NOVEL THERAPEUTIC USE FOR TREATING OF LEUKAEMIA

This invention relates to the treatment of leukaemias, in particular myeloid leukaemias.

Leukaemia is a cancerous disease of the bone marrow and the blood. Four types of leukaemia can be distinguished: chronic myeloid leukaemia, acute myeloid leukaemia, chronic lymphoid leukaemia and acute lymphoid leukaemia.

Myeloid leukaemias of the acute type with a rapid progression are called AML or acute myeloid leukaemia. Myeloid leukaemias of the chronic type with a gradual, less aggressive progression are called CML or chronic myeloid leukaemia. These are clonal diseases of the bone marrow characterized by a clonal expansion of myeloid cells which cannot differentiate normally and accumulate in the bone marrow and the blood.

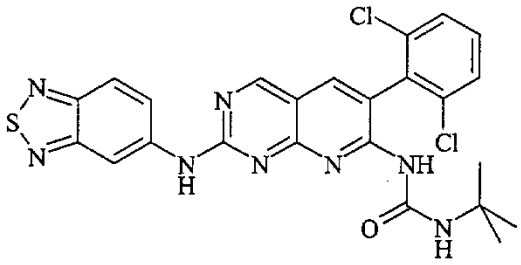
According to a study by the American Cancer Society, it is estimated that 11,930 new cases of AML and 4,500 new cases of CML will be diagnosed in 2006 in the United States. Over the period from 2002 to 2006, the 5 year survival rate is 20.4% for AML and 42.3% for CML (Cancer Facts and Figures 2006, American Cancer Society, www.leukemia-lymphoma.org/).

According to the French-American-British (FAB) classification of 1976, there are 8 subtypes of AML, referred to as M0 to M7, depending on the type of cells from which the leukaemia develops (Bennett et al, 1976, "Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group". *Br J Haematol* **33** (4): 451-8).

About 95% of patients suffering from CML bear a gene translocation between chromosomes 9 and 22 of the leukaemic cells. This abnormality, known as Philadelphia chromosome (Ph1), causes proliferation and uncontrolled multiplication of all the types of white cells and platelets.

Currently, several drugs are available for the treatment of leukaemias. However, there remains a need for new active therapeutic compounds for the improvement of the strategies for treatment of patients suffering from leukaemia or the development of a treatment alternative to the treatments already known (Plo et al, Mol Pharmacol, 2002, 62:304-312).

The product N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl) pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea is described in the international application WO2007/003765. Its formula is shown below:



A process for preparation of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea is also described.

Although this compound can display a significant anti-tumour activity on cells in tests in vitro, new parameters such as the distribution of the compound in the tissues, the quantity of product in the serum, the pharmacokinetics and the metabolism are involved in the obtention of an effect in vivo, not predictable on the basis of in vitro tests. It has moreover been demonstrated that in vitro antitumour activity is not always predictive of in vivo activity (Cancer Res. 1988 Oct 1; 48(19): 5447-54, Cancer Chemother Pharmacol. 1996 38: 548-552).

By in vivo tests, it has been demonstrated that the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea displays significant in vivo anti-tumour activity in animals bearing human leukaemias.

The object of the present invention is the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias. Leukaemia is understood to mean leukaemias such as chronic myeloid leukaemia, acute myeloid leukaemia, chronic lymphoid leukaemia, acute lymphoid leukaemia, and the various myeloproliferative syndromes.

In particular, the present invention relates to the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido-[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of myeloid leukaemias. More particularly, the present invention relates to the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido-[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the AML type. More particularly, the present invention relates to the utilization of

the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)-pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the CML type.

The object of the present invention relates to the utilizations cited above for the treatment of mammals, in particular of man.

In the present invention, the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea can be administered to the animal tested by the oral route, the intravenous route, the intraperitoneal route or again by the intravenous route followed by an intraperitoneal route or again by the intravenous route followed by an oral route. In man, a conventional administration route is the intravenous route and/or the oral route.

One object of the present invention is the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the AML type where the drug is intended to be used by administration by the intravenous route.

One object of the present invention is the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the AML type where the drug is intended to be used by administration by the oral route.

One object of the present invention is the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the AML type where the drug is intended to be used by administration by the intravenous route and oral route.

One object of the present invention is the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the CML type where the drug is intended to be used by administration by the intravenous route.

