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Diphenylsulfone Muscarinic Antagonists: Piperidine Derivatives with High M_2 Selectivity and Improved Potency

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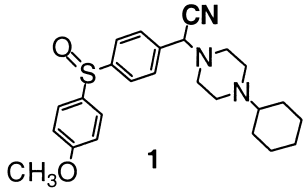
Abstract—Piperidine analogues of our previously described piperazine muscarinic antagonists are described. Piperidine analogues show a distinct structure–activity relationship (SAR) that differs from comparable piperazines. Compounds with high selectivity and improved potency for the M_2 receptor have been identified. The lead compound, **12b**, increases acetylcholine release in vivo. Compounds of this class may be useful for the treatment of cognitive disorders such as Alzheimer's disease (AD). © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a profound cognitive impairment that progresses eventually to an inability to function independently and ultimately to death. One of the consistent findings in brains of AD patients is loss of cholinergic markers, including levels of acetylcholine (ACh).[1] The cholinergic approach to treatment of AD involves counteracting this loss in cholinergic activity by pharmacologic intervention to increase cholinergic transmission. Currently available cholinergic therapy accomplishes this by inhibition of acetylcholinesterase, the major enzyme responsible for the degradation of ACh.[2] Cholinesterase inhibitors such as Aricept® have shown moderate efficacy in AD patients but also produce dose-limiting peripheral cholinergic side effects.[3] Acetylcholine levels can also be increased by blocking central presynaptic M_2 receptors. Centrally acting muscarinic M_2 antagonists may improve cognition without the side effects associated with other cholinergic approaches provided there is sufficient selectivity for the M_2 receptor over other muscarinic receptors, particularly the M_1 receptor, which mediates the cognitive effects of acetylcholine.[4,5] Very few compounds with the requisite selectivity are known, and many of these do not cross the blood–brain barrier effectively.

We have previously described a series of piperazine diphenylsulfoxides typified by **1**, that are potent and selective antagonists of the M_2 receptor.[6] As a part of our on-going follow-up to this discovery, we now describe our work in a related piperidine series of M_2 antagonists, **2**. Despite the obvious structural similarities, the piperidine series shows a distinct structure–activity relationship (SAR) which differs from the piperazine series in many respects but has nonetheless produced compounds with improved potency and high selectivity for the M_2 receptor.



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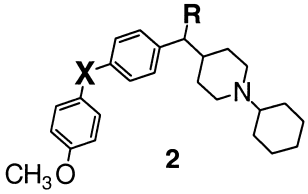

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Chemistry[7]

Piperidine analogues of **1** were prepared as shown in Scheme 1. Aldol condensation of compound **3**[8]

