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The discovery of tropane derivatives as nociceptin receptor ligands for the management of cough and anxiety

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Conditioned lick suppression (CLS) model in rats
Separation-induced guinea pig pups vocalization assay (GPPV)

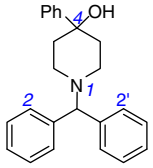
ABSTRACT

The discovery of **1** as a high-affinity ligand for the nociceptin receptor has led to the synthesis of a series of tropane (8-methyl-8-azabicyclo[3.2.1]octane) derivatives as optimized ligands. These compounds exhibit high affinity for the nociceptin receptor, moderate to excellent selectivity over the opioid μ receptor, and behave as full agonists. In this Letter, we present the synthesis and highlight the structure–activity relationship of tropane derivatives culminating in the identification of **24** and **32** as potent and orally active antitussive and anxiolytic agents. The in vitro and in vivo activities, pharmacokinetic profile, and the hPXR activity, which predicts the potential 3A4 induction in human, are disclosed.

The identification of nociceptin/orphanin FQ peptide (N/OFQ) in 1995 represented the first successful use of reverse pharmacology and led to deorphanization of the nociceptin receptor (NOP).[1,2] Subsequently, the N/OFQ–NOP system has been implicated in a wide range of biological functions, including cough, anxiety, urinary incontinence, sleep disturbance, pain, stress, feeding, learning and memory, locomotor activity, substance abuse, cardiovascular function, and Parkinson's disease.[3] Despite the high sequence homology between the nociceptin receptor and the opioid μ, κ, and δ receptors (MOP, KOP, and DOP), and high similarity between N/OFQ and the opioid peptides, endogenous opioid receptor ligands lack affinity for NOP and N/FQ fails to activate the classical opioid receptors.

Previously, we have disclosed a series of *N*-benzhydryl substituted 4-hydroxy-4-phenylpiperidines as nociceptin receptor ligands.[4] In this Letter, we report the results of an expanded SAR study to identify a series of tropane derivatives as nociceptin receptor agonists. This has led to the discovery of potent and orally active antitussive and anxiolytic agents.

The lead compound **1** displays high affinity for NOP with binding affinity of 13 nM and moderate to excellent selectivity over MOP. KOP, and DOP.



NOP K_i = 13 nM
DOP K_i = 1666 nM
KOP K_i = 364 nM
MOP K_i = 233 nM

1

Since 4-aryl-4-hydroxypiperidine is known to metabolize to the potentially neurotoxic 4-arylpyridinium species,[5] our SAR development has focused on the modification of the piperidine ring. The

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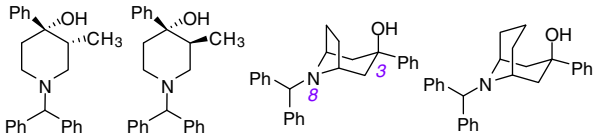
Table 1
SAR of the modified piperidine ring of **1**



2 **3** **4** **5**

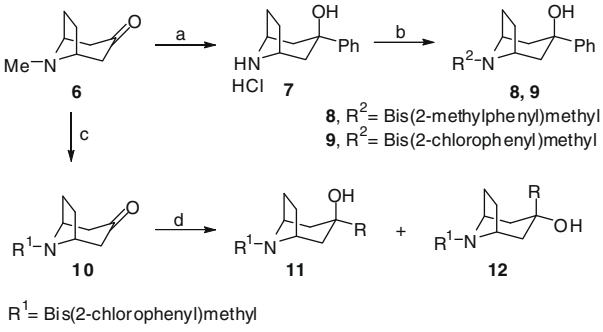
Compds	MW	*c*Log*P*	K_i[a] (nM)		EC_{50}[a] (nM) (% stim. @ 10 μM)	
			NOP	MOP	NOP	MOP
2	357.5	4.8	142	738	(70%)	nd
3	357.5	4.8	1571	nd	nd	nd
4	**369.5**	**4.6**	**2.3**	**94**	**161**	**nd**
5	383.5	5.2	7.5	514	(101%)	nd

[a] Values are means of at least 2–3 experiments (nd = not determined).

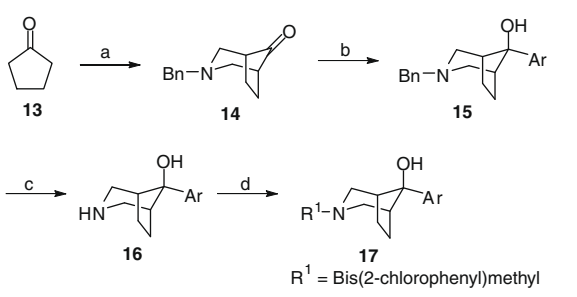
binding and properties of the modified piperidine analogs **2**–**5** are shown in Table 1. Since these compounds generally have better selectivity over KOP and DOP, only selectivity over MOP will be presented.