One object of the present invention is the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-

yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the CML type where the drug is intended to be used by administration by the oral route.

One object of the present invention is the utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea, or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias of the CML type where the drug is intended to be used by administration by the intravenous route and oral route.

In the present invention, the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea is typically formulated for administration in the form of a composition acceptable at the pharmaceutical level. These pharmaceutical compositions contain an effective dose of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea or a pharmaceutically acceptable salt, a hydrate or solvate of the said compound, as well as at least one pharmaceutically acceptable excipient.

The said excipients are selected depending on the desired pharmaceutical form and mode of administration, from the normal excipients which are known to the person skilled in the art.

In the pharmaceutical compositions of the present invention for oral or intravenous administration, the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea or possibly a salt, solvate or hydrate thereof can be administered to animals and to human beings in unit dosage form, mixed with conventional pharmaceutical excipients, for the prophylaxis or the treatment of the above disorders or diseases.

A PEG400 22% / Solutol 5% / G5 73% formulation is preferably used for the treatment by the intravenous route of mice bearing Kasumi1 tumours.

A Labrasol 21% / Solutol 5% / HCl 0.001N 74% formulation is preferably used for the treatment by the oral route of mice bearing Kasumi1 or KG1 tumours.

A PEG400 22% / Solutol 5% / G5 73% formulation is preferably used for the treatment by the intraperitoneal route of mice bearing EOL-1 tumours.

A PEG400 22% / Solutol 5% / G5 73% formulation is preferably used for the treatment, by the intravenous route followed by an intraperitoneal route, of mice bearing CTV1 tumours.

A DMSO 5% / Tween80 10% / H_2O 85% formulation is preferably used for the treatment, by the oral route, or by the intravenous route followed by an

intraperitoneal route, or again by the intravenous route followed by an oral route, of mice bearing KG1a tumours.

A DMSO 5% / Tween80 10% / H_2O 85% formulation is preferably used for the treatment, by the intravenous route followed by an intraperitoneal route, of mice bearing K562 or CMLT1 tumours

A DMSO 5% / Tween80 10% / H_2O 85% formulation is preferably used for the treatment, by the intravenous route, of mice bearing KG1 tumours.

The appropriate unit dosage forms include forms by the oral route such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions and intravenous administration forms.

There may be special cases where higher or lower dosages are appropriate; such dosages do not fall outside the scope of the invention. According to the normal practice, the dosage appropriate for each patient is determined by the doctor depending on the mode of administration, and the weight and response of the said patient.

The therapy with the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea according to the present invention can be utilized at the same time as other therapies. In particular, the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea according to the invention can be administered in combination with one (or more) anti-cancer active principle(s), in particular antitumour compounds such as

alkylating agents such as the alkylsulphonates (busulfan), dacarbazine, procarbazine, cloretazine, the nitrogen mustards (chlormethine, melphalan, chlorambucil, cyclophosphamide, ifosfamide), the nitrosoureas such as carmustine, lomustine, semustine, streptozocine and altretamine;

antineoplastic alkaloids such as vincristine, vinblastine, vinorelbine and vindesine;

taxanes such as paclitaxel or taxotere;

antineoplastic antibiotics such as actinomycin and bleomycin;

intercalating agents such as mitoxantrone;

antineoplastic antimetabolites: folate antagonists, methotrexate; inhibitors of purine synthesis; purine analogues such as mercaptopurine and 6-thioguanine; inhibitors of pyrimidine synthesis, aromatase inhibitors, capecitabine, pyrimidine

analogues such as fluorouracil, gemcitabine, cytarabine and cytosine arabinoside; brequinar and nelarabine;

topoisomerase inhibitors such as irinotecan, exatecan, topotecan, teniposide, camptothecin or etoposide;

anticancer hormone agonists and antagonists including tamoxifen;

kinase inhibitors such as imatinib, nilotinib and dasatinib, midaustorin, sorafenib, lestaurtinib and tandutinib;

growth factor inhibitors;

antiinflammatories such as pentosan polysulphate, corticosteroids, prednisone and dexamethasone;

ceplene (histamine dihydrochloride);

anthracyclines such as daunorubicin, epirubicin, pirarubicin, idarubicin, zorubicin, aclarubicin, annamycin, doxorubicin, mitomycin and methramycin;

anticancer metal complexes, platinum complexes, cisplatin, carboplatin, oxaliplatin and satraplatin;

alpha interferon,

triphenylthiophosphoramide;

antiangiogenic agents;

thalidomide;

farnesyl transferase inhibitors such as tipifarnib;

DNA methyl transferase inhibitors such as MG98;

immunotherapy adjuvants such as gemtuzumab ozogamicin and HuM 195;

biotherapeutic agents such as CT388-IL3;

antisense agents such as GTI-2040;

vaccines.

