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Isopropyl amide derivatives of potent and selective muscarinic M_2 receptor antagonists

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Abstract—Low molecular weight amide derivatives were synthesized and evaluated as M_2 receptor antagonists for the treatment of Alzheimer's disease. Isopropyl amides **19** and **31** are highly potent, selective and low molecular weight M_2 receptor antagonists with structural features different from our clinical candidate **1**.

Alzheimers's disease (AD) is a neurodegenerative disease characterized by a progressive loss of cognitive function which leads to severe memory loss accompanied by behavioral changes. Current treatment for AD involves increasing acetylcholine (ACh) levels in the synapse through administration of acetylcholinesterase inhibitors.[1] An alternate method which we are pursuing is to enhance acetylcholine levels through antagonism of presynaptic M_2 muscarinic receptors.[2,3] Selective binding to the M_2 receptor over other muscarinic subtypes is an important criteria for the program, as M_1 antagonism would negate the therapeutic effects of increased ACh levels, and blockade of other muscarinic receptors would increase the potential for unwanted side effects. Recently, co-workers from our laboratories have disclosed low molecular weight sulfoxide analogues **2** and (+)-**3** derived from our clinical candidate **1**. Compound (+)-**3** showed oral efficacy in animal models comparable to that of **1**.[2b,4] We report here the identification of isopropyl amides **19** and **31** as potent and selective M_2 receptor antagonist which possess structural features different from those of **2** and **3** (Fig. 1).

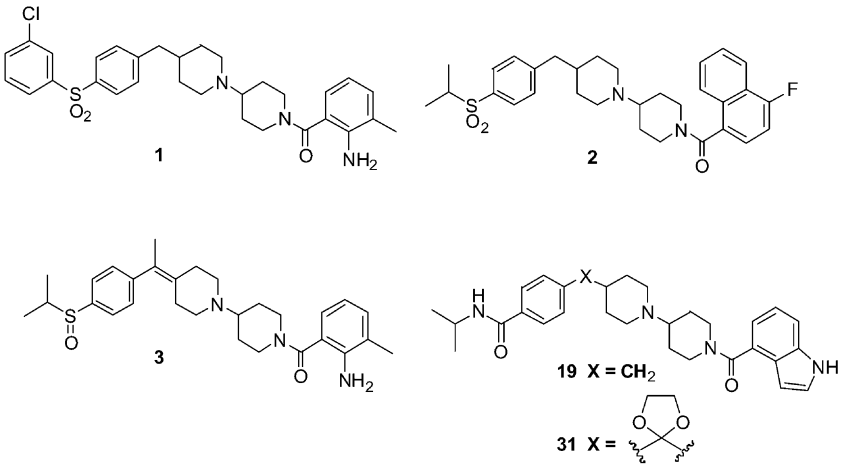

Figure 1. M_2 receptor antagonists.

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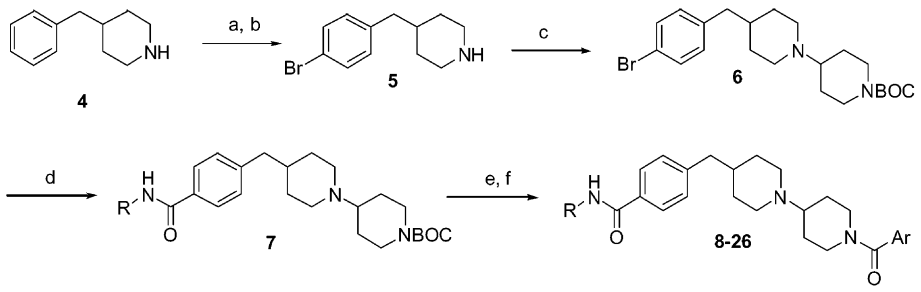
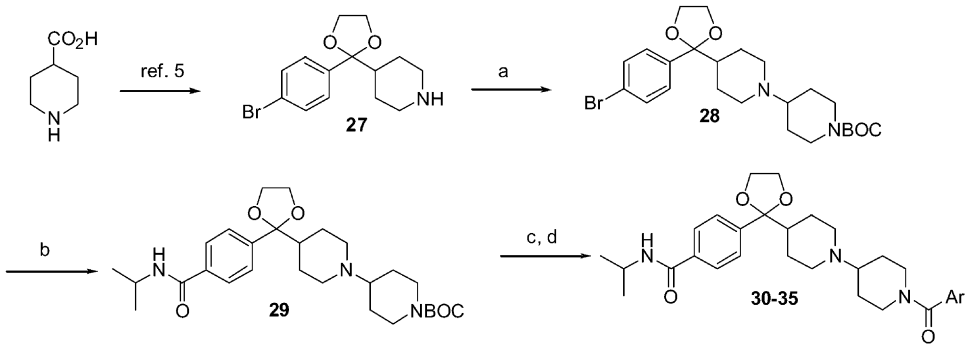
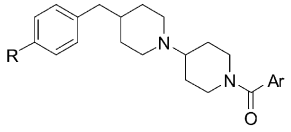


