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Synthesis and structure–activity relationships of 4-hydroxy-4-phenylpiperidines as nociceptin receptor ligands: Part 1

Ginny D. Ho,[a,*] Ana Bercovici,[a] Deen Tulshian,[a] William J. Greenlee,[a] Ahmad Fawzi,[b] April Smith Torhan[b] and Hongtao Zhang[b]

[a]*Department of Chemical Research—CV & CNS, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

[b]*Department of Neurobiology, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

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Abstract—A series of 4-hydroxy-4-phenylpiperidines have been synthesized and bind to the nociceptin receptor with high affinity. The synthesis and structure–activity relationships at the N-1 and C-4 are described.

Following the discovery of the nociceptin receptor, there has been remarkable progress toward understanding its pharmacological relevancy. The nociceptin receptor, NOP (previously termed ORL-1 (opioid receptor-like-1) or OP_4), was cloned as an 'orphan receptor' in 1994.[1] It is a member of the G protein-coupled receptor (GPCR) superfamily and is widely distributed throughout the brain and spinal core. The nociceptin receptor expresses ~50% sequence homology to the classic δ, κ, and μ opioid receptors (DOP, KOP, and MOP, respectively). Even with this degree of homology, the nociceptin receptor has low affinity for the endogenous opioid peptides and synthetic opioid receptor ligands. Its endogeneous ligand, nociceptin (or orphanin FQ), is a 17-amino acid neuropeptide isolated from the brain in 1995,[2] which also exhibits high structural similarities to the known opioid peptides, particularly dynorphin, but fails to activate the classic opioid receptors. Therefore, the nociceptin receptor is pharmacologically distinct from the classic opioid receptors. Since the nociceptin receptor is widely distributed throughout the nervous system, it may participate in a broad spectrum of pharmacological processes. Intensive pharmacological studies with the nociceptin receptor and its peptide ligand and analogs over the past several years have resulted in significant advances in understanding the interaction of nociceptin with biological systems. In our in-house studies, either central (ICV) or peripheral (iv) administration of nociceptin in conscious guinea pigs produces inhibition of capsaicin-induced cough.[3] Other accounts also demonstrate that the nociceptin/NOP system may play important roles in the regulation of urinary incontinence, pain, stress and anxiety, feeding, learning and memory, locomotor activity, substance abuse, cardiovascular function, sleep disturbance, and Parkinson's disease.[4]

High-throughput screening of the Schering compound collection has identified a number of hits with varying affinities for the nociceptin receptor. In this report, we disclose our early SAR studies based on the 4-hydroxy-4-phenyl piperidine scaffold. 4-Hydroxy-4-phenyl piperidines have been investigated extensively in the literature and are key moieties in a variety of biologically active compounds. The piperidine framework has also been reported in a number of small molecule nociceptin receptor ligands.[5] Our initial lead in this series is compound **1** with affinity for the nociceptin receptor of 613 nM. Initial SAR development focuses on substitution of the piperidine nitrogen in order to determine the optimal linker between the piperidine nitrogen and the phenyl (Table 1). Comparison of compounds **3**, **4**, and **6** indicates that the benzyl analog **6** exhibits the highest affinity for the nociceptin receptor. Branching at the α-position to the piperidine nitrogen (cf. **4** and **5**)

Keywords: Nociceptin/orphin FQ; Nociceptin receptor (NOP); Opioid receptor-like-1 (ORL-1); Opioid receptors (MOP, KOP, DOP); G protein-coupled receptor.
* Corresponding author. Tel.: +1 908 740 3502; fax: +1 908 740 7152; e-mail: ginny.ho@spcorp.com

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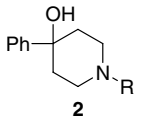
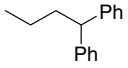
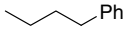
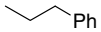
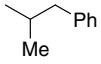
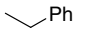
Table 1. Nociceptin receptor binding of **2**

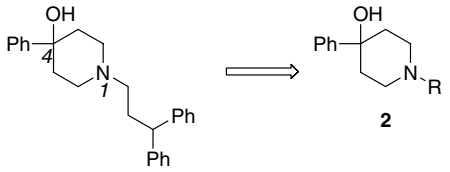


2

Compound	-R	NOP K_i (nM)[a] (% inh, at 10 μM)	MW	*C*LogP
1		613	371.51	4.9
3		(60%)	295.42	3.46
4		(46%)	281.39	3.07
5		(82%)	295.42	3.56
6		**1983** (**75**%)	**267.37**	**2.94**

[a] Values are means of at least two experiments.

