Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 5, pp. 677-682, 1994

0960-894X/94 $6.00+0.00

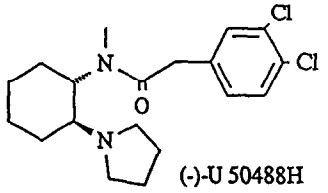
0960-894X(94)E0030-I

EMD 61 753 AS A FAVOURABLE REPRESENTATIVE OF STRUCTURALLY NOVEL ARYLACETAMIDO-TYPE K OPIATE RECEPTOR AGONISTS

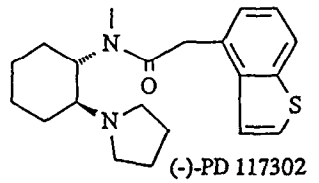
R. Gottschlich, K. A. Ackermann*, A. Barber#, G. D. Bartoszyk#, H. E. Greiner#*
** Medicinal Chemistry Department, # Biological Research Department*
E. Merck, D-64271 Darmstadt, Federal Republic of Germany

Abstract: K opiate agonists like (-)-U 50488H, (-)-PD 117302, etc. contain an acetamido group which is *mono*substituted in the α-position by an aromatic moiety. In contrast, EMD 61 753 is disubstituted in this position by two phenyl rings and is thus the first representative of the new class of diarylacetamide-type κ opiates. Derivates of EMD 61 753 are described and structure-activity relationships are discussed. In the formalin test in mice EMD 61 753 shows a profile similar to that of the antiinflammatory drugs rather than that of the centrally acting opiates.

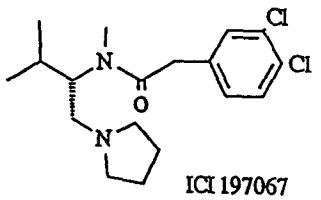
All the well known selective κ opiate agonists like (-)-U 50488H[1], (-)-PD 117302[2], ICI 197067[3] and EMD 60 400[4][5]



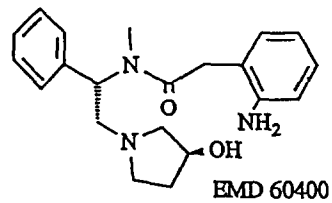
(-)-U 50488H



(-)-PD 117302



ICI 197067



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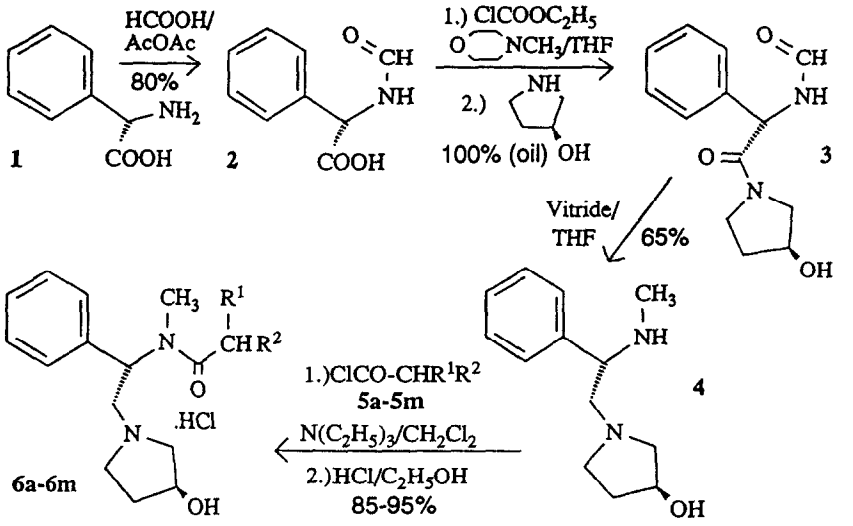
possess as a common structural element an arylacetyl group which is ***not*** substituted in the α-position. Only a few examples of α-substituted κ agonists have been described in the literature and these are mostly compounds in which the α-substituent forms a ring with either the amide-nitrogen or the aromatic moiety thus stiffening the molecular structure [6][7]. In addition, it has been found that the introduction of the small methyl group into the α-position of the arylacetyl moiety of (-)-PD 117302 leads to a decrease in κ-activity[6].

However, this individual result can certainly not be generalized to mean that α-substitution is an unfavourable variation in the molecular structure of the arylacetamido-type κ agonists. Thus, being interested to find out whether or not bulky α-substituents are an obstacle to good biological activity we synthesized some corresponding derivatives of EMD 60 400 and tested them in opiate binding assays.