The conformationally constrained analogs **4** and **5** have improved the NOP affinity and selectivity over MOP and produce a full agonist response. Compound **4** shows a 70-fold decrease in the functional activity relative to its binding affinity and is not efficacious in the capsaicin-induced cough model in guinea pigs.[3a] Since **4** has higher affinity for NOP and lower *c*Log*P*, further SAR development has centered on **4** to improve the functional and in vivo activities.

The preparations of the *N*-benzhydryl modified analogs **8** and **9** and the 3-phenyl modified analogs having the general structures **11** and **12** are shown in Scheme 1. Generally diastereomer **11** is isolated predominantly as the major product. The synthetic routes



Scheme 1. Reagents and conditions: (a) (1) PhLi/THF, −78 °C; (2) $ClC(O)CH(Cl)CH_3/(CH_2Cl)_2$, reflux; (3) MeOH, reflux; (b) R^2Br, K_2CO_3,/CH_3CN, 80 °C; (c) (1) $ClC(O)CH(Cl)CH_3/(CH_2Cl)_2$, reflux; (2) MeOH, reflux; (3) R^1Br, K_2CO_3/CH_3CN, 80 °C; (d) RLi, RMgBr, RMgCl/THF or Et_2O or $NaBH_4$/MeOH.



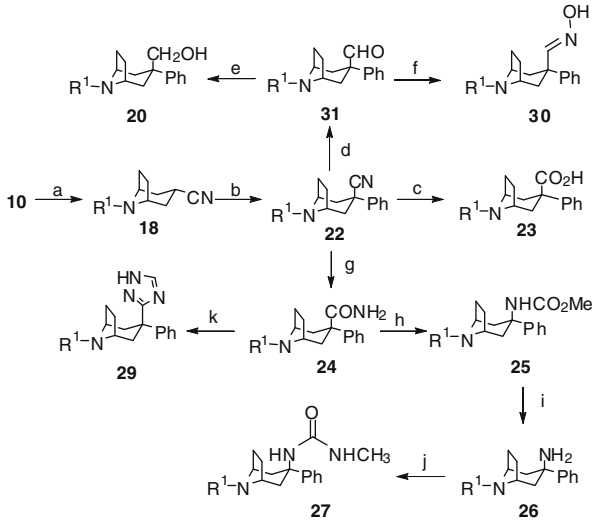
Scheme 2. (a) $(HCHO)_n$, $BnNH_2$, AcOH/MeOH, reflux; (b) ArLi/THF or Et_2O; (c) HCO_2NH_4, $Pd(OH)_2/C$, MeOH, 50 °C; (d) R^1Br, K_2CO_3/CH_3CN, 80 °C.

employed to prepare isotropane derivatives having the general structure **17** is diagramed in Scheme 2, while the C-3 hydroxy modified analogs is outlined in Scheme 3.[6]

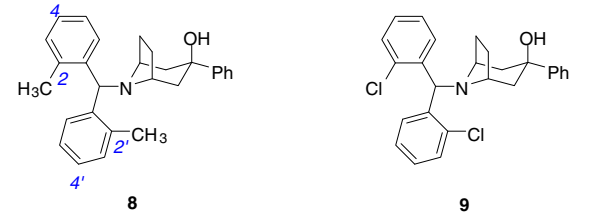
Target compounds were tested for affinity at the cloned human nociceptin receptor expressed in CHO cell membranes by measuring their ability to compete with [^{125}I][Tyr^{14}]nociceptin FQ. The opioid receptor binding assays were performed on CHO cell membranes expressing the human opioid receptors using [^{3}H]-diprenorphine as the radioligand. The K_i values were determined from dose–response curves. The functional activities of selected compounds were evaluated by 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.[7]

Selected compounds were evaluated for their antitussive and anxiolytic-like activity via oral administration. The antitussive activity was tested in the capsaicin-induced cough model in guinea pigs.[3a] The anxiolytic-like effects were assessed in the conditioned lick suppression (CLS) model in rats and the separation-induced guinea pig pups vocalization assay (GPPV).[8]

For the N-8 modifications, a variety of small substituents (Me, Et, F, Cl, Br, OMe, CN, CH_2OH) appear to be tolerated at the C-2 position of one or both of the phenyl rings on the benzhydryl (data not shown). Consistent with previous studies on the N-1 modifications of **1**,[4] introduction of a methyl or chlorine at C-2 of the benz-



Scheme 3. Reagents and conditions: (a) $TsCH_2NC$, *t*-BuOK/EtOH, DME; (b) KHMDS, PhF/$PhCH_3$; (c) $NaOH/(CH_2OH)_2$; (d) DIBAL/toluene; (e) $NaBH_4$/MeOH; (f) $NH_2OH{\cdot}HCl$, Py., EtOH; (g) concd H_2SO_4; (h) $PhI(OAc)_2$, KOH/MeOH; (i) TMSI; (j) MeN=C=O/THF; (k) (1) $Me_2NCH(OMe)_2$; (2) $NH_2NH_2{\cdot}H_2O$.



