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Substituted 2-thio-3,5-dicyano-4-aryl-6-aminopyridines and their use

The present invention relates to substituted 2-thio-3,5-dicyano-4-aryl-6-amino-pyridines, to a process for their preparation and to their use as active compounds for medicaments.

The present invention furthermore provides the use of adenosine-receptor-selective ligands for the prophylaxis and/or treatment of various disorders.

Adenosine, a nucleoside consisting of adenine and D-ribose, is an endogenous factor having cell-protective activity, in particular under cell-damaging conditions with limited oxygen and substrate supply, such as, for example, in the case of ischemia in various organs (for example heart and brain).

Adenosine is formed intracellularly as an intermediate during the degradation of adenosine 5'-monophosphate (AMP) and S-adenosylhomocysteine, but it can be released from the cell, in which case it acts as a hormone-like substance or neurotransmitter by binding to specific receptors.

Under normoxic conditions, the concentration of free adenosine in the extracellular space is very low. However, under ischemic or hypoxic conditions, the extracellular concentration of adenosine in the affected organs is increased dramatically. Thus, it is known, for example, that adenosine inhibits platelet degradation and increases the blood supply to the coronary vessels of the heart. Furthermore, it acts on the heart rate, on the release of neurotransmitters and on lymphocyte differentiation.

The aim of these actions of adenosine is to increase the oxygen supply of the affected organs and/or to reduce the metabolism of these organs in order to adjust the metabolism of the organ to the blood supply of the organ under ischemic or hypoxic conditions.



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The action of adenosine is mediated via specific receptors. To date, subtypes A1, A2a, A2b and A3 are known. The actions of these adenosine receptors are mediated intracellularly by the messenger cAMP. In the case of the binding of adenosine to the A2a or A2b receptors, the intracellular cAMP is increased via activation of the membrane-bond adenylate cyclase, whereas binding of adenosine to A1 or A3 receptors results in a decrease of the intracellular cAMP concentration via inhibition of adenylate cyclase.

According to the invention, "Adenosine-receptor-selective ligands" are substances which bind selectively to one or more subtypes of the adenosine receptors, thus either mimicking the action of adenosine (adenosine agonists) or blocking its action (adenosine antagonists).

According to their receptor selectivity, adenosine-receptor-selective ligands can be divided into different categories, for example ligands which bind selectively to the A1 or A2 receptors of adenosine and in the case of the latter also, for example, those which bind selectively to the A2a or the A2b receptors of adenosine. Also possible are adenosine receptor ligands which bind selectively to a plurality of subtypes of the adenosine receptors, for example ligands which bind selectively to the A1 and the A2, but not to the A3 receptors of adenosine.

The abovementioned receptor selectivity can be determined by the effect of the substances on cell lines which, after stable transfection with the corresponding cDNA, express the receptor subtypes in question (see the publication M.E. Olah, H. Ren, J. Ostrowski, K.A. Jacobson, G.L. Stiles, "Cloning, expression, and characterization of the unique bovine A1 adenosine receptor. Studies on the ligand binding site by site-directed mutagenesis." in *J. Biol. Chem.* **267** (1992) pages 10764-10770, the disclosure of which is hereby fully incorporated by way of reference).

The effect of the substances on such cell lines can be monitored by biochemical measurement of the intracellular messenger cAMP (see the publication K.N. Klotz,

J. Hessling, J. Hegler, C. Owman, B. Kull, B.B. Fredholm, M.J. Lohse, "Comparative pharmacology of human adenosine receptor subtypes - characterization of stably transfected receptors in CHO cells" in *Naunyn Schmiedebergs Arch. Pharmacol.* **357** (1998) pages 1-9, the disclosure of which is hereby fully incorporated by way of reference).

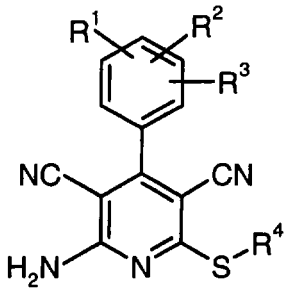
The "adenosine-receptor-specific" ligands known from the prior art are mainly derivatives based on natural adenosine (S.-A. Poulsen and R.J. Quinn, "Adenosine receptors: new opportunities for future drugs" in *Bioorganic and Medicinal Chemistry* **6** (1998) pages 619-641). However, most of the adenosine ligands known from the prior art have the disadvantage that their action is not really receptor-specific, that their activity is less than that of natural adenosine or that they have only very weak activity after oral administration. Thus, because of the disadvantages mentioned above, they are mainly only used for experimental purposes.

It is now an object of the following invention to find or provide compounds which have a wide therapeutic range and can serve as active compounds for the prophylaxis and/or treatment of various diseases.

In particular, it is an object of the present invention to find or provide substances which preferably act as adenosine-receptor-selective ligands and are suitable for the prophylaxis and/or treatment of various disorders, in particular disorders of the cardiovascular system (cardiovascular disorders) or inflammatory disorders, but additionally also disorders of the urogenital system, the respiratory tract, the central nervous system, the diabetes (in particular diabetes mellitus) and cancer.

It is a further object of the present invention to find or provide adenosine-receptor-selective ligands having a high specificity of action for the abovementioned purposes.

Accordingly, the present invention relates to compounds of the general formula (I)



(I),

in which :

R^1, R^2, R^3 are identical or different and independently of one another are selected from the group of the following substituents:

hydrogen;

hydroxyl;

optionally substituted (C_1-C_8)-alkyl;

optionally substituted (C_6-C_{10})-aryl;

optionally substituted (C_1-C_8)-alkoxy;

-O-$(CH_2)_n$-CH=CH_2 where n = 0, 1 or 2;

halogen;

nitro;

cyano;

-C(O)-R^5;

-C(O)-NR^6R^7;

-NR^6R^7;

-NR^6-C(O)-R^8;

-O-C(O)-R^8;

-SO_2-NR^6R^7; and

-NR^6-SO_2R^8,

where:

R^5 denotes:

hydrogen;

hydroxyl;
optionally substituted (C_1-C_8)-alkyl;
optionally substituted (C_3-C_7)-cycloalkyl;
optionally substituted (C_1-C_8)-alkoxy;
optionally substituted (C_6-C_{10})-aryl;
optionally substituted (C_6-C_{10})-aryloxy; or
-O-$(CH_2)_n$-[(C_6-C_{10})-aryl] where n = 1, 2 or 3,

where the (C_6-C_{10})-aryl group may be fused via two adjacent ring atoms to optionally substituted (C_4-C_7)-cycloalkyl,

or

R^5 represents a 5- to 7-membered saturated or unsaturated heterocycle which for its part may be mono- or polysubstituted by
an oxo group (=O);
halogen;
optionally substituted (C_1-C_8)-alkyl;
nitro;
cyano;
hydroxyl;
optionally substituted (C_6-C_{10})-aryl; or
by (C_1-C_8)-alkoxy,

or

R^5 represents optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S,

where the heterocycle and the heteroaryl ring may each optionally be fused via two adjacent ring atoms to optionally substituted (C_6-C_{10})-aryl or optionally substituted (C_4-C_7)-cycloalkyl,

and

R^6 and R^7 are identical or different and represent

hydrogen;

optionally substituted (C_1-C_8)-alkyl;

optionally substituted (C_6-C_{10})-aryl; or

represent optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S

or

R^6 and R^7 together with the nitrogen atom to which they are optionally attached form a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of

an oxo group (=O);

halogen;

(C_1-C_8)-alkyl;

nitro;

cyano;

hydroxyl;

(C_6-C_{10})-aryl; or

(C_1-C_8)-alkoxy,

and

R^8 represents hydroxyl;
NR^6R^7 where R^6 and R^7 are as defined above;
optionally substituted (C_1-C_8)-alkyl;
(C_1-C_8)-alkoxy;
optionally substituted (C_6-C_{10})-aryl;
(C_6-C_{10})-aryloxy; or
-O-$(CH_2)_n$-[(C_6-C_{10})-aryl] where n = 1, 2 or 3,

and

R^4 represents straight-chain or branched (C_1-C_8)-alkyl or (C_2-C_8)-alkenyl which are optionally mono- or polysubstituted by
hydroxyl;
halogen;
cyano;
-C(O)-R^5 where R^5 is as defined above;
-C(O)-NR^6R^7 where R^6 and R^7 are as defined above;
-NR^6R^7 where R^6 and R^7 are as defined above;
-NR^6-C(O)-R^8 where R^6 and R^8 are as defined above;
-SO_2-NR^6R^7 where R^6 and R^7 are as defined above;
-NR^6-SO_2-R^8 where R^6 and R^8 are as defined above;
-C(O)-$(CH_2)_n$-C(O)-R^8 where n = 0 to 2 and R^8 is as defined above;
(C_1-C_8)-alkoxy;
optionally substituted (C_6-C_{10})-aryloxy;
optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S;
optionally substituted (C_6-C_{10})-aryl; or
by a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S which for its part may optionally be mono- or polysubstituted by identical or different substituents

from the group consisting of an oxo group (=O); halogen; (C_1-C_8)-alkyl; nitro; cyano; hydroxyl; (C_6-C_{10})-aryl; or by (C_1-C_8)-alkoxy,

where the heterocycle and the heteroaryl ring may each optionally be fused via two adjacent ring atoms to optionally substituted (C_6-C_{10})-aryl,

or

R^4 represents a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S, which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of an oxo group (=O); halogen; (C_1-C_8)-alkyl; nitro; cyano; hydroxyl; (C_6-C_{10})-aryl; or by (C_1-C_8)-alkoxy, and which may optionally be fused via two adjacent ring atoms to optionally substituted (C_6-C_{10})-aryl or optionally substituted (C_4-C_7)-cycloalkyl,

and their tautomers and their respective salts, hydrates and alkoxides,

except for the following compounds of the general formula (I), in which the radicals R^1, R^2, R^3 and R^4 are as defined below:

- $R^1 = R^2 = H$; R^3 = para-OH; $R^4 = -CH_2$-Z where Z = CN, C(O)-OC_2H_5, 4-Br-C_6H_4-CO, 4-n-butyl-C_6H_4-CO, H, C_6H_5, C(O)-O-CH_2-C_6H_5, C(O)-OCH_3, C(O)-OH, 2-oxo-benzo-pyranyl-3-carbonyl, 4-Cl-C_6H_4-CO, 3-Br-C_6H_4-CO, 4-C_6H_5-C_6H_4-CO, 4-CH_3-C_6H_4-CO, 3,4-Cl_2-C_6H_3-CO;
- $R^1 = R^2 = H$; R^3 = meta-OH; $R^4 = -CH_2$-Z where Z = 4-Br-C_6H_4-NH-CO, 2-oxo-benzo-pyranyl-3-carbonyl, 4-Cl-C_6H_4-CO;
- $R^1 = R^2 = H$; R^3 = para-O-C(O)-CH_3; $R^4 = -CH_2$-Z where Z = 4-CH_3-C_6H_4-CO, H, 2-oxo-benzopyranyl-3-carbonyl, $(CH_2)_3$-CH_3, 4-C_6H_5-C_6H_4;
- $R^1 = R^2 = R^3 = H$; $R^4 = -CH_2$-Z where Z = CH_3, CN , 2-naphthyl;

- $R^1 = R^2 = H$; R^3 = para-butoxy; $R^4 = -CH_2-Z$ where Z = 4-Cl-C_6H_5, C(O)-OCH_3, C(O)-C_6H_5, $CH=CH_2$, C(O)-NH_2, H, 4-Br-C_6H_4-CO, 4-Cl-C_6H_4-CO, C(O)-OC_2H_5, C(O)-O-CH_2-C_6H_5, 2-oxo-benzopyranyl-3-carbonyl, C(O)-NH-C_6H_5, CN;
- $R^1 = R^2 = H$; R^3 = para-bromo; $R^4 = -CH_2-Z$ where Z = 4-Br-C_6H_4-CO, 4-Cl-C_6H_4-CO, C(O)-NH_2, C(O)-OCH_3, 4-Cl-C_6H_5, 4-Br-C_6H_4-NH-CO;
- $R^1 = R^2 = H$; R^3 = meta-fluoro; $R^4 = -CH_2-Z$ where Z = 4-Br-C_6H_4-CO, C(O)-NH_2, C(O)-O-CH_2-C_6H_5, CN;
- $R^1 = R^2 = H$; R^3 = para-chloro; $R^4 = -CH_2-Z$ where Z = 2-naphthyl, CH_3;
- $R^1 = R^2 = H$; R^3 = para-OCH_3; $R^4 = -CH_2-Z$ where Z = 2-naphthyl, CH_3;
- $R^1 = R^2 = H$; R^3 = meta-NO_2; $R^4 = -CH_2-Z$ where Z = CH_3.

Some of the abovementioned substances which can be used in accordance with the present invention for the prophylaxis and/or treatment of disorders are novel, and some are also known from the literature (see *Dyachenko et al.*, Russian Journal of Chemistry, Vol. 33, No. 7, 1997, pages 1014-1017 and Vol. 34, No. 4, 1998, pages 557-563; *Dyachenko et al.*, Chemistry of Heterocyclic Compounds, Vol. 34, 1998, pages 188-194; *Elnagdi et al.*, Zeitschrift für Naturforschung, Vol. 47b, 1992, pages 572-578; *Riguera et al.*, Eur. J. Med. Chem. 33, 1998, pages 887-897; *J. Vaquero, Thesis,* University of Alcala de Henares, Madrid, Spain, 1981). However, in the literature, a therapeutic use of the known compounds has hitherto not been described. The first time this has happened is in the context of the present invention.

Accordingly, the present invention also provides the use of the abovementioned compounds of the general formula (I), including the compounds excluded above, for the prophylaxis and/or treatment of disorders.

Depending on the substitution pattern, the compounds of the formula (I) can exist in stereoisomeric forms which are either like image and mirror image (enantiomers) or not like image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and to their respective mixtures. The racemic forms, like

the diastereomers, can be separated in a known manner into the stereoisomerically uniform components. Likewise, the present invention also relates to the other tautomers of the compounds of the formula (I) and their salts.

Physiologically acceptable salts of the compounds of the formula (I) can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulfonic acids. Particular preference is given, for example, to salts with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalene disulfonic acid, trifluoroacetic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Salts which may be mentioned include salts with customary bases, such as, for example, alkali metal salts (for example sodium or potassium salts), alkaline earth metal salts (for example calcium or magnesium salts) or ammonium salts, derived from ammonia or organic amines such as, for example, diethylamine, triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine, 1-ephenamine or methylpiperidine.

Definitions in the context of the present invention:

- Halogen generally represents fluorine, chlorine, bromine or iodine. Preference is given to fluorine, chlorine or bromine. Very particular preference is given to fluorine or chlorine.

- In the context of the present invention, (C_1-C_8)-alkyl, (C_1-C_6)-alkyl and (C_1-C_4)-alkyl represent a straight-chain or branched alkyl radical having 1 to 8; 1 to 6 and 1 to 4 carbon atoms, respectively. Examples which may be mentioned are: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl and n-octyl. Preference is given to a straight-chain or branched alkyl radical having 1 to 6 carbon atoms. Particular

preference is given to a straight-chain or branched alkyl radical having 1 to 4 carbon atoms.

- Optionally substituted (C_1-C_8)-alkyl, (C_1-C_6)-alkyl and (C_1-C_4)-alkyl, as used in the present invention, denotes an above-defined straight-chain or branched alkyl radical having 1 to 8; 1 to 6 and 1 to 4 carbon atoms, respectively, which for its part can be mono- or polysubstituted by identical or different substituents. Substituents which may be mentioned are in particular the following substituents: halogen (fluorine, chlorine, bromine, iodine); cyano; nitro; carboxyl; hydroxyl; straight-chain or branched (C_1-C_8)-alkoxy, preferably (C_1-C_6)-alkoxy, in particular (C_1-C_4)-alkoxy, where the alkoxy radical for its part may optionally be substituted; straight-chain or branched (C_2-C_8)-alkenyl, preferably (C_2-C_6)-alkenyl, in particular (C_2-C_4)-alkenyl, where the alkenyl radical for its part may optionally be substituted; (C_6-C_{10})-aryl, in particular phenyl or naphthyl, where the (C_6-C_{10})-aryl radical for its part may optionally be substituted; (C_1-C_4)-alkylsulfonyloxy, where the (C_1-C_4)-alkylsulfonyloxy radical for its part may optionally be substituted; phenylsulfonyl or p-tolylsulfonyl; straight-chain or branched (C_1-C_8)-thioalkyl, where the thioalkyl radical for its part may optionally be substituted; straight-chain or branched mono-, di- and/or trihalogeno-(C_1-C_8)-alkyl, in particular trifluoromethyl; straight-chain or branched mono-, di- and/or trihalogeno-(C_1-C_8)-alkoxy, in particular trifluoromethoxy; acyl; amino, N-[(C_1-C_8)-alkyl]-amino and/or N-di-[(C_1-C_8)-alkyl]-amino, where the alkyl radical for its part may optionally be substituted; and (C_1-C_8)-alkoxycarbonyl, where the alkoxycarbonyl radical for its part may optionally be substituted.

- In the context of the present invention, (C_6-C_{10})-aryl represents an aromatic radical having 6 to 10 carbon atoms. Preferred aryl radicals are phenyl and naphthyl.

- In the context of the present invention, the term optionally substituted (C_6-C_{10})-aryl represents an aromatic radical as defined above having 6 to 10 carbon atoms which for its part may be mono- or polysubstituted by identical or different substituents, in particular by: halogen (fluorine, chlorine, bromine, iodine); cyano; nitro; carboxyl; hydroxyl; straight-chain or branched (C_1-C_8)-alkyl, preferably (C_1-C_6)-alkyl, in particular (C_1-C_4)-alkyl, where the alkyl radical for its part may optionally be substituted; straight-chain or branched (C_1-C_8)-alkoxy, preferably (C_1-C_6)-alkoxy, in particular (C_1-C_4)-alkoxy, where the alkoxy radical for its part may optionally be substituted; straight-chain or branched (C_2-C_8)-alkenyl, preferably (C_2-C_6)-alkenyl, in particular (C_2-C_4)-alkenyl, where the alkenyl radical for its part may optionally be substituted; straight-chain or branched (C_1-C_8)-thioalkyl, where the thioalkyl radical for its part may optionally be substituted; straight-chain or branched mono-, di- and/or trihalogeno-(C_1-C_8)-alkyl, in particular trifluoromethyl; straight-chain or branched mono-, di- and/or trihalogeno-(C_1-C_8)-alkoxy, in particular trifluoromethoxy; acyl; amino, N-[(C_1-C_8)-alkyl]-amino and/or N-di-[(C_1-C_8)-alkyl]-amino, where the alkyl radical for its part may optionally be substituted; N-[(C_1-C_6)-alkoxy]-aldimino; (C_1-C_8)-alkoxycarbonyl, where the alkoxycarbonyl radical for its part may optionally be substituted; and (C_6-C_{10})-aryl, in particular phenyl or naphthyl, where the (C_6-C_{10})-aryl radical for its part may optionally be substituted.

- (C_6-C_{10})-Aryloxy represents a group -O-(C_6-C_{10})-aryl, in particular a group -O-phenyl or -O-naphthyl, where otherwise reference may be made to the above definition of (C_6-C_{10})-aryl.

- Optionally substituted (C_6-C_{10})-aryloxy denotes a group -O-(C_6-C_{10})-aryl as defined above where, with respect to the substituents of the (C_6-C_{10})-aryl group, reference may be made to the above definition under optionally substituted (C_6-C_{10})-aryl.

- (C_1-C_8)-Alkoxy, (C_1-C_6)-alkoxy and (C_1-C_4)-alkoxy, as used in the present invention and also in the definitions of (C_1-C_8)-alkoxycarbonyl represents a straight-chain or branched alkoxy radical having 1 to 8; 1 to 6 and 1 to 4 carbon atoms, respectively. Examples which may be mentioned are: methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy, isopentoxy, n-hexoxy, isohexoxy, n-heptoxy and n-octoxy. Preference is given to a straight-chain or branched alkoxy radical having 1 to 6 carbon atoms. Particular preference is given to a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms.

- In the context of the present invention, optionally substituted (C_1-C_8)-alkoxy, (C_1-C_6)-alkoxy and (C_1-C_4)-alkoxy denotes a straight-chain or branched alkoxy radical as defined above having 1 to 8, 1 to 6 and 1 to 4 carbon atoms, respectively, which may optionally be mono- or polysubstituted by identical or different substituents, in particular by the following substituents: halogen (fluorine, chlorine, bromine, iodine); cyano; nitro; carboxyl; hydroxyl; straight-chain or branched (C_2-C_8)-alkenyl, preferably (C_2-C_6)-alkenyl, in particular (C_2-C_4)-alkenyl, where the alkenyl radical for its part may optionally be substituted; straight-chain or branched (C_1-C_8)-thioalkyl, where the thioalkyl radical for its part may optionally be substituted; straight-chain or branched mono-, di- and/or trihalogeno-(C_1-C_8)-alkyl, in particular trifluoromethyl; straight-chain or branched mono-, di- and/or trihalogeno-(C_1-C_8)-alkoxy, in particular trifluoromethoxy; acyl; amino, N-[(C_1-C_8)-alkyl]-amino and/or N-di-[(C_1-C_8)-alkyl]-amino, where the alkyl radical for its part may optionally be substituted; or (C_1-C_8)-alkoxycarbonyl, where the alkoxycarbonyl radical for its part may optionally be substituted.

- In the context of the invention, (C_3-C_7)-Cycloalkyl generally represents a carbon ring having 3 to 7 carbon atoms, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

- In the context of the invention, optionally substituted (C_3-C_7)-cycloalkyl generally represents a (C_3-C_7)-cycloalkyl radical as defined above which may optionally be mono- or polysubstituted by identical or different substituents, in particular by a (C_1-C_8)-alkyl radical, preferably a (C_1-C_6)-alkyl radical, very particularly preferably a (C_1-C_4)-alkyl radical, which for its part may in turn be mono- or polysubstituted as defined above.

- In the context of the invention, a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and O generally represents a monocyclic heteroaromatic radical which is attached via a ring carbon atom of the heteroaromatic radical and, if appropriate, also via a ring nitrogen atom of the heteroaromatic radical. Examples which may be mentioned are: furanyl (for example furan-2-yl, furan-3-yl), pyrrolyl (for example pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl), thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, pyridyl, pyrimidyl, pyridazinyl. Preference is given to pyridyl, pyrimidyl, pyridazinyl, furanyl, imidazolyl and thiazolyl.

- In the context of the invention, an optionally substituted 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and O generally represents a heterocycle as defined above which may be mono- or polysubstituted by identical or different substituents from the group consisting of nitro; amino; guanidino; aminocarbonyl; halogen, preferably chlorine or fluorine; (C_1-C_6)-alkyl, preferably (C_1-C_4)-alkyl, as defined above, which for its part may optionally be substituted; or by (C_6-C_{10})-aryl as defined above which for its part may optionally be substituted.

Compounds which are preferred in the context of the invention are compounds of the general formula (I),

in which:

R^1, R^2, R^3 are identical or different and independently of one another are selected from the group of the following substituents:

hydrogen;

hydroxyl;

optionally substituted (C_1-C_6)-alkyl;

optionally substituted phenyl or naphthyl;

optionally substituted (C_1-C_6)-alkoxy;

-O-$(CH_2)_n$-CH=CH_2 where n = 1 or 2;

fluorine, chlorine, bromine;

nitro;

cyano;

-C(O)-R^5;

-C(O)-NR^6R^7;

-NR^6R^7;

-NR^6-C(O)-R^8;

-O-C(O)-R^8;

-SO_2-NR^6R^7; and

-NR^6-SO_2R^8,

where:

R^5 denotes:

hydrogen;

hydroxyl;

optionally substituted (C_1-C_6)-alkyl;

optionally substituted (C_3-C_7)-cycloalkyl;

optionally substituted (C_1-C_6)-alkoxy;

optionally substituted phenyl or naphthyl;

optionally substituted phenyloxy or naphthyloxy; or

-O-$(CH_2)_n$-phenyl where n = 1, 2 or 3,

where the phenyl or naphthyl group may be fused via two adjacent ring atoms to optionally substituted (C_4-C_7)-cycloalkyl,

or

R^5 represents a 5- to 7-membered saturated or unsaturated heterocycle which for its part may be mono- or polysubstituted by
an oxo group (=O);
fluorine, chlorine, bromine;
optionally substituted (C_1-C_6)-alkyl;
nitro;
cyano;
hydroxyl;
optionally substituted phenyl or naphthyl; or
by (C_1-C_6)-alkoxy,

or

R^5 represents optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S,

where the heterocycle and the heteroaryl ring may each optionally be fused via two adjacent ring atoms to optionally substituted phenyl or naphthyl or optionally substituted (C_4-C_7)-cycloalkyl,

and

R^6 and R^7 are identical or different and represent
hydrogen;
optionally substituted (C_1-C_6)-alkyl;
optionally substituted phenyl or naphthyl; or

represent optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S

or

R^6 and R^7 together with the nitrogen atom to which they are optionally attached form a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of
an oxo group (=O);
fluorine, chlorine, bromine;
(C_1-C_6)-alkyl;
nitro;
cyano;
hydroxyl;
phenyl or naphthyl; or
(C_1-C_6)-alkoxy,

and

R^8 represents NR^6R^7 where R^6 and R^7 are as defined above;
optionally substituted (C_1-C_6)-alkyl;
(C_1-C_6)-alkoxy;
optionally substituted phenyl or naphthyl;
phenyloxy or naphthyloxy; or
$-O-(CH_2)_n$-phenyl where n = 1, 2 or 3,

and

R^4 represents straight-chain or branched (C_1-C_6)-alkyl or (C_2-C_6)-alkenyl which are optionally mono- or polysubstituted by

hydroxyl;

fluoro, chloro, bromine;

cyano;

-C(O)-R^5 where R^5 is as defined above;

-C(O)-NR^6R^7 where R^6 and R^7 are as defined above;

-NR^6R^7 where R^6 and R^7 are as defined above;

-NR^6-C(O)-R^8 where R^6 and R^8 are as defined above;

-SO_2-NR^6R^7 where R^6 and R^7 are as defined above;

-NR^6-SO_2-R^8 where R^6 and R^8 are as defined above;

-C(O)-$(CH_2)_n$-C(O)-R^8 where n = 0 to 2 and R^8 is as defined above;

(C_1-C_6)-alkoxy;

optionally substituted phenyloxy or naphthyloxy;

optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S;

optionally substituted phenyl or naphthyl; or

by a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S, which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of an oxo group (=O); fluorine, chlorine, bromine; (C_1-C_6)-alkyl; nitro; cyano; hydroxyl; phenyl or naphthyl; or by (C_1-C_6)-alkoxy,

where the heterocycle and the heteroaryl ring may each optionally be fused via two adjacent ring atoms to optionally substituted phenyl or naphthyl,

or

R^4 represents a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S,
which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of an oxo group (=O); fluorine, chlorine, bromine; (C_1-C_6)-alkyl; nitro; cyano; hydroxyl; phenyl or naphthyl; or by (C_1-C_6)-alkoxy and
which may optionally be fused via two adjacent ring atoms to optionally substituted phenyl or naphthyl or optionally substituted (C_4-C_7)-cycloalkyl,

and their tautomers and their respective salts, hydrates and alkoxides,

except for the following compounds of the general formula (I), in which the radicals R^1, R^2, R^3 and R^4 are as defined below:

- $R^1 = R^2 = H$; R^3 = para-OH; $R^4 = -CH_2-Z$ where Z = CN, C(O)-OC_2H_5, 4-Br-C_6H_4-CO, 4-n-butyl-C_6H_4-CO, H, C_6H_5, C(O)-O-CH_2-C_6H_5, C(O)-OCH_3, C(O)-OH, 2-oxo-benzo-pyranyl-3-carbonyl, 4-Cl-C_6H_4-CO, 3-Br-C_6H_4-CO, 4-C_6H_5-C_6H_4-CO, 4-CH_3-C_6H_4-CO, 3,4-Cl_2-C_6H_3-CO;
- $R^1 = R^2 = H$; R^3 = meta-OH; $R^4 = -CH_2-Z$ where Z = 4-Br-C_6H_4-NH-CO, 2-oxo-benzo-pyranyl-3-carbonyl, 4-Cl-C_6H_4-CO;
- $R^1 = R^2 = H$; R^3 = para-O-C(O)-CH_3; $R^4 = -CH_2-Z$ where Z = 4-CH_3-C_6H_4-CO, H, 2-oxo-benzopyranyl-3-carbonyl, $(CH_2)_3$-CH_3, 4-C_6H_5-C_6H_4;
- $R^1 = R^2 = R^3 = H$; $R^4 = -CH_2-Z$ where Z = CH_3, CN, 2-naphthyl;
- $R^1 = R^2 = H$; R^3 = para-butoxy; $R^4 = -CH_2-Z$ where Z = 4-Cl-C_6H_5, C(O)-OCH_3, C(O)-C_6H_5, $CH=CH_2$, C(O)-NH_2, H, 4-Br-C_6H_4-CO, 4-Cl-C_6H_4-CO, C(O)-OC_2H_5, C(O)-O-CH_2-C_6H_5, 2-oxo-benzopyranyl-3-carbonyl, C(O)-NH-C_6H_5, CN;
- $R^1 = R^2 = H$; R^3 = para-bromo; $R^4 = -CH_2-Z$ where Z = 4-Br-C_6H_4-CO, 4-Cl-C_6H_4-CO, C(O)-NH_2, C(O)-OCH_3, 4-Cl-C_6H_5, 4-Br-C_6H_4-NH-CO;
- $R^1 = R^2 = H$; R^3 = meta-fluoro; $R^4 = -CH_2-Z$ where Z = 4-Br-C_6H_4-CO, C(O)-NH_2, C(O)-O-CH_2-C_6H_5, CN;

- $R^1 = R^2 = H$; R^3 = para-chloro; $R^4 = -CH_2-Z$ where Z = 2-naphthyl, CH_3;
- $R^1 = R^2 = H$; R^3 = para-OCH_3; $R^4 = -CH_2-Z$ where Z = 2-naphthyl, CH_3;
- $R^1 = R^2 = H$; R^3 = meta-NO_2; $R^4 = -CH_2-Z$ where Z = CH_3.

