Ron Bihovsky, Ph.D.

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Organic Chemistry and Medicinal Chemistry Expert with Laboratory. Specialist in pharmaceutical patent cases requiring laboratory investigation. Testifying experience. Extensive drug discovery and lead optimization accomplishments in the pharmaceutical industry. Discovered novel, potent heterocyclic and peptide mimetic enzyme inhibitors and receptor antagonists. Good working knowledge of biochemistry and pharmacology. Good communication and interpersonal skills. Strong patent and publication record.

Expertise includes:

- Medicinal Chemistry
- Organic Synthesis
- Drug Design
- Lead Optimization
- Structure-Activity Relationships
- Molecular Modeling
- Intellectual Property
- Hatch-Waxman Patent Litigation

EXPERT WITNESS EXPERIENCE:

2001-Present KEY SYNTHESIS LLC, Wynnewood, PA. President and Founder.

- Organic chemistry and medicinal chemistry expert witness or fact witness in ~50 Hatch-Waxman pharmaceutical patent litigation cases. Have been deposed and testified in three high-profile cases with favorable outcomes. Consult for intellectual property firms and perform experiments to establish the validity of patent claims. Perform custom organic synthesis. Specialize in pharmaceutical patent cases requiring laboratory investigation. Patent and literature searching capability. Wrote the genus and examples for my 15 granted US patents, and worked closely with patent attorneys and patent agents to construct the claims.

- Steering Committee (2007 – present), Treasurer (2007-2008) and Chairman (2009-2012) of Chemical Consultants Network, a topical group of the American Chemical Society.

RESEARCH EXPERIENCE AND ACCOMPLISHMENTS:

2001-Present KEY SYNTHESIS LLC, Wynnewood, PA. President and Founder.
Custom Organic Synthesis, Medicinal Chemistry, Expert Witness, Consultant.

- Founded Key Synthesis LLC. Responsible for all aspects of the company: Located and equipped the laboratory, developed business strategy, attracted customers. Key Synthesis prepares compounds including enzyme inhibitors, receptor antagonists, enzyme substrates, and synthetic intermediates for the pharmaceutical and biotechnology industries. Pharmaceutical chemistry, biotechnology, and intellectual property consultant. .

1992-2001 CEPHALON, INC., West Chester, PA. Principal Project Chemist and Senior Scientist, Medicinal Chemistry. Treatment of Cerebral Ischemia, Cancer.

- PARP Inhibitors - Principal Project Chemist: Designed novel, potent, selective heterocyclic inhibitors of poly(ADP-ribose) polymerase. Optimized potency and properties of screening hit to provide lead molecule. Lead compounds crossed blood-brain barrier, reduced infarct volume in cerebral ischemia, and inhibited tumor growth in vivo.

- Calpain Inhibitors - Team Leader and Principal Project Chemist: Designed and synthesized novel peptide-mimetic and non-peptide cell-permeable calpain inhibitors with new enzyme-reactive groups for neurodegenerative therapy. Coordinated multidisciplinary team of 20 biochemists, pharmacologists, cell biologists and medicinal chemists. Supervised team of 7-10 medicinal chemists in calpain inhibitor program. Collaborated with directors of chemistry, biochemistry and pharmacology to evaluate hypotheses and plan new directions. Recruited the chemistry staff. Designed the laboratories.

1987-1992 **BERLEX LABORATORIES, Cedar Knolls, NJ.** Scientist, Medicinal Chemistry. Cardiovascular Research.

- Project Leader - Directed group of medicinal chemists in synthesis of enzyme inhibitors and peptide mimetics. Represented medicinal chemistry on core team of biochemists and pharmacologists.
- Designed and synthesized highly potent endothelin converting enzyme inhibitors.
- Investigated mechanism of epoxysuccinate class of cysteine protease inhibitors.
- Identified novel peptide-mimetic construct which was incorporated into angiotensin II.
- Performed molecular modeling on peptides, peptide mimetics, and enzyme inhibitors.

1980-1987 **STATE UNIVERSITY OF NEW YORK, Stony Brook, NY.** Assistant Professor of Chemistry. Synthetic Organic and Bio-organic Chemistry.

- Synthesized biologically significant natural products: biotin, oudenone, civet acid, C-glycoside antibiotics, lignans, tetrahydroisoquinolines.
- Generation and utilization of α-halo ethers and oxonium ions in synthesis.
- Regioselectivity of Pictet-Spengler reaction.
- Determined structures of crown gall tumor metabolites.
- Wrote computer software programs for literature reference retrieval and elemental analysis.
- Supervised research of 2 Postdoctoral Fellows, 9 Graduate Students, and 20 Undergraduates.
- Taught Graduate Synthetic Organic Chemistry and Undergraduate Organic Chemistry courses.

