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Biaryl piperidines as potent and selective delta opioid receptor ligands

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ABSTRACT

The design and synthesis of novel opiates are reported. Based on the message-address principle a novel class of 4,4- and 3,3-biaryl piperidines was designed and synthesized. Biological evaluation confirmed that these compounds exhibit high affinity and selectivity for the delta opioid receptor. Key structure–activity relationships that influence affinity, selectivity, functional activity and clearance are reported.

Opioid ligands of the three receptor subtypes mu, delta, and kappa have been implicated in the modulation of several disease states of the central nervous system spanning from addiction and pain, to depression and bipolar disorder.[1] Thus, the quest for novel and selective tools that would aid the pharmacological characterization of these receptor subtypes is an active research area for medicinal chemistry. Our initial interest in the opioid family focused on the delta receptor. There is an emerging body of knowledge which suggests that agonists of the receptor could be effective pain therapeutics.[2] Antagonists of the receptor have been implicated as suppressors of ethanol addiction.[3] Our research aimed to probe the latter hypothesis. Hence, at the start of the investigation we set as key project objectives the discovery of novel, potent, and selective delta receptor antagonists with sufficient exposure in the CSF relative to in vitro receptor affinity. Subsequently, our goal was to characterize these compounds in preclinical models with disease relevance.

The design of selective delta opioid receptor ligands has been largely influenced by the message-address principle which describes essential structural features for affinity and selectivity.[4] A powerful application of the message-address principle, which led to the identification of naltrindole is represented by the work of Portoghese et al.[5,6] Additional delta selective ligands such as TAN-67 (Fig. 1) have emerged from the application of the message-address principle.[7] Both naltrindole and TAN-67 represent delta opiates with phenyl groups as the address component. The hypothesis that the address portion of delta opiates may not be strictly limited to aromatic moieties has been postulated. For example, computational studies have suggested that the piperazine delta receptor agonist SNC-80[8] (Fig. 1) shares receptor binding elements with molecules derived from the application of the message-address principle.[9] This recognition led to the discovery of novel molecules that contain polar functionality, such as the diethyl amide, as the address component responsible for selectivity.

Based on molecular modeling, we were compelled to investigate whether biaryl piperidines (Fig. 2) would furnish potent and selective delta opiates. As a structural class, biaryl piperidines offer many design advantages. The biaryl piperidines represent an evo-

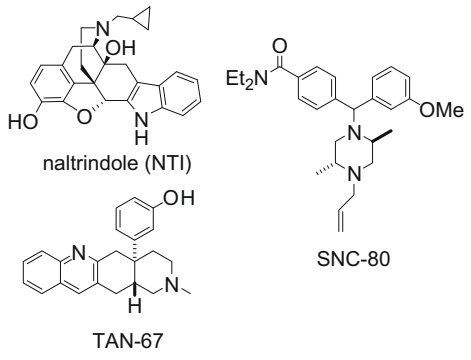

Figure 1. Naltrindole (NTI), TAN-67 and SNC-80.

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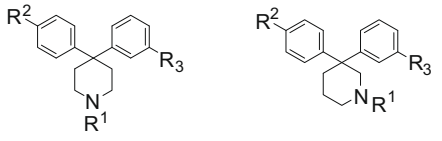


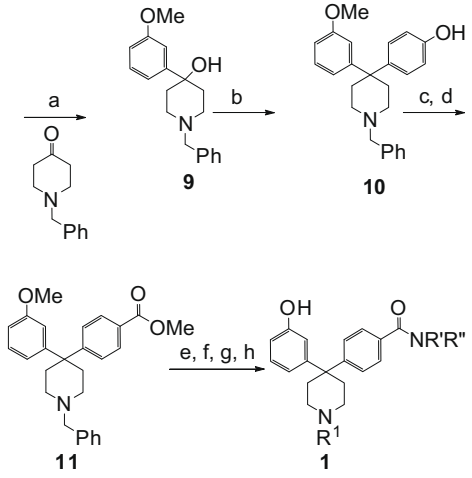
1: R^1 alkyl, R^2 CONR'R", R^3 OH
2: R^1 alkyl, R^2 C(OH)R'R", R^3 OH
3: R^1 alkyl, R^2 CONR'R R^3 $CONH_2$
4: R^1 alkyl, R^2 C(OH)R'R", R^3 $CONH_2$

