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Synthesis and SAR of potent and selective tetrahydropyrazinoisoquinolinone 5-HT$_{2C}$ receptor agonists

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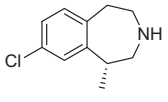
ABSTRACT

The 5-HT$_{2C}$ receptor has been implicated as a critical regulator of appetite. Small molecule activation of the 5-HT$_{2C}$ receptor has been shown to affect food intake and regulate body weight gain in rodent models and more recently in human clinical trials. Therefore, 5-HT$_{2C}$ is a well validated target for anti-obesity therapy. The synthesis and structure–activity relationships of a series of novel tetrahydropyrazinoisoquinolinone 5-HT$_{2C}$ receptor agonists are presented. Several members of this series were identified as potent 5-HT$_{2C}$ receptor agonists with high functional selectivity against the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors and reduced food intake in an acute rat feeding model upon oral dosing.

Serotonin (5-HT) plays an integral role in a broad range of cardiovascular, metabolic, and central nervous system pharmacological pathways.[1] Of the 14 known 5-HT receptor subtypes, the 5-HT$_{2C}$ receptor in particular has been implicated as a critical regulator of appetite. 5-HT$_{2C}$ knockout mice are obese, hyperphagic, hyperinsulinemic and are insensitive to the action of 5-HT$_{2C}$ agonists.[2] The 5-HT$_{2C}$ receptor is a well validated target for anti-obesity therapy since activation of this receptor has been shown to affect food intake and regulate body weight gain in rodent models[3] and human clinical trials.[4] A challenge of this target has been to identify a potent 5-HT$_{2C}$ receptor agonist with high selectivity versus other 5-HT receptors, primarily the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors, to avoid side effects such as hallucinogensis and valvular hypertrophy disease.[5] The latter finding led to the withdrawal of the non-selective 5-HT$_{2C}$ agonists fenfluramine and the (*S*)-enantiomer dexfenfluramine from the market.[6] Recently, the modestly selective 5-HT$_{2C}$ receptor agonist lorcaserin (**1**)[7] (Fig. 1) has received FDA approval for treatment of obesity on the basis of showing statistically significant weight loss in several phase 3 trials.[8]

Numerous 5-HT$_{2C}$ receptor agonists have been reported in the literature over the last two decades.[9] A common structural motif in 5-HT$_{2C}$ receptor agonist design has been the presence of a basic amine attached to a phenyl ring through a linkage (replicating the indole and primary amine pharmacophore of 5-HT), in which length and orientation of the groups ultimately contribute to the potency and selectivity of the compound. Our efforts were focused on identification of novel structural motifs with potent 5-HT$_{2C}$ agonism and high selectivity over both the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors (preferably with no functional activity at 5-HT$_{2B}$). Previously, we had reported that unsubstituted tetrahydropyrazinoisoindolone (**2**) was a moderately potent 5-HT$_{2C}$ agonist (5-HT$_{2C}$, K_i = 630 nM, EC$_{50}$ = 1500 nM) with ninefold functional selectivity for the 5-HT$_{2C}$ receptor over the 5-HT$_{2B}$ receptor, and 14-fold over the 5-HT$_{2A}$ receptor; moreover, substitution on the aryl ring,



Lorcaserin (**1**)
5-HT$_{2C}$ EC$_{50}$ = 9 nM (IA = 1)
5-HT$_{2B}$ EC$_{50}$ = 943 nM (IA = 1)
5-HT$_{2A}$ EC$_{50}$ = 168 nM (0.75)

Figure 1. FDA-approved selective 5-HT$_{2C}$ agonist as anti-obesity medication.

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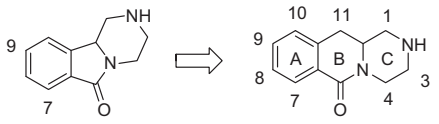


Figure 2. Known and proposed 5-HT_{2C} agonists.

especially at the 7-position, enhanced 5-HT_{2C} potency as much as 20-fold[10] (Fig. 2). We envisioned that the conceptual expansion of the central five-membered ring of the tetrahydropyrazinoisoindolone core (**2**) to generate the closely related tetrahydropyrazinoisoquinolinone core (**3**) could possibly lead to more potent 5-HT_{2C} agonists with better selectivity against the 5-HT_{2A} and 5-HT_{2B} receptors. Our confidence in this hypothesis was bolstered by overlaying low energy conformations of the (*R*)-tetrahydropyrazinoisoquinolinone core (**22**) onto the 7-trifluoromethyl tetrahydropyrazinoisoindolone analog (**4**), the lead compound in the series[10] (Fig. 3). This analysis predicted that (1) the *R* enantiomers of the tetrahydropyrazinoisoquinolinones would be required for 5-HT_{2C} activity as was the case for the tetrahydropyrazinoisoindolone series and (2) only a small (or no) 7-substutution might be required for 5-HT_{2C} potency and selectivity against the 5-HT_{2A} and 5-HT_{2B} receptors. Our strategy involved sequential evaluation of the effect of substitutions at each position on the tetrahydropyrazinoisoquinolinone core to enhance potency and selectivity prior to identification of potent and selective agonists produced by optimal additive effects from di-substitution at different positions.

