Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 3053–3056

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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

James B. Thomas,[a] Xavier M. Herault,[a] Richard B. Rothman,[b] Jason P. Burgess,[a] S. Wayne Mascarella,[a] Heng Xu,[b] Robert B. Horel,[b] Christina M. Dersch,[b] and F. Ivy Carroll[a,*]

[a]*Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, NC 27709, U.S.A.*
[b]*Clinical Psychopharmacology Section, NIDA Addiction Research Section,5500 Nathan Shock Dr., Baltimore, MD 21224, U.S.A.*

Received 16 August 1999; accepted 15 September 1999

**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. 

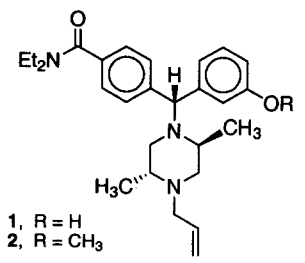
## Introduction

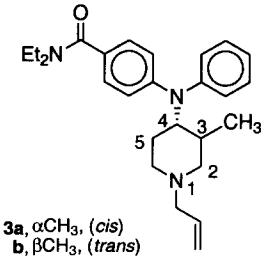
In search of analgesics possessing a reduced side-effect profile relative to morphine, much effort has been expended towards finding opioids that operate via δ or κ opioid receptors as opposed to the μ opioid receptor, which meditates the actions of morphine and its congeners.[1] BW373U86 (**1**)[2] 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

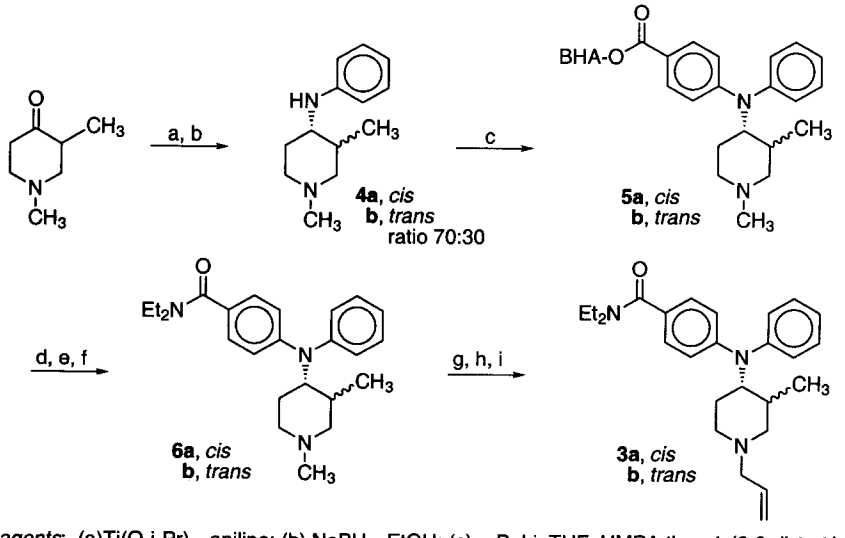
Preparation of **3a,b** began with reductive amination of 1,3-dimethyl-4-piperidone with aniline using titanium (IV) isopropoxide[5] which gave **4a,b** as a mixture of *cis* and *trans* diastereomers in 75% yield in a ratio of 70:30. These were separated by column chromatography and carried forward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

0960-894X/99/$ - see front matter 
*PII:* S0960-894X(99)00525-9




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$_2$O; (f) Et$_2$NH, BOP, Et$_3$N; (g) PhOCOCl; (h) KOH, i-PrOH, H$_2$O; (i) allyl-Br, EtOH, K$_2$CO$_3$

## 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.

**Acknowledgment**: This research was supported by the National Institute on Drug Abuse, Grant DA09045.

## References

1. Aldrich, J. V. In *Burger's Medicinal Chemistry and Drug Discovery*; M. E. Wolff, Ed.; John Wiley & Sons: New York, 1996; Vol. 3.
2. Chang, K. J.; Rigdon, G. C.; Howard, J. L.; McNutt, R. W. *J. Pharm. Exp. Ther.* **1993**, *267*, 852.
3. Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125.
4. Dondio, G.; Ronzoni, S.; Eggleston, D. S.; Artico, M.; Petrillo, P.; Petrone, G.; Visentin, L.; Farina, C.; Vecchietti, V.; Clarke, G. D. *J. Med. Chem.* **1997**, *40*, 3192.
5. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.
6. Hattori, T.; Satoh, T.; Miyano, S. *Synthesis* **1996**, 514.
7. Thomas, J. B.; Zheng, X.; Mascarella, S. W.; Rothman, R. B.; Dersch, C. M.; Partilla, J. S.; Flippen-Anderson, J. L.; George, C. F.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *J. Med. Chem.* **1998**, *41*, 4143.
8. Xu, H.; Lu, Y.-F.; Partilla, J. S.; Brine, G. A.; Carroll, F. I.; Rice, K. C.; Lai, J.; Porreca, F.; Rothman, R. B. *Analgesia* **1997**, *3*, 35.
9. Befort, K.; Tabbara, L.; Kling, D.; Maigret, B.; Kieffer, B. L. *J. Biol. Chem.* **1996**, *271*, 10161.
10. Liao, S.; Alfaro-Lopez, J.; Shenderovich, M. D.; Hosohata, K.; Lin, J.; Li, X.; Stropova, D.; Davis, P.; Jernigan, K. A.; Porreca, F.; Yamamura, H. I.; Hruby, V. J. *J. Med. Chem.* **1998**, *41*, 4767.