

Description

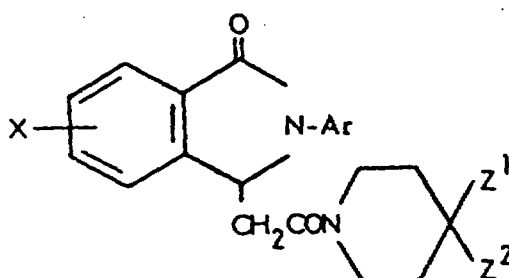
This invention relates to novel isoindolinone derivatives which are useful as drugs.

In the field of antianxiety drugs which fall within the category of drugs acting on the central nervous system (CNS), too, studies have been made on various novel compounds.

As far as isoindolinone derivatives are concerned, there are already a number of relevant reports (e.g. South African patent nos. 7208795 and 7309139, and EP—A—0 091 241. The latter discloses *inter alia* compounds of the below formula (I) in which Z¹ and Z² are both hydrogen.

CNS drugs, inclusive of antianxiety drugs, are required, for example, to be orally administrable and free of adverse effects such as muscle relaxant effect. Any compounds which are satisfactory from this viewpoint have not yet been found.

The invention provides a compound of the formula



wherein X is hydrogen, halogen or nitro; Ar is phenyl or naphthyridinyl which may have one or two substituents selected from halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, nitro, amino, methylenedioxy, phenoxy, benzyloxy, C₂₋₅ alkanoyloxy, α- or ω-hydroxy-C₁₋₄ alkyl, benzoyl, amido, cyano, trifluoromethyl, C₁₋₄ alkylthio, C₂₋₅ alkanoyloxy-C₁₋₃ alkyl, C₂₋₅ alkanoylamino, and C₁₋₄ alkoxy-carbonyl; and either one of Z¹ and Z² is hydrogen and the other is C₁₋₄ alkanoyloxy or hydroxy, each of Z¹ and Z² is C₁₋₄ alkoxy, or Z¹ and Z² combinedly represent hydroxyimino, oxo or a group of the formula:



in which Y is oxygen or sulfur and A is a branched or unbranched C₂₋₄ alkylene chain which may have one or more C₁₋₄ alkyl side chains; or a salt thereof, which act on the central nervous system and are useful, in particular, as antianxiety drugs.

Referring to X in the above formula (I), the halogen represented by X includes fluorine, chlorine, bromine and iodine and preferably chlorine, and X is preferably hydrogen.

The phenyl or naphthyridinyl represented by Ar may have one or two substituents and such substituents include, among others, halogen (e.g. fluorine, chlorine, bromine, iodine), hydroxy, (C₁₋₄) alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl), (C₁₋₄) alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy), nitro, amino, methylenedioxy, phenoxy, benzyloxy, (C₂₋₅) alkanoyloxy (e.g. acetoxy, propionyloxy, butyryloxy), α- or ω-hydroxy-lower (C₁₋₄) alkyl (e.g. hydroxymethyl, 2-hydroxyethyl), benzoyl, amido, cyano, trifluoromethyl, (C₁₋₄) alkylthio (e.g. methylthio, ethylthio, propylthio, butylthio), (C₂₋₅) alkanoyloxy (C₁₋₃) alkyl (e.g. acetyloxymethyl, acetyloxyethyl, propionyloxymethyl), (C₂₋₅) alkanoylamino (e.g. acetylamino, propionylamino) and alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, isopropoxycarbonyl, propoxycarbonyl).

The above-mentioned substituent or substituents may be located at any position or positions on the benzene or naphthyridine ring. Preferred are those compounds which have such a substituent, preferably (C₁₋₄) alkoxy, at position 4 of the benzene ring or a substituent, preferably halogen or (C₁₋₄) alkyl, at position 5 or 7 of a naphthyridine ring, for example the 1,8-naphthyridine ring. The 1,8-naphthyridine is preferably bonding to N at position 2 thereof.

Ar is preferably a naphthyridinyl group, in particular a 7-halogen substituted-1,8-naphthyridinyl group.

Referring to Z¹ and Z², the (C₁₋₄) alkanoyloxy is, for example, formyloxy, acetoxy, propionyloxy, isopropionyloxy or butyryloxy, and the (C₁₋₄) alkoxy is, for example, methoxy, ethoxy, propoxy or isopropoxy.

When Z¹ and Z² combinedly represent a group of the formula



Y is preferably oxygen and the alkylene chain represented by A is preferably of C₂₋₄ and may have one or

more (C₁₋₄) alkyl side chains (e.g. methyl, ethyl, propyl, isopropyl, butyl). In particular, it is preferable that Z¹ and Z² form ethylenedioxy.

When they are basic, the compounds (I) according to the invention may be in the form of acid addition salts, in particular in the form of physiologically acceptable acid addition salts, such as salts with inorganic acids (e.g. hydrochloric acid, nitric acid, phosphoric acid, hydrobromic acid) or with organic acids (e.g. acetic acid, propionic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

The compounds (I) can be produced, for example, by subjecting, to condensation reaction, a compound of the formula



wherein X and Ar are as defined above and Y' is a hydroxyl group or a reactive derivative thereof and a compound of the formula



wherein Z¹ and Z² are as defined above.

Referring to the compound (II), Y', when it is a reactive derivative of hydroxy, is, for example, halogen (e.g. fluorine, chlorine, bromine, iodine; preferably chlorine or bromine), (C₁₋₄) alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy) or N-hydroxydiacylimide ester (e.g. N-hydroxysuccinimide ester, N-hydroxyphthalimide ester, N-hydroxy-5-norbornene-2,3-dicarboximide ester).

That compound in which Y' is halogen, namely acid halide, can be produced by halogenating that compound in which Y' is hydroxy, namely carboxylic acid, by a *per se* known method, for example by treating with a halogenating agent (e.g. phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride, phosphorus pentabromide, phosphorus trichloride, phosphorus, tribromide, thionyl chloride, thionyl bromide, sulfonyl chloride, oxalyl chloride, cyanuric chloride, boron tribromide, hydrogen iodide).

The solvent to be used in halogenation may be any solvent which is in common use. Chloroform, dichloromethane, dichloroethane, benzene and toluene are preferred examples.

The reaction of compound (II) and compound (III) is carried out by a *per se* known method. For instance, the compound (I) can be produced by deriving a compound (II: Y' = hydroxy) to a compound (II: Y' = halogen) by a *per se* known method, and then reacting the latter with a compound (III), by reacting a compound (II: Y' = hydroxy) as it is with a compound (III) in the presence of an acid activating agent such as carbonyldiimidazole, dicyclohexylcarbodiimide, diethyl phosphorocyanidate or diphenylphosphoryl azide, or by reacting a compound (II: Y' = C₁₋₄ alkoxy) directly with a compound (III). In each case, the reaction can generally be effected in an organic solvent such as a hydrocarbon solvent (e.g. pentane, hexane, benzene, toluene), a halogenated hydrocarbon solvent (e.g. dichloromethane, chloroform, dichloroethane, carbon tetrachloride), an ether solvent (e.g. ethyl ether, tetrahydrofuran, dioxane, dimethoxyethane), an ester solvent (e.g. ethyl acetate, butyl acetate, ethyl propionate), and amide solvent (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphotriamide) or dimethyl sulfoxide, with cooling (-10°C to 10°C), at room temperature (11°C to 40°C) or with heating (41°C to 120°C). The reaction time is generally 10 minutes to 12 hours. The compound (III) is preferably used in an amount of 1.0 to 3.0 equivalents based on the compound (II). If necessary, the reaction is conducted in the presence of an organic base such as pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylamine, triethylenediamine or tetramethylethylenediamine, or inorganic base such as sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide or potassium hydroxide.

