SPOOR & FISHER

FORM P.8
(To be lodged in duplicate)

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

PUBLICATION PARTICULARS AND ABSTRACT

(Section 32(3)(a) – Regulation 22(1)(g) and 31)

OFFICIAL APPLICATION NO.			LODGING DATE		ACCEPTANCE DATE	
21	01	2003/2452	22	10 OCT 2001	43	24 3 04

INTERNATIONAL CLASSIFICATION		NOT FOR PUBLICATION
51	C07D; A61K; A61P	CLASSIFIED BY: WIPO

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EARLIEST PRIORITY CLAIMED

COUNTRY		NUMBER		DATE	
33	ES	31	P 200002532	32	20 OCT 2000

TITLE OF INVENTION

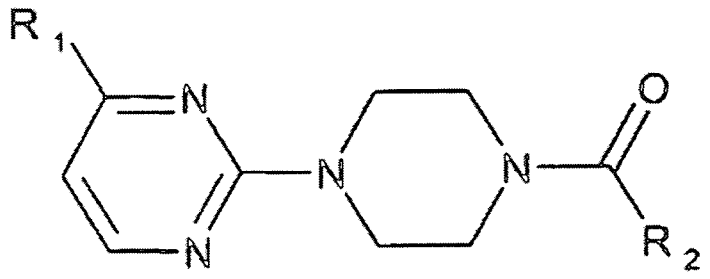
54	DERIVATIVES OF CYANO-ARYL (OR CYANOHETEROARYL)-CARBONYL-PIPERAZINYL-PYRIMIDINES, THEIR PREPARATION AND APPLICATION AS MEDICATION

57	ABSTRACT (NOT MORE THAT 150 WORDS)	NUMBER OF SHEETS	53

If no classification is finished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

Abstract

The invention relates to new derivatives of cyano-aryl (or cyanoheteroaryl)-carbonyl-piperazinyl-pyrimidines (I), wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical deriving from a saturated hydrocarbon with a linear or branched chain of 1 to 4 carbon atoms and R_2 represents a phenyl radical substituted at least by a cyano radical (-C≡N), or a radical of a 5 or 6-membered heteroaromatic ring substituted by at least one cyano radical (-C≡N). The physiologically acceptable salts of said derivatives can be used in human and/or veterinary therapeutic applications as sedatives, anticonvulsivants, hypnotics and general anesthetics.

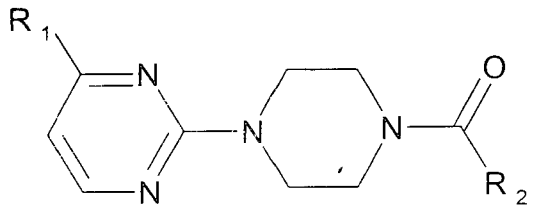


(I)

NEW DERIVATIVES OF CYANO-ARYL (OR CYANOHETEROARYL)-CARBONYL-PIPERAZINYL-PYRIMIDINES, THEIR PREPARATION AND APPLICATION AS MEDICATION

Field of the invention

The present invention relates to new cyanoaryl (or cyanoheteroaryl)-carbonyl-piperazinyl-pyrimidines, with the general formula (I), as well as to their physiologically acceptable salts, to their preparation procedures, their application as medicines in human and/or veterinary therapeutic use and the pharmaceutical compositions which contain them.



(I)

The new compounds object of the present invention may be used in the pharmaceutical industry as intermediates and to prepare medications.

Background of the invention

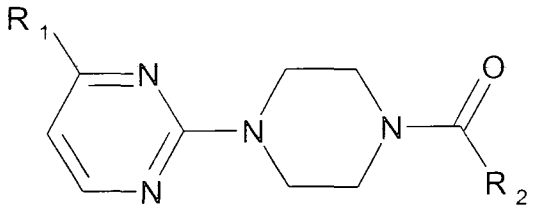
In our patent application WO 99/05121 we describe several derivatives of acyl-piperazinyl-pyrimidines, among which are the compounds with general formula (I), as products with sedative, anticonvulsivant, hypnotic and general anaesthetic activity. In said patent derivatives with the general formula (I) are described, in which R_2 represents, among others, an aryl radical and a heteroaryl radical. The term "aryl" represents a phenyl radical, not substituted or substituted by 1, 2 or 3 like or different substituents, such as fluorine, chlorine, bromine, amine, acetamide, nitro, methyl, trifluoromethyl or methoxy. The term "heteroaryl" represents a heteroaromatic ring of 5 or 6 members substituted or not substituted, or fused heteroaromatic systems of 9 or 10 members substituted or not substituted comprising 1 or 2 heteroatoms such as nitrogen, oxygen or sulphur, with the substituents being groups such as fluorine, chlorine, bromine, amine, acetamide, nitro, methyl, trifluoromethyl or methoxy.

We have now discovered that the introducion of a cyano group (-C≡N) in aryl or heteroaryl radicals results in new compounds with the general formula (I) which are more powerful than those previously described, having interesting biological properties which make them particularly suitable for use in human and/or veterinary therapeutics. The compounds object of this invention are useful as agents which are active on the central nervous system of mammals, including man. Specifically, the new compounds are useful as sedatives, anticonvulsivants, hypnotics and general anaesthetics.

Detailed description of the invention

The present invention provides new compounds with the following properties: sedative, anticonvulsivant, analgesic, muscular relaxant, antitussive, anxiolytic, antipsychotic, antidepressive, anti-cerebral ischaemia, antimigraine, for sleep disorders, for neurodegenerative diseases, cognitive disorders and Alzheimer's disease, hypnotic or general anaesthetic in mammals, including man. Specifically, the new compounds of the invention are capable of causing conscious sedation, acting as hypnotic agents and agents capable of bringing about or maintaining general anaesthesia, depending on the dose and route of administration.

The compounds object of the present invention have the general formula (I)



(I)

wherein R_1 represents an alkoxy radical and R_2 represents a cyanoaryl or a cyanoheteroaryl radical.

In the present invention the term "alkoxy" represents an OR_3 radical, wherein R_3 is alkyl C_1-C_4 (i.e., an alkyl radical deriving from a saturated hydrocarbon with a linear or branched chain with 1 to 4 carbon atoms), such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy or *tert*-butoxy.

The term "cyanoaryl" represents a phenyl radical substituted by at least one cyano radical (-C≡N).

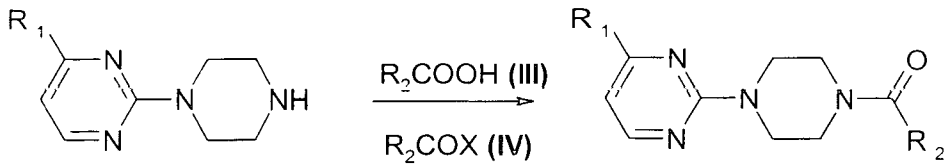
The term "cyanoheteroaryl" represents a radical of a heteroaromatic ring of 5 or 6 members or a radical of fused heteroaromatic systems of 9 or 10 members substituted or not substituted comprising 1 or 2 heteroatoms such as nitrogen, oxygen or sulphur, all of them substituted at least by a cyano radical (-C≡N), such as, for example, 3-cyano-2-furyl, 3-cyano-2-thienyl, 5-cyano-2-thienyl, 3-cyano-2-pirrolyl, 3-cyano-2-pyridyl, 2-cyano-3-pyridyl, 2-cyano-4-pyridyl, 3-cyano-2-indolyl, 2-cyano-3-indolyl, 3-cyano-2-benzo[b]thienyl or 2-cyano-3-benzo[b]thienyl.

The present invention also relates to the physiologically acceptable salts of the compounds with the general formula (I), particularly to the salts from addition of mineral acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, and organic acids such as *p*-toluensulphonic or metansulphonic acid.

The new derivatives of general formula (I) can be prepared by the methods A-G indicated below:

METHOD A:

Compounds with the general formula (I) can be obtained by reaction of the amine with general formula (II), in which R_1 is as described above, with a carboxylic acid with general formula R_2COOH (III), in which R_2 has the above described meaning, or with a salt of this acid or a reaction derivative R_2COX (IV), (Diagram 1).



(II) **(I)**

Diagram 1

Examples of these salts include salts of alkali metals, such as sodium and potassium salts, alkaline-earth metals such as calcium and magnesium salts,

ammonium salt and salts of organic bases such as triethylamine, trimethylamine, pyridine and picoline.

Examples of reaction derivatives with the general formula R_2COX (IV) include those in which X is a halogen atom, preferably a chlorine or bromine atom, an azide group ($-N_3$), a 1-imidazolyl group, an O-CO-R_4 group, wherein R_4 can be an alkyl radical with 1 to 6 carbon atoms or an aryl radical, optionally substituted by one or more halogen atoms, or an OR_5 group, wherein R_5 represents an aromatic group with one or two rings, substituted by one or more halogen atoms or nitro radicals, preferably by the groups 4-nitrophenyl, 2,4-dinitrophenyl, pentachlorophenyl, pentafluorophenyl, 1-benzotriazolyl or N-succinimide. Likewise, instead of using the aforementioned reaction derivatives the compounds with the general formula (I) can be prepared directly by reaction of the amine (II) with a carboxylic acid with the general formula R_2COOH (III), in which case it is preferable to have the reaction occur in the presence of carbonyl group activation reagents, such as N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide or 3-(3-dimethylamino)propyl-1-ethylcarbodiimide. This reaction can also take place using the aforementioned carbodiimides in the presence of 1-benzotriazole or N-hydroxysucciminide. Acids with the general formula (III) and the amine with the general formula (II) also react directly in the presence of N,N'-carbonyldiimidazole or of the anhydride of propanophosphonic acid.

The reaction occurs in an organic solvent, for example an organic chlorinated hydrocarbon, such as dichloromethane or chloroform, a linear or cyclic ether such as 1,2-dimethoxyethane, tetrahydrofuran or dioxane, a polar aprotic solvent such as pyridine, dimethylsulphoxide, acetonitrile or dimethylformamide, or any other suitable solvent. The reaction may occur in the presence of a mineral or organic base, such as an aliphatic amine, preferably triethylamine or N-methylmorpholine and is stirred at a temperature between room temperature and the boiling point of the solvent for a period between ten minutes and twenty-four hours, with the preferred conditions being between thirty minutes and five hours.

METHOD B:

The new derivatives with the general formula (I), wherein R_1 is as described above and R_2 represents a cyanoaryl radical, can be prepared according to the

method shown in Diagram 2:

The reaction of the amine with the general formula (II), wherein R_1 is as described above, with 3-bromophtalide (V) provides the aldehyde with the general formula (VI), wherein R_1 is as described above (Alonso, R., Castedo, L., Domínguez, D., J. Org. Chem. 1989, 54 (2), 424).

The reaction takes place in an organic solvent, for example an organic chlorinated hydrocarbon such as dichloromethane or chloroform, a linear or cyclic ether such as 1,2-dimethoxyethane, tetrahydrofuran or dioxane, a polar aprotic solvent such as pyridine, dimethylsulphoxide, acetonitrile or dimethylformamide, or any other suitable solvent. The reaction may occur in the presence of a mineral or organic base, such as an aliphatic amine, preferably triethylamine or N-methylmorpholine and is stirred at a temperature between room temperature and the boiling point of the solvent for a period between ten minutes and twenty-four hours, with the preferred conditions being between thirty minutes and five hours.

