Probes for Narcotic Receptor-Mediated Phenomena. 27.[1] Synthesis and Pharmacological Evaluation of Selective δ-Opioid Receptor Agonists from 4-[(α*R*)-α-(2*S*,5*R*)-4-Substituted-2,5-dimethyl-1-piperazinyl-3-methoxybenzyl]-*N*,*N*-diethylbenzamides and Their Enantiomers

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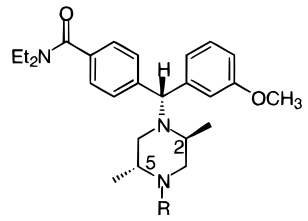
Potent, selective, and efficacious δ-opioid receptor agonists such as (+)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl-3-methoxybenzyl]-*N*,*N*-diethylbenzamide [SNC80, (+)-**2**] have been found to be useful tools for exploring the structural requirements which are necessary for ligands which interact with the δ-receptor. To determine the necessity for the 4-allyl moiety in (+)-**2**, this substituent was replaced with a variety of 4-alkyl, 4-arylalkyl, and 4-alkenyl substituents. The corresponding enantiomers of these compounds were also synthesized. The binding affinities for the μ-, δ-, and κ-opioid receptors and efficacies in the functional GTPγS binding assay were determined for the (+)-**2** related compounds and their enantiomers. The 4-crotyl analogue was found to have similar δ-receptor affinity and efficacy as (+)-**2**, but the 4-cyclopropylmethyl analogue, in the functional assay, appeared to be a partial agonist with little antagonist activity.

Introduction

Selective δ-opioid receptor agonists produce antinociception with fewer side effects than are commonly noted from the activation of μ- and κ-opioid receptors.[2,3] Unlike μ-opioid receptor agonists, δ-receptor agonists have little or no tendency to cause respiratory depression or physical dependence.[4] Thus, highly potent and efficacious compounds which selectively interact with the δ-receptor have broad clinical potential as analgesics, immunoregulatory agents, and treatment agents for drug addiction.[2,3]

Recently, we reported the synthesis and structure−activity relationship studies of a potent and selective systemically active δ-receptor agonist: (+)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl-3-methoxybenzyl]-*N*,*N*-diethylbenzamide [SNC80, (+)-**2**].[5−7] We examined the role of the piperazine nucleus,[5] the importance of several substituents on the aromatic site,[6] and the role of the diethylamide moiety.[7] We now report the effect of chemical modification of the *N*-substituent of (+)-**2**, interchanging the *N*-allyl moiety in (+)-**2** with an *N*-H, *N*-alkyl (methyl, ethyl, butyl, pentyl, hexyl), *N*-alkenyl (2-methylallyl, 3-methylallyl (crotyl)), *N*-benzyl, *N*-phenylethyl, *N*-phenylpropyl, and an *N*-cyclopropylmethyl, and their enantiomers in this 4-[(α*S*)-α-(2*R*,5*S*)-4-substituted-2,5-dimethyl-1-piperazinyl-3-methoxybenzyl]-*N*,*N*-diethylbenzamide series (Table 1).

Table 1. Binding Affinities of **3a** and Its *N*-Alkyl Derivatives in the (α*R*)-α-(2*S*,5*R*)-Series **3a**−**l** for δ-Opioid Receptors



		K_i (nM ± SEM)	[^{35}S]GTPγS binding[b]	
compd	R	δ-binding[a]	% stim	% inhib
(+)-**2**	allyl	1.5 ± 0.2	128 ± 6	0
3a	H	4.7 ± 0.5	63 ± 4	11 ± 2
3b	methyl	4.5 ± 0.2	25 ± 5	18 ± 9
3c	ethyl	5.2 ± 0.3	45 ± 4	13 ± 1
3d	*n*-butyl	2.7 ± 0.1	66 ± 8	19 ± 5
3e	*n*-pentyl	4.7 ± 0.3	26 ± 3	28 ± 6
3f	*n*-hexyl	10.4 ± 0.6	21 ± 8	34 ± 3
3g	2-methylallyl	4.8 ± 0.3	119 ± 9	2.3 ± 1.5
3h	crotyl	1.9 ± 0.2	130 ± 8	6.3 ± 4.7
3i	cyclopropylmethyl	3.5 ± 0.2	48 ± 4	18 ± 4
3j	benzyl	6.2 ± 0.2	144 ± 8	0
3k	2-phenylethyl	30.6 ± 1.4	10 ± 8	30 ± 5
3l	3-phenylpropyl	16.7 ± 0.8	18 ± 6	13 ± 8

[a] Inhibitory effect to [^{3}H]DADLE in rat brain membranes. K_i values at μ ([^{3}H]DAMGO in rat brain) and κ ([^{3}H]U69,593 in guinea pig brain membranes) receptors were not determined since their IC_{50} values were all >1 μM. [b] Percent (%) stimulation of [^{35}S]GTPγS binding and percent (%) inhibition of SNC80 (10 μM)-stimulated [^{35}S]GTPγS binding by **3a** and its *N*-alkyl derivatives (10 μM).