1978-1980 **UNIVERSITY OF WISCONSIN, Madison, WI.** NIH Postdoctoral Fellow. Organic Synthesis and Structure Elucidation.

- Synthesized natural products; introduced chirality via microbial transformation. Isolated and elucidated structures of compounds with smooth muscle-contracting activity (Leukotriene and G-acid) from animal tissue; determined mechanism of action.
- Performed smooth-muscle contractility assays.

1972-1978 **UNIVERSITY OF CALIFORNIA, Berkeley, CA.** Graduate student, Organic Chemistry. Organic Synthesis and Structure Elucidation.

- Synthesized anatoxin-a via intramolecular cyclization of iminium ion.
- Isolated and determined structure of saxitoxin, potent marine neurotoxin.
- Developed sensitive oxidative fluorescence assay for saxitoxin.
- Cultured microscopic marine algae, isolated toxins, performed bioassay, and determined structures.

Additional Academic Experience:

2001-2003 **Villanova University, Villanova, PA.** Adjunct Professor of Chemistry.

- Created and taught graduate Medicinal Chemistry course.

Education: Ph.D. 1977, Organic Chemistry, University of California, Berkeley (Advisor: H. Rapoport)
B.S. 1970, Chemistry, Magna cum laude, Honors in Chemistry,
State University of New York, Stony Brook

Languages: Reading and Speaking – English, German
Scientific Reading – English, German, French, Italian, Spanish

Computer Experience: Windows, UNIX, Fortran, Basic, ISIS Base, Beilstein, CAS-Scifinder, Reaxys, Excel, Word, Powerpoint, Firefox, Internet Explorer, etc.

Publications: (Note: Ron Bihovsky previously published under the name H. Bates)

1. S. Patil,* R. Bihovsky, S. Smith, W. Potter, V. Stella, Novel Prodrug PRX-P4-003, Selectively Activated by Gut Enzymes, May Reduce the Risk of Iatrogenic Addiction and Abuse." *Drug and Alcohol Dependence 186,* 159-166 (2018).

2. M. Tao,* C. H. Park, R. Bihovsky, G. J. Wells, J. Husten, M. A. Ator, R. L. Hudkins, "Synthesis and Structure-Activity Relationships of Novel Poly(ADP-ribose) Polymerase-1 Inhibitors." *Bioorg. Med. Chem. Lett. 16,* 938-942 (2006).

3. G. W. Wells,* R. Bihovsky, R. L. Hudkins, M. A. Ator, and J. Husten, "Synthesis and Structure-Activity Relationships of Novel Pyrrolocarbazole Lactam Analogs as Potent and Cell-Permeable Inhibitors of Poly(ADP-ribose)polymerase-1 (PARP-1)." *Bioorg. Med. Chem. Lett. 16,* 1151-1155 (2006).

4. R. Bihovsky, M. Tao, J. P. Mallamo, and G. Wells,* "1,2-Benzothiazine 1,1-Dioxide α-Ketoamide Analogues as Potent Calpain I Inhibitors." *Bioorg. Med. Chem. Lett. 14,* 1035-1038 (2004).

5. S. J. Miknyoczki, S. Jones-Bolin, S. Pritchard, K. Hunter, H. Zhao, W. Wan, M. Ator, R. Bihovsky, R. Hudkins, S. Chatterjee, A. Klein-Szanto, C. Dionne, and B. Ruggeri, "Chemopotentiation of temozolomide, irinotecan, and cisplatin activity by CEP-6800, a poly(ADP-ribose) polymerase inhibitor." *Mol. Cancer Ther. 2*, 371-382 (2003).

6. G. J. Wells, M. Tao, K. A. Josef, and R. Bihovsky,* "1,2-Benzothiazine 1,1-dioxide P_2 - P_3 Peptide Mimetic Aldehyde Calpain I Inhibitors." *J. Med. Chem. 44,* 3488-3503 (2001).

7. K. A. Josef,* F. W. Kauer, and R. Bihovsky, "Potent α-Ketohydroxamate Inhibitors of Recombinant Human Calpain I." *Bioorg. Med. Chem. Lett. 11,* 2615-2617 (2001).

8. S. Chatterjee,* D. Dunn, M. Tao, G. Wells, Z.-Q. Gu, R. Bihovsky, M. A. Ator, R. Siman, and J. P. Mallamo, "P_2-Achiral, P'-Extended α-Ketoamide Inhibitors of Calpain." *Bioorg. Med. Chem. Lett. 9*, 2371-2374 (1999).

