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Synthesis and structure–activity relationships of N-substituted spiropiperidines as nociceptin receptor ligands

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Abstract—A series of N-substituted analogs based upon the spiropiperidine core of **1** was synthesized and exhibited high binding affinity to the nociceptin (NOP) receptor. The selectivities against other known opioid receptors were determined.
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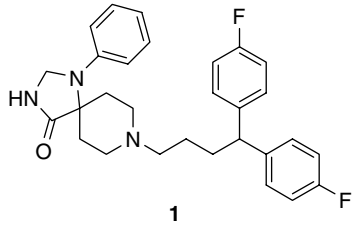
Since its discovery in 1994, many advances have been made regarding the biological significance and functions of the opioid receptor-like-1 (ORL1/OP4/NOP) receptor and its endogenous peptide ligand, nociceptin [orphanin FQ (OFQ) or nociceptin/orphanin FQ (N/OFQ) peptide]. The 17 amino-acid G protein coupled NOP receptor has been found to share a 47% overall homology (65% homology in the transmembrane domains) with the classical opioid receptors, μ, κ, and δ; however, the pharmacology of nociceptin has a low binding affinity to the classical opioids and opioid antagonists such as naltrexone do not block the activity of nociceptin.[1]

Opioids, such as codeine and butorphanol, are the most effective drugs available to treat cough associated with pulmonary diseases. However, these drugs, which activate μ receptors, possess significant side effect liabilities including respiratory depression, constipation, and physical dependency. We have reported that OFQ, a functional agonist, displays the potential to inhibit cough through a central and peripheral CNS mechanism.[2] This antitussive effect is blocked by the small-molecule selective NOP antagonist, J113397. Therefore, NOP agonists represent a novel therapeutic approach for the treatment of cough. Here, we report our SAR of small-molecule NOP agonists and their selectivity against the classical opioid receptors.



1

From high-throughput screening of our chemical library, compound **1** was identified as a lead showing moderate affinity for NOP with a K_i of 500 nM. Our SAR development plan was to investigate substitution on the piperidine nitrogen of the spiropiperidine core of **1**. As summarized in Scheme 1, the commercially available 1-phenyl-1,3,8-triazaspiro-[4,5]deacan-4-one, **2**, was either alkylated in the presence of various benzyl halides or treated under reductive amination conditions with benzyl aldehydes to produce **3**, where R consists of primarily benzhydryl, benzyl, and tetralinyl analogs.

The necessary halides were generated via treatment of the corresponding alcohols with $SOCl_2$ as described in Scheme 2.

Keywords: Nociceptin; Orphanin FQ; NOP receptor; Agonist.
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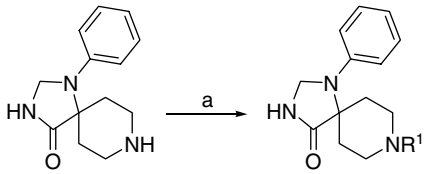
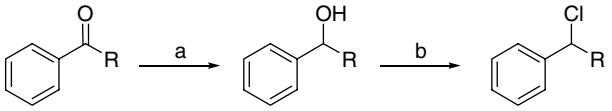


2 3

Scheme 1. Reagents and conditions: (a) R^1Br, K_2CO_3, CH_3CN, reflux or R^1Cl, K_2CO_3, KI, CH_3CN, reflux or R^1CHO, $Na(OAc)_3BH$, CH_2Cl_2.

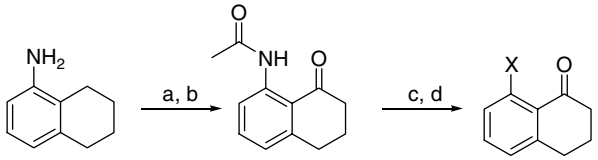


4 5 6

Scheme 2. Reagents: (a) $NaBH_4$, MeOH; (b) $SOCl_2$, CH_2Cl_2.

