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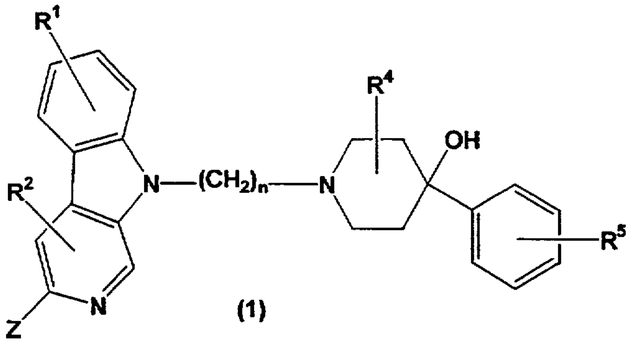
(56) Documents Cited
WO 96/34863 A1 **US 4539407 A**

(58) Field of Search
Online: CAS ONLINE

(54) Abstract Title
beta-Carboline derivatives for use in treatment of pain, trauma, spasticity and movement disorders

(57) Pharmaceutical compositions comprising a compound of formula (1), wherein n = 2, 3 or 4; Z is an ester group of formula R^3-O-CO- wherein R^3 is C_{1-6} alkyl or C_{2-6} alkenyl;



(1)

R^1, R^2 and R^5 are, independently, halogen, H, OH, CF_3, OMe, NO_2; and R^4 = H or C_{1-6} alkyl, are useful in the treatment of pain, trauma, spasticity and movement disorder other than that resulting from epilepsy. The compounds may be in free base form or in the form of an acid addition salt, such as the hydrochloride salt. Compounds according to formula (1) are inhibitors of the uptake of GABA (gamma-amino-butyric acid) by the GABA transporter protein GAT-3/4.

GB 2 355 659 A

β-CARBOLINE DERIVATIVES

Background of the invention

Field of the invention

The invention relates to the use of β-carboline derivatives for analgesic and related purposes.

Description of the related art

Nerve impulses pass along the specialised cells known as neurones. Neurones communicate with each other at synapses, mainly by chemical means. Neurotransmiters are small molecules which pass from vesicles within the neurone to the presynaptic membrane which is distanced from the postsynaptic membrane on a neighbouring neurone or an effector cell such as a muscle cell by the synaptic cleft. Neurotransmitters transmit a signal across the cleft.

Neurotransmitters can be inhibited by other molecules known as inhibitors, especially by gamma-aminobutyric acid (GABA). The actions of GABA at the synapse are terminated by re-uptake of GABA into the pre-synaptic neurones or into glial cells

The inhibition of this GABA uptake results in enhanced availability of this inhibitory neurotransmitter in the synaptic cleft and thus to increased "GABA-ergic" activity. Increased GABA-ergic activity can be useful in the treatment, for example of anxiety, pain and epilepsy, as well as muscular and movement disorders [see, for example, P. Krogsgaard-Larsen *et al.*, Progress in Medicinal Chemistry, *22*, 68-112 (1985)].

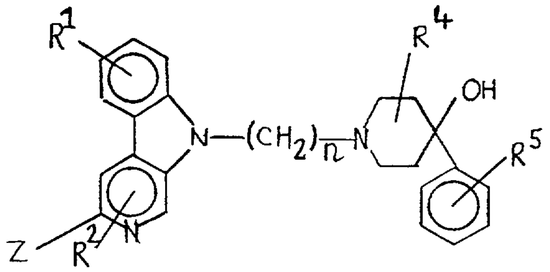
A well-known and potent inhibitor of GABA uptake from the synaptic cleft into presynaptic nerve terminals and glial cells is 3-piperidinecarboxylic acid (nipecotic acid). However, being a relatively polar compound and therefore unable to cross the blood-brain barrier, 3-piperidinecarboxylic acid itself has found no practical utility as a drug.

During the 1990s a new class of proteins have been found, known as GABA transporters. They have been classified as GAT-1, GAT-2, GAT-3 and GAT-4.

