Synthesis of Selective Serotonin Reuptake Inhibitor Analogs
Sarah Candiello, Elyssa Kantor, Bernandie Jean, †R. B. Lettan II, ‡Jeffry D. Madura
Duquesne University and Chatham University
∗SCandiello@yahoo.com; †RLettan@chatham.edu; ‡Madura@duq.edu

Background
▶ Inhibition of the serotonin transporter, SERT, using a selective serotonin reuptake inhibitor (SSRI) has been proposed to increase serotonin concentration in the synapse and remediate depression behavior.¹ ²
▶ SSRIs containing halogen substituents have increased binding affinity to the halogen binding pocket (HBP).³
▶ Dr. Madura and colleagues developed a structure-based pharmacophore to analyze SERT selectivity and examine the binding pocket.⁴
▶ SM-11 had the highest binding affinity of the fifteen compounds studied.⁴

Fig. 1: The figure on the left shows the area of interest in SERT.⁴ The second figure (right) depicts the binding of SM-10, an SSRI candidate, to the S2 substrate pocket in SERT.⁴

Methods
Scheme 1: The procedure was implemented in the synthesis of the SM-11 analogs.⁵ ⁶ ⁷

Results
6-((4-(4-methoxybenzyl)piperazin-1-yl)methyl)-1, 3, 5-triazine-2, 4-diamine:
▶ Mass: 16 mg
▶ Mass after further high vac: 4 mg
▶ Percent yield: 6%
▶ Sample Purity: 99.0% ± 3%

6-((4-(3, 4- dichlorobenzyl)piperazin-1-yl)methyl)-1, 3, 5-triazine-2, 4-diamine:
▶ Mass: 21 mg
▶ Too many impurities to continue
▶ Percent yield: 14%
▶ Percent purity: 95% ± 8%

Conclusions
▶ Analogs have been synthesized, partially validating practicality of computational results.
▶ Future pharmacological study of the compounds is required to support or refute the second half of the hypothesis.
▶ Further evaluation of the synthetic process is required to increase the purity greater than 90% while still yielding 10 mg or greater.

Future Work
▶ Refine TLC profile for reversed phase chromatography
▶ Potentially implement only reverse phase column for purification
▶ Optimize synthetic procedure

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Hypothesis:
Synthesizing analogs of a computationally derived compound will validate the implementation of a SERT structure-based pharmacophore. Competitive binding assays will corroborate the dichloro analog as having the greatest inhibition of SERT based on the Topliss operational scheme.

Specific Aims:
▶ Synthesize, purify, and analyze SM-11 analogs
▶ Conduct pharmacological study of novel SSRIs via competitive binding assays

References