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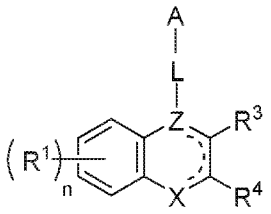
(54) Title: PHENOTHIAZINE ANTIPSYCHOTICS FOR USE IN THE TREATMENT OF GLIOBLASTOMA



(I)

(57) Abstract: The invention provides compounds of formula (I), stereoisomers, and pharmaceutically acceptable salts thereof for use in the treatment of cancer: Formula (I) wherein: X is CH, S, N or NH; Z is C or N; A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system; L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more -CH_2- groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl); each R^1 is independently selected from: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -OH, -SH, halogen, and an optionally substituted aryl group; n is an integer from 0 to 4; R^3 and R^4 are each independently selected from: hydrogen, C_{2-6}alkenyl, and C_{2-6} alkynyl, or R^3 and R^4, together with the intervening ring carbon atoms, form an optionally substituted aryl ring; and represents an optional bond between two adjacent carbon atoms in the ring. The compounds of formula (I), their stereoisomers and pharmaceutically acceptable salts find particular use in the treatment of glioblastoma.

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PHENOTHIAZINE ANTIPSYCHOTICS FOR USE IN THE TREATMENT OF GLIOBLASTOMA

Field of the invention

The present invention relates to compounds for use in the treatment of cancer, in particular for use in the treatment of glioblastoma. It further relates to certain novel compounds, to pharmaceutical compositions containing them, and to their use in such treatment.

Background to the invention

The worldwide load of cancer has steadily risen over the years and the number of cancer cases is still increasing. Cancer represents a considerable cause of human suffering and early death and its treatment puts extensive pressure on global health economies.

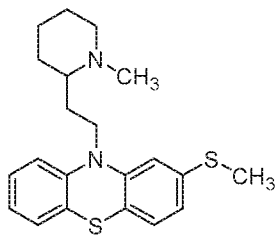
Glioblastoma (also known as glioblastoma multiforme or "GBM") is an incurable form of brain cancer. It is particularly difficult to treat due to its location and highly aggressive characteristics, however it can be treated for relief and prolongation of life. Conventional treatment involves highly invasive (open brain) surgery, followed by radiation treatment and chemotherapy. Treatment may also involve Gamma Knife radiosurgery in which beams of radiation are highly focused on the tumour thereby minimising radiation damage to surrounding healthy tissues. Surgery is performed to remove as much of the tumour as possible. In high-risk areas of the brain, however, it may not be possible to remove all of the tumour by surgery alone. Radiotherapy is used to kill remaining tumour cells after surgery and can also reduce tumour size, as well as the rate of tumour growth. However, radiotherapy does not have a major effect on tumours such as GBM due to its tendency to spread and the radio-resistance of the cancer cells. Furthermore, radiotherapy is not specific in destroying cancerous cells versus normal tissues.

In addition to radiotherapy, chemotherapy may also be used although there are relatively few chemotherapeutics in clinical use for the treatment of GBM. Temozolomide and the nitrogen mustard β-chloro-nitrosourea carmustine, which are both alkylating agents, can be used as a first line treatment but these are mainly cytostatic as the cancer cells eventually develop resistance and render the

treatment no longer effective. Temozolomide is a prodrug which is activated by a first pass metabolic decomposition process in the liver that produces methyl diazonium ions which can penetrate the blood-brain barrier. Its mechanism of action involves alkylation of the guanine groups of DNA by the methyl diazonium ions.

Despite current treatments, GBM is usually accompanied by recurrence with re-growth of tumours which requires repeated treatment. The poor prognosis of GBM is mainly due to the tumour's high degree of invasiveness and the development of chemotherapy resistance. Tumours such as GBM thus remain particularly difficult to treat and existing therapies only offer a minimal increase in survival rates. The development of alternative treatments is urgently required, in particular treatments which have improved efficacy and which show high selectivity for the target cancer cells.

Thioridazine (Mellaril) is a known antipsychotic drug belonging to the phenothiazine group of drugs. It has the following structure:



Thioridazine

10-[2-[(RS)-1-methylpiperidin-2-yl]ethyl]-2-methylsulfanyl-phenothiazine

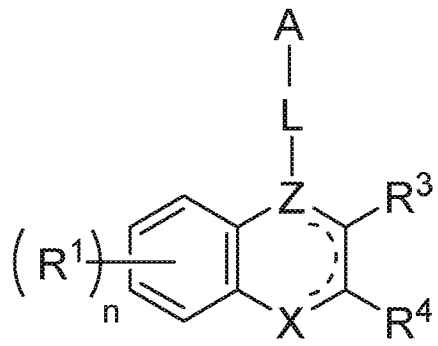
Thioridazine has primarily been used in the treatment of schizophrenia, but also for various psychiatric indications in patients with dementia. However, severe side-effects such as cardiac arrhythmias have been observed leading to its discontinued use. Its serious side-effects suggest that the agent possesses poor selectivity towards its drug target. In fact, Johannessen et al. (Int. J. Cancer 144: 1735-1745, 2019) recently discovered that thioridazine gives rise to inhibition of cellular autophagy. As a result, it has been investigated as a means to sensitize GBM cells to the chemotherapeutic agent temozolomide. Autophagy is a natural cellular

process that involves lysosome degradation in which cells capture unnecessary or dysfunctional intracellular components, such as proteins, lipids, and organelles, and deliver them to the lysosomal compartment where they are degraded. This effect has been observed in the context of cancer treatment, where the effect of the cytotoxic compound is minimized by degradation via the autophagy process. To date, however, there have been no reports of any cytotoxic effects associated with thioridazine or related phenothiazine compounds.

The inventors have now found that certain compounds, in particular phenothiazine derivatives and related anthracene compounds, show high cytotoxicity and selectivity versus glioblastoma cells in *in vitro* tests in a range of glioblastoma cell lines. These compounds also have the advantage of high lipophilicity that will allow penetration across the blood-brain barrier. As a result of these findings, such compounds are proposed herein for use in the treatment of glioblastomas. *In vitro* tests conducted by the inventors in melanoma cell lines demonstrate the cytotoxicity of the compounds against other cancer cells. The inventor's findings relating to the cytotoxic effects of the compounds herein described can thus be expected to extend to the treatment of other types of cancer.

Summary of the invention

In one aspect, the invention relates to a compound of formula (I), a stereoisomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer:



(I)

wherein:

X is CH, S, N or NH;

Z is C or N;

A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{2-6} alkenyl (preferably C_{2-4} alkenyl),

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),

-OH,

-SH,

halogen (e.g. F, Cl or Br), and

an optionally substituted aryl group (e.g. optionally substituted phenyl);

n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2;

R^3 and R^4 are each independently selected from:

hydrogen,

C_{2-6} alkenyl (preferably C_{2-4} alkenyl), and

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

or

R^3 and R^4, together with the intervening ring carbon atoms, form an optionally substituted aryl ring (e.g. an optionally substituted phenyl ring); and

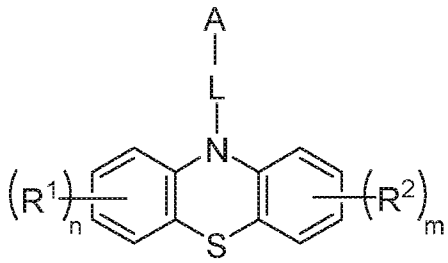
 represents an optional bond between two adjacent carbon atoms in the ring.

In another aspect the invention relates to a compound of formula (Ia), (Ib) or (Ic) as herein described, a stereoisomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

In another aspect the invention relates to the use of a compound of formula (I), (Ia), (Ib) or (Ic), a stereoisomer, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer.

In another aspect, the invention relates to a method of treatment of cancer, said method comprising the step of administering to a subject in need thereof (e.g. a human patient) a pharmaceutically effective amount of a compound of formula (I), (Ia), (Ib) or (Ic), a stereoisomer, or a pharmaceutically acceptable salt thereof.

In a further aspect, the invention relates to novel compounds of formula (II), their stereoisomers and their pharmaceutically acceptable salts:



(II)

wherein:

A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system, preferably an optionally substituted carbocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 and R^2 is independently selected from:

- C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),
- C_{2-6} alkenyl (preferably C_{2-4} alkenyl),
- C_{2-6} alkynyl (preferably C_{2-4} alkynyl),
- C_{1-6} haloalkyl (e.g. $-CF_3$),
- $-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),
- $-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),
- -OH,
- -SH,
- halogen (e.g. F, Cl or Br), and
- an optionally substituted aryl group (e.g. optionally substituted phenyl);

n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2; and

m is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2;
with the proviso that the compound is other than thioridazine.

