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Trans N-Methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl] cycloprop-2-ene-1-carboxamides: Novel Lipophilic Kappa Opioid Agonists

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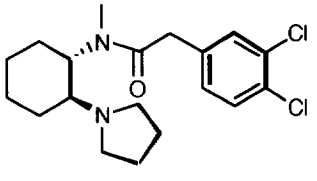
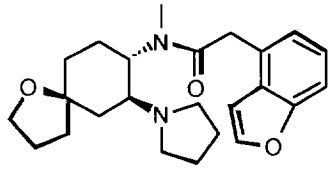
Abstract: The synthesis and kappa opioid agonist activities of some lipophilic analogues of the kappa opioid agonist **U-50488** incorporating motifs bearing two aromatic rings in place of the 3,4-dichlorophenyl group are described. *Trans* 2,3-diphenyl-*N*-methyl-*N*[2-(1-pyrrolidinyl)cyclohexyl]-2-cyclopropene-1-carboxamide, **7**, is a potent kappa opioid agonist. A diphenylcyclopropene analogue of **CI-977**, *trans* 2,3-diphenyl-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-cyclopropene-1-carboxamide, **13**, is a highly lipophilic chemically novel potent selective kappa opioid agonist.

Trans N-(2-aminocyclohexyl)arylacetamides such as **U-50488**[1] and **CI-977**[2] are potent selective agonists of the kappa opioid receptor. The development of agonists selective for the kappa opioid receptor has been the subject of considerable research during recent years, with the aim of identifying a compound which is a potent analgesic devoid of the adverse effects (constipation, respiratory depression and dependence) associated with activation of the mu subtype.



U-50488



CI-977

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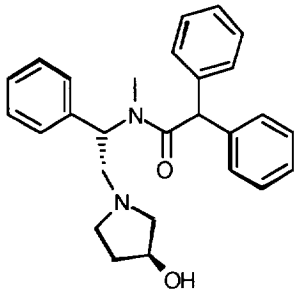
In addition to the antinociceptive effects of such kappa opioid agonists, agonism at the kappa receptor in the CNS is also believed to be associated with sedation, diuresis and dysphoria. A kappa opioid agonist which cannot penetrate the blood brain barrier should be a valuable agent against peripheral inflammatory pain, but without the centrally-associated side effects.[3] The lipophilicity of a compound, measured in terms of the partition coefficeint (log P) or distribution coefficeint (log D) is an important factor in determining whether or not it will readily cross the blood brain barrier. It has been reported that the relationship between the ability of compounds to penetrate the CNS and their lipophilicities is often parabolic, with optimum penetration when log P is close to 2.[4] Therefore, approaches to the development of peripherally selective compounds are to lower the log P well below 2 by incorporating a hydrophilic group such as a carboxylic acid,[5] or to raise log P considerably above 2 by increasing lipophilicity. The limited ability of the kappa opioid agonist **EMD 61753** to penetrate the blood brain barrier has been attributed to the presence of the highly lipophilic diphenylmethyl unit.[6]

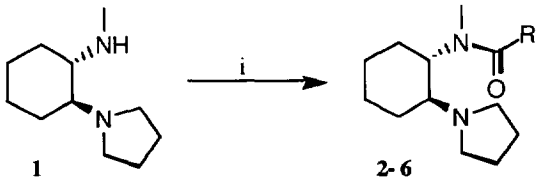


EMD 61753

This paper describes the preparation of some lipophilic *N*-(2-aminocyclohexyl)arylacetamides, in which the 2,3-dichloro substituent of **U-50488** has been replaced with some highly lipophilic motifs bearing two phenyl rings, and their agonist properties at kappa receptors which were evaluated in a rabbit vas deferens (LVD) assay.[7]

The arylacetamides **2** to **6** were obtained by coupling the appropriate acid chlorides (prepared from the carboxylic acids using thionyl chloride) with the diamine **1**[8] (Scheme 1) and were purified by recrystallisation of their hydrochloride salts.[9] The carboxylic acid precursors for compounds **2** to **4** were commercially available. 2,2-Diphenylcyclopropanecarboxylic acid was prepared by adding diphenyldiazomethane[10] to methyl acrylate in toluene at 80°C, followed by saponification of the methyl ester using lithium hydroxide. Carbenoid addition of ethyl diazoacetate to *cis* stilbene in the presence of rhodium acetate dimer followed by saponification gave *cis* 2,3-diphenylcyclopropanecarboxylic acid. Table 1 shows the relative agonist properties of compounds **2** to **6** for the kappa receptor in the LVD assay.