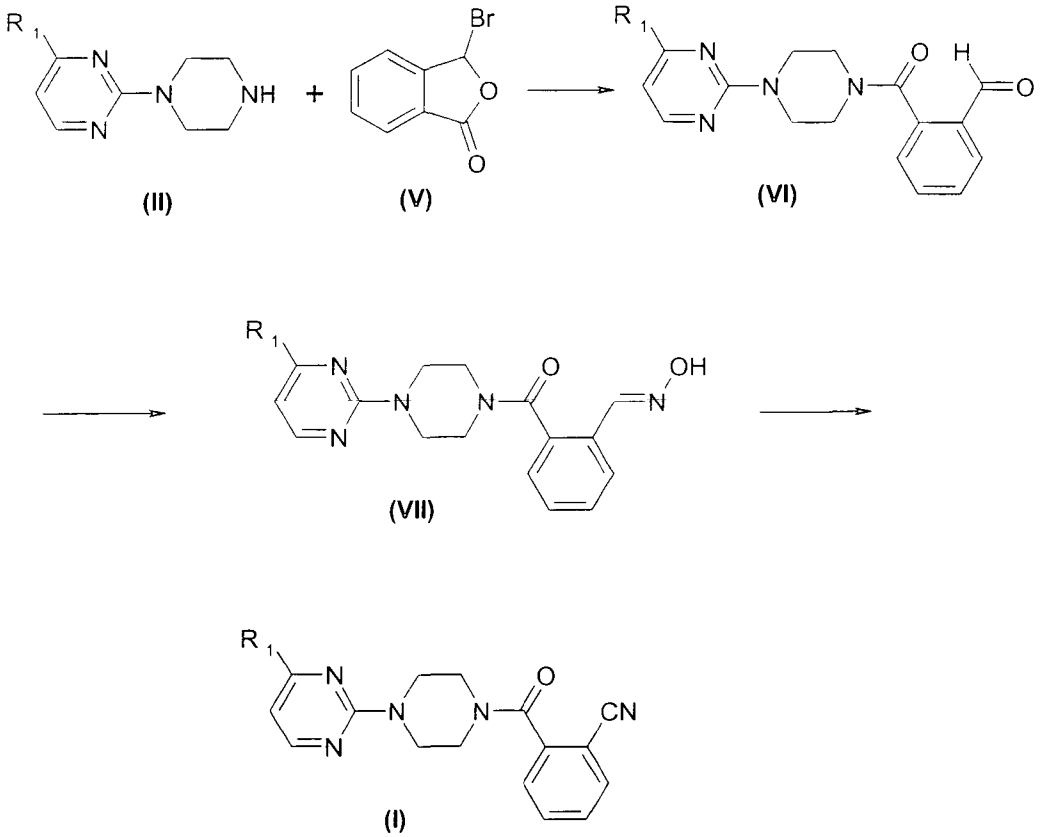


Diagram 2

The oxime with general formula (VII), in which R_1 is as described above, is obtained by the reaction of the aldehyde with general formula (VI) with hydroxylamine or a hydroxylamine salt. The reaction takes place in an organic solvent such as ethanol, or a mixture of ethanol and water or any other suitable solvent. The reaction occurs in the presence of a base such as sodium hydroxide, sodium carbonate or sodium acetate, or an aliphatic amine, preferably pyridine, triethylamine or N-methylmorpholine and is stirred at a temperature between the room temperature and the boiling point of the solvent for a period between one hour and twenty-four hours.

The transformation of the oxime with the general formula (VII), in which R_1 is as described above, into the cyano derivative with general formula (I) wherein R_1 is as described above is obtained by the reaction of the oxime (VII) with several dehydration reagents, such as $(PhO)_2PHO$, p-$ClC_6H_4OC(=S)Cl$, N,N'-carbonyldiimidazole, as well as in the presence of Cu(II) ions such as $Cu(AcO)_2$, or by acylation of the aldoxime with acetic anhydride or trifluoroacetic anhydride and later formation of the cyano radical with bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, pyridine or triethylamine. The reaction takes place at a temperature between room temperature and the boiling point of the solvent for a period between one hour and 4 days.

METHOD C:

The new derivatives with the general formula (I), wherein R_1 is as described above and R_2 represents a cyanoaryl or cyanopyridyl radical can be prepared according to the method represented in Diagram 3:

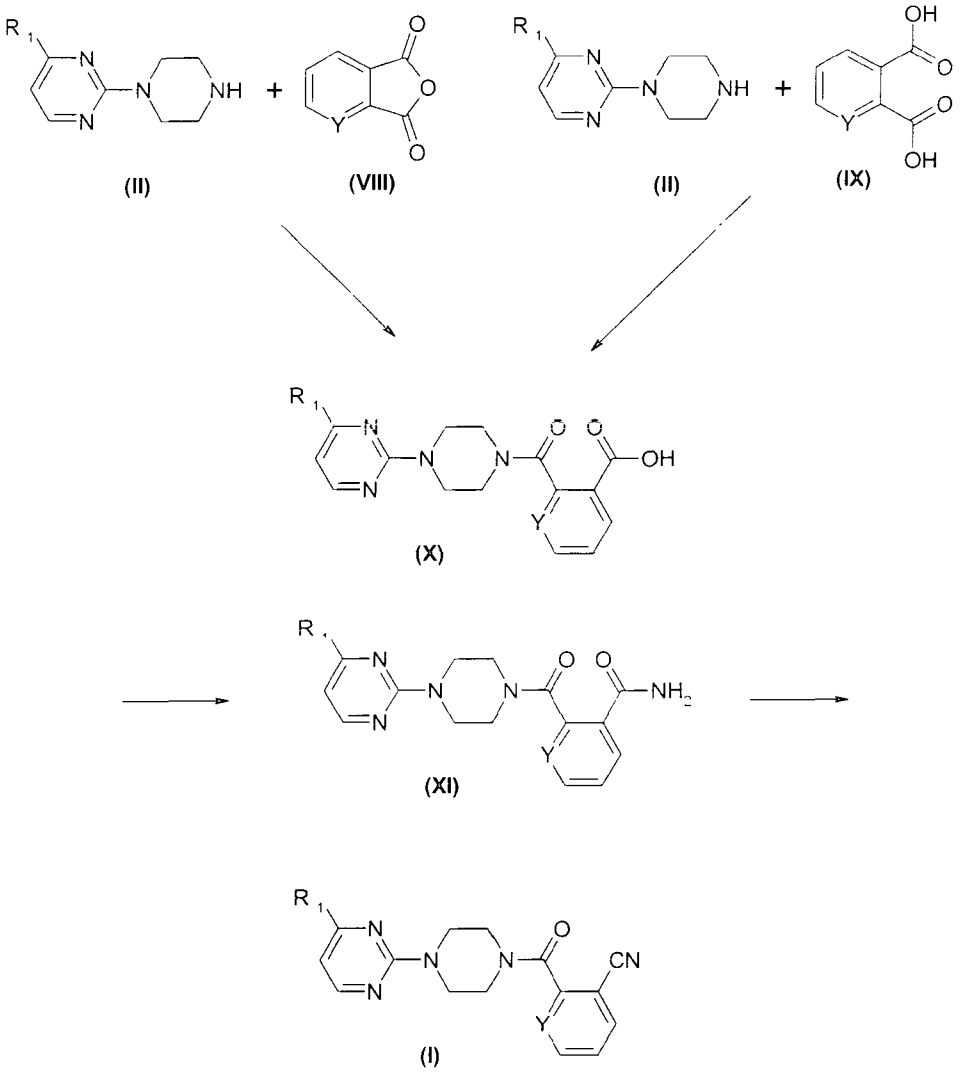


Diagram 3

The reaction of the amine with general formula (II), in which R_1 is as described above, with an anhydride with the general formula (VIII) wherein Y represents a nitrogen atom (N) or an aromatic carbon atom joined to a hydrogen atom (CH), or the reaction of the amine with the general formula (II), in which R1 is as described above, with an acid with the general formula (IX) wherein Y represents a nitrogen atom (N) or an aromatic carbon atom joined to a hydrogen atom (CH) produces the acid with the general formula (X) wherein R_1 and Y are as described above.

The reaction with the anhydride (VIII) takes place in an organic solvent, for example an organic chlorinated hydrocarbon such as dichloromethane or

chloroform, a linear or cyclic ether such as 1,2-dimethoxyethane, tetrahydrofuran or dioxane, a polar aprotic solvent such as pyridine, dimethylsulphoxide, dimethylformamide, or acetonitrile or any other suitable solvent. The reaction may occur in the presence of a mineral or organic base, such as an aliphatic amine, preferably triethylamine or N-methylmorpholine and is stirred at a temperature between room temperature and the boiling point of the solvent for a period between ten minutes and twenty-four hours, with the preferred conditions being between thirty minutes and five hours.

The reaction of the acid with general formula (IX) takes place in the presence of carbonyl group activation reagents such as N,N'-dicyclohexycarbodiimide, N,N'-diisopropylcarbodiimide or 3-(3-dimethylamino)propyl-1-ethylcarbodiimide. This reaction can also occur using said carbodiimides in the presence of 1-benzotriazole or N-hydroxysucciminide or by reaction of the acid (IX) with reagents such as thionyl chloride, oxalyl chloride, ethyl chloroformiate, pivaloyl chloroformiate or methansulfonyl chloride. The acid with the general formula (IX) and the amine with the general formula (II) also react directly in the presence of N,N'-carbonyldiimidazole or the anhydride of propanophosphonic acid. The reaction occurs in an organic solvent such as methylene chloride, chloroform, pyridine or any other suitable solvent. The reaction occurs in the presence of a base such as sodium hydroxide, sodium carbonate or sodium acetate or an aliphatic amine, preferably pyridine, triethylamine or N-methylmorpholine and is stirred at a temperature between the room temperature and the boiling point of the solvent for a period between one hour and twenty-four hours.

The amide with the general formula (XI), in which R_1 and Y are as indicated above, is obtained by reacting the acid with the general formula (X) with carbonyl group activation reagents and later treatment with ammonia. Activation of the carbonyl group of the acid with the general formula (X) is obtained by reacting (X) with reactants such as thionyl chloride, oxalyl chloride, ethyl chloroformiate, pivaloyl chloroformiate or methansulfonyl chloride. The reaction of the acid (X) with ammonia can also take place in the presence of carbonyl group activation reagents such as N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide or 3-(3-dimethylamino)propyl-1-ethylcarbodiimide. This reaction can also occur using the aforementioned carbodiimides in the presence of 1-benzotriazole or N-

hydroxysucciminide. The acid with the general formula (X) and the ammonia also react directly in the presence of N,N'-carbonyldiimidazole. The reaction occurs in an organic solvent such as methylene chloride, chloroform, pyridine or any other suitable solvent. The reaction occurs in the presence of a base such as sodium hydroxide, sodium carbonate or sodium acetate, an aliphatic amine, preferably pyridine, triethylamine or N-methylmorpholine and is stirred at a temperature between room temperature and the boiling point of the solvent for a period between one and twenty-four hours.

The transformation of the amide with the general formula (XI), in which R_1 and Y are as described above, into the cyano derivative with the general formula (I) wherein R_1 and Y are as described above is achieved by dehydration of the amide (XI) with several reagents, such as thionyl chloride, oxalyl chloride, trifluoroacetic anhydride, catalytic Bu_2SnO or preferably methansulfonyl chloride (A.D. Dunn, M.J. Mills and W. Henry, Org. Prep. Proced. Int., 1982 Vol. 14(6) 396-399) or other dehydration reagents. The reaction occurs in an organic solvent such as dimethylformamide, methylene chloride, toluene and in the presence of a base such as triethylamine or pyridine at a temperature between 0°C and the boiling point of the solvent for a period between one hour and twenty-four hours.

METHOD D:

The new derivatives with the general formula (I), wherein R1 is as described above and R_2 represents a cyanoaryl or cyanopyridyl radical can be prepared according to the method represented in Diagram 4.

