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(±)-4-[(N-ALLYL-*CIS*-3-METHYL-4-PIPERIDINYL)PHENYLAMINO]-*N,N*-DIETHYLBENZAMIDE DISPLAYS SELECTIVE BINDING FOR THE DELTA OPIOID RECEPTOR

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Abstract: Racemic 4-[(N-allyl-*cis*-3-methyl-4-piperidinyl)phenylamino]-*N,N*-diethylbenzamide (**3a**) was synthesized and found to have good affinity and selectivity for the δ receptor. These compounds can be viewed as an analog of BW373U86 and SNC-80 where an internal piperazine nitrogen has been transposed with a benzylic carbon. Functionally, **3a** behaves as an agonist at the δ receptor with no measurable stimulation of either the μ or κ receptor subtypes and was found to be devoid of any measurable amount of antagonist activity for any opioid receptor. A comparison of **3a** to SNC-80 and DPDPE in the [^{35}S]GTPγS functional assay suggests that **3a** may be more like the peptide DPDPE.

Introduction

In search of analgesics possessing a reduced side-effect profile relative to morphine, much effort has been expended towards finding opioids that operate via δ or κ opioid receptors as opposed to the μ opioid receptor, which meditates the actions of morphine and its congeners.[1] BW373U86 (**1**)[2] and SNC-80 (**2**)[3] represent one class of opioid agonists discovered to be selective for the δ opioid receptor. Due to the lack of a clear opioid message substructure (i.e., a tyramine component similar to the enkephalins), compounds **1** and **2** have been referred to as nonclassical opioid ligands.[4] The piperazine subunit of **1** and **2** is not commonly found in compounds showing activity at the opioid receptors. In contrast, piperidine ring compounds are found in many different classes of opioids.[1] If the internal nitrogen atom in compounds **1** or **2** is transposed with the benzylic carbon, piperidine ring analogs such as **3** are obtained. Even though there are obvious differences between structures **1**, **2**, and **3**, there is sufficient similarity to suggest that **3** might interact with opioid receptors similar to **1** or **2** and thus possess δ selectivity. In this communication, we describe the syntheses of compounds **3a,b** and report that compound **3a** possesses good affinity and selectivity for the opioid δ receptor in radioligand binding assays. Furthermore, racemic **3a** was found to stimulate [^{35}S]GTPγS binding only in the δ receptor functional assay.

Chemistry

Preparation of **3a,b** began with reductive amination of 1,3-dimethyl-4-piperidone with aniline using titanium (IV) isopropoxide[5] which gave **4a,b** as a mixture of *cis* and *trans* diastereomers in 75% yield in a ratio of 70:30. These were separated by column chromatography and carried forward independently. These intermediates were

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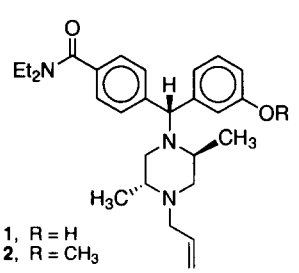
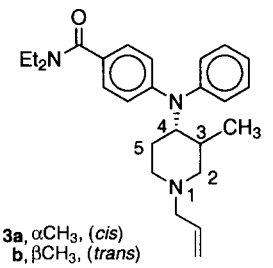
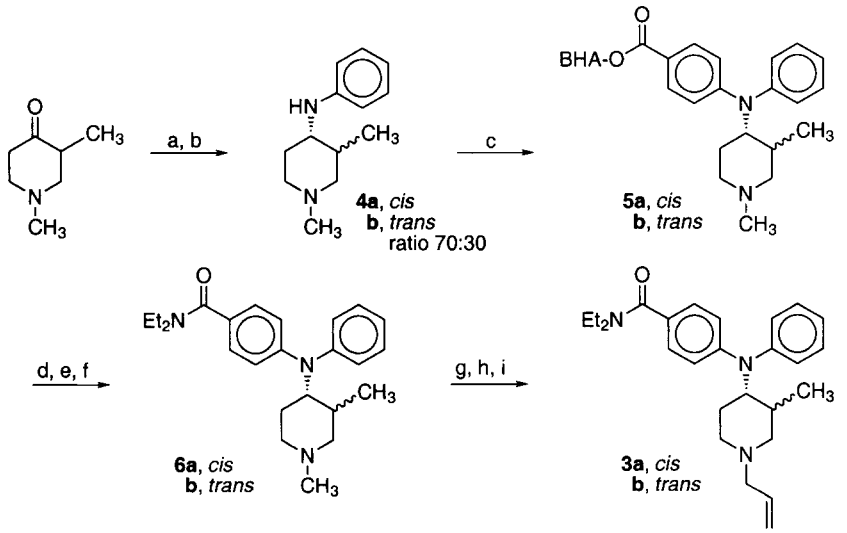