These proteins transport GABA from the synaptic cleft back into the neurone. Both GAT-1 and GAT-3/4 (GAT-3 is the rat and human homologue of GAT-4 in mice) are located exclusively within the central nervous system (CNS). Whilst GAT-1 is widely distributed, GAT-3/4 site expression is regionally specific. There are high levels of GAT-3/4 in the mid-brain, brain stem and spinal cord, key regions involved in pain control. Stimulation of peripheral sensory neurones known as C-fibres results in release of excitatory neurotransmitters in the spinal cord which result in the transmission and perception of pain. Pre-synaptic GABA receptors (GABA-B receptors) inhibit release of these neurotransmitters and reduce the perception of pain. Thus, activation of GABA receptors by GABA released from GABA-ergic neurones in the spinal cord and brainstem leads to a reduced release of neurotransmitters from these fibres and further ascending neurones and so to an analgesic effect.

The antiepileptic drug tiagabine is a selective inhibitor of GAT-1 and has analgesic properties, see M. D. Swedberg, J. Pharmacol. Exp. Ther. *269*, 1021-1028 (1994). However, tiagabine potentiates GABA-ergic transmission in all regions of the CNS and can therefore have sedative side effects. Compounds capable of increasing GABA function in the spinal cord and brainstem would therefore have the potential to produce analgesic without sedation.

Certain β-carboline derivatives which are potent inhibitors of GAT-3/4 are disclosed in PCT Patent Application WO 96/34865 (filed by Novo Nordisk A/S and assigned to the present applicant). These are principally compounds of formula (1):



(1)

wherein

n is 1 to 5,

R^1 and R^2 independently are principally hydrogen, halogen, hydroxy, nitro, $-NR^9R^{10}$, $-SONR^{11}R^{12}$, $-COOR^{13}$, $-CONR^{14}R^{15}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl or trifluoromethoxy wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} independently are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6} alkynyl; and

R^4 is hydrogen or C_{1-6}-alkyl; and

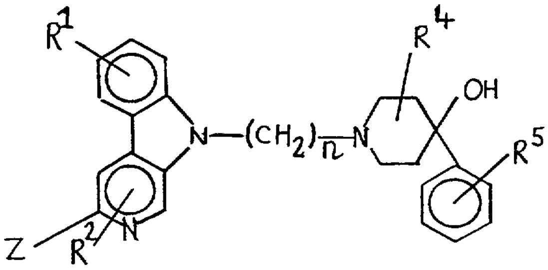
R^5 and R^6 independently are hydrogen, halogen, hydroxy, nitro, $-NR^{16}R^{17}$, $-COOR^{18}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl or trifluoromethoxy wherein R^{16}, R^{17} and R^{18} independently are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl; and Z is any of several defined 5-membered ring heterocyclic groups, preferably 3-substituted-1,2,4-oxadiazol-5-yl groups;

in the form of a free base or a pharmaceutically acceptable salt thereof.

The problem of the present invention is to find further potent GAT-3/4 inhibitors, preferably with a high selectivity for GAT-3/4 inhibition relative to GAT-1 inhibition.

Summary of the invention

It has now been found that compounds of formula (2):



(2)

wherein:

n is 2, 3 or 4;

Z is an ester group of formula R^3-O-CO- wherein R^3 is C_{1-6} alkyl or C_{2-6} alkenyl; and

R^1, R^2 and R^5 are independently selected from the group consisting of hydrogen, halogen, hydroxy, methoxy, nitro, and trifluoromethyl; and

R^4 is hydrogen or C_{1-6} alkyl;

in the form of the free base or an acid addition salt thereof are useful for any novel purpose involving the inhibition of GABA uptake via a GAT-3 or GAT-4 subtype carrier, preferably as analgesics, as well as for treatment of trauma, movement disorders (other than resulting from epilepsy) and spasticity.

These compounds are known from US Patent 4,539,407 to have anticonvulsant activity and thus to be useful in the treatment of epilepsy. However, no other effect is disclosed in that patent.

The invention extends to the further medical use of the compounds of formula (2), in any terms permitted by patent law of individual countries or regions. In particular it includes the use of compounds of formula (2) in the preparation of a medicament for the purposes described above and particularly as an analgesic.

The compounds of formula (2) differ from those of WO 96/34865 in that the 3-position substituent in the β-carboline ring system is an ester group instead of a heterocyclic group.

Description of the preferred embodiments

The compounds of formula (2) may exist as geometric and optical isomers and all isomers and mixtures thereof are included herein. Isomers may be separated by means of standard methods such as chromatographic techniques or fractional crystallisation of suitable salts.