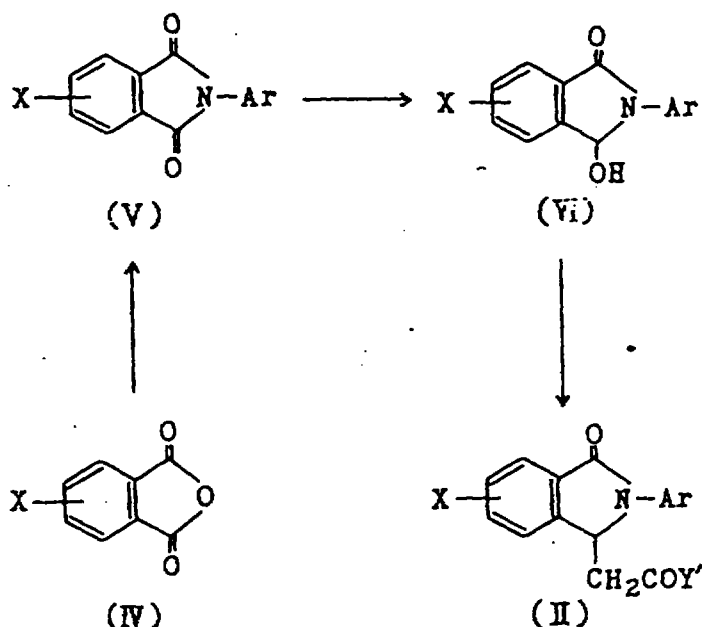
When the reactive derivative of the above compound (II: Y' = hydroxy) is an N-hydroxydiacylimide ester, the reaction of such reactive derivative and the compound (III) is generally carried out in a solvent such as dichloromethane, tetrahydrofuran, chloroform, dimethylformamide, acetonitrile or water. Any other solvents inert to the reaction may also be used. The reaction is performed, if desired, in the presence of an organic amine base or inorganic base such as mentioned above. The reaction temperature is generally -10°C to 100°C, preferably 0°C to 30°C.

As far as the compound (II) is concerned, such compound in which Y' is hydroxy can readily be obtained by hydrolyzing the corresponding ester in which Y' is C₁₋₄ alkoxy by a *per se* known method, for example by treatment with an alkali metal hydroxide (e.g. sodium hydroxide, lithium hydroxide, potassium hydroxide), an alkali metal carbonate (e.g. potassium carbonate, sodium carbonate, lithium carbonate), an inorganic acid (e.g. hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid) or an organic acid (e.g. acetic acid, propionic acid, trifluoroacetic acid, monochloroacetic acid, trichloroacetic

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acid, methanesulfonic acid, toluenesulfonic acid). Any solvent which is generally usable may be used as the solvent in conducting hydrolysis. Water, (C₁₋₄) alkanols (e.g. methanol, ethanol, propanol, butanol), dioxane and dimethylformamide are preferred examples. When an organic acid is used, particular use of a solvent is not always needed. The reaction is conducted generally at a temperature of about -5°C to about 120°C, preferably 0°C to 80°C.

The compound (II: Y' = C₁₋₄ alkoxy) can be produced by the following reactions:



In the above formulas, X, Ar and Y' are as defined above.

The starting compound of general formula (VI) can be produced according to the method described in J. Org. Chem., 26, 2273 (1961) or in Chem. Commun., 245 (1968). Thus, for example, the compound (VI) can be produced easily by first producing a compound (V) by reaction of a compound (IV) with an amine of the formula



wherein Ar is as defined above by the method described in Chem. Ber., 40, 4850 (1907), Bull. Soc. Chim. France, 26, 749 (1959), Il Farmaco Ed. Sc., 23, 448 (1968) or Arzneim.-Forsch., 12, 1207 (1962) or a modification thereof and then following the procedure described in J. Org. Chem., 26, 2273 (1961) or Chem. Commun., 245 (1968).

The compound (II: Y' = lower alkoxy) can be produced by reacting the compound (VI) with a compound of the formula



wherein Y' is lower alkoxy. The reaction of compound (VI) and compound (VIII) is carried out in an organic solvent such as toluene, benzene, xylene, ethyl acetate, dimethoxyethane or dichloromethane. Any other organic solvent which will not disturb the reaction may also be used. The reaction is conducted generally at a temperature of about 10°C to about 160°C, preferably 25°C to 120°C, for about 10 minutes to about 12 hours, preferably 30 minutes to 2 hours.

The compound (III) can be produced easily by the *per se* known method (tetrahedron, 27, 411 (1971); J. Chem. Soc., (B), 1087 (1971) or J. Chem. Soc., (B), 127 (1970)) or a modification thereof.

For each compound (I) according to the invention, there exist optical isomers, and these isomers and the racemic modification all fall within the scope of the present invention. The compound (I) according to the invention is generally obtained in the racemic form. The respective optical isomers can be obtained as necessary by optical resolution according to a *per se* known method. It is also possible, for example, to produce the compound (I) in an optically active form by first subjecting the compound (II: Y' = hydroxy) to optical resolution by a *per se* known method and then reacting the thus-obtained optically active (II) with a compound (III) according to the above-mentioned method. As resolving agents usable for the compound (II: Y' = hydroxy), there may be mentioned, for example, optically active amines such as cinchonine, brucine, quinine and amino acids.

The compounds (I) according to the invention act on the central nervous system of mammals. Having strong specific binding activity to benzodiazepine receptors, they show strong and lasting antianxiety

activity in the anticonflict test in rats. The minimum lethal doses (MLDs) for the compounds of the invention are not less than 1,000 mg/kg (p.o.) in rats, hence very large as compared with minimum effective doses (MEDs) thereof, so that the safety margins for said compounds are very broad. For the compound (I: Ar = 7-chloro-1,8-naphthyridin-2-yl), for instance, the MED for the above-mentioned antianxiety activity in rats is not higher than 20 mg/kg (p.o.).

As compared with the known isoindolinone derivatives mentioned above or those benzodiazepine drugs which are currently on the market as antianxiety drugs, the compounds (I) of the invention are broader in safety margin, very good in distinctness of their activity or activities from the hypnotic, muscle relaxant or like activity as a side effect, and very weak or slight in activity to produce such adverse effects as the so-called drowsiness and dizziness. Even peroral administration of said compounds can produce remarkable therapeutic effects. Therefore, said compounds are useful as antianxiety drugs for mammals, inclusive of humans.

As diseases to be treated with the compounds of the invention, there may be mentioned various psychosomatic diseases and anxiety neuroses, such as autonomic imbalance, neurotic emesis, neurodermatitis, alopecia areata, angina pectoris nervosa and dyspnoeoneurosis, and said compound can be used in the prevention or treatment of such diseases. The compounds according to the invention also have anti-convulsant activity. Therefore, they can also be used in the treatment of epilepsy or traumatic convulsion.

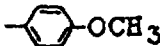
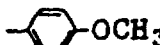
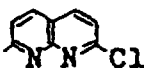
The compounds of the invention are administered to mammals, inclusive of humans, in the dosage form of tablets, granules, capsules, injections, suppositories and so forth. The dose varies depending on the disease to be treated, symptoms thereof and other factors. Generally, however, the oral dose for adult humans is 0.01 mg to 200 mg, preferably 0.1 mg to 20 mg, per day.

Biochemical Test Example

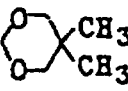
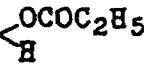
The compounds (I) according to the invention were tested for their affinity for benzodiazepine receptors using radioactive [^3H]diazepam.

