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Design and Synthesis of (2-(5-Chloro-2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)cyclopropyl)methanamine as a Selective Serotonin 2C Agonist

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Abstract

A conformationally restricted analog of a selective cyclopropane-bearing serotonin 2C agonist was designed and synthesized. A 2,2-dimethyl-2,3-dihydrobenzofuran scaffold was investigated as a constrained variant of a biologically active isopropyl phenyl ether. Construction of the required dimethyl-2,3-dihydrobenzofuran intermediate began using a procedure that relied on a microwave-assisted alkylation reaction. The synthesis of the designed compound as its HCl salt is reported in a total of 12 steps and 17% overall yield. Biological evaluation revealed the constrained analog to be a selective serotonin 2C agonist with modest potency.

Keywords

Serotonin 2C; Agonist; Benzofuran; Cyclopropylmethanamine

Introduction

The serotonin 2C (5-HT_{2C}) receptor has been found to represent a promising drug target in the search for new treatments for a variety of disorders, including obesity and various mental diseases, such as schizophrenia, depression, and anxiety.[1,2,3] One of the many advantages of the 5-HT_{2C} receptor as a central nervous system (CNS) drug target stems from the fact that it is almost exclusively found in the CNS,[4,5] and thus compounds that selectively activate this receptor should have limited impact on peripheral tissues. However, the activation of two other closely related 5-HT_2 receptor subtypes, namely the 5-HT_{2A} and 5-HT_{2B}

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This article is dedicated to the lasting memory of Harry H. Wasserman, a connoisseur of heterocycles.

Supplementary data Supplementary data including synthetic procedures and details of the functional assay on 5-HT_2 receptors associated with this article can be found, in the online version.

receptors, has been reported to be associated with hallucinatory effects and life threatening cardiac valvulopathy, respectively.[6,7,8] Therefore, the identification of ligands possessing exquisite selectivity for the 5-HT_{2C} versus the 5-HT_{2A} and 5-HT_{2B} receptor subtypes is a key requirement for therapeutic advancement of 5-HT_{2C} agonists.[3] However, the achievement of such selectivity has proven to be challenging because of the high amino acid sequence homology shared by members of the 5-HT_2 subfamily.

During our studies aimed at designing selective 5-HT_{2C} agonists for possible use in CNS diseases, compound (+)-**1** was found to be a relatively potent and selective 5-HT_{2C} agonist (5-HT_{2C}: EC_{50} = 71 nM, E_{max} = 100% (of 5-HT); 5-HT_{2B}: EC_{50} = 682 nM, E_{max} = 57%; 5-HT_{2A}: EC_{50} = 7190 nM, E_{max} = 17%). Based on the sum total of the structure activity relationship (SAR) data we had assembled for this lead candidate, we considered the possibility of exploring the activity of a dimethyl-2,3-dihydrobenzofuran analog **2**, which represents a conformationally constrained version of the isopropyl phenyl ether **1**. Conformational restriction is, of course, a well-recognized medicinal chemistry strategy for enhancing the binding affinity as well as the target selectivity of small molecules.[9] This particular structure was also of interest as the heterocyclic benzofuran system is present in a number of drugs.[10,11] For example, the 2,2-dimethyl-2,3-dihydrobenzofuran scaffold is found in the drug zatosetron (**3**),[12] which is a 5-HT_3 antagonist that is able to induce antinausea effects without affecting gastrointestinal motility.[13] Zatosetron was also found to be an effective anxiolytic in both animal studies and human trials.[14] The similarity of compound **2** with **3**, and the fact that both compounds **1** and **3** act through serotonin receptors thus encouraged us to synthesize compound **2** for biological evaluation.

Result and discussion

The retro-synthetic analysis of compound (±)-**2** is outlined in Figure 2. Benzaldehyde **4** was selected as a key intermediate, as the cyclopropylmethylamine side chain of **2** can be installed from this aldehyde, using methods similar to those that we have reported previously.[15] This benzaldehyde could in turn be prepared from its corresponding benzoate **5**.[16, 17] As compound **5** has previously served as an intermediate in the synthesis of zatosetron (**3**), a synthetic approach to this intermediate starting from methyl 5-chloro-2-hydroxybenzoate (**6**) has been reported.[12,18] We note that no spectroscopic data have been reported previously for the intermediates prepared in the synthesis of **5**, and that this compound had previously been obtained in only very low yield.

