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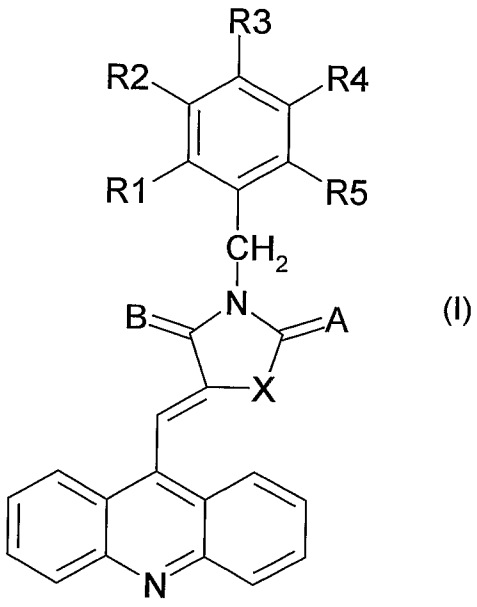
(54) Title: ACRIDINE DERIVATIVES WITH ANTITUMORAL ACTIVITY



(I)

(57) Abstract: The present invention discloses new acridine derivatives according to general formula (I) below, useful as antitumor agents, methods for its preparation as well as pharmaceutical compositions containing the same are also disclosed: (Formula **I).**

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

AcRiDiNE DERIVATIVES WITH ANTITU MORAL ACTIVITY

Description

Field of the Invention

The present invention is related to acridine-thiazolidinic and acridine-imidazolidinic derivatives denominated, respectively, thiazacridine - TZA - and imidazacridine - IZA - , which displayed an antitumor activity, and the respective processes for their chemical synthesis as well as their therapeutic use as anticancer agents.

Background of the invention

It is known that azolidines and acridines are effective compounds against infectious diseases, specially against tumors and extensive research has made in this field, including several patents. As example, document WO 94/25439 prepared acridine compounds with antitumor activity, and among the studied compounds, the (3,6-bis-dimethylamine-acridin-4-yl)-methanol presented the most important activity.

Also several other patents disclosed acridine derivatives as antitumor agents. Some patent literature include: Document FR 2716454 discloses the synthesis of 4-(aminomethyl)-3-dimethylaminoacridine compounds as anticancer agents, and the 4-(3,6-bis-dimethylamino-acridin-4-yl)-butan-2-one. The latter compounds showed an *in vitro* anticancer activity (in cells ATCC HTB1) which was higher than that of adriamicine in the same assay conditions. WO 93/23094 disclosed acridine derivatives of the 3-(9-acridinylamino)-5-hydroxy-methylaniline type; US 6,114,332 disclosed acridine derivatives of the bis(acridinecarboxamide) type; US 6,521,635 disclosed acridine derivatives of the acridinecarboxamide type; WO 03/074490 disclosed acridine derivatives of the 9-aminoacridine type; US 6,589,691 disclosed acridine derivatives of the 9-alkylamino-1-nitroacridine type; and WO 05/007643 disclosed acridine derivatives of the diazacycloalkyl-(thio)carbonyl-substituted acridine type.

As scientific studies, the work of Fiszer-Maliszewska *et al.* (Arch. Immunol. Ther. Exp. 1993, v. 41, n. 1), reported an important therapeutic activity in the transplanted tumors of linfosarcoma X19 in mice, when treated intra-peritoneally with the 9-oxo-10-acridineacetic acid. A cytotoxic activity has been reported for compounds obtained by condensation of the porfirinic acid with 9-aminoacridine derivatives (Karagianis & James, Aust. J. Chem. 1995, v. 48, n. 10, p. 1693-1705).