The assay for specific binding to benzodiazepine receptors was performed according to the method described in the literature (Nature, 266, 732 (1977); European J. Pharmacol., 46, 263 (1978)). Thus, a crude mitochondrial fraction obtained from the cerebral cortex of SD strain male rats aged 9 to 10 weeks was suspended in 50 mM Tris-HCl buffer (pH 7.4), followed by addition of the test drug at several concentration levels and of [^3H]diazepam (final concentration 2 nM). Each suspension was incubated at 4°C for 20 minutes and then filtered through a Whatman GF/B glass fiber filter, and the radioactivity of [^3H]diazepam on the filter was measured with a liquid scintillation counter. In this manner, the IC_{50} value, namely the concentration of the test drug at which the [^3H]diazepam binding was inhibited by 50%, was determined.

The results obtained are shown in Table 1.

compound (I) X	Ar	Z ¹ , Z ²	IC ₅₀ (nM)
5-Cl		-NOH	3.47
5-Cl	"	=O	2.40
5-NO ₂	"		21.9
5-Cl			8.71
5-NO ₂	"	=O	6.16
5-NO ₂	"	-NOH	7.94
H		=O	0.537

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compound (I)	Ar	Z ¹ , Z ²	IC ₅₀ [nM]
H	•		0.380
H	•		1.29
H	•	-NOH	0.645
H	•		2.40
H	•		4.90
H	•		0.562
H	•		1.23
H	•		0.501
H	•		1.00
H	•		0.794

Pharmacological Test Example

The compounds (I) of the invention were examined for antianxiety, muscle relaxant and sleep-inducing activities.

(1) Antianxiety activity

The antianxiety activity measurement was performed in accordance with Vogel et al [Psychopharmacologia, 21, 1 (1970)] as follows: An apparatus comprising a large clear box with a stainless steel grid floor and a smaller opaque dark box provided with a drinking tube was arranged such that a rat placed therein could receive, on the sole, electric shocks through the grid floor following each twentieth lick. The test compound was orally administered to each male rat (SD/JCL) deprived of water for 48 hours prior to the test, which rat was then, 30, 60 or 180 minutes after administration, placed in the apparatus mentioned above and the number of licks was recorded over 3 minutes. The increase in the number of licks as compared with a physiological saline group was determined and taken as a measure of antianxiety potency, and the minimum effective dose determined accordingly.

(2) Muscle relaxant activity

Groups of 6 rats were used. The rats were placed on a rotating rod with a diameter of 3.5 cm. The rod rotated with a speed of 8 revolutions per minute. The animals were observed for whether they fell off the rod within 1 minute or not. The dose, ED₅₀, of the test compound as required to make 50% of the rats fall off the rod was calculated [J. Am. Pharmaceutical Association, 46, 208 (1957)].

(3) Sleep-inducing activity

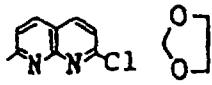
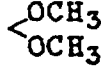
Mice, in groups of eight, were orally administered the test compound and, 30 minutes later, intraperitoneally administered 25 mg/kg of pentobarbital. The loss of righting reflex which lasted for 2 minutes or longer during the 30-minute period following pentobarbital administration was taken as an

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indication of sleep potentiation. The dose, ED₅₀, of the test compound as required to achieve sleep potentiation in 50% of mice was calculated.

The antianxiety, muscle relaxant and sleep-inducing activities of three typical examples of the compound (I) are shown in Table 2.

Table 2

X	Compound (I)		Antianxiety activity	Muscle relaxant activity	Sleep-inducing activity
	Ar	Z ¹ , Z ²	MED (mg/kg)	ED ₅₀ (mg/kg)	ED ₅₀ (mg/kg)
H			5	>80	>50
H	"	=O	20	>80	24.8
H	"		>20	>40	≈50
H	"		>20	>80	40.2

Example

The following examples are intended to illustrate this invention in further detail and should by no means be construed as limiting the scope of the invention.

Example 1

5-Chloro-3-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-carbonylmethyl-2-(4-methoxyphenyl)isoindolin-1-one
 With ice-cooling and stirring, 1.57 g of 1,4-dioxo-8-azaspiro[4.5]decan-8-yl, 2.3 ml of triethylamine and 2.12 g of diethyl phosphorocyanidate were successively added to a solution of 3.32 g of 6-chloro-2-(4-methoxyphenyl)-3-oxoisoindoline-1-acetic acid in 30 ml of dimethylformamide. The mixture was stirred with ice-cooling for an hour. To the reaction mixture was added 150 ml of ice water and the mixture was allowed to stand to give a crystalline precipitate, which was collected by filtration, washed with water and dried. Recrystallization from ether gave 4.13 g of colorless crystals melting at 156—157°C.

Elemental analysis

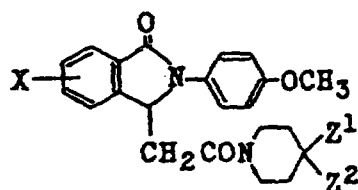
Calcd. for C₂₄H₂₅ClN₂O₅: C 63.08; H 5.52; N 6.13

Found: C 63.26; H 5.54; N 5.92

Example 2

In the same manner as Example 1, there were obtained the compounds listed in Table 3.

Table 3



X	Z ¹ , Z ²	m.p. (°C)	Molecular Formula	Elemental Anal. Calcd. (Found)		
				C	H	N
5-Cl	-NOH	209-211	C ₂₂ H ₂₂ ClN ₃ O ₄	61.75 (61.82)	5.18 5.23	9.82 9.89
5-Cl	-O	171-173	C ₂₂ H ₂₁ ClN ₂ O ₄	64.00 (64.11)	5.13 5.21	6.79 6.68
5-NO ₂		197	C ₂₄ H ₂₅ ClN ₃ O ₇	61.66 (61.56)	5.39 5.39	8.99 8.87
H		164-166	C ₂₄ H ₂₅ N ₂ O ₅	68.23 (68.21)	6.20 6.19	6.63 6.54
5-NO ₂	-O	166-167	C ₂₂ H ₂₁ N ₃ O ₆	62.41 (62.72)	5.00 5.05	9.92 9.84
5-NO ₂	-NOH	199-200	C ₂₂ H ₂₂ N ₄ O ₆	60.27 (60.39)	5.06 5.01	12.78 12.71
5-Cl		180-182	C ₂₂ H ₂₃ N ₂ O ₄	63.69 (63.12)	5.59 5.53	6.75 6.71
5-NO ₂		204-205	C ₂₂ H ₂₃ N ₃ O ₆	62.11 (62.33)	5.45 5.53	9.88 9.90

Example 3

2-(7-Chloro-1,8 naphthyridin-2-yl)-3-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)carbonylmethylisoindolin-1-one

To a mixture of 20.4 g of 2-(7-chloro-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetic acid and 250 ml of dimethylformamide were added 16 ml of triethylamine, 10.4 g of 1,4-dioxo-8-azaspiro[4.5]decane and 16 ml of diethyl phosphorocyanidate, and the mixture was stirred for 20 minutes. After addition of water, the resulting crystalline precipitate was collected by filtration, washed with water and dried to give 26.4 g of crude crystals. Recrystallization from methylene chloride-ethyl acetate gave 27.1 g of colorless crystals melting at 238-239°C.

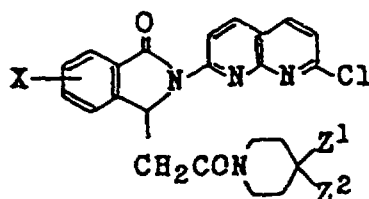
Elemental analysis Calcd for C₂₅H₂₃ClN₄O₄: C 62.70; H 4.84; N 11.70

Found: C 62.84; H 4.90; N 11.67

Example 4

In the same manner as Example 3, there were obtained the compounds listed in Table 4.

