



**Technical Reports**  
Volume 12, No. 17

## **Special Technical Report**

### **AMRI Contributions to Science: Review of Scientific Publications in 2007**

**John W. Lippert, Ph.D. and R. Jason Herr, Ph.D.**  
**Medicinal Chemistry Department**

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**Abstract:** *As the year 2007 drew to a close, we wished to provide a summary of the technological communications that Albany Molecular Research, Inc. (AMRI) scientists contributed to the scientific community during the year. This document provides a full list of abstracts (as they appeared within the original documents) for all of the publications, presentations and patent applications that appeared during 2007. We hope to make this bibliographical summary a regular year-end contribution.*

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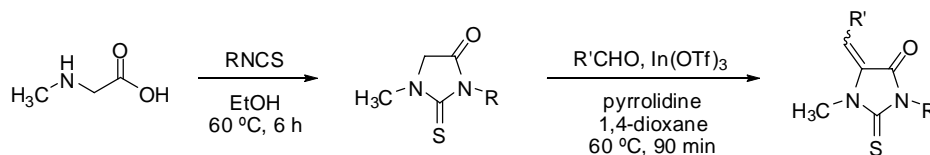
## 2007 AMRI Research Publications

During 2007, thirteen research articles appeared in peer-reviewed scientific journals that described innovations conceived by AMRI scientists. In most of these cases, the manuscripts were written by AMRI lead authors to communicate independent research, or were co-authored with customers to communicate research in collaboration with AMRI. Below are the bibliographies for these publications, including the abstracts, as they appeared with the original documents. The underlined name(s) indicate the lead author(s).

**“*Expedient Lewis acid catalyzed synthesis of a 3-substituted 5-arylidene-1-methyl-2-thiohydantoin library*”**, *Journal of Combinatorial Chemistry* **2007**, 9(6), 1036-1040.

Brian T. Gregg, Kathryn C. Golden, John F. Quinn, Dmytro O. Tymoshenko, William G. Earley, Dacia A. Maynard, Dana A. Razzano, W. Martin Rennells and Jennifer Butcher  
Medicinal Chemistry Department, AMRI

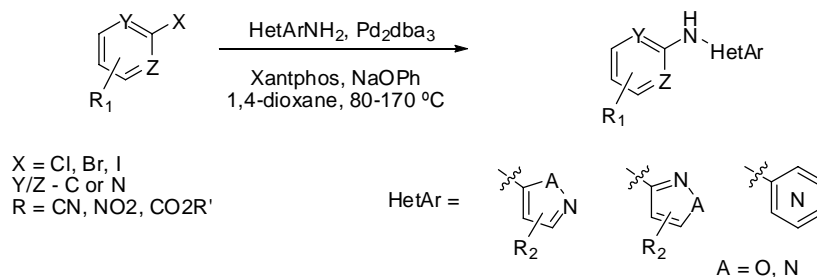
**Abstract.** An efficient and rapid solution phase combinatorial synthesis of a 3-substituted 5-arylidene-1-methyl-2-thiohydantoin library was developed. The salient feature for this library production procedure is the addition of the Lewis acid catalyst, indium(III) trifluoromethanesulfonate, which serves to facilitate the direct condensation of aldehydes with 3-substituted 1-methyl-2-thiohydantoin. Use of this Lewis acid catalyst has resulted in faster reaction times, higher conversions and better purity profiles for these condensation reactions as compared to traditional uncatalyzed reactions. The resulting 315 member library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoin is described.



**“*Palladium-catalyzed couplings of heteroaryl amines with aryl halides using sodium phenolate as the stoichiometric base*”**, *Synlett* **2007**, 15, 2331-2336.

James P. Schulte II and Scott R. Tweedie  
Medicinal Chemistry Department, AMRI

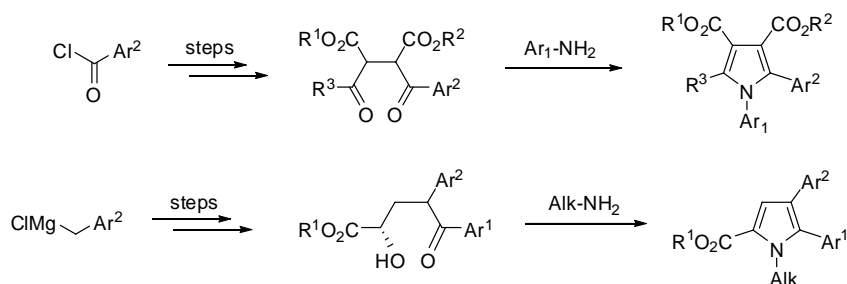
**Abstract.** Heteroaryl amines are efficiently coupled (in two hours) to aryl halides with catalytic Pd<sub>2</sub>dba<sub>3</sub> and Xantphos to provide the corresponding biaryl amines under microwave and standard thermal conditions. The use of organic-soluble sodium phenolate (NaOPh) as the stoichiometric base promotes facile coupling of a variety of substrates in excellent yields.



**“Regioselective synthesis of highly aryl-substituted pyrrole carboxylates as useful medicinal chemistry leads”**, *Synthetic Communications* **2007**, 37(16), 2793–2806.

