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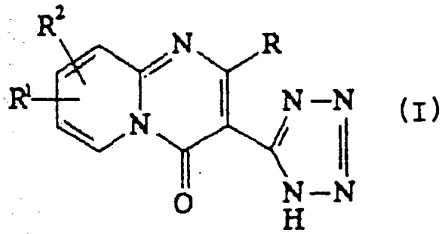
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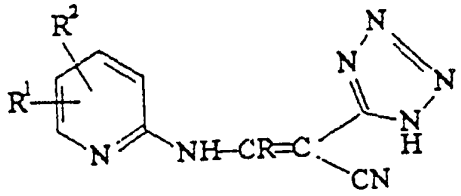
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(54) Title: 3-(1H-TETRAZOL-5-YL)-4H-PYRIDO[1,2-A]PYRIMIDINE-4-ONES, PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME AND THE PREPARATION THEREOF



(I)



(II)

(57) Abstract

The invention relates to partly new 3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-ones of general formula (I) and pharmaceutically acceptable salts and/or hydrates and the preparation thereof. These compounds possess significant antiallergic or antiulcer activity. The subjects of our invention are compounds of general formula (I) and pharmaceutically acceptable salts and/or hydrates thereof, wherein R stands for hydrogenatom, C_{1-4} alkyl group, or C_{6-10} aryl group; R^1 stands for hydrogenatom, C_{1-4} alkyl group, halogenatom, hydroxyl group, nitro group, carboxyl group, C_{2-5} alkoxycarbonyl group or C_{7-12} aralkoxy group; R^2 represents hydrogenatom, C_{1-4} alkyl group, or halogenatom; and a process for the preparation thereof. The invention also relates to a process for the preparation of compounds of general formula (I) and pharmaceutically acceptable salts and/or hydrates thereof, which comprises cyclising a 3-(2-pyridylamino)-2-(1H-tetrazol-5-yl)acrylnitrile of general formula (II), (wherein the meanings of R, R^1 and R^2 are the same as defined above) in acidic media and converting the compound of general formula (I) thus obtained into a pharmaceutically acceptable salt thereof or, if desired, liberating the base from its salt, or converting it into another salt thereof in a way known *per se*.

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3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidine-4-ones, pharmaceutical compositions containing the same and the preparation thereof

The invention relates to partly new 3-(1H-tetrazol--5-yl)-4H-pyrido[1,2-a]pyrimidin-4-ones of the general formula (I) and pharmaceutically acceptable salts and/or hydrates and the preparation thereof. These compounds possess significant antiallergic or antiulcer activity.

3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4--ones of general formula (I), where R represents hydrogenatom, are described in US-PS Nos. 4122274 and 4209620 as antiallergic agents, whereas in US-PS No. 4457932 as antiulcer agents.

The starting materials and the methods applied in the above patent specifications, however, are not very favourable for the preparation of the compounds of general formula (I), where R stands for hydrogen, as they result very low yields even lower than shown in the description and/or they use hazardeous reactants, such as the aluminium chloride-sodium azide 1:3 mixture in tetrahydrofuran.

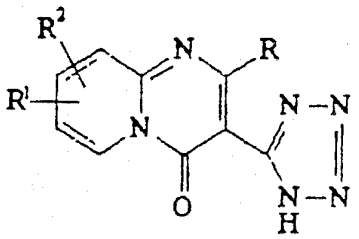
The reactants and the reaction conditions given in US-PS No. 4474953 are more favourable, but the yields of 60-70 % given in the examples do not relate to pure (1H--tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-ones of general formula (I), wherein R stands for hydrogen. After repeating the process we identified and isolated from the product, in about 30 % yield, an isomeric mixture consisting of the 3-(2-ethyl-tetrazol-5-yl) derivative of general formula (III), and the 3-(1-ethyl-tetrazol-5-yl) derivative of general formula (IV). These isomers may be separated from each other by crystallisation.

Identification of the compound of general formula (IV)

was accomplished by X-ray diffractometry. The formation of these compounds may be explained by an ethylation reaction where the ethanol resulting from the ring closure reaction of the ethyl-[3-(2-pyridylamino)-2-(1H-tetrazol-5-yl)acrylates] of general formula (V) in polyphosphoric acid, alkylates the products of the ring closure, i.e. the compounds of general formula (I), wherein R stands for hydrogen. Thus, beside the compound of general formula (I), significant amount of compounds of general formulae (III) and (IV) are also obtained.