Particularly preferred compounds are the compounds of the general formula (I)

in which:

R^1, R^2, R^3 are identical or different and independently of one another are selected from the group of the following substituents:
hydrogen;
hydroxyl;
optionally substituted (C_1-C_4)-alkyl;
optionally substituted phenyl;
optionally substituted (C_1-C_4)-alkoxy;
$-O-(CH_2)_n-CH=CH_2$ where n = 1;
fluorine, chlorine;
nitro;
cyano;
$-C(O)-R^5$;
$-C(O)-NR^6R^7$;
$-NR^6R^7$;
$-NR^6-C(O)-R^8$;
$-O-C(O)-R^8$;
$-SO_2-NR^6R^7$; and
$-NR^6-SO_2R^8$,

where:

R^5 denotes:
hydrogen;

hydroxyl;
optionally substituted (C_1-C_4)-alkyl;
optionally substituted (C_3-C_7)-cycloalkyl;
optionally substituted (C_1-C_4)-alkoxy;
optionally substituted phenyl;
optionally substituted phenyloxy; or
-O-$(CH_2)_n$-phenyl where n = 1,

where the phenyl group may be fused via two adjacent ring atoms to optionally substituted (C_5-C_6)-cycloalkyl,

or

R^5 represents a 5- to 7-membered saturated or unsaturated heterocycle which for its part may be mono- or polysubstituted by
an oxo group (=O);
fluorine, chlorine;
optionally substituted (C_1-C_4)-alkyl;
nitro;
cyano;
hydroxyl;
optionally substituted phenyl; or
by (C_1-C_4)-alkoxy,

or

R^5 represents optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S, selected from the group consisting of furanyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, pyridyl, pyrimidyl and pyridazinyl,

where the heterocycle and the heteroaryl ring may each optionally be fused via two adjacent ring atoms to optionally substituted phenyl or optionally substituted (C_5-C_6)-cycloalkyl,

and

R^6 and R^7 are identical or different and represent
hydrogen;
optionally substituted (C_1-C_4)-alkyl;
optionally substituted phenyl; or
represent optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S selected from the group consisting of furanyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, pyridyl, pyrimidyl and pyridazinyl,

or

R^6 and R^7 together with the nitrogen atom to which they are optionally attached form a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of
an oxo group (=O);
fluorine, chlorine;
(C_1-C_4)-alkyl;
nitro;
cyano;
hydroxyl;
phenyl; or
(C_1-C_4)-alkoxy,

and

R^8 represents NR^6R^7 where R^6 and R^7 are as defined above;
optionally substituted (C_1-C_4)-alkyl;
(C_1-C_4)-alkoxy;
optionally substituted phenyl;
phenyloxy; or
$-O-(CH_2)_n$-phenyl where n = 1,

and

R^4 represents straight-chain or branched (C_1-C_4)-alkyl or (C_2-C_4)-alkenyl which are optionally mono- or polysubstituted by
hydroxyl;
fluorine, chlorine;
cyano;
$-C(O)-R^5$ where R^5 is as defined above;
$-C(O)-NR^6R^7$ where R^6 and R^7 are as defined above;
$-NR^6R^7$ where R^6 and R^7 are as defined above;
$-NR^6-C(O)-R^8$ where R^6 and R^8 are as defined above;
$-SO_2-NR^6R^7$ where R^6 and R^7 are as defined above;
$-NR^6-SO_2-R^8$ where R^6 and R^8 are as defined above;
$-C(O)-(CH_2)_n-C(O)-R^8$ where n = 0 to 2 and R^8 is as defined above;
(C_1-C_4)-alkoxy;
optionally substituted phenyloxy;
optionally substituted 5- to 6-membered heteroaryl having up to 3 heteroatoms from the group consisting of N, O and S selected from the group consisting of furanyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, pyridyl, pyrimidyl and pyridazinyl;
optionally substituted phenyl; or

by a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of an oxo group (=O); fluorine, chlorine; (C_1-C_4)-alkyl; nitro; cyano; hydroxyl; phenyl; or by (C_1-C_4)-alkoxy,

where the heterocycle and the heteroaryl ring may each optionally be fused via two adjacent rings atoms to optionally substituted phenyl,

or

R^4 represents a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of N, O and S,
which for its part may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of an oxo group (=O); fluorine, chlorine; (C_1-C_4)-alkyl; nitro; cyano; hydroxyl; phenyl; or by (C_1-C_4)-alkoxy and
which may optionally be fused via two adjacent ring atoms to optionally substituted phenyl or optionally substituted (C_5-C_6)-cycloalkyl,

and their tautomers and their respective salts, hydrates and alkoxides,

except for the following compounds of the general formula (I), in which the radicals R^1, R^2, R^3 and R^4 are as defined below:

- $R^1 = R^2 = H$; R^3 = para-OH; $R^4 = -CH_2-Z$ where Z = CN, C(O)-OC_2H_5, 4-Br-C_6H_4-CO, 4-n-butyl-C_6H_4-CO, H, C_6H_5, C(O)-O-CH_2-C_6H_5, C(O)-OCH_3, C(O)-OH, 2-oxo-benzo-pyranyl-3-carbonyl, 4-Cl-C_6H_4-CO, 3-Br-C_6H_4-CO, 4-C_6H_5-C_6H_4-CO, 4-CH_3-C_6H_4-CO, 3,4-Cl_2-C_6H_3-CO;
- $R^1 = R^2 = H$; R^3 = meta-OH; $R^4 = -CH_2-Z$ where Z = 4-Br-C_6H_4-NH-CO, 2-oxo-benzo-pyranyl-3-carbonyl, 4-Cl-C_6H_4-CO;

- $R^1 = R^2 = H$; R^3 = para-O-C(O)-CH_3; R^4 = -CH_2-Z where Z = 4-CH_3-C_6H_4-CO, H, 2-oxo-benzopyranyl-3-carbonyl, 4-C_6H_5-C_6H_4;
- $R^1 = R^2 = R^3 = H$; R^4 = -CH_2-Z where Z = CH_3, CN;
- $R^1 = R^2 = H$; R^3 = para-butoxy; R^4 = -CH_2-Z where Z = 4-Cl-C_6H_5, C(O)-OCH_3, C(O)-C_6H_5, $CH=CH_2$, C(O)-NH_2, H, 4-Br-C_6H_4-CO, 4-Cl-C_6H_4-CO, C(O)-OC_2H_5, C(O)-O-CH_2-C_6H_5, 2-oxo-benzopyranyl-3-carbonyl, C(O)-NH-C_6H_5, CN;
- $R^1 = R^2 = H$; R^3 = meta-fluoro; R^4 = -CH_2-Z where Z = 4-Br-C_6H_4-CO, C(O)-NH_2, C(O)-O-CH_2-C_6H_5, CN;
- $R^1 = R^2 = H$; R^3 = para-chloro; R^4 = -CH_2-Z where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = para-OCH_3; R^4 = -CH_2-Z where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = meta-NO_2; R^4 = -CH_2-Z where Z = CH_3.

Particular preference according to the invention is given to compounds of the general formula (I)

in which:

R^1, R^2, R^3 are identical or different and independently of one another are selected from the group of the following substituents:

hydrogen;

hydroxyl;

methyl;

trifluoromethyl;

methoxy;

radicals of the formulae -O-CH_2-CH_2-OH, -O-CH_2-COOH or -O-CH_2-$CH=CH_2$;

fluorine, chlorine or bromine;

nitro;

cyano;

-C(O)OH or –C(O)OCH_3;

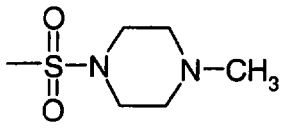
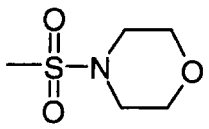
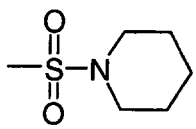
$-C(O)NH_2$;

$-NH_2$;

$-NH-C(O)-CH_3$;

$-O-C(O)-CH_3$ or $-O-C(O)-C_2H_5$;

radicals of the formulae


,

or

;

and

$-NH-SO_2CH_3$ or $-NH-SO_2C_6H_5$,

and

R^4 represents straight-chain or branched (C_1-C_4)-alkyl which is optionally mono- or polysubstituted by

hydroxyl;

amino;

$-C(O)-OCH_3$;

$-C(O)-NH_2$, $-C(O)-HNCH_3$, $-C(O)-HNC_2H_5$, or $-C(O)-HNC_6H_5$;

$-NHC(O)NH_2$, $-NHC(O)NHCH_3$, $-NHC(O)NHC_2H_5$, $-NHC(O)OCH_3$ or $-NHC(O)OC_2H_5$;

$-SO_2-NH_2$;

$-NH-SO_2-CH_3$ or $-NH-SO_2-C_2H_5$;

$-OCH_3$;

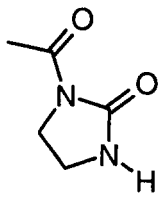
phenyl, which may be substituted by nitro, cyano, fluorine, methoxy, difluoromethoxy, methoxycarbonyl or p-tolylsulfonylmethyl;

pyridyl, furyl, imidazolyl, benzimidazolyl or thiazolyl, which may in each case be mono- or disubstituted by identical or different substituents from the group consisting of methyl, nitro and chlorine;

oxadiazolyl which may be substituted by phenyl or methoxyphenyl;

or

a radical of the formula



or

R^4 represents allyl or 3,3-dimethylallyl,

and their tautomers and their respective salts, hydrates and alkoxides,

except for the following compounds of the general formula (I), in which the radicals R^1, R^2, R^3 and R^4 are as defined below:

- $R^1 = R^2 = H$; R^3 = para-OH; $R^4 = -CH_2-Z$ where Z = H, C_6H_5, C(O)-OCH_3;
- $R^1 = R^2 = H$; R^3 = para-O-C(O)-CH_3; $R^4 = -CH_2-Z$ where Z = H;
- $R^1 = R^2 = R^3 = H$; $R^4 = -CH_2-Z$ where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = meta-fluoro; $R^4 = -CH_2-Z$ where Z = C(O)-NH_2;
- $R^1 = R^2 = H$; R^3 = para-chloro; $R^4 = -CH_2-Z$ where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = para-OCH_3; $R^4 = -CH_2-Z$ where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = meta-NO_2; $R^4 = -CH_2-Z$ where Z = CH_3.

Very particular preference according to the invention is given to compounds of the general formula (I)

in which:

R^1, R^2, R^3 are identical or different and independently of one another are selected from the group of the following substituents:

hydrogen;

hydroxyl;

methyl;

methoxy;

radicals of the formulae -O-CH_2-CH_2-OH, -O-CH_2-COOH or -O-CH_2-CH=CH_2;

fluorine or chlorine;

nitro;

cyano;

-C(O)OH or –C(O)OCH_3;

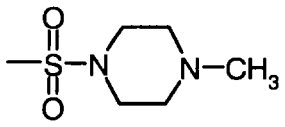
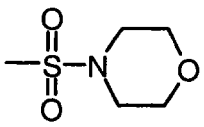
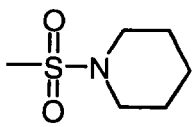
-C(O)NH_2;

-NH_2;

-NH-C(O)CH_3;

-O-C(O)-CH_3 or -O-C(O)-C_2H_5;

radicals of the formulae


, 
or 
;

and

–NH-SO_2CH_3 or –NH-$SO_2C_6H_5$,

and

R^4 represents straight-chain or branched (C_1-C_4)-alkyl which is optionally mono- or polysubstituted by

hydroxyl;

amino;

-C(O)-OCH_3;

$-C(O)-NH_2$, $-C(O)-HNCH_3$, $-C(O)-HNC_2H_5$, or $-C(O)-HNC_6H_5$;

$-NHC(O)NH_2$, $-NHC(O)NHCH_3$, $-NHC(O)NHC_2H_5$, $-NHC(O)OCH_3$ or $-NHC(O)OC_2H_5$;

$-SO_2-NH_2$;

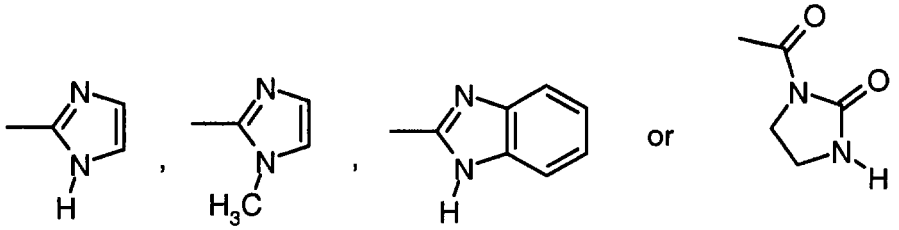
$-NH-SO_2-CH_3$ or $-NH-SO_2-C_2H_5$;

$-OCH_3$;

phenyl;

ortho-nitrophenyl; or

a radical of the formula



or

R^4 represents allyl,

and their tautomers and their respective salts, hydrates and alkoxides,

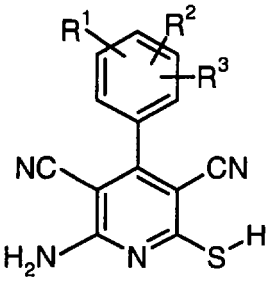
except for the following compounds of the general formula (I), in which the radicals R^1, R^2, R^3 and R^4 are as defined below:

- $R^1 = R^2 = H$; R^3 = para-OH; $R^4 = -CH_2-Z$ where Z = H, C_6H_5, $C(O)-OCH_3$;
- $R^1 = R^2 = H$; R^3 = para-$O-C(O)-CH_3$; $R^4 = -CH_2-Z$ where Z = H;
- $R^1 = R^2 = R^3 = H$; $R^4 = -CH_2-Z$ where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = meta-fluoro; $R^4 = -CH_2-Z$ where Z = $C(O)-NH_2$;
- $R^1 = R^2 = H$; R^3 = para-chloro; $R^4 = -CH_2-Z$ where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = para-OCH_3; $R^4 = -CH_2-Z$ where Z = CH_3;
- $R^1 = R^2 = H$; R^3 = meta-NO_2; $R^4 = -CH_2-Z$ where Z = CH_3.

The present invention also provides a process for preparing the compounds of the general formula (I).

According to a first variant of the process according to the invention, the compounds of the general formula (I) are prepared by

reacting compounds of the general formula (II)



(II),

in which the radicals R^1, R^2 and R^3 are as defined above

with compounds of the general formula (III)

$$R^4\text{-}X \quad \text{(III)},$$

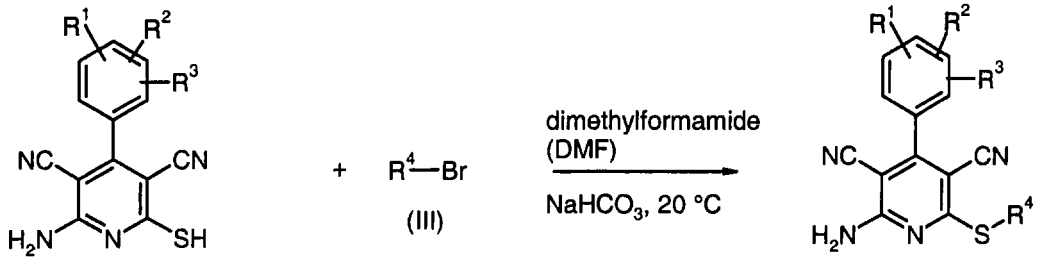
in which R^4 is as defined above

and

X represents a nucleofugic group (preferably halogen, in particular chlorine, bromine or iodine, or mesylate, tosylate, triflate or 1-imidazolyl),

in inert solvents, if appropriate in the presence of a base.

The process described above can be illustrated in an exemplary manner by the equation below:



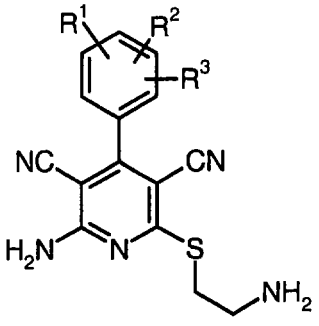
(II) (I)

If the radical R^4 in the general formula (I) has the meaning of

alkyl, substituted by the radicals $-NR^6-C(O)-R^8$, $-NR^6-C(O)-NR^6R^7$, $-NR^6-SO_2-R^8$,

where the radicals R^6, R^7 and R^8 are as defined above,

it is alternatively, according to a second variant of the process according to the invention, also possible to prepare the compounds of the general formula (I) by initially reacting the compounds of the general formula (II) with 2-bromoethylamine to give compounds of the general formula (IV)



(IV)

which are then reacted with compounds of the general formula

R^9-Y (V),

in which

R^9 has the meaning $-C(O)-R^8$, $-C(O)-O-R^8$, $-C(O)-NR^6R^7$, $-SO_2-R^8$ where R^8 is as defined above

and

Y represents a nucleofugic group, preferably halogen, in particular chlorine, bromine or iodine, or mesylate, tosylate, triflate or 1-imidazolyl,

or else

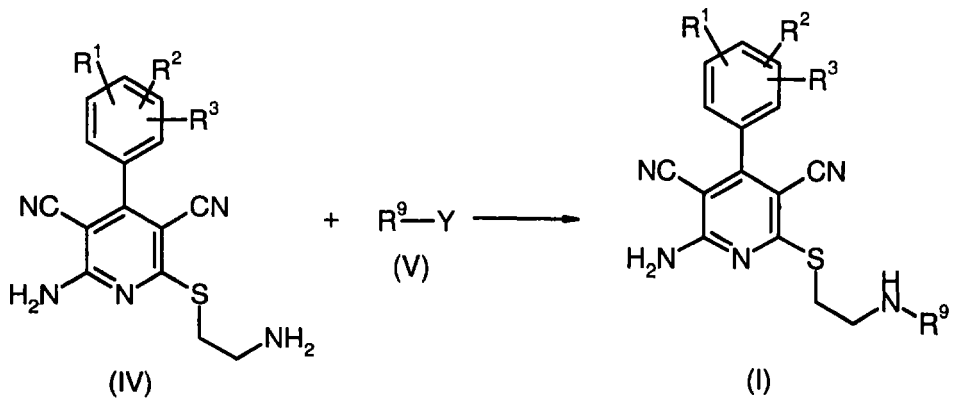
R^9 has the meaning R^6

and

Y represents the group O=C=N-,

in inert solvents, if appropriate in the presence of a base.

The second variant, described above, of the process according to the invention can be illustrated in an exemplary manner by the following equation:



The nucleofugic group X, which is sometimes also referred to as leaving group, can be introduced into the reaction separately or else be generated in situ by customary methods, for example by the "Mitsunobu reaction".

Suitable solvents for the process according to the invention are all organic solvents which are inert under the reaction conditions. These include alcohols such as methanol, ethanol and isopropanol, ketones such as acetone and methyl ethyl ketone, acyclic and cyclic ethers such as diethyl ether and tetrahydrofuran, esters such as ethyl acetate or butyl acetate, hydrocarbons such as benzene, xylene, toluene, hexane or cyclohexane, dimethylformamide, acetonitrile, pyridine, dimethyl sulfoxide (DMSO), chlorinated hydrocarbons such as dichloromethane, chlorobenzene or dichloroethane or hexamethylphosphoric triamide. Water is also suitable for use as solvent. Particular preference is given to dimethylformamide. It is also possible to use mixtures of the solvents mentioned above.

Suitable bases are the customary inorganic or organic bases. These preferably include alkali metal hydroxides, such as, for example, sodium hydroxide or potassium hydroxide, or alkali metal carbonates, such as sodium carbonate or potassium carbonate or sodium bicarbonate or potassium bicarbonate, or sodium methoxide or potassium methoxide or sodium ethoxide or potassium ethoxide or potassium tert-butoxide, or else amides, such as sodium amide, lithium bis-(trimethylsilyl)amide or lithium diisopropylamide, or organometallic compounds, such as butyllithium or phenyllithium, or else amines, such as triethylamine and pyridine. Preference is given to the alkali metal carbonates and alkali metal bicarbonates.

Here, the base can be employed in an amount of from 1 to 10 mol, preferably from 1 to 5 mol, in particular from 1 to 4 mol, based on 1 mol of the compounds of the general formula (II) or (IV).

The reaction generally takes place in a temperature range of from -78°C to reflux temperature. preferably in the range from –78°C to +40°C, in particular at room temperature.

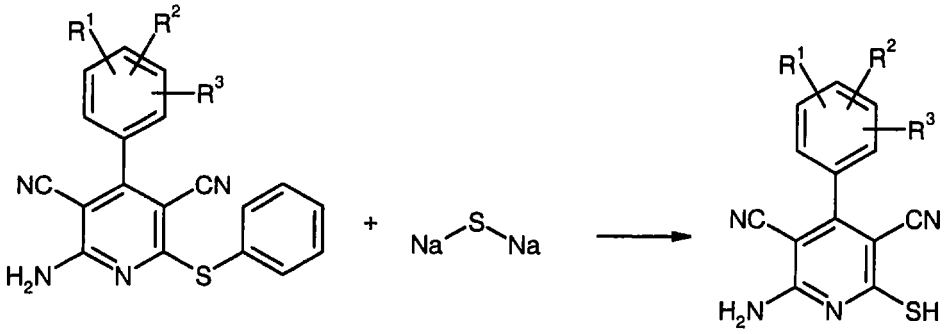
The reaction can be carried out at atmospheric, elevated or reduced pressure (for example in the range from 0.5 to 5 bar). In general, the reaction is carried out at atmospheric pressure.

The person skilled in the art is familiar with numerous modifications of the conditions mentioned above which are within the knowledge of the average expert and within the scope of the present invention.

The compounds of the general formulae (II) are likewise known per se to the person skilled in the art or can be prepared by customary methods known from the literature. Reference may be made in particular to the following publications, the respective content of which is expressly incorporated herein by way of reference:

- *Dyachenko et al.*, Russian Journal of Chemistry, Vol. 33, No. 7, 1997, pages 1014-1017 and Vol. 34, No. 4, 1998, pages 557-563;
- *Dyachenko et al.*, Chemistry of Heterocyclic Compounds, Vol. 34, No. 2, 1998, pages 188-194;
- *Qintela et al.*, European Journal of Medicinal Chemistry, Vol. 33, 1998, pages 887-897;
- *Kandeel et al.*, Zeitschrift für Naturforschung 42b, 107-111 (1987).

It is also possible to prepare the compounds of the general formula (II) from compounds of the general formula (VI) by reaction with an alkali metal sulfide. This preparation method can be illustrated in an exemplary manner by the equation below:



(VI) (II)

The alkali metal sulfide used is preferably sodium sulfide in an amount of from 1 to 10 mol, preferably from 1 to 5 mol, in particular from 1 to 4 mol, based on 1 mol of the compounds of the general formula (VI).

Suitable solvents are all organic solvents which are inert under the reaction conditions. These include N,N-dimethylformamide, N-methylpyrrolidinone, hexamethylphosphoric triamide, pyridine and acetonitrile. Particularly preference is given to N,N-dimethylformamide. It is also possible to use mixtures of the solvents mentioned above.

The reaction is generally carried out in a temperature range of from +20°C to reflux temperature, preferably in the range from +20°C to +120°C, in particular at from +60°C to +100°C.

The reaction can be carried out at atmospheric, elevated or reduced pressure (for example in the range from 0.5 to 5 bar). In general, the reaction is carried out at atmospheric pressure.

The person skilled in the art is familiar with numerous modifications of the conditions mentioned above which are within the knowledge of the average expert and within the scope of the present invention.

The compounds of the general formulae (VI) are likewise known per se to the person skilled in the art or can be prepared by customary methods known from the literature. Reference may be made in particular to the publication *Kambe et al., Synthesis, 531 (1981)* the content of which is expressly incorporated herein by way of reference.

The compounds of the general formulae (III) or (V) are either commercially available or known per se to the person skilled in the art or can be prepared by customary methods.

Surprisingly, the compounds of the general formula (I) have an unforeseeable useful pharmacological activity spectrum and are therefore suitable in particular for the prophylaxis and/or treatment of disorders.

This is because it has now been found, unexpectedly, that the substances of the formula (I) above are suitable for the prophylaxis and/or treatment of a large number of disorders, i.e. in particular, for example, disorders of the cardiovascular system (cardiovascular disorders); urogenital disorders; respiratory disorders; inflammatory and neuroinflammatory disorders; diabetes, in particular diabetes mellitus; cancer; and finally also neurodegenerative disorders, such as, for example, Parkinson's disease, and also pain.

In the context of the present invention, cardiovascular disorders are to be understood as meaning, in particular, for example the following disorders: coronary heart disease; hypertension (high blood pressure); restinosis such as, for example, restinosis after balloon dilatation of peripheral blood vessels; arteriosclerosis; tachycardia; arrhythmias; peripheral and cardiovascular disorders; stable and unstable angina pectoris; and atrial fibrillation.

The compounds of the general formula (I) are furthermore also suitable for reducing the myocardial area effected by an infarct.

The compounds of the general formula (I) are furthermore suitable for the treatment and prophylaxis of thromboembolic disorders and ischemias such as myocardial infarction, stroke and transitory ischemic attacks.

A further area of indication for which the compounds of the general formula (I) are suitable is the prophylaxis and/or therapy of urogenital disorders, such as, for example, irritable bladder, erectile dysfunction and female sexual dysfunction, and additionally also the prophylaxis and/or treatment of inflammatory disorders, such as, for example, asthma and inflammable dermatoses, of neuroinflammatory disorders of the central nervous system, such as, for example, conditions after cerebral infarction, Alzheimer's disease, furthermore also neurodegenerative disorders such as Parkinson's disease, and also pain.

A further area of indication is respiratory disorders such as, for example, asthma, chronic bronchitis, pulmonary emphysema, bronchiectases, cystic fibrosis (mucoviscidosis) and pulmonary hypertension.

The compounds of the general formula (I) are furthermore also suitable for the prophylaxis and/or therapy of hepatic fibrosis and cirrhosis of the liver.

Finally, the compounds of the general formula (I) are also suitable for the prophylaxis and/or therapy of diabetes, in particular diabetes mellitus.

Accordingly, the present invention also relates to the use of the substances of the general formula (I) for preparing medicaments and pharmaceutical compositions for the prophylaxis and/or treatment of the clinical features mentioned above.

The present invention furthermore relates to a method for the prophylaxis and/or the treatment of the clinical pictures mentioned above using substances of the general formula (I).

The pharmaceutical activity of the abovementioned compounds of the general formula (I) can be explained by their action as selective ligands on individual subtypes or a plurality of subtypes of the adenosine receptors, in particular as selective ligands on adenosine A1, adenosine A2a and/or adenosine A2b receptors, preferably as selective ligands on adenosine A1 and/or adenosine A2b receptors.

In the context of the present invention, "selective" are adenosine receptor ligands where, firstly, a clear effect on one or more adenosine receptor subtypes and, secondly, no or a considerably weaker effect on one or more other adenosine receptor subtypes can be observed, where, with respect to the test methods for the selectivity of action, reference is made to the test methods described in section A. II.

Compared to adenosine receptor ligands of the prior art, the substances of the general formula (I) are much more selective. Thus, for example, compounds of the general formula (I) in which R^4 represents (C_1-C_4)-alkyl which is substituted by a group of the formula $-C(O)NR^6R^7$, where R^6 and R^7 are identical or different and are hydrogen or optionally substituted (C_1-C_3)-alkyl, are generally selective on adenosine A2b receptors.

On the other hand, compounds of the general formula (I) in which R^4 represents (C_1-C_4)-alkyl substituted by one or more hydroxyl groups generally act selectively on adenosine A1 receptors.

Compounds of the general formula (I) in which R^4 represents (C_1-C_4)-alkyl substituted by imidazolyl or optionally substituted benzyl, in turn, generally act selectively on adenosine A1 and adenosine A2b receptors.

This receptor selectivity can be determined by biochemical measurement of the intracellular messenger cAMP in cells which specifically only express one subtype of the adenosine receptors. In the case of agonists, an increase in the intracellular cAMP concentration is observed; in the case of antagonists, a decrease in the intracellular

cAMP concentration after prior stimulation with adenosine or adenosine-like substances is observed (see the publications B. Kull, G. Arslan, C. Nilsson, C. Owman, A. Lorenzen, U. Schwabe, B.B. Fredholm, "Differences in the order of potency for agonists but not antagonists at human and rat adenosine A2A receptors", *Biochem. Pharmacol.*, **57** (1999) pages 65-75; and S.P. Alexander, J. Cooper, J. Shine, S.J. Hill, "Characterization of the human brain putative A2B adenosine receptor expressed in Chinese hamster ovary (CHO.A2B4) cells", *Br. J. Pharmacol.*, **119** (1996) pages 1286-90, the respective disclosure of which is hereby expressly incorporated by way of reference).

Accordingly, the present invention also provides the use of selective adenosine receptor ligands, in particular of selective adenosine A1, adenosine A2a and/or adenosine A2b receptor ligands, for preparing medicaments and pharmaceutical compositions for the prophylaxis and/or treatment of disorders, in particular, for example, disorders of the cardiovascular system (cardiovascular disorders); urogenital disorders; inflammatory and neuroinflammatory disorders; neurodegenerative disorders; respiratory disorders; hepatic fibrosis, cirrhosis of the liver; cancer; and finally diabetes, in particular diabetes mellitus, where, with respect to the individual areas of indication, reference is also made to what has been said above.

Thus, compounds of the general formula (I) which bind selectively to adenosine A1 receptors are preferably suitable for myocardial protection and for the prophylaxis and/or treatment of tachycardias, atrial arrhythmias, cardiac insufficiency, of acute kidney failure, diabetes and of pain. Compounds of the general formula (I) which bind selectively to adenosine A2a receptors, on the other hand, are preferably suitable for the prophylaxis and/or treatment of thromboembolic disorders, of neurodengenerative disorders such as Parkinson's disease and also for wound healing. Compounds of the general formula (I) which bind selectively to adenosine A2b receptors, in turn, are preferably suitable for the prophylaxis and/or therapy of hepatic fibrosis, of myocardial infarction, of neuroinflammatory disorders,

Alzheimer's disease, of urogenital incontinence and also of respiratory disorders such as, for example, asthma and chronic bronchitis.

The present invention also provides medicaments and pharmaceutical compositions comprising at least one selective adenosine and/or adenosine A2b receptor ligand, preferably at least one compound of the general formula (I), together with one or more pharmacologically acceptable excipients or carriers, and their use for the purposes mentioned above.

Suitable for administering the compounds of the general formula (I) are all customary administration forms, i.e. oral, parenteral, inhalative, nasal, sublingual, rectal or external, such as, for example, transdermal, with particular preference oral or parenteral. In the case of parenteral administration, particular mention may be made of intravenous, intramuscular and subcutaneous administration, for example as a subcutaneous depot. Very particular preference is given to oral administration.

Here, the active compounds can be administered on their own or in the form of preparations. Suitable preparations for oral administration are inter alia tablets, capsules, pellets, sugar-coated tablets, pills, granules, solid and liquid aerosols, syrups, emulsions, suspensions and solutions. Here, the active compound has to be present in such a quantity that a therapeutic effect is obtained. In general, the active compound can be present in a concentration of from 0.1 to 100% by weight, in particular from 0.5 to 90% by weight, preferably from 5 to 80% by weight. In particular, the concentration of the active compound should be 0.5-90% by weight, i.e. the active compound should be present in quantitites sufficient to achieve the dosage range mentioned.

To this end, the active compounds can be converted in a manner known per se into the customary preparations. This is achieved using inert nontoxic pharmaceutically suitable carriers, excipients, solvents, vehicles, emulsifiers and/or dispersants.

Excipients which may be mentioned are, for example: water, nontoxic organic solvents such as, for example, paraffins, vegetable oils (for example sesame oil), alcohols (for example ethanol, glycerol), glycols (for example polyethylene glycol), solid carriers, such as natural or synthetic ground minerals (for example talc or silicates), sugars (for example lactose), emulsifiers, dispersants (for example polyvinylpyrrolidone) and glidants (for example magnesium sulfate).

In the case of oral administration, tablets may, of course, also contain additives such as sodium citrate, together with adjuvants such as starch, gelatin and the like. Aqueous preparations for oral administration may furthermore be admixed with flavor enhancers or colorants.

In general, it has been found to be advantageous to administer, in the case of parenteral administration, quantities of from about 0.1 to about 10 000 µg/kg, preferably from about 1 to about 1 000 µg/kg, in particular from about 1 µg/kg to about 100 µg/kg, of bodyweight, to obtain effective results. In the case of oral administration, the quantity is from about 0.1 to about 10 mg/kg, preferably from about 0.5 to about 5 mg/kg, in particular from about 1 to about 4 mg/kg, of bodyweight.

In spite of this, it may still be required, depending on bodyweight, administration route, individual response to the active compound, the type of preparation and the time or interval at which administration takes place, to deviate from the quantities mentioned.

The present invention is illustrated by the examples below; however, these examples are only intended to facilitate a better understanding of the invention and not to restrict the invention in any way.

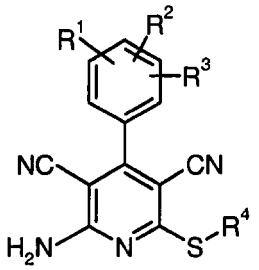
A. Evaluation of the physiological activity

I. Demonstration of the cardiovascular action

Langendorff heart of the rat:

After opening the thoracic cage of anesthetized rats, the heart is removed quickly and introduced into a conventional Langendorff apparatus. The coronary arteries are perfused at a constant volume (10 ml/min), and the resulting perfusion pressure is recorded via an appropriate pressure sensor. In this arrangement, a decrease of the perfusion pressure corresponds to a relaxation of the coronary arteries. At the same time, the pressure which is developed by the heart during each contraction is measured via a balloon introduced into the left ventricle and a further pressure sensor. The frequency of the isolated beating heart is calculated from the number of contractions per time unit.

In this test arrangement, the following values were obtained for the coronary perfusion pressure (the stated percentage refers to the reduction of the coronary perfusion pressure in percent at the respective concentration):

	Reduction of the coronary perfusion pressure in percent at a concentration of	
Compound of the formula (I) used 	**10^{-7} g/ml**	**10^{-6} g/ml**
$R^1 = R^2 = H$ R^3 = para-CH_3 R^4 = -CH_2-CH(OH)(CH_2OH) (compound of example A 198)	no effect observed	about 26%
$R^1 = R^2 = H$ R^3 = para-CH_3 R^4 = -CH_2-phenyl (compound of example A 189)	no effect observed	about 37%
$R^1 = R^2 = H$ R^3 = meta-OH R^4 = -CH_2-CH_2OH (compound of example A 43)	about 42%	about 68%
$R^1 = R^2 = H$ R^3 = para-OH R^4 = -CH_2-CH_2OH (compound of example 21)	about 40%	about 75%
$R^1 = R^2 = H$ R^3 = para-OH R^4 = 2-imidazolylmethyl (compound of example A 379)	about 64%	about 63%

At the stated concentrations, the substances tested had no effect on the pressure developed during the contraction in the left ventricle and no effect on the heart rate. Thus, it was demonstrated that the substances act selectively only on coronary perfusion.

II. Demonstration of the receptor selectivity (adenosine A1, A2a, A2b and A3 receptor selectivity)

Cells of the permanent line CHO (Chinese Hamster Ovary) were stably transfected with cDNA for the adenosine receptor subtypes A1, A2a, A2b and A3. Binding of the substances to the A2a or A2b receptor subtypes was determined by measuring the intracellular cAMP concentration in these cells using a conventional radioimmunological assay (cAMP-RIA, IBL GmbH, Hamburg, Germany).

In the case of the action of the substances as agonists, binding of the substances is expressed in an increase of the intracellular cAMP concentration. In these experiments, the adenosine analogue NECA (5-N-ethylcarboxamido-adenosine), which binds unselectively, but with high affinity, to all adenosine receptor subtypes and has agonistic action (Klotz, K.N., Hessling, J., Hegler, J., Owman, C., Kull, B., Fredholm, B.B., Lohse, M.J., Comparative pharmacology of human adenosine receptor subtypes - characterization of stably transfected receptors in CHO cells, Naunyn Schmiedebergs Arch Pharmacol, 357 (1998), 1-9) was used as reference compound.

The adenosine receptors A1 and A3 are coupled to a Gi protein, i.e. stimulation of these receptors results in an inhibition of adenylate cyclase and thus a reduction of the intracellular cAMP level. To identify A1/A3 receptor agonists, the adenylate cyclase is stimulated using forskolin. However, additional stimulation of the A1/A3 receptors inhibits adenylate cyclase, so that it is possible to detect A1/A3 receptor agonists by a comparatively low concentration of cAMP in the cell.

