Analogs of the Dual Sigma Receptor Antagonist Dopamine Uptake Inhibitor, CM699, as Potential Pharmacotherapy for Stimulant Abuse

W. F. Alsharif 1, T. Kopajtic 2, M. Kandasamy 1, B. A. Avery 1, T. Hiranita 2, J. L. Katz 2, C. R. McCurdy 1
1 University of Mississippi, 2 National Institutes of Health (NIH)

Purpose
To develop analogs of the dual sigma receptor antagonist/dopamine uptake inhibitor, CM699 to improve druggability.

Methods
Synthesis of the CM699 derivatives was accomplished by treating 1-methyl-2-benzimidazolinone with the proper dibromoalkyl in the presence of K2CO3 in dimethylformamide (DMF) to give bromoalkyl derivatives that were then coupled with 3H-spiro[isobenzofuran-1,4'-piperidine] in the presence of K2CO3 in DMF to afford the respective analogs.

Results
CM699 produced dose-related and selective decreases in cocaine self-administration, likely due to dual actions at sigma receptors and dopamine transporter. The affinities of CM699 derivatives were synthesized and their affinities toward sigma receptors and dopamine transporter measured using radioligand binding assays. Among the tested compounds, WA378 had affinities of 5.70, 0.967, and 203 nM at σ1Rs, σ2Rs and DAT, respectively, while CM699 had affinities of 14.0, 2.30 and 318 nM at the same respective sites. These compounds were also screened for their stability in liver microsome assays. All analogs showed superior metabolic stability to CM699.

Conclusion
Based on the effects of CM699 on cocaine self-administration we synthesized a series of CM699 analogs, and some compounds (WA241, WA378, and WA429) retained comparable affinities toward DAT and sigma receptors. Further, in vivo testing of these compounds in rat cocaine self-administration assays and pharmacokinetic paradigms is underway. These results suggest that WA378 may be useful as a pharmacological tool in developing new treatments for cocaine abuse, and this novel approach could be a turning point in the development of medications to treat drug addiction.