More particularly, the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea according to the invention can be administered in combination with one or more compound(s) of the anthracycline family.

More particularly, the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea according to the invention can be administered in combination with daunorubicin or in combination with cytosine arabinoside, or indeed in combination with daunorubicin and cytosine arabinoside.

According to the present invention, the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea can also be administered in combination with one or more

other active principles useful in one of the pathologies mentioned above, for example an anti-emetic, analgesic, anti-inflammatory or anti-cachexia agent.

It is also possible to combine the compounds of the present invention with a radiation treatment.

These treatments can be administered simultaneously, separately, sequentially and/or spaced in time. The treatment will be adapted by the doctor depending on the patient to be treated.

In the present invention, the product N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea is administered according to a dosage scheme which enables the treatment of leukaemias. The dosage scheme varies depending on the administration route and depending on the physical characteristics of the patient. The dosage schemes suitable for this purpose include those which display therapeutic efficacy for the treatment of disorders resulting from abnormal cellular proliferation. The product N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]-pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea can be administered as often as is necessary to obtain the therapeutic effect sought.

The efficacy of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea against leukaemias can be determined experimentally as in the following example which illustrates the invention.

EXAMPLE

Materials and methods

Scid CB-17 mice (supplied by Charles River, Lyon, France) are used. At the time of the randomization, the animals have an average weight of 20-22 g and are aged from 6 to 9 weeks.

The animals are received at least one month before the experiment so as to allow perfect acclimatization. The health of the animals is examined the day before the implantation of the tumour and before the randomization so as to ensure that only animals in good health will be used for the experimental work. They are placed in type III macrolon cages with filtering hoods (maximum 8 mice per cage) in a sterile room where the air is continuously filtered to avoid all contamination. The sterility of the room is checked once a month. The cages are sterilized at 121°C before use and changed twice a week. The temperature of the room is maintained at 22°C and the relative humidity at 60+/-10%. The animals are placed in a natural

light cycle condition. The water is sterilized at 121°C for 30 minutes. The water consumption is followed visually each day, and the bottles are changed twice a week. Food and water are given *ad libitum*. The litter is sterilized at 121°C for 30 minutes and changed twice a week.

The day before the first administration of a compound, the animals bearing tumours are classified into several groups. Only animals bearing two tumours which are palpable or of determined weight are selected and distributed at random into the treated groups and control groups. Each group is made up of 5 to 10 mice. At the start of the study, each cage is labelled with a card indicating the day of implantation of the tumour, the type of tumour, the compound tested and the mode of administration.

The implantation of the tumours is effected as follows: after removal of the tumour from the donor mouse, the tumour is cut up into fragments 2 to 3 mm in diameter, placed in a saline phosphate buffer, and implanted bilaterally with an adapted trocar.

Determination of antitumour activity

The volume of the tumours and its conversion into weight is estimated according to the formula: weight: (in mg) = $(a \times b^2) / 2$, where a and b are respectively the length and the width of the tumour (mm). The tumours are measured twice a week with callipers. In the following tables, P indicates the weight of the tumours at the start of treatment.

Two parameters for estimation of antitumour activity are used: $\log_{10}$ of the cells killed (Log cell kill) and T/C.

- Calculation of $\log_{10}$ of the cells killed = $(T - C) / 3.32 \times Td$, where $(T - C)$ is the delay in tumour growth and Td the volume (and weight) doubling time of the tumour (expressed in days). T is the median time in days for reaching a defined value (e.g.1000 mg) in the treated group and C is the median time in days for reaching this same value in the control group. A value of $\log_{10}$ of the cells killed > 0.7 is indicative of antitumour activity of the molecule. A value of $\log_{10}$ of the cells killed > 2.8 is indicative of a very high antitumour activity of the molecule (J Liang et al, Invest New Drugs 2005;23(3):213-24).

