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Ligand conformation has a definitive effect on 5-HT$_{1A}$ and serotonin reuptake affinity

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Abstract—Conformationally constrained aryl cyclohexanes and cyclohexenes based on aryl cyclohexanols **1** were prepared. Locking the aryl ring in plane with the cyclohexane moiety provided potent SSRIs **3**. Conversely, fixing the aryl ring perpendicular to the cyclohexane ring via a spiro lactone provided balanced 5-HT$_{1A}$ antagonists with mid-nanomolar range SSRI potency (compounds **2**).

1. Introduction

Depression is a mood disorder, which affects an estimated 121 million people worldwide.[1] In the U.S. alone, depression has a monetary impact in the tens of billions of dollars per year in medical costs and lost productivity, and an immeasurable toll on quality of life.[2] The molecular basis for depression is not fully understood; however, deficits in the activity of serotonin-mediated neurons in the brain are clearly central to the disease.[3] Other neurotransmitter systems, such as norepinephrine and dopamine are also implicated.[4] The introduction of serotonin-selective reuptake inhibitors (SSRI's) to the market has done much to treat the symptoms of depression; however, their efficacy is not yet optimal. One major drawback of these compounds is the delayed onset of efficacy, which can be as long as two to four weeks.[5] During this time, patients may choose to discontinue drug therapy, or try to harm themselves. It is understood that the desired accumulation of serotonin in the synapse as a result of serotonin reuptake blockade also increases occupancy of the 5-HT$_{1A}$ autoreceptor on the presynaptic neuron, causing a decrease in neuron firing. With continuous SSRI treatment, the autoreceptor becomes desensitized, and neuronal firing is restored contemporaneously with observed clinical benefit.[6] Administration of an antagonist of the 5-HT$_{1A}$ autoreceptor prevents the decrease in neuronal firing normally observed upon autoreceptor occupancy by serotonin. In keeping with the above discussion, clinical co-administration of a SSRI and a 5-HT$_{1A}$ antagonist reduces the time to onset of efficacy.[7] The goal of our research program is to incorporate both activities in a single molecule.

2. Design and synthesis

In the course of previous investigations on serotonin modulators, benzylpiperidine and benzylpiperazine moieties attached to the 4-position of arylcyclohexanol (and congeners thereof) (compounds **1**) provided a basis for

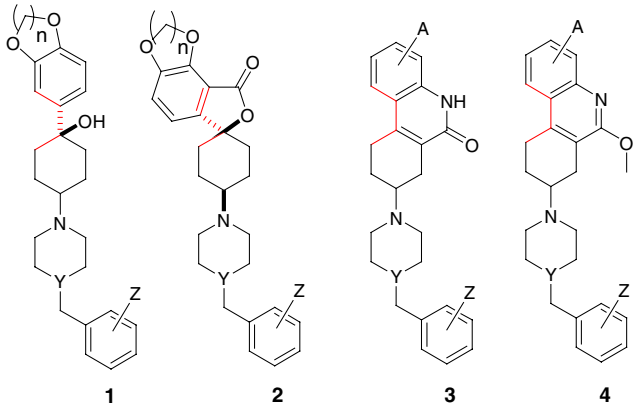

Figure 1. Prototype **1** and target molecules **2**–**4**. 'A' is dimethoxy or (m)ethylenedioxy.

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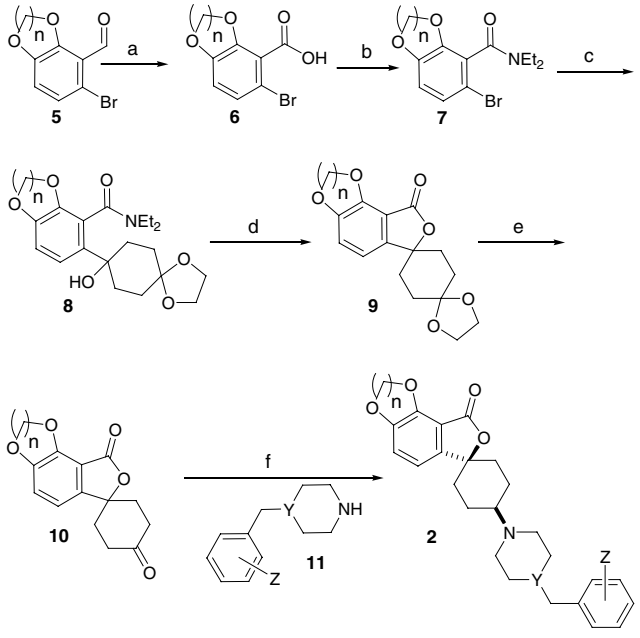
SAR investigation (Fig. 1).[8] Based on these early studies, we developed a hypothesis that the angle formed between the dialkoxyphenyl head group and the cyclohexane ring was a determinant of potency at h-SERT and 5-HT_{1A}. Specifically, we sought an optimized angle, which would maximize both activities simultaneously.

