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Arylacetamides as Peripherally Restricted Kappa Opioid Receptor Agonists

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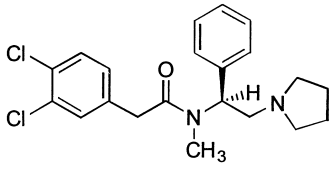
Abstract—Analogues of the kappa (κ) opioid receptor agonist, ICI 199441, were prepared. K_i values for these analogues at the cloned human κ opioid receptor ranged from 0.058 to 25 nM. Trifluoromethylaryl derivatives were potent analgesics when administered subcutaneously in the rat and were more peripherally restricted than the parent compound, ICI 199441.

Introduction

During the past several years a number of groups have synthesized kappa (κ) opioid agonists and demonstrated that these compounds were antinociceptive agents that lacked the adverse side effects of constipation, respiratory depression, and drug abuse and dependence liabilities associated with mu (μ) opioid agonists such as morphine.[1a–c] Most of these compounds were developed as centrally active analgesics. However, preclinical and clinical studies with centrally active κ agonists have revealed that these agents have their own profile of side effects, including sedation, diuresis, and dysphoria.[2,3] More recently the presence of opioid receptors in the peripheral nervous system has been described, and it has been postulated that activation of these receptors may produce antinociception without inducing centrally-mediated side effects. Our strategy is to synthesize peripherally restricted κ receptor agonists as antinociceptive agents that are improvements over the peripheral κ agonists that have been reported in the literature.[1c] To achieve this goal, we have chosen the centrally active κ agonist ICI 199441 (**1**),[4] an analogue of U-50488,[5] as a template and initially we have focused on modifications of the arylacetamide moiety to give compounds of general structure **2**.



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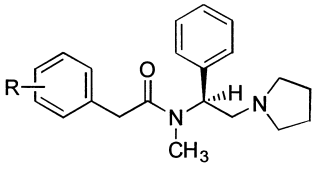

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Chemistry

The syntheses of these compounds required the diamine (**3**), which was prepared following the literature procedure[6] from (*S*)-(+)-phenyl glycine. Condensation of the diamine with various aryl acetic acids was accomplished in the presence of *N*-hydroxybenzotriazole hydrate (HOBT), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), and *N,N′*-diisopropylethylamine to give compounds of general structure **2** (Scheme 1).[7]

The nitro analogues (**2a**–**d**) were prepared following the above procedure, and reduction with either Raney

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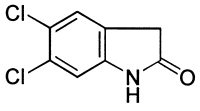
nickel/hydrazine hydrate[8] or PtO_2 gave the reported anilines[9] (**2e–h**). Mesylation of these anilines with methanesulfonyl chloride/triethylamine resulted in the bis-sulfonamide derivatives, **2i–l** (Scheme 2).

A number of derivatives of the intermediate 3,4-dichloroaniline (**2e**) were planned to develop the structure–activity relationship for peripheral κ agonists. However, this aniline turned out to be sensitive to the bases used. During base catalyzed reactions of **2e** such as acylations, sulfonation, and alkylations, the desired compounds were isolated as minor components while the predominant product from each of these reactions was 5,6-dichloro-2-oxo-indole (**4**).



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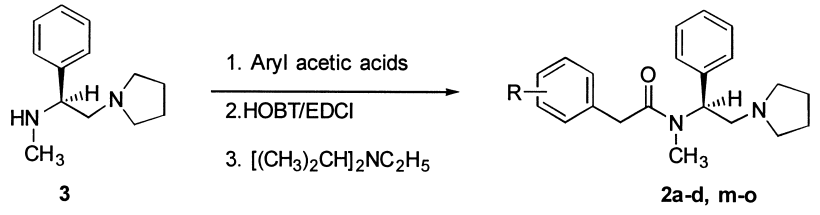
It was presumed that due to the presence of dichloro on the aniline, the intermediate nitrogen anion might favor the internal cyclization by expelling the diamine portion of **2e** to give **4** instead of reacting with electrophiles.

To circumvent this problem, a surrogate for the 3,4-dichlorophenyl acetic acid was sought. In a closely related series of κ agonists, the ICI group has reported[10] that the replacement of both chlorines of the phenyl acetyl of ICI 197067 with trifluoromethyl resulted in compounds with enhanced binding affinity at the κ opioid receptor, despite increased electron withdrawing effects and lipophilicity of the trifluoromethyl group. Encouraged by these findings, the analogues **2m–o** were prepared from the diamine (**3**) and from trifluoromethyl phenyl acetic acids (Scheme 1).