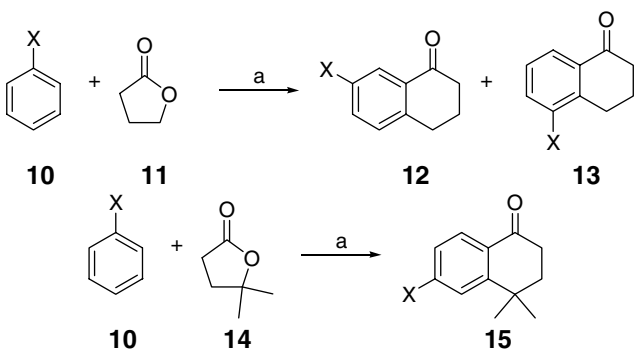
The requisite 8-halo-tetralones were prepared as described in Scheme 3.[3] As outlined in Scheme 4, the 5- and 7-halo-tetralones (**12** and **13**) were furnished by subjecting the phenyl halide and butyrolactone **11** under Friedel–Crafts acylation conditions.[4] However, under similar conditions, the gem-dimethyl butyrolactone **14** gave rise to the 6-halo regioisomer **15**.

The compounds described were evaluated in radioligand binding assays. K_i values against the human NOP receptor were determined from competition binding assays



7 8 9

Scheme 3. Reagents and conditions: (a) Ac_2O, py, rt; (b) $KMnO_4$, 9/1/acetone/15% $MgSO_{4(aq)}$; (c) $NaOH_{(aq)}$, EtOH, reflux; (d) for X = Cl: $NaNO_2$ 0 °C, Cu(I)Cl in 20% $HCl_{(aq)}$, 0 °C 30 min, then rt for 30 min, then reflux 2 h—for X = F: $NOBF_4$, DCM, 0 °C, add 1,2-dichlorobenzene, distill DCM, then reflux 2 h.



10 11 12 13

10 14 15

Scheme 4. Reagents and conditions: (a) $AlCl_3$, heat, 0 °C to 100 °C, 3 h.

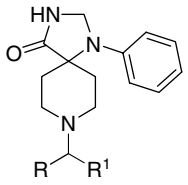
using [^{125}I]Nociceptin and h-NOP receptor expressing Chinese hamster ovary (CHO) cell membranes as described.[5] K_i values for human μ-, κ-, and δ-opioid receptors were determined using [^{3}H]diprenorphine and CHO cell membranes expressing the opioid receptors as described.[5b] The functional [^{35}S]GTPγ S binding assays for h-NOP receptor were carried out in CHO cell membranes as described.[5a] In cases where the chiral products were obtained, the compounds were screened as racemates.

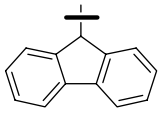
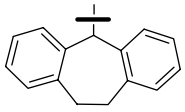
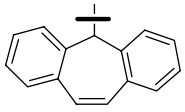
The SAR of the benzyl and benzyhdryl analogs are shown in Table 1. The benzyl analog **16** exhibited high affinity for NOP (K_i = 11.0 nM) and was ≅18-fold selective over KOP. By comparison the cyclohexylmethyl analog **17** was less potent at NOP and with less selectivity over KOP (≅8.5-fold). In the case of the pyridyl variants (**18**–**20**), NOP binding affinity dropped significantly. Although the thienyl analog **21** displayed high binding affinity at NOP, selectivity over KOP remained marginal. Introduction of chloro substituents on the benzyl ring resulted in single-digit nanomolar potency at NOP; yet, only slight selectivity at KOP was observed for **22** and slight selectivity over MOP was observed for **23**. NOP binding was tolerant of a wide variety of alkyl substitutions (**24**–**29**) at the benzylic position; however, selectivity over the KOP receptor remained at modest levels. Introduction of the benzhydryl moiety (**30**) produced low double-digit nanomolar potency at NOP and was ≅6-fold selective over KOP. Constrained analogs of the benzhydryl varied in NOP binding affinity with the fluorenyl variant **31** being completely inactive while **33** regained similar potency as **30**.