Ulhas Bhatt,<sup>1</sup> Bryan C. Duffy,<sup>1</sup> Peter R. Guzzo,<sup>1</sup> Leifeng Cheng<sup>2</sup> and Thomas Elebring<sup>2</sup>  
<sup>1</sup>Medicinal Chemistry Department, AMRI and <sup>2</sup>AstraZeneca R&D Mölndal, Mölndal, Sweden

**Abstract.** The regioselective syntheses of two pharmaceutically relevant pyrrole scaffolds are described. A synthetic route for the preparation of differentially substituted pyrrole-3,4-dicarboxylates is presented and exemplified. This route circumvents some of the problems and limitations associated with previous butynedioic diester condensations and 1,3-dipolar cycloaddition reactions. A route to the related 4,5-diarylpyrrole-2-carboxylic acid scaffold is also presented. Both routes allow for the regiocontrolled preparation of highly substituted pyrrole pharmacophore cores.



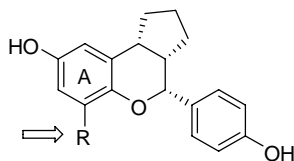
**“Benzopyrans as selective estrogen receptor-beta agonists (SERBAs). Part 4: Functionalization of the benzopyran A-ring”**, *Bioorganic & Medicinal Chemistry Letters* **2007**, 17(18), 5082–5085.

Bryan H. Norman,<sup>1</sup> Timothy I. Richardson,<sup>1</sup> Jeffrey A. Dodge,<sup>1</sup> Lance A. Pfeifer,<sup>1</sup> Gregory L. Durst,<sup>1</sup> Yong Wang,<sup>1</sup> Jim D. Durbin,<sup>1</sup> Venkatesh Krishnan,<sup>2</sup> Sean R. Dinn,<sup>3</sup> Shengquan Liu,<sup>3</sup> John E. Reilly<sup>3</sup> and Kendal T. Ryter<sup>3</sup>

<sup>1</sup>Discovery Chemistry and <sup>2</sup>Musculoskeletal Research Departments, Eli Lilly and Company and <sup>3</sup>Medicinal Chemistry Department, AMRI

**Abstract.** Benzopyrans are selective estrogen receptor-beta (ER-beta) agonists (SERBAs), which bind the ER receptor subtypes alpha and beta in opposite orientations. We have used structure based drug design to show that this unique phenomena can be exploited via substitution at the 8-position of the benzopyran A-ring to disrupt binding to ER-alpha, thus improving ER-beta subtype selectivity. X-ray cocrystal structures with

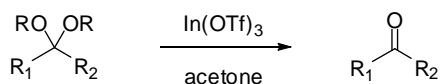
ER-alpha and ER-beta are supportive of this approach to improve selectivity in this structural class.



**“Indium(III) trifluoromethanesulfonate as an efficient catalyst for the deprotection of acetals and ketals”**, *Journal of Organic Chemistry* **2007**, 72(15), 5890-5893.

Brian T. Gregg, Kathryn C. Golden and John F. Quinn  
Medicinal Chemistry Department, AMRI

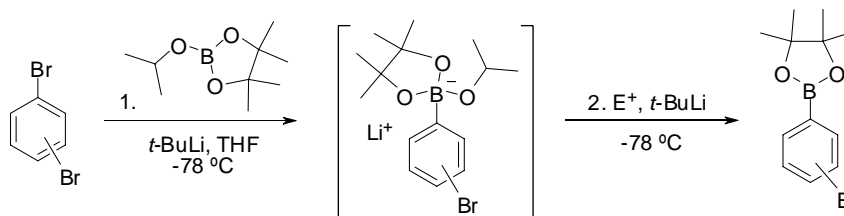
**Abstract.** Acetals and ketals are readily deprotected under neutral conditions in the presence of acetone and catalytic amounts of indium(III) trifluoromethanesulfonate (<0.8 mol %) at room temperature or under mild microwave heating conditions to give the corresponding aldehydes and ketones in good to excellent yields.



**“Use of in situ isopropoxide protection in the metal-halogen exchange of arylboronates”**, *Journal of Organic Chemistry* **2007**, 72(17), 6618-6620.

Qin Jiang, Meagan Ryan and Paul Zhichkin  
Medicinal Chemistry Department, AMRI

**Abstract.** Isopropoxide protection of arylboronates allowed their use in metal-halogen exchange reactions. The isopropoxide-protected borate species were obtained from a boronate or in situ from dibromoarenes. *Meta*- and *para*-dibromoarenes were converted via these intermediates into functionalized arylboronates in a one-pot manner.

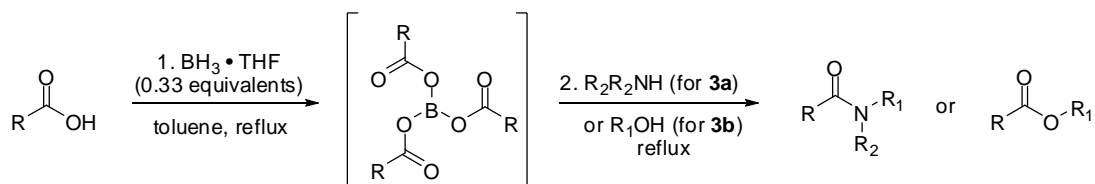


**“An efficient synthesis of amides and esters via triacyloxyboranes”**, *Synlett* **2007**, 7, 1026-1030.

Zhongping Huang, John E. Reilly and Ronald N. Buckle  
Medicinal Chemistry Department, AMRI

**Abstract.** Borane-tetrahydrofuran complex or borane-methyl sulfide complex is used to activate carboxylic acids to generate triacyloxyboranes. The triacyloxyboranes can be effectively reacted with various nucleophiles including alkylamines, arylamines,

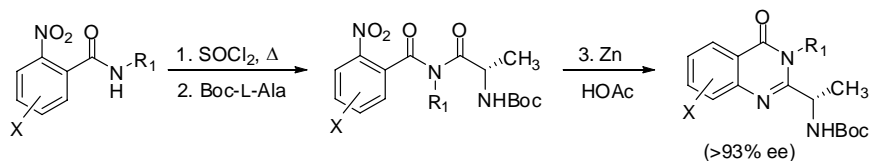
hydrazides, alcohols and phenols at reflux in toluene to provide the corresponding amides and esters in excellent yield. Aliphatic carboxylic acids are selectively esterified in the presence of aromatic carboxylic acids under the borane conditions. Thus, reaction of hexanoic acid with borane-tetrahydrofuran complex toluene followed by reaction with butylamine at reflux for 12 hour gave >99% of N-butylhexanamide.



