

Philip F. Hughes, PhD

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Synopsis:

I am a medicinal chemist with extensive drug discovery experience in both large pharmaceutical companies and biotech startups. I have broad experience in synthetic, analytical and medicinal chemistry and the development and application of new technologies for drug discovery.

WORK EXPERIENCE:

- 8/10- present Senior Research Scientist in Tim Haystead's lab, Duke University, Pharmacology and Cancer Biology. Provide chemistry support for the lab's drug discovery efforts. Currently developing new methods for targeted delivery of diagnostic and therapeutic agents. Give a Medicinal Chemistry Lecture to incoming graduate Pharmacology students.

- 12/14 Medicinal Chemistry Consultant for ADS Pharma Consulting

- 11/14-present Retained Consultant for Goodwin Proctor LLP. NYC, NY. on rapamycin chemistry expertise

- 4/13-present Medicinal Chemistry Consultant for Esanex.

- 9/10-10/11 Medicinal Chemistry Consultant for Synereca Pharmaceuticals, Inc.

- 2/10- 12/10 Scientific Review Officer (part-time) SRA Inc. Run scientific review panels for research grants submitted to CDMRP for breast cancer research. CDBRP is administered by the US Army.

- 1/10-12/11 Retained Consultant for King & Spalding LLP. Atlanta, Ga. on rapamycin chemistry expertise

- 4/06-9/08 Staff Scientist, Serenex, Inc. Durham, NC. Medicinal chemist in Hsp90 program. Serenex was acquired by Pfizer and closed 9/30/08. SNX-5422, from the Hsp90 program, entered late-stage Phase I clinical studies.

- 4/05-4/06 Research Investigator, Scynexis, Inc. RTP, NC Lead Generation group

- 3/04-present Founder and President, InnovaSyn, LLC, Chapel Hill, NC - InnovaSyn provides products for high throughput chemical synthesis and experimentation.

- 1/98-3/04 Senior Research Scientist, Lilly Research Triangle Park Laboratories, Eli Lilly and Co., RTP, NC - Responsible as a Medicinal Chemist for the development and application of synthetic technologies for lead generation and optimization. Directed the analytical chemistry group. Led development of new technologies for rapid parallel synthesis and analytical data delivery and storage.

- 9/94-12/97 Research Scientist, Sphinx Laboratories, Eli Lilly and Co., RTP, NC - Responsible for development and implementation of high throughput synthesis technology and

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methodology at Sphinx. Responsible for the invention, development and delivery of content and technology associated with three technology transfers to Japanese partners. Managed a group (seniors and associates) involved in lead generation, lead optimization, analytical chemistry and technology development.

- 9/94 Sphinx acquired by Lilly
2/91-9/94 Senior Scientist I, Sphinx Pharmaceuticals, Responsible for establishing and developing combinatorial chemistry efforts at Sphinx Durham. Medicinal Chemist in research related to Protein Kinase C. including the total synthesis of (-)-Balanol and numerous analogues. Management of scientists at the BS/MS and PhD level. Set up and management of molecular modeling system.
- 1/88-2/91 Research Scientist, Wyeth-Ayerst Research, Princeton, NJ
11/83-1/88 Senior Scientist, Wyeth-Ayerst Research, Princeton, NJ - Medicinal Chemist in antiinflammatory and immunomodulator therapeutic areas including NSAIDS, bradykinin inhibitors, PLA₂ inhibitors and rapamycin analogs. Responsible for the design and synthesis of novel compounds as potential drug candidates. This includes writing proposals to define new approaches, developing new synthetic methods, developing improved processes and training and managing other scientists.
- 5/83-11/83 Ayerst Postdoctoral Fellow, Department of Chemistry, Cornell University, Ithaca, NY - Isolated and determined the structure of an antibiotic from Erwinia herbicola.
- 6/76-8/78 Chemist II, Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, NC worked under Bob Jeffcoat - Carried out the isolation, structural elucidation and synthesis of xenobiotic metabolites. Synthesized radio-labeled compounds.

EDUCATION:

Ph.D. Cornell University, Ithaca, N.Y. **1983**, Advisor: Jon Clardy
Major field: Organic Chemistry Minor fields: Analytical and Biological Chemistry
Thesis: Total Synthesis of Some Unusual Amino Acids.
(<http://catalog.hathitrust.org/Record/010005625>)
NIH Predoctoral Fellow.