9. G. J. Wells* and R. Bihovsky, "Calpain Inhibitors as Potential Treatment for Stroke and Other Neurodegenerative Diseases. Recent Trends and Developments." *Expert Opin. Ther. Patents 8,* 1707-1727 (1998).

10. M. Tao,* R. Bihovsky, G. J. Wells, and J. P. Mallamo, "Novel Peptidyl Phosphorous Derivatives as Inhibitors of Human Calpain I." *J. Med. Chem. 41*, 3912-3916 (1998).

11. S. Chatterjee,* Z.-Q. Gu, D. Dunn, M. Tao, K. Josef, R. Tripathy, R. Bihovsky, S. E. Senadhi, T. M. O'Kane, B. A. McKenna, S. Mallya, M. A. Ator, D. Bozyczko-Coyne, R. Siman, and J. P. Mallamo, "D-Amino Acid Containing High Affinity Inhibitors of Recombinant Human Calpain I." *J. Med. Chem. 41*, 2663-2666 (1998).

12. S. Chatterjee,* M. A. Ator, D. Bozyczko-Coyne, K. Josef, G. Wells, R. Tripathy, M. Iqbal, R. Bihovsky, S. Mallya, S. E. Senadhi, T. M. O'Kane, B. A. McKenna, R. Siman, and J. P. Mallamo, "Synthesis and Biological Activity of a Series of Potent Fluoromethyl Ketone Inhibitors of Recombinant Human Calpain I." *J. Med. Chem. 40,* 3820-3828 (1997).

13. R. Bihovsky* and M. A. Ator, "Calpains: Their Role in Pathology, and New Therapeutic Opportunities." Investigational Drugs Weekly Highlights, 22-25, May, 1997.

14. M. Iqbal, P. Messina, B. Freed, M. Das, S. Chatterjee, R. Tripathy, M. Tao, K. A. Josef, B. Dembofsky, D. Dunn, E. Griffith, R. Siman, S. E. Senadhi, W. Biazzo, D. Bozyczko-Coyne, S. L. Meyer, M. A. Ator, and R. Bihovsky*, "Subsite Requirements for Peptide Aldehyde Inhibitors of human Calpain I." *Bioorg. Med. Chem. Lett., 7,* 539-544 (1997).

15. M. Tao*, R. Bihovsky, and J. C. Kauer "Inhibition of Calpain by Peptidyl Heterocycles." *Bioorg. Med. Chem. Lett., 6,* 3009-3012 (1996).

16. R. Bihovsky*, and I. Pendrak, "Synthesis of Cystamidin A (Pyrrole-3-propanamide), a Reported Calpain Inhibitor." *Bioorg. Med. Chem. Lett., 6,* 1541-1542 (1996).

17. S. Chatterjee*, K. Josef, G. Wells, M. Iqbal, R. Bihovsky, J. P. Mallamo, M. Ator, D. Bozyczko-Coyne, S. Mallya, S. Senadhi, and R. Siman "Potent Fluoromethyl Ketone Inhibitors of Recombinant Human Calpain I." *Bioorg. Med. Chem. Lett., 6,* 1237-1240 (1996).

18. S. L. Meyer*, D. Bozyczko-Coyne, S. K. Mallya, C. M. Spais, R. Bihovsky, J. K. Kawooya, D. M. Lang, R. W. Scott, and R. Siman "Biologically Active Monomeric and Heterodimeric Recombinant Human Calpain I Produced Using the Baculovirus Expression System". *Biochem. J. 314,* 511-519 (1996).

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20. R. Bihovsky*, J. C. Powers, C.-M. Kam, R. Walton, and R. Loewi, "Further Evidence for the Importance of Free Carboxylate in Epoxysuccinate Inhibitors of Thiol Proteases," *J. Enzyme Inhib. 7,* 15-25 (1993).

21. R. Bihovsky*, "Reactions of α,ß-Epoxy Carbonyl Compounds with Methanethiolate: Regioselectivity and Rate," *J. Org. Chem., 57*, 1029-1031 (1992).

22. R. Bihovsky*, "Applications of Cyclic α-Haloethers and Unsaturated Oxonium Ions to Natural Product Synthesis: Carbon-Carbon Bond Formation," *Trends in Organic Chemistry, 3,* 1-6 (1992).

23. R. Mohan*, Y. L. Chou, R. Bihovsky, W. C. Lumma, Jr. P. Erhardt, and K. Shaw, "Synthesis and Biological Activity of Angiotensin II Analogs Containing a Val-His Replacement, ValΨ[CH($CONH_2$)NH]His," *J. Med. Chem., 34*, 2402-2410, (1991).