The basis of our invention is the unexpected discovery that the acrylnitriles of general formula (II) may be transformed in a simple manner, in good yield, and without the formation of by-products into the pyrido-[1,2-a]pyrimidines of general formula (I).

The subjects of our invention are compounds of general formula (I)



(I)

and pharmaceutically acceptable salts and/or hydrates thereof, wherein

R stands for hydrogenatom, C_{1-4} alkyl group, or C_{6-10} aryl group;

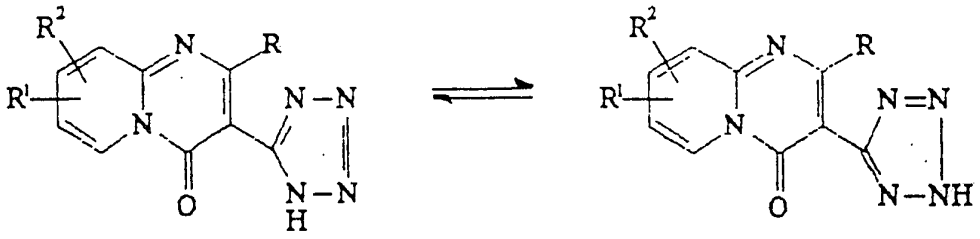
R^1 stands for hydrogenatom, C_{1-4} alkyl group, halogenatom, hydroxyl group, nitro group, carboxyl group, C_{2-5} alkoxycarbonyl group or C_{7-12} aralkoxy group;

R^2 represents hydrogenatom, C_{1-4} alkyl group, or halogenatom;

and a process for the preparation thereof.

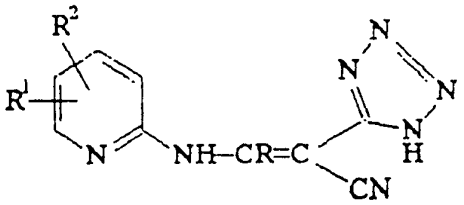
As used herein, the term "C_{1-4} alkyl group" means - in itself or in moieties, for instance in alkoxy groups - straight or branched chain aliphatic saturated hydrocarbon groups having one to four carbon atoms (such as e.g. methyl, ethyl, n-propyl and tert.-butyl group). As used herein the term "C_{6-10} aryl group" means phenyl group or naphthyl group, optionally bearing a C_{1-4} alkyl group.

Compounds of general formula (I) may give equilibrium mixture with compounds of general formula (IA) as demonstrated on Scheme A.



Scheme A

The present invention also relates to a process for the preparation of compounds of general formula (I) and pharmaceutically acceptable salts and/or hydrates thereof, which comprises cyclising a 3-(2-pyridylamino)--2-(1H-tetrazol-5-yl)acrylnitrile of general formula (II)



(II)

(wherein the meanings of R, R^1 and R^2 are the same as defined above) in acidic media and converting the compound of general formula (I) thus obtained into a pharmaceutically acceptable salt thereof or, if desired, liberating the base from its salt, or converting it into

another salt thereof in a way known per se.

The application of compounds of general formula (II) implies the application of compounds of general formula (IIA) (wherein R, R^1 and R^2 are the same as defined above) which constitute tautomeric equilibrium mixtures with the compounds of general formula (II) (see Scheme B), as well as the tetrazole ring tautomers of the compounds of general formulae (II) and (IIA), and the E-Z geometric isomers of the compounds of general formula (II).

As acidic agents, organic and inorganic acids may be applied. If desired, the reaction may be carried out in the presence of solvent, preferably in the presence of water.

As for organic acids alkanecarboxylic acids and arylsulfonic acids may be used. For inorganic acids preferably hydrogenhalides, sulfonic acid and various acids of the phosphor may be applied. The reaction may be accomplished, if desired, at elevated temperature. The temperature may be chosen according to the properties of the acidic agent and, if the reaction is carried out in the presence of solvent, according to the properties of the solvent. The reaction is preferably carried out at a temperature different from room temperature.

The compound of general formula (I) obtained in the reaction precipitates from the reaction mixture after dilution with water or after adjusting the pH of the reaction mixture to neutral and may be recovered for instance by filtration.

