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Synthesis and structure–activity relationships of N-substituted spiropiperidines as nociceptin receptor ligands: Part 2

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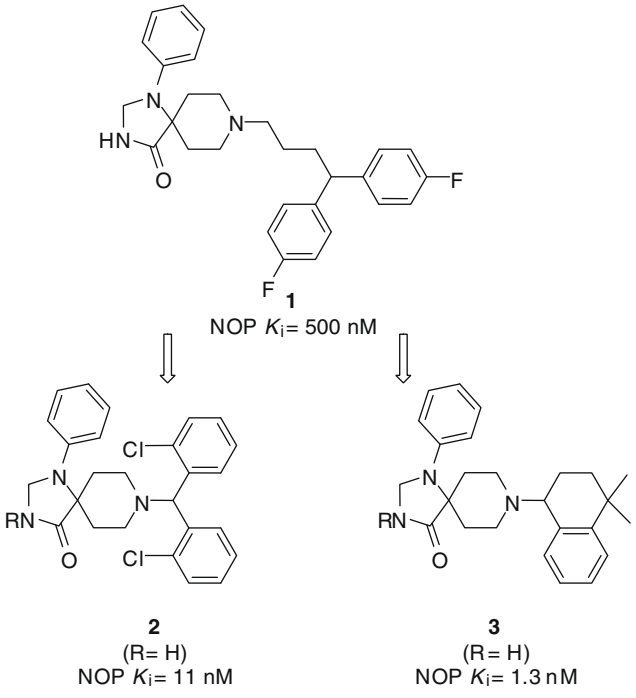
ABSTRACT

A series of N-8 substituted analogs based upon the spiropiperidine core of the original lead compound **1** was synthesized. This lead has been elaborated to compounds to give compounds **2** and **3** (**R** = H) that exhibited high NOP binding affinity as well as selectivity against other known opioid receptors. These two series have been further functionalized at the amido nitrogen. The synthesis and structure–activity relationship (SAR) of these and related compounds are discussed.

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 previous paper[1a] detailed the initial efforts to explore modifications at the piperidine nitrogen resulting in compounds such as **2** and **3** which exhibited high NOP binding affinity as well as selectivity against the other known opioid receptors. It is worth noting that others have incorporated this spiropiperidine motif in similar efforts exploring NOP agonism.[1b]

However, despite the treasure trove of data focused around substitution of the piperidine nitrogen, it was apparent that exploration was rather limited with respect to substitution on the amido nitrogen. Capitalizing on this opportunity, we set forth to investigate the SAR focusing on substitution at the amido nitrogen of the spiropiperidine core of **1** using the optimized moieties we have previously discussed.[1a]

As summarized in Scheme 1, the commercially available 1-phenyl-1,3,8-triazaspiro-[4,5]deacan-4-one, **4**, was either alkylated in the presence of various benzyl halides or treated under reductive amination conditions with benzyl aldehydes to produce **5**, where R^1 consists of primarily benzhydryl, benzyl, and tetralinyl analogs. The amido nitrogen of **5** was further functionalized under phase-transfer alkylation conditions to produce derivatives such as **6**.[2] When **5** is subjected under the phase-transfer alkylation conditions using 1,2-bromochloroethane as the alkylating agent, the resultant product is **7**. The chloride of **7** may be readily displaced by secondary or primary amines to produce compounds such as **8**.



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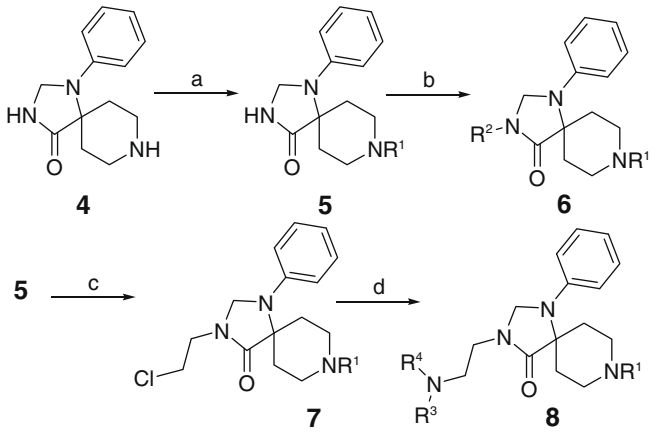