8

MW = 397.6, cLogP = 5.5
NOP K_i = 0.3 nM, EC_{50} = 12 nM
MOP K_i = 65 nM, EC_{50} = 693 nM
KOP K_i = 131 nM
DOP K_i = 2854 nM

9

MW=438.4, cLogP=6.0
NOP K_i = 3.4 nM, EC_{50} = 4 nM
MOP K_i = 22 nM, EC_{50} = 337 nM
KOP K_i = 109 nM
DOP K_i = 3143 nM

Figure 1. Binding and functional activities of **8** and **9**.

Table 2
Antitussive and anxiolytic-like activity of **8** and **9**

Compds	Antitussive activity ED_{50}[a,b](mg/kg)	Anxiolytic-like activity ED_{50}[a,b] (mg/kg)	
		GPPV	Rat CLS
8	0.07	0.5	1.6
9	0.4	0.4	1.4

[a] Activity was determined 2 h after oral dosing.
[b] $n = 10$ for antitussive and GPPV assay; $n = 12$–14 for rat CLS assay.

hydryl moiety produces potent NOP agonists (Fig. 1). Moving the substituents from the C-2 to the C-4 position decreases the potency. In general, replacement of the benzhydryl with a benzyl derivative produces a partial agonist (data not shown). Compared to **4**, the 2,2′-dimethyl and 2,2′-dichloro analogs (**8** and **9**) have improved functional activity. The in vitro data and the in vivo investigation of **8** and **9** are presented in Figure 1 and Table 2.

Compounds **8** and **9** produce dose-dependent antitussive and anxiolytic-like activity. The antitussive activity of **8** and **9** in the capsaicin-induced cough model in guinea pigs is attenuated by the NOP antagonist, J-113397,[9] but not the classic opioid receptor antagonist naltrexone or naloxone, demonstrating that the antitussive activity is mediated by NOP. The anxiolytic-like activity and side-effect profile of **8** were assessed in a variety of models and disclosed recently.[8] The specificity of the anxiolytic-like effect of **8** has also been confirmed with the NOP antagonist, J-113397, and the opioid receptor antagonist naltrexone.[8] Encouraged by the in vivo activity of **8** and **9**, we have further examined the tropane ring modifications and variations of the C-3 substitution. Since the methyl groups in **8** were metabolized to the corresponding carboxylic acids in rats (Fig. 2), compound **9** was selected for follow-up studies.

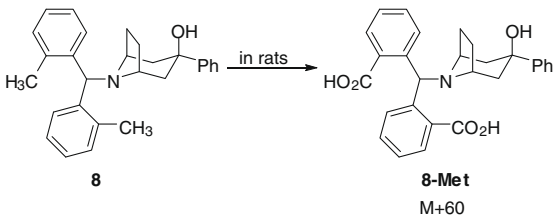


Figure 2. Metabolism of **8** in rats.

Table 3
Binding affinities of representative axial and equatorial isomers

R^1 = Bis(2-chlorophenyl)methyl

R	Compds	K_i[a] (nM)		Compds	K_i[a] (nM)	
		NOP	MOP		NOP	MOP
H	**11a**	198	nd	**12a**	1090	nd
	**11b**	19	1487	**12b**	2999	nd
	**11c**	10	470	**12c**	3759	nd

[a] Values are means of at least 2–3 experiments (nd = not determined).

To determine whether the hydroxy is tolerated at the equatorial position, the NOP affinities of the axial and equatorial isomers have been investigated (Table 3). The hydroxyl group in the axial position appears to be essential for the nociceptin receptor binding since the hydroxyl group in the equatorial position decreases the NOP affinity considerably (**11a–c** vs **12a–c**).

The NOP affinity of the isotropane analog, an alternative conformationally constrained structure has also been examined (Table 4). Compared to the corresponding isotropane analogs **17d** and **17e**, the tropane derivatives **11d** and **11e** display improved affinity for NOP.

