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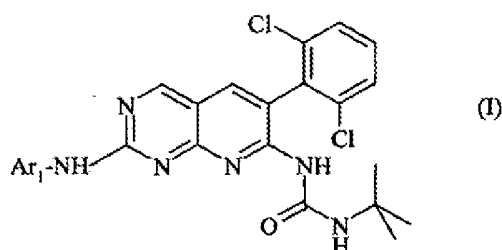
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EP-B- 0 790 997
WO-A-01/55147
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WO-A-2004/085436
SCHROEDER M C ET AL: "SOLUBLE 2-SUBSTITUTED AMINOPYRIDO[2,3-D]PYRIMIDIN-7-YL UREAS. STRUCTURE-ACTIVITY RELATIONSHIPS AGAINST SELECTED TYROSINE KINASES AND EXPLORATION OF IN VITRO AND IN VIVO ANTICANCER ACTIVITY" 7 juin 2001 (2001-06-07), JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, PAGE(S) 1915-1926 , XP001152609 ISSN: 0022-2623 * le document en entier *
ANDREW M. THOMPSON ET AL.: "Synthesis and Structure-Activity Relationships of soluble 7-Substituted 3-(3,5-Dimethoxyphenyl)-1,6-naphthyridin-2 -amines and Related Ureas as Dual Inhibitors of the Fibroblast Growth Factor Receptor-1 and Vascular Endothelial growth factor Receptor-2 Tyrosine Kinases" JOURNAL OF MEDICINAL CHEMISTRY., vol. 48, no. 14, 17 juin 2005 (2005-06-17), pages 4628-4653-, XP002372558 USAMERICAN CHEMICAL SOCIETY.

Fortsættes ...

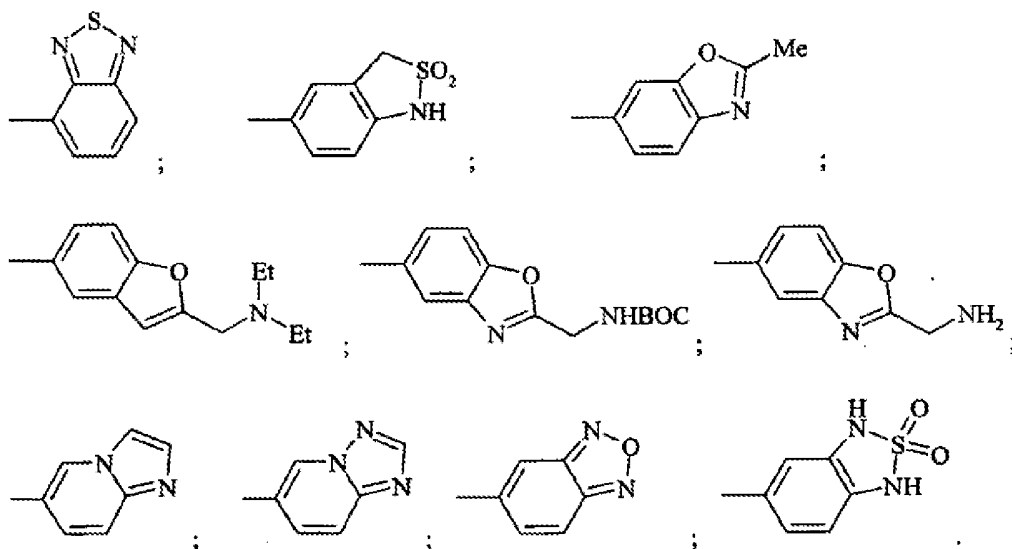
Description

The present invention relates to pyrido[2,3-d]pyrimidine derivatives, to the preparation thereof and to the therapeutic use thereof.

Compounds derived from pyrido[2,3-d]pyrimidine are described in patent applications WO 01/55 147 and WO 03/000 011 and in patents EP-B-790 997 and US 5 733 913. These compounds are potentially useful for treating cell proliferation conditions. Thus, and according to a first aspect, a subject of the present invention is compounds corresponding to formula (I):



in which Ar₁ is chosen from:



The compounds of the examples which follow are a subject of the present invention.

A compound in accordance with the invention can (i) be in a

non-chiral form, or a racemic form, or a form enriched in one stereoisomer, or enriched in one enantiomer; (ii) be optionally salified, and (iii) be optionally hydrated or solvated.

5

The compounds of formula (I) can contain one or more asymmetrical carbon atoms. They can therefore exist in the form of enantiomers or of diastereoisomers. These enantiomers and diastereoisomers and also mixtures thereof, including
10 racemic mixtures, are part of the invention.

The compounds of formula (I) can exist in the form of bases or of addition salts with acids. When compounds of formula (I) contain free acid functions, for example carboxylic, sulphonic
15 or phosphonic, these acid functions can be salified using bases so as to form addition salts. Such addition salts are part of the invention.

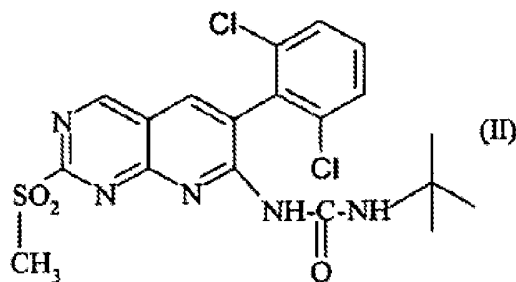
The addition salts with acids or with bases are advantageously
20 prepared with, respectively, pharmaceutically acceptable acids or bases, but the salts of other acids or of bases that are useful, for example, for the purification or the isolation of the compounds of formula (I) are also part of the invention.

The compounds of formula (I) can also exist in the form of
25 hydrates or of solvates, i.e. in the form of associations or of combinations with one or more molecules of water or with a solvent. Such hydrates and solvates are also part of the invention.

30 In the context of the present invention:

- the term "a halogen atom" is intended to mean: a fluorine, a chlorine, a bromine or an iodine.

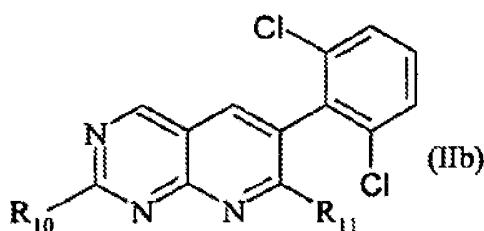
The compounds of formula (I) are prepared by reaction between a compound of formula (II):



and an amine of formula $\text{Ar}'_1\text{NH}_2$ (III) in which Ar'_1 is Ar_1 , as defined for (I) or a precursor of Ar_1 ; where appropriate, the Ar'_1 group of the compound thus obtained is converted to an Ar_1 group.

In accordance with the invention, the compounds of formula (I) can be prepared according to a process characterized in that the following are reacted:

(i) a compound of formula:



in which R_{10} is a leaving group such as: (a) halogen, in particular Cl or Br, or (b) alkyl-S(O) m - with $m = 0, 1$, or 2 ; R_{11} is NHC(O)-NH-tBu ; and

(ii) an amine of formula $\text{Ar}'_1\text{NH}_2$ (III) in which Ar'_1 is Ar_1 as defined for (I) or a precursor of Ar_1 ; where appropriate, the Ar'_1 group of the compound thus obtained is converted to an Ar_1 group.

