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Spiro[pyrrolidine-3,3′-oxindoles] as 5-HT$_7$ receptor ligands

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ABSTRACT

Here we report the design and synthesis of spiro[pyrrolidine-3,3′-oxindole] derivatives representing a novel scaffold of 5-HT$_7$ receptor ligands. The synthesized analogues were validated as low nanomolar ligands showing selectivity in a panel of related serotonin receptor subtypes including 5-HT$_{1A}$R, 5-HT$_{2A}$R and 5-HT$_6$R.

The serotonin receptor subtype-7 (5-HT$_7$R) is expressed in both the central nervous system (CNS) and peripheral tissues, and coupled positively to $G_{\alpha s}$ (activation raises cAMP levels)[1] or $G_{\alpha 12}$ protein. The 5-HT$_7$R plays role in the regulation of body temperature, sleep-wake rhythm, circadian rhythm, and mood. Thus the receptor has become rapidly an important target for several important CNS-related indications with proved in vivo efficacy in the animal models of depression,[2,3] sleep disorders,[4] anxiety,[5] learning and memory deficits,[6] and autism spectrum disorders.[7]

To date the candidate drug with the pyrazolo[3,4-*d*]azepine core (JNJ-18308683 **1**) has reached the clinic (a phase 2 study is currently recruiting[8]), and a number of selective and non-selective antagonists[1] (e.g. SB-656104 **2**, DR-4004 **3**) and agonists have been proved as investigational compounds (see Fig. 1 for examples).

An early *3D* pharmacophore model was built on the basis of thirty known 5-HT$_7$R antagonists including DR-4004 and analogues, SB-258719 (structure not shown) and analogues, SB-269970 (structure not shown) analogue etc.[9] The 5-HT$_7$R binding pharmacophore has been updated[10] using broad structure-activity relationship (SAR) data and structure-based docking validated by site-directed mutagenesis experiments. Pharmacophore features of 5-HT$_7$R ligands include an aromatic ring (in stacking interactions with Phe$^{3.28}$ and Tyr$^{7.43}$), two further hydrophobic regions HYD$_1$ and HYD$_2$ (facing towards Phe$^{6.52}$), a hydrogen bond acceptor (binding to Ser$^{5.42}$ and/or Thr$^{5.43}$) next to HYD$_1$, and a positive ionizable moiety located at 5–6 Å distance from HYD$_1$ that contacts Asp$^{3.32}$ (Fig. 2).

Tetrahydrobenzindoles (e.g. DR-4004 (**3**))[11,12] and corresponding oxindoles[13,14] were validated as potent 5-HT$_7$R scaffolds. As an attempt to synthesize new, selective and less lipophilic compounds we designed spiro[pyrrolidine-3,3′-oxindoles] (**4**) as potential 5-HT$_7$R ligands. Arylpiperazine analogues attached to the common spiro[pyrrolidine-3,3′-oxindole] core could provide ligands with more favourable ADME characteristics by exchanging the carbocycle of the tetrahydrobenzindole to the more polar and less rigid pyrrolidine ring. In order to design selective compounds against other serotonin receptors (5-HT$_{1A}$R, 5-HT$_{2A}$R, 5-HT$_6$R) we used the pharmacophore models by López *et al.*[9,10] and further modified by Medina *et al.*[15] These models suggest that decreasing the distance between PI (positive ionizable) and HBA (H-bond acceptor) features, facilitating interactions to Ser$^{6.55}$ (Ala$^{6.55}$ at 5-HT$_{1A}$R), introducing polar substituents at HYD$_1$-HYD$_2$ to contact Arg$^{7.36}$ (that is absent in 5-HT$_{1A}$R) would be beneficial. Following these suggestions we set our objective for exploring selectivity drivers around the spiro[pyrrolidine-3,3′-oxindoles] core.

The 5-HT$_7$R pharmacophore suggested that we need a four-atom linker between the spiro carbon *C-3* to the pyrrolidine-nitrogen and therefore connected this with two methylenes (Fig. 2) to the basic moiety of compounds with General Structure **4**. Thus in line with other studies[12,11,16–19] we focused on compounds with two atom spacer (Fig. 3, compound **5**, although compound **6** was also synthesized in

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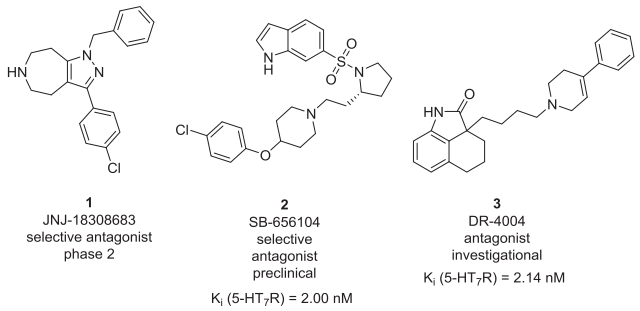
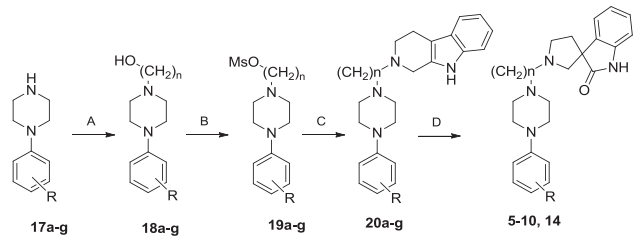


Fig. 1. Structures of the most prominent 5-HT$_7$R antagonists.



