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N-Alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)phenylmethyl]-benzamides, μ and δ opioid agonists: a μ address

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Abstract—The tertiary amide δ opioid agonist **2** is a potent antinociceptive agent. Compound **2** was metabolized in vitro and in vivo to secondary amide **3**, a potent and selective μ opioid agonist. The SAR of a series of *N*-alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)phenylmethyl]benzamides was examined.

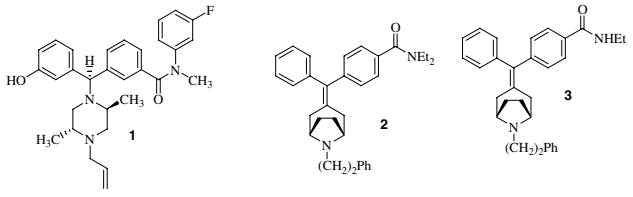
Delta opioid agonists have been seen as potentially safer alternatives to conventional μ agonists as pain relieving agents.[1] More recently, the therapeutic potential of δ opioid agonists as agents to treat acute pain has been questioned.[2] Alternative therapeutic roles for these agents, in neuropathic or inflammatory pain,[3] depression,[4] Parkinson's disease,[5] and lung cancer[6] have been suggested.

The use of δ opioid agonists to potentiate μ opioid-induced analgesia has also been mentioned as a possible therapeutic role for these agents.[1] As early as 1979, it was recognized that leu-enkephalin, a δ selective agonist, could potentiate the antinociceptive effects of morphine.[7] Further studies with DPDPE and morphine led to the postulation of a μ–δ receptor complex.[8] Importantly, the nonpeptide δ agonist, BW373U86, was found to antagonize respiratory depression caused by the μ agonist alfentanil without attenuating antinociception[9] raising the possibility of favorable μ–δ interactions.

In order to make use of the cooperative effects of δ and μ agonists, the mixed δ/μ agonist, DPI3290, **1**, was developed.[10] In an initial clinical trial via the iv route, **1** was reported to produce a 'significant increase in pain tolerance with a possible respiratory sparing effect'.[11]

Evaluation of the behavioral effects of the δ selective agonist **2**[12] revealed unexpectedly robust antinociception. In the mouse 55° hot plate test,[13] a stringent antinociceptive model, **2** had an ED_{50} value of 25 μmol/kg, po suggestive of clinical use against severe pain. Importantly, the mice showed 'straub tail', a behavior often associated with μ opioid activity. The antinociceptive activity of **2** was partially blocked by the δ opioid antagonist, naltrindole. Its antinociception was also attenuated by the μ opioid antagonist, β-FNA, suggesting μ opioid component to the pharmacologic activity.

The in vitro binding profile of compound **2**, however, gave little indication of μ opioid involvement. It bound to the δ opioid receptor with a K_i of 0.2 nM while binding to the μ opioid receptor with a K_i of 72 nM and to the κ opioid receptor with a K_i of 62 nM. It was a full agonist at the δ opioid receptor as demonstrated by its stimulation of [^{35}S]GTPγS binding[12] but only a weak antagonist at the μ opioid receptor as assessed by the same technique.



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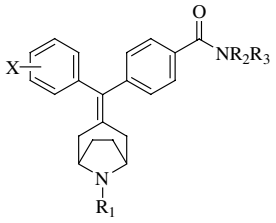
Examination of the metabolism[14] of **2** both in vitro by isolated hepatocytes, and in vivo, after oral administration to rats, revealed that the major metabolite of **2** was the secondary amide, **3**. This metabolite was found to be a potent and selective μ agonist (see Table 1). It bound to the μ opioid receptor with a K_i of 0.26 nM while binding to the δ opioid receptor with a K_i of 46.7 nM. It was a full agonist at the μ opioid receptor as demonstrated by its stimulation of [^{35}S]GTPγS binding (while DAMGO, at 1 μM, stimulated [^{35}S]GTPγS binding by 522%, **3** at 10 μM stimulated [^{35}S]GTPγS binding by 490%).