Additionally, Alex A. Adjei (Investigational New Drugs 1999, v.17, p.43-48), synthesized pyrazoloacridines combining the acridines activity by intercalate the DNA with selectivity hypoxia conferred by reduction of nitro group of acridinic ring. The 9-methoxypyrazoloacridine (pyrazolo acridine, PZA_1NSC 366140) presented activity for hypoxic cells and cytotoxicity in cells that are not in cell cycle. PZA was also active against others antitumoral resistant cells based on P-glycoprotein or MPR (multidrug resistance-associated protein) overexpression. PZA presented a broad spectrum of antitumoral activity in pre-clinic models *in vivo.*

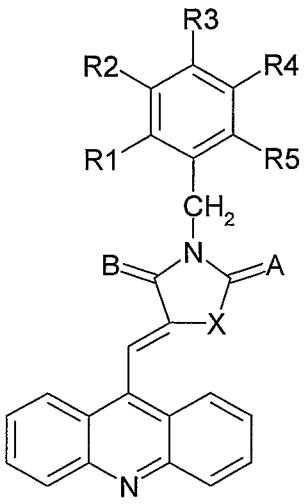
Ferlin M.G. *et al.* (Eur. J. Med. Chem. 2000, v.35, p.827-837), prepared substituted derivate of 9-acridine and of azacridine (analogous of m-AMSA) as potent antitumoral agents with topoisomerase II inhibitory effects. Some derivatives showed remarkable cytotoxicity in HL-60 human cells and HeLa cells in culture.

The closest work related to the derivatives of the present invention is WO 2004/024058, which also discloses acridine-thiazolidinic and acridine-imidazolidinic derivatives. However, the derivatives disclosed herein are not encompassed by this application or any other application found in the state of the art.

Summary of the Invention

It is an object of the invention the use of acridine-thiazolidinic and acridine-imidazolidinic derivatives as antitumor agents. More specifically, it is a

further object of the invention the use of acridine derivatives as antitumor agents according to general formula (I):



(I)

wherein:

X is N or S;

A is O or S;

B is O or S;

R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, C1-C5 alkyl, aryl, nitro, F, Cl, Br, I and mixtures of the same;

with the proviso that:

when X is S, A is O, B is O, R1, R2, R4 and R5 are all H, R3 is not H, Cl, or F;

when X is S, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not Br;

when X is N, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not H, nitro or Cl;

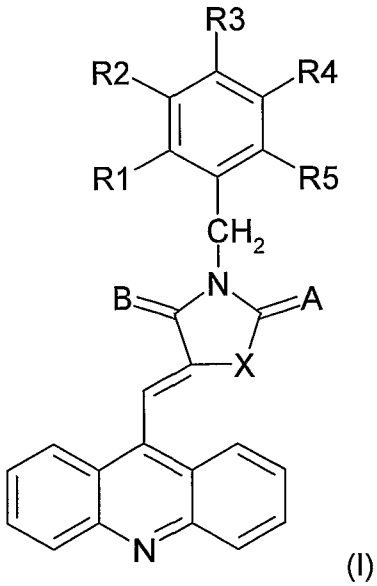
It is a further object of the invention the use of acridine-thiazolidinic and acridine-imidazolidinic derivatives as antitumor agents in pharmaceutical compositions.

These and other objects of the invention will be more readily appreciated with the hereinbelow detailed description of the invention.

Detailed Description of the Invention

The following examples described herein are not intended to limit the scope of the invention, but rather to exemplify some of the preferred embodiments thereof. Several other embodiments possible, readily achieved by the teachings herein presented are to be deemed as within the scope of the invention.

The synthesized compounds described in this invention belong to a new series of thiazacridine derivatives, thiazolidines couples with the acridinic ring, 5-(acridin-9-ylmethylene)-3-(benzyl)-thiazolidin-2,4-dione substituted at the aromatic ring in position 3; 5-(acridin-9-ylmethylene)-3-benzyl-4-thio-oxo-thiazolidin-2-one substituted at the aromatic ring in position 3; imidazacridinic derivatives, imidazolidines couples with the acridinic ring, 5-acridin-9-ylmethylene-3-benzyl-4-thio-oxo-imidazolidin-2-one substituted at the aromatic ring in position 3 and 5-(acridin-9-ylmethylene)-3-benzyl-2-thio-oxo-imidazolidin-4-one; All these compounds have pharmacological and antitumor activities. These compounds are according to general formula (I) below:



(I)

wherein:

X is N or S;

A is O or S;

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R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, C1-C5 alkyl, aryl, nitro, F, Cl, Br, I and mixtures of the same;

with the proviso that:

when X is S, A is O, B is O, R1, R2, R4 and R5 are all H, R3 is not H, Cl, or F;

when X is S, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not Br;

when X is N, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not H, nitro or Cl.