Compounds of general formula (I), if desired, may be converted into their pharmaceutically acceptable salts and/or hydrates on the effect of acids or bases. From the salts the bases may be liberated and, if desired, converted into another salt thereof. By this method acid addition salts with e.g. hydrochloric acid, hydrobromic

acid, sulphuric acid, acetic acid, citric acid ets. may favourably be prepared, as well as the sodium, potassium and calcium salts.

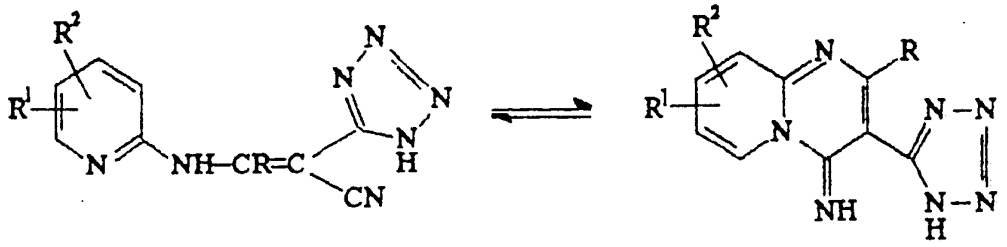
The compound of general formula (I) or its pharmaceutically acceptable salts may therapeutically be used in the form of pharmaceutical compositions containing the active ingredient in an admixture with inert non-toxic solid or liquid diluents and carriers.

These pharmaceutical compositions may be formulated as solids (tablet, capsule, dragée) or as liquids (solution, suspension, emulsion).

For carriers the usual materials (such as e.g. talc, calcium carbonate, magnesium stearate, water, poly(ethylene glycol) may be used.

The preparations, if desired, may contain supplementary materials such as e.g. emulsifying agents, or dissolution materials.

The starting materials of general formulae (II) and (IIA) forming tautomeric equilibrium mixtures (see Scheme B),

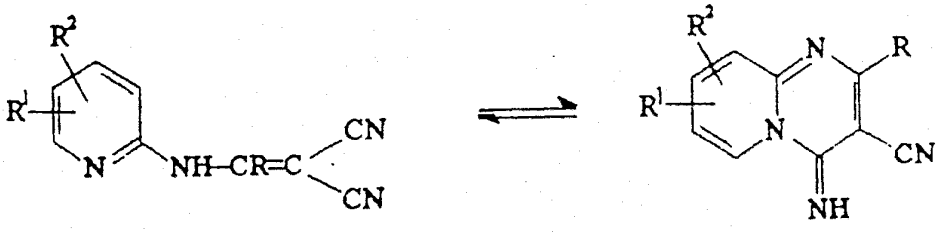


(II) (IIA)

Scheme B

may be prepared from the malonitriles of general formula (VI)

(wherein R, R^1 and R^2 are the same as defined above) giving tautomeric equilibrium mixtures with the 3-cyano--4-imino-4H-pyrido[1,2-a]pyrimidines of general formula (VIA) (see Scheme C)

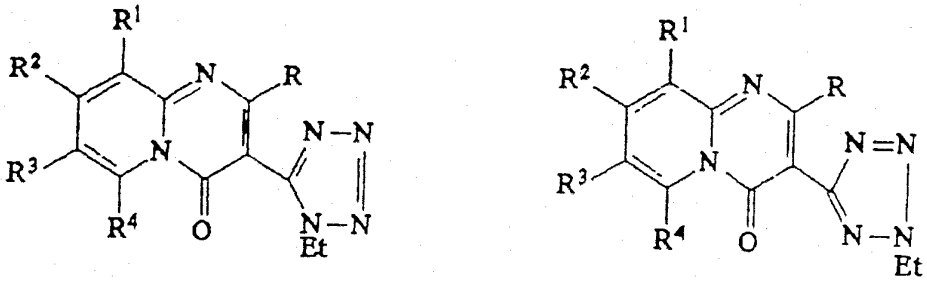


(VI) (VIA)

Scheme C

by reacting them with ammonium azide.

Compounds of general formulae (VI) and (VIA) may be synthetized in a simple way known from the literature [Journal of Organic Chemistry, 1986, 51, 2988] by the reaction of 2-amino-pyridines, malonitrile and orthoesters which are available on the market.



III IV

The invention is illustrated in detail by the following non-limiting Examples.

