ACS Medicinal Chemistry Letters

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Synthesis of Novel Analogs of Cabergoline: Improving Cardiovascular Safety by Removing 5-HT$_{2B}$ Receptor Agonism

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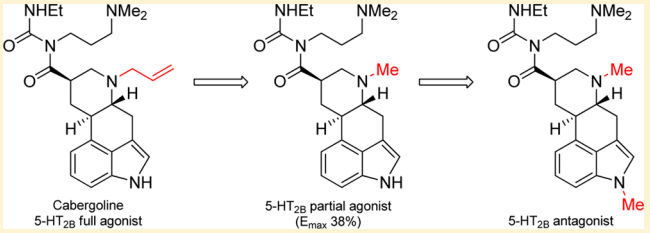
Supporting Information

ABSTRACT: The dopamine agonist cabergoline has been used to treat prolactinomas, Parkinson's disease, Cushing's disease, and sexual dysfunction. However, its clinical use was severely curtailed when it was found that patients taking cabergoline had an increased risk of developing cardiac-valve regurgitation. This potentially life-threatening condition has been associated with drugs, such as cabergoline, that are 5-HT$_{2B}$ receptor agonists. We prepared analogs of cabergoline and have identified several that have limited or no agonism at the 5-HT$_{2B}$ receptor.



KEYWORDS: *Cabergoline, 5-HT2B, ergot alkaloid, sexual dysfunction, dopamine agonist*

Cabergoline is a dopamine agonist that has been used clinically to treat prolactinomas,[1] Parkinson's disease,[2] and Cushing's disease[3] and has been reported to have positive effects in patients suffering from depression.[4,5] We became interested in this ergot alkaloid because of its potential to treat sexual dysfunction. Cabergoline has been used clinically to treat patients suffering from male sexual dysfunction, especially those with elevated prolactin levels.[6−8] An elevated level of prolactin is a known risk factor for sexual dysfunction, and cabergoline lowers the level of this hormone by binding to D_2 receptors in the pituitary gland and inhibiting prolactin synthesis.[9] Cabergoline is also an agonist at the D_4 and 5-HT$_{1A}$ receptors,[10−12] which are believed to play important roles in regulating sexual function in both males and females.[13−16]

Unfortunately, cabergoline is also a potent agonist of the 5-HT$_{2B}$ receptor (with a reported K_i of 1.2 nM)[11] and, like other 5-HT$_{2B}$ agonists such as nor-dexfenfluramine, is known to cause cardiac-valve regurgitation (CVR) in patients.[17,18] This potentially fatal complication has greatly limited the clinical use of cabergoline, especially in indications requiring high doses of the drug. A close analog of cabergoline without the propensity to cause CVR could potentially be of significant therapeutic use.

We believed that it should be possible to find safer analogs of cabergoline using design techniques developed to ameliorate 5-HT$_{2B}$ agonism in other therapeutics. Recent studies have shown that it is indeed possible to find safer analogs of drugs that have seen their clinical use limited due to a tendency to cause CVR. For instance, Arena Pharmaceuticals recently received FDA approval for the antiobesity agent lorcaserin, a 5-HT$_{2C}$ agonist which is structurally related to nor-fenfluramine but with greatly reduced 5-HT$_{2B}$ agonism (Figure 1).[19] Clinical studies showed that, unlike nor-dexfenfluramine, this drug does not appear to cause heart-valve damage in patients.[20]

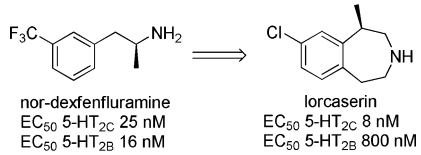


Figure 1. The antiobesity agents nor-dexfenfluramine and lorcaserin are both potent 5-HT$_{2C}$ agonists, but lorcaserin is a much weaker agonist at the 5-HT$_{2B}$ receptor and, unlike nor-dexfenfluramine, does not cause heart-valve damage clinically.

As the connection between 5-HT$_{2B}$ agonists and CVR had not yet been discovered when cabergoline was first developed, no apparent effort was made to minimize 5-HT$_{2B}$ agonism at that time.[21] There are two strategies for removing the potential to cause heart-valve damage from cabergoline analogs: either their activity at the 5-HT$_{2B}$ receptor can be reduced, or they can be converted from agonists into antagonists, which are not believed to cause CVR.[22,23] We set out to try both approaches.