By reaction of the amine with the general formula (II), in which R1 is as described above, with a carboxylic acid with the general formula (XII), wherein R_6 represents an alkyl radical such as methyl or ethyl and Y represents a nitrogen atom (N) or an aromatic carbon atom joined to a hydrogen atom (CH), the amide with the general formula (XIII) is obtained wherein R_1, R_6 and Y are as described above.

The reaction takes place by treating the acid with general formula (XII) with activation reactants for the carbonyl group and later treatment with the amine with the general formula (II). The activation of the carbonyl group of the acid with the general formula (XII) is achieved by treatment with reagents such as thionyl chloride, oxalyl chloride, ethyl chloroformiate, pivaloyl chloroformiate or

methansulphonyl chloride. The reaction of the acid (XII) and the amine with the general formula (II) can also occur in the presence of carbonyl group activation reagents such as N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide or 3-(3-dimethylamino)propyl-1-ethylcarbodiimide. This reaction can also be effected with the aforementioned carbodiimides in the presence of 1-benzotriazole or N-hydroxysucciminide. The acid with the general formula (XII) and the amine (II) also react directly in the presence of N,N'-carbonyldiimidazole or the anhydride of propanophosphonic acid. The reaction takes place in an organic solvent such as methylene chloride, chloroform, pyrimidine or any other suitable solvent. The reaction occurs in the presence of a base such as sodium hydroxide, sodium carbonate, sodium acetate or an aliphatic amine, preferably pyrimidine, triethylamine or N-methylmorpholine and is stirred at a temperature between the room temperature and the boiling point of the solvent for a period between one hour and twenty-four hours.

The hydrolysis of the ester group of the amide with the general formula (XIII), in which R_1, R_6 and Y are as described above leads to formation of the acid with the general formula (XIV) wherein R_1 and Y are as described above. Hydrolysis is achieved by conventional methods, such as saponification with sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate or potassium carbonate or by hydrolysis in an acid medium, such as hydrochloric acid. The reaction occurs in a solvent such as methanol, ethanol, water, tetrahydrofuran or in a mixture thereof at a temperature between room temperature and the boiling point of the solution for a period between one hour and twenty-four hours.

The amide with the general formula (XV) in which R_1 and Y are as described above is obtained by reaction of the acid with the general formula (XIV) with carbonyl group activation reactants and later treatment with ammonia. The activation of the carbonyl group of the acid with the general formula (XIV) is achieved by reagents such as thionyl chloride, oxalyl chloride, ethyl chloroformiate, pivaloyl chloroformiate or methansulphonyl chloride. Reaction of the acid (XIV) with ammonia can also occur in the presence of carbonyl group activation reactants such as N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide or 3-(3-dimethylamino)propyl-1-ethylcarbodiimide. This reaction can also take place with the aforementioned carbodiimides in the presence of 1-benzotriazole or N-

hydroxysuccinimide. The acid with the general formula (XIV) and ammonia also react directly in the presence of N,N'-carbonyldiimidazole. The reaction occurs in an organic solvent such as methylene chloride, chloroform or pyridine, or any other suitable solvent. The reaction occurs in the presence of a base such as sodium hydroxide, sodium carbonate, sodium acetate or an aliphatic amine, preferably pyridine, triethylamine or N-methylmorpholine and is stirred at a temperature between the room temperature and the boiling point of the solvent for a period between one hour and twenty-four hours.

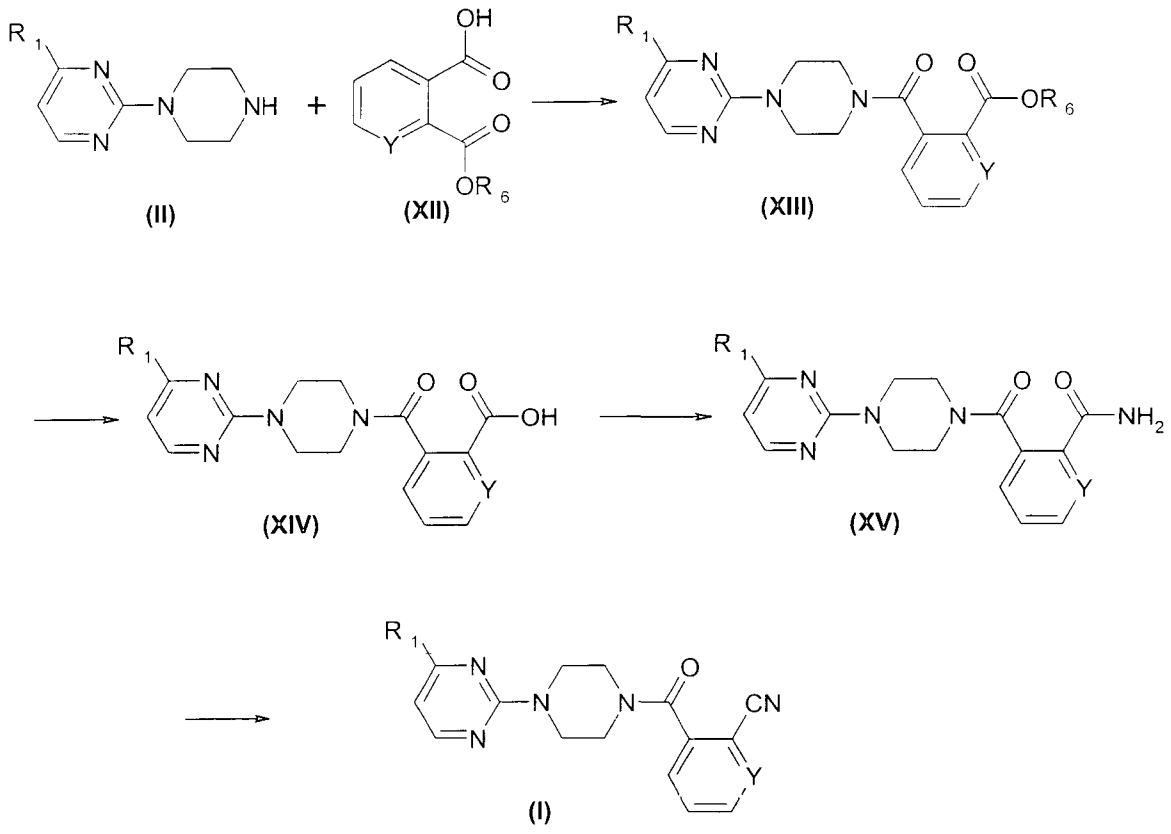


Diagram 4

The transformation of the amide with the general formula (XV), in which R_1 and Y are as described above, into the cyano derivate with the general formula (I), wherein R_1 and Y are as described above, is achieved by dehydration of the amide (XV) by several reagents such as thionyl chloride, oxalyl chloride, trifluoroacetic

anhydride, catalytic Bu_2SnO or preferably methansulfonyl chloride (A.D. Dunn, M.J. Mills and W. Henry, Org. Prep. Proced. Int., 1982 Vol. 14(6) 396-399) or other dehydration reactants. The reaction takes place in an organic solvent such as DMF, methylene chloride or toluene and in the presence of a base such as triethylamine or pyridine at a temperature between 0°C and the boiling point of the solvent for a period between one hour and twenty-four hours.

METHOD E:

The new derivatives with the general formula (I), wherein R1 is as described above and R_2 represents cyanothienyl or cyanofuryl radical can be prepared by the method represented in Diagram 5:

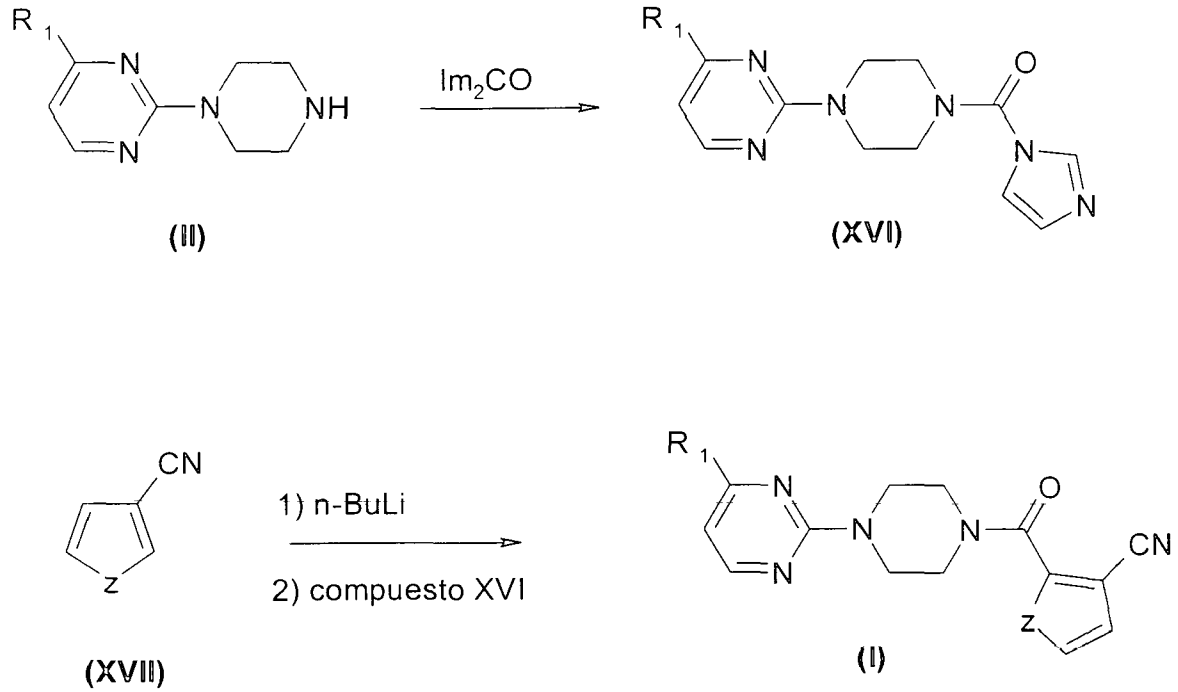


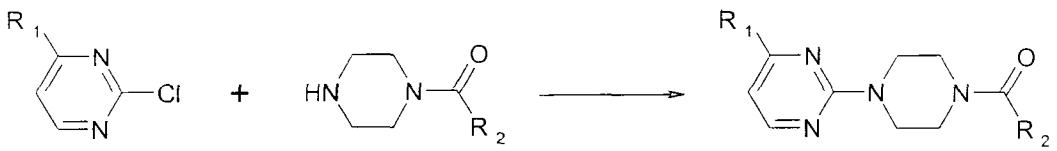
Diagram 5

The reaction of the amine with the general formula (II), in which R_1 is as described above, with N,N'-carbonyldiimidazole gives the compound with the general formula (XVI). The reaction takes place in an anhydrous organic solvent, such as tetrahydrofuran or dimethylformamide, at a temperature ranging between 0°C and room temperature for a time between one and twenty-four hours.

The metallation of a compound with the general formula (XVII) wherein Z represents a sulphur atom (S) or an oxygen atom (O) with *n*-BuLi, *sec*-BuLi or *tert*-BuLi in an anhydrous solvent such as tetrahydrofuran at a temperature of -78°C and later addition of the compound (XVI) gives the cyano derivative with the general formula (I), wherein R_1 and Z are as described above.