Scheme 1. (a) TFAA, CF_3SO_3H, 1,3-dibromo-5,5-dimethylhydantoin, CH_2Cl_2, 50–60%; (b) K_2CO_3, MeOH, 98%; (c) $NaBH(AcO)_3$, 1,2-DCE, 1-*t*-butoxycarbonyl-4-piperidone, 60%; (d) *n*-BuLi, RNCO, THF, 70–90%; (e) TFA, CH_2Cl_2, 90%; (f) ArCOOH, EDCI, DMAP, CH_2Cl_2, 85–95%.



Scheme 2. (a) $NaBH(AcO)_3$, 1,2-DCE, 1-*t*-butoxycarbonyl-4-piperidone, 50%; (b) *n*-BuLi, *i*PrNCO, THF, 71%; (c) TFA, CH_2Cl_2, 90%; (d) ArCOOH, EDCI, DMAP, CH_2Cl_2, 85–95%.

Table 1. Effect of left hand amide modifications on receptor binding and selectivity



Compd	R	Ar	M_2 K_i (nM)	M_1/M_2	M_3/M_2	M_4/M_2	M_5/M_2
1	—	—	0.89	734	787	69	95
2	^{i}PrSO$_2$		17	21	na	na	na
(+)-3	—	—	0.89	101	170	22	36
8	^{i}PrNHCO		2.1	77	6.6	12	48
9	^{i}PrNHCO		7	121	na	na	na
10	^{t}BuNHCO		18	72	1.6	na	na
11	^{t}BuNHCO		106	12	10	5	14
12	*c*-hexylNHCO		1300	1	na	na	na
13	*c*-hexylNHCO		15	31	na	na	na
14	PhNHCO		104	9	na	na	na
15	PhNHCO		122	5	na	na	na

na, not available.

Synthesis of the amide targets is outlined in Scheme 1. Selective bromination of commercially available 4-benzyl piperidine afforded *p*-bromobenzyl piperidine trifluoroactamide which upon hydrolysis afforded **5**. Reductive amination of **5** with 1-*tert*-butoxycarbonyl-4-piperidone provided piperidinyl piperidine **6**. The amides **7** were prepared by Br–Li exchange followed by reaction with the commercially available isocyanates. The final products **8**–**26** were obtained after deprotection followed by aryl amide formation with appropriate aromatic acids under standard conditions. The syntheses of the ketal targets are outlined in Scheme 2. Compound **27**, prepared according to a previously described procedure was converted to final targets **30**–**35** in a manner similar to non-ketal derivatives.[5]

The K_i values for receptor binding were determined using cloned human muscarinic receptors as previously described.[6] The results shown in Table 1 highlight the structure–activity relationships for left side amide modifications. First, for our initial structure–activity studies we fixed the right side aryl amide as either 4-fluoronaphthamide or *o*-toluamide based on our previous studies, which are optimal for providing good M_2 biding affinity and selectivity.[7]

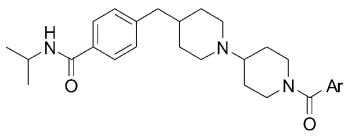
In general, M_2 affinity was sensitive to both terminal amide modifications. Isopropyl amides **8** and **9** were identified to be the best in terms M_2 potency and selectivity. 4-Fluoronaphthyl aromatic amides gave us good M_2 selective antagonists with exception of compounds **12** and **14**. Compound **9** containing *o*-toluamide provided a high degree of selectivity for M_2 versus M_1, but however for other compounds, this modification resulted in non selective and less active antagonists.

