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Studies towards the next generation of antidepressants. Part 4: Derivatives of 4-(5-fluoro-1*H*-indol-3-yl)cyclohexylamine with affinity for the serotonin transporter and the 5-HT$_{1A}$ receptor

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Abstract—Derivatives of the serotonin reuptake inhibitor 4-(5-fluoro-1*H*-indol-3-yl)cyclohexylamine, in which serotonin 1A (5-HT$_{1A}$) receptor pharmacophoric elements are incorporated, are reported. Analogs exhibiting affinity for both the serotonin transporter and the 5-HT$_{1A}$ receptor are described. Compounds containing 1-(4-indolyl)piperazine and 2-(1*H*-indol-4-yloxy)ethylamine are promising leads for further SAR studies.

Research aimed at the discovery and development of new antidepressant drugs has not diminished in recent years, despite the popularity of the selective serotonin (5-HT) reuptake inhibitors (SSRIs) as first-line antidepressant therapy. Although SSRIs generally cause fewer side effects than traditional tricyclic antidepressants (TCAs), they are not without their own shortcomings. For one, SSRIs are generally no more efficacious than the TCAs.[1] In addition, SSRIs are characterized by a delay in the onset of therapeutic efficacy of 2–6 weeks.[2] This delay is thought to be the result of the inhibitory action of somatodendritic 5-HT$_{1A}$ autoreceptors that are stimulated by the SSRI-induced increase in 5-HT levels; namely, inhibition of neuronal firing by the elevated 5-HT results in zero net increase of synaptic 5-HT.[3] Only after desensitization of the 5-HT$_{1A}$ autoreceptors do the serotonergic neurons resume normal firing, allowing an increase in synaptic 5-HT levels and observation of therapeutic antidepressant effects.[4] Several studies have provided evidence that antidepressant effects can be accelerated by the co-administration of a 5-HT$_{1A}$ antagonist and an SSRI.[5–10]

There has been a substantial amount of work in our laboratories[11] as well as by others[12–16] aimed at creating a single molecular entity that possesses both 5-HT$_{1A}$ antagonism and 5-HT reuptake inhibition. Such a molecule could prove to be a superior rapidly acting antidepressant.

During our preliminary investigations we learned that 4-(1*H*-indol-3-yl)cyclohexylamines possess fairly robust 5-HT uptake inhibition, but initial modifications resulted in only moderate affinity for the 5-HT$_{1A}$ receptor.[11a] This paper describes further efforts to combine both desired activities in the same molecule by using the 'overlapping type approach,'[13] in which 4-(5-fluoro-1*H*-indol-3-yl)cyclohexylamine (**1**, Fig. 1) is combined with prototypical 5-HT$_{1A}$ receptor phar- macophores by overlapping at the basic amine. Seven known 5-HT$_{1A}$ pharmacophoric moieties (**2**–**4**, Figure 1) were chosen for these initial studies.

The synthetic routes to the target molecules are shown in Schemes 1 and 2. In general, test compounds were

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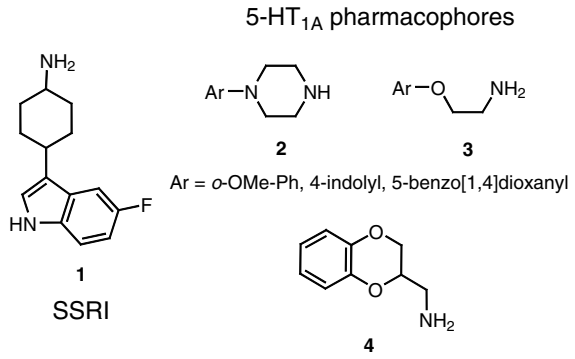
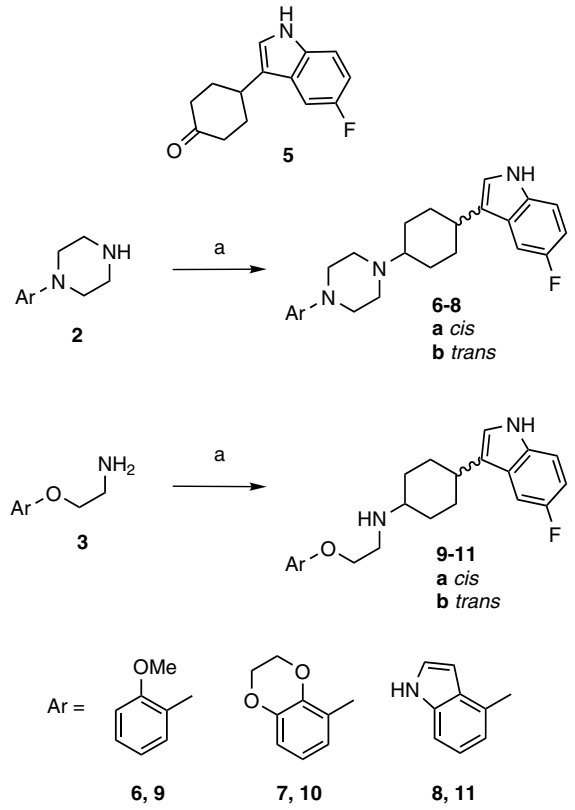


