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Lactam and oxazolidinone derived potent 5-hydroxytryptamine 6 receptor antagonists

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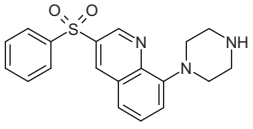
ABSTRACT

Lactam and oxazolidinone derived potent 5-hydroxytryptamine 6 (5-HT_6) receptor antagonists have been disclosed. One potent member from the lactam series, racemic compound **14** (K_i of 2.6 nM in binding assay, IC_{50} of 15 nM in functional cAMP antagonism assay) was separated into corresponding enantiomers that displayed the effect of chirality on binding potency (K_i of 1.6 nM and 3000 nM, respectively). The potent enantiomer displayed an IC_{50} of 8 nM in cAMP antagonism assay, selectivity against a number of family members as well as brain permeability in rats after 6 h post oral administration.

The 5-hydroxytryptamine 6 (5-HT_6) receptor is one of the prominent players of the serotonin receptor family.[1] Due to its exclusive distribution in the central nervous system (CNS), this receptor has emerged as a promising target for the pharmacological intervention for the treatment of several CNS-related disorders, for example, cognitive function in Alzheimer's disease and schizophrenia, anxiety, obesity, depression and sleep–wake activity.[2–5] Thus, the discovery of novel and potent inverse agonists/antagonists of this receptor has become a recent area of research for the pharmaceutical industries.[6,7] It had been revealed that SB-742457 (compound **I**, Fig. 1), a potent 5-HT_6 antagonist, demonstrated significant improvement in global function in the treatment of dementia in Alzheimer's disease in a phase IIb placebo-controlled study.[8]

In search of novel and potent 5-HT_6 receptor inverse agonists/antagonists, our team profiled our corporate chemical library on a high throughput screening (HTS) platform. From this exercise, the team encountered the 1-thia-4,7-diaza-spiro[4.4]nonane-3,6-dione-derived 'hit' compound **1a** [K_i of 5.70 μM against human 5-HT_6 (h5-HT_6) receptor, Fig. 2].[9] Subsequently, compound **1a** acted as a launching pad for additional exploration of the series. While a research program was aimed at developing the structure-activity relationship (SAR) around the central [5,5]-spiro motif (rings B/C),[9] a parallel program was initiated to answer to the query whether the motif itself was needed for the potency of this class of compounds.



I

Figure 1. Structures of compound **I**.

Accordingly, the spiro bicyclic system in compound **1a** was simplified to generate a pair of series around the central cyclic moiety (ring B). They are represented by generic structures **E** (lactam series) and **F** (oxazolidinone series), respectively, (Fig. 2) making them unique motifs for the receptor's antagonism. In addition, they were also notable for the absence of any sulfonamide or sulfone moiety in the framework, a frequent feature of literature reported potent inverse agonists/antagonists from various laboratories.[7] In this Letter, we disclose some preliminary results from our ongoing exploration from both series.

Scheme 1 depicts the representative synthesis of various *N*-substituted phenyl lactams. Commercially available appropriate aryl bromide **2** and 4-phenyllactam **3** were coupled under Buchwald condition to generate racemic lactams **4** and **6**–**17** (Table 1).[10]

Scheme 2 illustrates the route that was utilized to synthesize compound **5** (Table 1). Commercially available amine **18** and acid chloride **19** were coupled under basic condition to generate an intermediate amide (not shown) that was subsequently treated