**“A novel highly stereoselective synthesis of 2,3-disubstituted 3H-quinazoline-4-one derivatives”**, *Organic Letters* **2007**, 9(7), 1415-1418.

Paul Zhichkin,<sup>1</sup> Edward Kesicki,<sup>2</sup> Jennifer Treiberg,<sup>2</sup> Lisa Bourdon,<sup>1</sup> Matthew Ronsheim,<sup>1</sup> Hua Chee Ooi,<sup>2</sup> Stephen White,<sup>2</sup> Angela Judkins<sup>2</sup> and David J. Fairfax<sup>1</sup>  
<sup>1</sup>Medicinal Chemistry Department, AMRI and <sup>2</sup>ICOS Corporation, Bothell, WA

**Abstract.** An efficient three-step synthesis of chiral 3H-quinazolin-4-one derivatives from common materials is disclosed. The Mumm reaction of nitrobenzimidoyl chlorides with chiral L-alpha-amino acids, which were prepared by chlorination of nitrobenzamides, affords the corresponding (nitrobenzamido)oxoethylcarbamate derivatives. Reductive cyclocondensation of the (nitrobenzamido)oxoethylcarbamate derivatives affords enantiomerically pure (ee >93%) quinazolin-4-ones in good overall yield. A comparison with existing approaches indicates that this method is superior for hindered substrates.

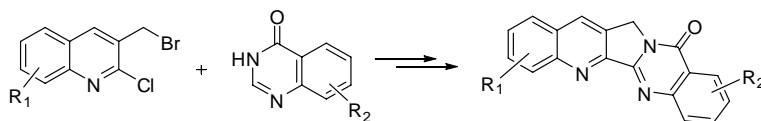


**“Synthesis and topoisomerase poisoning activity of A-ring and E-ring substituted luotonin A derivatives”**, *Bioorganic & Medicinal Chemistry* **2007**, 15(12), 4237-4246.

Kassoum Nacro,<sup>1</sup> Conxiang (Charles) Zha,<sup>1</sup> Peter R. Guzzo,<sup>1</sup> R. Jason Herr,<sup>2</sup> Denise Peace<sup>3</sup> and Thomas D. Friedrich<sup>3</sup>

<sup>1</sup>Discovery Research & Development, Chemistry and <sup>2</sup>Medicinal Chemistry Departments, AMRI and <sup>3</sup>Center for Immunology and Microbial Disease, Albany Medical College

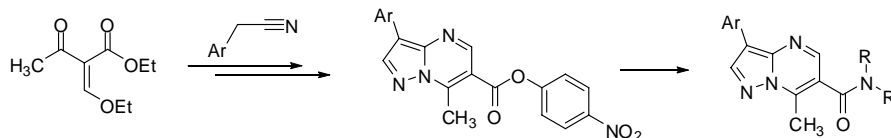
**Abstract.** A series of A-ring and E-ring analogs of the natural product luotonin A (I), a known topoisomerase I poison, was evaluated for growth inhibition in human carcinoma and leukemia cell lines. Rational design of structures was based on analogs of the related alkaloid camptothecin, which has been demonstrated to exert cytotoxic effects by the same mechanism of action. When compared to luotonin A, several compounds exhibited an improved topoisomerase I-dependent growth inhibition of a human leukemia cell line.



**“Pyrazolo[1,5-*a*]pyrimidines. identification of the privileged structure and combinatorial synthesis of 3-(hetero)arylpyrazolo[1,5-*a*]pyrimidine-6-carboxamides”**, *Journal of Combinatorial Chemistry* **2007**, 9(3), 507-512.

Brian T. Gregg, Dmytro O. Tymoshenko, Dana A. Razzano and Matthew R. Johnson  
Medicinal Chemistry Department, AMRI

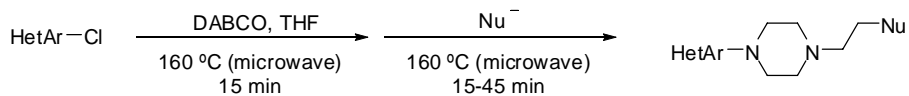
**Abstract.** The pyrazolo[1,5-*a*]pyrimidine class of compounds has been identified as a privileged structure for library synthesis on the basis of several key characteristics of the core molecule. A chemical set in excess of 400 compounds was synthesized to give 3,6,7-substituted pyrazolo[1,5-*a*]pyrimidinecarboxamides **9**. To facilitate the rapid preparation of this library, a preparative strategy included the synthesis of activated *p*-nitrophenyl esters, followed by subsequent scavenging of the *p*-nitrophenol leaving group. Excess reagents were also removed using scavenging reagents that were found to be compatible with the synthetic methodology and that afforded target compounds in acceptable purity and yields.



