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Design and synthesis of 4-phenyl piperidine compounds targeting the mu receptor

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Abstract—Small molecule mu agonists based on the 4-phenyl piperidine scaffold were designed and synthesized to further investigate the therapeutic potential of loperamide analogs. The resulting compounds show excellent agonistic activity towards the human mu receptor with interesting SAR trends within the series.

Opioid ligands exhibit a variety of physiological activities and have been utilized extensively in medicine, most prominently in the treatment of pain. To date, opioid agonists (more specifically mu agonists) such as morphine and its analogs are still the medicine of choice for the treatment of moderate to severe pain. However, the unwanted CNS mediated side effects such as respiratory depression, nausea and addiction have limited the usefulness of these opioids. The search for novel opioid agonists, which possess analgesic effects and better side effect profiles, has been a continuous goal of the medical community over the past 30 years. The design and synthesis of synthetic mu opioid receptor agonists is well documented in medicinal chemistry literature.[1] More recently, the 'Opioid Receptor Like' receptor 1 (ORL-1 receptor, formally named as NOP receptor) was discovered in 1994.[2] Subsequently its endogenous ligand nociceptin (N/OFQ), a novel heptadeca neuropeptide was isolated from brain and identified in 1995.[3] Previously we have reported the design and synthesis of 4-phenylpiperidine libraries targeting the NOP receptor. Potent NOP agonists and antagonists were obtained from lead generation and lead optimization libraries.[4,5] In this paper, we would like to report our efforts towards the discovery of small molecule mu receptor agonists based on the 4-phenyl piperidine scaffold. The syntheses, biological results and SAR trends of these new molecules will be presented.

Our design of this series of mu receptor agonists was based on the lead compounds **1** and **2** that were discovered in our NOP lead generation library (Fig. 1 and Table 1: compounds **1A**–**2CIII**).[4] The similarity among compounds **1**, **2** and loperamide has prompted our interests in the design and synthesis of more potent mu agonists based on the 4-phenyl piperidine scaffold. Loperamide is the active component of oral antidiarrheal drugs such as Imodium, Imotil and Maalox. In recent years, the antihyperalgesic properties of this opiate antidiarrheal agent were investigated by several groups in a variety of inflammatory pain models.[6,7] In all animal models examined, the potency of loperamide after local administration was comparable to, or better than

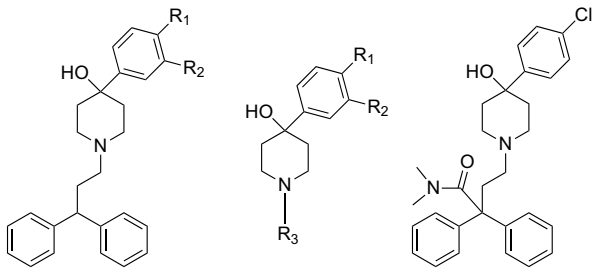

Figure 1. Representative mu receptor agonists.

Keywords: Mu receptor; ORL-1 receptor; Agonist; SAR; Structure activity; Chemistry; Design; Mu agonist.
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Table 1. Mu and NOP receptor binding and assays

Compds	R1	R2	R3	Mu K_i[a] (nM)	Mu functional	NOP K_i[a] (nM)	NOP functional
1A	H	CF_3		1 (±0)	Agonist[b]	116 (±3)	Agonist
1B	Cl	H		37 (±14)	PA[c,d]	372 (±105)	PA
1C	Cl	CF_3		4 (±1)	Agonist	225 (±70)	PA
2CI	Cl	CF_3	2-Naphthylmethyl	2.5 (±1)	ND[e]	879 (±260)	PA
2CII	Cl	CF_3	4-Trifluoromethyl-phenylmethyl	104 (±30)	PA	1194 (±4489)	ND
2CIII	Cl	CF_3	4-Cyanophenylmethyl	>10,000	ND	>10,000	ND
8A	H	CF_3		0.16 (±0.05)	Agonist	505 (±23)	Agonist
8B (loperamide)	Cl	H		0.53 (±0.32)	Agonist	>10,000	ND
8C	Cl	CF_3		0.11 (±0.04)	Agonist	2151 (±975)	ND
9A	H	CF_3		0.11 (±0.04)	Agonist	78 (±21)	Agonist
9B	Cl	H		0.23 (±0.11)	Agonist	590 (±105)	Agonist
9C	Cl	CF_3		0.3 (±0.1)	Agonist	149 (±49)	Agonist
10A	H	CF_3		331 (±46)	Agonist	>10,000	ND
10B	Cl	H		1461 (±387)	Agonist	>10,000	ND
10C	Cl	CF_3		489 (±132)	Agonist	>10,000	ND
11A	H	CF_3	3,3-Diphenylpropyl	8128 (±3681)	ND	>10,000	ND
11CI	Cl	CF_3	2-Naphthylmethyl	>10,000	ND	>10,000	ND
11CII	Cl	CF_3	3,3-Diphenylpropyl	>10,000	ND	>10,000	ND

