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# Modulation of selective serotonin reuptake inhibitor and 5-HT$_{1A}$ antagonist activity in 8-aza-bicyclo[3.2.1]octane derivatives of 2,3-dihydro-1,4-benzodioxane

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**Abstract**—2,3-Dihydro-1,4-benzodioxanes with aryl 8-aza-bicyclo[3.2.1]oct-3-ene attachments **2** produce compounds with potent 5-HT-T affinity, and weak 5-HT$_{1A}$ affinity and $\alpha_1$ affinity. This compares with 2,3-dihydro-1,4-benzodioxanes containing 8-aza-bicyclo[3.2.1] octan-3-ol attachments **4** which possess potent 5-HT$_{1A}$ affinity, moderate to good selectivity over $\alpha_1$ and little 5-HT-T affinity. A 3-benzothiophene analogue of **4** (**30**) was synthesized which possesses potent 5-HT$_{1A}$ affinity and especially good selectivity over both $\alpha_1$ and 5-HT-T.


Inhibition of serotonin (5-HT) receptors, namely the serotonin transporter (5-HT-T), has led to the development of many clinically approved agents for depression and anxiety.[1] However, these drugs have noticeable side effects as well as a delayed onset of action. Selective antagonists for the 5-HT$_{1A}$ receptor have been postulated to be useful in the treatment of CNS disorders such as anxiety,[2] and Alzheimer's disease.[3] In addition, 5-HT$_{1A}$ antagonists may have an important role in treating depression in that they could facilitate the onset of action of selective serotonin receptor inhibitors (SSRIs) by blocking 5-HT$_{1A}$ autoreceptors which are believed to decrease the firing of serotonergic neurons in the presence of 5-HT.[4] Thus, an agent with both activities (SSRI and 5-HT$_{1A}$ antagonism) would be a significant improvement on currently approved therapies. As proof of concept, co-administration of 5-HT$_{1A}$ antagonists/partial antagonists and SSRIs has been clinically shown to induce faster antidepressant action than administration of SSRIs alone.[5,6]

In the course of our study of novel ligands that would possess both SSRI and 5-HT$_{1A}$ antagonist activities, we began synthesizing molecules containing the aryl 8-aza-bicyclo[3.2.1]oct-3-ene moiety **1**. Benzodioxane derivatives of **1** (**2**) were found to possess potent affinity and inhibitory activity for the 5-HT-T (Fig. 1). Interestingly changing the aryl 8-aza-bicyclo[3.2.1]oct-3-ene moiety in **1** to an 8-aza-bicyclo[3.2.1] octan-3-ol **3** produces **4**, a series of molecules with potent 5-HT$_{1A}$ affinity and relatively little 5-HT-T affinity. In addition, many of the members of series **4** were found to possess potent 5-

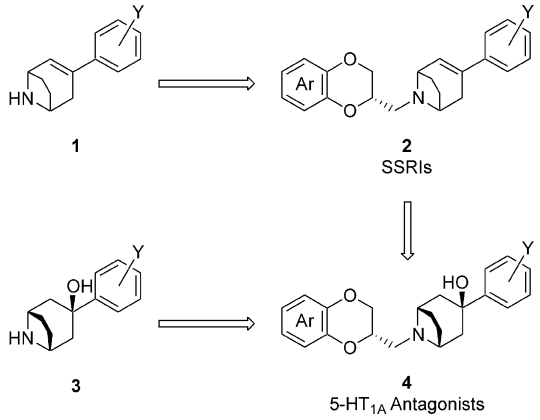


**Figure 1.** Aryl 8-aza-bicyclo[3.2.1] octanes of interest.

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$HT_{1A}$ antagonist activity. We now wish to report the synthesis and initial structure–activity relationships (SARs) of these two new classes of 5-HT antagonist compounds.