1, R = H
2, R = CH_3



3a, αCH_3, (*cis*)
b, βCH_3, (*trans*)

then coupled to the butylated hydroxyanisole (BHA) ester of 4-fluorobenzoic acid to give (**5a,b**) in 91% and 68% yields.[6] Removal of the BHA group was accomplished by transesterification with refluxing sodium methoxide in toluene/N-methylpyrrolidinone followed by saponification of the methyl ester. The zwitterionic intermediates were isolated as HCl salts and converted directly into diethylamides using benzotriazol-1-yl-oxy-tris-(dimethylamino) phosphonium hexafluorophosphate (BOP a.k.a. Castro's reagent), diethylamine, and triethylamine in a tetrahydrofuran (THF) slurry to give **6a** and **6b** in 90% and 59% yields, respectively. Conversion to the N-allyl group was accomplished by treating **6a,b** with phenyl chloroformate followed by hydrolysis of the resulting carbamates with potassium hydroxide in isopropyl alcohol. N-Alkylation with allyl bromide then gave **3a,b** in 40% and 20% yield, respectively. Compound structures were based on elemental analysis and proton and carbon NMR spectral analyses including COSY and HMQC. The *cis* relative stereochemistry of **3a** was based on a large vicinal coupling constant (J = 13.0 Hz) between H5-axial and H4 which established the equatorial position for the 4-diarylamine group and a correlation in the NOESY spectrum between H5-axial proton and the 3-methyl group which places this group *cis* to the 4-diarylamine group.



Reagents: (a)Ti(O-i-Pr)$_4$, aniline; (b) $NaBH_4$, EtOH; (c) *n*-BuLi, THF, HMPA then 1-(2,6-di-*tert*-butyl-4-methoxyphenyl)-4-fluorobenzoate; (d) N-methylpyrrolidinone, $NaOCH_3$, toluene; (e) EtOH, H_2O; (f) Et_2NH, BOP, Et_3N; (g) PhOCOCl; (h) KOH, i-PrOH, H_2O; (i) allyl-Br, EtOH, K_2CO_3

Results and Discussion

The radioligand binding data at all three opioid receptors[7] for the compounds **3a,b** along with comparative data for BW373U86 (**1**) and SNC-80 (**2**) are shown in Table 1. Compound **3a** (the *cis* isomer) is more potent and more selective for the δ opioid receptor relative to both the μ and κ opioid receptors than **3b** (the *trans* isomer). This difference in selectivity is due to a significantly lower affinity of the *trans* isomer for the δ receptor relative to the μ or κ opioid receptors. The 11.9 nM K_i value for **3a** combined with the 1212 nM K_i value at the μ receptor compare favorably to the K_i values for **1** and **2** particularly when one considers that **3a** is racemic and does not possess all the structural features present in **1** and **2**, namely the 3'-hydroxy and 3'-methoxy groups, respectively, on the aromatic ring and a methyl group comparable to the piperazine 2-methyl group.

Table 1. Radioligand Binding Results at the μ, δ, and κ Opioid Receptors for (±)-4-[(N-Allyl-3-methyl-4-piperidinyl)phenylamino]-*N*,*N*-diethylbenzamide

	K_i (nM±SD)			
Compd	μ [^{3}H]DAMGO[a]	δ [^{3}H]DADLE[b]	κ [^{3}H]U69,593[c]	μ/δ
1, BW373U86	36 ± 3.4	0.91 ± 0.05	NA	40
2, SNC-80	1614 ± 131	1.57 ± 0.19	3535 ± 1841	1030
3a, (±)-*cis*-isomer	1212 ± 132	11.9 ± 0.9	3284 ± 299	102
3b, (±)-*trans*-isomer	1589 ± 86	126 ± 5	8695 ± 978	13

[a] [^{3}H]DAMGO [(D-Ala^2,MePhe^4,Gly-ol^5)enkephalin]. Tritiated ligand selective for μ opioid receptor. [b] [^{3}H]DADLE [(D-Ala^2,D-Leu^5)enkephalin]. Tritiated ligand selective for δ opioid receptor. [c] [^{3}H]U69,593 {[^{3}H](5α,7α,8β)-(-)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide}. Tritiated ligand selective for κ opioid receptor.