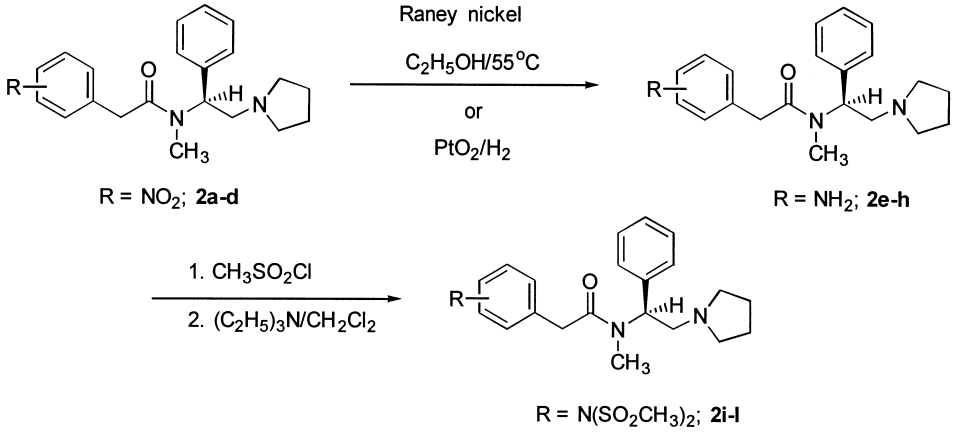
Biological Results

In Vitro:[11] Kappa (κ) opioid receptor affinity was determined by the displacement of bound [^{3}H]U69,593 and mu (μ) and delta (δ) opioid receptor affinities were obtained by displacement of bound [^{3}H]diprenorphine (Table 1) using membranes prepared from cells expressing the cloned human opioid receptors. The selectivity for the opioid receptors was defined by the ratio of the K_i values. The intermediate nitro and amino compounds (**2a–h**) exhibited high affinities for κ receptors with K_i values in the subnanomolar to low nanomolar range. However, the receptor selectivity was compromised depending upon the positional attachment of the substituents. For example, compound **2c** with 4-NO_2 on the phenyl ring was less selective for the κ receptor than compounds **2a** (2-NO_2) and **2b** (3-NO_2). The amino compounds had similar activities in κ receptor binding relative to their precursors. However, compound **2e** was also the least selective among the opioid receptors.

The peripheralization of these amines as bis-sulfonamide derivatives resulted in compounds **2i–l** that were 2- to 463-fold less potent at the κ receptor than ICI 199441. Among the bis-sulfonamides, **2j** was the most potent at the κ receptor ($K_i = 0.096$ nM); however, its receptor selectivity relative to the δ opioid receptor was less than 50-fold (Table 1).



Scheme 1.



Scheme 2.

The search for a surrogate of 3,4-dichloro substituents on the phenyl acetyl group resulted in the preparation of the trifluoromethyl compounds **2m–o**. These compounds not only maintained potent κ receptor affinity but also retained the selectivity profile relative to the other opioid receptors (Table 1). The 4-trifluoromethyl derivative (**2o**) was the most potent with a K_i value of 0.06 nM for the κ receptor, which is comparable to that of ICI 199441 (**1**).

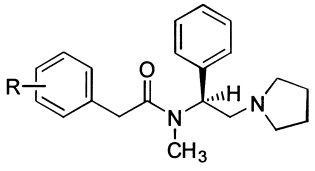
In Vivo:[11] Compounds were evaluated in vivo for their ability to inhibit formalin-induced flinching in rats. Selected compounds that were efficacious when administered intrapaw (antagonism of flinching $\geqslant$80% at 300 μg) were titrated to determine A_{50} values. Otherwise data are reported as % inhibition values at the indicated dose (Table 2). Compounds were also evaluated in the same assay by the sc route at an initial dose of 10 or 30 mg/kg and % inhibition or A_{50} values were determined (Table 2). The 3- and 4-anilines (**2g** and **2h**) were less active than the corresponding 2-amino derivatives (**2e** and **2f**). In contrast, the bis-sulfonamide derivatives (**2i–l**) of these amino compounds were equally active in this assay. Similarly, the trifluoromethyl compounds (**2m–o**) showed equal efficacy in the formalin assay when given intrapaw.

However, the difference in analgesic activity of these compounds became evident when compounds were given by the sc route in the same assay. Bis-sulfonamides (**2i**, **2k**, and **2l**) were inactive despite being effective analgesics when administered locally to the paw. These compounds lack systemic bioavailability, but are active when applied directly at the site of injury, and therefore may be useful as topical analgesic agents.