In a further aspect, the invention relates to a compound of formula (II), a stereoisomer, or a pharmaceutically acceptable salt thereof, for use in therapy or for use as a medicament.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of formula (II), a stereoisomer, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Detailed description of the invention

Definitions

As used herein, the term "alkyl" refers to a saturated hydrocarbon group and is intended to cover both straight-chained and branched alkyl groups. Examples of such groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, sec-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl. An alkyl group preferably contains from 1-6 carbon atoms, more preferably 1-4 carbon atoms, e.g. 1-3 carbon atoms. Unless otherwise specified, any alkyl group may be substituted in one or more positions with a suitable substituent. Where more than one substituent group is present, these may be the same or different. Suitable substituents include -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

As used herein, the term "alkenyl" refers to an alkyl group having one or more carbon-carbon double bonds and includes both straight-chained and branched alkenyl groups. The term "C_{2-6} alkenyl" refers to an alkenyl group having from 2 to 6 carbon atoms and one or more (e.g. one or two) double bonds. Examples of such groups include vinyl, allyl, propenyl, iso-propenyl, butenyl, iso-butenyl, crotyl, pentenyl and hexenyl. Unless otherwise stated, any alkenyl group mentioned herein may optionally be substituted by one or more groups, which may be identical or different. Suitable substituents include -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

As used herein, the term "alkynyl" refers to an alkyl group having one or more carbon-carbon triple bonds and includes both straight-chained and branched alkynyl groups. Unless otherwise stated, any alkynyl group mentioned herein may optionally be substituted by one or more groups, which may be identical or different. Suitable substituents include -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

The term “carbocyclic ring system” as used herein refers to a monovalent, saturated or unsaturated cyclic carbon system. Such systems may include one or more carbon-containing rings. Where more than one ring is present the rings may be linked by a bond or they may be fused. Unless otherwise specified, any carbocyclic ring system may be substituted in one or more positions with a suitable substituent. Where more than one substituent group is present, these may be the same or different. Suitable substituents include -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

The term “heterocyclic ring system” as used herein refers to a monovalent, saturated or unsaturated cyclic carbon system in which one or more carbon atoms are replaced by a heteroatom selected from oxygen, nitrogen or sulfur, preferably nitrogen. Such systems may include one or more rings in which at least one ring contains at least one heteroatom. Where more than one ring is present the rings may be linked by a bond or they may be fused. Unless otherwise specified, any heterocyclic ring system may be substituted in one or more positions with a suitable substituent. Where more than one substituent group is present, these may be the same or different. Suitable substituents include -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

The term “cycloalkyl” refers to a monovalent, saturated cyclic carbon system. It includes monocyclic, bicyclic and polycyclic (e.g. tricyclic) rings. Monocyclic rings may contain from 3 to 8 carbon atoms, bicyclic rings may contain from 7 to 14 carbon atoms, and tricyclic rings may contain from 10 to 14 carbon atoms. Where these contain more than one ring, the rings may be fused or bridged. In fused compounds, two rings share two adjacent atoms. In bridged compounds, two rings share three or more atoms thereby forming a bridge which contains at least one

atom. Examples of monocyclic cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc. Examples of bicyclic cycloalkyl groups include, but are not limited to, norbornyl. Examples of tricyclic cycloalkyl groups include, but are not limited to, adamantyl. Unless otherwise specified, any cycloalkyl group may be substituted in one or more positions with a suitable substituent. Where more than one substituent group is present, these may be the same or different. Suitable substituents include -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

The term "cycloalkenyl" refers to a monovalent, partially unsaturated cyclic carbon system. It includes monocyclic, bicyclic and polycyclic (e.g. tricyclic) rings. Unless otherwise specified, any cycloalkenyl group may be substituted in one or more positions with a suitable substituent. Where more than one substituent group is present, these may be the same or different. Suitable substituents include -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

As used herein, the term "alkylene" refers to a linking alkyl group and is intended to cover any straight-chained or branched alkylene group. Examples of such groups include methylene, ethylene, ethane-1,1-diyl, propylene, propane-2,2-diyl, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, etc. Such groups may optionally be substituted by one or more groups selected from -O-C_{1-3} alkyl and halogen atoms (e.g. F, Cl or Br).

The term "halogen" or "halogen atom" as used herein refers to -F, -Cl, -Br or -I.

The term "haloalkyl" refers to an alkyl group as defined herein in which at least one of the hydrogen atoms of the alkyl group is replaced by a halogen atom, preferably F, Cl or Br. Examples of such groups include -CH_2F, -CHF_2, -CF_3, -CCl_3, -$CHCl_2$, -CH_2CF_3, etc.

The term "aryl" as used herein refers to aromatic ring systems. Such ring systems may be monocyclic or bicyclic and contain at least one unsaturated aromatic ring. Where these contain bicyclic rings, these may be fused. Preferably such systems contain from 6-20 carbon atoms, e.g. either 6 or 10 carbon atoms. Examples of such groups include phenyl, 1-napthyl and 2-napthyl. A preferred aryl group is

phenyl. Unless stated otherwise, any aryl group may be substituted by one or more substituents as described herein. Where more than one substituent group is present, these may be the same or different.

The term "heterocyclic ring" as used herein refers to a saturated or partially unsaturated, 4- to 6-membered (preferably 5- or 6-membered) carbocyclic system in which at least one ring atom is a heteroatom selected from nitrogen, oxygen and sulfur, the remaining ring atoms being carbon. The heterocyclic ring structure may be linked to the remainder of the molecule through a carbon atom or through a nitrogen atom. Examples of heterocyclic rings include, but are not limited to, tetrahydrofuran, piperidine, pyrrolidine, dioxane, morpholine, etc. Unless otherwise stated, any heterocyclic ring mentioned herein may optionally be substituted by one or more groups, which may be identical or different, for example hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, cyano, or nitro groups, or halogen atoms (e.g. F, Cl or Br).

Unless otherwise stated, all substituents are independent of one another.

In the case where a subscript is the integer 0 (i.e. zero), it is intended that the group to which the subscript refers is absent.

The compounds herein described may contain one or more stereocenters and may therefore exist in different stereoisomeric forms. The term "stereoisomer" refers to compounds which have identical chemical constitution but which differ in respect of the spatial arrangement of the atoms or groups. Examples of stereoisomers are enantiomers and diastereomers. The term "enantiomers" refers to two stereoisomers of a compound which are non-superimposable mirror images of one another. The term "diastereoisomers" refers to stereoisomers with two or more stereocenters which are not mirror images of one another. The invention is considered to extend to diastereomers and enantiomers, as well as racemic mixtures and enantioenriched mixtures in which the ratio of enantiomers is other than 1:1.

The compounds herein described may be resolved into their enantiomers and/or diastereomers. For example, where these contain only one chiral center, these may be provided in the form of a racemate or racemic mixture (a 50:50 mixture of

enantiomers) or may be provided as pure enantiomers, i.e. in the R- or S-form. Any of the compounds which occur as racemates may be separated into their enantiomers by methods known in the art, such as column separation on chiral phases or by recrystallization from an optically active solvent. Those compounds with at least two asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallization, and where these compounds are obtained in racemic form, they may subsequently be resolved into their enantiomers.

The term "pharmaceutically acceptable salt" as used herein refers to any pharmaceutically acceptable organic or inorganic salt of any of the compounds herein described. A pharmaceutically acceptable salt may include one or more additional molecules such as counter-ions. The counter-ions may be any organic or inorganic group which stabilises the charge on the parent compound. If the compound is a base, a suitable pharmaceutically acceptable salt may be prepared by reaction of the free base with an organic or inorganic acid. If the compound is an acid, a suitable pharmaceutically acceptable salt may be prepared by reaction of the free acid with an organic or inorganic base. Non-limiting examples of suitable salts are described herein.

The term "pharmaceutically acceptable" means that the compound or composition is chemically and/or toxicologically compatible with other components of the formulation or with the patient to be treated.

By "a pharmaceutical composition" is meant a composition in any form suitable to be used for a medical purpose.

As used herein, the term "cancer" refers to cells undergoing abnormal proliferation. Growth of such cells typically causes the formation of a tumor. Cancerous cells may be benign, pre-malignant or malignant. Such cells may be invasive and/or have the ability to metastasize to other locations in the body. The term cancer, as used herein, includes cancerous growths, tumours, and their metastases. The term "tumour", as used herein, refers to an abnormal mass of tissue containing cancerous cells.

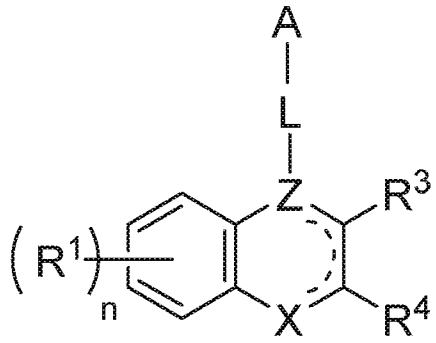
As used herein, the term "metastasis" refers to the spread of malignant tumour cells from one organ or part of the body to another non-adjacent organ or part of the body. Cancer cells may break away from a primary tumour, enter the lymphatic and blood systems and circulate to other parts of the body (e.g. to normal tissues). Here they may settle and grow within the normal tissues. When tumour cells metastasize, the new tumours may be referred to as a "secondary" or metastatic cancer or tumour.

As used herein, "treatment" includes any therapeutic application that can benefit a human or non-human animal (e.g. a non-human mammal). Both human and veterinary treatments are within the scope of the present invention, although primarily the invention is aimed at the treatment of humans. Where not explicitly stated, treatment encompasses prevention.

As used herein, a "pharmaceutically effective amount" relates to an amount that will lead to the desired pharmacological and/or therapeutic effect, i.e. an amount of the agent which is effective to achieve its intended purpose. While individual subject (e.g. patient) needs may vary, determination of optimal ranges for effective amounts of the active agent(s) herein described is within the capability of one skilled in the art. Generally, the dosage regimen for treating a disease, condition or disorder with any of the compounds described herein may be selected by those skilled in the art in accordance with a variety of factors including the nature of the condition and its severity.

The term "subject" refers to any individual who is the target of the administration or treatment. The subject may be, for example, a mammal. Thus the subject may be a human or non-human animal. The term "patient" refers to a subject under the treatment of a clinician. Preferably, the subject will be a human.

In one aspect, the invention relates to a compound of formula (I), a stereoisomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer:



(I)

wherein:

X is CH, S, N or NH;

Z is C or N;

A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 is independently selected from:

- C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),
- C_{2-6} alkenyl (preferably C_{2-4} alkenyl),
- C_{2-6} alkynyl (preferably C_{2-4} alkynyl),
- C_{1-6} haloalkyl (e.g. $-CF_3$),
- $-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),
- $-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),
- -OH,
- -SH,
- halogen (e.g. F, Cl or Br), and
- an optionally substituted aryl group (e.g. optionally substituted phenyl);

n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2;

R^3 and R^4 are each independently selected from:

- hydrogen,
- C_{2-6} alkenyl (preferably C_{2-4} alkenyl), and
- C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

or

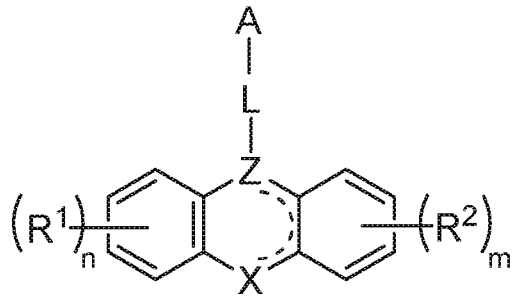
R^3 and R^4, together with the intervening ring carbon atoms, form an optionally substituted aryl ring (e.g. an optionally substituted phenyl ring); and

 represents an optional bond between two adjacent carbon atoms in the ring.