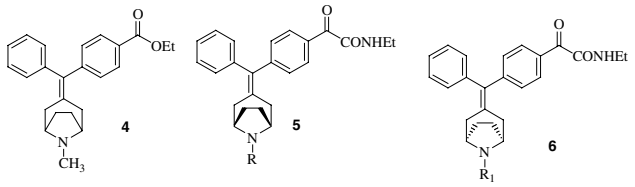
Table 1. Opioid receptor binding



Compd	R_1	R_2,R_3	X	Stereochemistry	δ K_i, nM	μ K_i, nM	μ/δ
2	2-Phenethyl	Et_2	H	1*R*,5*S*	0.24	72	305
3	2-Phenethyl	H,Et	H	1*R*,5*S*	46.7	0.26	0.0056
7	2-Phenethyl	Et_2	H	1*S*,5*R*	42.1	317	7.53
8	2-Phenethyl	H,Et	H	1*S*,5*R*	4.69	7.16	1.53
9	2-Phenethyl	H,*n*-Pr	H	*rac*	22	1.6	0.073
10	2-Phenethyl	H_2	H	*rac*	35.9	39.6	1.1
11	2-Phenethyl	H,*n*-Bu	H	*rac*	49.3	21.7	0.44
12	2-Phenethyl	H,Me	H	*rac*	13	0.14	0.011
13	2-Phenethyl	H,cycloPr	H	*rac*	20	1.01	0.05
14	2-Phenethyl	H,cyclohexyl	H	*rac*	924	717	0.78
15	2-Phenethyl	2-H,methoxy-ethyl	H	*rac*	103	163	1.58
16	2-Phenethyl	H,2-thiazolyl	H	*rac*	49.53	53	1.08
17	2-Phenethyl	H,2-fluoroethyl	H	*rac*	32	2.99	0.093
18	2-Phenethyl	H,*t*-Bu	H	*rac*	352	608	1.73
19	2-Phenethyl	H,phenyl	H	*rac*	1517	4242	2.8
20	3-Phenylpropyl	H,Et	H	*rac*	12.3	4.8	0.39
21	2-Phenoxyethyl	H,Et	H	*rac*	63.4	93	1.46
22	2-(3-Indolyl)-ethyl	H,Et	H	*rac*	23.7	84	3.55
23	5-Methyl-imidazol-4-methyl	H,Et	H	*rac*	15.9	61	3.84
24	2-Hydroxyethyl	H,Et	H	*rac*	26.17	76	2.89
25	Imidazol-4-ylmethyl	H,Et	H	*rac*	3.88	101	25.9
26	2-Pyridylmethyl	H,Et	H	*rac*	0.86	17	19.7
27	1-Methylpyrrol-2-yl	H,Et	H	*rac*	20.77	59	2.83
28	H	H,Et	4-OH	*rac*	4.5	265	58.32
29	3,3-Dimethylallyl	H,Et	3-CH_3O	*rac*	0.72	2.04	2.85
30	Allyl	H,Et	3-CH_3O	*rac*	1.45	13.8	9.54
31	H	H,Et	3-CH_3O	*rac*	13.16	96.0	7.3
32	3,3-Dimethylallyl	H,Et	3-OH	*rac*	2.02	2.52	1.25
33	Allyl	H,Et	3-OH	*rac*	0.384	9.58	24.94
34	2-Phenethyl	H,Et	4-CH_3O	*rac*	11.29	6.1	0.54
35	2-Thienylmethyl	H,Et	4-CH_3O	*rac*	1.32	13.48	10.23
36	2-Chlorobenzyl	H,Et	4-CH_3O	*rac*	5.67	122	21.63
37	2-Phenethyl	H,Et	4-OH	*rac*	7.8	21.7	2.79
38	2-Thienylmethyl	H,Et	4-OH	*rac*	0.25	6.77	27.05
39	2-Chlorobenzyl	H,Et	4-OH	*rac*	0.93	8.72	9.37
40	2-Phenethyl	H,Et	3-CH_3O	*rac*	19.79	0.654	0.033
41	2-Thienylmethyl	H,Et	3-CH_3O	*rac*	0.51	3.79	7.2
42	2-Chlorobenzyl	H,Et	3-CH_3O	*rac*	6.66	57.74	8.67
43	2-Phenethyl	H,Et	3-OH	*rac*	4.14	0.222	0.05
44	2-Thienylmethyl	H,Et	3-OH	*rac*	0.152	0.664	4.37
45	2-Chlorobenzyl	H,Et	3-OH	*rac*	2.09	14.98	7.17
46	CH_3	H,Et	H	1*S*,5*R*	6.39	42.46	6.65
47	H	H,Et	H	1*S*,5*R*	5.48	74.73	13.63
48	Allyl	H,Et	H	1*S*,5*R*	2.24	10.52	4.69
49	CH_3	H,Et	H	1*R*,5*S*	292	304	1.04
50	Allyl	H,Et	H	1*R*,5*S*	7.72	19.09	2.47

An in vivo study of **3** revealed powerful antinociceptive activity. It showed an ED_{50} of 25 μmol/kg, po in the mouse 55° hot plate test. An SAR study was carried out to define the features, which lead to μ opioid activity in this structural class, which had previously been associated with only δ opioid activity.