In the trifluoromethyl series of compounds (**2m–o**), the 4-trifluoromethyl compound (**2o**) was more potent when given by the sc route than the 2- and 3-substituted trifluoromethyl derivatives (**2m** and **2n**, 60-fold and 21-fold respectively). The compound **2o** was also nearly 6-fold more active in this assay than ICI 199441 (**1**), thus indicating that both electron withdrawing properties and lipophilicity of the substituents play a significant role in enhancing the analgesic activity.

The compounds (**2d**, **2f**, **2m**, **2n**, and **2o**) that showed significant activity in the formalin assay following sc administration were evaluated for sedation, a centrally mediated side effect. For this purpose, the rotarod performance assay was chosen. A peripheral restriction index, as an indicator of the CNS liability of compounds, was calculated by the ratio of the rotarod ED_{50} compared to the A_{50} to inhibit formalin-induced flinching by the sc route (Table 2). The intermediates **2d** and **2f** had a peripheral restriction index of 4 and 6, respectively, and the centrally active ICI 199441 (**1**) had a ratio of 3, indicating improvement in peripheral restriction for compound **2f**. Among the trifluoromethyl derivatives, the 3- and 4-substituted compounds (**2n** and **2o**) had peripheral restriction indices of 9 and 13, respectively, 3- to 4-fold higher than ICI 199441. However, the 2-trifluoromethyl analogue (**2m**) produced sedation in

Table 1. In vitro binding affinities to cloned human opioid receptors



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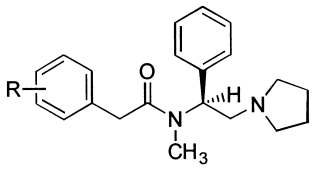
2	R	Yield (%)	Kappa binding K_i (nM)[a] [^{3}H]U69,593	Selectivity for κ μ K_i/κ K_i	Selectivity for κ δ K_i/κ K_i
a	2-NO_2[b]	87	0.41 (0.18–0.93)	>1000	>1000
b	3-NO_2[b]	95	0.065 (0.046–0.093)	>1000	>1000
c	4-NO_2[b]	93	1.1 (0.37–3.0)	52	410
d	2-NO_2, 3,4-dichloro[b]	60	0.091 (0.058–0.14)	430	580
e	2-NH_2, 3,4-dichloro[b]	55	0.086 (0.029–0.26)	260	140
f	2-NH_2[b]	70	0.58 (0.20–1.7)	>1000	>1000
g	3-NH_2[b]	47	0.93 (0.38–2.30)	>1000	>1000
h	4-NH_2[b]	73	0.93 (0.43–2.0)	>1000	>1000
i	2-N(SO_2CH_3)$_2$	94	8.6 (7.0–11.0)	>1000	>1000
j	2-N(SO_2CH_3)$_2$, 3,4-dichloro	49	0.096 (0.085–0.11)	320	33
k	3-N(SO_2CH_3)$_2$	42	6.0 (3.0–12.0)	>1000	>1000
l	4-N(SO_2CH_3)$_2$	68	25.0 (22.0–30.0)	>1000	>1000
m	2-CF_3	82	0.13 (0.93–0.18)	>1000	>1000
n	3-CF_3	67	0.064 (0.03–0.14)	>880	>1000
o	4-CF_3	93	0.058 (0.046–0.073)	>800	>1000
	3,4-Dichloro (ICI 199441) (**1**)		0.054 (0.039–0.076)	>1000	600

[a]Values are the means of three to six experiments and 95% confidence intervals are given in parentheses.
[b]Known compounds (ref 9).