To demonstrate an antagonistic effect on adenosine receptors, the recombinant cells transfected with the corresponding receptor were prestimulated with NECA, and the effect of the substances on a reduction of the intracellular cAMP concentration by this prestimulation was examined. In these experiments, XAC (xanthine amine congener), which binds unselectively, but with high affinity, to all adenosine receptor

subtypes and has antagonistic action (Müller, C.E., Stein, B., Adenosine receptor antagonists: structures and potential therapeutic applications, Current Pharmaceutical Design, 2 (1996), 501-530) was used as reference compound.

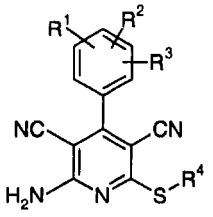
In the experiments below, the intracellular cAMP concentration in CHO cells which had been transfected with cDNA for the A2b receptor was determined. What is stated is the cAMP concentration in percent in all cells in a well of a microtiter plate, based on the control value obtained without any substances acting on the cells:

	Concentration of intracellular cAMP in percent at a concentration of				
Compound of the formula (I) used 	**10^{-9} M**	**10^{-8} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**
NECA (reference)	363	340	858	1226	1263
$R^1 = R^2 = H$ R^3 = para-OH $R^4 = -CH_2-C(O)NH_2$ (compound of example A 1)			837	947	900
$R^1 = R^2 = H$ R^3 = para-OH $R^4 = -CH_2-CH_2OH$ (compound of example 21)			253	432	384
$R^1 = R^2 = H$ R^3 = meta-OH $R^4 = -CH_2-CH_2OH$ (compound of example A 43)			347	674	784
$R^1 = R^2 = H$ R^3 = meta-OH $R^4 = -CH_2-CH(CH3)OH$ (compound of example A 46)			463	716	753
$R^1 = R^2 = H$ $R^3 = H$ $R^4 = -CH_2-CH_2OH$ (compound of example A 104)	100	178	438	586	571
$R^1 = R^2 = H$ R^3 = para-OH R^4 = 2-imidazolylmethyl (compound of example A 379)	870	846	861	936	1140

In these experiments, it was possible to block the action of all substances by the antagonist XAC, which is unselective, but highly specific for adenosine receptors.

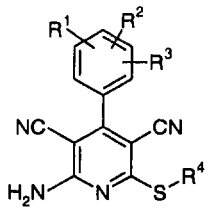
In the experiments below, the intracellular cAMP concentration in CHO cells which had been transfected with cDNA for the A2a receptor was determined. What is stated is the cAMP concentration in percent in all cells in a well of a microtiter plate, based on the control value obtained without any substances acting on the cells:

5

	Concentration of intracellular cAMP in percent at a concentration of				
Compound of the formula (I) used 	**10^{-9} M**	**10^{-8} M**	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**
NECA (reference)	585	800	1301	1992	2075
$R^1 = R^2 = H$ R^3 = para-OH $R^4 = -CH_2-C(O)NH_2$ (compound of example A 1)			92	117	208
$R^1 = R^2 = H$ R^3 = para-OH $R^4 = -CH_2-CH_2OH$ (compound of example 21)			143	117	
$R^1 = R^2 = H$ R^3 = meta-OH $R^4 = -CH_2-CH_2OH$ (compound of example A 43)			117	200	317
$R^1 = R^2 = H$ R^3 = meta-OH $R^4 = -CH_2-CH(CH3)OH$ (compound of example A 46)			67	108	183
$R^1 = R^2 = H$ $R^3 = H$ $R^4 = -CH_2-CH_2OH$ (compound of example A 104)	104	107	107	146	212
$R^1 = R^2 = H$ R^3 = para-OH R^4 = 2-imidazolylmethyl (compound of example A 379)	93	160	218	235	291

In these experiments, it was possible to block the action of all substances by the antagonist XAC, which is unselective, but highly specific for adenosine receptors.

In the following experiments, the intracellular cAMP concentration in CHO cells transfected with the cDNA for the A1 receptor was determined. What is stated is the cAMP concentration in percent in all cells of a well of a microtiter plate, based on the control value obtained without the action of any substance but after prestimulation with 1 μM of forskolin for 15 min (in these measurements, the cAMP concentration without prestimulation with forskolin is 18%):

	Concentration of intracellular cAMP in percent at a concentration of		
Compound of the formula (I) used 	**10^{-7} M**	**10^{-6} M**	**10^{-5} M**
NECA (reference)	24	24	28
$R^1 = R^2 = H$ R^3 = meta-OH R^4 = -CH_2-CH_2OH (compound of example A 43)	18	24	22
$R^1 = R^2 = H$ $R^3 = H$ R^4 = -CH_2-CH_2OH (compound of example A 104)	28	23	21
$R^1 = R^2 = H$ R^3 = para-OH R^4 = 2-imidazolylmethyl (compound of example A 379)	34	34	35

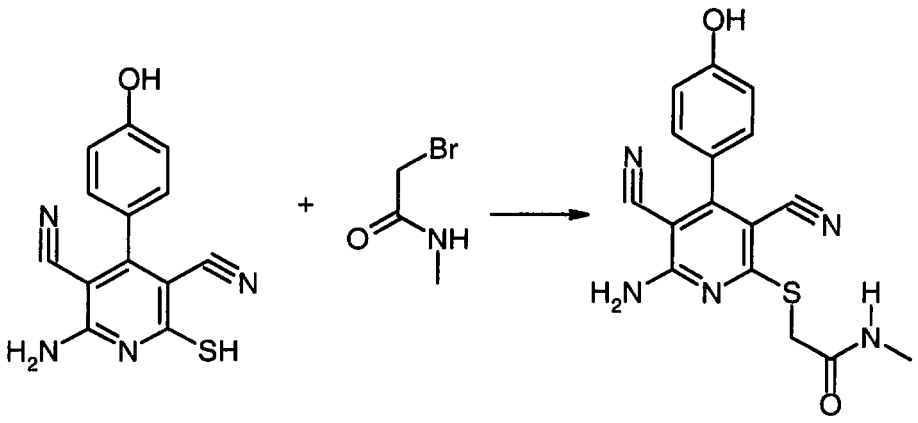
Thus, the compound of example A 1 has a clear agonistic effect on cells which express the adenosine receptor A2b and virtually no effect on cells with the A2a receptor. In contrast, the compounds from example A 43 and A 104 have a clear agonistic effect on cells with the A 1 receptor, virtually no effect on cells with A2a receptors and a considerably weaker effect on cells with the A2b receptor and are therefore selective adenosine A1 receptor agonists. The compound of example

A 379, on the other hand, has a clear agonistic effect on cells with the A2b receptor, virtually no effect on cells with A2a receptors and a comparably weaker effect on cells with the A1 receptor and is thus a selective adenosine A2b receptor agonist.

B. Synthesis examples

Example 1

2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}-N-methyl-acetamide



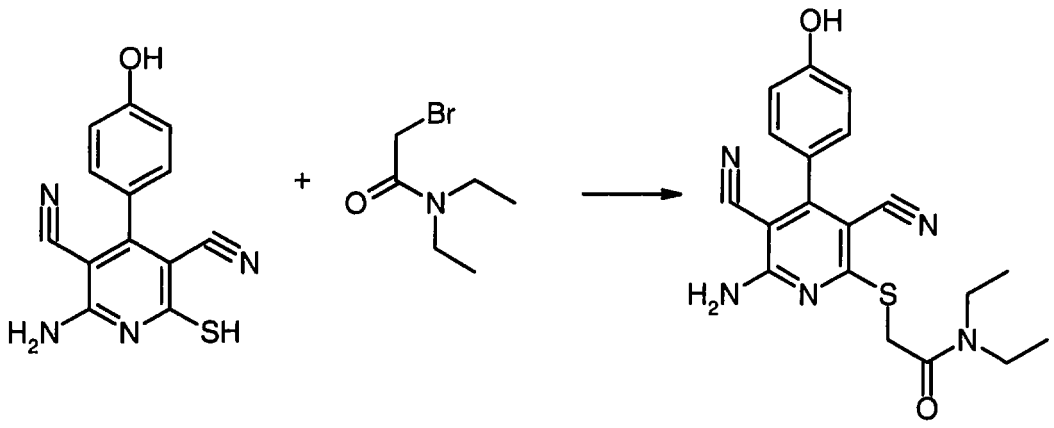
At room temperature (RT), 53.6 mg (0.2 mmol) of 2-amino-4-(4-hydroxyphenyl)-6-sulfanyl-3,5-pyridinedicarbonitrile and 45.6 mg (0.3 mmol) of N-methylbromo-acetamide are stirred in 0.5 ml of dimethylformamide (DMF) together with 33.6 mg (0.4 mmol) of $NaHCO_3$ for 4 hours. Thin-layer chromatography (TLC) (CH_2Cl_2/CH_3OH 10:1) shows complete conversion. The entire mixture is diluted with water and ethyl acetate (EA) and the EA phase is dried with $MgSO_4$ and concentrated under reduced pressure. The residue crystallizes from methanol.

Yield: 45 mg (66.3% of theory), white crystals

Mass spectrum: molecular mass calculated: 339, found $[M+H]^+$=340.3

Example 2

2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}-N,N-diethylacetamide



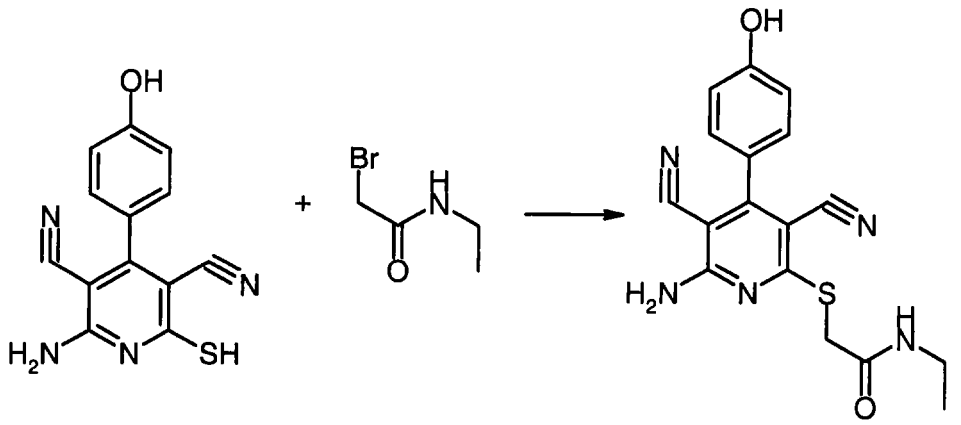
At RT, 53.6 mg (0.2 mmol) of 2-amino-4-(4-hydroxyphenyl)-6-sulfanyl-3,5-pyridinedicarbonitrile and 58.2 mg (0.3 mmol) of N,N-diethylbromoacetamide are stirred in 0.5 ml of DMF together with 33.6 mg (0.4 mmol) of $NaHCO_3$ for 4 hours. TLC (CH_2Cl_2/CH_3OH 10:1) shows complete conversion. The entire mixture is diluted with water and ethyl acetate and the EA phase is dried with $MgSO_4$ and concentrated under reduced pressure. The residue crystallizes from methanol.

Yield: 50 mg (65.5% of theory), white crystals

Mass spectrum: molecular mass calculated: 381, found $[M+H]^+=382$

Example 3

2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}-N-ethylacetamide



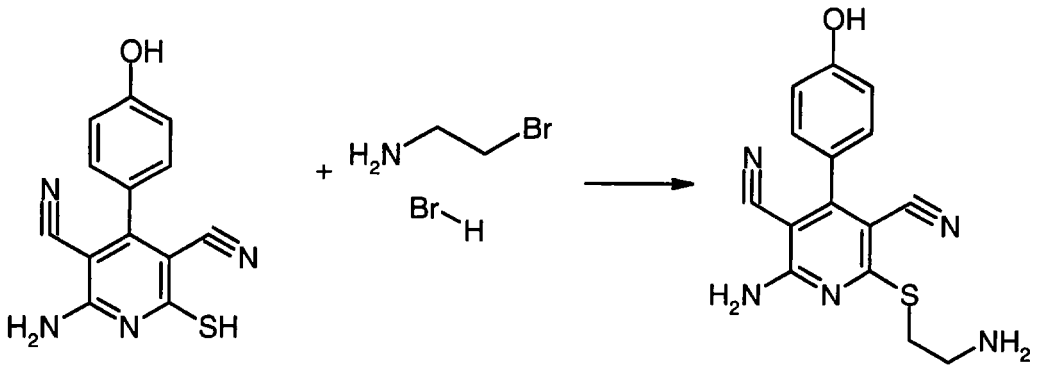
At RT 0.76 g (2 mmol) of 2-amino-4-(4-hydroxyphenyl)-6-sulfanyl-3,5-pyridinedicarbonitrile and 0.5 g (3 mmol) of N-ethylbromoacetamide are stirred in 5 ml of DMF together with 0.34 g (4 mmol) of $NaHCO_3$ for 4 hours. After dilution with water, the mixture is extracted with ethyl acetate and the ethyl acetate phase is dried with $MgSO_4$ and concentrated under reduced pressure. The solid residue obtained after concentration is stirred with methanol. The crystals are filtered off with suction and dried under reduced pressure.

Yield: 0.49 g (69.5% of theory), crystals

Mass spectrum: molecular mass calculated: 353, found $[M+H]^+$=354.2

Example 4

2-Amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile



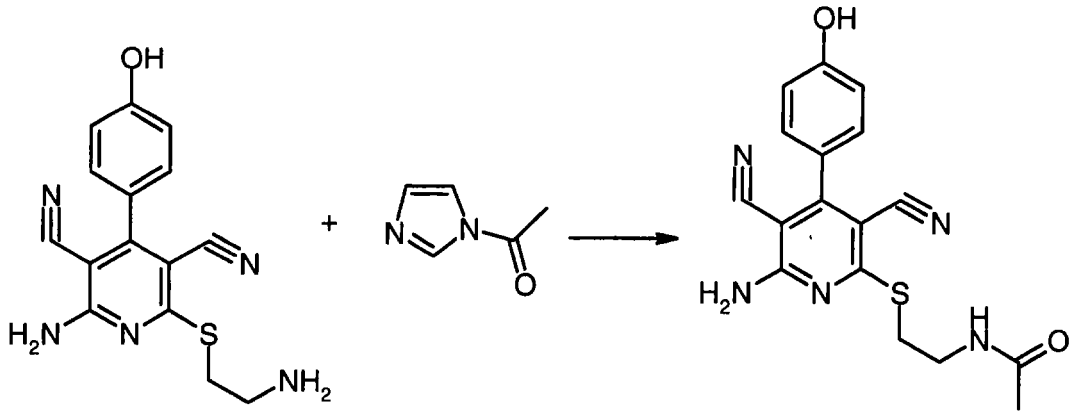
268 mg (1 mmol) of 2-amino-4-(4-hydroxyphenyl)-6-sulfanyl-3,5-pyridinedicarbonitrile, 105 mg (1 mmol) of 2-bromoethylamine hydrobromide and 168 mg (2 mmol) of $NaHCO_3$ are stirred in 1 ml of DMF for 1 hour. The entire mixture is diluted with a few milliliters of 1N HCl. The crystals are filtered off with suction and dried under reduced pressure.

Yield: 200 mg (64.2% of theory), yellow crystals

Mass spectrum: molecular mass calculated: 311, found $[M+H]^+=312$

Example 5

N-(2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}ethyl)-acetamide



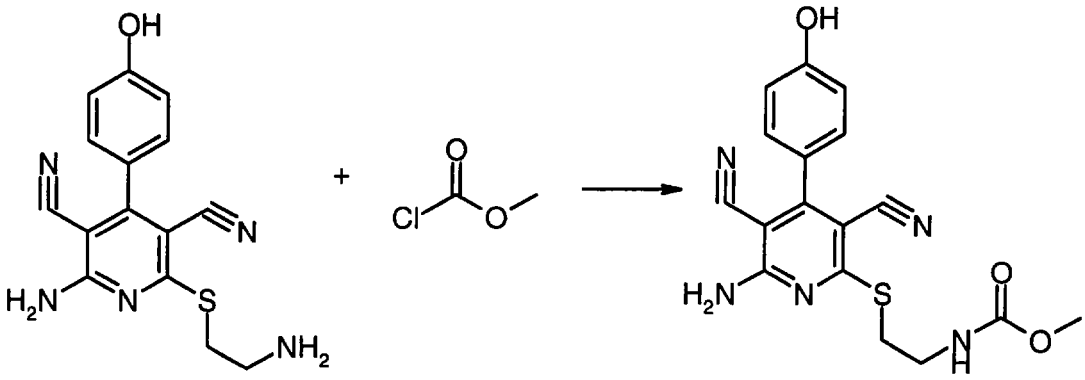
At RT 60 mg (0.2 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile and 30 mg (0.3 mmol) of N-acetylimidazole are stirred in 0.5 ml of DMF for 1 hour. Water is slowly added dropwise, the mixture becomes slightly turbid and the crude product crystallizes out. The product is filtered off with suction, washed with water and dried under reduced pressure. This gives 53 mg of yellow crystals. The crystals are dissolved in 1 ml of a 1:1 mixture of CH_2Cl_2/CH_3OH, and a few drops of concentrated ammonia are added (removal of diacetylated byproduct). The mixture is stirred at RT for 5 hours. The product crystallizes out when the reaction solution is concentrated. The product is filtered off with suction and washed with methanol.

Yield: 37 mg (52.3% of theory), almost white crystals

Mass spectrum: molecular mass calculated: 353, found $[M+H]^+=354$

Example 6

2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}methyl-carbamate



Under argon, 31.1 mg (0.1 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile are suspended at RT in 1 to 2 ml of dichloromethane, and the mixture is cooled to from -20 to –25°C. At this temperature, 30.3 mg (0.3 mmol) of triethylamine and 28,3 mg (0.3 mmol) of methyl chloroformate are added. The mixture is stirred at –20 C for 30 minutes and then allowed to warm to 0°C over a period of 1 hour. The mixture is concentrated under reduced pressure, 4 ml of a 2 molar NH_3 solution in methanol are added and the mixture is stirred at RT for 1 hour. The mixture is then concentrated, dissolved in 600 µl of DMSO and purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5µ 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15µ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B = water + 0.1% trifluoroacetic acid

0 min: 10% A; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

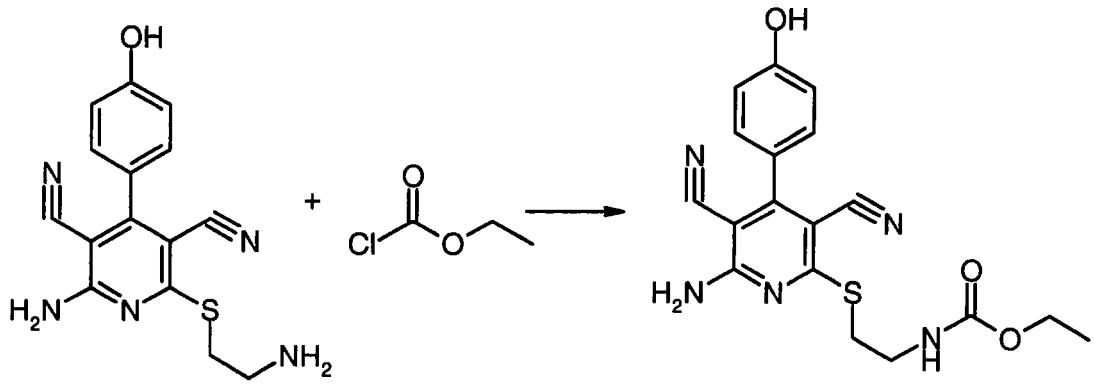
Injection volume: 600 µl of DMSO solution

Yield: 21.7 mg (58.7% of theory) of product

Mass spectrum: molecular mass calculated: 369, found $[M+H]^+$=370.1

Example 7

2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}ethyl-carbamate



Under argon, 31.1 mg (0.1 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile are suspended at RT in 1 to 2 ml of dichloromethane, and the mixture is cooled to from -20 to -25°C. At this temperature, 30.3 mg (0.3 mmol) of triethylamine and 32.6 mg (0.3 mmol) of ethyl chloroformate are added. The mixture is stirred at -20°C for 30 minutes and then allowed to warm to 0°C over a period of 1 hour. The mixture is concentrated under reduced pressure, 4 ml of a 2 molar NH_3 solution in methanol are added and the mixture is stirred at RT for 1 hour. The mixture is then concentrated, dissolved in 600 µl of DMSO and purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5µ 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15µ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B= water + 0.1% trifluoroacetic acid

0 min: 10% A; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

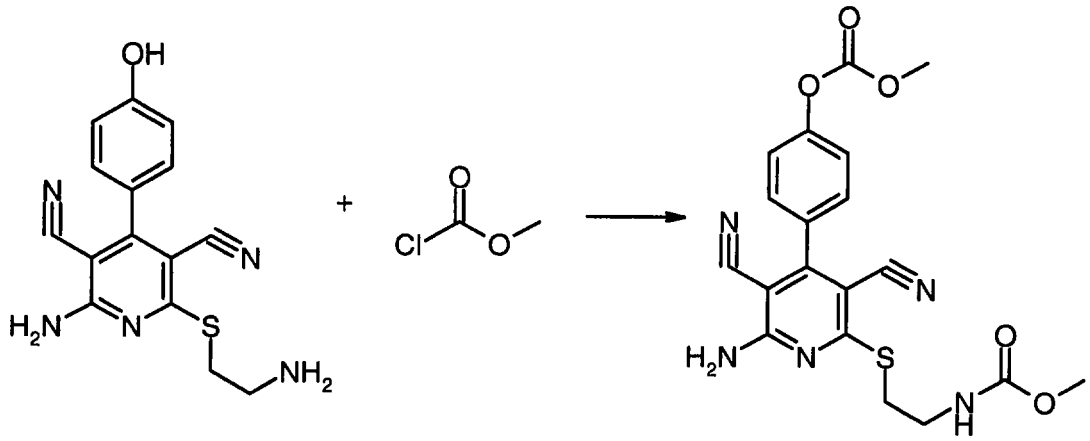
Injection volume: 600 µl of DMSO solution

Yield: 20.5 mg (53.5% of theory) of product

Mass spectrum: molecular mass calculated: 383, found $[M+H]^+$=384.2

Example 8

4-[2-Amino-3,5-dicyano-6-({2-[(methoxycarbonyl)amino]ethyl}sulfanyl)-4-pyridinyl]phenyl-methylcarbonate



Under argon, 31.1 mg (0.1 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile are suspended at RT in 1 to 2 ml of dichloromethane, and the mixture is cooled to from -20 to -25°C. At this temperature, 10.1 mg (0.1 mmol) of triethylamine and 9.4 mg (0.1 mmol) of methyl chloroformate are added. The mixture is stirred at -20°C for 30 minutes and then allowed to warm to 0°C over a period of 1 hour. The mixture is then concentrated dissolved in 600 µl of DMSO and purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5µ 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15µ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B= water + 0.1 % trifluoroacetic acid

0 min: 10% A; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A;

8.1 min. 10% A; 9 min. 10% A

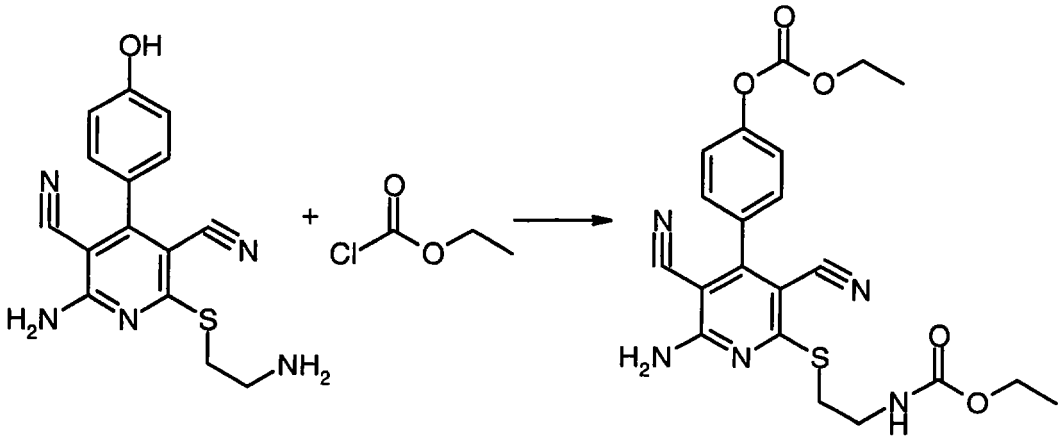
Injection volume: 600 µl of DMSO solution

Yield: 11.2 mg (26.2% of theory) of product

Mass spectrum: molecular mass calculated: 427, found $[M+H]^+$= 428.2

Example 9

4-[2-Amino-3,5-dicyano-6-({2-[(methoxycarbonyl)amino]ethyl}sulfanyl)-4-pyridinyl]phenyl-ethylcarbonate



Under argon 31.1 mg (0.1 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile are suspended at RT in 1 to 2 ml of dichloromethane, and the mixture is cooled to from -20 to –25°C. At this temperature, 10.1 mg (0.1 mmol) of triethylamine and 10.9 mg (0.1 mmol) of ethyl chloroformate are added. The mixture is stirred at–20°C for 30 minutes and then allowed to warm to 0°C over a period of 1 hour. The mixture is then concentrated, dissolved in 600 µl of DMSO and purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5µ 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15µ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B= water + 0.1% trifluoroacetic acid

0 min: 10% A; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A;

8.1 min. 10% A; 9 min. 10% A

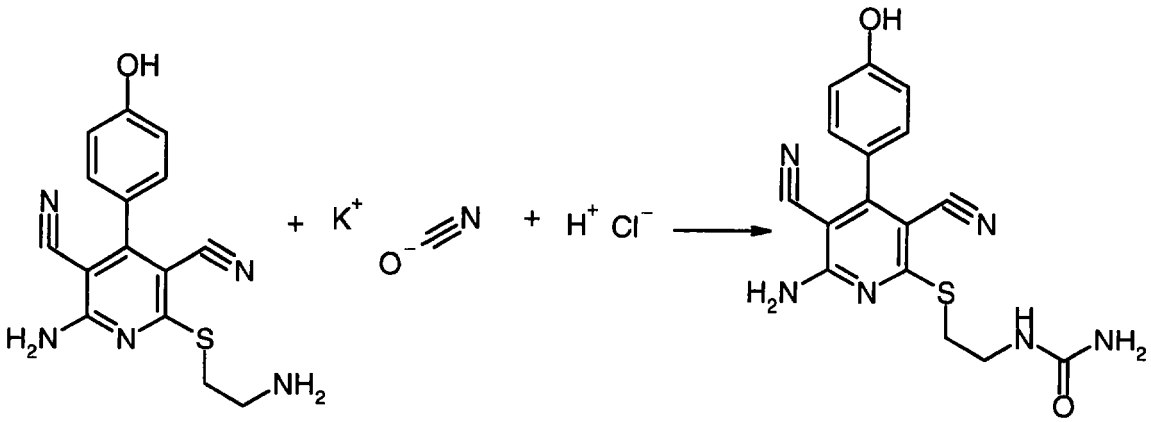
Injection volume: 600 µl of DMSO solution

Yield: 15.2 mg (33.4% of theory) of product

Mass spectrum: molecular mass calculated: 455, found $[M+H]^+$= 456.2

Example 10

N-(2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}-ethyl)urea



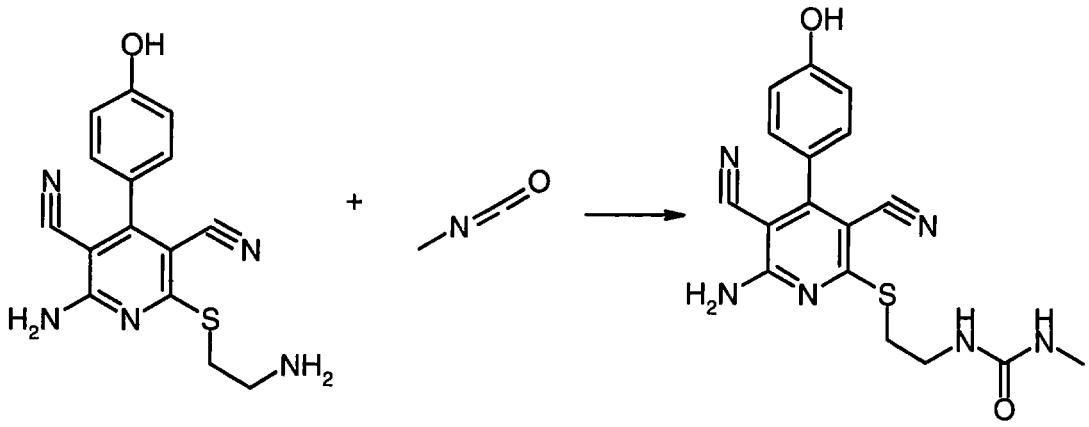
31.1 mg (0.1 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile are suspended in 0.91 ml of 1N HCl, and 8.1 mg (0.1 mmol) of potassium cyanate are added. After the addition of a few drops of methanol, the mixture is stirred at 50°C for a total of 10 hours. The crystals are filtered off with suction and washed with water and ether.

Yield: 16 mg (45.1% of theory) of product

Mass spectrum: molecular mass calculated: 354, found $[M+H]^+$= 355.1

Example 11

N-(2-{[6-Amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}ethyl)-N'-methylurea



62.2 mg (0.2 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile are suspended in 0.4 ml of DMF, and 11.4 mg (0.2 mmol) of methyl isocyanate are added at room temperature. The mixture is stirred overnight, filtered and purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5μ 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15μ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B= water + 0.1% trifluoroacetic acid

0 min: 10% A; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

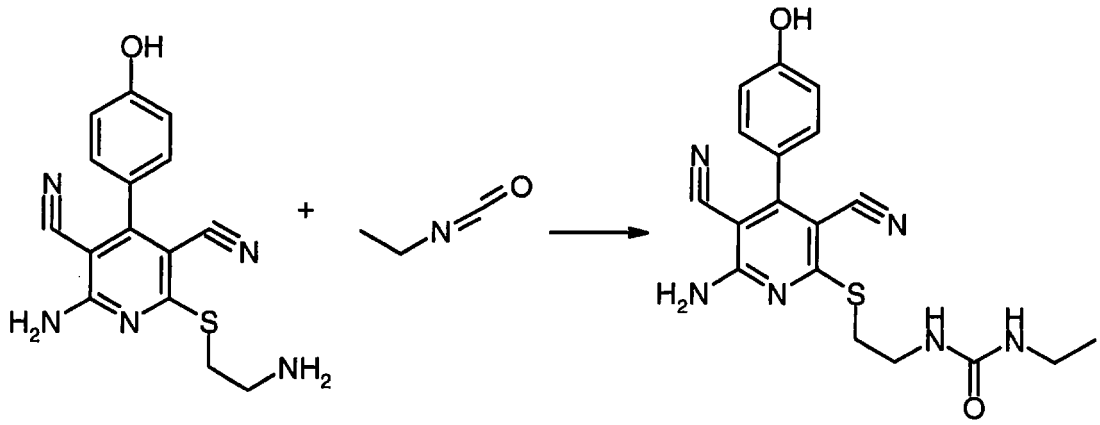
Injection volume: 400 μl of DMF solution

Yield: 45.9 mg (62.3% of theory) of product

Mass spectrum: molecular mass calculated: 368, found $[M+H]^+$=369.2

Example 12

N-(2-{[6-amino-3,5-dicyano-4-(4-hydroxyphenyl)-2-pyridinyl]sulfanyl}ethyl)-N'-methylurea



62.2 mg (0.2 mmol) of 2-amino-6-[(2-aminoethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile are suspended in 0.4 ml of DMF, and 14.2 mg (0.2 mmol) of ethyl isocyanate are added at room temperature. The mixture is stirred overnight, filtered and purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5μ 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15μ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B= water + 0.1% trifluoroacetic acid

0 min: 10% A; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A;

8.1 min. 10% A; 9 min. 10% A

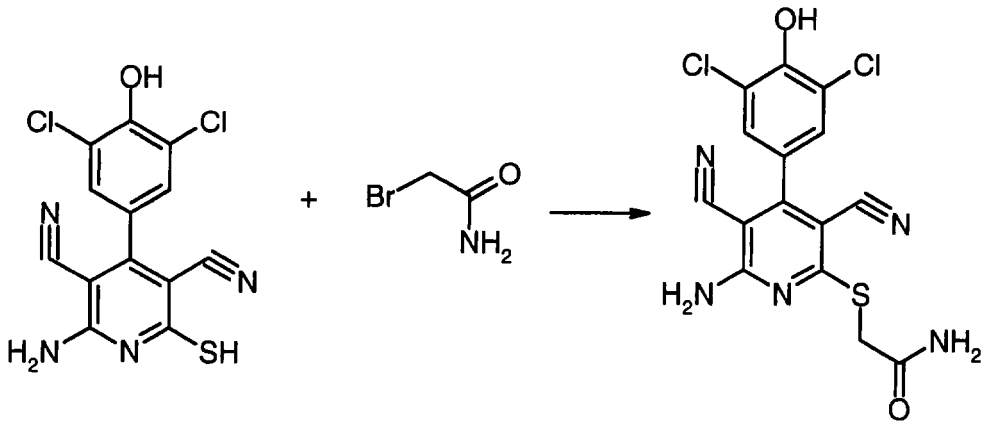
Injection volume: 400 μl of DMF solution

Yield: 37.6 mg (49.2 % of theory) of product

Mass spectrum: molecular mass calculated: 382, found $[M+H]^+$=383.2

Example 13

3,5-Dicyano-4-(3,5-dichloro-4-hydroxyphenyl)-2-carbamoylmethyl-6-amino-pyridine



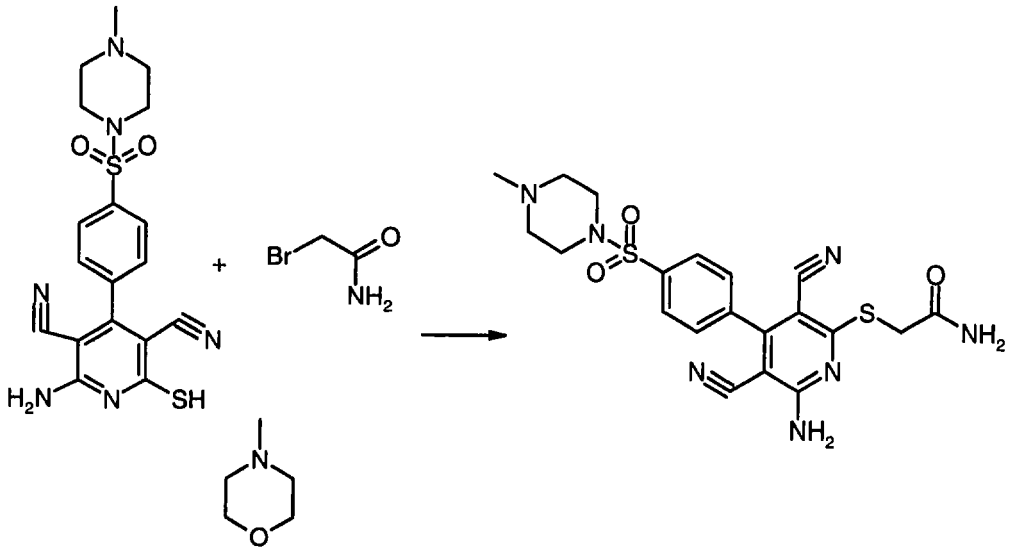
337.2 mg (1 mmol) of 2-amino-4-(3,5-dichloro-4-hydroxyphenyl)-6-sulfanyl-3,5-pyridinedicarbonitrile and 207 mg (1.5 mmol) of bromoacetamide are dissolved in 4 ml of DMF, 336 mg (4 mmol) of $NaHCO_3$ are added and the mixture is stirred at RT for 8 hours. The mixture is diluted with water and washed with ethyl acetate. The aqueous phase is acidified with 1N HCl and the resulting crystals are filtered off with suction and dried.