5: R^1 alkyl, R^2 CONR'R", R^3 OH
6: R^1 alkyl, R^2 C(OH)R'R", R^3 OH
7: R^1 alkyl, R^2 CONR'R R^3 $CONH_2$
8: R^1 alkyl, R^2 C(OH)R'R", R^3 $CONH_2$

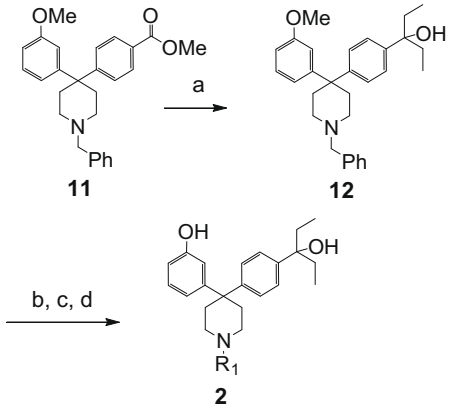
Figure 2. Biaryl piperidine targets.

lution of phenyl piperidines, compounds with significant presence in the literature as opioid agonists and antagonists.[10] The significant body of knowledge regarding phenyl piperidines aids the design of biaryl piperidine compounds with desired CNS disposition and appropriate pharmacokinetic characteristics. The structure provides the opportunity for the parallel SAR investigation of key functionality at the aromatic rings and at the piperidine nitrogen. Thus, we aimed to probe the effect of amine substitutions ($\mathbf{R}^1$) on binding and functional activity. Additionally, we sought to identify address moieties beyond amides ($\mathbf{R}^2$) and examine the impact on affinity and selectivity. Finally, we intended to probe the significance of the phenol moiety ($\mathbf{R}^3$) and to identify low molecular weight phenol replacements which would mitigate the potential risk posed by zwitterions on brain penetration.

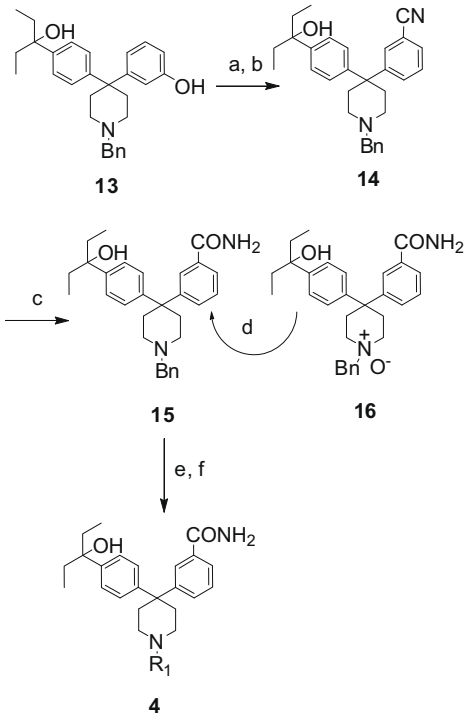
The reduction to practice of the plan for the synthesis of 4,4-biaryl piperidines (compounds **1**–**4**) is shown below (Schemes 1–3). We devised a common strategy for the synthesis of the corresponding 3,3-biaryl piperidines which afforded compounds **5**–**8**. Our work commenced with the addition of *m*-methoxy phenyl magnesium bromide, generated in situ, to *N*-benzyl-4-piperidi-



Scheme 1. Synthesis of 4,4-biaryl piperidine **1**. Reagents and conditions: (a) 3-bromoanisole, Mg, I_2, THF, 95%; (b) phenol $AlCl_3$, $(CH_2)_2Cl_2$, 73%; (c) triflic anhydride, Et_3N, DMAP, 75%; (d) $Pd(OAc)_2$, DPPP, CO, MeOH, TEA, DMSO, 70 °C, 84%; (e) R'R"NH_2, $AlMe_3$, toluene, rt to reflux, 72–84%; (f) HBr, AcOH, 120 °C, 88%; (g) H_2, $Pd(OH)_2$–C, AcOH, rt, 83%; (h) various aldehydes, $NaBH(OAc)_3$, $(CH_2)_2Cl_2$, 62–91%.