The SAR of 3-phenyl modifications of **9** is highlighted in Table 5. Substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl are tolerated at the C-3 equatorial position and produce potent and selective NOP agonists with moderate to good selectivity over MOP. Replacement of the phenyl with a heteroatom containing moiety to reduce the lipophilicity appears to decrease both NOP and MOP functional activities.

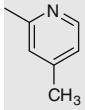
The SAR of the analogs modified at the C-3 hydroxy is shown in Table 6. It appears that the 3-hydroxy can be replaced with a wide variety of functional groups. In general, these modifications generate potent and selective NOP agonists with the exception of **21**. Based on the rapid rat PK data, potent NOP agonists were evaluated for the antitussive and anxiolytic-like activities.

The in vivo activities of the most potent compound, **24**, and the control compounds, codeine and chlordiazepoxide (CDP), are presented in Table 7. Compound **24** produces dose-dependent antitussive and anxiolytic-like activities. It demonstrates superior activity in animal models of cough and anxiety. The anxiolytic-like effect of **24** in the rat conditioned lick suppression test can be attenuated by the NOP antagonist, J-11897, demonstrating that this effect is mediated by NOP. The pharmacokinetic data collected after dosing at 3 mg/kg in rats are shown in Table 8. Compound **24** is void of enzyme induction in rats and does not inhibit cytochrome P450 isoforms 2D6 and 3A4. However it shows high clearance in rats.

To determine the potential 3A4 enzyme induction in human, compound **24** was evaluated in the human pregnane X receptor (hPXR) reporter gene assay by comparing its activity with the positive control, rifampicin (RIF). A ratio of induction level relative to RIF of 0.4 has been set as a practical screening cut-off to minimize the possibility of generating false positives.[10] In this assay **24** displays a ratio of 0.89 relative to RIF at 1 μM. The SAR development to reduce the hPXR activity of **24** is shown in Table 9. In general,

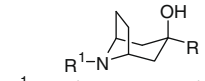
Table 4
Binding affinities of tropane and isotropane derivatives

R^1 = Bis(2-chlorophenyl)methyl

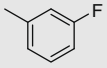
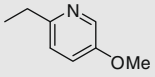
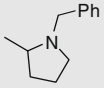
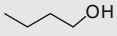
R	Compds	K_i[a] (nM)		Compds	K_i[a] (nM)	
		NOP	MOP		NOP	MOP
	**11d**	3	42	**17d**	908	7255
	**11e**	7.3	708	**17e**	385	3586

[a] Values are means of at least 2–3 experiments (nd = not determined).

Table 5
Highlights of 3-phenyl modification



R^1 = Bis(2-chlorophenyl)methyl

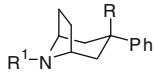
Compds	R	K_i[a] (nM)		EC_{50}[a] (nM) (E_{max})	
		NOP	MOP	NOP	MOP
11f		2.7	57	16	894
11g		5.2	535	50	1695
11h		13	384	90	(31%)
11i		1.9	104	16	709
11j		3.6	781	48	(60%)
11k		14	1553	nd	nd
11l		3	622	62	(29%)
11m		7.4	306	nd	nd

[a] Values are means of at least 2–3 experiments (nd = not determined).

incorporation of a substituent at the *para*-position of the 3-phenyl leads to the reduction of the hPXR activity while retaining the antitussive and anxiolytic-like activities, whereas a substituent on the amide nitrogen increases the hPXR activity. Introduction of a fluorine at the *para*-position of the 3-phenyl (**32**) provides a threefold decrease in the hPXR activity and a tenfold improvement in the antitussive activity compared to **24** (Table 10). The pharmacokinetic data collected after dosing at 3 mg/kg in rats are shown in Table 11. Compared to **24**, compound **32** demonstrates an improved pharmacokinetic profile. It exhibits higher exposure, lower clearance, and improved bioavailability.

In summary, we have discovered a series of tropane derivatives as high-affinity ligands for the nociceptin receptor. These compounds produce a full agonist response. Compound **24** demon-

Table 6
SAR of representative 3-hydroxy modification analogs

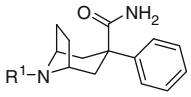


R^1 = Bis(2-chlorophenyl)methyl

Compds	R	K_i[a] (nM)		EC_{50}[a] (nM) (% stim. @ 10 μM)	
		NOP	MOP	NOP	MOP
19	OCH_3	8	636	50	545
20	CH_2OH	6	627	136	2144
21	CH_2F	3151	nd	nd	nd
22	CN	100	nd	nd	nd
23	CO_2H	3	123	nd	nd
24	$CONH_2$	1.7	38	6	376
25	$NHCO_2CH_3$	6	576	54	782
26	NH_2	4	458	76	4525
27	$NHCONHCH_3$	2	27	nd	nd
28	NHCO(cPr)	11	996	35	(25%)
29	1*H*-1,2,4-triazol-3-yl)	5.3	100	nd	nd
30	CH=NOH	20	601	107	(29%)

[a] Values are means of at least 2–3 experiments (nd = not determined).

