTERIC INHIBITORS OF THE HEPATITIS C VIRUS NS5B POLYMERASE: TOWARDS NOVEL ANTI-HCV THERAPIES
   Pierre L. Beaulieu

2 THE DISCOVERY OF BENZO[1,2,4]THIADIAZINES AS NON-NUCLEOSIDE HEPATITIS C VIRUS NS5B POLYMERASE INHIBITORS
   Kevin J. Duffy

3 MECHANISM OF ACTION AND SAR OF 2'-MODIFIED NUCLEOSIDE INHIBITORS OF HEPATITIS C VIRUS RNA REPLICATION

4 THE DESIGN AND SYNTHESIS OF BILN 2061, A POTENT INHIBITOR OF THE HEPATITIS C VIRUS: FROM THE NMR TUBE TO THE CLINIC
   Youla S. Tsantrizos

5 ARCHIVES ON THE POWER OF CHEMICAL SYNTHESIS
   Samuel J. Danishefsky

6 NUCLEAR HORMONE RECEPTORS: STRUCTURE, FUNCTION, LIGANDS AND IMAGING
   John Katzenellenbogen

7 DISCOVERY, SAR, AND PRE-CLINICAL EVALUATION OF A NOVEL SELECTIVE ESTROGEN RECEPTOR MODULATOR FOR THE TREATMENT OF LEIOMYOMA (UTERINE FIBROIDS)
   Jeffrey A. Dodge*, Conrad W. Hummel, Ilene Cohen, Robert D. Dally, Scott Frank, Ronald Hinklin, Dennis McCann, Norman E. Hughes, Scott Jones, George Lewis, Timothy A. Shepherd, Owen Wallace, Yong Wang, Henry U. Bryant, Andrew Geiser

8 EXPLOITING NEW SCAFFOLDS TOWARD THE DISCOVERY OF ERβ SELECTIVE LIGANDS

9 NOVEL, SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)-PAST, PRESENT AND FUTURE
   Duane D. Miller*, Dong Jin Hwang, Renukadevi Patil, Vinod Nair, Suni M. Mustafa, Michael L. Mohler, Igor M. Rakov, Seoung Soo Hong, Yali He, Karen Veverka, Mitch S. Steiner, K. Gary Barnette, Robert Boger, Donghua Yin, Weiqing Gao, Jeffrey D. Kearbey, Huiping Xu, Juhyun Kim, Jiyun Chen, Casey Bohl, and James T. Dalton

10 A NOVEL BENZIMIDAZOLE CLASS OF ANDROGEN RECEPTOR MODULATORS
    Yuntae Kim*, Barbara A. Hanney, Jeffrey D. Muselman, Keith L. Spencer, George D. Hartman, Mark E. Duggan

11 HIGHLY POTENT AND MUSCLE SELECTIVE BICYCLIC N-ARYL HYDANTOIN SARMS

12 SYSTEMS BASED RESEARCH IN THE KINOME
    Karen E. Lackey

* denotes presenter
13 RECENT PROGRESS IN THE DESIGN OF TYROSINE KINASE INHIBITORS
Peter Traxler

14 OPTIMIZATION OF THE 1H-INDOL-2-YL-1H-QUINOLIN-2-ONE CLASS OF KDR (VEGFR-2) KINASE INHIBITORS: IN VITRO AND IN VIVO CHARACTERIZATION OF A CLINICAL CANDIDATE
Mark Fraley

15 EVALUATION OF COMPOUNDS THAT BIND P38 MAP KINASE IN A [PHE OUT] CONFORMATION
Neil Moss

16 THE DEVELOPMENT OF NON-ATP COMPETITIVE MEK INHIBITORS AS POTENTIAL ANTICANCER DRUGS.
Haile Tecle

17 GLYCOSYLTRANSFERASES INVOLVED IN ANTIBIOTIC BIOSYNTHESIS AND TAILORING
Christopher Walsh

18 NATURAL PRODUCT GLYCORANDOMIZATION
Jon S. Thorson

19 MANIPULATION OF SECONDARY METABOLIC PATHWAYS FOR DRUG DISCOVERY
Ben Shen

20 KOSAN BIOSCIENCES: A CASE STUDY FOR DRUG LEAD DISCOVERY BY COMBINATORIAL BIOSYNTHESIS
C. Richard Hutchinson

21 THE DISCOVERY AND OPTIMIZATION OF TRIAZOLE BASED NK-1 ANTAGONISTS

22 POTENT NEW NK1 ANTAGONISTS FROM A MODIFIED PIPERIDINE TEMPLATE: DIASTEREOSELECTIVE SYNTHESIS OF 2,3,6-TRISUBSTITUTED PIPERIDINES.
John M. Humphrey*, Brian T. O’Neill, Thomas A. Chappie, Eric Arnold, Stafford McLean, Dianne K. Bryce-Pritt, Angela C. Doran, Bill J. Smith, F. David Tingley

23 RECENT PROGRESS IN ORALLY ACTIVE NK1 ANTAGONISTS
Paul E. Finke

24 DESIGN AND SYNTHESIS OF POTENT AND SELECTIVE, ORALLY ACTIVE NK1 RECEPTOR ANTAGONISTS
Patrick Schnider*, Theresa M. Ballard, Michael Bös, Guido Galley, Thierry Godel, Guy A. Higgins, Torsten Hoffmann, Walter Hunkeler, Sonia M. Poli, Andrew J. Sleight and Heinz Stadler

25 PHOSPHODIESTERASES AS A RICH SOURCE OF NOVEL DISEASE TARGETS AND DRUG MOLECULES
N.K. Terrett*, R.J. Chambers, and K. Lam

26 THE DESIGN AND INCORPORATION OF AN INTRA-MOLECULAR HYDROGEN BOND TO INCREASE CNS PENETRATION
Russell A Lewthwaite

27 FILTERING IN DRUG DISCOVERY: THE IMPORTANCE OF THE CHEMISTRY QUALITY MESSAGE
Christopher A. Lipinski

28 DISCOVERY OF MK-0431: A POTENT, SELECTIVE DIPEPTIDYL PEPTIDASE IV INHIBITOR FOR THE TREATMENT OF TYPE 2 DIABETES
29 DISCOVERY OF POTENT NON-STEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS
Prabhakar K. Jadhav*, Donald P. Matthews, Jonathan Green, Kevin Fales, James Nixon, Anthony Borel, Sally Kelley, Karen Zimmerman, Mitchell I. Steinberg

30 DISCOVERY AND DEVELOPMENT OF THE CXCR3 ANTAGONIST T487 AS THERAPY FOR TH1 MEDIATED IMMUNE DISORDERS
Julio Medina*, Tassie Collins, Michael Johnson, An-Rong Li, Zice Fu, Jiwen Liu, Andrew Marcus, George Tonn, Thomas Schall, Qiuping Ye

31 A NEW MECHANISM WITH THE POTENTIAL TO TREAT ERECTILE DYSFUNCTION: THE MEDICINAL CHEMISTRY AND PHARMACOLOGY OF D₄ AGONISTS

32 NOVEL INHIBITORS OF T CELL PROLIFERATION
Dave Donald

33 NOVEL ANTIMICROTUBULE AGENTS FOR THE TREATMENT OF CANCER
Arie Zask*, Gary Birnberg, Joshua Kaplan, Chuan Niu, Frank Loganzo, Carolyn M. Discafani, Lee M. Greenberger, Semiramis Avrak-Kaloustian

34 DISCOVERY OF CP-724714, A POTENT AND SELECTIVE ERBB2 RECEPTOR TYROSINE KINASE INHIBITOR

Posters
Abstracts #35 - 116

35 THE DESIGN OF INHIBITORS OF THE HCV NS3•4A PROTEASE. THE IDENTIFICATION OF A CLINICAL DEVELOPMENT CANDIDATE, VX-950

36 PEPTIDOMIMETIC ALPHA-KETOAMIDE INHIBITORS OF HEPATITIS C NS3 PROTEASE EXHIBIT A SLOW-BINDING MECHANISM
Cynthia A. Gates*, Lawrence F. Courtney, Yu-Ping Luong, Shawn D. Britt, John C. Court, Wayne C. Schairer, Janos Pitlik, Scott L. Raybuck and Robert B. Perni

37 TOWARDS NOVEL THERAPEUTICS AGAINST HIV INFECTION AND DRUG RESISTANCES
Ye Che*, Bernard R. Brooks and Garland R. Marshall

38 NOVEL OXINDOLES AS POTENT ANTI-HIV AGENTS
Yun He*, Tao Jiang, David A. Ellis, Beth Anacletio, Kelli L. Kuhen, Karen Wolff, Hong Yin, Kimberly Bieza, Badry Bursulaya, Tom Yao-Hsing Wu, Tove Tuntland, Kanyin Zhang, Jeremy S. Caldwell

39 CHEMICAL PROBES OF THE CATALYTIC MECHANISM OF UDP-GALACTOPYRANOSE MUTASE
Erin E. Carlson*, Michelle S. Higgin, John F. May, Todd D. Gruber, and Laura L. Kiessling

40 DIASTEREOSELECTIVE CONDENSATION OF SERINAL DERIVATIVES WITH AZOLID YLIDES: A SYNTHESIS OF β-AZOLYL-β-HYDROXYL-α-AMINO ACIDS
Craig A. Zificsak*, Dennis J. Hlants
THE SELECTIVE ESTROGEN RECEPTOR MODULATOR ZK 186619

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF SUBSTITUTED NAPHTHALENES AS ESTROGEN RECEPTOR LIGANDS

NOVEL PROBES FOR THE ESTROGEN RECEPTOR LIGAND BINDING DOMAIN
Robert N. Hanson

UTILITY OF BORON CLUSTERS FOR DRUG DESIGN. QSAR BETWEEN ESTROGEN RECEPTOR BINDING AFFINITY AND HYDROPHOBICITY OF CARBORANYLPHENOLS
Kiminori Ohta*, Keisuke Yamamoto, Yasuyuki Endo

MODULATING NONGENOMIC/GENOMIC ESTROGEN SIGNALING WITH MODIFIED SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)
Joseph Trebley

DESIGN, SYNTHESIS AND SAR OF QUINOLINE-BASED ESTROGEN RECEPTOR BETA-SELECTIVE LIGANDS.
An T. Vu*, Stephen T. Cohn, Eric S. Manas, Heather A. Harris, Richard E. Mewshaw

LGD2226 AS A NOVEL SELECTIVE ANDROGEN RECEPTOR MODULATOR (SARM)
Arjan Van Oeveren*, Keith B. Marschke, Francisco J. Lopez, Lin Zhi

NEW ANTIESTROGENS FROM A LIBRARY OF HOMOALLYLIC AMINES, ALLYLIC AMINES AND CYCLOpropylALKALAMINES
Jelena M. Janjic*, Christopher Kendall, Corey R.J. Stephenson, Ying Mu, Wen Xie, Raghavan Balachandran, Brianne Raccor, Ying Lu, Guangyu Zhu, Peter Wipf, Billy W. Day

DEVELOPEMENT OF BICYCLIC PYRAZOLONES AS CYTOKINE SYNTHESIS INHIBITORS
Roger Bookland*, Michael Clark, Steve Laughlin, Matthew Laufersweiler, Todd Brugel, Adam Golebiowski, Mark Sabat, Jane Djung, Michael Natchus, Jennifer Townes, John vanRens, Biswanath De, Lily Hsieh, Susan Xu, Rick Walter, Michael Janusz

MONOCYCLIC PYRAZOLONES AS CYTOKINE SYNTHESIS INHIBITORS

NOVEL BICYCLIC PYRIMIDINE DERIVATIVES AS P38 MAP KINASE INHIBITORS
Jian Jeffrey Chen, Stacie A. Dalrymple, Nolan James Dewdney*, Pete Dunten, David M. Goldstein, Eva Papp, Rick Roberts, Mary Welch, Haixia Wang

DISCOVERY OF A NOVEL CLASS OF ORALLY ACTIVE P38 MAP KINASE INHIBITORS

PYRIDAZINES AS A NEW CHEMOTYPE FOR ALZHEIMER’S DISEASE DRUG DISCOVERY THAT TARGETS DISEASE PROGRESSION
Wenhui Hu*, Laurie K. McNamara, Sakti Roy, Jeffrey M. Craft, Magdalena Zasadzki, Linda J. Van Eldik and D. Martin Watterson

NOVEL AND POTENT TGF-β TYPE I INHIBITOR: 7-AMINO 4-(2-PYRIDIN-2-YL-5,6-DIHYDRO-4H-PYRROLO[1,2-B]PYRAZOL-3-YL)-QUINOLINES
Hong-yu Li*, Yan Wang, Lei Yan, Robert M. Campbell, Bryan D. Anderson
55 DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 7-AZAINDOYL-
HETEROARYLMALEIMIDES AS POTENT AND SELECTIVE GLYCOGEN SYNTHASE KINASE-
$\beta\beta\beta\beta\beta$ (GSK-$\beta\beta\beta\beta\beta$) INHIBITORS
David J. O’Neill*, Lan Shen, Catherine Prouty, Bruce R. Conway, Jun Z. Xu, Han-Cheng Zhang, Bruce E.
Maryanoff, William V. Murray, Keith T. Demarest and Gee-Hong Kuo

56 MOLECULAR MODELING QUEST FOR INHIBITORS OF THE CDK5/P35 INTERACTION
Felipe Opazo, Gerald Zapata-Torres, Ricardo B. Maccioni, Bruce K. Cassels*

57 INHIBITION OF SRC KINASE ACTIVITY BY 4-ANILINO-7-PYRIDINYL-3-
QUINOLINECARBONITRILES
Biqi Wu*, Nan Zhang, Diane H. Boschelli, Jennifer M. Golas and Frank Boschelli

58 THE DISCOVERY OF POTENT AND SELECTIVE INSULIN-LIKE GROWTH FACTOR I
RECEPTOR KINEASE INHIBITORS
Hofmann

59 PEPTIDES IDENTIFIED BY PHAGE DISPLAY THAT BIND TO DIFFERENT EPITOPES OF THE
SAME TARGET CAN BE DIMERIZED WITH A NOVEL LINKING STRATEGY TO IMPROVE
POTENCY OVER MONOMERS AS MUCH AS 250-FOLD FOR THE TYROSINE KINASES KDR/
VEGFR-2 AND CMET
Radhakrishna Pillai, Palaniappa Nanjappan, Edmund R. Marinelli, Rolf E. Swenson*, Ajay Shrivastava,
Mathew von Wronska, Nancy Bogdan, Adrian D. Nunn, Michael F. Tweedle, Aaron K. Sato, Robert Ladner,
Daniel Dransfield, Daniel Sexton, Mary Devlin, Greg Conley, Qing Chang

60 SAR OF IMPROVED COMPOUNDS FOR TARGETED RADIOTHERAPY OF HUMAN SOLID
TUMORS EXPRESSING GASTRIN RELEASEING PEPTIDE RECEPTORS
Rolf E. Swenson*, Luciano Lattuada, Enrico Cappelletti, Natarajan Raju, Hanh Nguyen, Jianqin Chen,
Karen E. Linder, Laura E. Lantry, Thangavel Arunachalam, Adrian D. Nunn, Michael F. Tweedle

61 BIOSYNTHESIS OF ENEDIynes AND THEIR RESISTANCE MECHANISMS
Qunjie Gao*, Changsheng Zhang, Heather Johnson, Yu Huang, In-Kyoung Lee, Martin H. Hager, Jon S.
Thorson

62 METHYLTRANSFERASE DEPENDENT DNA ALKYLATION WITH AZIRIDINE-BASED
COFACTOR MIMICS
Lindsay R. Comstock* and Scott R. Rajski

63 SYNTHESIS AND CYTOTOXICITY OF 1,2-DISUBSTITUTED IMIDAZO[4,5-G]QUINOLINE-5,8-
DIONE DERIVATIVES
Seon Hee Jeong, Seung Hoon Cheon*

64 IDENTIFICATION OF A NOVEL CLASS OF CELL CYCLE INHIBITORS AS ANTI-CANCER
AGENTS
Michael S. Saporito, Alexander Ochman, Laura Hong, Kyoung-Jin Lee, Martha J. Kelly, Bruce Dorsey*,
Brad Zerler.

65 THE TUMOR CELL MIGRATION INHIBITOR MIGRASTATIN: ANALYSIS OF ITS
BIOSYNTHETIC GENE CLUSTER IN STREPTOMYCES PLATENSIS AND ENGINEERING FOR
NOVEL ANALOGS
Si-Kyu Lim*, Jian-Hua Ju, and Ben Shen

66 $\gamma$-RADIATION INDUCED DNA-DAMAGED PRODUCTS: INSIGHT INTO STEREOCHEMICALLY
FAVORED 6-(a-THYMINYL)-5,6-DIHYDROTHYMINE DERIVATIVES
Javier Ulises Ortiz Mayo, Francois-Yves Dupradeau, Dominique Guillaume, Jean-Louis Fourrey, and
Pascale Clivio*
67 THE SYNTHESIS OF NOVEL C-5'-MODIFIED GLYCOSIDIC FLUOROINDOLOCARBAZOLES AS TOPOISOMERASE I INHIBITORS
Edward Ruediger*, Byron Long, Carol Bachand, Francis Beaulieu, Craig Fairchild, David Frennesson, Miaka Mahler, Alain Martel, Mark Saulnier, Denis St. Laurent, Dolatrai Vyas, Balu Balasubramanian

68 DISCOVERY OF POTENT ANTAGONISTS OF THE ANTI-APOPTOTIC PROTEIN XIAP FOR THE TREATMENT OF CANCER

69 HIT-TO-LEAD PROCESS AT SCHERING AG

70 ADVANTAGES OF USING SPECIES-SPECIFIC LOG D IN DRUG DESIGN AND ADMET ANALYSES
Robert A. Scherrer*, Stephen F. Donovan

71 THE EFFECTS OF SUBSTITUTION ON PYAN-LACTONE CONTAINING DIHYDROPYRIDINE ATP-SENSITIVE POTASSIUM CHANNEL OPENERS.
Robert J. Altenbach, Victoria E. Scott, Kristi L. Whiteaker, Ivan Milicic, Steven A. Buckner, Murali Gopalakrishnan, Michael J. Coghlan* and William A. Carroll


73 DISCOVERY OF POTENT PROSTAGLANDIN EP2 AND EP4 RECEPTORS AGONISTS THAT EXHIBIT BONE ANABOLIC PROPERTIES IN RATS
Zhong Zhao*, Bagna Bao, Nadia Brugger, David Fischer, Claudio Giachetti, Lucia Golzio, Srinivasa Karra, Paolo Marinelli, Sean McKenna, Elizabeth Palmer, Adulla Reddy, YuFang Xiao, Gian Luca Araldi

74 RATIONAL DESIGN OF POTENT AND SELECTIVE NH-LINKED ARYL/HETEROARYL CATHEPSIN K INHIBITORS
Joel Robichaud*, Christopher Bayly, Renata Oballa, Peppi Prasit, Christophe Mellon, Jean-Pierre Falgueyret, David Percival, Gregg Wesolowski, Sevgi B. Rodan

75 SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-FLUORO-2-CYANOPYRROLIDINE DIPEPTIDE INHIBITORS OF DPP-IV.
Richard Caldwell, Istvan Kaldor, Curt D. Haffner, Darryl L. McDougald, Steven M. Reister, Kate Dwornik, Sab Randhawa, Brian Thompson, David Cowan, Brad Henke, James M. Lenhard, Dallas Croom, Daphne Clancy, Donovanon McConn, Kevin M. Hedeen*, Kevin J. Wells-Knecht, Melissa Secosky, Wenhai Zhang

76 STRUCTURE-ACTIVITY RELATIONSHIPS OF PIPERIDINYLGLYCINYL-4,5-METHANOPROPYLENETRILE: POTENT DIPEPTIDYL PEPTIDASE IV INHIBITORS FOR THE TREATMENT OF TYPE II DIABETES
Chet Kwon*, Guohua Zhao, Charles R. Dorso, Mark S. Kirby, Qi Huang, Rex A. Parker, Benoni Abbo-Offe, James G. Robertson, Ayiing Wang, Lori Hilden, Mandar V. Dali, Ashish Khanna, and Lawrence G. Hamann

77 RATIONAL DESIGN OF INDOLE-BASED PPAR AGONISTS
Neeraj Mahindroo*, Chien-Fu Huang, Chiung-Chiu Wang, Tzu-Wen Lien, Xin Chen, Tsu-An Hsu, Hsings-Pang Hsieh

78 DESIGN, SYNTHESIS AND STABILITY STUDIES OF KETOJYRROLIDINES AND KETOAZETIDINES AS POTENT DIPEPTIDYL PEPTIDASE IV (DPP IV) INHIBITORS
Dana Ferraris*, Yao-Sen Ko, Bert Thomas, Susan Lautar, David Calvin, Ajit Thomas, Krystyna Wozniak, Camilo Rojas, Sergei Belyakov
DESIGN AND SYNTHESIS OF MC4-FOCUSED TARGET LIBRARY AROUND NOVEL SPIRO[IMIDAZOLIDINEQUINOLINE]-2,4-DIONE SCAFFOLD
Tom Webb*, Luyong Jiang, Doug McGrath, Rongshi Li

SUBSTITUTED IMIDAZOLES AS POTENT AND SELECTIVE CANNABINOID-1 RECEPTOR INVERSE AGONISTS
Linda L. Chang*, Jonathan E. Wilson, Ihor Kopka, Jing Chen, Ruey-Ruey C. Huang, Julie Z. Lao, Chun-Pyn Shen, Tung Fong, William K. Hagemann, and Mark T. Goulet

THE SYNTHESIS AND BIOLOGICAL EVALUATION OF ENAMINONE ISOXAZOLE AMIDE DERIVATIVES AS POTENTIAL ANTICONVULSANT AGENTS
K. Scott, P. Jackson, C. Hanson*

EFFECTS OF VARYING SPACER LENGTH ON ACTIVITY OF 1,2,5-ThIAZIAZOLE DERIVATIVES OF 1,2,5,6-TETRAHYDROPYRIDINE AT MUSCARINIC RECEPTOR SUBTYPES
Frederick R. Tejada*, Yang CAo, Peter I. Nagy, Min Xu, Jason Dorsey, Tricia Katz and William S. Messer, Jr.

N-ARYLOXYETHYL-INDOLALKYLAMINE DERIVATIVES WITH DUAL SSRI AND 5-HT1A RECEPTOR ACTIVITIES

NOVEL CYTISINE ANALOGUES: SYNTHESIS AND BIOLOGICAL ACTIVITY
Lenka Munoz*, Stephanie Hennen, Daniela Gündisch

PHOTOAFFINITY LABELING LIGANDS OF THE PRO-LEU-GLY-NH2 BINDING SITE

A POLY-L-PROLINE HELIX II MIMIC WITH A 5.6.5 SPIROBICYCLIC FRAMEWORK AS A PLG PEPTIDOIMIMETIC
Bhooma Raghavan*, Vaneeta Varma, Ram K. Mishra and Rodney L. Johnson

SYNTHESIS OF TYPE VI BETA-TURN MIMICS OF L-PROLYL-L-PROLYL-L-PROLINAMIDE
Ashish P. Vartak* and Rodney L. Johnson

EFFICIENT PREPARATION OF ADRAFINIL ISOMERS
John Podobinski*, Bryan Roth, Thomas Prisinzano

2,3,7-TRISUBSTITUTED PYRAZOLO[1,5-D][1,2,4]TRIAZINES: FUNCTIONALLY SELECTIVE GABA-A ALPHA2/ALPHA3-SUBTYPE SELECTIVE AGONISTS.