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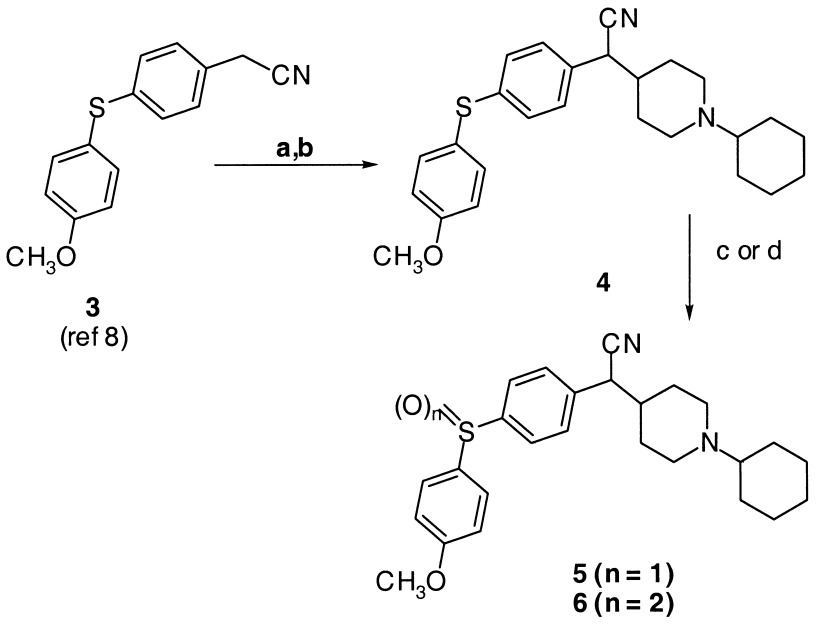
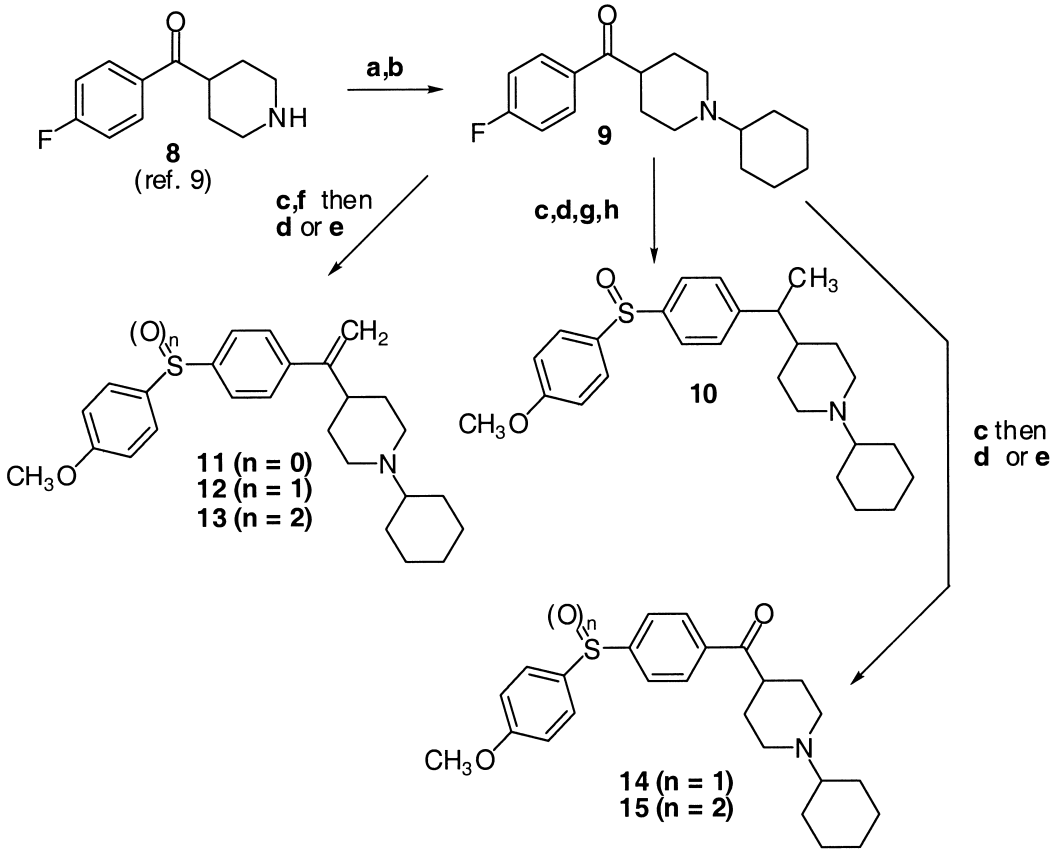
followed by reduction of the resulting olefin provided **4**. This was oxidized to the corresponding sulfoxide **5** or sulfone **6** using either one equivalent or excess sodium perborate.