In the receptor binding assay, compound **3a** was about 17-fold less potent than SNC-80 at δ receptors (Table 1). Consistent with these binding data, compound **3a** was 10-fold less potent than SNC-80 in the [^{35}S]GTPγS functional assay (Table 2).[8] The lower affinity and efficacy of **3a** relative to **1** and **2** could be due in part to the absence of several structural features present in **1** and **2**. Importantly, **3a** was unable to reverse agonist stimulated [^{35}S]GTPγS binding at any opioid receptor thus indicating a lack of antagonist activity. As indicated in Table 2, compound **3a** acts as an agonist at the δ receptor since its stimulation of [^{35}S]GTPγS binding was eliminated by addition of the δ-selective antagonist naltrindole while the μ- and κ-selective antagonists CTAP and nor-binaltorphimine (nor-BNI) had relatively little affect on stimulation. In this respect, compound **3a** behaves more like the peptide agonist cyclic [penacillamine,^{2} penacillamine^5]enkephalin (DPDPE).

Conclusions

We have demonstrated that (±)-4-[(N-allyl-*cis*-3-methyl-4-piperidinyl)phenylamino]-*N*,*N*-diethylbenzamide (**3a**) is selective for δ receptors in the radioligand binding assay and acts as an agonist at δ receptors, as assessed in the [^{35}S]GTPγS functional assay. Even though **3a** is structurally more similar to BW373U86 and SNC-80 than the δ-selective peptide DPDPE, its efficacy in the [^{35}S]GTPγS assay is more like that of DPDPE. In light of data that SNC-80 and peptidic δ agonists bind to different domains of the δ receptor,[9] it is possible that **3a** may be a peptidic-like nonpeptide compound, as has been reported by Liao et al.[10] Alternatively, **3a** may be a partial

SNC-80 like agonist. These considerations suggest that further structural alterations of **3a**, as well as its optical resolution, may lead to novel types of δ agonist compounds.

Table 2. Functional K_d and E_{max} Values of DAMGO, SNC-80, U69,593, and (±)-4-[(N-Allyl-3-methyl-4-piperidinyl)phenylamino]-*N*,*N*-diethylbenzamide Using GTPγS Binding Assays in Guinea Pig Caudate Membranes

	Unblocked Condition (nM ± Sd)	Blocked with 20 nM NTI[d]	Blocked with 6 nM nor-BNI[e]	Blocked with 6000 nM CTAP[f]
DAMGO[a] K_d	592 ± 105	1850 ± 287	509 ± 111	
E_{max}	123 ± 6	124 ± 6	135 ± 7	No stimulation
SNC-80[b] K_d	317 ± 54		629 ± 71	673 ± 108
E_{max}	142 ± 6	No stimulation	143 ± 4	131 ± 5
U69,593[c] K_d	684 ± 74	1980 ± 269	4894 ± 2172	2142 ± 223
E_{max}	177 ± 5	178 ± 8	58 ± 11	167 ± 6
3a K_d	3500 ± 500		3722 ± 1094	4667 ± 1937
E_{max}	63 ± 5	No stimulation	60 ± 7	55 ± 9
DPDPE K_d	577 ± 150			
E_{max}	51.4 ± 2.8			

[a] DAMGO [(D-Ala^2,MePhe^4,Gly-ol^5)enkephalin]. Agonist selective for μ opioid receptor. [b] SNC-80 ([(+)-4-[(αR)-α-(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide). Agonist selective for δ opioid receptor. [c] U69,593 [(5α,7α,8β)-(-)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide]. Agonist selective for κ opioid receptor. [d] Naltrindole (NTI). Antagonist selective for δ opioid receptor. [e] nor-Binaltorphimine (nor-BNI). Antagonist selective for κ opioid receptor. [f] CTAP. Antagonist selective for μ opioid receptor.

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