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# Novel aryloxy-8-azabicyclo[3.2.1]oct-3-enes with 5-HT transporter and 5-HT$_{1A}$ affinity

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**Abstract**—Joining aryl 8-azabicyclo[3.2.1]oct-3-enes with aryloxyethanes and aryloxypropanes produces novel series of compounds **11** and **12** with potent 5-HT-T affinity and moderately potent 5-HT$_{1A}$ affinity. Moreover, several of these compounds possess functional 5-HT$_{1A}$ antagonism. Optimal compounds are, 4-indolyloxyethane **21**, 4-indolyloxypropanes **25**, and **27**, which possess potent 5-HT-T affinity (5-HT-T $K_i$: **21**: 1.2 nM, **25**: 0.54 nM, **27**: 0.38 nM) and good 5-HT$_{1A}$ affinity/antagonism (5-HT$_{1A}$ $K_i$, [$^{35}$S]GTPγS: $E_{max}$ (%): **21**: 111.1 nM, 0%; **25**: 173.2 nM, 0%; **27**: 107 nM, 0%).


## 1. Introduction

Although used for many years as effective antidepressants, first generation selective serotonin reuptake inhibitors (SSRIs) possess shortcomings that might be remedied with agents that have additional desired properties. The major drawback with the current line of SSRIs is that they have a delayed onset before the beneficial therapeutic effect is observed. One approach to create a fast-acting SSRI is to combine, in a single molecule, an agent with SSRI activity + 5-HT$_{1A}$ antagonist activity since activation of 5-HT$_{1A}$ autoreceptors by serotonin (5-HT) is believed to decrease the firing of serotonergic neurons.[1] 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.[2,3]

Recently our laboratories[4–7] and others[8–13] have disclosed efforts toward discovering a potentially new class of antidepressant agents based on 'the overlapping type approach'. This strategy uses a common nitrogen to amalgamate the 5-HT$_{1A}$ and 5-HT uptake site pharmacophore (Fig. 1). In Part 2 we discovered that compounds that fell into the generic structure **1** had both 5-HT$_{1A}$ antagonism and 5-HT uptake site activity.[6] In this article we will expand upon template **1** by replacing the piperidinyl moiety with the tropane framework, as well as tethering either the 2-aryloxyethyl or 3-aryloxy-2-propanol side chains (i.e., **2**).

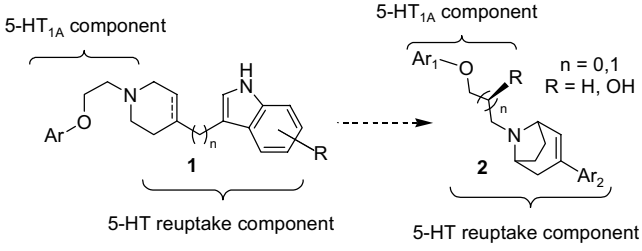


**Figure 1.** Design strategy.

## 2. Chemistry

Target molecules were synthesized according to the procedures outlined in Schemes 1–3. Aryloxyethyl chlorides

