Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 795–798

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Structure–Activity Relationships of M_2-Selective Muscarinic Receptor Ligands in the 1-[4-(4-Arylsulfonyl)-phenylmethyl]-4-(4-piperidinyl)-piperazine Family

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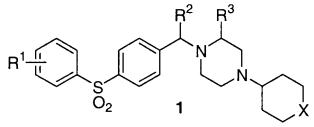
Received 19 October 2001; accepted 21 December 2001

Abstract—The synthesis and muscarinic binding properties of compounds based on the 1-[4-(4-arylsulfonyl)phenylmethyl]-4-(1-aroyl-4-piperidinyl)-piperazine skeleton are described. For compounds, substituted with appropriately configured methyl groups at the benzylic center and at the piperazine 2-position, high levels of selective, M_2 subtype affinity could be obtained, particularly when the terminal *N*-aroyl residue was *ortho*-substituted.

Alzheimer's Disease (AD), characterized by a progressive loss of cognitive function, is a serious medical problem. Since AD is largely a disease of the elderly, the percentage of affected persons is expected to grow, as overall life expectancy continues to increase. Currently, therapeutic intervention in AD involves enhancing levels of the key neurotransmitter acetylcholine (ACh)[1] by treatment with inhibitors of acetylcholinesterase, which retard the breakdown of ACh in the synapse. An alternative way to elevate ACh levels is via the cholinergic receptor system. Our approach has been to pursue antagonists of the presynaptic M_2 receptor.[2,3] Selective binding to M_2 relative to the other muscarinic receptor subtypes is an important goal: the postsynaptic M_1 receptor is believed to mediate the effects of ACh in learning and memory, and the peripheral M_3 receptor is involved in the regulation of gastro-intestinal functions.

In the accompanying paper,[4] we described novel, M_2-selective ligands of general structure **1**, and showed that enhanced selectivity over the postsynaptic M_1 receptor is obtained when R^2 and R^3 are (*S*)-Me and (*R*)-Me, respectively. Initial modification of the aromatic ring substitution pattern and the piperidine *N*-substituent led to **2**, which exhibited acceptable selectivity [$K_i(M_1)/K_i(M_2) = 109$] and also elevated brain acetylcholine levels when administered orally to rats.



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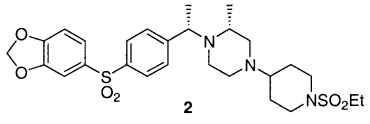

2

In this paper, we describe chemical and biological results which illustrate the optimization of the affinity for the M_2 receptor over the M_1 and M_3–M_5 subtypes, for the diaryl sulfone series. The effects of changes in the aryl ring of the $ArSO_2$ moiety, the methylation pattern on the piperazine ring, and the 1-substituent on the piperidine ring are described. In the latter position, we

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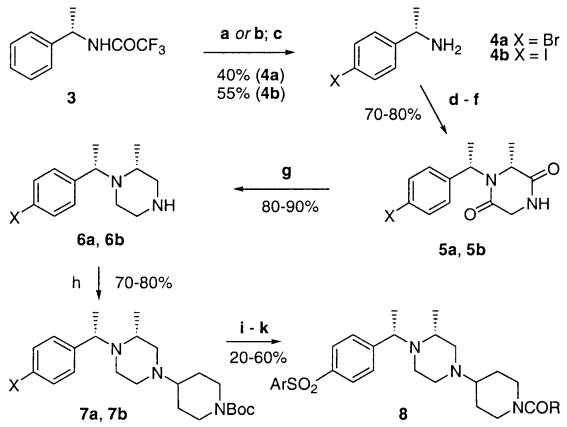
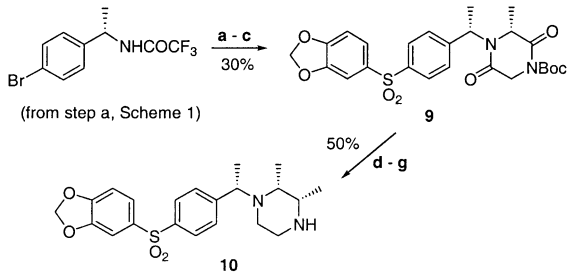