Scheme 2. Synthesis of diethyl carbinols as amide replacements. Reagents and conditions: (a) EtMgBr, THF, 0–50 °C, 91%; (b) EtSH, NaH, DMF, 130 °C, 68%; (c) H_2, $Pd(OH)_2$–C, EtOH, 84%; (d) various aldehydes, $NaBH(OAc)_3$, $(CH_2)_2Cl_2$, 60–89%.



Scheme 3. Synthesis of primary amides replacing the phenol. Reagents and conditions: (a) triflic anhydride, ET_3N, DMAP, CH_2Cl_2, 79%; (b) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 120 °C, 93%; (c) H_2O_2, H_2O, EtOH, Na_2CO_3, rt; (d) Raney-nickel, DME, 70% overall for steps c and d; (e) H_2, $Pd(OH)_2$–C, EtOH, 84%; (f) various aldehydes, $NaBH(OAc)_3$, $(CH_2)_2Cl_2$ 62–91%.

none. The resulting tertiary alcohol **9** was treated with $AlCl_3$ and phenol in refluxing dichloromethane to furnish phenol **10**. Phenol **10** was converted readily to the ester **11** by treatment with triflic anhydride/pyridine and subsequent elaboration under standard carbonylation conditions with $Pd(OAc)_2$, DPPP, carbon monoxide in methanol and triethylamine in DMSO at 70 °C.[11] Elaboration to the final products of general structure **1** was accomplished via the following sequence: (a) conversion of the ester to the amides under the influence of trimethyl aluminum and various secondary amines, (b) dealkylation of the methyl ether with HBr/AcOH, (c) hydrogenolysis of the benzyl group with palladium hydroxide in acetic acid, and (d) reductive alkylation under standard conditions with various aldehydes.

As intended, the flexibility of the synthetic route allowed us to quickly probe the potential for replacing the amide moiety with other functionalities, such as tertiary carbinols. The approach to these compounds is described in Scheme 2. Ester **11** was converted to the diethyl carbinol **12** via exhaustive addition of ethyl magnesium bromide. The targeted phenols **2** were obtained following a three step sequence which involved methyl ether deprotection employing sodium hydride and ethanethiol in DMF, debenzylation with palladium hydroxide–carbon in ethanol, and reductive alkylation with conditions as reported in Scheme 1 above.

Replacement of the phenol moiety with low molecular weight isosteres such as primary carboxamides proceeded in a straightforward manner as described in Scheme 3. Phenol **13** was readily converted to the corresponding triflate with triflic anhydride and triethylamine/DMAP and the resulting aryl triflate was subsequently transformed to the nitrile with $Zn(CN)_2$ and palladium catalysis.[12] Treatment of the nitrile moiety in compound **14** with aqueous hydrogen peroxide[13] under controlled conditions proceeded to afford a mixture of the desired amine/amide product **15** and the *N*-oxide/amide **16** as the predominant side product. The *N*-oxide side product **16** was formed almost exclusively with prolonged reaction times but could be readily reduced to the desired amine/amide by treatment with Raney-nickel in DME in nearly quantitative yield. Debenzylation of the amine with $Pd(OH)_2$–carbon in ethanol followed by reductive alkylation with various aldehydes yielded the desired compounds of general structure **4**. The preparation of related compounds covered by the general structures **3**, **7**, and **8** was accomplished by similar routes.

Analogs[14] from both structural motifs were tested in radioligand assays measuring binding affinity. Binding assays on membranes from CHO cells expressing human kappa, mu, and delta opioid receptors were performed according to standard procedures.[15] Briefly, frozen cell paste (70–80 mg per 96 well plate) was homogenized in 50 mM Tris–HCl buffer (pH 7.4 at 4 °C) containing 2.0 mM $MgCl_2$ using a Polytron and spun in a centrifuge at 40,000*g* for 10 min. The final pellet was re-suspended in assay buffer (50 mM Tris–HCl buffer (pH 7.4) containing 1 mM EDTA, 5 mM $MgCl_2$). Incubations were initiated by the addition of tissue to 96-well plates containing test drugs and 0.6 nM [^{3}H]diprenorphine in a final volume of 250 μL). Non-specific binding was determined by radioligand binding in the presence of a saturating concentration of naltrexone (10 μM). After a one hour incubation period at room temperature, assay samples were rapidly filtered through Whatman GF/B filters and rinsed with ice-cold 50 mM Tris buffer (pH 7.4). Membrane bound [^{3}H]diprenorphine levels were determined by liquid scintillation counting of the filters in Beta-Scint. The IC_{50} value (concentration at which 50% inhibition of specific binding occurs) was calculated by linear regression of the concentration–response data. K_i values were calculated according to the Cheng–Prusoff equation, $K_i = IC_{50}/(1 + (L/K_d))$, where L is the concentration of the radioligand used in the experiment and the K_d value is the dissociation constant for the radioligand (determined previously by saturation analysis).