Schemes 1–4 show the synthesis of the target molecules. The aryl 8-aza-bicyclo[3.2.1] oct-3-ene derivatives **1**, were prepared by demethylation of tropinone **5** with 1-chloroethyl chloroformate,[7] protection of the secondary amine with $(BOC)_2O$ to form **6**,[8] addition of an aryl lithium, followed by dehydration/deprotection with TFA (Scheme 1).

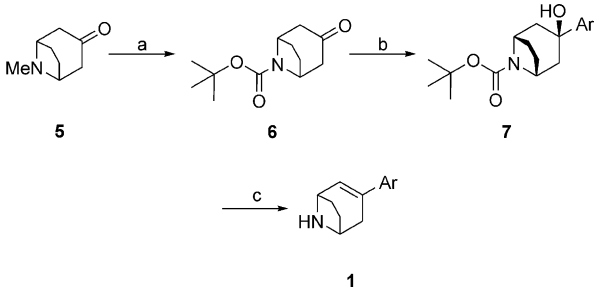
The aryl 8-aza-bicyclo[3.2.1] octan-3-ol derivatives **3** were prepared by demethylating tropinone **5** with 1-chloroethyl chloroformate,[7] protection of the resulting secondary amine with BnBr to give **8**, addition of an aryl lithium to exclusively give the *endo*-alcohol product **9**,[9] followed by removal of the benzyl group with Pd/C, $HCO_2NH_4$ (Scheme 2).[10]

The 8-OMe and 8-OEt benzodioxane headpieces were synthesized as tosylates **16** (R = Me and R = Et), as shown in Scheme 3. The sequence features a Baeyer–Villiger oxidation/basic hydrolysis conversion of aldehyde **12** to phenol **13**, the attachment of (2*R*)-(−)-glycidyl tosylate, debenzylation with concomitant ring closure/epoxide opening to produce **15**, and tosylation with TsCl to produce **16** (Scheme 3).

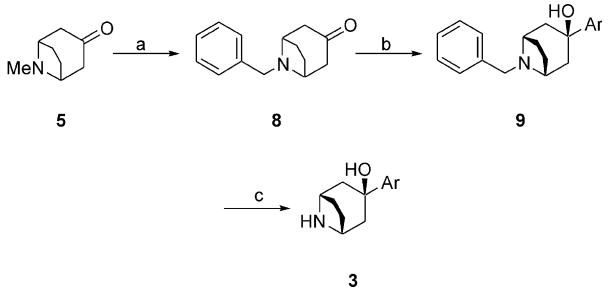
The target aryl 8-aza-bicyclo[3.2.1] oct-3-ene benzodioxanes **2** and aryl 8-aza-bicyclo[3.2.1] octan-3-ol benzodioxanes **4**[11] were prepared by heating **1** or **3** with **16** in the presence of $K_2CO_3$ in MeCN or by heating 2 equivalent of **1** or **3** with 1 equivalent of **16** in warm DMSO (Scheme 4).

All aryl 8-aza-bicyclo[3.2.1] oct-3-ene benzodioxanes **2** and aryl 8-aza-bicyclo[3.2.1] octan-3-ol benzodioxanes **4** were tested in vitro to determine affinity for the 5-$HT_{1A}$, 5-HT transporter (5-HT-T) and $\alpha_1$ receptors. Human 5-$HT_{1A}$ (HC-5-$HT_{1A}$) receptor binding was determined via the displacement of [$^3$H]-8-OH-DPAT from human 5-$HT_{1A}$ transfected CHO cells according to the method of Dunlop et al.[12] Assessment of compound agonism/antagonism on the HC 5-$HT_{1A}$ receptor was determined using a [$^{35}$S]-GTP$\gamma$S[13] and/or a forskolin stimulated cyclic AMP assay (*c*-AMP). A protocol similar to that of Cheetham et al. was used to determine 5-HT transporter affinity (RB5-HT-T).[14] $IC_{50}$ values (HC-5-HT-T) were calculated from the $K_i$ values according to the method of Cheng et al.[15] Selectivity over the $\alpha_1$ receptor was determined by displacement of [$^3$H]-prazosin ($\alpha_1$)[16] since $\alpha_1$ receptor affinity could lead to unwanted side effects for a selective 5-HT agent. An optimal compound would have potent 5-HT-T/5-$HT_{1A}$ inhibitory activity and weak or no ($\alpha_1$) affinity.

