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Identification of 3-substituted *N*-benzhydryl-nortropane analogs as nociceptin receptor ligands for the management of cough and anxiety

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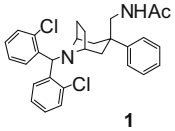
ABSTRACT

A series of nortropane analogs based on previously reported compound **1** have been synthesized and shown to bind to the nociceptin receptor with high affinity. The synthesis and structure–activity relationships around the C-3 nortropane substitution are described. From the SAR study and hPXR screening effort, compound **15** was identified to possess potent oral antitussive and anxiolytic-like activities in the guinea pig models.

The nociceptin receptor (NOP, ORL-1), first discovered in 1994, displays low binding affinity for the classical opioid ligands, albeit its sequence has ~50% homology to those of the opioid receptor family μ, κ, and δ (or MOP, KOP, and DOP, respectively).[1] 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. The NOP endogenous ligand (nociceptin)[2] does not interact with the other opioid receptors, and has been reported to mediate various physiological processes, for instance, pain, cough, anxiety, cognition, feeding, sleep, substance abuse and urinary incontinence.[3] Thus, selective NOP agonists or antagonists might have clinical potential for the treatment of related diseases.

Nociceptin has been shown to display antitussive activity in the guinea pig model through peripheral (IV) or central (ICV) administration.[4] Thus, selective NOP agonists provide a novel therapeutic approach for the management of cough.



1

NOP Ki: 20 nM
NOP (GTPγS) EC_{50}: 269 nM
Antitussive activity:
ED_{50}: 0.19 mg/kg at 2 h

Genetic and pharmacological studies indicate that NOP modulates the anxiety response.[5,6] It was found that local (ICV) administration of nociceptin neuropeptide or IP administration of NOP agonist Ro64-6198 led to anxiolytic-like activity in rats.[6,7] Recently, NOP agonist SCH 221510, a nortropane analog structurally distinct from nociceptin and Ro64-6198, was disclosed to possess the oral anxiolytic-like activity in various animal models including the rat conditioned lick suppression (CLS) model and the separation-induced guinea pig pup vocalization (GPPV) model.[8] The reported data for SCH 221510 suggested that NOP agonists have the potential to be developed as a novel class of anxiolytic agents.

In our nociceptin agonist program, we have reported structure–activity relationships (SAR) based on the 4-hydroxy-4-phenyl piperidinyl scaffold.[9] Further SAR development was focused on the conformationally-restricted nortropane scaffold. Compound **1** was identified previously as a potent NOP agonist with potent in vivo antitussive activity in the guinea pig model from a series of 3-axial-aminomethyl-*N*-benzhydryl-nortropane analogs.[10] In this paper, we describe our continuing efforts to explore SAR at the C-3 position to modulate the binding affinity and selectivity profile (e.g., human pregnane X receptor (hPXR)). Synthesis and SAR of a new 3-axial-substituted-*N*-benzhydryl-nortropane series including carboxylamide, amine, and carbamate series are disclosed along with our strategy to identify potent dual antitussive and axiolytic agents.

The synthetic route to the C-3-α-substituted nitrile is summarized in Scheme 1. The commercially available tropinone (**2**) was

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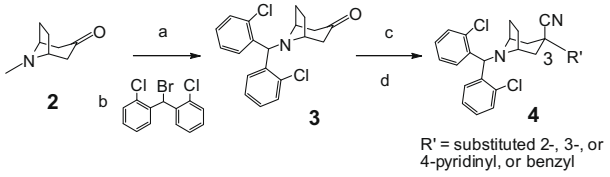
de-methylated and subsequently alkylated using previously established procedure to afford the ketone intermediate (**3**).[9,10] Transformation of **3** to the nitrile and subsequent nucleophilic addition of a benzyl or pyridyl group through the less hindered α face was achieved using the corresponding benzyl halides or pyridyl halides under the basic condition to give **4**.[10] The C-3 stereochemistry was confirmed with the NOE experiments of the hydrolyzed products (**5**). The NOE correlations were observed between the amide protons and the protons on the ethylene bridge in the NOESY experiment, confirming the β position of the amide group. The detail NMR and high-resolution mass data of one example of **5** are presented in the reference.[11]

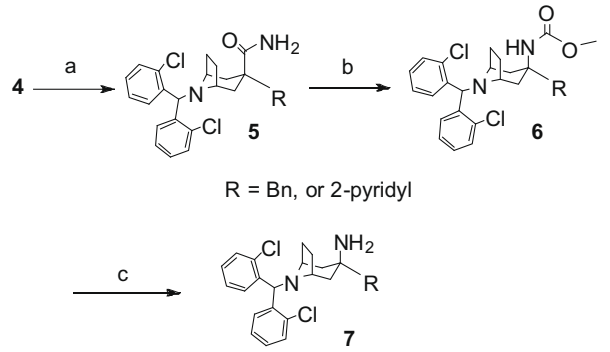
Further transformation of the C-3 nitrile (**4**) to the carboxylamide, carbamate, and amino functional groups is detailed in Scheme 2. Thus, the nitriles (**4**) were hydrolyzed to the carboxylamides (**5**) with concd H_2SO_4, and then rearranged through Hofmann rearrangement to afford the corresponding methyl carbamates (**6**) using bis(acetoxy)iodobenzene and KOH/MeOH. The 3-amino analogs (**7**) were obtained by removal of the $-CO_2Me$ group with TMSI in dichloromethane and then in MeOH under reflux.