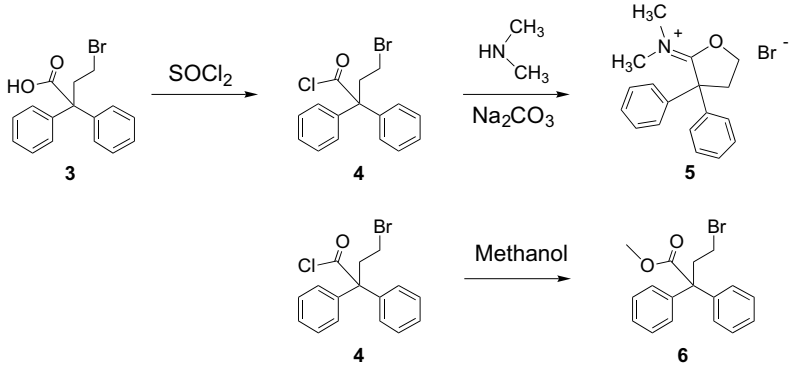
[a] Values are means of at least three experiments, standard deviation is given in parentheses.
[b] A compound was considered to be a full agonist when its ability to stimulate GTPγS binding was >75% in comparison to N/OFQ (NOP) or DAMGO (mu).
[c] An antagonist (ANT) stimulated GTPγS binding with efficacy ⩽ 10% in comparison to N/OFQ (NOP) or DAMGO (mu).
[d] A partial agonist (PA) stimulated GTPγS binding with efficacy >10% but <75% in comparison to N/OFQ (NOP) or DAMGO (mu).
[e] ND = not determined.

that of, systemically administered morphine. It was suggested that loperamide and its analogs have potential therapeutic use as peripherally selective opiate antihyperalgesic agents that lack many of the side effects generally associated with administration of centrally acting opiates.[6,8]

Although some medicinal chemistry work around the 3,3-diphenylpropylpiperidine scaffold was published decades ago in the search for novel antidiarrheal agents, very few of these molecules were evaluated for their ability to bind to cloned human opioid receptor subtypes and for their antihyperalgesic activities.[9,10] To further understand the therapeutic potential and SAR of the mu receptor agonists comprised of the 4-phenylpiperidine scaffold, we investigated the SAR around this moiety in the following directions: (1) 3-substitution of the 3,3-diphenylpropyl tail group; (2) the importance of the basic amino group on the piperidine ring; (3) the substitution effect on the 4-phenyl aromatic ring system.

The synthesis starts with the preparation of tail groups **5** and **6** (Scheme 1). A mixture of 4-bromo-2,2-diphenylbutyric acid **3**, thionyl chloride and trace amounts of dimethylformamide in chloroform was heated under reflux for 4 h. After completion of the reaction, the solvent was concentrated under reduced pressure to provide the 4-bromo-2,2-diphenylbutyric chloride **4** as a pale-yellow oil. The acid chloride **4** was treated with a 2 M solution of dimethylamine in THF under basic conditions to afford the dimethyl-(tetrahydro-3,3-diphenyl-2-furylidene)-ammonium bromide **5** as a solid. In addition, the acid chloride **4** was also converted into the ester **6** by reaction with methanol.