We began our efforts to reduce 5-HT$_{2B}$ activity by replacing the dimethylamino side chain of cabergoline with a less basic morpholine group (compound **1** in Figure 2), as a similar change has previously been shown to help reduce activity at 5-

Received: November 7, 2012
Accepted: December 22, 2012
Published: January 14, 2013

   dx.doi.org/10.1021/ml3003814 | ACS Med. Chem. Lett. 2013, 4, 254−258

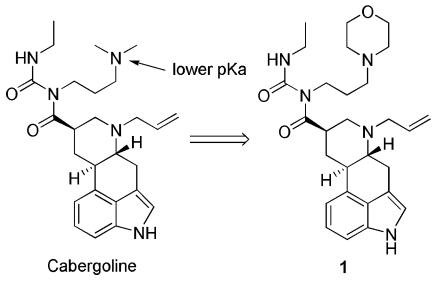
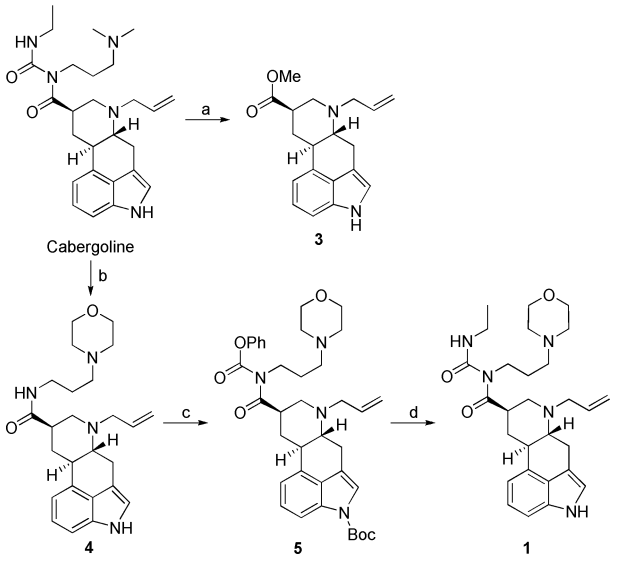


Figure 2. Hypothesis 1: Lowering the pK_a of the basic amine could decrease 5-HT_{2B} activity.

HT_2 receptors.[24] The synthesis of **1** proved to be more problematic than expected. Most published syntheses of cabergoline start from cabergolinic acid **2** or its methyl ester **3**, shown in Schemes 2 and 1, respectively.[21,25] However,

Scheme 1. Synthesis of Morpholino Analog of Cabergoline[a]

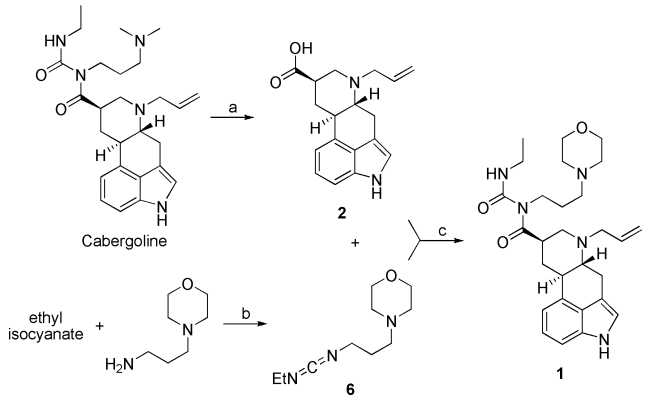


[a]Reagents and conditions: (a) Methanol, NEt_3. (b) 3-Morpholinopropylamine, 65 °C. (c) i. Boc_2O, DMAP, THF; ii. NaHMDS; iii. PhOCOCl. (d) i. $EtNH_2$·HCl, 2-propanol, 50 °C; ii. HCl, H_2O.

extensive attempts to acquire either of these compounds commercially were unsuccessful. Fortunately, it is possible to synthesize **3** directly from cabergoline using the method of Wang and co-workers, who found that simply stirring cabergoline in methanol and triethylamine leads to the near quantitative recovery of methyl ester **3** (Scheme 1).[26] Further investigation showed that it was possible to bypass methyl ester **3** and instead generate amide **4** directly in one step by heating cabergoline with 3-morpholinopropylamine (Scheme 1). An attempt to access the desired final *N*-acylurea **1** directly from amide **4** by heating **4** with ethyl isocyanate[21] led to an inseparable mixture of products. We instead used a multistep synthetic route through Boc-protected phenyl carbamate **5** to obtain **1** from **4** (Scheme 1).[25] As this multistep synthesis proved to be rather time-consuming, we later developed a faster route to **1**, by reacting cabergolinic acid (**2**) with the morpholino-analog of EDC, which was prepared from 3-morpholinopropylamine and ethyl isocyanate (Scheme 2).