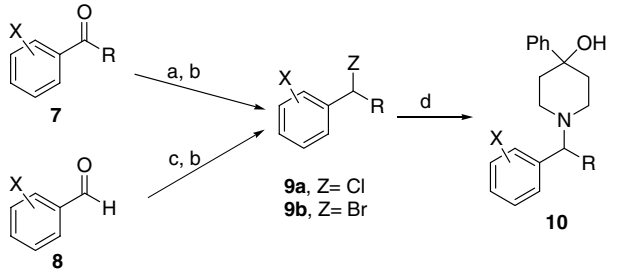
or introduction of an additional phenyl group α to the phenyl (cf. **1** and **3**) enhances the affinity at the nociceptin receptor. Since the benzyl analog **6** displays a better overall profile including the potency and physical properties (highlighted in bold), it is selected for further optimization. The extended study on compound **6** centers on evaluating benzylic substitution.



1
NOP K_i= 613 nM

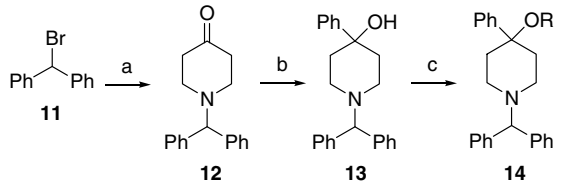
2

Scheme 1 outlines the general routes for preparing 4-hydroxy-4-phenylpiperidine analogs of type **10**. The chloride and bromide intermediates of type **9a** or **9b** are either purchased or prepared by bromination or chlorination of the corresponding alcohol with thionyl chloride or thionyl bromide, respectively. The alcohols are either purchased or prepared by reduction of the corresponding ketones of type **7** with sodium borohydride or reaction of the aldehydes of type **8** with an appropriate lithium or Grignard reagent. Compounds of type **10** are obtained by alkylation of 4-hydroxy-4-phenyl piperidine hydrochloride with the chloride or bromide intermediates of type **9a** or **9b** in acetonitrile in the presence of potassium carbonate with or without sodium iodide.



7
8
9a, Z= Cl
9b, Z= Br
10

Scheme 1. Reagents and condition: (a) $NaBH_4$, MeOH; (b) $SOCl_2$ or $SOBr_2$, CH_2Cl_2; (c) RLi or RMgBr, THF; (d) 4-hydroxy-4-phenylpiperidine hydrochloride, K_2CO_3, NaI (Z = Cl), MeCN, 80 °C.



11
12
13
14

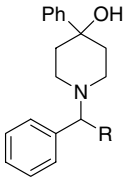
Scheme 2. Reagents: (a) 4-piperidone monohydrate hydrochloride, K_2CO_3·MeCN; (b) PhLi or PhMgBr, THF; (c) NaH, RI, DMF.

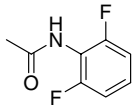
Compounds of type **14**, containing an ether substituent, are synthesized as described in Scheme 2. Alkylation of 4-piperidone hydrochloride with bromodiphenylmethane (**11**) produces the 4-piperidone intermediate **12**. Treatment of **12** with phenyl lithium or phenyl magnesium bromide yields **13**. Reaction of **13** with sodium hydride and an appropriate alkyl iodide provides compounds of type **14**.

Target compounds are tested for their affinity at the cloned human nociceptin receptor expressed in CHO cell membranes by measuring their ability to compete with [^{125}I][Tyr^{14}]nociceptin FQ. The opioid receptor binding assays are performed with CHO cell membranes expressing the human opioid receptors using [^{3}H]-diprenorphine as the radioligand. The K_i values have been determined from dose–response curves. The functional activities of these compounds are evaluated as their ability to enhance the binding of [^{35}S]GTPγS in the presence of GDP, using membranes isolated from cells transfected with the nociceptin receptor.[6]