Scheme 1. Reagents and conditions: (a) R^1Br, K_2CO_3, CH_3CN, reflux or R^1Cl, K_2CO_3, KI, CH_3CN, reflux or R^1CHO, $Na(OAc)_3BH$, CH_2Cl_2; (b) R^2Br, NaOH, K_2CO_3, Bu_4NHSO_4, toluene, 70 °C; (c) $Cl(CH_2)_2Br$, NaOH, K_2CO_3, Bu_4NHSO_4, toluene, 70 °C; (d) NR^3R^4, EtOH, reflux.

The compounds described were evaluated in radioligand binding assays. K_i values against the human NOP receptor were determined from competition binding assays using [^{125}I]nociceptin and *h*-NOP receptor expressing Chinese hamster ovary (CHO) cell membranes as described.[3a] 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.[3b] In cases where the products yielded an enantiomeric mixture, the resultant mixture was screened as such.

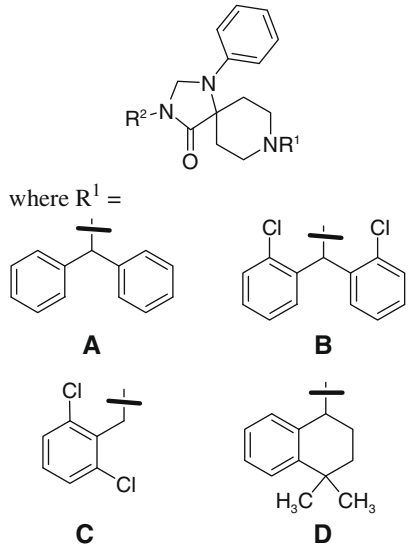
The SAR of the spiropiperidine analogs are shown in Table 1.

The SAR exploration began using the unsubstituted benzhydryl moiety at the piperdinyl nitrogen (R^1 = **A**). In general, alkylation at the amido nitrogen (**10**–**19**) decreased potency at the NOP receptor while retaining good selectivity over DOP and only marginal selectivities over KOP and MOP throughout the series.

We turned to the 1,1′-bischlorobenzhydryl substituent (R^1 = **B**) which was proven to provide excellent potency at NOP with high selectivity over the opioid receptors (**2**). Substitution at the amido nitrogen with simple alkyl (**20**, **21**) as well as oxygen containing derivatives (**22**–**24**) displayed a decrease in NOP potency. However, potency at NOP was regained by introduction of an alkylaminoalkyl side chain (**26**–**39**) while maintaining an acceptable selectivity profile.

In light of this finding, the 2,6-dichlorobenzyl substituted counterparts (R^1 = **C**) were explored. The incorporation of the alkylaminoethyl units resulted in numerous examples (**41**–**49**) of subnanomolar potency at NOP; yet, these compounds were also highly potent at KOP.

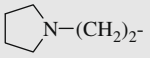
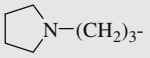
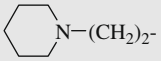
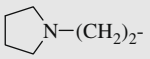
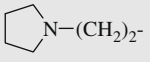
Table 1
Binding affinities of spiropiperidine analogs



Compound	R^1	R^2	K_i (nM)			
			NOP	DOP	KOP	MOP
9	A	H–	23	37,890	137	489
10	A	Me	31	33,095	150	692
11	A	Et	84	23,175	506	2283
12	A	Pr	34	15,325	1342	11,755
13	A	Bu	57	59,420	773	8438
14	A	*i*-Pr	66	9111	543	4042
15	A	c-PrCH_2–	83	5412	633	5279
16	A	*c*-BuCH_2–	53	8210	1846	nt
17	A	*c*-HexylCH_2–	89	187,050	2316	nt
18	A	Propargyl	234	44,025	1268	4314
19	A	Allyl	203	45,335	694	63,020
2	B	H–	6.8	150,385	5887	5945
20	B	Bu–	48.7	192,050	81,010	33,120
21	B	*i*-Amyl	56	60,980	46,515	13,000
22	B	$CH_3OC(O)CH_2$–	19.5	122,080	2274	683