Table 4



X	Z ¹ , Z ²	m.p. (°C)	Molecular Formula	Elemental Anal.		
				Calcd. (Found)	C	H
H	-NOH	245-247	C ₂₃ H ₂₀ ClN ₅ O ₃	6140 448 1557 (6115 449 1531)		
H	-O	263	C ₂₃ H ₁₉ ClN ₄ O ₃	6352 440 1288 (6364 446 1283)		
H		207-208	C ₂₅ H ₂₅ ClN ₄ O ₄	6243 524 1165 (6266 519 1177)		
H		203-204	C ₂₇ H ₂₉ ClN ₄ O ₄	6371 574 1101 (6394 557 1113)		
H		218-221	C ₂₈ H ₂₉ ClN ₄ O ₄	6455 561 1075 (6450 545 1080)		
H		281-282	C ₂₆ H ₂₅ ClN ₄ O ₄	6335 511 1137 (6234 508 1118)		
H		225-227	C ₂₆ H ₂₅ ClN ₄ O ₂ S ₂	5947 480 1067 (5940 476 1063)		
H		249-250	C ₂₅ H ₂₃ ClN ₄ O ₂ S ₂	5876 454 1096 (5865 446 1086)		
5-Cl	-O	259-260	C ₂₃ H ₁₈ Cl ₂ N ₄ O ₃	5886 387 1194 (5843 385 1151)		
5-NO ₂	=O	290-292	C ₂₃ H ₁₈ ClN ₅ O ₅	5757 378 1459 (5733 374 1447)		
5-Cl		263-264	C ₂₅ H ₂₂ Cl ₂ N ₄ O ₄	5849 432 1091 (5834 412 1064)		
5-NO ₂		295-297	C ₂₅ H ₂₂ ClN ₅ O ₆	5731 423 1337 (5721 416 1340)		
6-NO ₂		295-297	C ₂₅ H ₂₂ ClN ₅ O ₆	5731 423 1337 (5703 419 1313)		
H		234-235	C ₂₅ H ₂₃ ClN ₄ O ₄	6270 484 1170 (6299 473 1187)		
H		233-234	C ₂₆ H ₂₅ ClN ₄ O ₄	6335 511 1137 (6346 518 1126)		

X	Z ¹ , Z ²	m.p. (°C)	Molecular Formula	Elemental Anal.		
				Calcd. (Found)		
				C	H	N
6-NO ₂	=O	>300	C ₂₃ H ₁₈ ClN ₅ O ₅	57.56 (57.50)	3.78 3.85	14.60 14.41
H		270-271	C ₂₃ H ₂₁ ClN ₄ O ₃	63.23 (63.00)	4.84 4.78	12.82 12.72

Example 5

2-(7-Chloro-5-methyl-1,8-naphthyridin-2-yl)-3-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)carbonylmethylisoindolin-1-one

With ice-cooling and stirring, 1.6 g of 1,4-dioxo-8-azaspiro[4.5]decan-8-yl, 2 ml of triethylamine and 2.2 g of diethyl phosphorocyanidate were successively added to a solution of 3.5 g of 2-(7-chloro-5-methyl-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetic acid in 30 ml of dimethylformamide. The mixture was stirred with ice-cooling for an additional 2 hours and 200 ml of ice-water was added thereto. The mixture was allowed to stand, and the resulting crystalline precipitate was collected by filtration, washed with water and dried. Recrystallization from dichloromethane-ether (1:4) gave 4.23 g of colorless crystals melting at 259-262°C.

Elemental analysis Calcd. for C₂₆H₂₅ClN₄O₄: C 63.34; H 5.11; N 11.37
Found: C 63.39; H 5.10; N 11.41

Example 6

2-(7-Chloro-5-methyl-1,8-naphthyridin-2-yl)-3-(4-piperidon-1-yl)carbonylmethylisoindolin-1-one

With ice-cooling and stirring, 1.2 g of 4-piperidone, 1.5 ml of triethylamine, 0.5 g of 4-methylaminopyridine and 1.6 g of diethyl phosphorocyanidate were successively added to a solution of 2.1 g of 2-(7-chloro-5-methyl-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetic acid in 35 ml of dimethylformamide. After stirring with ice-cooling for an additional 3 hours, 200 ml of ice water was added, and the resulting crystalline precipitate was collected by filtration, washed with water and dried. Recrystallization from dichloromethane gave 2.13 g of colorless crystals melting at 312-314°C.

Elemental analysis Calcd. for C₂₄H₂₁ClN₄O₃: C 64.21; H 4.72; N 12.48
Found: C 64.33; H 4.69; N 12.60

Example 7

2-(7-Chloro-1,8-naphthyridin-2-yl)-3-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)carbonylmethylisoindolin-1-one

(1) To 2.6 g of 2-(7-chloro-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetic acid was added 6 ml of thionyl chloride. The mixture was stirred at room temperature for 30 minutes and then heated at 60°C for 15 minutes. Removal of the excess thionyl chloride by distillation gave 2.66 g of 2-(7-chloro-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetyl chloride. This product was directly submitted to the next step without purification.

(2) A solution of 2.66 g of the acetyl chloride derivative obtained by the above procedure in 20 ml of dichloromethane was added to a solution of 2.1 g of 1,4-dioxo-8-azaspiro[4.5]decan-8-yl and 3 ml of triethylamine in 50 ml of dichloromethane with ice-cooling and stirring. After stirring with ice-cooling for 30 minutes, 300 ml of water was added and the dichloromethane layer was separated, washed with water and dried on anhydrous magnesium sulfate. Removal of the solvent by distillation gave 2.71 g of crude crystals. This product was recrystallized from methylene chloride-ether (1:2) to give the same compound as that obtained in Example 3. It melted at 238-239°C.

Formulation Example 1

- | | | |
|-----|--|------|
| (1) | 2-(7-Chloro-1,8-naphthyridin-2-yl)-3-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)carbonylmethylisoindolin-1-one | 1 g |
| (2) | Lactose | 89 g |
| (3) | Corn starch | 29 g |
| (4) | Magnesium stearate | 1 g |

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The above ingredients (1) and (2) and 15 g of corn starch were mixed and granulated with a paste prepared from 8 g of corn starch. To the granules were added 6 g of corn starch and ingredient (4), and the mixture is compressed on a tableting machine to give 1000 tablets of 5 mm diameter each containing 1 mg of ingredient (1).

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Reference Example 1

2-(7-Chloro-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetic acid

(1) A mixture of 46.0 g of 2-(7-chloro-1,8-naphthyridin-2-yl)-3-hydroxyisindolin-1-one, 78 g of t-butyloxycarbonylmethylenetriphenylphosphorane and 800 ml of toluene was refluxed for 5 hours. The mixture was concentrated and the residue was purified by silica gel column chromatography (dichloro-methane-ethyl acetate) to give 54.5 g of t-butyl 2-(7-chloro-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetate. Recrystallization from toluene-ether gave colorless crystals melting at 210—211°C.

Elemental analysis Calcd. for $C_{22}H_{20}ClN_3O_3$: C 64.47; H 4.92; N 10.25

Found: C 64.66; H 4.97; N 10.27

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(2) In 270 ml of trifluoroacetic acid was dissolved 54.5 g of the t-butyl ester obtained in the above. The solution was allowed to stand for 2 hours and then concentrated, followed by addition of ether. The resulting crystalline precipitate was collected by filtration to give 47.0 g of crystals melting at 225—226°C.

Elemental analysis Calcd. for $C_{19}H_{12}ClN_3O_3$: C 61.11; H 3.42; N 11.88

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Found: C 61.30; H 3.46; N 11.82

Reference Example 2

6-Chloro-2-(4-methoxyphenyl)-3-oxoisindoline-1-acetic acid

(1) A solution of 20 g of 5-chloro-2-(4-methoxyphenyl)-3-hydroxyisindolin-1-one and 27 g of ethoxycarbonylmethylenetriphenylphosphorane in 200 ml of dry toluene was heated at 110°C for 3 hours. After cooling, the resulting triphenylphosphine oxide was removed. Recrystallization of the crude crystals gave 19.6 g of ethyl 6-chloro-2-(4-methoxyphenyl)-3-oxoisindoline-1-acetate as colorless crystals melting at 129—131°C.