SEARCH FOR BENZODIAZEPINE/GABA, SUBTYPE SELECTIVE BIVALENT LIGANDS THAT REVERSE ALCOHOL SELF-ADMINISTRATION
Wenyuan Yin*, Siritama Sarma V.U.Pollela, Chunchun Zhang, Harry June and James Cook

INHIBITION OF MONOAMINE OXIDASES A AND B BY FLUORINATED PHENYLCYCLOPROPYLAMINES
Song Ye, Shinichi Yoshida, Thomas C. Rosen, Oliver G. J. Meyer, Milton J. Sloan, Guenter Haufe, Kenneth L. Kirk*

DESIGN AND SYNTHESIS OF NOVEL AND POTENT PPAR-Delta AGONISTS
James Knobelsdorf*, Jeff Schkeryantz, Guoxin Zhu, Nathan Mantlo, Chahrzad Montrose-Rafizadeh, Robert Barr, Don Jett, Rick Zink, and Nathan Yumibe

TOWARD IN VIVO GLYCORANDOMIZATION
Dirk Hoffmeister*, Jon S. Thorson

COMBINATORIAL APPROACHES TOWARD GLYCORANDOMIZED NATURAL PRODUCTS
Joseph M. Langenhan*, Jon S. Thorson
SYNTHESIS OF L-ALTROSE DERIVATIVES TO PROBE THE SUBSTRATE SPECIFICITY OF MUTANT GALACTOKINASES
Lesley Liu*, Jie Yang, Jon S. Thorson

RAPID DRUG DIVERSIFICATION BY ENZYME ENGINEERING AND EVOLUTION
Jie Yang*, Dirk Hoffmeister, Lesley Liu, Martin Hager, Rocco Moretti, Jon S. Thorson

INACTIVATION OF THE LNME GENE REVEALING NEW INSIGHTS INTO THE BIOSYNTHESIS OF THE ANTIBIOTIC LEINAMYCIN IN STREPTOMYCES ATROOLIVACEUS
Bong-Sik Yun*, Gong-Li Tang, Yi-Qiang Cheng, Yong Huang, Hirak S. Basu, George Wilding, and Ben Shen

BIOSYNTHESIS OF THE ANTITUMOR ANTIBIOTIC ENEDIynes C-1027 AND NEOCARZINOSTATIN AND PRODUCTION OF ANALOGS BY METABOLIC PATHWAY MANIPULATION
Jian Zhang*, Jianhua Ju, Steven Van Lanen*, Juyun Bae, and Ben Shen

RADIAL SYMMETRY IN LEAD DISCOVERY AND LEAD OPTIMIZATION: THE STRUCTURE-ACTIVITY RELATIONSHIP OF A HIGH AFFINITY NK-1 RECEPTOR LIGAND
Angie R. Angeles*, Cheryl McVaugh, Gary Chicchi, Marc Kurtz, Dennis Underwood, Amos B. Smith, III and Ralph F. Hirschmann

ANTIETMIC CYCLOHEXYLAMINE NK1 ANTAGONISTS
Jason M. Elliott*, Emma J. Carlson, Gary G. Chicchi, Natalie Clark, Laura C. Cooper, Olivier Dirat, Gregory J. Hollingworth, Marc M. Kurtz, Wayne Rycroft, Christopher J. Swain

SYNTHESIS AND EVALUATION OF PYRIDYL-TRIAZOLE DERIVATIVES AS NK1 ANTAGONISTS
K. Jeff Thrasher*, Louis N. Jungheim, Erik Hembre, Kevin Gardinier, Doug Schober, Brian Getman, Daniel Smith, Dominic Li, Smriti Iyengar, Don Gehlert

DESIGN, SYNTHESIS AND EVALUATION OF SR 48,968 ANALOGUES AS NEUROKININ-2 RECEPTOR SELECTIVE ANTAGONISTS
Shih-Chung Huang, Vijaya L. Korlipara*, and Bradley J. Undem

2-(AMINOMETHYL)BENZAMIDE INHIBITORS OF GLYT2

OPIOID RECEPTOR LIKE (ORL-1) AGONISTS AS NOVEL ANALGESICS
Duncan McArthur

DIAZABICYCLO[4.2.0]OCTANE LIGANDS AS POTENT NNR AGONISTS

HETEROAROMATIC SIDE-CHAIN ANALOGS OF PREGABALIN
Robert Schelkun*, Po-wai Yuen, Stephen Johnson, David Wustrow, Mark Field, Mark Vartanian

NEOCLERODANE DITERPENES AS NOVEL OPIOID RECEPTOR LIGANDS: ISOLATION AND EVALUATION

SUBSTITUTED BENZODIAZEPINES AS SELECTIVE BRADYKININ B2 RECEPTOR ANTAGONISTS
Carmen Leung*, V. Santhakumar, Mirek Tomaszewski, Christopher Walpole, Simon Woo, Lynda Adam, Joanne Butterworth, Claude Godbout, Kemal Payza, Marie Roumi
109 5-CHLOROPYRIDOTHIOSEMICARBAZIDE COMPOUNDS AS SELECTIVE BRADYKININ B2 RECEPTOR ANTAGONISTS
Yun-xing Cheng*, Mirek Tomaszewski, Xuehong Luo, Mehmaz Pourashraf, Christopher Walpole, Joanne Butterworth, Lynda Adam, Claude Godbout, Kemal Payza, Marie Roumi

110 SYNTHESIS AND EVALUATION OF THIAZEPINES AS ICE INHIBITORS

111 DISCOVERY OF A NEW CLASS OF ANTI-INFLAMMATORY AGENTS: NON-INDOLE CPLA_{2α} INHIBITORS
Steven J. Kirincich*, John C. McKew, Jason Xiang, Steve Tam, Wen Zhang, Marina Shen, Jing Lun Wu, and James D. Clark

112 TRYP bottom line of page 112

113 TOWARD VLA1 INTEGRIN INHIBITORS: PARALLEL SYNTHESIS OF NOVEL HYDANTOIN SCAFFOLDS
Allen A. Thomas*, Jason De Meese, Scott C. Miller, Steve Boyd, Mark Lupher, Don Staunton

114 SOLID-PHASE SYNTHESIS OF HYDANTOINS AS CASPASE INHIBITORS
Jesus Vazquez*, Jaime Rubio, Enrique Perez-Paya, Fernando Albericio

115 DISCOVERY OF POTENT INHIBITORS OF DIHYDRONEOPTERIN ALDOLASE

116 INVESTIGATIONS ON THE BIOSYNTHETIC PATHWAYS OF BLEOMYCIN, PHLEOMYCIN, AND TALLYSOMYCIN IN WILD-TYPE AND RECOMBINANT STRAINS OF THE RESPECTIVE PRODUCER ORGANISMS
Jane Coughlin, Ute Galm*, Nicholas P. George*, Evelyn Wendt-Pienkowski, Bong-Sik Yun, Ben Shen

117. CHALLENGES OF MODELLING INTERACTIONS BETWEEN KINASE INHIBITORS AND THEIR TARGET PROTEINS
Robert D. Clark, Sun Choi, Richard Foster, Michael S. Lawless and Jon Swanson

118. HOMOLOGY MODELING, DYNAMICS OF RAT AND HUMAN EXTRACELLULAR DOMAIN OF A4ß2 AND A7 NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR SUBTYPES
William H. Bisson*, Gerrit Westera, P. Augustus Schubiger, Leonardo Scapozza

119. SYNTHESIS OF 3-(4-SUBSTITUTED P Piperazinylmethyl)-5,6-DIMETHOXYINDOLES AND THEIR 5,6-DIHYDROXY ANALOGUES AS NOVEL ANTIHYPERTENSION AGENTS
Wen-Chuan Hsu*, Yung-Yun Huang and Chieh-Nan Ko
1. ALLOSTERIC INHIBITORS OF THE HEPATITIS C VIRUS NS5B POLYMERASE: TOWARDS NOVEL ANTI-HCV THERAPIES

Pierre L. Beaulieu
Boehringer Ingelheim (Canada) Ltd.

It is estimated that approximately 3% of the world population (~160 million people) suffers from chronic HCV infection causing a progressive liver disease that can lead to fatal conditions such as cirrhosis or hepatocellular carcinomas. The leading cause for liver transplants in the US results from HCV infection, and some 10,000 deaths occur annually in that country that can be linked directly to the disease. Current therapies for HCV are based on combinations of pegylated interferon (IFN-α) and ribavarin, a broad spectrum antiviral agent. Specific anti-HCV chemotherapies are required for patients that fail to achieve a sustained response (50% in the case of the predominant genotype 1) or can not tolerate the adverse side effects associated with this treatment.

The NS5B polymerase is a virally-encoded enzyme that is essential for HCV replication and offers opportunities for the development of novel antiviral therapies. We recently highlighted the use of a uniquely modified NS5B polymerase construct with a lower affinity than mature NS5B for RNA substrate, for the identification of specific benzimidazole 5-carboxamide compounds (e.g. 1) that inhibit productive RNA binding to the polymerase. These compounds are non-competitive inhibitors of NTP incorporation, but exhibit a mixed-mode of inhibition with a significant competitive component with respect to template/primer substrate. The design of a fluorescent analogue and its use as a probe allowed direct KD determinations. NMR techniques were used to confirm interaction of compounds with the polymerase in the absence of RNA, and to determine the solution confirmation of a bound inhibitor. Photo-affinity labeling experiments identified a putative binding region for these inhibitors which is located in the upper-thumb domain of the enzyme. The evolution of this class of compounds towards novel diamide derivatives (2) which show activity in a cell-based assay of subgenomic HCV RNA replication (replicons) will be described. Generation of resistant replicons using these analogs re-enforced the existence of an allosteric binding site for this class of inhibitors. Resistant mutations identified in the polymerase complemented the photo-affinity labeling experiments and localized in the vicinity of a previously reported GTP binding site in the upper-thumb domain. Resistant mutations were re-introduced in replicon cell lines and the effects on inhibitory potency of the compounds and RNA replication fitness of the clones was assessed. Moreover, the effect of these inhibitors was evaluated against NS5B genotypes 2 and 3. Using the cell-based replicon system, we also demonstrated that a combination of HCV protease and polymerase inhibitors are complementary in cell culture models of HCV RNA replication in suppressing the emergence of resistant variants, and expand the repository of potential treatments for chronic HCV infection.

![Chemical structures](image1.png)

initial hit structure (IC$_{50}$ = 12 μM)
diamide analogs active in replicon

2. THE DISCOVERY OF BENZO[1,2,4]THIADIAZINES AS NON-NUCLEOSIDE HEPATITIS C VIRUS NS5B POLYMERASE INHIBITORS

Kevin J. Duffy
GlaxoSmithKline

Hepatitis C virus (HCV), a positive strand RNA virus of the Flaviviridae family, is the etiological agent of post-transfusion and sporadic non-A, non-B hepatitis. An estimated 2-3% of the world population are chronically infected with HCV which causes significant liver disease, cirrhosis, and can eventually lead to the development of hepatocellular carcinoma.

* denotes presenter
High-throughput screening for the inhibition of one of the essential Hepatitis C Virus, non-structural gene products, the RNA-depandent RNA polymerase NS5B, was carried out at GlaxoSmithKline and resulted in several structurally-distinct classes of hits. Lead optimization of one chemical series of benzo[1,2,4]thiadiazine inhibitors will be discussed in this presentation. SAR investigations around this heterocyclic template revealed several key positions which could be utilized to improve both biological potency and drug-like “developability” properties. Several inhibitor-bound x-ray crystal structures were obtained which identified a novel allosteric binding site in close proximity to the interface of the palm and thumb domains of NS5B.

This presentation will discuss the process from identifying the initial hit series through optimization of biological activities and physical properties resulting in the selection of clinical candidate molecules.

![benzo[1,2,4]thiadiazine screening hit](image)

3. MECHANISM OF ACTION AND SAR OF 2'-MODIFIED NUCLEOSIDE INHIBITORS OF HEPATITIS C VIRUS RNA REPLICATION

David B. Olsen1*, Steven S. Carroll1, Licia Tomei2, Sergio Altamura2, Balkrishen Bhat4, Michele R. Bosserman1, Lawrence F. Colwell3, Raffaele De Francesco2, Anne B. Eldrup4, Osvaldo A. Flores1, Krista Getty1, Daria J. Hazuda1, Robert L. LaFemina1, Steven W. Ludmerer1, Malcolm MacCoss3, Daniel R. McMasters1, Giovanni Migliaccio2, Mark W. Stahlhut1 & Joanne E. Tomassini1

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Hepatitis C virus (HCV) is estimated to have infected 3.9 million Americans and 170 million people worldwide, causing serious liver disease in approximately 70% of chronically infected individuals. The number of new infections per year has decreased significantly with the onset of routine blood bank screening from 240,000 in the 1980s to an estimated 25,000 in 2001, with the majority of new infections due to ongoing, illegal intravenous drug use. HCV infection, therefore, constitutes a significant health problem that would benefit from additional therapies. Purine nucleosides modified at the 2'-position have been identified as potent inhibitors of HCV RNA replication in the cell-based replicon assay (1, 2).

Their corresponding triphosphates are potent in vitro inhibitors of HCV RNA polymerase and function as non-obligate chain terminators. Resistance studies have confirmed that the intracellular target for these modified nucleosides is the HCV NS5b polymerase (2). A detailed medicinal chemistry effort within this series has demonstrated a fairly tight structure-activity-relationship. In particular, the data suggest that the 2'- and 3'-hydroxyl groups are important pharmacophores for inhibition of HCV RNA replication in the context of the cell-based replicon assay. Initial pharmacokinetic parameters obtained for lead compounds indicate that they have good oral bioavailability. Details of these data will be discussed with the goal being the identification of a potent and safe clinical candidate.
4. **THE DESIGN AND SYNTHESIS OF BILN 2061, A POTENT INHIBITOR OF THE HEPATITIS C VIRUS: FROM THE NMR TUBE TO THE CLINIC**

*Youla S. Tsantrizos*

**Boehringer Ingelheim Ltd.**

The virally encoded enzyme NS3 protease is essential to the life cycle of the hepatitis C virus (HCV), an important human pathogen causing chronic hepatitis, cirrhosis of the liver and hepatocellular carcinoma. In spite of intensive efforts, the design of inhibitors for the HCV NS3 protease has been limited to large peptidomimetic compounds, making drug discovery an extremely challenging endeavor. In our quest for the discovery of a small-molecule lead which could block replication of the Hepatitis C virus (HCV) by binding to the HCV NS3 protease, the critical protein-polypeptide interactions between the virally encoded NS3 serine protease and its polyprotein substrate were investigated. The design and synthesis of macrocyclic inhibitors of the NS3 protease, which are orally absorbed and inhibit replication of the HCV RNA in the cell-based replicon assay, will be described. These 15-membered ring peptides include the clinical candidate BILN 2061, which was found to reduce the viral load of HCV in infected humans when administered for 2 days. Some of the critical structural studies which guided the design of these β-strand scaffolds, mimicking the key molecular recognition elements between the NS3 protease and its NS3-NS5B polyprotein substrate, will also be presented. The results of this investigation highlight the staying-power of structure-based drug design, a valuable alternative to high-throughput random screening of compounds which has become the modern approach to drug discovery.

5. **ARCHIVES ON THE POWER OF CHEMICAL SYNTHESIS**

*Samuel J. Danishefsky*

**Department of Chemistry, Columbia University and Laboratory of Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research**
6. NUCLEAR HORMONE RECEPTORS: STRUCTURE, FUNCTION, LIGANDS AND IMAGING

John Katzenellenbogen
University of Illinois

The receptors for steroid hormones are nuclear proteins that function as transcription factors, having distinct for DNA binding and ligand/activation functions. The transcriptional activity of these nuclear hormone receptors (NHRs) is regulated by the interaction of hormonal ligands with the ligand-binding domains, an interaction that stabilizes specific conformations that reflect the size and shape of the ligand. The rigidified external surface features of the ligand-receptor complex then serve as specific docking sites with which various coregulatory factors bind. The overall result is that ligand binding to the receptor alters the rate of transcription of specific regulated genes.

Crystal structures of NHR ligand binding domains show them to have a unique alpha-helical triple sandwich fold, with an upper part that is tightly packed and a lower part that envelopes the ligand. When agonists bind, the C-terminal helix-12, wraps back over the ligand binding pocket, completing the formation of a hydrophobic groove in which coactivators dock. By contrast, antagonist binding ejects helix-12 so that it reorients, binding in the hydrophobic groove and blocking coactivator binding.

Our major focus has been on the estrogen receptor (ER), a principal regulator of estrogen action in various target tissues. Many steroidal and non-steroidal estrogens are known, and some of them act as Selective Estrogen Receptor Modulators (SERMs) that exhibit intriguing tissue-specific effects that make them of use for the prevention and treatment of breast cancer and for postmenopausal hormone replacement. There are also two ERs, ER-alpha and ER-beta; they have different tissue distributions and different biological functions.

To explore how progressive changes in ligand structure affect the affinity and efficacy of various estrogens, we developed an ER pharmacophore model to guide ER ligand design, and with it we have created various ER ligands of novel structure in a combinatorial fashion. Some of these ligands have very pronounced selectivity for ER-alpha or ER-beta, either in terms of potency, efficacy or both, and they are proving to be useful as pharmacological probes of the functions of the ER subtypes.

To investigate ER-ligand interactions, we developed fluorescence-based methods for monitoring the conformation and dynamics in the ERs and the interaction they have with coregulators. We have tagged the receptor with fluorophores directly, in a site specific manner, and then used fluorescence resonance energy transfer and fluorescence polarization methods to reveal that ligands function in a pharmacological class-specific manner to induce a stabilization of the receptor dimer interface and cause regional alterations in the conformational mobility of the helix11-helix 12 loop. We have also characterized the effect of coactivator binding on these processes by excimer formation using pyrene-labeled receptors, and we have developed protein arrays of ER-alpha and ER-beta with which we can monitor subtype-specific ligand binding and coactivator recruitment.

Elevated levels of steroid receptors are found in many tumors that develop in hormone target tissues (ER and progesterone receptors (PR) in breast tumors and androgen receptors (AR) in prostate tumors). We have designed high affinity receptor ligands, labeled with various radionuclides, as receptor-targeted tumor imaging agents. Ligands for ER, AR, and PR, labeled with the positron-emitting radionuclide fluorine-18, have been developed for use with positron emission tomographic (PET) imaging, and with these agents, we have imaged receptor-positive breast and prostate tumors. Clinical research imaging protocols have been developed through which an early assessment of the response of ER-positive breast cancers to hormone therapy can be made.

7. DISCOVERY, SAR, AND PRE-CLINICAL EVALUATION OF A NOVEL SELECTIVE ESTROGEN RECEPTOR MODULATOR FOR THE TREATMENT OF LEIOMYOMA (UTERINE FIBROIDS)

Jeffrey A. Dodge*, Conrad W. Hummel, Ilene Cohen, Robert D. Dally, Scott Frank, Ronald Hinklin, Dennis McCann, Norman E. Hughes, Scott Jones, George Lewis, Timothy A. Shepherd, Owen Wallace, Yong Wang, Henry U. Bryant, Andrew Geiser

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Uterine leiomyomas or fibroids are benign tumors arising from smooth muscle cells of the myometrium. They are the most common type of solid tumor in adult women, clinically apparent in at least 25% of those of reproductive
Lieomyoma are dependent on estrogen thereby making the receptor for this steroid hormone a viable therapeutic target for the treatment of fibroids. The estrogen receptor (ER) is a ligand-dependent transcription factor that belongs to the nuclear hormone receptor superfamily. ER plays an essential role in mediating the action of estrogens in a variety of biological processes that include the reproductive, skeletal, cardiovascular, and central nervous systems. Tissue-selective pharmacology on bone, breast, and uterus has been clinically observed in women with ER ligands such as raloxifene, a selective estrogen receptor modulator (SERM). SERMs have been shown to reduce leiomyoma size in post-menopausal women. However, in pre-menopausal women they are considerably less efficacious due, in part, to their inability to overcome the higher relative levels of endogenous estrogen in this patient population. SERMs can also act as antagonists on the hypothalamic-pituitary-ovarian (HPO) axis resulting in undesirable stimulation of the ovaries.

In structure-activity studies we have found that replacement of one of the SERM phenol pharmacophores with a methylsulfone group is a key structural determinant of uterine versus ovarian tissue selectivity. Crystallographic studies indicate that the sulfone moiety retains hydrogen-bonding interactions with the His-524 in the ligand binding domain of ERalpha. Further refinement of receptor affinity and functional activity in breast and uterine cell lines coupled with in vivo efficacy in rodents led to the discovery of 6-(4-methanesulfonyl-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol (1). This naphthalene-derived SERM has high affinity to both ERalpha (Ki = 0.47 nM) and ERbeta (Ki = 1.48 nM) as well as functional estrogen antagonist activity in uterine Ishikawa cells (IC50 = 10.7 nM) and in MCF-7 breast cells (IC50 = 0.86 nM). In animal models of efficacy, compound 1 blocked all of the uterine wet weight gain induced by co-administered estrogen with an ED50 of 0.07 mpk. Studies in mature ovary intact rats demonstrated the ability of 1 to decrease uterine wet weight by 51% after 35 days treatment and with an ED50 of 0.1 mpk. These data confirm potent in vivo activity at the desired target tissue in the presence of circulating levels of estradiol over several estrous cycles in the rat. Studies designed to assess bone effects showed that treatment of ovariectomized rats with 1 for 6 weeks prevented bone loss at doses as low as 0.01 mg/kg. In contrast to the potent uterine and bone effects of 1, negligible ovarian stimulatory effects were observed as assessed by serum estradiol levels and histologic evaluation.

In summary, we have identified a novel, orally active, and tissue selective SERM for the treatment of uterine fibroids. This naphthalene-derived compound is a potent inhibitor of uterine hypertrophy that does not stimulate the ovaries or cause bone loss.
8. EXPLOITING NEW SCAFFOLDS TOWARD THE DISCOVERY OF ERβ SELECTIVE LIGANDS

Richard E. Mewshaw1*, Richard J. Edsall1, Cuijian Yang1, An Vu1, Stephen Cohn1, S. Marc Bowen1, Eric S. Manas1, James C. Keith3, Jr., Yelena Leathurby3, Leo M. Albert3, and Heather A. Harris2

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In 1996 a second estrogen receptor (ERβ) was discovered that has added a new level of uncertainty to our understanding of the role of the estrogen receptor and prompted intense interest by both academic and industrial scientists. Over the last several years our laboratories have been committed to elucidating ERβ function with the use of ERβ selective ligands. This has been a very challenging problem due to the similarity of the ERα and ERβ ligand binding domains with only two conservative amino acid differences occurring in the binding pockets of these two isoforms. Recently our company discovered numerous molecules from several different series that were observed to be highly selective for ERβ. Using a modestly ERβ selective ligand (genistein) as a starting point, we will discuss how we simplified its structure while mimicking crucial molecular properties, enabling us to systematically evolve and identify many compounds having 50-130 fold ERβ selectivity. This seminar will highlight our design strategy in which we reveal several isomeric ligands that exploit different binding modes to achieve similar ERβ selectivity. We will also show how we employed the oxime moiety as a C-ring hydroxyl mimic of genistein and reveal an x-ray structure supporting our findings. In addition, we will discuss how we designed and prepared one molecule to exploit two potential binding modes simultaneously in order to further enhance selectivity. Throughout this presentation, docking models and x-ray structures will be presented to support our rationale and to provide an understanding of the selectivity we achieved. This seminar will briefly highlight the most important aspects of the
SAR, which led to the discovery of WAY-202196, a selective ERβ agonist that is currently in development (ERB-196). WAY-202196 binds to ERβ with an IC50 of 3 nM, similar to 17β-estradiol, but it is 77 fold selective for ERβ relative to ERα. WAY-202196 is also nonuterotrophic and inactive in several other estrogen-responsive models where nonselective estrogens (e.g. 17β-estradiol) are known to have robust effects. However, WAY-202196 does have a dramatic beneficial effect in both the HLA-B27 transgenic rat model of inflammatory bowel disease and the Lewis rat adjuvant-induced arthritis model.

9. NOVEL, SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)-PAST, PRESENT AND FUTURE

Duane D. Miller*, Dong Jin Hwang, Renukadevi Patil, Vinup Nair, Suni M. Mustafal, Michael L. Mohler, Igor M. Rakov, Seoung Soo Hong, Yali He, Karen Veverka, Mitch S. Steiner, K. Gary Barnette, Robert Boiger, Donghua Yin, Weiquing Gao, Jeffrey D. Kearbey, Huiping Xu, Juhyun Kim, Jiyoung Chen, Casey Bohl, and James T. Dalton

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Steroid hormones are important chemical messengers throughout the body and are widely recognized for an array of essential physiological responses. Androgen therapy has been used for many years to treat a variety of male hormone disorders. Testosterone, the principal natural androgen, regulates a variety of hormonal actions including growth and function of external gentitalia and accessory glands, growth of body hair and sebum production, muscle development, maturation of bone and bone density, and erythropoesis. However, the lack of a highly efficacious orally active agent, with an acceptable safety profile, has limited the use of androgen therapy. We first reported on the action of nonsteroidal androgens in 1998. We have been able to create a desired profile of activity with these new agents that target the androgen receptor and provide a number of desired selective therapeutic applications. New drug development based upon a significant improvement in the understanding of the natural ligands and the nuclear receptor activation process and the overall understanding of the importance of such agents in the regulation of the cell nucleus and to selectively modulate the gene expression to produce important actions in the cell and throughout the body should lead to a new and broader acceptance of this therapeutic approach. The fact that we now have compounds that are selective in the type of action that they have on the different nuclear receptors including androgens, estrogens, progestins and gluccocorticoids, provides for an improvement in therapeutic applications. Tissue specific expression of cofactors (including both co-activators and co-repressors) appears to allow for needed selective cellular responses.

Although injectable, gel and transdermal steroidal preparations have been available, we have focused on the development of orally active nonsteroidal androgens with a spectrum of anabolic and androgenic activity. With the accepted use of term SERM (Selective Estrogen Receptor Modulator) we now refer to this new class of agents as SARMs (Selective Androgen Receptor Modulators). Our ARTA (Androgen Receptor Targeting Agent) program has been successful in the preclinical and Phase I clinical development of agents for (a) building muscle and increasing lean body mass (b) prevention and treatment of osteoporosis and bone fractures and (c) reduction of prostate size while maintaining muscle and bone in man. The action of testosterone and other synthetic steroids on the prostate has been a major concern with normal androgen steroid therapy. The future is very bright for orally active SARMs since they should be of value in the previously mentioned therapies, as well as in the treatment of (a) andropause (treatment of symptoms of aging men), (b) male contraception and (c) the therapy osteoporosis in women. Overall, the new SARMs should provide a fundamental change for the health of men and women in the future.

10. A NOVEL BENZIMIDAZOLE CLASS OF ANDROGEN RECEPTOR MODULATORS

Yuntae Kim*, Barbara A. Hanney, Jeffrey D. Musselman, Keith L. Spencer, George D. Hartman, Mark E. Duggan

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It is well-documented that androgens stimulate bone formation in post-menopausal women. Despite this beneficial effect, use of androgens for treating post-menopausal osteoporosis is limited due to unwanted virilizing
effects such as facial hair growth. Thus, a tissue selective androgen receptor modulator (SARM) that stimulates bone formation, without eliciting virilizing effects, would be a desirable therapeutic agent for the treatment of postmenopausal osteoporosis. Toward this objective, we have optimized a series of non-steroid benzimidazole derivatives to produce high affinity ligands for the androgen receptor. We will report the application of an SAR-guided library approach that resulted in the identification of these novel non-steroidal SARM’s from a screening lead, as well as, the in vitro and in vivo profiles for key compounds in this structural class.

11. HIGHLY POTENT AND MUSCLE SELECTIVE BICYCLIC N-ARYL HYDANTOIN SARMS

Bristol-Myers Squibb Company

Age-related deterioration of muscle mass and strength in men is closely linked to declining circulating levels of testosterone, and androgen replacement therapy has proven to be efficacious at restoring muscle function. However, testosterone has low oral bioavailability, and the side effects associated with androgens (e.g. prostate enlargement and, for oral androgens, liver toxicity) limit their therapeutic utility. Therefore, the development of an orally active, tissue selective androgen receptor modulator (SARM) that improves muscle mass and function in aging men with minimal effects on the prostate and without liver toxicity, represents an enormous opportunity to address an unmet medical need for an ever-increasing aging population.

High-throughput screening and lead optimization has led to the discovery of a novel bicyclic N-aryl hydantoin series of SARMs. The lead compounds in the series show high affinity and selectivity for the androgen receptor (AR) (Ki <5nM for AR and Ki > 1,000nM for other steroid nuclear hormone receptors). In a rat atrophied levator ani muscle model, the lead compounds are orally active and demonstrate efficacy at restoring levator ani muscle mass with >30 fold selectivity for the muscle over the prostate. The discovery, SAR and preclinical profiles of select compounds from this series will be presented.

12. SYSTEMS BASED RESEARCH IN THE KINOME

Karen E. Lackey
GlaxoSmithKline

Approximately half of the anticipated small-molecule drug targets fall into just six gene families: G-protein-coupled receptors (GPCRs), protein kinases, zinc metallo-peptidases, serine proteases, nuclear hormone receptors, and phosphodiesterases.1 A systems based research (SBR) approach groups proteins into classes based on sequence and common motifs that form 3D space receptive for small molecule interactions. The goal of small-molecule drug discovery is to modulate the activity of a biological target via interactions with an externally administered molecule at optimal drug intervention points to afford the maximum therapeutic index.

Key to achieving this mechanistic approach to drug discovery is the design, synthesis and evaluation of biologically effective compounds. Working within a system of related targets allows scientists to apply learnings from one member to accelerate identification of ligands for other disease-associated targets. The focus of this presentation will be on generating signaling inhibitors targeting members of the kinome and understanding their selectivity in this chemically connected target family. The discussion will include the critical SBR components to create sustainable kinase drug discovery programs in multiple therapeutic areas along with specific protein target examples to show how these components are utilized.