The receptor affinity values included in Tables 1 and 2 represent averages of 2–6 screening runs. Results from the in vitro biological studies of the 4,4 biaryl piperidine series are included in Table 1. The results yielded several useful conclusions and also revealed certain consistent limitations regarding the structural class. From the affinity standpoint the design generally succeeded in its objectives. Most compounds exhibited significant affinity for the delta receptor. A variety of nitrogen tethers which included aliphatic chains of variable lengths delivered compounds with high affinity for the delta receptor. In vitro selectivity for the delta receptor was high with a variety of nitrogen substitutions; especially over the mu receptor (e.g., compounds **1a**–**1d**). Amide alkyl group variations were broadly tolerated. Our studies revealed that larger amide alkyl groups offered no advantage with respect to molecular properties, affinity and ligand efficiency. Therefore, we focused our emphasis on low molecular weight amide groups (e.g., **1e**). Replacement of the amides with tertiary carbinols[16] produced compounds that retained high affinity and selectivity. Finally, the impact of phenol substitutions on binding was probed. We observed that primary carboxamides were well tolerated and delivered compounds with high affinity and appreciable selectivity (e.g., **4a** and **4b**). The major limitation of the class appeared to be high clearance measured in vitro by human and rat liver microsomes. In vitro clearance for key compounds measured by human liver microsomes is included in Table 1. A body of data suggested that for the 4,4-biaryl piperidines increased microsomal stability could be achieved by decreasing lipophilicity as measured by *Clog P*.[17]

Regarding the 3,3-biaryl piperidines, affinity for the delta receptor was consistently high for this class as well. A variety of substitutions at the piperidine nitrogen yielded compounds with high delta receptor affinity. Selectivity was modest for some small alkyl chains (e.g., **5a**, **5c,** and **5d**) but was generally high with most other substitutions (e.g., **5b** and **5f**). Reductive alkylations with small

Table 1
Binding affinities for delta, mu and kappa receptors and in vitro (HLM) clearance activity of select 4,4-biaryl-piperidines

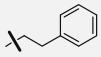
Compound	R^1	R^2	R^3	δ Ki (nM)	μ Ki (nM)	κ Ki (nM)	Clog *P*	Clint (ml/min/kg)
1a		$CONEt_2$	OH	9.0	>890	440	4.1	62.9
1b		$CONEt_2$	OH	1.9	>890	347	3.8	34.6
1c		$CONEt_2$	OH	0.9	66.5	95.0	5.1	239
1d		$CONEt_2$	OH	1.8	>890	>890	5.7	NA
1e		$CONMe_2$	OH	11.0	>890	150	4.7	80
4a		$C(OH)Et_2$	$CONH_2$	2.3	>890	79.0	4.4	26.1
4b		$C(OH)Et_2$	$CONH_2$	2.0	380	45.0	6.1	108

Table 2
Binding affinities for delta, mu and kappa receptors and in vitro clearance (HLM) of select 3,3-biaryl-piperidines

Compound	R^1	R^2	R^3	δ Ki (nM)	μ Ki (nM)	κ Ki (nM)	Clog *P*	Clint (ml/min/kg)
5a		$CONEt_2$	OH	0.8	35.0	24.0	4.1	89
5b		$CONEt_2$	OH	6.2	>890	>890	4.9	113
5c		CON(Me)Et	OH	2.2	52.0	66.0	3.6	70
5d		$CONEt_2$	OH	2.9	>890	24.0	3.98	>300
5e		$CONEt_2$	OH	3.5	>890	163	3.48	>300
5f		$CONEt_2$	OH	1.2	>890	>890	2.97	230
6a		$C(OH)Me_2$	OH	39.0	110	41.0	4.30	22
7a		$CONEt_2$	$CONH_2$	7	>890	>890	2.15	NA