Elemental analysis Calcd. for $C_{19}H_{18}ClNO_4$: C 63.42; H 5.04; N 3.89

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Found: C 63.47; H 5.06; N 3.87

(2) To a solution of 16 g of the ester compound obtained by the above procedure (1) in 200 ml of methanol were added 50 ml of water and 27 g of potassium carbonate. The mixture was stirred at 80°C for 3 hours. After cooling, the excess methanol was distilled off and 150 ml of 3N hydrochloric acid was added to the residue. The resulting crystalline precipitate was collected by filtration, washed with water, dried and recrystallized from methanol to give 14.2 g of the title compound melting at 250—251°C.

Elemental analysis Calcd. for $C_{17}H_{14}ClNO_4$: C 61.54; H 4.25; N 4.22

Found: C 61.53; H 4.26; N 4.30

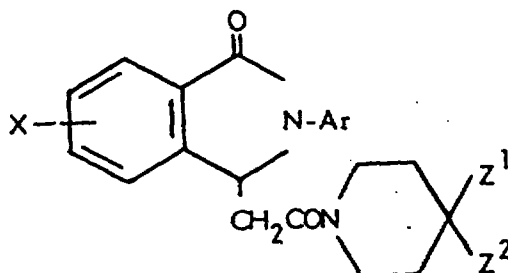
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Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula

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wherein X is hydrogen, halogen or nitro; Ar is phenyl or naphthyridinyl which may have one or two substituents selected from halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, amino, methylenedioxy, phenoxy, benzyloxy, C_{2-5} alkanoyloxy, α - or ω -hydroxy- C_{1-4} alkyl, benzoyl, amido, cyano, trifluoromethyl, C_{1-4} alkylthio, C_{2-5} alkanoyloxy- C_{1-3} alkyl, C_{2-5} alkanoylamino, and C_{1-4} alkoxy carbonyl; and either one of Z^1 and Z^2 is hydrogen and the other is C_{1-4} alkanoyloxy or hydroxy, each of Z^1 and Z^2 is C_{1-4} alkoxy, or Z^1 and Z^2 together represent hydroxyimino, oxo or a group of the formula:

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The above ingredients (1) and (2) and 15 g of corn starch were mixed and granulated with a paste prepared from 8 g of corn starch. To the granules were added 6 g of corn starch and ingredient (4), and the mixture is compressed on a tableting machine to give 1000 tablets of 5 mm diameter each containing 1 mg of ingredient (1).

Reference Example 1

2-(7-Chloro-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetic acid

(1) A mixture of 46.0 g of 2-(7-chloro-1,8-naphthyridin-2-yl)-3-hydroxyisindolin-1-one, 78 g of t-butyloxycarbonylmethylenetriphenylphosphorane and 800 ml of toluene was refluxed for 5 hours. The mixture was concentrated and the residue was purified by silica gel column chromatography (dichloromethane-ethyl acetate) to give 54.5 g of t-butyl 2-(7-chloro-1,8-naphthyridin-2-yl)-3-oxoisindoline-1-acetate. Recrystallization from toluene-ether gave colorless crystals melting at 210–211°C.

Elemental analysis Calcd. for $C_{22}H_{20}ClN_3O_3$: C 64.47; H 4.92; N 10.25
Found: C 64.66; H 4.87; N 10.27

(2) In 270 ml of trifluoroacetic acid was dissolved 54.5 g of the t-butyl ester obtained in the above. The solution was allowed to stand for 2 hours and then concentrated, followed by addition of ether. The resulting crystalline precipitate was collected by filtration to give 47.0 g of crystals melting at 225–226°C.

Elemental analysis Calcd. for $C_{18}H_{12}ClN_3O_3$: C 61.11; H 3.42; N 11.88
Found: C 61.30; H 3.46; N 11.82

Reference Example 2

6-Chloro-2-(4-methoxyphenyl)-3-oxoisindoline-1-acetic acid

(1) A solution of 20 g of 5-chloro-2-(4-methoxyphenyl)-3-hydroxyisindolin-1-one and 27 g of ethoxycarbonylmethylenetriphenylphosphorane in 200 ml of dry toluene was heated at 110°C for 3 hours. After cooling, the resulting triphenylphosphine oxide was removed. Recrystallization of the crude crystals gave 19.6 g of ethyl 6-chloro-2-(4-methoxyphenyl)-3-oxoisindoline-1-acetate as colorless crystals melting at 129–131°C.

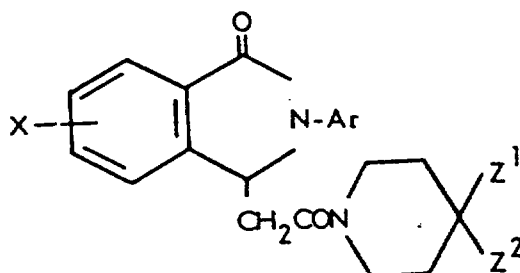
Elemental analysis Calcd. for $C_{19}H_{18}ClNO_4$: C 63.42; H 5.04; N 3.89
Found: C 63.47; H 5.06; N 3.87

(2) To a solution of 16 g of the ester compound obtained by the above procedure (1) in 200 ml of methanol were added 50 ml of water and 27 g of potassium carbonate. The mixture was stirred at 80°C for 3 hours. After cooling, the excess methanol was distilled off and 150 ml of 3N hydrochloric acid was added to the residue. The resulting crystalline precipitate was collected by filtration, washed with water, dried and recrystallized from methanol to give 14.2 g of the title compound melting at 250–251°C.

Elemental analysis Calcd. for $C_{17}H_{14}ClNO_4$: C 61.54; H 4.25; N 4.22
Found: C 61.53; H 4.26; N 4.30

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula



wherein X is hydrogen, halogen or nitro; Ar is phenyl or naphthyridinyl which may have one or two substituents selected from halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, amino, methylenedioxy, phenoxy, benzyloxy, C_{2-5} alkanoyloxy, α - or ω -hydroxy- C_{1-4} alkyl, benzoyl, amido, cyano, trifluoromethyl, C_{1-4} alkylthio, C_{2-5} alkanoyloxy- C_{1-3} alkyl, C_{2-5} alkanoylamino, and C_{1-4} alkoxycarbonyl; and either one of Z^1 and Z^2 is hydrogen and the other is C_1 – C_4 alkanoyloxy or hydroxy, each of Z^1 and Z^2 is C_1 – C_4 alkoxy, or Z^1 and Z^2 together represent hydroxyimino, oxo or a group of the formula:





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in which Y is oxygen or sulfur and A is a branched or unbranched C_2-C_4 alkylene chain which may have one or more C_1-C_4 alkyl side chains; or a salt thereof.

2. A compound according to Claim 1, wherein Ar is phenyl.
3. A compound according to Claim 1, wherein Ar is naphthyridinyl.
- 5 4. A compound according to Claim 2, wherein the phenyl is substituted by C_1-C_4 alkoxy.
5. A compound according to Claim 3, wherein the naphthyridinyl is substituted by halogen or/and C_1-C_4 alkyl.
6. A compound according to Claim 1, wherein X is hydrogen.
7. A compound according to Claim 1, wherein either one of Z^1 and Z^2 is hydrogen and the other is
- 10 hydroxy.
8. A compound according to Claim 1, wherein Z^1 and Z^2 combinedly represent oxo.
9. A compound according to Claim 1, wherein Z^1 and Z^2 together represent a group of the formula:

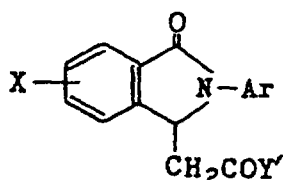


10. A compound according to Claim 9, wherein Y is oxygen.
- 20 11. A compound according to Claim 1, wherein X is hydrogen, Ar is naphthyridinyl which is substituted by halogen, and Z^1 and Z^2 together represent a group of the formula:



wherein Y is oxygen and A is unbranched C_2-C_4 alkylene.