- Calculation of T/C: the treated groups and the control groups are evaluated when the tumours of the control group reach approximately 1000 mg (median value of the group). The median weight of the tumours of each treated group is then determined. The T/C value ((weight of the tumours of the treated groups / weight of the tumours of the control groups) x 100) in percent is an indication of the antitumour efficacy: a T/C value less than or equal to 42% is indicative of anti-

tumour activity according to the American National Cancer Institute (NCI). A T/C value less than 10% is representative of very high anti-tumour activity.

- The number of mice no longer displaying tumours a long time after the last administration (TFS = tumour-free survival), and considered as cured, can also constitute a parameter of activity of the molecule.

- Evaluation of the toxicity of the compound tested: a weight loss greater than or equal to 20% or the appearance of any lethality in connection with the compound is considered as an excessively toxic treatment.

As examples, the results obtained with the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethyl-ethyl)-urea are given in the following Tables 1 to 7.

TABLE 1

Activity of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea in mice bearing KG1a tumours (AML)

Formulation	P mg	Dose mg/kg/injection	Route	Administration on days:	Total dose mg/kg	T/C at 22 days	Log_{10} cells killed (TFS)
DMSO 5% Tween80 10% H_2O 85%	91-98	17	IV/IP	5-13,15/16, 18-20,22,24-26,29,31	340	0%	>>6 80% on day 120)
DMSO 5% Tween80 10% H_2O 85%	147	40 × 2 (2 administrations per treatment day)	oral	15-44	2400	14.9%	3.0
DMSO 5% Tween80 10% H_2O 85%	1000	25 / 40 × 2 (2 oral administr-ations per treatment day)	IV/oral	22-30/31-44	225 / 1120	not relevant	>> 6

IV/IP is understood to mean administration by the intravenous route followed by an intraperitoneal route, here the transition is effected between day 15 and day 16. IV/oral is understood to mean administration by the intravenous route followed by an oral route, here the transition is effected between day 30 and day 31. Treatment of tumours at the very advanced stage (1000 mg) by the IV route from days 22 to 30 at the dose of 25 mg/kg leads to a reduction in the tumour weight by 80%. On day 31, the compound is administered by the oral route until day 44. At the end of this second treatment period, the tumours are no longer measurable (< 63 mg).

The cell line KG-1a (AML) is described by Koeffler et al., Blood 56: 265 (1980), and supplied by DSMZ ACC No. 421, Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) Mascheroder Weg 1b, 38124 Brunswick, Germany).

TABLE 2

Activity of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea in mice bearing KG1 tumours (AML)

Formulation	P mg	Dose mg/kg/injection	Route	Administration on days:	Total dose mg/kg	T/C at 28 days	Log_{10} cells killed (TFS)
DMSO 5% Tween80 10% H_2O 85%	127-130	17	IV	19-28, 30, 32, 34, 36, 38	255	0%	>6 (100%)
Labrasol 21% Solutol 5% HCl 0.001N 74%	130-132	40 × 2 (2 administrations per treatment day)	Oral	18-24, 26, 28, 30, 32, 34, 36, 38, 40	1200	0%	4.3

IV is understood to mean administration by the intravenous route.
The cell line KG-1 (AML) is described by Koeffler et al., Science 200: 1153-1154 (1978), and supplied by DSMZ ACC No. 14.

TABLE 3

Activity of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea in mice bearing Kasumi1 tumours (AML)

Formulation	P mg	Dose mg/kg/injection	Route	Administration on days:	Total dose mg/kg	T/C at 28 days	Log_{10} cells killed
PEG400 22% Solutol 5% G5 73%	178	15 × 2 (2 administrations per treatment day)	IV	25-31;33;34. (One single administration on day 30)	255	20%	3
Labrasol 21% Solutol 5% HCl 0.001N 74%	178	40 × 2 (2 administrations per treatment day)	oral	25-31;33;34. (One single administration on day 30)	680	17.5%	2,4

IV is understood to mean administration by the intravenous route.
The cell line Kasumi-1 (AML) is described by Asou et al., Blood 77: 2031 (1991), and supplied by DSMZ ACC No. 220.