13. RECENT PROGRESS IN THE DESIGN OF TYROSINE KINASE INHIBITORS

Peter Traxler
Novartis Institutes for BioMedical Research, Research Oncology, CH-4002 Basel/Switzerland

Protein kinases play a crucial role in signal transduction as well as in cellular proliferation, differentiation and various regulatory mechanisms. The inhibition of growth related kinases, especially tyrosine kinases, might therefore provide new therapies for diseases such as cancer. Due to the enormous progress that has been made in the past few years in the identification of the human genome, combined with advances made in molecular, biochemical and cell
biology technologies, as well as synthetic chemistry, computer-assisted molecular modeling and crystallography, the number of receptor and non-receptor tyrosine kinases that have been identified as valuable molecular targets has greatly increased. Currently, worldwide over 20 different tyrosine kinases are under evaluation in drug discovery projects in oncology. Meanwhile clinical proof of concept (POC) has been achieved with several antibodies and small molecules targeted against tyrosine kinases. With Herceptin, Gleevec, Iressa and Avastin, the first kinase drugs have entered or will enter the market.

The progress made in the crystallization of protein kinases, in most cases complexed with ATP-site directed inhibitors, has confirmed that the ATP-binding domain of tyrosine kinases is an attractive target for rational drug design. Currently, there are more than twenty ATP-competitive low molecular weight inhibitors in various phases of clinical evaluation. We have used a pharmacophore model of the ATP-binding site of tyrosine kinases (e.g., the EGFR kinase) that has been refined over the last years for the rational design of tyrosine kinase inhibitors. Three successful examples of rational drug design at Novartis using a tyrosine kinase as a molecular target will be presented: The anilino-phthalazine derivative PTK787/ZK222584 (Phase I/II, co-developed by Schering AG, Berlin) was identified in a HTScreen. PTK/ZK is a potent and selective inhibitor of the family of VEGFR tyrosine kinases with interesting anti-angiogenic and pharmacokinetic properties (orally bioavailable). The compound is currently in Phase III trials. AEE788, a 7H-pyrrolo[2,3-d]pyrimidine, is a potent dual family EGFR/ErbB2 and VEGFR tyrosine kinase inhibitor, active on the isolated enzyme level as well as in cellular systems. Oral administration of AEE788 to tumor bearing animals leads to high and persistent levels of the compound in the tumor tissue. AEE788 is able to efficiently inhibit growth factor-induced EGFR and ErbB2 phosphorylation in tumors derived from tumor-bearing mice and it inhibits the growth of subcutaneously transplanted tumors which overexpress EGFR and/or ErbB2. In addition, AEE788 inhibits VEGF-induced angiogenesis in a murine model. The anti-angiogenic activity is also apparent by measurement of tumor vascular permeability and interstitial leakage space using DCE-MRI. AEE788 entered Phase I studies in June 2003. Glivec (Gleevec, STI571), is a phenylamino-pyrimidine derivative, which was also obtained through systematic optimisation of a random screening lead structure. It is a potent inhibitor of the Abl tyrosine kinase, which is present in 95% of patients with chronic myeloid leukemia (CML). Exciting data from phase II and III clinical trails in CML patients (90 % haematological response rate) support the fact that Glivec represents a new treatment modality for CML. In addition, potent inhibition of the PDGFR and c-Kit tyrosine kinases also indicates its clinical use in solid tumors (e.g., gastrointestinal stromal tumors (GIST)). To overcome the occurrence of resistance in late stage CML patients offers a new challenge for medicinal chemists.

14. OPTIMIZATION OF THE 1H-INDOL-2-YL-1H-QUINOLIN-2-ONE CLASS OF KDR (VEGFR-2) KINASE INHIBITORS: IN VITRO AND IN VIVO CHARACTERIZATION OF A CLINICAL CANDIDATE

Mark Fraley
Merck Research Laboratories

Aberrant angiogenesis is operative in the pathogenesis of diseases such as diabetic retinopathy, rheumatoid arthritis, osteoarthritis, psoriasis, and cancer. In particular, the growth and metastatic potential of solid tumors are highly dependent on vascularization. The extent of tumor vascularization is related to patient survival and has correlated with clinical outcomes for a variety of tumor types. Thus, inhibition of angiogenesis has been regarded as an attractive approach for the treatment of solid tumors. Vascular endothelial growth factor (VEGF) and its mitogenic receptor KDR (VEGFR-2), a ligand-dependent receptor tyrosine kinase expressed exclusively on endothelial cells, have been identified as promising therapeutic targets because of the importance of their mechanistic roles in the angiogenic process. Several lines of evidence indicate that the expression and signaling of VEGF are critical for tumor angiogenesis. Among these, antibodies against VEGF and its receptor KDR, and small molecule inhibitors of the KDR kinase domain have been shown to inhibit angiogenesis and the growth of tumors in animal models. Most importantly, Avastin (bevacizumab), an anti-VEGF monoclonal antibody, has demonstrated survival benefit in colorectal cancer patients when dosed in combination with standard chemotherapy, providing valuable proof-of-concept for an anti-angiogenesis agent in a clinical setting and basis for its recent FDA approval. Clinical trials have also been initiated with an anti-KDR receptor antibody as well as a number of ATP-competitive, small molecule inhibitors of KDR kinase activity. Previously, we reported the discovery and evolution of the indolyl quinolinone class of potent ATP-competitive KDR kinase inhibitors. Oral dosing of a prototypical member of this series caused
tumor growth inhibition and anti-angiogenic effects in HT1080 nude mice xenografts. Herein we describe the optimization of this series with an emphasis on design modifications that provided potent leading compounds with excellent pharmacokinetics and minimal hERG binding. A detailed description of a clinical candidate will be presented including key in vitro and in vivo data that were utilized for its selection.


15. EVALUATION OF COMPOUNDS THAT BIND P38 MAP KINASE IN A [PHE OUT] CONFORMATION

Neil Moss
Boehringer Ingelheim Pharmaceuticals, Inc

Inhibition of p38 MAP kinase has become a popular strategy for the potential development of anti-inflammatory agents. Industry’s quest for inhibitors of p38 MAP kinase has resulted in the discovery and design of a wide range of structurally unique compounds. X-ray crystallographic and molecular modeling analysis of these structural classes has revealed at least two distinct binding modes distinguished from each other primarily by the location of the C-terminal region of the activation loop. We colloquially refer to these two modes as either [Phe in] or [Phe out]. This phenomenon is not unique to p38 MAP kinase. While the majority of kinase inhibitors bind in the [Phe in] mode, clinical candidates have emerged from kinase inhibitors that bind in a [Phe out] mode, including our p38 inhibitor, BIRB 796. This lecture will contrast features of these binding modes together with implications for kinase inhibitor drug design.

16. THE DEVELOPMENT OF NON-ATP COMPETITIVE MEK INHIBITORS AS POTENTIAL ANTICANCER DRUGS.

Haile Tecle
Pfizer Global R and D, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

Our interest to discover novel anticancer drugs led us to screen our compound libraries for inhibitors of MAP kinase kinase (MEK). Any structures remotely resembling those of known kinase (ATP-competitive) inhibitors were discarded from the hit list leaving us, among others, with N-aryl anthranilic acids which were micromolar MEK inhibitors. Since the crystal structure of MEK was not known at the time, we used conventional medicinal chemistry to explore the SAR of the anthranilic acids and prepared potent single digit nanomolar inhibitors of MEK. The anthranilic acids, although potent inhibitors of isolated MEK enzyme, failed to inhibit MEK in intact cells. Hydroxamic acid and hydroxamate derivatives of the anthranilic acids were prepared and found to be potent inhibitors of MEK in our cellular assays and our in vivo animal tumor models. CI-1040, a hydroxamate, was the first MEK inhibitor to undergo clinical evaluation. In a Phase I clinical trial, in cancer patients, CI-1040 was safe at doses as high as 800 mg/kg bid and, demonstrated significant target (pERK) suppression. While there were encouraging hints of clinical activity in the Phase I trial, CI-1040 was subsequently withdrawn from further development due to insufficient efficacy in Phase II trials. The Phase I results encouraged us to prepare more potent MEK inhibitors with improved PK properties and increased systemic exposures. SAR optimization to improve the solubility of CI-1040 led to the synthesis of PD-0325901. PD-0325901, like CI-1040 is a non-ATP competitive MEK inhibitor. It is 200-fold more soluble than CI-1040, ca. 500-fold more potent than CI-1040 in cellular assays and significantly more potent in our in vivo animal tumor models. PD-0325901 is currently in Phase I clinical trials. SAR and pre-clinical pharmacology of CI-1040 and PD-0325901 will be discussed as well as Phase I/II results for CI-1040. Kinetic studies show that CI-1040 and PD-0325901 are non competitive with MEK substrates ATP and ERK, explaining
their exquisite selectivity for MEK. The exact binding site of the inhibitors on MEK has hitherto eluded investigation mainly due to the lack of structural knowledge of the MEK protein. We, and others, have tried to crystallize MEK for a long time without success. We are pleased to report that we have successfully used our inhibitors to crystallize and solve the structure of MEK. The x-ray structure of a ternary complex of MEK, ATP and one of our CI-1040 analogs will be discussed.

17. GLYCOSYLTRANSFERASES INVOLVED IN ANTIBIOTIC BIOSYNTHESIS AND TAILORING
   Christopher Walsh
   Harvard Medical School
   Many natural products with antibiotic activity require glycosylation for biological target recognition. For polyketides and nonribosomal peptides the scaffolds are constructed on multimodular enzymatic assembly lines and then glycosylation occurs by the action of tailoring glycosyltransferases (Gtfs). This lecture will discuss progress in our group on purification and characterization of Gtfs involved in vancomycin type glycopeptide antibiotic maturation, in anthracycline antiumor agent maturation, and in aminocoumarin antibiotic construction in the context of specificity, structure, and permissivity.

18. NATURAL PRODUCT GLYCORANDOMIZATION
   Jon S. Thorson
   University of Wisconsin-Madison, School of Pharmacy
   In nature, the attachment of sugars to small molecules is often employed to mediate targeting, mechanism of action, and/or pharmacology. As an alternative to pathway engineering or total synthesis, we report merging three promiscuous enzymes (a sugar kinase - ‘E1’, a nucleotidylyltransferase - ‘E2’, and a glycosyltransferase) with upstream synthetic chemistry and downstream chemoselective ligation provides a powerful method (in vitro glycorandomization or IVG) to diversify the glycosylation patterns of complex natural products. Glycorandomization development, the proof of concept, biological activity of glycorandomized natural product-base drug analogs and the implications for general therapeutic development will be discussed. In addition, our progress toward an in vivo fermentation-based glycorandomization process will also be presented.
19. MANIPULATION OF SECONDARY METABOLIC PATHWAYS FOR DRUG DISCOVERY

Ben Shen
University of Wisconsin-Madison

Microorganisms produce a large variety of biologically active metabolites representing a vast diversity of fascinating molecular architecture not available in any other systems. The study of bacterial metabolism is continuing to push the frontier of modern chemistry, biochemistry, and molecular biology by revealing novel chemical reactions, complex enzyme systems, and intricate regulatory mechanism of the biosynthetic machinery. Genetic manipulations of genes governing natural product biosynthesis offer a promising alternative to preparing complex natural products biosynthetically for drug discovery and development. The success of this approach depends critically on (1) the development of novel strategies for combinatorial manipulation of secondary metabolite biosynthesis gene clusters and (2) the continuous discovery and characterization of biosynthetic machinery that catalyzes novel chemistry. Examples from our current study on biosynthesis of various antitumor antibiotics and engineering of the various biosynthetic machinery will be presented to highlight the progress in this field, with the emphasis on (1) novel chemistry and biology involved in natural product biosynthesis and (2) application of combinatorial biosynthesis methods to microbial biosynthetic machinery to generate natural structural diversity for drug discovery and development.

20. KOSAN BIO SCIENCES: A CASE STUDY FOR DRUG LEAD DISCOVERY BY COMBINATORIAL BIOSYNTHESIS

C. Richard Hutchinson
University of Wisconsin-Madison

Microbial natural products have been a rich source of drugs and drug leads during the past 60 years: for instance, at least 60% of the antitumor drugs in current use have come from microorganisms. Kosan Biosciences, an eight year old biotechnology company located in Hayward, CA, has embraced “combinatorial biosynthesis”, which
uses genetic engineering of biosynthetic pathway genes to create new microbial metabolites, as the principal means
to discover new drug leads and develop them for various therapeutic indications. This approach will be illustrated
for analogs of the erythromycins, epothilones and geldanamycin.

21. THE DISCOVERY AND OPTIMIZATION OF TRIAZOLE BASED NK-1 ANTAGONISTS

E. Hembre*, A. Amegadzie, J. Bishop, J. Cohen, J. Cramer, K. Gardinier, D. Gehlert, S. Green, E. Hong,
S. Iyengar, L. Junghem, D. Li, B. Muehl, M. Robertson, K. Savin, D. Schober, D. Smith, J. Thrasher

Eli Lilly and Company

Substance P is an undecapeptide (HOOC-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH2) that is a
member of the tachykinin family of neurotransmitters. The biological activity of substance P is mediated by the
neurokinin receptors NK-1, NK-2, and NK-3 that belong to the super family of seven-transmembrane G-protein
coupled receptors. While Substance P can act at the NK-2 and NK-3 receptors, it is the endogenous ligand for NK-
1 receptors, binding with an affinity in the range of 0.05-0.5 nM. Substance P and NK-1 receptors are widely
expressed in both the central and the peripheral nervous systems and are involved in a variety of centrally and
peripherally mediated processes. Antagonists of the NK-1 receptor are of interest for the treatment of a wide range
of stress related disorders. Peptide antagonists of the NK-1 receptor were first identified in the 1960s and high
affinity tri- and di-peptide antagonists were subsequently developed. However, the utility of these compounds was
limited due to poor oral bioavailability and CNS penetration. The first non-peptide small molecule NK-1 antagonists
CP-96345 and CP-99994 were reported in the early 1990s by researchers at Pfizer. This work precipitated a deluge
of activity in the search for potent, brain penetrant, orally active NK-1 antagonists that has continued to this day.
Through the many years of research in this area, several obstacles have been identified that must be overcome to
develop an efficacious, orally acting NK-1 antagonist. Due to the strong affinity that substance P has for the NK-1
receptor, a small molecule antagonist must possess potent receptor binding affinity to effect biological activity. The
relatively large molecular weight and lipophilic nature of most NK-1 antagonists lead to potential problems with
their pharmacokinetic profile, including low bioavailability, high metabolic liability, poor brain penetration, and
limited aqueous solubility. This presentation will discuss our recent efforts in tackling the significant challenges in
this arena. Through a combination of rational design and directed screening we identified a novel NK-1 antagonist
lead molecule containing a 1,2,3-triazole scaffold. The initial lead structure was optimized for binding affinity at the
NK-1 receptor through a systematic SAR investigation of the substituents at the N-1, C-4 and C-5 positions of the
triazole. Subsequently, the series was optimized for drug-like pharmacokinetic and physical properties to provide
potent, orally bioavailable and efficacious NK-1 antagonists. The details of these investigations will be presented.

22. POTENT NEW NK1 ANTAGONISTS FROM A MODIFIED PIPERIDINE TEMPLATE:
DIASTEREOSELECTIVE SYNTHESIS OF 2,3,6-TRISUBSTITUTED PIPERIDINES.

John M. Humphrey*, Brian T. O’Neill, Thomas A. Chappie, Eric Arnold, Stafford McLean, Dianne K.
Bryce-Pritt, Angela C. Doran, Bill J. Smith, F. David Tingley

Pfizer Inc., Eastern Point Rd, Groton, CT, 06340

Modification of the 2-phenyl-3-benzylaminopiperidine series of NK-1 antagonists via alkyl substitution at
the piperidine 6-position yields potent new compounds and interesting SAR. The requisite piperidine templates are
available in good yield and without chromatography through parallel synthetic routes originating from a common
intermediate. Stereoselective synthesis of the various piperidine isomers presents a challenge, particularly with
respect to the 2,6-trans relationship. Two successful methods for establishing this stereochemistry will be presented.
Also highlighted will be an efficient thermodynamic resolution of a key crystalline intermediate. The synthesis of
various diastereomers of structure 1 will be presented in detail, and select biological data and SAR within this new
series will be discussed.
23. RECENT PROGRESS IN ORALLY ACTIVE NK1 ANTAGONISTS

Paul E. Finke
Merck and Co

A biological role for the tachykinin Substance P (SP), an agonist of the neurokinin-1 receptor (NK1), has been implicated in numerous inflammatory conditions and central nervous disorders, as well as chemotherapy-induced nausea and vomiting (CINV) and post operative nausea and vomiting (PONV). The utility of the potent, orally active NK1 antagonist aprepitant (5-[[2(R)-[1(R)-(3,5-bistrifluoromethylphenyl)ethoxy]-3(S)-(4-fluorophenyl)morpholin-4-yl]methyl]-2,4-dihydro-[1,2,4]triazol-3-one) for the treatment of CINV has recently been demonstrated in a phase III clinical program. The results of these trials led to the approval of aprepitant for marketing in the USA for the prevention of CINV under the trade name EMEND®.

During the clinical evaluation of aprepitant, several strategies were formulated targeting the development of back-up NK1 antagonist candidates possessing good brain penetration, manageable drug interaction profiles, and improved water solubility relative to aprepitant. Several alternative structures possessing a similar heterocyclic scaffold were identified and have previously been reported. The primary emphasis of the current presentation will be the development of the non-heterocyclic scaffold shown in 1 in which the morpholine was replaced with a cyclopentane (n = 1) or cyclohexane (n = 2) moiety. The unexpected stereochemical outcome that the all trans isomer afforded the highest NK1 affinity and the ability to incorporate a more basic exocyclic amine lead to the cyclopentyl derivative 2 (NK1 IC₅₀ = 0.2 nM). This compound maintained the efficacy of aprepitant while also having several other desirable properties. Further evaluation of other structural features of 1 (n, R¹ and R²) led to the identification of cyclopentane derivatives having sub-nanomolar NK1 affinity, good efficacy in several in vivo assays, and excellent oral bioavailability and pharmacokinetic characteristics. This presentation will describe the optimization process that led to selection of a member of this series for further development as a possible clinical back-up candidate for aprepitant.

24. DESIGN AND SYNTHESIS OF POTENT AND SELECTIVE, ORALLY ACTIVE NK1 RECEPTOR ANTAGONISTS

Patrick Schnider*, Theresa M. Ballard, Michael Bös, Guido Galley, Thierry Godel, Guy A. Higgins, Torsten Hoffmann, Walter Hunkeler, Sonia M. Poli, Andrew J. Sleight and Heinz Stadler
F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, CH-4070 Basel, Switzerland

Neurokinin (NK) receptors belong to the family of G-protein coupled receptors and can be divided into three subtypes: NK1, NK2 and NK3. The endogenous ligand for NK1 receptors is the neuropeptide Substance P, one of
the five mammalian tachykinins. Following the discovery of the first non-peptide NK1 receptor antagonist CP-96,345 in 1991, a remarkable number of small molecule NK1 receptor antagonists were identified by many pharmaceutical companies in the last decade. Moreover, recent clinical trials have demonstrated an important therapeutic application for NK1 receptor antagonists in the control of cancer chemotherapy-induced nausea and vomiting and in the treatment of mood disorders such as anxiety and depression. MK-869 (aprepitant) was the first NK1 receptor antagonist to receive marketing approval. In March 2003 it was approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting.

Following random screening of our corporate library, a unique compound cluster of achiral aryl substituted isoxazole derivatives was discovered which showed moderate affinity for the human NK1 receptor (e.g. RO0162515). This presentation will describe the design, synthesis, structure activity relationship and biological evaluation of a variety of derivatives emerging from this hit structure which led to the rapid identification of potent and selective, orally active NK1 receptor antagonists that are currently in clinical development at Roche.

25. PHOSPHODIESTERASES AS A RICH SOURCE OF NOVEL DISEASE TARGETS AND DRUG MOLECULES
N.K. Terrett*, R.J. Chambers, and K. Lam
Research Technology Center, Pfizer Inc.

The growth in our knowledge of the phosphodiesterase (PDE) gene family has accelerated considerably following Pfizer’s discovery of sildenafil (VIAGRA™) and with the decoding of the human genome. Across the industry, in addition to three PDE 5 inhibitors currently marketed for the treatment of male erectile dysfunction, there are also two PDE4 inhibitors in preregistration for chronic obstructive pulmonary disease and asthma, and many other compounds in earlier clinical development. There exists considerable potential for other low molecular weight drug molecules with significant disease impact that act through inhibition of the PDEs.

Although the PDEs constitute a relatively small gene family, with only 21 members, and only two endogenous substrates - cyclic AMP and cyclic GMP - there is considerable variation between the isozymes in both tissue distribution and cyclic nucleotide binding site structure. Consequently, not only is there enormous value in targeting the individual enzymes from a disease perspective, but selectivity between isozymes can often be a feasible objective.

This presentation will start with a review of the well documented discovery of sildenafil, the first commercially exploited cyclic GMP inhibitor, and will demonstrate how our knowledge of the PDE gene family has changed since the early 1990s. The research paradigm of focussing on an entire gene family of disease-relevant targets – as pursued by the Pfizer Research Technology Center based in Cambridge, Massachusetts – and using high throughput screening followed by hit to lead chemistry to discover novel pharmacological tools will be described. The value of this approach in elucidating the function of PDE isozymes will also be presented.

26. THE DESIGN AND INCORPORATION OF AN INTRA-MOLECULAR HYDROGEN BOND TO INCREASE CNS PENETRATION
Russell A Lewthwaite
Pfizer

CI-1021 is a high affinity, selective NK1 antagonist with moderate brain penetration. We sought to increase the brain penetration by removing one of the hydrogen-bond donors via an intra-molecular hydrogen-bond. PD-174424 (above) incorporates an –NMe2 which was designed to form a hydrogen bond to one of the neighbouring NH’s via a 5-(carbamates NH) or 6-(amide NH) membered ring. Data will be presented showing the existence of an
intra-molecular hydrogen-bond to one of the neighbouring N-H’s. Also data will be presented showing the synthesis, consequences of incorporating this group on biological activity, brain penetration, and consequently dose size.

27. FILTERING IN DRUG DISCOVERY: THE IMPORTANCE OF THE CHEMISTRY QUALITY MESSAGE
Christopher A. Lipinski
Pfizer Global R&D, Groton New London Labs (retired)

Progress in filtering in drug discovery over the last decade has been remarkable. From the purely technical perspective of drug discovery industry best practices the ADMET properties of chemistry screening libraries are very much improved. The “rule of five” is but one of many filters that have been widely adopted with positive results. Differences between drug-like and non drug-like chemistry structures are now well understood and have been extended to the concept of lead-like screening libraries. The hit to lead process that is so critical for continued industry productivity is greatly improved. The long timelines of the pharmaceutical industry mean that the well understood and long since corrected chemistry failed learnings of 1994 are only now in 2004 losing their influence. Unfortunately, the popular press has largely missed the improvement resulting from research in chemical technology and chemistry quality. The result is that this industry chemistry success story has been under appreciated in the public policy arena.

Despite successes, a challenge remains in terms of chemistry quality and filters. State of the art best practices are not universally distributed. This can be seen in the large numbers of poor quality commercial compounds still available for sale for screening. Medicinal chemistry pattern recognition skills are typically not widely accessible within the academic biology community. There is a danger that the well-characterized progress in filtering technology by knowledgeable pharma may not translate well when the “drug discovery” against orphan or developing world disease targets is carried out in academic biology. The translation of industry best practices in chemistry quality is most likely to be problematical when the targets are the most difficult. In this context, it is to be hoped that the NIH molecular library small molecule repository initiative proves successful in making quality chemistry subject matter readily accessible to the academic biology research community.

28. DISCOVERY OF MK-0431: A POTENT, SELECTIVE DIPEPTIDYL PEPTIDASE IV INHIBITOR FOR THE TREATMENT OF TYPE 2 DIABETES
Departments of Medicinal Chemistry, Metabolic Disorders, Pharmacology, and Preclinical Drug Metabolism; Merck & Co. Inc., P.O. Box 2000, Rahway, NJ 07065

Dipeptidyl peptidase IV (DP-IV) is a proline selective serine dipeptidase that is responsible for the N-terminal inactivation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulino tropic peptide (GIP), incretin hormones that are released from the gut in response to an oral nutrient load and evoke glucose stimulated insulin secretion. GLP-1 also stimulates insulin biosynthesis, inhibits glucagon release, slows gastric emptying and reduces appetite. In addition, GLP-1 appears to regulate the growth and differentiation of the insulin producing β cells in
pancreatic islets in rodents. Chronic infusion of GLP-1 to type 2 diabetics resulted in decreased fasting and 8-h blood glucose and glycosylated hemoglobin HbA1c, a marker for glucose control. In both animal models and human studies with normal volunteers and type 2 diabetic patients, DP-IV inhibitors have been shown to increase circulating levels of GLP-1, resulting in improved glucose tolerance. Following chronic administration to type 2 diabetics, decreases in fasting and 24-h glucose and HbA1c have been observed. Thus, DP-IV inhibitors represent a potential new therapy for the treatment of type 2 diabetes mellitus. We have recently reported the identification of two novel screening leads, a β-amino 4-phenylbutanoylproline amide and a β-amino 3-phenylpropylpiperazine derivative, which inhibit DP-IV with IC50s of 1.9 and 11 µM, respectively. SAR studies in the first series led to the discovery of sub nanomolar compounds with excellent selectivity over related proline peptidases. Addition of fluorine at the 2-position of the phenyl ring proved crucial for the activity of these compounds. The 2,5-difluoro, and 2,4,5-trifluoro analogs were the most potent; however, these derivatives suffered from poor oral absorption in rats. In the second series, fluorination of the phenyl ring led to modest improvements in potency. A dramatic increase in potency was seen when the 3-phenylpropyl group was replaced with the β-amino 4-phenylbutanoyl moiety from the first series, leading to hybrid β-amino 4-phenylbutanoyl piperazines. These derivatives also proved to have low oral bioavailability in rats, due in part to extensive metabolism on the piperazine ring. In an effort to stabilize this ring, a series of bicyclic derivatives were prepared, culminating in the identification of a potent and selective triazolopiperazine series. Unlike their monocyclic counterparts, these analogs typically showed excellent pharmacokinetic properties in preclinical species. One of these, MK 0431, was chosen for clinical development.