Scheme 1. (a) 1,3-dibromo-5,5-dimethylhydantoin, $MeSO_3H$, CH_2Cl_2, rt, 48 h; *or* (b) $PhI(OCOCF_3)_2$, I_2, CH_2Cl_2, rt, 48 h; (c) KOH, MeOH, rt, 2 h; (d) (*S*)-$MeCH(OSO_2CF_3)CO_2Et$, CH_2Cl_2, K_2CO_3–H_2O, rt, 6 h; (e) $ClCH_2COCl$, 1,2-$C_2H_4Cl_2$, 90 °C, 4 h; (f) NH_3, NaI, DMSO–H_2O, rt, 24 h; (g) $NaBH_4$, $BF_3{\cdot}Et_2O$, DME, 80 °C, 6 h; (h) 1-(*tert*-butoxycarbonyl)-4-piperidone, $NaBH(OAc)_3$, CH_2Cl_2, rt, 24 h; (i) *n*-BuLi, THF-hexanes, −70 °C, then $ArSO_2F$, −70 to −20 °C; (j) TFA, 1 h; (k) RCOCl, CH_2Cl_2, K_2CO_3–H_2O, rt, 2 h *or* RCO_2H, EDCI, HOBt, *i*-Pr_2NEt, DMF, rt, 24 h.

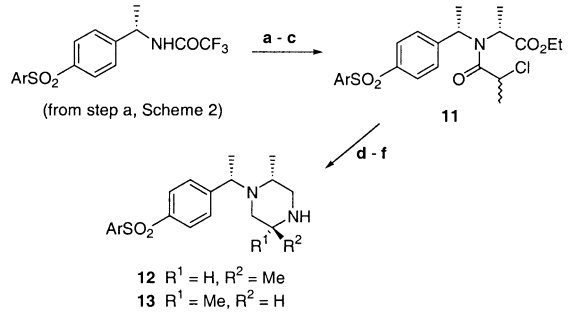
show that certain *ortho*-substituted aromatic amides confer exceptional selectivity for the M_2 receptor.

Our initial objective was to develop a versatile synthesis from available 'chiral pool' substances, such that intermediates along the route could be diverted to generate a variety of substitution patterns. We chose diketopiperazines as the key intermediates, with late-stage introduction of the arylsulfonyl substituent, as shown in Scheme 1.

Bromination or iodination of *N*-trifluoroacetyl-(*S*)-1-phenylethylamine, crystallization to obtain the dominant[5] *para* isomers and subsequent alkaline hydrolysis gave **4a** and **4b**, respectively. Sequential *N*-alkylation with the triflate derived from ethyl (*S*)-lactate, *N*-chloroacetylation[6] and final treatment with ammonia gave the crystalline diketopiperazines **5a** and **5b**, which were converted by reduction followed by reductive amination to **7a** and **7b**, the first intermediates in the sequence which needed chromatographic purification. The sulfones were prepared by Br(I)–Li exchange followed by reaction with the appropriate arylsulfonyl fluoride.[7] Yields were high except when the aryl residue carried an oxy-substituent, *meta* to the fluorosulfonyl group. In those cases, substantial amounts of the des-bromo compound (X = H in structure **7a**) were formed, and the sulfonyl fluoride was decomposed. We ascribe this to competing H-abstraction by the aryllithium species of the proton between the two electron withdrawing groups (–OR and $–SO_2F$). In these cases, yields were improved by adding 1.1 equivalents of anhydrous magnesium bromide to the intermediate aryl lithium, with warming to 0 °C before adding the sulfonyl fluoride. Following diaryl sulfone isolation, the sequence was completed by *N*-deprotection and amide formation under standard conditions, to afford the target compounds **8**.



Scheme 2. (a) 1.1 equiv MeLi, then 1.2 equiv *n*-BuLi, THF-hexanes, −70 °C then 1.2 equiv 3,4-(methylenedioxy)-benzenesulfonyl fluoride, −70 to −20 °C; (b) steps c–f, Scheme 1; (c) di-*tert*-butyl dicarbonate, Et_3N, THF, rt, 5 h; (d) MeMgBr, THF, 0 °C, 15 min; (e) CCl_3CO_2H, $NaBH_3CN$, CH_2Cl_2, rt, 2 h; (g) $NaBH_4$, $BF_3{\cdot}Et_2O$, DME, 80 °C, 6 h.



Scheme 3. (a) KOH, MeOH, rt, 2 h; (b) (*S*)-$MeCH(OSO_2CF_3)CO_2Et$, CH_2Cl_2, K_2CO_3–H_2O, rt, 6 h; (c) rac-MeCH(Cl)COCl, 1,2-$C_2H_4Cl_2$, 90 °C, 12 h; (d) NaN_3, DMSO, 80 °C, 6 h; (e) H_2, Pd/C, EtOH, 50 psi, rt, 2 h; (f) $NaBH_4$, $BF_3{\cdot}Et_2O$, DME, 80 °C, 6 h.