This is a new series of intercalating agents, with the ability of planar acridine radical to insert themselves between the layers of base pairs of nucleic acids, deforming the double helix and stopping replication and transcription and the target thiazolidine part has been shown to be closely related to the nuclear receptor.

Many antitumor antibiotics, such as the actinomicine-D, adriamicine and proflavine, an amino-acridine, act as intercalating agents. (Patrick, G. L., An Introduction Medicinal to Chemistry, Oxford University Press, 1995, Oxford).

A) Compound synthesis

The synthetic route used to obtain the compounds of the present invention is similar to the synthetic procedures of document WO 04/024058: it begins with oxidation of 9-methyl-acridine, prepared from diphenylamine, to acridin-9-carboxyaldehyde, followed by condensation in alkaline medium with ethyl cyanoacetate to obtain ethyl cyano-acridin-9-ylacrylate. The synthesis of the thiazolidinic or imidazolidinic moiety of the molecule is performed by benzylation of thiazolidin-2,4-dione or imidazolidin-2,4-dione with benzyl halides in alkaline medium, followed by thionation in position 4 by phosphorus pentassulfide or by Lawesson's reagent 2,4-bis(4-methoxy-phenyl)-1 ,3-dithio-2,4-diphosphetane-2,4-disulfide.

The thiazolidinic and imidazolidinic derivatives through an addition reaction with ethyl ester of 2-cyano-acridin-9-ylacrylate of ethyl in presence of piperidine produce thiazacridines and imidazacridines. The preparation of compound 5-(acridin-9-ylmethylene)-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one required initially, the addition of ethyl ester of 2-cyano-acridin-9-ylacrylate with 2-thioxo-imidazolidin-4-one in presence of piperidine, followed by benzylation of 5-(acridin-9-ylmethylene)-2-thioxo-imidazolidin-4-one with 1-chloro-methyl-4-nitro-benzene.

The TZAs and the IZAs object of the present invention were synthesized according to the experimental procedures described bellow.

Example 1 - Preparation procedure of acridin-9-carboxyaldehvde :

Diphenylamine, acetic acid and zinc chloride are heated at a temperature of 220 ^{0}C, for 8 hours. The reaction mixture was treated, initially, with 10% sulfuric acid followed by alkalinization with 30% ammonia solution. The 9-methyl-acridine was isolated though benzene extraction and purified trough flash chromatography in silica gel 60.

In the 9-methyl-acridine oxidation, piridinium chlorochromate (PCC) and magnesium sulfate are put in a flask, in presence of dichloromethane, with stirring, followed by addition of 9-methyl-acridine. The agitation was kept at room temperature, under inert atmosphere, for 48 hours. The acridine-9-carboxyaldehyde compound was extracted from the medium with ethylic ether and evaporated to dryness. The aldehyde obtained was purified trough flash chromatography in silica gel 60.

Example 2 - Preparation procedure of ethyl ester of 2-cvano-acridin-9-ylacrylate:

Acridin-9-carboxyaldehyde and ethyl cyanoacetate in presence of piperidine, and anhydrous benzene, as solvent are put into a flask. The mixture is refluxed at a temperature of 110 ^{0}C, for 8 hours. The ethyl ester of 2-cyano-

acridin-9-ylacrylate was kept in the refrigerator for 12 hours. The cyanoacridinic ester obtained was purified trough flash chromatography in silica gel 60.

Example 3 - General preparation procedure of substituted thiazolidinediones:

Thiourea and chloroacetic acid previously dissolved in 5OmL of water were added to a flask. The mixture was heated for 40 hours. The product obtained was put for 24 hours in the refrigerator. Yellow crystals were formed from the thiazolidin-2,4-dione which was purified by successive crystallizations.