Table 2. In vivo profile of peripherally restricted κ agonists



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2	R	Formalin flinching A_{50}, μg (i.paw)[a]	Formalin flinching A_{50}, mg/kg (sc)[a]	Rotarod ED_{50}, mg/kg (sc)[a]	Peripheral restriction index
a	2-NO_2	29 (12–69)			
b	3-NO_2	95% @ 300[b]			
c	4-NO_2	Not tested			
d	2-NO_2, 3,4-dichloro	5.3 (2.2–11)	0.24 (0.18–0.49)	0.97 (0.37–2.3)	4
e	2-NH_2, 3,4-dichloro	7 (3.5–11)	Not tested		
f	2-NH_2	65 (27–192)	1.5 (0.85–2.2)	8.9 (3.2–20)	6
g	3-NH_2	58% @ 300[b]			
h	4-NH_2	52% @ 300[b]			
i	2-N(SO_2CH_3)$_2$	17 (4.8–62)	21% @ 30[b]		
j	2-N(SO_2CH_3)$_2$, 3,4-dichloro	28 (9.7–65)	Not tested		
k	3-N(SO_2CH_3)$_2$	91% @ 300[b]	15% @ 10[b]		
l	4-N(SO_2CH_3)$_2$	95% @ 1000[b]	30% @ 30[b]		
m	2-CF_3	98% @ 300[b]	0.54 (0.21–1.23)	71% @ 3[c]	
n	3-CF_3	97% @ 300[b]	0.02 (0.006–0.04)	0.18 (0.06–0.46)	9
o	4-CF_3	0.82 (0.32–1.7)	0.009 (0.002–0.02)	0.12 (0.04–0.34)	13
	3,4-Dichloro (ICI 199441) (**1**)	0.74 (0.24–1.69)	0.05 (0.02–0.09)	0.14 (0.06–0.34)	3

[a]Numbers in parentheses are the 95% confidence intervals.
[b]Data are the % antagonism of flinching at the doses indicated.
[c]Data are the % decrease from baseline at the doses indicated.

the rotarod consistent with central activity, demonstrating sedation with compounds having electron withdrawing and lipophilic groups at this position.

Thus, replacement of the 3,4-dichlorophenyl portion of ICI 199441 with 3- or 4-trifluoromethylphenyl acetyl resulted in compounds with reduced CNS liabilities. Work is in progress to develop the SAR of the peripherally restricted κ opioid receptor agonists using compounds **2n** and **2o** as templates.

Conclusions

A series of novel arylacetamides was prepared as peripherally restricted κ opioid receptor agonists based on the centrally active agonist, ICI 199441, with κ receptor binding affinities from 0.05 to 25 nM. Bis-sulfonamides (**2i**, **2k**, and **2l**) were antinociceptive in the formalin-induced flinching assay in rats when administered locally (intrapaw) but not systemically (sc). These compounds may have potential utility as topical or local antihyperalgesics. Replacement of 3,4-dichlorophenyl with 3- or 4-trifluoromethylphenyl resulted in compounds **2n** and **2o**, with enhanced analgesic activity in rats and improved peripheral restriction indices three and four times higher than ICI 199441. The development of the SAR around compounds **2n** and **2o** is in progress to further improve the peripheral restriction of the series.

References and Notes

1. (a) Barber, A.; Gottschlich, R. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1351. (b) Szmuszkovicz, J. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser Verlag: Basel, 1999; Vol. 52, pp 167–195. (c) Szmuszkovicz, J. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser Verlag: Basel, 1999; Vol. 53, pp 1–51.
2. Giardina, G.; Clarke, G. D.; Grugni, M.; Sbacchi, M.; Vecchietti, V. *Il Farmaco* **1995**, *50*, 405.
3. Scopes, D. I. C. *Drugs Future* **1993**, *18*, 933.
4. Costello, G. F.; Main, B. G.; Barlow, J. J.; Carroll, J. A.; Shaw, J. S. *Eur. J. Pharm.* **1988**, *151*, 475.
5. Szmuszkovicz, J.; VonVoigtlander, P. F. *J. Med. Chem.* **1982**, *25*, 1125.
6. Costello, G. F.; James, R.; Shaw, J. S.; Slater, A. M.; Stutchbury, N. C. J. *J. Med. Chem.* **1991**, *34*, 181.
7. Compounds were purified on a silica gel column and converted to either HCl or CH_3SO_3H salts. All the new compounds (**2i**–**o**) reported here gave satisfactory ^{1}H NMR, MS (FAB), and elemental analyses.
8. Chang, A.-C.; Takemori, A. E.; Ojala, W. H.; Gleason, W. B.; Portoghese, P. S. *J. Med. Chem.* **1994**, *37*, 4490.
9. Weerawarna, S. A.; Davis, R. D.; Nelson, W. L. *J. Med. Chem.* **1994**, *37*, 2856.
10. Barlow, J. J.; Blackburn, T. P.; Costello, G. F.; James, R.; Le Count, D. J.; Main, B. G.; Pearce, R. J.; Russel, K.; Shaw, J. S. *J. Med. Chem.* **1991**, *34*, 3149.
11. DeHaven-Hudkins, D. L.; Cortes-Burgos, L.; Cassel, J. A.; Daubert, J. D.; DeHaven, R. N.; Mansson, E.; Nagasaka, H.; Yu, G.; Yaksh, T. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 494 and references therein.