Yield: 180 mg (45.7 % of theory) of product

Mass spectrum: molecular mass calculated: 393, found $[M+H]^+$=394.1

Example 14

2-[(6-Amino-3,5-dicyano-4-{4-[(4-methylpiperazino)sulfonyl]phenyl}-2-pyridinyl)sulfanyl]acetamide



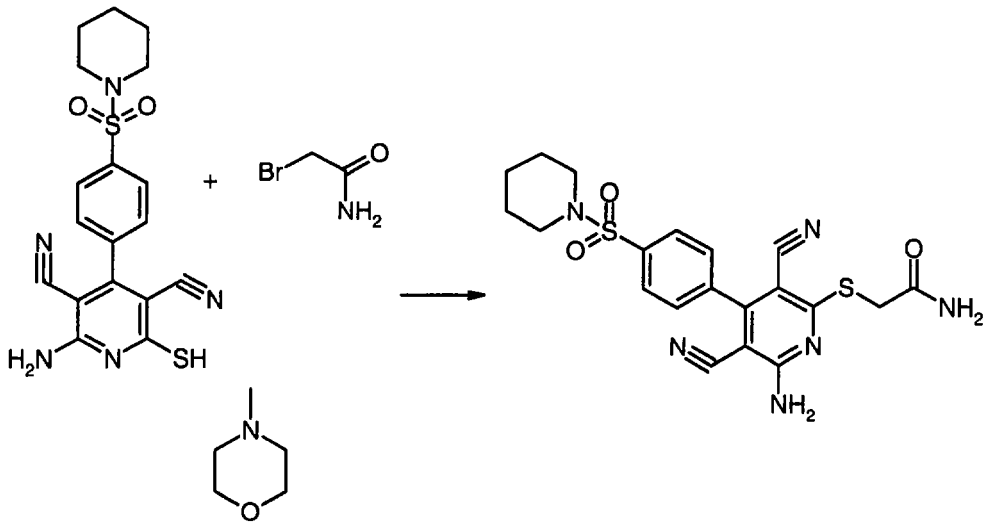
84 mg (0.163 mmol) of 2-amino-4-{4-[(4-methylpiperazino)sulfonyl]phenyl}-6-sulfanyl-3,5-pyridinedicarbonitrile N-methylmorpholinium salt together with 53.3 mg (0.244 mmol) of bromoacetamide and 54.7 mg (0.65 mmol) of $NaHCO_3$ are stirred in 0.5 ml of DMF overnight. After filtration, the reaction solution is initially purified by preparative HPLC. The isolated fraction is reconcentrated under reduced pressure and the residue is purified by preparative thin-layer chromatography.

Yield: 14 mg (18.2 % of theory) of product

Mass spectrum: molecular mass calculated: 471, found $[M+H]^+$=472.1

Example 15

2-({6-Amino-3,5-dicyano-4-[4-(piperidinosulfonyl)phenyl]-2-pyridinyl}-sulfanyl)acetamide



82 mg (0.164 mmol) of 2-amino-4-{4-(piperidinosulfonyl)phenyl}-6-sulfanyl-3,5-pyridinedicarbonitrile N-methylmorpholinium salt together with 53.5 mg (0.246 mmol) of bromoacetamide and 55 mg (0.65 mmol) of $NaHCO_3$ are stirred in 0.5 ml of DMF overnight. After filtration, the reaction solution is purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5μ 50 x 20 mm

Precolumn: GROM-SIL ODS 4 HE 15 μ 10 x 20 mm

Wavelength: 220 mm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B = water + 0.1% trifluoroacetic acid

0 min: 10%; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

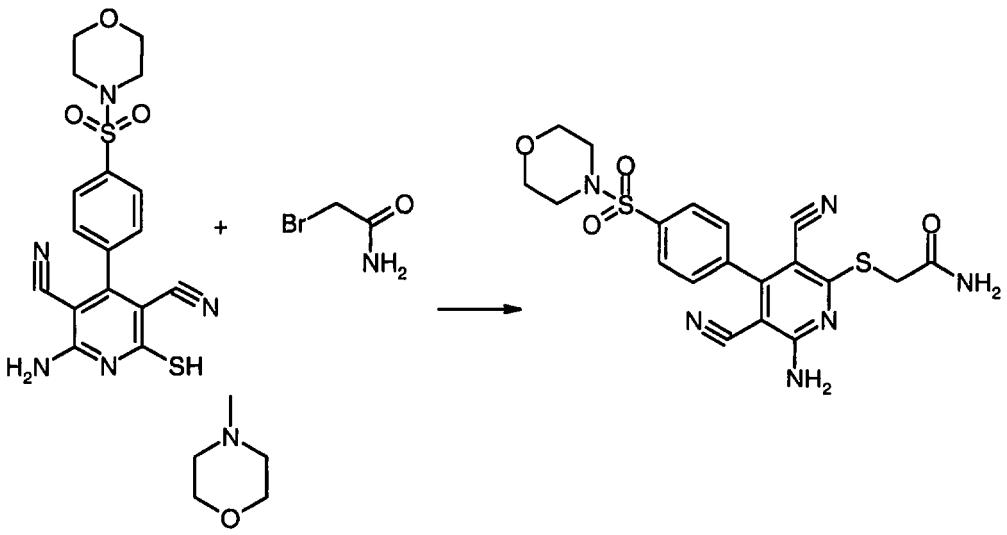
Injection volume: 400 μl of DMF solution

Yield: 42.8 mg (57.2% of theory) of product

NMR [400 MHz, DMSO-d_6]: 1.4 m (2H), 1.6 m (4H), 3.0 tr (4H), 3.9 s (2H), 7.25 s (1H), 7.5 s (1H), 7.8 d (2H), 7.9 d (2H), 8.1 s broad (2H)

Example 16

2-({6-Amino-3,5-dicyano-4-[4-(morpholinosulfonyl)phenyl]-2-pyridinyl}-sulfanyl)acetamide



90 mg (0.179 mmol) of 2-amino-4-{4-(morpholinosulfonyl)phenyl}-6-sulfanyl-3,5-pyridinedicarbonitrile N-methylmorpholinium salt together with 58.5 mg (0.269 mmol) of bromoacetamide and 60 mg (0.71 mmol) of $NaHCO_3$ are stirred in 0.5 ml of DMF overnight. After filtration, the reaction solution is purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5μ 50 x 20 mm

Precolumn: GROM-SIL ODS 4 HE 15 μ 10 x 20 mm

Wavelength: 220 mm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B = water + 0.1% trifluoroacetic acid

0 min: 10%; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

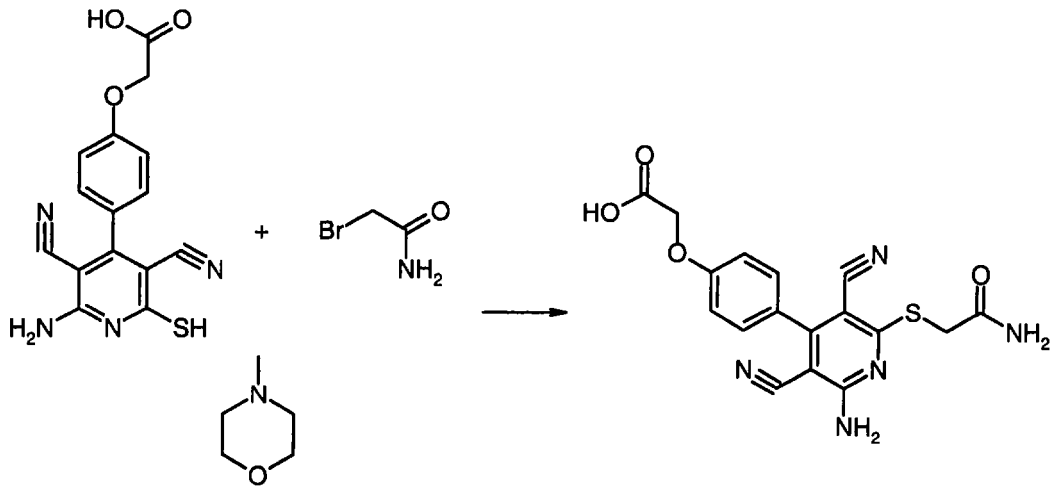
Injection volume: 400 µl of DMF solution

Yield: 43.7 mg (53.2% of theory) of product

NMR[400 MHz, DMSO-d_6]: 2.9 tr (4H), 3.65 tr (4H), 3.9 s (2H), 7.25 s (1H), 7.5 s (1H), 7.85 d (2H), 7.95 d (2H), 8.15 s broad (2H)

Example 17

2-(4-{2-Amino-6-[(2-amino-2-oxoethyl)sulfanyl]-3,5-dicyano-4-pyridinyl}-phenoxy)acetic acid



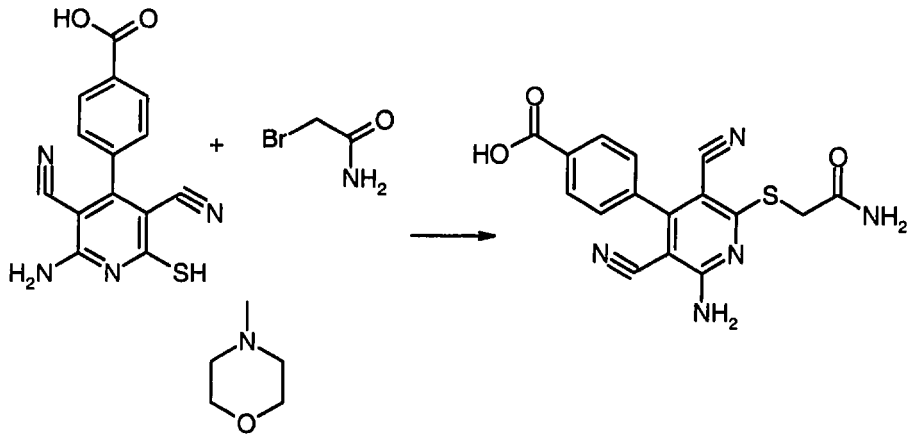
135 mg (0.316 mmol) of 2-[4-(2-amino-3,5-dicyano-6-sulfanyl-4-pyridinyl)-phenoxy]acetic acid N-methylmorpholinium salt together with 103.3 mg (0.474 mmol) of bromoacetamide and 106.1 mg (1.263 mmol) of $NaHCO_3$ are stirred in 0.5 ml of DMF overnight. After filtration, the reaction solution is prepurified by preparative HPLC. The isolated fraction is reconcentrated under reduced pressure and the residue is purified by preparative thin-layer chromatography.

Yield: 14 mg (11.6 % of theory) of product

Mass spectrum: molecular mass calculated: 383, found $[M+Na]^+$=406.2

Example 18

4-{2-Amino-6-[(2-amino-2-oxoethyl)sulfanyl]-3,5-dicyano-4-pyridinyl}-benzoic acid



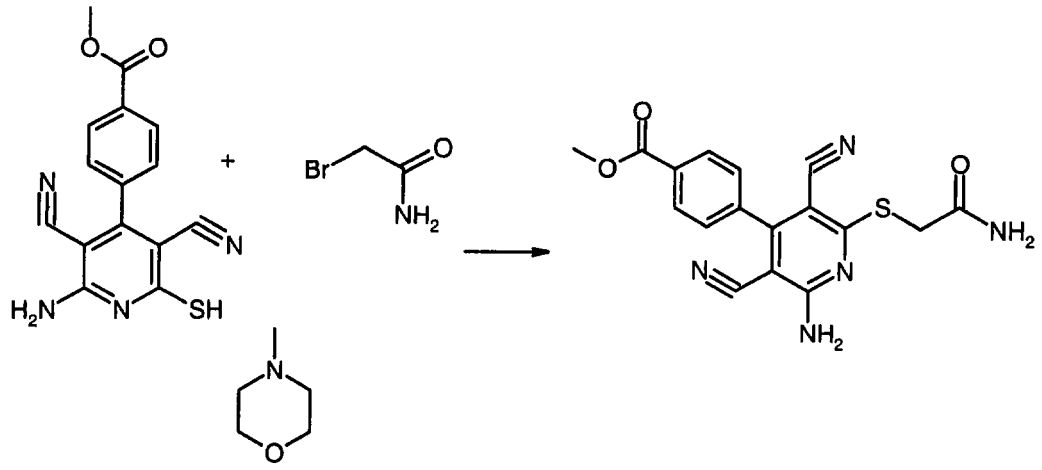
72 mg (0.18 mmol) of 2-[4-(2-amino-3,5-dicyano-6-sulfanyl-4-pyridinyl)benzoic acid N-methylmorpholinium salt together with 59.2 mg (0.27 mmol) of bromo-acetamide and 60.9 mg (0.72 mmol) of $NaHCO_3$ are stirred in 0.5 ml of DMF overnight. After filtration, the reaction solution is prepurified by preparative HPLC. The isolated fraction is reconcentrated under reduced pressure and the residue is purified by preparative thin-layer chromatography.

Yield: 11 mg (17.2 % of theory) of product

Mass spectrum: molecular mass calculated: 353, found $[M+H]^+$=353.9

Example 19

Methyl 4-{2-amino-6-[(2-amino-2-oxoethyl)sulfanyl]-3,5-dicyano-4-pyridinyl}-benzoate



89 mg (0.216 mmol) of methyl 4-(2-amino-3,5-dicyano-6-sulfanyl-4-pyridinyl)-benzoate N-methylmorpholinium salt together with 70.7 mg (0.324 mmol) of bromoacetamide and 72.7 mg (0.86mmol) of $NaHCO_3$ are stirred in 0.5 ml of DMF overnight. After filtration, the reaction solution is purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5μ 50 x 20 mm

Precolumn: GROM-SIL ODS 4 HE 15 μ 10 x 20 mm

Wavelength: 220 mm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B = water + 0.1% trifluoroacetic acid

0 min: 10%; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

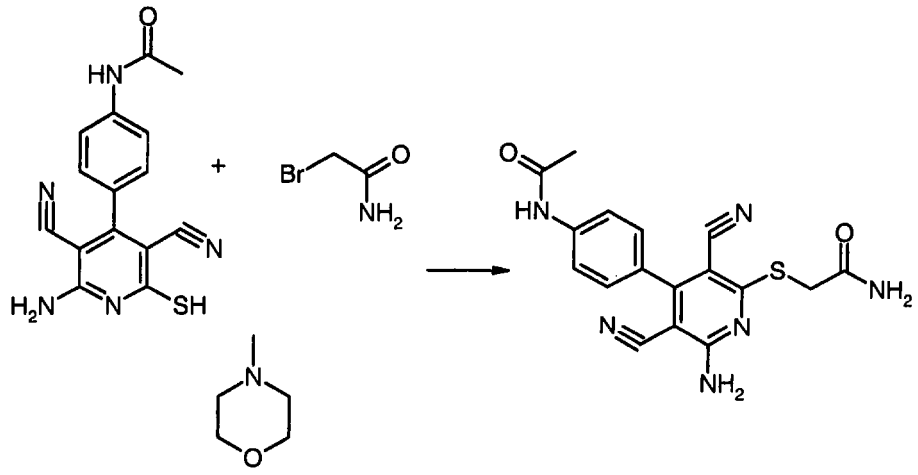
Injection volume: 400 μl of DMF solution

Yield: 40.4 mg (50.8% of theory) of product

NMR [400 MHz, DMSO-d_6]: 3.9 s (2H), 7.25 s (1H), 7.5 s (1H), 7.7 d (2H), 8.1 d (2H), 8.1 s broad (2H)

Example 20

2-({4-[4-(Acetylamino)phenyl]-6-amino-3,5-dicyano-2-pyridinyl}sulfanyl)-acetamide



44 mg (0.11 mmol) of N-[4-(2-amino-3,5-dicyano-6-sulfanyl-4-pyridinyl)phenyl]-acetamide N-methylmorpholinium salt together with 35 mg (0.16 mmol) of bromoacetamide and 36 mg (0.43 mmol) of $NaHCO_3$ are stirred in 0.5 ml of DMF overnight. After filtration, the reaction solution was purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5μ 50 x 20 mm

Precolumn: GROM-SIL ODS 4 HE 15 μ 10 x 20 mm

Wavelength: 220 mm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B = water + 0.1% trifluoroacetic acid

0 min: 10%; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

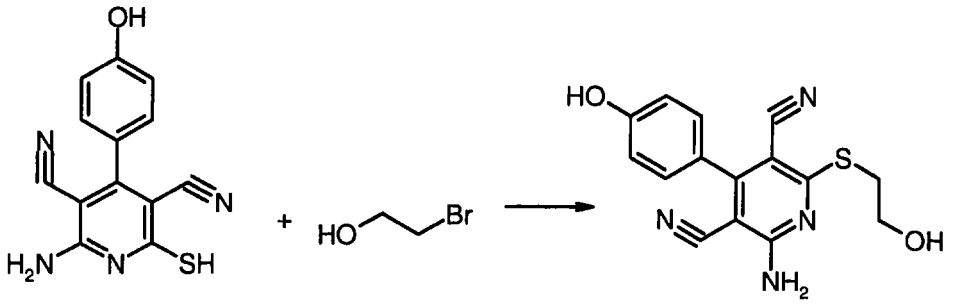
Injection volume: 400 μl of DMF solution

Yield: 18.3 mg (46.6% of theory) of product

NMR [400 MHz, DMSO-d_6]: 2.1 s (3H), 3.9 s (2H), 7.25 s (1H), 7.5 d (3H), 7.7 d (2H), 8.0 s broad (2H), 10.25 s (1H)

Example 21

2-Amino-6-[(2-hydroxyethyl)sulfanyl]-4-(4-hydroxyphenyl)-3,5-pyridinedicarbonitrile



26.8 mg (0.1 mmol) of 2-amino-4-(4-hydroxyphenyl)-6-sulfanyl-3,5-pyridinedicarbonitrile are dissolved in 0.2 ml of dimethylformamide. 20 mg (0.238 mmol) of solid sodium bicarbonate are added, followed by a solution of 18.74 mg (0.15 mmol) of 2-bromoethanol in 0.06 ml of dimethylformamide. The reaction mixture is shaken overnight and, after filtration, purified by preparative HPLC.

HPLC conditions:

Column: GROM-SIL 120 ODS 4 HE 5μ 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15μ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B= water + 0.1% trifluoroacetic acid

0 min: 10% A; 1.75 min. 10% A; 5.5 min. 90% A; 8 min. 90% A; 8.1 min. 10% A; 9 min. 10% A

Injection volume: 300 μl of DMSO solution

Retention time: 3.97 min

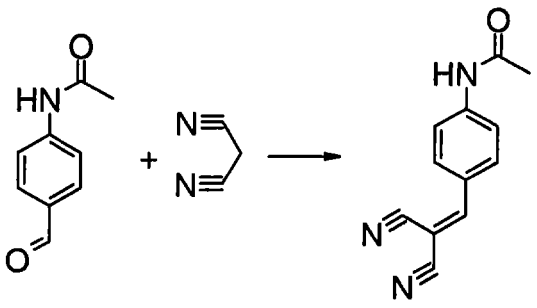
Yield: 14.1 mg (45.1% of theory)

Mass spectrum: molecular mass calculated: 312, found $[M+H]^+$=313

Example 22

1. Step:

N-[4-(2,2-Dicyanovinyl)phenyl]acetamide



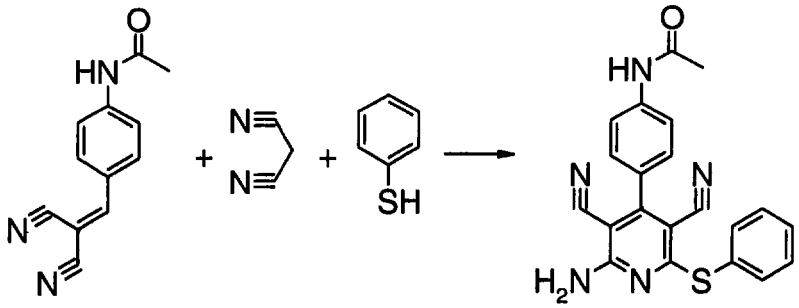
32.6 g (0.2 mol) of 4-acetaminobenzaldehyde and 13.74 g (0.208 mol) of malononitrile are initially charged in 140 ml of ethanol, and 24 drops of piperidine are added. The mixture is stirred at reflux for 30 min. After cooling, the crystals are filtered off with suction and dried.

Yield: 38.6 g (90.6% of theory) of product

Mass spectrum: molecular mass calculated: 211, found $[M+H]^+ = 212$

2. Step

N-{4-[2-Amino-3,5-dicyano-6-(phenylsulfanyl)-4-pyridinyl]phenyl}acetamide



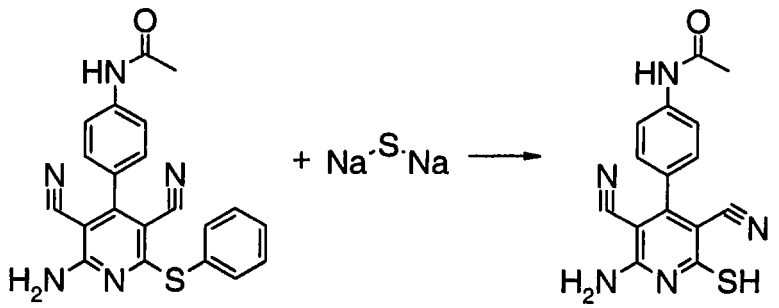
19 g (0.09 mol) of N-[4-(2,2-dicyanovinyl)phenyl]acetamide, 5.95 g (0.09 mol) of malononitrile and 9.91 g (0.09 mol) of thiophenol are initially charged in 120 ml of ethanol, and 0.4 ml of triethylamine are added. The mixture is stirred at reflux for 2 h, during which the product crystallizes. After cooling, the product is filtered off with suction and dried under reduced pressure.

Yield: 10.25 g (29.6% of theory) of product

Mass spectrum: molecular mass calculated: 385, found $[M+H]^+ = 386$

3. Step

N-[4-(2-Amino-3,5-dicyano-6-sulfanyl-4-pyridinyl)phenyl]acetamide



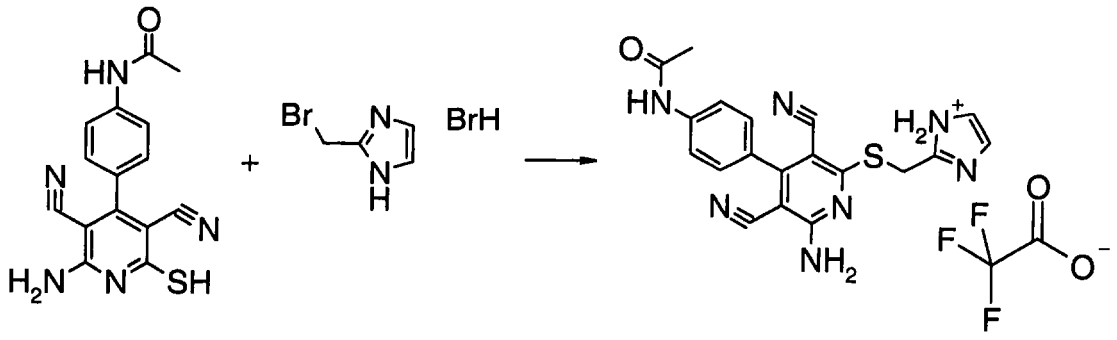
Under argon, 1.16 g (3 mmol) of N-{4-[2-amino-3,5-dicyano-6-(phenylsulfanyl)-4-pyridinyl]phenyl}-acetamide are dissolved in 10 ml of DMF, 0.78 g (10 mmol) of sodium sulfide are added and the mixture is stirred at 80°C for 2 h. 20 ml of 1N HCl are then added and the resulting crystals are filtered off with suction and dried under reduced pressure.

Yield: 428 mg (46.1 % of theory) of product

Mass spectrum: molecular mass calculated: 309, found $[M+H]^+ = 310.1$

4. Step

2-[({4-[4-(Acetylamino)phenyl]-6-amino-3,5-dicyano-2-pyridinyl}sulfanyl)-methyl]-1H-imidazol-1-ium trifluoracetate



309 mg (1 mmol) of N-[4-(2-amino-3,5-dicyano-6-sulfanyl-4-pyridinyl)phenyl]-acetamide, 241 mg (1 mmol) of 2-(bromomethyl)-1H-imidazole hydrobromide and 336 mg (4 mmol) of $NaHCO_3$ in 2 ml of DMF are stirred at RT. After 2 h, 4 to 5 ml of water are added and the beige crystals are filtered off with suction and dried under reduced pressure. The crystals (310 mg) are dissolved in DMSO and purified by prep. HPLC using 9 injections. The corresponding fraction is concentrated under reduced pressure and the crystalline residue is suspended in water, filtered off with suction and dried under reduced pressure.

HPLC conditions:

Column: Kromasil 100 C18 5μm 50 X 20 mm

Precolumn: GROM-SIL ODS 4 HE 15μ 10 X 20 mm

Wavelength: 220 nm

Flow rate: 25 ml/min

Gradient: A = acetonitrile + 0.1% trifluoroacetic acid

B= water + 0.1% trifluoroacetic acid

0 min: 10% A; 2 min. 10% A; 6 min. 90% A; 7 min. 90% A;

7.1 min. 10% A; 8 min. 10% A

Injection volume: 500 μl of DMSO solution

Retention time: 3.6 min

Yield: 234 mg (60% of theory) of product

Mass spectrum: molecular mass calculated: 389, found $[M+H]^+ = 390.1$

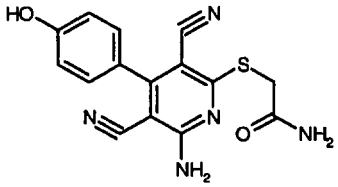
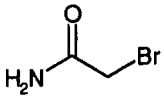
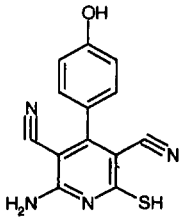
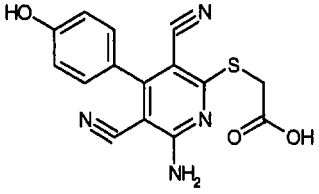
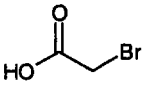
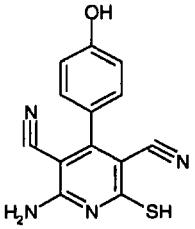
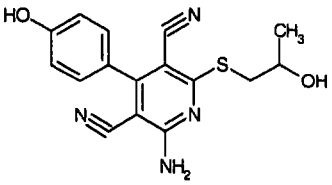
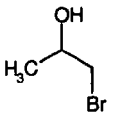
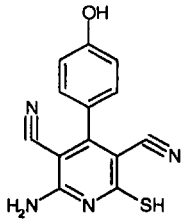
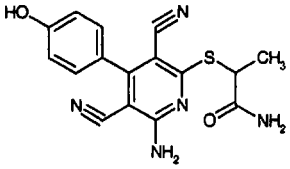
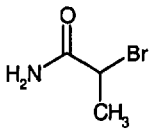
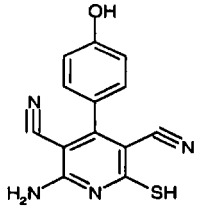
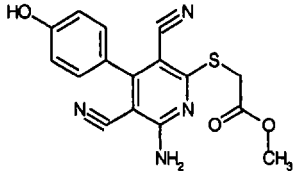
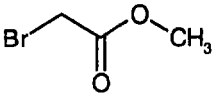
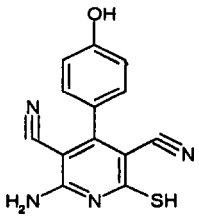
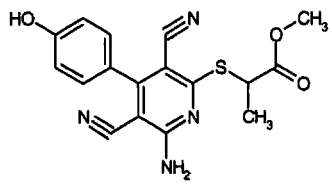
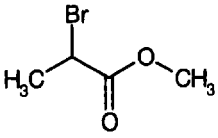
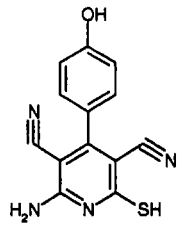
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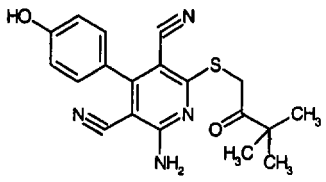
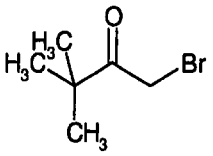
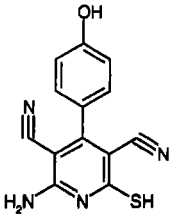
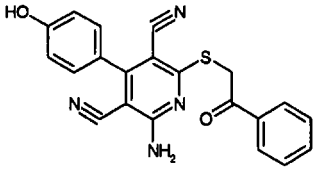
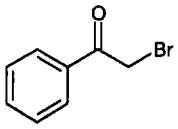
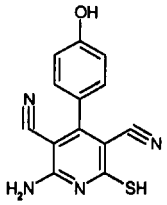
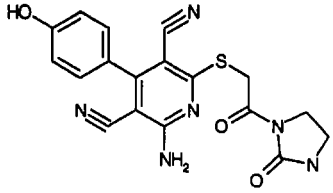
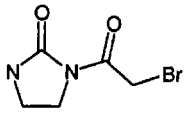
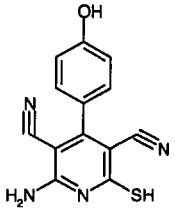
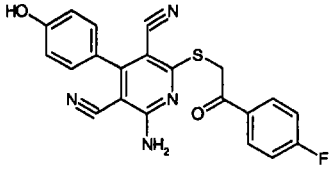
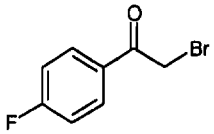
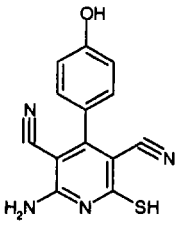
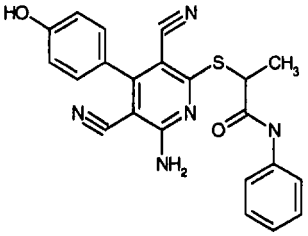
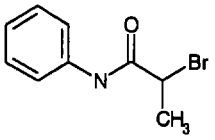
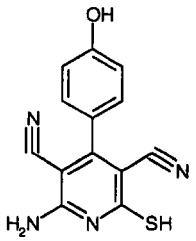
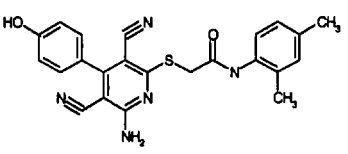
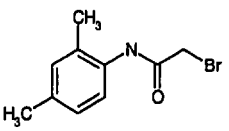
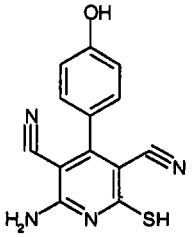
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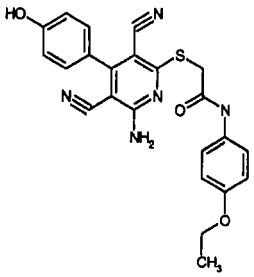
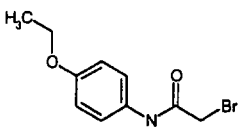
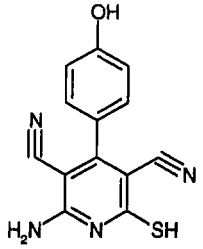
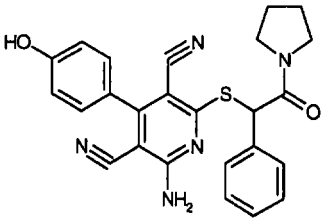
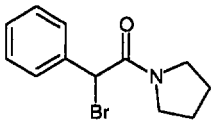
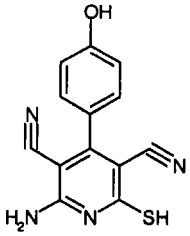
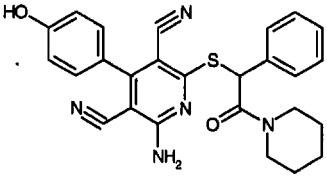
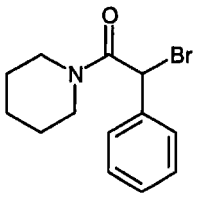
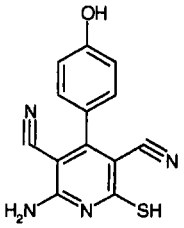
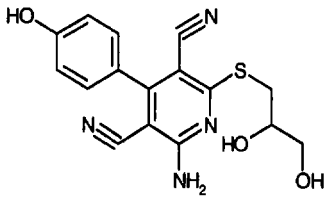
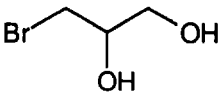
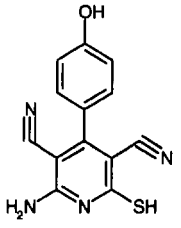
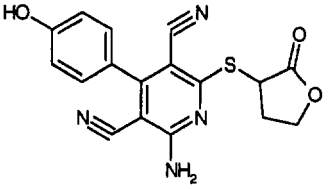
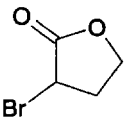
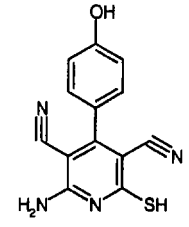
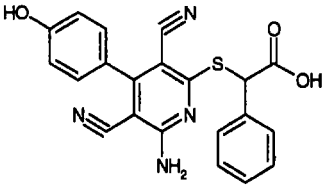
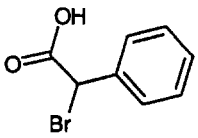
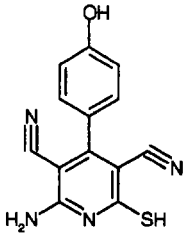
The compounds of examples A 1 to A 413 were either isolated as crystals or, if they did not crystallize directly from the reaction solution, purified by preparative HPLC.