In certain embodiments, the compounds for use according to the invention are those of formula (I) in which R^3 and R^4 are both hydrogen.

In certain embodiments, the compounds for use according to the invention are those of formula (I) in which R^3 and R^4, together with the intervening ring carbon atoms, form an optionally substituted aryl group. In one embodiment, the aryl group which is formed can be an optionally substituted phenyl ring.

Thus, in certain embodiments, the compounds for use according to the invention are those of formula (Ia), their stereoisomers, or pharmaceutically acceptable salts thereof:



(Ia)

wherein X, Z, A, L, R^1 and n are as herein defined;

 represents an optional bond between two adjacent carbon atoms in the ring;

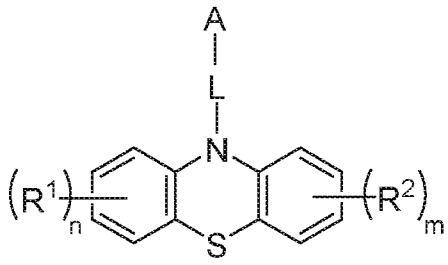
R^2 is selected from any of the groups defined herein for R^1; and

m is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2.

In one embodiment, the compounds for use according to the invention are those of formula (I) or (Ia) in which X is CH or S, preferably S.

In one embodiment, the compounds for use according to the invention are those of formula (I) or (Ia) in which X is S and Z is N.

In certain embodiments, the compounds for use according to the invention are based on a phenothiazine scaffold. Such compounds are those of formula (Ib), their stereoisomers, or pharmaceutically acceptable salts thereof:

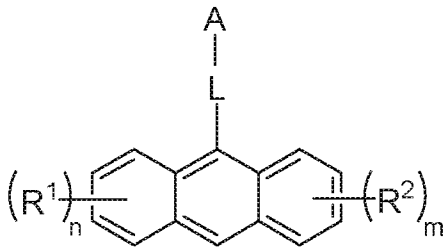


(Ib)

wherein A, L, R^1, R^2, n and m are as herein defined.

In one embodiment, the compounds for use according to the invention are those of formula (I) or (Ia) in which X is CH and Z is C.

In certain embodiments, the compounds for use according to the invention are based on an anthracene scaffold. Such compounds are those of formula (Ic), their stereoisomers, and pharmaceutically acceptable salts thereof:



(Ic)

wherein A, L, R^1, R^2, n and m are as herein defined.

In any of the formulae herein defined, group A may be an optionally substituted amine. For example, group A may be a group of the formula $-NR^aR^b$ wherein R^a and R^b are independently selected from H, optionally substituted $C_{1\text{-}6}$ alkyl, and optionally substituted aryl. Examples of such groups include, but are not limited to, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-N(CH_3)(C_2H_5)$, and $-N(C_2H_5)_2$.

Alternatively, in any of the formulae herein defined, group A may be an optionally substituted carbocyclic or heterocyclic ring system. Such ring systems may

comprise from 3 to 14 ring atoms, preferably from 5 to 12 ring atoms, e.g. from 6 to 14 ring atoms. In one embodiment, group A is an optionally substituted carbocyclic ring system.

In certain embodiments, group A may be an optionally substituted cycloalkyl or cycloalkenyl group. Such groups may be mono-, bi- or tricyclic. Where more than one ring is present, these may be bridged or fused.

In one embodiment, A is a cycloalkyl group containing two or three rings which are fused or bridged.

In one embodiment, A is an optionally substituted aryl group. For example, it may be an optionally substituted phenyl ring.

In one embodiment, A is an optionally substituted heterocyclic group. Such groups may be mono-, bi- or poly-cyclic. Where more than one ring is present, these may be bridged or fused. Such groups may be saturated or unsaturated. Where these are saturated, they may be heteroaromatic.

Non-limiting examples of group A include adamantyl, phenyl, quinuclidinyl (1-azabicyclo[2.2.2]octanyl), DABCO (1,4-diazabicyclo[2.2.2]octanyl), tropanyl (*N*-methyl-8-azabicyclo[3.2.1]octanyl), nortropanyl (8-azabicyclo[3.2.1]octanyl), norbornyl, norbornenyl, norbornadienyl, bornyl, pyrrolyl, pyrrolidinyl, piperidinyl, pyridinyl, morpholinyl, azepanyl (azacycloheptanyl), decahydroquinolyl, azonanyl, octahydrocyclopenta[c]pyrrolyl, azecanyl, octahydropyrrolo[3,4-*c*]pyrrolyl, indolyl, 4-t-butylpiperidinyl and azocanyl groups.

In a preferred embodiment, group A is selected from substituted or unsubstituted adamantyl, phenyl, quinuclidinyl, piperidinyl and azepanyl. In another embodiment, group A is substituted or unsubstituted adamantyl or piperidinyl, preferably substituted or unsubstituted adamantyl. In one embodiment, group A is unsubstituted adamantyl.

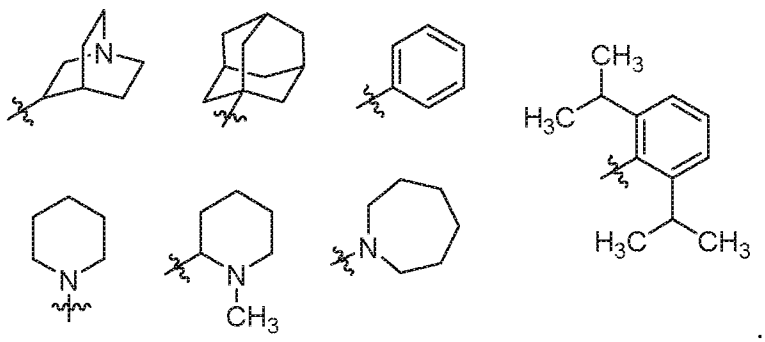
Group A may be bonded to group L either through a ring carbon or ring nitrogen atom. In one embodiment, group A is bonded to the group L via a ring carbon atom.

Group A may be substituted or unsubstituted. Where it is substituted, one or more substituent groups (e.g. 1, 2, or 3 substituent groups) may be present on the ring. Each substituent may, independently of one another, be linked either to a ring carbon atom or to a ring nitrogen atom.

In one embodiment, group A is substituted by one or more groups independently selected from -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br). Preferred substituents include, but are not limited to, methyl, ethyl, n-propyl and isopropyl groups.

In one embodiment, group A is not substituted at any ring carbon atom. Where it is substituted, it is preferably substituted at a ring nitrogen. In another embodiment, group A is not substituted at any point on the ring, i.e. it is unsubstituted. The presence of a hydrogen atom on a ring nitrogen atom is not considered to be a "substituent".

Preferred examples of group A include the following (where ~~~~ denotes the point of attachment to the rest of the molecule):



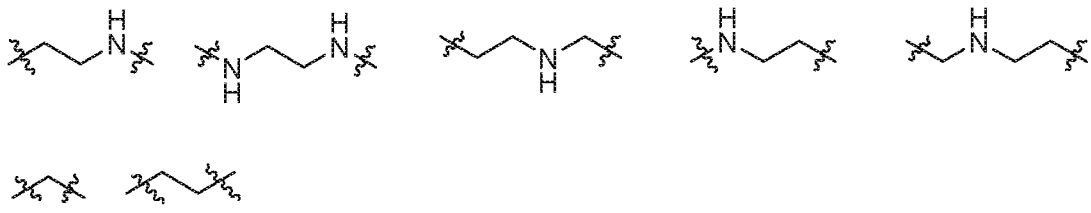
Linking group L serves to link the group A to the remainder of the molecule. Group L may be an optionally substituted, straight-chained or branched C_{1-6} alkylene group. In one embodiment, L is an optionally substituted, straight-chained or branched C_{1-3} alkylene group.

In one embodiment, linking group L is an unsubstituted, straight-chained C_{1-6} alkylene group, preferably an unsubstituted, straight-chained C_{1-3} alkylene group, such as methylene or ethylene.

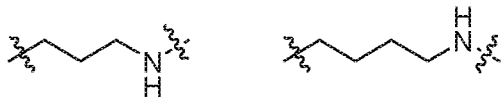
In another embodiment, L may be an optionally substituted C_{1-6} alkylene group, preferably C_{2-6} alkylene group, in which one or more $-CH_2-$ groups of the alkylene chain are replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl). For example, L may be an optionally substituted C_{2-6} alkylene, C_{3-6} alkylene or C_{4-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain are replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl). In one embodiment, the alkylene chain is straight-chained. In one embodiment, group L may be propylene or butylene in which one or two of the $-CH_2-$ groups are replaced by a group -NR'-, preferably by a group -NH- or $-N(CH_3)-$. In another embodiment, group L may be pentylene in which one or two of the $-CH_2-$ groups are replaced by a group -NR'-, preferably by a group -NH- or $-N(CH_3)-$.

In one embodiment, one or more $-CH_2-$ groups of the alkylene chain in group L are replaced by a group -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl). In one embodiment, one or two $-CH_2-$ groups of the alkylene chain are replaced by such a group.

Non-limiting examples of linking group L include the following (where ~~~ denotes the point of attachment to the rest of the molecule):



Other examples of linking group L include the following (where ~~~ denotes the point of attachment to the rest of the molecule):



Where present, substituent groups R^1 and R^2 may be the same or different.

In one embodiment, each R^1 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),

-OH,

-SH,

halogen (e.g. F, Cl or Br), and

an optionally substituted aryl group (e.g. optionally substituted phenyl).

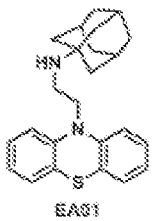
In one embodiment, each R^1 is independently selected from C_{1-3} alkyl (e.g. $-CH_3$), $-CF_3$, $-O-C_{1-3}$ alkyl (e.g. $-OCH_3$ or $-OCH_2CH_3$), $-S-C_{1-3}$ alkyl (e.g. $-SCH_3$ or $-SCH_2CH_3$), F, Cl, Br and phenyl. In a preferred embodiment each R^1 is independently selected from $-CH_3$, $-CF_3$, $-OCH_3$, $-SCH_3$, and $-SCH_2CH_3$.