Table 2 details the effect of substitution on the benzylic carbon of compound **6**. In general, introduction of a substitution at the benzylic position leads to an increase of potency with the exception of **24** and **27**–**29**. Addition of an alkyl substituent containing three to six carbons produces potent NOP ligands with 2- to 19-fold selectivity over the MOP receptor. We found that the four-carbon linear chain is optimal (**18**, K_i = 5 nM, and **20**, K_i = 9 nM). Introduction of a benzyl group provides good affinity toward NOP and displays partial agonist response (compound **23**). Introduction of the hydroxymethyl group in **24** produces a substantial loss of potency. However, potency is enhanced by converting the hydroxyl analog **24** to the corresponding methyl ether **25** or ethyl ether **26**. The phenyl analog **13** shows a dramatic improvement in affinity toward NOP, moderate selectivity over KOP and MOP, and excellent selectivity over DOP (highlighted in bold). Replacement of one of the phenyls in **13** with a pyridine leads to

Table 2. SAR of the benzylic modification analogs



Compound[a]	R	K_i (nM)[b]			
		NOP	DOP	KOP	MOP
6	H	1983	nd	nd	nd
15	Me	323	33,110	4149	6265
16	Et	135	20,890	1427	2298
17	*n*-Pr	19	4126	245	341
18	*n*-Bu	5	441	36	29
19	*n*-Pent	14	184	220	37
20	*i*-Pent	9	348	185	125
21	*n*-Hex	18	550	335	144
22	*c*-Pent	41	5323	312	787
23	CH_2Ph	16	187	288	24
24	CH_2OH	4035	nd	nd	nd
25	CH_2OMe	295	32,960	1771	780
26	CH_2OEt	134	15,250	1028	451
27	CO_2Me	1887	121,800	6753	59,810
28	CN	10,000	nd	nd	nd
29		8183	22295	4381	3736
13	**Ph**	**13**	**1666**	**364**	**233**
30	2-Pyridinyl	214	21,890	5935	9324
31	3-Pyridinyl	323	10,920	2993	819
32	2-Thienyl	35	7845	971	405

[a] All compounds are racemates except for **6** and **13**.
[b] Values are means of at least two (nd, not determined).

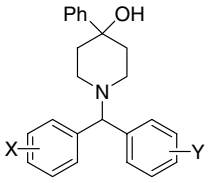
decreases in potency (**30** and **31**). Substitution of a 2-thiophene at the benzylic position of **6** yields a potent NOP ligand **32** with 11.5-fold selectivity over MOP and excellent selectivity over DOP. Introduction of an electron withdrawing substituent results in significant decreases or loss in the affinity at the NOP receptor (**27**–**29**). Table 3 shows the functional activity of compounds of type **10** (X = H) that have NOP binding affinity less than 20 nM.

Table 3. Functional activity of selected benzylic modification analogs

Compound	R	GTPγS % Stim at (μM)
13	Ph	107 at 10
17	*n*-Pr	99 at 10
18	*n*-Bu	102 at 1
19	*n*-Pent	101 at 10
20	*i*-Pent	74 at 10
21	*n*-Hex	117 at 10
23	Bn	49 at 100

Encouraged by the potency and selectivity of compound **13**, we then examined variations of the aromatic substitution pattern in **13**. A variety of substituents have been introduced on one or both of the phenyl rings of the benzhydryl moiety. The receptor binding data for the benzhydryl modifications are summarized in Table 4. It appears that nociceptin receptor binding affinities are influenced by the substitution pattern. With the exception of **50**, addition of substituents to the ortho position of one or both of the phenyls of the benzhydryl yields analogs with improved potency. Introduction of a methyl at the ortho position produced a potent NOP agonist **33** with greater than 400-fold selectivity over DOP and KOP, and greater than 100-fold selectivity

Table 4. SAR of the benzhydryl modification analogs



Compound[a]	X	Y	K_i (nM)[b]			
			NOP	DOP	KOP	MOP
13	H	H	13	1666	364	233
33	H	2-Me	2	969	802	246
(−)**34**	H	2-Me	0.7	503	295	35
(+)**35**	H	2-Me	23	8765	1205	361
36	H	3-Me	3	2437	1095	147
37	H	4-Me	53	9365	2687	3728
38	H	2-CF_3	12	1271	1362	127
39	H	3-CF_3	357	7355	6621	714
40	H	4-CF_3	225	10,124	4294	1207
41	H	2-Et	0.6	237	535	9
42	H	2-Cl	4	1674	1136	609
43	H	3-Cl	26	3029	1971	201
44	H	4-Cl	132	1431	164	793
45	H	2-F	5	2945	1479	177
46	H	2-Br	11	2110	1144	170
47	H	4-Br	125	4458	2443	2449
48	H	2-OMe	1	975	519	28
49	H	2-CH_2OH	9	1977	1174	120
50	H	2-CO_2H	6753	>100,000	8057	2864
51	2-Me	2-Me	4	5791	1712	2147
52	2-Cl	2-Cl	2	1665	635	256
53	2-F	2-F	6	1783	1172	148
54	4-F	4-F	42	584	123	183
55	2-Br	2-Br	21	nd	nd	nd
56	2-OMe	2-OMe	3	18160	306	843
57	4-OMe	4-OMe	439	13715	2878	843
58	$(CH_2)_0$		325	8287	17	758
59	$(CH_2)_2$		155	302	381	126

