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Piperazinyl Benzamidines: Synthesis and Affinity for the Delta Opioid Receptor

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Abstract—Piperazinyl benzamidines were prepared and found to bind to the rat delta (δ) opioid receptor. The most active compounds had a *N,N*-diethylcarboxamido group and a *N*-benzyl piperazine. The most potent among these was *N,N*-diethyl-4-[4-(phenylmethyl)-1-piperazinyl][2-(trifluoromethyl)phenyl]iminomethyl]benzamide (**27**) with a 1.22 nM K_i for the rat δ opioid receptor and ca. 1000× selectivity relative to the μ opioid subtype.

There has been intensive research in the past 20 years leading to the identification of three opioid receptor subtypes, referred to as mu (μ), delta (δ), and kappa (κ). Compounds that are δ opioid receptor agonists are analgesic agents in animal models, and selective non-peptide δ opioid agonists have been reported in the literature.[1–6] Selective δ agonists are less likely to have the liabilities associated with marketed opiate analgesics, which bind at the μ opioid site, such as constipation and respiratory depression. Most small-molecule δ-opioid agonists are piperidines or piperazines, such as SNC 80 (**1**) and the racemic hydroxy analogue BW373U86 (**2**).[7,8] 4-Aminopiperidines of structure **3** have also been shown to have activity at the δ opioid receptor site (Fig. 1).[9–11]

One of the limitations associated with piperazines **1** and **2** is their complicated stereochemistry. In order to obtain achiral δ opioid agonists, we synthesized amidino piperazines **4** (Table 1). Additionally, data from high-throughput screening of our corporate compound collection at the human δ opioid receptor suggested that amidine functionality incorporated as in **4** would be tolerated with retention of biological activity.

The synthetic route to compounds of type **4** is shown in Scheme 1.[12] Substituted piperazines **5** reacted with terephthalic acid monomethyl ester chloride **6** under Schotten–Baumann conditions to give benzamides **7**. These intermediates were then condensed with anilines utilizing phosphorus oxychloride to provide amidines **8**. The esters of **8** were then converted to dialkylamides **9** via the acid chloride.

Delta opioid receptor affinity was calculated from the inhibition of ^{3}H-DPDPE binding to δ opioid receptors from rat brain membranes. In a similar manner, μ

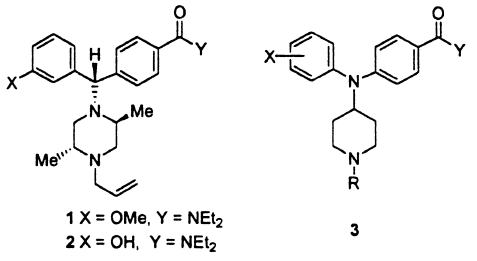
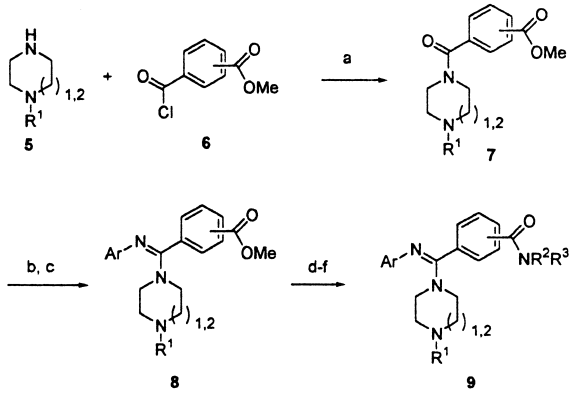


Figure 1. Nonpeptide opioid agonists.



Scheme 1. (a) 1 N NaOH, CH_2Cl_2; (b) $POCl_3$, H_2O; (c) $ArNH_2$; (d) 3 N NaOH, 80 °C; (e) 3 N HCl, $SOCl_2$; (f) R^2R^3NH.