Table 7
Antitussive and anxiolytic-like activity of **24**



24

R^1 = Bis(2-chlorophenyl)methyl

MW = 465.4, cLogP = 5.4
NOP K_i = 1.7 nM, EC_{50} = 6 nM
DOP K_i = 2326 nM
KOP K_i = 268 nM
MOP K_i = 38 nM, EC_{50} = 376 nM

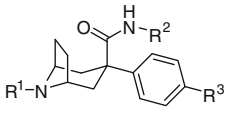
Compds	Antitussive activity ED_{50}[a,b] (mg/kg)	Anxiolytic-like activity ED_{50}[a,b] (mg/kg)	
		GPPV	Rat CLS
24	0.3	0.4	1.4
Codeine	6.8	nd	nd
CDP	nd	3.2	8.8

[a] Activity was determined 2 h after oral dosing (nd = not determined).
[b] n = 10 for antitussive and GPPV assay; n = 12–14 for rat CLS assay.

Table 8
Pharmacokinetic data of compound **24**

Rat PK (3 mg/kg, p.o.)	
$AUC_{(0-24\,h)}$	540 nM h
C_{max}	80 nM
$t_{1/2}$	1.8 h
Bioavailability	37%
Clearance	73 mL/min/kg
Vd(ss)	9.1 L/kg
P450 enzyme inhibition (IC_{50})	2D6, 3A4: >30 μM 2C9: 8 μM, 19 M (co, pre)
14-Day rat enzyme Induction	No issue @ 30 mg/kg
Human hepatocyte clearance	3.0 μL/min/10^6 cells

Table 9
hPXR activity of C-3 modification analogs

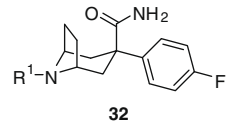


R^1 = Bis(2-chlorophenyl)methyl

Compds	R^2	R^3	K_i[a] (nM)		hPXR
			NOP	MOP	Ratio to RIF (1 μM)
24	H	H	2	38	0.89
32	**H**	**F**	**16**	**126**	**0.27**
33	H	Cl	31	55	0.05
34	H	Br	40	nd	0.05
35	H	OCH_3	22	59	0.06
36	H	OCF_3	285	nd	0.10
37	H	$C(O)NH_2$	678	nd	0.05
38	CH_3	H	4.9	50	1.29
39	C_2H_5	H	7	215	1.49
40	$CH(CH_3)_2$	H	10	333	2.21
41	$CH_2CH_2OCH_3$	H	8.2	60	2.35
42	$CH_2CH(CH_3)OH$	H	11	57	2.38

[a] Values are means of at least 2–3 experiments (nd = not determined).

Table 10
Antitussive and anxiolytic-like activity of **32**



32

MW = 483.4, cLogP = 5.5
NOP K_i = 16 nM, EC_{50} = 14 nM
DOP K_i = 1039 nM
KOP K_i = 752 nM
MOP K_i = 126 nM, EC_{50} = 947 nM

R^1 = Bis(2-chlorophenyl)methyl

Compds	Antitussive activity ED_{50}[a,b] (mg/kg)	Anxiolytic-like activity ED_{50}[a,b] (mg/kg)	
		GPPV	Rat CLS
32	0.03	0.2	2.7

[a] Activity was determined 2 h after oral dosing.
[b] n = 10 for antitussive and GPPV assay; n = 12–14 for rat CLS assay.

Table 11
Pharmacokinetic data of compound **32**

Rat PK (3 mg/kg, p.o.)	
$AUC_{(0-24\,h)}$	1270 nM h
C_{max}	250 nM
$t_{1/2}$	1.8 h
Bioavailability	45%
Clearance	33 mL/min/kg
Vd(ss)	1.8 L/kg

strates superior activity in animal models of cough and anxiety to codeine and chlordiazepoxide. The potential 3A4 enzyme induction in human has been evaluated in the human pregnane X receptor reporter gene assay.[10] Introduction of a fluorine at the *para*-position of the 3-phenyl (**32**) provides a threefold decrease in the hPXR activity and a tenfold improvement in the antitussive activity and a better pharmacokinetic profile. Further SAR development on C-3 has been explored. For instance, the SAR studies of 3-aminomethyl have been presented recently.[11] Other C-3 modifications will be disclosed in due course.

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