In one embodiment, n is selected from 0, 1 or 2, preferably 0 or 1.

In one embodiment each R^2, where present, is independently selected from C_{1-3} alkyl (e.g. $-CH_3$), $-CF_3$, $-O-C_{1-3}$ alkyl (e.g. $-OCH_3$ or $-OCH_2CH_3$), $-S-C_{1-3}$ alkyl (e.g. $-SCH_3$ or $-SCH_2CH_3$), F, Cl, Br and phenyl. In a preferred embodiment each R^2 is independently selected from $-CH_3$, $-CF_3$, $-OCH_3$, $-SCH_3$, and $-SCH_2CH_3$.

In one embodiment, m is selected from 0, 1 or 2, preferably 0 or 1.

Examples of compounds for use in accordance with the invention include, but are not limited to, the following, their stereoisomers, and their pharmaceutically acceptable salts: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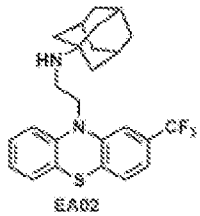
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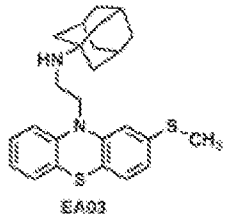
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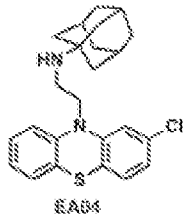
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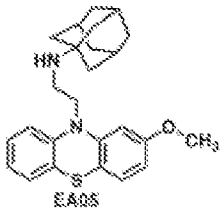
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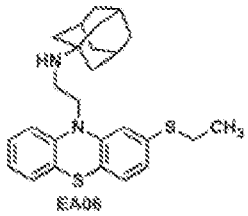
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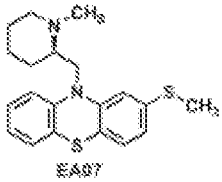
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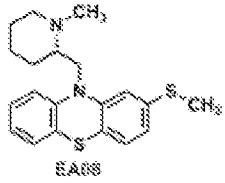
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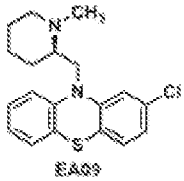
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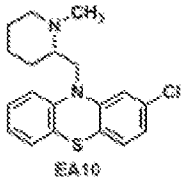
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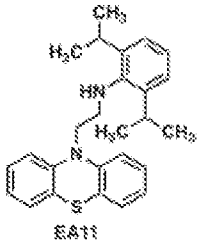
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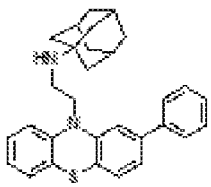
EA12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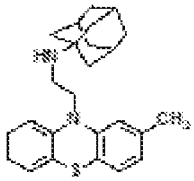
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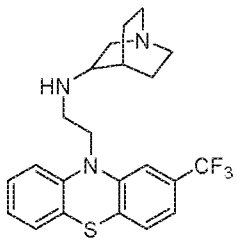
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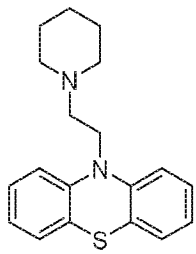
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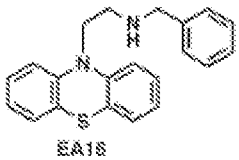
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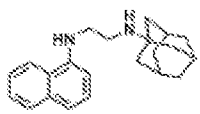
EA18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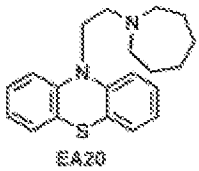
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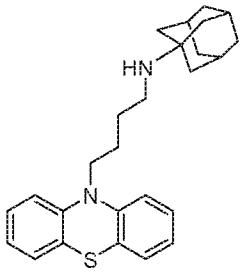
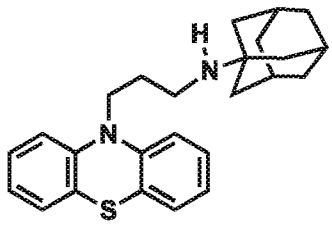


EA22



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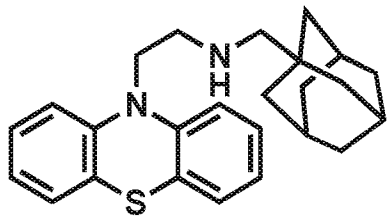
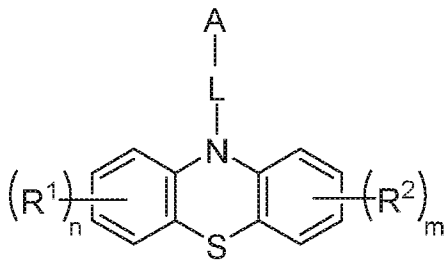


EA24

Certain compounds described herein are novel and these form a further aspect of the invention. Thus, in another aspect, the present invention provides compounds of formula (II), their stereoisomers and their pharmaceutically acceptable salts:



(II)

wherein:

A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 and R^2 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{2-6} alkenyl (preferably C_{2-4} alkenyl),

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),

-OH,

-SH,

halogen (e.g. F, Cl or Br), and

an optionally substituted aryl group (e.g. optionally substituted phenyl);
n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2; and
m is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2;
with the proviso that the compound is other than thioridazine.

In one embodiment, the compound of formula (II) is other than 10-((1-methylpiperidin-2-yl)methyl)-2-(methylthio)-10*H*-phenothiazine or 10-(2-(piperidin-1-yl)ethyl)-10*H*-phenothiazine.

Where appropriate, any of the definitions for A, L, R^1, R^2, n and m listed herein in respect of the compounds of formulae (I), (Ia), (Ib) and (Ic) similarly apply to the compounds of formula (II).

In one embodiment, the invention provides compounds of formula (II), their stereoisomers and their pharmaceutically acceptable salts, in which A is an optionally substituted carbocyclic ring system. In one embodiment of formula (II), A is an optionally substituted cycloalkyl group, for example an optionally substituted cycloalkyl group containing two or three rings which are fused or bridged. In a particular embodiment of formula (II), A is substituted or unsubstituted adamantyl, for example unsubstituted adamantyl.

In a further aspect, the invention relates to a compound of formula (II), a stereoisomer, or a pharmaceutically acceptable salt thereof, for use in therapy or for use as a medicament.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of formula (II), a stereoisomer, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Any of the compounds herein described may be converted into a salt thereof, particularly into a pharmaceutically acceptable salt thereof with an inorganic or organic acid or base. Acids which may be used for this purpose include hydrochloric acid, hydrobromic acid, sulfuric acid, sulfonic acid, methane sulfonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric

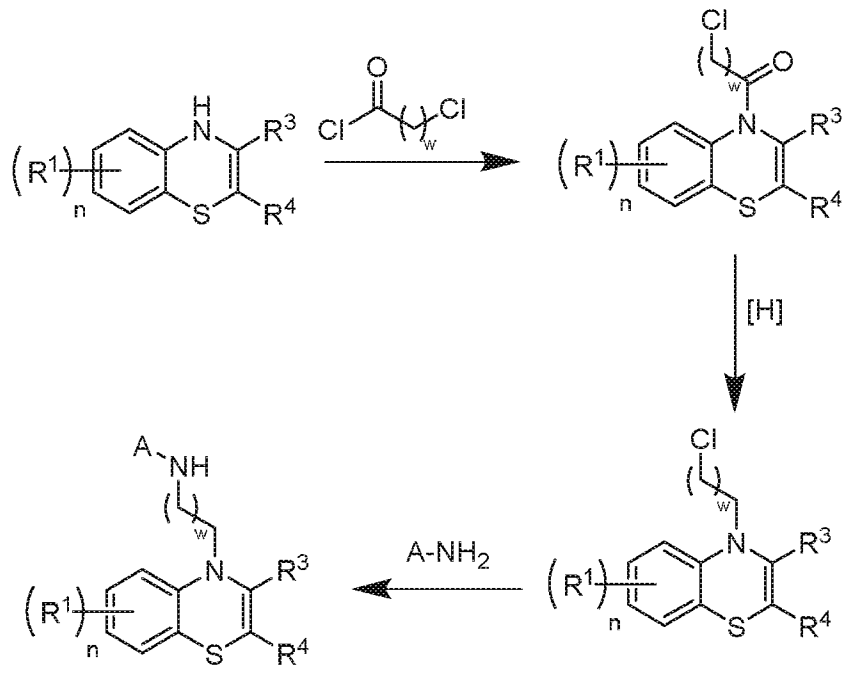
acid, maleic acid, acetic acid, trifluoroacetic acid and ascorbic acid. Bases which may be suitable for this purpose include alkali and alkaline earth metal hydroxides, e.g. sodium hydroxide, potassium hydroxide or cesium hydroxide, ammonia and organic amines such as diethylamine, triethylamine, ethanolamine, diethanolamine, cyclohexylamine and dicyclohexylamine. Procedures for salt formation are conventional in the art.

As will be understood, the compounds described herein may exist in various stereoisomeric forms, including enantiomers, diastereomers, and mixtures thereof. The invention encompasses all optical isomers of the compounds described herein and mixtures of optical isomers. Hence, compounds that exist as diastereomers, racemates and/or enantiomers are within the scope of the invention.

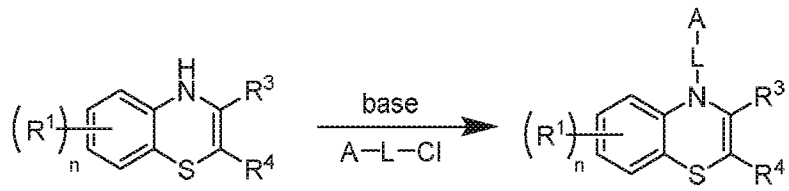
The compounds for use in the invention are either known in the art, or can be prepared by methods known to those skilled in the art using readily available starting materials. Some of the compounds for use in the invention may be commercially available.