We appreciated that compounds **1** sampled conformations about the cyclohexanol/aryl ring bond in solution. We wished to add conformational constraint to this bond to more closely match the (unknown) bound-state conformation of the ligand. To study the issue in detail, we envisioned two classes of molecules with fixed and orthogonal relationships (compounds **2** and **3**). In compound **2**, the aryl ring occupies a perpendicular (~90°) relationship to the cyclohexanol unit, while in compound **3**, the aryl ring is fixed in a planar conformation with respect to the cyclohexene ring. Taken together, these molecules probe the binding requirements of the h-SERT and 5-HT_{1A} proteins.

Compounds **2** were synthesized starting from the known 5-bromobenzo[*d*][1,3]dioxole-4-carbaldehyde[9] (**5**) (Scheme 1). Silver nitrate oxidation to the corresponding bromoacid and standard functional group manipulation furnished the amide **7**. Halogen–metal exchange afforded a stable nucleophile, producing the tertiary alcohol adduct **8** upon addition of 1,4-cyclohexanedione monoethylene ketal. Treatment with sodium methoxide formed the lactone **9**, which was then subjected to 3 M HCl and acetone to provide the ketone **10**. Reductive amination with appropriately substituted benzylpiperazines and benzylpiperidines utilizing a titanium isopropoxide/sodium borohydride protocol provided the desired *cis*-cyclohexane spirolactones **2**, with



Scheme 1. Reagents and conditions: (a) $AgNO_3$, NaOH, rt, 1 h; (b) i. $SOCl_2$, CH_2Cl_2, reflux, ii. $HNEt_2$, CH_2Cl_2, reflux (88% from **5**); (c) *s*-BuLi, 1,4-cyclohexanedione monoethylene ketal, −78 °C to rt; (d) NaOMe, MeOH, (78%, two steps); (e) 3 M HCl, acetone, reflux, 93%; (f) i. Ti(O*i*-Pr)$_4$, amine, 120 °C, ii. $NaBH_4$, EtOH, (18%, two steps).

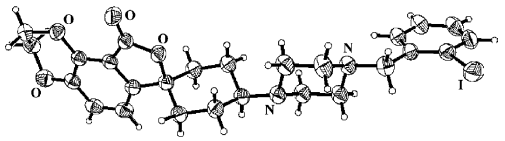
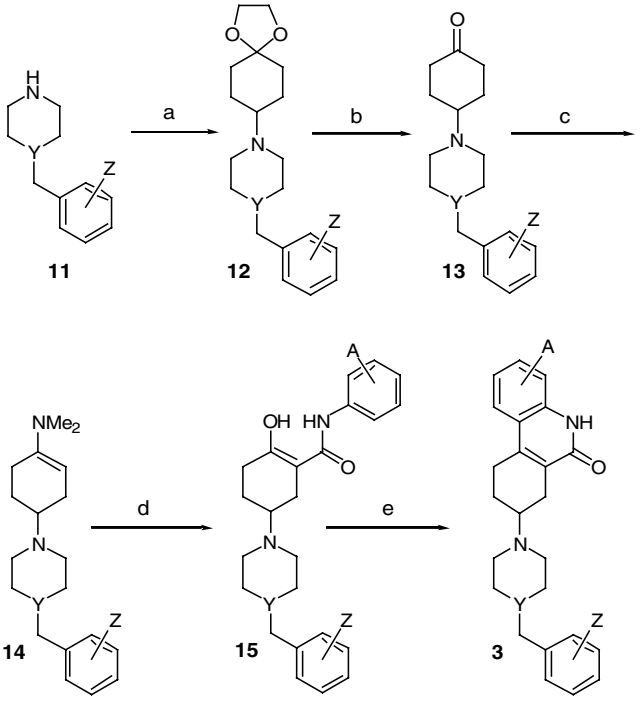


Figure 2. ORTEP drawing of **2b** with thermal ellipsoids at 40% probability for non-H atoms and open circles for H-atoms.

no *trans* isomer detected. This was verified by single-crystal X-ray analysis of compound **2b**[10] (Fig. 2).