METHOD F:

The new derivatives with general formula (I), wherein R_1 and R_2 are as described above, can be obtained by reaction of the chloropyrimidine derivative with the general formula (XVIII), wherein R_1 is as described above, with a piperazine derivative with the general formula (XIX), wherein R_2 is as described above, according to the method represented in Diagram 6:



(XVIII) **(XIX)** **(I)**

Diagram 6

The reaction takes place in an organic solvent, such as a chlorinated organic hydrocarbon as dichloromethane or chloroform, a linear or cyclic ether such as 1,2-dimethoxyethane, tetrahydrofuran or dioxane, an aprotic polar solvent such as pyridine, dimethylsulphoxide, dimethylformamide or acetonitrile, a protic polar solvent such as methanol, ethanol, isopropanol or n-butanol or any other suitable solvent for effecting an aromatic nucleophilic substitution reaction. The reaction may take place in the presence of a mineral base such as sodium carbonate or potassium carbonate, or an organic one such as an aliphatic amine, preferably triethylamine or N-methylmorpholine and is stirred at a temperature between the room temperature and the boiling point of the solvent for a period ranging between ten minutes and twenty-four hours, with the period between thirty minutes and five hours being the preferred conditions.

METHOD G:

Salts of compounds with the general formula (I) are prepared by reaction with a mineral acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid or with an organic acid such as *p*-toluensulphonic acid or methansulphonic acid in a suitable solvent, such as methanol, ethanol, ethyl ether, ethyl acetate or acetone, with the corresponding salts obtained by the conventional precipitation or crystallisation techniques.

The carboxylic acids used in the preparation of the cyano derivatives with the general formula (I), wherein R_1 and R_2 are as described above, according to the methods described in the present invention are commercially available or have been prepared by several procedures described in the scientific literature (Kenneth A. Hold and Phillip Shadbolt, Br. Polym. J., 1983, 15 (4), 201-207; Carol K. Sauers and Robert J. Cotter, J. Org. Chem., 1961, 26, 6-10; Louis A. Carpino, J. Am. Chem. Soc., 1962, 84, 2196-2201; A.D. Dunn, M.J. Mills and W. Henry, Org. Prep. Proced. Int., 1982, 14(6), 396-399; Pierre Dubus, Bernard Decroix, Jean Morel et Paul Pastour, Bull. Soc. Chim. Fr., 1976. (3-4. Pt. 2), 628-634; William M. Murray and J. Edward Semple, Synthesis, 1996, 1180-1182; Luc I. M. Spiessens and Marc J. OR. Anteunis, Bull. Soc. Chim. Belg., 1980, 89 (3), 205-231; I. Thunus et M. Dejardin-Duchêne, J. Pharm. Belg., 1969, 51, 3-21; S. Fallab und H. Erlenmeyer, Helv. Chim. Acta, 1951, 34, 488-496).

The following examples describe the preparation of new compounds in accordance with the invention. Also described are some typical uses in the various fields of application, as well as galenical formulations applicable to the compounds object of the invention.

The methods described below are provided for purposes of illustration only and should not be taken as a definition of the limits of the invention.

METHOD A:

Example 1.- Preparation of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-methoxypyrimidine.

To a suspension of 2.0 g (14 mmol) of 2-cyanobenzoic acid in 100 mL of CH_2Cl_2 are added 1.5 mL (17.5 mmol) of oxalyl chloride and a catalytic amount of pyridine. The suspension is left stirred at room temperature for 3 hours. The solvent is evaporated at reduced pressure, giving a crude which is suspended in 100 mL of CH_2Cl_2 and which is slowly added on a solution of 2.45 g (12.6 mmol) of 4-methoxy-2-(1-piperazinyl)pyrimidine and 4 mL (28 mmol) of triethylamine in 50 mL of CH_2Cl_2 cooled to 0°C in an ice bath. The solution is kept at 0°C for one hour and is allowed to reach room temperature. The reaction mixture is washed with H_2O, dried with Na_2SO_4 and the solvent removed at reduced pressure. The resulting crude is purified by chromatography on silica gel, using ethyl acetate as eluent, providing 2.06 g (6.4 mmol) of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-methoxipyrimidine with m.p. = 166-168°C.

METHOD B:

Example 3: Preparation of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine.

To a solution of 2.08 g (10 mmol) of 4-ethoxy-2-(1-piperazinyl)pyrimidine and 5 mL of triethylamine in 60 mL of dry THF are added 2.15 g (10 mmol) of 3-bromophtalide and kept stirred at room temperature for 4 hour. The triethylamine hydrobromide is filtered and washed with THF, and the solvent removed at reduced pressure, providing a crude which is purified by chromatography on silica gel, using ethyl acetate as eluent, yielding 2.45 g (7.20 mmol) of 4-ethoxy-2-[4-(2-formylbenzoyl)-1-piperazinyl]pyrimidine with m.p.= 134-136°C.

To a solution of 2.45 g (7.2 mmol) of 4-ethoxy-2-[4-(2-formylbenzoyl)-1-piperazinyl]pyrimidine in ethanol-H_2O (80:20) are added 2.5 g (18.4 mmol) of AcONax3H_2O and 0.75 g (8.6 mmol) of hydroxylamine hydrochloride. The reaction mixture is taken to reflux and its evolution monitored by TLC. The solvent is removed at reduced pressure, diluted in CH_2Cl_2 and washed with H_2O. The organic solvent is evaporated at reduced pressure, giving an oil which is crystallised in ethyl ether, yielding 0.5 g (1.40 mmol) of 4-ethoxy-2-{4-[2-(hidroxyiminomethyl)benzoyl]-1-piperazinyl}pyrimidine with m.p.= 136-140°C.

To a solution of 0.5 g (1.40 mmol) of 4-ethoxy-2-{4-[2-(hidroxyiminomethyl)benzoyl]-1-piperazinyl}pyrimidine in 30 mL of ethyl acetate are

added 0.15 mL of acetic anhydride and taken to reflux for 2 hours. The solvent is evaporated under reduced pressure providing the acetylated oxime.

The acetylated oxime is dissolved in 20 mL of acetonitrile and added K_2CO_3 in excess and left stirring at room temperature for 78 hours. The solid is filtered, the solvent removed at reduced pressure, diluted in CH_2Cl_2 and washed with H_2O. The solvent is evaporated at reduced pressure, giving a crude which crystallises in ethyl ether, yielding 0.2 g (0.60 mmol) of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine with m.p. = 151-154°C.

METHOD C:

Example 15.- Preparation of 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine.

To a suspension of 0.75 g (5.04 mmol) of quinolinic anhydride in 25 mL of acetonitrile are added 1.05 g (5.04 mmol) of 4-ethoxy-2-(1-piperazinyl)pyrimidine and 0.8 mL (5.07 mmol) of triethylamine and taken to reflux for 18 hours. The solvent is evaporated at reduced pressure and the resulting crude is purified by chromatography on silica gel, using as eluents $CHCl_3$:MeOH 3:2 obtaining 0.6 g (1.68 mmol) of 2-[4-(3-carboxy-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine with m.p.= 186-189°C.

To a suspension of 0.3 g (0.8 mmol) of 2-[4-(3-carboxy-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine in 20 mL of methylene chloride are added 0.5 mL (3.6 mmol) of triethylamine, taken to 0°C and added 0.1 g (0.92 mmol) of ethyl chloroformiate keeping the solution at this temperature for 30 minutes. Through the resulting mixture is bubbled NH_3 (gas) for 1 minute and the temperature kept at 0°C for 2 hours. The solution is allowed to reach room temperature and washed with H_2O, the methylene chloride is removed at reduced pressure obtaining a paste which solidifies yielding 184 mg (0.51 mmol) of 2-[4-(3-carbamoyl-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine with m.p.= 161-163°C.

To a solution of 84 mg (0.23 mmol) of 2-[4-(3-carbamoyl-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine in 15 mL of methylene chloride are added 0.2 mL of triethylamine and 0.1 mL of methansulfonyl chloride. The resulting mixture is left stirring for 18 hours at room temperature. The organic solution is washed with a solution of CO_3Na_2, the solvent removed at reduced pressure obtaining a crude

which is purified by chromatography on silica gel, using ethyl acetate as an eluent yielding 42 mg (0.12 mmol) of 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine with m.p.=137-140°C.

METHOD D:

Example 19.- Preparation of 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine.

To a solution of 1.33 g (7.45 mmol) of 2-methoxycarbonylnicotinic acid in 15 mL of DMF cooled in an ice bath are added 1.20 g (7.45 mmol) of N,N'-carbonyldiimidazole and stirred for 40 minutes. To the reaction mixture is added 1.53 g (7.45 mmol) of 4-ethoxy-2-(1-piperazinyl)pyrimidine and left at room temperature for two hours. The solution is then diluted with ethyl acetate and washed with H_2O, dried with Na_2SO_4 and the solvent removed at reduced pressure, obtaining an oil which crystallises in ethyl ether, yielding 1.5 g (4.04 mmol) of 4-ethoxy-2-[4-(2-methoxycarbonyl-3-pyridylcarbonyl)-1-piperazinyl]pyrimidine with m.p.= 126-128°C.

To a solution of 1.4 g (3.77 mmol) of 4-ethoxy-2-[4-(2-methoxycarbonyl-3-pyridylcarbonyl)-1-piperazinyl]pyrimidine in 25 mL of THF and 10 mL of MeOH are added 0.158 g (3.77 mmol) of $LiOHxH_2O$ and left stirred at room temperature for two hours. Through the solution is bubbled SO_2 and the solvent is removed at reduced pressure. The resulting crude is suspended in 30 mL of methylene chloride and 0.45 mL (3.3 mmol) of triethylamine added, and it is taken to 0°C and 0.3 g (2.76 mmol) of ethyl chloroformiate are added, keeping the solution at this temperature for 30 minutes. Through the resulting mixture is bubbled NH_3 (gas) for 1 minute and the temperature kept at 0°C for 2 hours. The solution is allowed to reach room temperature and washed with H_2O. The methylene chloride is removed at reduced pressure, and a paste is obtained which solidifies to a crude which crystallises in ethyl acetate, yielding 0.12 g (0.34 mmol) of 2-[4-(2-carbamoyl-3-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine with m.p.= 152-156°C.

To a solution of 100 mg (0.28 mmol) of 2-[4-(2-carbamoyl-3-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine in 5 mL of pyridine are added 1.0 mL of methansulphonyl chloride. The resulting mixture is stirred for 24 hours at room temperature. The solvent is evaporated to dryness and distributed in methylene

chloride and water, washed with $NaHCO_3$ and the solvent removed at reduced pressure, providing a crude which is purified by chromatography on silica gel using as eluent ethyl acetate, yielding 60 mg (0.18 mmol) of 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine with m.p.=177-178°C.

METHOD E:

Example 9.- Preparation of 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine.

To a solution of 1.5 g (7.7 mmol) of 4-methoxy-2-(1-piperazinyl)pyrimidine in 20 mL of THF cooled to 0°C are added 1.25 g (7.7 mmol) of N,N'-carbonyldiimidazole. The mixture is left stirring at room temperature for 3 hours. The solvent is removed at reduced pressure and H_2O is added, forming a precipitate which is filtered to obtain 1.8 g (6.24 mmol) of 2-[4-(1-imidazolilcarbonyl)-1-piperazinyl]-4-methoxypyrimidine with m.p.= 125-126°C.

To a solution of 0.62 mL (6.8 mmol) of 3-cyanothiofene in 25 mL of anhydrous THF cooled to –78°C and under argon atmosphere are slowly added 4.26 mL (6.8 mmol) of *n*-BuLi 1.6M in hexane. The mixture is kept at –78°C during 30 minutes and later is slowly added a solution of 1.8 g (6.2 mmol) of 2-[4-(1-imidazolilcarbonyl)-1-piperazinyl]-4-methoxypyrimidine in 25 mL of anhydrous THF. The mixture is allowed to slowly reach room temperature and it is kept at this temperature for 2 hours. The solution is poured over water and extracted with ethyl acetate, producing a crude which is purified by chromatography over silica gel using as eluent a mixture of ethyl acetate:hexane 7:3 , yielding 1.0 g (3.0 mmol) of 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine with m.p.= 140-142°C.

METHOD F:

Example 1.- Preparation of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-methoxypyrimidine.