When R_{10} is halogen or alkyl-S(O) m -, with $m = 2$, the reaction is carried out in a solvent, preferably a polar solvent:

(i) for example tetrahydrofuran, dimethyl sulphoxide or ethanol, optionally in the presence of a trace of acid such as

hydrochloric acid; or

(ii) in dimethyl sulphoxide in the presence of a strong base such as tBuOK;

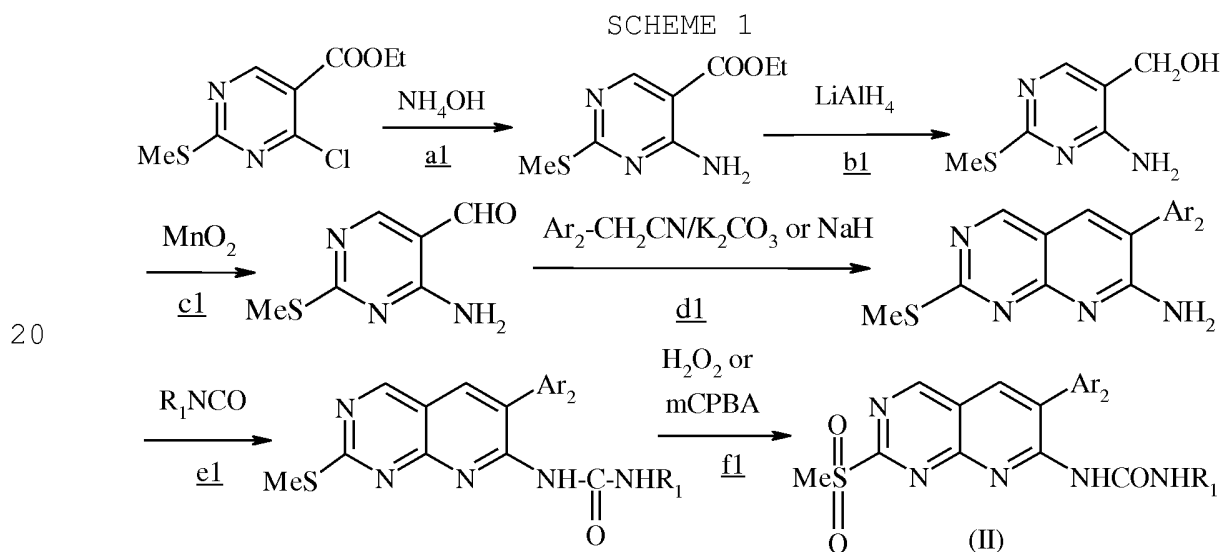
5

at a temperature between ambient temperature and the reflux temperature of the solvent.

When R_{10} is alkyl-S(O)m- with $m = 0$ or 1 , the reaction can be carried out with Ar'_1NH_2 (III) in the molten state, preferably at a temperature in the region of $200^\circ C$, without catalyst.

Where appropriate, the amine functions present in the Ar'_1 group of compound (III) are salified or protected beforehand.

The compounds of formula (II) are prepared by following the procedure described in European patent 790 997 and patent US 5 733 913, as described in scheme 1 below:



mCPBA: *mé*ta-chloroperbenzoic acid.

The amines of formula (III) Ar'_1NH_2 are known or prepared by known methods from the corresponding nitrated derivatives Ar'_1NO_2 (IV), by reduction either (i) in an acidic medium in the presence of a metal such as powdered zinc or iron, or (ii) by hydrogen in the presence of a catalyst such as Pd/C. Ar' is Ar or a precursor of Ar.

30

The compounds of formula (IV) are known or prepared by known methods.

The compounds according to the invention are obtained in
5 racemic form; the optically pure isomers can then be prepared
using resolving methods known to those skilled in the art,
such as crystallization by formation of salts with chiral
agents. Compounds according to the invention in optically pure
form can also be prepared using methods of asymmetric or
10 stereospecific synthesis, the use of chromatographic
techniques using a chiral phase. Moreover, the products of the
invention can be separated via the formation of
diastereoisomers, separation thereof, and then the
decomposition of the pharmaceutically useful diastereoisomer
15 into its enantiomerically pure active product. Enzymatic
techniques can also be used. Additional known separating
techniques can be used. They include those disclosed in:
Enantiomers, Racemates, and Resolutions, John Wiley and Sons,
New York (1981).

20 The compounds according to the invention can also be prepared
in a form enriched in one stereoisomer as soon as there is
preparation of the synthesis intermediates. Thus, the
resolving of the enantiomers of the amines of formula (III) or
25 of the nitrated precursors (IV) can be carried out by one of
the abovementioned methods.

The following examples describe the preparation of certain
intermediates and of compounds in accordance with the
30 invention. These examples are not limiting and merely
illustrate the present invention.

In the examples, the following abbreviations are used:

35 Boc: *tert*-butoxycarbonyl

BOP: benzotriazol-1-yloxytris(dimethylamino)phosphonium
hexafluorophosphate

THF: tetrahydrofuran

AT: ambient temperature
TFA: trifluoroacetic acid
DCM: dichloromethane
DMSO: dimethyl sulphoxide
5 DMF: dimethylformamide
MeOH: methanol
DCCI: dicyclohexylcarbodiimide
DIPEA: diisopropylethylamine
KHSO₄ / K₂SO₄: 5% solution of KHSO₄ / K₂SO₄.

10

The proton nuclear magnetic resonance (NMR) spectra are recorded at 200 or 250 MHz in DMSO-d₆, unless otherwise indicated. The DMSO-d₆ signal is at 2.5 ppm and serves as a reference. For the interpretation of the spectra, the
15 following abbreviations are used: s: singlet, d: doublet, t: triplet, m: unresolved peak, mt: multiplet, bs: broad singlet, dd: doublet of a doublet, qd: quadruplet, qt: quintuplet.

Mp: melting point (in degrees Celsius) as measured on a Büchi
20 B545 apparatus with a temperature gradient of 1°C per minute.

MH+: Mass spectrum. The compounds are analyzed by HPLC - UV - MS (liquid chromatography - UV detection - mass spectrometry) coupling. The device used, sold by Agilent, is composed of an
25 HP1100 chromatograph equipped with an Agilent diode array detector and an MSD Quad quadrupolar mass spectrometer.

The analytical conditions are as follows:

30 Column: C 18 Symmetry (50 x 2.1 mm; 3.5 µm)

Eluent A: H₂O + 0.005% TFA at pH 3.15

Eluent B: CH₃CN + 0.005% TFA

Gradient:

	Time (min)	% B
35	0	0
	10	90
	15	90
	16	0


```
5   tr: retention time
    v: volume.
```

10 Preparation 1

CC(C)NC(=O)Nc1nc2nc3c(nc12)nc(S(=O)(=O)C)c3c4cc(Cl)cc(Cl)c4

15

20

30

210 ml of a 1M solution of LiAlH_4 in THF are added, in 45 minutes, while maintaining the temperature below 30°C , to

39.68 g of ester obtained in the previous stage dissolved in 1 litre of THF. The mixture is stirred for a further hour and the temperature is then decreased to 5°C and 9 ml of water, 6.5 ml of 5N sodium hydroxide and then 32 ml of water are successively added dropwise. After stirring for 10 minutes, the solid is filtered off and then rinsed with THF. The filtrate is concentrated to dryness under vacuum and the residue is then redissolved in 600 ml of boiling toluene, the product is rapidly filtered under hot conditions in order to remove some of the insoluble material and the filtrate is left to cool overnight. The white crystals obtained are filtered, washed with a small amount of toluene and then of ether and dried, Mp = 124-127°C, m = 23.9 g.

