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Tricyclic dihydroquinazolinones as novel 5-HT$_{2C}$ selective and orally efficacious anti-obesity agents

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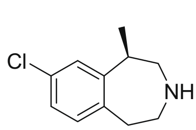
ABSTRACT

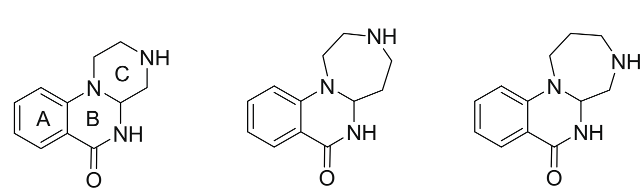
Agonists of the 5-HT$_{2C}$ receptor have been shown to suppress appetite and reduce body weight in animal models as well as in humans. However, agonism of the related 5-HT$_{2B}$ receptor has been associated with valvular heart disease. Synthesis and biological evaluation of a series of novel and highly selective dihydroquinazolinone-derived 5-HT$_{2C}$ agonists with no detectable agonism of the 5-HT$_{2B}$ receptor is described. Among these, compounds (+)-**2a** and (+)-**3c** were identified as potent and highly selective agonists which exhibited weight loss in a rat model upon oral dosing.

The biological effects of the neurotransmitter serotonin (5-HT) are mediated through at least 14 distinctly different receptor subtypes. The serotonin subtype 5-HT$_{2C}$ receptor has been the focus of considerable attention within the pharmaceutical community because of its implication in a variety of conditions including obesity, diabetes and schizophrenia.[1,2] Pre-clinical studies show that 5-HT$_{2C}$ agonists reduce food intake and body weight in rats[3] and the feeding effects can be reversed with selective 5-HT$_{2C}$ antagonists.[4] 5-HT$_{2C}$ receptor knockout mice are obese, hyperphagic, hyperinsulinemic and insensitive to the 5-HT$_{2C}$ agonist fenfluramine.[5,6] Furthermore, clinical studies have shown that 5-HT$_{2C}$ agonism can suppress appetite and reduce body weight in humans.[7] Thus, 5-HT$_{2C}$ is a well validated target for obesity.

While 5-HT$_{2C}$ agonists have the potential to treat obesity, it has been hypothesized that agonism of the closely related 5-HT$_{2B}$ receptor may be associated with heart valvulopathy in humans.[8,9] In addition, agonists of the related 5-HT$_{2A}$ receptor can also have unfavorable characteristics as they can be vasoconstrictive as well as lead to undesirable CNS effects.[10] Thus, the design and identification of a selective 5-HT$_{2C}$ agonist is a necessary requisite for a program targeting this receptor. There have been several reports in the recent literature describing 5-HT$_{2C}$ agonists with significant selectivity over 5-HT$_{2A}$ and 5-HT$_{2B}$ including lorcaserin (**1**), a compound currently in clinical development for the treatment of obesity.[11] In the course of our efforts to identify a potential development candidate, we set a criterion of no-to-minimal activation



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 (IA = 0.75)
(data reported in ref. 11a)



2 **3** **4**

of the 5-HT$_{2B}$ receptor. This paper outlines the synthesis and biological evaluation of a series of novel and selective 5-HT$_{2C}$ receptor agonists, represented by structures **2**–**4**, based on the known 5-HT$_{2C}$ agonist mCPP.[7] A summary of the SARs leading to the

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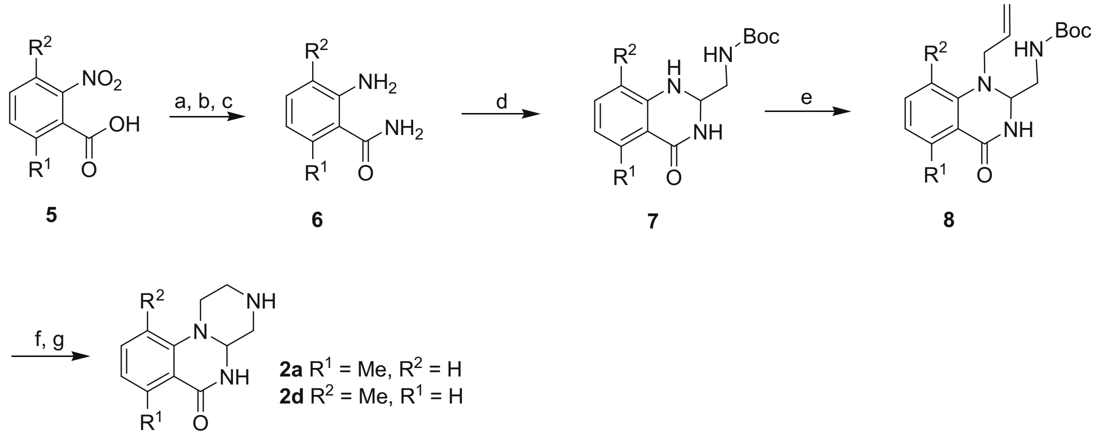
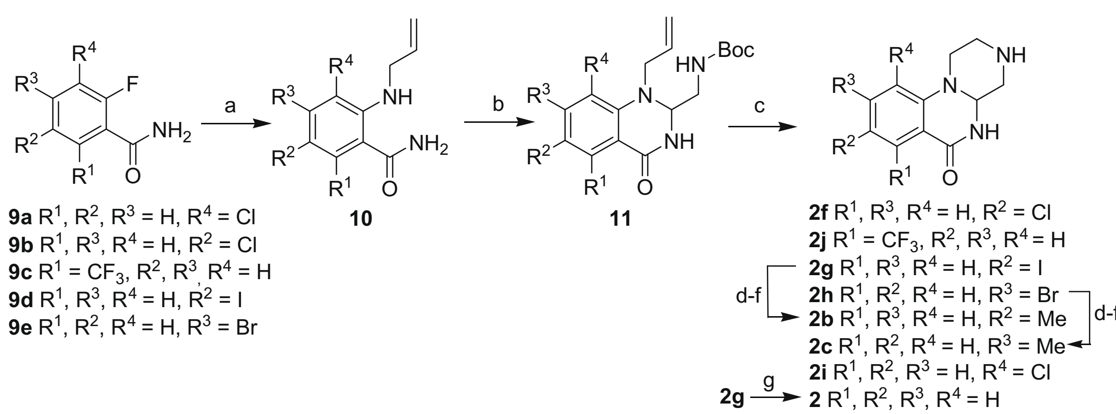
identification of compounds with potent in vitro 5-HT_{2C} agonist activity and no detectable activation of the 5-HT_{2B} and 5-HT_{2A} receptors is described. Finally, the in vivo evaluation of select compounds in rat feeding and weight loss models is described.