Mono-substitution (**34**–**37**) on the benzhydryl substituent produced compounds with acceptable NOP binding affinity and excellent selectivity over the opioid receptors. Furthermore, bis-substitution (**38**–**43**) enhances the NOP binding affinity while maintaining this exceptional degree of selectivity over the other opioid receptors.

The SAR of the tetralinyl analogs are shown in Table 2. In general, these compounds displayed very high affinity for the NOP receptor with K_is ranging from 15.1 to 0.3 nM as well as high selectivity over DOP. The indanyl (**44**) and tetralinyl (**45**) analogs displayed NOP K_is of 1.2 and 1.4 nM, respectively. The suberonyl derivative, **46**, had a comparatively lower affinity for NOP (K_i = 14.5 nM). Since **45** had a higher degree of selectivity over the opioids than **44** (46-fold against KOP vs 16-fold against MOP), we focused our efforts on the tetralinyl series. The geminal di-methyl analog **47** retained its NOP potency and increased the selectivity against KOP but decreased the selectivity against MOP relative to the parent tetralone. The fluoro derivatives (**48**–**50**) yielded subnanomolar affinity for NOP; yet **48** had single-digit nanomolar at MOP, while **49** and **50** displayed low double-digit binding affinities at KOP. While not displaying as high NOP affinity as their corresponding fluoro counterparts, the chloro derivatives (**51**–**53**) exhibited a similar trend in terms of selectivity, with

Table 1. Binding affinities of benzyl and benzhydryl analogs



Compound	R	R^1	K_i (nM)			
			NOP	DOP	KOP	MOP
16	Ph	H	11.0	2946	196	500
17	Cyclohexyl	H	61.2	73655	517	887
18	2-Pyridyl	H	119.0	31935	321	1761
19	3-Pyridyl	H	133.0	3791	252	233
20	4-Pyridyl	H	824.0	nt	nt	nt
21	3-Thienyl	H	14.0	8999	26.2	133
22	2-Cl-Ph	H	3.2	724.5	16.4	37.4
23	2,6-Cl_2-Ph	H	2.3	1633	52.3	29.5
24	Ph	Me	3.5	1035	50	74
25	Ph	Et	17.0	6846	60.5	355
26	Ph	Propyl	2.4	3373	22.5	244
27	Ph	Butyl	1.1	1421	13	22
28	Ph	Isoamyl	1.5	736	25.5	30
29	Ph	Cyclopentyl	4.6	4680	26	398
30	Ph	Ph	23.0	37890	137	486
31			na	nt	nt	nt
32			225.0	9784	1672	2454
33			36.5	11510	776	475
34	2-F-Ph	Ph	10.8	15715	1183	818
35	2-Cl-Ph	Ph	9.0	14770	1086	778
36	2-Me-Ph	Ph	11.5	6042	579	1109
37	4-Cl-Ph	Ph	140.0	24805	3529	5081
38	2-Me-Ph	2-Me-Ph	9.0	8600	1602	346
39	2-Cl-Ph	2-Cl-Ph	6.8	150385	5887	595
40	3-Cl-Ph	3-Cl-Ph	249.0	26515	4628	1616
41	2-F-Ph	2-F-Ph	6.3	16035	858	567
42	3-F-Ph	3-F-Ph	250.0	10360	1448	3187
43	4-F-Ph	4-F-Ph	49.0	5598	2009	787

Values are means of 2–3 experiments (na, not active; nt, not tested).

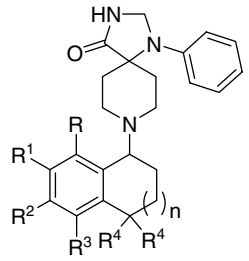
51 having a high binding affinity at MOP, while **52** and **53** displayed double-digit binding affinities at KOP.