Potassium hydroxide was dissolved in methanol. This solution was added, by drops, in a thiazolidin-2,4-dione suspension. Ten minutes after, substituted benzyl chloride was added. The mixture was heated to 60 ^{0}C temperature for 25 hours. After cooling, the substituted thiazolidin-2,4-dione was separated and purified trough successive crystallizations. The thionation could be performed by the dissolution of the thiazolidinic derivatives in dioxane in presence of phosphorus pentasulfide or by Lawesson's reagent under inert atmosphere. The reaction mixture was heated at 60-75^{0}C followed by thin layer chromatography. After evaporation to dryness, the 4-thioxo-thiazolidin-2-one substituted in position 3 was washed with distillated water.

Example 4 - General preparation procedure of 3-benzyl-4-thioxo-imidazolidin-2-ones:

The imidazolidin-2,4-dione and methanol were added in a flask. Potassium hydroxide was dissolved in methanol and this solution was added, by drops, in the imidazolidin-2,4-dione suspension. Ten minutes later, benzyl chloride was added. The mixture was heated at 6O^{0}C for 18 hours. After the cooling the 3-benzyl-imidazolidine-2,4-dione is separated, and purified through successive crystallizations. This imidazolidinic derivate is dissolved in dioxane in the presence of Lawesson's reagent under inert atmosphere. The reactional mixture was heated at 60-75^{0}C and followed by thin layer chromatography. After the evaporation to dryness, the 3-benzyl-4-thioxo-imidazolidine-2-one was washed with distillated water.

Example 5 - General preparation procedure of thiazacridines and imidazacridines:

By heating the substituted thiazolidines or imidazolidines, dissolved in anhydrous ethanol, with the ethyl ester of 2-cyano-acridin-9-ylacrylate at 50-80^{0}C temperature for 2-4 hours in presence of piperidine, the precipitation of the thiazacridines and imidazacridines intended will occur, which are filtrated and purified.

Example 6 - Preparation procedure of imidazacridines 5-acridin-9-ylmethylene-3-benzyl-2-thioxo-imidazolidine-4-one :

The 2-thioxo-imidazolidine-4-one and methanol were added into a flask. Potassium carbonate was dissolved in methanol and this solution was added, by drops, to the 2-thioxo-imidazolidin-4-one suspension. Ten minutes later, 1-chloro-methyl-benzene was added. The mixture was agitated at room temperature for 10 hours. After the cooling, the formed imidazacridine was separated, and purified trough successive crystallizations.

B) Structural confirmation

The confirmation of the synthesized compounds structures was performed by infrared spectra of KBr pellets recorded on an IFS 66 Bruker spectrometer. Proton nuclear magnetic resonance was recorded on a AC 300 P Bruker spectrometer in DMSO d_6 as solvent. Electronic impact mass spectra (70 eV) was recorded on HP 5987. The spectroscopic characteristics in the infrared and proton nuclear magnetic resonance of the thiazacridine and imidazacridine compounds are in agreement with their proposed structures. The observed fragmentations and the intensity of the peaks of the isotopes on mass spectra also agree with the proposed structures.

Synthesized compounds:

5-acridin-9-ylmethylene-3-biphenyl-4-ylmethyl-thiazolidine-2,4-dione (AC30);

5-acridin-9-ylmethylene-3-(4-bromo-benzyl)-thiazolidine-2,4-dione (AC7);
5-acridin-9-ylmethylene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (AC4);
5-acridin-9-ylmethylene-3-(4-nitro-benzyl)-thiazolidine-2,4-dione (AC6);
5-acridin-9-ylmethylene-3-(3-chloro-benzyl)-thiazolidine-2,4-dione (AC34);
5-acridin-9-ylmethylene-3-(2-nitro-benzyl)-thiazolidine-2,4-dione (AC109);
5-acridin-9-ylmethylene-3-(4-methyl-benzyl)-4-thioxo-thiazolidin-2-one (AC99);
5-acridin-9-ylmethylene-3-(4-chloro-benzyl)-4-thioxo-thiazolidin-2-one (AC1 19);
5-acridin-9-ylmethylene-3-(3-chloro-benzyl)-4-thioxo-thiazolidine-2-one (AC129);
δ-acridin- 9-ylmethylene-i-benzyM-thioxo-imidazolidin^-one (AC124);
5-acridin-9-ylmethylene-3-(2-nitro-benzyl)-4-thioxo-imidazolidin-2-one (AC128);
5-acridin-9-ylmethylene-3-(2-chloro-benzyl)-4-thioxo-imidazolidin-2-one (AC100);
5-acridin-9-ylmethylene-3-(4-nitro-benzyl)-2-thioxo-imidazolidin-4-one (AC97).