To a solution of 1.0 g (6.8 mmol) of 2-cyanobenzoic acid in 20 mL of anhydrous DMF cooled to 0°C are added 1.1 g (6.8 mmol) of N,N'-carbonyldiimidazole and kept stirred for 40 minutes. Later are added 1.26 g (6.8 mmol) of 1-(*tert*-butoxycarbonyl)piperazine and left at room temperature for 2 hours. It is poured on water and extracted with ethyl ether. The organic phase is dried and

evaporated at reduced pressure, giving a crude which solidifies in petroleum ether to yield 1.24 g (3.94 mmol) of 4-(*tert*-butoxycarbonyl)-1-(2-cyanobenzoyl)piperazine with m.p.= 126-128°C.

To a solution of 1.2 g (3.81 mmol) of 4-(*tert*-butoxycarbonyl)-1-(2-cyanobenzoyl)piperazine in 10 mL of methylene chloride cooled to 0°C are added 10 mL of trifluoroacetic acid and left stirred at room temperature for 2 hours. The reaction mixture is evaporated to dryness and the resulting crude crystallises in methylene chloride:ethyl ether, yielding 1.04 g (3.16 mmol) of 1-(2-cyanobenzoyl)piperazine trifluoroacetate with m.p.= 136-141°C.

A mixture of 1.0 g (3.04 mmol) of 1-(2-cyanobenzoyl)piperazine trifluoroacetate, 0.5 g (3.35 mmol) of 2-chloro-4-methoxypyrimidine and 1.0 g (6.68 mmol) of potassium carbonate in 20 mL of DMF is heated to 100°C for 1 hour. The solvent is removed at reduced pressure and water is added. The resulting solid is filtered, washed with water and purified by chromatography over silica gel, using as eluent ethyl acetate, yielding 0.51 g (1.58 mmol) of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-methoxypyrimidine.

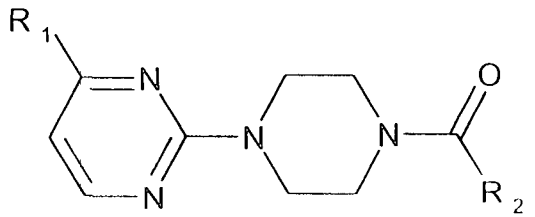
METHOD G:

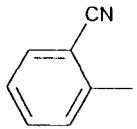
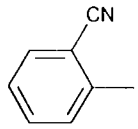
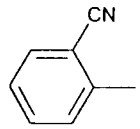
Example 4.- Preparation of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine hydrochloride.

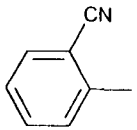
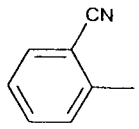
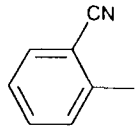
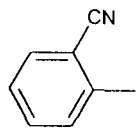
4.76 g (14.12 mmol) of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine are dissolved in acetone and a few drops of ethyl ether/HCl and ethyl ether are added, forming a precipitate which is filtered and dried, providing 3.85 g (10.31 mmol) of 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine hydrochloride with m.p.= 147-151°C.

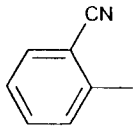
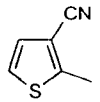
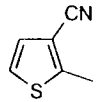
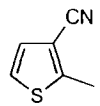
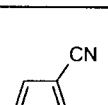
In Table 1 a few compounds which are illustrative of the invention are described, indicating their method of obtention, melting point and spectroscopic characteristics.

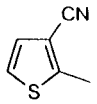
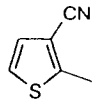
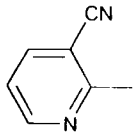
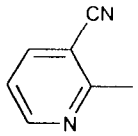
TABLE 1

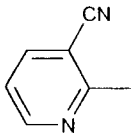
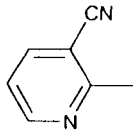
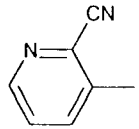
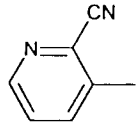


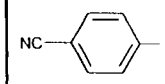
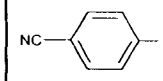
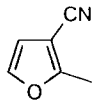
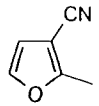
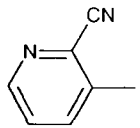
Example	R_1	R_2	Base or salt	METHOD	m.p.(°C)	^{1}H RMN (MHz) (Solvent) δ	IR, cm^{-1}
1	CH_3O-		Base	A, B or F	166-168	(300 MHz) ($CDCl_3$) 3.35 (m, 2H) 3.78-4.02 (a.c., 9H, (δ = 3.85. s)), 6.01 (d, J= 5.7 Hz, 1H), 7.50 (m, 2H), 7.66 (t, J= 7.5 Hz, 1H), 7.72 (d, J= 7.5 Hz, 1H), 8.03 (d, J= 5.7 Hz, 1H).	(KBr) 2226. 1632. 1598. 1565. 1431. 1259. 987.
2	CH_3O-		HCl	G	154-156	(300 MHz) ($CDCl_3$) 3.52 (broad band, 2H), 3.85-4.38 (a.c., 9H, (δ= 4.05. s)), 6.28 (d, J= 6.8 Hz, 1H), 7.46 (d, J= 7.6 Hz, 1H), 7.56 (t, J= 7.6 Hz, 1H), 7.71 (m 2H), 8.70 (d, J= 6.8 Hz, 1H).	(KBr) 3700-2300 (broad band), 2228. 1644. 1609. 1485. 1257.
3	CH_3CH_2O-		Base	A, B or F	151-154	(300 MHz) ($CDCl_3$) 1.34 (t, J= 7.1 Hz, 3H), 3.34 (m, 2H), 3.77-3.99 (a.c., 6H), 4.29 (q, J= 7.1 Hz, 2H), 5.99 (d, J= 5.8 Hz, 1H), 7.50 (m, 2H), 7.66 (t, J= 7.7 Hz, 1H), 7.72 (m, 1H), 8.03 (d, J= 5.8 Hz, 1H)	(KBr) 2220. 1632. 1560. 1491. 1432. 1256. 1002.

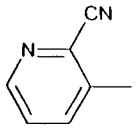
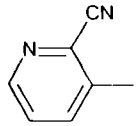
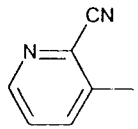
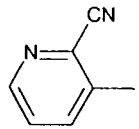
4	CH_3CH_2O-		HCl	G	147-151	(300 MHz) ($CDCl_3$) 1.43 (t, J= 7.3 Hz, 3H), 3.52 (broad band, 2H), 3.85-4.35 (a.c., 6H), 4.48 (q, J= 7.3 Hz, 2H), 6.25 (d, J= 6.7 Hz, 1H), 7.46 (d, J= 8.0 Hz, 1H), 7.56 (t, J= 8.0 Hz, 1H), 7.70 (m, 2H), 8.06 (d, J= 6.7 Hz, 1H).	(KBr) 3700-2300 (broad band), 2228. 1638. 1605. 1481. 1433. 1254.
5	$CH_3[CH_2]_2O$-		Base	A, B or F	118-121	(300 MHz) ($CDCl_3$) 0.97 (t, J= 7.4 Hz, 3H), 1.73 (m, 2H), 3.34 (broad band, 2H), 3.77-3.98 (a.c., 6H), 4.18 (t, J= 6.7 Hz, 2H), 6.00 (d, J= 5.7 Hz, 1H), 7.50 (m, 2H), 7.66 (t, J= 8.0 Hz, 1H), 7.71 (d, J= 8.0 Hz, 1H), 8.02 (d, J= 6.7 Hz, 1H).	(KBr) 2220. 1629. 1586. 1559. 1428. 1240. 1005.
6	$CH_3[CH_2]_2O$-		HCl	G	147-149	(300 MHz) ($CDCl_3$) 1.02 (t, J= 7 0 Hz, 3H), 1.82 (m, 2H), 3.52 (broad band, 2H), 3.84-4.17 (a.c., 4H), 4.36 (m, 4H), 6.27 (d, J= 6.6 Hz, 1H), 7.45 (d, J= 7.4 Hz, 1H), 7.56 (t, J= 7.5 Hz, 1H), 7.70 (m, 2H), 8.05 (d, J= 6.6 Hz, 1H).	(KBr) 3300-2300 (broad band), 2235. 1647. 1601. 1485. 1452. 1283. 1261.
7	$CH_3[CH_2]_3O$-		Base	A, B or F	71-73	(300 MHz) ($CDCl_3$) 0.93 (t, J= 7 3 Hz, 3H), 1.42 (m, 2H), 1.69 (m, 2H), 3.35 (broad singlet, 2H), 3.75-4.00 (a.c., 6H), 4.23 (t, J= 6.5 Hz, 2H), 5.99 (d, J= 5.7 Hz, 1H), 7.50 (m, 2H), 7.66 (dt, J= 7.7 Hz, J'= 1.0 Hz, 1H), 7.72 (d, J= 7.7 Hz, 1H), 8.02 (d, J= 5.7 Hz, 1H).	(KBr) 2966. 2225. 1632. 1561. 1500. 1464. 1240. 1006.

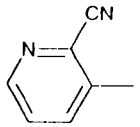
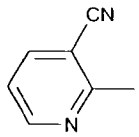
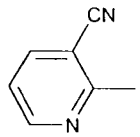
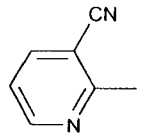
8	$CH_3[CH_2]_3O$-		HCl	G	137-138	(300 MHz) ($CDCl_3$) 0.97 (t, J= 7.6 Hz, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 3.52 (broad band, 2H), 3.83-4.50 (a.c., 8H), 6.26 (d, J= 7.1 Hz, 1H), 7.46 (d, J= 7.5 Hz, 1H), 7.56 (t, J= 7.6 Hz, 1H), 7.70 (m, 2H), 8.05 (d, J= 7.1 Hz, 1H).	(KBr) 3200-2300 (broad band), 1648. 1609. 1483. 1259. 1005.
9	CH_3O-		Base	A or E	140-142	(300 MHz) ($CDCl_3$) 3.58-4.80 (broad band, 4H), 3.86 (s, 3H), 3.93 (m, 4H), 6.02 (d, J= 5.6 Hz, 1H), 7.25 (d, J= 5.1 Hz, 1H), 7.50 (d, J= 5.1 Hz, 1H), 8.04 (d, J= 5.6 Hz, 1H).	(KBr) 2220. 1626. 1587. 1563. 1511. 1434. 1340. 1259. 988.
10	CH_3O-		HCl	G	136-138	(300 MHz) ($CDCl_3$) 3.84 (broad singlet, 4H), 4.00-4.45 (a.c., 7H, (δ= 4.07. s)), 6.30 (d, J= 6.8 Hz, 1H), 7.28 (d, J= 5.1 Hz, 1H), 7.55 (d, J= 5.1 Hz, 1H), 8.10 (J= 6.8 Hz, 1H).	(KBr) 3200-2300 (broad band), 2231. 1634. 1612. 1481. 1355. 1259. 1003.
11	CH_3CH_2O-		Base	A or E	152-155	(300 MHz) ($CDCl_3$) 1.35 (t, J= 7.1 Hz, 3H), 3.71 (broad band, 4H), 3.92 (broad band, 4H), 4.31 (q, J= 7.1 Hz, 2H), 6.00 (d, J= 5.6 Hz, 1H), 7.25 (d, J= 5.1 Hz, 1H), 7.50 (d, J= 5.1 Hz, 1H), 8.04 (d, J= 5.6 Hz, 1H).	(KBr) 2230. 1626. 1436. 1338. 1253. 1002.
12	CH_3CH_2O-		HCl	G	171-174	(300 MHz) ($CDCl_3$) 1.44 (t, J= 7.1 Hz, 3H), 3.83 (broad band, 4H), 4.05 (m, 2H), 4.40 (m, 2H), 4.49 (q, J= 7.1Hz, 2H), 6.27 (d, J= 6.7 Hz, 1H), 7.28 (d, J= 5.1 Hz, 1H), 7.55 (d, J= 5.1 Hz, 1H), 8.07 (d, J= 6.7 Hz, 1H).	(KBr) 3200-2300 (broad band), 2228. 1637. 1610. 1462. 1439. 1257.