Methylidine, ketone, and methylated analogues were prepared as shown in Scheme 2. Fluorophenyl ketone **8** was alkylated with cyclohexenyl bromide followed by reduction to give **9**. Reaction with the sodium salt of



Scheme 1. Synthesis of piperidine analogues of **1**: (a) 1-cyclohexyl-4-piperidinone, NaOEt/EtOH, reflux; (b) Mg/MeOH; (c) 1.05 equiv $NaBO_3{\cdot}4H_2O$; (d) 2.7 equiv $NaBO_3{\cdot}4H_2O$.



Scheme 2. Synthesis of methylidine, ketone, and methylated analogues of **1**: (a) 3-bromocyclohexene; (b) H_2 Pd–C 95%; (c) 4-methoxythiophenol, NaH 75%; (d) 1.04 equiv $NaBO_3{\cdot}4H_2O$ 92%; (e) 2.7 equiv $NaBO_3{\cdot}4H_2O$ 55%; (f) Tebbe reagent, THF, 0 °C, 51%; (g) MeMgBr/$CeCl_3$; (h) Et_3SiH, TFA.

4-methoxythiophenol converted **9** to a diarylsulfide ketone, which served as a common intermediate for other compounds as shown.

Racemic sulfoxides were resolved via HPLC using a Chiracel OJ column.[10]

Results

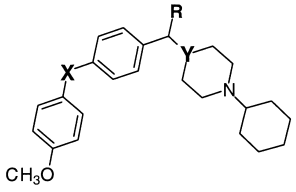
Our initial efforts focused on direct analogues of **1** and related compounds in the piperidine series (Table 1). In earlier work, we observed that both the benzylic nitrile and the (*S*)-sulfoxide of **1** were important for potency and selectivity for the M_2 receptor. These effects did not carry over to the analogous piperidine series. For instance, (*R*)-sulfoxide **1a** is significantly less selective than its (*S*)-sulfoxide isomer **1b** due to a small loss in M_1 potency but a larger loss in M_2 potency for the (*R*)-enantiomer versus the (*S*)-isomer. By contrast, the sulfoxide enantiomers of the corresponding piperidine **5a** and **5b** show comparable potency and selectivity, and both are less potent and selective than **1b**. Changing the benzylic nitrile to a methyl group **10** significantly increases potency in the piperidine series but has only a modest impact on potency in the piperazine series, **7**. In all cases, benzylic methyl derivatives are less selective than benzylic nitriles, and sulfones are less selective than sulfoxides, although in the piperidine series, sulfone **6** is more potent than either sulfoxide enantiomer.

We investigated a number of alternative substituents at the benzylic position, motivated in part by a desire to limit the chirality of compounds. Among these, the most promising was a series of methylidine and related ketone derivatives (Table 2). The methylidine compounds are 10–100× more potent than the benzylic methyl or nitrile analogues but display SARs which are similar to the piperazine series. Thus, (*S*)-sulfoxide **12b** is ~50× more potent than **1b** but shows comparable selectivity versus the M_1 receptor. The corresponding (*R*)-sulfoxide isomer **12a** is significantly less selective, but unlike in the piperazine series, the decrease in selectivity is due almost entirely to an increase in potency at M_1. Ketone analogues **14a** and **14b** show a similar preference for one sulfoxide enantiomer. The preferred enantiomer in the ketone series **14b** is only slightly less selective than **12b** but is about 60× less potent. Sulfones **13** and **15** are consistently less selective than sulfoxides.

The effect of **12b** on acetylcholine release in rat brain was investigated using microdialysis as previously described for **1b**[6,13] (Fig. 1). After ip administration, **12b** caused a rapid and sustained increase in acetylcholine release comparable to what was observed with **1b**. Peak acetylcholine levels were reached about 30 min after dosing, and significant increases over baseline were maintained for at least 2 h. Peak acetylcholine levels were significantly lower after oral administration and were achieved about 2 h after dosing, suggesting slow absorption of compound. However, acetylcholine levels at 2 h were comparable after either po or ip administration.