Scheme 1:



The compounds were synthesized as shown in scheme 1: Compound **2** was obtained by treating (S)-α-aminobenzeneacetic acid **1** with formic acid and acetic acid anhydride. It was converted to the amide **3** by reacting the carboxylic acid function with ethyl chloroformate and subsequently with (S)-pyrrolidin-3-ol[8]. Reduction of the amido groups with sodium dihydrobis (2-methoxyethoxy) aluminate (Vitride) gave the diamine **4**. Compounds **6a-m** were obtained by reacting **4** with the acid chlorides **5a-m**.

In the case of **5b** and **5c** the racemic acid chlorides were used and the resulting epimers **6b** and **6c** were separated by column chromatography on silica gel 60 (E. Merck). The bases were subsequently converted to the corresponding hydrochlorides **6a-m** by means of hydrogen chloride in ethanol. Analytical data (elemental analysis and FAB-MS) were in agreement with the given stuctures.

The epimeric compounds **6b** and **6c** with unknown configuration of the α-disubstituted acetamido group were denoted **6b (1)**, **6c (1)** for the stereoisomers with the higher $(\alpha)_D^{20}$-value and **6b (2)**, **6c (2)** for those characterized by the lower optical rotation, respectively.

K-opioid binding was determined in the presence of the ligand [^{3}H]U 69593 in 50 mM Tris buffer using membranes prepared from guinea-pig cerebellum [5].

Table 1: Chemical structures, physical data and κ binding values of the standard compounds (-)-U 504488H and EMD 60 400 (**6a**) and of compounds **6b - 6d** to the κ opioid receptor

Comp see scheme 1	**R^1**	**R^2**	**mp (°C)**	**$(\alpha)_D^{20}$ (c=1; MeOH)**	**κ-binding (Ki; nMol/l)**
(-)-U 50488H	---	---	220-225 [1]	---	1
6a (EMD 60 400)	H	2-Aminophenyl	168-170	---	1 ± 0,2[2]
6b (1)	Isopropyl	Phenyl	155-155	97.7	3
6b (2)	Isopropyl	Phenyl	205-207	50.9	10
6c (1)	Cyclohexyl	Phenyl	175-177	98.1	10
6c (2)	Cyclohexyl	Phenyl	265-267	28.3	10
6d (EMD 61 753)	Phenyl	Phenyl	197-198	---	2 ± 0,1[2]

[1] Hydrochloride of (-)-U 50488H [2] mean ± s.d. (n=3)

Table 1 illustrates to what degree the affinity of these opiates for the κ receptor is altered by the introduction of a bulky substituent R^1. The binding data for **6b** and **6c** show that such structural variation leads - at least with these type of compound - to κ opiates with only a slightly diminished activity. It is noteworthy that the difference in the biological activity of the epimers **6b (1)** and **6b (2)** is small and in the case of **6c (1)** and **6c (2)** not existent. Surprisingly, by converting the cyclohexyl ring into a phenyl ring compound **6d** (EMD 61 753) with an improved activity is obtained. EMD 61 753, a representative of the novel class of diarylacetamido-type κ opiates exhibits high affinity for the κ receptor as characterized by binding values in the low nanomolar range and is thus, to a certain degree comparable to the reference substances U 50 488 and EMD 60 400.

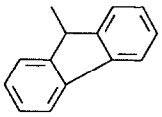
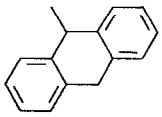
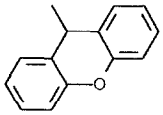
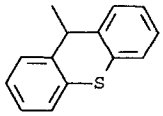
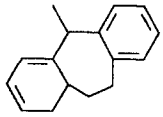
This unexpected finding prompted us to further vary the structure of this compound. The κ binding values for some derivatives with substituted phenylacetyl groups as well as one analogue with a dithienylacetyl group are given in table 2.

Table 2: Chemical structures, melting points and κ binding values of compounds **6d-6h**

Comp see scheme 1	R^1	R^2	mp (°C)	κ-binding (Ki; nMol/l)
6d (EMD 61 753)	Phenyl	Phenyl	197-198	2
6e	4-Fluorophenyl	4-Fluorophenyl	225	7
6f	4-Chlorophenyl	4-Chlorophenyl	252	5
6g	4-Methylphenyl	4-Methylphenyl	258-260	20
6h	2-Thienyl	2-Thienyl	178-180	4

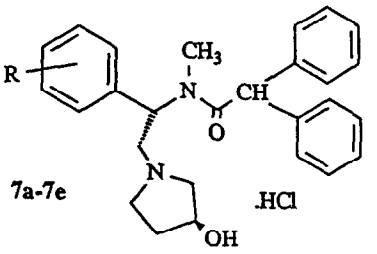
Although compounds **6e-6h** exhibit high affinity for the κ-receptor none of them exceeds **6d** in this respect. The structure of **6d** was further varied by combining both phenyl rings to a tricyclic system.