B.S. Chemistry, University of North Carolina at Chapel Hill **1976**.

ACCOMPLISHMENTS:

Developed a highly selective affinity probe for the chaperone protein Hsp90. Besides aiding purification of native Hsp90, the probe is being developed for delivery of diagnostic and therapeutic agents to cells overexpressing Hsp90, notably cancer cells. Provided basis for \$10M DOD innovation award grant.

Contributed to Serenex Hsp90 program resulting in a clinical candidate and eventual purchase of the company by Pfizer.

Founded InnovaSyn, LLC, a company which provides elegant high throughput organic synthesis solutions for practicing Medicinal Chemists.

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Faculty member of the Drew University Residential School on Medicinal Chemistry from 1998-2005.

Conceived of and managed the development of **LINEA**, a web-based program for archiving and distributing analytical data (LC/MS, NMR, MS, images, documents). LINEA enabled Lilly scientists world wide to quickly access analytical data with spectral manipulation capabilities and structural display.

Developed world class parallel synthesis technology and methods. Automation, robotics, apparatus and software offer functionality, flexibility and ease of use unmatched in commercial offerings. One compound discovered using this technology is currently in Phase 1 clinical trials and numerous others are in advanced pre-clinical development.

Managed analytical chemistry group delivering routine high throughput NMR and LC/MS with paperless archiving and delivery of high quality analytical data. Throughput per instrument was generally > 10-fold other company groups.

Developed a novel piperidone chemical library that led to a 3.7 nM competitive inhibitor of farnasyltransferase.

Received the Lilly Research Labs President's Recognition Award in 1995 and 1997.

Primarily responsible for invention and delivery of parallel synthesis technology in 3 technology transfers to Japanese partners, resulting in multi-million dollar (~\$70M) income for Eli Lilly.

Total synthesis of Balanol, a potent natural product inhibitor of Protein Kinase C.

Contributed to the development of rapamycin and analogs, currently on the market for transplant and cancer indications.

RELATED EXPERIENCE:

Strong organic synthesis and medicinal chemistry skill set. Conversant in analytical chemistry, liquid handling robotics, CAD for equipment design, molecular modeling and chemistry database programs. Extensive experience in chromatography, especially preparative HPLC. Experience with radiochemical methods and peptide and amino acid synthesis. Original member of the Apple Computer Pharmaceutical Advisory Council. Organized registration for the 1990 Princeton ACS Fall Organic Symposium (attendance >500). Extensive programming experience in Visual Basic 6.0. Experience with JavaScript, PHP/MySQL, XHTML/CSS, SQL and Java though I've forgotten much of it.

PUBLICATIONS:

Identification of a Novel Allosteric Small Molecule Inhibitor of the Inducible Form of Heat Shock Protein 70, Matthew K. Howe, Khaldon Bodoor, David A. Carlson, Philip F. Hughes, David R. Loiselle, Alex M. Jaeger, David B. Darr, Jamie L. Jordan, Lucas M. Hunter, Eileen T. Molzberger, Theodore A. Gobillot, Dennis J. Thiele, Jeffrey L. Brodsky, Neil L. Spector and Timothy A. J. Haystead, *Chemistry and Biology*, **2014**; *21*, 1648–1659.

Timothy Haystead and Philip Hughes; Discovery of the Serenex Hsp90 Inhibitor, SNX5422 In *Inhibitors of Molecular Chaperones as Therapeutic Agents* Eds. Timothy D Machajewski,

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Zhenhai Gao, Royal Society of Chemistry: London, **2014**; pp 241-258.

Fluorescence Linked Enzyme Chemoproteomic Strategy for Discovery of a Potent and Selective DAPK1 and ZIPK Inhibitor, David A Carlson , Aaron S Franke , Douglas Weitzel , Brittany L Speer , Philip F Hughes , Laura Hagerty , Christopher N Fortner , James M Veal , Thomas E Barta , Bartosz J Zieba , Avril V Somlyo , Cindy Sutherland , Jing Ti Deng , Michael P Walsh , Justin A MacDonald , and Timothy A.J. Haystead, *ACS Chem. Biol.*, **2013**, *8*, 2715.