Having established the left hand isopropyl amide as a suitable amide, we then investigated diverse substitution patterns on the right side aromatic region. Representative examples are shown in Table 2. The difluorinated naphthyl compound **16** showed good selectivity for M_2 versus M_1 and M_3, but with 2-fold loss of M_2 affinity as compared to **8**. Compound **18** is the best among the several quinoline derivatives which were studied as a potential replacement for the naphthyl ring. The indole heterocyclic amide derivative **19** showed excellent M_2 receptor binding affinity and selectivity versus other subtypes except M_4. Earlier results have suggested that introducing polar 2-amino-3-methylphenyl group can be advantageous for improving not only potency and selectivity but also in vivo activity.[2b] However, in this series, introduction of 2-amino-3-methyl phenyl group gave low M_2 affinity and poor selectivity (**25**). The 3-amino-2-methyl phenyl group as in **26** was found to be excellent and showed a high level of selectivity and potency. From these SAR investigations, we identified compounds **19** and **26** with desired binding and selectivity profile for further investigation.

Earlier studies have shown that replacement of the benzylic methylene unit with a ketal could improve metabolic stability, M_2 receptor affinity and selectivity.[8] Therefore we investigated a panel of isopropyl amides containing ketals at the benzylic position. The target compounds were prepared using approaches similar to those in Scheme 1, starting from isonipecotic acid as shown in Scheme 2. As expected, ketal analogues **30** and **34** showed excellent affinity and 2- to 3-fold improvement in selectivity relative to **8** and **19**. Surprisingly, 2-amino-3-methyl group which was found to be less favorable in the earlier series demonstrated excellent M_2 binding affinity and selectivity in the ketal series. Note that the introduction of double bond at the benzylic position similar to **3** in the isopropyl amide series resulted in potent and non-selective muscarinic antagonists antagonists (Table 3).

In summary, we have identified structurally new, selective and high affinity M_2 receptor ligands by manipulation of the substitution pattern on the two amide

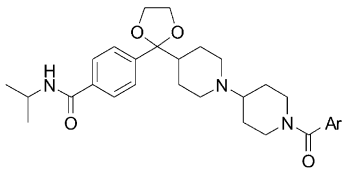
Table 2. Effects of aryl amide modifications on receptor binding and selectivity



Compd	Ar	M_2 K_i (nM)	M_1/M_2	M_3/M_2	M_4/M_2	M_5/M_2
8		2.1	77	6.6	12	48
16		5	113	97	14	19
17		9	72	na	na	na
18		40	7	na	na	na
19		1.6	107	382	7	164
20		27	7	na	na	na
21		5	60	na	na	na
22		6	51	na	na	na
23		78	12	na	na	na
24		12	62	54	10	58
25		9	40	na	na	na
26		1.6	201	na	na	na

na, not available.

Table 3. Effects of aryl amide modifications on receptor binding and selectivity in the benzylidene ketal series



Compd	Ar	M_2 K_i (nM)	M_1/M_2	M_3/M_2	M_4/M_2	M_5/M_2
30		2.4	214	116	19	84
31		1.1	120	259	22	234
32		9	49	na	na	na
33		35	28	na	na	na
34		2.7	364	222	42	25
35		1.9	60	na	na	na

na, not available.

moieties of the target molecule, along with ketal modification. Compounds **19** and **31** with >100-fold selectivity for the M_2 receptor, relative to M_1, M_3 and M_5 were obtained, particularly with a combination of isopropyl amide and indole aryl amide. Further development of these leads will be reported in due course.

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