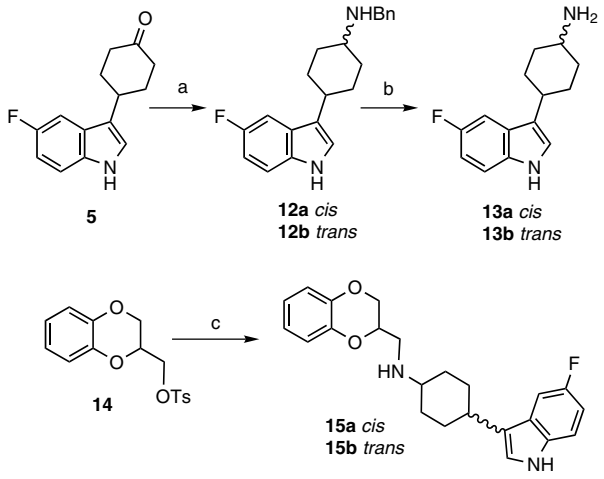
Figure 1. Compound design elements: 5-HT uptake inhibitor and 5-HT_{1A} pharmacophore moieties.



Scheme 1. Reagents and conditions: (a) **5**, $NaBH(OAc)_3$, HOAc, $ClCH_2CH_2Cl$.

prepared by reductive amination of 4-(5-fluoro-1*H*-indol-3-yl)cyclohexanone (**5**, prepared as previously reported[11a]) with the amine of the 5-HT_{1A} component (e.g., **2** or **3**, Scheme 1). The resulting mixture of *cis* and *trans* isomers (**6**–**8**,**9**–**11**) was separated by flash chromatography. The starting arylpiperazines (**2**) and aryloxyethylamines (**3**) were either commercially available or were prepared by literature methods.[11c,17]

1,4-Benzodioxan-2-methylamine derivatives **15a** and **15b** were more conveniently prepared from isomerically pure *cis*- and *trans*-4-(5-fluoro-1*H*-indol-3-yl)cyclohexylamines **13a** and **13b** by alkylation with 2-tosyloxymethyl-1,4-benzodioxane (**14**, Scheme 2). Although the primary



Scheme 2. Reagents and conditions: (a) $BnNH_2$, $NaBH(OAc)_3$, HOAc, THF; (b) (i) HCO_2NH_4, 10% Pd/C, MeOH, reflux; (ii) chromatography on SiO_2; (c) **13a** or **13b**, *i*-Pr_2EtN, DMSO, 80 °C.

amines **13a** and **13b** could be prepared directly from the ketone **5** by reductive amination with ammonium acetate, it was found that *cis*/*trans* isomer separation was more facile at the intermediate benzylamine stage (**12a**,**b**, Scheme 2).

Serotonin transporter affinity (r-5-HT-T), 5-HT_{1A} receptor affinity (h-5-HT_{1A}) and 5-HT_{1A} intrinsic activity (GTPγS E_{max}) are tabulated in Table 1. Consistent with our earlier report,[11a] the compounds of this study

Table 1. Serotonin transporter and $5HT_{1A}$ receptor affinities for compounds **6**–**11**, and **15**

Compd	r-5-HT-T[a] K_i, nM	h-5-HT_{1A}[b] K_i, nM	GTPγS[c] E_{max} (%)
6a	3.30	129	5
6b	46.1	14.3	29
7a	5.31	65.7	0
7b	67.2	11.3	57
8a	5.39	36.7	10
8b	48.5	4.62	43
9a	3.98	307	22
9b	6.48	22.4	80
10a	12.1	484	27
10b	1.05	18.9	43
11a	12.6	147	7
11b	1.73	1.08	59
15a	23.2	332	44
15b	14.1	194	94

[a] Affinity for the 5-HT transporter (r-5-HT-T) was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[19] K_i values were calculated from IC_{50}s by the method of Cheng and Prusoff,[20] and are the average of 2–3 independent determinations.

[b] Affinity for the 5-HT_{1A} receptor (h-5-HT_{1A}) was determined by displacement of [^{3}H]-8-OH-DPAT from human 5-HT_{1A} receptors transfected into CHO cells.[21] K_i values were calculated from IC_{50}s by the method of Cheng and Prusoff,[20] and are the average of 2–3 independent determinations.