Examples of pharmaceutically acceptable acid addition salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, phthalate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically acceptable inorganic or organic acid addition salts.

R^1 and R^2 are preferably hydrogen.

R^4 is preferably hydrogen or methyl.

R^5 is preferably hydrogen or a 3- or 4- chloro, bromo or trifluoromethyl substituent.

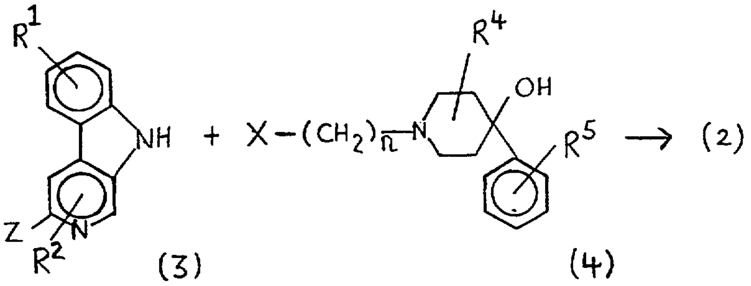
Within the definition of the ester group, Z, the alkyl and alkenyl groups R^3 may have straight or branched chains; ethyl and n-propyl are currently preferred, but chain branching at the α-carbon atom is specifically included.

A propylene bridge is preferred, i.e. n is preferably 3.

It has been demonstrated that the novel compounds of formula (2) which selectively inhibit the uptake of GABA, via the GAT-3/4 subtype carrier, from the synaptic cleft, possess useful pharmacological properties in the central nervous system, in that they cause a selective enhancement of GABA-ergic activity. They are primarily useful to treat pain.

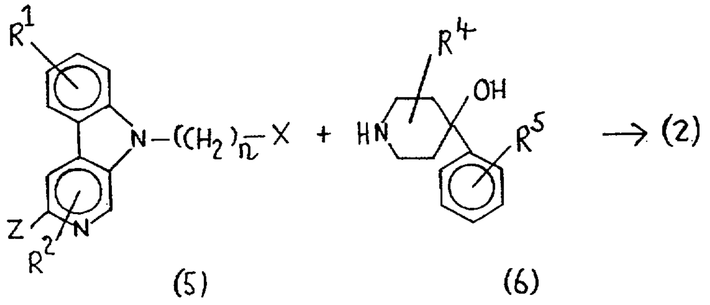
The compounds of formula (2) may be prepared as follows:

Method A:



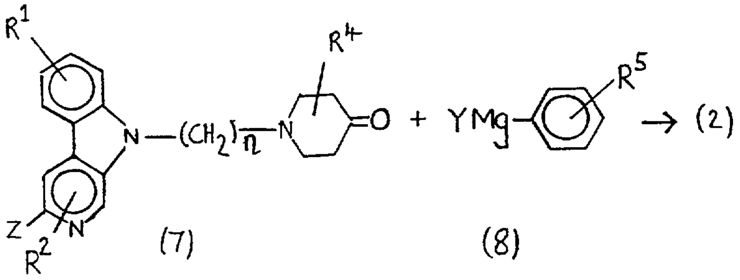
A compound of formula (3) wherein R^1, R^2 and Z are as defined above, may be reacted with an azaheterocyclic compound of formula (4) wherein n, R^4 and R^5 are defined above and X is a suitable leaving group such as halogen, p-toluene sulphonate or mesylate. This alkylation reaction may be carried out in a suitable solvent such as acetone, dibutylether, 2-butanone, tetrahydrofuran, methylisobutylketone, methylisopropylketone, toluene, benzene or DMF in the presence of a base e.g. potassium carbonate, sodium hydride or potassium tert.-butoxide at a temperature up to reflux for the solvent used, for e.g. 1 to 200 h.

Method B:



A compound of formula (5) wherein R^1, R^2, n, Z and X are as defined above may be reacted with an azaheterocyclic compound of formula (6) wherein R^4 and R^5 are as defined above. This reaction may be carried out in a suitable solvent as defined above in the presence of a base as defined above and possibly a catalyst, e.g. an alkali metal iodide, at a temperature up to reflux for the solvent used, for e.g. 1 to 200 h.