29. DISCOVERY OF POTENT NON-STEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS
Prabhakar K. Jadhav*, Donald P. Matthews, Jonathan Green, Kevin Fales, James Nixon, Anthony Borel, Sally Kelley, Karen Zimmerman, Mitchell I. Steinberg
Lilly Research Laboratories, A Division of Eli Lilly and Company
Aldosterone is an endogenous ligand of the Mineralocorticoid Receptor (MR). Mineralocorticoid Receptors are so named for their role in regulation of mineral ions such as sodium, potassium, and magnesium. MR is a member of the steroid subfamily of Nuclear Hormone Receptors (NHR). Elevated levels of Aldosterone have been implicated in various cardiovascular disorders including high blood pressure, cardiac and perivascular fibrosis, and potentiation of catecholamines. MR blockade is emerging as an important mechanism of action for identification of therapeutic agents for the treatment of cardiovascular diseases. Spironolactone and Eplerenone (INSPRA™) are the only two steroid based MR blockers available for the treatment of mineralocorticoid excess. We have identified and optimized non-steroidal ligands for MR which are potent, selective and orally active. The evolution of SAR leading to benzofused heterocyclic replacements as phenol mimics and the evaluation of non-steroid MR antagonist in the aldosterone infusion animal model of hypertension will be discussed.

30. DISCOVERY AND DEVELOPMENT OF THE CXCR3 ANTAGONIST T487 AS THERAPY FOR TH1 MEDIATED IMMUNE DISORDERS
Julio Medina†*, Tassie Collins†, Michael Johnson†, An-Rong Li†, Zice Fu†, Jiwen Liu†, Andrew Marcus†, George Tonn†, Thomas Schall‡, Qiuping Ye†
†Tularik Inc., ‡ChemoCentryx
The CXCR3 receptor is predominantly expressed on activated T cells of the Th1 phenotype and plays a role in their migration into sites of inflammation. Ligands for CXCR3 [MIG (CXCL9), IP10 (CXCL10) and ITAC (CXCL11)] are produced in inflamed tissues and have been implicated in a variety of inflammatory and autoimmune diseases such as psoriasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, type 1 diabetes and solid organ transplant rejection. We have discovered and optimized a novel series of quinazolinone-derived CXCR3 antagonists from which we have selected T487 for clinical development. In binding assays, T487 inhibits binding of 125I-IP10 and 125I-ITAC to CXCR3 with IC50 values of 7.7 nM and 8.2 nM, respectively. T487 inhibits CXCR3-mediated cell migration to IP10, ITAC and MIG with IC50 values of 8 nM, 15 nM and 36 nM, respectively. T487 also inhibits calcium mobilization in response to ITAC (IC50 5 nM). In the presence of human plasma, T487 inhibits 125I-IP10 binding (50% plasma, IC50 46 nM) and ITAC-mediated migration (100% plasma, IC50 182 nM). T487 shows >1000-fold selectivity for CXCR3 vs. a large panel of other receptors, including 11 chemokine receptors.
T487 is efficacious in several animal models of inflammation. T487 reduces inflammation and cartilage damage in mouse and rat models of collagen-induced arthritis. Furthermore, T487 reduces infiltration of T cells into the pancreas in a mouse model of type 1 diabetes. T487 also blocks cellular infiltration into the lung in a mouse bleomycin model. T487 has good oral bioavailability and moderate systemic clearance and is well tolerated in animals at doses significantly higher than those required for efficacy. T487 is currently undergoing Phase 2a proof-of-concept evaluation in psoriasis and rheumatoid arthritis.

31. A NEW MECHANISM WITH THE POTENTIAL TO TREAT ERECTILE DYSFUNCTION: THE MEDICINAL CHEMISTRY AND PHARMACOLOGY OF D₄ AGONISTS

Abbott Laboratories, Neuroscience Research

There has been a surge of interest in finding effective and safe treatments for male erectile dysfunction. PDE-5 inhibitors are now entering routine clinical use, but there are also other pharmacotherapeutic mechanisms with potential in this area. We have recently found that D₄ agonists act via central mechanisms to promote erections in animals without inducing side effects mediated by dopaminergic receptors. The discovery of the pharmacological profile of these agents, their SAR, and behavioral characteristics will be described.

32. NOVEL INHIBITORS OF T CELL PROLIFERATION

Dave Donald
AstraZeneca

33. NOVEL ANTIMICROTUBULE AGENTS FOR THE TREATMENT OF CANCER

Arie Zask*, Gary Birnberg, Joshua Kaplan, Chuan Niu, Frank Loganzo, Carolyn M. Discafani, Lee M. Greenberger, Semiramis Ayral-Kaloustian
Wyeth Research, Chemical and Screening Sciences, and Oncology Research, 401 North Middletown Road, Pearl River, NY 10965

A major therapeutic approach for the treatment of cancer is through disruption of the dynamics of microtubule formation with tubulin interactive compounds. The taxanes (e.g. paclitaxel and docetaxel) and Vinca alkaloids (e.g. vinorelbine, vinblastine and vincristine) are two classes of tubulin inhibiting natural products currently in use as anti-cancer agents. These compounds may be distinguished by their mode of interaction with microtubules. Whereas agents such as the taxanes stabilize microtubules against depolymerization, the Vinca alkaloids bind to the tubulin heterodimer and lead to the depolymerization of existing microtubules. Both mechanisms result in cell cycle arrest leading to tumor cell death. Despite the successes of the taxanes and Vinca alkaloids in inhibiting the progression of some cancers, inherent resistance to these agents in many tumors types, and acquired resistance during multiple cycles of therapy limit their utility. In addition, side effects due to the compounds themselves or the vehicle required for their administration are significant. Therefore, there has been great activity in investigating novel antimicrotubule drugs that overcome various modes of resistance and have improved pharmacology profiles. Numerous experimental antimicrotubule agents are currently in development.

We currently have in clinical and preclinical development novel tubulin inhibitors, active in a variety of tumor models, including paclitaxel-resistant ones. These agents are structurally diverse and work by either stabilization or destabilization of microtubules towards polymerization. Two agents that are currently in clinical trials, MAC-321,1,2 a novel paclitaxel analog, and HTI-286,3,4 an analog of the tripeptide marine natural product hemiasterlin, will be described. Synthesis and structure-activity relationships of HTI-286 analogs, as well as structural investigation of their interaction with the tubulin heterodimer and their relationship to other peptide tubulin inhibitors, will be presented.
34. DISCOVERY OF CP-724714, A POTENT AND SELECTIVE ERBB2 RECEPTOR TYROSYNE KINASE INHIBITOR


Pfizer Global Research and Development, MS 8118W-311, Eastern Point Road, Groton, CT; Iwata, K., OSI Pharmaceuticals, Boulder, CO.

The ErbB2 (Her-2/neu) proto-oncogene is overexpressed in various human malignancies such as breast, ovary and stomach. Herceptin, an erbB2 targeted antibody increases survival for patients with breast cancers that over express erbB2. In our laboratories, we have discovered CP-724714 as a potent (IC_{50} 8nM) small molecule inhibitor that is selective for the erbB2 receptor (>100x relative to other relevant kinases). Oral administration of CP-724714 demonstrates significant anti-tumor activity in multiple human tumor xenograft models. We will be presenting drug discovery efforts including the synthetic chemistry, biology and SAR trends leading to the discovery of CP-724714, which is currently in Phase I human clinical trials.
Notes
Poster Abstracts
THE DESIGN OF INHIBITORS OF THE HCV NS3•4A PROTEASE. THE IDENTIFICATION OF A CLINICAL DEVELOPMENT CANDIDATE, VX-950


1Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA, 2Eli Lilly and Company, Indianapolis IN, USA

Hepatitis C virus infection currently represents an important unmet medical need. At present the standard therapies are far from optimal in terms of efficacy and are associated with significant morbidity. The current standard of care is immunomodulatory and not directly antiviral. The inhibition of viral enzymes responsible for replication represents a potentially more effective approach. Among the enzymes available for intervention, the inhibition of the hepatitis C NS3•4A protease may be the most appealing based on the success of HIV protease inhibitors. Significant specificity may be possible because of the unusually flat and extended binding site. This approach has been the subject of intense research efforts over the last few years. Significant advances in the field have recently been reported including the clinical proof-of-concept for one such inhibitor. The evolution of a practical inhibitor scaffold from the HCV NS5A-5B natural substrate to a prototype tetrapeptide inhibitor exhibiting moderate binding affinity, $K_i=12\,\mu M$, to a series of compounds with nM potency will be described. Surprising findings from the P2 subsite optimization will highlighted. This presentation will also discuss the in vitro and in vivo characteristics of the clinical candidate that arose from this effort, VX-950.

PEPTIDOMIMETIC ALPHA-KETOAMIDE INHIBITORS OF HEPATITIS C NS3 PROTEASE EXHIBIT A SLOW-BINDING MECHANISM

Cynthia A. Gates*, Lawrence F. Courtney, Yu-Ping Luong, Shawn D. Britt, John C. Court, Wayne C. Schairer, Janos Pitlik, Scott L. Raybuck and Robert B. Perni

Vertex Pharmaceuticals, Inc.

An activated carbonyl is a frequent motif found in serine protease inhibitors. Fluorinated ketones and ketoamides replace the scissile amide bond of a substrate-like molecule. The mechanism of action for these electrophilic moieties involves nucleophilic addition by the active site serine hydroxyl to the carbonyl of the inhibitor. The ensuing metastable hemiketal enzyme-inhibitor complex mimics the tetrahedral species formed during catalysis. Among the many warheads we explored for inhibitor design were the alpha-ketoamides. Because this type of serine protease inhibitor often shows time dependent inhibition, a number of ketoamide peptidomimetic compounds were tested for this phenomenon and indeed, exhibited slow binding inhibition. For a wide range of scaffold and subsite variations, we observed a two-step binding mechanism, and found similar values for the forward rate constant of the onset of the slow transition. More variation is apparent in the reverse rate constant. The forward rate constants for the various compounds indicate that formation of the hemiketal intermediate largely contributes to slow binding. However, solvent isotope effects are moderate (~2) which suggest that hemiketal formation is not the sole rate-determining component of slow binding.

TOWARDS NOVEL THERAPEUTICS AGAINST HIV INFECTION AND DRUG RESISTANCES

Ye Che, Bernard R. Brooks and Garland R. Marshall

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The HIV/AID pandemic continues to spread around the world at an alarming rate. The success of current therapy is limited by the rapid emergence of drug-resistant viruses, the necessity of sustained adherence to complex regimens, and the potential for toxic effects. Therefore, there is a desperate need to circumvent the drug resistance problem by focusing on novel viral and cellular targets for new compounds capable of suppressing HIV strains that are resistant to the currently available anti-HIV therapies. The development of resistance in the virus due to the appearance of specific mutations is basically inevitable under the pressure of chemical therapeutics; but, the secondary
structures, instead of the primary structures, are usually invariable during evolution. Chemical scaffolds that are capable of mimicking protein secondary structures and incorporating different amino acid side-chains, are suitable as chemical templates for modulating protein-protein interactions that are necessary for HIV infection and replication. Based on this hypothesis, we have developed a series of small molecules mimicking important protein recognition motifs, including cis-amide, α-helix, β-sheet and reverse turns, and we are trying to circumvent the drug resistance problem with a library of small molecules based on common scaffolds, instead of searching for a single or a few “magic bullets” for all different kinds HIV variants. The development of such molecular library is undergoing for several protein interactions necessary for HIV infection, including viral attachment to host coreceptors, gp41-mediated membrane fusion, subunit interactions in HIV reverse transcriptase, integrase and protease, and the maturation and assembly of HIV capsid protein.

38. NOVEL OXINDOLES AS POTENT ANTI-HIV AGENTS

Yun He1*, Tao Jiang1, David A. Ellis1, Beth Anaclerio1, Kelli L. Kuhen1, Karen Wolff1, Hong Yin1, Kimberly Bieza1, Badry Bursulaya1, Tom Yao-Hsing Wu2, Tove Tuntland1, Kanyin Zhang1, Jeremy S. Caldwell1
1Genomics Institute of Novartis Research Foundation (GNF), 10675 John Hopkins Drive, San Diego, CA 92121 and 2The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla CA 92037

Non-nucleoside reverse transcriptase inhibitors (NNRTI’s) are a major component of the current therapy for AIDS. However, in recent years, significant resistance has been generated against the marketed NNRTI’s (nevirapine, delavirdine and efavirenz) due to viral mutations. New NNRTI’s are needed to overcome the increasing resistance. We have discovered a novel series of oxindoles that exhibit single digit nanomolar potency against WT HIV and drug-resistant mutants. The synthesis and SAR of this novel series of NNRTI’s will be discussed.

39. CHEMICAL PROBES OF THE CATALYTIC MECHANISM OF UDP-GALACTOPYRANOSE MUTASE

Erin E. Carlsonf*, Michelle S. Higgint, John F. May1, Todd D. Gruber1, and Laura L. Kiessling t,f
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In 1993, tuberculosis (TB) was declared a “global health emergency” by the World Health Organization. TB now infects one-third of the world’s population and kills 2 million people annually. Thus, need for leads that work by new mechanisms of action has become increasingly dire. To address this growing concern, an understanding of the enzymes that mediate cell wall biosynthesis of bacteria is essential. This complex cell wall acts as a formidable barrier against destruction, and it has been shown that compromised structural integrity can result in the loss of cell viability. UDP-galactopyranose mutase (UGM) is the enzyme responsible for the isomerization of UDP-galactopyranose (UDP-Galp) into UDP-galactofuranose (UDP-Galf) during cell wall construction of a number of bacteria, protozoa and fungi. Although the catalytic mechanism of the isomerization is controversial, it has been determined that enzymatic activity is dependent on a fully reduced flavin adenine dinucleotide cofactor (FAD). We propose that FAD is directly involved in catalysis, and, instead of performing a redox or structural role, the reduced flavin acts as a nucleophile. Recently, we have obtained data in support of this proposal. We plan to monitor enzymatic activity in the presence of several FAD analogs. Synthetic routes to both 1-deaza and 5-deazariboflavin are known; however, both have proven to be difficult to carry out and irreproducible. Thus, new synthetic pathways to both riboflavin analogs were designed and executed. Design and application of a high-throughput screen for UGM is also currently under investigation. Several inhibitors of UGM from K. pneumoniae and M. tuberculosis with Ki values in the micromolar range have been identified. The activities of these hits are being analyzed, and the design and synthesis of a directed library of compounds is being pursued.

40. DIASTEREOSELECTIVE CONDENSATION OF SERINAL DERIVATIVES WITH AZOLIUM YLIDES: A SYNTHESIS OF β-ARYL-β-HYDROXYL-α-AMINO ACIDS

Craig A. Zificsak*, Dennis J. Hlasta
Johnson & Johnson Pharmaceutical Research & Development, LLC

β-Hydroxyl-α-amino acids in either the erythro or threo relative configuration are components of a variety of natural products and drugs. A large number of polypeptide antibiotics (e.g. vancomycin) contain a β-aryl-β-hydroxyl-
α-amino acid residue within their architecture and other polypeptides containing similar fragments (e.g. bleomycin) are known anti-cancer agents. The 1,3-azoles (imidazole, thiazole, oxazole and others) are commonly found as a structural motif in drugs and natural products. The two (or more) heteroatoms within the aromatic five-membered ring are available as hydrogen bond acceptors, and for the N-unsubstituted imidazoles, as hydrogen bond donors. 1,3-Azoles are often implicated in the chelation of transition metals within enzymes, which has lead to their investigation as matrix metalloprotease inhibitors. Apart from bleomycin and its analogs, relatively few β-azolyl-β-hydroxyl-α-amino acids have been investigated as drug candidates or as building blocks for bioactive polypeptides. This lack of investigation is partially related to a limited number of methods for the preparation of this type of amino acid analog.

Previously it was found that the addition of in situ generated azolium ylides to aldehydes allows for the substitution of 1,3-azoles at C2 in a mild and selective manner. Additionally, it was found that Garner’s aldehyde (a configurationally stable, protected serinal) afforded the diastereomeric carbamates in a high diastereomeric ratio (92:8, 84% de), favoring the anti-adduct. Unfortunately, upon further examination a decrease in the enantiomeric purity of the product was observed, dropping from >97% ee for the aldehyde to 80% ee for the carbamate product. Our success to improve these reaction conditions for this transformation is described in this poster. The use of Garner’s aldehyde under various conditions and other non-enolizable protected serinals, such as the N-phenylfluorenyl oxazolidone, will be discussed. The product carbamates are fully functionalized and are orthogonally protected which permits the preparation of β-azolyl-β-hydroxyl-α-amino acids via a short synthetic sequence.


41. THE SELECTIVE ESTROGEN RECEPTOR MODULATOR ZK 186619


Schering AG, 13342 Berlin

At present, the postmenopausal period represents approximately a third of a woman’s life. In this era long term estrogen depletion increases the risk of osteoporosis, coronary heart disease and cognitive disorders. Existing therapies like the chronic monotherapy with pure estrogens causes an increased risk of endometrial hyperplasia, possibly leading to carcinoma. This can be avoided by continuous or sequential application of progestins. However,
the combination therapy with progestins may attenuate some of the beneficial effects of estrogens and result in undesirable effects, e.g. uterine bleeding. The undesired effects associated with estrogen replacement therapy and the increased risk of cancer (either real or suspected) reduces compliance with this therapy.

Selective estrogen receptor modulators (SERMs) which antagonize the effects of estrogen on uterine and mammary tissue, while mimicking the effect of estrogen on bone and the cardiovascular system, are considered as a possible alternative to estrogen replacement therapy[1]. All currently known SERM’s are estrogen receptor partial agonists/antagonists. This is the molecular basis of these compounds to act as estrogens or antiestrogens in a tissue specific manner. For example tamoxifen, originally developed as an estrogen receptor antagonist and widely administered for the treatment of breast cancer, has been found to act as a partial estrogen receptor agonist on the uterus and to display estrogen agonist effects on bone and on the cardiovascular system. The treatment of endometriosis is a very important option for the application of this new compound. Moreover raloxifene hydrochloride, which is on the market for the treatment and prevention of osteoporosis, exhibits tissue selectivity.

Structure and physio-chemical characteristics of ZK 186619
ZK 186619[2] is a nonsteroidal benzocycloheptene derivative with the following structural formula:

[Structure of ZK 186619]

Steroid receptor binding profile of ZK 186619 The profile of ZK 186619 binding to the steroid hormone receptors ERα and ERβ, progestogen (PR), glucocorticoid (GR), androgen (AR) and mineralocorticoid receptor (MR) - was determined by competition experiments. The study was performed by incubating the respective human receptors produced in Sf-9 insect cells with a saturating concentration of the appropriate radioactive ligand and different concentrations of ZK 186619. Displacement curves were established and the relative binding affinity (RBA) was determined as percent of reference affinity. The RBA values are listed in the Table.

| Table: Relative Binding Affinities for ZK 186619 RBA [%] |
|-----------------|-----|-----|-----|-----|-----|
| ERα  | ERβ | PR  | GR  | AR  | MR  |
| 106  | 209 | n.c.| n.c.| <0.1| n.c.|


42. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF SUBSTITUTED NAPHTHALENES AS ESTROGEN RECEPTOR LIGANDS


GlaxoSmithKline Inc., Five Moore Drive, Research Triangle Park, NC 27709, USA

The estrogen receptors (ERs) are members of the superfamily of ligand-modulated nuclear receptors (NR). They are implicated with many normal biological functions, including sexual development, cardiovascular and bone physiology, as well as lipid metabolism. Hormone replacement therapy (HRT) is effective in postmenopausal women for the treatment of osteoporosis and hot flush, however, the Women’s Health Initiative (July 2002) showed that HRT was associated with increased risk for cardiovascular disease and breast cancer. Selective estrogen receptor modulators (SERMs) represent a class of therapeutic agents with affinity for ERs that have been developed in order to provide the benefits of estrogen without the associated liabilities.

In this poster, we describe a series of synthetic routes used to synthesize substituted naphthalenes. Efforts focused on preparing a wide range of analogues with substitution at the R3 position of the naphthalene ring. The binding affinities of all new analogues vs the ER-alpha and ER-beta receptor subtypes will be reported.
43. NOVEL PROBES FOR THE ESTROGEN RECEPTOR LIGAND BINDING DOMAIN

Robert N. Hanson

Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA

As part of our program to develop new agents for the diagnosis and treatment of breast cancer we have focused on the estrogen receptor (ER) as our target. Based upon our previous studies and those of other investigators we have prepared new series of steroidal and non-steroidal probes for the ER-ligand binding domain. Receptor binding assays coupled with cell-based in vitro studies and in vivo evaluations provided the data for structure-activity relationships. We have used molecular modeling including conformational analysis (NMR) to evaluate the interactions between our ligands and the ER-LBD.

44. UTILITY OF BORON CLUSTERS FOR DRUG DESIGN. QSAR BETWEEN ESTROGEN RECEPTOR BINDING AFFINITY AND HYDROPHOBICITY OF CARBORANYLPHENOLS

Kiminori Ohta¹ *, Keisuke Yamamoto², Yasuyuki Endo¹

¹Tohoku Pharmaceutical University, ²The University of Tokyo

Carboranes (dicarba-closo-dodecaborane) are a class of carbon-containing boron cluster compounds, and exhibit remarkable thermal and chemical stability. Since carboranes are generally nontoxic and not metabolized in vivo, they will certainly possess the potential of a wide range of applications in the field of medicinal chemistry. We have focused on the possible utility of carboranes as a hydrophobic component in biologically active molecules, which interact hydrophobically with receptors. Recently, we reported the development of nuclear estrogen receptor (ER) ligands containing carboranes as the hydrophobic pharmacophore.¹ We have reported that 4-(12-hydroxymethyl-p-carboran-1-yl)phenol (BE120, 1) exhibited estrogenic activity greater than that of 17β-estradiol. Moreover, p-carboran-1-ylphenol (2) has significant potency despite lack of a hydroxymethyl group for hydrogen bonding to one of the hydrogen-bonding site on ER.
In view of the potential application of carboranes in the design of a wide range of drugs, we have experimentally measured the partition coefficients, logP, for carboranylphenols by means of an HPLC method, and determined the values of the Hansch-Fujita hydrophobic parameter \( \pi \) of the carboranyl groups. We designed and synthesized eight carboranylphenols having the same molecular geometry for the determination of the hydrophobic parameter \( \pi \) of the carboranyl group.\(^2\) In addition, the acidity of the phenolic group may affect the binding affinity for ER through hydrogen-bonding as well as the hydrophobicity of the carboranes. Therefore, we investigated a quantitative structure-activity relationship between two parameters, logP and \( pK_a \) in these carboranylphenols.\(^3\)

The \( C \)-substituted carboranylphenols were more hydrophobic than those of \( B \)-substituted analogues and \( p \)-carboran-1-ylphenol (2) showed the highest logP value (logP = 5.89). The \( \pi \) values (2.71-4.47) calculated from logP vary depending on the position of substitution on the carborane cage and the isomeric form (\( o \)-, \( m \)-, \( p \)-carborane), though carboranylphenols have the same molecular geometry. The \( pK_a \) values of carboranylphenols were in the range of one pH unit (\( pK_a = 9.16-10.25 \)). \( p \)-Carboran-1-ylphenol (2, IC\(_{50} = 0.59 \) nM) showed most potent binding affinity, which was measured by competitive inhibition of \([6,7-^3\text{H}]17\beta\)-estradiol-binding for ER\( \alpha \) and the other \( C \)-substituted phenols, 3 and 4, also exhibited more potent affinity than \( B \)-substituted phenols (5-9).

A quantitative structure-activity relationship analysis based on the values of logP and the \( pK_a \) of the phenolic group showed that the hydrophobicity of these compounds is highly correlated to the ER\( \alpha \)-binding affinity except for \( m \)-carboran-9-ylphenol (8) and \( o \)-carboran-9-ylphenol (9). The results may effectively represent the microscopic QSAR at the ligand-binding cavity of the ER\( \alpha \) and the spherical carborane cage seems to be produced a strong hydrophobic interaction with hydrophobic residues of the receptor cavity. In case of 8 and 9, one CH on the cage of these compounds may have an electrostatic interaction with ER\( \alpha \), His-524, which forms hydrogen-bonding with alcoholic hydroxyl group of 17\( \beta \)-estradiol.

These results should be useful for application of these spherical carboranes as hydrophobic pharmacophores in drug design, as well as for microscopic analysis of ER-ligand interaction.