12. A compound according to Claim 1, which is 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(4-hydroxy-piperidin-1-yl)carbonylmethylisoindolin-1-one.
- 30 13. A compound according to Claim 1, which is 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(4-piperidon-1-yl)-carbonylmethylisoindolin-1-one.
14. A compound according to Claim 1, which is 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)carbonylmethylisoindolin-1-one.
15. A method of producing the compound according to Claim 1, which comprises condensing a
- 35 compound of the formula:



wherein X and Ar are as defined above and Y' is hydroxy or reactive derivative thereof, with a compound of

45 the formula:



wherein Z^1 and Z^2 are as defined above.

16. A pharmaceutical composition which contains an effective amount for acting on the central nervous system of the compound according to Claim 1 and a pharmaceutically acceptable carrier, vehicle or diluent therefor.

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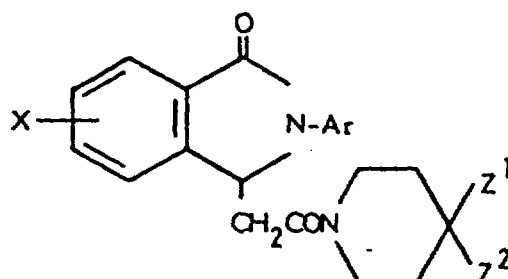
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Claims for the Contracting State: AT

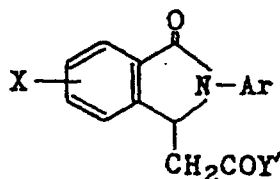
1. A method of preparing a compound of the formula



wherein X is hydrogen, halogen or nitro; Ar is phenyl or naphthyridinyl which may have one or two substituents selected from halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, nitro, amino, methylenedioxy, phenoxy, benzyloxy, C₂₋₅ alkanoyloxy, α- or ω-hydroxy-C₁₋₄ alkyl, benzoyl, amido, cyano, trifluoromethyl, C₁₋₄ alkylthio, C₂₋₅ alkanoyloxy-C₁₋₃ alkyl, C₂₋₅ alkanoylamino, and C₁₋₄ alkoxy-carbonyl; and either one of Z¹ and Z² is hydrogen and the other is C₁₋₄ alkanoyloxy or hydroxy, each of Z¹ and Z² is C₁₋₄ alkoxy, or Z¹ and Z² together represent hydroxyimino, oxo or a group of the formula:



in which Y is oxygen or sulfur and A is a branched or unbranched C₂₋₄ alkylene chain which may have one or more C₁₋₄ alkyl side chains; or a salt thereof, which comprises condensing a compound of the formula:

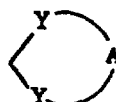


wherein X and Ar are as defined above and Y' is hydroxy or reactive derivative thereof, with a compound of the formula:



wherein Z¹ and Z² are as defined above.

2. A method according to Claim 1, wherein Ar is phenyl.
3. A method according to Claim 1, wherein Ar is naphthyridinyl.
4. A method according to Claim 2, wherein the phenyl is substituted by C₁₋₄ alkoxy.
5. A method according to Claim 3, wherein the naphthyridinyl is substituted by halogen or/and C₁₋₄ alkyl.
6. A method according to Claim 1, wherein X is hydrogen.
7. A method according to Claim 1, wherein either one of Z¹ and Z² is hydrogen and the other is hydroxy.
8. A method according to Claim 1, wherein Z¹ and Z² together represent oxo.
9. A method according to Claim 1, wherein Z¹ and Z² together represent a group of the formula:



10. A method according to Claim 9, wherein Y is oxygen.

11. A method according to Claim 1, wherein X is hydrogen, Ar is naphthyridinyl which is substituted by halogen, and Z¹ and Z² together represent a group of the formula:





wherein Y is oxygen and A is unbranched C₂₋₄ alkylene.

12. A method according to Claim 1, wherein the compound produced is 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(4-hydroxypiperidin-1-yl)carbonylmethylisoindolin-1-one.

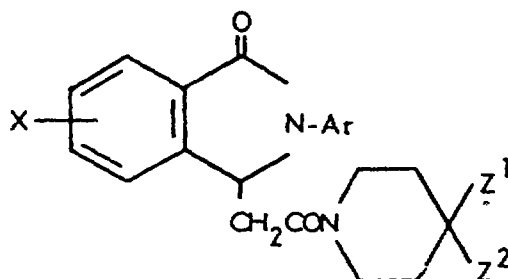
13. A method according to Claim 1, wherein the compound produced is 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(4-piperidon-1-yl)carbonylmethylisoindolin-1-one.

14. A method according to Claim 1, wherein the compound produced is 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)carbonylmethylisoindolin-1-one.

15. A pharmaceutical composition which contains an effective amount for acting on the central nervous system of the compound produced by the method according to any of Claims 1 to 14, and a pharmaceutically acceptable carrier, vehicle or diluent therefor.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel



worin X Wasserstoff, Halogen oder Nitro ist; Ar gegebenenfalls durch ein oder zwei Substituenten gewählt aus Halogen, Hydroxy, C₁₋₄ Alkyl, C₁₋₄ Alkoxy, Nitro, Aminto, Methylendioxy, Phenoxy, Benzyloxy, C₂₋₅ Alkanoyloxy, α- oder ω-Hydroxy-C₁₋₄ Alkyl, Benzoyl, Amido, Cyano, Trifluormethyl, C₁₋₄ Alkylthio, C₂₋₅ Alkanoyloxy-C₁₋₃ Alkyl, C₂₋₅ Alkanoylamino und C₁₋₄ Alkoxy-carbonyl substituiertes Phenyl oder Naphthyridinyl bedeutet; und entweder Z¹ oder Z² Wasserstoff und das andere C₁₋₄ Alkanoyloxy oder Hydroxy ist, Z¹ und Z² jeweils C₁₋₄ Alkoxy bedeuten oder Z¹ und Z² zusammen Hydroxyimino, Oxo oder eine Gruppe der Formel



darstellen, worin Y Sauerstoff oder Schwefel bedeutet und A eine verzweigte oder unverzweigte C₂₋₄ Alkylkette ist, die eine oder mehrere C₁₋₄ Alkylseitenketten aufweisen kann; oder ein Salz derselben.

2. Verbindung nach Anspruch 1, worin Ar für Phenyl steht.
3. Verbindung nach Anspruch 1, worin Ar Naphthyridinyl ist.
4. Verbindung nach Anspruch 2, worin das Phenyl substituiertes C₁₋₄ Alkoxy bedeutet.
5. Verbindung nach Anspruch 3, worin das Naphthyridinyl durch Halogen und/oder C₁₋₄ substituiert ist.
6. Verbindung nach Anspruch 1, worin X Wasserstoff bedeutet.
7. Verbindung nach Anspruch 1, worin entweder Z¹ oder Z² Wasserstoff bedeutet und das andere Hydroxy ist.
8. Verbindung nach Anspruch 1, worin Z¹ und Z² kombiniert Oxo darstellen.
9. Verbindung nach Anspruch 1, worin Z¹ und Z² zusammen eine Gruppe der Formel



bedeuten.