Method C:

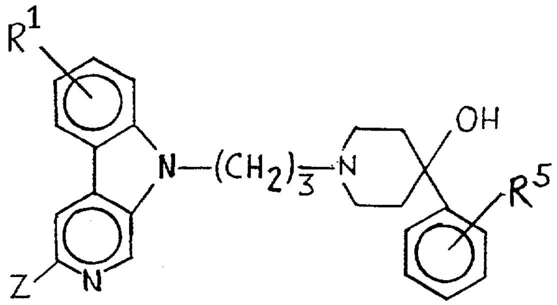


An azaheterocyclic ketone of formula (7) wherein R^1, R^2, n, R^4 and Z are as defined above may be reacted with a Grignard reagent of formula (8) wherein R^5 is as defined above and Y is chloro, bromo or iodo. This reaction may be carried out in a suitable solvent such as diethyl ether, THF, toluene or benzene at a suitable temperature up to reflux temperature for the solvent used, for e.g. 1 to 5 h.

Pharmacological Data

^{3}H-GABA uptake was measured by a modification of the method of Fjalland *et al.*, (1978). A crude membrane preparation was prepared from selected brain areas of male Wistar rats. To test for GAT-1 inhibition, whole forebrain was used. To test for GAT-4 inhibition the fresh inferior colliculus was used, this being an area of the brain associated with GAT-4 activity. The tissue was homogenised in 20 ml of ice-cold 0.32 M sucrose with a hand driven teflon/glass Potter-Elvehjem homogeniser. The homogenate was centrifuged at 4°C for 10 min. at 1,000 x g, and the pellet was discarded. The supernatant was recentrifuged at 4°C for 20 min. at 10,000 x g. The pellet was then homogenised in 50 volumes 0.32 M sucrose. To 300 µl (GAT-1) or 200 µl (GAT-4) of uptake-buffer (200 nM NaCl, 15.3 mM KCl, 6.67 mM $MgSO_4$, 3.83 mM $CaCl_2$, 16.67 mM glucose, 66.67 mM Tris, pH 7.5 at 30°C) was added 100 µl test substance and 50 µl tissue suspension. In the GAT-4 inhibition test 100 µl of 1-(2-(((diphenylmethylene)amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid (1 nM final concentration) was also added. The samples were mixed and incubated at 30°C for 8 min. Then ^{3}H-GABA (0.9 nM final concentration) and unlabelled GABA (25 nM final concentration) was added, and the incubation was continued for an additional 8 min. The reaction was terminated by rapid filtration through Whatman GF/F glass fiber filters under vacuum. The filters were then washed twice in 10 ml of ice-cold isotonic (0.9%) saline, and the tritium trapped on the filters was quantified by conventional scintillation spectroscopy. Non-specific binding was determined in duplicate using nipecotic acid (500 µM final concentration). Total binding minus non-specific binding gives the specific binding.

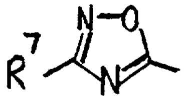
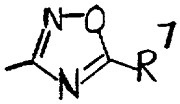
Values for non-GABA uptake carrier-mediated uptake of ^{3}H-GABA for some representative compounds of the present invention, along with the best results from the compound of PCT Application WO 96/34865, are shown below. Comparing the compound of present Example 1 with the best compounds of WO 96/34865, which are those of Examples 4 and 7 thereof, it will be seen that the compound of the invention shows greater GAT-4 inhibition. Substitution of the rings is generally less favourable, although the 3-chloro substituent in the right-hand benzene ring gave a particularly good result. Replacement of the ester group Z by a -COOH group was unfavourable, as shown by the comparison included ("Comp"). In several instances the compounds of the invention display high ratios of IC_{50}, GAT-1:GAT-4. Thus, for the compound of Example 1 of the present invention, the ratio is about 41 compared with 14 for the best compound (in that respect) of WO 96/34865, the compound of Example 28.



