

FENG HONG, Ph. D

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OBJECTIVE

To pursue an opportunity in drug discovery and development research applying my knowledge of medicinal chemistry and synthetic expertise.

SUMMARY OF QUALIFICATIONS

Creative, well-organized, a strong problem solver with proven track record and more than eight year experiences in drug discovery research. Having very good knowledge of drug discovery such as SAR, drug-like properties and pharmacokinetics. Excel in working both independently and as a team player. Highly dedicated, self-motivated, a continuous learner and good communicator.

PROFESSIONAL EXPERIENCE AND ACCOMPLISHMENTS

Ceptyr Inc, Consultant, Medicinal Chemistry (01/06-03/06)

Ceptyr Inc, Consultant, Medicinal Chemistry (03/05-07/05)

Ceptyr Inc, Scientist II, Medicinal Chemistry (04/04-11/04)

Design and synthesis of protein-tyrosine phosphatase 1B (PTP1b) inhibitors as potential therapeutic agents for treating diabetes.

- For the purpose of SAR study and with the hope of finding better PTP 1b inhibitors, a class of hetero-aromatic compounds with unique multiple functional groups were efficiently synthesized.
- Designed and synthesized a novel class of compounds as PTP 1b inhibitors.

CELL THERAPEUTICS, Senior Scientist, Discovery Chemistry (01/01-09/03)

Design and synthesis of LPAAT-beta inhibitors as novel anti-cancer agents. Guided by the insight of SAR, a novel class of compounds, *diamino-C,N-diaryl-pyrimidines*, were designed and synthesized. This class of the compounds (compared with existing compounds) had improved potency, enhanced anti-proliferation, better solubility and metabolic stability, stronger in-cell LPAAT-beta inhibition and promising *in vivo* activity.

- By applying the knowledge of SAR and drug-like properties, a series of *diamino-C,N-diaryl-pyrimidines* were designed and synthesized as LPAAT-beta inhibitors.
- Took and successfully completed the challenging synthesis of *diamino-C,N-diaryl-pyridines* (all three isomers) and *diamino-C,N-diaryl-benzenes* for SAR study and the protection of CTI's intellectual property.
- Design and synthesis of *diamino-C,N-diaryl-triazines*, *aryl-bezoxazoles* and *aryl-benzothiozoles* as LPAAT-beta inhibitors aimed at achieving improved drug-like properties.
- Finished the synthesis of a novel polyglutamate(PG)-conjugated anti-cancer entity.

UNIVERSITY OF WASHINGTON, Senior Research Fellow, Biomolecular Structure Center (11/98-1/01)

Design and synthesis of novel *dihydrofolate reductase* (DHFR) inhibitors and heat-labile enterotoxin and cholera toxin receptors.

- Design and synthesis of novel *dihydrofolate reductase* (DHFR) inhibitors as potential therapeutics for treating *tuberculosis* (TB).
- Devised a novel strategy for solution phase synthesis of water-soluble galactose derivatives library as heat-labile enterotoxin and cholera toxin receptors.
- Performed solid phase synthesis of galactose-containing peptides library as heat-labile enterotoxin and cholera toxin receptors.
- Synthesis of *thio-guanosine* for X-ray crystal structural elucidation of the binding pattern between human *topoisomerase-I* and *camptothecin*.

MAYO CLINIC, Research Fellow, Research Department (11/95-10/98)

Design and synthesis of non-peptidic *Neurotensin(8-13)*, ($\text{Arg}^8\text{Arg}^9\text{Pro}^{10}\text{Tyr}^{11}\text{Ile}^{12}\text{Leu}^{13}$), analogs and *acetylcholinesterase* inhibitors.

- Designed and synthesized *bis-guanidinoalkyl/bis-aminoalkyl substituted indoles, pyrroles* and *quinolines* as non-peptidic mimetics of neurotensin(8-13).
- Developed several convenient methods for the synthesis of alkylene-linked *bis-tacrines* and *bis-pyridiniumaldoximes* as acetylcholinesterase inhibitors.
- Synthesis of *neo-tryptophan* for incorporating into neurotensin analogs with improved potency and stability.

NEW YORK UNIVERSITY, Postdoctoral Fellow, Department of Chemistry (06/94-10/95)

- Discovered a novel method for the selective and high yield preparation of *alpha-and beta-glycosides* using glycosyl phosphorimidates as glycosyl donors.

SKILLS

Familiar with using various instruments including NMR (Bruker, Varian), LC-MS, HPLC, IR etc.

EDUCATION

Ph. D., The Chinese Academy of Sciences, Shanghai Institute of Organic Chemistry (07/90-06/93).

