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Structure–activity relationships of 3-substituted *N*-benzhydryl-nortropane analogs as nociceptin receptor ligands for the treatment of cough

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ABSTRACT

A series of 3-axial-aminomethyl-*N*-benzhydryl-nortropane analogs have been synthesized and identified to bind to the nociceptin receptor with high affinity. Many of these analogs showed high binding selectivity over classic opioid receptors such as μ receptor. The synthesis and structure–activity relationships around the C-3 nortropane substitution are described. Selected compounds with potent oral antitussive activity in the guinea pig model are disclosed.

The nociceptin receptor (NOP, ORL-1), an orphan opioid receptor, was discovered as a member of the G protein-coupled receptor superfamily in 1994.[1] Its sequence has ~50% homology to those of the opioid receptor family μ, κ, and δ (also known as MOP, KOP, and DOP, respectively). However NOP displays low binding affinity for the classical synthetic and endogenous opioid ligands. NOP is widely distributed throughout the brain and spinal cord and thus is expected to participate in various physiological processes. Following the discovery of NOP, there has been remarkable advance toward understanding its pharmacological significance. Nociceptin (orphanin FQ or OFQ), the NOP endogenous ligand,[2] does not interact with the other opioid receptors. It has been reported to mediate various physiological processes, for instance, pain, cough, anxiety, feeding, sleep, substance abuse, and cognition.[3] Thus, selective NOP agonists or antagonists might have clinical potential for the treatment of related diseases with better side effect profile associated with the other opioid receptors, such as physical dependency, respiratory depression, and constipation.

Codeine is the most widely used narcotic antitussive agent. However it is not long acting and possesses significant adverse effects such as drowsiness, constipation, respiratory depression, and unpleasant withdrawal symptoms. There is an unmet medical need for the treatment of cough. Nociceptin has been shown to display antitussive activity in guinea pig model through peripheral (IV) or central (ICV) administration, and this effect was blocked by a NOP selective antagonist, J113397.[4] Thus, selective NOP agonists provide a novel therapeutic approach for the management of cough.

In our nociceptin agonist program, we have reported structure–activity relationships (SAR) related to two early lead series based on the 4-hydroxy-4-phenyl piperidinyl[5,6] and spiropiperidinyl[7] scaffolds, originally derived from high throughput screening. In the 4-hydroxy-4-phenyl piperidinyl series, the *N*-2,2′-dichlorobenzhydryl analogs demonstrated improved binding affinity.[5,6] Further SAR development was focused on the *N*-2,2′-dichlorobenzhydryl substituted nortropane scaffold, a conformationally-restricted analog of piperidine. In this paper, we disclose synthesis and SAR of a new 3-axial-aminomethyl-*N*-benzhydryl-nortropane series as potential replacement of the C-3 hydroxyl group which could undergo elimination. Furthermore the aminomethyl functionality allowed us to explore different chemical functionality on the C-3 axial position to further modulate DMPK profile of the tropane series.

The synthetic route to the 4-α-substituted nitrile is outlined in Scheme 1. Commercially available tropinone (**1**) was de-methylated

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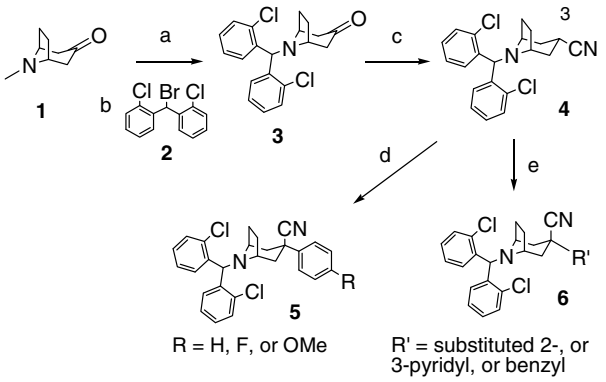


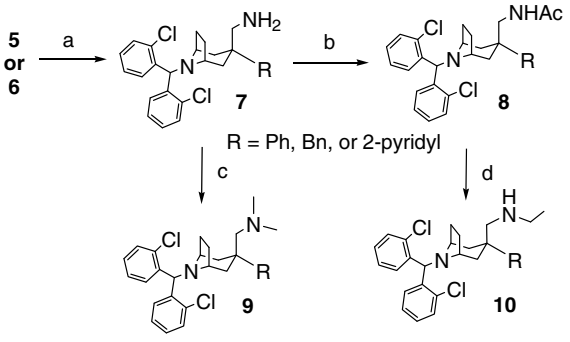
Scheme 1. Reagents and conditions: (a) α-chloroethyl chloroformate, DCE, reflux; (b) **2**, K_2CO_3, CH_3CN, reflux; (c) KO-*t*-Bu, tosylmethyl isocyanide, DME, −40 °C to rt; (d) RPhF, KHMDS, neat, microwave, 100 °C; (e) NaHMDS, R'X, THF, −78 °C to rt.