(9)

PCT Application WO 96/34865

Z = oxadiazolyl

Ex. of WO 96/34865	Z	R^7	R^1	R^5	IC_{50} nM	
					GAT-1	GAT-4
4.		C_2H_5	H	H	6700	890
7.	"	△	H	H	3700	890
10.	"	Ph	H	H	not done	1440
26.	"	CH_3	H	H	12200	1640
28.		CH_3	H	H	17000	1240

Present invention

Z = ester group (carboxylic acid group for comparison)

Ex. of this specification	Z	R^1	R^5	IC_{50} (nM)	
				GAT-1	GAT-4
1	n-C_3H_7OOC	H	H	8900	430
2	C_2H_5OOC	H	H	18400	450
3	C_2H_5OOC	6-NO_2	H	>3000	960
4	C_2H_5OOC	H	4-F	6100	1130
Comp.	HOOC	H	4-Cl	not done	11280
5	iso -C_3H_7OOC	H	4-Cl	7200	1500
6	C_2H_5OOC	H	4-Br	10800	1860
7	C_2H_5OOC	H	4-CF_3	15000	2170
8	C_2H_5OOC	H	4-OCH_3	21200	1760
9	C_2H_5OOC	H	3-Cl	12700	690
10	C_2H_5OOC	H	3-CF_3	14400	1380

The compounds of formula (2) are preferably formulated with a pharmaceutical carrier or diluent. The compositions containing the compounds of formula (2) may be prepared by conventional techniques and in conventional forms, for example capsules, tablets, solutions or suspensions.

The pharmaceutical carrier employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water.

Similarly, the carrier or diluent may include any time delay material known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier for oral administration is used, the preparation can be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely, but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Generally, the compounds of formula (2) are dispended in unit dosage form comprising 50-200 mg of active ingredient in or together with a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds of formula (2) is 1-500 mg/day, e.g. about 100 mg per dose, when administered to patients, e.g. humans, as a drug.

A typical tablet, which may be prepared by conventional tabletting techniques contains:

<u>Core</u>:

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide ("Aerosil", TM)	1.5 mg
Cellulose, microcryst. ("Avicel", TM)	70 mg
Modified cellulose gum ("Ac-Di-Sol", TM)	7.5 mg
Magnesium stearate	

<u>Coating</u>:

HPMC	Approx.	9 mg
*Mywacett, TM 9-40 T	Approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intraurethral, intramuscular, topical, intransal, ophthalmic solution or an ointment, the oral route being preferred.

The following Examples illustrate the preparation of the compounds used in the invention.

Preparative Examples

Example 1

Propyl 9-(3-(4-Phenyl-4-hydroxypiperidino)propyl)-β -carboline-3-carboxylate.

Propyl-9H-pyrido[3,4-b]indolecarboxylate 2.5g (10 mmol) was dissolved in N,N-dimethylformamide (125 mL) and 0.55g (14 mmol) NaH was added under nitrogen, the mixture was stirred 1h at room temperature. 4.72 g (30 mmol) 2-bromo-1-chloropropane was added and the reaction mixture was stirred for 20 h. at room temperature. The mixture was evaporated *in vacuo* and redissolved in CH_2Cl_2 (125ml). 2N HCl (100 mL) was added and the mixture was filtered. The organic phase was washed with 5% $NaHCO_3$(aq) (100 mL) and NaCl (brine) (25 mL). It was then dried with $MgSO_4$, filtered and evaporated *in vacuo* to give the crude propyl (9H-1-(3-chloro/bromopropyl)pyrido[3,4-b]indolecarboxylate. Recrystallisation from 2-propanol gave 3.19g (98% in yield).

This compound was a bromo/chloro mixture and was used below without any further purification.

2.0g (6 mmol) of propyl 9H-1-(3-chloro/bromopropyl)pyrido[3,4-b]indolecarboxylate prepared above was dissolved in N,N-dimethylformamide (100 mL). 4-Phenyl-4-hydroxypiperidine 1.07g (6 mmol) and triethylamine (1 mL) were added. The reaction mixture was stirred under nitrogen at 60°C for 12 h. The reaction mixture was evaporated *in vacuo* and redissolved in CH_2Cl_2 (100 mL), washed with 5% $NaHCO_3$ (aq) (50 mL) and NaCl (brine) (50 mL) and then dried with magnesium sulfate. Evaporation *in vacuo* gave the crude product as an brown oil. Further purification was performed on a silica gel column (150g; CH_2Cl_2/EtOH/ NH_4OH(25%aq); 185:14:1 as eluant). 2.48g was isolated as the free amine. To 700mg of the free amine was added HCl (2.3M in ethanol), the solvent was evaporated and the product (as hydrochloride salt) recrystallised from ethanol and diethyl ether, yield 752 mg. For physical data, see list after Examples 3-10.