M. Sc., The Chinese Academy of Sciences, Shanghai Institute of Organic Chemistry (09/87-06/90).

B. Sc., Department of Chemistry, Sichuan University, Chengdu, China (09/83-07/87).

HONORS

LPAAT-beta team award (CTI, 2003); First Prize Scholarship (SIOC, 1993); Outstanding College Graduate (Sichuan University, 1987); Grand Prize Scholarship (Sichuan University, 1986); Grand Prize Scholarship (Sichuan University, 1985); First Prize Scholarship (Sichuan University, 1984).

PUBLICATIONS AND PATENTS

26 publications in peer-reviewed journals (please see attached sheet) and six pending patents.

LANGUAGES: Fluent reading, speaking, and writing in both *English* and *Chinese*.

REFERENCES: Available upon request.

SELECTED PUBLICATIONS

1. "Synthesis of Three Isomers of Diamino-C,N-Diaryl-Pyridines" **F. Hong**, D. Hollenback, J. Singer and P. Klein *Bioorg. & Med. Chem.*, **2005**, *15*, 4703
2. "Synthesis, SAR and Antitumor Properties of Diamino-C,N-Diaryl-Pyrimidine Positional Isomers: Inhibitors of Lysophosphatidic Acid Acyltransferase-beta" B. Gong, **F. Hong**, C. Kohm, J. Tulensky, R. Bhatt, P. DeVry, S. Jenkins and P. Klein *Bioorg. & Med. Chem.*, **2004**, *14*, 2303.
3. "Synthesis and SAR of 2-Aryl-Benzoxazoles, -Benzothiazoles and -Benzimidazoles as Inhibitors of Lysophosphatidic Acid Acyltransferase-beta" B. Gong, **F. Hong**, C. Kohm, L. Bonham and P. Klein *Bioorg. & Med. Chem. Lett.*, **2004**, *14*, 1455.
4. "Rational design of alkylene-linked bis-pyridiniumalldoximes as improved acetylcholinesterase reactivators" Y. P. Pang, T. M. Kollmeyer, **F. Hong**, J. C. Lee, P. I. Hammond, S. P. Haugabouk and S. Brimijoin *Chem. Biol.*, **2003**, *10*, 491.
5. "Synthesis and biological studies of novel neurotensin(8-13) mimetics" **F. Hong**, J. Zaidi, B. Cusack and E. Richelson *Bioorg. & Med. Chem.*, **2002**, *10*, 3849.
6. "A Convenient Approach for the Solution Phase Synthesis of Water-Soluble Galactose Derivatives Library" **F. Hong** and E. Fan, *Tetrahedron Lett.*, **2001**, *42*, 6073.
7. "Using a Galactose Library for Exploration of Novel, Hydrophobic Pocket in the Receptor Binding Site of the *E. coli* Heat-Labile Enterotoxin" W. E. Minke, **F. Hong**, C. L. M. Verlinde, W. G. J. Hol and E. Fan *J. Biol. Chem.*, **1999**, *274*, 33469.
8. "Synthesis of (S)-2-Amino-3-(1H-4-indol-4-yl)-propionic Acid, a Novel Tryptophan Analogue for Structural Modification of Bioactive Peptides" A. Fauq, **F. Hong**, Y. P. Pang and E. Richelson, *Tetrahedron Asymmetry*, **1998**, *9*, 4127.
9. "Peptidic and Non-peptidic Neurotensin Analogs" **F. Hong**, B. Cusack, A. Fauq and E. Richelson, *Current Medicinal Chemistry*, **1997**, *4*, 421.
10. "Design, Synthesis, and Pharmacological Evaluation of Active Pyrrole-based, Nonpeptidic Analogs of Neurotensin(8-13)" **F. Hong**, J. Zaidi, Y.-P. Pang, B. Cusack and E. Richelson, *J. Chem. Soc. Perkin Trans I*, **1997**, 2997.
11. "Glycosyl Donors with Phosphorimidate Leaving Groups for Either α - or β -Glycosidation" S. Pan, H. Li, **F. Hong**, B. Yu and K. Zhao, *Tetrahedron Lett.*, **1997**, *38*, 6139.
12. "Design, Synthesis, and Pharmacological Test of a Quinoline-based Nonpeptidic Analog of Neurotensin(8-13)" **F. Hong**, Y.-P. Pang, B. Cusack, and E. Richelson *J. Chem. Soc. Perkin Trans I*, **1997**, 2083.
13. "Synthesis of Alkylene Linked Bis-THA and Alkylene Linked Benzyl-THA as Highly Potent and Selective Inhibitors and Molecular Probes of Acetylcholinesterase" Y.-P. Pang, **F. Hong**, P. Quiram, T. Jelacic, and S. Brimijoin *J. Chem. Soc. Perkin Trans I*, **1997**, 171.
14. " α -Trifluoromethyl-Substituted β -Ethoxyl Zinc Reagent: Preparation and Palladium-Catalyzed Cross-Coupling as a Novel Route to Functionalized CF₃-Containing Compounds" G. Shi, X. Huang and **F. Hong** *J. Org. Chem.*, **1996**, *61*, 3200.
15. "A Novel and Convenient Method for the Synthesis of (Z)-3,3,3-Trifluoropropenyl Alkyl Ethers and CF₃-Substituted Acetals as Versatile CF₃-Containing Building Blocks" **F. Hong** and C. Hu *J. Chem. Soc. Chem. Commun.*, **1996**, 57.
16. "Zinc Promoted Barbier-type Reaction of 2-Bromo-3,3,3-trifluoropropene with Aldehydes" **F. Hong**, X. Tang and C. Hu *J. Chem. Soc. Chem. Commun.*, **1994**, 289.
17. "Palladium-catalyzed Carbocyclization Reaction of Organophosphorus Compounds---A Novel and Effective Method for the Synthesis of Cyclic Organophosphorus Compounds Including the Phosphorus Analogs of α -methylene lactones" **F. Hong**, J. Xia and Y. Xu *J. Chem. Soc. Perkin Trans. I*, **1994**, *13*, 1665.