**Figure 1. BE120(1) and designed carboranylphenols (2-9)**

![Diagram of carboranylphenols]

**Table 1. \( \pi \), LogP and \( pK_a \), and IC\(_{50} \) for ER\( \alpha \) binding affinity of carboranylphenols (2-9)**

<table>
<thead>
<tr>
<th>Carboranylphenol</th>
<th>( \pi )</th>
<th>LogP</th>
<th>( pK_a )</th>
<th>IC(_{50} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-(( p )-Carboran-1-yl)phenol (2)</td>
<td>+4.47</td>
<td>5.89</td>
<td>9.56</td>
<td>0.59</td>
</tr>
<tr>
<td>4-(( o )-Carboran-1-yl)phenol (3)</td>
<td>+4.33</td>
<td>5.75</td>
<td>9.16</td>
<td>2.85</td>
</tr>
<tr>
<td>4-(( m )-Carboran-1-yl)phenol (4)</td>
<td>+4.29</td>
<td>5.71</td>
<td>9.46</td>
<td>3.60</td>
</tr>
<tr>
<td>4-(( m )-Carboran-2-yl)phenol (5)</td>
<td>+4.11</td>
<td>5.53</td>
<td>9.67</td>
<td>9.57</td>
</tr>
<tr>
<td>4-(( p )-Carboran-2-yl)phenol (6)</td>
<td>+4.04</td>
<td>5.46</td>
<td>9.91</td>
<td>6.88</td>
</tr>
<tr>
<td>4-(( o )-Carboran-3-yl)phenol (7)</td>
<td>+3.74</td>
<td>5.16</td>
<td>9.61</td>
<td>71.6</td>
</tr>
<tr>
<td>4-(( m )-Carboran-9-yl)phenol (8)</td>
<td>+3.20</td>
<td>4.62</td>
<td>10.19</td>
<td>23.4</td>
</tr>
<tr>
<td>4-(( o )-Carboran-9-yl)phenol (9)</td>
<td>+2.71</td>
<td>4.13</td>
<td>10.25</td>
<td>3.92</td>
</tr>
</tbody>
</table>

Estrogen-mimicking small molecules have long been of therapeutic benefit for women suffering from a myriad of maladies including breast cancer, heart disease, and post-menopausal symptoms. The classic mechanism of estrogen action involves a ligand-dependent gene transcription factor called the estrogen receptor (ER), a member of the nuclear receptor super family. Recently, however, rapid nongenomic effects of estrogen have drawn a great deal of attention. It is thought that rapid estrogen signaling is mediated through a membrane associated receptor, but researchers in the field have yet to accept a definitive model describing the receptor(s) through which estrogen exhibits its nongenomic effects. In addition, it is still unclear what role nongenomic effects play overall in estrogen signaling. The purpose of the presented work is to chemically modify both estradiol, the prominent endogenous estrogen in women, and tamoxifen, a leading SERM used in breast cancer treatment and prevention, in order to modulate their nongenomic and genomic effects with the goal that these chemical tools will help begin to elucidate the mechanism and the relevance of nongenomic estrogen and SERM signaling. Our work involves screening compounds with cell-based and in vitro assays that measure estrogen activity. MAPK signaling was measured in MCF-7 cells using Western blotting techniques. eNOS activity was measured also by Western blotting techniques in COS-7 cells transiently transfected with ER and eNOS. Genomic signaling was measure using luciferase gene reporter assays utilizing the estrogen response element (ERE) promoter transiently transfected in Hela, Cos-7, and MCF-7 cells. Binding to both subtypes of the estrogen receptor (ERα and ERβ) were measured using fluorescence polarization. All assays were used to measure pharmacological properties of both well-characterized and novel SERM’s with the goal of discovering small or large molecules that differentially activate nongenomic versus genomic signaling of estrogen. Although most compounds are at the initial stage of testing in the above model systems, some progress has been made in diminishing the genomic response while maintaining MAPK activity. 4-hydroxytamoxifen, the active metabolite of tamoxifen, the active metabolite of tamoxifen, when functionalized with a primary amine on the extending arm of the triphenylethylethylene core shows at least a 10-fold decrease in potency in competition with estradiol in gene reporter assays with both ERα and ERβ but maintains binding affinity and MAPK activity. Work is in progress to place the same extension, among others, on the 11-position of estradiol in hopes to modulate the estrogenic response. Another tamoxifen analogue has been synthesized containing a linker that serves as a chemical handle attaching to a mono-dispersed functionalizable polymer synthesized through atomic transfer radical polymerization. We hypothesize that attaching steroid mimics to a large polymer will render the resulting bioconjugate impermeable to the cell. This will allow for selective activation of membrane-associated estrogen receptors. Initial studies with the tamoxifen polymer show that the polymer binds to ER, is a poor inhibitor of transcriptional activity, and maintains MAPK activity. Work is currently being done to synthesize and test a cell-impermeable estradiol conjugate. Through this work we hope to use small and large molecules to modulate genomic and nongenomic signaling of estradiol. These small molecules will be useful tools in identifying and characterizing the receptors responsible for nongenomic signaling and for determining the role rapid estrogen action plays in estrogen signaling pathways important to women’s health.

The recent discovery of estrogen receptor beta (ERβ) in nontraditional estrogen target tissues such as prostate, lung, and bladder has prompted intense research to elucidate the physiological functions and identify the therapeutic targets for this second subtype of estrogen receptor. Our approach towards this goal is to exploit the use of highly selective ERβ agonists. Recently, we have designed and developed a series of substituted quinolines as a novel class of ERβ selective ligands. A number of these substituted quinolines exhibit high affinity and selectivity for ERβ receptor. The design, synthesis and SAR, as well as proposed binding mode within the ligand binding domain of this class of compounds will be discussed.
LGD2226 AS A NOVEL SELECTIVE ANDROGEN RECEPTOR MODULATOR (SARM)
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The androgen receptor (AR) is a member of the extended family of nuclear receptors, and is widely distributed throughout the body. The natural ligands for the AR are testosterone (T) and dihydrotestosterone (DHT). Deficiencies of T and DHT can be compensated for by administrating exogenous androgens. Androgen therapy has been used for treatment of hypogonadal men, age-related deterioration of bone and muscle, cancer cachexia, and many other indications. Drawbacks of currently available androgen therapies however, are livertoxicity, overstimulation of prostate, or dosing is done through patches, gels, or injections. We have identified LGD 2226 as an orally available, nonsteroidal androgen, that displays good tissue selectivity in a ORDX rat model, with strong activity on muscle and bone, and moderate activity on prostate and seminal vesicle.

NEW ANTIESTROGENS FROM A LIBRARY OF HOMOALLYLIC AMINES, ALYLLIC AMINES AND CYCLOPROPYLALKYLAMINES
Jelena M. Janjic2*, Christopher Kendall1, Corey R.J. Stephenson1, Ying Mu2, Wen Xie2, Raghavan Balachandran2, Brianne Raccor1, Ying Lu1, Guangyu Zhu1, Peter Wipf1, Billy W. Day1.2
1Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA, 2Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA 15261, USA

We describe a new structural scaffold of potential antiestrogens identified from a library screen of homoallylic amines, allylic amines and cyclopropylalkylamines. Five compounds from a 67-membered library inhibited estradiol (E2)-induced transcriptional activity of the ERα in a transcriptional activation assay at classical ERE. All library members proved to be inactive in inducing ERα transcriptional activation at a classical estrogen response element (ERE). The most active compound in the transcriptional assay, CK1-183 [ O-Ethyl-N-2-{[(1R,2R)-2-{[(R)\]

DEVELOPEMENT OF BICYCLIC PYRAZOLONES AS CYTOKINE SYNTHESIS INHIBITORS
Roger Bookland*, Michael Clark, Steve Laughlin, Matthew Laufersweiler, Todd Brugel, Adam Golebiowski, Mark Sabat, Jane Djung, Michael Natchus, Jennifer Townes, John vanRens, Biswanath De, Lily Hsieh, Susan Xu, Rick Walter, Michael Janusz
Procter & Gamble Pharmaceuticals, Inc., Health Care Research Center, 8700 Mason-Montgomery Rd., Mason, OH 45040-8006

Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), when over expressed, are believed to be involved in the generation of inflammatory disorders such as rheumatoid arthritis (RA), osteoarthritis (OA), and Crohn’s Disease. The development of an orally available, low molecular weight cytokine synthesis inhibitors based on a [5,5] or [5,6]-bicyclic pyrazolone core containing a vicinal 4-aryl, 5-pyrimidinyl appendage are described. By making substitutions on the pyrimidinyl ring we were able to do the SAR necessary to improve solubility, metabolic stability, bioavailability as well as potency. Many analogs showed low
nanomolar activity against LPS-induced TNF-α in monocyctic cells. Lead candidates were tested in a rat iodoacetate model for osteoarthritis and showed in vivo efficacy at a dosing level of 15 mg/kg (BID).

50. MONOCYCLIC PYRAZOLONES AS CYTOKINE SYNTHESIS INHIBITORS

Procter & Gamble Pharmaceuticals, Inc., Health Care Research Center, 8700 Mason-Montgomery Rd., Mason, OH 45040-8006

The overexpression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) has been implicated in several inflammatory disorders. We are currently investigating lead drug targets for cytokine synthesis inhibition that could be used to treat inflammatory diseases such as osteoarthritis (OA) by potentially reducing cartilage degradation and promoting analgesia. These efforts have led to the development of a vicinal bis-aryl class of cytokine inhibitors containing a monocyclic pyrazolone core. Several symmetrically substituted monocyclic compounds (NR₁ = NR₂) containing ether and amino functionalities have been synthesized and tested for TNF-α inhibition in a THP-1 whole cell assay. Many of these compounds showed low nanomolar activity. Further modifications of this monocyclic pyrazolone scaffold to include asymmetrically substituted analogs (NR₁ not equal to NR₂) have been made and tested. Improved solubility and metabolic stability was observed with several of these analogs, versus the symmetrically substituted monocyclic pyrazolones. Lead candidates in this series were further tested in a rat iodoacetate model for osteoarthritis. Of the candidates that were screened in the in vivo model, the symmetrically substituted lead compound showed in vivo efficacy at a dosing level of 25 mg/kg (BID).

51. NOVEL BICYCLIC PYRIMIDINE DERIVATIVES AS P38 MAP KINASE INHIBITORS

Jian Jeffrey Chen, Stacie A. Dalrymple, Nolan James Dewdney*, Pete Dunten, David M. Goldstein, Eva Papp, Rick Roberts, Mary Welch, Haixia Wang
Department of Medicinal Chemistry, Roche Palo Alto LLC

The proinflammatory cytokines tumor necrosis factor - α (TNFα), and interleukin -1β (IL-1β) have been clinically validated as targets for the treatment of Rheumatoid Arthritis (RA). p38α Mitogen Activated Protein (MAP) Kinase is an intracellular soluble threonine kinase which regulates the production and signaling of IL-1β and TNFα. Inhibiting p38 MAP kinase suppresses TNFα and IL-1β, as well as cyclooxygenase (COX) expression, which would indicate that p38 inhibitors are likely to be effective in the treatment of RA and other inflammatory diseases. Orally active small-molecule inhibitors of p38α remain attractive therapeutic agents, and several p38 inhibitors are currently in Phase II clinical trials. Herein, we report the SAR of a novel class of bicyclic pyrimidine p38 MAP kinase inhibitors.

52. DISCOVERY OF A NOVEL CLASS OF ORALLY ACTIVE P38 MAP KINASE INHIBITORS

Departments of Chemistry, Biology and Modeling, Pharmacopeia, Departments of Discovery Chemistry, Macromolecular Structure, and Immunology, Bristol-Myers Squibb, PO Box 4000, Princeton, NJ 08543-4000 USA

Overproduction of cytokines such as TNF-alpha and IL-beta are implicated in a wide variety of inflammatory diseases, including rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease and endotoxic shock, among others. There is convincing clinical evidence that protein antagonists of cytokines such as the soluble TNF-a receptor
Fusion protein (etanercept), anti-TNF antibody (infliximab) and the IL-1 receptor antagonist (anakinra) can effectively treat chronic inflammatory diseases. The stress-activated signal transduction pathway leading to inflammatory cytokine production in stimulated immune cells is known to be regulated in part by p38alpha mitogen activated protein (MAP) kinase. To this end, we and others have searched for inhibitors of p38alpha as a means to inhibit inflammatory cytokine production. Herein, we describe our initial efforts in developing a potent, selective triaminotriazine amide as an inhibitor of p38alpha MAP kinase. Our initial hit was identified through screening the Pharmacopeia compound collection. The lead compound possesses oral activity in vivo models of acute and chronic inflammatory disease and represents a unique structural class compared to known p38 inhibitors. A description of the SAR, in vivo activity and X-ray crystallography will be presented.

53. PYRIDAZINES AS A NEW CHEMOTYPE FOR ALZHEIMER’S DISEASE DRUG DISCOVERY THAT TARGETS DISEASE PROGRESSION

Wenhui Hu*, Laurie K. McNamara, Sakti Roy, Jeffrey M. Craft, Magdalena Zasadzki, Linda J. Van Eldik and D. Martin Watterson

Drug Discovery Program, Northwestern University Feinberg School of Medicine, Chicago, IL USA

Alzheimer’s disease (AD) has an unmet medical need for therapies that target disease progression. The neuroinflammation hypothesis posits that attenuation of the cycle of glial activation, neuronal dysfunction, and further glia activation is a potential point of intervention in AD progression. We directly addressed this hypothesis using an integrative chemical biology approach (1,2). We used bioavailable pyridazine-based inhibitors (3,4) in a new mouse model of human amyloid-beta-induced hippocampal injury (1). We showed that compounds which target glial activation (3) can attenuate neuroinflammatory responses, neuronal dysfunction and loss, and spatial learning deficits (1,2). Our results provide strong evidence that targeting the neuroinflammatory cycle is a viable AD discovery approach with potential to modulate disease progression. The bioavailable inhibitors used for the proof of concept investigations clearly have adequate properties for penetration of the blood brain barrier and are not toxic, as determined by high dose and chronic administration, as well as analysis of cardiotoxicity (5). However, their molecular properties are not ideal for oral bioavailability (see computed properties for MW01-070C below). Therefore, current research is focused on lead compound discovery using a de novo approach, starting with the core pyridazine chemotype and synthesizing families of compounds with good computed molecular properties diversified at each of several positions on the pyridazine core. While requiring more extensive demands on the chemists and biologists, this approach has a potential for discovery of orally bioavailable compounds with desired ADMET properties. We describe here a proof of concept that compounds with good molecular properties (see MW01-2-151WH), discovered by our unbiased de novo approach, are able to mimic many of the therapeutic functions of the MW01-070C and related inhibitors developed as part of the integrative chemical biology studies. This new group of pyridazines are more appropriate for lead compound refinement as a foundation for new drug development.

Computed Molecular Properties

MW01-2-151WH —
MW: 344.4; LogP: 3.06 +/- 0.51; H-donors: 0; H-acceptors: 6; PSA (A2): 58.04; Rotatable bonds: 1.

MW01-070C —
MW: 527.7; LogP: 5.22 +/- 0.81; H-donors: 1; H-acceptors: 8; PSA (A2):88.78; Rotatable bonds: 12.


Supported in part by grants from the NIH (NS47586, AG13939, AG21184, AG00260, NS46942) & ISOA.
54. NOVEL AND POTENT TGF-β TYPE I INHIBITOR: 7-AMINO 4-(2-PYRIDIN-2-YL-5,6-DIHYDRO-4H-PYRROLO[1,2-B]PYRAZOL-3-YL)-QUINOLINES

Hong-yu Li\textsuperscript{a,*}, Yan Wang\textsuperscript{a}, Lei Yan\textsuperscript{b}, Robert M. Campbell\textsuperscript{c}, Bryan D. Anderson\textsuperscript{c}
\textsuperscript{a}Discovery Chemistry Research, \textsuperscript{b}Cancer Research, and \textsuperscript{c}Lead Optimization Biology Lilly Research Laboratory
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285, USA

A novel series of 7-amino 4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolines was synthesized and their TGF-β R1 inhibitory, p38 MAPK inhibitory, and TGF-β R1-dependent cellular activity were evaluated. Compound 5a was found to be a highly potent in the enzyme assay and TGF-β R1-dependent cellular assays. In addition, dimer (4g), with a urea linker, shows a similar enzyme and cellular activity despite a bulky substitution.

55. DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 7-AZAINDOLYL-HETEROARYLMALEIMIDES AS POTENT AND SELECTIVE GLYCOGEN SYNTHASE KINASE-3β (GSK-3β) INHIBITORS

David J. O’Neill\textsuperscript{*}, Lan Shen, Catherine Prouty, Bruce R. Conway, Jun Z. Xu, Han-Cheng Zhang, Bruce E. Maryanoff, William V. Murray, Keith T. Demarest and Gee-Hong Kuo
Johnson & Johnson PRD

Two approaches were developed to synthesize novel 7-azaindolyl-heteroarylmaleimides. The first approach was based upon a palladium-catalyzed Suzuki cross-coupling or Stille cross-coupling of a 2-chloro-maleimide with various aryboronic acids or arylstannanes. The second approach was based upon the condensation of ethyl 7-azaindolyl-3-glyoxylate with various acetamides. The hydroxypropyl-substituted 7-azaindolylmaleimide template was first used to screen different heteroaryls attached to the maleimide. Replacement of hydroxypropyl with different chain lengths and different functional groups were studied next. Many compounds synthesized were demonstrated to have high potency at GSK-3β, good GS activity in HEK293 cells and good to excellent metabolic stability in human liver microsomes. Three representative compounds were demonstrated to have good selectivity against a panel of 80 kinase assays. Among them, one exhibited very weak inhibition at the other 79 kinase assays, and behaved as a GSK-3β “specific inhibitor.”

56. MOLECULAR MODELING QUEST FOR INHIBITORS OF THE CDK5/P35 INTERACTION

Felipe Opazo, Gerald Zapata-Torres, Ricardo B. Maccioni, Bruce K. Cassels\textsuperscript{*}
Millennium Institute for Advanced Studies in Cell Biology and Biotechnology

Cdk5 is an atypical member of the cyclin-dependent kinase family, as it is not involved in control of the cell cycle. Instead, Cdk5 plays a fundamental role in the development of the CNS, in apoptosis, neuronal migration, neurite outgrowth and synapse formation. Also, it is activated by p35, its proteolytic fragment p25, and other proteins which are not cyclins, and its deregulation is a key element in the hyperphosphorylation of tau protein leading to the formation of neurofibrillary tangles, a hallmark of Alzheimer’s disease. Earlier research in our Institute has shown that Cdk5 inhibition is cytoprotective in neuronal cell cultures exposed to neurotoxic oligomeric beta amyloid (Aβ) peptide. We recently built a homology-based model of Cdk5 bound to its substrate ATP, derived from the crystal structure of cocrystallized Cdk2-cyclin A with ATP, and carried out docking studies with a series of Cdk5-inhibitory and inactive flavonoids. The high degree of similarity between the active sites of different Cdk’s led us to the
conclusion that the pursuit of drugs with good selectivity for Cdk5 over other Cdk’s, based on binding to the ATP site, may not be worth the effort. Using the recently published X-ray structure of the Cdk5/p25 complex, we have now modeled the interface between these two proteins as a basis for the design of more specific inhibitors. This interface includes the T-loop and the PSSALRE α-helix of Cdk5. Using InsightII and other software, we designed and optimized peptide mimics of the surface of the PSSALRE helix. Using AutoDock, we were able to predict that some of these peptides should have higher affinity for p25 than PSSALRE itself.

57. INHIBITION OF SRC KINASE ACTIVITY BY 4-ANILINO-7-PYRIDINYL-3-QUINOLINECARBONITRILES

Biqi Wu*, Nan Zhang, Diane H. Boschelli, Jennifer M. Golas and Frank Boschelli
Chemical & Screening Sciences and Oncology, Wyeth Research, 401 N. Middletown Road, Pearl River, NY, 10965.

Src, a non-receptor tyrosine kinase plays an essential role in disease states including cancer. Previously we established that several 7-alkoxy-4-anilino-3-quinolinecarbonitriles were potent inhibitors of Src kinase activity. In order to increase the Src inhibitory activity, the C-7 alkoxy group was replaced by a pyridine ring containing various basic solubilizing groups. In this poster, we present the synthesis of 4-anilino-7-pyridinyl-3-quinolinecarbonitriles and discuss the effect of varying the 4-anilino and 7-pyridinyl groups on the inhibition of Src kinase activity. The most potent activity was observed with the derivative bearing a 2,4-dichloro-5-methoxyaniline at C-4 and a 5-[(4-methyl-1-piperazinyl)methyl]-2-pyridyl group at C-7.

\[
\begin{align*}
R' & = \text{N} \\
R & = 2,4\text{-diCl-5-OMe} \\
& \quad 2,4\text{-diCl} \\
& \quad 3,4,5\text{-triOMe}
\end{align*}
\]

58. THE DISCOVERY OF POTENT AND SELECTIVE INSULIN-LIKE GROWTH FACTOR I RECEPTOR KINASE INHIBITORS

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IGF-IR (Insulin-like growth factor I receptor) is a membrane-bound tetramer (αββα) with intrinsic tyrosine kinase activity. High levels of IGF-IR and/or its activating growth factors have been associated with various types of cancers and found to be correlated with increased invasiveness and metastatic potential. Targeting IGF-IR via different approaches (e.g. antisense oligonucleotides or antibodies) has reversed the transformed phenotype of cancer cells in vitro and inhibited tumour formation in vivo. In our drug discovery approach for this receptor, we have targeted its intracellular kinase domain by interfering with ATP binding. Following high-throughput screening of our in-house compound collection, we identified a series of pyrrolo[2,3-d]pyrimidine derivatives that were equipotent against the tyrosine kinase activities of the IGF-IR and insulin receptor. Due to the high level of sequence identity between these two receptors (84% in the kinase domains and 100% in the ATP binding sites), a major medicinal chemistry effort was devoted to achieve selectivity against the insulin receptor. Our lead optimisation strategy resulted in the identification of IGF-IR kinase inhibitors that showed 5- to 50-fold higher potency over the insulin receptor in inhibiting receptor autophosphorylation in cellular settings. Representative examples from this new class of potent and selective IGF-IR kinase inhibitors will be selected to highlight the in vitro and in vivo effects of blocking IGF-IR signalling in tumour cells.
59. **PEPTIDES IDENTIFIED BY PHAGE DISPLAY THAT BIND TO DIFFERENT EPITOPIES OF THE SAME TARGET CAN BE DIMERIZED WITH A NOVEL LINKING STRATEGY TO IMPROVE POTENCY OVER MONOMERS AS MUCH AS 250-FOLD FOR THE TYROSINE KINASES KDR/VEGF-R2 AND CMET**

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In an effort to optimize the binding of high affinity monomeric peptides identified by phage display to multiple motifs on the extracellular portion of KDR/VEGFR-2 and CMET, we constructed homo- and hetero- multimers. First, we assessed the binding ability of heterotetrameric complexes of biotinylated peptides on Neutravidin-HRP. We found that mixtures of two non-competing peptides (that bind different epitopes on KDR) bound much better than the homotetrameric complexes of either peptide. Based on these results, fully synthetic heterodimeric and homodimeric peptides were made and tested. Using glutaryl bissuccinate we were able to prepare heterodimers joined at the N-terminus, C-terminus or N- and C- terminus, with a number of different linkers and reporting groups for imaging or biological evaluation. The best heterodimers had K_D's of about 0.5 nM, 6-fold lower than the best monomer. In addition, heterodimers were more than 40-fold more potent in blocking VEGF binding to KDR than the best monomer. In bioassays that measure the ability of compounds to block VEGF’s effects on KDR activation, cell migration, and proliferation in endothelial cells, heterodimers were up to 250-fold more potent than the best monomeric KDR-binding peptide (IC_50 0.5 to 11 nM vs IC_50 100 to >1000 nM). Heterodimers constructed with a site for attachment of a reporter group for imaging did not lose binding affinity. Homodimers generally performed no better than monomeric peptides with the same sequences. Thus, the heterodimeric peptides bind to two different epitopes on the KDR receptor simultaneously, achieving increased avidity from multimeric binding. The dimers were highly specific for the external domain of the KDR receptor as evidenced by a lack of binding to related receptors and non-KDR-expressing cell lines. To further test the generality of this approach we prepared heterodimers of phage-derived peptides to CMET. In this case, we prepared dimers from peptides that bound to different epitopes on CMET. One dimer of a 880 nM and a 220 nM peptide produced a compound with 0.79 nM binding. This 250+ improvement was obtained from a limited set of noncompetitive binding monomers. We believe that designing appropriate heteromultimers can greatly extend the value of phage display overall in generating useful therapeutic and diagnostic imaging molecules.

60. **SAR OF IMPROVED COMPOUNDS FOR TARGETED RADIOTHERAPY OF HUMAN SOLID TUMORS EXPRESSING GASTRIN RELEASING PEPTIDE RECEPTORS**

Rolf E. Swenson*, Luciano Lattuada, Enrico Cappelletti, Natarajan Raju, Hanh Nguyen, Jianqing Chen, Karen E. Linder, Laura E. Lantry, Thangavel Arunachalam, Adrian D. Nunn, Michael F. Tweedle

Ernst Felder Laboratories, Bracco Research USA Inc.

The Gastrin Releasing Peptide Receptor (GRP-R) is over-expressed in many cancers, including prostate, breast and small cell lung cancer. Bombesin (BBN), a naturally occurring peptide, is a potent GRP agonist with homology to 12 of the 24 amino acids of native Gastrin Releasing Peptide (GRP). The last 8 amino acids (QWA VGHLM-NH2) have been shown to be critical for biological activity. Clinically, radiolabelled octreotate derivatives (somatostatin analogs) have shown efficacy for the radiotherapeutic treatment of somatostatin receptor positive cancer demonstrating the utility of targeted radiotherapy for peptide receptor positive cancers using internalizing peptide agonists. Previously, it was shown that BBN[7-14] linked via 8-aminooctanoic acid to a DOTA-chelate containing a beta emitting isotope such as 90Y or 177Lu, binds to GRP-R(+) tumor cells in vitro and increases the survival of GRP-R(+) tumor bearing mice. We found that optimization of the linker between the DOTA-chelate and Bombesin [7-14] produced compounds with substantially improved efficacy in vivo. SAR of the linker allowed the selection of 177Lu-DOTA-G-(4-aminobenzoyl)-QWAVGHLM-NH2 (177Lu-AMBA) as a candidate for clinical development. In a long term radiotherapy study (120 day) using a human prostate xenograft model (PC3), mice were administered a single bolus subcutaneous injection (30 mCi/kg) of 177Lu-AMBA. Treatment demonstrated 39% survival at 30 days versus 5.5% survival in the control group; and 26%, 22%, and 17% overall survival at 60,
90 and 120 days respectively in the treatment group. The compound was four times as effective as the 8-aminoocanoic acid compound, at half the radiotherapy dose. The chemistries of $^{177}$Lu-AMBA and related analogs and the pharmacological studies that demonstrate the utility of these compounds in targeted radiotherapy will be presented.

61. BIOSYNTHESIS OF ENEDIYNES AND THEIR RESISTANCE MECHANISMS

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The enediyne antibiotics are potent antitumor agents with an extremely unique molecular architecture, mode of action and clinical promise. Their extremely high toxicity, which is unrivaled by any other known secondary metabolite, is based on their ability to attack and cleave DNA. This mode of action represents a major challenge for the producing organism and requires an elaborate resistance mechanism. Calicheamicin and dynemicin, prominent of the 10-membered enediyne family, are excellent targets for the study of natural product biosynthesis and self-resistance. Cloning and characterization of biosynthetic gene loci for the both of antibiotics revealed an unusual iterative polyketide synthase, biosynthetic genes responsible for four unusual deoxysugar motifs and novel resistance gene. Heterologous expression and biochemical characterization of the biosynthetic loci/gene will give insight into the key steps of enediyne warhead assembly, resistance protein mechanism and aryltetrasaccharide biosynthesis.

62. METHYLTRANSFERASE DEPENDENT DNA ALKYLATION WITH AZIRIDINE-BASED COFACTOR MIMICS

Lindsay R. Comstock* and Scott R. Rajski
University of Wisconsin, Madison

The synthesis and evaluation of DNA modifying agents deriving sequence specificity from DNA-modifying proteins will be presented. Specifically, DNA methyltransferases will be utilized in combination with aziridine-based cofactor mimics to alkylate DNA. Construction of two cofactor mimics capable of substrate adenylatation bearing an azide on the C8 of the adenine based will be described. The resulting lesion will be capable of undergoing further conjugation under abiotic conditions using the Staudinger ligation and “Click” chemistry to ultimately create conjugates capable of DNA damage.