Tethered Hsp90 Inhibitors Carrying Optical or Radioiodinated Probes Reveal Selective Internalization of Ectopic Hsp90 in Malignant Breast Tumor Cells, Jared J. Barrott, Philip F. Hughes, Takuya Osada, Xiao-Yi Yang, Zachary C. Hartman, David R. Loisel, Neil L. Spector, Len Neckers, Narasimhan Rajaram, Fangyao Hu, Nimmi Ramanujam, Ganesan Vaidyanathan, Michael R. Zalutsky, H. Kim Lysterly and Timothy A. Haystead. *Chemistry and Biology*, **2013**, *20*, 1187.

A Highly Selective Hsp90 Affinity Chromatography Resin with a Cleavable Linker, Philip F Hughes, Jared J Barrott, David A Carlson, David R Loisel, Brittany L Speer, Khaldon Bodoor, Laretta A Rund, and Timothy A J Haystead. *Bioorg. Med. Chem.* **2012**, *20*, 3298.

Discovery of novel aminoquinazolin-7-yl 6,7-dihydro-indol-4-ones as potent, selective inhibitors of heat shock protein 90. Kenneth H. Huang, Thomas E. Barta, John W. Rice, Emilie D. Smith, Andy J. Ommen, Wei Ma, James M. Veal, R. Patrick Fadden, Amy F. Barabasz, Briana E. Foley, Philip F. Hughes, Gunnar J. Hanson, Christopher J. Markworth, Melanie Silinski, Jeffrey M. Partridge, Paul M. Steed and Steven E. Hall. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1593.

Application of Chemoproteomics to Drug Discovery: Identification of a Clinical Candidate Targeting Hsp90, Patrick Fadden, Kenneth H. Huang, James M. Veal, Paul M. Steed, Amy F. Barabasz, Briana Foley, Mei Hu, Jeffrey M. Partridge, John Rice, Anisa Scott, Laura G. Dubois, Tiffany A. Freed, Melanie A. Rehder Silinski, Thomas E. Barta, Philip F. Hughes, Andy Ommen, Wei Ma, Emilie D. Smith, Angela Woodward Spangenberg, Jeron Eaves, Gunnar J. Hanson, Lindsay Hinkley, Matthew Jenks, Meredith Lewis, James Otto, Gijsbertus J. Pronk, Katleen Verleysen, Timothy A. Haystead and Steven E. Hall. *Chemistry & Biology*, **2010**, *17*, 686-694.

Discovery of Novel 2-Aminobenzamide Inhibitors of Heat Shock Protein 90 as Potent, Selective and Orally Active Antitumor Agents, Kenneth H. Huang, James M. Veal, R. Patrick Fadden, John W. Rice, Jeron Eaves, Jon-Paul Strachan, Amy F. Barabasz, Briana E. Foley, Thomas E. Barta, Wei Ma, Melanie A. Silinski, Mei Hu, Jeffrey M. Partridge, Anisa Scott, Laura G. DuBois, Tiffany Freed, Paul M. Steed, Andy J. Ommen, Emilie D. Smith, Philip F. Hughes, Angela R. Woodward, Gunnar J. Hanson, W. Stephen McCall, Christopher J. Markworth, Lindsay Hinkley, Matthew Jenks, Lifeng Geng, Meredith Lewis, James Otto, Bert Pronk, Katleen Verleysen, and Steven E. Hall. *J. Med. Chem.*; **2009**, *52*, 4288-4305.

High throughput evaluation of the production of substituted acetylenes by the Sonogashira reaction followed by the Mizoroki–Heck reaction in ionic liquids, in situ, using a novel array reactor, Md. Taifur Rahman, Takahide Fukuyama, Ilhyong Ryu, Kanae Suzuki, Koichi Yonemura, Philip F. Hughes and Kiyoshi Nokihara, *Tet. Lett.* **2006**, *47*, 2703–2706.

Array Reactors for Parallel Synthesis. Philip F. Hughes, Thomas H. Graham and Jose S. Mendoza. *J. Comb. Chem.*; **2004**, *6*, 308-311.