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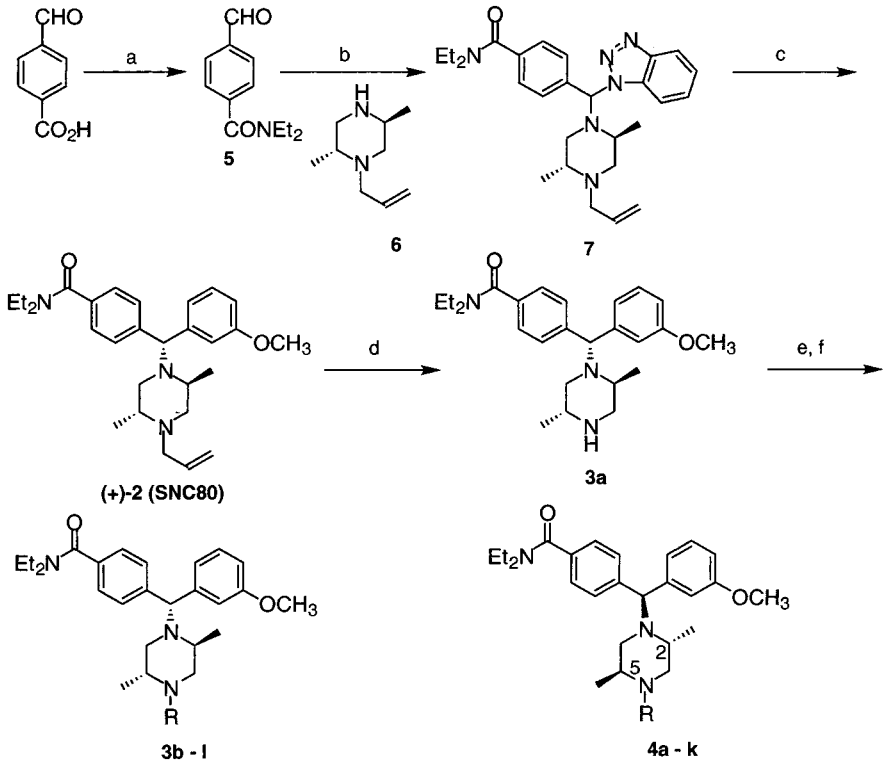
Scheme 1[a]



	R=		R=
3b	Me	**3h**	Crotyl
3c	Et	**3i**	CPM
3d	*n*-Butyl	**3j**	Benzyl
3e	*n*-Pentyl	**3k**	Phenethyl
3f	*n*-Hexyl	**3l**	Phenylpropyl
3g	Methallyl		

	R=		R=
4a	H	**4g**	Methallyl
4b	Me	**4h**	Crotyl
4c	Et	**4I**	CPM
4d	*n*-Butyl	**4j**	Benzyl
4e	*n*-Pentyl	**4k**	Phenethyl
4f	*n*-Hexyl		

[a] The synthetic scheme shown is based on one enantiomer and applies to both enantiomers synthesized in these series. Reagents: (a) Et_2NH, EDCI, CH_2Cl_2; (b) benzotriazole, benzene, reflux; (c) 3-methoxyphenylmagnsium bromide, THF; (d) Pd/C, AcOH, H_2O; (e) R-X, K_2CO_3, DMF; (f) flash chromatography. Procedures a−c, see refs 1, 10, 11; procedure d, see ref 13, 14.

The synthesis and pharmacological properties of the high-affinity and δ-selective *N*-propyl-substituted compound have been previously reported.[8,9]

Chemistry

The synthetic pathways leading to the novel analogues of (+)-**2** are outlined in Scheme 1. A diastereoselective synthesis has been previously described[10,11] that affords 60% of (±)-**1** in a ratio of approximately 93:7 in favor of the desired benzylic epimer. Modifying[1] this stereoselective methodology to the synthesis of (+)-**2** and its (−)-enantiomer enabled us to prepare either desired enantiomer in 70% yield. In this approach, the required enantiomers[5,6] of *trans*-1-allyl-2,5-dimethylpiperazine (**6**) were synthesized by an optical resolution−enantiomer interconversion procedure[12] which afforded the optically pure antipodes of >99% optical purity as determined by HPLC of the ureas formed with 1-naphthyl isocyanate on a Chiralpak AD chiral column. Next, the allyl group of (+)-**2** or its (−)-enantiomer was removed by a simple one-pot procedure involving a palladium-mediated allylic isomerization[13,14] followed by in situ hydrolysis of the resultant enamine. The use of this method yielded enantiomers **3a** and **4a** which were ultimately used as precursors for all of the new analogues. Finally, alkylation of enantiomers **3a** and **4a** was accomplished by reaction with the corresponding halides and potassium carbonate to yield the novel *N*-alkylated (+)-**2** analogues **3b**−**l** and their enantiomers **4b**−**k**.

