# Curriculum Vitae

**Name:** Susan L. Mercer

**Degree and Date to be Conferred:** Ph.D., 2008

**Collegiate Institutions Attended:**

**Seton Hill University,** Greensburg, PA 15601 **– 2000-2004**
**B.S.** awarded May 2004
Major: Chemistry
Minor: Forensic Science

**University of Maryland, Baltimore**, Baltimore, MD 21201 – **2004-2008**
**Ph.D.** awarded August 2008
Major: Pharmaceutical Sciences
Focus: Medicinal Chemistry

**Professional Publications:**

1. Koek W, Chen W, **Mercer SL**, Coop A, France CP. Discriminative stimulus effects of gamma-hydroxybutyrate (GHB): role of training dose. *J. Pharmacol. Exp. Ther.* **2006**; 317(1): 409-417.

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 $GABA_B$ 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.

**Selected Professional Abstracts:**

1. **SL Mercer**, CW Cunningham, HE Hassan, ND Eddington, A Coop. The Relative Activity of Meperidine Analogs as P-glycoprotein Substrates. University of Maryland, Baltimore, School of Pharmacy Annual Research Day. Baltimore, MD. May **2006**.

2. CW Cunningham, **SL Mercer**, HE Hassan, ND Eddington, A Coop. Effect of 3- and 6-Substitution on P-gp substrate activity of morphine analogs. University of Maryland, Baltimore, School of Pharmacy Annual Research Day. Baltimore, MD. May, **2006**.

3. **SL Mercer**, CW Cunningham, HE Hassan, ND Eddington, A Coop. The Relative Activity of Opioids as P-glycoprotein Substrates. Abstracts of the College on Problems of Drug Dependence. Scottsdale, AZ. June **2006**.

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**.

5. **SL Mercer**, CW Cunningham, HE Hassan, ND Eddington, A Coop. The Relative Activity of Meperidine Analogs as P-glycoprotein Substrates. International Narcotics Research Conference. Berlin, Germany. July **2007**.

6. **SL Mercer**, CW Cunningham, HE Hassan, ND Eddington, A Coop. The Relative Activity of Meperidine Analogs as P-glycoprotein Substrates. University of Maryland, Baltimore, School of Pharmacy Annual Research Day. Baltimore, MD. April **2008**.

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**.

9. CW Cunningham, **SL Mercer**, HE Hassan, JR Traynor, ND Eddington, A Coop. The Effect of 3- and 6-Substitution on the Substrate Activity of Morphine Analogs at P-glycoprotein. National Medicinal Chemistry Symposium. Pittsburgh, PA. June **2008**.

**Professional Positions Held:**

Assistant Professor
Lipscomb University College of Pharmacy
1 University Park Drive
Nashville, TN 37204
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Graduate Research Assistant
University of Maryland, School of Pharmacy
Department of Pharmaceutical Sciences
Baltimore, MD 21201
*Mentor: Andrew Coop, Ph.D.*
July 2004 – August 2008

Chemistry Lab Work-Study/ Lab Assistant.
Seton Hill University
Chemistry Department
Greensburg, PA 15601
*Mentor: Susan Yochum, S.C., Ph.D.*
August 2000 – May 2004

Summer Undergraduate Research Student
Howard Hughes Medical Institute Fellow
Case Western Reserve University, School of Medicine
Department of Pharmacology
Cleveland, OH 44106
*Mentor: John Mieyal, Ph.D.*
May 2002 – August 2002

Summer Internship Student
Bayer Corporation
OEM Coatings and Colorants Laboratory
Pittsburgh, PA 15210
*Mentor: Patricia Jacobs, Ph.D.*
May 2001 – August 2001

**Current Committee Memberships:**

American Association of Colleges of Pharmacy (AACP)

American Association of Pharmaceutical Scientists (AAPS)

American Chemical Society (ACS)

Tennessee Pharmacists Association (TPA)

**Selected Leadership Positions:**

American Chemical Society – Maryland Section (MD-ACS)
- Committee Chair – MD ACS Student Grants (2006-2008)
- Student Affiliate Liaison to the Executive Committee (2006-2008)
- Election Committee (2006)

Pharmaceutical Sciences Graduate Student Association
University of Maryland, Baltimore
- Graduate Student Association Representative (2006-2007)
- Vice-President (2005-2006)

American Association of Pharmaceutical Scientists – Student Chapter
University of Maryland, Baltimore
- Events Coordinator (2005-2006)

Seton Hill University SA-ACS Chemistry Club
- President (2002-2003 and 2003-2004)
- Secretary (2001-2002)



**Selected Community Activities:**

University of Maryland, Baltimore
- Pharmaceutical Sciences Graduate Program Steering Committee (2007-2008)
- Mentor for Exploration in Science Research Awareness Program (2007)
- Coordinator and Participant in Ronald McDonald House Dinner (2006)
- Tutor for "A Bridge to Academic Excellence" (2005)

**Selected Special Awards:**

National Medicinal Chemistry Symposium Travel Award (2008)
ACS Leadership Development Award (Younger Chemists Committee) (2008)
Pharmaceutical Sciences Competitive Departmental Predoctoral Fellowship and Merit Award (University of Maryland, School of Pharmacy) (2007-2008)

# 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

Department of Pharmaceutical Sciences

University of Maryland, School of Pharmacy

20 Penn Street, HSF II Room 543

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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 S100β 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

*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*

## 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.

I am thankful for having the opportunity to have worked and/or collaborated with Dr. Natalie Eddington, Dr. Alexander MacKerell, and Dr. Angela Wilks who have provided numerous learning opportunities and reality checks! Additionally, Drs. Kellie Hom and Julie Ray have provided excellent technical assistance in NMR and MS, respectively. Many thanks also go to the Drug Evaluation Committee for performing the

opioid pharmacological analyses and Dr. Rae Matsumoto (West Virginia University School of Pharmacy) for performing the sigma binding analysis.

I am especially blessed and grateful to have such a wonderful and supportive family. My parents always wanted their children to succeed and have made personal sacrifices so that my sister I could excel and pursue our dreams. Their support and encouragement have been steadfast, especially at times when I needed it most throughout the years. A warm-hearted "You can do it!" from Mom always gave me encouragement and talks with Dad kept me "level-headed"…or so he tried! My sister, Chris, has been a constant friend in my life, who always reminds me of simpler ways and how to have fun. This is as much their success as it is mine.

During my graduate career, I was fortunate to have married a truly wonderful, compassionate, and supportive husband, Greg, who has remained patient and loving throughout the years. I am extremely grateful that he has been present in my life to deal with the day-to-day hardships and always remind me of the big picture. His family has also been supportive and enjoys celebrating in our successes.

Lastly, this work has been made possible from multiple funding resources including: the National Institute on Drug Abuse, National Institutes of Health (DA-13583), the University of Maryland, School of Pharmacy Collaborative Research Grant, and a Pre-doctoral Fellowship from the University of Maryland, School of Pharmacy, Department of Pharmaceutical Sciences.

*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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