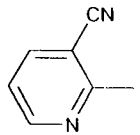
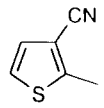
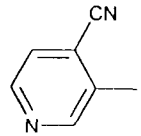
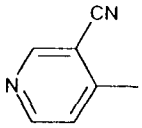
13	$CH_3[CH_2]_2O$-		Base	A or E	106-107	(300 MHz) ($CDCl_3$) 0.96 (t, J= 7.3 Hz, 3H), 1.75 (m, 2H), 3.71 (broad band, 4H), 3.91 (broad band, 4H), 4.20 (t, J= 6.6 Hz, 2H), 6.01 (d, J= 5.8 Hz, 1H), 7.25 (d, J= 5.1 Hz, 1H), 7.50 (d, J= 5.1 Hz, 1H), 8.05 (d, J= 5.8 Hz, 1H).	(KBr) 2230. 1628. 1582. 1560. 1436. 1255. 1003.
14	$CH_3[CH_2]_2O$-		HCl	G	147-149	(300 MHz) ($CDCl_3$) 1.02 (t, J= 7.3 Hz, 3H), 1.83 (m, 2H), 3.83 (broad band, 4H), 4.06 (broad band, 2H), 4.37 (broad triplet, J= 6.6 Hz, 4H), 6.28 (d, J= 6.8 Hz, 1H), 7.28 (d, J= 5.1 Hz, 1H), 7.54 (d, J= 5.1 Hz, 1H), 8.07 (d, J= 6.8 Hz, 1H).	(KBr) 3200-2300 (broad band), 2234. 1638. 1606. 1483. 1439. 1258. 998.
15	CH_3CH_2O-		Base	A or C	137-139	(300 MHz) ($CDCl_3$) 1.34 (t, J= 7.1 Hz, 3H), 3.42 (m, 2H), 3.78-4.00 (a.c., 6H), 4.30 (q, J= 7.1 Hz, 2H), 5.99 (d, J= 5.6 Hz, 1H), 7.48 (dd, J= 7.8 Hz, J'= 4.9 Hz, 1H), 8.03 (d, J= 5.6 Hz, 1H), 8.07 (d, J= 7.8 Hz, 1H), 8.78 (d, J= 4.9 Hz, 1H).	(KBr) 2230. 1637. 1607. 1558. 1444. 1341. 1316. 1258. 1002.
16	CH_3CH_2O-		HCl	G	170-172	(300 MHz) (CD_3OD) 1.43 (t, J= 7.2 Hz, 3H), 3.67 (broad band, 2H), 3.93 (broad band, 2H), 4.03 (broad singlet, 4H), 4.55 (q, J= 7.2 Hz, 2H), 6.46 (d, J= 7.0 Hz, 1H), 7.70 (dd, J= 7.8 Hz, J'= 5.0 Hz, 1H), 8.06 (d, J= 7.0 Hz, 1H), 8.35 (d, J= 7.8 Hz, 1H), 8.85 (m, 1H).	(KBr) 3200-2300 (broad band), 2235. 1638. 1612. 1443. 1260. 1210. 997.

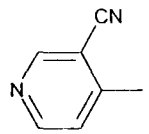
17	$CH_3[CH_2]_2O$		Base	A or C	93-95	(300 MHz) ($CDCl_3$) 0.98 (t, J= 7.4 Hz, 3H), 1.75 (m, 2H), 3.43 (m, 2H), 3.81-4.01 (a.c., 6H), 4.19 (t, J= 6.7 Hz, 2H), 6.01 (d, J= 5.6 Hz, 1H), 7.48 (dd, J= 7.8 Hz, J'= 5.0 Hz, 1H), 8.03 (d, J= 5.6 Hz, 1H), 8.08 (dd, J= 7.8 Hz, J'= 1.1 Hz, 1H) 8.79 (dd, J= 5.0 Hz, J'= 1.1 Hz, 1H).	(KBr) 2234. 1640. 1583. 1561. 1441. 1236. 1009.
18	$CH_3[CH_2]_2O$		HCl	G	152-155	(300 MHz) ($CDCl_3$) 1.02 (t, J= 7.4 Hz, 3H), 1.80 (m, 2H), 3.63 (broad band, 2H), 3.90-4.20 (a.c., 4H), 4.38 (m, 4H), 6.27 (d, J= 6.8 Hz, 1H), 7.52 (dd, J= 7.8 Hz, J'= 4.9 Hz, 1H), 8.09 (m, 2H), 8.78 (d, J= 4.9 Hz, 1H).	(KBr) 3200-2000 (broad band), 2239. 1643. 1606. 1442. 1415. 1260. 1210. 999.
19	CH_3CH_2O-		Base	A or D	177-178	(300 MHz) ($CDCl_3$) 1.34 (t, J= 7 1 Hz, 3H), 3.37 (broad band, 2H), 3.81-3.99 (a.c., 6H), 4.30 (q, J=7.1 Hz, 2H), 6.01 (d, J= 5.6 Hz, 1H), 7.60 (dd, J= 8.0 Hz, J'= 4.8 Hz, 1H), 7.84 (dd, J= 8.0 Hz, J'= 1.5 Hz, 1H), 8.04 (d, J= 5.6 Hz, 1H), 8.76 (dd, J= 4.8 Hz, J'= 1.5 Hz, 1H).	(KBr) 2235. 1628. 1601. 1544. 1433.
20	CH_3CH_2O-		HCl	G	173-176	(300 MHz) ($CDCl_3$) 1.42 (t, J= 7 1 Hz, 3H), 3.53 (broad singlet, 2H), 3.95 (broad singlet, 2H), 4.11 (broad singlet, 2H), 4.23 (broad singlet, 2H), 4.46 (q, J= 7.1 Hz, 2H), 6.24 (d, J= 6.6 Hz, 1H), 7.62 (dd, J= 7.6 Hz, J'= 4.7 Hz, 1H), 7.84 (d, J= 7.6 Hz, 1H), 8.05 (d, J= 6.6 Hz, 1H), 8.78 (d, J= 4.7 Hz, 1H).	(KBr) 3600-2300 (broad band), 2228. 1637. 1616. 1464. 1437. 1000.

21	CH_3CH_2O-		Base	A	132-134	(300 MHz) ($CDCl_3$) 1.34 (t, J= 7.1 Hz, 3H), 3.40 (m, 2H), 3.65-4.00 (a.c., 6H), 4.29 (q, J= 7.1 Hz, 2H), 6.00 (d, J= 5.9 Hz, 1H), 7.52 and 7.72 (System AB, J_{AB}= 8.3 Hz, 4H), 8.04 (d, J= 5.9 Hz, 1H).	(KBr) 2228. 1623. 1554. 1430. 1265.
22	CH_3CH_2O-		HCl	G	167-169	(300 MHz) ($CDCl_3$) 1.44 (t, J= 6.8 Hz, 3H), 3.50-4.35 (a.c., 8H), 4.49 (m, 2H), 7.51 and 7.74 (System AB, J_{AB}= 7.8 Hz, 4H), 8.07 (d, J= 6.9 Hz, 1H).	(KBr) 3200-2300 (broad band), 1628. 1483. 1457. 1343. 1262. 1213. 1007.
23	CH_3O-		Base	A or E	139-142	(300 MHz) ($CDCl_3$) 3.80 (m, 4H), 3.87 (s, 3H), 3.91 (m, 4H), 6.03 (d, J= 5.6 Hz, 1H), 6.73 (d, J= 1.7 Hz, 1H), 7.54 (d, J= 1.7 Hz, 1H), 8.05 (d, J= 5.6 Hz, 1H)	(KBr) 2239. 1626. 1650. 1438. 1340. 1306. 1239. 987. 794.
24	CH_3O-		HCl	G	143-145	(300 MHz) ($CDCl_3$) 3.80-4.45 (a.c., 11H, (δ= 4.07. s)), 6.31 (d, J=6.8 Hz, 1H), 6.77 (s, 1H), 7.57 (s, 1H), 8.11 (d, J= 6.8 Hz, 1H).	(KBr) 3600-2300 (broad band), 2228. 1629. 1490. 1444. 1267. 1001.
25	CH_3O-		Base	A or D	153-156	(300 MHz) ($CDCl_3$) 3.37 (m, 2H), 3.82-4.05 (a.c., 9H, (δ= 3.86. s)), 6.03 (d, J= 5.6 Hz, 1H), 7.60 (dd, J= 8.0 Hz, J'= 4.8 Hz, 1H), 7.84 (dd, J= 8.0 Hz, J'= 1.5 Hz, 1H), 8.04 (d, J= 5.6 Hz, 1H), 8.76 (dd, J= 4.8 Hz, J'= 1.5 Hz, 1H).	(KBr) 2239. 1628. 1560. 1414. 1265. 1008. 797.

26	CH_3O-		HCl	G	152-164	(300 MHz) ($CDCl_3$) 3.56 (broad singlet, 2H), 3.90-4.30 (a.c., 9H, (δ= 4.08. s)), 6.31 (d, J= 7.0 Hz, 1H), 7.63 (dd, J= 7.8 Hz, J'= 4.7Hz, 1H), 7.83 (m, 1H), 8.07 (d, J= 7.0 Hz, 1H), 8.80 (dd, J= 4.7 Hz, J'= 1.5 Hz, 1H).	(KBr) 3600-2300 (broad band), 2232. 1618. 1498. 1413. 1287.
27	$CH_3[CH_2]_2O$-		Base	A or D	165-168	(300 MHz) ($CDCl_3$) 0.97 (t, J= 7.3 Hz, 3H), 1.74 (m, 2H), 3.37 (m, 2H), 3.80-4.00 (a.c., 6H), 4.19 (t, J= 6.8 Hz, 2H), 6.01 (d, J= 5.9 Hz, 1H), 7.60 (dd, J= 8.0 Hz, J'= 4.9 Hz, 1H), 7.84 (d, J= 8.0 Hz, 1H), 8.03 (d, J= 5.9 Hz, 1H), 8.76 (d, J= 4.9 Hz, 1H).	(KBr) 2964. 2240. 1627. 1555. 1433. 1037. 1242. 1009. 790.
28	$CH_3[CH_2]_2O$-		HCl	G	168-171	(300 MHz) ($CDCl_3$) 1.02 (t, J= 7.3 Hz, 3H), 1.81 (m, 2H), 3.52 (m, 2H), 3.90-4.42 (a.c., 8H), 6.24 (d, J= 6.6 Hz, 1H), 7.62 (dd, J= 7.8 Hz, J'= 4.8 Hz, 1H), 7.83 (d, J= 7.8 Hz, 1H), 8.06 (d, J= 6.6 Hz, 1H), 8.80 (m, 1H).	(KBr) 3600-2300 (broad band), 2232. 1637. 1483. 1436. 1267. 1000.
29	$CH_3[CH_2]_3O$-		Base	A or D	163-164	(300 MHz) ($CDCl_3$) 0.93 (t, J= 7.3 Hz, 3H), 1.42 (m, 2H), 1.70 (m, 2H), 3.37 (m, 2H), 3.80-4.00 (a.c., 6H), 4.23 (t, J= 6.6 Hz, 2H), 6.00 (d, J= 5.6 Hz, 1H), 7.60 (dd, J= 7.8 Hz, J'= 4.9 Hz, 1H), 7.84 (dd, J= 7.8 Hz, J'= 1.5 Hz, 1H), 8.03 (d, J= 5.6 Hz, 1H), 8.76 (dd, J= 4.9 Hz, J'= 1.5 Hz, 1H).	(KBr) 2956. 2241. 1627. 1557. 1433. 1009. 791.