After sufficient quantities of **5** and **6** had been prepared, we used parallel synthesis for the construction of our target compounds. The reactions between dimethyl-(tetrahydro-3,3-diphenyl-2-furylidene)-ammonium bromide **5** and 4-phenylpiperidines **7** with 3 equiv of Na_2CO_3 in DMF went on smoothly at 80 °C and provided the desired product **8** in ca. 80% yield (Scheme

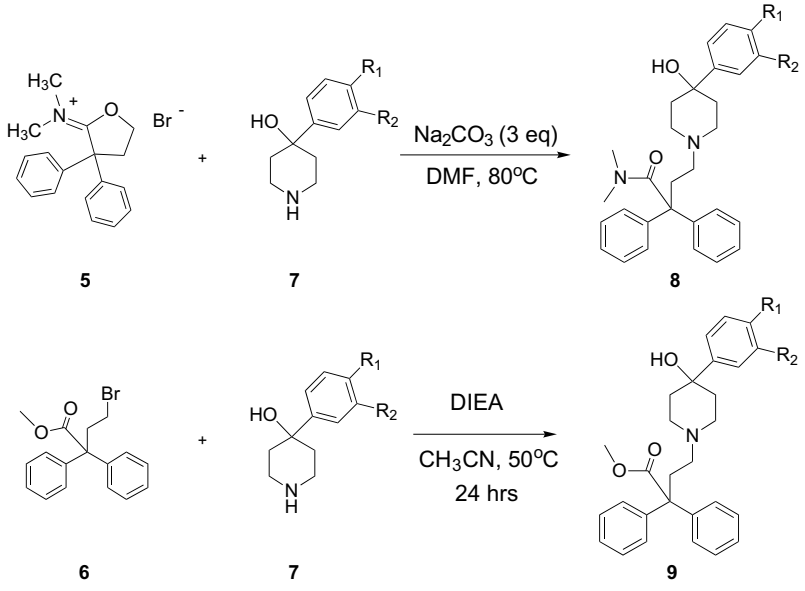


Scheme 1. Synthesis of tail groups **5** and **6**.

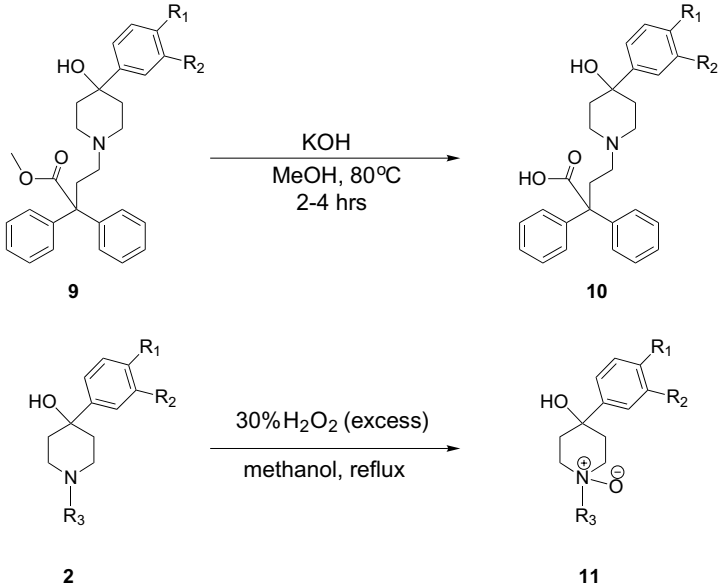
2).[11] On the other hand, the alkylation of 4-phenylpiperidines with bromide **6** required 24 h and afforded low to medium yields of final product **9**.[11] The yield of this reaction has not been optimized since a sufficient amount of desired product could be easily isolated from the reaction mixture. Products **8** and **9** were designed to evaluate the substitution effect at the 3-position of the 3,3-diphenylpropyl tail group.

The ester group in compound **9** was further converted to the corresponding acid **10** to introduce an acidic group at the 3-position of the 3,3-diphenylpropyl tail group (Scheme 3). To evaluate the importance of the basic amino group in terms of mu binding activity, we also synthesized the N-oxide of compound **2** (Scheme 3). A mixture of compound **2** and excess H_2O_2 in methanol was stirred and heated to reflux overnight to give product **11** as a white solid after work up.[11]

The compounds synthesized above were tested in NOP receptor binding and GTPγS functional assays using membrane preparations from recombinant HEK-293 cells as previously reported.[12] Recombinant human mu receptor membranes were purchased from Perkin Elmer Life Sciences (Boston, MA). Concentration inhibition binding assays using [^{3}H] diprenophine, were conducted according to the product inserts. The mu functional GTPγS assay was conducted using the commercially



Scheme 2. Synthesis of compounds **8** and **9**.



