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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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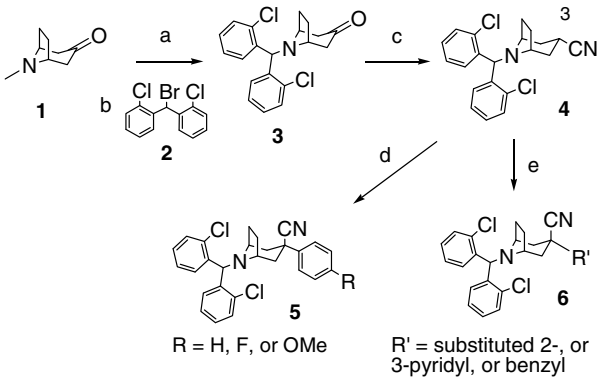


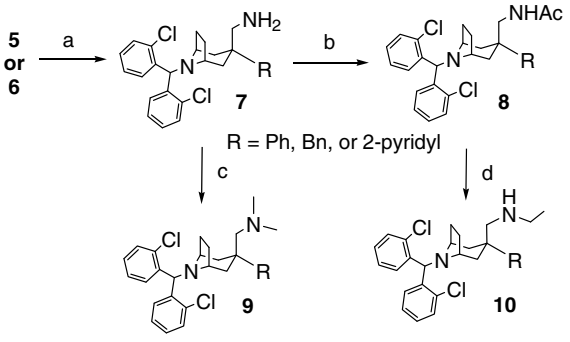
Scheme 1. Reagents and conditions: (a) α-chloroethyl chloroformate, DCE, reflux; (b) **2**, K_2CO_3, CH_3CN, reflux; (c) KO-*t*-Bu, tosylmethyl isocyanide, DME, −40 °C to rt; (d) RPhF, KHMDS, neat, microwave, 100 °C; (e) NaHMDS, R'X, THF, −78 °C to rt.

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]

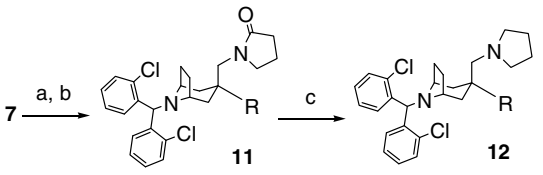
Further transformation of the C-3 nitrile to the aminomethyl or substituted aminomethyl group is detailed in Schemes 2–4. Thus, the nitriles (**5** or **6**) were reduced to aminomethyl **7** using LAH, and acetylated with acetic anhydride or di-methylated under reductive amination condition to afford 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**.

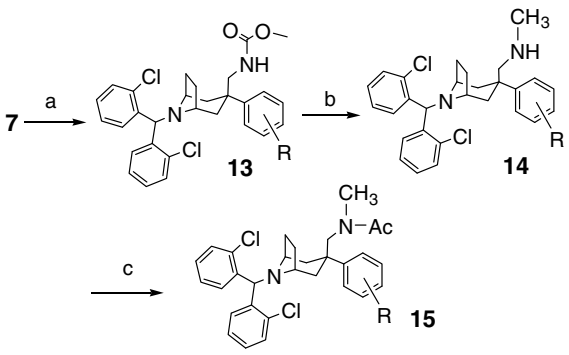
To prepare the *N*-methyl-*N*-acetyl substituted analog **15**, a three-step synthesis was carried out as shown in Scheme 4. Carbamate **13** generated from **7** and $ClCO_2Me$ under basic condition was



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.



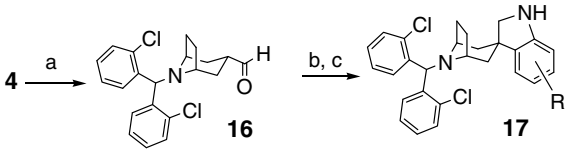
Scheme 4. Reagents and conditions: (a) $ClCO_2Me$, aq K_2CO_3, DCM, rt; (b) LAH, THF, reflux; (c) Ac_2O, pyridine, 0 °C.

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.