Discovery and Structure-Activity Relationships of Novel Piperidine Inhibitors of

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Farnesyltransferase. Shinji Nara, Rieko Tanaka, Jun Eishima, Mitsunobu Hara, Yuichi Takahashi, Shizuo Otaki, Robert J. Foglesong, Philip F. Hughes, Shelley Turkington, and Yutaka Kanda. *J. Med. Chem.*; **2003**, *46*, 2467-2473.

Synthesis and Protein Kinase Inhibitory Activity of Balanol Analogues with Modified Benzophenone Subunits. John W. Lampe, Christopher K. Biggers, Jean M. Defauw, Robert J. Foglesong, Steven E. Hall, Julia M. Heerding, Sean P. Hollinshead, Hong Hu, Philip F. Hughes, G. Erik Jagdmann, Jr., Mary George Johnson, Yen-Shi Lai, Christopher T. Lowden, Michael P. Lynch, José S. Mendoza, Marcia M. Murphy, Joseph W. Wilson, Lawrence M. Ballas, Kiyomi Carter, James W. Darges, Jefferson E. Davis, Frederick R. Hubbard, and Mark L. Stamper. *J. Med. Chem.*; **2002**; *45*(12) 2624 – 2643.

Total Synthesis of (-)- and (+)-Balanol. John W. Lampe, Philip F. Hughes, Christopher K. Biggers, Shelley H. Smith and Hong Hu. *J. Org. Chem.* **1996**, *61*, 4572.

Two Efficient Synthesis of (±)-*anti*-N-Benzyl-3-amino-4-hydroxyhexahydroazepine. Hong Hu, G. Erik Jagdmann, Philip F. Hughes and Jeffrey B. Nichols. *Tet. Lett.*, **1995**, 3659.

Two Chiral Syntheses of *Threo*-3-Hydroxylysine. Philip F. Hughes, Shelley H. Smith and John Olson. *J. Org. Chem.* **1994**, *59*, 5799.

Total Synthesis of (-)-Balanol, John W. Lampe, Philip F. Hughes, Christopher K. Biggers, Shelley H. Smith and Hong Hu. *J. Org. Chem.* **1994**, *59*, 5147.

The Isolation, Synthesis and Characterization of an Isomeric Form of Rapamycin. Philip Hughes, John Musser, Mary Conklin and Ralph Russo. *Tet. Lett.*, **1992**, 4739.

Synthetic Entries to 6-Fluoro-7-substituted Indole Derivatives. Brian McKittrick, Amedeo Failli, Robert J. Steffan, Richard. M. Soll, Philip Hughes, Jean Schmid, Andre A. Asselin, C. C. Shaw, R. Noureldin, and G. Gavin. *Journal of Heterocyclic Chemistry*, **1990**, *27*(7), 2151.

The Synthesis and Biological Evaluation of 4,6-Diethyl-1,3,4,5-tetrahydropyrano- [4,3-b]indole-4-acetic acid, an Isomer of Etodolac. Philip Hughes, J. DeVirgilio, L. Humber, T. Chau, B. Weichman and G. Neuman. *J. Med. Chem.* **1989**, *32*, 2134.

The Synthesis of 3(S)-Carboxy-4(S)-hydroxy-2,3,4,5- tetrahydropyridazine, a Novel Amino Acid Constituent of the Antitumor Agent, Luzopeptin. Philip Hughes and Jon Clardy. *J. Org. Chem.* **1989**, *54*, 3260.

The Total Synthesis of Amino Acids from *Atelia herbert smithii*. Philip Hughes and Jon Clardy. *J. Org. Chem.* **1988**, *53*, 4793.

Etodolac, A Novel Anti-inflammatory Agent. The Synthesis and Biological Evaluation of its Metabolites. L. G. Humber, E. Ferdinandi, C. A. Demerson, S. Ahmed, U. Shah, D. Mobilio, J. Sabatucci, B. DeLange, F. Labbadia, P. Hughes, J. DeVirgilio, G. Neuman, T. Chau and B. Weichman. *J. Med. Chem.* **1988**, *31*, 1712.