1.3 4-Amino-2-(methylthio)pyrimidine-5-carbaldehyde

79.5 g of active MnO₂ are added, in 2 minutes, to a suspension of 23.8 g of the alcohol obtained in the previous stage in 1600 ml of chloroform, and the mixture is stirred at ambient temperature overnight; the solid is filtered off, and washed with 3x75 ml of CHCl₃, and the filtrate is concentrated to dryness under vacuum; the white solid residue is taken up in ether, filtered and dried, Mp = 184-186°C, m = 21.05 g.

1.4 6-(2,6-Dichlorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7-amine

5.47 g of 60% NaH are added, in 5 minutes, to 21 g of the aldehyde obtained in the previous stage, dissolved in 240 ml of DMF and cooled to 5°C, followed by 29.05 g of 2,6-dichlorophenylacetonitrile, in 20 minutes, in small fractions. The stirring is continued for 30 minutes at 5°C and then at ambient temperature overnight. The reaction medium is cooled to 5°C and 65 ml of a saturated NH₄Cl solution and then 500 ml of a water/ice mixture are added; a red precipitate forms, which is filtered off, washed twice with water, filter-dried to a maximum, and washed with ether, with 100 ml of chloroform and then with ether again; after drying, a beige solid is

obtained, Mp = 250-253°C, m = 29.92 g.

The ether and chloroform washing phases are concentrated to dryness, and the product is taken up in a small amount of
5 chloroform, to which ether is added: a second cast of 3.15 g is obtained, total m = 33.07 g.

1.5 N-(*t*-Butyl)-N'-[6-(2,6-dichlorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7-yl]urea

10

4.6 g of 60% NaH are added, in 10 minutes and while maintaining the temperature below 25°C, to 29.9 g of the amine obtained above in solution in 300 ml of DMF; the mixture is stirred for a further 20 minutes and then 12.2 ml of *tert*-
15 butyl isocyanate are added in 20 minutes and the mixture is stirred overnight. The reaction medium is poured slowly onto 800 ml of a water/ice mixture +100 ml of 6N HCl; the precipitate formed is filtered, washed with water, filter-dried, and then stirred for 1 hour in 300 ml of ether, then
20 filtered, washed with ether and dried. A beige solid is obtained, Mp = 195-196°C (decomp.), m = 26.5 g.

1.6 N-(*t*-Butyl)-N'-[6-(2,6-dichlorophenyl)-2-(methylsulphonyl)pyrido[2,3-d]pyrimidin-7-yl]urea

25

27 g of meta-chloroperbenzoic acid (77%) are added, in 25 minutes and while maintaining the temperature below 25°C, to 21.95 g of urea obtained above in solution in 300 ml of chloroform. A precipitate forms. After 2 hours, the reaction
30 medium is diluted with 1 litre of dichloromethane and Na₂SO₄ followed by 14 g of Ca(OH)₂ are added. After stirring for 30 minutes, the solid is filtered off and washed with dichloromethane and the filtrate is then concentrated to dryness. The residue is triturated in 80 ml of ether under hot
35 conditions; the product is left to cool, and the white solid is then filtered off, washed with ether and dried, Mp = 138-140°C, m = 20.5 g.

NMR: 1.40: s: 9H; 3.50: s: 3H; 7.50-7.70: m: 3H; 8.55: s: 1H;
9.10: s: 1H; 9.60: s: 1H; 9.95: s: 1H.

Preparation of the compounds of formula (III)

5 The preparation numbers used refer to the numbers of the
compounds in Table 2 hereinafter.

Preparation 18

10 Commercial product.

Preparation 19

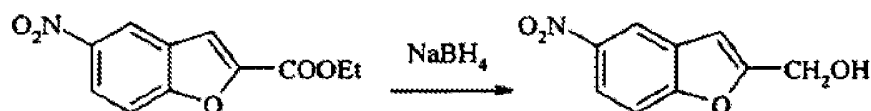
Prepared according to *J. Hetero. Chem.* 1986, **23**, 1645-1649 and
15 isolated in hydrochloride form.

Preparation 20

Prepared according to *J. Chem. Soc.* 1928, 121.

20 Preparation 21

21.1

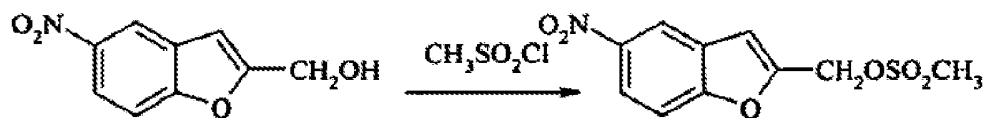


25

2.27 g of NaBH₄ are added, in small portions over a period of
8 hours, to 1.12 g of ethyl 5-nitrobenzo[b]furan-2-carboxylate
in 50 ml of THF, and the mixture is then stirred for 40 hours.
5 ml of methanol and then 5 ml of water are added. The
30 reaction medium is extracted with EtOAc, and the organic phase
is washed with water, with a 5% KHSO₄/K₂SO₄ solution, with
water, and then with a saturated NaCl solution. After drying
and concentration under reduced pressure, 0.74 g of the
expected product are recovered in solid form.

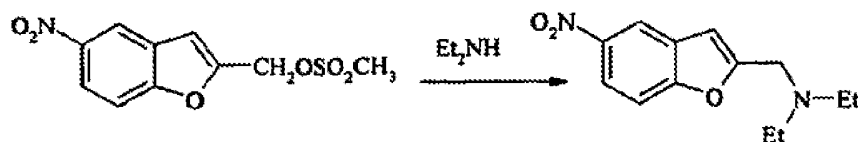
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21.2



730 mg of the product obtained in stage 21.1 are dissolved in
 5 9 ml of DCM and maintained at 5°C. 1 ml of triethylamine is
 added at 5°C, and then 536 mg of methanesulphonyl chloride are
 added in 15 minutes. The temperature is maintained at 5°C for
 15 minutes, and the reaction medium is then allowed to return
 to ambient temperature for 55 minutes. The reaction medium is
 10 then diluted with DCM and water. The organic phase is
 separated by settling out, washed with water and with a
 saturated NaCl solution, dried and evaporated under reduced
 pressure. 0.98 g of oil, comprising a mixture of mesylate
 (expected product) and of chloride (product from substitution
 15 of the CH₂OH in the 2-position of benzo[*b*]furan with CH₂Cl), is
 obtained.