Compound **1** and cabergoline were evaluated in a competitive binding assay at the 5-HT_{2B} receptor against ^{125}I-

Scheme 2. Alternate Synthesis of Morpholino Analog 1[a]



[a]Reagents and conditions: (a) i. NaOH, H_2O, methanol; ii. HCl. (b) i. CH_2Cl_2, 0 °C; ii. NEt_3, *p*-toluenesulfonyl chloride, reflux. (c) NEt_3, CH_2Cl_2.

radiolabeled 2,5-dimethoxy-4-iodoamphetamine, as well as in a 5-HT_{2B} functional assay using HTRF quantitation of IP1 accumulation. Unfortunately, the results of these assays showed that compound **1** (K_i 7.1 nM in the binding assay, EC_{50} 13 nM in the functional assay) was not significantly less active at the 5-HT_{2B} receptor than cabergoline (K_i 1.4 nM, EC_{50} 13 nM). As expected, both compounds were full agonists at the 5-HT_{2B} receptor (see Figure 4 for a listing of all in vitro data and the structures of compounds evaluated).

We then turned our efforts to finding analogs of cabergoline that were 5-HT_{2B} antagonists instead of agonists. We based our initial approach on the results of a study by Pertz and co-workers, who found that while the ergot alkaloid pergolide (which is 6-propyl substituted) is a functional agonist at 5-HT_{2B} receptors in porcine pulmonary arteries, 6-methylpergolide is a 5-HT_{2B} antagonist (Figure 3).[27] Both compounds are full

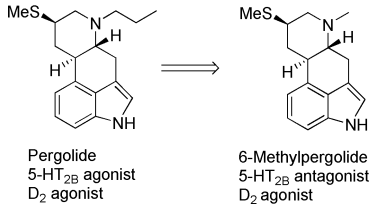


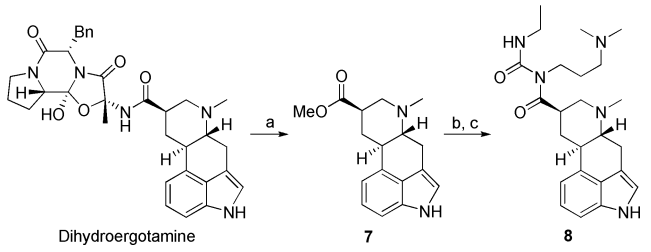
Figure 3. Replacing the 6-propyl group of pergolide with a methyl group switches the functionality at the 5-HT_{2B} receptor but not at the D_2 receptor.

agonists at the D_2 receptor. We therefore decided to prepare an analog of cabergoline in which the 6-allyl moiety is replaced by a methyl group. As we were also unable to obtain the 6-methyl analog of compound **3** commercially, we instead began our synthesis by hydrolyzing dihydroergotamine and converting the resulting acid into a methyl ester in order to ease purification (Scheme 3). From methyl ester **7**, hydrolysis followed by coupling to EDC[21] yielded the desired 6-methylated cabergoline analog **8**.

Compound **8** demonstrated similar potency as cabergoline and compound **1** in a 5-HT_{2B} radioactive binding assay (K_i 2.2 nM; see Figure 4). A 5-HT_{2B} functional assay showed that the change from a 6-allyl group to a 6-methyl group did significantly reduce 5-HT_{2B} agonism but was not enough to

dx.doi.org/10.1021/ml3003814 | ACS Med. Chem. Lett. 2013, 4, 254−258

Scheme 3. Synthesis of 6-Methylcabergoline[a]



[a]Reagents and conditions: (a) i. NaOH, H_2O, methanol; ii. H_2SO_4, methanol. (b) NaOH, H_2O, methanol. (c) NEt_3, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide HCl, CH_2Cl_2.

completely eliminate it, as compound **8** is a partial agonist, with an EC_{50} of 16 nM and a E_{max} of 38%.