Scheme 1



1 2-6

Reagents and Conditions: i. RCOCl, CH_2Cl_2, 30 min, room temp, 40-54%

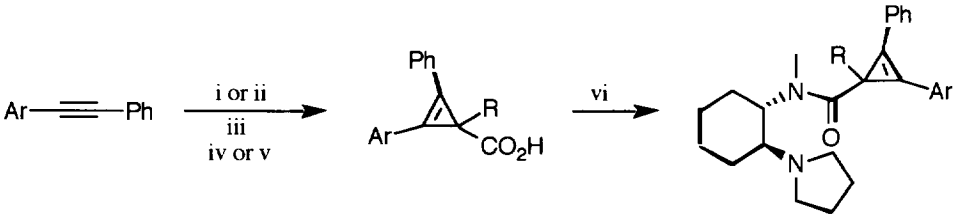
Table 1

compound	R	EC_{50} (LVD)
2	diphenylmethyl	> 10 μM
3	2,2-diphenylethyl	> 10 μM
4	fluorenyl	22 nM
5	2,2-diphenylcyclopropyl	> 10 μM
6	*cis* 2,3-diphenylcyclopropyl	> 10 μM

Compound **2**, an analogue of **EMD 61753**, had very poor activity as a kappa agonist (EC_{50} > 10 μM). Compound **3**, in which an extra methylene spacer makes the aromatic portion of the molecule more flexible, and **5** and **6**, in which flexibility is reduced by appending the phenyl groups to cyclopropane rings, were also of low activity. Only when the two phenyl rings of the diphenylacetyl group were constrained into a planar configuration, as in the fluorene derivative **4**, was a high affinity for the kappa opioid receptor observed (EC_{50} = 22 nM).

Considering the apparent need for planarity of the aromatic portion, a series of compounds based on the planar 1,2-diphenylcyclopropene motif were prepared. 2,3-Diarylcyclopropenecarboxylic acids were obtained by the carbenoid addition of ethyl diazoacetate or dimethyl diazomalonate[11] to diarylacetylenes[12] (catalysed by rhodium acetate dimer or copper(II) acetylacetonate respectively) followed by saponification. The acids were converted to acid chlorides using thionyl chloride, and coupled to the diamine **1**, to give compounds **7** to **12** (Scheme 2). The kappa opioid agonist properties of compounds **7** to **12** are shown in Table 2.

Scheme 2



7 - 12

Reagents and conditions: i. (R = H) Ethyl diazoacetate, rhodium acetate dimer, CH_2Cl_2, 35°C, 15-29%; ii. (R = CO_2Me) Dimethyl diazomalonate, copper(II) acetylacetonate, 140°C, 15%; iii. (Ar = 3-AcOPh to Ar = 3-MeOPh) $NaHCO_3$, H_2O, MeOH, then MeI, K_2CO_3, acetone, 33%; iv. (R = H) KOH, MeOH, 4 h, reflux, 42-78%; v. (R = CO_2Me) 1 equiv. LiOH, MeOH, CH_2Cl_2, 2 h, 60°C, 58%; vi. $SOCl_2$, $CHCl_3$, 2 days, room temp, then **1**, CH_2Cl_2, 30 min, room temp, 14-43%.

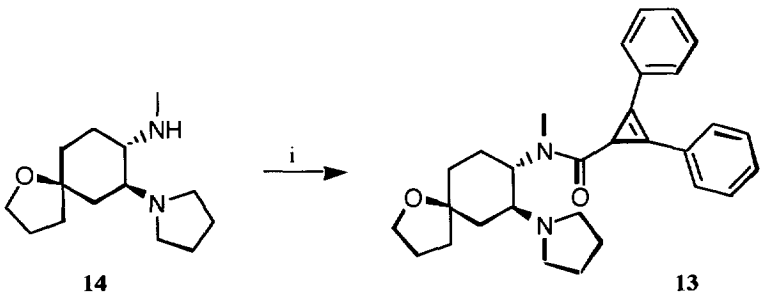
Table 2

Compound	Ar	R	EC_{50} (LVD)
7	Ph	H	32 nM
8	3-ClPh	H	141 nM
9	3-MeOPh	H	300 nM
10	4-ClPh	H	>10 μM
11	Ph	CO_2Me	3 μM
12	Ph	CO_2H	>10 μM

We were delighted to find that compound **7**, the 1,2-diphenylcyclopropene, had high agonist potency at the kappa receptor (EC_{50} = 32 nM). However, addition of substituents to one of the phenyl rings resulted in a decrease in activity, substitution at the 4-position (**10**) being much more detrimental than at the 3-position (**8** and **9**). The presence of the extra carboxylate groups in **11** and **12** also lead to a great reduction in affinity.