Fused polycycles **3** were synthesized by effecting a reductive amination of 1,4-cyclohexanedione monoethylene ketal with appropriately substituted benzylpiperazines and benzylpiperidines. Deprotection of the ketal, followed by enamine formation provided intermediates **14**. Condensation with appropriate aryl isocyanates in refluxing chloroform, followed by acid-mediated ring closure provided the desired compounds **3** (Scheme 2).

Binding at the h-SERT and 5-HT_{1A} receptors were measured[11] by published methodology[12,13] (using [^{3}H]-citalopram and (±)-[^{3}H]-8-hydroxydipropylaminotetralin, respectively) and the data expressed as IC_{50} values with the radioligand at the K_d concentration (Table 1). Compounds **2** may be classified as dual 5-HT_{1A} and h-SERT modulators, the 5-HT_{1A} activity being dominant and in the lower-to mid-nanomolar range. Selectivities range from ~2.5-fold (**2a**) to ~40-fold (**2s**, **2t**). Consistent with the SAR of the cyclohexanol analogs, 2-halo substituents on the benzylpiperidine/piperazine moiety



Scheme 2. Reagents and conditions: (a) 1,4-cyclohexanedione monoethylene ketal, $NaBH(OAc)_3$, THF, HOAc, 77%; (b) 3 M HCl, acetone, reflux, 100%; (c) Me_2NSiMe_3, *p*-TsOH, 100%; (d) aryl isocyanate, $CHCl_3$, reflux, 93%; (e) HCl, MeOH, reflux, 6%.

Table 1. Inhibition assay results for compounds **2**–**4**

Compds	*n*	Y	Z	h-SERT, IC_{50}, nM[a]	5-HT_{1A}, IC_{50}, nM[a]
2a	1	N	2-I	48	18
2b	2	N	2-I	54	9.6
2c	1	CH	2-Br	45	9.6
2d	2	CH	2-Br	73	9.8
2e	1	CH	2-Cl	140	10
2f	2	CH	2-Cl	100	19
2g	1	CH	2-F	410	14
2h	2	CH	2-F	480	12
2i	1	CH	2-CF_3	180	67
2j	2	CH	2-CF_3	510	43
2k	1	CH	3-OMe	150	6.7
2l	2	CH	3-OMe	59	4.3
2m	1	CH	2-Br-5-F	82	14
2n	2	CH	2-Br-5-F	77	11
2o	1	CH	2,5-Di-F	250	22
2p	2	CH	2,5-Di-F	110	14
2q	1	CH	2-F-5-OMe	400	NT
2r	2	CH	2-F-5-OMe	430	11
2s	1	CH	2-Br-5-OMe	91	2.4
2t	1	CH	2,5-Di-Cl	92	2.3
3a	1	N	2-I	23	>1000
3o	1	CH	2,5-Di-F	5.0	440
3u	$(OMe)_2$	N	2-I	5.5	>1000
4o	1	CH	2,5-Di-F	14	450

[a] See Ref. 11; (NT = not tested).

provide potently active molecules at 5-HT_{1A}, with the 3-methoxy substituent also providing potent agents (**2k**, **2l**). Superposition of these substituents (**2s**) provided a very potent 5-HT_{1A} modulator, however the h-SERT activity remained at a modest level. Ring size at the alkylated catechol (*n* in Scheme 1) effected binding in an unpredictable manner, although the effects at 5-HT_{1A} were less than at h-SERT (**2c** vs **2d** and **2g** vs **2h**). Compounds **3** showed a reversal in selectivity, being devoid of activity at 5-HT_{1A}, while enjoying potent activities at h-SERT. *O*-Methylation of the lactam gave the corresponding cyclic imidate **4o**, which retained potency at h-SERT. The retention of activity in **4** versus **3** demonstrates that the hydrogen-bonding network by the lactam functionality itself is not responsible for the high levels of h-SERT activity observed. Taken together, this data provides evidence that the conformation of the aryl ring relative to the cyclohexyl ring is an important factor in determining relative potencies at h-SERT and 5-HT_{1A}.

Compounds **2a** and **2l** were shown to be partial antagonists at the 5-HT_{1A} autoreceptor by published methods,[14] having intrinsic activities of 0.1 and 0.37, respectively.

Manipulation of the global conformation of serotonin modulators provided two unique series of compounds. In the first, a balance of nanomolar 5-HT_{1A} (antagonist) and h-SERT (antagonist) activities was achieved by fixing the aryl ring in a perpendicular orientation via a spiro lactone. The SSRI activity was shown to improve dramatically at the expense of 5-HT_{1A} activity upon rotation of the aryl ring to an orthogonal, planar, conformation. By manipulating the topology of the ligand via judicious conformational constraint, potent, dual antagonists at the 5-HT_{1A} and h-SERT receptors were obtained.

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