30	$CH_3[CH_2]_3O$-		HCl	G	141-143	(300 MHz) ($CDCl_3$) 0.95 (t, J= 7.3 Hz, 3H), 1.44 (m, 2H), 1.76 (m, 2H), 3.55 (broad singlet, 2H), 3.80-4.53 (a.c., 8H), 6.27 (d, J= 6.8 Hz, 1H), 7.62 (dd, J= 7.8 Hz, J'= 4.8 Hz, 1H), 7.82 (m, 1H), 8.05 (d, J= 6.8 Hz, 1H), 8.79 (dd, J= 4.8 Hz, J'= 1.5 Hz, 1H).	(KBr) 3700-2300 (broad band), 2236. 1640. 1608. 1488. 1437. 1257. 998.
31	CH_3O-		Base	A or C	137-139	(300 MHz) ($CDCl_3$) 3.42 (m, 2H), 3.80-4.06 (a.c., 9H, ((δ= 3.86. s)), 6.02 (d, J= 5.6 Hz, 1H), 7.48 (dd, J= 7.8 Hz, J'= 4.9 Hz, 1H), 8.04 (d, J= 5.6 Hz, 1H), 8.08 (d, J= 7.8 Hz, 1H), 8.79 (d, J= 4.9 Hz, 1H).	(KBr) 2230. 1647. 1560. 1471. 1415. 1288. 1256. 1014. 989.
32	CH_3O-		HCl	G	170-172	(300 MHz) ($CDCl_3$) 3.65 (m, 2H), 3.98 (m, 2H), 4.08 (broad singlet, 5H), 4.35 (m, 2H), 6.30 (d, J= 6.8 Hz, 1H), 7.54 (dd, J= 8.0 Hz, J'= 4.9 Hz, 1H), 8.10 (m, 2H), 8.79 (m, 2H).	(KBr) 3600-2300 (broad band), 2231. 1630. 1604. 1482. 1406. 1354. 1265. 1009. 988. 806.
33	$CH_3[CH_2]_3O$-		Base	A or C	73-75	(300 MHz) ($CDCl_3$) 0.93 (t, J= 7.3 Hz, 3H), 1.42 (m, 2H), 1.70 (m, 2H), 3.41 (m, 2H), 3.80-4.01 (a.c., 6H), 4.24 (t, J= 6.6 Hz, 2H), 5.99 (d, J= 5.6 Hz, 1H), 7.48 (dd, J= 8.0 Hz, J'= 4.9 Hz, 1H), 8.03 (d, J= 5.6 Hz, 1H), 8.08 (d, J= 8.0 Hz, 1H), 8.78 (m, 1H).	(KBr) 2957. 2233. 1640. 1560. 1439. 1255. 1008. 793.

34	$CH_3[CH_2]_3O$-		HCl	G	129-131	(300 MHz) ($CDCl_3$) 0.97 (t, J= 7.3 Hz, 3H), 1.46 (m, 2H), 1.78 (m, 2H), 3.64 (broad singlet, 2H), 3.90-4.18 (a.c., 4H), 4.21-4.50 (a.c., 4H), 6.26 (d, J= 6.8 Hz, 1H), 7.53 (dd, J= 7.8 Hz, J'= 4.8 Hz. 1H), 8.09 (m, 2H), 8.78 (d, J= 4.8 Hz, 1H).	(KBr) 3600-2300 (broad band), 2238. 1617. 1480. 1458. 1261. 1217. 1004. 799.
35	$CH_3[CH_2]_3O$-		Base	A or E	79-82	(300 MHz) ($CDCl_3$) 0.94 (t, J= 7 3 Hz, 3H), 1.42 (m, 2H), 1.70 (m, 2H), 3 71 (broad band, 4H), 3.91 (m, 4H), 4.24 (t, J= 6.6 Hz, 2H), 6.00 (d, J= 5.9 Hz, 1H), 7.25 (d, J= 5.2 Hz, 1H), 7.49 (d, J= 5.2 Hz, 1H), 8.03 (d, J= 5.9 Hz, 1H).	(KBr) 2957. 2231. 1637. 1582. 1438. 1338. 1237. 1001.
36	$CH_3[CH_2]_3O$-		Base	A	97-100	(300 MHz) ($CDCl_3$) 0.96 (t, J= 7.3 Hz, 3H), 1.44 (m,2H), 1.72 (m, 2H), 3 39 (broad band, 2H), 3.80-4.05 (a.c., 6H), 4.25 (t, J= 6.6 Hz, 2H), 6.03 (d, J= 5.7 Hz, 1H), 7.61 (d, J= 4.9 Hz, 1H), 8.05 (d, J= 5.7 Hz, 1H), 8.82 (s, 1H), 8.85 (d, J= 4.9 Hz, 1H).	(KBr) 2957. 2236. 1627. 1556. 1434. 1307.1265. 1008. 790.
37	$CH_3[CH_2]_3O$-		Base	A	124-127	(300 MHz) ($CDCl_3$) 0.95 (t, J= 7.5 Hz, 3H), 1.44 (m, 2H), 1.72 (m, 2H), 3.34 (m, 2H), 3.80-4.02 (a.c., 6H), 4.25 (t, J= 6.6 Hz, 2H), 6.03 (d, J= 5.7 Hz, 1H), 7.43 (d, J= 5.0 Hz, 1H), 8.05 (d, J= 5.7 Hz, 1H), 8.90 (d, J= 5.0 Hz, 1H), 8.96 (s, 1H).	(KBr) 2956. 2238. 1630. 1602. 1556. 1434. 1308. 1265. 1012. 790.

38	$CH_3[CH_2]_3O$-		HCl	G	171-173	(300 MHz) ($CDCl_3$) 0.99 (t, J= 7.3 Hz, 3H), 1.47 (m, 2H), 1.80 (m, 2H), 3.54 (m, 2H), 3.80-4.50 (a.c., 8H), 6.30 (d, J= 6.7 Hz, 1H), 7.44 (broad band, 1H), 8.08 (d, J= 6.7 Hz, 1H), 8.94 (d, J= 4.9 Hz, 1H), 9.00 (s, 1H).	(KBr) 3600-2300 (broad band), 2229. 1637. 1609. 1437. 1288. 1264. 1029. 1003.

General anaesthetic activity

Studies have been performed on three species, mouse, rat and dog, following the protocols described below.

a) Anaesthetic activity in mice.

The anaesthetic activity was determined after intravenous (IV) administration of the product under study in three different doses (15, 10 and 5 mg/kg) in the caudal vein of the mouse. The percentage of anaesthetised animals was recorded and the average time of anaesthesia calculated. Mice were considered to be anaesthetised when losing the three reflexes: positional reflex, response reflex to painful stimulus (tail pinch) and palpebral reflex.

The results obtained in this trial show that the products object of the invention are powerful anaesthetics as compared to one of the most widely used anaesthetics in human clinical use, propofol (table 2).

TABLE 2.- Anaesthetic activity in mice

Example	% anaesthetised (time of anaesthesia) Dose (mg/kg, iv)		
	15	10	5
4	100 (5.8')	100 (2.6')	0
6	100 (9.6')	100 (7.6')	90 (1.2')
8	100 (13.3')	100 (6.8')	60 (0.9')
12	100 (5.4')	100 (1.6')	0
14	100 (8.9')	100 (2.2')	0
18	100 (4.6')	100 (3.9')	0
Propofol	80 (1.3')	80 (1')	0

b) Anaesthetic activity in dogs.

A saline solution of the products in study was perfused by means of a perfusion pump in a concentration and rate of 5 mg/ml/minute, through a cannula inserted in a vein of the front leg. The i.v. infusion was stopped when the animal was fully anaesthetised (loss of motor coordination, sedation, loss of response to painful stimulus – prick in the fingers of the front leg – and loss of the palpebral reflex) and the anaesthetic dose was determined (Table 3).

TABLE 3.- Anaesthetic activity in dogs

(i.v. infusion)

Example	Anaesthetic dose (mg/kg)
4	10.1
6	17.4
8	21.2
18	14
Propofol	21.6*

*Animals treated with propofol only fell asleep, as they maintained the palpebral and pain reflexes.

The results obtained for dogs show that the products of the invention are clearly superior to Propofol, as they achieved full anaesthesia.

c) Anaesthetic activity in rats.

In this test, through the cannulated caudal vein of a rat was perfused a solution of the products under study with a concentration of 10 mg/kg. The rate of perfusion was varied to keep the rats anaesthetised for 1 hour. The total dose administered was determined, showing that the products of the invention were more active than Propofol (Table 4).

TABLE 4.- Anaesthetic activity in rats: i.v. infusion required to maintain full anaesthesia for 1 hour

Example	Total dose (mg/kg)
4	56.8
6	42.1
8	33.1
18	66.2
Propofol	67

Anticonvulsivant activity

This test studied the products' capacity to antagonise convulsions induced by i.v. injection of pentamethylentetrazole (cardiazol) at a dose of 45 mg/kg in the

caudal vein of the mouse. The results show that the products under study have a greater anticonvulsivant activity than propofol (Table 5).

TABLE 5.- Anticonvulsivant activity in mice (Convulsions induced by cardiazol)

Example	% Activity (mg/kg, i.p.)				
	80	40	20	10	ED-50
2	100	73	36	-	26.1
4	87	69	40	-	25.1
6	93	63	69	0	24.1
8	100	70	56	25	25.0
Propofol	100	46	33	-	32.5

Sedative activity

The sedative activity was studied by observing the animals' behaviour after intraperitoneal (i.p.) administration of a dose of 80 mg/kg. This observation was conducted at different times, allowing to know the sedative effect and its duration. The results obtained show that the products under study had a sedative effect, in some cases comparable to that of zolpidem and in other cases of longer duration (Table 6).

TABLE 6.- Sedative activity in mice (80 mg/kg, i.p.)

Example	30'	1h	2h	3h	4h	5h	24h
4	90	75	75	35	0	0	0
8	98	100	98	27	27	22	0
14	30	33	38	35	20	10	0
16	100	100	20	0	0	0	0
Zolpidem	100	90	30	0	0	0	0

Activity as muscular relaxant

The activity as muscular relaxant of the products of the invention was studied, by evaluating the effect on body tone and abdominal tone of the rats, following the method described by S. IRWIN (Gordon Res.Conf. on Medicinal Chem., 1959, p.133). The rats received the products under study in a i.p. dose of 80 mg/kg and at several times after administration (1/2, 1, 2, 3, 4 and 5 hours) the body and abdominal tone were evaluated, comparing muscle tension to that of the control

animals. The results of Table 7 show that many products have a remarkable activity as muscular relaxants, with this effect lasting longer than with propofol, which was used as the product of reference.

TABLE 7.- Myorelaxant activity in the IRWIN test in rats (80 mg/kg, i.p.)