Compounds herein described which are not known in the art may be prepared from readily available starting materials using synthetic methods known in the art such as those described in known textbooks, for example, in Advanced Organic Chemistry (March, Wiley Interscience, 5th Ed. 2001) or Advanced Organic Chemistry (Carey and Sundberg, KA/PP, 4th Ed. 2001).

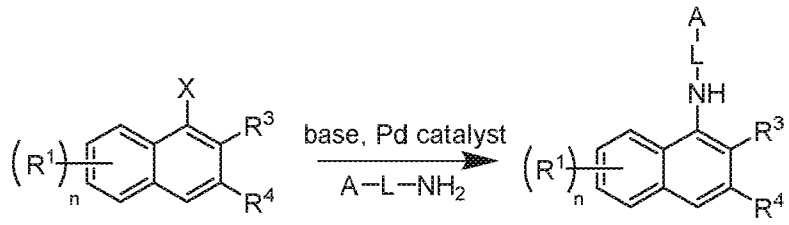
The following schemes illustrate general methods for preparing some of the compounds herein described. The compounds used as starting materials are either known from the literature or may be commercially available. As will be understood, other synthetic routes may be used to prepare the compounds using different starting materials, different reagents and/or different reaction conditions.



wherein R^1, R^2, A and n are as herein defined, and w is an integer from 0-5.



wherein R^1, R^2, R^3, R^4, A, L and n are as herein defined.



wherein R^1, R^2, R^3, R^4, A, L and n are as herein defined; and

X is a halogen atom.

Cancers which may be treated in accordance with the invention include, but are not limited to, any of the following: leukemias, lymphomas, colon cancer (e.g. colorectal cancer), breast cancer, glioblastoma, pancreatic cancer, bladder cancer, lung cancer and skin cancer. Metastatic disease arising from any of these tumours may also be treated using any of the compounds herein described. However, the invention finds particular use in the treatment of deep lying cancerous lesions that are difficult to access non-invasively. Treatment of gliomas (e.g. GMB) forms a preferred aspect of the invention.

The compounds described herein find use in the treatment of glioblastoma in a subject or patient and, in particular, in the treatment or prevention of astrocytomas, oligodendrogliomas or ependymomas. In a particular embodiment, the compounds described herein can be used in the treatment of astrocytomas, such as pliocytic astrocytoma, diffuse or low grade astrocytoma, anaplastic astrocytoma or grade 4 astrocytoma.

The compounds described herein also find particular use in the treatment of skin cancers, for example in the treatment of basal cell carcinoma, squamous cell carcinoma, and melanoma.

As used herein, a “subject” or “patient” encompasses any animal, preferably a mammal. Examples of mammalian subjects include, without limitation, humans, dogs, cats, rodents (e.g. mouse, rat, guinea pig, etc.), horses, cattle, sheep, and pigs. Preferably, the subject is a human.

In one embodiment, the compounds of the invention are suitable for preventing and/or retarding cancer cell proliferation, differentiation and/or survival, or for preventing and/or retarding metastasis of cancer cells. As used herein, the term "proliferation" refers to cells undergoing mitosis. The term "retarding proliferation" indicates that the compounds inhibit proliferation of a cancer cell. In preferred embodiments, "retarding proliferation" indicates that DNA replication is at least 10% less than that observed in untreated cells, more preferably at least 25% less, yet more preferably at least 50% less, e.g. 75%, 90% or 95% less than that observed in untreated cancer cells.

For use in a therapeutic treatment, the compounds herein described will typically be formulated as a pharmaceutical formulation together with one or more pharmaceutically acceptable carriers, excipients or diluents. Acceptable carriers, excipients and diluents for therapeutic use are well known in the art and can be selected with regard to the intended route of administration and standard pharmaceutical practice. Examples include binders, lubricants, suspending agents, coating agents, solubilizing agents, preserving agents, wetting agents, emulsifiers, surfactants, sweeteners, colorants, flavouring agents, antioxidants, odorants, buffers, stabilizing agents and/or salts.

The compounds for use according to the invention may be formulated with one or more conventional carriers and/or excipients according to techniques well known in the art. Typically, the compositions will be adapted for oral or parenteral administration, for example by intradermal, subcutaneous, intraperitoneal, or intravenous injection. For example, these may be formulated in conventional oral administration forms, e.g. tablets, coated tablets, caplets, capsules, powders, granulates, solutions, dispersions, suspensions, syrups, emulsions, etc. using conventional excipients, e.g. solvents, diluents, binders, sweeteners, aromas, pH modifiers, viscosity modifiers, antioxidants, etc. Suitable excipients can readily be determined by those skilled in the art. The formulations may be prepared using conventional techniques, such as dissolution and/or mixing procedures.

Where parenteral administration is employed this may, for example, be by means of intravenous, subcutaneous, intraperitoneal or intramuscular injection. For this purpose, sterile solutions containing the active agent may be employed, such as an oil-in-water emulsion. Where water is present, an appropriate buffer system (e.g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions.

The use of orally administrable compositions, e.g. tablets, coated tablets, capsules, syrups, etc. is preferred. Compounds having a partition coefficient, Log P, greater than or equal to 3 and less than or equal to 5 are particularly suitable for oral administration due to their ability to cross the blood brain barrier.

Alternatively, any pharmaceutical formulation may be administered locally (e.g. by injection or topically) at or near the affected site. Topical pharmaceutical formulations include gels, creams, ointments, sprays, lotions, salves, sticks, powders, solutions and any of the other conventional pharmaceutical forms in the art. Ointments, gels and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Any thickening or gelling agents used should be non-toxic and non-irritant. Lotions may be formulated with an aqueous or oily base and will, in general, also contain one or more emulsifying, dispersing, suspending, thickening or colouring agents. Powders may be formed with the aid of any suitable powder base. Sprays and solutions may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing, solubilising or suspending agents.

The formulations herein described may be prepared using conventional techniques, such as dissolution and/or mixing procedures, tableting, etc.

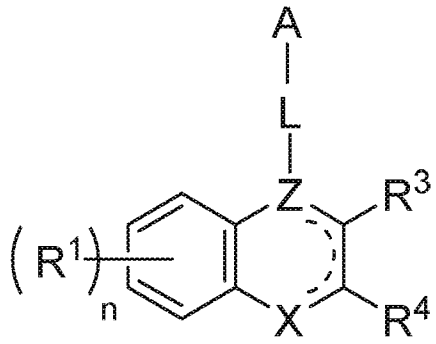
The dosage required to achieve the desired activity of the compounds herein described will depend on various factors, such as the compound selected, its mode and frequency of administration, whether the treatment is therapeutic or prophylactic, and the nature and severity of the disease or condition, etc. Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon factors such as the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age of the patient, the mode and time of administration, and the severity of the particular condition. The compound and/or the pharmaceutical composition may be administered in accordance with a regimen from 1 to 10 times per day, such as once or twice per day. For oral and parenteral administration to human patients, the daily dosage level of the agent may be in single or divided doses.

Suitable daily dosages of the compounds herein described may readily be determined by those skilled in the art, but are expected to be in the range from 0.1 mg to 1 g of the compound; 1 mg to 500 mg of the compound; 1 mg to 300 mg of

the compound; 5 mg to 100 mg of the compound, or 10 mg to 50 mg of the compound. By a "daily dosage" is meant the dosage per 24 hours.

Embodiments of the invention include, but are not limited to, the following:

Embodiment 1: A compound of formula (I), a stereoisomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer:



(I)

wherein:

X is CH, S, N or NH;

Z is C or N;

A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{2-6} alkenyl (preferably C_{2-4} alkenyl),

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),

-OH,

-SH,

halogen (e.g. F, Cl or Br), and

an optionally substituted aryl group (e.g. optionally substituted phenyl);

n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2;

R^3 and R^4 are each independently selected from:

hydrogen

C_{2-6} alkenyl (preferably C_{2-4} alkenyl), and

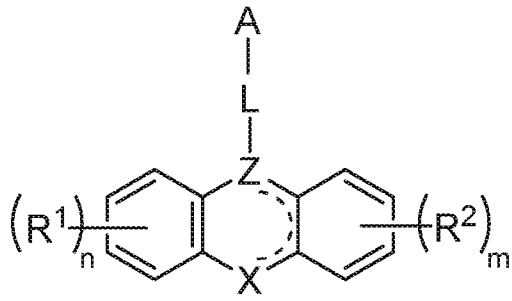
C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

or R^3 and R^4, together with the intervening ring carbon atoms, form an optionally substituted aryl ring (e.g. an optionally substituted phenyl ring); and

 represents an optional bond between two adjacent carbon atoms in the ring.

Embodiment 2: A compound for use as described in embodiment 1, wherein R^3 and R^4, together with the intervening ring carbon atoms, form an optionally substituted aryl group.

Embodiment 3: A compound for use as described in embodiment 1 or embodiment 2 which is a compound of formula (Ia), a stereoisomer, or a pharmaceutically acceptable salt thereof:



(Ia)

wherein X, Z, A, L, R^1 and n are as defined in embodiment 1;

 represents an optional bond between two adjacent carbon atoms in the ring;

each R^2 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{2-6} alkenyl (preferably C_{2-4} alkenyl),

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),

-OH,

-SH,

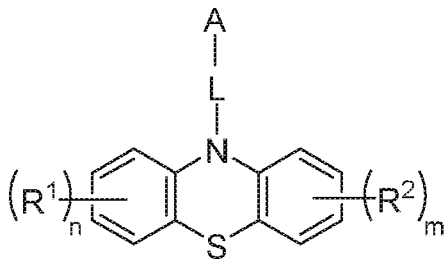
halogen (e.g. F, Cl or Br), and

an optionally substituted aryl group (e.g. optionally substituted phenyl); and

m is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2.

Embodiment 4: A compound for use as described in any one of embodiments 1 to 3, wherein X is CH or S, preferably S.

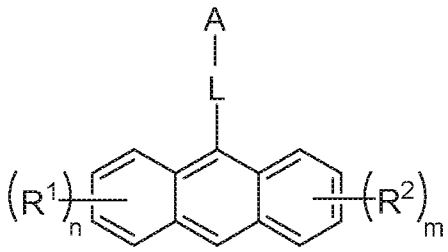
Embodiment 5: A compound for use as described in embodiment 4 which is a compound of formula (Ib), a stereoisomer, or a pharmaceutically acceptable salt thereof:



(Ib)

wherein A, L, R^1 and n are as defined in embodiment 1; and
R^2 and m are as defined in embodiment 3.