(*continued on next page*)

Table 1 (*continued*)

Compound	R^1	R^2	K_i (nM)			
			NOP	DOP	KOP	MOP
23	B	$HO(CH_2)_2$–	18.5	5612	1747	483
24	B	$MeO(CH_2)_2$–	26	28,990	1830	726
25	B	$NH_2(CH_2)_2$–	47.8	32	852	886
26	B	$CH_3NH(CH_2)_2$–	4.05	578	871	1069
27	B	$EtNH(CH_2)_2$–	2.1	868	497	776
28	B	*i*-$PrNH(CH_2)_2$–	2.55	955	469	745
29	B	*c*-$PentylNH(CH_2)_2$–	8.65	1525	247	625
30	B	*c*-$HexylNH(CH_2)_2$–	5	759	224	400
31	B	$(CH_3)_2N(CH_2)_2$–	3.5	933	320	421
32	B	*c*-$PrNH(CH_2)_2$–	3.7	1136	1014	978
33	B	$(i\text{-}Pr)_2N(CH_2)_2$–	12.1	4758	674	1921
34	B	$BuNH(CH_2)_2$–	2.15	1033	165	2546
35	B	*i*-$BuNH(CH_2)_2$–	2.75	878	238	1376
36	B	*c*-$HexylCH_2NH(CH_2)_2$–	3.8	1535	271	1800
37	B		2.25	906	254	436
38	B		3.2	2381	64	436
39	B		8	3176	279	683
40	C	H–	2.3	1633	52	29
41	C	$CH_3NH(CH_2)_2$–	0.8	2270	68	146
42	C	$EtNH(CH_2)_2$–	0.7	1676	54	167
43	C	*i*-$PrNH(CH_2)_2$–	0.7	1080	40	136
44	C	*c*-$PrCH_2NH(CH_2)_2$–	0.5	445	25	89
45	C	*c*-$BuNH(CH_2)_2$–	0.5	370	29	112
46	C	$PrNH(CH_2)_2$–	0.6	516	13	28
47	C	*i*-$BuNH(CH_2)_2$–	0.5	376	8	26
48	C	$BuNH(CH_2)_2$–	0.4	867	10	36
49	C	$Et_2N(CH_2)_2$–	1.0	379	56	122
50	C		2.3	538	15	37
3	D	H–	1.3	1790	540	48
51	D	Pr–	5.4	3103	1392	142
52	D	$CH_3C(O)CH_2$–	4.5	795	56	14
53	D	$HO(CH_2)_2$–	1.7	2639	655	59
54	D	$CH_3NH(CH_2)_2$–	2.1	1298	48	35
55	D	$EtNH(CH_2)_2$–	1.6	2064	39	37
56	D	*i*-$PrNH(CH_2)_2$–	1.4	5016	68	69
57	D	*c*-$PentylNH(CH_2)_2$–	0.9	1615	49	96
58	D	*c*-$HexylNH(CH_2)_2$–	0.9	1951	33	120
59	D	$PrNH(CH_2)_2$–	1.0	2340	45	43
60	D	$CH_2{=}CHCH_2NH(CH_2)_2$–	0.9	2515	208	198
61	D	*c*-$BuNH(CH_2)_2$–	1.5	2096	45	64
62	D	*c*-$PrCH_2NH(CH_2)_2$–	0.8	2879	174	239
63	D	*i*-$BuNH(CH_2)_2$–	0.5	1802	65	61
64	D	$(i\text{-}Pr)_2NH(CH_2)_2$–	6.7	2980	86	82
65	D		1.4	1224	169	69
66	**D**	**$BuNH(CH_2)_2$–**	**0.5**	**3948**	**138**	**66**
67	D	*i*-$AmylNH(CH_2)_2$–	0.4	2600	82	204
68	D	*c*-$HexylCH_2NH(CH_2)_2$–	0.7	1693	26	102
69	D	$BnNH(CH_2)_2$–	3.6	1279	151	139

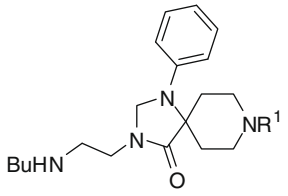
Values are means of 2–3 experiments. nt, not tested.