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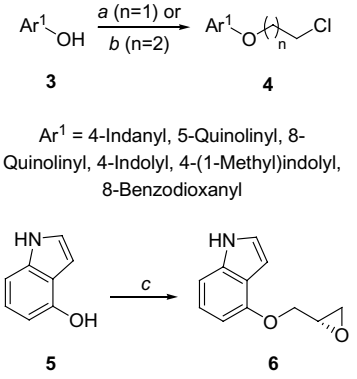
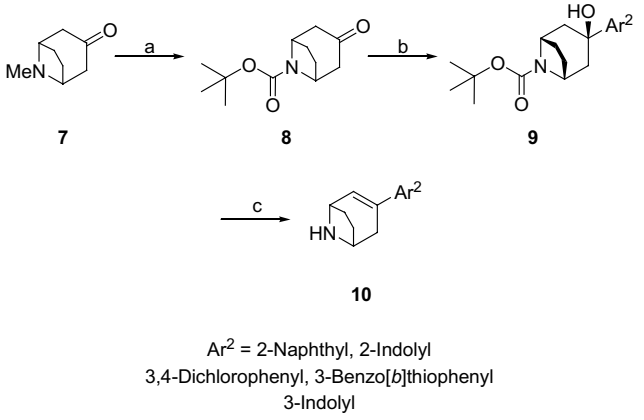
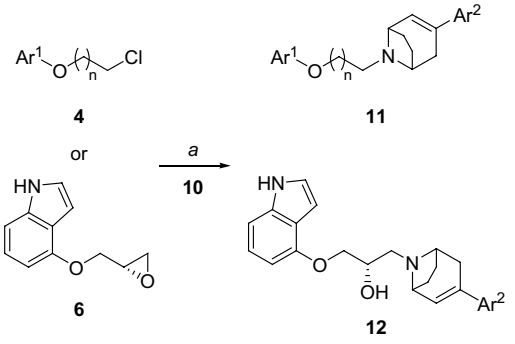



**Scheme 1.** Reagents and conditions: (a) 2-chloroethanol, $Ph_3P$, DEAD, THF, 0–23 °C, (b) 3-chloropropanol, $Ph_3P$, DEAD, THF, 0–23 °C, (c) NaH, (2*R*)-(−)-glycidyl tosylate, THF, 23 °C.




**Scheme 2.** 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 3.** Reagents and conditions: (a) $K_2CO_3$, MeCN, 80 °C.

and aryloxypropyl chlorides were prepared via a Mitsunobu reaction between phenols **3** and 2-chloroethanol or 3-chloropropanol.[14] 4-Oxiranylmethoxy-(1*H*)-indole **6** was prepared from 4-hydroxyindole **5** via deprotonation with NaH followed by reaction with (2*R*)-(−)-glycidyl tosylate.

Aryl 8-azabicyclo[3.2.1]oct-3-ene derivatives **10**, were prepared by demethylation of tropinone **7** with 1-chloroethyl chloroformate,[15] protection of the secondary amine with $(Boc)_2O$ to form **8**,[16] addition of an aryl lithium, followed by dehydration/deprotection with TFA (Scheme 2). Aryloxyalkyl chlorides **4** and aryloxyepoxide **6** were combined with aryl 8-azabicyclo[3.2.1]oct-3-enes **10** by heating in MeCN in the presence of $K_2CO_3$ to produce target compounds **11** and **12** (Scheme 3).

$^1$H NMR, IR, and ESMS spectroscopy confirmed the structures of all newly prepared compounds. The enantiomers of **11** and diastereomers of **12** were not separated and were tested as racemic/diastereomeric mixtures, respectively.

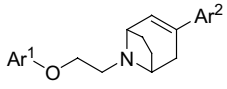
## 3. Pharmacology

All new aryloxy-8-azabicyclo[3.2.1]oct-3-enes **11** and **12** were tested in vitro to determine affinity for the 5-$HT_{1A}$ receptor, and 5-HT transporter (5-HT-T). 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.[17] Assessment of compound agonism/antagonism on the HC-5-$HT_{1A}$ receptor was determined using a [$^{35}$S]GTP$\gamma$S assay.[18] A protocol similar to that of Cheetham et al. was used to determine rat 5-HT transporter affinity (RB5-HT-T).[19]