Example	% muscular relaxation after:					
	½ h.	1 h.	2 h.	3 h.	4 h.	5 h.
4	100	100	100	70	33	0
8	100	100	100	0	0	0
16	100	100	100	66	44	0
Propofol	100	100	70	0	0	0

Pharmaceutical formulations

1. Injectable intramuscular/intravenous (im/iv):

Example 4	5 mg
Sodium chloride	q.s.
HCl 0.1 N or NaOH 0.1 N	q.s.
Water for injection q.s.p.	3 mL

2. Capsules

Example 4	0.5 to 4.0 mg
Colloidal silicon dioxide	0.5 mg
Magnesium stearate	1.0 mg
Lactose q.s.p.	100 mg

3. Tablets

Formula A (direct compression)

Example 4	0.5 to 4.0 mg

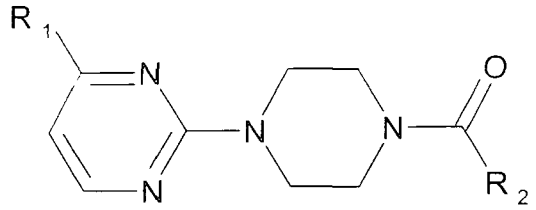
Colloidal silicon dioxide	0.5 mg
Magnesium stearate	1.0 mg
Sodium Croscarmelose	3.0 mg
Microcrystalline cellulose	60 mg
Lactose q.s.p.	100 mg

Formula B (wet granulation)

Example 4	0.5 a 4.0 mg
Colloidal silicon dioxide	0.5 mg
Magnesium stearate	1.0 mg
Povidone K-30	5.0 mg
Sodium carboxy methyl starch	5.0 mg
Microcrystalline cellulose	20 mg
Lactose q.s.p.	100 mg

CLAIMS

1. A cyanoaryl (or cyanoheteroaryl)-carbonyl-piperazinyl-pyrimidine derivative with the general formula (I)



(I)

wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon with a linear or branched chain, with 1 to 4 carbon atoms, and R_2 represents a phenyl radical substituted at least by one cyano radical (-C≡N), or a radical of a heteroaromatic ring of 5 or 6 members substituted at least by one cyano radical (-C≡N); and their physiologically acceptable salts.

2. A compound with the general formula (I), according to claim 1, chosen from among the following:

[1] 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-methoxypyrimidine

[2] 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-methoxypyrimidine hydrochloride

[3] 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine

[4] 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine hydrochloride

[5] 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-propoxypyrimidine

[6] 2-[4-(2-cyanobenzoyl)-1-piperazinyl]-4-propoxypyrimidine hydrochloride

[7] 4-butoxy-2-[4-(2-cyanobenzoyl)-1-piperazinyl]pyrimidine

[8] 4-butoxy-2-[4-(2-cyanobenzoyl)-1-piperazinyl]pyrimidine hydrochloride

[9] 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine

[10] 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine hydrochloride

[11] 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine

[12] 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine hydrochloride

[13] 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-propoxypyrimidine

[14] 2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]-4-propoxypyrimidine hydrochloride

[15] 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine

[16] 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine monohydrochloride

[17] 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-propoxypyrimidine

[18] 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-propoxypyrimidine monohydrochloride

[19] 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine

[20] 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-ethoxypyrimidine monohydrochloride

[21] 2-[4-(4-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine

[22] 2-[4-(4-cyanobenzoyl)-1-piperazinyl]-4-ethoxypyrimidine hydrochloride

[23] 2-[4-(3-cyano-2-furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine

[24] 2-[4-(3-cyano-2-furylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine hydrochloride

[25] 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine

[26] 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine monohydrochloride

[27] 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-propoxypyrimidine

[28] 2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]-4-propoxypyrimidine monohydrochloride

[29] 4-butoxy-2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]pyrimidine

[30] 4-butoxy-2-[4-(2-cyano-3-pyridylcarbonyl)-1-piperazinyl]pyrimidine monohydrochloride

[31] 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine

[32] 2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]-4-methoxypyrimidine monohydrochloride

[33] 4-butoxy-2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]pyrimidine

[34] 4-butoxy-2-[4-(3-cyano-2-pyridylcarbonyl)-1-piperazinyl]pyrimidine monohydrochloride

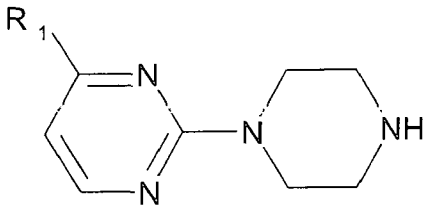
[35] 4-butoxy-2-[4-(3-cyano-2-thienylcarbonyl)-1-piperazinyl]pyrimidine

[36] 4-butoxy-2-[4-(4-cyano-3-pyridylcarbonyl)-1-piperazinyl]pyrimidine

[37] 4-butoxy-2-[4-(3-cyano-4-pyridylcarbonyl)-1-piperazinyl]pyrimidine

[38] 4-butoxy-2-[4-(3-cyano-4-pyridylcarbonyl)-1-piperazinyl]pyrimidine monohydrochloride

3. A procedure for preparing a compound with the general formula (I) according to claim 1, which involves reacting an amine with the general formula (II)



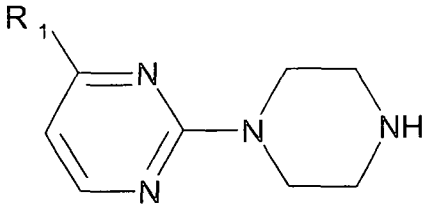
(II)

wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon, with a linear or branched chain, with 1 to 4 carbon atoms; with a carboxylic acid with the general formula (III) or with a salt of this acid,

$$R_2CO_2H \qquad \text{(III)}$$

wherein R_2 represents a phenyl radical substituted at least by one cyano radical (-C≡N), or a radical of a heteroaromatic ring of 5 or 6 members substituted at least by one cyano radical (-C≡N).

4. A procedure for preparing a compound with the general formula (I) according to claim 1, which involves reacting an amine with the general formula (II)



(II)

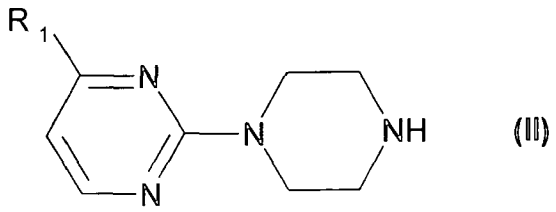
wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon, with a linear or branched chain of 1 to 4 carbon atoms; with a derivative of a carboxylic acid with the general formula (IV)

R_2COX **(IV)**

wherein R_2 represents a phenyl radical substituted at least by one cyano radical (-C≡N), or a radical of a heteroaromatic ring of 5 or 6 members substituted at least by one cyano radical (-C≡N); and

X represents a halogen atom, an azide group ($-N_3$), a 1-imidazolyl group, an O-CO-R_4 group wherein R_4 represents an alkyl radical of 1 to 6 carbon atoms or an aryl radical, optionally substituted by one or several halogen atoms, or an OR_5 group wherein R_5 represents an aromatic group of one or two rings substituted by one or more halogen atoms or nitro radicals, or N-succinimide.

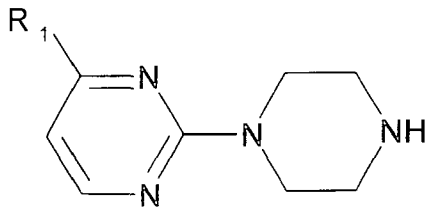
5. A procedure for preparing a compound with the general formula (I) according to claim 1, wherein R_2 represents a phenyl radical substituted at least by one cyano radical (-C≡N), which involves reacting an amine with the general formula (II)



(II)

wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon, with a linear or branched chain of 1 to 4 carbon atoms; with 3-bromophtalide to obtain an aldehyde which is reacted with hydroxylamine or a salt thereof to give an oxime which (i) is reacted with a dehydration reagent in the presence of Cu(II) ions, or (ii) is acylated with acetic anhydride or trifluoroacetic anhydride and treated with an organic or inorganic base.

6. A procedure for preparing a compound with the general formula (I) according to claim 1, wherein R_2 represents a phenyl radical substituted at least by one cyano radical (-C≡N), or a pyridyl radical substituted, at least, by one cyano radical (-C≡N), which involves reacting an amine with the general formula (II)

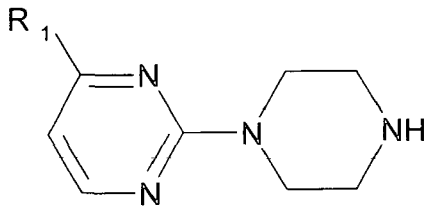


(II)

wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon, with a linear or branched chain of 1 to 4 carbon atoms;

with phthalic anhydride, phthalic acid, 2,3-pyridindicarboxylic anhydride or 2,3-pyridindicarboxylic acid to give an acid which is reacted with a carbonyl group activation reagent, and later with ammonia, in order to obtain an amide which is reacted with a dehydration reagent.

7. A procedure for preparing a compound with the general formula (I) according to claim 1, wherein R_2 represents a phenyl radical substituted at least by one cyano radical (-C≡N), or a pyridyl radical substituted at least by one cyano radical (-C≡N), which involves reacting an amine with the general formula (II)

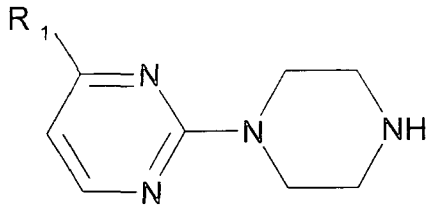


(II)

wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon, with a linear or branched chain of 1 to 4 carbon atoms;

with monomethyl phthalate or with 2-methoxycarbonylnicotinic acid, followed by hydrolysis of the ester previously formed in order to obtain an acid which is reacted with a carbonyl group activation reagent, and later with ammonia, in order to obtain an amide which is reacted with a dehydration reagent.

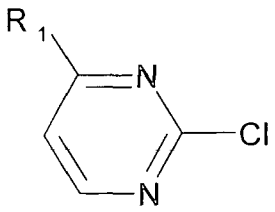
8. A procedure for preparing a compound with the general formula (I) according to claim 1, wherein R_2 represents a cyanothienyl or cyanofuryl radical, which involves reacting an amine with the general formula (II)



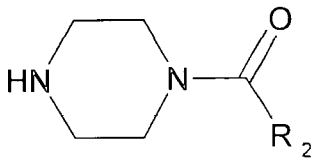
(II)

wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon, with a linear or branched chain of 1 to 4 carbon atoms; with 1,1'-carbonyldiimidazole and the product obtained reacted with the lithiated derivative of 3-cyanothiophene or 3-cyanofuran.

9. A procedure for preparing a compound with the general formula (I) according to claim 1, which involves reacting a derivative of chloropyrimidine with the general formula (XVIII) with a derivative of piperazine with the general formula (XIX),



(XVIII)



(XIX)

wherein R_1 represents an OR_3 radical, wherein R_3 represents a radical derived from a saturated hydrocarbon, with a linear or branched chain of 1 to 4 carbon atoms, and R_2 represents a phenyl radical substituted at least by one cyano radical (-C≡N), or a radical of a heteroaromatic ring of 5 or 6 members substituted at least by one cyano radical (-C≡N).

10. A procedure for preparing the physiologically acceptable salts of compounds with the general formula (I) according to claim 1, which involves reacting a compound with the general formula (I) with a mineral acid or an organic acid in a suitable solvent.

11. A pharmaceutical composition characterised in that it contains, in addition to a pharmaceutically acceptable excipient, at least one compound with the general formula (I) or one of its physiologically acceptable salts, according to any of claims 1 or 2.

12. Use of a compound with the general formula (I) or its pharmaceutically acceptable salts, according to any of claims 1 or 2, in the preparation of a medicament which is active on the central nervous system of mammals, including man.

13. Use of a compound with the general formula (I) or its pharmaceutically acceptable salts, according to any of claims 1 or 2, in the preparation of a medicament with activity as a sedative, anticonvulsivant, analgesic, muscular relaxant, antitussive, anxiolytic, antipsychotic, antidepressant, anti-cerebral ischaemia, antimigraine, in sleep disorders, in neurodegenerative diseases, in cognitive disorders and Alzheimer's disease, hypnotic or general anaesthetic in mammals, including man.