Embodiment 6: A compound for use as described in any one of embodiments 1 to 3 which is a compound of formula (Ic), a stereoisomer, or a pharmaceutically acceptable salt thereof:



(Ic)

wherein A, L, R^1 and n are as defined in embodiment 1; and
R^2 and m are as defined in embodiment 3.

Embodiment 7: A compound for use as described in any one of embodiments 1 to 6, wherein A is an optionally substituted carbocyclic or heterocyclic ring system.

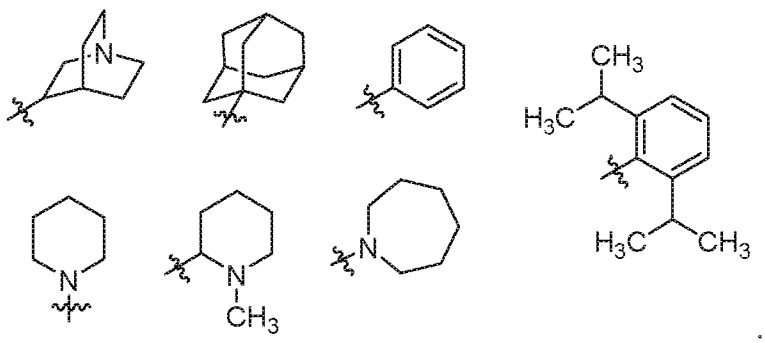
Embodiment 8: A compound for use as described in embodiment 7, wherein A is an optionally substituted cycloalkyl or cycloalkenyl group, preferably an optionally substituted cycloalkyl group containing two or three rings which are fused or bridged.

Embodiment 9: A compound for use as described in embodiment 7, wherein A is an optionally substituted heterocyclic group.

Embodiment 10: A compound for use as described in embodiment 8 or embodiment 9, wherein A is selected from substituted or unsubstituted adamantyl, phenyl, quinuclidinyl, piperidinyl and azepanyl.

Embodiment 11: A compound for use as described in any one of embodiments 1 to 10, wherein A is substituted by one or more groups independently selected from -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

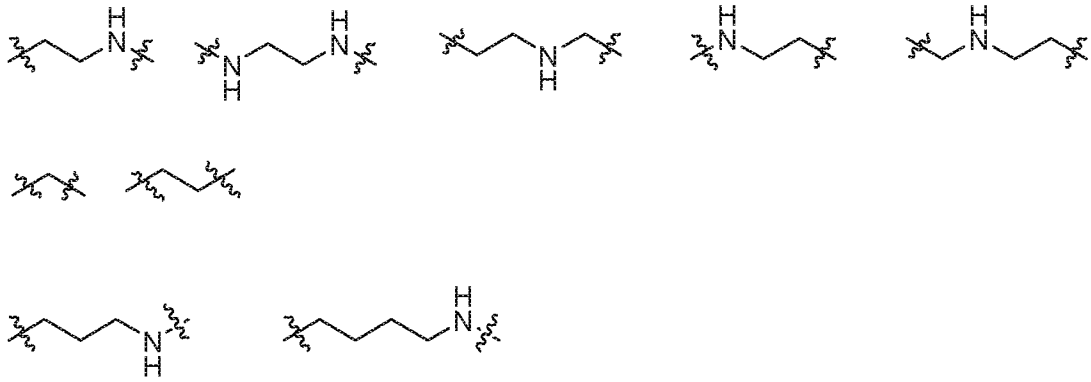
Embodiment 12: A compound for use as described in any one of embodiments 1 to 11, wherein A is selected from the following:



Embodiment 13: A compound for use as described in any one of embodiments 1 to 12, wherein L is an optionally substituted, straight-chained or branched C_{1-6} alkylene group.

Embodiment 14: A compound for use as described in any one of embodiments 1 to 12, wherein L is an optionally substituted C_{1-6} alkylene group, preferably C_{2-6} alkylene group, in which one or more $-CH_2-$ groups of the alkylene chain are replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl).

Embodiment 15: A compound for use as described in any one of embodiments 1 to 14, wherein L is selected from the following:



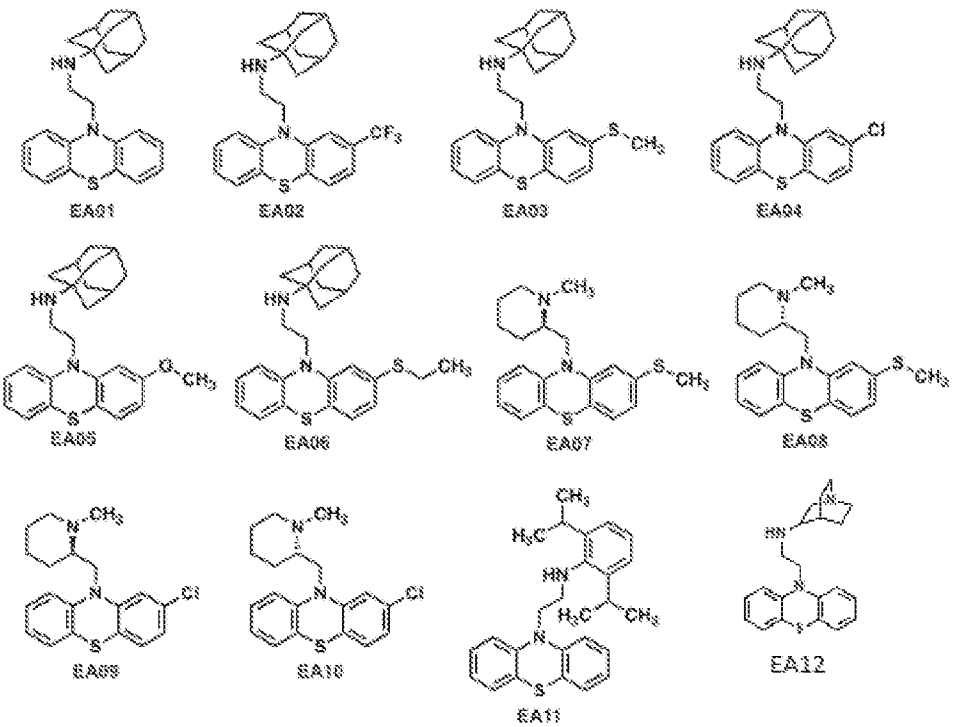
Embodiment 16: A compound for use as described in any one of embodiments 1 to 15, wherein each R^1 is independently selected from C_{1-3} alkyl (e.g. $-CH_3$), $-CF_3$, -O-C_{1-3} alkyl (e.g. $-OCH_3$ or $-OCH_2CH_3$), -S-C_{1-3} alkyl (e.g. $-SCH_3$ or $-SCH_2CH_3$), F, Cl, Br and phenyl.

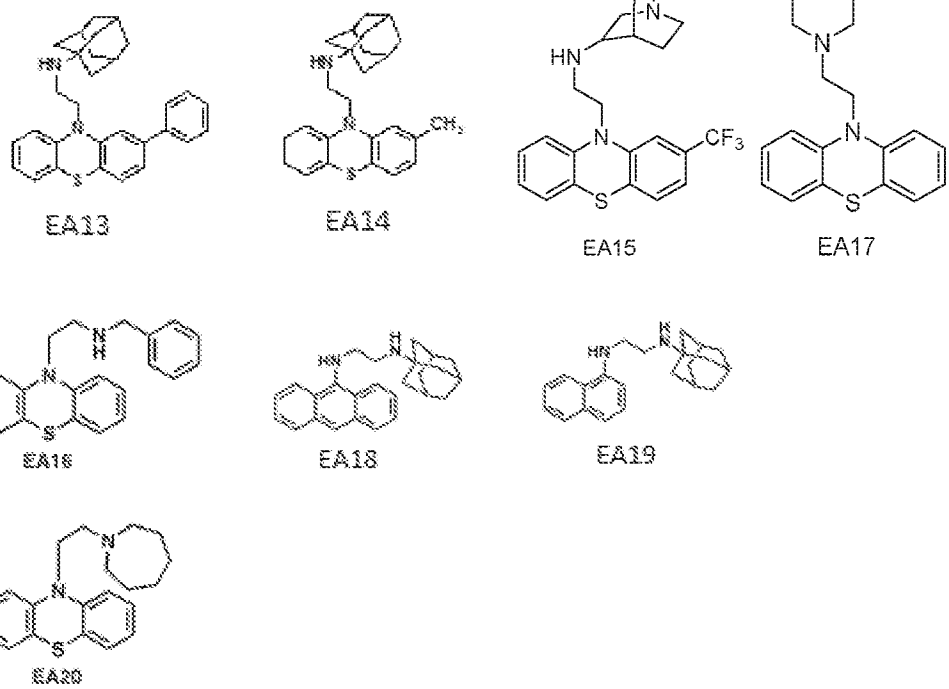
Embodiment 17: A compound for use as described in any one of embodiments 1 to 16, wherein n is 0, 1 or 2, preferably 0 or 1.

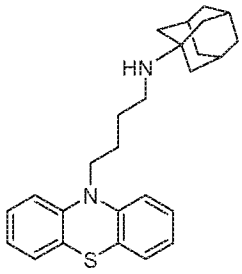
Embodiment 18: A compound for use as described in any one of embodiments 3 to 17, wherein each R^2 is independently selected from C_{1-3} alkyl (e.g. $-CH_3$), $-CF_3$, -O-C_{1-3} alkyl (e.g. $-OCH_3$ or $-OCH_2CH_3$), -S-C_{1-3} alkyl (e.g. $-SCH_3$ or $-SCH_2CH_3$), F, Cl, Br and phenyl.

Embodiment 19: A compound for use as described in any one of embodiments 3 to 18, wherein m is 0, 1 or 2, preferably 0 or 1.