Results and Discussion

The δ K_i values and the GTPγS functional assay data are listed in Table 1. The (+)- and (−)-enantiomeric compounds were found to be relatively inactive at the μ- and κ-receptors (K_i >1 μM); all of the compounds stereochemically related to (+)-**2** (**3a**−**l**) showed substantial binding to the δ-opioid receptor. The 2-phenylethyl **3k** and 3-phenylpropyl **3l** congeners showed the least affinity for the δ-receptor. The enantiomeric (+)-**2** analogues **4a**−**k** generally showed little affinity for the μ-, κ-, and δ−receptors; only the *N*-H **4a** and *N*-benzyl **4j** analogues showed δ-affinity < 1 μM (58 and 66 nM, respectively). In the functional assays, the *N*-2-methylallyl **3g**, *N*-crotyl **3h**, and *N*-benzyl **3j** derivatives stereochemically related to (+)-**2** showed similar δ-agonist efficacy as (+)-**2** itself. The other compounds examined were less efficacious than (+)-**2** as δ-agonists. The *N*-H **4a** analogue showed little stimulation and inhibition (1.3% and 7%, respectively), and the *N*-benzyl **4j** analogue gave 79% stimulation and 4% inhibition.

None of the examined compounds significantly inhibited δ-agonist-stimulated GTPγS binding and thus show little or no efficacy as δ-opioid receptor antagonists.

We have, thus, synthesized a series of 4-substituted analogues of (+)-**2** and found that they were all δ-selective ligands (since their affinity to both the μ- and κ-opioid receptors was slight (K_i > 1 μM)). Their δ-receptor affinities and efficacies, however, were quite different. The 4-crotyl, 2-methylallyl, and benzyl compounds **3h**,**g**,**j** were the most interesting. The 4-crotyl analogue **3h** had the highest affinity (comparable to the affinity of the previously reported *N*-propyl-substituted analogue)[9] and was as efficacious as (+)-**2** in the GTPγS functional assay. The 4-(2-methylallyl) **3g** and benzyl **3j** analogues had efficacies comparable to that of (+)-**2**, but their affinities for the δ-opioid receptor were slightly lower. The 4-cyclopropylmethyl analogue, as well as the 4-H, and 4-alkyl analogues (methyl, ethyl, butyl to hexyl), on the other hand, had much less efficacy in the GTPγS assay, and the 4-(2-phenyl)ethyl and 4-(3-phenyl)propyl analogues had even less efficacy than the 4-alkyl-substituted compounds. The effect of the *N*-cyclopropylmethyl, *N*-allyl, and *N*-benzyl substituents, among others in the (α*R*)-α-(2*S*,5*R*)-diethylbenzamide series, at the δ-opioid receptor, is distinctly different from their μ-receptor effects in the morphinan system, and the observed structure−activity relationships indicate that the absolute stereochemistry of these analogues is critical for high δ-binding affinity. The experimental data indicating that naltrindole, an *N*-cyclopropylmethyl-substituted noroxymorphindole, is a potent δ-opioid antagonist[15] and that **3i**, the (α*R*)-α-(2*S*,5*R*)-*N*-cyclopropylmethyl derivative of the diethylbenzamide, is an agonist without efficacy in the GTPγS assay (Table 1), as well as the agonist activity of the *N*-benzyl and 2-methylallyl analogues of (+)-**2** (Table 1), give further credence to the LMC recognition pharmacophore.[16] Thus, *N*-substituted morphinans and oxymorphindoles appear to have quite different effects than comparably substituted analogues of (+)-**2**. The LMC δ-recognition pharmacophore[16] noted that the *N*-substituents in diethylbenzamides based on (+)-**2** exist in a different three-dimensional spatial area than those in the morphinans and oxymorphindoles, and thus, comparably *N*-substituted compounds from these series should be pharmacologically dissimilar.