Examples

Example 1

53.3 g (0.25 mol) of 3-(2-pyridylamino)-2-(1H-

-tetrazol-5-yl)-acrylnitrile are heated in 500 ml of conc. hydrochloric acid under reflux conditions for 1 hour. After 10-15 mins of heating the original crystals dissolve, and the crystals of the product appear. The resulting suspension is cooled, diluted with 1000 ml of water, and neutralized with 25 % aqueous ammonia solution. The crystals are collected, washed with water.
Product: 41.48 g (87.9 %) of 3-(1H-tetrazol-5-yl)-4-oxo--4H-pyrido[1,2-a]pyrimidine.
Mp.: 316 °C (decomp.)
Analysis for $C_9H_6N_6O$

calculated: C 50.47 %; H 2.82 %; N 39.24 %;
found: C 49.73 %; H 2.77 %; N 39.48 %.

Example 2

23.7 g (0.1 mol) of 3-[(3-methyl-2-pyridyl)amino]--2-(1H-tetrazol-5-yl)acrylnitrile are heated n 200 ml of conc. hydrochloric acid under reflux conditions for 1 hour. After 10-15 mins. of heating the original crystals dissolve, and the crystals of the product appear. The resulting suspension is cooled, diluted with 400 ml of water, and neutralized with 25 % aqueous ammonia solution (pH = 6.5). The crystals are collected, washed with water.
Product: 19.57 g (85.76 %) of 3-(1H-tetrazol-5-yl)-9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine.
Mp.: 312 °C decomp. (dimethylformamide)
Analysis for $C_{10}H_8N_6O$

calculated: C 52.62 %; H 3.53 %; N 36.83 %;
found: C 52.66 %; H 3.44 %; N 37.27 %.

Example 3

13.3 g (0.059 mol) of 3-[(6-methyl-2-pyridyl)--amino]-2-(1H-tetrazol-5-yl)acrylnitrile are added under stirring to 70 g of polyphosphoric acid at 60 °C. The

reaction mixture is heated and stirred in a 130-140 °C oil bath for 2 hours, then it is cooled to 30-40 °C, cautiously diluted with 210 ml of water and neutralized under ice cooling with 75 ml of 25 % aqueous ammonia solution (pH = 6.5-7). The precipitated crystals are collected, washed with water. Product: 12.7 g (94.8 %) of 3-(1H-tetrazol-5-yl)-6-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine.

Mp: 286 °C decomp. (dimethylformamide)

Analysis for $C_{10}H_8N_6O$

calculated: C 52.62 %; H 3.53 %; N 36.83 %;

found: C 52.80 %; H 3.48 %; N 37.01 %.

Example 4

2.41 g (0.01 mol) of 3-methyl-3-[(6-methyl-2-pyridyl)-amino]-2-(1H-tetrazol-5-yl)acrylnitrile are added under stirring to 20 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirred in a 130-140 °C oil bath for 4 hours, then it is cooled to 50-60 °C, cautiously diluted with 28 ml of water and neutralized under ice cooling with 28 ml of 25 % aqueous ammonia solution (pH = 7). The precipitated crystals are collected, washed with water.

Product: 1.47 g (60.8 %) of 3-(1H-tetrazol-5-yl)-2,6-dimethyl-4-oxo-4H-pyrido[1,2-a]pyrimidine.

Mp: 258-260 °C decomp. (dimethylformamide)

Analysis for $C_{11}H_{10}N_6O$

calculated: C 54.54 %; H 4.16 %; N 34.70 %;

found: C 54.58 %; H 4.12 %; N 34.33 %.

Example 5

2.47 g (0.01 mol) of 3-[(5-chloro-2-pyridyl)-amino]-2-(1H-tetrazol-5-yl)acrylnitrile are added under stirring to 12 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirring in a 130-140 °C

oil bath for 1 hour, then it is cooled to 50-60 °C, cautiously diluted with 50 ml of water and neutralized under ice cooling with 25 ml of 25 % aqueous ammonia solution (pH = 6.5-7). The precipitated crystals are collected, washed with water. Product: 1.7 g (68.6 %) of 3-(1H-tetrazol-5-yl)-7-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidine. Mp: 304 °C decomp.

Analysis for $C_9H_5N_6OCl$

calculated: C 43.48 %; H 2.03 %; N 33.80 %; Cl 14.26 %;

found: C 43.71 %; H 2.50 %; N 33.53 %; Cl 14.60 %.