The synthesis of intermediate **5** is depicted in Scheme 1. The alkylation of the starting material methyl 5-chloro-2-hydroxybenzoate (**6**) was accomplished using 3-chloro-2-methylprop-1-ene under reflux conditions in acetone, however, this led to only a 29% yield of product **7**.[12] In order to improve the yield of this alkylation reaction, 3-bromo-2-methylprop-1-ene was used as the alkylating reagent and the reaction was carried out under microwave conditions (80 °C). This method gave an improved yield (81%) of the product **7**, and the reaction time was reduced from overnight to 1.5 h. The Claisen rearrangement of intermediate **7** turned out to be sluggish. Heating of **7** in NMP at 200 °C for 8 h provided a 65% yield of product **8**, with a 24% recovery of the starting material. The subsequent cyclization of compound **8** was brought about by refluxing in 95% formic acid, which gave

an excellent yield of intermediate **5**. With the assistance of microwave conditions, intermediate **5** was prepared in 52% yield from **6** in three steps, compared to an overall 20% yield as reported previously.[12]

The ester **5** was then subjected to a sequence of lithium aluminum reduction and pyridinium dichromate (PDC) oxidation to give the benzaldehyde **4** in good yield. Wittig reaction of **4** with a commercially available reagent *N*-methoxy-*N*-methyl(triphenylphosphoranylidene)acetamide in dichloromethane at room temperature provided the Weinreb amide **10** in high yield. The double bond was obtained in solely the *E* form, without the observation of its *Z* isomer. The coupling constant of the two protons attached to the double bond is 16.0 Hz, which is consistent with the data reported for similar compounds.[15] Subsequent Corey-Chaykovsky cyclopropanation of the *E* double bond, with the sulfur ylide which was generated from trimethylsulfoxonium iodide upon treatment with sodium hydride, gave the cyclopropane **11** as its *trans* isomer. The Weinreb amide was then reduced with diisobutylaluminium hydride at low temperature to give aldehyde **12**, which was subsequently reduced to the corresponding alcohol **13** in excellent yield using sodium borohydride. The primary amine **2** was prepared from its alcohol **13** through a sequence of steps involving a Mitsunobu reaction employing phthalimide to afford the Gabriel imide **14**, followed by de-protection with hydrazine. Finally, the hydrochloride salt of **2** was prepared using HCl in diethyl ether. This sequence of transformations provided the target compound in 9 steps from **5**, with an overall yield of 33%. While preparative chiral HPLC methods were investigated for the separation of the optically pure enantiomers of the racemic Boc derivative of compound (±)-**2**, no separation was observed using either OD or OJ columns employing various solvent systems. Therefore, the biology activity of compound **2** was evaluated using its racemate.

Functional activity at the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors was determined using the calcium flux assay (for details of the assay, see supplementary data) for the racemic form of compound **2**. Moderate potency was observed for compound **2** at the 5-HT_{2C} receptors (EC_{50} = 600 nM) where it acts as a partial agonist (E_{max} = 66% of 5-HT). No activity was observed at either the 5-HT_{2A} or 5-HT_{2B} receptors. The absence of any 5-HT_{2B} activity for compound **2** is beneficial, as this would preclude any undesirable cardiac toxicity as noted above. The decreased activity of this compound at 5-HT_{2C} receptors may be a result of its increased steric size compared to compound **1**, as previous SAR studies have shown that increasing the length of the ether chain by one carbon led to a significant decrease in 5-HT_{2C} activity.[15]

Conclusion

In this letter we report the design and synthesis of a selective 5-HT_{2C} agonist compound **2** bearing a dimethyl-2,3-dihydrobenzofuran moiety. An improved synthesis of the dimethyl-2,3-dihydrobenzofuran scaffold is reported that makes use of a microwave-assisted alkylation reaction followed by a Claisen rearrangement and a formic acid promoted cyclization. The 2-phenylcyclopropylmethylamine side chain of the target compound was synthesized using a sequence of steps involving a Wittig reaction, Corey-Chaykovsky cyclopropanation, reduction of a Weinreb amide, and a Mitsunobu reaction followed by