Structure-Activity Relationships Among Analogs of Pemedolac, *cis*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl- pyrano[3,4-b]indole-1-acetic Acid, a Potent Analgesic Agent. D. Mobilio, L. G. Humber, A. H. Katz, C. A. Demerson, P. Hughes, R. Brigance, K. Conway, U. Shah, G. Williams, F. Labbadia, B. DeLange, J. Schmidt, J. Newburger, N. P. Jensen, B. Weichman, T. Chau, G.

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Neuman, D. D. Wood, D. Van Engen and N. Taylor. *J. Med. Chem.* **1988**,*31*, 2211.

Conformational Properties of 2,4-Methanoproline (2-Carboxy-2,4-Methanopyrrolidine) in Peptides: Determination of Preferred Peptide Bond Conformation in Aqueous Solution by Proton Overhauser Measurements. G.T. Montelione, P.F. Hughes, J. Clardy and H.A. Sheraga. *J. Am. Chem. Soc.* **1986**, *108*, 6765.

2-Amino-4-acetylamino butyric acid, 2,4-diaminobutyric acid and 2-amino-6N-oxalylureidopropionic acid (oxalylalbizziine) in seeds of *Acacia angustissima*. C.A. Evans, J. Clardy, P.F. Hughes and E.A. Bell. *Phytochemistry*, **1985**, *24*, 2273.

Zinc Pyridinethione: Serum Metabolites of Zinc Pyridinethione in Rabbits, Rats, Monkeys and Dogs after Oral Dosing. W.B. Gibson, R.A. Jeffcoat, P.A. T.S. Turan, R.H. Wendt, P.F. Hughes and M.T. Twine. *Toxicol. Appl. Pharmacol.*, **1982**, *62*(1), 237-250.

Synthesis of 2,4-Methanoproline. Philip Hughes, Michael Martin and Jon Clardy. *Tet. Lett.*, **1980**, 4579.

Zinc pyridinethione: Urinary Metabolites of Zinc Pyridinethione in Rabbits, Rats, Monkeys and Dogs after Oral Dosing. R.A. Jeffcoat, W.B. Gibson, P.A. Rodriguez, T.S. Turan, P.F. Hughes and M.T. Twine. *Toxicol. Appl. Pharmacol.*, **1980**, *56*(1), 141-154.

Structural Studies of Organosulfur Compounds. D.M. Frieze, P.F. Hughes, R.L. Merrill Jr., and S.A. Evans. *J. Org. Chem.*, **1977**, *42*, 2206.

PATENTS:

Timothy Haystead and Philip Floyd Hughes "Compounds and methods for targeting Hsp90 " WO/2014/025395A1 February 13, **2014**., US20150191471 A1 July 9, **2015**.

Kenneth He Huang, Andy J. Ommen, Thomas E. Barta , Philip F. Hughes, James Veal, Wei Ma, Emilie D. Smith, Angela R. Woodward and W. Stephen McCall "Tetrahydroindole And Tetrahydroindazole Derivatives" WO/2008/130879A2 October 30, **2008**.

Kenneth H. Huang, John Mangette, Thomas Barta, Philip Hughes, Steve Hall and James Veal "Benzene, pyridine, and pyridazine derivatives" WO/2008/024978 February 28, **2008**.

Kenneth H. Huang, Philip Hughes, Wei Ma, Andy Ommen, Angela Woodward, James Veal and Thomas Barta "Benzene, pyridine, and pyridazine derivatives" WO/2008/024970 February 28, **2008**.

Kenneth H. Huang, Philip Hughes, Thomas Barta and James Veal "Dihydropyridazine, tetrahydropyridine, chromanone, and dihydronaphthalenone derivatives as heat-shock protein 90 inhibitors" WO/2008/024961 February 28, **2008**.

Sean P. Hollinshead, Michael A. Staszak, John S. Ward, Joseph W. Wilson, Bret E. Huff, Philip F. Hughes, Jose S. Mendoza, and Charles H Mitch. "Indane derivatives for antipsychotic compositions". U. S. Patent 6,429,317 Aug. 6, **2002**

Neil Alexander Castle, Sean Patrick Hollinshead, Philip Floyd Hughes, Jose Serafin Mendoza,

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Joseph Wendell Wilson, George Salvatore Amato, Serge Beaudoin, Michael Gross Grant McNaughton-Smith. "Potassium channel inhibitors." U. S. Patent 6,083,986 July 4, **2000**.