Herein we report the synthesis and structure–activity relationship of a series of 5-HT_{2C} receptor agonists by the optimization of the tetrahydropyrazinoisoquinolinone core. All the tetrahydropyrazinoisoquinolinone analogs were synthesized by two general synthetic routes. The first route, based on the work of Singh,[11] was developed for the synthesis of the analogs at C4 (Scheme 1) beginning with readily available D-phenylalanine methyl esters **5**, which were acylated with triphosgene, followed by treatment with alumnium trichloride, to give (*R*)-methyl tetrahydroisoquinolinone carboxylic acid esters **6**. Treatment with NaH concurrently promoted racemization and alkylation with substituted ethyl bromoacetates to generate racemic diesters **7**. Lithium borohydride reduction of diesters **7** and subsequent reaction with thionyl chloride afforded dichlorides **8**. Treatment with benzyl amine in the presence of potassium carbonate yielded the corresponding benzyl

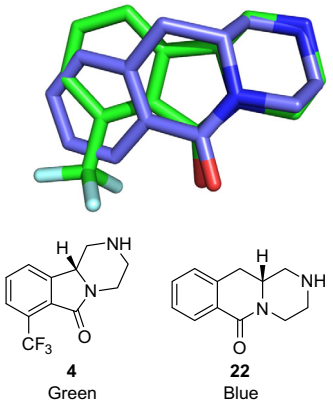
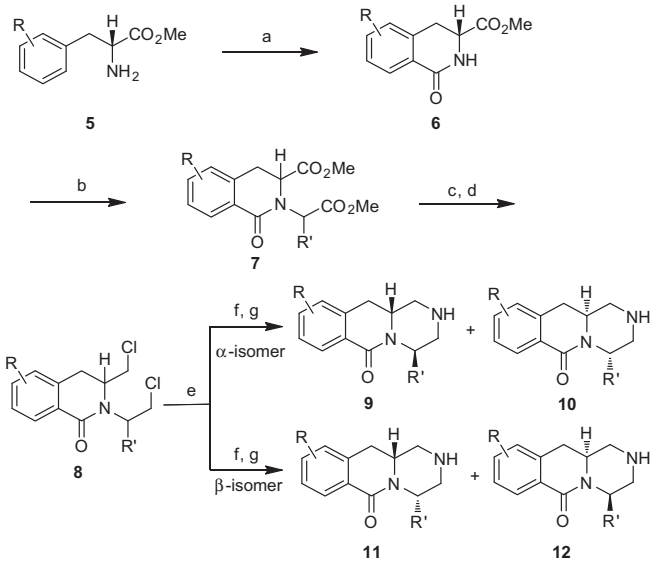


Figure 3. Low energy conformation overlay of known and proposed 5-HT_{2C} agonists.



Scheme 1. Reagents and conditions: (a) triphosgene, $ClCH_2CH_2Cl$, then $AlCl_3$, 0 °C to reflux (40–50%); (b) NaH, R′BrCHCO$_2$Me, DMF, rt to 40 °C (61–75%); (c) $LiBH_4$, THF, reflux (89–96%); (d) $SOCl_2$, CH_3Cl (69–78%); (e) $BnNH_2$, K_2CO_3, diglyme (52–67%, α:β = 2:1); (f) H_2, 10% Pd/C, EtOAc, OD Chiral HPLC separation, OD column, 30% MeOH/EtOH/70% heptane (39–44%).

tetrahydropyrazinoisoquinolinones with α:β = 2:1 ratio after separation, which were respectively, subjected to debenzylation under standard conditions (H_2, Pd/C) and chiral separation to provide compounds **9**–**12** in good yield. Absolute configuration was determined by X-ray crystallography of the (1*S*)-(+)-10-camphor-sulfonamide of the final product.

Having established the absolute configuration of the active enantiomer to be *R*, we developed an enantioselective synthesis for the analogs at other positions, which began with commercially available D-Boc-phenylalanines **13** (Scheme 2). Coupling of acids **13** with optically pure *N*-benzyl glycine or alanine ethyl ester yielded amides **14**. Boc-deprotection and subsequent thermal cyclization gave diones **15**. Carbamates **16** were formed by lithium aluminium hydride reduction of diones **15** followed by treatment with methyl chloroformate. P_2O_5/$POCl_3$ catalyzed cyclization and debenzylation under standard conditions (H_2, Pd/C or CH_3CHClO-COCl/MeOH) provided the final products **17** in good yield. Where the D-Boc-phenylalanines were not commercially available, as was the case with some alkyl and cyano analogs in Table 2, the synthesis was carried out from intermediate bromides **18**. Alkylation of bromides **18** under Negishi, Suzuki, or Stille conditions or copper catalyzed cyanidation with CuCN, followed by debenzylation under standard conditions (H_2, Pd/C or $CH_3CHClOCOCl$/MeOH), afforded the corresponding alkyl and cyano analogs **17**, respectively. Analogue **21** was synthesized from intermediate methyl ether **19** generated using the procedure as described above. O-demethylation of ether **19** with boron tribromide, followed by propargylation of the resulting phenol, formed ether **20**, which was cyclized to give the final product **21** after debenzylation under acidic conditions. *N*-Methyl analog **23** was generated under reductive amination conditions from analog **22** (produced by either of the above two routes).

The primary goal of our research was to design a 5-HT_{2C} agonist with a K_i and EC_{50} of less than 25 nM which exhibits greater than 100-fold functional selectivity over the 5-HT_{2B} and 5-HT_{2A} receptors. The preliminary binding and functional assay results for the unsubstituted tetrahydropyrazinoisoquinolinone core were very encouraging. As predicted by modeling, the 5-HT_{2C} binding affinity (24 nM K_i) of the *R*-enantiomer tetrahydropyrazinoisoquinolinone