24. S. Rosenblum and R. Bihovsky*, "Synthesis of the Papulacandin *C*-Arylglucosylspiroketal Nucleus," *J. Amer. Chem. Soc., 112,* 2746-2748 (1990).

25. R. Bihovsky* and V. Bodepudi, "Synthesis of (+)-Biotin: Efficient Resolution of Key Intermediates," *Tetrahedron, 46,* 7667-7676, (1990).

26. R. Bihovsky*, M. U. Kumar, S. Ding, and A. Goyal, "Oxonium Ions in Organic Synthesis: Condensation of 2,3-Dihydrofuran and 3,4-Dihydro-2*H*-pyran with 1,3-Dicarbonyl Compounds," *J. Org. Chem., 54*, 4291-4293 (1989).

27. R. Bihovsky*, C. Selick, and I. Giusti, "Synthesis of *C*-Glucosides by Reactions of Glucosyl Halides with Oranocuprates," *J. Org. Chem., 53,* 4026-4031 (1988).

28. H. Bates*, K. Bagheri, and P. Vertino, "Effect of pH on the Regioselectivity of Pictet-Spengler Reactions of 3-Hydroxyphenethylamines with Formaldehyde and Acetaldehyde," *J. Org. Chem. 51*, 3061-3063 (1986).

29. H. Bates*, J. Farina, and M. Tong, "An Approach to Pseudomonic Acids from Acetylenic Precursors: Synthesis of 2-(Hydroxymethyl)-3-butyn-1-ol," *J. Org. Chem., 51*, 2637-2641 (1986).

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31. H. Bates, "Structure of Crown Gall Tumor Metabolites: Chemical Mediators of Parasitism," *Anal. New York Acad. Sci., 471,* 289-290 (1986).

32. H. Bates*, N. Condulis, and N. Stein, "Reduction of Cyclic Ureas with Lithium Aluminum Hydride," *J. Org. Chem., 51,* 2228-2229 (1986).

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34. H. Bates* and J. Farina, "Oxonium Ion Electrophiles: Synthesis of the Hypotensive Oudenone," *J. Org. Chem., 50,* 3843-3845 (1985).

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36. H. Bates*, L. Smilowitz, and S. Rosenblum, "A Practical Stereospecific Synthesis of the Biotin Precursor (3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-d]imidazol-2(3*H*)-one 1,1-Dioxide," *J. Chem. Soc., Chem. Commun.,* 353-354 (1985).

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38. H. Bates*, L. Smilowitz, and J. Lin, "Preparation of (3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-d]imidazol-2(3*H*)-one: A Key Biotin Intermediate," *J. Org. Chem., 50,* 899-901 (1985).

39. H. Bates* and J. Garelick, "Synthesis of Tetrahydro-4,6,7-Isoquinolinetriols and Tetrahydro-4,7,8-isoquinolinetriols," *J. Org. Chem., 49,* 4552-4557 (1984).

40. H. Bates*, A. Kaushal, P. Deng, and D. Sciaky, "Structure and Synthesis of Histopine, a Histidine Derivative Produced by Crown Gall Tumors," *Biochemistry, 23,* 3287-3290 (1984).

41. H. Bates* and P. Deng, "Synthesis of the Civet Constituent *cis*-(6-Methyltetrahydropyran-2-yl)acetic Acid," *J. Org. Chem., 48,* 4479-4481 (1983).

42. H. Bates, "Characterization of Tetrahydroisoquinolines Produced by Pictet-Spengler Reactions of Norepinephrine with Formaldehyde and Acetaldehyde," *J. Org. Chem., 48,* 1932-1934 (1983).

43. H. Bates, "Decarbonylation of Tetrahydrofuran-2-carboxylic Acids and Tetrahydropyran-2-carboxylic Acids in Concentrated Sulfuric Acid: Formation of Oxonium Ions," *J. Am. Chem. Soc., 104,* 2490-2493 (1982).

44. H. Bates*, "Pictet-Spengler Reactions of Epinephrine with Formaldehyde," *J. Org. Chem., 46,* 4931-4935 (1981).

45. H. Bates and C. Sih*, "Arachidonic Acid is Responsible for the Smooth Muscle-Contracting Activity of G-Acid," *Proc. Nat. Acad. Sci., 76,* 2712-2714 (1979).

46. H. Bates and H. Rapoport*, "Synthesis of Anatoxin a via Intramolecular Cyclization of Iminium Salts," *J. Am. Chem. Soc., 101,* 1259-1265 (1979).

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