KONSTANTINOS A. AGRIOS, Ph.D.

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SUMMARY

SYNTHETIC ORGANIC/MEDICINAL CHEMIST with industry as well as academic experience in drug discovery.

Skilled in the discovery of small molecule therapeutics. Creative and team-oriented in rapidly advancing drug discovery projects into clinical development (Abbott Laboratories, now Abbvie; Anadys Pharmaceuticals; Incyte Corp.)

Lecturer/instructor and research mentor for undergraduate and M.Sc. students (Villanova University, Chemistry and Biochemistry)

- *Inventor, co-inventor of 5 published and/or issued patents; co-author of 22 peer-reviewed publications*
- *Rapid hit to lead advancement – experience in drug design and lead-optimization strategies*
- *Experience in optimization of pharmaceutical properties (HERG activity, permeability, metabolism, PK)*
- *Experience in selection of robust clinical candidates*
- *Excellent synthetic organic chemistry skills*

PROFESSIONAL EXPERIENCE

VILLANOVA UNIVERSITY, Villanova, PA **2008-2021**
Visiting Assistant Professor (2008-2013) and Continuing Assistant Professor (2013-2021)

Teaching: Lecturer for organic and medicinal chemistry courses as well as instructor for organic chemistry laboratory courses.

Research: Established, worked on and managed a drug discovery project on second-generation **Factor D** inhibitors as potential therapeutics for **complement mediated rare diseases**. Production of recombinant human Factor D, medicinal chemistry, assay development. Novel and potent Factor D inhibitors were synthesized (provisional patent application in preparation). Mentored undergraduate and graduate students in the practice of medicinal chemistry (2017-2021).

New synthetic methodologies for privileged heterocyclic structures (2016).

Synthesis of small molecules as Nrf2 activators (in collaboration with Prof. A. Eggler, Villanova University, 2015).

Visiting Scholar: The University of Pennsylvania Medical School, Department of Pathology, hosted by Professor John Lambris an expert in **complement** biology. **Synthesis of albumin binding tags to improve the bioavailability of Compstatin, an experimental complement therapeutic** (Summer 2016).

Oral presentation: **Efficient Synthesis of Drug-like Polycyclic Compounds such as Naphthyridines and Aza-Indoles**". Paper number: ORGN 614; Division: Organic Chemistry; Session: Heterocycles and Aromatics. 251st ACS National Meeting in San Diego, California, **March 13-17, 2016.**

Invited speaker: Penn Radiology Oncology - Smilow Center for Translational Research. "**Medicinal Chemistry Strategies towards Druggable Targets**" (October 29, 2015**)**.

Visiting Scientist: The Institut de Science et d'Ingenierie Supramoleculaires (ISIS), University de Strasbourg – CNRS, Strasbourg, France, hosted by Prof. Nicolas Winssinger. Synthesis of AXL kinase covalent inhibitors (Summer 2011).

ARMGO Pharma, Inc., New York City **2013**
Consultant

INCYTE CORPORATION, San Diego, CA and Wilmington, DE **2003-2012**
Principal Research Investigator

Design of novel RXR activators for the treatment of type 2 diabetes. Contributed in the execution of the synthetic route for large-scale synthesis of an orally active Her-2 sheddase inhibitor clinical candidate. Design of novel 11β-HSD1 inhibitors for the treatment of diabesity.

- Synthesized novel RXR activators with acceptable overall pharmaceutical profile; **Lead optimization (less than three months) resulted in significant aqueous solubility improvement.**
- Designed and synthesized novel 11β-HSD1 inhibitors with excellent cell potency (1-10nM), no HERG and PXR activities, good overall PK profile. **Advancement of the initial hit into a patentable lead series in less than two months.** Co-inventor in one granted patent. Clinical candidate completed **phase II** trials in type 2 diabetes patients.

ANADYS PHARMACEUTICALS, INC., San Diego, CA **2001-2003**
Principal Research Investigator

Myxopyronin and analogs thereof targeting the bacterial RNA polymerase.
Member of the Roche-Anadys collaboration team for the lead optimization of MDM2-p53 inhibitors.

ABBOTT LABORATORIES, Chicago, IL **1998-2001**
Research Chemist

Discovery of potent and selective potassium channel activators for the treatment of bladder over-activity.

- **Efficient modification of preliminary lead unfolded a novel series of potassium channel openers with excellent cellular and *in vivo* activities.**
- Inventor and co-inventor on four published patents.
- Project team nominated clinical candidate.

Postdoctoral Work:

THE SCRIPPS RESEARCH INSTITUTE, La Jolla, CA **1996-1998**
Research Associate

Member of the project team that accomplished the synthesis of Brevetoxin A ending successfully a 10-year effort.

THE UNIVERSITY OF KANSAS, Lawrence, KS **1995-1996**
Postdoctoral Associate – Department of Chemistry and Medicinal Chemistry

- Synthetic Methodology: Developed Lewis acid promoted cycloaddition reactions and Azido-Mannich reactions.
- Total Synthesis: Accomplished synthesis of two natural products (pterocarpans – inhibitors of HIV reverse transcriptase; curacin A – anticancer activity).
- Pharmaceutical Chemistry: β-Turn mimetics, studied the effect of stereochemistry on their transport through biological membranes.