heterocyclic aldehydes yielded compounds with high affinity and excellent selectivity. Trends with amide alkyl substitutions were similar to those observed for the 4,4 class and consequently we focused on small amide replacements (e.g., **5c**). Tertiary carbinols replacing the amide moiety delivered compounds with appreciable affinity for the delta receptor; although the delta receptor affinity for dimethyl carbinols specifically was lower (e.g., **6a**). Replacement of the phenol moiety with a primary carboxamide delivered compounds which retained similar affinity and selectivity profiles with the corresponding phenols (e.g., **7a**). Clearance, as measured in vitro by human liver microsomes (HLM) was generally high. Compounds with small alkyl piperidine nitrogen substitutions and small amide groups exhibited the better clearance profiles. Nitrogen substitutions containing heterocyclic moieties did not improve clearance (e.g., **5e** and **5f**).

Based on a balance of properties, which included delta receptor affinity, selectivity and microsomal stability a number of key compounds were characterized for functional activity at the delta receptor by a GTP-γ S assay. Results from the investigation are depicted in Table 3. Functional activity values included represent the average of minimally two screening runs. IC_{50} values are reported for antagonists. Within the 4,4-biaryl piperidine class good antagonists were identified with long aliphatic and branched alkyl chains (e.g., compounds **1e** and **4b**). Compounds **1a** and **4a** with small aliphatic chains showed significantly reduced functional activity relative to their binding affinity and this is a phenomenon we are studying further. Within the 3,3-biaryl piperidine class good antagonists were identified with small and medium size alkyl chains (e.g., compounds **5a** and **5b**) and with larger substitutions containing heterocyclic moieties (compounds **5e** and **7a**). Replacing the diethyl amide with carbinols or the phenol with carboxamides in 4,4- and 3,3-biaryl piperidines did not impact the functional activity.

Table 3
Delta receptor functional activity for representative biaryl piperidines

Compound	δ IC_{50} (nM)
1a	155
1e	72
4a	282
4b	4.7
5a	7.1
5b	55
5e	16
7a	12

In conclusion, we have demonstrated that biaryl piperidines are potent and selective ligands for the delta opioid receptor. We have been able to identify selective antagonists of the delta opiate receptor which will aid the pharmacological characterization of the receptor. While receptor affinity and selectivity can be rationalized on the basis of the message-address principle, the structural and conformational requirements that deliver delta receptor antagonists are subject to additional investigation. Lead compounds from this investigation are generally characterized by high in vitro clearance. Further progress towards delivering pharmacological tools with desirable pharmacokinetic properties and characterization of these probes in disease relevant models of ethanol intake reduction will be disclosed in subsequent reports.

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14. All compounds were characterized by ^1H NMR and mass spectroscopy and gave satisfactory spectral data. For example, Compound **4a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, *J* = 1.8 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.38–7.22 (m, 6H), 6.09 (br, 1H), 5.83 (br, 1H), 2.61–2.40 (m, 7H), 2.15–2.13 (m, 2H), 1.94 (br, 1H), 1.81–1.73 (m, 5H), 0.82–0.78 (m, 1H), 0.71 (t, *J* = 7.5 Hz, 6H), 0.48–0.40 (m, 2H), 0.04–0.01 (m, 2H); MS (M+1) 421.2.*Compound* **4b**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, *J* = 1.66 Hz, 1H), 7.50 (ddd, *J* = 7.76, 1.41, 1.17 Hz, 1H), 7.39–7.16 (m, 6H), 6.00 (br, 1H), 5.71 (br, 1H), 3.45 (s, 1H), 2.44 (br, 7H), 1.99 (dd, *J* = 19.42,

7.32 Hz, 2H), 1.82–1.52 (m, 7H), 1.38–1.29 (m, 3H), 1.01–0.96 (m, 1H), 0.84 (t, *J* = 7.03, 2H), 0.82 (d, *J* = 6.64, 3H), 0.71 (t, *J* = 7.42 Hz, 6H); MS (M+1) 451.3. For complete experimental conditions describing the preparation of final compounds and intermediates please see: Liras, S. PCT Int. Patent Appl. WO 2000/14066.

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