Faculty

School of Pharmacy
Medical Sciences Campus
University of Puerto Rico

Contact Information

School of Pharmacy
Office 314 and Annex Door 325
3rd Floor
School of Pharmacy Building
Medical Sciences Campus
San Juan, PR 00931

PO Box 365067
San Juan, PR 00936-5067

Phone: 787-758-2525
Exts.: 5412/5432
Fax: 787-767-2796

cornelis.vlaar@upr.edu

Rank/Discipline

Associate Professor
Medicinal Chemistry
Department of Pharmaceutical Sciences

Education & Specialty Certification

PhD, VRYE Universiteit-Amsterdam 1994; Post Doctoral Organic Chemistry, Louisiana State University, 1994-95; Post Doctoral Organic Chemistry, Louisiana State University, 1994-95; Post Doctoral Chemistry, Scripps Research Institute-California 1995-96.

Cornelis Vlaar, Ph.D.

Research Areas and Active Projects

The most current research has been focused in the area of medicinal chemistry related to the synthesis and pharmacological evaluation of novel compounds with potential anti-cancer and anti-malarial activity. Specifically, a short summary of the main projects is described below:

- **Synthesis of cyclic disulfides as potential inhibitors of enzymes with cysteine redox couples in their active site:** A variety of redox enzymes with key biological functions have a redox-active cysteine couple in their active site. In the redox process, the sulfhydryl groups of each of the cysteine residues is alternately oxidized to form a disulfide group and reduced to form two thiol groups. We have synthesized a variety of novel cyclic disulfide derivatives that specifically interact, presumably via interaction of the cyclic disulfide group of the inhibitor with the cysteine redox couple of the enzyme. Thus far, selective cyclic disulfide inhibitors of three different redox enzymes have been identified: ***a.*** Selective cyclic disulfide inhibitors of the oxidizing enzyme *Plasmodium falciparum* DHODH have been identified, which possibly could be developed into novel antimalarial drugs (in collaboration with Dr. Glenn McConkey, University of Leeds). ***b.*** Inhibitors of glutathione reductase have been identified. Molecular docking is applied to be able to identify, and subsequently synthesize selective inhibitors of *Plasmodium falciparum* glutathione reductase inhibitors as antimalarials, or inhibitors of human glutathione reductase as potentially useful compounds for drug-resistance reversal. ***c.*** Selective cyclic disulfide inhibitors of thioredoxin reductase have been identified, of which the most potent compounds identified thus far were also shown to inhibit *in vitro* growth of breast cancer cell lines at 1-2 micromolar concentrations (in collaboration with Dr. Marianela Pérez-Torres School of Pharmacy, UPR), thus providing an interesting avenue for the synthesis of novel more potent compounds as potentially novel anti-cancer drugs.

- **Synthesis of novel, dual inhibitors of Rac1 and cdc42:** Rac1 and

cdc42 are both important GTPase enzymes involved in signal transduction in cell metastases. We have an interest to synthesize and develop novel inhibitors for these GTPases in order to be able to prevent cell cancer growth (with Dr. Surangani Dharmawardhane, Department of Biochemistry, UPR, and Eliud Hernández, School of Pharmacy, UPR).

- **Plant extracts with pharmacological effects:** We are interested to study locally available flora for their potential pharmacological effects. Specifically, we have found an extract with significant anxiolytic effects (in collaboration with Dr. Nivia Pérez, Department of Anatomy and Neurobiology).
  Unfortunately, due to lack of financial support for maintenance of essential instrumentation, and insufficient availability of funds for the purchase of materials, these projects are currently inactive. Because the laboratory work is on hold, the focus of the research will be reoriented towards the area of clinical research.

Publications

- **Vlaar, C.P.** and Hernandez, L.; "Symposium Review: Drug Discovery and Development in Academia" *Puerto Rico Health Sciences Journal*, **2009**; Invited contribution to special "Biotechnology" issue in June. *Accepted for publication.*

- Espinosa, S, Solivan, M. and **Vlaar, C.P.**; "Synthesis and redox-modulation by amino-1,4-dihydro-benzo[d][1,2]dithiine derivatives". *Tetrahedron Lett.,* **2009**, *50*, 3023-3026.
- Hernández, E., Jessica M. Vélez. J.M. and Vlaar, C.P.; "Synthesis of 1,4-dihydro-benzo[*d*][1,3]-oxazin-2-ones from phthalides via an aminolysis-Hofmann rearrangement protocol". *Tetrahedron Lett.*, **2007**, *48,* 8972-8975.

- Rudolph, J. Sennhenn, P., **Vlaar, C.P.** and Sharpless, K.B.;. "Smaller Substituents on Nitrogen Facilitate the Osmium Catalyzed Asymmetric Aminohydroxylation Process". *Angew. Chem*., **1996**, *35*, 2810.

