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# 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.

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## 1. Introduction

Due to its emerging role in various central nervous system (CNS) disorders, the 5-hydroxytryptamine 6 (5-HT$_6$) 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-HT$_6$ receptor ($K_i$ of 5,700 nM against human 5-HT$_6$ receptor (h5-HT$_6$R), 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, $K_i$ of 26 nM against h5-HT$_6$R) [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** ($K_i$ of 10 nM against h5-HT$_6$R, Figure 1) [7].

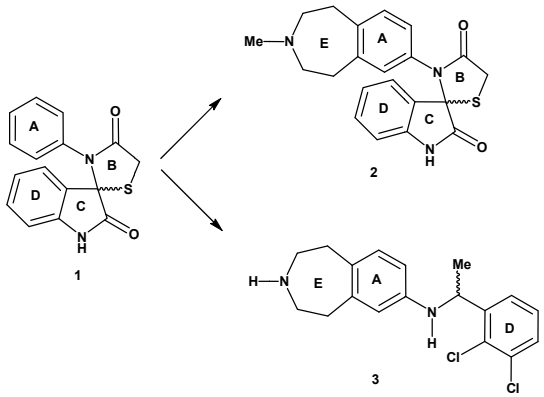


**Figure 1.** Structures of compounds **1**, **2** and **3**.

Emergence of the above-mentioned pair of potent antagonists inspired us to explore additional *de novo* designed series.


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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.

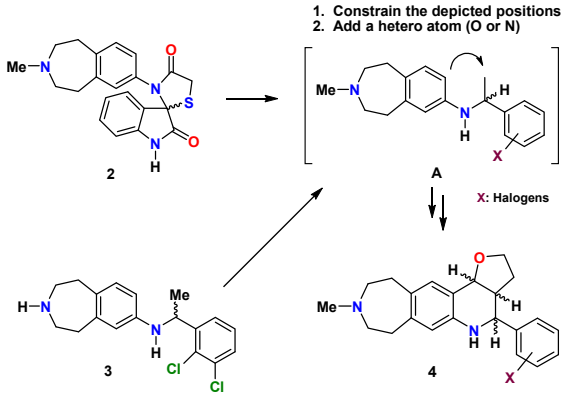



**Figure 2.** Evolution of compound **4**.

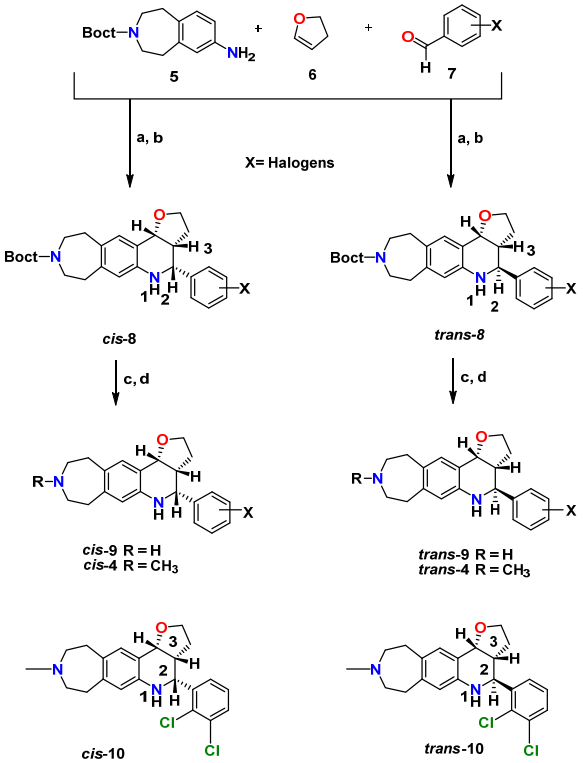
## 2. Experimental

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 acidic 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 $^1$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-HT$_6$R following previously disclosed assay procedure [7]. Compound *cis*-**10** displayed a $K_i$ of 90 nM, while the corresponding *trans*-isomer was ca. six-fold less active indicating the influence of three-dimensional structural architecture on activity. The result is the first example of a furanoquinoline-based active 5-HT$_6$ receptor antagonist.




Reagents and conditions: (a) Ceric ammonium nitrate (CAN), $CH_3CN$, 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-HT$_6$R antagonism. Compound *cis*-**10** displaying a $K_i$ of 90 nM offered a new platform for further exploration of the series.

## Acknowledgement

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