Scheme 3. Synthesis of compounds **10** and **11**.

available membrane preparation under conditions previously described for the NOP receptor.[12] The activity of the mu agonist DAMGO was used for data normalization (maximal effect elicited by 10 μM DAMGO = 100%; background GTPγS binding in the absence of agonist = 0%).

Table 1 shows the results from mu and NOP receptor binding and functional assays for the compounds described above. In general, these compounds show better affinity towards the mu receptor than the NOP receptor. A number of compounds have shown subnanomolar affinities against mu while only a few compounds possess ~100 nM affinities for the NOP receptor. The substitution patterns on the 4-phenyl ring have certain effects on the ligands' affinities towards mu receptor, which is evidenced by compounds **1A**–**C** with a rank order of 3-CF_3 (1 nM) > 3-CF_3, 4-Cl (4 nM) > 4-Cl (37 nM). However, this 4-phenyl ring substitution effect is reduced to a negligible level with tail groups such as *N*,*N*-dimethyl-2,2-diphenylbutyramide group and 2,2-diphenylbutyric acid methyl ester group. For example, compounds **8A**–**9C** have affinities ranging from 0.11 to 0.53 nM. It is interesting that the N-1 substitutions have a dramatic effect on the affinity of the ligand. For compounds **2CI**–**2CIII**, the 4-cyano substitution on the phenylmethyl tail group resulted in an inactive compound, while the 4-trifluoromethyl analog binds with an affinity of 104 nM and the 2-naphthylmethyl analog binds with an affinity of 2.5 nM. This comparison of the tail group also illustrates another SAR trend within this series, which is the 3-substitution effect at the 3,3-diphenylpropyl tail group. Changing from a hydrogen (**1A**–**C**) to *N*,*N*-dimethylamide group (**8A**–**C**) or 3-methoxycarbonyl group (**9A**–**C**) dramatically increased the mu affinities ranging approximately from 6-fold (**1A** vs **8A**) to 4000-fold (**1C** vs **8C**). These amide and ester groups may serve three purposes: (1) a polar function capable of hydrogen bonding with an electrophilic site (or amino acid residues) in the mu receptor; (2) steric interaction with the two phenyl groups causing them to take a better orientation to interact more effectively with the mu receptor; (3) hydrophobic interaction with a small pocket in the mu receptor. It is also interesting to see that a carboxylic acid group at the 3-position of the 3,3-diphenylpropyl tail group (compounds **10A**–**C**) lowers the ligand's affinity for mu receptor (331, 1461 and 489 nM, respectively). This indicates that the small pocket in the mu receptor cannot tolerate an acidic group.

Finally, the observation that the N-oxides **11A**–**11CII** are almost inactive at the mu receptor indicates that a basic nitrogen on the piperidine ring is essential for high affinity mu binding. This basic amino group could be involved in an electrostatic/ionic interaction with a negatively charged amino acid in the mu receptor or forms H-bond to an amino acid residue of the mu receptor.[13]

In conclusion, based on the 4-phenylpiperidine scaffold, which was utilized in our lead generation and lead optimization libraries towards NOP receptor, we designed potent mu receptor agonists by introducing substitution groups at the 3-position of the 3,3-diphenylpropyl tail group. The SAR for the 3-substitution effects indicates that groups like amides and esters will increase the mu affinity while an acidic group will decrease the mu affinity. In addition, we have also evaluated the importance of the basic nitrogen on the piperidine ring by introducing the N-oxide group. The lack of affinity of these N-oxides towards the mu receptor is consistent with previous findings about the antidiarrheal agent loperamide oxide.[14] The SAR trends described in this paper may allow a better understanding of mu receptor recognition for the 4-phenylpiperidine mu ligands. The therapeutic potential of these loperamide analogs may also be of interest for the scientific community in light of our recent discovery of DiPOA, a novel, systemically available and peripherally restricted mu opioid agonist with antihyperalgesic activity.[15,16]

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