Example 2

Ethyl 9-(3-(4-Phenyl-4-hydroxypiperidino)-propyl)-β-carboline-3-carboxylate.

Ethyl 9H-1-(3-chloro/bromopropyl)pyrido[3,4-6]indole carboxylate was synthesised in the same manner as in Example 1.

The title compound (hydrochloride salt) was then synthesised in the same manner as in Example 1, to give 1 g white crystals, yield 54%.

Examples 3-10

The other compounds of the Table shown above were synthesised in the same manner as Example 1.

Physical data

Compound 1: Hydrochloride.

Mp: 168-170°C.

Sample for NMR contains ethanol and 2HCl, Mp:179-180°C.

^{1}H-NMR: (D6-DMSO 200MHz) 1.05(d,t;3H); 1.7(d;2H); 1.8(q;1H); 2.4(m;2H); 2.55(d,d;1H); 3.2(m;4H); 4.4(t;2H); 4.35(t;2H); 5.4(broad s;3H); 7.25(t;1H); 7.35(t;2H); 7.45(d,t;2H); 7.8(t;1H); 8.1(d,1H); 8.6(d;1H); 9.2(s;1H); 9.6(s;1H); 11.5(s;1H).

Compound 2: Hydrochloride.

Mp: amorphous, about 113°C.

Contains ethanol.

^{1}H-NMR: ($CDCl_3$;200MHz) 1.25(t;3H); 1.5(t;3H); 1.65(s;1H); 2.05-2.2(m;4H); 3.45(d,t;4H); 3.7(d;2H); 3.75(q;1,5H); 4.6(m;4H); 7.3(d;1,5H); 7.4(d,t;2,5H); 7.5(d;2H); 7.65(d,d;2H); 8.2(d;1H); 8.9(s;1H); 9.05(s;1H).

Compound 3: Hydrochloride.

3HCl salt,

Mp: 182-185°C.

FAB MS 502.2 ($M^+ + 1$). The sample crystallised was reckoned to contain 0.38 mole H_2O as water of crystallisation.

Sample for NMR contains ethanol.

^{1}H-NMR: (CD_3OD; 200MHz) 1.5(t;3H); 1.9(d;2H); 2.4-2.7(m;4H); 3.6(m;6H); 4.65(q;2H); 5.0(t;2H); 7.2-7.4(m;3H); 7.5(d,2H); 8.3(d,1H); 8.7(d;1H); 9.5(d;2H); 9.9(s;1H).

Compound 4:

Liquid chromatography mass spectrometry (LC-MS): M+1=475; Retention time (Rt)=3.00 min; area; 82%.

Compound 5: Hydrochloride.

Contains ethanol.

Mp: 201-205°C.

^{1}H-NMR: (D6-DMSO 200MHZ) 1.3(t;3H); 1.6(d;2H); 2.0-2.4(m;4H); 2.6-3.2(broad m;6H); 4.4(q;2H); 4.7(m;2H); 5.5(broad s; 1H); 7.3(d;1H); 7.4(t;4H); 7.6(t;1H); 7.8(d;1H); 8.4(d;1H); 8.9(s;1H); 9.2(S;1H).

Comparative compound (acid): Hydrochloride.

Mp>250°C.

^{1}H-NMR: (D6-DMSO 200MHz) 1.7(d;2H); 2.35(m;4H); 3.1-3.5(m; 7H); 4.7(t;2H); 5.6(s;1H); 7.4(m;5H); 7.7(t;1H); 7.9 (d;1H); 8.5(d;1H); 9.0(s;1H); 9.3(s;1H); 10.6(s;1H).

Compound 6: Hydrochloride. Mp: amorphous.

Contains ethanol.

^{1}H-NMR: (D6-DMSO 200MHz) 1.4(d;6H); 1.7(d;2H); 2.45(m;2H); 3.1-3.3(m;4H); 3.45(d;2H); 4.7(t;2H); 5.2(h;1H); 7.35(d;2H); 7.45(t;3H); 7.8(t;1H); 8.05(d;1H); 8.6(d;1H); 9.2(s;1H); 9.5(s;1H); 11.3(s;1H).