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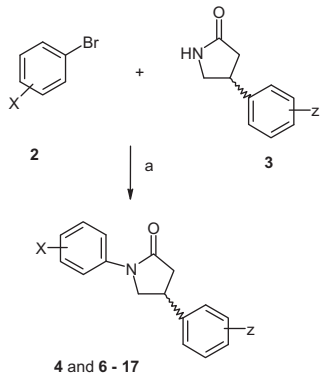
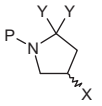
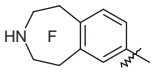
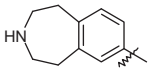
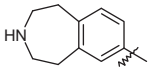
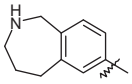
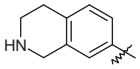
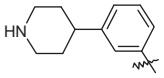
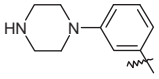
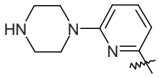
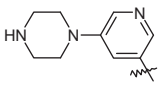
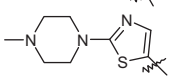
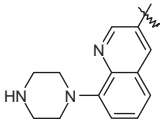
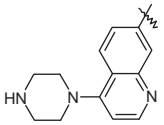
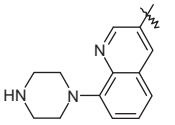
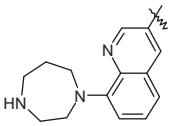


Scheme 1. Reagents and conditions: (a) CuI, K_2CO_3, K_3PO_4, trans-N,N-dimethyl-1,2-cyclohexanediamine, 1,4-dioxane, 110 °C, 50–60%.

Table 1
Biological data for compounds **1a–b** and **4–17**[a,b]



Compound	P	X	Y, Y	h5-HT$_6$[c] (K_i nM)
1a	—	—	—	5700
1b				88
4		Ph	O	54
5		2-Cl-Ph	O	100
6		2-Cl-Ph	H, H	650
7		Ph	O	1200
8		Ph	O	140
9		Ph	O	70
10		Ph	O	84
11		Ph	O	48
12		Ph	O	4100
13		Ph	O	>30,000
14		Ph	O	2.6[d]
15		Ph	O	55
16		H	O	4900
17		Ph	O	10

[a] Binding assay against recombinant h5-HT$_6$; internal ligand [^{3}H]LSD (binding of this ligand to the h5-HT6 membranes was saturable with B_{max} = 6.2 pmol/mg protein and K_d = 2.3 nM). K_i value of a test compound was then calculated according to the Cheng-Prusoff method.
[b] All compounds were tested as racemates.
[c] Average of three experiments.
[d] SEM: ±0.3 (n = 3).

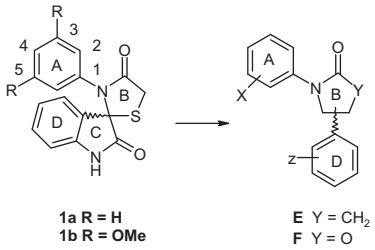
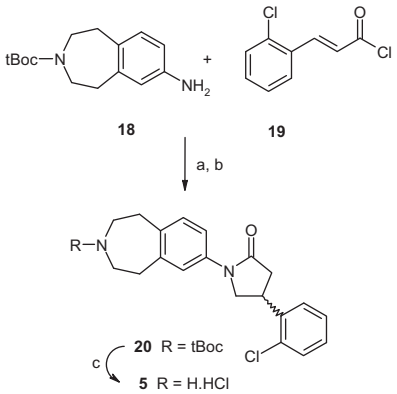


Figure 2. Structures of HTS-hit compound **1a**, **1b** and current series of lactams **E** and oxazolidinones **F**.



Scheme 2. Reagents and conditions: (a) $iPrNEt_2$, CH_2Cl_2, MeOH, 0 °C to room temp, quantitative; (b) Me_3S^+–O^-, 60% NaH in oil, DMSO 0 °C to room temp, overnight, 40–50%; (c) 4 N HCl in dioxane, room temp; 2 h, quantitative.

with the carbanion generated from trimethylsulfoxide to generate lactam **20**.[11] Deprotection of the *t*-boc group in compound **20** generated compound **5**.

Scheme 3 displays a representative synthesis of oxazolidinone derivatives containing a benzazepine moiety. Commercially available bromoketone of general structure **21** was reduced to corresponding bromohydroxy derivative of general structure **22** that was subsequently coupled with compound **18** (Scheme 2) to generate the carbamate **23**. Cyclization of the carbamate **23** generated the *t*Boc-protected oxazolidinone **24** that on subsequent deprotection generated the oxazolidinone derivatives **25–29** (Table 2).

Binding properties of the target compounds were assessed against recombinant human 5-HT$_6$ (h5-HT$_6$) receptors by