**“An efficient one-pot, two-step synthesis of 4-substituted 1-heteroarylpiperazines under microwave irradiation conditions”**, *Tetrahedron Letters* **2007**, 48(17), 3043-3046.

Hong-Jun Wang, William G. Earley, Robert M. Lewis, Rajiv R. Srivastava, Andrew J. Zych, David M. Jenkins and David J. Fairfax  
Medicinal Chemistry Department, AMRI

**Abstract.** A highly efficient one-pot, two-step microwave procedure was developed for the synthesis of 4-substituted 1-heteroarylpiperazines. Microwave heating of heteroaryl chlorides with 1,4-diazabicyclo[2.2.2]octane (DABCO) at 160 °C for 15 minutes yielded 1-heteroaryl-4-(2-chloroethyl)piperazines, which could be further reacted with various nucleophiles, again under microwave irradiation conditions, to give an array of 4-substituted 1-heteroarylpiperazines in good to excellent yields.

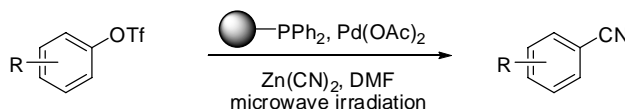


**“Application of polymer-supported triphenylphosphine and microwave irradiation to the palladium-catalyzed cyanation of aryl triflates”**, *Synthetic Communications* **2007**, 37(3), 431-438.

Rajiv R. Srivastava, Andrew J. Zych, David M. Jenkins, Hong-Jun Wang, Zhen-Jia Chen and David J. Fairfax

Medicinal Chemistry Department, AMRI

**Abstract.** A variety of aryl nitriles were prepared in excellent yield from the palladium(II) acetate-catalyzed cross-coupling of aryl triflates and zinc cyanide under microwave irradiation conditions. To facilitate purification, polymer-supported triphenylphosphine was used as the palladium ligand. Comparison to the corresponding thermal conditions revealed much shorter reaction times with comparable yields.

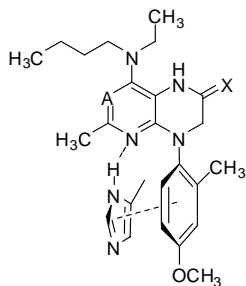


**“Dihydropyridopyrazinones and dihydropteridinones as corticotropin-releasing factor-1 receptor antagonists: Structure-activity relationships and computational modeling”**, *Journal of Medicinal Chemistry* **2007**, 50(9), 2269-2272.

Carolyn D. Dzierba,<sup>1</sup> Andrew J. Tebben,<sup>1</sup> Richard G. Wilde,<sup>1</sup> Amy G. Takvorian,<sup>1</sup> Maria Rafalski,<sup>1</sup> Padmaja Kasireddy-Polam,<sup>1</sup> John D. Klaczkiwicz,<sup>1</sup> Anthony D. Pechulis,<sup>2</sup> Amy L. Davis,<sup>2</sup> Mark P. Sweet,<sup>2</sup> Alex M. Woo,<sup>2</sup> Zhicai Yang,<sup>2</sup> Sarah M. Ebeltoft,<sup>2</sup> Thaddeus F. Molski,<sup>1</sup> Ge Zhang,<sup>1</sup> Robert C. Zaczek,<sup>1</sup> George L. Trainor,<sup>1</sup> Andrew P. Combs<sup>1</sup> and Paul J. Gilligan<sup>1</sup>

<sup>1</sup>Discovery Chemistry, Neuroscience Biology (Wallingford, CT) and Computer Aided Drug Design (Princeton, NJ), Bristol-Myers Squibb Pharmaceutical Research Institute and <sup>2</sup>Medicinal Chemistry Department, AMRI

**Abstract.** The CRF antagonist pharmacophore is a heterocyclic ring bearing a critical hydrogen-bond acceptor nitrogen and an orthogonal aromatic ring. CRFR1 antagonists have shown a 40-fold and 200-fold loss in potency against the CRFR1 H199V and M276I mutant receptors, suggesting key interactions with these residues. We have derived a two component computational model that correlates CRFR1 binding affinity within the reported series to antagonist/H199 complexation energy and M276 hydrophobic contacts.



**1a** A = CH<sub>2</sub>, X = O; CRF<sub>1</sub> IC<sub>50</sub> = 0.92 nM

**1b** A = CH<sub>2</sub>, X = H<sub>2</sub>; CRF<sub>1</sub> IC<sub>50</sub> = 4.2 nM

**1c** A = N, X = O; CRF<sub>1</sub> IC<sub>50</sub> = 95 nM

**1d** A = N, X = H<sub>2</sub>; CRF<sub>1</sub> IC<sub>50</sub> = 11.7 nM

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## 2007 AMRI Review Publications (including Book Chapters)

AMRI scientists were also lead authors on eleven book chapters during 2007, many appearing in serial book series. In addition, five review articles written by AMRI employees appeared in scientific journals or in trade publications available to a wider audience. Two book reviews were also contributed by AMRI scientists, which appear in scientific journals and are abstracted in scientific databases.

**“Chapter 9. Cardiovascular and Metabolic Diseases: Angiotensin AT1 antagonists for hypertension”** in *The Art of Drug Synthesis*, D. S. Johnson and J.-J. Li, Eds. John Wiley & Sons, Inc: Hoboken, NJ, USA, 2007, pgs 129-141.

Larry Yet

Discovery Research & Development, Chemistry Department, AMRI

**“Chapter 15. Central Nervous System Diseases: GABA<sub>A</sub> receptor agonists for insomnia: zolpidem (Ambien), zaleplon (Sonata), eszopiclone (Estorra, Lunesta) and indiplon”** in *The Art of Drug Synthesis*, D. S. Johnson and J.-J. Li, Eds. John Wiley & Sons, Inc: Hoboken, NJ, USA, 2007, pgs 215-223.