The synthesis of analogues of **3** in racemic form was carried out using methodology described previously.[12,15] The homochiral compounds, **5** (1*R*,5*S*) and **6** (1*S*,5*R*), were prepared by two routes. Most arose from ester **4**, which was separated into enantiomers by chiral HPLC. The chiral esters were hydrolyzed and converted to amides. The exceptions were **3** and **5**, which were obtained by hydrolysis of **2** and **4** followed by conversion of the respective acids to *N*-ethylamides. The absolute configurations of **45**–**49** were inferred by conversion of **46** to **8**.



The opioid binding affinities of analogues of **3** are shown in Table 1. Interestingly, compound **3** itself was found to embody the optimal structural features within this new structural subclass of μ agonists. A secondary amide is necessary for significant μ agonist activity. The group attached to the nitrogen of the secondary amide could not deviate far in size from ethyl in order to retain good μ activity. Methyl, *n*-propyl, cyclopropyl, and 2-fluoroethyl retained activity but 2-methoxyethyl, *N*-cyclohexyl, and *N*-phenyl were inactive. The group on the tropanylidene nitrogen could not deviate far in size from phenethyl without loss of μ selectivity. Compound **20** with a phenylpropyl group on tropanylidene nitrogen maintained slight μ selectivity but all other substitutions led to loss of μ selectivity, loss of potency or both. Methoxy and hydroxyl groups at the 3- and 4-positions of the phenyl, which do not bear the carboxamido function, were well tolerated.

Interestingly, the compounds with a phenethyl group on nitrogen had a different stereochemical preference than compounds bearing a smaller group. Compound **3** with an *N*-phenethyl and 1*R*,5*S* configuration had a 179-fold preference for the μ receptor over δ, whereas its enantiomer **8** with a 1*S*,5*R* configuration had a 1.53-fold preference for the δ receptor over μ and was less potent than **3**. In contrast, the *N*-methyl, 1*S*,5*R* compound, **46**, was δ selective (δ K_i 6.39) while its 1*R*,5*S* enantiomer, **49**, bound only weakly to both μ and δ receptors. The *N*-allyl, 1*S*,5*R* compound, **48**, was nearly twice as potent as its 1*R*,5*S* enantiomer, **50** at μ.

In 1988, Portoghese et al. described the first nonpeptide δ opioid ligand, the antagonist naltrindole.[16] He introduced the concept that the portion of naltrindole resembling morphine constituted an opioid 'message,' whereas the pendent indole moiety constituted an 'address,' making the drug selective for the δ opioid receptor versus the highly homologous μ and κ receptors. The message–address concept was broadened with the suggestion that the *N*,*N*-diethylbenzamide function of SNC80 represented a δ address.[17] Studies with chimeric δ opioid receptors[18] have implicated the third extracellular loop as a site likely to embrace the *N*,*N*-diethylamide function of SNC80 analogues. In particular, change of the Trp^{284} residue at the top of transmembrane six to leucine yielded a receptor with a 42-fold weaker affinity for SNC80. The corresponding amino acid in the μ opioid receptor is lysine.

If the *N*,*N*-diethylbenzamide function of SNC80 is termed a δ address, then the *N*-ethylbenzamide function of **3** might be termed a μ address. The presence of the secondary amide in **3** suggests that a hydrogen bond interaction is part of the μ address. The rather narrow SAR requirements for μ selectivity imply that the ligand must be precisely oriented in order to find its μ address in the receptor. The phenethyl group must anchor the compound in the receptor site. The difference in stereochemical preference between **3** and **46**–**50** implies that the tropane bridge plays a role in orienting the molecule.

In summary, it was discovered that the potent δ opioid agonist, **2**, is metabolically converted from an *N*,*N*-diethylamide to a monoethyl secondary amide **3** and that **3** and closely related substances are potent μ agonists.

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