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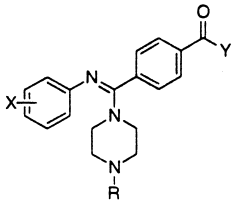
opioid receptor affinity was determined by competition experiments using ^{3}H-DAMGO in the same rat brain membrane preparations.[13] The binding affinities of morphine and SNC 80 are also included in Table 1.

The piperazinyl benzamidines bind to the δ opioid receptor, with lesser affinity for the μ opioid subtype. Variations on the core structure investigated included *N*-substitution on the piperazine, replacement of the carboxamide with an ester, and substitution on the *N*-phenyl ring (X). Prototype structure **10**, where R = Et and bearing a 4-(diethyl)carboxamido group revealed a 16 nM K_i for the δ opioid receptor, prompted us to continue to investigate this series. Further, the ratio of δ to μ opioid receptor affinity for **10** was 62.5, which we reasoned could be improved by subsequent structural changes. Two- and three-substitution on the *N*-phenyl ring were examined to the greatest extent. 2-Chloro compound **11** showed a relative decrease in activity at δ (91.1 nM K_i), but the δ/μ selectivity increased. Dipropyl amide **12** was less active than **11**. Surprisingly, methyl ester **13** showed comparable activity to **12**. When X involved 3-substitution, some of the compounds had a higher affinity for the δ opioid receptor than for 2- or 4-substituted derivatives. For example, compound **14** (δ, 63 nM K_i) was more active than **11** (δ, 91.0 nM K_i). Additionally, **17** (δ, 58.5 nM K_i) was more active than **16** (δ, 118 nM K_i). However, the reverse was observed with compounds **23** (δ, 20.5 nM K_i) and **24** (δ, 157.4 nM K_i). 3,5-Dichlorophenyl **15**, fluoro compounds **16** and **17**, and 3-bromophenyl **18** were active, but incorporation of the electron-releasing methoxy group into the 2-position as in **19** decreased δ affinity (1023 nM K_i), being less active than directly-comparable 2-chloro analogue **12** (292 nM K_i).

When the *N*-ethyl group of **10**–**19** was replaced with propyl (**20** and **21**) or allyl (**22**–**24**), less affinity for the δ opioid receptor was observed, except for allyl derivative **23** (δ, 20.5 nM K_i). The most active members of this series were those with *N*-benzyl substitution (**25**–**28**). For example, the most potent compounds were where X was 2-trifluoromethyl (**27**, 1.22 nM K_i) and 2-chloro (**26**, 11.8 nM K_i). 4-Chloro compound **28** was less active, as was unsubstituted **25**. Amidine **27** had a higher affinity for the δ-opioid receptor than SNC 80, and has the advantages of being achiral and easier to prepare. Importantly, **26** and **27** have ca. 1000× selective affinity for the δ relative to the μ opioid receptor. Compounds **26** and **27** were full δ opioid agonists as determined in a GTP-γ-S functional test. Extending *N*-substitution on the piperazine with phenethyl (**29**) or thienylethyl (**30** and **31**) groups lessened activity. For example, thienylethyl **31** (δ, 95.3 nM K_i) had less δ opioid receptor affinity than *N*-benzyl derivative **26** (δ, 11.8 nM K_i). *N*-(2-Methoxyethyl) substitution was tolerated, with **32** and

Table 1. Binding affinity of piperazinyl benzamidines to δ and μ opioid receptors