Table 3: Chemical structures, melting points and κ binding values of compounds **6i-m**

Comp see scheme 1	-CH R^1R^2	mp (°C)	κ-binding (Ki; nMol/l)
6i		203	6
6j		231-232	4
6k		257-258	4
6l		231-232	10
6m		228-229	20

The binding data in table 3 reveal that the molecules containing a methylene or an oxygen bridge (**6j** and **6k**) exhibit the highest activities. These structure activity relationships may be particulary useful for the evaluation of the biologically relevant spatial arrangement of the two rings in EMD 61 753 (**6d**). All the compounds **6a-6h** and **6j-6m** possess negligible affinities (K_i ≥100n Mol/l) for the μ and δ opioid receptors (rat cerebrum; [^{3}H] PL 017 and [^{3}H] [D-Pen^{2,5}] enkephalin, respectively). Only **6i** shows moderate affinities: Ki=40 nMol/l (μ) and 60nMol/l (δ).

Variation of the "amine-part" of EMD 61 753 led to compounds **7a-7e**:



7a was synthetized as shown in scheme 1 the only difference being that the commercially available (S)-α-amino-4-hydroxybenzeneacetic acid was used instead of the unsubstituted **1**. If in this synthesis the 4-hydroxy analogue of intermediate **3** was methylated to the 4-methoxy derivative compound **7b** was obtained as the final product. The synthesis of **7c** started from (S)-α-amino-3-nitrobenzeneacetic acid, which can be obtained by nitration of **1** as described in the literature.[9] The following steps were again carried out as shown in scheme 1. For the reduction of the amido groups to the amines in presence of the nitro group boranedimethylsulfide was used instead of vitride. **7c** was converted to **7d** by catalytic hydrogenation of the nitro group.Acetylation of **7d** with acetic acid anhydride led to **7e**.

Table 4: Chemical structures, melting points and κ binding values of compounds **7a-7e**

Comp	R	mp (°C)	κ-binding (Ki; nMol/l)
7a	4-hydroxy	152	6
7b	4-methoxy	119	7
7c	3-nitro	241-242	20
7d	3-amino	196-200	6
7e	3-acetamido	125*)	6

*) decomposition

The data given in table 4 show that the introduction of substituent into the phenyl ring of the "amine part" of EMD 61 753 leads to compounds with a slightly diminished affinity for the κ-opioid receptor; only in the case of the electron withdrawing nitro group a more distinct decrease in biological activity can be observed. Taken together, none of the variations in the structure of EMD 61 753, the parent compound of the diarylacetamide-type κ-opiates, led to an improved affinity or selectivity for the κ opioid receptor.

Peripherally selective opiates (i.e. opioid compounds which exert their analgesic effects by interacting with opiate receptors in the inflamed tissue rater than with opiate receptors in the CNS) may be a novel type of therapeutic agents useful in the treatment of inflammatory pain[10]. Since EMD 61 753 contains the diphenylmethyl group, a structural element which is also present in some lipophilic drugs devoid of central effects (e.g. non-sedating antihistaminics[11][12]) we tested EMD 61 753 in the formalin test, a test in which opioid activity against noninflammatory and inflammatory pain can be distinguished[13].

Table 5: ID_{50}-values of the centrally acting κ agonist ICI 197 067, the centrally acting μ agonist morphine and EMD 61 753 in the formalin test in mice

	ID_{50} mg/kg s.c.	
	early phase	late phase
ICI 197 067	0.04	0.02
Morphine	1.7	3.4
EMD 61 753 (6d)	> 2	0.24

Table 5 shows that centrally acting opiates like ICI 197 067 or morphine possess a comparable activity in the early and late phase of the formalin test. In contrast, antiinflammatory drugs like the NSAIDs are preferentially active in the late phase which is considered to represent a pain response to acute inflammation (e.g. indomethacin at doses of and above 30 mg/kg i.p. causes a significant inhibition in the late phase but not in the early phase).[13] EMD 61 753 exerts a distinctly higher activity in the late compared to the early phase and, thus, shows a profile similar to that of antiinflammatory drugs rather than that of the centrally acting opiates. Further-more, EMD 61 753 is active in the late phase after oral application (ID50 = 3.8 mg/kg).

The pharmacological profile and in particular the peripheral selectivity of EMD 61 753 are further investigated.

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(*Received in Belgium* 23 *November* 1993; *accepted* 12 *January* 1994)