Biological data for all newly prepared aryloxyethyl 8-azabicyclo[3.2.1]oct-3-enes **11** is presented in Table 1. Thus 2-naphthyl 8-azabicyclo[3.2.1]oct-3-ene **1** was initially combined with a 4-indanyl-ethyl group to produce **13** (**11**: $Ar^1$ = 4-indanyl, $Ar^2$ = 2-naphthyl), a compound with very potent 5-HT-T affinity but no 5-$HT_{1A}$ affinity. The $Ar^1$ = 5-quinolinyl (**14**) and $Ar^1$ = 8-quinolinyl (**15**) analogs possess sub-nM affinity for the 5-HT-T with increasing 5-$HT_{1A}$ affinity compared to **13**. Changing the $Ar^2$ = 2-naphthyl moiety of **15** to an $Ar^2$ = 2-indolyl moiety produces an important increase in 5-$HT_{1A}$ affinity the resulting compound **16** possesses potent 5-HT-T affinity and moderately potent 5-$HT_{1A}$ antagonism (**16**: 5-HT-T: 11 nM; 5-$HT_{1A}$: 320 nM, $E_{max}$: 0%). Compound **17** has a similar potency profile as **16** however this compound possesses partial 5-$HT_{1A}$ antagonism (**17**: 5-HT-T: 0.2 nM, 5-$HT_{1A}$: 295 nM; $E_{max}$: 25%). Since **17** has very potent affinity for 5-HT-T, it was decided to keep the $Ar^1$ = 4-indolyl substituent and make further variations at $Ar^2$.

Two isosteric modifications of the $Ar^2$ = 2-naphthyl moiety give compounds with reduced 5-$HT_{1A}$ affinity—**18** ($Ar^2$ = 3,4-dichlorophenyl; 39% @ 1000 nM) and **19** ($Ar^2$ = 3-benzothiophenyl; 11% @ 1000 nM). The corresponding N(Me) analog of **17** shows reduced 5-$HT_{1A}$ and 5-HT-T affinity (**20**: $Ar^1$ = 4-(1-methyl)indolyl; 5-HT-T: 4.4 nM; 5-$HT_{1A}$: 33% @ 1000 nM; $E_{max}$: 100%). However a jump in 5-$HT_{1A}$ potency was seen with **21** where the $Ar^2$ = 2-naphthyl moiety of **17** was changed to an $Ar^2$ = 3-indolyl group. Moreover, this compound possesses potent 5-HT-T affinity and is a functional antagonist at the 5-$HT_{1A}$ receptor (**21**: 5-HT-T: 1.2 nM, 5-$HT_{1A}$: 111.1 nM, $E_{max}$: 0%). Addi-

**Table 1.** Serotonin transporter affinity, 5-$HT_{1A}$ affinity and [$^{35}$S]GTPγS: $E_{max}$ values for aryloxytropenes **11**

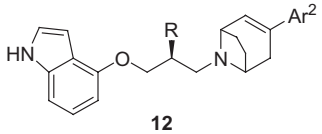



**11**

| Compound | $Ar^1$ | $Ar^2$ | RB5-HT-T $K_i$ (nM)[a] | HC5-HT1A $K_i$ (nM)[a] | [$^{35}$S]GTPγS: $E_{max}$ (%)[b] |
|---|---|---|---|---|---|
| **13** | 4-Indanyl | 2-Naphthyl | 5.0 | 0% @ 1000 nM | Not tested |
| **14** | 5-Quinolinyl | 2-Naphthyl | 0.4 | 15% @ 1000 nM | 29 |
| **15** | 8-Quinolinyl | 2-Naphthyl | 0.5 | 44% @ 1000 nM | 95 |
| **16** | 5-Quinolinyl | 2-Indolyl | 11.0 | 320 | 0 |
| **17** | 4-Indolyl | 2-Naphthyl | 0.2 | 295 | 25 |
| **18** | 4-Indolyl | 3,4-Dichlorophenyl | 0.5 | 39% @ 1000 nM | 5 |
| **19** | 4-Indolyl | 3-Benzo[*b*]thiophenyl | 15.0 | 11% @ 1000 nM | Not tested |
| **20** | 4-(1-Methyl)indolyl | 2-Naphthyl | 4.4 | 33% @ 1000 nM | 100 |
| **21** | 4-Indolyl | 3-Indolyl | 1.2 | 111.1 | 0 |
| **22** | 8-Benzodioxanyl | 3-Indolyl | 4.0 | 85.5 | 65 |

[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] $E_{max}$ values are reported from one experimental run at six different concentrations.