Peter R. Guzzo

Discovery Research & Development, Chemistry Department, AMRI

**“Section 16. Fermentation and Bioindustrial Chemistry: Microbial transformations”** in the *Kirk-Othmer Encyclopedia of Chemical Technology, 5th Edition*, A. Seidel, Ed. John Wiley & Sons, Inc: Hoboken, NJ, USA, 2006, pgs 395-419.

Peter C. Michels, Yuri L. Khmel'nitsky and Joseph O. Rich

Discovery Research & Development, Metabolism and Biotransformation Department

**“Part 1. Central Nervous System Diseases: Chapter 2. Recent developments in monoamine reuptake inhibitors”** in *Annual Reports in Medicinal Chemistry, Volume 42*, J. E. Macor, Ed. Academic Press of Elsevier, Inc: Oxford, UK, 2007, pgs 13-26.

Shuang Liu and Bruce F. Molino

Discovery Research & Development, Chemistry Department, AMRI

**“Product Subclass 8: N-Silylenamines”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 451-473.

Steven J. Collier

Singapore Research Centre, AMRI

**“Product Subclass 9: N-Borylenamines”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 475-485.

Steven J. Collier

Singapore Research Centre, AMRI

**“Product Subclass 10: N-Haloenamines”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 487-492.

Steven J. Collier

Singapore Research Centre, AMRI

**“Product Subclass 11: N-Alk-1-enylhydroxylamines”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 493-502.

Steven J. Collier

Singapore Research Centre, AMRI

**“Product Subclass 12: N-Alk-1-enylaminosulfur compounds”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 503-520.

Steven J. Collier

Singapore Research Centre, AMRI

**“Product Subclass 13: Alk-1-enylhydrazines”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 521-540.

Steven J. Collier and Mark D. McLaws

Singapore Research Centre and Chemical Development Department, AMRI

**“Product Subclass 14: Alk-1-enyl azides”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 541-563.

Steven J. Collier

Singapore Research Centre, AMRI

**“Product Subclass 15: N-Alk-1-enylaminophosphorous compounds”** in *Science of Synthesis Houben-Weyl Methods of Molecular Transformations, Category 4, Volume 33: Ene-X Compounds (X=S, Se, Te, N, P)*, G. A. Molander, Ed. Georg Thieme: Stuttgart, Germany, 2007, pgs 565-576.

Steven J. Collier

Singapore Research Centre, AMRI

**“AMRI and Singapore: Driving discovery in Asia”**, *Biotechnology Journal* **2007**, 2(11, Special Issue: Singapore Biotech Crossroads), 1330.

Mark W. Sawicki

Business Development Department, AMRI

**“Safety Notables: Information from the literature”**, *Organic Process Research & Development* **2007**, 11(6), 1087-1090.

Gerald A. Weisenburger<sup>1</sup> and Paul F. Vogt<sup>2</sup>

<sup>1</sup>Process Safety Laboratory, Pfizer Inc. and <sup>2</sup>cGMP Manufacturing, AMRI

**“Enhanced hit-to-lead process using bioanalogous lead evolution and chemogenomics: application in designing selective matrix metalloprotease inhibitors”**, *Expert Opinion on Drug Discovery* **2007**, 2(5), 707-723.

Ákos Papp,<sup>1</sup> Tamás Szommer,<sup>1</sup> László Barna,<sup>2</sup> Gergely Gyimesi,<sup>2</sup> Péter Ferdinandy,<sup>3</sup> Cesare Spadoni,<sup>1</sup> Ferenc Darvas,<sup>4</sup> Toshio Fujita,<sup>5</sup> László Úrge<sup>6</sup> and György Dormán<sup>1</sup>

<sup>1</sup>AMRI Hungary, Inc, Budapest, Hungary; <sup>2</sup>Institute of Enzymology, Budapest, Hungary;

<sup>3</sup>University of Szeged, Cardiovascular Research Group and PharmaHungary Ltd,

Department of Biochemistry, Szeged, Hungary; <sup>4</sup>Cominnex, Inc., Budapest, Hungary;

<sup>5</sup>EMIL-Project, Sakyoku, Japan and <sup>6</sup>ThalesNano, Inc., Budapest, Hungary

**“Vascular disrupting agents”**, *Bioorganic & Medicinal Chemistry* **2007**, 15(2), 605-615.

John W. Lippert

Medicinal Chemistry Department, AMRI

**“Tetrazoles as carboxylic acid bioisosteres in drug discovery”**, *PharmaChem* **2007**, 6(4), 21-24.

Andrew J. Zych and R. Jason Herr

Medicinal Chemistry Department, AMRI

**“MMP inhibitors in cardiac diseases: an update”**, *Recent Patents on Cardiovascular Drug Discovery* **2007**, 2(3), 186-194.

György Dormán,<sup>1</sup> Katalin Kocsis-Szommer,<sup>1</sup> Cesare Spadoni<sup>1</sup> and Péter Ferdinandy<sup>2</sup>

<sup>1</sup>AMRI Hungary, Inc, Budapest, Hungary and <sup>2</sup>University of Szeged, Cardiovascular Research Group and PharmaHungary Ltd, Department of Biochemistry, Szeged, Hungary

**“Book Review of ‘The Chemistry of Process Development in the Fine Chemical and Pharmaceutical Industry, 2nd Edition,’ by C. Someswara Rao”**, *Synthesis* **2007**, 11, 1738.