The N-substituted analogs were synthesized as described in Scheme 3. Acetylation and methylation of **7** gave **8** and **9**, respectively.

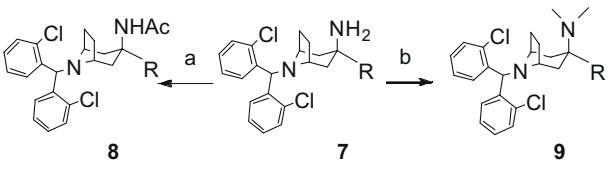
To prepare the amide homolog (**13**), a five-step synthesis was designed as shown in Scheme 4. The nitrile **4** was reduced to the aldehyde intermediate using DIBAL, and further reduced to the alcohol (**11**) with $NaBH_4$. Mesylation of the alcohol and the subsequent replacement with a cyano group gave nitrile **12**. Finally, the nitrile (**12**) was hydrolyzed to the carboxylamide (**13**) under the same acidic condition described above.



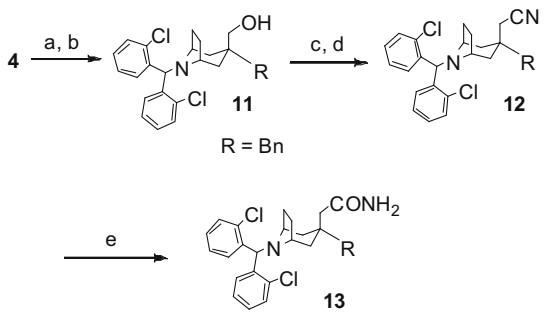
Scheme 1. Reagents and conditions: (a) α-chloroethyl chloroformate, DCE, reflux; then MeOH, reflux; (b) **2**, K_2CO_3, CH_3CN, reflux; (c) KO–*t*Bu, tosylmethyl isocyanide, DME, −40 °C to rt; (d) NaHMDS, RX, THF, −78 °C to rt.



Scheme 2. Reagents and conditions: (a) concd H_2SO_4, neat, rt; (b) $PhI(OAc)_2$, KOH, MeOH, 0 °C to rt; (c) TMSI, DCM, reflux, then MeOH reflux.



Scheme 3. Reagents and conditions: (a) Ac_2O, pyridine, rt; (b) HCHO, HCO_2H, rt; $NaBH(OAc)_3$, DCE, rt.



Scheme 4. Reagents and conditions: (a) DIBAL in toluene, 0 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) MsCl, Et_3N, DCM, 0 °C; (d) KCN, 18-crown-6, DMF, 110 °C; (e) concd H_2SO_4, neat, rt.

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. The opioid receptor binding assays were performed with CHO cell membranes expressing the human opioid receptors using [^{3}H]-diprenorphine as the radioligand. 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 CHO cells transfected with the human nociceptin gene. Since most of the nortropane analogs identified previously showed good selectivity over DOP and KOP,[10] only selectivity over MOP will be presented. To limit the number of the compounds for further evaluation, the compounds with the NOP K_i less than 15 nM and selectivity (NOP vs MOP) higher than ~10-fold were selected.

The C-3 2-pyridyl carboxylamide **14** showed potent NOP binding affinity with a K_i of 4 nM. Thus a series of the substituted pyridyl analogs were prepared. Introduction of a small substituent (e.g., F, Cl, Me, or OMe) at the 5 position of the pyridine ring slightly reduced NOP affinity (**15–19,** K_i between 6 and 22 nM, Table 1). Substitutions of the polar groups (OH or NH_2), cyano, or relatively large groups (e.g., Br, CF_3 or $CONH_2$) at the 5-position of the pyridine ring were found to decrease the NOP binding affinity significantly (**17**, **20–25**). The binding selectivity of this series of compounds for the NOP receptor versus MOP is around 4–17-fold.

The promising result of the 5-fluoro analog (**15**) triggered additional studies on the fluoro-substituted pyridyl analogs. Moving the fluoro atom from the 5-position to the 6-position retained NOP affinity and improved selectivity over MOP (**26**, 35-fold). Most of the di-fluoro compounds (**27–31**) showed slightly reduced NOP affinity (K_i 9–19 nM), and were selected for further hPXR evaluation. A dramatic loss of NOP affinity was observed while carboxylic acid was introduced to the 4-position of the pyridine ring (**32**). In general the polar or large substitutions were not preferred at the 4- or 5-position of the 2-pyridine ring (Table 2).

To further explore the C-3 axial substitution, the C-3 nitrogen directly-attached analogs were prepared. The binding affinity data of these analogs are listed in Table 3. The C-3 unsubstituted amino analogs **33** and **34** exhibited potent NOP affinity (K_i 10 nM; 7 nM, respectively) and decent selectivity over MOP (32-fold). The acetyl analogs (**35** and **36**) of **33** and **34** retained NOP affinity (K_i 6 and 10 nM) and increased selectivity over MOP to 52- and 60-fold, respectively. The methyl carbamates (**37–39**) displayed similar NOP affinity (K_i 10–12 nM) and improved selectivity (74–80-fold) over MOP. However, the *N,N*-di-methyl substitution resulted in