C) Evaluation of antitumoral activity

To evaluate the *in vitro* antitumoral activity of the acridine-thiazolidinic derivates and acridine-imidazolidinic derivates, these compounds were tested in a fixed concentration of 25 ug/ml_ in the follow cell lines SF295 (SNC); HCT-8 (colon) and MDA-MB-435 (mamma). The percentual of tumor growth inhibition was higher than 80% for some compounds in the cell lines mentioned above. IC50 was determined in several lineages, where TZAs and IZAs showed cytotoxic potential for solid tumors. Several samples showed IC50 lower than 5ug/mL, for HCT-8 (Colon) and SF-295 (SNC) lineages. No sample showed hemolytic potential, therefore showing that the action is likely due to interference on DNA.

To evaluate the antitumoral activity *in vivo* of TZA and IZA derivatives, albine swiss mice *(Mus musculus)* from Biotery of Antibiotic Department of UFPE, at 60 days of age were selected and separated in groups of 06 animals per cage. The dose in study was calculated according the body mass index of the animals, the compounds being solubilized in tween 80 and isotonic saline

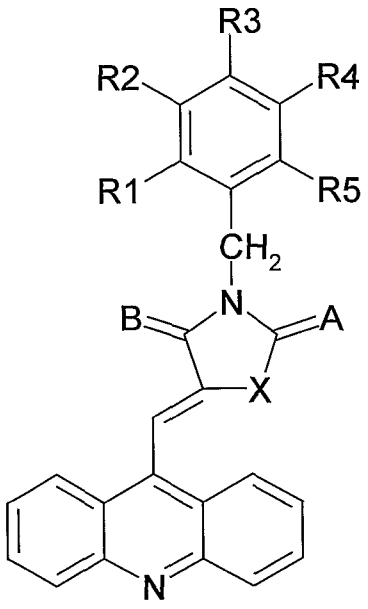
(0.9%) solution. Malignant tumors had been used (sarcoma 180) from tumor carrying animals with 8 days of implantation. The donor animals had their hair removed in a surgery room, all hygienized previously and anesthetized to extirpation of tumor mass. The tumor was put in Ringer's solution, followed by fragmentation and introduction in the receptors animals. The technique was the implantation of the tumor fragments with a little incision on axillary area and introduced with the help of trocater by subcutaneous route. After 48 hours of surgery the administration of the compound being tested begins in the doses of 50, 25, 12.5 and 6.25 mg/Kg of body mass, for 8 days. The control group received the vehicle, and the standard group received the methotrexate as reference antitumoral. The administration was intraperitoneal. After the treatment period, the animals had been sacrificed, tumor of each animal was removed, in order to observe the macroscopic morphologic alterations as well as the tumor extension. An important reduction of tumoral mass was observed and to some animals an almost total regression of sarcoma 180 with small doses was also observed.

The skilled in the art will readily understand that the exemplary teachings provided herein also enable other forms of performing the present invention. Accordingly, such other embodiments are to be considered as within the spirit of the invention and of the scope of the appended claims.

AcRiDiNE DERIVATIVESWITH ANTITUMORAL ACTIVITY

Claims

1. Acridine derivatives for antineoplastic use characterized by comprising an active ingredient of formula (I):



(I)

wherein:

X is N or S;

A is O or S;

B is O or S;

R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, C1-C5 alkyl, aryl, nitro, F, Cl, Br, I and combinations of the same;

with the proviso that:

when X is S, A is O, B is O, R1, R2, R4 and R5 are all H, R3 is not H, Cl, or F;

when X is S, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not Br;

when X is N, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not H, nitro or Cl.