Experimental Section

(+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide [(+)-2]. This material was prepared by Zhang's[1,10] modification of Bishop's application[11] of the Katritzky tertiary amine method used for the synthesis of (+)-BW373U86. A solution of 3-methoxyphenylmagnesium bromide was prepared by dropwise addition of 3-bromoanisole (8.49 g, 45.4 mmol) to a mixture of magnesium turnings (1.10 g, 45.4 mmol) in THF (40 mL), followed by a 1 h reflux. The Grignard solution was cooled and transferred via cannula into a three necked round-bottomed flask equipped with a mechanical stirrer. The imine adduct **7** was prepared by refluxing **5**[1] (4.66 g, 22.7 mmol), (−)-1-allyl-(2*R*,5*S*)-*trans*-dimethylpiperazine (**6**)[5,6,12] (3.5 g, 22.7 mmol) and benzotriazole (2.70 g, 22.7 mmol) overnight in 60 mL of anhydrous benzene with a Dean−Stark trap attached to remove water. The imine solution was cooled and transferred dropwise to the chilled (0 °C) vigorously stirred Grignard solution by means of a cannula. The mixture became very cloudy and viscous. After stirring for 3 h at room temperature, the reaction was quenched with saturated NH_4Cl solution (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were combined, evaporated, redissolved in Et_2O (100 mL), and extracted with 10% HCl (2 × 100 mL). The combined aqueous layers were washed with Et_2O (3 × 75 mL). The aqueous layer was then carefully free based at 0 °C with concentrated NH_4OH to pH 10 and extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated to give a light brown solid. This solid was recrystallized in 4:1 acetonitrile:water to afford 8.1 (79%) of **2** as white crystals: mp 122.7−123.1 °C (lit.[6] mp 122−123 °C); ^{1}H NMR and MS data were identical with those previously published.[6] Anal. ($C_{28}H_{39}N_3O_2$) C, H, N.

(+)-4-[(α*R*)-α-((2*S*,5*R*)-2,5-Dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (3a). A suspension of (+)-**2** (1.15 g, 2.56 mmol), AcOH (0.3 mL, 5.2 mmol) and 10% Pd/C (0.1 g) in H_2O (2 mL) was heated at reflux overnight. The solution was cooled, the catalyst was filtered through Celite, and the aqueous filtrate was free based with concentrated NH_4OH. The mixture was extracted with $CHCl_3$ (3×) and dried with Na_2SO_4. After removal of the solvent, the resultant brown oil was chromatographed with $CHCl_3$:CH_3OH:NH_4OH (80:20:2) to afford 1.0 g (95%) of the pure product as a viscous yellow oil. This was dissolved in a minimum amount of Et_2O, and a 1.0 M solution of HCl in Et_2O was added until the resulting mixture was acidic to moist pH paper. Removal of the solvent, and drying overnight in a vacuum oven afforded **3a**·HCl as a light yellow amorphous powder: mp 75 °C (soften); ^{1}H NMR δ 0.93−0.95 (d, J = 6.4 Hz, 3 H), 1.04−1.34 (m, 9 H), 1.57−1.64 (t, J = 9.0 Hz, 1 H), 2.38−2.47 (m, 2 H), 2.65−2.78 (m, 2 H), 2.83−2.96 (m, 2 H), 3.19−3.68 (pair of br s, 4 H), 3.79 (s, 3 H), 5.33 (s, 1 H), 6.70−6.88 (m, 3 H), 7.25−7.31 (m, 3 H), 7.43−7.49 (d, 2 H); CIMS *m*/*z* 410 (MH^+); $[\alpha]^{20}_D$ = +24.9° (*c* 0.3, MeOH). Anal. ($C_{25}H_{35}N_3O_2$·HCl·2.25 H_2O) C, H, N.

Representative Synthesis: (+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Methyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (3b). A mixture of **3a** (0.61 g, 1.5 mmol), iodomethane (103 μL, 1.65 mmol), and K_2CO_3 (0.25 g, 4.5 mmol) in DMF (2 mL) was heated to 85 °C for 2 h whereby TLC showed completion of reaction. The solution was cooled, water was added, and the aqueous mixture was extracted with ether (3 × 25 mL). The combined organic extracts were dried with Na_2SO_4, and the solvent was evaporated. Chromatography with ethyl acetate afforded 0.47 g (75%) of the pure product as a viscous yellow oil. This was dissolved in a minimum amount of ether, and a 1.0 M solution of HCl in ether was added until the resulting mixture was acidic to moist pH paper. Removal of the solvent and drying overnight in a vacuum oven afforded the salt **3b** as a white amorphous powder: mp 82 °C dec; ^{1}H NMR δ 0.88−1.00 (δ, J = 6.3 Hz, 3 H), 1.01−1.38 (m, 9 H), 1.79−1.86 (t, J = 9.0 Hz, 1 H), 2.15−2.31 (m, 4 H), 2.53−2.79 (m, 4 H), 3.17−3.64 (pair of br s, 4 H), 3.80 (s, 3 H), 5.35 (s, 1 H), 6.68−6.87 (m, 3 H), 7.19−7.39 (m, 3 H), 7.43−7.56 (d, 2 H); CIMS *m*/*z* 424 (MH^+); $[\alpha]^{20}_D$ = +20.2° (*c* 0.5, MeOH). Anal. ($C_{26}H_{37}N_3O_2$·HCl·2.0H_2O) C, H, N.

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Supporting Information Available: Remaining syntheses, biological methods, and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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