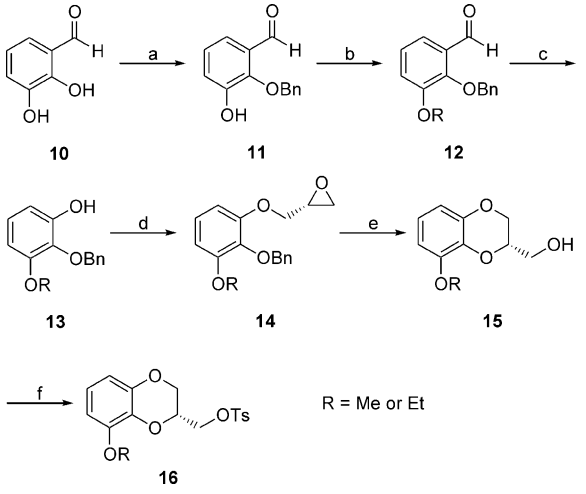
Biological data for all newly prepared aryl 8-aza-bicyclo[3.2.1]oct-3-enes **2** are presented in Table 1. In all



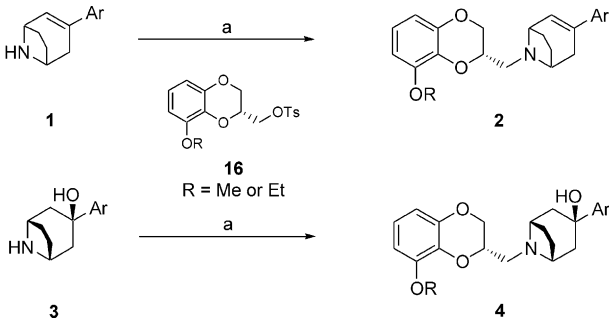

**Scheme 1.** Reagents and conditions: (a) (1) 1-chloroethyl chloroformate, DCE, 80 °C; (2) MeOH, 50 °C; (3) $(BOC)_2O$, *i*-PrOH, $H_2O$, NaOH, 23 °C; (b) ArLi, THF, −78 to 23 °C; (c) TFA, $CH_2Cl_2$, 23 °C.




**Scheme 2.** Reagents and conditions: (a) (1) 1-chloroethyl chloroformate, DCE, 80 °C; (2) MeOH, 50 °C; (3) BnBr, $Et_3N$, THF, 23 °C; (b) ArLi, THF, −78 to 23 °C; (c) 10% Pd/C, $HCO_2NH_4$, MeOH, 50 °C.




**Scheme 3.** Reagents and conditions: (a) NaH, BnBr, THF, 23 °C; (b) NaH, MeI or EtI, DMF, 23 °C; (c) (1) *m*-CPBA, $CH_2Cl_2$, 23 °C; (2) $Al_2O_3$, MeOH, 23 °C; (d) NaH, (2*R*)-(−)-glycidyl tosylate, solvent, X°C; (e) 5% Pd/C, 1,4-cyclohexadiene, $NaHCO_3$, EtOH, 80 °C; (f) TsCl, TEA, DMAP, $CH_2Cl_2$, 23 °C.



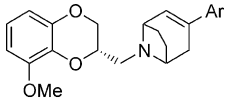

**Scheme 4.** Reagents and conditions: (a) $K_2CO_3$, MeCN, 80 °C or 1 equiv **16**, 2 equiv **1** or **9**, DMSO, 80 °C.