deprotection of the thus formed Gabriel imide. The HCl salt of the target compound was prepared in 12 steps in an overall yield of 17%. The functional activity of this compound at the 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors was then determined using a calcium flux assay, and compound **2** was found to be a selective 5-HT_{2C} partial agonist of moderate potency. The design of other analogs of **2** would thus appear to be valuable to explore.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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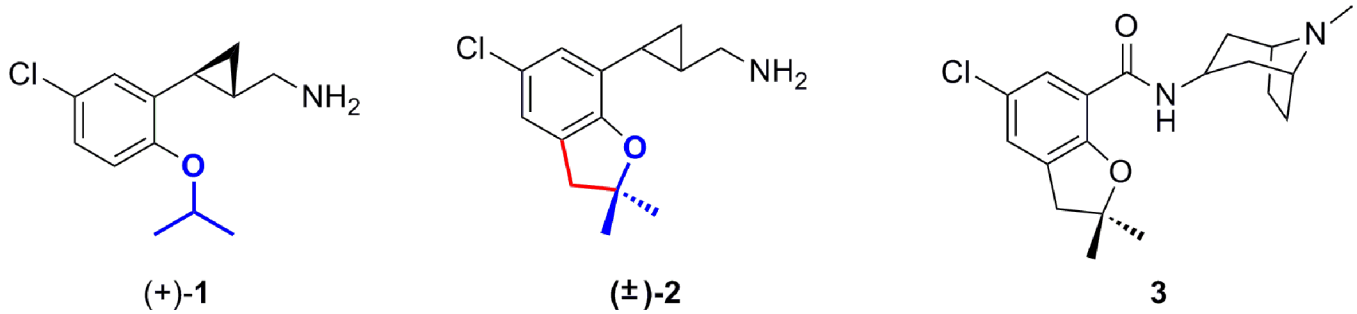


Figure 1.
Structures of compounds (+)-**1**, (±)-**2** and zatosetron (**3**).

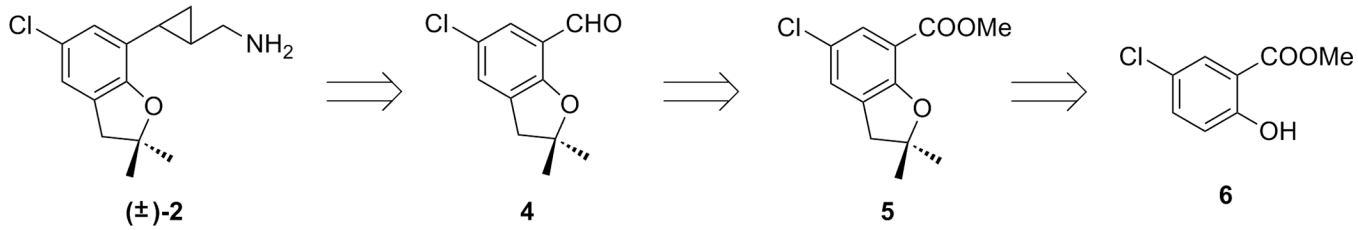
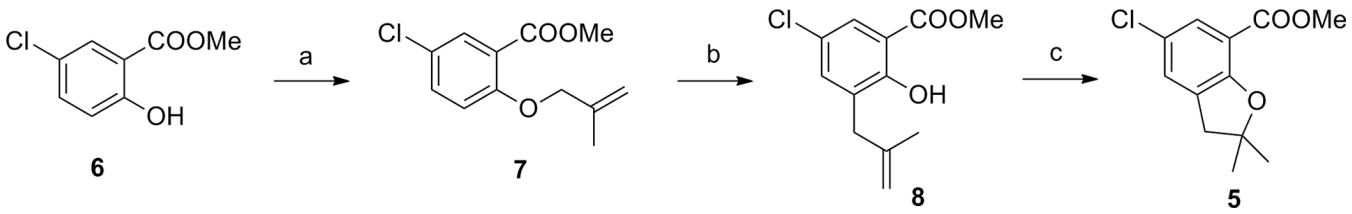
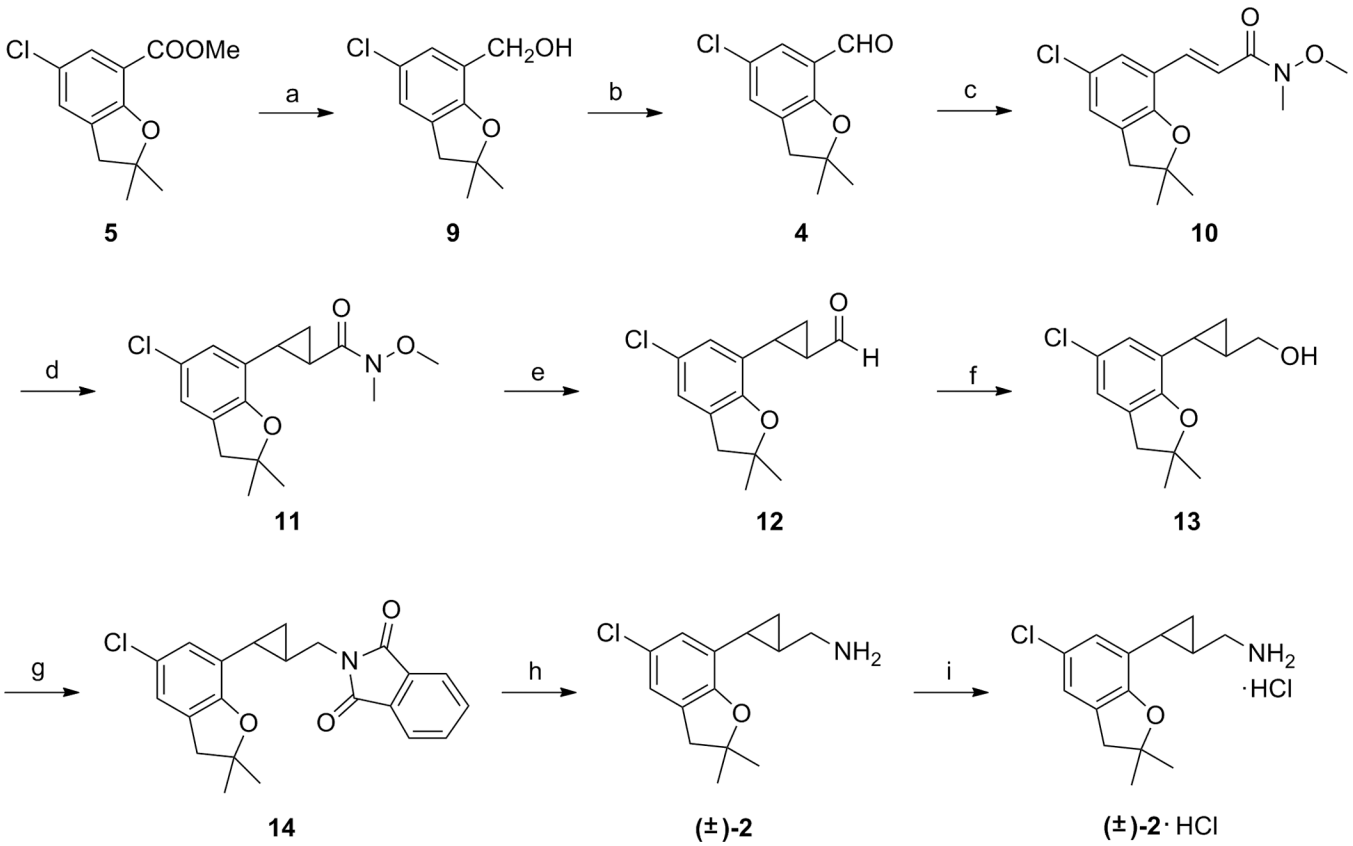