Example 6

2.27 g (0.01 mol) of 3-[(5-methyl-2-pyridyl)--amino]-2-(1H-tetrazol-5-yl)-acrylnitrile are added under stirring to 12 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirred on a 140 °C oil bath for 1 hour, then it is cooled to room temperature, cautiously diluted with 50 ml of water and neutralized under ice cooling with 20 ml of 25 % aqueous ammonia solution. The precipitated crystals are collected, washed with water.

Product: 2.3 g (93.5 %) of 3-(1H-tetrazol-5-yl)-7-methyl--4-oxo-4H-pyrido[1,2-a]pyrimidine monohydrate. Mp: 297 °C decomp.

Analysis for $C_{10}H_8N_6O \cdot H_2O$

calculated: C 48.78 %; H 4.09 %; N 34.13 %;

found: C 49.34 %; H 4.18 %; N 34.57 %.

Example 7

2.27 g (0.01 mol) of 3-[(4-methyl-2-pyridyl)--amino]-2-(1H-tetrazol-5-yl)acrylnitrile are added under stirring to 20 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirred on a 140 °C oil bath for 1 hour, then it is cooled to room temperature, cautiously diluted with 60 ml of water and neutralized

under ice cooling with 28 ml of 25 % aqueous ammonia solution (pH = 6.5-7). The precipitated crystals are collected, washed with water. Product: 2.24 g (94.5 %) of 3-(1H-tetrazol-5-yl)-8-methyl-4-oxo-4H-pyrido[1,2-a]-pyrimidine hemihydrate. Mp: 288 °C decomp.

Analysis for $C_{10}H_8N_6O \cdot \frac{1}{2}H_2O$

calculated: C 50.63 %; H 3.82 %; N 35.42 %;

found: C 50.26 %; H 3.90 %; N 35.38 %.

Example 8

2.41 g (0.01 mol) of 3-[(4,6-dimethyl-2-pyridyl)--amino]-2-(1H-tetrazol-5-yl)acrylnitrile are added under stirring to 12 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirred in a 140 °C oil bath for 1 hour, then it is cooled to room temperature, cautiously diluted with 50 ml of water and neutralized under ice cooling with 18 ml of 25 % aqueous ammonia solution. The precipitated crystals are collected, washed with water. Product: 1.43 g (59.1 %) of 3-(1H-tetrazol-5--yl)-6,8-dimethyl-4-oxo-4H-pyrido[1,2-a]pyrimidine.

Mp: 350 °C decomp.

Analysis for $C_{11}H_{10}N_6O$

calculated: C 54.54 %; H 4.16 %; N 34.69 %;

found: C 54.35 %; H 4.21 %; N 33.94 %.

Example 9

2.3 g (0.01 mol) of 3-[(3-hydroxy-2-pyridyl)amino]--2-(1H-tetrazol-5-yl)acrylnitrile is heated in 20 ml of conc. hydrochloric acid under reflux conditions for 1 hour. The reaction mixture is cooled to room temperature and poured on 30 ml of water, and the pH adjusted to 6.5 with 10 ml of 25 % aqueous ammonia solution. The crystals are collected, washed with water. Product: 2.4 g (90.2 %) of 3-(1H-tetrazol-5-yl)-9-hydroxy-4-oxo-4H-pyrido[1,2-a]-pyrimidine hydrochloride salt.

Mp.: 324 °C decomp.

Analysis for $C_9H_6N_6O_2 \cdot HCl$

calculated: C 40.54 %; H 2.65 %; N 31.52 %;

found: C 40.82 %; H 2.78 %; N 31.26 %.

Example 10

1.1 g (0.004 mol) of 3-[(3,5-dichloro-2-pyridyl)--amino]-2-(1H-tetrazol-5-yl)-acrylnitrile are added under stirring to 12 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirred in a 130-140 °C oil bath for 30 minutes, then it is cooled to 60 °C, cautiously diluted with 50 ml of water and neutralized under ice cooling with 15 ml of 25 % aqueous ammonia solution (pH = 7). The precipitated crystals are collected, washed with water. Product: 1.04 g (90.4 %) of 3-(1H-tetrazol-5-yl)-dichloro-4-oxo-4H-pyrido[1,2-a]-pyrimidine.

Mp: 291 °C decomp. (dimethylformamide).