63. SYNTHESIS AND CYTOTOXICITY OF 1,2-DISUBSTITUTED IMIDAZO[4,5-G] QUINOLINE-5,8-DIONE DERIVATIVES

Seon Hee Jeong, Seung Hoon Cheon*
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To search for potential anticancer drug candidates, we have synthesized a number of 1,2-disubstituted imidazo[4,5-g]quinoline-5,8-diones. According to the in vitro test results, most of them were more potent than the clinical agent doxorubicin in five different human tumor cell lines. In general, C-6 substituted products are more active than C-7 substituted products. Especially, compound with n-propylamino group substituted at C-6 showed strong potency in SK-OV-3. 6- and 7-amino analogs that seem to be a key pharmacophore for the biological activities of lavendamycin were synthesized in four steps from commercially available 8-hydroxyquinoline in excellent overall yield.

64. IDENTIFICATION OF A NOVEL CLASS OF CELL CYCLE INHIBITORS AS ANTI-CANCER AGENTS

Michael S. Saporito, Alexander Ochman, Laura Hong, Kyoung-Jin Lee, Martha J. Kelly, Bruce Dorsey*, Brad Zerler.
Locus Pharmaceuticals

Retinoids consist of natural and synthetic derivatives of vitamin A that inhibit cellular proliferation, promote differentiation and induce programmed cell death. These properties indicate that retinoids could be useful as cancer chemotherapeutic agents. In fact, retinoic acid (ATRA) is approved for the treatment of acute myeloid leukemias and there are a number of synthetic retinoids in clinical trials for the treatment of a variety of cancer types. However,
the chemotherapeutic activities of ATRA are limited by the occurrence of retinoid-specific toxicities and by the development of tolerance with repeat administration. ATRA promotes cellular responses via activation of a subclass of nuclear hormone receptors designated as retinoic acid receptors (RARs). Using a proprietary computational design technology a series of novel RAR-specific retinoid mimetics were designed and synthesized. These compounds were evaluated for their anti-proliferative activity on a series of tumorigenic cell types. One compound evoked an inhibition of cellular proliferation in a array of tumor cell lines and promoted a dramatic increase in the ratio of cells in the G2/M phase of the cell cycle. In some cell types including several leukemic T-cell types, this compound produced a G2/M cell cycle block that was followed by apoptosis. The cell cycle block activities were distinct from those associated with natural and synthetic retinoids, suggesting that an alternative non-RAR activity was driving the cell cycle inhibitory response. The data that will be presented will explore alternative cellular mechanisms that drive the cell cycle block activity and describe the potential of this class of compounds as a unique therapeutic for a number of cancer types.

65. THE TUMOR CELL MIGRATION INHIBITOR MIGRASTATIN: ANALYSIS OF ITS BIOSYNTHETIC GENE CLUSTER IN STREPTOMYCES PLATENSIS AND ENGINEERING FOR NOVEL ANALOGS

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Migrastatin (MGS) exhibits potent inhibitory effects on tumor cell migration, serving as a lead to target tumor metastasis for anticancer drug discovery. Genome scanning of Streptomyces platensis NRRL18993 unveiled a gene cluster featuring acyltransferase (AT)-less type I polyketide synthases (PKSs) with discrete ATs to provide the essential AT activity in trans for MGS biosynthesis. The MGS gene cluster consists of eleven genes, whose involvement in MGS biosynthesis was confirmed by gene inactivation via the PCR-targeting, λ-red mediated gene replacement method. Both discrete ATs (MgsB; AT-TE and MgsH; AT-Ox) are essential for MGS biosynthesis. An amidotransferase (MgsD) and a discrete acyl carrier protein (ACP) (MgsC) are proposed to constitute the loading module of the MGS megasynthase, responsible for the assembly of the glutarimide moiety of MGS. A transcriptional activator (MgsA) has a bacterial transcriptional activator domain (BTAD) in a SARP (streptomyces antibiotic regulator protein) family, is required for MGS production. An oxidoreductase (MgsI), a methyltransferase (MgsJ), and a P-450 monoxygenase (MgsK) are responsible for the tailoring steps of MGS biosynthesis. Remarkably, inactivation of genes within the mgs cluster abolished not only MGS production but also that of dorrigocin (DGN), another family of metabolites known to this organism. These results confirm that the cloned gene cluster in fact encodes the biosynthesis of both MGSs and DGNs. Genetic and biochemical characterizations of the mgs gene cluster, engineering of the MGS pathway for the production of novel MGS and DGN analogs, isolation and structural determination of these new compounds, and evaluation of their inhibitory effects on tumor cell migration will be presented.

66. γ-RADIATION INDUCED DNA-DAMAGED PRODUCTS: INSIGHT INTO STEROECHOICALLY FAVORED 6-(α-THYMINYL)-5,6-DIHYDROTHYMINE DERIVATIVES

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The 6-(α-thyminyl)-5,6-dihydrothymine adduct (1) represents the major product formed under the direct effect of γ-radiation on thymidine.1 In the light of its probable formation within DNA, this compound deserves full consideration, particularly when a permanent manned station on the moon and a manned mission to Mars are currently being envisaged. We herein report on the synthesis and stability of two intra-strand-derived 6-(α-thyminyl)-5,6-dihydrothymine diastereomers. Far UV photolysis of 4-thiothymidylyl(3'-5')thymidine (2) led to the formation of two 6-(α-thyminyl)-5,6-dihydrothymine derivatives diastereomers at positions C5 and C6 (3 and 4) that likely derived from an hydrogen abstraction from the thymine methyl group by the excited thiocarbonyl group then radical combination according to two stereochemical pathways (Scheme). The major pathway occurred when the 5'-base
glycosidic bond had an *anti* conformation leading to Scheme an *S* configuration of the C₆Tp-end. The minor pathway involved a 5'-base in a *syn* conformation leading consequently to the R configuration at the C₆Tp-end. The resultant thioenolate equilibrates with its thiocarbonyl form by protonation on the C₃ position exclusively from the less hindered side of the 5,6-dihydropyrimidine (side opposite to the thyminyl substituent) to afford the kinetic adducts (3 or 4). Upon standing in alkaline aqueous solution, these two compounds quantitatively convert into the thermodynamic adducts 5 and 6; respectively, leading to a *trans* diaxially 5,6-disubstituted-5,6-dihydro pyrimidine. Free energy difference (ΔG) calculations in the gas phase between the two C₅ epimers of the major adduct (3 and 5) confirmed these observations and generalized our previously established rules concerning the stereochemistry of hC₅(6-4) photoproducts.C² This study demonstrates that among the four 6-(α-thymyl) diastereomers, only the two *trans*-diaxially substituted are stable over a long period of time.

\[
\begin{align*}
\text{Scheme 1} \\
\text{Major} \quad + \quad \text{Minor} \\
\text{3 (5R, 6S)} \quad + \quad \text{4 (5S, 6R)} \\
\text{5 (5S, 6S)} \quad + \quad \text{6 (5R, 6R)}
\end{align*}
\]


67. THE SYNTHESIS OF NOVEL C-5'-MODIFIED GLYCOSIDICFLUOROINDOLOCARBAZOLES AS TOPOISOMERASE I INHIBITORS

*Edward Ruediger*¹ *, Byron Long*³ , Carol Bachand¹ , Francis Beaulieu¹ , Craig Fairchild³ , David Frennesson² , Mikael Mahler¹ , Alain Martel¹ , Mark Saulnier² , Denis St. Laurent² , Dolatri Vyas² , Balu Balasubramanian²

Bristol-Myers Squibb Pharmaceutical Research Institute, ¹Candiac, QC, Canada; ²Wallingford, CT; ³Lawrenceville, NJ

Topoisomerase I has been clinically validated as an important therapeutic target in cancer chemotherapy. In recent years, non-camptothecins, such as the indolocarbazoles NB-506 (1) and BMS-250749 (2), have emerged as clinical candidates with potent topoisomerase I inhibitory activity. Staurosporine (3) is a related indolocarbazole
microbial metabolite, bearing an intriguing C-5'-bridged glycosidic linkage, which exhibits potent protein kinase C activity, but which is devoid of topoisomerase I activity.

During the course of our investigation of the SAR of potent topoisomerase I inhibitors related to BMS-250749 (2), we sought to explore a series of C-5'-modified glycosides (e.g., 6) using a selective deprotection strategy (e.g., 4 → 5). The details of the synthesis of a series of novel C-5'-substituted glycosidic fluoroindolocarbazoles will be described, as will the in vitro topoisomerase I and cytotoxic activity of these and related analogs.

68. DISCOVERY OF POTENT ANTAGONISTS OF THE ANTI-APOPTOTIC PROTEIN XIAP FOR THE TREATMENT OF CANCER

Thorsten K. Oost1*, Chaohong Sun1, Robert C. Armstrong2, Ali-Samer Al-Assaad2, Stephen F. Betz1, Thomas L. Deckwerth2, Hong Ding1, Steven W. Elmore1, Robert P. Meadows1, Edward T. Olejniczak1, Andrew X. Oleksijew1, Tilman Oltersdorf2, Saul H. Rosenbg1, Alexander R. Shoemaker1, Hua Zou2, Stephen W. Fesik1

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Apoptosis plays a critical role in the development and homeostasis of multicellular organisms. In many cancers the cell death machinery is inhibited by the upregulation of anti-apoptotic proteins, suggesting that the restoration of apoptotic activity might be an effective approach for treating these cancers. Inhibitor of apoptosis proteins (IAPs) are overexpressed in many cancers and have been implicated in tumor growth, pathogenesis and resistance to chemotherapeutic or radiotherapy. Human X-linked IAP (XIAP), the best-characterized among the IAPs, is believed to directly inhibit particular caspases via its ~70-amino acid BIR domains. The BIR3 domain of XIAP binds directly to the small subunit of caspase-9, the initiator caspase in the mitochondrial pathway of apoptosis. Based on the NMR structure of a SMAC peptide complexed with the BIR3 domain of XIAP [1], a novel series of proteolytically stable XIAP antagonists was discovered and optimized using high-throughput parallel chemistry. The most potent compounds in this series bind to the BIR3 domain of XIAP with single-digit nanomolar affinity and promote cell death in several human cancer cell lines with EC50 values as low as <10 nM. In a breast cancer mouse xenograft model, these XIAP
antagonists inhibited the growth of tumors. Results from cellular experiments are consistent with a mechanism in which ligands for the BIR3 domain of XIAP disrupt the XIAP-caspase 9 protein-protein complex, thereby activating downstream caspases and resulting in apoptosis. The present study validates the BIR3 domain of XIAP as a target and supports the use of small molecule XIAP antagonists as a potential therapy for cancers that overexpress XIAP.

\[
\begin{align*}
K_d &= 12 \text{ nM (XIAP-BIR3)} \\
EC_{50} &= 15 \text{ nM (BT-549 cells)}
\end{align*}
\]


69. HIT-TO-LEAD PROCESS AT SCHERING AG


Schering AG, Research Center Europe

High Throughput Screening (HTS) has become a widely used technology for lead finding in pharmaceutical industry. In most cases HTS produces large hit numbers of different quality. The phase between the end of HTS and the start of a full Lead Optimization (LO) project is called Hit-to-Lead. The challenge is to filter the initial hits to obtain a few high quality lead structures which will allow a successful and rapid Lead Optimization. To achieve this goal we established a process with defined decision points. Major selection criteria are: Biological activity/selectivity, chemical optimization potential, lead/druglikeness, and patentability. Clear guidance and parallelization of the workflow allow rapid filtering of the initial HTS hits. Our HitL process will be presented and illustrated with examples.

70. ADVANTAGES OF USING SPECIES-SPECIFIC LOG D IN DRUG DESIGN AND ADMET ANALYSES

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13M Co. and (currently) BIOpK, 2FMC Corp.

The use of log D in QSAR studies and in correlations, such as binding to serum albumin, is routine. One problem with using log D is that the properties of the neutral and ionized species are lumped together. Two compounds with the same log D at pH 7.4 can differ markedly in the percent ionized. A better alternative to log D is the use of species-specific log D (an A. Avdeef term). The required property information has been difficult to obtain, but is now available through a new titration procedure. (Automated Titrations in KCl/Water-Saturated Octanol, 3rd International Lipophilicity Symposium, Zurich 2/29-3/4/04; see this poster.) The octanol pK\textsubscript{a}” (double prime) and aqueous pK\textsubscript{a} are used in the calculations. For bases, D\textsuperscript{1} = (P\times 10^{(pK\textsubscript{a}” - pH)}(1 + 10^{(pK\textsubscript{a} - pH)}), and D\textsuperscript{N} = P/(1 + 10^{(pK\textsubscript{a} - pH)}). For acids, the pK\textsubscript{a} and pH terms are reversed. Log D = log (D\textsuperscript{N} + D\textsuperscript{1}).

71. THE EFFECTS OF SUBSTITUTION ON PYAN-LACTONE CONTAINING DIHYDROPYRIDINE ATP-SENSITIVE POTASSIUM CHANNEL OPENERS.

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We have previously reported on pyran-lactone containing dihydropyridines (DHPs) as potent ATP-sensitive potassium channel openers (KCOs). KCOs relax smooth muscle by increasing potassium efflux which results in cell membrane hyperpolarization and reduced smooth muscle excitability and may be useful in the treatment of the spontaneous bladder contractions associated with urinary urge incontinence.
We investigated the effects of substitution off of the pyran and lactone rings at positions A, B and C of compound 1. Compounds were evaluated for their potassium channel opening activity using primary cultured guinea pig bladder (GPB) cells. The synthesis and biological results will be presented.

Roche Palo Alto

Prostaglandin E2 acts on at least four pharmacologically distinct receptors and exerts a number of physiological effects when administered systemically. The prostanoid receptor subtype EP4 is one of the receptors and it plays a critical role in bone biology. A hypothesis was forwarded that the selective stimulation of the EP4 receptor would lead to preferential effects in bone tissue. By extension, an orally active selective EP4 agonist would be beneficial in the treatment of osteoporosis. A drug discovery program was initiated based on the finding that chemically simplified 8-aza-11-deoxy-prostaglandin E derivatives are selective agonists at the prostanoid EP4 receptor.

The optimization of the α-chain towards high EP4 subtype selectivity and assessment by functional activity has been previously reported. The native heptanoic acid (α-chain) of prostaglandins is subject to rapid degradation and leads to nor acids (e.g. A) of much diminished activity. We sought to improve the in vivo half-life of active EP4 agonists. Lactams with unnatural features in the α-chain (B and C) were assessed for their pharmacokinetic properties in rat. This poster will present the preparation of novel γ-lactams bearing unnatural α-chains, selected structure-activity relationships and receptor profiling of those lactams as well as early pharmacokinetic information.
73. DISCOVERY OF POTENT PROSTAGLANDIN EP2 AND EP4 RECEPTORS AGONISTS THAT EXHIBIT BONE ANABOLIC PROPERTIES IN RATS
Zhong Zhaoa*, Bagna Baob, Nadia Bruggera, David Fischerc, Claudio Giachettid, Lucia Golziod, Srinivasa Karraa, Paolo Marinellid, Sean McKennab, Elizabeth Palmere, Adulla Reddya, YuFang Xiaoa, Gian Luca Araldia*

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The subfamily Prostaglandin E2 (PGE2) receptors includes four subtypes: EP1, EP2, EP3 and EP4 receptors. The major phenotype of EP2 knockout mice indicated impaired ovulation and fertilization. Recent studies also showed that an EP2 agonist can induce bone healing. The major phenotype of EP4 knockout mice showed impaired bone metabolism and patent ductus arteriosus. PGE2, despite its high potency, lacks selectivity toward the EP receptors and is chemically unstable under physiological conditions. In order to improve its selectivity profile and to prevent the chemical and metabolic degradation of PGE2, analogues with an improved activity/duration profile have been designed and synthesized. This report details the synthesis and structure-activity relationship of a series of novel γ-lactam derivatives of general formula 1 bearing different groups in the ω-chain. In vivo PK profiling data of one of the analogues and efficacy studies of prevention of bone loss in a rat ovariectomy model are also presented.

Analogues of PGE2, wherein, the hydroxyl cyclopentanone ring has been replaced by a γ-lactam ring and the alkenyl α-chain been replaced with the phenethyl chain, were found to exhibit potent and selective agonist activity at the EP2 and EP4 receptors. In particular, synthesis of 15-hydroxy-15-alkyl derivatives led to potent and mixed EP2/EP4 agonists while the preparation of derivatives of formula 1 wherein R is CH2-aryl led to selective EP4 receptor agonist. These compounds displayed a high degree of selectivity amongst the other prostanoid receptors with an improved in vivo half-life as compared to PGE2. These analogues are shown to be potent bone anabolic agents.

74. RATIONAL DESIGN OF POTENT AND SELECTIVE NH-LINKED ARYL/HETEROARYL CATHEPSIN K INHIBITORS
Joel Robichaud1*, Chistopher Bayly,1 Renata Oballa,1 Peppi Prasit,1 Christophe Mellon,1 Jean-Pierre Falgueyret,1 David Percival,1 Gregg Wesolowski,2 Sevgi B. Rodan,2

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Cathepsin K (Cat K), a cysteine protease selectively expressed in osteoclasts, plays a pivotal role in the degradation of bone collagen. The inhibition of this enzyme results in reduced bone resorption, making Cat K a prime therapeutic target for the treatment of osteoporosis.

Prior reports from our laboratories have identified the non-peptidic nitrile 1. Examination of this compound modeled into the active site of Cat K suggested that the introduction of a NH linker between the P3 biaryl moiety and the P2-P1 leucinamide acetonitrile moiety would allow the formation of a favorable hydrogen bonding interaction with the Gly66 residue of Cat K. The aniline 2 was prepared and found to be equipotent to its predecessor 1.

Further modeling pointed out that a 2-substituted five-membered ring would more adequately place the P3 moiety of our inhibitors inside the S3 pocket of Cat K. This hypothesis was confirmed by the identification of the 2-
substituted thiophene 3 which had a 10-fold increase in potency relative to 1. Compound 3 is a 0.2 nM inhibitor of Cathepsin K, is >500-fold selective over Cathepsins B, L, and S, and also displays an increased potency in the functional bone resorption assay (10 nM) versus its predecessor 1 (95 nM).

75. SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-FLUORO-2-CYANOPYRROLIDINE DIPEPTIDE INHIBITORS OF DPP-IV.

Richard Caldwell1, Istvan Kaldor1, Curt D. Haffner1, Darryl L. McDougald1, Steven M. Reister1, Kate Dwornik1, Sab Randhawa1, Brian Thompson1, David Cowan1, Brad Henke1, James M. Lenhard2, Dallas Croom2, Daphne Clancy2, Donovon McCorn3, Kevin M. Hedeen3*, Kevin J. Wells-Knecht4, Melissa Secosky4, Wenhai Zhang4

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Dipeptidyl peptidase IV (DPP-IV), first identified by Hopsu-Havu and Glenner, is a widely expressed post proline cleaving serine protease. A large number of peptide substrates for DPP-IV have been discovered and several biological functions in humans have been identified. DPP-IV contributes to extracellular matrix binding, it functions as an adenosine deaminase (ADA)-binding protein, and it exhibits post proline or alanine cleaving properties from oligo or polypeptides at the N-terminus. Incretins such as glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptepide (GIP) play an important role in insulin homeostasis and have been shown to be inactivated by DPP-IV. We describe the synthesis and biological evaluation of a series of potent, selective and orally active DPP-IV inhibitors 1.

76. STRUCTURE-ACTIVITY RELATIONSHIPS OF PIPERIDINYLGLYCINYL-4,5-METHANOPROLINENITRILES: POTENT DIPEPTIDYL PEPTIDASE IV INHIBITORS FOR THE TREATMENT OF TYPE II DIABETES

Chet Kwon*, Guohua Zhao, Charles R. Dorso, Mark S. Kirby, Qi Huang, Rex A. Parker, Benoni Abboa-Offei, James G. Robertson, Aiying Wang, Lori Hilden, Mandar V. Dali, Ashish Khanna, and Lawrence G. Hamann

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It has been clinically demonstrated that the inhibition of dipeptidyl peptidase-IV (DPP-IV) mediated degradation of the incretin hormone glucagon-like peptide-1 (GLP-1) results in the improvement of both post-prandial and fasting glucose control in type II diabetics. As a result, DPP IV has become a particularly attractive target for small-molecule antidiabetic pharmaceutical development for the treatment of this widespread disease. In previous disclosures from these laboratories, we have shown that the presence of β-branched N-terminal amino acid moieties confers additional chemical stability to prolinenitrile and methanoprolinenitrile based inhibitors. A series of 4-substituted piperidinyl glycelyn 2-cyano-4,5-methano pyrrolidines have been synthesized and their structure-activity relationship as DPP-IV inhibitors has been investigated. It appears that the introduction of bulky groups at the 4 position of the piperidinyl glycine leads to an improvement in the inhibitory potency, and, as previously demonstrated in a related cycloalkyglycine series, the introduction of quaternary center at the β-position leads to chemical stability of these series of compounds.
77. RATIONAL DESIGN OF INDOLE-BASED PPAR AGONISTS

Neeraj Mahindroo1*, Chien-Fu Huang2, Chiung-Chiu Wang1, Tzu-Wen Lien2, Xin Chen2, Tsu-An Hsu2, Hsing-Pang Hsieh1

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Type II diabetes is one of the most common chronic diseases with estimated 143 million patients worldwide and the number expected to double by 2030. The total medical costs incurred annually on diabetes in the US alone are close to $100 billion. The disease is largely associated with obesity, which contributes to insulin resistance. The insulin resistance is also implicated in the pathogenesis of other major diseases including atherosclerotic cardiovascular disease, dyslipidemias and polycystic ovarian syndrome. Currently available therapies for type II diabetes include insulin and various oral agents: sulfonylureas; metformin; α-glucosidase inhibitors; thiazolidinediones, like pioglitazone and rosiglitazone (BRL49653).

In an effort to identify novel PPAR agonists, we have rationally designed a series of compounds with indole as a core skeleton. Compounds were prepared from commercially available indole scaffolds with desired chemical groups attached at various positions on the nucleus. The synthesized compounds were evaluated for binding with PPARα, γ and δ receptors using scintillation proximity assay (SPA) and transactivation assay (TA). The compounds have shown potent PPAR agonist activity in low nM range. The structure-activity relationship (SAR) has been elucidated.

78. DESIGN, SYNTHESIS AND STABILITY STUDIES OF KETOPYRROLIDINES AND KETOAZETIDINES AS POTENT DIPEPTIDYL PEPTIDASE IV (DPP IV) INHIBITORS

Dana Ferraris*, Yao-Sen Ko, Bert Thomas, Susan Lautar, David Calvin, Ajit Thomas, Krystyna Wozniak, Camilo Rojas, Sergei Belyakov

Guilford Pharmaceuticals, Inc

Dipeptidyl peptidase IV (DPP IV) is a proline specific serine protease responsible for the cleavage and degradation of many endogenous peptides and neuropeptides throughout the body. The most prominent substrates for DPP IV are GLP-1, neuropeptide Y, Substance P and casmormin. The inhibition of DPP IV and prevention of the degradation of these substrates produces pharmacological effects in conditions as wide ranging as diabetes, pain, obesity, neurologic disorders and cancer. In this poster, two series of DPP IV inhibitors, the ketopyrrolidines and ketoazetidines will be discussed as warhead-based proline mimetics with nanomolar potencies. Biological evaluation
of these compounds as well as stability studies will be presented. The most stable members of these series inhibit DPP IV in the plasma for up to several hours

79. DESIGN AND SYNTHESIS OF MC4-FOCUSED TARGET LIBRARY AROUND NOVEL SPIRO[IMIDAZOLIDINEQUINOLINE]-2,4-DIONE SCAFFOLD

Tom Webb*a, Luyong Jiongb, Doug McGrathc, Rongshi Lib

bDepartment of High Throughput Chemistry, cDepartment of Biology, aChemBridge Research Laboratories, aChemBridge Corporation

An important goal in medicinal chemistry has been to develop an understanding and a set of tools that will allow for the planned introduction of the important pharmacophores exhibited by the numerous potent bioactive peptides onto small synthetic drug-like scaffolds.[1] As a starting point in our efforts to develop a conceptual approach for the general exploration of the numerous interesting potential combinatorial pharmacophoric possibilities, we noted the recent groundbreaking work by Garland and Dean.[2] These authors demonstrated that cluster analysis and recombination of the observed patterns yielded consensus positioning of the C-alpha atoms among the various beta-turn types. They also showed that this relationship could be visualized as three independent specific three-point (triangular) distance-geometries that are common to all beta-turn types. In this presentation, design and synthesis of the focused library around 7'-hydroxy-2',3'-dihydro-1'H,2H,5H-spiro[imidazolidine-4,4'-quinoline]-2,4-dione (1) targeting MC-4 receptor will be discussed. The chemistry to install four important pharmacophoric groups on the hetero-atoms shown in 1 to mimic Arg, His, Phe and Trp using their surrogates will be presented. Their activities on MC-4 and other GPCR receptors will be reported.

80. SUBSTITUTED IMIDAZOLES AS POTENT AND SELECTIVE CANNABINOID-1 RECEPTOR INVERSE AGONISTS

Linda L. Chang*a, Jonathan E. Wilsona, Ihor Kopkaa, Jing Chenb, Ruey-Ruey C. Huangb, Julie Z. Laob, Chun-Pyn Shenb, Tung Fongb, William K. Hagmanna, and Mark T. Gouleta

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The cannabinoid receptor family (CB) includes two G-protein coupled receptor subtypes: CB-1 and CB-2. The CB-1 receptor is found primarily in the brain, spinal cord and mainly associated with CNS effects while the CB-2 receptor is present mostly in peripheral tissues. There are three known endogenous ligands for the CB receptor: anandamide, 2-arachinonyl glycerol and 2-arachidonyl glycerol ether. These are agonists with an activity profile similar to ∆9-tetrahydrocannabinol [∆9-THC, a major active ingredient in cannabis sativa (marijuana)], e.g., anticonvulsion, sedation, and appetite stimulation. In mice, CB-1r-/-knock-outs have been shown to be resistant to diet-induced obesity, suggesting that a CB-1 receptor antagonist or inverse agonist may reverse the effects of CB-1 agonism and could be useful in body weight reduction. This is consistent with the pharmacology of known CB-1r inverse agonists such as SR 141716 which is in Phase III trials for the treatment of obesity. Screening of our sample collection showed that the imidazole 1, 2-butyl-4-chloro-4[{(treityloxy)methyl]-1H-imidazole, exhibited high affinity
for the CB-1 receptor (hCB1 IC<sub>50</sub> = 7 nM). The SAR studies performed on this lead toward potent and selective CB-1 receptor inverse agonists will be described.

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\text{\includegraphics[width=0.5\textwidth]{CB1_receptor_inverse_agonist}}
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81. **THE SYNTHESIS AND BIOLOGICAL EVALUATION OF ENAMINONE ISOXAZOLE AMIDE DERIVATIVES AS POTENTIAL ANTICONVULSANT AGENTS**

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Unfortunately, fifty million people are affected with epilepsy, which is the second leading neurological disorder world wide. Due to the vast complications with treatment, there is a high demand for more potent, selective, and safer anticonvulsant agents. We anticipate that the unreported methylated and fluorinated enaminone isoxazole derivatives will act as potential probes for the mechanism of action for anticonvulsant agents.