Steven J. Collier

Singapore Research Centre, AMRI

**“Book Review of ‘Life Saving Drugs: The Elusive Magic Bullet,’ by John Mann”**, *Journal of Natural Products* **2007**, 70(4), 711.

Romila D. Charan

Analytical Quality Services Department, AMRI

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## AMRI Research Presented (Oral Papers and Posters)

Several presentations were given by AMRI scientists during the year 2007, both as talks given at scientific meetings and as posters presented. At this year's American Chemical Society Meetings, five presentations were given either by representatives of AMRI or by research collaborators, to audiences between fifty and 200 attendees. Two posters detailing research conducted by AMRI scientists were also presented at the Fall Meeting.

**Oral Presentation:** "*Azepine inhibitors of plasma cholesteryl ester transfer protein,*" MEDI 222 (Division of Medicinal Chemistry), 233<sup>rd</sup> ACS National Meeting, Chicago, IL, March 25-29

Nathan B Mantlo,<sup>1</sup> Todd Fields,<sup>1</sup> Xiaodong Wang,<sup>1</sup> Maria-Carmen Fernandez,<sup>1</sup> Ana I. Mateo,<sup>1</sup> Ana Escribano,<sup>1</sup> Eva M. Martin de la Nava,<sup>1</sup> Saravanan Parthasarathy,<sup>1</sup> Matthew W. Giese,<sup>1</sup> Matthew Carson,<sup>1</sup> Thomas P. Beyer,<sup>1</sup> Sandra L. Cockerham,<sup>1</sup> Guoqing Cao,<sup>1</sup> Karl Kovach,<sup>1</sup> Stephanie Sweetana,<sup>1</sup> Anthony Borel,<sup>1</sup> Timothy M. Jones,<sup>1</sup> Ellen Annette Cannady,<sup>1</sup> Christopher Cioffi,<sup>2</sup> Xinchao Chen<sup>2</sup> and Sean Dinn<sup>2</sup>

<sup>1</sup>Department of Chemistry, Eli Lilly and Company and <sup>2</sup>Medicinal Chemistry Department, AMRI

**Oral Presentation** "*Structure-based design of aminohydantoin s as highly potent, selective and orally active BACE1 inhibitors,*" COMP 407 (Division of Computers in Chemistry), 234<sup>th</sup> ACS National Meeting, Boston, MA, August 19-23

Michael S. Malamas,<sup>1</sup> Jim Erdei,<sup>1</sup> Iwan Gunawan,<sup>1</sup> Nowak Pawel,<sup>1</sup> Keith Barnes,<sup>3</sup> Matthew Johnson,<sup>3</sup> Albert J Robichaud,<sup>1</sup> Ping Zhou,<sup>1</sup> Jonathan Bard,<sup>2</sup> Jim Turner,<sup>2</sup> Yun Hu,<sup>2</sup> Eric Wagner,<sup>2</sup> Suzan Aschmies,<sup>2</sup> Thomas Comery,<sup>2</sup> Rajiv Chopra,<sup>4</sup> and Kristi Fan<sup>1</sup>

<sup>1</sup>Chemical and Screening Sciences and <sup>2</sup>Discovery Neuroscience, Wyeth Research; <sup>3</sup>Medicinal Chemistry Department, AMRI and <sup>4</sup>Novartis Institutes for BioMedical Research

**Oral Presentation:** "*Substituted-pyridine 2-amino-3,5-dihydro-4H-imidazol-4-ones as highly potent, and selective BACE1 inhibitors,*" MEDI 236 (Division of Medicinal Chemistry), 234<sup>th</sup> ACS National Meeting, Boston, MA, August 19-23

Michael S. Malamas,<sup>1</sup> Keith Barnes,<sup>3</sup> Yu Hui,<sup>3</sup> Ping Zhou,<sup>1</sup> Albert J Robichaud,<sup>1</sup> Jonathan Bard,<sup>2</sup> Jim Turner,<sup>2</sup> Yun Hu,<sup>2</sup> Kristi Fan,<sup>1</sup> Rajiv Chopra,<sup>4</sup> and Matthew Johnson<sup>3</sup>

<sup>1</sup>Chemical and Screening Sciences and <sup>2</sup>Discovery Neuroscience, Wyeth Research; <sup>3</sup>Medicinal Chemistry Department, AMRI and <sup>4</sup>Novartis Institutes for BioMedical Research

**Oral Presentation:** "*8,8-Disubstituted-2,3,4,8-tetrahydroimidazo[1,5-a]pyrimidin-6-amines as highly potent, selective and orally active BACE1 inhibitors,*" MEDI 237 (Division of Medicinal Chemistry), 234<sup>th</sup> ACS National Meeting, Boston, MA, August 19-23

Michael S. Malamas,<sup>1</sup> Keith Barnes,<sup>3</sup> Yu Hui,<sup>3</sup> Jim Erdei,<sup>1</sup> Iwan Gunawan,<sup>1</sup> Nowak Pawel,<sup>1</sup> Albert J Robichaud,<sup>1</sup> Jonathan Bard,<sup>2</sup> Jim Turner,<sup>2</sup> Yun Hu,<sup>2</sup> Eric Wagner,<sup>2</sup> Suzan Aschmies,<sup>2</sup> Kristi Fan,<sup>1</sup> Rajiv Chopra<sup>4</sup> and Matthew Johnson<sup>3</sup>