Analysis for $C_9H_4N_6Cl_2O$

calculated: C 38.19 %; H 1.42 %; N 29.69 %; Cl 25.05 %;

found: C 37.80 %; H 1.58 %; N 29.77 %; Cl 25.02 %.

Example 11

1.25 g (4 mmol) of 3-(5-bromo-2-pyridylamino)-2--(1H-tetrazol-5-yl)-acrylnitrile are heated in 10 ml of conc. hydrochloric acid under reflux conditions for 1 hour. The reaction mixture is cooled to room temperature and poured on 30 ml of water, and neutralized with 10 ml of 25 % aqueous ammonia solution (pH = 7). The crystals are collected, washed with water.

Product: 1.25 g (99.0 %) of 3-(1H-tetrazol-5-yl)-7-bromo--4-oxo-4H-pyrido[1,2-a]pyrimidine. Mp: 298-300 °C decomp.

Analysis for $C_9H_5N_6BrO$

calculated: C 36.88 %; H 1.72 %; N 28.67 %; Br 27.26 %;

found: C 36.76 %; H 1.62 %; N 28.86 %; Br 27.13 %.

Example 12

1.41 g (4.6 mmol) of 3-phenyl-[(6-methyl-2--pyridyl)-amino]-2-(1H-tetrazol-5-yl)-acrylnitrile are added under stirring to 12 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirred in a 130-140 °C oil bath for 1 hour, then it is cooled to 60 °C, cautiously diluted with 60 ml of water and neutralized under ice cooling with 14 ml of 25 % aqueous ammonia solution (pH = 7). The precipitated crystals are collected, washed with water.

Product: 1.05 g (75.0 %) of 3-(1H-tetrazol-5-yl)-2--phenyl-6-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine.

Mp.: 280 °C decomp.(dimethylformamide)

Analysis for $C_{16}H_{12}N_6O$

calculated: C 63.15 %; H 3.97 %; N 27.62 %;

found: C 63.39 %; H 3.66 %; N 27.72 %.

Example 13

0.65 g (2.5 mmol) of 3-(3-nitro-2-pyridylamino)-2--(1H-tetrazol-5-yl)acrylnitrile are heated in 10 ml of conc. hydrochloric acid under reflux conditions for 1 hour. The reaction mixture is cooled to room temperature and poured on 35 ml of water, and neutralized with 9 ml of 25 % aqueous ammonia solution (pH = 7). The crystals are collected, washed with water.

Product: 0.49 g (75.0 %) of 3-(1H-tetrazol-5-yl)-9-nitro--4-oxo-4H-pyrido[1,2-a]pyrimidine. Mp.: 283-285 °C decomp.

Analysis for $C_9H_5N_7O_3$

calculated: C 41.71 %; H 1.94 %; N 37.83 %;

found: C 41.20 %; H 2.30 %; N 38.20 %.

Example 14

1.4 g (0.005 mol) of 3-[(-ethoxycarbonyl-2-pyri--dyl)-amino]-2-(1H-tetrazol-5-yl)acrylnitrile are added

under stirring to 12 g of polyphosphoric acid at 60 °C. The reaction mixture is heated and stirred in a 130-140 °C oil bath for 1 hour, then it is cooled to 60 °C, cautiously diluted with 50 ml of water and neutralized under ice cooling with 16 ml of 25 % aqueous ammonia solution (pH = 7). The precipitated crystals are collected, washed with water.

Product: 3-(1H-tetrazol-5-yl)-9-ethoxycarbonyl-6-methyl--4-oxo-4H-pyrido[1,2-a]pyrimidine. Mp.: 247-250 °C decomp.

Analysis for $C_{12}H_{10}N_6O$

calculated: C 50.35 %; H 3.52 %; N 29.36 %;

found: C 50.12 %; H 3.45 %; N 29.87 %.

Example 15

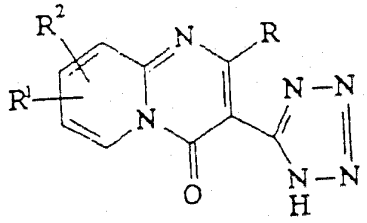
Preparation of 50, 100, 200 and 400 mg tablets.

750 mg of 3-(1H-tetrazol-5-yl)-2,6-dimethyl-4-oxo--4H-pyrido]1,2-a]pyrimidine potassium salt are homogenized with 1050 g of crystalline cellulose and 15 g of arnidopectine.