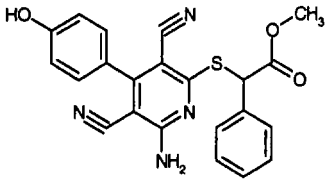
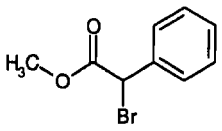
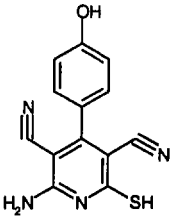
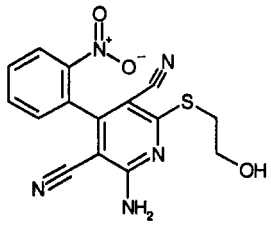
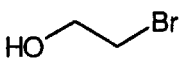
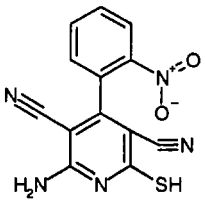
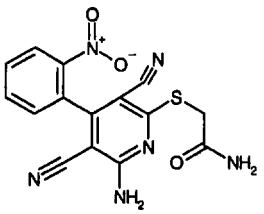
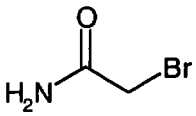
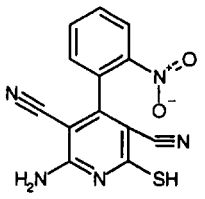
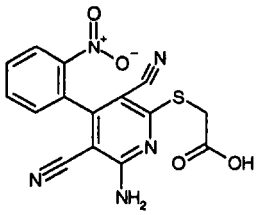
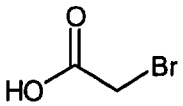
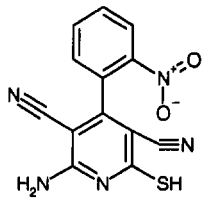
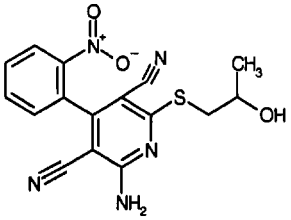
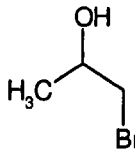
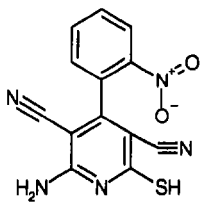
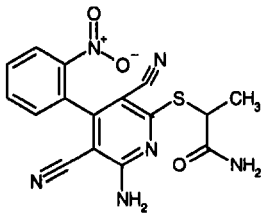
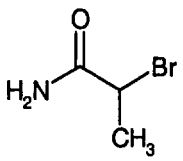
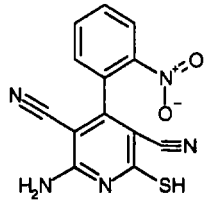
The compounds of examples B 1 to B 375 were prepared on a 10 μmol scale, analogously to the procedures above. These compounds were purified and identified by a preparative HPLC-MS system.

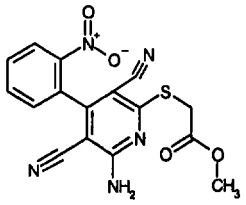
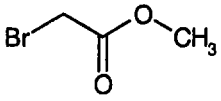
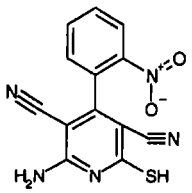
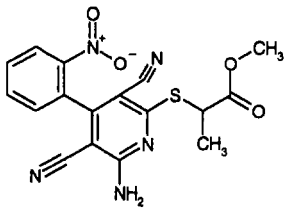
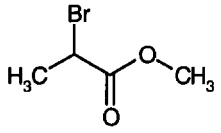
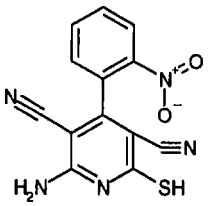
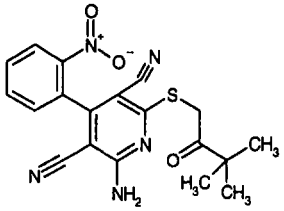
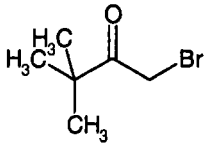
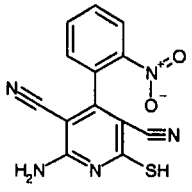
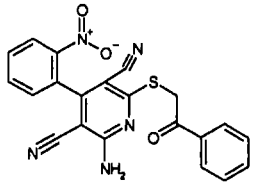
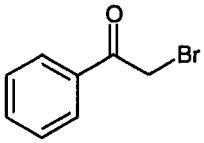
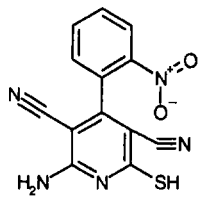
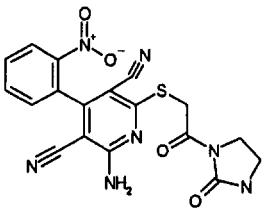
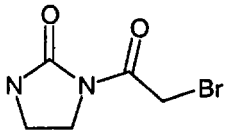
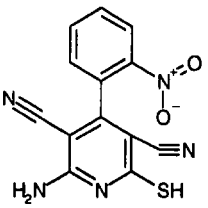
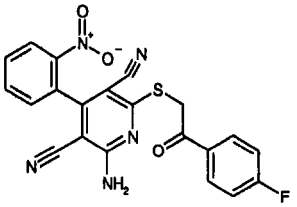
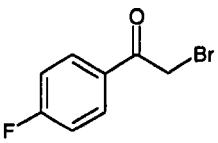
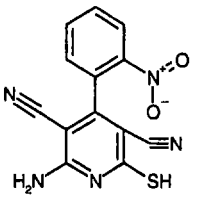
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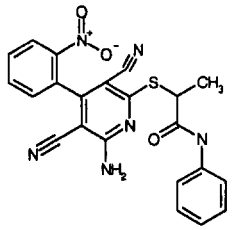
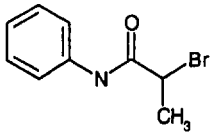
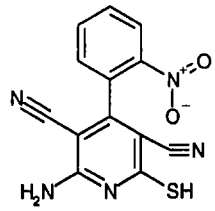
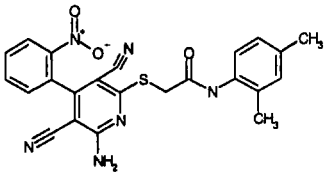
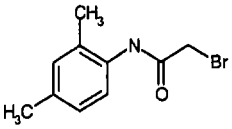
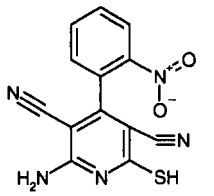
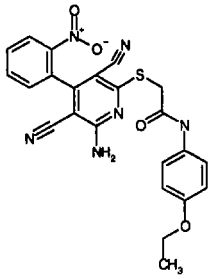
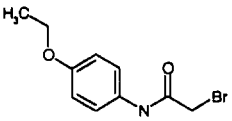
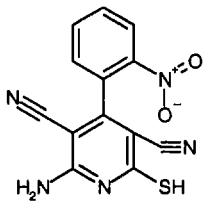
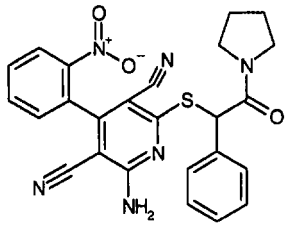
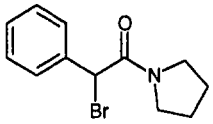
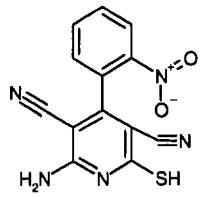
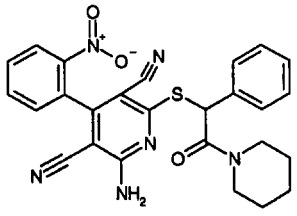
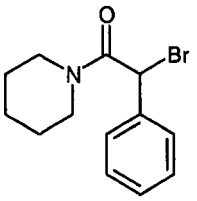
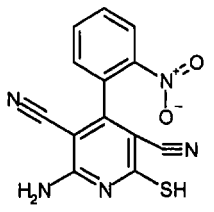
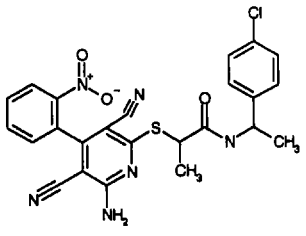
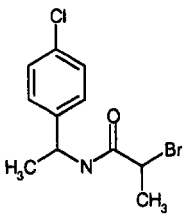
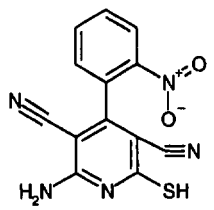
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A2				326	327	7.0
A3				326	327	52.7
A4				339	340	67.5
A5				340	341	60.8
A6				354	355	53.6

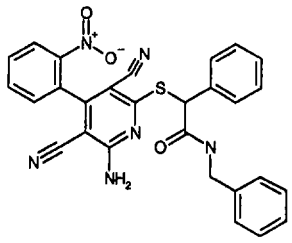
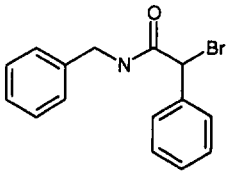
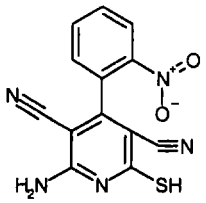
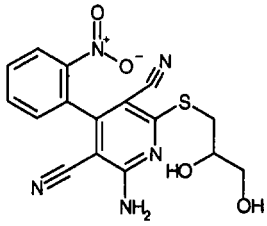
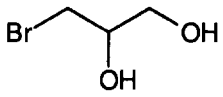
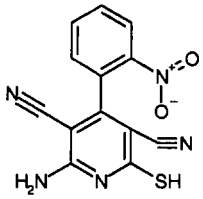
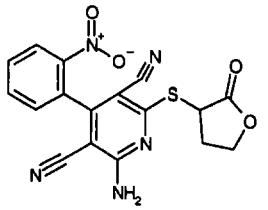
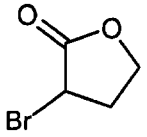
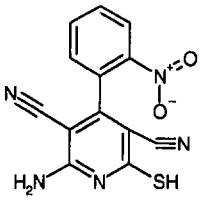
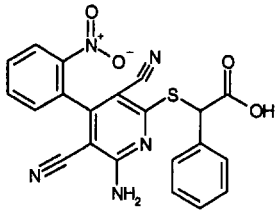
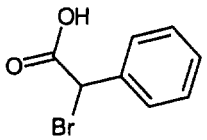
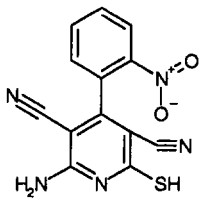
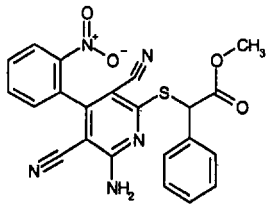
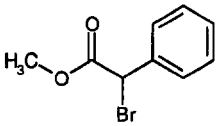
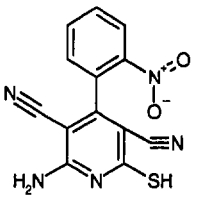
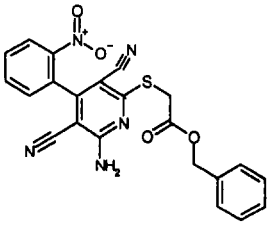
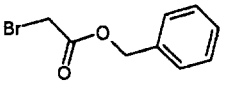
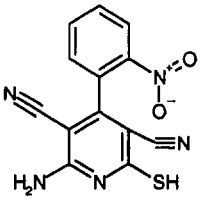
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A8				386	387	57.2
A9				394	395	12.2
A10				404	405	39.3
A11				415	416	58.2
A12				430	431	25.1

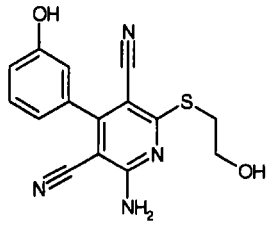
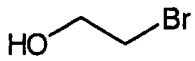
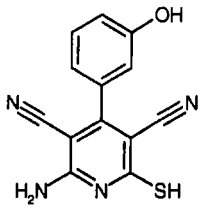
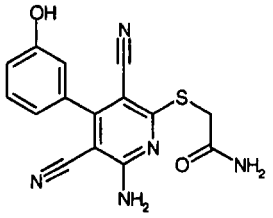
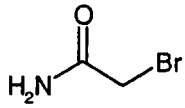
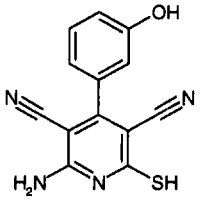
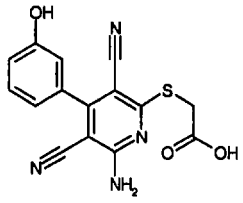
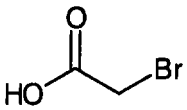
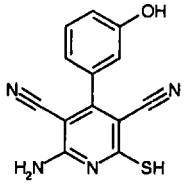
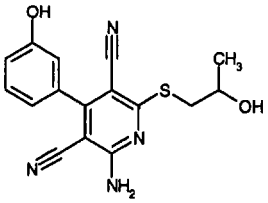
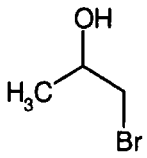
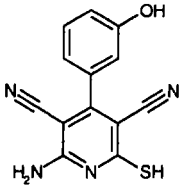
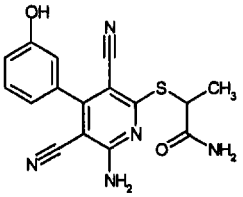
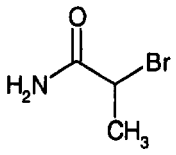
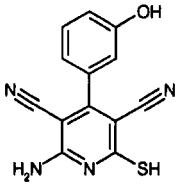
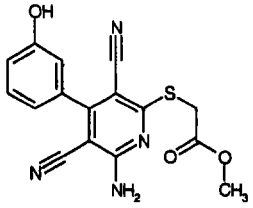
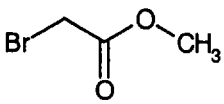
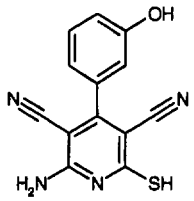
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A14				456	457	29.6
A15				470	471	62.2
A16				342	343	54.0
A17				352	353	73.8
A18				402	403	65.6

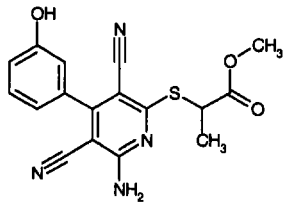
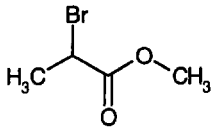
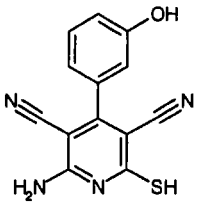
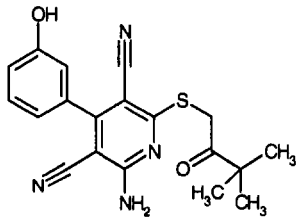
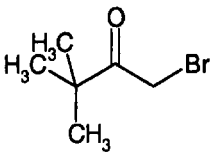
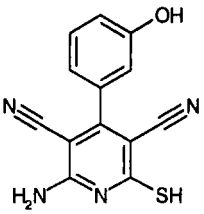
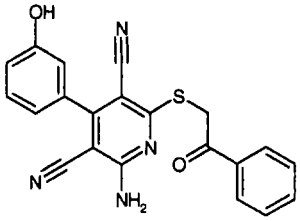
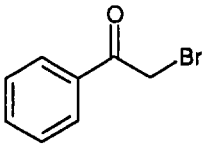
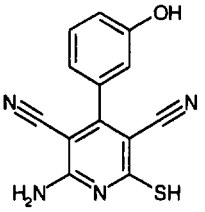
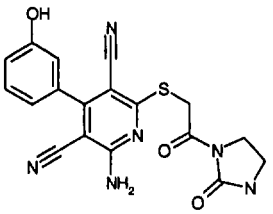
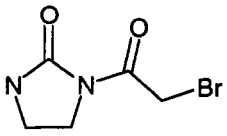
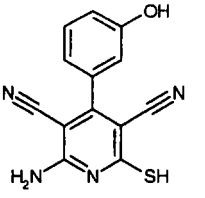
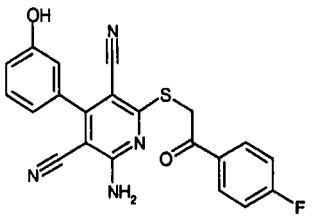
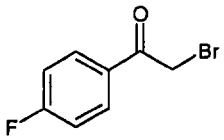
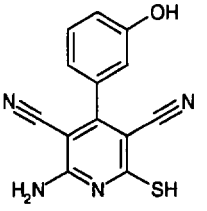
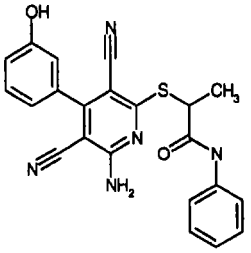
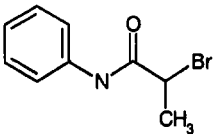
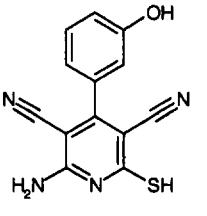
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A19				416	417	51.9
A20				341	342	29.7
A21				354	355	84.4
A22				355	356	10.0
A23				355	356	35.2
A24				368	369	77.1

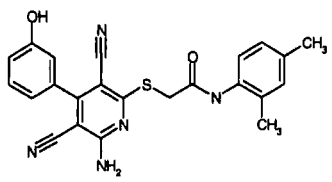
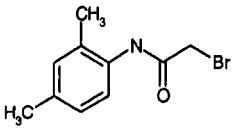
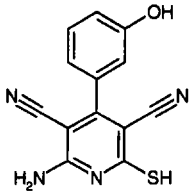
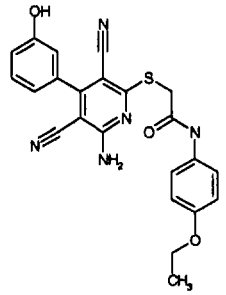
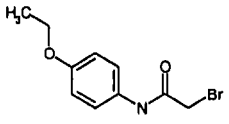
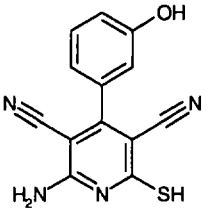
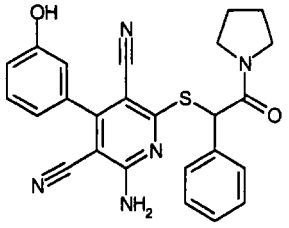
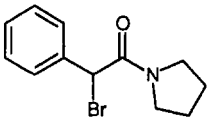
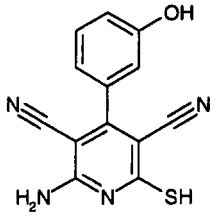
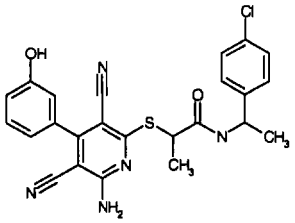
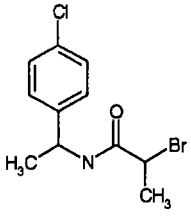
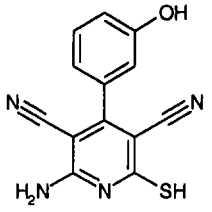
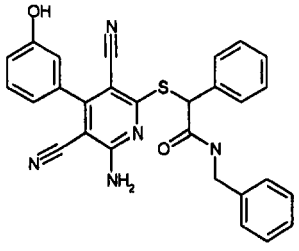
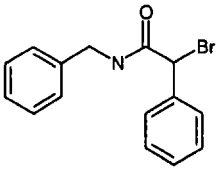
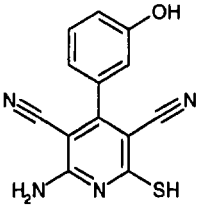
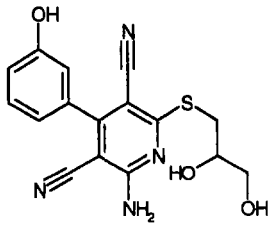
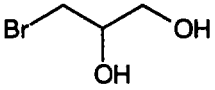
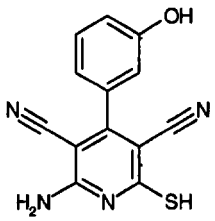
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A25				369	370	70.9
A26				383	384	68.1
A27				395	396	60.2
A28				415	416	58.0
A29				423	424	31.2
A30				433	434	36.2

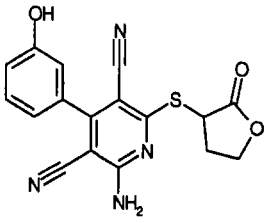
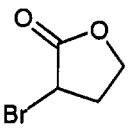
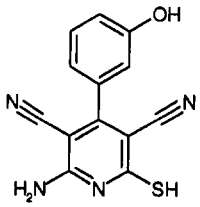
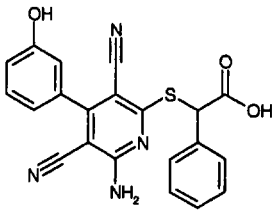
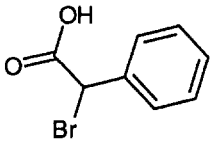
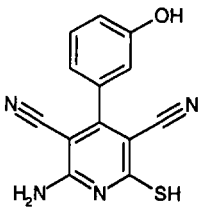
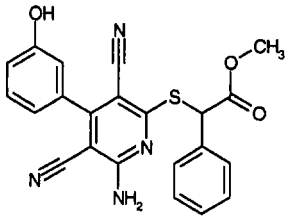
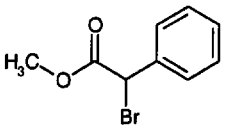
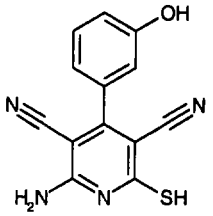
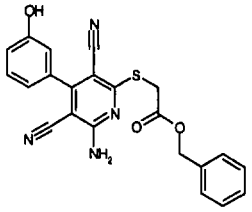
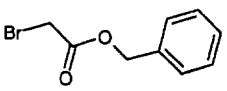
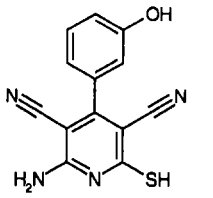
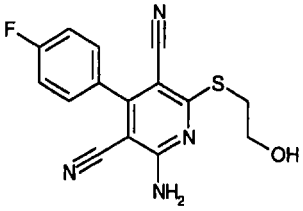
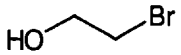
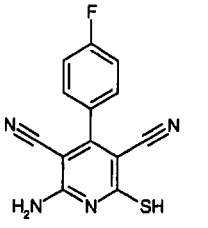
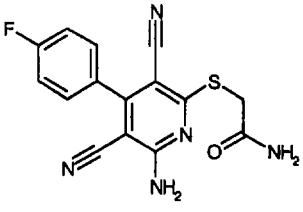
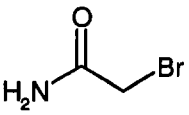
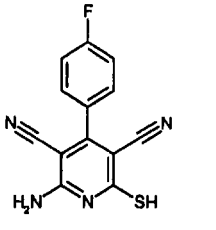
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A32				459	460	46.7
A33				475	476	49.7
A34				485	486	47.1
A35				499	500	64.0
A36				507	508	37.5

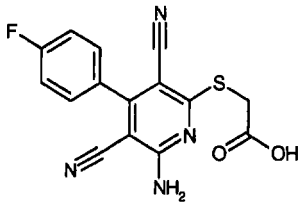
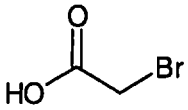
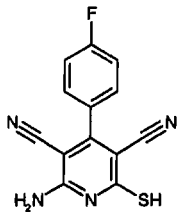
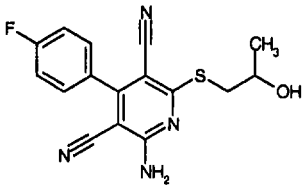
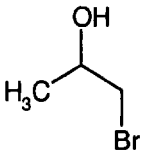
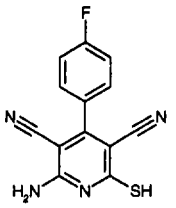
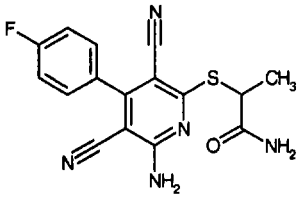
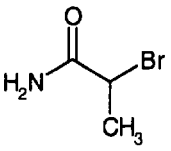
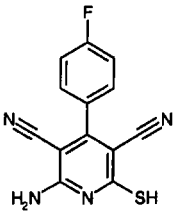
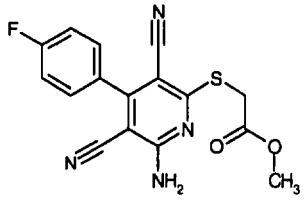
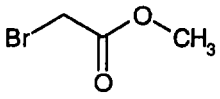
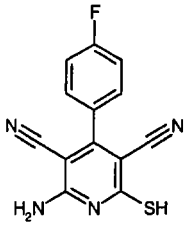
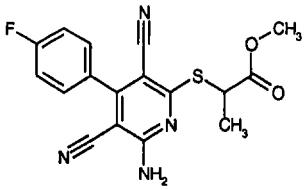
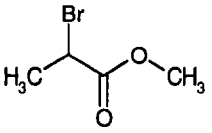
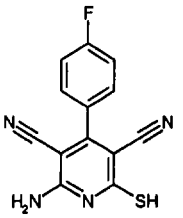
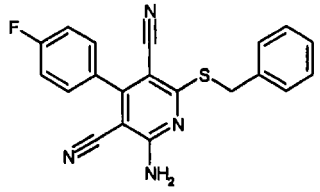
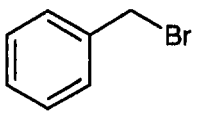
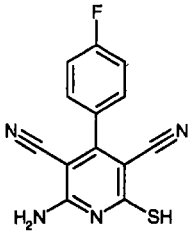
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A37				521	522	61.5
A38				371	372	63.8
A39				381	382	50.3
A40				431	432	40.8
A41				445	446	71.9
A42				445	446	32.6

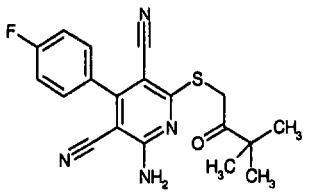
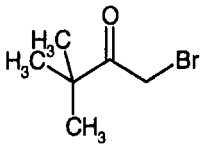
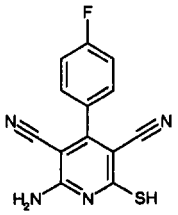
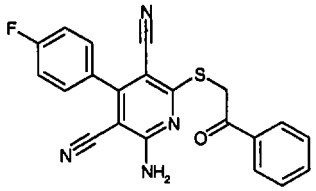
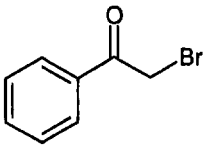
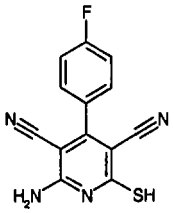
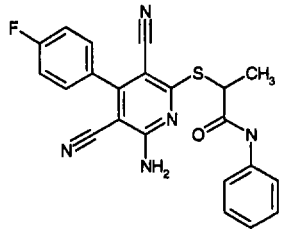
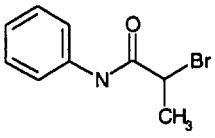
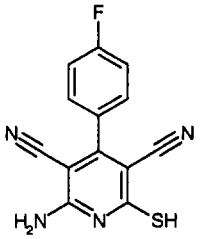
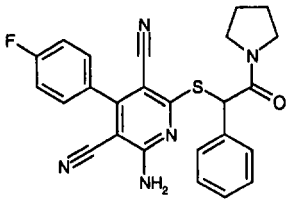
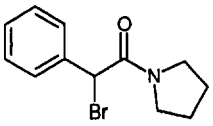
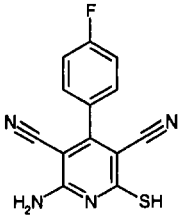
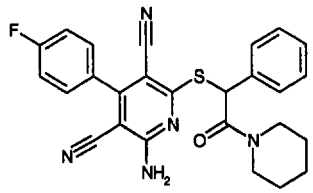
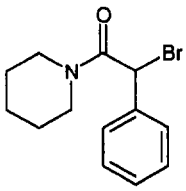
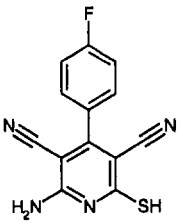
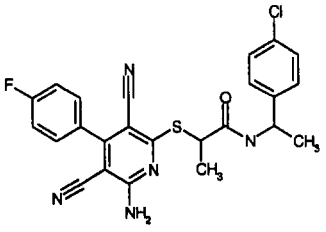
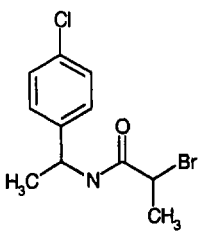
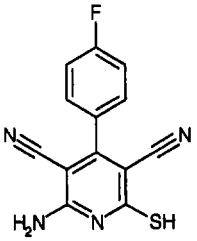
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A44				325	326	78.4
A45				326	327	13.9
A46				326	327	17.8
A47				339	340	89.6
A48				340	341	77.6