Compound **13**, an anologue of **CI-977** incorporating the diphenylcyclopropene motifs, was prepared by coupling 2,3-diphenylcyclopropene carbonyl chloride to the chiral amine **14**[13] (Scheme 3). The activities of **13** and **CI-977** at the kappa receptor and their log P and log D values[14] are compared in Table 3.

Scheme 3



14 **13**

Reagents and Conditions: i. 2,3-diphenylcycloprop-2-ene carbonyl chloride CH_2Cl_2, 30 min, room temp, 20%

Table 3

Compound	EC_{50} (LVD)	Log P	Log $D_{7.4}$
CI-977	3.3 nM	3.13	1.55
13	9.6 nM	4.39	2.37

The diphenylcyclopropene **13** has an EC_{50} comparable to that of **CI-977**; the log P and log D values indicate that it is more lipophilic. **CI-977** and **13** have been evaluated in radioligand binding assays to determine their affinities at kappa and mu receptors, and in mouse *in vivo* models designed to test antinociception (formalin paw and phenylbenzylquinone induced writhing) and sedation (rotarod). The results of these experiments (Table 4) indicate that both compounds are highly selective for the kappa opioid receptor and are potent analgesics *in vivo*. However, the sedative effect of **13** in the rotarod test provides evidence that its increased lipophilictiy compared with **CI-977** is not sufficient to significantly limit its access to the CNS.

Table 4

Compound	**rKOR[a] (K_i, nM)**	**μ[b] (K_i, nM)**	**Formalin Paw[c] ED_{50} (mg/kg)**	**Writhing[c] ED_{50} (mg/kg)**	**Rotarod[c] ED_{50} (mg/kg)**
CI-977	0.1	87.4	0.016	0.06	0.13
13	0.64	>1000	0.19	0.2	0.6

a: see reference 15; b: see reference 16; c: performed as described in reference 17.

In summary, a novel lipophilic arylacetamide, **13**, has been synthesised and its pharmacological properties determined in a series of *in vivo* and *in vitro* assays. **13** is a chemically novel potent selective agonist at the kappa opioid receptor.

References and Notes

1. Von Voigtlander, P. F.; Lahti, R. A.; Ludens, J. H. *J. Pharmacol. Exp. Ther.*, **1983**, *224*, 7.
2. Halfpenny, P. R.; Horwell, D. C.; Hughes, J.; Hunter, J. C.; Rees, D. C. *J. Med. Chem.*, **1990**, *33*, 286.
3. Barber, A.; Gottschlich, R. *Med. Res. Rev.*, **1992**, *12*, 525.
4. Hansch, C.; Bjorkroth, J. P.; Leo, A. *J. Pharm. Sci.*, **1987**, *76*, 663 and references therein.
5. Shaw, J. S.; Carroll, J. A.; Alcock, P.; Main, B. G. *Br. J. Pharmacol.*, **1989**, *96*, 986.
6. Gottschlich, R.; Ackermann, K. A.; Barber, A.; Bartoszyk, G. D.; Greiner, H. E. *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 677.
7. Compounds were evaluated for their ability to inhibit the contractions af electrically stimualted rabbit vas deferens. The procedure was based on that of Oka, T.; Negishi, K.; Suda, M.; Matsumiya, T.; Inazu, T.; Ueki, M. *Eur. J. Pharmacol.*, **1980**, *73*, 235.
8. Clark, C. R.; Halfpenny, P. R.; Hill, R. G.; Horwell, D. C.; Hughes, J.; Jarvis, T. C.; Rees, D. C.; Schofield, D. *J. Med. Chem.*, **1988**, *31*, 831.
9. All new compounds gave satisfactory spectroscopic and analytical data.
10. Smith, L. I.; Howard, K. L. *Org. Synth. Coll. Vol. 3*, 351.
11. Prepared according to the procedure of Hermann, W. A. *Chem. Ber.*, **1979**, 1731.
12. Diphenylacetylene was commercially available. 2(3 and 4-chlorophenyl)phenylacetylene were prepared following the procedure of Stevens, D.; Castro, C. E. *J. Org. Chem.*, **1963**, *28*, 3313. 2(3-acetoxyphenyl)phenylacetylene was prepared following the procedure of Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, 4467.
13. Kaplan, L. J. US Patent 4,438,130, March 20, **1984**; *Chem Abstr.*, **1984**, *101*, 54912w.
14. The Log P and interpolated Log D values were determined at Sirius Analytical Instruments, East Sussex, UK.
15. Evaluated with [^{3}H]-U-69593 in cloned rat kappa opioid receptor, expressed in CHO cell line.
16. Evaluated with [^{3}H]-DAGO in rat brain mu opioid receptor.
17. Leighton, G. E.; Johnson, M. A.; Meecham, K. G.; Hill, R. G.; Hughes, J. *Br. J. Pharmacol.*, **1987**, *92*, 915.

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