

## Curriculum Vitae

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2. **Mercer SL**, Hassan HE, Cunningham CW, Eddington ND, Coop A. Opioids and efflux transporters. Part 1: P-Glycoprotein substrate activity of *N*-substituted analogs of meperidine. *Bioorg. Med. Chem. Lett.* **2007**; 17(5): 1160-1162.
3. Koek W, **Mercer SL**, Coop A. Cataleptic effects of GHB, its precursor GBL, and GABA<sub>B</sub> agonists: differential antagonism by CGP35348. *Psychopharmacology* **2007**; 192(3): 407-414.
4. Cunningham CW, **Mercer SL**, Hassan HE, Traynor JR, Eddington ND, Coop A. Opioids and efflux transporters. Part 2: P-Glycoprotein substrate activity of 3- and 6-substituted morphine analogs. *J Med Chem.* **2008**; 51(7): 2316-2320.
5. **Mercer SL**, Shaikh J, Traynor JR, Matsumoto RR, Coop A. Nitrile analogs of meperidine as high affinity and selective sigma-1 receptor ligands. *Eur. J. Med. Chem.* **2008**; 43(6): 1304-1308.
6. **Mercer SL**, Cunningham CW, Eddington ND, Coop A. Opioids and efflux transporters. Part 3: P-glycoprotein substrate activity of 3-hydroxyl addition to meperidine analogs. *Bioorg. Med. Chem. Lett.* **2008**; 18(12): 3638-3640.

7. Hassan HE, **Mercer SL**, Cunningham CW, Coop A, Eddington ND. Evaluation of the P- glycoprotein affinity status of a series of novel and currently available morphine analogs: comparative study with meperidine analogs to identify opioids with minimal P-gp interactions. *Int. J. Pharmaceutics*. Accepted.
8. **Mercer SL** and Coop A. Opioid analgesics and P-glycoprotein efflux transporters: A potential systems-level contribution to analgesic tolerance. *Curr. Top. Med. Chem.* In Review.

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4. CW Cunningham, HE Hassan, **SL Mercer**, ND Eddington, A Coop. Diminished P-gp Substrate Activity of 3- and 6-Substituted Morphine Analogs. International Narcotics Research Conference. Minneapolis, MN. July, **2006**.
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7. TN Stephenson, **SL Mercer**, A Coop. UMB24 Analogs as Potential Methamphetamine Treatments. University of Maryland, Baltimore County (UMBC) Undergraduate Research and Creative Achievement Day. April **2008**.
8. **SL Mercer**, CW Cunningham, ND Eddington, A Coop. Synthesis and Characterization of Meperidine Analogs at the P-glycoprotein Efflux Transporter. National Medicinal Chemistry Symposium. Pittsburgh, PA. June **2008**.

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## Abstract

Title of Dissertation: Synthesis and Characterization of Meperidine Analogs at  
the P-Glycoprotein Efflux Transporter

Susan L. Mercer, Doctor of Philosophy, 2008

Dissertation Directed by: Andrew Coop, Ph.D.

Professor and Chair

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Chronic clinical pain remains poorly treated. The use of mu opioid analgesics is effective in treating chronic pain, but the rapid development of tolerance to the analgesic effects necessitates ever increasing doses to be administered. However, tolerance to the constipatory effects occurs at a slower rate, a condition we refer to as differential tolerance. There is a great need to develop opioids to which differential tolerance does not develop in order to reduce the severity of constipation. Our hypothesis is that the efflux transporter, P-glycoprotein (P-gp), contributes to the development of central tolerance by actively pumping morphine out of the CNS. P-gp is present at the BBB, morphine is a known P-gp substrate, and P-gp is up-regulated in morphine and oxycodone tolerant animals. As analgesia is primarily central and constipation is primarily peripheral, up-regulation of P-gp would be expected to lead to lower brain

concentrations of morphine compared to naïve animals; therefore, contributing to tolerance.

The design of opioids with decreased activity as P-gp substrates is anticipated to produce analgesics with reduced differential tolerance and therefore, diminished constipation. Meperidine, a moderately potent mu opioid receptor agonist causes less constipation than morphine clinically and has lower P-gp substrate activity than morphine. We have worked towards the optimization of meperidine by 1) employing opioid *N*-substituent SAR to increase its potency similar to morphine, 2) synthesizing isosteric replacements of the 4-ester to increase duration of action, and 3) introducing steric hinderance into the piperidine ring at the 2- and 6-positions to eliminate toxic metabolite formation. All analogs were analyzed for opioid receptor binding and P-gp substrate affinity. Results showed the optimal *N*-substituent was *N*-methyl; the ester was superior in the 4-position, and the introduction of a *m*-OH into the phenyl ring increased P-gp substrate affinity. Progress towards introducing steric hindrance is reported along with the strategy for their completion.

Additional work on the synthesis and development of 1) selective sigma-1 ligands for stimulant abuse and 2) a dual profile inhibitor of the S100 $\beta$  and p53 interaction involved in malignant melanoma is presented.

**Synthesis and Characterization of Meperidine Analogs at the P-  
Glycoprotein Efflux Transporter**

By

**Susan L. Mercer**

Dissertation submitted to the faculty of the Graduate School  
of the University of Maryland, Baltimore in partial fulfillment  
of the requirements for the degree of  
Doctor of Philosophy  
2008

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PREVIEW

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*This work is dedicated to my parents,*

*Edward and Peggy Gillenberger, III*

*My sister, Chris Gillenberger*

*And my husband, Greg Mercer*

*For their unconditional love, support, and encouragement*

PREVIEW

## Acknowledgments

I first and foremost would like to thank my advisor, Dr. Andrew Coop. His enduring support, guidance, and encouragement have fostered my development as a scientist. I am truly grateful that Andy has allowed me the freedom to explore additional scientific disciplines of personal interest so that I could truly become an interdisciplinary scientist and understand the many facets of drug design and discovery. Andy has been a great mentor, providing invaluable advice towards my career development, teaching me how to handle failure and how to celebrate success!

I thank my Ph.D. Committee Members, Dr. Sarah Michel, Dr. Edward Moreton, Dr. Amy Newman, and Dr. James Polli for their professional attention during my graduate training as well as their invaluable advice relating to career opportunities.

My time in graduate school has been made more enjoyable through working and interacting with my past and present labmates: Dr. Matthew Metcalf, Christopher Cunningham, Trudy Smith, Dr. Marilyn Matthews, and Lidiya Stavitskaya. Their support and constructive criticism of my work and future plans have encouraged me to work harder and excel as a scientist. I will truly miss our coffee breaks, group lunches, and trips to the pub to converse and celebrate the many milestones we have achieved individually and as a group.

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*As I reflect on my journey and development through graduate school and the family, friends, and mentors I have interacted with along the way, I realize that I am truly blessed.*

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