Research Summary (Prior to 2004)

Feng Hong, Ph. D

1. Design and Synthesis of LPAAT-beta Inhibitors As Novel Anti-cancer Agents

Lysophosphatidic acid acyltransferases (LPAATs) catalyze the sn-2 acylation of 1-acyl-sn-glycerol-3-phosphate (lysophosphatidic acid, LPA) to produce 1, 2-diacyl-sn-glycerol-3-phosphate (phosphatidic acid, PA). The majority of LPAAT activity in mammalian cells has been attributed to two isoforms, LPAAT- α and LPAAT- β . Both isoforms are integral membrane proteins. While LPAAT- α is uniformly expressed in all human tissues tested, LPAAT- β displays distinct tissue distribution and is highly expressed in a wide variety of tumor cells and their surrounding stroma.

PA is an important lipid cofactor that has been implicated in cell signaling events including Raf translocation to membranes, mTOR activation, epidermal growth factor receptor (EGFR) internalization, and activation of PKC. RNAi knockdown of LPAAT- β blocked tumor cell proliferation. Accordingly, LPAAT- β may provide a novel target for cancer therapy.

- By applying the knowledge of SAR, drug-like properties, I designed and synthesized a new class of compounds, *diamino-C,N-diaryl-pyrimidines*, (**1**, **2** & **3**, Figure 1) as LPAAT-*beta* inhibitors with improved potency, enhanced anti-proliferation, stronger in-cell LPAAT-beta inhibition, promising *in vivo* activity, better solubility and metabolic stability. This class of compounds were subsequently become the focus in Cell Therapeutics' on going LPAAT-beta inhibitor-based drug discovery program.