21.3

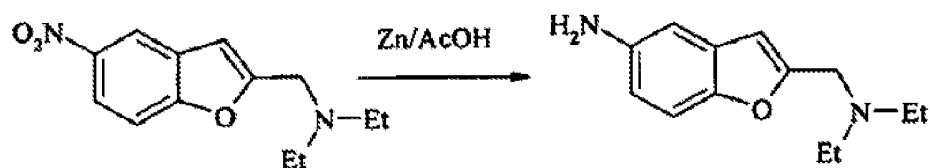


20

0.97 g of the product obtained in stage 21.2, in 10 ml of DMF,
 are treated with 1.05 g of diethylamine for 18 hours. The
 reaction medium is extracted with EtOAc, the organic phase is
 25 washed with water and with a saturated NaCl solution and
 dried, and the solvents are then evaporated off under reduced
 pressure. 0.93 g of oil is obtained.

21.4

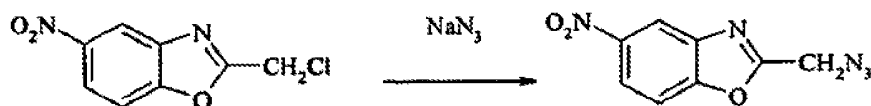
30



4.48 g of powdered Zn are added to 1.16 g of product obtained in stage 21.3 in 40 ml of THF, followed, at -5°C, by 5 ml of acetic acid, over a period of 25 minutes. After 1h 15 of reaction, the residual solid is eliminated from the reaction medium by filtration, the solid is washed with a small amount of THF, and the organic phases are combined, diluted with EtOAc and water, and then brought to pH = 9 with 10N NaOH. After separation by settling out, the organic phase is isolated and washed with a 15% Na₂CO₃ solution, with water and with a saturated NaCl solution, dried and evaporated. 900 mg of oil are obtained.

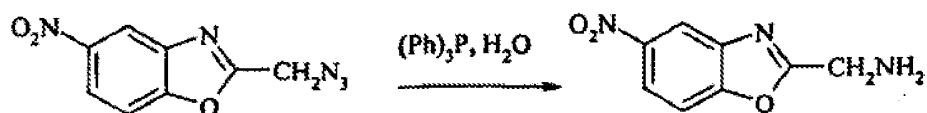
Preparation 22

22.1



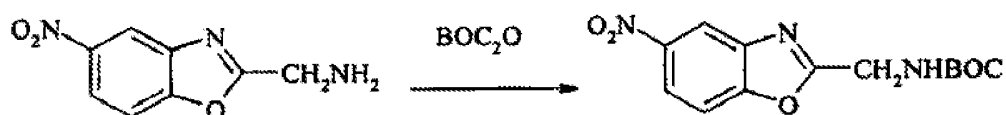
1.26 g of sodium azide are added to 1.64 g of 2-chloromethyl-5-nitrobenzoxazole (prepared according to *Synth. Communications* 1989, **19**, 2921-2924) in 25 ml of DMF and the mixture is stirred at ambient temperature overnight. The reaction medium is poured onto 150 ml of EtOAc and washed twice with ice-cold water and then with a saturated NaCl solution. The organic phase is dried and concentrated under reduced pressure. 1.42 g of black oil are recovered.

22.2



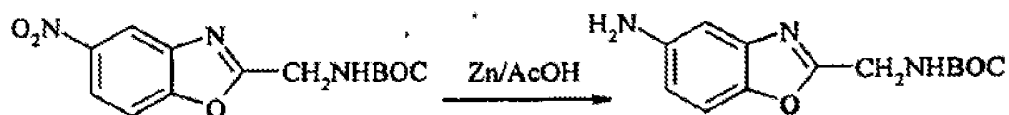
2.84 g of triphenylphosphine are added, in 10 minutes to 1.40 g of the product obtained in stage 22.1 in 30 ml of EtOAc, and then, after 10 minutes, 1.16 ml of water are added in 2 minutes. After 24 hours with stirring at 60°C , and then cooling, the reaction medium is diluted with EtOAc, and the organic phase is washed with water and then with a saturated NaCl solution. The organic phase is dried and concentrated under reduced pressure. The residue is taken up in Et_2O and is extracted twice with 1N HCl. The acid phases are combined, brought into contact with EtOAc, and brought to pH = 10 with 10N NaOH. After separation by settling out, the organic phase is washed with water and then with a saturated NaCl solution. The organic phase is dried and concentrated under reduced pressure, to give 468 mg of the expected product in the form of an oil.

22.3



The product obtained in stage 22.2 is dissolved in 10 ml of DCM, and then 0.4 equivalent of triethylamine followed by 1.1 equivalents of BOC_2O are added. After 5 h, the reaction medium is diluted with CH_2Cl_2 and then washed successively with a 5% $\text{KHSO}_4/\text{K}_2\text{SO}_4$ solution, water and a saturated NaCl solution. The crude is dried and evaporated under reduced pressure, so as to obtain 388 mg of the expected product.

22.4



The product obtained in stage 19.3 is reduced quantitatively with Zn/AcOH, so as to obtain an oil, according to the method
5 described in preparation 18.4.

Preparation 23

23.1

10

Prepared according to *J. Hetero. Chem.* 1973, **10**, 755.

23.2

15 Reduction of the product obtained in stage 23.1 with Sn/HBr in water according to *Chem. Abstr.* 1950, 4474.

Preparation 24

20 Prepared according to *J. Hetero. Chem.* 1970, **7**, 1019-1027.

Preparation 25

25 Prepared according to *Boll. Sci. Fac. Chim. Ind. Bologna* 1964 vol.22 pages 33-37

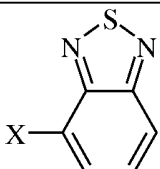
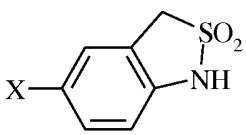
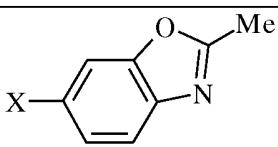
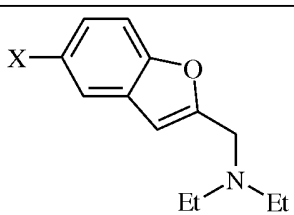
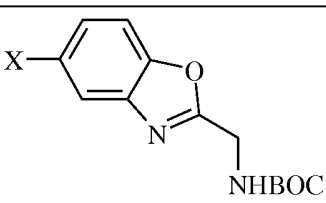
Preparation 26

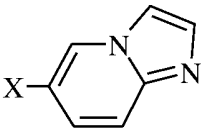
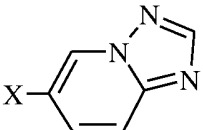
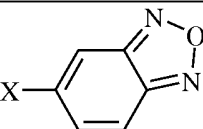
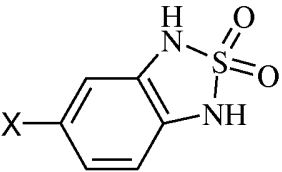
30 Prepared according to the procedure described in patent application W092/05164.

The compounds of formula (III) are characterized in Table 2 below:

TABLE 2

Preparations of the compounds of formula (III).