<sup>1</sup>Chemical and Screening Sciences and <sup>2</sup>Discovery Neuroscience, Wyeth Research;  
<sup>3</sup>Medicinal Chemistry Department, AMRI and <sup>4</sup>Novartis Institutes for BioMedical Research

**Oral Presentation:** “*Synthesis and topoisomerase poisoning activity of A-ring and E-ring substituted luotonin A derivatives*,” MEDI 455 (Division of Medicinal Chemistry), 234<sup>th</sup> ACS National Meeting, Boston, MA, August 19-23

Kassoum Nacro,<sup>1</sup> Conxiang Zha,<sup>1</sup> Peter R. Guzzo,<sup>1</sup> R. Jason Herr,<sup>2</sup> Denise Peace<sup>3</sup> and Thomas D. Friedrich<sup>3</sup>

<sup>1</sup>Discovery Research & Development, Chemistry and <sup>2</sup>Medicinal Chemistry Departments, AMRI and <sup>3</sup>Center for Immunology and Microbial Disease, Albany Medical College

**Poster Presentation:** “*Discovery of 2-arylbenzoxazole carboxamides as 5-HT<sub>3</sub> receptor antagonists*”, MEDI 366 (Division of Medicinal Chemistry), 234<sup>th</sup> ACS National Meeting, Boston, MA, August 19-23

Catherine M. Beer,<sup>1</sup> Lisa H. Borden,<sup>1</sup> Kevin L. Christensen,<sup>2</sup> Svetlana Dobritsa,<sup>2</sup> David J. Fairfax,<sup>1</sup> Soshanna Isaacson,<sup>1</sup> John P. Lindsay,<sup>3</sup> Jun-Ho Maeng,<sup>4</sup> David D. Manning,<sup>4</sup> Liaqat Masih,<sup>4</sup> Vadim V. Mozhaev,<sup>3</sup> Dana A. Razzano,<sup>1</sup> W. Martin Rennells,<sup>1</sup> Justin Richardson,<sup>1</sup> Timothy Rust,<sup>1</sup> Alexander Usyatinsky,<sup>4</sup> Zhicai Yang<sup>4</sup> and Julianne V. Zaremba<sup>3</sup>

<sup>1</sup>Medicinal Chemistry, <sup>2</sup>Discovery Research & Development, In Vitro Biology, <sup>3</sup>Discovery Research & Development, Metabolism and Biotransformation and <sup>4</sup>Discovery Research & Development, Chemistry Departments, AMRI

**Poster Presentation:** “*Highly active enzyme formulations for use in nonaqueous media*”, BIOT 368 (Division of Biochemical Technology), 234<sup>th</sup> ACS National Meeting, Boston, MA, August 19-23

Anne L. Serdakowski,<sup>1</sup> John P. Lindsay<sup>2</sup> and Jonathan S. Dordick<sup>3</sup>

<sup>1</sup>Department of Biochemistry and Biophysics and <sup>3</sup>Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute and <sup>2</sup>Discovery Research & Development, Metabolism and Biotransformation Department, AMRI

**“Early stage chemical process development of DPP-4 inhibitors SYR-322, SYR-619 and SYR-085”**, GEN-059, 41<sup>st</sup> Western Regional ACS Meeting, San Diego, CA, October 9-13, 2007

Jayachandra Reddy, Guntha Sreenivasulu, Silvina Garcis-Rubio, Debasis Patra, Thomas Sattelberg, Edward C. Gersten, Bernard J. Paul, Grant Palmer, Luckner G. Ulysse, Bingidimi I. Mobebe; Gregory J. Reid, Zhiyuan Zhang, Michael B. Wallace, Stephen L. Gwaltney, Jeffrey A. Stafford  
Chemical Development and Analytical Quality Services Departments, AMRI and Takeda Pharmaceutical Company Limited

**Oral Presentation:** “*Managing drug discovery data with ChemFinder*”, CambridgeSoft Conference and User Meeting, Boston, MA, August 6

E. James Schermerhorn

Discovery R&D Chemistry & Computer-Aided Drug Discovery Departments, AMRI

**Oral Presentation:** “*A Pragmatic Approach to Polymorph and Particle Size Control in Chemical Development: Case Studies from Development to Manufacturing*”, 7<sup>th</sup>

Polymorphism and Crystallization Conference (Scientific Update); Tampa, FL, Nov 29-30

Luckner G. Ulysse

Chemical Development Department, AMRI

**Oral Presentation:** “*An Integrated Approach to Solid-Form Selection and Production*”, 7<sup>th</sup> Annual Polymorphism and Crystallization Scientific Forum (Pharma IQ), Philadelphia, PA, December 3-5

Paul K. Isbester

Analytical Quality Services Department, AMRI

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## Patent Applications Filed and Issued containing AMRI Scientists

The process of obtaining a patent for an invention often takes several years, from the filing of the application through the subsequent review and issuance by various national patent offices. During this year, five patent applications were filed by AMR Technology, Inc, USA—our corporate holding company for patents assigning all rights to AMRI as the owner of the intellectual property—and two previously filed patent applications were issued as full US patents. In all cases, AMRI scientists were named as co-inventors. Several other patent applications filed by customers and collaborators were also published during the year, in which AMRI scientists were named as co-inventors.