using α-chloroethyl chloroformate and subsequently alkylated using 2,2′-dichloro-benzhydryl bromide (**2**)[5] in the presence of K_2CO_3 to afford the ketone intermediate **3**. Single step transformation of **3** to the nitrile intermediate **4** was carried out using tosylmethyl isocyanide and KO-*t*-Bu in DME.[8] Further nucleophilic addition of a phenyl group through the less hindered α-equatorial direction was achieved under neat microwave condition with excess fluorobenzene and KHMDS as base at 100 °C (∼78% when R = H) to obtain **5**. The benzyl or pyridinyl derivatives (**6**) could be prepared using the corresponding benzyl halides or pyridinyl halides and NaHMDS as base.[9]

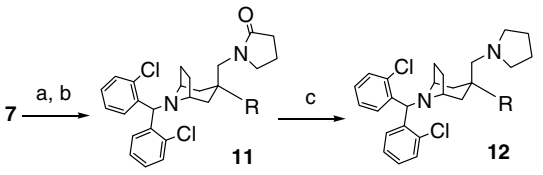
Further transformation of the C-3 nitrile to the aminomethyl or substituted aminomethyl group is detailed in Schemes 2–4. Thus, the nitriles (**5** or **6**) were reduced to aminomethyl **7** using LAH, and acetylated with acetic anhydride or di-methylated under reductive amination condition to afford the target analogs **8** and **9**, respectively. The *N*-ethyl analogs (**10**) were obtained by reduction of *N*-acetyl **8** with DIBAL in THF. The stereochemistry of C-3 for **8** was confirmed by the NOE experiment. The methylene protons between C-3 and the nitrogen displayed significant NOE correlations with the protons on the top ethylene bridge.

The pyrrolidinone and pyrrolidine analogs were synthesized as described in Scheme 3. Acylation of **7** with 4-chloro-butyryl chloride and further cyclization in the presence of KO-*t*-Bu produced pyrrolidinone **11** in one pot.[10] Reduction of the cyclic amide (**11**) with LAH generated pyrrolidine **12**.

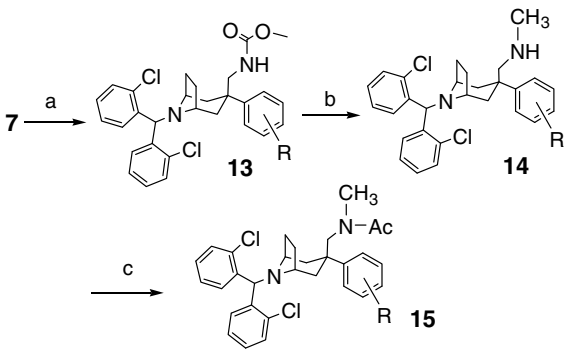
To prepare the *N*-methyl-*N*-acetyl substituted analog **15**, a three-step synthesis was carried out as shown in Scheme 4. Carbamate **13** generated from **7** and $ClCO_2Me$ under basic condition was



Scheme 2. Reagents and conditions: (a) LAH, ether, rt; (b) Ac_2O, Pyr, 0 °C; (c) HCHO, HCO_2H, 100 °C (R = Ph) or HCHO, AcOH, $NaBCNH_3$, MeOH, rt; (d) DIBAL, THF, −78 °C to rt.



Scheme 3. Reagents and conditions: (a) $Cl(CH_2)_3COCl$, Et_3N, DCM, rt; (b) KO-*t*-Bu, THF, rt; (c) LAH, THF, reflux.



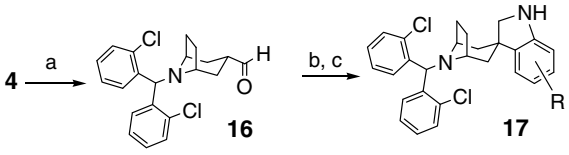
Scheme 4. Reagents and conditions: (a) $ClCO_2Me$, aq K_2CO_3, DCM, rt; (b) LAH, THF, reflux; (c) Ac_2O, pyridine, 0 °C.

reduced by LAH to afford the *N*-methyl analog **14**. Further acetylation of **14** gave the target **15**.