Compound 7: Free amine.

Mp: amorphous.

LC-MS: M+1=538; Rt=2.88 min; area 96%.

Compound 8: Hydrochloride.

Mp: amorphous.

LC-MS: M+1=526; Rt=3.50 min; area 97%.

Compound 9: Free amine.

LC-MS: M+1=488; Rt=2.92 min; area: 72%.

Compound 10: Free amine. Mp: amorphous.

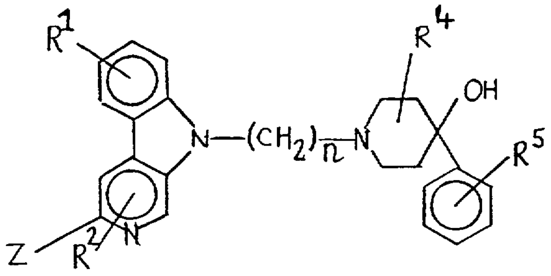
LC-MS: M+1=493; Rt=3.33 min; area: 100%.

Compound 11: Free amine. Mp: amorphous.

LC-MS: M+1=526; Rt=3.50 min; area: 99%.

CLAIMS

1. A method of treating a patient suffering from pain, trauma, a movement disorder, other than resulting from epilepsy, or spasticity, which comprises administering to said patient an effective amount of a compound of formula (2):



(2)

wherein:

n is 2, 3 or 4;

Z is an ester group of formula R^3-O-CO- wherein R^3 is C_{1-6} alkyl or C_{2-6} alkenyl; and

R^1, R^2 and R^5 are independently selected from the group consisting of hydrogen, halogen, hydroxy, methoxy, nitro, and trifluoromethyl; and

R^4 is hydrogen or C_{1-6} alkyl;

in the form of the free base or an acid addition salt thereof.

2. The method of Claim 1, wherein R^1 and R^2 are both hydrogen atoms.

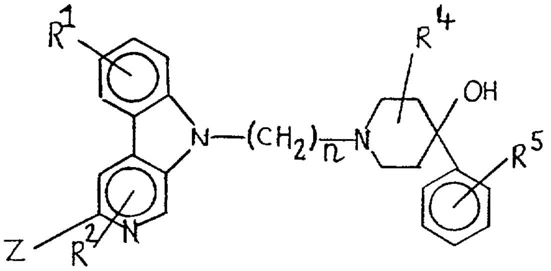
3. The method of Claim 2, wherein n is 3.

4. The method of Claim 3, wherein R^3 is ethyl or n-propyl.

5. The method of Claim 1, wherein Z is C_2H_5-O-CO- or n-C_3H_7-O-CO-, n is 3 and R^1 and R^2 are both hydrogen atoms.

6. The method of Claim 5, wherein R^4 and R^5 are hydrogen atoms.

7. Use of a compound of formula (2):



(2)

wherein:

n is 2, 3 or 4;

Z is an ester group of formula R^3-O-CO- wherein R^3 is C_{1-6} alkyl or C_{2-6} alkenyl; and

R^1, R^2 and R^5 are independently selected from the group consisting of hydrogen, halogen, hydroxy, methoxy, nitro, and trifluoromethyl; and

R^4 is hydrogen or C_{1-6} alkyl;

in the preparation of a formulation for treating a patient suffering from pain, trauma, a movement disorder, other than resulting from epilepsy, or spasticity.

8. Use according to Claim 7, wherein the compound of formula (2) is as further defined in any one of Claims 2 to 6.

INVESTOR IN PEOPLE

Application No:	GB 0026485.3	**Examiner:**	Dr Lawrence Cullen
Claims searched:	1-8	**Date of search:**	6 February 2001

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.S):

Int Cl (Ed.7):

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
Y	WO 96/34863 A1	(NOVO NORDISK) see page 4, formula I; page 6, lines 15-21; page 8, line 17 to page 10, line 25; page 11, lines 5-10.	1-8
Y	US 4539407 A	(AMERICAN HOME PRODUCTS) see whole document	1-8

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
		E	Patent document published on or after, but with priority date earlier than, the filing date of this application.
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