Alternatively, the same organolithium species could be reacted with the appropriate aryl disulfide, and the resulting product oxidized (HOAc, H_2O_2 or $NaBO_3$) to the sulfone. The same sulfides could also be obtained from the iodocompound **7b** and $ArSH/K_2CO_3/CuI$. Direct reactions of **7b** with $ArSO_2Na/CuI$, a satisfactory process in simple systems,[8] gave low yields of the sulfones.

Diketopiperazines were also the key to obtaining different piperazine ring methylation patterns. The route to the *cis*-2,3-dimethyl compound is shown in Scheme 2. Activation of the lactam carbonyl permitted the highly selective addition of methyl magnesium bromide to give a stable, *N*-*tert*-butoxycarbonyl hemiaminal. Mild reduction, *N*-deprotection, and final reduction of the remaining carbonyl group with borane afforded **10**, for further elaboration. Only the *cis* isomer was produced in the acyliminium ion reduction step, reflecting attack of the hydride donor *anti* to the 2-methyl group.

To access 2,5-dimethylpiperazines (Scheme 3), the chloroacetyl chloride in Scheme 2 was replaced with racemic 2-chloropropionoyl chloride. Reaction of the resulting amide **11** with ammonia was unsatisfactory, but displacement with azide followed by catalytic reduction gave the separable, diastereoisomeric 2,5-disubstituted diketopiperazines. Final reduction with borane afforded the piperazines **12** and **13**, for further elaboration.

Using cloned human M_1–M_5 receptors, K_i values for receptor binding were determined as previously described.[9] Briefly, membranes were incubated with [^{3}H]-*N*-methyl scopolamine and test compounds for 1 h at room temperature, followed by rapid filtration and scintillation counting to measure bound radioactivity. Values shown are averages of four determinations; inter-replicate variability was below 10%.

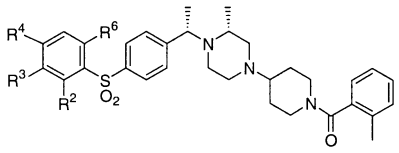
The results shown in Table 1, selected from a large panel of amides, in which the 3,4-(methylenedioxy)-phenylsulfonyl moiety, the methylation pattern and the absolute stereochemistry were kept constant, highlight the structure–activity relationships.

Although the M_2 affinity was not unduly sensitive to the nature of the *N*-acyl group, the receptor subtype selectivity was dramatically affected. Simple, aliphatic amides (typified by **14**) were not selective. In the aromatic amides, the substitution pattern proved to be the key: a variety of *ortho* substituents conferred a high degree of selectivity for M_2 versus the M_1 and M_3 receptors, and acceptable selectivity versus M_5 (entries **18**–**21**). In general, relatively non polar substituents were preferred, although the 2-hydroxy benzamide (**23**) and particularly the 2-amino benzamide (**21**) were also M_2-selective. Compounds **24** and **25** show that large substituents were tolerated with respect to binding affinity, but did not affect selectivity in a consistent fashion. For more highly substituted amides, 2,4- and 2,6-disubstitution (**17** and **27**, respectively) were not helpful, but the 2,3-(methylenedioxy)-benzamide **26** had excellent selectivity. We also evaluated heterocyclic amides, with mixed results. The thiophene analogue **28** of the *o*-chlorobenzamide demonstrated high affinity and selectivity, whereas the pyridine analogue **29** of the *o*-toluamide was nonselective, and a relatively weak binder.

Having established those structural requirements in the terminal amide residue, which maximized M_2 selectivity, we then investigated diverse substitution patterns on the aromatic ring of the arylsulfonyl group. Representative compounds are shown in Table 2.

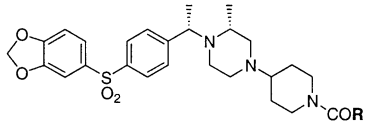
In general, we were not able to significantly improve upon the affinity–selectivity profile exhibited by the best compounds shown in Table 1, but some interesting trends emerged. Comparison of entries **19** and **30** shows that for *o*-toluamides, like sulfonamides, the 3,4-(methylenedioxy)-phenylsulfonyl compounds have greater affinity than their *p*-methoxy counterparts. 2,4-Dimethoxy substitution (entry **31**) also conferred acceptable selectivity, but 2,3,4-trisubstitution was tolerated only when the substituents adjacent to the sulfonyl group were tied back to form a bicyclic system (entry **33** vs **32** and **35**). Although earlier results[3] had suggested that strongly electron-donating substituents were important when the piperidine carries an *N*-sulfonyl substituent, this was not true for the corresponding *o*-toluamides, where a *m*-methyl or