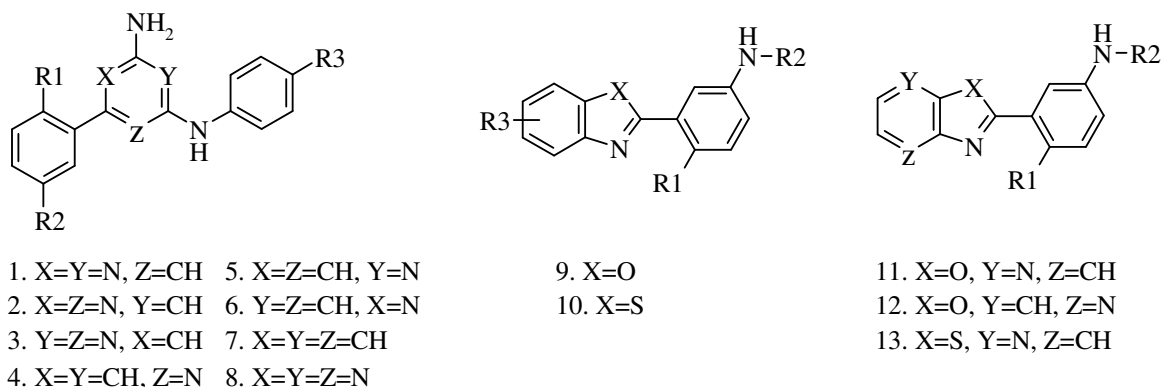


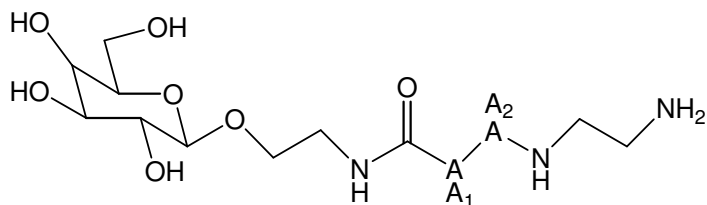
Figure 1

- After discovering *diamino-C,N-diaryl-pyrimidines*, I took and successfully completed the challenging synthesis of *diamino-C,N-diaryl-pyridines* (**4**, **5** & **6**, Figure 1) and *diamino-C,N-diaryl-benzenes* (**7**, Figure 1) for SAR study and the protection of Cell Therapeutics' intellectual property.
- In addition, I also designed and synthesized some *diamino-C,N-diaryl-triazines* (**8**, Figure 1), *aryl-bezoxazoles* and *aryl-benzothiozoles* (**9**, **10**, **11**, **12** & **13** Figure 1) as LPAAT-*beta* inhibitors aimed at achieving improved drug-like properties.

2. Design and Synthesis of Nonpeptidic Neurotensin (8-13) Analogs

being either volatile or soluble in organic solvent. Therefore, the excess reagents and by-products may be removed by evaporation and organic solvent extraction. The desired products could then be obtained in high purity after lyophilization in final step. A total of 72 compounds were obtained.

In addition to the solution phase library synthesis, solid phase synthesis was also employed to make galactose containing peptide library. The hydrophobic moieties giving the best results in solution phase library were adopted (in position AA₁, synthetic amino acids). Natural amino acids (in AA₂) were used to explore the sialic acid binding sites. Solid phase synthesis was applied to obtain the desired compounds. However, these compounds did not yield better binding as compared with compounds in the first generation library.



5. Glycosyl Phosphoramidates As Dual Purpose Glycosyl Donors: Selective Preparation of 1, 2-Cis- and 1, 2-Trans-linked Glycosides

Glycosylation is a key step for the chemical synthesis of sugar-containing compounds with important biological activities. A convenient glycosylation method was developed using glycosyl phosphoramidates as glycosyl donors to generate either α - or β - predominant glycosides in high yields.

6. Building Block Approach Applied to The Preparation of Trifluoromethyl-containing Compounds Including Fluorinated Natural Product Analogs

Trifluoromethyl moiety has been useful in drugs, pesticides, and other materials due to its unique lipophilic and electron withdrawing properties. Applying building block approach using 2-bromo-3,3,3-trifluoropropene as starting material, ten novel and convenient methods were developed for the preparation of various kinds of functionalized CF₃-containing compounds including fluorinated analogs of three natural products: *Siccayne*, *Naproxen* and *Pyrethroid*.

7. Preparation of Cyclic Organophosphorus Compounds

Some six-exo-trig and seven-endo-trig cyclic phosphinates and cyclic 6-endo-trig phosphine oxides were prepared using palladium-catalyzed P-C and C-C bonds formation reactions.

8. Synthesis of (2S)-3-[1-(tert-Butoxycarbonyl)-1H-4-indolyl]-2-[[9H-fluorenylmethoxy]-carbonyl]amino}-propanoic Acid, An Fmoc-Boc-Protected L-neo-Tryptophan

Synthetic amino acids are useful in modifying biologically important native peptides. Substitution of certain amino acids with synthetic ones often enhances affinity, stability, oral availability and other properties of the peptides. To obtain peptidic and non-peptidic NT (8-13) mimetics with improved affinity, oral activity and stability, an Fmoc-Boc-protected neo-L-tryptophan (**17**, Figure 3) was synthesized.

9. Synthesis of N²-Isobutyryl-2', 5'-dideoxy-5'-[4, 4'-(dimethoxytriphenylmethyl)thio]-guanosine 3'-O-(2-cyanoethyl N, N-diisopropylphosphoramidite)

DNA oligomers containing base(s) with 5'-oxygen substituted by sulfur have been utilized in DNA-protein interaction study. The title compound (**18**, Figure 3) was synthesized for X-ray crystal structural elucidation of the binding pattern between human *topoisomerase-I* and *camptothecin*.

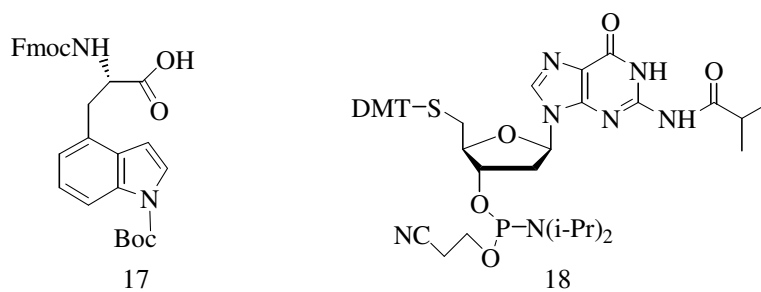


Figure 3