EDUCATION

University of Toledo - Ph.D. in Organic Chemistry,
University of Ioannina, Ioannina, Greece – Diploma of Chemistry,

PROFESSIONAL DEVELOPMENT

Attended Medicinal Chemistry Course at Drew University, 1999
Attended Antibacterial Short Course, Washington DC, 2001

Patents

Amido compounds and their use as pharmaceuticals. Wenquing Yao; Coleen Zhang; Meixong Xu; **Konstantinos Agrios**; Brian Metcalf; Jincong Zhuo. (Incyte Corporation). WO 2006/002350 A1. This patent covers 11β-HSD1 inhibitors. THE CLINICAL CANDIDATE COMPLETED PHASE II STUDIES IN TYPE 2 DIABETES PATIENTS.

Dihydronaphthyridine- and Dihydropyrrolopyridine-derivated compounds as potassium channel openers. **Agrios, Konstantinos**. (Abbott Laboratories, USA). WO 2002/010164

Pyrano, piperidino, and thiopyrano compounds and methods of use. Carroll, William A.; **Agrios, Konstantinos A**.; Altenbach, Robert J.; Drizin, Irene; Kort, Michael J. (Abbott Laboratories, USA). United States Patent 6642222.

Pyrano, piperidino, and thiopyrano compounds and methods of use. Carroll, William A.; **Agrios, Konstantinos A**.; Altenbach, Robert J.; Drizin, Irene; Kort, Michael J. (Abbott Laboratories, USA). UnitedStatesPatent6191140.

Dihydropyridine compounds and their use as potassium channel openers. Carroll, William A.; **Agrios, Konstantinos A**.; Basha, Fatima, Z.; Chen, Yiyuan; Kort, Michael J.; Kym, Philip R.; Tang, Rui; Turner, Sean C.; YI, Lin (Abbott Laboratories, USA). WO 2000/024741

Publications

Novel Insights into Factor D Inhibition. Eleni Gavriilaki, Anna Papakonstantinou; Konstantinos A. Agrios, submitted to *Int. J. Mol. Sci.*, May **2022**.

Discovery of a Potent, Selective, and Orally Active Human Epidermal Growth Factor Receptor-2 Sheddase Inhibitor for the Treatment of Cancer. Wenqing Yao,* Jincong Zhuo, David M. Burns, Yun-Long Li, Qiyan Lin, **Costas Agrios** *et al*., *J. Med. Chem*., **2007**, 50(4), pp 603-606.

Asymmetric synthesis of conformationally constrained trans-2,3-piperidinedicarboxylic acid derivatives. Zhuo, J., Burns, D., Agrios, C., Metcalf, B., Yao, W. *Synlett*, **2007**, 3, pp 460-464.

Syntheses of novel myxopyronin B analogs as potential inhibitors of bacterial RNA polymerase. R. Lira, A. Xiang, T. Doundoulakis, W. Biller, **K. A. Agrios**, K. Simonsen, S. Webber *et al*., *Biorganic and Medicinal Chemistry Letters*, **2007**, 17(24), pp 6797-6800.

An Efficient Synthesis of *rac*-Myxopyronin B via versatile pyridone intermediates. **K. A. Agrios** and R. Lira *Heterocycles*, **2006**, 68(6), pp 1099-1103.

Myxopyronin B Analogs as Inhibitors of RNA Polymerase, Synthesis and Biological Evaluation. T. Doundoulakis, A. Xiang, R. Lira, **K. A. Agrios**, S. Webber, K. Simonsen *et al*. *Bioorg. & Med. Chem. Lett.*, 14(**2004**), 5667-5672.

Synthesis and Structure-Activity Relationships of a Novel Series of Tricyclic Dihydropyridine-Based KATP Openers That Potently Inhibit Bladder Contractions in Vitro. W. A. Carroll, **K. A. Agrios**, R. J. Altenbach, Y. Chen, I. Drizin et al. *J. Med. Chem.*, 47(12), **2004**, 3180-3192.

5-Amino-2H-pyran-3(6H)-one, a Convenient Intermediate in the Synthesis of Pyran Containing 1,4-Dihydropyridines. R. J. Altenbach, **K. A. Agrios**, I. Drizin, W. A. Carroll. *Synthetic Communications* 34(4), **2004**, 557-565.

Reactions of Alkyl Azides and Ketones as Mediated by Lewis Acids: Schmidt and Mannich Reactions Using Azide Precursors. Desai, Pankaj; Schildknegt, Klaas; **Agrios, Konstantinos** A.; Mossman, Craig; Milligan, Gregory L.; Aube, Jeffrey. *JACS* (**2000**), 122(30), 7226-7232.

Total synthesis of brevetoxin A: Part 4: final stages and completion. Nicolaou, K. C.; Gunzner, Janet L.; Shi, Guo-Qiang; **Agrios, Konstantinos A**.; Gartner, Peter; Yang, Zhen.
Chemistry – A European Journal (**1999**), 5(2), 646-658.