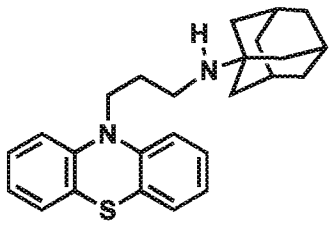
Embodiment 20: A compound for use as described in embodiment 1 which is selected from the following compounds, their stereoisomers, and their pharmaceutically acceptable salts:



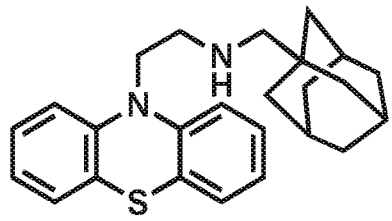




EA22



EA23



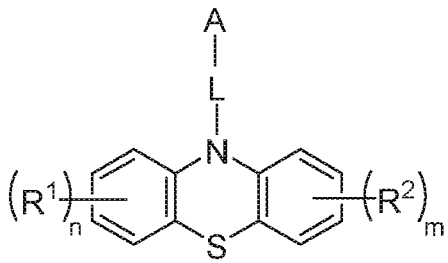
EA24

Embodiment 21: A compound for use as described in any one of embodiments 1 to 20, wherein said cancer is selected from the group consisting of: leukemias, lymphomas, colon cancer, breast cancer, glioblastoma, pancreatic cancer, bladder cancer, lung cancer and skin cancer.

Embodiment 22: A compound for use as described in embodiment 21 in the treatment of glioblastoma, preferably in the treatment of an astrocytoma, oligodendroglioma or ependymoma.

Embodiment 23: A compound for use as described in embodiment 21 in the treatment of basal cell carcinoma, squamous cell carcinoma, or melanoma.

Embodiment 24: A compound of formula II, a stereoisomer or a pharmaceutically acceptable salt thereof:



(II)

wherein:

A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 and R^2 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{2-6} alkenyl (preferably C_{2-4} alkenyl),

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),

-OH,

-SH,

halogen (e.g. F, Cl or Br), and

an optionally substituted aryl group (e.g. optionally substituted phenyl);

n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2; and

m is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2;

with the proviso that the compound is other than thioridazine.

Embodiment 25: A pharmaceutical composition comprising a compound of formula (II), a stereoisomer, or a pharmaceutically acceptable salt thereof as described in embodiment 24, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

The invention will now be described in more detail in the following non-limiting Examples and with reference to the accompanying figures:

Figure 1: Monitoring cell growth and morphology during treatment with 4 µM Compound EA01 after treatment for 72 h. (A) Left: Normal Human Astrocytes (NHA) (DMEM alt), right: NHA with 4 µM Compound EA01. (B) Left: U87-MG Control (DMEM alt), right: U87-MG with 4 µM Compound EA01. (C) Left: U251 Control (DMEM alt), right: U251 with 4 µM Compound EA01.

Figure 2: IncuCyte Zoom Analysis of U87-MG, p44-46, n=3 for various treatment conditions of Compounds EA01 and EA02 with and without combination with temozolomide (TMZ), normalized to the confluency [%] to time point 0 h. (A) Monitored change fold of confluency (confluency of each time point normalised to the confluency of t=0 h) for U87-MG, p44-46 over 72 h. Shown are means of the measured confluency [%]. (B) 72 h values of change fold confluency. Statistical

analysis was carried out using Dunnett's multiple comparisons test (Ordinary One-Way ANOVA, parametric): Significant results are indicated by asterisks: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Whiskers indicate SEM.

Figure 3: Cell viability assessed via WST1-assay of two generations of FRBO treated with Compounds EA01 and EA02 for 72 h (n=2). (A) Cell viability curve for FRBO treated with Compound EA01. (B) Cell viability curve for FRBO treated with Compound EA01.

Figure 4: Treatment of tumor spheroids and fetal rat brain organoids (FRBO) with Compounds EA01 and EA02. (A) Co-culture pf P3-GFP tumor spheroids with FRBO after 72 h-treatment with indicated concentrations of Compounds EA01 and EA02. (B) Co-culture pf BG5-GFP tumor spheroids with FRBO after 72 h-treatment with indicated concentrations of Compounds EA01 and EA02.

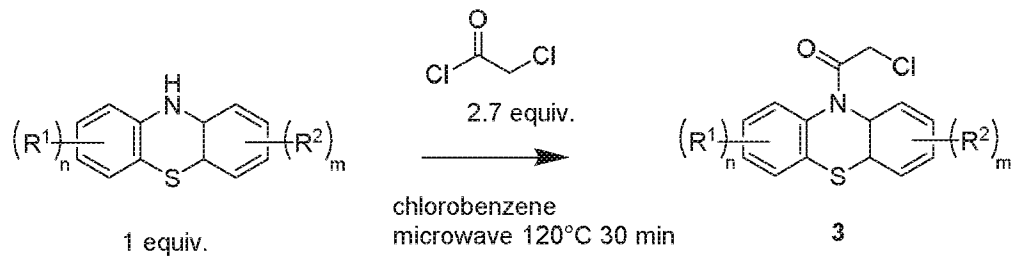
Figure 5: Initial testing of survivability of different cell lines after treatment with 4 µM Compounds EA01 and EA02 versus control (0.1 % DMSO) using the clonogenic assay. (n=1).

Examples

General procedure for synthesis of phenothiazine derivatives:

The synthesis of the various phenothiazine derivatives was conducted by means of a three-step synthetic pathway. In the following reaction schemes, A, R^1, R^2, n and m are as herein defined.

Step 1 – method A:



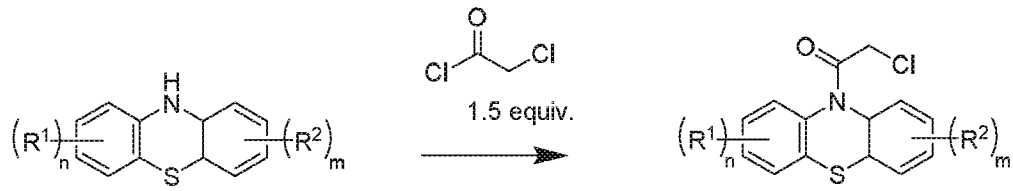
1 equiv.

1

3

The 10*H*-phenothiazine derivative (1 eq.) **1** was treated with chloroacetyl chloride (2.7 eq.) **2** under microwave irradiation. When the microwave reaction was finished, water was added and the mixture was extracted with ethyl acetate, the extracts were combined and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The compound **3** was purified by recrystallization in methanol.

Step 1 – method B:



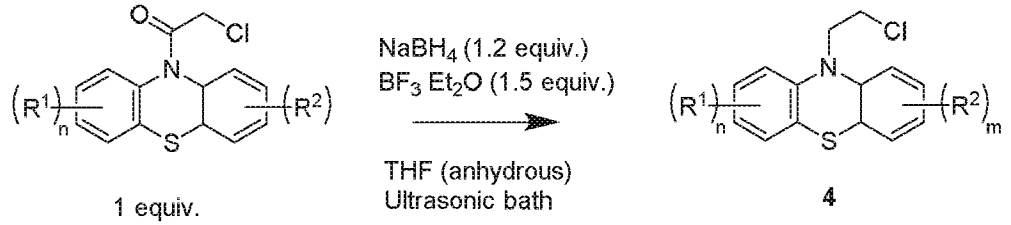
1 equiv.

1

3

The 10*H*-phenothiazine derivative (1 eq.) **1** and toluene were added to a round bottle flask equipped with a magnetic stirring bar. The mixture was then placed in an ice-water bath and stirred while chloroacetyl chloride (1.5 eq.) **2** was carefully added by a syringe. The mixture was heated and left stirring. The mixture was then cooled to room temperature and the solvent was removed *in vacuo*. The compound **3** was then purified by recrystallization in methanol.

Step 2:



1 equiv.

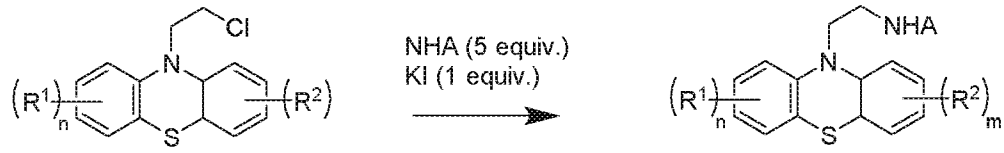
3

4

The 2-chloro-1-(10H-phenothiazin-10-yl)ethan-1-one derivative (1 eq.) **3** and dry THF were added to a dry round bottle flask equipped with a magnetic stirring bar. The mixture was flushed with nitrogen, put in an ice water bath and $BF_3 \cdot Et_2O$ (1.5 eq.) carefully added by syringe while stirring. $NaBH_4$ (1.2 eq.) was added and the mixture was stirred before it was put in an ultrasonic bath. After removing the

mixture from the ultrasonic bath, it was quenched with $NaHCO_3$ and extracted with ethyl acetate. The organic phases were combined and dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo.*

Step 3 – method A:



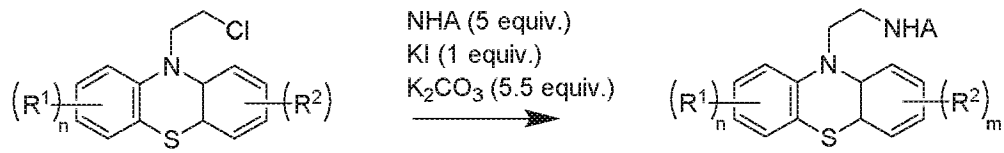
1 equiv.

4

5

The 10-(2-chloroethyl)-10*H*-phenothiazine derivative (1 eq.) **4**, KI (1 eq.), amine (5 eq.) and DMF were added to a round bottle flask equipped with a magnetic stirrer. The mixture was heated and left stirring. When the reaction was finished it was cooled to room temperature and an aqueous solution of NH_4Cl was added, before it was extracted with ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were filtered, and the solvent removed *in vacuo*. The compound **5** was purified using flash column chromatography.

Step 3 – method B:



1 equiv.

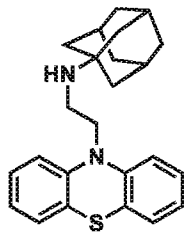
4

5

The 10-(2-chloroethyl)-10*H*-phenothiazine derivative (1 eq.) **4**, amine (5 eq.), K_2CO_3 (5.5 eq.), KI (1 eq.) and THF were added to a round bottle flask equipped with a condenser and a magnetic stirrer. The mixture was heated to reflux and stirred. When the reaction was finished it was cooled to room temperature and water added before it was extracted with ethyl acetate. The organic extracts were dried over

Na_2SO_4, filtered and the solvent was removed *in vacuo*. The compound **5** was purified using flash column chromatography.