The mono-halogenated derivatives **54** and **55** in the geminal di-methyl tetralones produced compounds which retained single-digit potency at NOP; however, still demonstrated modest affinity at MOP. The dichlorinated tetralone (**56**) showed acceptable binding at NOP with excellent selectivity over all of the opioid receptors with DOP $K_i \cong 11.7\ \mu M$ and near micromolar binding affinities at KOP and MOP. Compound **56** was characterized as a full agonist in the functional assay, as shown in Table 3, since it increased [^{35}S]GTPγS binding. Furthermore, **56** displayed an acceptable 7% inhibition of the hERG channel at 5 mg/mL; as well as good oral bioavailabilty in rat at 10 mpk with an $AUC_{(0-6h)} = 2106$ nM h, $C_{max} = 518$ nM at 4h, and $C_{6h} = 467$ nM.

In summary, we have developed several small-molecule NOP agonists which display excellent selectivity over the other opiate receptors. Further work in this area will be presented in due course.

Compound 28: ^{1}H NMR ($CDCl_3$)δ 7.55 (s, 1H), 7.25–7.45 (m, 7H), 7.02 (d, 2H), 6.96 (t, 1H), 4.77 (br s, 2H), 3.44 (dd, $J = 8.8$, 5.2 Hz, 1H), 3.07 (m, 1H), 2.60–2.90 (m, 5H), 2.00 (m, 1H), 1.65–1.86 (m, 3H),

Table 2. Binding affinities of tetralinyl analogs



Compound	R	R^1	R^2	R^3	R^4	n	K_i (nM)			
							NOP	DOP	KOP	MOP
44	H	H	H	H	H	0	1.2	1854	32	19
45	H	H	H	H	H	1	1.4	3511	65	346
46	H	H	H	H	H	2	14.5	1906	203	673
47	H	H	H	H	CH_3	1	1.3	1790	540	48
48	F	H	H	H	H	1	0.3	1231	145	5.1
49	H	F	H	H	H	1	0.9	2650	33.5	133
50	H	H	H	F	H	1	0.8	2400	13.7	72.3
51	Cl	H	H	H	H	1	2.6	1375	143	11.1
52	H	Cl	H	H	H	1	10.8	2511	66.5	162
53	H	H	H	Cl	H	1	2.0	2266	94.5	130.5
54	H	H	Cl	H	CH_3	1	1.4	1291	282	49.1
55	H	H	F	H	CH_3	1	8.4	2461	169	59.1
56	H	Cl	Cl	H	CH_3	1	15.1	11655	938	977

Values are means of 2–3 experiments.

Table 3. Functional activity of selected compounds

Compound	% Stimulation of [^{35}S]GTPγS at μM
34	87 at 10
35	87 at 10
39	90 at 10
41	104 at 10
56	104 at 0.1

1.25 (m, 1H), 1.0 (m, 1H), 1.07 (m, 1H), 0.93 (d, J = 6.8 Hz, 6H). Mass Spec ESI (M+1) = 392, 232.

Compound 39: ^{1}H NMR ($CDCl_3$)δ 7.65 (d, J = 7.2 Hz, 1H), 6.90–7.40 (m, 12H), 5.49 (s, 1H), 4.74 (s, 2H), 3.00 (t, 2H), 2.60–2.80 (m, 4H), 1.67 (d, J = 13.6 Hz, 2H). Mass Spec ESI (M+1) = 466, 235.

Compound 56: ^{1}H NMR ($CDCl_3$)δ 8.01 (s, 1H); 7.60 (s, 1H); 7.39 (s, 1H); 7.37 (d, 1H); 7.35 (d, 1H); 6.99 (d, 2H); 6.88 (t, 1H); 4.77 (q, 2H); 3.77 (dd, J = 10.2, 5.1 Hz, 1H); 3.40 (dt, J = 10.2, 2.9 Hz, 1H); 2.97–2.80 (m, 3H); 2.63 (dt, J = 12.8, 5.1 Hz, 1H); 2.44 (d, 1H); 1.97–1.71 (m, 4H); 1.64 (m, 2H); 1.29 (s, 3H); 1.22 (s, 3H); Mass Spec ESI (M+1) = 458, 232.

Acknowledgments

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