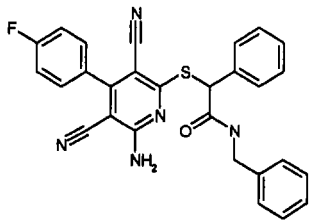
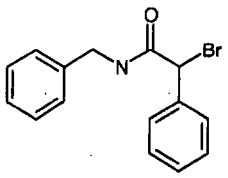
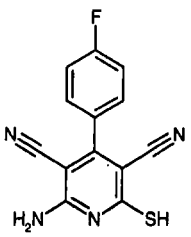
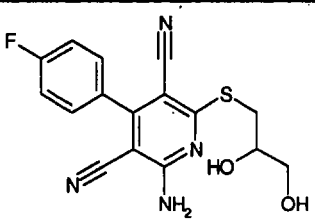
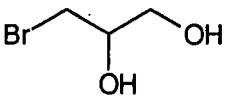
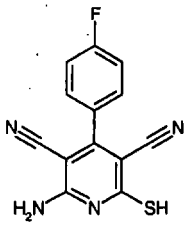
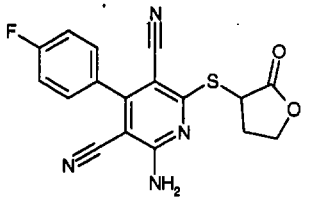
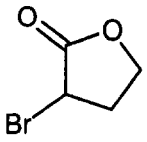
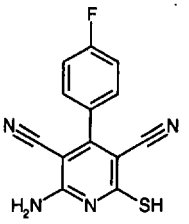
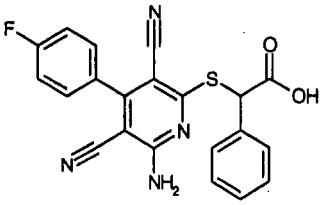
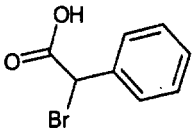
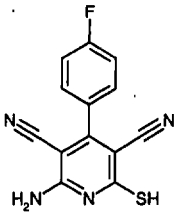
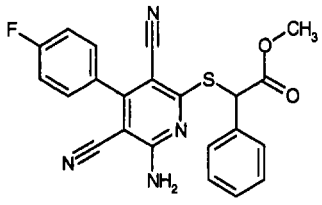
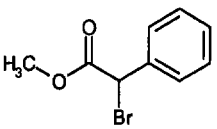
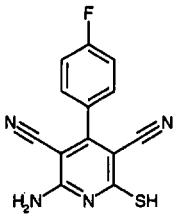
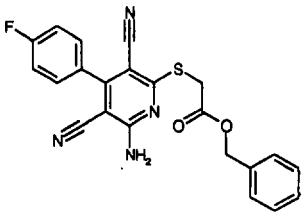
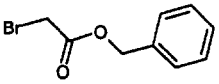
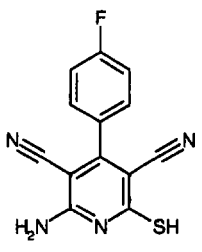
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A50				366	367	47.5
A51				386	387	36.5
A52				394	395	20.5
A53				404	405	58.8
A54				415	416	18.3

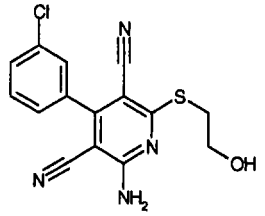
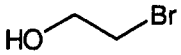
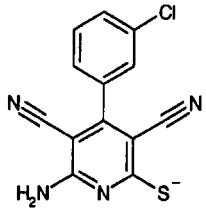
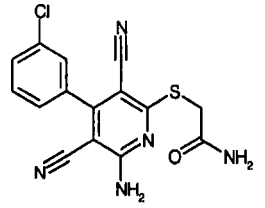
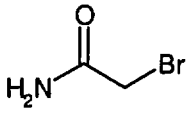
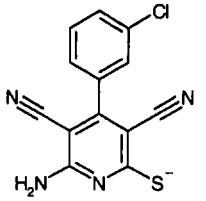
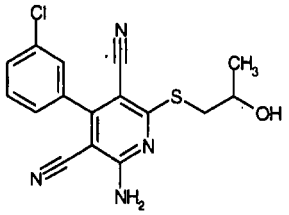
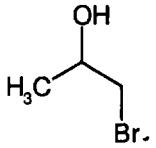
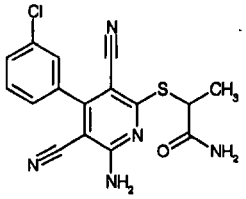
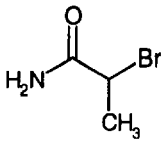
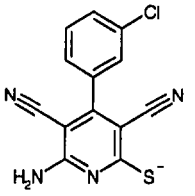
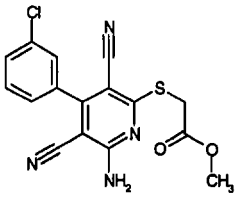
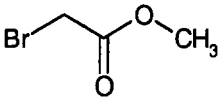
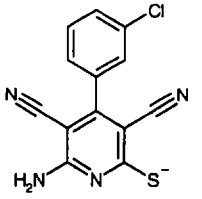
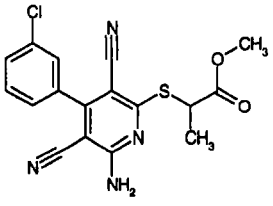
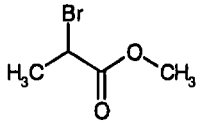
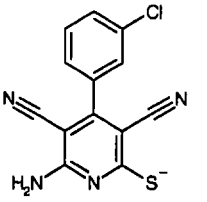
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A55				430	431	29.8
A56				446	447	42.2
A57				456	457	9.2
A58				478	479	54.2
A59				492	493	66.3
A60				342	343	73.6

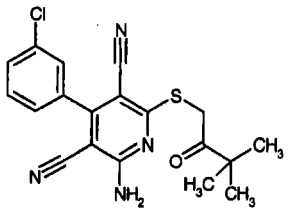
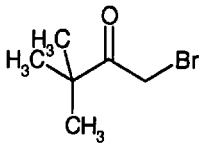
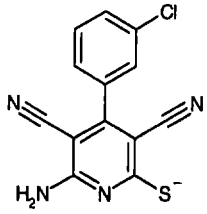
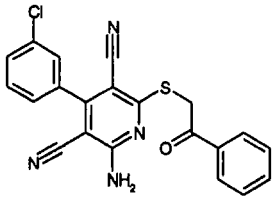
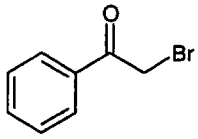
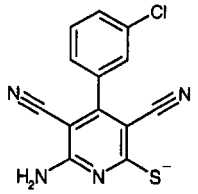
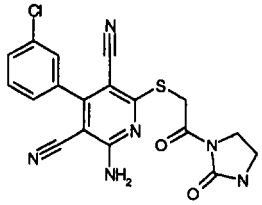
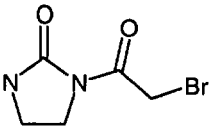
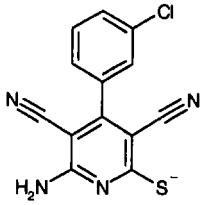
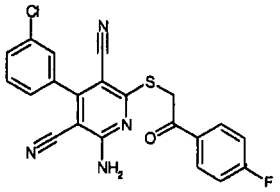
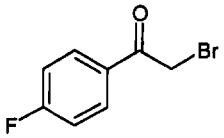
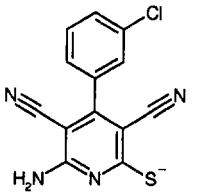
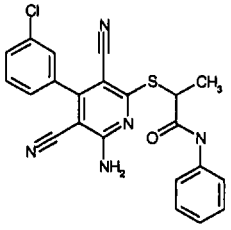
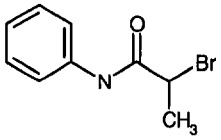
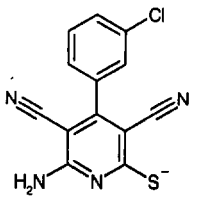
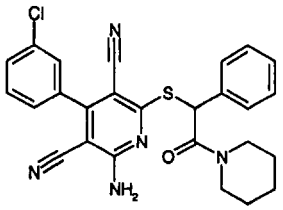
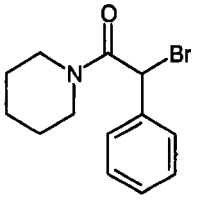
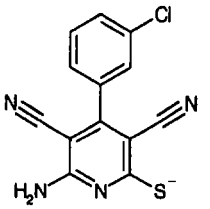
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A62				402	403	41.2
A63				416	417	52.1
A64				416	417	52.6
A65				314	315	62.7
A66				327	328	58.0

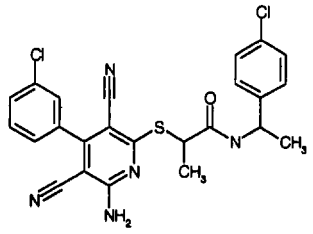
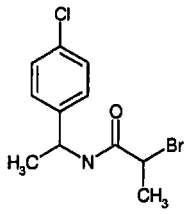
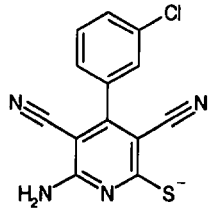
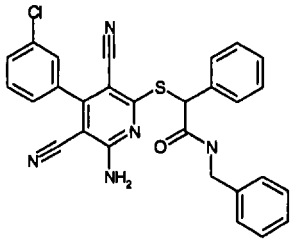
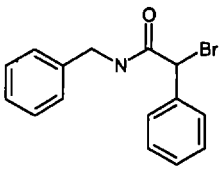
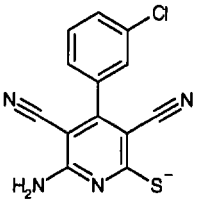
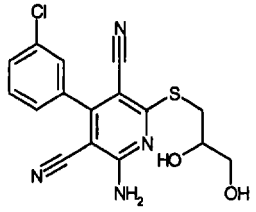
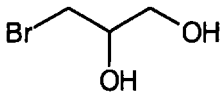
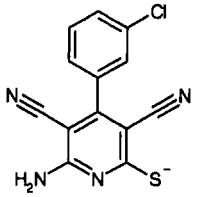
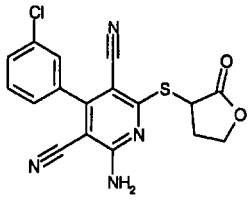
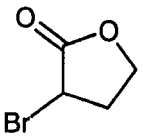
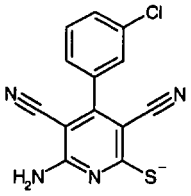
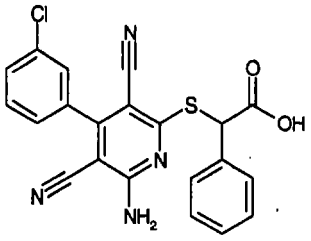
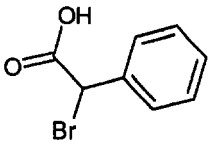
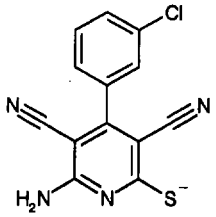
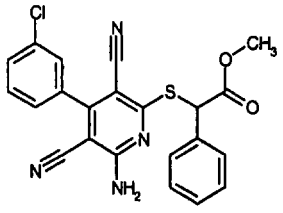
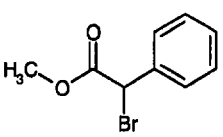
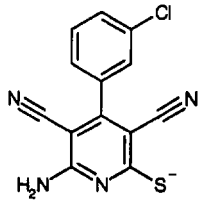
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A67				328	329	17.1
A68				328	329	53.9
A69				341	342	57.7
A70				342	343	35.6
A71				356	357	49.7
A72				360	361	43.3

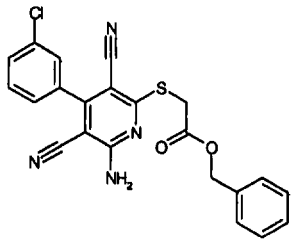
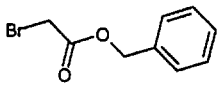
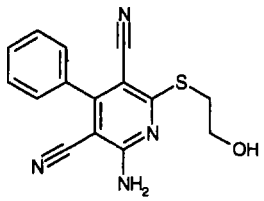
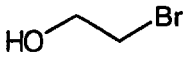
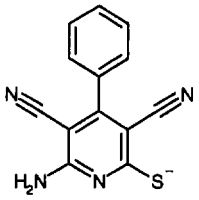
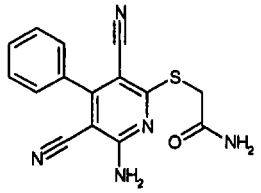
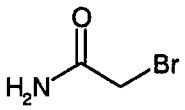
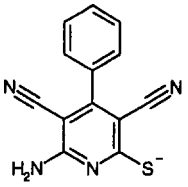
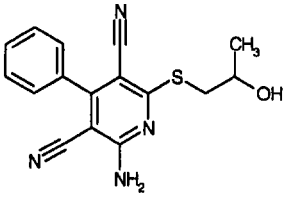
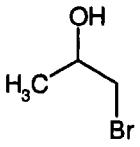
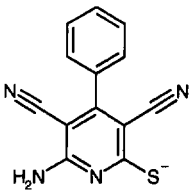
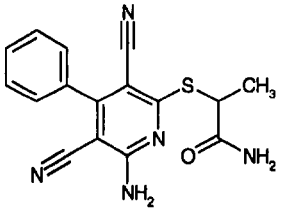
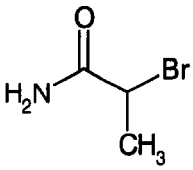
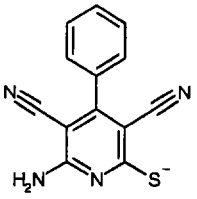
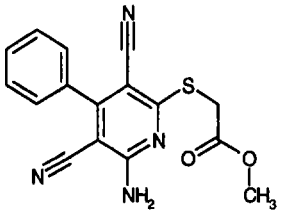
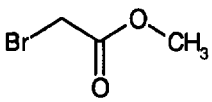
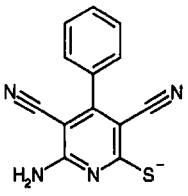
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A74				388	389	17.5
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A76				458	459	19.5
A77				472	473	41.8
A78				480	481	32.9

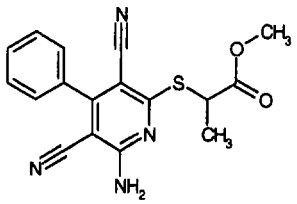
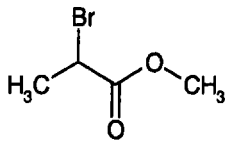
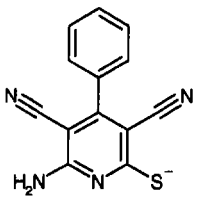
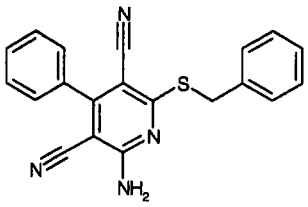
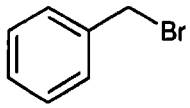
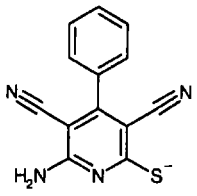
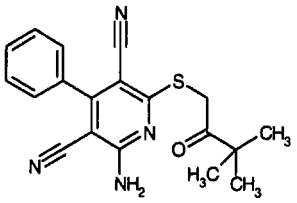
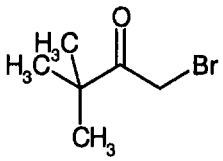
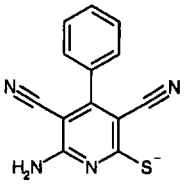
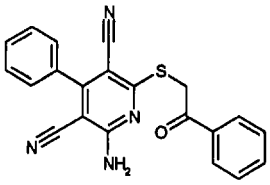
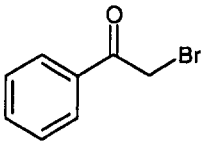
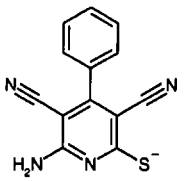
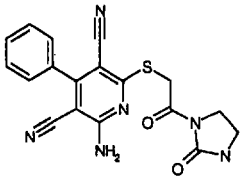
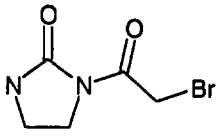
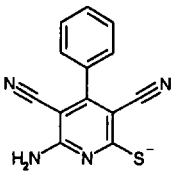
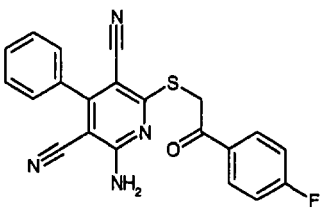
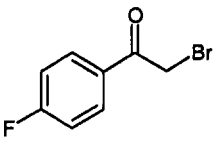
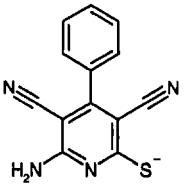
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A79				494	495	29.0
A80				344	345	45.6
A81				354	355	37.2
A82				404	405	37.6
A83				418	419	63.3
A84				418	419	21.5

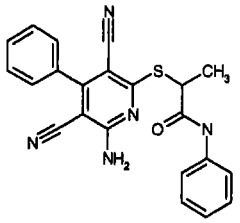
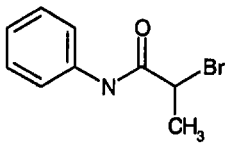
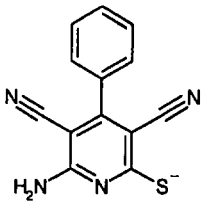
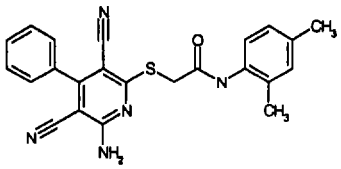
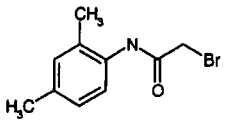
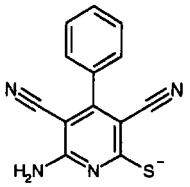
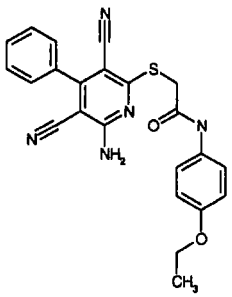
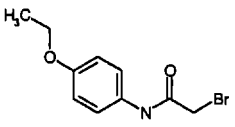
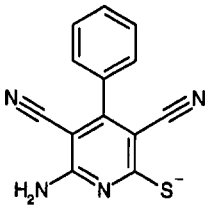
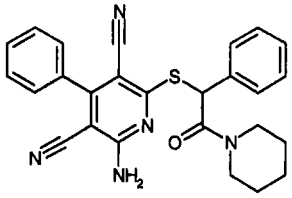
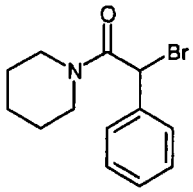
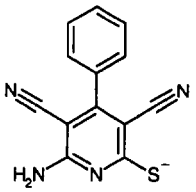
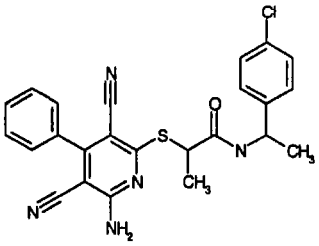
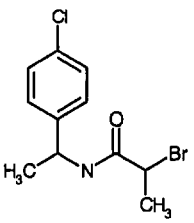
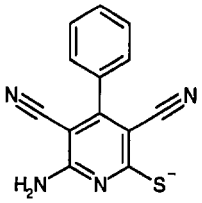
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A86				344	345	66.9
A87				345	346	76.3
A88				358	359	83.8
A89				359	360	89.7
A90				373	374	70.5

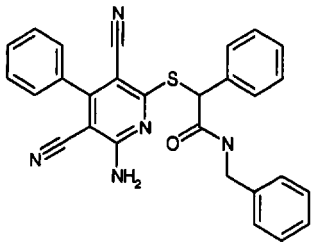
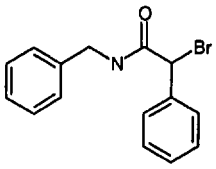
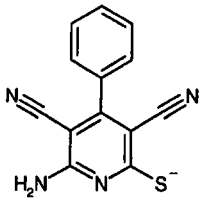
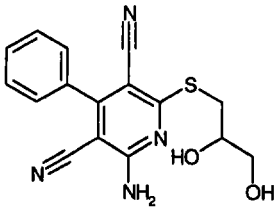
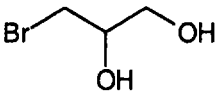
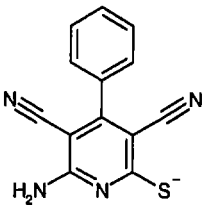
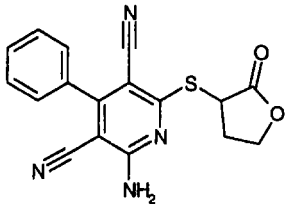
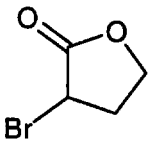
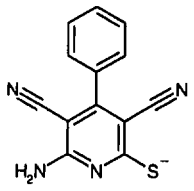
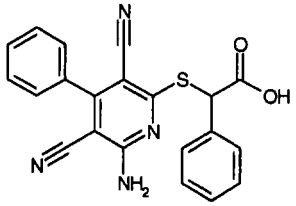
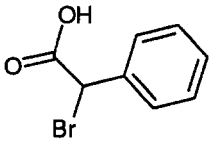
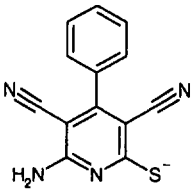
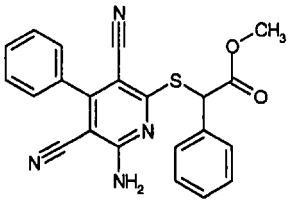
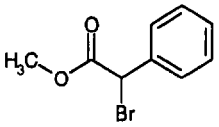
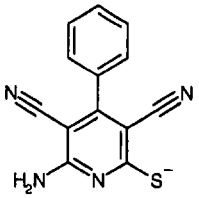
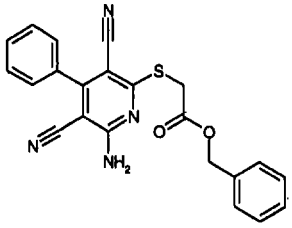
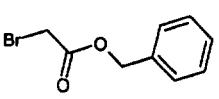
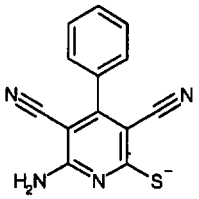
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A92				405	406	84.0
A93				413	414	12.1
A94				423	424	23.6
A95				434	435	67.3
A96				488	489	67.4

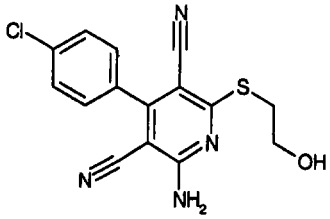
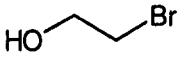
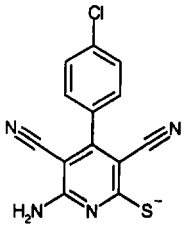
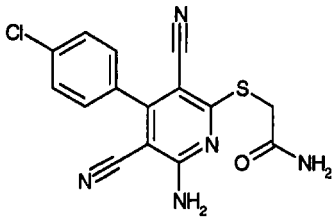
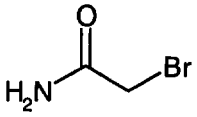
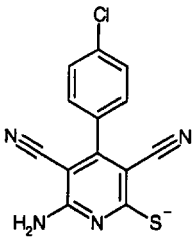
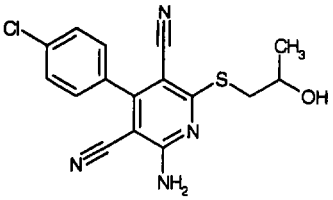
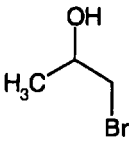
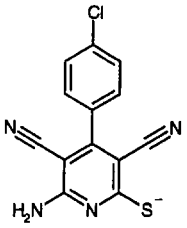
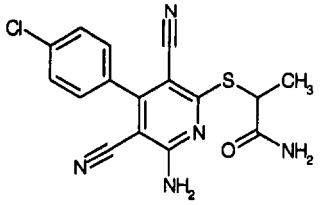
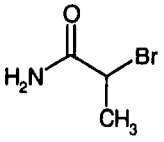
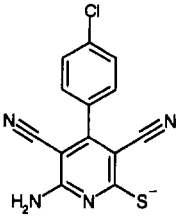
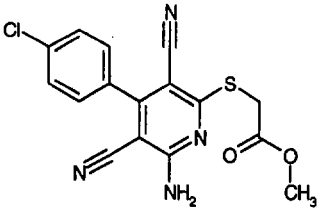
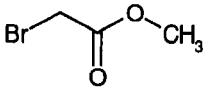
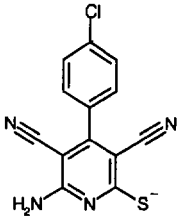
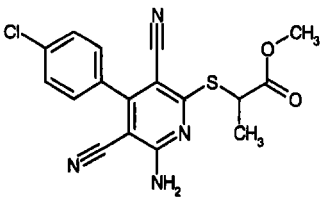
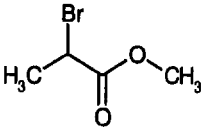
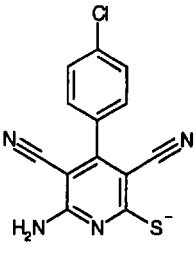
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A97				496	497	90.2
A98				510	511	55.7
A99				361	362	103.1
A100				371	372	48.3
A101				421	422	97.9
A102				435	436	51.7

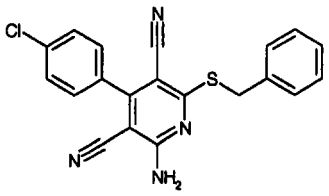
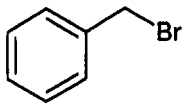
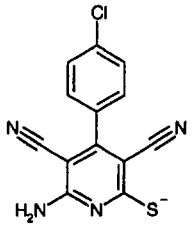
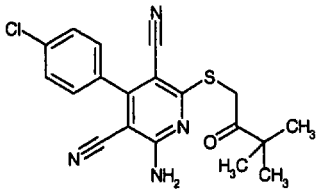
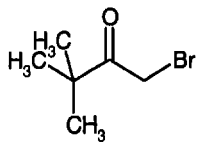
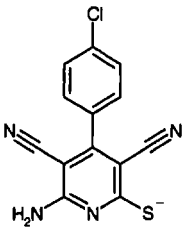
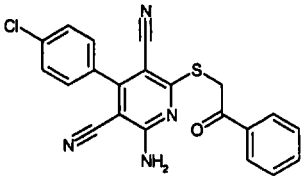
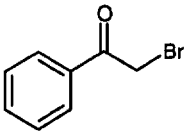
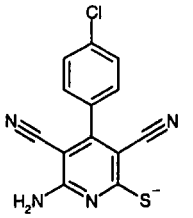
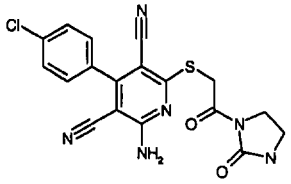
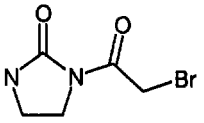
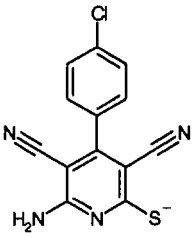
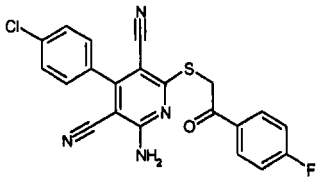
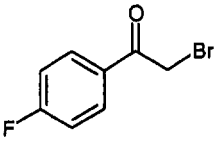
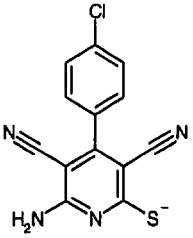
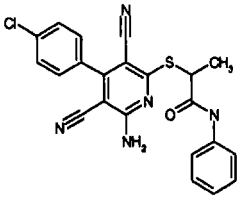
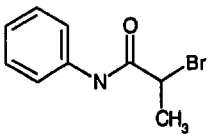
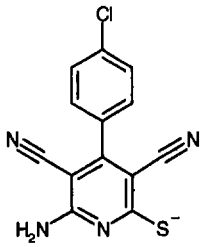
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A103				435	436	63.7
A104				296	297	82.0
A105				309	310	75.6
A106				310	311	72.5
A107				323	324	84.4
A108				324	325	67.8

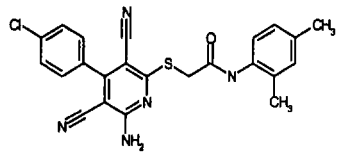
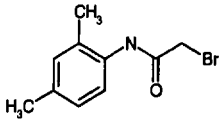
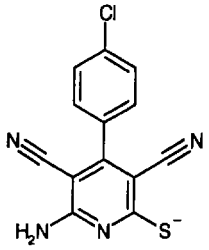
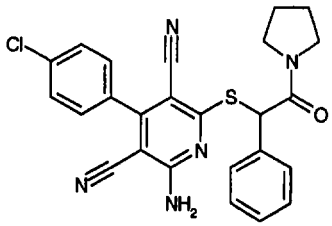
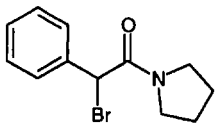
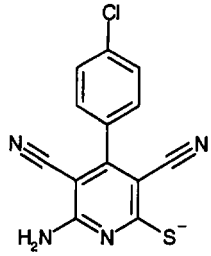
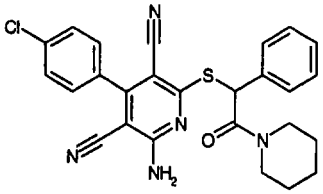
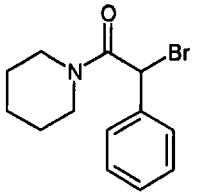
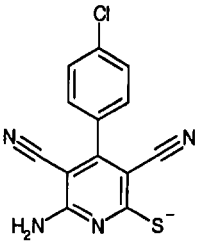
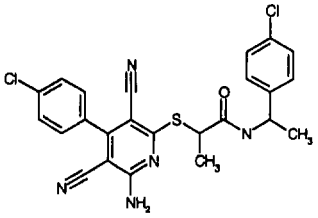
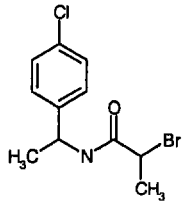
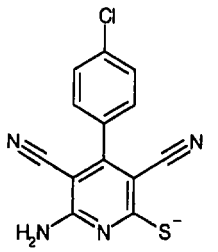
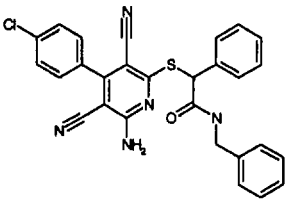
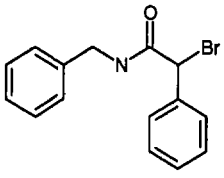
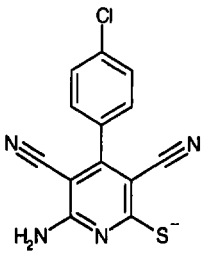
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A109				338	339	71.8
A110				342	343	44.7
A111				350	351	18.5
A112				370	371	73.2
A113				378	379	46.8
A114				388	389	91.4

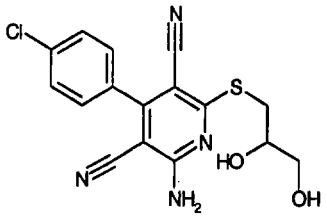
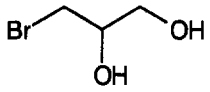
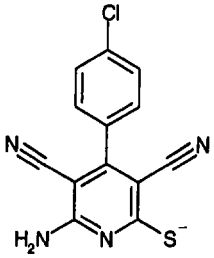
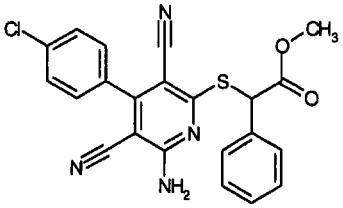
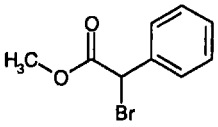
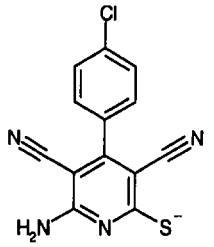
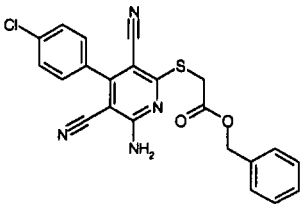
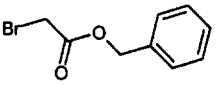
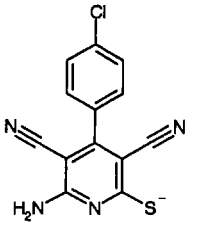
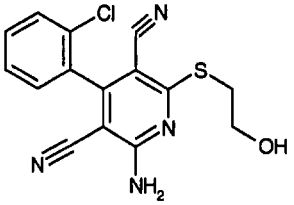
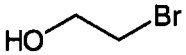
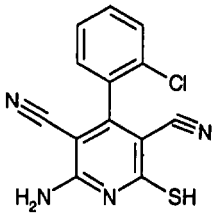
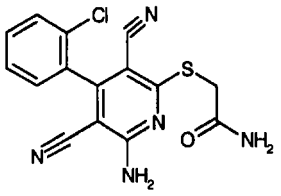
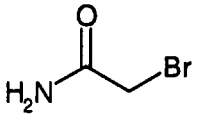
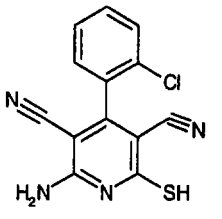
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A115				399	400	17.5
A116				414	415	16.7
A117				430	431	31.4
A118				454	455	58.4
A119				462	463	77.1