2. Acridinde derivatives, according to claim 1, characterized by the fact that X is S, A is O, B is O, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, methyl, phenyl, nitro, Cl and Br.

3. Acridine derivatives, according to claims 1 and 2, characterized by the fact that the compounds are selected from the group consisting of:
5-acridin-9-ylethylene-3-biphenyl-4-ylmethyl-thiazolidine-2,4-dione (AC30);
5-acridin-9-ylmethylene-3-(4-bromo-benzyl)-thiazolidine-2,4-dione (AC7);
5-acridin-9-ylmethylene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (AC4);
5-acridin-9-ylmethylene-3-(4-nitro-benzyl)-thiazolidine-2,4-dione (AC6);
5-acridin-9-ylmethylene-3-(3-chloro-benzyl)-thiazolidine-2,4-dione (AC34);
5-acridin-9-ylmethylene-3-(2-nitro-benzyl)-thiazolidine-2,4-dione (AC109);
and combinations thereof.

4. Acridine derivatives, according to claim 1, characterized by the fact that X is S, A is O, B is S, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, methyl and Cl.

5. Acridine derivatives, according to claims 1 and 4, characterized by the fact that the compounds are selected from the group consisting of:
5-acridin-9-ylmethylene-3-(4-methyl-benzyl)-4-thioxo-thiazolidine-2-one (AC99);
5-acridin-9-ylmethylene-3-(4-chloro-benzyl)-4-thioxo-thiazolidine-2-one (AC119);
5-acridin-9-ylmethylene-3-(3-chloro-benzyl)-4-thioxo-thiazolidine-2-one (AC129);
and combinations thereof.

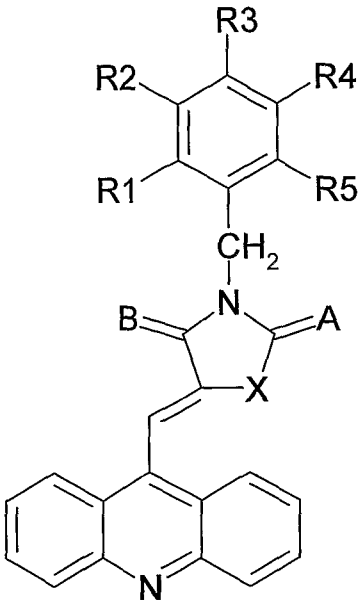
6. Acridine derivatives, according to claim 1, characterized by the fact that X is N, A is O, B is S, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, nitro, F and Cl.

7. Acridine derivatives, according to claims 1 and 6, characterized by the fact that the compounds are selected from the group consisting of:
5-acridin-9-ylmethylene-3-(4-fluoro-benzyl)-4-thioxo-imidazolidine-2-one (AC124);
5-acridin-9-ylmethylene-3-(2-nitro-benzyl)-4-thioxo-imidazolidine-2-one (AC128);
5-acridin-9-ylmethylene-3-(2-chloro-benzyl)-4-thioxo-imidazolidine-2-one (AC100);
and combinations thereof.

8. Acridine derivatives, according to claim 1, characterized by the fact that X is N, A is S, B is O, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H and nitro.

9. Acridine derivatives, according to claims 1 and 8, characterized by the fact that the compound is 5-acridin-9-ylmethylene-3-(4-nitro-benzyl)-2-thioxo-imidazolidine-4-one (AC97).

10. Pharmaceutical composition for the antineoplastic treatment characterized by comprising a pharmaceutically acceptable vehicle and, as active ingredient, at least one acridine derivative of formula (I):



(I)

wherein:

X is N or S;

A is O or S;

B is O or S;

R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, C1-C5 alkyl, aryl, nitro, F, Cl, Br, I and mixtures of the same;

with the proviso that:

when X is S, A is O, B is O, R1, R2, R4 and R5 are all H, R3 is not H, Cl, or F;

when X is S, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not Br;

when X is N, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not H, nitro or Cl.