The conformationally restrained analog **17** was designed by connecting the C-3 aminomethyl to the *ortho*-position of the phenyl group. The synthesis was achieved in two steps as shown in Scheme 5. Aldehyde **16** was prepared by reduction of the nitrile **4** using DIBAL. Formation of the 3*H*-indole on C-3 was achieved using phenylhydrazine and trifluoroacetic acid in DCM at 40 °C. Further reduction of the 3*H*-indole to the spiro 2,3-dihydro-1*H*-indole (**17**) was accomplished by subsequently adding $NaBH(OAc)_3$ to the above reaction mixture.[11]

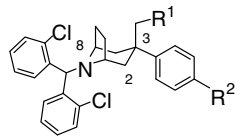
Target compounds were tested for their affinity at the cloned human nociceptin receptor expressed in CHO cell membranes by measuring their ability to compete with [^{125}I][Tyr^{14}]nociceptin FQ. The opioid receptor binding assays were performed with CHO cell membranes expressing the human opioid receptors 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 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.

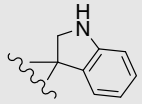
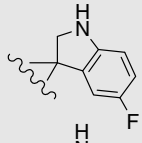
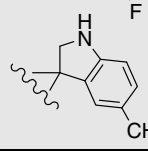
Compound **18** showed potent NOP binding affinity with K_i 6 nM and superior selectivity over MOP binding (∼112-fold). Additional methyl, dimethyl, or acetyl substitution on the nitrogen (**19**–**21**) slightly reduced NOP binding affinity (K_i between 10 and 20 nM, Table 1). The carbamate substitution (**22**) was tolerated, whereas the *N*-methyl-*N*-acetyl analog **23** showed poor NOP affinity (K_i 210 nM) and reduced selectivity over MOP receptor (∼13-fold). Large substitutions at the nitrogen such as pyrrolidine in **24** and



Scheme 5. Reagents and conditions: (a) DIBAL, toluene, −78 °C to rt; (b) *R*-phenylhydrazine, TFA, DCM, 40 °C; (c) $NaBH(OAc)_3$, DCM, rt.

Table 1
SAR of the C-3 phenyl substituted analogs.

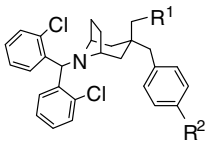


Compound	R^1	R^2	NOP K_i (nM)	MOP K_i (nM)
18	NH_2	H	6	674
19	$NHCH_3$	H	10	566
20	$N(CH_3)_2$	H	17	1486
21	NHAc	H	20	777
22	$NHCO_2CH_3$	H	20	905
23	$N(CH_3)$(Ac)	H	210	2620
24		H	70	4169
25		H	68	nd
26	NHAc	4-F	31	2106
27	NHAc	4-OMe	118	2407
28		[a]	50	1204
29		[a]	39	1706
30		[a]	74	998

[a] Partial structures represent C-3 substitution.

pyrrolidinone in **25** led to ~10-fold reduction in binding affinity compared to **18**.

Table 2
SAR of the C-3 benzyl substituted analogs.



Compound	R^1	R^2	NOP K_i (nM)	MOP K_i (nM)
31	NH_2	H	11	1336
32	NHAc	H	12	458
33	NHEt	H	39	nd
34	$N(CH_3)_2$	H	55	nd
35		H	116	nd
36		H	336	nd
37	NH_2	4-F	34	1414
38	NHAc	4-F	15	782
39		4-F	58	nd

nd, not determined.

Since the *para*-position of the phenyl ring is a potential site of metabolism, the SAR of the *para*-substitution on the phenyl ring was evaluated. Fluoro substitution at the *para*-position (**26**) maintained binding affinity for NOP with a better selectivity (68-fold) for MOP, when compared to **21**. In contrast, the *para*-methoxyl substitution caused ~6-fold reduction of NOP binding affinity, and led to poor selectivity, as concluded from comparison of K_i data from **21** and **27**. The spiro 2,3-dihydro-1*H*-indole analogs (**28–30**) displayed decreased NOP affinity (K_i 39 to 74 nM).

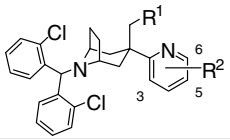
SAR of the C-3 benzyl substituted analogs (**31**–**39**) was summarized in Table 2. Additional carbon extension of the phenyl group was tolerated (**31**–**33**, **38**). Compound **31** showed potent NOP binding affinity (K_i 11 nM) and excellent selectivity (~121-fold) over MOP. Large alkyl substitution on the nitrogen reduced binding affinity (**35**, **36**). The fluoro substitution at the *para*-position did not affect binding significantly (**37**–**39**).