The primary objective of this research is to design, synthesize, and pharmacologically evaluate enaminone isoxazoles. Based on our previous research, and available literature, the enaminone system has shown to be a pharmacophore as an antiepileptic agent. Currently, our lab group has successfully synthesized several intermediates for the target compounds, as well as a series of non amide-ester enaminone isoxazole derivatives. The synthesis and molecular properties of the known methylated and fluorinated isoxazole amide precursors will be presented.

Condensation of cyclic 1,3-diketone compounds with 5-methyl-isoxazole derivatives led to a series of non amide-ester enaminone isoxazole derivatives: 3-(5-methyl-isoxazol-3-yl-amino)-cyclohex-2-enone (ONMe) 1, 5-Methyl-3-(5-methyl-isoxazole-3-yl-amino)-cyclohex-2-enone (5MeON5Me) 2, and 5,5-Dimethyl-isoxazol-3-yl-amino)-cyclohex-2-enone (5,5MeONMe) 3, which have been tested by the National Institute of Neurological Disorders and Stroke (NINDS). The screening data showed that ONMe had unusual protection in mice against the subcutaneous pentylenetetrazol (scMET) test with 4/5 animals protected at 300 mg/kg at 0.5h without toxicity. In rats, ONMe showed activity against the maximal electroshock (MES) at 50 mg/kg at 1.0 and 4.0 h. For the compounds, 5MeON5Me and 5,5MeONMe, they were active in mice at 100 mg/kg and 300 mg/kg, respectively, with toxicity at 100 mg/kg at 0.5h. All target compounds will undergo similar testing at NINDS.

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\text{\includegraphics[width=0.5\textwidth]{enaminone_isoxazole_derivatives}}
\]

82. **EFFECTS OF VARYING SPACER LENGTH ON ACTIVITY OF 1,2,5-THIADIAZOLE DERIVATIVES OF 1,2,5,6-TETRAHYDROPYRIDINE AT MUSCARINIC RECEPTOR SUBTYPES**

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The dopamine hypothesis of schizophrenia has had pronounced effect on the strategies for developing antipsychotics. However, even the new atypical antipsychotics do not completely relieve all schizophrenic symptoms.
Consequently, muscarinic receptors are being considered as targets in the therapy of schizophrenia. The M4 muscarinic receptor plays an important role in balancing dopamine activity indicating a potential use of M4 agonists in treating psychosis. Recently CDD-0304 was identified as a potential antipsychotic displaying agonist activity at M1, M2 and M4 muscarinic receptors. We hypothesize that derivatives capable of allosteric binding to key amino acid residues found in the extracellular loops can potentially improve M1/M4 receptor selectivity and reduce M2 activity, which could produce side effects such as bradycardia. An M1/M4 agonist profile could provide efficacy in a broad range of symptomatic domains of schizophrenia including enhancement of cognitive function. Preliminary chimeric receptor data suggest that amino acids found in the second and third extracellular loops of the M1 receptor are critical for agonist binding and activity, respectively. Two sets of compounds, a symmetrical series and an unsymmetrical series were synthesized and evaluated for muscarinic receptor binding and activity. Introduction of various spacer lengths generated compounds with altered binding and activity at M1 and M2 receptors. For both set of compounds, the binding affinity at M1 receptors peaks at a spacer length \( n = 3 \) with pKi values of 10 ± 0.23 and 7.6 ± 0.26 for CDD-0273 and CDD-0304, respectively. The biological data suggest that an optimal spacer length is required for selective interaction with M1 receptors.

Keywords: muscarinic agonists/schizophrenia/allosteric binding

83. N-ARYLOXYETHYL-INDOLYALKYLAMINE DERIVATIVES WITH DUAL SSRI AND 5-HT1A RECEPTOR ACTIVITIES

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A series of N-aryloxyethyl-indolealkylamines have been prepared. These novel compounds had been evaluated for 5-HT reuptake inhibition and 5-HT1A receptor affinity. The effects of the placement of a heteroatom in the aryl ring and the length of the linkage used to tether the indoles moiety were assessed. Several compounds were identified with excellent affinity for the 5-HT transporter and 5-HT1A receptor. However, the profile of intrinsic activity was varied from full agonists to antagonists.

84. NOVEL CYTISINE ANALOGUES: SYNTHESIS AND BIOLOGICAL ACTIVITY

Lenka Munoz\(^*\), Stephanie Hennen, Daniela Gündisch


Cytisine, a chiral quinolizidine alkaloid, belongs together with nicotine and epibatidine to the group of naturally occuring prototypical agonists for nicotinic acetylcholine receptors (nAChRs). In the past, halogenated analogues or N-derivatives of cytisine were synthesized in order to get more insight into structure activity relationships for nAChRs. However, little is known about the impact of bulkier substituents at the pyridone fragment on the affinity for nAChRs.

We developed a four-step synthesis of 3- and 5-substituted analogues of cytisine via palladium-mediated Suzuki cross-coupling of either N-protected 3- or 5-bromo-cytisine with different boronic acids under microwave-accelerated conditions. The affinities for different nAChR subtypes were determined by competition assays with \(^{3}\)H]epibatidine (\(\alpha 4\beta 2^*, \alpha 3\beta 4^*, \) muscle type) and \(^{3}\)H]MLA (\(\alpha 7^*\)), respectively, using membrane fractions of native tissues (rat brain, calf/pig adrenals and Torpedo californica electroplax). Structure activity relationships of this series of compounds are described.
label has been placed at various positions on 4 so as to identify the residues within the binding site where the binding interaction takes place. Supported by NIH grant NS20036 and a NIH minority supplement.

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\begin{align*}
1: R^1 &= \text{trans 4-azido-benzoylamino}; R^2 = H \\
2: R^1 &= \text{cis 4-azido-benzoylamino}; R^2 = H \\
3: R^1 &= H; R^2 = 4-azido-benzoylaminoethyl
\end{align*}
\]

86. A POLY-L-PROLINE HELIX II MIMIC WITH A 5.6.5 SPIROBICYCLIC FRAMEWORK AS A PLG PEPTIDOMIMETIC

Bhooma Raghavan\(^{1\ast}\), Vaneeta Varma\(^{2}\), Ram K. Mishra\(^{2}\) and Rodney L. Johnson\(^{1}\)

\(^{1}\)University of Minnesota, \(^{2}\)McMaster University

L-Prolyl-L-leucyl glycinamide (PLG), an endogenous tripeptide, has been found to modulate dopamine receptors by increasing the affinity of dopamine and dopamine agonists to the dopamine D2 receptor. The bioactive conformation of PLG is postulated to be a type II \(\beta\)-turn. Various constrained analogs of PLG, containing a spirobicyclic framework, have been synthesized to provide evidence for this hypothesis. However Pro-Pro-Pro-NH\(_2\) (1), which can exist in a poly-L-proline II helix conformation, has also been found to have significant activity in modulating dopamine receptors. Compound 2 has been synthesized to test the hypothesis that compounds possessing a poly-L-proline II helix conformation are also capable of modulating dopamine receptors. This work is supported by NIH grant NS20036.
87. SYNTHESIS OF TYPE VI BETA-TURN MIMICS OF L-PROLYL-L-PROLYL-L-PROLINAMIDE
Ashish P. Vartak* and Rodney L. Johnson
University of Minnesota
L-Prolyl L-leucyl glycaminamide (PLG) or melanostatin is an endogenous tripeptide known to modulate dopamine receptors. Its bioactive conformation is purported to be a type II beta-turn, a hypothesis that has been supported by the activity profile of a large number of peptidomimetics that restrict PLG in such a conformation. In one series of PLG analogs, all three residues were replaced by prolyl residues to give L-prolyl-L-prolyl-L-prolinamide (1) and L-prolyl-L-prolyl-D-prolinamide (2). Compound 1, which cannot form a beta-turn, was surprisingly more active than 2; a fact which questions the postulated type II beta-turn bioactive conformation of PLG. Since the prolyl residue supports a cis amide linkage, 1 could assume a type VI beta-turn conformation. To determine if such a conformation may be involved in the activity of 1, two peptidomimetics 3 and 4 that constrain the “all-L” triproline 1 and L-prolyl-L-leucyl-L-prolinamide, respectively, in a type VI beta-turn have been synthesized.

88. EFFICIENT PREPARATION OF ADRAFINIL ISOMERS
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1Division of Medicinal & Natural Products Chemistry, The University of Iowa, Iowa City, and 2Case Western Reserve University, School of Medicine, Cleveland, Ohio
Attention-deficit/hyperactivity disorder (ADHD) affects approximately 5% of the school age population and is treated with central nervous system stimulants. Stimulants are highly efficacious and safe for treatment of ADHD, however, a subset of patients will either fail to respond to stimulants or have side effects which preclude their use. Furthermore, narcolepsy, another CNS syndrome, is characterized by excessive sleepiness, cataplexy, hypnagogic hallucinations and disturbed night-time sleep. Current pharmacotherapy for narcolepsy which affects approximately 0.06% of the population in North America and Western Europe, involves the use of CNS stimulants to control sleepiness and promote wakefulness. Unfortunately, CNS stimulants are able to produce tolerance and have a strong potential for illicit use. Because of these barriers, other CNS stimulants, such as modafinil, (2-[(diphenylmethanesulfinyl)]-acetic acid) and adrafinil (2-[(diphenylmethanesulfinyl)-hydroxy-acetamide) are being developed for ADHD and narcolepsy. Experimental and clinical data suggest that the pharmacological profile of modafinil differs from those of amphetamine and methylphenidate, two classical psychostimulants. The brain targets which modafinil acts on to induce wakefulness, however, remains unknown. Recently, though, it has been shown that the dopamine transporter (DAT) plays a role in promoting wakefulness. This suggests that the mechanism of action of modafinil might involve the DAT. This is interesting because DAT inhibitors have been shown to reduce self-administration of cocaine in rhesus monkeys. As such, modafinil and adrafinil are potential new leads in the development of therapeutics for stimulant abuse. Chemical and biological results to date will be presented.
89. **2,3,7-TRISUBSTITUTED PYRAZOLO[1,5-D][1,2,4]TRIAZINES: FUNCTIONALLY SELECTIVE GABA-A ALPHA2/ALPHA3-SUBTYPE SELECTIVE AGONISTS.**
Departments of Medicinal Chemistry, Biochemistry, and Pharmacology, Merck Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK.

The major inhibitory neurotransmitter in the central nervous system is gamma-aminobutyric acid (GABA). GABA-A receptors are ligand-gated chloride ion channels. Several subtypes of GABA-A receptors (containing 5 subunits selected from alpha 1-6, beta 1-3, gamma 1-3, delta, epsilon, pi and theta subunits) have now been identified. Allosteric modulatory sites on GABA-A receptors exist for various ligands, of which the benzodiazepine (BZ) binding site has attracted the most attention. Agonists at the BZ site enhance GABAergic inhibition, inverse agonists reduce inhibition, whilst antagonists elicit no functional response. Agonists acting at the BZ site have long been used as anxiolytics, but exhibit side-effects such as cognitive impairment, sedation, and abuse potential. Our laboratory has previously reported the discovery of triazolo[4,3-b]pyridazines as functionally selective partial agonists at alpha2/3-containing receptors, which act as non-sedating anxiolytics in animal models. In this communication, we report that novel 2,3,7-trisubstituted pyrazolo[1,5-d][1,2,4]triazines 1 are also functionally selective alpha2/3 ligands, and describe the synthetic and medicinal chemistry that led to their discovery and optimization.

90. **SEARCH FOR BENZODIAZEPINE/GABA_A SUBTYPE SELECTIVE BIVALENT LIGANDS THAT REVERSE ALCOHOL SELF-ADMINISTRATION**
Wenyuan Yin*, Srirama Sarma V.U.Pullela, Chunchun Zhang, Harry June, and James Cook
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To elucidate the role of specific GABA_A/benzodiazepine receptor subtypes in regulating alcohol reinforcement, a number of active β-carbolines has been synthesized and evaluated. Previously, a study with orally active β-carboline-3-carboxylate t-butyl ester(βCCt) examined the role of α1 receptor subtypes within the ventral pallidum (VP) on alcohol self-administration. Currently, bivalent βCCt ligands which contain two antagonist pharmacophores within the same molecule were synthesized and tested for receptor binding affinity. Examination of the α1 pharmacophore/receptor model with these bivalent ligands supports a linear binding conformation and supports the hypothesis that the GABA_A/BzR receptor contains a large binding pocket in the LDi region. These results support a new avenue for the design of clinically safe and effective drugs against alcoholism. Recent synthetic studies as well as affinities of these ligands will be presented.

![βCCt](image1.png)

![βCCt Bivalent Ligand](image2.png)
91. INHIBITION OF MONOAMINE OXIDASES A AND B BY FLUORINATED
PHENYL C YCLOPROPYLAMINES

Song Ye1, Shinichi Yoshida2, Thomas C. Rosen3, Oliver G. J. Meyer3, Milton J. Sloan1, Guenter Haufe3, Kenneth L. Kirk1∗

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Cyclopropylamines make up an important class of amine oxidase inhibitors. Similarly, fluorine substitution near the site of enzymatic activation of a substrate has been used effectively in the design of inhibitors of many enzymes, including monoamine oxidases (MAO). Fluorinated phenylcyclopropylamines and alkylamines were prepared as compounds incorporating both of these structural features. These have been examined as inhibitors of recombinant human liver MAO A and MAO B.

For a series of Z- and E-2-fluoro-2-phenylcyclopropylamine analogues, the presence of fluorine in the cyclopropane ring resulted in a modest increase in inhibitory activity towards both MAO A and MAO B. In addition, p-substitution of electron-withdrawing groups such as Cl and F in the aromatic ring of the Z-isomers increased the inhibition of both enzymes. Similar to the effects of absolute stereochemistry seen with E-2-phenylcyclopropylamine (tranylcypromine), (1S,2S)-2-fluoro-2-phenylcyclopropylamine was a more potent inhibitor of both MAO A and B than was the (1R,1R)-enantiomer.

A dramatic reversal of isozyme selectivity resulted from fluorination at the 2-position of 1-phenylcyclopropylamine, which is known to be a selective inhibitor of MAO B relative to MAO A. Both Z- and E-isomers of 2-fluoro-1-phenylcyclopropyl amine were much more potent as inhibitors of MAO A than of MAO B. p-Substituted analogues (Cl, OMe) of the E-isomer were prepared and shown also to be potent and selective MAO A inhibitors.

All inhibitors showed time- and concentration-dependent inactivation of both enzymes, with the exception of (Z-2-fluoro-2-phenylcyclopropyl)ethylamine, which acts as a competitive and reversible MAO A-selective inhibitor. The effects of fluorine substitution on inhibition of MAO A and B by these analogues differ from previously reported effects on inhibition of tyramine oxidase (a copper-containing amine oxidase).1 We are investigating the mechanistic aspects of the effects of fluorine substitution on the behavior of these compounds as amine oxidase inhibitors.


92. DESIGN AND SYNTHESIS OF NOVEL AND POTENT PPAR-DELTA AGONISTS

James Knobelsdorf*, Jeff Schkeryantz, Guoxin Zhu, Nathan Mantlo, Chahrzad Montrose-Rafizadeh, Robert Barr, Don Jett, Rick Zink, and Nathan Yumibe

Eli Lilly & Company

Selective PPARδ agonists have been shown to affect marked changes in the lipid profile in an obese rhesus monkey model. These results suggested that selective PPARδ agonists could provide a new treatment for dyslipidemia and atherosclerotic cardiovascular disease associated with metabolic syndrome X. In search of potent and selective PPARδ agonists, a new class of compounds featuring 1,3,4-substituted oxazoles were designed and synthesized.

93. TOWARD IN VIVO GLYCORANDOMIZATION

Dirk Hoffmeister*, Jon S.Thorson

University of Wisconsin – Madison, School of Pharmacy

In Vitro Glycorandomization (IVG) is a promising strategy for natural product glycoside diversification, e.g. in antibiotic and anticancer drug development. Initially designed as an enzymatic three-step in vitro process, IVG activates a library of free sugars as anomeric phosphates, nucleotide-bound analogs and finally provides for the transfer of the sugars to drug backbones by the concerted action of an anomeric sugar kinase, a nucleotidylyltransferase, and a glycosyltransferase (Figure 1). The advantage of establishing the entire process in vivo would be threefold. First, the process could be scaled up easily. Second, expensive cosubstrates, such as ATP and dTTP would be provided by the host. Third, with streptomyces as host strains, their diverse intrinsic metabolites could be tapped
as a vastly rich source for drug backbone structures, thereby circumventing tedious purifications or aglycon solubility issues. We recently started assembling this pathway in Streptomyces (S.) lividans. As anomeric kinase for glycorandomization in a Streptomyces host, we have chosen GalK from S. coelicolor. We have cloned its gene, followed up by characterization and functional overexpression of the enzyme in both E.coli and S. lividans. Parallel extensive directed evolution and structure-based engineering on E.coli GalK provides a map for further manipulations. Results from overexpression of the nucleotidylyltransferase gene rmlA in S.lividans will also be presented.
94. COMBINATORIAL APPROACHES TOWARD GLYCORANDOMIZED NATURAL PRODUCTS

Joseph M. Langenhan*, Jon S. Thorson  
University of Wisconsin-Madison

The natural product pool, which includes many glycosylated secondary metabolites, is the source of over half of the world’s drug leads. For example, the antibiotics vancomycin and erythromycin, the antitumor compounds bleomycin and doxorubicin, and the antifungal agents amphotericin and nystatin all contain essential sugar attachments. Carbohydrate groups of natural product-based drugs have long been known to generally influence pharmacokinetic properties and there is an increasing recognition that these carbohydrate appendages also play a key role in drug-target interactions. These findings suggest that the alteration of glycosylation patterns on secondary metabolites is a potential strategy for the generation of novel therapeutics.

We are currently exploring combinatorial approaches toward glycorandomized natural products. Here, two complementary strategies will be described. The first strategy, termed “In vitro glycorandomization” involves the regio- and stereoselective enzymatic coupling of synthetic sugar phosphates to complex aglycon structures, and subsequent chemoselective ligation to further elaborate the glycosylated natural products. The second strategy involves the selection of relatively simple aglycon structures upon which a uniquely reactive functional group, such as an N-methyl-hydroxylamine group, can be easily installed. These aglycon derivatives can then be reacted with a pool of reducing sugars to generate the corresponding neoglycoconjugates.

95. SYNTHESIS OF L-ALTROSE DERIVATIVES TO PROBE THE SUBSTRATE SPECIFICITY OF MUTANT GALACTOKINASES

Lesley Liu*, Jie Yang, Jon S. Thorson  
University of Wisconsin-Madison

Many therapeutically-valuable natural products are glycosylated. Since the sugar moieties of these compounds often significantly influence their biological activity, altering the glycosylation of natural product aglycones is a method to generate new compounds with novel or enhanced bioactivity. One way to access libraries of novel, natural product based glycoconjugate libraries is to use the “glycorandomization” strategy. This approach involves providing chemically-synthesized libraries of free hexoses to a set of three promiscuous enzymes that act consecutively to phosphorylate, activate, and glycosidate the sugars. Recently, the structure-based enhancement of a galactokinase enzyme was reported. This engineered enzyme, which carries out the first chemical transformation in the “glycorandomization” sequence, was shown to catalyze the anomeric phosphorylation of many new sugar substrates in addition to its natural substrate, D-galactose. Here, we report the synthesis of a set of L-altrose derivatives as substrates to explore the scope of the activity of the enhanced galactokinase mutant in the context of “glycorandomization.”

96. RAPID DRUG DIVERSIFICATION BY ENZYME ENGINEERING AND EVOLUTION

Jie Yang*, Dirk Hoffmeister, Lesley Liu, Martin Hager, Rocco Moretti, Jon S. Thorson  
School of Pharmacy, University of Wisconsin-Madison

Glycorandomization is a chemoenzymatic strategy to rapidly diversify complex glycosidic natural products, such as antibiotics and anticancer agents, by converting libraries of free sugars into libraries of glycosidic compounds. Three enzymatic steps are required: sugar phosphorylation by a kinase, sugar activation by a nucleotidylyltransferase, and sugar attachment to a drug backbone by a glycosyltransferase. The more flexible these enzymes are, the wider open the sugar pipeline that can be included in the process. To generate glycorandomized libraries based on natural product structures, we apply directed evolution techniques as well as structure-based engineering to members of these groups of enzymes.
97. INACTIVATION OF THE LNME GENE REVEALING NEW INSIGHTS INTO THE BIOSYNTHESIS OF THE ANTIBIOTIC LEINAMYCIN IN STREPTOMYCES ATROOLIVACEUS
Bong-Sik Yun1*, Gong-Li Tang1, Yi-Qiang Cheng1, Yong Huang1, Hirak S. Basu2, George Wilding2, and Ben Shen1,2,3
1Division of Pharmaceutical Sciences, 2Comprehensive Cancer Center, 3Department of Chemistry, University of Wisconsin-Madison

Leinamycin (LNM), a novel antitumor antibiotic produced by Streptomyces atroolivaceus, is a thiazole-containing hybrid peptide-polyketide natural product with an unusual 1,3-dioxo-1,2-dithiolane moiety, which is essential for its biological activity. The LNM biosynthetic gene cluster has been recently cloned and characterized. It consists of 27 open reading frames (ORFs), five of which encode nonribosomal peptide synthetase (NRPS), polyketide synthase (PKS), and hybrid NRPS-PKS enzymes responsible for the biosynthesis of the 18-membered macrolactam ring. The six PKS modules lack their cognate AT domain, and this essential activity is provided in trans by a discrete AT protein. These findings for the LNM macrolactam ring formation unveiled a novel PKS architecture characterized by a discrete, iteratively acting AT protein that loads the extender units in trans to AT-less type I PKS for polyketide biosynthesis. However, the post-NRPS/PKS tailoring steps leading to the unusual 1,3-dioxo-1,2-dithiolane moiety remain unknown. Sequence analysis of the LNM gene cluster revealed several genes of unknown function, serving as candidates that could be involved in the biosynthesis of 1,3-dioxo-1,2-dithiolane moiety. To assign the functions of these genes and to delineate the pathway for 1,3-dioxo-1,2-dithiolane biosynthesis, these genes were inactivated by gene replacement, and the resultant mutants were analyzed for metabolite production. While inactivation of \( \text{lnmE} \) completely abolished LNM production, the \( \Delta \text{lnmE} \) mutant produced four new LNM analogs. Isolation and structural characterization of these compounds support the hypothesis of \( \text{lnmE} \) to be involved in 1,3-dioxo-1,2-dithiolane biosynthesis. Proposed function of LnmE, its role in LNM biosynthesis, and details of structure determination and biological activity of the new LNM analogs will be presented.

98. BIOSYNTHESIS OF THE ANTITUMOR ANTIBIOTIC ENEDIYNES C-1027 AND NEOCARZINOSTATIN AND PRODUCTION OF ANALOGS BY METABOLIC PATHWAY MANIPULATION
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The enediyne polyketides, a relatively new and steadily growing family of natural products, are the most potent, highly active anticancer agents in existence today. A significant challenge has been to develop methods to harness this unprecedented potency and to produce enediyines and their analogs with favorable clinical attributes. In an effort to address this issue, we have recently cloned and characterized the biosynthetic pathways for two enediyines, C-1027 and neocarzinostatin. Discovery of the machinery responsible for the biosynthesis of both secondary metabolites, along with primary sequence analysis of the gene products, has allowed us to functionally predict the biosynthesis of both the enediyne core and peripheral moieties of C-1027 and neocarzinostatin. The availability of the gene clusters, as presented here, has allowed us to rationally prepare gene disruption mutants to generate new enediyines as well as to engineer novel enediyines by applying combinatorial biosynthetic methods, in hopes of improving the overall therapeutic characteristics.

99. RADIAL SYMMETRY IN LEAD DISCOVERY AND LEAD OPTIMIZATION: THE STRUCTURE-ACTIVITY RELATIONSHIP OF A HIGH AFFINITY NK-1 RECEPTOR LIGAND
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Privileged structures comprise tools often used in lead discovery by the pharmaceutical industry. The receptor binding promiscuity exhibited by these structures increases the probability of discovering a receptor ligand during
biological screening. Monosaccharide-based peptidomimetics typified by (±)-1 have been established as privileged structures because of their unique radial symmetry. This property is absent in L363-301, the cyclic hexapeptide, which was the basis of design of (±)-1. This structural difference explains why (±)-1, but not L363-301, can bind both the SRIF and the NK-1 receptors. The former binds the two receptors via different side chains and the latter requires an amino acid substitution to realize NK-1 receptor binding. Exploitation of the glycoside radial symmetry in lead optimization resulted in the discovery of a novel and potent NK-1 ligand.

![Structural formula of L363,301 and (±)-1]

**L363,301**
Potent SRIF Agonist

**(+)-1**
SRIF Agonist $K_i = 1.5$ nM  
NK-1 Antagonist $I_{C50} = 150$ nM

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**100. ANTIEMETIC CYCLOHEXYLAMINE NK1 ANTAGONISTS**

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The utility of neurokinin-1 (NK1) antagonists for the treatment of chemotherapy-induced emesis has now been established. We have previously reported the development of novel cyclohexylamine based NK1 antagonists with high affinity and encouraging *in vivo* properties. We have now established that it is possible to replace the amide linker with a lactam without loss of affinity or selectivity. This gives compounds with improved *in vivo* properties, capable of blocking cisplatin induced emesis *in vivo*. 


101. SYNTHESIS AND EVALUATION OF PYRIDYL-TRIAZOLE DERIVATIVES AS NK1 ANTAGONISTS

*K. Jeff Thrasher*, Louis N. Jungheim, Erik Hembre, Kevin Gardinier, Doug Schober, Brian Getman, Daniel Smith, Dominic Li, Smriti Iyengar, Don Gehlert

**Eli Lilly and Company**

There is continued interest in the use of NK1 antagonists for the treatment of stress related disorders. During the course of our work, we identified a series of 1,2,3-triazole-4-benzamides as highly potent NK1 antagonists. One of our goals was to improve the solubility characteristics and reduce the potential for metabolism, as measured in microsomal assays. We investigated the potential for replacing the benzyl substituent in the lead molecule with variously substituted pyridines. These compounds were prepared via regioselective metallation of the requisite pyridine moieties. Several derivatives exhibited excellent receptor binding affinity $K_i < 1 \text{ nM}$ as well as activity in a relevant in vivo model. The syntheses, in vitro and in vivo activity of various 1,2,3-triazole derivatives will be presented.