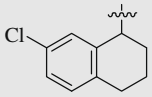
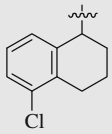
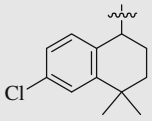
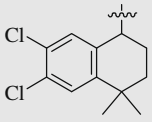
Additionally, we pursued the SAR of the *gem*-dimethyltetralinyl analogs (R^1 = **D**). In this SAR, single-digit nanomolar potency was achieved at NOP regardless of the amido substitution. Indeed, the alkylaminoalkyl side chain could be replaced by other amido modifications which were tolerated, as well (**51**–**53**). Several examples in this series displayed subnanomolar potency at NOP while exhibiting tremendous selectivity over the other opioids (**60**, **62**, **66**, and **67**).

The SAR of various tetralinyl analogs was explored where the amido nitrogen was substituted with the butylaminoethyl side chain as in compound **66**. The results are shown in Table 2. Although NOP potency ranged from subnanomolar (**72**) to low double digit nanomolar (**70** and **73**), the selectivity against KOP for all compounds in this series decreased markedly relative to compound **66**.

Compound **66** was selected for further profiling. Compound **66** increases [^{35}S]GTPγS binding thereby acting as a full agonist in the *h*-NOP functional assay as shown in Table 3. Compound **66** possessed an acceptable pharmacokinetic profile at a 10 mpk oral dose in rat with an $AUC_{(0-6\,h)}$ of 1165 nM h and a C_{max} at 6 h = 279 nM. Moreover, compound **66** had improved solubility compared to the parent compound **3** (data not shown). Additionally, compound

Table 2
Binding affinities of tetralinyl analogs



Compound	R^1	K_i (nM)			
		NOP	DOP	KOP	MOP
70		15.9	1062	11	297
71		1.8	1316	14	141
72		0.6	883	25	50
73		12.2	5022	158	306

Values are means of 2–3 experiments.

Table 3
Functional activity of compound **66**

% stimulation of [^{35}S]GTPγS	At [μM]
119	10
92	1
60	0.1

66 was efficacious in a pharmacological model of cough, namely the capsaicin-induced guinea pig model,[4a,b] and displayed antitussive activity with an ED_{50} < 3 mg/kg, po at 2 h. Furthermore, compound **66** was tested in a hERG rubidium efflux FLIPR assay and exhibited modest activity of 40% inhibition at a concentration of 5 μg/ml.

In summary, we have developed several small-molecule NOP agonists through two-point modification which display excellent selectivity over the other opiate receptors. Furthermore, compound **66** was identified as a compound displaying in vivo efficacy in the guinea pig model of capsaicin-induced cough.

Compound ***32***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (t, 2H); 7.30–7.37 (m, 4H); 7.24 (t, 2H); 7.14 (t, 2H); 6.98 (d, 2H); 6.90 (t, 1H); 7.63 (t, 2H); 5.49 (s, 1H); 7.63 (t, 2H); 4.69 (s, 2H); 3.52 (t, 2H); 3.04 (t, 2H); 7.63 (t, 2H); 2.95 (t, 2H); 2.69 (d, 2H); 7.63 (t, 2H); 2.58 (t, 2H); 2.17 (m, 1H); 1.63 (br s, 1H); 0.43 (dt, 2H); 0.29 (dt, 2H). Mass Spec. ESI (M+1) = 549.1 (100), 315.1 (52).

Compound ***66***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (t, 1H); 7.33 (m, 4H); 7.19 (m,1H); 7.01 (d, 2H); 6.88 (t, 1H); 4.77 (q, 2H); 3.84 (t, 1H); 3.55 (t, 2H); 3.52 (t, 2H); 2.88 (t, 2H); 2.85 (m, 3H); 2.64 (t, 2H); 2.44 (m, 1H); 1.93 (m, 2H); 1.76 (d, 2H); 1.63 (m, 1H); 1.58 (d,1H); 1.45 (t, 2H); 1.35 (m, 2H); 1.32 (s, 3H); 1.24 (s, 3H); 0.89 (t, 3H). Mass Spec. ESI (M+1) = 489.1 (92), 331.1 (100).

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References and notes

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