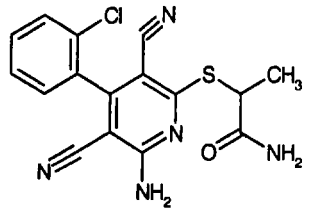
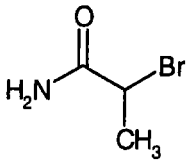
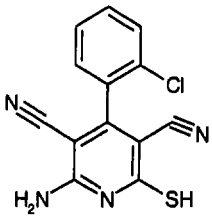
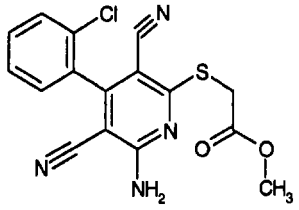
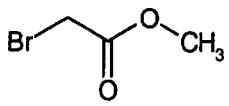
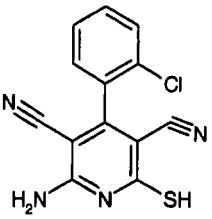
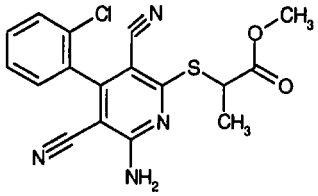
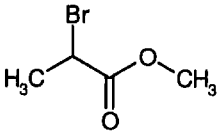
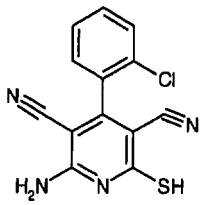
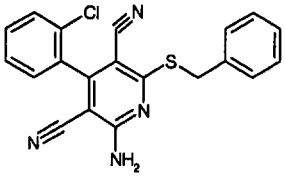
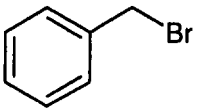
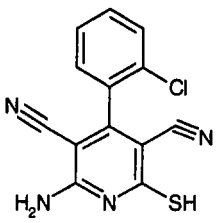
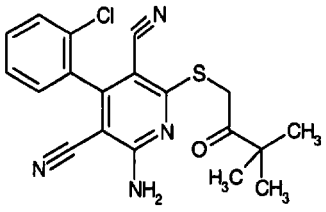
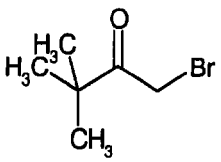
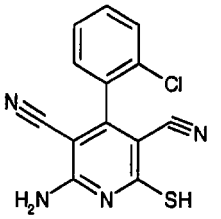
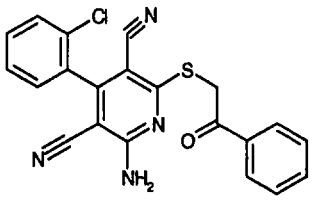
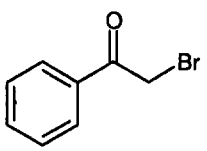
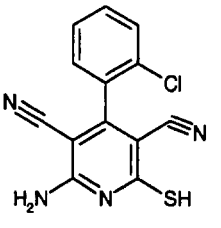
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A120				476	477	13.0
A121				326	327	89.8
A122				336	337	69.3
A123				386	387	73.2
A124				400	401	66.9
A125				400	401	74.2

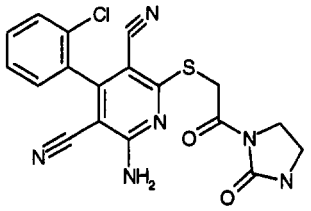
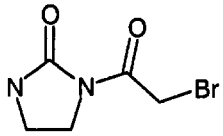
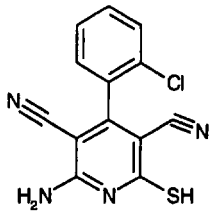
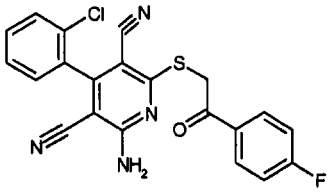
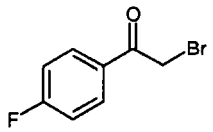
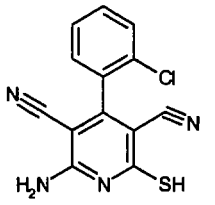
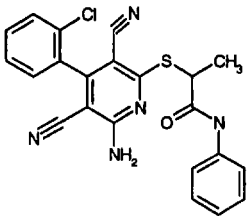
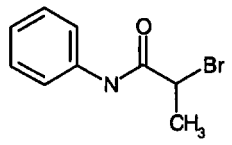
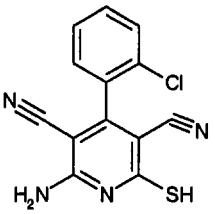
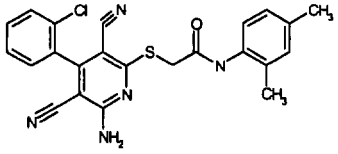
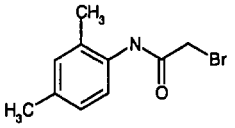
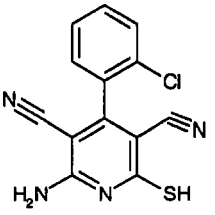
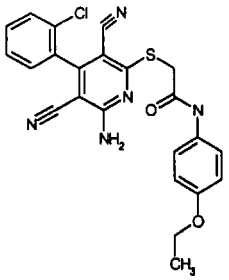
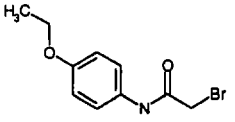
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A127				344	345	68.1
A128				345	346	70.2
A129				358	359	72.4
A130				359	360	44.3
A131				373	374	57.7

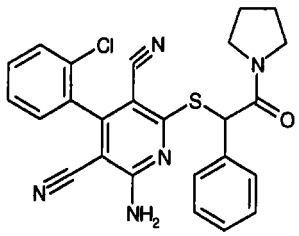
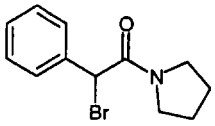
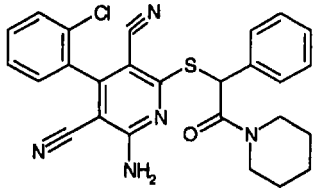
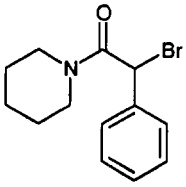
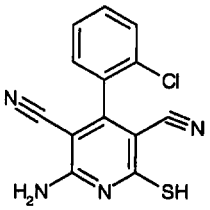
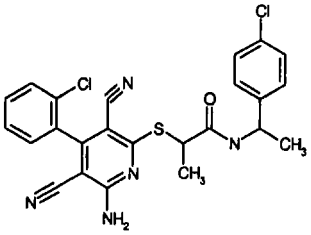
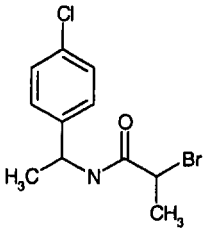
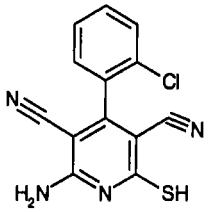
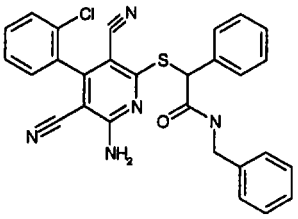
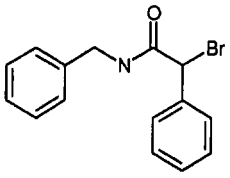
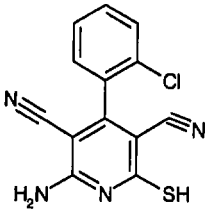
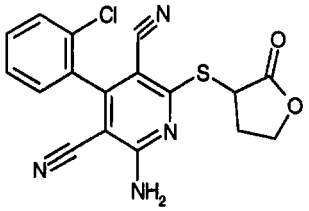
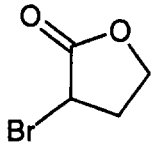
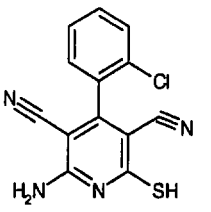
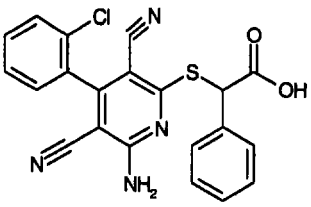
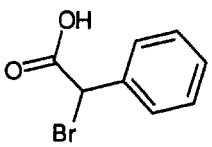
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A133				385	386	14.0
A134				405	406	8.9
A135				413	414	17.2
A136				423	424	12.8
A137				434	435	10.1

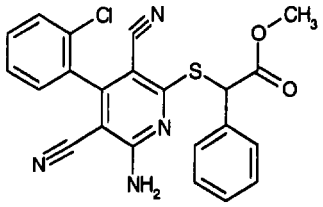
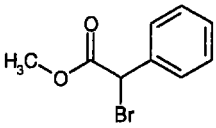
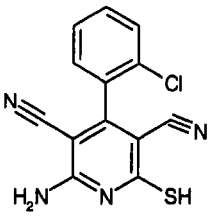
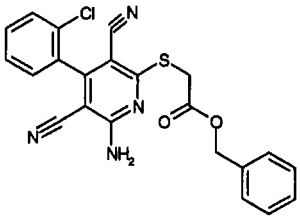
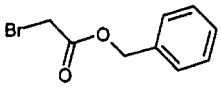
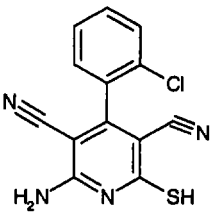
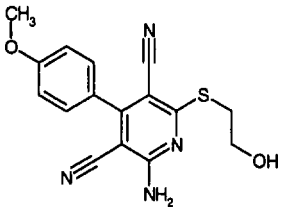
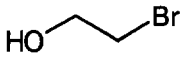
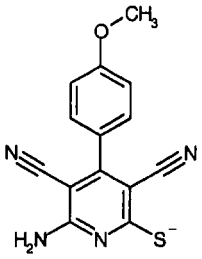
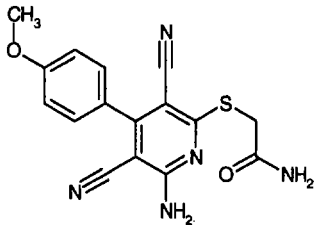
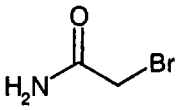
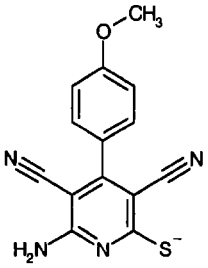
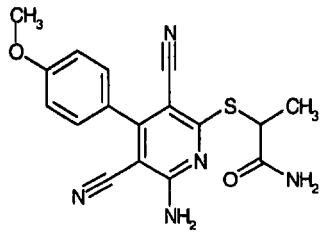
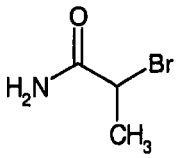
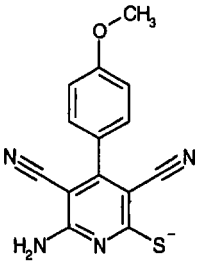
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A140				488	489	52.3
A141				496	497	50.2
A142				510	511	43.5

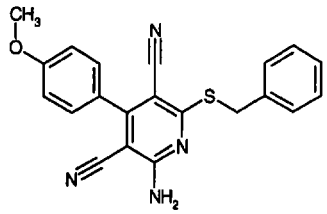
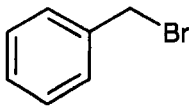
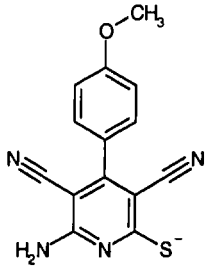
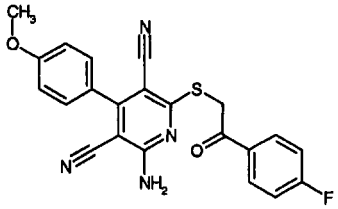
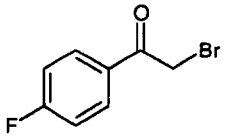
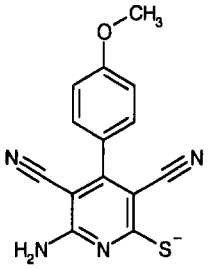
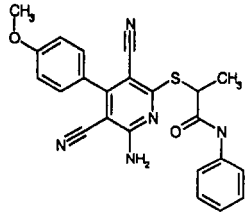
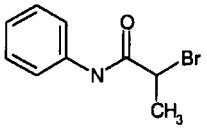
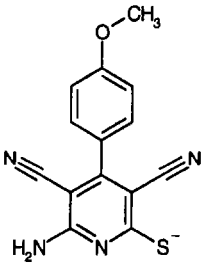
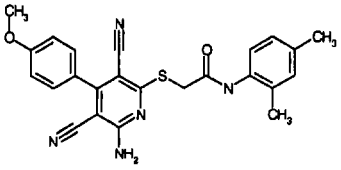
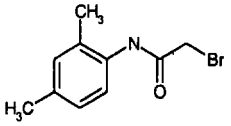
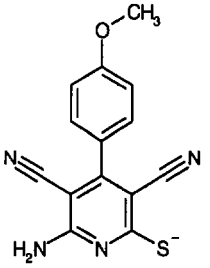
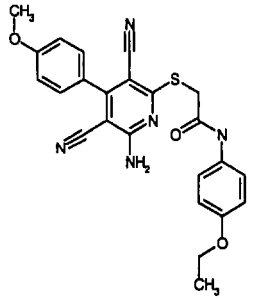
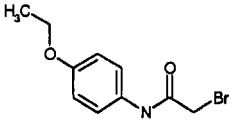
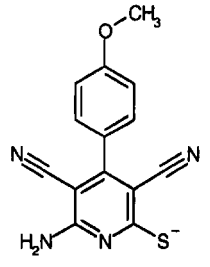
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A143				361	362	56.0
A144				435	436	3.7
A145				435	436	67.4
A146				331	332	64.1
A147				344	345	70.7

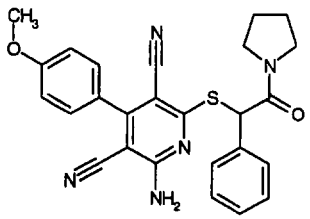
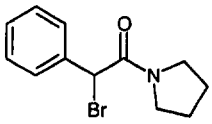
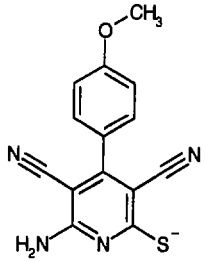
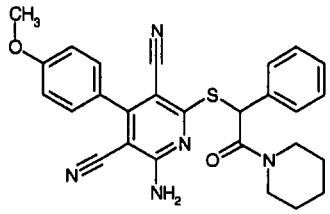
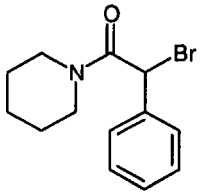
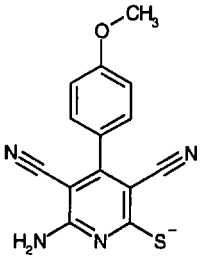
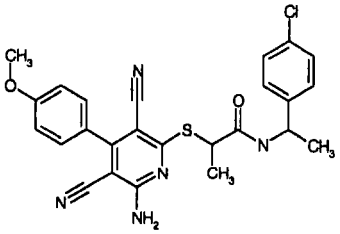
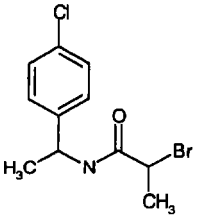
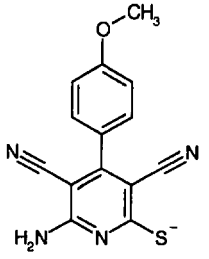
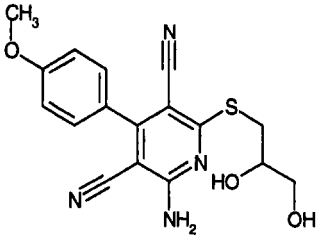
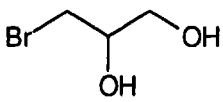
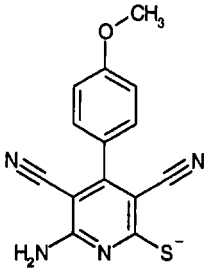
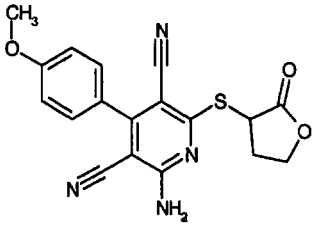
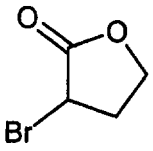
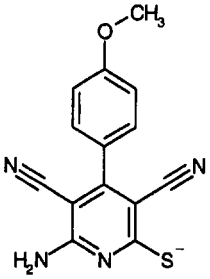
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A148				358	359	72.7
A149				359	360	58.8
A150				373	374	56.3
A151				377	378	55.5
A152				385	386	64.2
A153				405	406	32.4

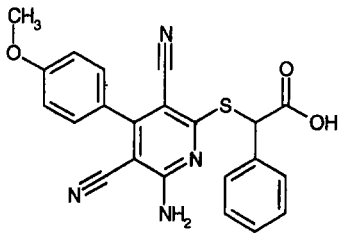
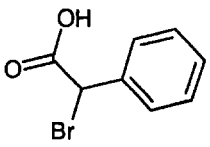
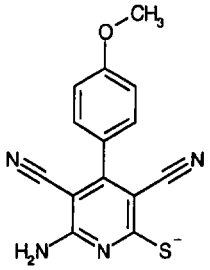
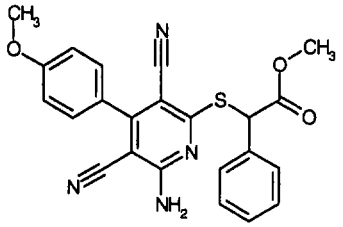
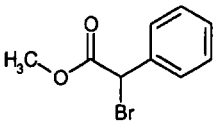
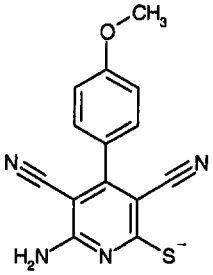
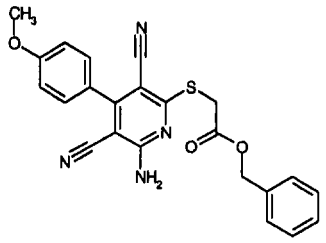
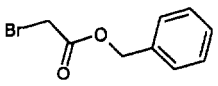
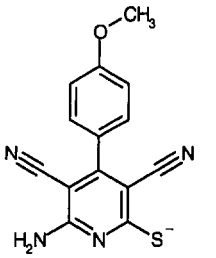
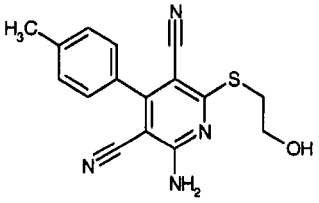
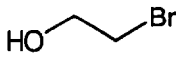
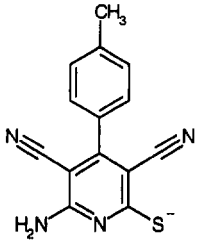
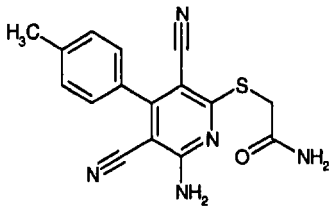
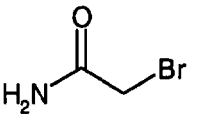
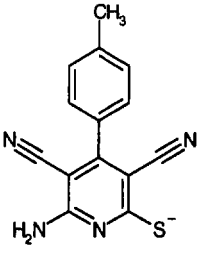
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A154				413	414	55.7
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A156				434	435	74.9
A157				448	449	69.0
A158				464	465	72.0

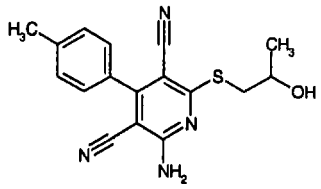
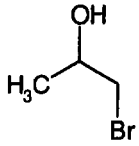
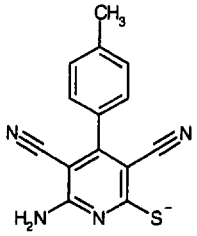
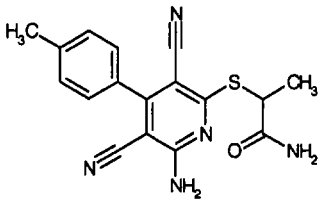
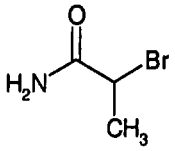
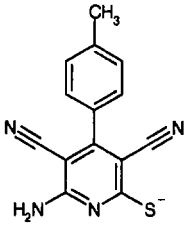
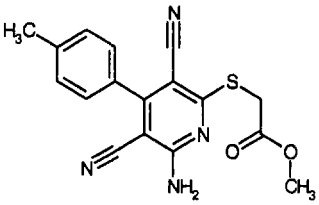
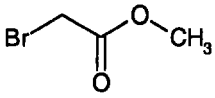
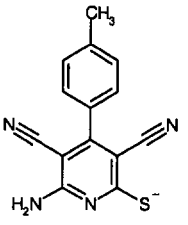
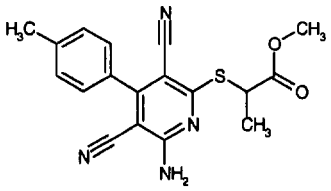
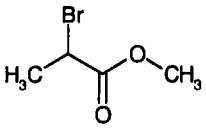
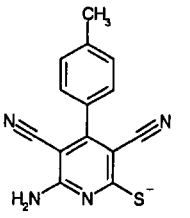
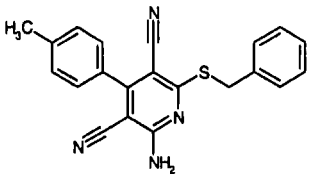
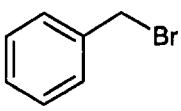
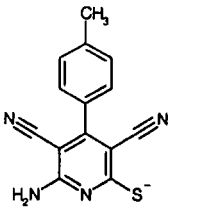
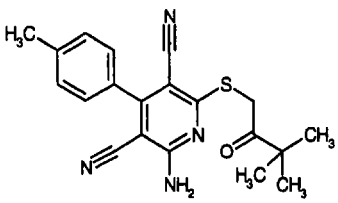
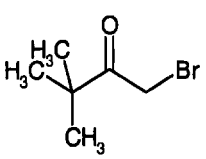
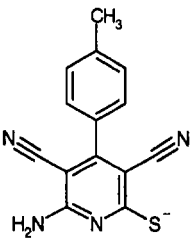
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A159				474	475	73.0
A160				488	489	75.2
A161				496	497	75.5
A162				510	511	67.4
A163				371	372	75.2
A164				421	422	57.7

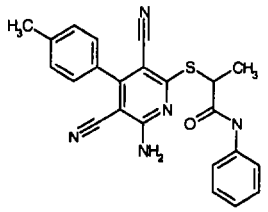
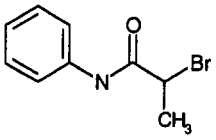
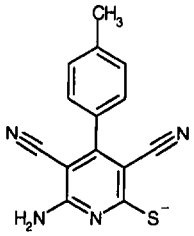
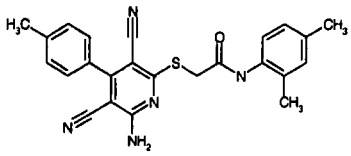
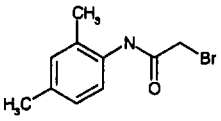
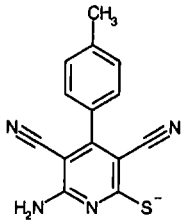
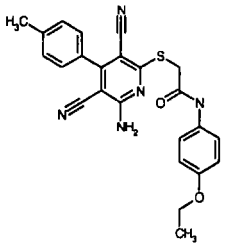
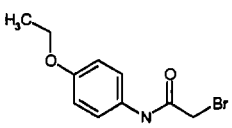
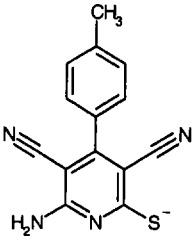
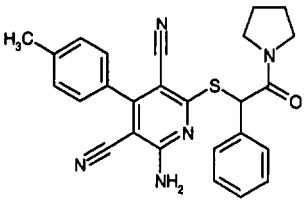
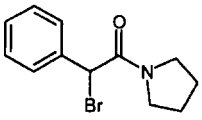
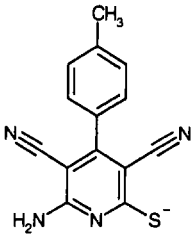
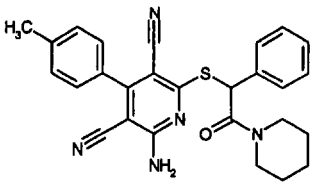
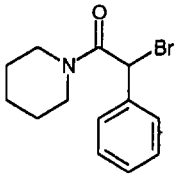
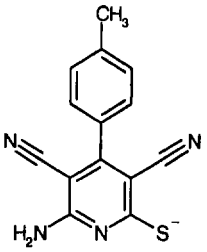
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A165				435	436	71.3
A166				435	436	54.0
A167				326	327	50.9
A168				339	340	76.3
A169				353	354	50.4

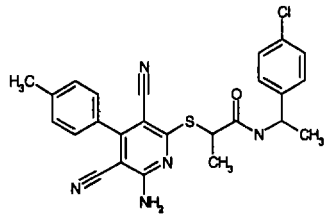
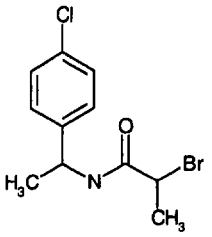
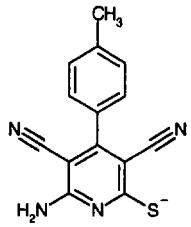
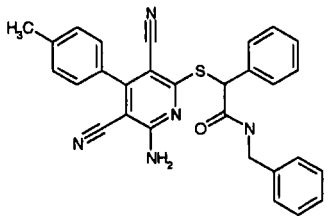
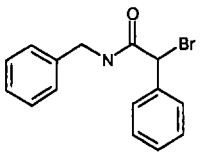
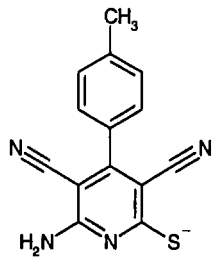
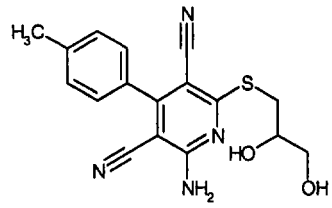
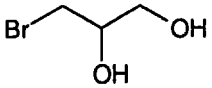
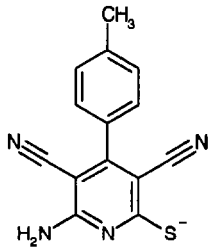
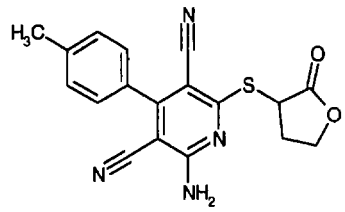
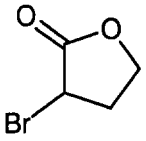
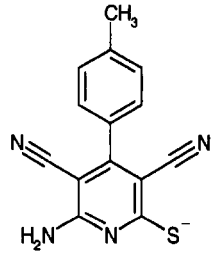
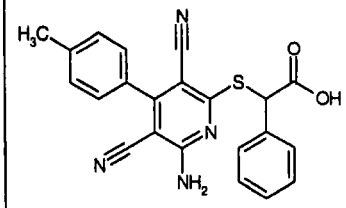
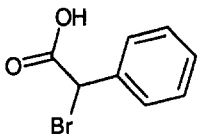
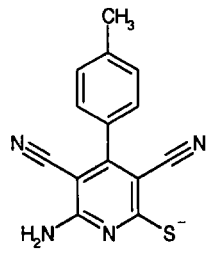
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A171				418	419	13.6
A172				430	431	63.8
A173				444	445	26.2
A174				460	461	32.2

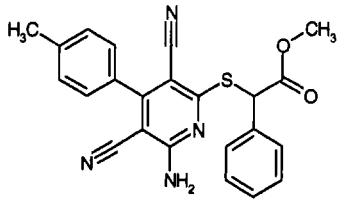
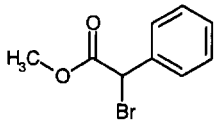
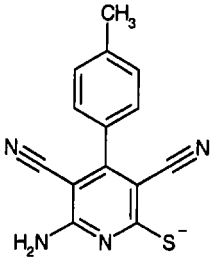
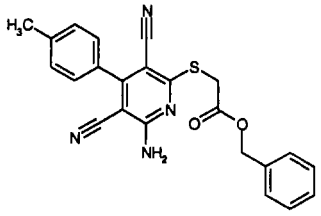
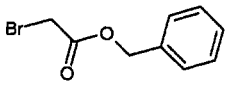
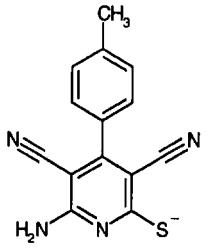
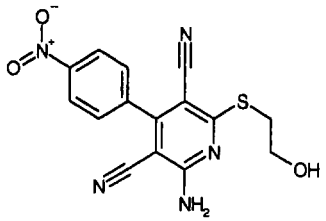
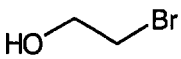
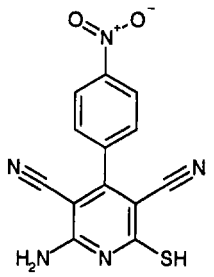
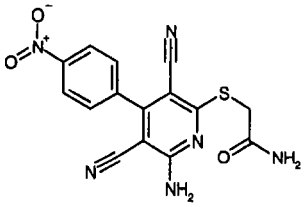
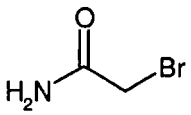
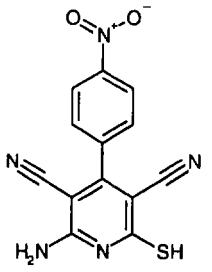
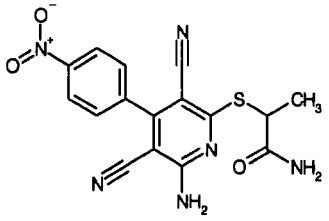
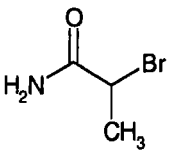
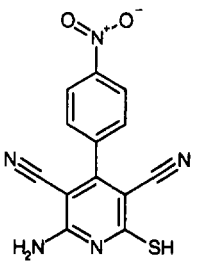
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A175				470	471	96.9
A176				484	485	18.2
A177				492	493	78.5
A178				356	357	17.1
A179				366	367	31.1

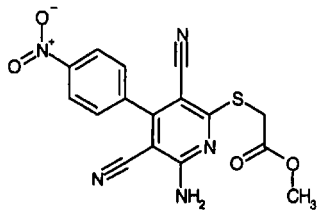
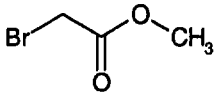
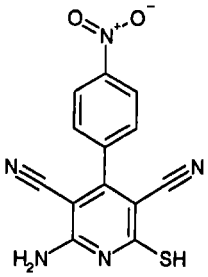
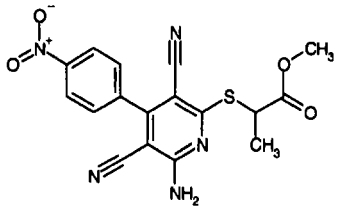
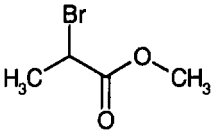
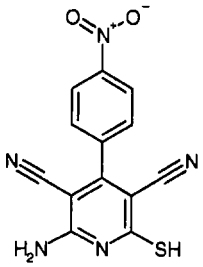
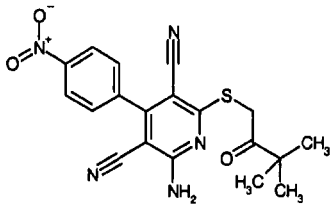
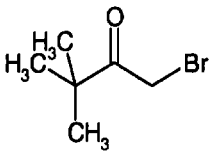
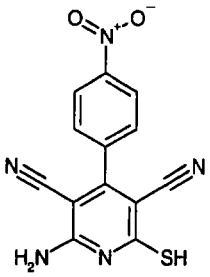
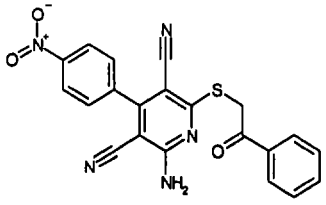
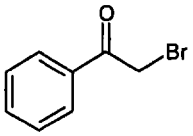
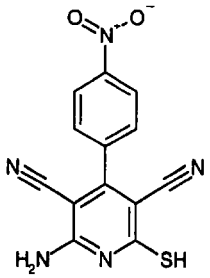
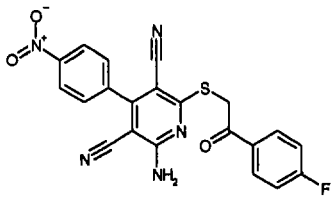
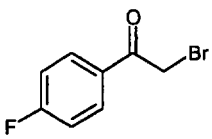
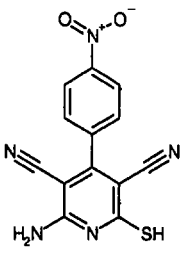
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A180				416	417	80.0
A181				430	431	66.2
A182				430	431	73.6
A183				310	311	28.4
A184				323	324	39.3