**Table 2.** Serotonin transporter affinity, 5-$HT_{1A}$ affinity and [$^{35}$S]GTPγS: $E_{max}$ values for aryloxytropenes **12**




**12**

| Compound | R | $Ar^2$ | RB5-HT-T $K_i$ (nM)[a] | HC5-HT1A $K_i$ (nM)[a] | [$^{35}$S]GTPγS: $E_{max}$ (%)[b] |
|---|---|---|---|---|---|
| **23** | H | 3-Indolyl | 0.65 | 49% @ 1000 nM | 14 |
| **24** | H | 2-Naphthyl | 0.14 | 46% @ 1000 nM | 81 |
| **25** | OH | 2-Naphthyl | 0.54 | 173.2 | 0 |
| **26** | H | 3,4-Dichlorophenyl | 0.65 | 44% @ 1000 nM | Not tested |
| **27** | OH | 3,4-Dichlorophenyl | 0.38 | 107 | 0 |

[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] $E_{max}$ values are reported from one experimental run at six different concentrations.

tional 5-$HT_{1A}$ potency is seen with **22**, but this compound functions as a partial agonist (**22**: 5-HT-T: 4.0 nM; 5-$HT_{1A}$: 85.5 nM; $E_{max}$: 65%).

Extension of the 4-indolyloxyethyl chain to a 4-indolyloxypropyl linker produces the compounds in Table 2. Compound **23**, the 3-carbon analog of **21**, comparatively has similar 5-HT-T affinity and weaker 5-$HT_{1A}$ affinity (**23**: 5-HT-T: 0.65 nM; 5-$HT_{1A}$: 49% @ 1000 nM, $E_{max}$: 14%). The corresponding $Ar^2$ = 2-naphthyl analogs (**24**) has a similar biological profile as **23** and shows 5-$HT_{1A}$ agonism ($E_{max}$: 81%). However, introduction of an (*S*)-OH group produces **25**, which has substantially more affinity for the 5-$HT_{1A}$ receptor compared to **24**, and is a full 5-$HT_{1A}$ antagonist (**25**: 5-HT-T: 0.54 nM, 5-$HT_{1A}$: 173.2 nM; $E_{max}$: 0%). This result is consistent with the fact that **25** contains the structure of pindolol, a known 5-$HT_{1A}$ antagonist in the dorsal raphe.[20] A similar strategy has been used to induce 5-$HT_{1A}$ antagonism in aryloxypropyl piperidine analogs.[11] Like the propyloxy analogs **23** and **24**, **26** possesses excellent 5-HT-T affinity but weak 5-$HT_{1A}$ affinity (**26**: 5-HT-T: 0.65 nM, 5-$HT_{1A}$: 44% @ 1000 nM). Incorporation of the pindolol (*S*)-OH group gives **27**, a compound with excellent 5-HT-T affinity and good 5-$HT_{1A}$ affinity/antagonism (**27**: 5-HT-T: 0.38 nM, 5-$HT_{1A}$: 107 nM, $E_{max}$: 0%).

## 4. Summary

We have disclosed a series of novel aryloxy-8-azabicyclo[3.2.1]octanes that have potent affinity for the 5-HT-T and good to moderate 5-$HT_{1A}$ affinity. In addition, structure–activity relationships have been delineated such that these compounds can have 5-$HT_{1A}$ antagonist functional activity via the optimization of the $Ar^1$ and $Ar^2$ groups in **11** and **12**. Most interestingly, indole analog **21** (Table 1) and pindolol analogs **25** and **27** (Table 2) possesses potent 5-HT-T affinity and moderately potent 5-$HT_{1A}$ affinity. Moreover, these compounds function as full 5-$HT_{1A}$ antagonists. 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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