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#	R	X	Y	δ K_i (nM)	μK_i (nM)	δ/μ ratio
10	Et	H	NEt_2	16	1000	62.5
11	Et	2-Cl	NEt_2	91.1	>1000	>111
12	Et	2-Cl	NPr_2	292	3930	13
13	Et	2-Cl	OMe	222	>1000	>45
14	Et	3-Cl	NEt_2	63	>1000	>159
15	Et	3,5-Cl_2	NEt_2	277	>1000	>36
16	Et	2-F	NEt_2	118	>1000	>85
17	Et	3-F	NEt_2	58.5	>10,000	>171
18	Et	3-Br	NEt_2	57.6	>10,000	>174
19	Et	2-MeO	NPr_2	1023	3910	3.8
20	Pr	2-Cl	OMe	87.3	2070	24
21	Pr	3-Cl	NEt_2	177	9530	54
22	Allyl	H	NEt_2	859	1000	1.2
23	Allyl	2-Cl	NEt_2	20.5	7600	370
24	Allyl	3-Cl	NEt_2	157	>10,000	>64
25	$PhCH_2$	H	NEt_2	212	>10,000	64
26	$PhCH_2$	2-Cl	NEt_2	11.8	>10,000	>847
27	$PhCH_2$	2-CF_3	NEt_2	1.22	1200	984
28	$PhCH_2$	4-Cl	NEt_2	142	>10,000	70
29	$Ph(CH_2)_2$	2-CF_3	NEt_2	545	1000	1.8
30	2-Thienyl-$(CH_2)_2$	H	NEt_2	764	>10,000	>13
31	2-Thienyl-$(CH_2)_2$	2-Cl	NEt_2	95.3	>10,000	>105
32	MeO-$(CH_2)_2$	2-CF_3	NEt_2	22.9	2960	117
33	MeO-$(CH_2)_2$	2-Cl	NEt_2	53.5	>10,000	>437
Morphine		—	—	90	1.8	0.02
SNC 80 (**1**)		—	—	1.7	1300	765

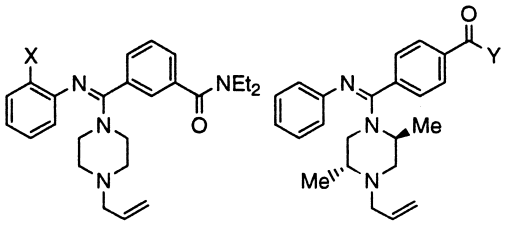
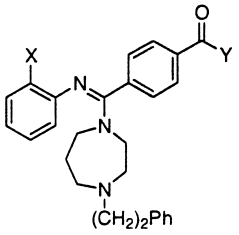


Figure 2. Additional piperazinyl benzamidines.

Table 2. Binding affinity of homopiperazine benzamidines to δ and μ opioid receptors



#	X	Y	δ K_i (nM)	μ K_i (nM)	δ/μ ratio
36	H	NEt_2	543	396	0.73
37	Cl	NEt_2	29.6	618	21
38	H	OMe	820	232	0.28
39	Cl	OMe	101	197	2.0

33 being somewhat less active than their *N*-benzyl comparators **26** and **27**, respectively. Moving the carboxamido substituent to the *meta* position resulted in a significant loss of activity. Compounds **34** and **35** were much less active than their *para*-substituted counterparts (δ, 7030 and 487 nM K_i's for **34** and **35**, respectively, vs 859 and 20.5 for **22** and **23**) (Fig. 2).

Homopiperazine analogues were prepared by variation of the chemistry shown in Scheme 1 and **36**–**39** are listed in Table 2. 2-Chloro derivative **37** (δ, 29.6 nM K_i) was quite active, with a 21× selectivity relative to the μ subtype. The activity with the homopiperazines led us to further vary this central ring and prepare dimethyl piperazine analogues **40** and **41**, which are direct analogues of SNC 80. These compounds showed only modest activity (δ, 170 and 405 nM K_i's, respectively), suggesting that the most active piperazinyl benzamides (e.g., **27**) may bind to the δ opioid receptor in a different or additional orientation as does SNC 80.

We have synthesized a new class of piperazinyl benzamides **4** that bind to the δ opioid receptor. Both *N*,*N*-diethylcarboxamides, *N*,*N*-dipropylcarboxamides, and methyl esters have at least some affinity for the δ opioid receptor. The best compounds (**26** and **27**) had electron-withdrawing groups on the 2-position of the *N*-phenyl ring and *N*-benzyl substitution (δ 11.8 and 1.22 nM K_i's, respectively). These two compounds also displayed very little μ opioid binding, and are among those selected for extensive in vivo evaluation. Structural modifications involving the piperazinyl benzamidines have provided potent and selective ligands for the δ opioid receptor, and further structural changes in the future may result in additional derivatives that provide further insight in this area.

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