Prep.	Ar ₁	X = NO ₂ (IV), HCl NMR	X = NH ₂ (III) NMR
18		—	Commercial product
19		—	Prepared according to <i>J. Hetero. Chem.</i> 1986, 23 , 1645-1649 and isolated in hydrochloride form
20		—	Prepared according to <i>J. Chem. Soc.</i> 1928, 121
21		21.3 1.00 ppm: t: 6H; 2.50 ppm: qd: 4H; 3.75 ppm: s: 2H; 7.00 ppm: s: 1H; 7.75 ppm: d: 1H; 8.15 ppm: d: 1H; 8.50 ppm: d: 1H.	21.4 1.00 ppm: t: 6H; 2.55 ppm: qd: 4H; 3.65 ppm: s: 2H; 4.90 ppm: bs: 2H; 6.45 ppm: s: 1H; 6.50 ppm: dd: 1H; 6.65 ppm: d: 1H; 7.15 ppm: d: 1H.
22		22.3 1.40 ppm: s: 9H; 4.45 ppm: d: 2H; 7.65 ppm: t: 1H; 7.95 ppm: d: 1H; 8.30 ppm: dd:	22.4 1.35 ppm: s: 9H; 4.25 ppm: d: 2H; 4.95: bs: 2H; 6.55 ppm: dd: 1H; 6.75 ppm: d:

		1H; 8.60 ppm: d: 1H.	1H; 7.25 ppm: d: 1H; 7.45 ppm: t: 1H.
23		23.1 Prepared according to <i>J.</i> <i>Hetero. Chem.</i> 1973, 10 , 755	23.2 Prepared according to <i>Chem. Abstr.</i> 1950, 4474.
24		—	Prepared according to <i>J.</i> <i>Hetero. Chem.</i> 1970, 7 , 1019- 1027
25		—	Prepared according to <i>Boll. Sci. Fac.</i> <i>Chim. Ind.</i> <i>Bologna</i> 1964 vol.22 pages 33- 37
26		—	Prepared according to the procedure described in patent application W092/05164

The numbers of the compounds exemplified refer to those given in Table 3 hereinafter, which illustrates the chemical structures and the physical properties of some compounds according to the invention. When they contain an asymmetrical carbon, these compounds are obtained in racemic form.

EXAMPLE 1: (Compound No. 2) N-[2-(2,1,3-benzothiadiazol-4-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea

Compound 2 is prepared in the same way as compound 1, starting with the amine of preparation 18 in Table 2.

5 EXAMPLE 2: (Compound No. 3) N-[6-(2,6-dichlorophenyl)-2-[(1,3-dihydro-2,2-dioxido-2,1-benzisothiazol-5-yl)amino]pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea

10 A mixture of 437 mg of the amine of preparation 19 in Table 2, in hydrochloride form, and of 750 mg of the urea of preparation 1 in Table 1, are heated in 15 ml of ethanol for 5 hours. The reaction medium is evaporated to dryness and then taken up in 50 ml of CHCl_3 and 20 ml of a saturated NaHCO_3
15 solution. The organic phase is separated by settling out, and washed with water and then with a saturated NaCl solution. The organic phase is dried and saturated under reduced pressure. The residue is purified by flash chromatography with a gradient of 0 to 20% (v/v) of EtOAc in chloroform. 275 mg of a
20 yellow solid are obtained. MH^+ : 572.

EXAMPLE 3: (Compound No. 4) N-[6-(2,6-dichlorophenyl)-2-[(2-methyl-6-benzoxazolyl)amino]pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea

25 210 mg of the amine of preparation 20 in Table 2 and 562 mg of the urea of preparation 1 in Table 1 are heated for 8 hours at 45°C in 20 ml of ethanol containing 0.02 ml of concentrated HCl . After concentration under reduced pressure, the residue
30 is chromatographed on silica gel, the eluent being $\text{CHCl}_3/\text{MeOH}$: 98/2 (v/v). 300 mg of product in the form of a yellow solid are isolated. MH^+ : 536.

EXAMPLE 4: (Compound No. 5) N-[6-(2,6-dichlorophenyl)-2-[[2-[(diethylamino)methyl]-5-benzofuranyl]amino]pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea

Compound 5 is prepared in the same way as compound 4, starting

from the amine 21.4 of preparation 21 in Table 2.

EXAMPLE 5: (Compound No. 6) 1,1-dimethylethyl [[5-[[6-(2,6-dichlorophenyl)-7-[[[(1,1-dimethylethyl)amino]carbonyl]amino]pyrido[2,3-d]pyrimidin-2-yl]amino]-2-benzoxazolyl]methyl]carbamate

Compound 6 is prepared in the same way as compound 4, starting from the amine 22.4 of preparation 22 in Table 2.

EXAMPLE 6: (Compound No. 7) N-[2-[[2-(aminomethyl)-5-benzoxazolyl]amino]-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea

190 mg of compound 6 are treated for 1 hour with 3 ml of TFA in 2 ml of DCM. After concentration under reduced pressure, the residue is taken up in a DCM/water mixture and the pH is then brought to 9 by adding a 15% Na₂CO₃ solution. After separation by settling out, the organic phase is washed with water and then with a saturated NaCl solution, dried, and concentrated under reduced pressure. The crude is purified by flash chromatography on silica gel, the eluant being 0 to 10% (v/v) of methanol in DCM. 100 mg of yellow solid are isolated. MH⁺: 551.

EXAMPLE 7: (Compound No. 8) N-[6-(2,6-dichlorophenyl)-2-(imidazo[1,2-a]pyridin-6-ylamino)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea

Compound 8 is prepared in the same way as compound 4, starting from the amine 23.2 of preparation 23 in Table 2.

EXAMPLE 8: (Compound No. 9) N-[6-(2,6-dichlorophenyl)-2-([1,2,4]triazolo[1,5-a]pyridin-6-ylamino)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea

Compound 9 is prepared in the same way as compound 4, starting from the amine of preparation 24 in Table 2.

EXAMPLE 9: (Compound No. 10) N-[2-(2,1,3-benzoxadiazol-5-

ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-
N'-(1,1-dimethylethyl)urea

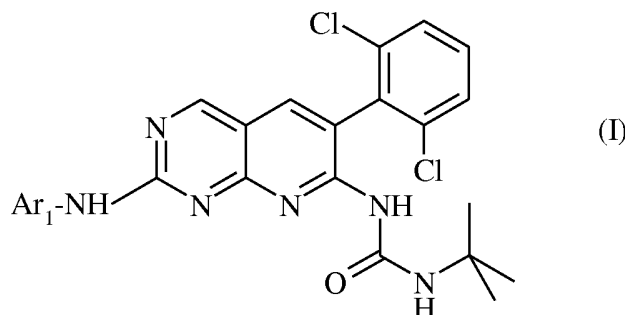
0.168 g of tBuOK is added in 25 min, to a mixture of 0.468 g
of the product of preparation 1 and 0.202 g of the amine (III)
of preparation 25 in Table 2, in 6 ml of DMSO, and then a
further 0.168 g is added in 1 hour. After stirring for
2 hours, the reaction medium is extracted with ethyl acetate
which is washed successively with water and a saturated NaCl
solution. After drying over Na₂SO₄ and evaporation of the ethyl
acetate, the crude product is purified by flash chromatography
on silica gel with a gradient of 0 to 8% (v/v) of ethyl
acetate in dichloromethane. A beige powder is obtained, m=
0.22 g. MH⁺=523.