Sean P. Hollinshead, Philip F. Hughes, Jose S. Mendoza, Charles H. Mitch, John S. Ward and Joseph W. Wilson "Combinatorial process for preparing substituted indane libraries," WO/1997/026300 July 24, **1997**.

Steven Edward Hall, Lawrence M. Ballas, Palaniappan Kulanthaivel, Christie Boros, Jack B. Jiang, Gunnar Erik Jagdmann, Yen-Shi Lai, Christopher K. Biggers, Hong Hu, Yali Hallock, Philip F. Hughes, Jean Marie Defauw, Michael Patrick Lynch, John William Crossley Lampe, David Steven Menaldino, Julia Marie Heerding, William P. Janzen and Sean Patrick Hollinshead "Balanoids," WO/1994/020062A2 September 15, **1994**.

Philip F. Hughes, "Oxepane Isomers of Rapamycin Useful as Immunosuppressive Agents," U. S. Patents 5,221,740, Jun. 22, **1993** and 5,344,833, Sept. 6, **1994**

Jack B. Jiang and Philip F. Hughes, "Polyhydroxylated dibenz (c,e) azepines as protein kinase C inhibitors" WO/1993/020695, October 28, **1993**.

Philip F. Hughes, "Rapamycin Alkoxyesters," U. S. Patent 5,233,036, Aug. 3, **1993**.

Philip F. Hughes, John H. Musser "Rapamycin analog as immunosuppressant," U. S. Patent 5,202,332, April 13, **1993**

Philip F. Hughes, John H. Musser "Rapamycin analog as immunosuppressant and antifungals," U. S. Patents 5,138,051, Aug. 11, **1992** and 5,169,851 Dec. 8, **1992**.

Philip F. Hughes, Dominick Mobilio and Leslie G. Humber, "Process for the Production of Substituted 2-Oxocyclohexaneacetic Acid Esters," U.S. Patents 4,861,910, **1989** and 4,898,967, Feb. 6, **1990**.

Philip F. Hughes, Dominick Mobilio and Leslie G. Humber, "Substituted 2-Oxocyclohexaneacetic Acid Esters," U.S. Patent 4,748,266, **1988**.

Philip F. Hughes, Dominick Mobilio and Leslie G. Humber, "New 1-Alkyl-3-halo-4- substituted-2-oxocyclohexaneacetic Acid Compounds Used in the Preparation of 1-Alkyl-4-substituted-2-oxocyclohexaneacetic Acid Intermediates to Analgesic and Anti-inflammatory Agents," EP 247-779-A, **1987**.

PRESENTATIONS:

Medicinal Chemistry Lecture, Duke University, Pharmacology 533 - Essentials of Pharmacology and Toxicology, **November 2012-14**.

A Simple Approach to Liquid Handling Robotics in Parallel Synthesis. Philip F. Hughes, Matthew S. Clapham and Thomas H. Graham, **The 56th Southeast Regional ACS Meeting, November 2004**.

Faculty member at **Drew University Residential School of Medicinal Chemistry**, Lectured on Chemical Diversity **1998-2005**.

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High-throughput Analytical Data Handling, Philip F. Hughes, **PittCon 2003, March 2003.**

Diverse Scaffolds for Lead Generation, Philip F. Hughes. **213th ACS National Meeting, Division of Organic Chemistry, April 1997.**

The Synthesis of Combinatorial Chemistry Libraries using the Pfau Enamine Alkylation Chemistry, Philip F. Hughes. **Lilly Expo '96.**

Total Synthesis of (-)-Balanol, Philip F. Hughes, John W. Lampe, Christopher K. Biggers, Shelley H. Smith, Hong Hu and John Olson. **24th National Medicinal Chemistry Symposium, 1994.**

The Isolation, Synthesis and Characterization of an Isomeric Form of Rapamycin. Philip Hughes, John Musser, Mary Conklin and Ralph Russo. **Gordon Conference on Natural Products, 1992.**

Structural Studies of Organosulfur Compounds. D.M. Frieze, P.F. Hughes, R.L. Merrill Jr., and S.A. Evans, **ACS Meeting in Minature, NCSU Raleigh 1976.**