SAR data of the C-3 2-pyridinyl analogs (**40**–**56**) are listed in Table 3. Replacement of the C-3 phenyl with a 2-pyridinyl group was tolerated. All four derivatives **40**–**43** with or without simple *N*-substitution showed K_i with single digit nM and high selectivity over MOP receptor binding ranging from 75- to 124-fold. With the 6-fluoro substitution on the pyridine ring (**44**–**46**), the potency of the ligands dropped ~4- to 15-fold. The NOP binding affinity was not affected significantly by the 6-methoxyl substitution on the pyridine ring (**47**–**49**), however the selectivity over MOP binding dropped notably. The substitution on the 3-position of the pyridine ring with a methyl or piperidinyl-methyl group reduced NOP binding activity (**50**–**53**).

Replacement of the C-3 phenyl with a 3-pyridinyl group showed reduced NOP binding affinity. The values of K_i increased to 82 and 35 nM for compounds **57** and **58**, respectively, as shown in Table 4. The racemic 2-piperidinyl analogs **59** and **60** were prepared by reduction of the 2-pyridinyl analogs **40** and **41**, respectively, using PtO_2 as catalyst under 1 atm H_2 atmosphere. Both **59** and **60** showed potent NOP binding affinity.

Selected compounds (**18**, **20**, **21**, **31**, **32**, **40**, and **47**) were evaluated for selectivity over DOP and KOP receptors. These compounds from different series displayed excellent selectivity over

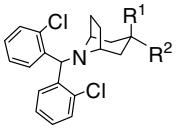
Table 3
SAR of the C-3 2-pyridinyl substituted analogs.



Compound	R^1	R^2	NOP K_i (nM)	MOP K_i (nM)
40	NH_2	H	7	617
41	NHAc	H	5	374
42	NHEt	H	6	743
43	$N(CH_3)_2$	H	7	785
44	NH_2	6-F	29	nd
45	NHAc	6-F	24	1284
46	$N(CH_3)_2$	6-F	104	3976
47	NH_2	6-OCH_3	11	123
48	NHAc	6-OCH_3	4	251
49	NHEt	6-OCH_3	20	442
50	NH_2	3-CH_3	50	nd
51	NHAc	3-CH_3	173	nd
52	NH_2	3-Piperidinyl-methyl	245	nd
53	NHAc	3-Piperidinyl-methyl	670	758
54	NHAc	5-OCH_3	62	3447
55	NHAc	5-Br	27	752
56	NHAc	5-Piperidinyl	99	nd

nd, not determined.

Table 4
SAR of the 3-pyridinyl and 2-piperidinyl substituted analogs.



Compound	R^1	R^2	NOP K_i (nM)
57	CH_2NH_2		82
58	CH_2NHAc		35
59	CH_2NH_2		17
60	CH_2NHAc		27

DOP receptor (300- to 780-fold) and medium to good selectivity over KOP receptor (30- to 190-fold).

Functional activity (EC_{50}) was evaluated for selected compounds using a GTPγS assay. The data listed in Table 5 showed EC_{50} of the compounds **20**, **21**, **37**, **38**, and **43**, which demonstrated full agonist activity in the GTPγS functional assay.

Some compounds demonstrated decent DMPK profiles (data not shown) were evaluated for the in vivo antitussive activity using the capsaicin-induced guinea pig model.[4] Compound **21** demonstrated potent oral antitussive activity with an ED_{50} of 0.19 mg/kg at 2 h, comparable to the previous lead compound possessing piperidinyl skeleton.[6] Compounds **20** and **38** showed antitussive activity at 0.3 mg/kg with 36% and 23% of cough suppression, respectively, compared to the placebo. Compound **26** did not display oral antitussive activity at low dose (0.3 mg/kg).

In conclusion, several potent NOP receptor agonists were identified with excellent selectivity in C-3 axial aminomethyl nortropane series. Large substitution on the axial aminomethyl nitrogen led to reduced NOP binding activity in general. The fluoro substitution on the *para*-position of the phenyl or benzyl ring only slightly diminished NOP binding affinity and selectivity over MOP receptor. In general, substitution on 2-pyridinyl ring led to reduced NOP affinity. Among the potent NOP agonists identified, **21** showed potent oral antitussive activity in the capsaicin-induced guinea pig model with an ED_{50} of 0.19 mg/kg at 2 h.

Table 5
Functional activity of selected compounds.

Compound	GTPγS EC_{50} (nM)	GTPγS % Stim, conc. [μM]
20	483	104%, 5.5
21	269	122%, 10
37	124	87%, 5.5
38	129	124%, 10
43	156	97%, 5.5

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