Application of a multi-component cyclocondensation to develop a bioactive molecular scaffold

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ABSTRACT

A molecular scaffold containing a furanoquinoline motif that offered a unique molecular architecture for 5-hydroxytryptamine 6 receptor antagonism was generated by a multi-component cyclization reaction.

1. Introduction

Due to its emerging role in various central nervous system (CNS) disorders, the 5-hydroxytryptamine 6 (5-HT6) has emerged as a promising target for the pharmacological intervention for the treatment of cognitive function in Alzheimer’s disease and schizophrenia, anxiety, obesity, depression and sleep-wake activity [1-4]. In the first generation of literature reported antagonists of this receptor, a frequent feature was the presence of a sulfonamide or a sulfone moiety [5]. While profiling a chemical library we encountered compound 1, a moderately active antagonist of the 5-HT6 receptor (K of 5,700 nM against human 5-HT6 receptor [h5-HT6R], Figure 1).

Compound 1 contained a hitherto unknown motif the 1-thia-4,7-diaza-spiro[4.4]nonane-3,6-dione for the receptor’s antagonism. Thus a program was initiated around this scaffold to expand the scope of the series. This research culminated in the potent antagonist, compound 2 (Figure 1, K, of 26 nM against h5-HT6R) [6]. While the research program aimed at developing the SAR around the central [5,5]-spiro motif (rings B/C) was ongoing, a parallel program also was initiated to explore whether the motif itself was needed for the potency of this class of compounds. Accordingly, the spiro bicyclic system in compound 1 was deconstructed into a linear array generating the potent antagonist, compound 3 (K, of 10 nM against h5-HT6R, Figure 1) [7].

Figure 1. Structures of compounds 1, 2 and 3.

Emergence of the above-mentioned pair of potent antagonists inspired us to explore additional de novo designed series.
Telescoping features from both compounds 2 and 3, respectively, the structural fragment A was envisioned followed by addition of an element of constrain between the positions as shown, as well as inclusion of a hetero atom near the constrained region (cf. compound 2). This concept gave rise to a furanoquinoline motif as exemplified in compound 4 (Figure 2, X represents varying halogen substituents) that became the scaffold to explore.

![Figure 2](image)

**Figure 2.** Evolution of compound 4.

2. Experimental

As depicted in Scheme 1, commercially available N-protected amine (compound 5), dihydrofuran 6 and various aromatic benzaldehydes (compound 7, X = variable substituents), in presence of ceric ammonium nitrate, underwent an one pot-three components cyclocondensation reaction to generate a mixture of compounds cis-8 and trans-8 compounds, respectively [8]. To the best of our knowledge, this was the first example of a Povarov-type reaction employing a benzazepine nucleus. Each separated individual isomer then underwent following series of transformations. Deprotection of t-Boc group in acid medium of compounds cis-8 and trans-8 generated compounds cis-9 and trans-9, respectively. Subsequent reductive amination of compounds cis-9 and trans-9 with paraformaldehyde generated compounds cis-4 and trans-4, respectively. Based on the partial structural feature of the active compound 3 (Figure 2), the pair cis-10 and trans-10 (generated utilizing 2,3-dichlorobenzaldehyde as one of the starting materials) became further focus of the study (vide infra).

3. Results and discussion

In 'H NMR spectra of the cis-adduct, the coupling constant between 2-H and 3-H (quinoline numbering, Scheme 1) was 5 Hz due to syn-orientations of the hydrogens whereas in the trans-adduct, the corresponding value was 10 Hz due to anti-orientation of the hydrogens. Similar trends also were reported in coupling constants between similar hydrogens in a different set of recently disclosed cis- and trans-adducts [9].

Activity of both compounds cis-10 and trans-10 were assessed against recombinant h5-HT6R following previously disclosed assay procedure [7]. Compound cis-10 displayed a K of 90 nM, while the corresponding trans-isomer was ca. sixfold less active indicating the influence of three-dimensional structural architecture on activity. The result is the first example of a furanoquinoline-based active 5-HT6 receptor antagonist.

Reagents and conditions: (a) Ceric ammonium nitrate (CAN), CH2CN, room temp., overnight, 75%; (b) chromatographic separation of the isomers; (c) Individual isomer from above step [b], 4 N HCl in dioxane, room temp., 2 h, quantitative; (d) Individual isomer from above step c, formalin, methanol, catalytic gl. acetic acid, sodium triacetoxyborohydride, 0 °C to room temp., 3 h, 70-75%.

**Scheme 1**

4. Conclusions

Based on the structural information gleaned from previously disclosed potent compounds 2 and 3, a series of compounds represented by compound 4 containing a furanoquinoline motif was conceptualized, synthesized and profiled for h5-HT6R antagonism. Compound cis-10 displaying a K of 90 nM offered a new platform for further exploration of the series.

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References