10. Verbindung der Formel 9, worin Y für Sauerstoff steht.
11. Verbindung nach Anspruch 1, worin X Wasserstoff ist, Ar für durch Halogen substituiertes Naphthyridinyl steht und Z¹ und Z² zusammen eine Gruppe der Formel



bedeuten, worin Y Sauerstoff darstellt und A ein unverzweigtes C₂₋₄ Alkyl ist.



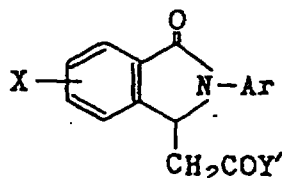
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12. Verbindung nach Anspruch 1, die 2-(7-Chlor-1,8-naphthyridin-2-yl)-3-(4-hydroxypiperidin-1-yl)-carbonylmethylisoindolin-1-on ist.

13. Verbindung nach Anspruch 1, die 2-(7-Chlor-1,8-naphthyridin-2-yl)-3-(4-piperidon-1-yl)carbonylmethylisoindolin-1-on ist.

14. Verbindung nach Anspruch 1, die 2-(7-Chlor-1,8-naphthyridin-2-yl)-3-(1,4-dioxa-8-azaspiro[4.5]-decan-8-yl)carbonylmethylisoindolin-1-on ist.

15. Verfahren zur Herstellung der Verbindung nach Anspruch 1, das das Kondensieren einer Verbindung der Formel



worin X und Ar die vorstehend angeführte Bedeutung besitzen und Y' Hydroxy oder ein reaktionsfähiges Derivat desselben darstellt, mit einer Verbindung der Formel

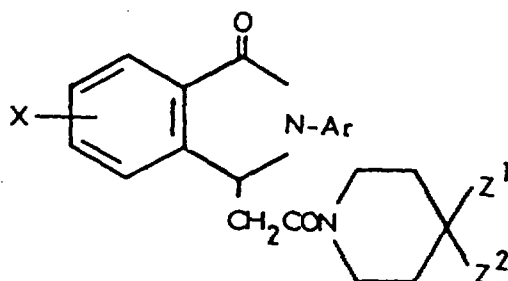


umfaßt, worin Z¹ und Z² die vorstehend angeführte Bedeutung besitzen.

16. Pharmazeutische Zusammensetzung, die eine für die Wirkung auf das zentrale Nervensystem ausreichende Menge der Verbindung nach Anspruch 1 und ein pharmazeutisch verträgliches Trägermittel, Vehikulum oder Verdünnungsmittel für diese enthält.

Patentansprüche für den Vertragsstaat: AT

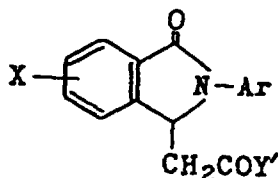
1. Verfahren zur Herstellung einer Verbindung der Formel



worin X Wasserstoff, Halogen oder Nitro ist; Ar gegebenenfalls durch ein oder zwei Substituenten gewählt aus Halogen, Hydroxy, C₁₋₄ Alkyl, C₁₋₄ Alkoxy, Nitro, Aminto, Methylendioxy, Phenoxy, Benzyloxy, C₂₋₅ Alkanoyloxy, α- oder ω-Hydroxy-C₁₋₄ Alkyl, Benzoyl, Amido, Cyano, Trifluormethyl, C₁₋₄ Alkylthio, C₂₋₅ Alkanoyloxy-C₁₋₃ Alkyl, C₂₋₅ Alkanoylamino und C₁₋₄ Alkoxycarbonyl substituiertes Phenyl oder Naphthyridinyl bedeutet; und entweder Z¹ oder Z² Wasserstoff und das andere C₁₋₄ Alkanoyloxy oder Hydroxy ist, Z¹ und Z² jeweils C₁₋₄ Alkoxy bedeuten oder Z¹ und Z² zusammen Hydroxyimino, Oxo oder eine Gruppe der Formel



darstellen, worin Y Sauerstoff oder Schwefel bedeutet und A eine verzweigte oder unverzweigte C₂₋₄ Alkylkette ist, die eine oder mehrere C₁₋₄ Alkylseitenketten aufweisen kann; oder ein Salz derselben, umfassend das Kondensieren einer Verbindung der Formel





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worin X und Ar die vorstehend angeführte Bedeutung besitzen und Y' Hydroxy oder ein reaktionsfähiges Derivat desselben darstellt, mit einer Verbindung der Formel

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worin Z¹ und Z² die vorstehend angeführte Bedeutung besitzen.

2. Verfahren nach Anspruch 1, worin Ar für Phenyl steht.
3. Verfahren nach Anspruch 1, worin Ar Naphthyridinyl ist.
4. Verfahren nach Anspruch 2, worin das Phenyl substituiertes C₁₋₄ Alkoxy bedeutet.
5. Verfahren nach Anspruch 3, worin das Naphthyridinyl durch Halogen und/oder C₁₋₄ substituiert ist.
6. Verfahren nach Anspruch 1, worin X Wasserstoff bedeutet.
7. Verfahren nach Anspruch 1, worin entweder Z¹ oder Z² Wasserstoff bedeutet und das andere Hydroxy ist.
8. Verfahren nach Anspruch 1, worin Z¹ und Z² kombiniert Oxo darstellen.
9. Verfahren nach Anspruch 1, worin Z¹ und Z² zusammen eine Gruppe der Formel

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bedeuten.

10. Verfahren nach Anspruch 9, worin Y für Sauerstoff steht.
11. Verfahren nach Anspruch 1, worin X Wasserstoff ist, Ar für durch Halogen substituiertes Naphthyridinyl steht und Z¹ und Z² zusammen eine Gruppe der Formel

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bedeuten, worin Y Sauerstoff darstellt und A ein unverzweigtes C₂₋₄ Alkyl ist.

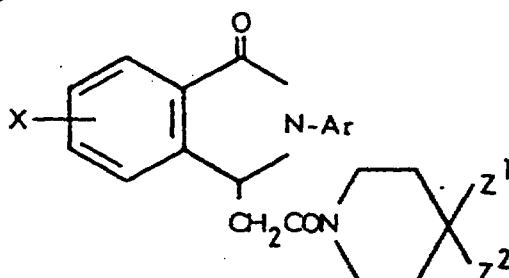
12. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 2-(7-Chlor-1,8-naphthyridin-2-yl)-3-(4-hydroxypiperidin-1-yl)carbonylmethylisindolin-1-on ist.
13. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 2-(7-Chlor-1,8-naphthyridin-2-yl)-3-(4-piperidon-1-yl)carbonylmethylisindolin-1-on ist.
14. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 2-(7-Chlor-1,8-naphthyridin-2-yl)-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)carbonylmethylisindolin-1-on ist.
15. Pharmazeutische Zusammensetzung, die eine für die Wirkung auf das zentrale Nervensystem ausreichende Menge der nach dem Verfahren nach einem der Ansprüche 1 bis 14 hergestellten Verbindung und ein pharmazeutisch verträgliches Trägermittel, Vehikulum oder Verdünnungsmittel für diese enthält.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

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1. Composé de formule

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dans laquelle X est l'hydrogène, un halogène ou un groupe nitro; Ar est un groupe phényle ou naphthyridinyle qui peut porter un ou deux substituants choisis parmi les halogènes, l'hydroxy, les groupes C₁₋₄-alkyle, C₁₋₄-alkoxy, nitro, amino, méthylènedioxy, phénoxy, benzyloxy, C₂₋₅-alkanoyloxy, — ou -hydroxy-C₁₋₄-alkyle, benzoyle, amido, cyano, trifluorométhyle, C₁₋₄-alkylthio, C₂₋₅-alkanoyloxy-C₁₋₃-alkyle, C₂₋₅ alkanoylamino et C₁₋₄ alkoxy-carbonyl; et l'un ou l'autre de Z¹ et Z² est l'hydrogène et l'autre est un groupe C₁₋₄-alkanoyloxy ou hydroxy, ou l'un et l'autre de Z¹ et Z² sont des groupes C₁₋₄-alkoxy ou Z¹ et Z² ensemble représentent un groupe hydroxyimino, oxo ou un groupe de formule:

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dans laquelle Y est l'oxygène ou le soufre et A est une chaîne C_2-C_4 -alkylène ramifiée ou non ramifiée qui peut porter une ou plusieurs chaînes latérales C_1-C_4 -alkyle; ou un sel de celui-ci.