Scheme 1. Synthesis of the aryl-piperazine derivatives (**5–10**, **14**). Reagents and conditions: (A) 2-bromoethanol (or 3-bromopropanol in case of **6**), K_2CO_3, MeCN, RT, overnight,; (B) MsCl, TEA, DCM, reflux, 2 h; (C) tryptoline/tetrahydro-β-carboline, K_2CO_3, MeCN, reflux, overnight; (D) NBS, cc. AcOH, THF, water, 1.5 h, 0 °C.

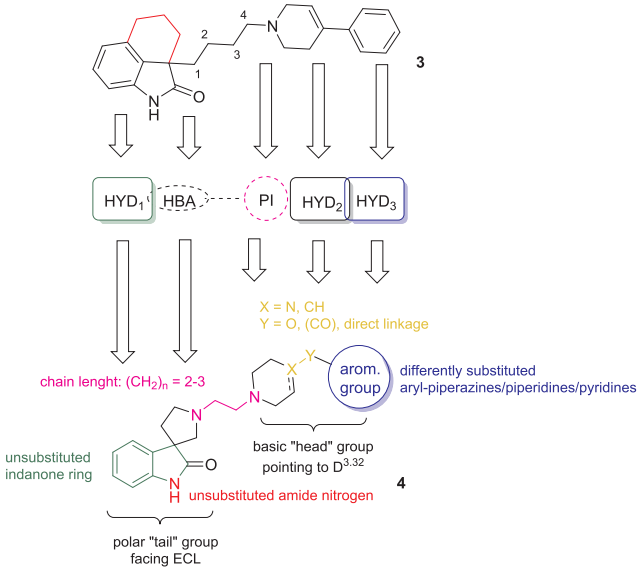


Fig. 2. Design concept for the SAR analysis of spiro[pyrrolidine-3,3′-oxindoles] (**4**).

order to investigate its effect on flexibility and HBA-PI distances.

Halo-scan, however, was planned to explore the substituent effects around the phenyl ring of the aryl-piperazine moiety comparing the profile of the unsubstituted **7** and the meta-Cl **8**, ortho-Cl **9**, para-Cl **5**, and 3,4-dichloro-derivatives **10**. Halo-scan methodology explores the functionalization of the ligands thus filling subpockets, and probing the impact of introducing lipophilic, and possibly H-bonding halogen atoms.[20]

In order to explore the impact of the HYD$_2$/HYD$_3$ features on the 5-HT$_7$R affinity and selectivity we replaced the canonical aryl-piperazine by phenyl-, and phenoxy-piperidines **11**, **12**, **15**, 5,6-dihydropyridine **13**, and benzoyl-piperazine **16** moieties.

Aryl-piperazine derivatives **5–10**, **14** were synthesized from the corresponding secondary amines **17a–g**. First, cyclic secondary amines were alkylated by 2-bromoethanol (in case of 1-(4-chlorophenyl)piperazine **17a** either by 3-bromopropanol) followed by the mesylation of the appropriate alcohols using mesyl chloride. A protecting group on the basic nitrogen of the tryptoline is necessary to avoid decomposition during the spiro-rearrangement reaction. As depicted in Scheme 1, *N*-alkylation by the corresponding mesylates leading to intermediates **20a–g** provided the desired protection of the tetrahydro-β-carboline nitrogen for the final spirocyclization step to afford derivatives **5–10** and **14**.[21]

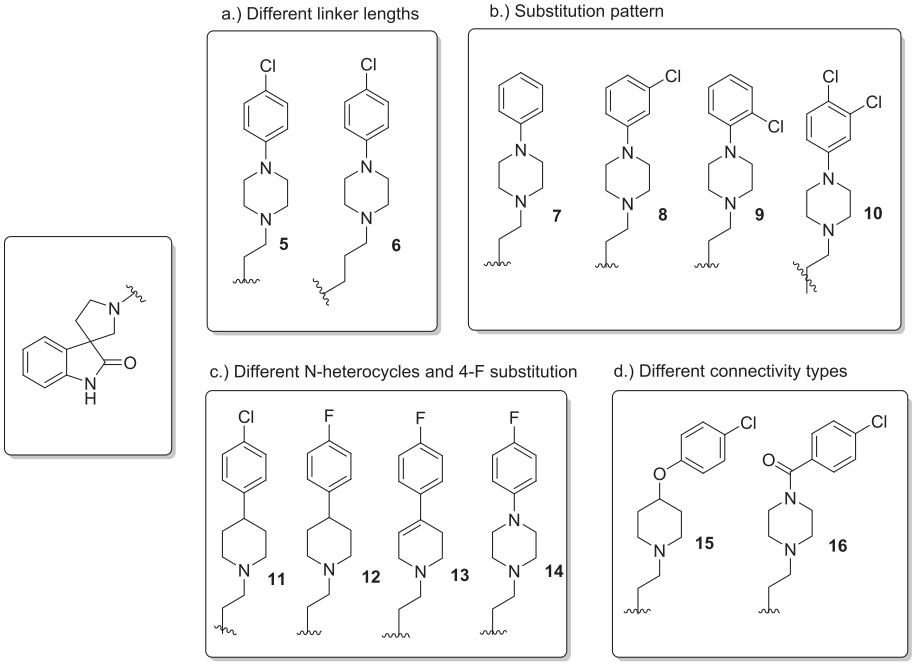


Fig. 3. Spiro[pyrrolidine-3,3′-oxindoles] designed for SAR studies.