cases, the 2(*R*) enantiomers were prepared since is known that the 2(*R*) enantiomer of (2,3-dihydro-benzo[1,4]dioxin-2-yl)-methylamines show stronger 5-HT receptor affinity/function compared to the 2(*S*) enantiomer.[17] 2-Naphthyl analogue **16** was initially prepared since 2-naphthyl 8-aza-bicyclo[3.2.1] oct-3-ene is known to have potent 5-HT-T affinity.[18] This compound shows potent 5-HT-T affinity/inhibition, good selectivity over the $\alpha_1$ receptor and some affinity for the 5-$HT_{1A}$ receptor. The 1-napthyl compound **17** comparably shows weaker 5-HT-T affinity but more 5-$HT_{1A}$ affinity. Indole **18** shows the best balance of 5-HT-T/5-$HT_{1A}$ affinity, but the potency at the $\alpha_1$ receptor increases as well. The 8-quinoline analogue **19** compares with the 1-naphtyl compound **17** except that it shows more $\alpha_1$ affinity, and the 3,4-dichlorophenyl molecule **20** shows a comparable activity profile to **16**. In general, the RB5-HT-T affinities are single to double digit nM while the HC5-HT-T functional $IC_{50}$s are much less potent ($\sim$2 orders of magnitude). The origin of this difference is not known.

At this point we were interested in exploring the biological profile of compounds where the 8-aza-bicyclo[3.2.1]oct-3-ene moiety **1** would be changed to an 8-aza-bicyclo[3.2.1] octan-3-ol **3**. This structural change produces compounds **4** with a dramatic activity profile shift compared to **2**. 2-Napthyl analogue **21** shows potent 5-$HT_{1A}$ affinity and only moderate 5-HT-T affinity (Table 2). This is a reverse of the activity profile seen for 2-naphtyl-8-aza-bicyclo[3.2.1]oct-3-ene compound **16**. Moreover, **21** shows potent 5-$HT_{1A}$ antagonist activity in both the [$^{35}$S]GTP$\gamma$S and *c*-AMP assays. In an effort to reduce the $\alpha_1$ affinity of **21**, compound **22** (R = Et) was prepared. This compound shows reduced $\alpha_1$ affinity compared to **21**, good 5-$HT_{1A}$ affinity and is devoid of 5-HT-T affinity at 100 nM.

Hoping to optimize **21** and **22** to produce selective 5-$HT_{1A}$ antagonists, different aryl groups were attached to the 8-aza-bicyclo[3.2.1] octan-3-ol benzodioxane core. Phenyl analogues **23** and **24** showed potent 5-

**Table 1.** 5-$HT_{1A}$ affinity, 5-$HT_{1A}$ functional activity, 5-HT-T affinity, 5-HT-T functional activity and $\alpha_1$ affinities for 8-aza-bicyclo[3.2.1]oct-3-ene 2,3-dihydro-1,4-benzodioxanes **2**

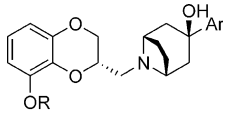



**2**

| Compd | Ar | HC5-$HT_{1A}$ $K_i$ (nM)[a] | RB5-HT-T $K_i$ (nM) | HC5-HT-T $IC_{50}$ (nM)[b] | $\alpha_1$ $K_i$ (nM) |
|---|---|---|---|---|---|
| **16** | 2-Naph | 43% @ 1000 nM | 1.4 | 76.7 | 229 |
| **17** | 1-Naph | 357 | 26.0 | 951 | 26% @ 100 nM |
| **18** | 3-(5-F-1*H*-indole) | 127.7 | 8.5 | 138 | 71 |
| **19** | 8-Quinoline | 307.1 | 33.0 | 109.0 | 46.2 |
| **20** | 3,4-Dichlorophenyl | 35% @ 1000 nM | 4.69 | 260.0 | >1000 |

[a] $K_i$ values are the mean of two experiments run at six different concentrations. 95% confidence limits were generally ±10% of the mean value.
[b] $IC_{50}$, $E_{max}$ and $I_{max}$ values are reported from one experimental run at six different concentrations.