TABLE 4

Activity of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea in mice bearing EOL-1 tumours (AML)

Formulation	P mg	Dose mg/kg/injection	Route	Administration on days:	Total dose mg/kg	T/C at 14 days	Log_{10} cells killed
PEG400 22% Solutol 5% G5 73%	133-146	15 x 2 (2 administrations per treatment day)	IP	8-10; 12-17; 19	300	5.7%	3.1

IP is understood to mean administration by the intraperitoneal route.
The cell line EOL-1 (AML) is described by Saito et al., Blood 66: 1233-1240 (1985), and supplied by DSMZ ACC No. 386.

TABLE 5

Activity of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea in mice bearing CTV1 tumours (AML)

Formulation	P mg	Dose mg/kg/injection	Route	Administration on days:	Total dose	T/C at 25	Log_{10} cells

					mg/kg	days	killed
PEG400 22% Solutol 5% G5 73%	100	25	IV/IP	17-23; 25-26 / 28-32	350	1.6%	1.7

IV/IP is understood to mean administration by the intravenous route followed by an intraperitoneal route, here the transition is effected between day 26 and day 28.

The cell line CTV1 (AML) is described by Chen et al., Gann 75: 660-664 (1984), and supplied by DSMZ ACC No. 40.

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TABLE 6

Activity of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea in mice bearing K562 tumours (CML)

Formulation	P mg	Dose mg/kg/injection	Route	Administration on days:	Total dose mg/kg	T/C at 28 days	Log_{10} cells killed (TFS)
DMSO 5% Tween80 10% H_2O 85%	63-80	25	IV/IP	4-11/12-25	550	0%	4,2 (43% on day 130)

IV/IP is understood to mean administration by the intravenous route followed by an intraperitoneal route, here the transition is effected between day 11 and day 12.
The cell line K-562 (CML) is described by Lozzio et al., J Natl Cancer Inst 50: 535 (1973) and by Lozzio et al., Blood 45: 321 (1975), and supplied by DSMZ ACC No. 10.

TABLE 7

Activity of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea in mice bearing CMLT1 tumours (CML)

Formulation	P mg	Dose mg/kg/injection	Route	Administration on days:	Total dose mg/kg	T/C at 22 days	Log_{10} cells killed (TFS)
DMSO 5% Tween80 10% H_2O 85%	palpable ~30	20	IV/IP	3-7 /10-14; 17-21	300	1%	1.5 (50% on day 42)

IV/IP is understood to mean administration by the intravenous route followed by an intraperitoneal route, here the transition is effected between day 7 and day 10.
The cell line CMLT1 (CML) is 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 supplied by DSMZ ACC No. 7.

CLAIMS

1. Utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of leukaemias.

2. Utilization of the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea or a hydrate, a salt or a solvate thereof, for the preparation of a drug intended for the treatment of myeloid leukaemias.

3. Utilization according to Claim 2, for the preparation of a drug intended for the treatment of leukaemias of the AML type.

4. Utilization according to Claim 3, for the preparation of a drug intended for the treatment of leukaemias of the AML type where the drug is intended to be used by administration by the intravenous route.

5. Utilization according to Claim 3, for the preparation of a drug intended for the treatment of leukaemias of the AML type where the drug is intended to be used by administration by the oral route.

6. Utilization according to Claim 3, for the preparation of a drug intended for the treatment of leukaemias of the AML type where the drug is intended to be used by administration by the intravenous route and oral route.

7. Utilization according to Claim 2, for the preparation of a drug intended for the treatment of leukaemias of the CML type.

8. Utilization according to Claim 7, for the preparation of a drug intended for the treatment of leukaemias of the CML type where the drug is intended to be used by administration by the intravenous route.

9. Utilization according to Claim 7, for the preparation of a drug intended for the treatment of leukaemias of the CML type where the drug is intended to be used by administration by the oral route.

10. Utilization according to Claim 7, for the preparation of a drug intended for the treatment of leukaemias of the CML type where the drug is intended to be used by administration by the intravenous route and oral route.

11. Utilization according to any one of Claims 1 to 10 characterized in that the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido-

[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea can be administered in combination with one or more compound(s) of the anthracycline family.

12. Utilization according to any one of Claims 1 to 10 characterized in that the compound N-[2-(2,1,3-benzothiadiazol-5-ylamino)-6-(2,6-dichlorophenyl)pyrido-[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea can be administered in combination with daunorubicin or in combination with cytosine arabinoside, or indeed in combination with daunorubicin and cytosine arabinoside.