Syntheses of the various compounds in the 6,6,6-tricyclic series (**2**) were carried out as outlined in Schemes 1–3. Readily available 2-nitrobenzoic acids **5** were converted to the corresponding 2-aminobenzamides **6** via their respective acid chlorides and 2-nitrobenzamides. Treatment of the aminobenzamides **6** with *N*-boc-aminoacetaldehyde in refluxing toluene (Dean–Stark trap) in the presence of catalytic *p*-toluenesulfonic acid afforded **7**.[12] Allylation of **7** at the 'aniline' nitrogen using allyl bromide and sodium or potassium carbonate in *N,N*-dimethylformamide (DMF) or *N,N*-dimethylacetamide (DMA) followed by treatment of the resulting olefins **8** with sodium periodate in THF–water in the presence of catalytic osmium tetroxide afforded the intermediate aldehydes. Finally, treatment of the aldehydes with excess trifluoroacetic acid and triethylsilane in dichloromethane provided target compounds **2a** and **2d** in 40–60% yield from **8**. In all cases the racemic compounds thus obtained were isolated as free amines and resolved by chiral chromatography affording enantiomerically pure analogs. While both enantiomers were tested for biological activity, Table 1 displays data for the enantiomers with more potent 5-HT_{2c} agonist activity.[13]

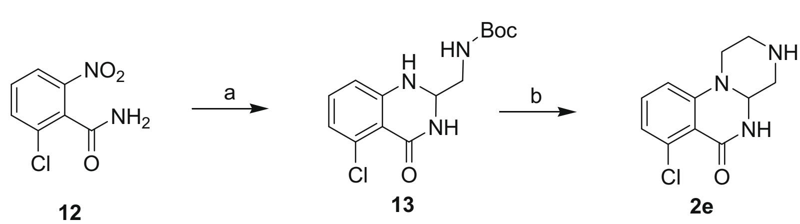
Other analogs related to **2** were prepared from the corresponding *ortho*-fluorobenzamides (Scheme 2) via introduction of the allylamine functionality prior to condensation with *N*-boc-aminoacetaldehyde. Thus, treatment of the readily available benzamides **9a–e** with allylamine in the presence of potassium carbonate in DMA at 130 °C afforded the corresponding allylated benzamides **10** which were converted via **11** to the respective tricyclic amines as described in Scheme 1. The 8- and 9-methyl analogs **2b** and **2c**,



Scheme 1. Reagents and conditions: (a) $(COCl)_2/CH_2Cl_2$/100%; (b) NH_3/MeOH–THF/90–100%; (c) H_2/10% palladium on carbon/MeOH/95%; (d) *N*-boc-aminoacetaldehyde/pTsOH/toluene/reflux/40–70%; (e) Na_2CO_3 or K_2CO_3/allyl bromide/DMF or DMA/140 °C/50–65%; (f) cat. $OsO_4/NaIO_4$/THF–water/50–65%; (g) TFA/Et_3SiH/CH_2Cl_2/40–60% (2 steps).



Scheme 2. Reagents and conditions: (a) allylamine/K_2CO_3/DMA/130 °C/61–100%; (b) *N*-boc-aminoacetaldehyde/catalytic pTsOH/dioxane or toluene/reflux/47–59%; (c) as in Scheme 1/40–60%; (d) boc anhydride/Et_3N/THF/100%; (e) $Me_4Sn/Pd(Ph_3P)_4$/LiCl/DMF/95 °C/45–85%; (f) TFA/CH_2Cl_2/100%; (g) H_2/10% palladium on carbon/MeOH/91%.



Scheme 3. Reagents and conditions: (a) Fe^o/AcOH/*N*-boc-aminoacetaldehyde/50–55 °C/22% yield; (b) as in Scheme 1 (ca. 10% overall yield).