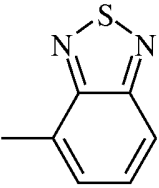
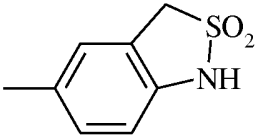
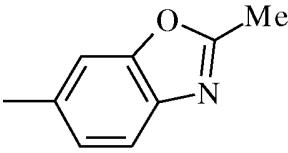
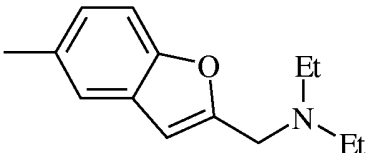
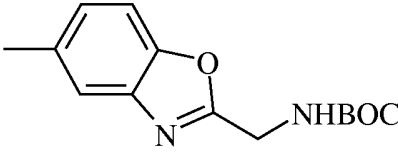
EXAMPLE 10: (Compound No. 11) N-[2-(1,3-dihydro-2,2-dioxido-
2,1,3-benzothiadiaazol-5-ylamino)-6-(2,6-
dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-
dimethylethyl)urea

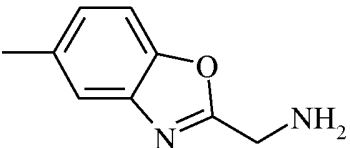
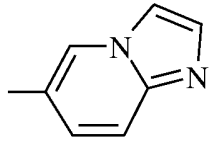
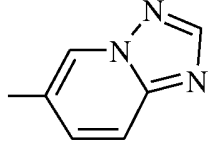
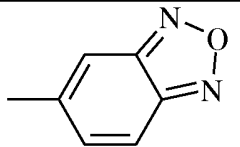
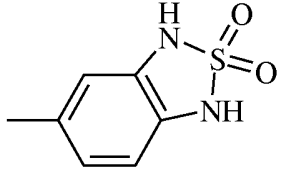
Compound 11 is prepared in the same way as compound 4,
starting from the amine of preparation 26 in Table 2.

Table 3 illustrates the chemical structures and the physical
properties of some examples according to the invention. In
these tables, Me, Et, iPr and tBu are, respectively, methyl,
ethyl, isopropyle and *tert*-butyl groups, and Boc (or BOC) is
the *tert*-butoxycarbonyl group.

TABLE 3



Compounds	Ar ₁	NMR characterization
2		1.40 ppm: s: 9H; 7.45 – 7.80 ppm: m: 5H; 8.15 ppm: s: 1H; 8.35 ppm: s: 1H; 8.80 ppm: d: 1H; 9.20 ppm: s: 1H; 9.55 ppm: s: 1H; 10.60 ppm: s: 1H.
3		1.45 ppm: s: 9H; 4.45 ppm: s: 2H; 6.75 ppm: d: 1H; 7.45 – 7.70 ppm: m: 3H; 7.80 ppm: de: 1H; 8.05 ppm: s: 1H; 8.15 ppm: bs: 2H; 9.05 ppm: s: 1H; 10.10 ppm: s: 1H; 10.20 – 10.30 ppm: bs: 1H; 10.60 ppm: s: 1H.
4		1.45 ppm: s: 9H; 2.60 ppm: s: 3H; 7.50 – 7.70 ppm: m: 5H; 8.10 ppm: s: 1H; 8.30 ppm: bs: 1H; 8.90 ppm: bs: 1H; 9.15 ppm: s: 1H; 10.45 ppm: s: 1H; 10.75 ppm: s: 1H.
5		1.00 ppm: t: 6H; 1.45 ppm: s: 9H; 2.50 ppm: qd: 4H; 3.70 ppm: s: 2H; 6.55 ppm: s: 1H; 7.40 – 7.70 ppm: m: 5H; 8.10 ppm: s: 2H; 8.55 ppm: bs: 1H; 9.10 ppm: s: 1H; 10.15 ppm: s: 1H; 10.65 ppm: s: 1H.
6		1.30 ppm: s: 9H; 1.40 ppm: s: 9H; 4.35 ppm: d: 2H; 7.45 – 7.60 ppm: m: 5H; 7.75 ppm: dd: 1H; 8.05 ppm: s: 1H; 8.10 ppm: bs: 1H; 8.65 ppm: s: 1H; 9.10

		ppm: s: 1H; 10.30 ppm: s: 1H; 10.60 ppm: s: 1H.
7		1.45 ppm: s: 9H; 2.10 ppm: bs: 2H; 3.90 ppm: s: 2H; 7.45 - 7.70 ppm: m: 4H; 7.80 ppm: dd: 1H; 8.05 ppm: s: 1H; 8.15 ppm: bs: 1H; 8.65 ppm: s: 1H; 9.10 ppm: s: 1H; 10.25 ppm: s: 1H; 10.70 ppm: s: 1H.
8		1.50 ppm: s: 9H; 7.40 - 7.70 ppm: m: 7H; 8.10 ppm: s: 1H; 8.20 ppm: s: 1H; 9.10 ppm: s: 1H; 9.65 ppm: s: 1H; 10.30 ppm: s: 1H; 10.60 ppm: s: 1H.
9		1.50 ppm: s: 9H; 7.45 - 7.70 ppm: m: 3H; 7.85 ppm: s: 2H; 8.15 ppm: s: 1H; 8.25 ppm: d: 1H; 8.40 ppm: s: 1H; 9.15 ppm: s: 1H; 10.10 ppm: s: 1H; 10.55 ppm: s: 1H; 10.60 ppm: s: 1H.
10		1.45 ppm: s: 9H; 7.50-7.70 ppm: mt: 3H; 7.75 ppm: d: 1H; 8.00 ppm: d: 1H; 8.20 ppm: s: 1H; 8.40 ppm: s: 1H; 9.15 ppm: s: 1H; 9.25 ppm: s: 1H; 10.65 ppm: s: 1H; 10.90 ppm: s: 1H.
11		1.45 ppm: s: 9H; 6.65 ppm: d: 1H; 7.40 ppm: s: 1H; 7.45-7.70 ppm: m: 4H; 8.05 ppm: s: 2H; 9.05 ppm: s: 1H; 10.00 ppm: s: 1H; 10.55 ppm: s:

		1H; 10.75 ppm: bs: 2H.
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The compounds according to the invention were subjected to pharmacological assays for determining their anticancer activity.

5

The compounds of formula (I) according to the present invention were tested in vitro on a panel of tumour lines of human origin, originating:

10 - from breast cancer: MDA-MB231 (American Type culture collection, Rockville, Maryland, USA, ATCC-HTB26), MDA-A1 or MDA-ADR (called multi-drug resistant MDR line, and described by E.Collomb et al., in Cytometry, 12(1):15-25, 1991), and MCF7 (ATCC-HTB22),

15

- from prostate cancer: DU145 (ATCC-HTB81) and PC3 (ATCC-CRL1435),

20 - from colon cancer: HCT116 (ATCC-CCL247) and HCT15 (ATCC-CCL225),

25 - from lung cancer: H460 (described by Carmichael in Cancer Research 47 (4):936-942, 1987 and provided by the National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, Maryland, USA),

30 - from glioblastoma: SF268 (described by Westphal in Biochemical & Biophysical Research Communications 132 (1): 284-289, 1985 and provided by the National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, Maryland, USA),

35 - from leukaemia: CMLT1 (described by Kuriyama et al. in Blood, 74: 1989, 1381-1387, by Soda et al. in British Journal of Haematology, 59: 1985, 671-679 and by Drexler, in Leukemia Research, 18: 1994, 919-927 and provided by the company DSMZ (Deutsche Sammlung von Mikroorganismen und

Zellkulturen GmbH) Mascheroder Weg 1b, 38124 Braunschweig, Germany), K-562 (described by Lozzio et al., J Natl Cancer Inst 50: 535 (1973), by Lozzio et al., Blood 45: 321 (1975), and provided by DSMZ No. ACC 10), KG-1a (described by Koeffler et al., Blood 56: 265 (1980), and provided by DSMZ No. ACC 421), and Kasumi-1 (described by Asou et al., Blood 77: 2031 (1991), and provided by DSMZ No. ACC 220).