After we finished our synthesis of 6-methylcabergoline, a new publication from the Pertz group reported that 6-methylcabergoline was a functional antagonist at endothelial 5-HT_{2B} receptors in porcine pulmonary arteries.[28] Because of the results obtained by Pertz, we retested compound **8** in a different human 5-HT_{2B} functional assay in which intracellular calcium mobilization was monitored using a FLIPR Tetra fluorescence imaging plate reader. Compound **8** was consistently a partial agonist at the human 5-HT_{2B} receptor in this assay, though the E_{max} varied from 5 to 49% (n = 5, average E_{max} of 23%). We believe that the most likely explanation for this discrepancy is interspecies differences in the 5-HT_{2B} receptor. While the pig and human 5-HT_{2B} receptors have been reported to possess a rather close 95% sequence homology,[29] there have been previous reports of compounds having significantly different activities at receptors having similar levels of interspecies homology, including at least two prior examples with ergot alkaloids at serotonin receptors.[30,31]

In an attempt to find compounds with less agonism at the human 5-HT_{2B} receptor, we next directed our attention to the preparation of **9** (shown in Scheme 4), the indole-methylated analog of **8**. We based this choice of target on the example of the ergot alkaloid methylergonovine, which is a partial agonist at the 5-HT_{2B} receptor, and its indole-methylated analog methysergide, which has significantly weaker activity at the receptor in both binding and functional assays.[17] Rather than begin the synthesis of **9** from dihydroergotamine, we chose instead to start from metergoline, which is significantly less expensive (1/25 the cost per mole) and already has a methyl group on the indole in place. Metergoline was first Cbz-deprotected with Pd/C and hydrogen in nearly quantitative yield to furnish **10** (Scheme 4). This primary amine was then converted into an aldehyde using a biomimetic procedure developed by Rapoport.[32] First the amine was condensed with 4-formyl-1-methylpyridinium benzenesulfonate to form a Schiff-base intermediate. The resulting imine was then deprotonated with DBU to form an anion (with resonance structures **11a** and **11b**). Next, protonation with oxalic acid occurred preferentially on the carbon closer to the highly electron-withdrawing quaternized pyridine nitrogen[32] and the resulting imine was then hydrolyzed to yield crude aldehyde **12**. This material was oxidized with Ag_2O[33] and converted into a methyl ester with H_2SO_4 and methanol in an overall 32% yield from metergoline. This procedure also yielded varying amounts of dimethyl acetal **15** (shown in Figure 4), which is presumably formed if not all aldehyde **12** is oxidized by Ag_2O prior to H_2SO_4 and methanol treatment. From methyl ester **13**, acetic acid catalyzed amide formation[21] furnished **14** in good yield. Finally, heating amide **14** with ethyl isocyanate gave the desired final product **9**.

Compounds **9** and **15** showed no agonism in the IP1 5-HT_{2B} functional assay (n = 1) or in the intracellular calcium mobilization 5-HT_{2B} functional assay (n = 5), while compound **14** showed minimal to no agonism in these assays (E_{max} < 12% in all cases). All three compounds were potent antagonists against serotonin at the 5-HT_{2B} receptor. These results demonstrated that it is indeed possible to synthesize a close analog of cabergoline in which 5-HT_{2B} agonism has been eliminated. Further investigation into **9** revealed that it is a full D_4 agonist, a potent but partial D_2 agonist (EC_{50} 1.4 nM, E_{max} 50%), and a weak 5-HT_{2A} antagonist (IC_{50} 11.5 μM).

When the screening results for all the products synthesized are taken as a whole, it is possible to make two tentative conclusions about the SAR of these novel cabergoline analogs. First, indole-methylation and replacement of the 6-allyl with 6-methyl both reduce the degree of functional agonism at the 5-HT_{2B} receptor. Second, while several of the compounds that were made had very different substitutions at the 8-position of the ergot alkaloid, the 5-HT_{2B} binding activity varied remarkably little among these compounds. These substitutions also had only a small effect on 5-HT_{2B} functional activity. These results suggest that any future efforts to reduce 5-HT_{2B} binding activity should focus elsewhere on the scaffold.