Figure 2.
Retrosynthetic approach of compound (±)-**2**.



Scheme 1.

Synthesis of benzaldehyde **5**. Reagents and conditions: (a) 3-bromo-2-methylprop-1-ene, K_2CO_3, DMF, microwave, 80 °C, 1.5h, 81%; (b) NMP, 200 °C, 8h, 65%; (c) formic acid (95%), reflux, 3h, 98%.



Scheme 2.

Synthesis of target compound **2**. (a) $LiAlH_4$, THF, 0 °C to rt, 2h, 92%; (b) PDC, CH_2Cl_2, rt, 2h, 65%; (c) $Ph_3P{=}CHC(O)N(OMe)Me$, CH_2Cl_2, rt, overnight, 92%; (d) $Me_3S^+(O)I^-$, NaH, DMSO, rt, overnight, 98%; (e) DIBAL-H, THF, −78 °C to rt, 95%; (f) $NaBH_4$, MeOH, 0 °C to rt, 96%; (g) Phthalimide, PPh_3, DEAD, THF, rt, 85%; (h) N_2H_4–H_2O, EtOH, reflux, 3h, 97%; (i) 2M HCl in Et_2O, rt, 2h, 81%.

Table 1

Pharmacological profiles of compound (+)-**1** and (±)-**2**.[a]

Compound	EC_{50}, nM (E_{max}; % 5-HT)		
	5-HT_{2C}	5-HT_{2B}	5-HT_{2A}
5-HT	0.20 (100%)	1.3 (100%)	2.1 (100%)
(+)-**1 (TFA salt)**	71 (100%)	682 (57%)	7190 (17%)
(±)-**2 (HCl salt)**	600 (66%)	NA	NA

[a] Functional data was acquired with recombinantly expressed human serotonin receptors in HEK-293 (5-HT_{2A} and 5-HT_{2B}) and PO1C (5-HT_{2C}) cell lines, fluorescence imaging plate reader (FLIPR) assay; “NA”, no activity at 10 μM.