The cell proliferation and viability were determined in a test using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium (MTS) according to Fujishita T. et al., Oncology, 2003, 64 (4), 399-406. In this test, the mitochondrial ability of the live cells to convert MTS to a coloured compound is measured after 72 hours of incubation of a compound of formula (I) according to the invention. The concentrations of compound according to the invention which result in a 50% loss of cell proliferation and cell viability (IC₅₀) are between 1 nM and 10 µM, depending on the tumor line and the compound tested. On the K-562 line, compound No. 5 has an IC₅₀ of 5 nM, compound No. 9 has an IC₅₀ of 19 nM. On the SF268, compound No. 7 has an IC₅₀ of 43 nM.

Thus, according to the present invention, it appears that the compounds of formula (I) bring about a loss of proliferation and of viability of the tumour cells. It therefore appears that the compounds according to the invention have an anticancer activity and an activity in the treatment of other proliferative diseases such as psoriasis, restenosis, atherosclerosis or AIDS, for example, and also in diseases caused by vascular smooth muscle cell proliferation and in rheumatoid arthritis.

Thus, according to another of its aspects, a subject of the invention is medicaments which comprise a compound of formula (I), or an addition salt of the latter with a pharmaceutically acceptable acid or a hydrate or a solvate of the compound of formula (I).

These medicaments find their use in therapeutics, in particular in the treatment or prevention of diseases caused or exacerbated by cell proliferation, and in particular tumour cell proliferation. A product in accordance with the invention
5 may be used for the manufacture of a medicament that is of use in the treatment of a pathological state, in particular a cancer.

As an inhibitor of tumour cell proliferation, these compounds
10 are of use in the prevention and treatment of leukaemias, both primary and metastatic solid tumours, carcinomas and cancers, in particular: breast cancer; lung cancer; cancer of the small intestine, colon cancer and rectal cancer; cancer of the respiratory tracts, of the oropharynx and of the hypopharynx;
15 œsophageal cancer; liver cancer, stomach cancer, cancer of the bile ducts, gall bladder cancer, pancreatic cancer; cancer of the urinary tracts, including kidney, urothelium and bladder; cancers of the female genital tract, including uterine cancer, cervical cancer, ovarian cancer, chloriocarcinoma and
20 trophoblastoma; cancers of the male genital tract, including prostate cancer, cancer of the seminal vesicles, testicular cancer, germinal cell tumours; cancers of the endocrine glands, including cancer of the thyroid, of the pituitary gland, of the adrenal glands; skin cancers, include
25 hemangiomas, melanomas, sarcomas, including Kaposi's sarcoma; brain tumours, nerve tumours, eye tumours, meningeal tumours, including astrocytomas, gliomas, glioblastomas, retinoblastomas, neurinomas, neuroblastomas, schwannomas, meningiomas; malignant hematopoietic tumours; leukaemias,
30 (acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL)), chloromas, plasmocytomas, T- or B-cell leukaemias, non-Hodgkin's lymphomas or Hodgkin's lymphomas, myelomas, various malignant hemopathies.

35 According to another of its aspects, the present invention relates to pharmaceutical compositions comprising, as active ingredient, a compound according to the invention. These

pharmaceutical compositions contain an effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt, a hydrate or a solvate of said compound, and also at least one pharmaceutically acceptable excipient. A pharmaceutical composition can also contain, in addition, another anticancer ingredient.

Said excipients are selected according to the pharmaceutical form and the method of administration desired, from the usual excipients which are known to those skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intratracheal, intranasal, transdermal or rectal administration, the active ingredient of formula (I) above, or its optional salt, solvate or hydrate, can be administered in unit administration form, as a mixture with conventional pharmaceutical excipients, to animals and to human beings for the prophylaxis or the treatment of the conditions or diseases above.

Appropriate unit administration forms include the oral administration forms such as tablets, soft or hard gelatin capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular and intranasal administration forms, forms of administration by inhalation, topical, transdermal, subcutaneous, intramuscular or intravenous administration forms, rectal administration forms, and implants. For topical application, the compounds according to the invention can be used in creams, gels, ointments or lotions.

By way of example, a unit administration form of a compound according to the invention in the form of a tablet can comprise the following components:

Compound according to the invention	50.0 mg
Mannitol	223.75 mg

Sodium croscarmellose	6.0 mg
Corn starch	15.0 mg
Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

5

The compounds of formula (I) above can be used at daily doses of 0.002 to 2000 mg per kilogram of body weight of the mammal to be treated, preferably at daily doses of 0.1 to 300 mg/kg. In human beings, the dose can range preferably from 0.02 to 10 000 mg per day, more particularly from 1 to 3000 mg, depending on the age of the individual to be treated or the type of treatment: prophylactic or curative.

There may be specific cases where higher or lower dosages are appropriate: such dosages do not depart from the scope of the invention. According to the usual practice, the dosage appropriate to each patient is determined by the physician according to the method of administration, and the weight and response of said patient.

20

According to another of its aspects, the present invention also relates to a method of treatment of the pathologies indicated above, which comprises the administration, to a patient, of an effective dose of a compound according to the invention, or one of its pharmaceutically acceptable salts or hydrates or solvates.

According to the present invention, the compound(s) of formula (I) can be administered in combination with one (or more) anticancer active ingredient(s), in particular antitumour compounds such as alkylating agents, for instance alkylsulphonates (busulphan), dacarbazine, procarbazine, nitrogenous mustards (chlormethine, melphalan, chlorambucil), cyclophosphamide, ifosfamide; nitrosoureas such as carmustine, lomustine, semustine, streptozocin; antineoplastic alkaloids such as vincristine, vinblastine; taxanes such as paclitaxel or taxotere; antineoplastic antibiotics such as actinomycin; intercalating agents, antineoplastic antimetabolites, folate

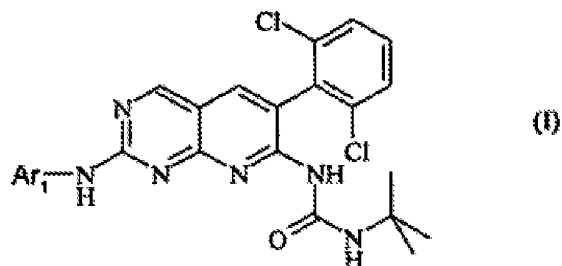
antagonists, methotrexate; purine synthesis inhibitors; purine analogues such as mercaptopurine, 6-thioguanine; pyrimidine synthesis inhibitors, aromatase inhibitors, capecitabine, pyrimidine analogues such as fluorouracil, gemcitabine, cytarabine and cytosine arabinoside; brequinar; topoisomerase inhibitors such as camptothecin or etoposide; anticancer hormone agonists and antagonists including tamoxifen; kinase inhibitors, imatinib; growth factor inhibitors; anti-inflammatories such as pentosane polysulphate, corticosteroids, prednisone, dexamethasone; antitopoisomerases such as etoposide, anthracyclines including doxorubicin, bleomycin, mitomycin and methramycin; anticancer metal complexes, platinum complexes, cisplatin, carboplatin, oxaliplatin; interferon alpha, triphenylthiophosphoramidate, altretamine; antiangiogenic agents; thalidomide; immunotherapy adjuvants; vaccines.