**Table 2.** 5-$HT_{1A}$ affinity, 5-$HT_{1A}$ functional activity, 5-HT-T affinity, 5-HT-T functional activity and $\alpha_1$ affinities for aryl 8-aza-bicyclo[3.2.1]octan-3-ol 2,3-dihydro-1,4-benzodioxanes **4**




**4**

| Compd | R | Ar | HC5-$HT_{1A}$ $K_i$ (nM)[a] | [$^{35}$S]GTP$\gamma$S: $I_{max}$ (%) $IC_{50}$ (nM)[b] | *c*AMP: $E_{max}$ (%) $IC_{50}$ (nM)[b] | RB5-HT-T $K_i$ (nM) | $\alpha_1$ $K_i$ (nM) |
|---|---|---|---|---|---|---|---|
| **21** | Me | 2-Naph | 0.81 | 100, 9.85 | 0, 21 | 216.5 | 42 |
| **22** | Et | 2-Naph | 5.87 | NA | NA | 0% @ 100 nM | 103.5 |
| **23** | Me | Ph | 1.53 | 100, 25 | 0, 21 | 0% @ 100 nM | NA |
| **24** | Et | Ph | 3.05 | NA | NA | 0% @ 100 nM | 32.7 |
| **25** | Me | 2-OMe-Ph | 39.0 | E40[c] | NA | 12% @ 100 nM | NA |
| **26** | Me | 3-$CF_3$-Ph | 0.33 | E90[d] | NA | 9% @ 100 nM | 9.9 |
| **27** | Et | 3-$CF_3$-Ph | 2.92 | NA | NA | 0% @ 100 nM | 12.9 |
| **28** | Me | 2-Pyr | 46.0 | 100, 1484 | NA | 0% @ 100 nM | NA |
| **29** | Et | 2-Pyr | 61.6 | NA | NA | 6% @ 100 nM | 147 |
| **30** | Me | 3-Benzothiophene | 1.6 | 92, 36 | 0, 130 | 0% @ 100 nM | 106 |
| **31** | Et | 3-Benzothiophene | 16.7 | NA | NA | 4% @ 100 nM | 123.5 |

[a] $K_i$ values are the mean of two experiments run at six different concentrations. 95% confidence limits were generally ±10% of the mean value.
[b] $IC_{50}$, $E_{max}$ and $I_{max}$ values are reported from one experimental run at six different concentrations.
[c] $E_{max}$ = 40%.
[d] $E_{max}$ = 90%. NA, not available.

$HT_{1A}$ affinity, no 5-HT-T affinity, but the R = Et analogue still possessed $\alpha_1$ affinity. Analogues **26** and **27** also show good 5-$HT_{1A}$ affinity, practically no 5-HT-T affinity, but these compounds behave as partial agonists/agonists at the 5-$HT_{1A}$ receptor. The 2-pyridyl compounds **28** and **29** show reduced 5-$HT_{1A}$ affinity compared to the corresponding phenyl analogues and the 3-benzothiophene molecules **30** and **31** compare favorably with **21** and **22**. Compound **30** is the most selective 5-$HT_{1A}$ antagonist that we have prepared (5-$HT_{1A}$: $K_i$: 1.6 nM [$^{35}$S]GTPγS: $I_{max}$: 92%, $IC_{50}$: 36 nM, $\alpha_1$: 106 nM).

Thus we have disclosed a series of aryl 8-aza-bicyclo[3.2.1] oct-3-ene benzodioxanes **2** and aryl 8-aza-bicyclo[3.2.1] octan-3-ol benzodioxanes **4** that have potent affinity for the 5-HT-T and 5-$HT_{1A}$ receptors respectively. In addition, several of the 8-aza-bicyclo[3.2.1] octan-3-ol analogues **4** show good 5-$HT_{1A}$ antagonist activity. A 3-benzothiophene 8-aza-bicyclo[3.2.1] octan-3-ol analogue **30** shows potent 5-$HT_{1A}$ affinity and antagonism, no 5-HT-T affinity and is $>50$ fold selective for the 5-$HT_{1A}$ receptor over $\alpha_1$. Further studies concerning agents that target the 5-$HT_{1A}$ and 5-HT-T receptors will be reported in due course.

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