- **Vlaar, C.P.** and Hammer, R.P. "Enantioselective synthesis of *H*-Phosphinate Amino Acids for Incorporation into Phosphonopeptides", Proceedings of the Fourteenth American Peptide Symposium (*Peptides: Chemistry, Structure and Biology*, Kaumaya, P.T.P and Hodges, R.S. (Eds.), Escom Leiden, The Netherlands, **1995**, 57.

- Fernandez, M.d.F; Vlaar, C.P. and Hammer, R.P. "Synthesis of

Phosphonate and Phosphonothioate Esters and Amides from Hydrogen-Phosphinates by a Novel One-Pot Activation-Coupling-Oxidation Procedure, *J. Org. Chem*. **1995**, *60*, 7390.

- **Vlaar, C.P.** and Klumpp, G.W. "Oxidative coupling of 7,7-dilithionorbornane: 7,7'-dilithio-7,7'-dinorbornyl, a New vic-Dilithioalkane Prone to a New Mode of Decomposition, " *Tetrahedron Lett.,* **1993**, *34*, 4651.

- **Vlaar, C.P.** and Klumpp, G.W. "Reduction of Geminal Dihalocyclopropanes with Lithium 4,4'-Di-tert-butylbiphenyl: Cyclopropyl Derivatives of Dilithiomethane and 1,2-Dilithioethane; Inferences Regarding the Intermediate Carbenoids". *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 574.

- **Vlaar, C.P.** and Klumpp, G.W. "Preparation and Some properties of 7,7-Dilithionorbornane". *Tetrahedron Lett*. **1991**, *32*, 2951.

PATENT:

- Miranda, E., **Vlaar, C.P.** and Zhu J.-Y. "A method for preparing irbesartan and derivatives thereof", **2007**, US patent # 7,211,676.

Presentations

- Madera, E., Espinosa, S. and **Vlaar, C.P.**; *Poster presentation:* "Synthesis of Cyclic Disulfides as Inhibitors of Redox Enzymes". XXVI Foro Annual de Investigacion y Educacion, Abstract R-013, April 1-3, 2009, UPR Medical Sciences Campus. [third prize poster award]

- **Vlaar, C.P.**, Espinosa, S., Solivan, M. *Accepted abstract:* "Synthesis of Novel Benzodithiine Derivatives as Modulators of Redox Enzymes" *Poster Presentation:* Chemistry in Cancer Research: A Vital Partnership in Cancer Drug Discovery and Development, New Orleans February 8-11, 2009. [Faculty Scholar Award].

- De La Mota-Peynado, A., Hernandez, E., **Vlaar, C.**, Cubano, L and Dharmawardhane, S.; *Poster presentation:* The American Society for Cell Biology, 48th Annual Meeting, San Francisco, CA; December 17, 2008; "Small Molecule Rac Inhibitors as Anti-Breast Cancer Invasive Compounds", S; 2948 B666. [first prize poster award]

- Quiñonez-Laracuente, K; Grana A., Reyes D., **Vlaar C.** and Pérez-Acevedo N.L.; *Poster presentation:* Annual Puerto Rico

Neuroscience Meeting, Rio Piedras, PR, December 06, 2008; "Acute exposure of the ethanol extract of *Hibiscus rosa sinensis* exerts an anxiolytics-like effect in pubertal male rats".

- **Vlaar Cornelis P.**; *Oral presentation*: Drug Discovery, Development and Clinical Research in Academia Symposium, San Juan, PR, September 18-19, 2008. "Synthesis of novel anti-proliferative agents".

- Espinosa, S., McConkey, G., Heikkilä, T. and **Vlaar, C.P.**; *Poster presentation:* 233rd ACS National Meeting, American Chemical Society, Chicago, March 25-29, 2007; "The synthesis of cyclic disulfides as possible antimalarial agents", Abstract # MEDI 56

- Villalobos and **C.P. Vlaar**, "Synthesis of Aryloxyquinolines as Potential Inhibitors of *Plasmodium falciparum* Dihydroorotate Dehydrogenase". XXVI Foro Annual de Investigacion y Educacion, Abstract C-01, April 5-7, 2006, UPR Medical Sciences Campus.

- M. Solivan and **C.P. Vlaar**, "Synthesis of Pyrazole Derivatives as Potential Inhibitors of Plasmosum Falciparum Dihydroorotate Dehydrogenase. XXVI Foro Annual de Investigacion y Educacion, Abstract C-04, April 5-7, 2006, UPR Medical Sciences Campus.

- J. Vélez and **C.P. Vlaar**, "A More Environmentally Friendly Route to Benzoxazinones", XXV Foro Annual de Investigacion y Educacion, Abstract 52, March 16-18, 2005, UPR Medical Sciences Campus.