Table 2. Effects of the arylsulfonyl group on receptor binding and selectivity



Entry	R^2	R^3	R^4	R^6	$K_i(M_2)$(nM)	M_1/M_2	M_3/M_2
19	H	–OCH$_2$O–		H	0.2	255	74
30	H	H	OMe	H	2.6	245	118
31	OMe	H	OMe	H	0.6	147	157
32	OMe	OMe	OMe	H	442	1	—
33	–OCH$_2$O–		OMe	H	4.7	121	188
34	OMe	–OCH$_2$O–		H	3.0	27	—
35	H	–OCH$_2$O–		OMe	53	2	—
36	H	Me	H	H	0.4	305	107
37	H	CF_3	H	H	1.8	170	108

Table 1. Effects of the terminal amide on receptor binding and selectivity



Entry	R	K_i (M_2) (nM)	M_1/M_2	M_3/M_2	M_4/M_2	M_5/M_2
14	*cyclo*-C_3H_5	1.3	12	23	3	23
15	C_6H_5	0.6	32	29	4	15
16	3,4-$Cl_2C_6H_3$	0.8	8	11	2	7
17	2,4-$Cl_2C_6H_3$	0.3	66	17	7	5
18	2-ClC_6H_4	0.1	298	69	4	25
19	2-MeC_6H_4	0.2	255	74	6	23
20	2-$MeOC_6H_4$	0.1	333	176	12	72
21	2-$H_2NC_6H_4$	0.5	239	70	7	24
22	2-$AcNHC_6H_4$	4.4	13	5	3	5
23	2-HOC_6H_4	1.0	84	15	7	18
24	2-$PhOC_6H_4$	0.1	22	33	6	6
25	2-($PhCO_2CH_2$)C_6H_4	0.2	266	73	9	47
26	2,3-(OCH_2O)C_6H_3	0.1	330	38	17	80
27	2,6-$Me_2C_6H_3$	0.8	37	57	8	2
28	3-Cl-2-thienyl	0.3	413	83	7	45
29	3-Me-2-pyridyl	77	8	0.3	4	3

m-trifluoromethyl group was also compatible with high levels of selectivity (entries **36** and **37**).

Additional methyl groups on the piperazine ring had a deleterious effect on selectivity. Reductive amination of the 2,3-dimethyl piperazine derivative **10**, and the 2,5-dimethylcompounds **12** and **13** with both cyclohexanone and 1-(*o*-toluoyl)-4-piperidinone gave the corresponding piperidinyl-piperazines, which proved to have high affinity, but poor subtype selectivity.

In conclusion, we have demonstrated that selective, high affinity M_2 receptor ligands may be obtained by manipulation of the substituent pattern on the two, terminal aromatic rings in a series of 1-[*1S*-(4-[4-arylsulfonyl]-phenyl)-ethyl]-*2R*-methyl-4-(1-aroyl-4-piperidinyl)-piperazines. Compounds with >100-fold selectivity for the M_2 receptor, relative to both the M_1 and M_3 subtypes, were obtained, particularly when the piperidine nitrogen bears an *ortho* substituted benzoyl group. Additional methyl groups in the piperazine ring reduced the receptor subtype selectivity.

Acknowledgements

The authors wish to thank the SPRI Physical-Analytical Department for spectroscopic and analytical data, and Drs. J. C. Clader, A. K. Ganguly, and C. Strader for support and discussions.

References and Notes

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5. In the crude products, the *p*- to *o*- ratios were approximately 5:2 for bromination and 6:1 for iodination; small amounts of di-halo compounds were also present.
6. *N*-Acylation of these hindered, moderately nucleophilic aminoesters was slow, and proceeded poorly in the presence of base, presumably because of more rapid formation and subsequent polymerization of chloroketene. Heating as indicated, to dissociate intermediate hydrochloride salts, gave quantitative conversion to the desired amides. After washing with aqueous sodium bicarbonate solution and evaporation, the crude amide was used directly in the next step.
7. The arylsulfonyl fluorides were obtained in excellent yields by treating the corresponding chlorides with potassium fluoride in aqueous acetone: Aitken, R.; Drysdale, A.; Ferguson, M. G.; Lough, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 875. Convenient routes to the non-commercial arylsulfonyl chlorides will be detailed elsewhere.
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