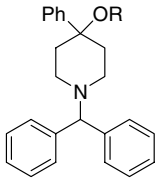
[a] Compounds **33**–**50** are racemates except for (−)**34** and (+)**35**.
[b] Values are means of at least two experiments (nd, not determined).

over MOP. Compound **33** displays an agonist response with an EC_{50} of 29 nM. The resolution of racemic **33** has been completed in order to determine the effect of stereochemistry on nociceptin receptor binding. The (−)-isomer **34** is more potent toward the NOP receptor and more selective over the MOP receptor than the (+)-isomer **35** and also produces a higher agonist response. The 2-ethyl analog **41** is highly potent, but without improved selectivity. Introduction of a trifluoromethyl, fluorine, chlorine, bromine, methoxy or hydroxymethyl at the ortho position of one or both of the phenyls provides excellent affinity for NOP, excellent selectivity over DOP and KOP, and moderate to excellent selectivity over MOP (**38**, **42**, **45**, **46**, **48**, **49**, **51**–**53**, and **56**). We observe that moving the substitution from the ortho to the para position of the phenyl(s) decreases the affinity for NOP (cf. **33** and **37**, **38** and **40**, **42** and **44**, **46** and **47**, **53** and **54**, **56** and **57**). Introduction of a conformationally restricted substituent at the piperidine nitrogen reduces the affinity at the NOP receptor (**58** and **59**). The 9-fluorenyl analog **58** exhibits high affinity for the KOP and little affinity for DOP. The dibenzosuberyl analog **59** has comparable affinities toward NOP and MOP. Table 5 summarizes the functional activity of the benzhydryl modification analogs when the nociceptin receptor

Table 5. Functional activity of selected benzhydryl modification analogs

Compound	GTPγS % Stim at [μM] (EC_{50})
33	107 at 0.1 (29 nM)
(−)**34**	101 at 1 (23 nM)
(+)**35**	94 at 10 (331 nM)
36	87 at 10
38	106 at 1
42	105 at 10
45	104 at 10
46	127 at 10
48	100 at 10 (26 nM)
49	122 at 10
51	95 at 10 (114 nM)
52	103 at 100 (222 nM)
53	98 at 10
56	107 at 1 (117 nM)

Table 6. SAR of the hydroxy modification analogs



Compound	R	K_i[a] (nM)			
		NOP	DOP	KOP	MOP
13	H	13	1666	364	233
60	Me	54	2651	343	412
61	Et	59	898	488	377
62	*n*-Pr	72	2767	1484	1649
63	Bn	162	3741	13,390	21,455

[a] Values are means of two–three experiments (nd, not determined).

Table 7. Functional activity of the hydroxy modification analogs

Compound	R	GTPgS % Stim at (μM)
60	Me	109 at 100
61	Et	104 at 100
62	*n*-Pr	96 at 100
63	Bn	86 at 100

affinity is less than 20 nM. All of these compounds display a good agonist response.

Extended SAR work on compound **13** has centered on evaluating the C-4 hydroxy modification (Table 6). It appears that an alkoxy substitution is tolerated at the C-4 position of the piperidine. Increasing the size of the substituent on the oxygen decreases the affinity and the agonist response at the nociceptin receptor (Table 7).

In summary, we have successfully identified a series of *N*-benzhydryl-substituted 4-hydroxy-4-phenylpiperidines as potent nociceptin receptor ligands. Introduction of a small substitution at the ortho position of one or both of the phenyl rings of the benzhydryl moiety provides excellent affinity and agonist response for the nociceptin receptor. Additional studies of nociceptin receptor agonists based on this scaffold will be reported in due course.

Acknowledgment

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