102. DESIGN, SYNTHESIS AND EVALUATION OF SR 48,968 ANALOGUES AS NEUROKININ-2 RECEPTOR SELECTIVE ANTAGONISTS

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The human neurokinin-2 (NK2) receptor has been identified and validated as a suitable target for development of novel drugs to be used for treatment of a number of diseases in the respiratory, gastrointestinal, and genitourinary tracts. Design and synthesis of NK2 receptor selective probes will serve useful in gaining a more detailed understanding of its structural and functional characteristics. Here we report the design and synthesis of a series of seventeen N-methylbenzamide analogues structurally derived from SR 48,968, a potent NK2 receptor antagonist ($pK_b 9.1$), using asymmetric synthesis. Isothiocyanato-N-methylbenzamide and Bromoacetamido-N-methylbenzamide derivatives have been designed to serve as potential electrophilic affinity labels. Nitro-N-methylbenzamide and acetamido-N-methylbenzamide were designed to serve as the nonelectrophilic controls for these ligands. Functional assay results using guinea pig trachea indicate that several members of this series exhibit potent NK2 receptor antagonist potencies with $pK_b$ values in the range of 9.1-9.7. Para-fluoro substituted analogue was found to be the most potent analogue with a $pK_b$ of 9.7. NK2 receptor antagonist activity of electrophilic N-methylbenzamide analogues was surmountable.
103. 2-(AMINOMETHYL)BENZAMIDE INHIBITORS OF GLYT2

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The amino acid glycine is a major neurotransmitter in the central nervous system (CNS) of vertebrates. Two major classes of transporters, glycine transporter type 1 (GlyT-1) and glycine transporter type 2 (GlyT-2), serve to control the synaptic levels of glycine in the CNS.1 GlyT-1 is widely distributed throughout the CNS and is thought to affect the excitatory action of glycine on postsynaptic N-methyl-D-aspartate (NMDA) receptors. However, GlyT-2 is localized primarily in the spinal cord and hindbrain, and modulates the inhibitory system mediated through the strychnine-sensitive glycine receptor (ssGlyR). Selective inhibition of GlyT-2 is expected to increase the synaptic glycine levels surrounding ssGlyR, which may result in muscle relaxation and antinociceptive effects. Thus, potent and selective GlyT-2 inhibitors might be useful as muscle relaxants, anesthetic, and/or analgesic reagents.

High-throughput screening (HTS) of Pharmacopeia's compound collection using a recombinant Chinese hamster ovary (CHO) cell line expressing human GlyT-2 provided a small molecule hit (1) with an IC50 = 1.8 µM. Hit-to-lead optimization provided compounds with IC50s less than 100 nM that were highly selective for hGlyT-2 compared to hGlyT-1 and ssGlyR. However, improvement was needed in selectivity against the dopamine (DAT), norepinephrine (NET), and 5-hydroxytryptamine (5HTT) transporters. Further optimization via constraint led to a compound (2) that exhibited excellent potency against GlyT-2 and >100 fold selectivity against these three monoamine transporters.


104. OPIOID RECEPTOR LIKE (ORL-1) AGONISTS AS NOVEL ANALGESICS

Duncan McArthur
Organon Laboratories Ltd

For several decades the focus of the field of pain has been to find an analgesic with the efficacy of morphine (µ opioid) but without the adverse side effect profile (e.g. respiratory depression, nausea, constipation, dysphoric effects and abuse potential). The ORL-1 receptor is the most recently discovered member of the opioid receptor family. It purportedly plays an important role in pain transmission, cognition and anxiety and carries a high degree of sequence homology with the other opioid receptors µ, κ and δ, but does not bind typical opioid ligands with high affinity.

Organon therefore initiated a program to develop potent ORL-1 receptor agonists as potential sedative analgesics for perioperative pain following surgery, which could replace the currently used combination of opioids (analgesic) with midazolam (sedative).
High throughput screening followed by hit optimisation led to a lead candidate that bound to the ORL1 receptor. This demonstrated full agonist activity and reversed hyperalgesia in a variety of animal models.

A successful lead optimisation program was initiated focusing on this compound to improve bio-activity (Ki <10 nM), selectivity (20-fold selectivity over other opioid receptors) and solubility (~2mg/ml).

This poster will detail SAR developed within this exciting series of compounds and explore the challenges involved in the development of an asymmetric synthetic route. A CoMFA model will be presented which was used to rapidly prioritise compounds based on the predicted ORL1 affinity. In-vivo data will also be disclosed for a selection of compounds showing effective analgesia. Details of a back-up series of compounds will also be described, illustrating some advantages over the original series.

105. DIAZABICYCLO[4.2.0]OCTANE LIGANDS AS POTENT NNR AGONISTS

Abbott Laboratories

ABT-594 is a novel analgesic which has been shown to act via interaction with the neuronal nicotinic acetylcholine receptors. In the course of our investigations to find a backup to ABT-594, we have synthesized and studied the diazabicyclo[4.2.0]octane series in which the core diamine was appended to numerous substituted pyridines. The synthesis of the diazabicyclo[4.2.0]octane core and the in vitro and in vivo characterization of this series will be presented.

106. HETEROAROMATIC SIDE-CHAIN ANALOGS OF PREGABALIN

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A NDA and MAA for Pregabalin (3-isobutyl-γ-aminobutyric acid) have recently been submitted for the treatment of epilepsy and neuropathic pain. Our research efforts focused on synthesizing pregabalin analogs with aromatic replacements of the 3-isobutyl side chain with the goal of finding new compounds with increased potency. The compounds were tested for their ability to displace [3H]gabapentin from the α2δ subunit of calcium channels, for
their ability to protect against seizures in the DBA2 mouse model, and for their analgesic effects in the CITH model. The synthesis and SAR of the compounds will be discussed.

107. **NEOCLERODANE DITERPENES AS NOVEL OPIOID RECEPTOR LIGANDS: ISOLATION AND EVALUATION**

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*Salvia divinorum*, a Mexican plant in the sage family, is gaining popularity as a hallucinogen in the United States. The main active component, Salvinorin A, is a neoclerodane diterpene and has been shown to be a selective and potent ligand for the kappa opioid receptor. Currently, there is little or no research into the effects of the use of this compound and due to the fact that it has only recently begun to enter the popular culture, it is still legal in the United States. Salvinorin A represents a structurally unique kappa receptor ligand and could lead to new treatments for substance abuse. The detailed pharmacological mode of action, as well as both short and long-term effects are not known and must be investigated. Kappa opioid agonists have been shown to antagonize the effects of CNS stimulants. By modulating the level of dopamine in the brain, they diminish the stimulating effects of cocaine, block its conditioned reinforcing effects and self-administration, and attenuate the reinstatement of extinguished drug-taking behavior. Kappa antagonists have been shown to have anti-depressant activity and block stress-induced behavior responses. In addition, kappa antagonists are potential therapeutic agents in the treatment of opioid dependence. To further the development of novel treatments for drug abuse we are exploring the structure activity relationship of Salvinorin A at opioid receptors. To accomplish these goals we have set out to derive a general extraction of Salvinorin A from *Salvia divinorum* leaves, to design a synthetic route to Salvinorin A and to synthesize and explore analogues of Salvinorin A for biological activity. Synthesis and biological results to date will be presented.

108. **SUBSTITUTED BENZODIAZEPINES AS SELECTIVE BRADYKININ B2 RECEPTOR ANTAGONISTS**

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Bradykinin (BK) is a nonapeptide produced by the action of kallikrein enzymes or a mixture of mast cell tryptase and elastase on kininogens. Two subtypes of BK receptors, B1 and B2, which belong to the family of G-protein coupled receptors (GPCRs), are expressed in a number of types of human tissue. Activation of these receptors by BK has been implicated in a number of disease states, suggesting B1 and B2 receptors as potential targets for therapeutic intervention. In particular, animal studies indicate that the activation of B2 receptors by kinins is involved in the initiation and maintenance of inflammatory pain, hinting at the potential of B2 receptor antagonists as analgesics. The discovery of a series of benzodiazepine compounds as potent and selective B2 receptor antagonists will be presented.
109. 5-CHLOROPYRIDOTHIOSEMICARBAZIDE COMPOUNDS AS SELECTIVE BRADYKININ B2 RECEPTOR ANTAGONISTS

Yun-xing Cheng1,*, Mirek Tomaszewski1, Xuehong Luo1, Mehrnaz Pourashraf1, Christopher Walpole1, Joanne Butterworth2, Lynda Adam2, Claude Godbout2, Kemal Payza2, Marie Roumi3

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Bradykinin B2 receptor belongs to the G-protein coupled receptor (GPCR) family and it is constitutively expressed in many human tissue types. Bradykinin is a nonapeptide in the kinin family with pro-inflammatory and pro-nociceptive activity. There are many studies in animals suggesting kinins contribute to the initiation and maintenance of inflammatory pain and the B2 receptor is involved in this process. For example, B2 antagonists are anti-nociceptive in mice (MAC, formalin tests) and rats (carrageenan test). On account of this, B2 receptor antagonists are expected to be useful in treatment of inflammatory pain. The preparation and SAR of a series 5-chloropyridothiosemicarbazide compounds as potent and selective bradykinin B2 receptor antagonists will be described.

![5-Chloropyridothiosemicarbazide](image)

110. SYNTHESIS AND EVALUATION OF THIAZEPINES AS ICE INHIBITORS


Procter & Gamble Pharmaceuticals

Interleukin-1β converting enzyme (ICE, Caspase-1) cleaves Pro IL-1β to IL-1β, which is an active component in the inflammation cascade. Inhibition of ICE may be important in treatment of inflammatory diseases such as osteoarthritis. A series of monocyclic thiazepine ICE inhibitors were synthesized in 8 steps from commercially available intermediates. Compound A was potent (30 nM) in the Caspase-1 enzyme inhibition assay. Additionally, this analog showed a 480 nM IC50 value in a THP-1 whole cell assay measuring IL-1β production. Compounds of this class possessed good selectivity against Caspase-3 and Caspase-8.

![Compound A](image)

111. DISCOVERY OF A NEW CLASS OF ANTI-INFLAMMATORY AGENTS: NON-INDOLE CPLA$_{2\alpha}$ INHIBITORS

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The phospholipase A$_2$ (PLA$_2$) group of enzymes are responsible for cleaving membrane associated fatty acid phospholipids. One particular member of this family, cPLA$_{2\alpha}$, is a 85 kDa, calcium-dependent, intracellular lipase that shows a strong affinity for arachidonic acid bound to the $sn$-2 position of phospholipids. Ultimately, arachidonic acid release triggers a cascade of reactions that produce such inflammatory mediators as leukotrienes, prostaglandins,
and thromboxanes. The other cleavage product, a lysophospholipid, can be converted to platelet activating factor (PAF), a potent broncho-constricting agent. Studies with cPLA$_2$ knockout mice in both a prostaglandin-driven animal model (CIA) and a leukotriene model (ARDS) have shown significantly reduced inflammation without the stomach ulcerations common to standard NSAID therapies. Unlike COX-2 inhibitors, which only affect the production of prostaglandins and thromboxanes, cPLA$_2$ inhibitors’ additional influence over the leukotriene biosynthetic pathway suggests that such molecules could treat both arthritis and asthma. Based on our experience with the SAR of indole-based inhibitors, we have found that the alternative quinazoline-2,4-dione core can be used in place of indole to provide active compounds when tested in a whole blood assay.

112. TRYPTASE INHIBITORS FOR THE TREATMENT OF ASTHMA


Aventis

Tryptase-$\beta$ is a serine protease involved in the inflammatory cascade responsible for the symptoms of asthma and related diseases. There is ample literature precedent showing that downregulation of this enzyme will reduce disease symptoms, thus making it a desirable target for drug development. Screening of a small protease library rapidly produced a collection of modest tryptase inhibitors. Molecular modeling and X-ray structure studies revealed two distinct binding modes for the inhibitors discovered. To optimize the interaction between the inhibitor and tyrosine-95 of $\beta$-tryptase, a collection of phenyl- and pyridyl-benzylamines were synthesized. Key biological properties for these molecules will be presented along with conclusions impacting follow-up studies for orally bioavailable tryptase inhibitors.

113. TOWARD VLA1 INTEGRIN INHIBITORS: PARALLEL SYNTHESIS OF NOVEL HYDANTOIN SCAFFOLDS

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Inhibition of the integrin $\alpha$1$\beta$1 (VLA1) binding to collagen IV, has been demonstrated to reduce inflammation in mouse models of delayed-type hypersensitivity (DTH), contact hypersensitivity (CHS) and arthritis. Hydantoins have been reported to be inhibitors of the related integrin LFA1 [WO 98/39303; J. Org. Chem. 2001, 66, 1903]. We were interested in whether they might also be VLA1 antagonists. The explosion step for these libraries involved two different strategies: Suzuki coupling using various boronic acids or cyclization of amino acids with a series of isocyanates. The synthesis of these hydantoins and their effect on VLA1 binding to collagen IV will be presented.

114. SOLID-PHASE SYNTHESIS OF HYDANTOINS AS CASPASE INHIBITORS

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Apoptosis is a key process in a wide variety of biological systems, including normal cell turnover, the immune system, embryonic development and metamorphosis. Inappropriate apoptosis is involved in many human pathologies, including neurodegenerative diseases.

Designs based on apopain structure have given potent peptidic and pseudopeptidic inhibitors,1,2 but with physical-chemistry and pharmacokinetic characteristics that limit their use to the intravenous treatment of acute episodes of some diseases. Non-peptidic inhibitors could solve this problem, but the few that have been synthesized3 to date present a low selectivity.

Here we discuss a new family of apopain inhibitors based on a hydantoin ring as scaffold. In silico studies demonstrated that the heterocycle fits into the active center of the enzyme, where its carboxylic moieties form hydrogen bonds with residues of the protein, which confers an improved interaction of the rest of the enzyme with the compound.

A first generation of compounds provided us with an appropriate skeleton and a second generation was synthesized bearing in mind these results. The in vitro evaluation, using recombinant caspase-3 and a fluorescent substrate, was performed.
Potent inhibitors of 7,8-dihydroneopterin aldolase (DHNA; EC 4.1.2.25) have been discovered using CrystaLEAD X-ray crystallographic high-throughput screening followed by structure-directed optimization. Screening of a 10,000 compound random library provided several low affinity leads and their corresponding X-ray crystal structures bound to the enzyme. The presence of a common structural feature in each of the leads suggested a strategy for the construction of a directed library of approximately 1000 compounds which were screened for inhibitory activity in a traditional enzyme assay. Several lead compounds with IC<sub>50</sub> values of about 1 µM against DHNA were identified and crystal structures of their enzyme-bound complexes obtained by co-crystallization. Structure-directed optimization of one of the leads thus identified afforded potent inhibitors with sub-micromolar IC<sub>50</sub> values.

DHNA IC<sub>50</sub> = 0.068 µM
116. INVESTIGATIONS ON THE BIOSYNTHETIC PATHWAYS OF BLEOMYCIN, PHLEOMYCIN, AND TALLYSOMYCIN IN WILD-TYPE AND RECOMBINANT STRAINS OF THE RESPECTIVE PRODUCER ORGANISMS

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The bleomycins (BLMs) are a family of glycopeptide-derived antibiotics produced by several Streptomyces species and exhibit strong antitumor activity. Structurally and biosynthetically related to the BLMs are the phleomycins (FLMs) and tallysomycins. The commercial product, Blenoxane, contains BLM A2 and B2 as the principle constituents. Production of these compounds usually is strongly dependent on proper regulation of the biosynthetic steps and on sufficient self-resistance of the producer strain. Sequence comparison of the three biosynthetic gene clusters revealed that the blm and tlm cluster both contain two different resistance determinants, blmA, a BLM binding protein, and blmB, a BLM acetyltransferase, while in the flm biosynthetic gene cluster the blmB homologue could not be found. Therefore, overexpression of these resistance genes as well as of regulatory genes in the respective producer strains may result in enhanced productivity. Another approach to generate mutants with increased product formation might be conventional UV-mutagenesis. Development of tools for in vivo engineering of this family of natural products and mechanistic characterizations of certain enzymatic reactions will also be discussed to set the stage to produce novel analogs for anticancer development by applying combinatorial biosynthetic methods to the BLM, FLM, and TLM biosynthetic machinery.

117. CHALLENGES OF MODELLING INTERACTIONS BETWEEN KINASE INHIBITORS AND THEIR TARGET PROTEINS

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Kinases are critically important as pharmacological targets. Rationalizing and – more importantly – anticipating details of their interaction with small molecule inhibitors have proven both rewarding and challenging. Modelling is complicated by the characteristic large changes in enzyme structure that typically take place as the substrates bind. The challenge is heightened by the need to identify inhibitory small molecules that discriminate between the specific target of interest and kinases in general. Despite these challenges, work on these systems has been well-rewarded in many cases, with careful rationally-directed programs producing important clinical candidates. This poster will examine several model cases, highlighting the complications encountered for each and the sorts of methods used to address the problems that arise.

118. HOMOLOGY MODELING, DYNAMICS OF RAT AND HUMAN EXTRACELLULAR DOMAIN OF A4ß2 AND A7 NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR SUBTYPES

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In recent years, it has become clear that the neuronal nicotinic acetylcholine receptor (nAChR) is a valid target for a variety of diseases, including Alzheimer disease, anxiety and nicotine addiction. As for most membrane proteins, information on the three dimensional structure of the nAChR is limited to data from electron microscopy with a resolution that makes difficult the application of structure-based design approaches to develop specific ligands. Based on a high-resolution crystal structure of AChBP, the homology-models of the extracellular domain of the neuronal rat and human a4ß2 and a7 nAChR subtypes (the most present subtypes in the brain) were built and their stability assessed for the first time with Molecular Dynamics (MD). All built models showed conformational stability over time confirming the quality of the starting 3D model. Lipophilicity and electrostatic potential studies were performed on the rat and human a4ß2 and a7 nicotinic models compared to AChBP revealing the importance of the hydrophobic aromatic pocket and the critical role of a-subunit Trp, homologue of AChBP-Trp 143, for ligand binding.
The presented models provide a valuable framework for structure-based design of specific α4β2 nAChR subtype ligands aiming at improving therapeutic and diagnostic applications.

119. SYNTHESIS OF 3-(4-SUBSTITUTED PIPERAZINYL METHYL)-5,6-DIMETHOXYINDOLES AND THEIR 5,6-DIHYDROXY ANALOOGUES AS NOVEL ANTIHYPERTENSIVE AGENTS

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The cardiovascular disorder hypertension afflicts between 10 and 20% of the adult population and is a major risk factor in many forms of cardiovascular disease.1 Because α-agonists cause vasoconstriction and raise blood pressure, one would expect α-antagonists to have antihypertensive activity. Prazosin, an α-adrenoceptor antagonist, has proven effective in the clinic uses. Of the variety of structural variants reported to have α-adrenoceptor antagonist effect, SGB1534 represents an interesting and potent α1-antagonist.2 Experimental results showed that noradrenalin, phenylephrine or histamine evoked the contraction in guinea-pig mesenteric artery, and this contraction was inhibited by SGB1534 over $1 \times 10^{-10}$ M.3

Since prazosin and SGB1534 are potent α-antagonists, we were very interested in the synthesis of a series of novel indole compounds which were built around similar structures. Starting from 3,4-dimethoxyaniline, a range of 3-(4-substituted piperazinylmethyl)-5,6-dimethoxyindoles and their corresponding 5,6-dihydroxy analogues have been prepared. Additionally, in order to compare the antihypertensive activity, the N-methylindole counterparts were also synthesized.

Author Index

A
Abbo-Offei B ........................................ 76
Adam L ........................................ 108, 109
Ahmed G ........................................ 52
Akwabi-Ameyaw A ......................... 42
Al-Assaad A-S .................................. 68
Albericio F ..................................... 114
Albert L M ..................................... 8
Altamura S ..................................... 3
Altenbach R J ................................ 71
Amegadzie A ..................................... 21
Anacleto B ....................................... 38
Anderson B ..................................... 54
Anderson D J ................................... 105
Andree T H ..................................... 83
Angeles A R ..................................... 99
Appell K C ...................................... 103
Araldi G L ....................................... 73
Armstrong C .................................... 68
Arnold E ........................................ 22
Arunachalam T ................................. 60
Attack J R ....................................... 89
Augeri D .......................................... 11
Ayral-Kaloustian S ............................ 33

B
Bachand C ........................................ 67
Bader B .......................................... 69
Bae J .............................................. 98
Balachandran R ............................... 48
Balasubramanian B ........................... 67
Baldwin J J .................................... 103
Baldwin J ......................................... 52
Ballard T M ..................................... 24
Bao B .............................................. 73
Barbacci-Tobin G ............................. 34
Barnette K G .................................... 9
Barr R ............................................ 92
Barrish J ......................................... 52
Basu H S ......................................... 97
Bayly C ......................................... 74
Beaulieu F ....................................... 67
Beaulieu P ....................................... 1
Beconi M ......................................... 28
Beeler B ......................................... 11
Belyakov S ....................................... 78
Bernard B R .................................... 37
Betebenner D Z ............................... 11
Betz S F ......................................... 115
Betz S ................................................ 68
Beutel B A ....................................... 115
Bhat B ............................................. 3
Bhattachar S K ................................. 34
Bi Y Z ........................................... 11
Bieza K .......................................... 38
Birmberg G ...................................... 33
Bishop J .......................................... 21
Bisson W H ...................................... 118
Boemer U ........................................ 69
Bogdan N ........................................ 59
Boger R ........................................... 9
Bohl C ............................................. 9
Bohlmann R .................................... 41
Bohnstedt A B .................................. 103
Bookland R G .................................. 49
Boos C A ......................................... 34
Borel A ........................................... 29
Bös M ............................................. 24
Boschelli D H .................................. 57
Boschelli F ....................................... 57
Boscoe B P ...................................... 34
Bosserman M R ................................ 3
Bowen S M ..................................... 8
Boyd S .......................................... 113
Brill E ............................................. 72
Brioni J D ....................................... 31
Britt S D ......................................... 35, 36
Britton J .......................................... 42
Brockunier L ................................... 28
Brueggen J ...................................... 58
Brugel T A ...................................... 49, 50
Brugger N ........................................ 73
Bryant H U ...................................... 7
Bryce-Pritt D K ................................ 22
Bryson J .......................................... 11
Buckley MJ ...................................... 105
Buckner S A .................................... 71
Bunnelle W H ................................... 105
Bursulaya B ..................................... 38
Butterworth J .................................. 108, 109
Byron Long ...................................... 67

C
Cairns J ........................................ 112
Caldwell J S .................................... 38
Caldwell R D ................................... 75
Calvin D .......................................... 78
Campbell M .................................... 34
Campbell R ..................................... 54
Cao Y ............................................. 82
Cappelletti E ................................... 60
Capraro H G .................................... 58
Carling R W .................................... 89
Carlson E ........................................ 39
Carlson E J ...................................... 100
Carrol S S ....................................... 3
Carroll W A .................................... 71
Cassels B K ..................................... 56
Chambers R J .................................. 25
Chandorkar G .................................. 35
Chang L L ....................................... 80
Chang Q .......................................... 59
Chappie T A .................................... 22
Che Y ............................................. 37
Chen J ............................................. 51
Chen J ............................................ 9, 80, 9
Chen S H ........................................ 35
Chen X .......................................... 112, 77
Cheng Y Q ....................................... 97
Cheng Y X ....................................... 109
Cheon S H ....................................... 63
Chicchi G G ..................................... 100
Chicchi G ........................................ 99
Choi J ............................................. 40
Choi J ............................................. 117
Chiu S .......................................... 72
Chu F ............................................. 72
Chun J ........................................... 60
Clancy D ......................................... 75
Clark C M ......................................... 50
Clark J D .......................................... 111
Clark M P ......................................... 49, 50
Clark N ........................................... 100
Clark R D ......................................... 117
Clivio P ........................................... 66
Coghlan M J .................................... 71
Cohen I C ......................................... 7
Cohen J .......................................... 21
Cohn S T ......................................... 46
Cohn S ............................................ 8
Coleman K G .................................... 34
Collins T ......................................... 30
Colwell L F ...................................... 3
Comstock L R ................................... 62
Condroski K R ................................... 115
Conley G ......................................... 59
Conway B R .................................... 55
Cook I ............................................. 90
Cooper L C ....................................... 100
Cottrell K M ..................................... 35
Coughlin J ....................................... 116
Court J ........................................... 35
Court J C .......................................... 36
Courtney L F .................................. 35, 36
Cowen D ......................................... 75
Cowart M ........................................ 31
Cox E D .......................................... 34
Craft J M ......................................... 53
Cramer J ......................................... 21
Croom D .......................................... 75
Currier J ........................................... 34
Currier P ......................................... 105

D
Daumen J F ...................................... 105
<table>
<thead>
<tr>
<th>Name</th>
<th>Page</th>
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<td>35, 36</td>
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<td>103</td>
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<td>24</td>
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<tr>
<td>Hoffmeister D</td>
<td>93, 96</td>
</tr>
<tr>
<td>Hofmann F</td>
<td>58</td>
</tr>
<tr>
<td>Holden K G</td>
<td>107</td>
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<td>108</td>
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<td>83</td>
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<td>Schairer W C</td>
<td>35, 36</td>
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<td>21, 101</td>
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<td>Schubiger P A</td>
<td>118</td>
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</table>

xxxix
Wyvratt M................................. 28

X
Xiang J................................. 111
Xiao J................................. 34
Xiao Y................................. 73
Xie W................................. 48
Xu H................................. 9
Xu J Z................................. 55
Xu J................................. 28
Xu M................................. 82
Xu S................................. 49

Y
Yamamoto K............................ 44
Yan L................................. 54
Yang C................................. 8
Yang J................................. 95, 96
Ye Q................................. 30
Ye S................................. 91
Yin D................................. 9
Yin H................................. 38
Yin W................................. 90
Yoshida S............................. 91
Yuen P............................... 106
Yumibe N............................. 92
Yun B S............................... 97, 116

Z
Zapata-Torres G....................... 56
Zasadzki M.......................... 53
Zask A............................... 33
Zerler B............................. 64
Zhang B B........................... 28
Zhang C.............................. 61
Zhang H C........................... 55
Zhang J............................... 98
Zhang K.............................. 38
Zhang N.............................. 57
Zhang W............................ 75, 111
Zhao G............................... 76
Zhao Z............................... 73
Zhi L................................. 47
Zhao X............................... 34
Zhou D............................... 83
Zhou P............................... 83
Zhu G............................... 48, 92
Zificsak C A.......................... 40
Zimmerman K........................ 29
Zink R............................... 92
Zou H............................... 68
Zou Y............................... 11
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