Our future plan is to test these compounds in animal models of SSRI-induced sexual dysfunction. Sexual dysfunction is a common side effect of SSRI administration and a leading cause of patient noncompliance.[34] Dopamine agonists, including cabergoline, have been reported to reverse SSRI-induced sexual

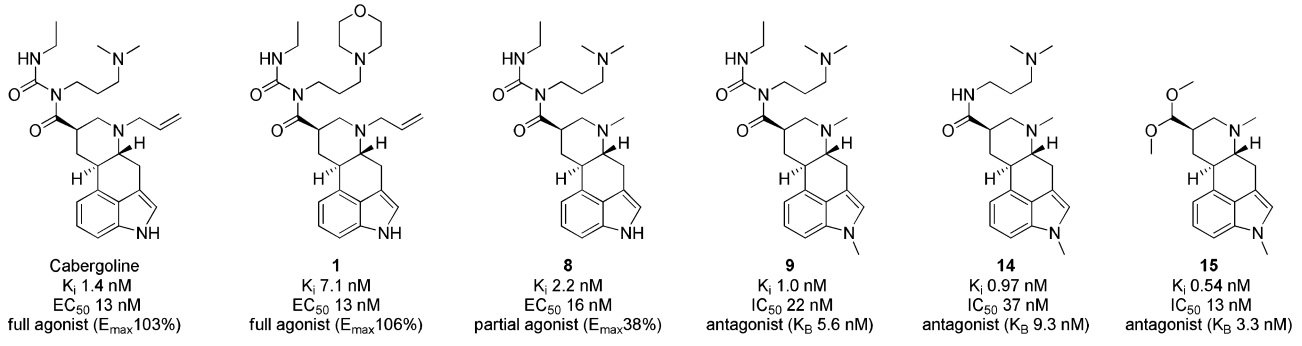


Figure 4. Structure and activity of cabergoline and analogs in 5-HT_{2B} binding (K_i) and functional assays (EC_{50} for agonists; IC_{50} and K_B for antagonists).

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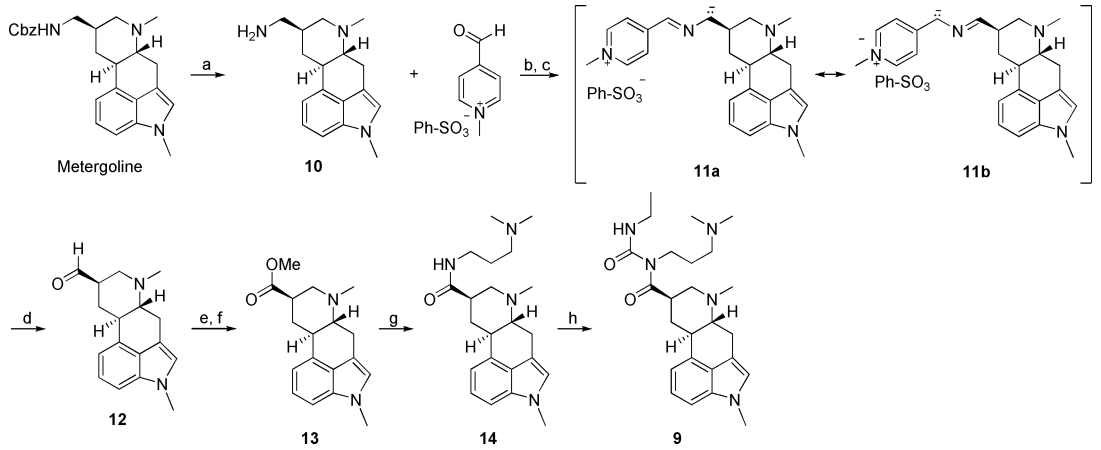
Scheme 4. Synthesis of 1,6-Dimethylcabergoline (9)[a]



[a]Reagents and conditions: (a) Pd/C, H_2, methanol. (b) CH_2Cl_2/DMF. (c) DBU. (d) Oxalic acid in H_2O, 0 °C to rt. (e) Ag_2O, THF, methanol, 10% NaOH in H_2O. (f) H_2SO_4, methanol. (g) 3-(Dimethylamino)-1-propylamine; acetic acid, 120 °C. (h) Ethyl isocyanate, toluene, 115 °C.

dysfunction in some patients,[35−37] and we intend to use our cabergoline analogs to help establish the pharmacological profile necessary for a drug to have therapeutic efficacy against this disorder in both men and women.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details of in vitro assays, synthetic procedures, and characterization of all final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding

This research was supported by a Grant Writers Workshop Seed Grant from the College of Pharmacy at the University of Minnesota.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

5-HT_{2B} binding and IP1 5-HT_{2B} functional assays were conducted by CEREP (France). All other functional data were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2008-00025-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, Ph.D., at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA.

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