2. Composé selon la revendication 1, dans lequel Ar est un phényle.

3. Composé selon la revendication 1, dans lequel Ar est un naphtyridinyle.

5 4. Composé selon la revendication 2, dans lequel le phényle est substitué par un C_1-C_4 -alkoxy.

5. Composé selon la revendication 3, dans lequel le naphtyridinyle est substitué par un halogène ou/et un C_1-C_4 -alkyle.

6. Composé selon la revendication 1, dans lequel X est l'hydrogène.

10 7. Composé selon la revendication 1, dans lequel l'un ou l'autre de Z^1 et Z^2 est l'hydrogène et l'autre est l'hydroxy.

8. Composé selon la revendication 1, dans lequel Z^1 et Z^2 ensemble représentent un groupe oxo.

9. Composé selon la revendication 1, dans lequel Z^1 et Z^2 ensemble représentent un groupe de formule:



10. Composé selon la revendication 9, dans lequel Y est l'oxygène.

20 11. Composé selon la revendication 1, dans lequel X est l'hydrogène, Ar est un naphtyridinyle qui est substitué par un halogène et Z^1 et Z^2 ensemble représentent un groupe de formule:



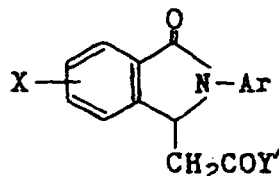
dans laquelle Y est l'oxygène et A est un C_2-C_4 -alkylène non ramifié.

12. Composé selon la revendication 1, qui est la 2-(7-chloro-1,8-naphtyridin-2-yl)-3-(4-hydroxy-pipéridin-1-yl)carbonylméthylisoindolin-1-one.

13. Composé selon la revendication 1, qui est la 2-(7-chloro-1,8-naphtyridin-2-yl)-3-(4-pipéridon-1-yl)-carbonylméthylisoindolin-1-one.

14. Composé selon la revendication 1, qui est la 2-(7-chloro-1,8-naphtyridin-2-yl)-3-(1,4-dioxa-8-azaspiro(4,5)décan-8-yl)carbonylméthylisoindolin-1-one.

15. Procédé de préparation du composé selon la revendication 1, qui comprend la condensation d'un composé de formule:



dans laquelle X et Ar sont tels que défini ci-dessus et Y' est l'hydroxy ou un dérivé réactif de celui-ci, avec un composé de formule:

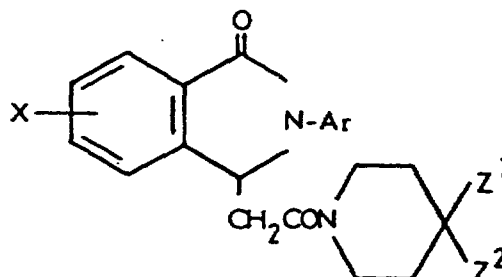


dans laquelle Z^1 et Z^2 sont tels que défini ci-dessus.

16. Composition pharmaceutique qui contient une quantité efficace pour une action sur le système nerveux central, du composé selon la revendication 1 et une matière de support, un véhicule ou diluant pharmaceutiquement acceptable pour ledit composé.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule:



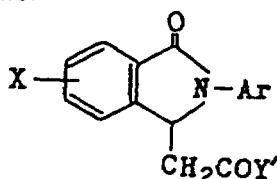


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dans laquelle X est l'hydrogène, un halogène ou un groupe nitro; Ar est un groupe phényle ou naphtyridinyle qui peut porter un ou deux substituants choisis parmi les halogènes, l'hydroxy, les groupes C₁₋₄-alkyle, C₁₋₄-alkoxy, nitro, amino, méthylènedioxy, phénoxy, benzyloxy, C₂₋₅-alkanoyloxy, — ou -hydroxy-C₁₋₄-alkyle, benzoyle, amido, cyano, trifluorométhyle, C₁₋₄-alkylthio, C₂₋₅-alkanoyloxy-C₁₋₃-alkyle, C₂₋₅ alkanoylamino et C₁₋₄ alkoxy-carbonyl; et l'un ou l'autre de Z¹ et Z² est l'hydrogène et l'autre est un groupe C₁—C₄-alkanoyloxy ou hydroxy, ou l'un et l'autre de Z¹ et Z² sont des groupes C₁—C₄-alkoxy ou Z¹ et Z² ensemble représentent un groupe hydroxyimino, oxo ou un groupe de formule:



dans laquelle Y est l'oxygène ou le soufre et A est une chaîne C₂—C₄-alkylène ramifiée ou non ramifiée qui peut porter une ou plusieurs chaînes latérales C₁—C₄-alkyle; ou d'un sel de celui-ci, qui comprend la condensation d'un composé de formule:



dans laquelle X et Ar sont tels que définis ci-dessus et Y' est l'hydroxy ou un dérivé réactif de celui-ci, avec un composé de formule:



dans laquelle Z¹ et Z² sont tels que définis ci-dessus.

2. Procédé selon la revendication 1, dans lequel Ar est un phényle.
3. Procédé selon la revendication 1, dans lequel Ar est un naphtyridinyle.
4. Procédé selon la revendication 2, dans lequel le phényle est substitué par un C₁₋₄-alkoxy.
5. Procédé selon la revendication 3, dans lequel le naphtyridinyle est substitué par un halogène ou/et un C₁₋₄-alkyle.
6. Procédé selon la revendication 1, dans lequel X est l'hydrogène.
7. Procédé selon la revendication 1, dans lequel l'un ou l'autre de Z¹ et Z² est l'hydrogène et l'autre est l'hydroxy.
8. Procédé selon la revendication 1, dans lequel Z¹ et Z² ensemble représentent un groupe oxo.
9. Procédé selon la revendication 1, dans lequel Z¹ et Z² ensemble représentent un groupe de formule:



10. Procédé selon la revendication 9, dans lequel Y est l'oxygène.
11. Procédé selon la revendication 1, dans lequel X est l'hydrogène, Ar est un naphtyridinyle qui est substitué par un halogène et Z¹ et Z² ensemble représentent un groupe de formule:



dans laquelle Y est l'oxygène et A est un C₂₋₄-alkylène non ramifié.

12. Procédé selon la revendication 1, dans lequel le composé produit est la 2-(7-chloro-1,8-naphtyridin-2-yl)-3-(4-hydroxypipéridin-1-yl)carbonylméthylisindolin-1-one.
13. Procédé selon la revendication 1, dans lequel le composé produit est la 2-(7-chloro-1,8-naphtyridin-2-yl)-3-(4-pipéridon-1-yl)carbonylméthylisindolin-1-one.
14. Procédé selon la revendication 1, dans lequel le composé produit est la 2-(7-chloro-1,8-naphtyridin-2-yl)-3-(1,4-dioxa-8-azaspiro(4,5)décan-8-yl)carbonylméthylisindolin-1-one.
15. Composition pharmaceutique qui contient une quantité efficace pour une action sur le système nerveux central, du composé préparé par le procédé selon l'une quelconque des revendications 1 à 14 et une matière de support, un véhicule ou diluant pharmaceutiquement acceptable pour ce composé.