[c] Intrinsic activity at the 5-HT_{1A} receptor was determined using a [^{35}S]-GTPγS binding assay similar to that of Lazareno and Birdsall.[22] Agonism (E_{max}) is reported as a percent of maximal response and is an average of 2–3 independent determinations.

possessed moderate to high affinity for the 5-HT transporter. Some degree of stereoselectivity was observed in the interaction with the transporter, but this varied in magnitude and direction depending on the chemical class of 5-HT_{1A} ligand. A *cis* arrangement of the indole and amine substituents across the cyclohexyl ring was preferred when the 5-HT_{1A} moiety was an arylpiperazine (**6a**–**8a**), with the highest selectivity (14-fold) being observed for the 1-(2-methoxyphenyl)piperazine analog **6a**. In contrast, the *trans* isomers are preferred by the transporter for two of the three aryloxyethylamines (**10b** and **11b**), while the transporter affinity of the 2-(2-methoxyphenoxy)ethylamine analogs **9a**,**b** revealed a slight (1.6-fold) preference for the *cis* isomer. Although aryloxyethylamines and arylpiperazines can both fulfill the pharmacophore requirements of biogenic amine receptors,[11b,11c,18] they do not behave as bioisosteric equivalents within the 5-HT transporter when coupled to 4-(5-fluoro-1*H*-indol-3-yl)cyclohexylamine **1**. Thus, for further SAR studies, compounds containing these 5-HT_{1A} pharmacophores must be treated as distinct chemical series that may not display the same pharmacologic trends.

The 1,4-benzodioxan-2-methylamine moiety **4** was initially viewed as a constrained aryloxyethylamine and it was not surprising that the transporter affinity for the analogs **15a**,**b** showed a preference for the *trans* isomer **15b**. The preference was small (1.6-fold), but was nonetheless in the same direction as the aryloxyethylamines **10a**,**b** and **11a**,**b**.

The 5-HT_{1A} affinity of the compounds in this study varied in magnitude to a greater extent than did the transporter affinity, but a clear stereochemical preference was observed: the *trans* isomers consistently had greater affinity for the 5-HT_{1A} receptor, regardless of the nature of the 5-HT_{1A} pharmacophoric moiety. The arylpiperazines and the aryloxyethylamines showed the same trend in the 5-HT_{1A} affinity of the *trans* isomers, following the order 4-indolyl > 5-benzodioxanyl > 2-methoxyphenyl in both series. Disappointingly, the higher 5-HT_{1A} affinity of the *trans* isomers appears to correlate with greater intrinsic activity as measured by the GTPγS assay (Table 1). The functional agonism of the *trans* isomers ranges from 29% (**6b**) to 94% (**15b**) while that of the *cis* isomers is in the range of 0% (**7a**) to 44% (**15a**). It appears from this limited set of compounds that a successful dual SSRI/5-HT_{1A} antagonist may require *cis* stereochemistry across the cyclohexyl ring.

The reduced 5-HT_{1A} affinity of the 1,4-benzodioxan-2-methylamine derivative **15b** was somewhat surprising, but could be due in part to the fact that the compound was tested as a racemate. It is well known that binding of 1,4-benzodioxan-2-methylamines to biogenic amine receptors is stereoselective, and that the (*S*)-enantiomer is preferred.[23] Further investigation of both the stereochemistry and the effect of substituents on the aromatic ring will be reported in a subsequent communication.

In summary, we have made an initial assessment of known 5-HT_{1A} ligands in combination with the SSRI 4-(5-fluoro-1*H*-indol-3-yl)cyclohexylamine in an effort toward identifying a more optimized template for the design of dual-acting SSRI/5-HT_{1A} antagonists. Based on these initial results, both arylpiperazines and aryloxyethylamines are attractive 5- HT_{1A} ligands for this purpose. Of the seven 5-HT_{1A} ligands tested in this study, the most promising in terms of binding affinities is 2-(1*H*-indol-4-yloxy)ethylamine in combination with the *trans* stereoisomer of the SSRI **1**; the resulting compound **11b** possessed potent and balanced affinities for the two molecular targets, but it also possessed significant 5-HT_{1A} agonism. Antagonism at the 5-HT_{1A} receptor was more readily attained by using the *cis* isomer of the SSRI, albeit at the cost of reduced 5-HT_{1A} binding affinity. The pharmacologic data for the 1-(4-indolyl)piperazine derivative **8a** approached the desired profile for a dual SSRI/5-HT_{1A} antagonist and therefore **8a** is a good lead for further SAR studies. Efforts aimed at achieving more balanced target binding affinities while reducing the the 5-HT_{1A} intrinsic activity to zero will be reported in due course.

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