11. Pharmaceutical composition, according to claim 10, characterized by the fact that X is S, A is O, B is O, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, methyl, phenyl, nitro, Cl and Br.

12. Pharmaceutical composition, according to claims 10 and 11, characterized by the fact that the compounds are selected from the group consisting of:
5-acridin-9-ylmethylene-3-biphenyl-4-ylmethyl-thiazolidine-2,4-dione (AC30);
5-acridin-9-ylmethylene-3-(4-bromo-benzyl)-thiazolidine-2,4-dione (ACT);
5-acridin-9-ylmethylene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (AC4);
5-acridin-9-ylmethylene-3-(4-nitro-benzyl)-thiazolidine-2,4-dione (AC6);
5-acridin-9-ylmethylene-3-(3-chloro-benzyl)-thiazolidine-2,4-dione (AC34);
5-acridin-9-ylmethylene-3-(2-nitro-benzyl)-thiazolidine-2,4-dione (AC109);
and combinations thereof.

13. Pharmaceutical composition, according to claim 10, characterized by the fact that X is S, A is O, B is S, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, methyl and Cl.

14. Pharmaceutical composition, according to claims 10 and 13, characterized by the fact that the compounds are selected from the group consisting of:
5-acridin-9-ylmethylene-3-(4-methyl-benzyl)-4-thioxo-thiazolidine-2-one (AC99);
5-acridin-9-ylmethylene-3-(4-chloro-benzyl)-4-thioxo-thiazolidine-2-one (AC119);
5-acridin-9-ylmethylene-3-(3-chloro-benzyl)-4-thioxo-thiazolidine-2-one (AC129);
and combinations thereof.

15. Pharmaceutical composition, according to claim 10, characterized by the fact that X is N, A is O, B is S, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, nitro, F and Cl.

16. Pharmaceutical composition, according to claims 10 and 15, characterized by the fact that the compounds are selected from the group consisting of:

5-acridin-9-ylmethylene-3-(4-fluoro-benzyl)-4-thioxo-imidazolidine-2-one (AC124);

5-acridin-9-ylmethylene-3-(2-nitro-benzyl)-4-thioxo-imidazolidine-2-one (AC 128);

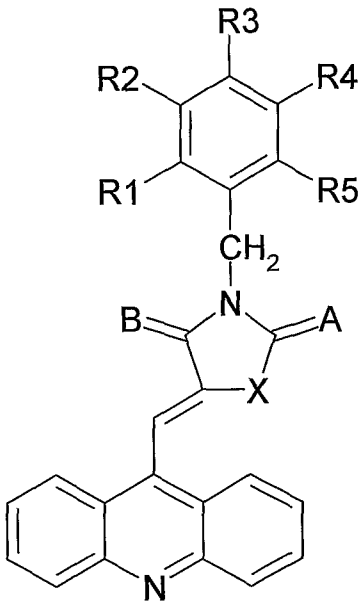
5-acridin-9-ylmethylene-3-(2-chloro-benzyl)-4-thioxo-imidazolidine-2-one (AC100);

and combinations thereof.

17. Pharmaceutical composition, according to claim 10, characterized by the fact that X is N, A is S, B is O, R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H and nitro.

18. Pharmaceutical composition, according to claims 10 and 17, characterized by the fact that the compound is 5-acridin-9-ylmethylene-3-(4-nitro-benzyl)-2-thioxo-imidazolidine-4-one (AC97).

19. Use, in the preparation of an antineoplastic medicament, of an acridine derivative of formula (I):



(I)

wherein:

X is N or S;

A is O or S;

B is O or S;

R1, R2, R3, R4 and R5 are, each independently, chosen from the group consisting of H, C1-C5 alkyl, aryl, nitro, F, Cl, Br, I and mixtures of the same;

with the proviso that:

when X is S, A is O, B is O, R1, R2, R4 and R5 are all H, R3 is not H, Cl, or F;

when X is S, A is O, B is S, R1, R2, R4 and R5 are all H, R3 is not Br;

when X is N, A is O, B is S_1 R1, R2, R4 and R5 are all H, R3 is not H, nitro or Cl.