### **Patents filed by AMRI covering novel intellectual property (IP) owned by AMR Technology, Inc., USA:**

*“Pharmaceutical compositions containing vinca alkaloid derivatives”*, PCT International Application WO 2005/055939 A2 (AMR Technology, Inc, USA)  
Ian L. Scott, Jeffrey M. Ralph and Matthew E. Voss  
Medicinal Chemistry Department, AMRI  
Issued as US 7,235,564 on June 26, 2007

*“Preparation of vinorelbine derivatives as antitumor agents”*, PCT International Application WO 2005/055943 A2 (AMR Technology, Inc, USA)  
Ian L. Scott, Jeffrey M. Ralph and Matthew E. Voss  
Medicinal Chemistry Department, AMRI  
Issued as US 7,238,704 on July 3, 2007

*“Preparation of cyclosporin alkyne/alkene analogues for preventing or treating viral-induced disorders”*, PCT International Application WO 2007/112352 A2 (AMR Technology, Inc, USA)  
Bruce F. Molino  
Discovery Research & Development, Chemistry Department, AMRI

*“Preparation of cyclosporin alkene analogues for preventing or treating viral-induced disorders”*, PCT International Application WO 2007/112345 A2 (AMR Technology, Inc, USA)  
Bruce F. Molino  
Discovery Research & Development, Chemistry Department, AMRI

*“Preparation of cyclosporin alkyne analogues for preventing or treating viral-induced disorders”*, PCT International Application WO 2007/112357 A2 (AMR Technology, Inc, USA)  
Bruce F. Molino  
Discovery Research & Development, Chemistry Department, AMRI

***“Process for preparation of (-)-delta-9-tetrahydrocannabinol and derivatives thereof”***, PCT International Application WO 2007/041167 A2 (AMR Technology, Inc, USA)  
David C. Burdick, Steven J. Collier, Frederic Jos, Betina Biolatto, Bernhard J. Paul, Harold Meckler, Mark A. Helle and Alicia J. Habershaw  
Generics Research & Development Department, AMRI

***“Preparation of oxoisoindolinylphenylpropanoates and its analogs for the treatment of spinal muscular atrophy and other uses”***, PCT International Application WO 2007/109211 A2 (United States Department of Health and Human Services, USA; Albany Molecular Research, Inc, USA and Science Applications International Corporation (SAIC), USA)  
Jill Heemskerk,<sup>1</sup> Keith D. Barnes,<sup>2</sup> John M. McCall,<sup>3</sup> Graham Johnson,<sup>3</sup> David J. Fairfax<sup>2</sup> and Matthew R. Johnson<sup>2</sup>  
<sup>1</sup>United States Dept. of Health and Human Services, Rockville, MD, USA; <sup>2</sup>Medicinal Chemistry Department, AMRI and <sup>3</sup>SAIC, San Diego, CA, USA

***“Aryl- and heteroaryl-substituted tetrahydrobenzazepines and use thereof to block reuptake of norepinephrine, dopamine, and serotonin”***, PCT International Application WO 2007/011820 A2 (AMR Technology, Inc, USA and Bristol-Myers Squibb Company, USA)  
Bruce F. Molino, Shuang Liu, Aruna Sambandam, Peter R. Guzzo, Min Hu, Congxiang Zha, Kassoum Nacro, David D. Manning, Matthew I. Isherwood, Kristen N. Fleming, Wenge Cui and Richard E. Olson  
Discovery Research & Development, Chemistry Department, AMRI and Bristol-Myers Squibb Company

**Some patents filed by collaborators/customers of AMRI containing AMRI scientists as co-inventors (NOT a fully inclusive list):**

***“Tricycloundecane compounds useful as modulators of nuclear hormone receptor function and their preparation and pharmaceutical compositions”***, PCT International Application WO 2007/088029 A1 (Bristol-Myers Squibb Company, USA)  
James A. Balog, David J. Fairfax, Gregory S. Martin, Mark E. Salvati and Hai-Yun Xiao  
Medicinal Chemistry Department, AMRI and Bristol-Myers Squibb Company

***“Preparation of new capped pyrazinoylguanidine-containing amino acid derivatives as sodium channel blockers”***, PCT International Application WO 2007/018640 A1 (Parion Sciences, Inc, USA)  
Michael R. Johnson, Bruce F. Molino, Bruce Sargent and Jianzhong Zhang  
Discovery Research & Development, Chemistry Department, AMRI and Parion Sciences, Inc, USA

***“Salts and polymorphs of a VEGF-R inhibitor”***, PCT International Application WO 2007/017740 A1 (Pfizer Inc., USA)  
Yi Li, Jia Liu, Anand Sistla, Bruce J. Elder, Yufeng Hong, Paul K. Isbester, Grant J. Palmer, Jonathan S. Salsbury and Luckner G. Ulysse

Chemical Development and Analytical Quality Services Departments, AMRI and Pfizer, Inc, USA

***“Process for preparation of N-alkylated pyrimidinediones”***, PCT International Application WO 2007/035629 A2 (Takeda Pharmaceutical Company Limited, Japan)  
Jun Feng, Stephen L. Gwaltney, Jeffrey A. Stafford, Zhiyuan Zhang, Bruce J. Elder, Paul K. Isbester, Grant J. Palmer, Jonathan S. Salsbury and Luckner Ulysse  
Chemical Development and Analytical Quality Services Departments, AMRI and Takeda Pharmaceutical Company Limited, Japan

***“Stable elsamitrucin salts suitable for pharmaceutical formulations”***, US Patent Application 2007/293445 A1 (Spectrum Pharmaceuticals, Inc., USA)  
Ashok Gore, Gred Defesche, Hermant Joshi, Guru Reddy, Luigi Lenaz, Paul K. Isbester, Olga V. Lapina, Grant J. Palmer and Jonathan S. Salsbury  
Analytical Quality Services Department, AMRI and Spectrum Pharmaceuticals, Inc, USA