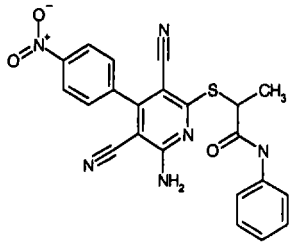
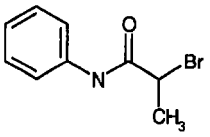
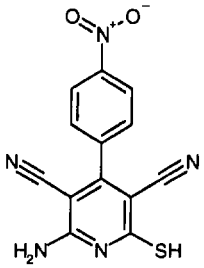
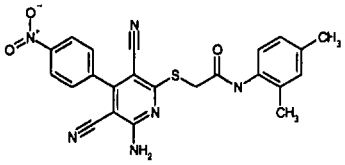
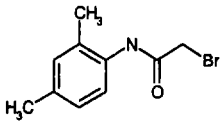
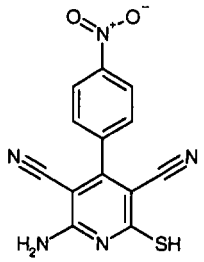
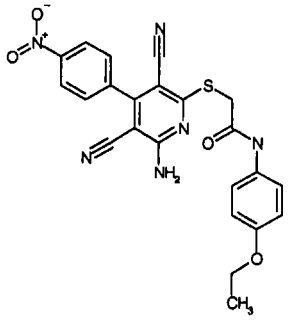
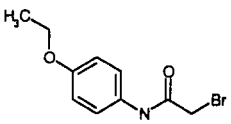
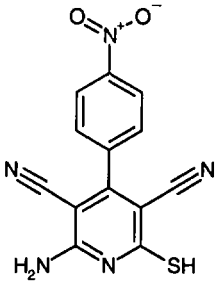
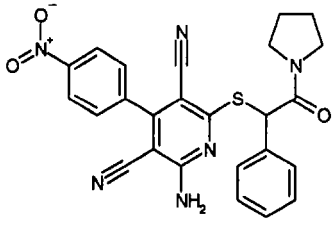
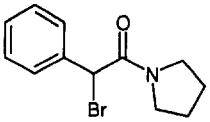
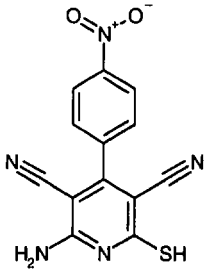
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A185				324	325	41.9
A186				337	338	40.9
A187				338	339	11.5
A188				352	353	29.2
A189				356	357	51.9
A190				364	365	77.4

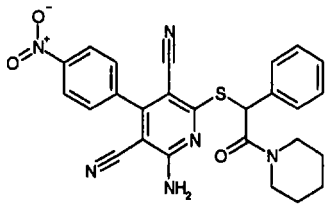
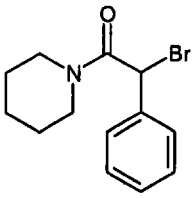
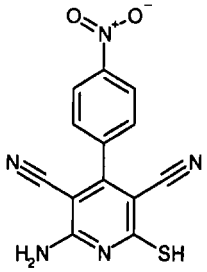
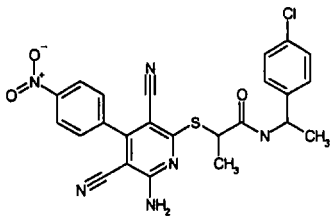
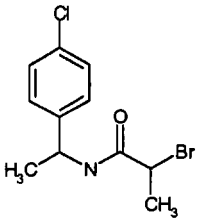
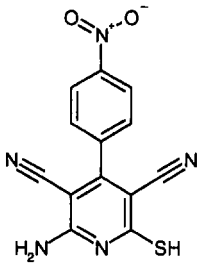
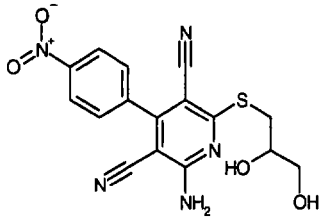
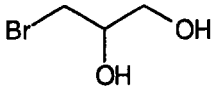
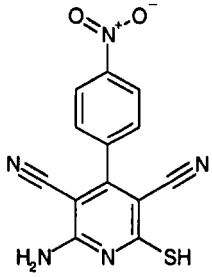
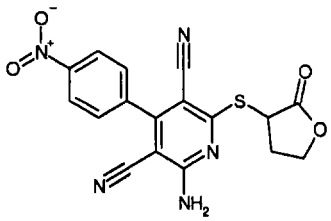
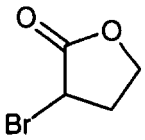
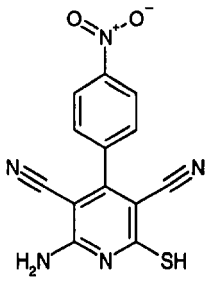
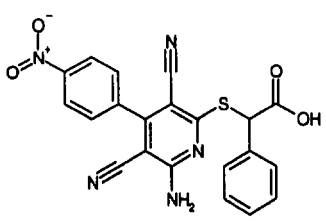
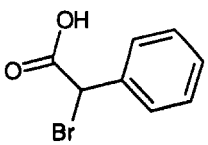
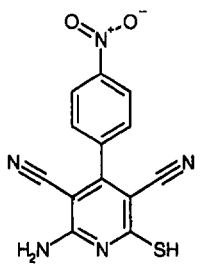
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A191				414	415	51.8
A192				428	429	58.2
A193				444	445	58.2
A194				454	455	29.5
A195				468	469	43.8

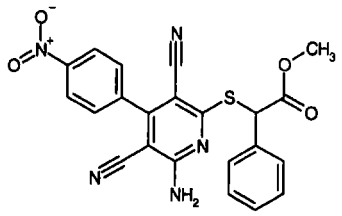
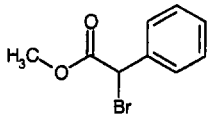
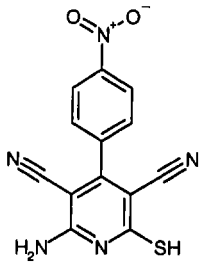
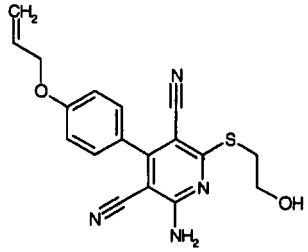
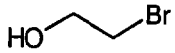
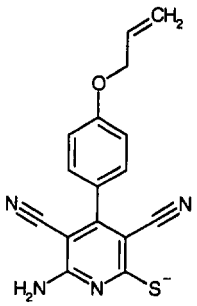
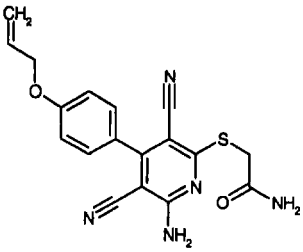
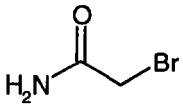
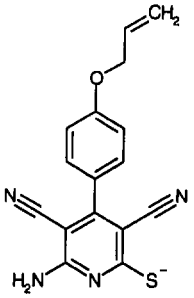
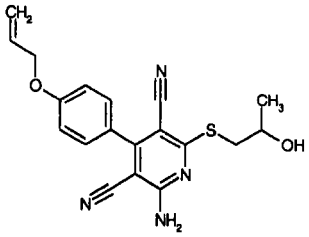
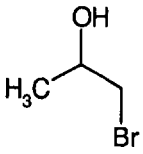
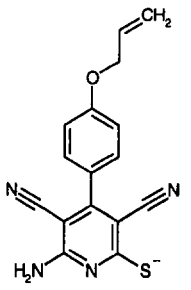
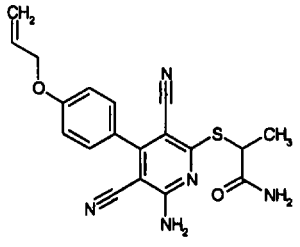
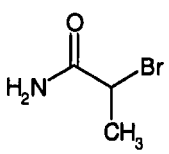
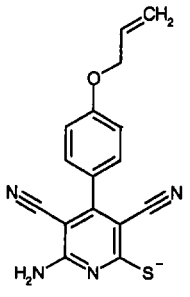
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A196				476	477	51.7
A197				490	491	73.9
A198				340	341	37.9
A199				350	351	80.8
A200				400	401	48.4

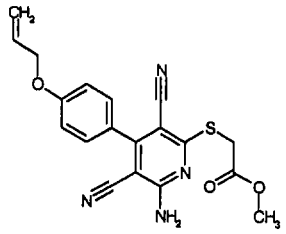
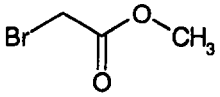
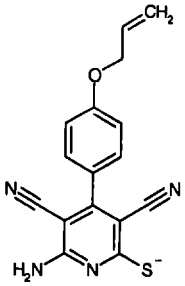
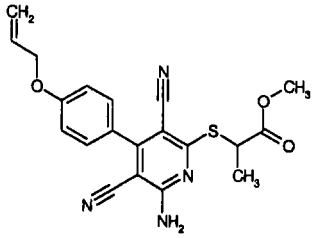
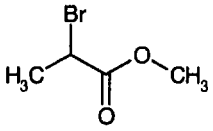
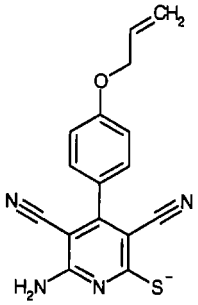
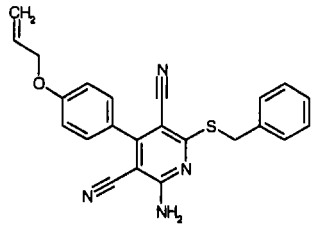
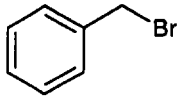
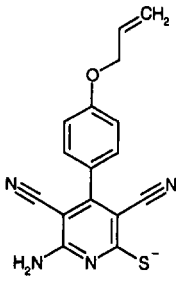
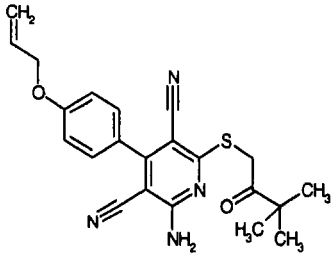
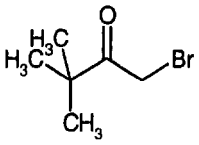
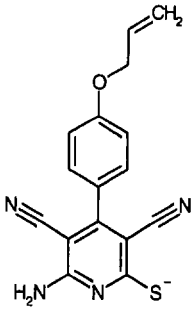
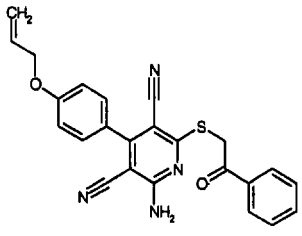
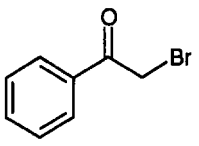
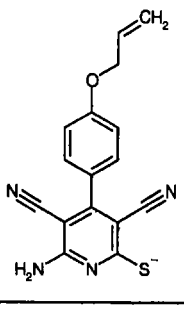
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A201				414	415	20.7
A202				414	415	61.0
A203				341	342	55.4
A204				354	355	38.4
A205				368	369	70.6

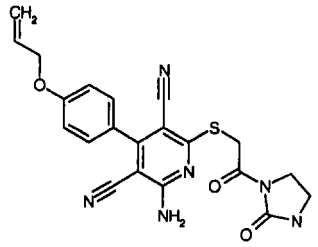
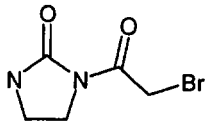
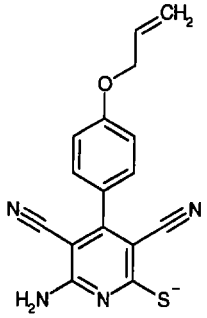
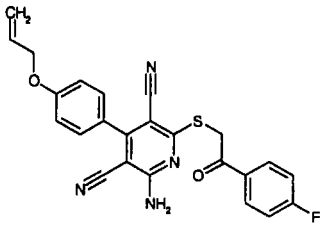
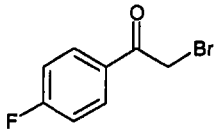
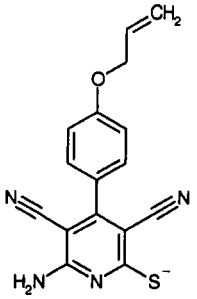
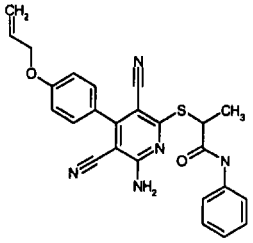
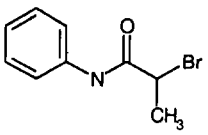
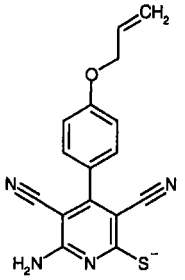
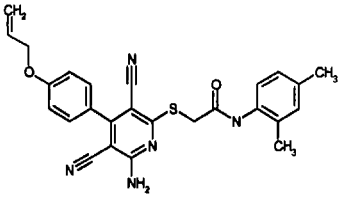
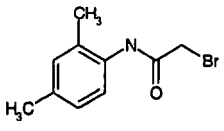
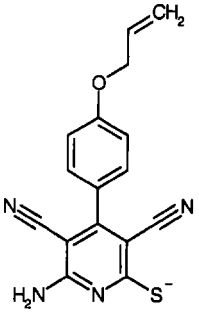
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A206				369	370	49.5
A207				383	384	65.5
A208				395	396	14.2
A209				415	416	22.9
A210				433	434	40.8

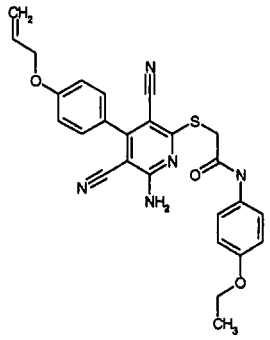
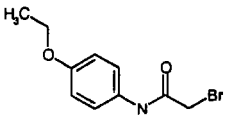
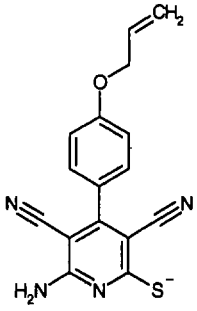
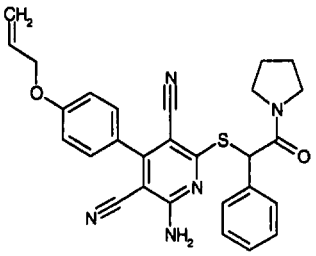
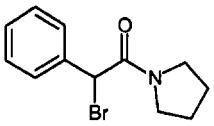
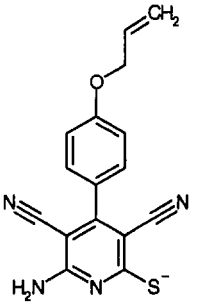
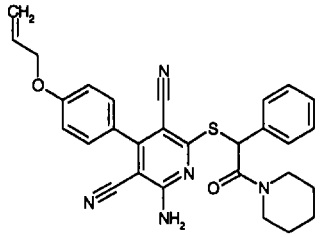
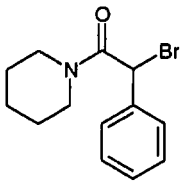
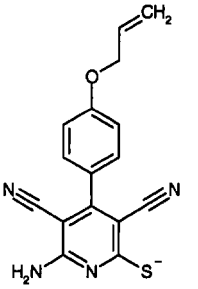
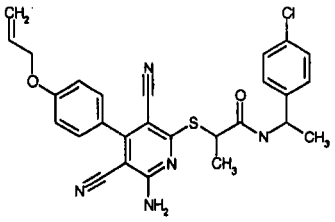
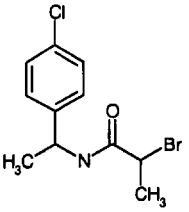
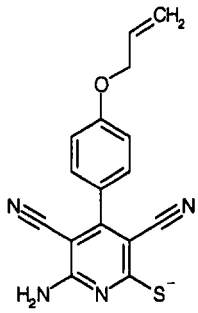
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A212				459	460	21.6
A213				475	476	57.5
A214				485	486	41.5

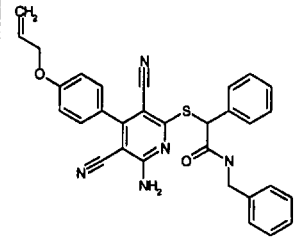
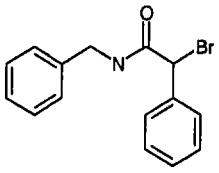
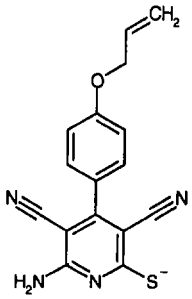
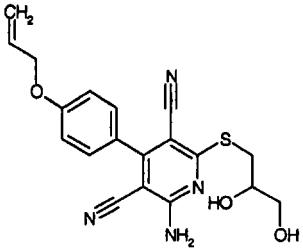
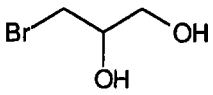
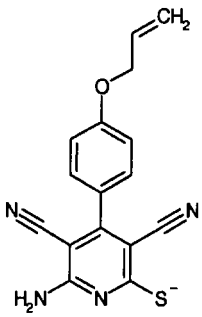
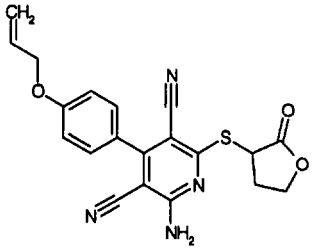
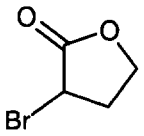
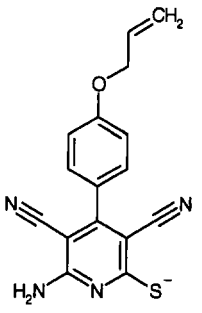
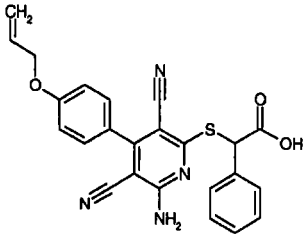
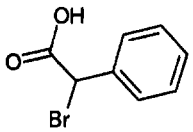
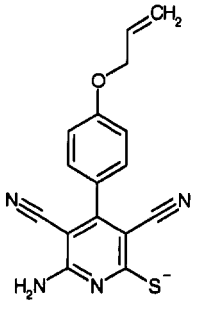
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A217				371	372	62.5
A218				381	382	39.9
A219				431	432	55.6

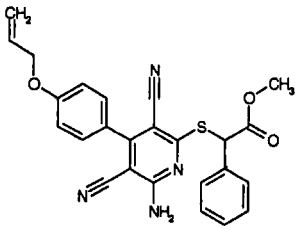
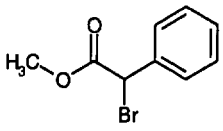
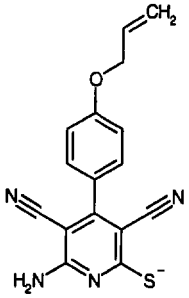
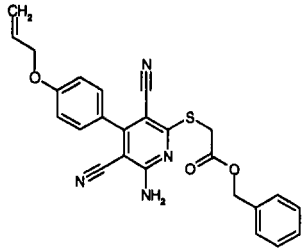
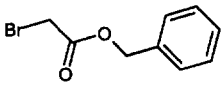
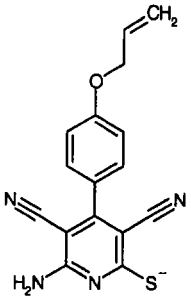
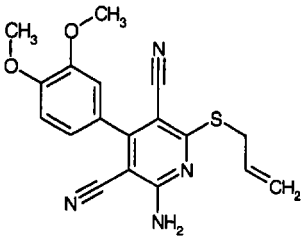
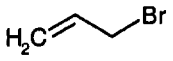
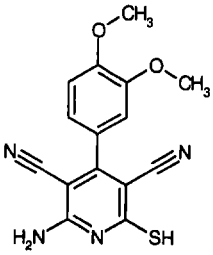
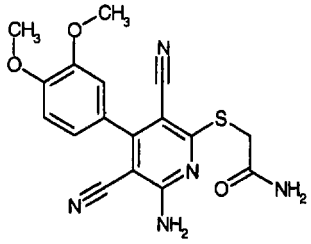
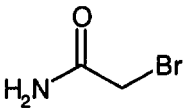
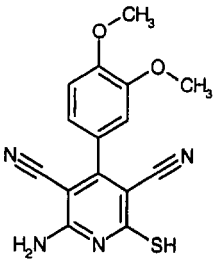
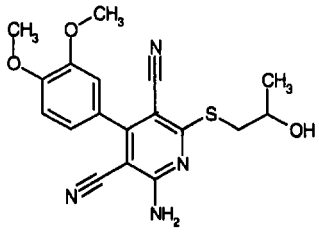
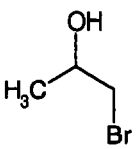
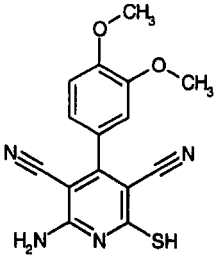
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A221				352	353	61.3
A222				365	366	80.2
A223				366	367	73.1
A224				379	380	81.7

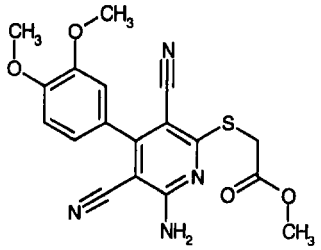
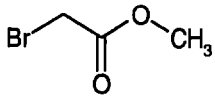
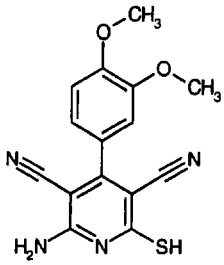
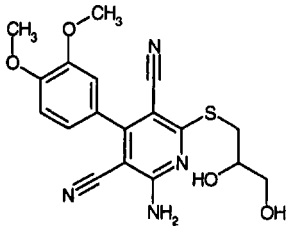
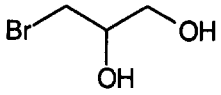
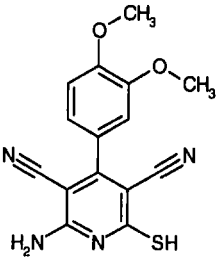
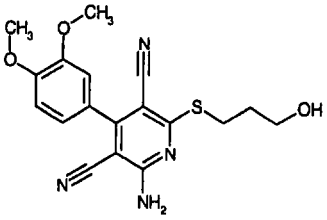
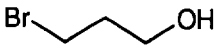
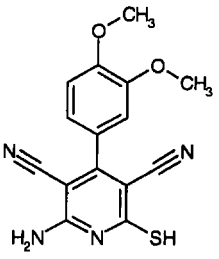
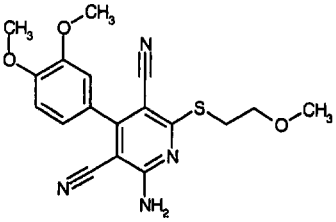
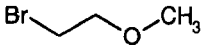
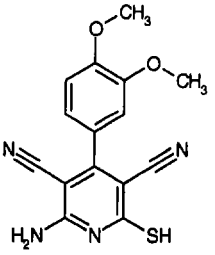
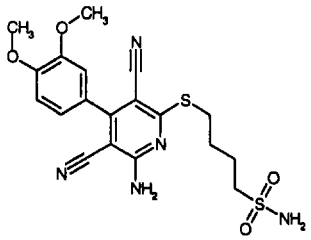
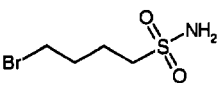
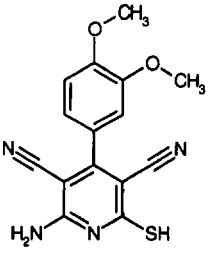
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A225				380	381	71.0
A226				394	395	65.9
A227				398	399	76.3
A228				407	408	79.7
A229				427	428	40.8

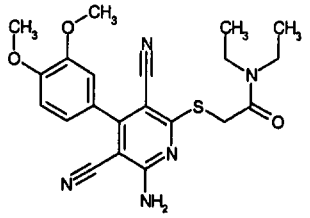
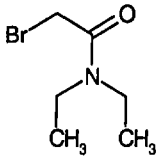
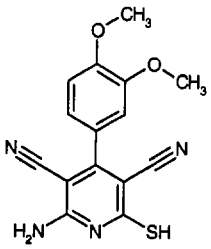
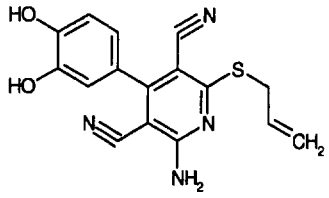
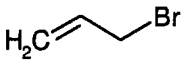
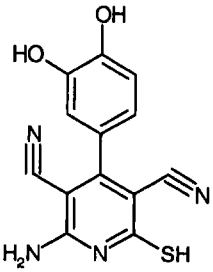
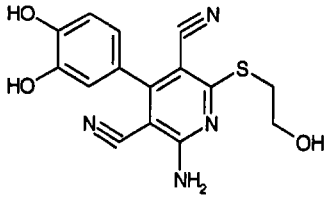
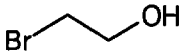
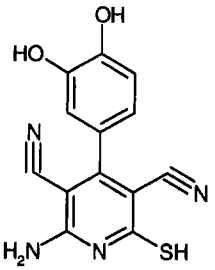
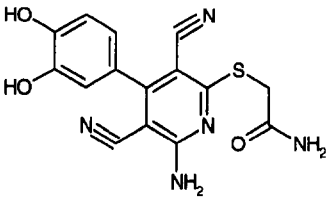
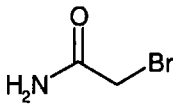
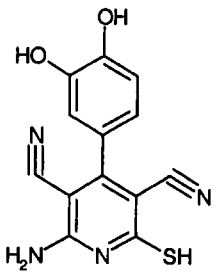
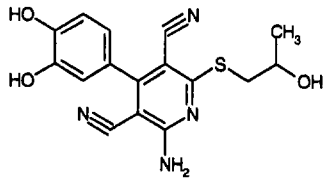
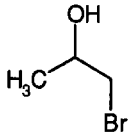
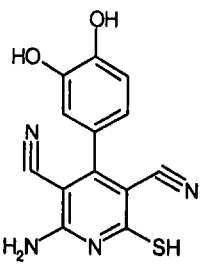
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A230				434	435	22.1
A231				444	445	9.7
A232				456	457	15.6
A233				470	471	43.7

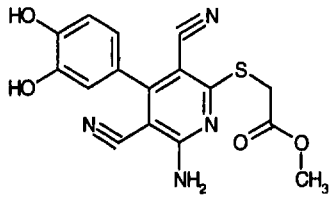
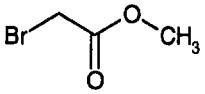
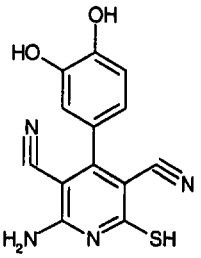
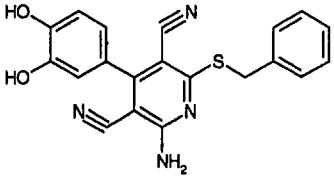
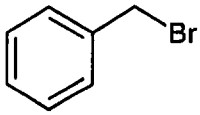
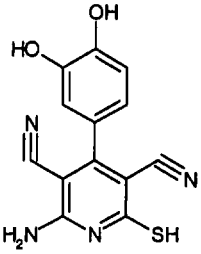
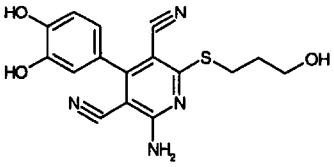
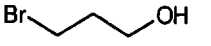
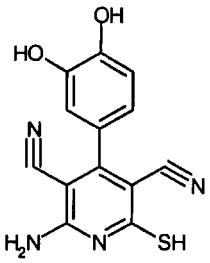
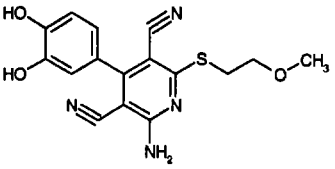
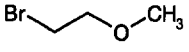
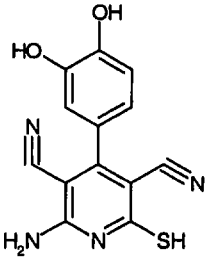
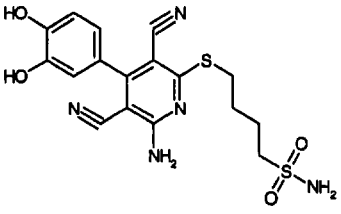
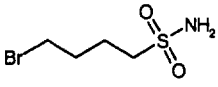
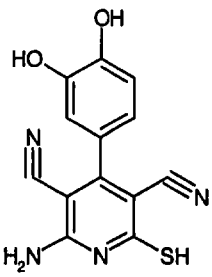
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A235				496	497	96.4
A236				510	511	84.6
A237				518	519	41.7

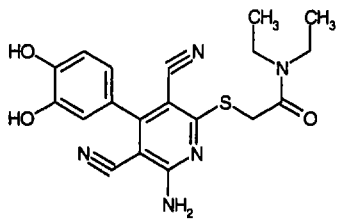
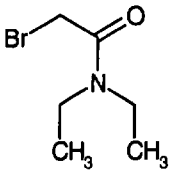
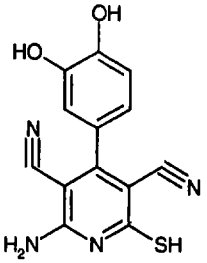
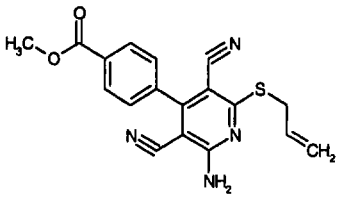
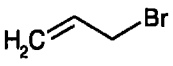
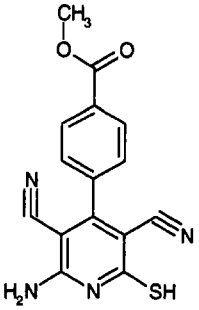
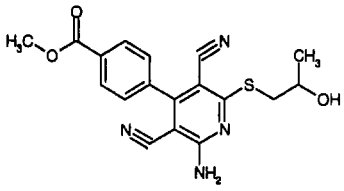
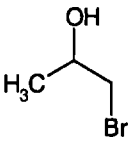
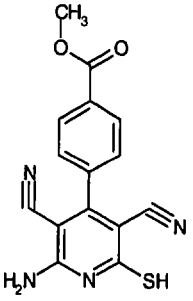
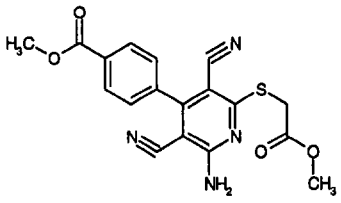
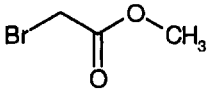
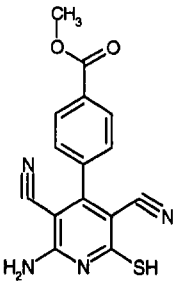
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
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A239				382	383	83.7
A240				392	393	54.8
A241				443	444	75.0

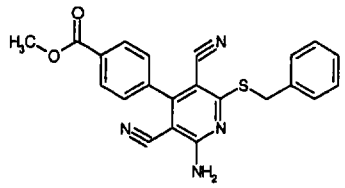
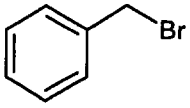
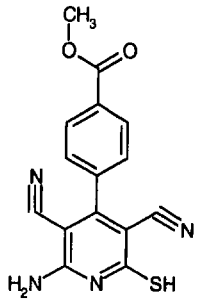
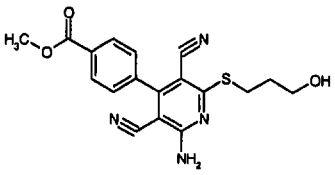
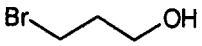
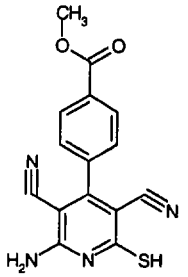
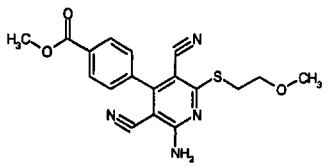
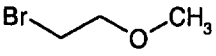
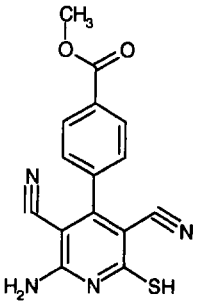
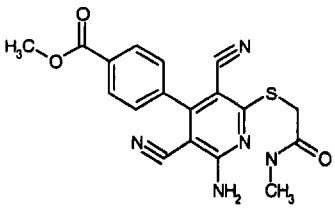
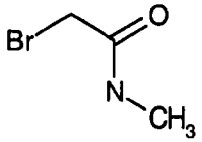
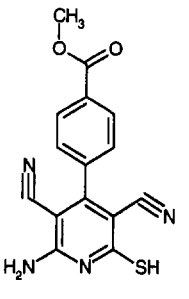
Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A242				457	458	50.2
A243				457	458	44.9
A244				352	353	54.5
A245				369	370	85.5
A246				370	371	60.7

Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A247				384	385	59.1
A248				386	387	79.7
A249				370	371	51.6
A250				370	371	49.4
A251				448	449	70.4

Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A252				426	427	39.0
A253				324	325	66.9
A254				328	329	90.1
A255				341	342	114.5
A256				342	343	70.7

Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A257				356	357	77.7
A258				374	375	87.1
A259				342	343	85.3
A260				342	343	73.3
A261				419	420	91.3

Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A262				397	398	66.2
A263				350	351	50.5
A264				368	369	49.1
A265				382	383	58.6

Ex. No.	Product	Starting material A	Starting material B	Molecular mass calculated	[M+H]+ found	Yield (% of theory)
A266				400	401	53.4
A267				368	369	48.9
A268				368	369	31.8
A269				381	382	30.2