Total synthesis of brevetoxin A: Part 3: construction of GHIJ and BCDE ring systems. Nicolaou, K. C.; Shi, Guo-Qiang; Gunzner, Janet L.; Gartner, Peter; Wallace, Paul A.; Ouellette, Michael A.; Shi, Shuhao; Bunnage, Mark E.; **Agrios, Konstantinos A**.; Veale, Chris A.; Hwang, Chan-Kou; Hutchinson, John; Prasad, C. V. C.; Ogilvie, William W.; Yang, Zhen.
Chemistry - A European Journal (**1999**), 5(2), 628-645.

Total synthesis of brevetoxin A: Part 2: second generation strategy and construction of EFGH model system. Nicolaou, K. C.; Wallace, Paul A.; Shi, Shuhao; Ouellette, Michael A.; Bunnage, Mark E.; Gunzner, Janet L.; **Agrios, Konstantinos A**.; Shi, Guo-Qiang; Gartner, Peter; Yang, Zhen.
Chemistry - A European Journal (**1999**), 5(2), 618-627.

Total synthesis of brevetoxin A: Part 1: first generation strategy and construction of BCD ring system. Nicolaou, K. C.; Bunnage, Mark E.; McGarry, Daniel G.; Shi, Shuhao; Somers, Patricia K.; Wallace, Paul A.; Chu, Xin-Jie; **Agrios, Konstantinos A**.; Gunzner, Janet L.; Yang, Zhen.
Chemistry - A European Journal (**1999**), 5(2), 599-617.

Mannich reactions using benzyl azide as a latent N-(phenylamino)methylating agent. Schildknegt, Klaas; **Agrios, Konstantinos A**.; Aube, Jeffrey. *Tetrahedron Letters* (**1998**), 39(42), 7687-7690.

Total synthesis of brevetoxin A. Nicolaou, K. C.; Yang, Zhen; Shi, Guo-qiang; Gunzner, Janet L.; **Agrios, Konstantinos A**.; Gartner, Peter. *Nature (London)* (**1998**), 392(6673), 264-269.

Effect of stereochemistry on the transport of Aca-linked β-turn peptidomimetics across a human intestinal cell line. Tamura, Kiyoshi; **Agrios, Konstantinos A**.; Velde, David Vander; Aube, Jeffrey; Borchardt, Ronald T. *Bioorganic & Medicinal Chemistry* (**1997**), 5(9), 1859-1866.
**THIS PAPER HAS BEEN CITED BY DR. LIPINSKY (The Rule of 5) IN ONE OF HIS PRESENTATIONS*

Total synthesis of (+)-curacin A, a marine cytotoxic agent. Hoemann, Michael Z.; **Agrios**, **Konstantinos A**.;

Aube, Jeffrey. *Tetrahedron* (**1997**), 53(32), 11087-11098.

Stereoselective syntheses of substituted pterocarpans with anti-HIV activity, and 5-aza-/5-thia-pterocarpan and 2-aryl-2,3-dihydrobenzofuran analogs. Engler, Thomas A.; LaTessa, Kenneth O.; Iyengar, Rajesh; Chai, Wenying; **Agrios, Konstantinos**. *Bioorganic & Medicinal Chemistry* (**1996**), 4(10), 1755-1769.

Total synthesis of curacin A. Hoemann, Michael Z.; **Agrios, Konstantinos A**.; Aube, Jeffrey. *Tetrahedron Letters* (**1996**), 37(7), 953-6.

Contrasting reactivity in Lewis acid-promoted reactions of thio- and silyl-allenes with 1,4-benzoquinones. Engler, Thomas A.; **Agrios, Konstantinos**; Reddy, Jayachandra P.; Iyengar, Rajesh. *Tetrahedron Letters* (**1996**), 37(3), 327-30.

Contrasting reactivity in lewis acid-promoted reactions of thio-and silyl-allenes with 1,4-benzoquinones. Engler, Thomas A.; **Agrios, Konstantinos**; Reddy, Jayachandra P.; Iyengar, Rajesh. Department Chemistry, University Kansas, Lawrence, KS, USA. Book of Abstracts, **210th ACS National Meeting**, Chicago, IL, August 20-24 (**1995**), (Pt. 2), ORGN-270.

Synthesis of 1,4-Dienes through the Regioselective Coupling of ((E)-1-Alkenyl)ethylzinc Reagents with Allylic Halides. The Effect of Catalyst and Solvent on the Outcome of This Reaction. **Agrios, Konstantinos A**.; Srebnik, Morris. *Journal of Organic Chemistry* (**1994**), 59(18), 5468-72.

Reduction of benzylic halides with diethylzinc using tetrakis(triphenylphosphine)palladium as catalyst. **Agrios, Konstantinos A**.; Srebnik, Morris. *Journal of Organic Chemistry* (**1993**), 58(24), 6908-10.

Trisubstituted alkenes from alkynes and aryl iodides by boron-to-zinc transmetalation and palladium(0) catalyzed cross coupling. **Agrios, Konstantinos A**.; Srebnik, Morris. *Journal of Organometallic Chemistry* (**1993**), 444(1-2), 15-19.