The mixture is granulated with the help of 150 g of Endragit-lac solution, then it is dried at 40 °C and re-granulated. The granulatum is homogenized with a powder mixture consisting of 20 g of talc and 20 g of magnesium stearate, then in a method known per se, with the help of the appropriate pressure tools, it is pressed into tablets of 50, 100, 200 and 400 mg.

Claims

1. Compounds of the general formula (I)



(I)

or pharmaceutically acceptable salts and/or hydrates thereof, wherein

R stands for hydrogen, C_{1-4} alkyl or C_{6-10} aryl group;

R^1 stands for hydrogen, C_{1-4} alkyl, halogen, hydroxy, nitro, carboxy, C_{2-5} alkoxycarbonyl or C_{7-12} aralkoxy,

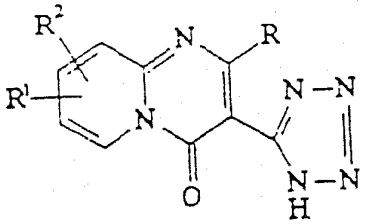
R^2 stands for hydrogen, C_{1-4} alkyl or halogen

with the proviso that

if R stands for hydrogen, R^1 is different from hydrogen, C_{1-4} alkyl or halogen.

2. Pharmaceutical composition which comprises as active ingredient a compound of general formula (I) or pharmaceutically acceptable salts and/or hydrates thereof wherein R, R^1 and R^2 are the same as defined in claim 1.

3. Process for the preparation of a compound of general formula (I)



(I)

or pharmaceutically acceptable salts and/or hydrates

thereof, wherein

R stands for hydrogen, C_{1-4} alkyl or C_{6-10} aryl group;

R^1 stands for hydrogen, C_{1-4} alkyl, halogen, hydroxy, nitro, carboxy, C_{2-5} alkoxycarbonyl or C_{7-12} aralkoxy,

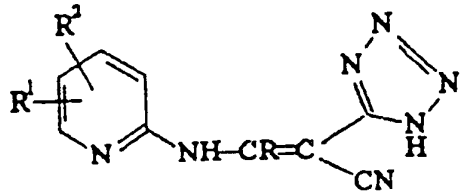
R^2 stands for hydrogen, C_{1-4} alkyl or halogen

which c o m p r i s e s

cyclising a 3-(2-pyridyl-amino)-2-(1H-tetrazol-5-yl)-acrylnitrile - wherein the meaning of R, R^1 and R^2 are defined above - in acidic media, and converting the compound of the general formula (I) thus obtained into a pharmaceutically acceptable salt and/or hydrate thereof, or liberating the base from the salt and converting it into another salt by methods known per se.

4. Process according to claim 3 which c o m p r i s e s applying as acidic media organic or inorganic acids, e.g. alkanecarboxylic acid, arylsulfonic acid, hydrogen halogenide, sulfuric acid or phosphoric acid.

5. Process according to claims 3-4, which c o m p r i s e s carrying out the cyclisation of the compound of general formula (II)



(II)

wherein the meaning of R, R^1 and R^2 is the same as defined in claim 1 - in the presence of a solvent.

6. Process according to claim 5, which c o m p r i s e s applying water as solvent.

7. Process according to claims 3-6, which c o m p r i s e s carrying out the cyclisation at a temperature between 25-50 °C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 93/00009

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: C 07 D 471/04; A 61 K 31/505 // (C 07 D 471/04, 239:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 07 D 471/04; A 61 K 31/55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, CHEMICAL ABSTRACTS

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Twelfth Collective Index, Volumes 106-115, 1987-1991, page 80 214CS, column 1, lines 90-93, Chemical Abstracts 111:89 703n, Yakuri to Chiryo 1989, 17(4), 1427-32 (Japan).	1
X	EP, A1, 0 462 834 (WAKO PURECHEMICAL) 27 December 1991 (27.12.91), page 3, line 30 to page 4, line 26; page 6, lines 1-7, 15-22, 38-40, 43-54.	3,4,7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 1993 (16.06.93)	18 June 1993 (18.06.93)

Name and mailing address of the ISA/ AT	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 93/00009

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A1 462834	27-12-91	CA AA 2044796 JP A2 4316579	22-12-91 06-11-92