According to the present invention, the compounds of formula (I) can also be administered in combination with one or more other active ingredients that are of use in one of the pathologies indicated above, for example an anti-emetic agent, pain-killer, anti-inflammatory, or anti-cachexia agent.

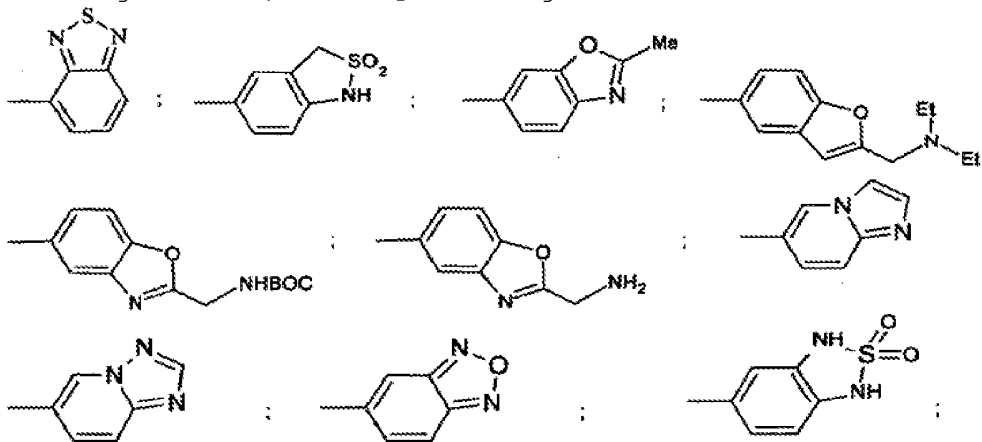
It is also possible to combine with the compounds of the present invention a radiation treatment. These treatments can be administered simultaneously, separately or sequentially. The treatment will be adapted by the practitioner according to the disease to be treated.

Patentkrav

1. Forbindelse, der svarer til formelen (I):



5 kendetegnet ved, at Ar₁ er valgt blandt:



2. Forbindelse ifølge krav 1

10 kendetegnet ved, at den er:

på ikke-chiral eller racemisk form eller en form, der er beriget med en stereoisomer eller en enantiomer;
ved, at den eventuelt er forsaltet;
og ved, at den eventuelt er hydratiseret eller solvatiseret.

15

3. Farmaceutisk præparat, k e n d e t e g n e t ved, at det omfatter en forbindelse ifølge krav 1 eller 2 samt mindst en farmaceutisk acceptabel bærer.

20 4. Farmaceutisk præparat ifølge krav 3, k e n d e t e g n e t ved, at det desuden indeholder mindst et andet kræftbekæmpende aktivt stof.

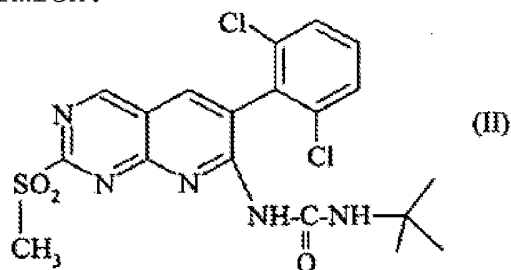
5. Lægemiddel, kendetegnet ved, at det omfatter en

forbindelse ifølge krav 1 eller 2 eller et additionssalt af forbindelsen med en farmaceutisk acceptabel syre eller et hydrat eller solvat af forbindelsen med formlen (I).

6. Anvendelse af en forbindelse ifølge krav 1 eller 2 til fremstilling af et lægemiddel, der er beregnet til behandling og forebyggelse af sygdomme, der forårsages eller forværres af cellernes prolifération.

7. Anvendelse ifølge krav 6 til forebyggelse og behandling af leukæmi, primære og metastatiske faste tumorer, karcinomer og cancere.

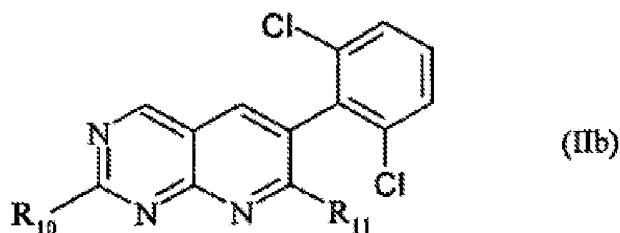
8. Fremgangsmåde til fremstilling af en forbindelse ifølge krav 1 eller 2, k e n d e t e g n e t ved, at en amin med formlen:



omsættes med en amin med formlen $\text{Ar}'_1\text{NH}_2$ (III), hvor Ar'_1 betegner Ar_1 , som defineret i krav 1 eller 2, eller en precursor for Ar_1 ; og hvor gruppen Ar'_1 i den således opnåede forbindelse eventuelt omdannes til en gruppe Ar_1 .

9. Fremgangsmåde til fremstilling af en forbindelse ifølge krav 1 eller 2, k e n d e t e g n e t ved, at der udføres en reaktion af:

(i) en forbindelse med formlen:



hvor R_{10} er en fraspaltelig enhed, såsom: (a) halogen, især Cl

eller Br eller (b) alkyl-S(O)m-, hvor $m = 0, 1$, eller 2 ; hvor R_{11} er NHC(O)-NH-tBu ; og

(ii) og en amin med formlen $\text{Ar}'_1\text{NH}_2$ (III), hvor Ar'_1 betegner Ar_1 , som defineret for (I), eller en precursor for Ar_1 ; og hvor gruppen Ar'_1 i den således opnåede forbindelse eventuelt omdannes til en gruppe Ar_1 ;
hvor:

10 (a) reaktionen udføres i et opløsningsmiddel ved en temperatur på mellem stuetemperatur og opløsningsmidlets refluksstemperatur, når R_{10} er halogen eller alkyl-S(O)m- med $m = 2$;

15 (b) reaktionen udføres med $\text{Ar}'_1\text{NH}_2$ (III) i smeltet tilstand, når R_{10} er alkyl-S(O)m- med $m = 0$ eller 1 ;
idet aminfunktionerne i gruppen Ar'_1 i forbindelsen (III) eventuelt forinden er forsaltet eller beskyttet.

20 10. Fremgangsmåde ifølge krav 9, hvor opløsningsmidlet er polært.

11. Fremgangsmåde ifølge krav 10, hvor opløsningsmidlet er
(i) tetrahydroduran, dimethylsulfoxid eller ethanol, eventuelt
25 anvendt i nærværelse af en spormængde syre såsom saltsyre;
eller
(ii) dimethylsulfoxid anvendt i nærværelse af en stærk base, såsom tBuOK.