In summary, we have identified a series of piperidines that are potent inhibitors of the muscarinic M_2 receptor

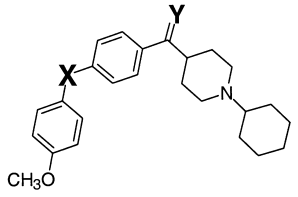
Table 1. Piperidine analogues of **1**



Compound	X	Y	R	Muscarinic binding K_i (nM)[a] M_1	M_2	M_3	M_4	M_5
1a	SO (*R*)	N	CN	253.3	17.3	NT	18.4	NT
1b	SO (*S*)	N	CN	111.9	2.78	29.4	14.8	308.6
2	SO_2	N	CN	71.8	7.3	6.8	18.6	NT
5a	SO (*R*)	CH	CN	136.3	7.14	58.8	45.05	NT
5b	SO (*S*)	CH	CN	113.1	7.67	37.04	12.74	NT
6	SO_2	CH	CN	16.4	1.3	NT	NT	NT
7	SO	N	CH_3	6.0	1.0	0.97	2.2	NT
10	SO	CH	CH_3	0.53	0.14	0.16	0.07	1.66

[a]Assay procedures are described in refs 11 and 12.

Table 2. Methylidine and ketone derivatives



Compound	Y	X	Muscarinic binding K_i (nM) M_1	M_2	M_3	M_4	M_5
11	CH_2	S	4.4	0.37	NT	NT	NT
12a	CH_2	SO (*R*)	0.68	0.03	0.13	0.09	NT
12b	CH_2	SO (*S*)	2.14	0.057	0.38	0.32	NT
13	CH_2	SO_2	2.8	0.17	0.48	0.33	NT
14a	O	SO (*R*)	69.5	10.8	20.1	15.2	NT
14b	O	SO (*S*)	103.8	3.58	27.8	17.9	NT
15	O	SO_2	31.09	3.07	13.76	9.05	NT

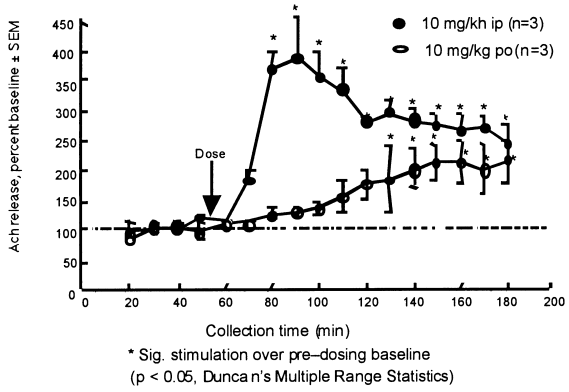


Figure 1. Effect of **12B** on ACh release from striatum of conscious rat following po and ip administration.

and show up to 38× selectivity versus the M_1 receptor. Compound **12b** increases acetylcholine release in rats, indicating that this class of compounds could be useful in treating the cognitive deficit of Alzheimer's disease. As both **1b** and **12b** show significant activity at the M_3 receptor, our on-going follow-up in both series is focused on improving selectivity versus the other muscarinic receptors.

Acknowledgements

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10. Sulfoxide enantiomers were separated using a preparative Chiracel OJ column, typically eluting with 10–20% 2-propanol/hexane. The first eluting enantiomer, designated (a), was tentatively assigned the (*R*) stereochemistry by analogy to the order of elution of **1b** and its enantiomer, whose stereochemistry was unambiguously assigned via asymmetric synthesis as described in ref 6. Although the assignment of stereochemistry via HPLC elution order is tentative, in cases where significant differences in activity were seen, the more selective enantiomer was consistently the one assigned the (*S*) stereochemistry.
11. Muscarinic receptor binding was determined using cloned human M_1–M_5 receptors as previous described (ref 12). Competition binding experiments were performed using ^{3}H-QNB as the radioligand. IC_{50} values were determined in triplicate and K_i values were derived from IC_{50} values using the Cheng–Prusoff equation.
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