Example 1 - Synthesis of *N*-(2-(10*H*-Phenothiazin-10-yl)ethyl)adamantan-1-amine (Compound EA01)



EA01

Synthesis of 2-chloro-1-(10H-phenothiazin-10-yl)ethan-1-one:

10*H*-phenothiazine (0.373 g, 1.87 mmol) and 5 mL of chlorobenzene were added to a microwave vial (20 mL) together with a magnetic stirrer bar. Chloroacetic chloride (0.40 mL, 5.02 mmol), was carefully added while stirring. After addition of chloroacetic chloride the mixture was capped and put in the microwave for 30 min at 120°C (in addition to 10 min of pre-stirring). When the reaction in the microwave was completed, water (5 mL) was added. The mixture was extracted with ethyl acetate (10 mL x 3), the extracts were combined and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The compound was recrystallized in methanol resulting in white crystals with a yield of 93% (0.479 g, 1.74 mmol).

Synthesis of 2-chloro-1-(10H-phenothiazin-10-yl)ethan-1-one:

10*H*-phenothiazine (5.00 g, 25.09 mmol) and 75 mL toluene were added to a 500 mL round bottle flask equipped with a magnetic stirring bar. The mixture was then placed in an ice-water bath and stirred before chloroacetyl chloride (3 mL, 37.67 mmol) was carefully added by a syringe. The mixture was heated at 80°C and stirred for 20 h. The mixture was then cooled at room temperature and the solvent was removed under reduced pressure. The compound was then purified by recrystallization in methanol to afford white crystals in a yield of 64% (4.400 g, 15.96 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 6.7 Hz, 2H), 4.12 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.07, 137.90, 128.18, 127.45, 127.36, 126.60, 42.72.

Synthesis of 10-(2-chloroethyl)-10H-phenothiazine:

2-Chloro-1-(10*H*-phenothiazin-10-yl)ethan-1-one (0.181 g, 0.65 mmol) and dry THF (5 mL) were added to a dry 25 mL round bottle flask equipped with a magnetic stirring bar. The mixture was flushed with nitrogen and put in an ice water bath and BF_3•Et_2O (0.15 mL, 1.22 mmol) carefully added by syringe while stirring. $NaBH_4$ (0.026 g, 0.69 mmol) was added and the mixture was stirred for 1 h. The mixture was then put in an ultrasonic bath for 2 h. After removing the mixture from the ultrasonic bath, it was quenched with $NaHCO_3$ and then extracted with ethyl acetate (10 mL x 3). The organic phases were combined and dried over Na_2SO_4, filtered, and solvent was removed under reduced pressure to provide a white solid in a yield of 89% (0.153 g, 0.58 mmol).

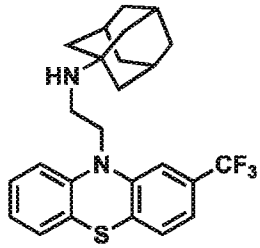
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 – 7.06 (m, 4H), 6.87 (td, *J* = 7.5, 1.1 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 2H), 4.18 – 4.13 (m, 2H), 3.74 – 3.69 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.35, 127.73, 127.48, 125.39, 123.11, 115.20, 49.24, 39.93.

Synthesis of N-(2-(10H-Phenothiazin-10-yl)ethyl)adamantan-1-amine EA01:

10-(2-Chloroethyl)-10*H*-phenothiazine (0.172 g, 0.66 mmol), a spatula tip of KI, adamantylamine (0.466 g, 3.08 mmol) and DMF (10 mL) were added to a 50 mL round bottle flask equipped with a magnetic stirrer. The mixture was heated to 100°C and stirred for 24 h. A NH_4Cl solution (10 mL) was then added, before it was extracted with (20 mL x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were then filtered and dried under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate: hexane 9:1 and 1% Et_3N), to obtain a purple waxy compound in the yield of 44% (0.110 g, 0.29 mmol). R_f = 0.36 (ethyl acetate: hexane 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (ddd, *J* = 7.5, 6.3, 1.7 Hz, 4H), 6.95 – 6.90 (m, 4H), 4.04 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.00 (s, 3H), 1.62 (d, *J* = 12.4 Hz, 4H), 1.52 (d, *J* = 2.9 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.11, 127.53, 127.30, 125.71, 122.73, 115.88, 50.83, 47.82, 42.31, 37.27, 36.58, 29.49.

Example 2 - Synthesis of *N*-(2-(2-(trifluoromethyl)-10*H*-phenothiazin-10-yl)ethyl)adamantan-1-amine (Compound EA02)



EA02

Synthesis of 2-Chloro-1-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)ethan-1-one: 2-Trifluormethyl-10*H*-phenothiazine (0.501 g, 1.87 mmol) and 5 mL of chlorobenzene were added to a 20 mL microwave vial together with a magnetic stirring bar. Chloroacetic chloride (0.4 mL, 5.02 mmol) was carefully added while stirring. After addition of chloroacetic chloride the mixture was capped and put in the microwave for 30 min at 120°C (in addition to 10 min of pre-stirring). When the reaction in the microwave was completed 5 mL of water was added. The mixture was extracted with ethyl acetate (10 mL x 3), the extracts were combined and washed with brine. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The compound was recrystallized in methanol resulting in light green crystals in a yield of 95% (0.615 g, 1.79 mmol).

Synthesis of 2-Chloro-1-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)ethan-1-one: 2-Trifluormethyl-10*H*-phenothiazine (6.701 g, 25.07 mmol) and 75 mL toluene were added to a 500 mL round bottle flask equipped with a magnetic stirring bar. The mixture was put in an ice water bath and stirred before chloroacetic chloride (3.00 mL, 37.67 mmol) was carefully added by syringe. The mixture was heated to 80°C and left stirring for 20 h. The mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The compound was then purified by recrystallization in methanol, resulting in light green crystals in a yield of 87% (7.504 g, 21.82 mmol).

^{1}H NMR (500 MHz, DMSO) δ 8.07 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.72 (dd, *J* = 20.7, 8.1 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 4.56 (d, *J* = 33.2 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 165.12, 137.87, 137.67, 136.82, 131.31, 128.97, 128.25, 128.03, 127.88, 126.83, 124.00, 123.78, 42.68, 39.50.

Synthesis of 10-(2-Chloroethyl)-2-(trifluoromethyl)-10H-phenothiazine:

2-Chloro-1-(2-(trifluoromethyl)-10*H*-phenothiazin-10-yl)ethan-1-one (0.340 g, 0.99 mmol) and dry THF (5 mL) were added to a dry 50 mL round bottle flask equipped with a magnetic stirring bar. The mixture was flushed with nitrogen and put in an ice water bath and BF_3•Et_2O (0.18 mL, 1.46 mmol) carefully added by syringe while stirring. $NaBH_4$ (0.044 g, 1.16 mmol) was added and the mixture was stirred for 1 h. The mixture was then put in an ultrasonic bath for 2 h. After removing the mixture from the ultrasonic bath, it was quenched with $NaHCO_3$ and then extracted with ethyl acetate (20 mL x 3). The organic phases were combined and dried over Na_2SO_4, filtered and solvent was removed under reduced pressure resulting in a white solid, and obtaining a yield of 87% (0.284 g, 0.86 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 3H), 7.15 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.03 (s, 1H), 6.99 (td, *J* = 7.5, 1.2 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 4.25 (t, *J* = 7.1 Hz, 2H), 3.81 – 3.76 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.98, 143.44, 127.89, 127.82, 124.64, 123.77, 119.79, 119.76, 115.64, 111.76, 49.37, 39.72.

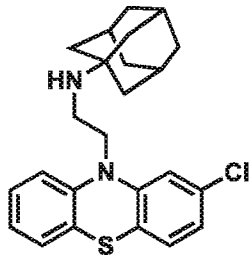
Synthesis of N-(2-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)ethyl)adamantan-1-amine EA02:

10-(2-Chloroethyl)-2-(trifluoromethyl)-10H-phenothiazine (0.205 g, 0.62 mmol), KI (0.137 g, 0.82 mmol), adamantylamine (0.459 g, 3.03 mmol) and DMF (5 mL) were added to a round bottle flask (25 mL) equipped with a magnetic stirrer bar. The mixture was heated to 100°C and stirred for 24 h. An NH_4Cl solution (5 mL) was then added, before it was extracted with (10 mL x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were then filtered and the solvent was removed under reduced pressure, to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate: hexane 9:1 and 1% Et_3N) which resulted in a waxy compound with a yield of 31% (0.085 g, 0.19 mmol). R_f = 0.29 (ethyl acetate: hexane 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 – 7.02 (m, 5H), 6.90 – 6.81 (m, 2H), 3.93 (t, *J* = 6.4 Hz, 2H), 2.88 (t, *J* = 6.4 Hz, 2H), 1.92 (s, 3H), 1.54 (d, *J* = 12.4 Hz, 3H), 1.49 – 1.37 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.67, 144.19, 127.67, 127.61,

127.48, 124.51, 123.31, 119.27, 116.15, 112.42, 50.33, 48.59, 42.61, 37.14, 36.64, 29.52.

Example 3 - Synthesis of *N*-(2-(2-Chloro-10*H*-phenothiazin-10-yl)ethyl)adamantan-1-amine (Compound EA04)



EA04

Synthesis of 2-Chloro-1-(2-chloro-10H-phenothiazin-10-yl)ethan-1-one:

2-Chloro-10H-phenothiazine (0.302 g, 1.29 mmol) and 5 mL of chlorobenzene were added to a 20 mL microwave vial together with a magnetic stirring bar. Chloroacetic chloride (0.28 mL, 3.52 mmol) was carefully added while stirring. After addition of chloroacetic chloride the mixture was capped and put in the microwave for 30 min at 120°C (in addition to 10 min of pre-stirring). When the reaction in the microwave was completed, 5 mL of water was added. The mixture was extracted with ethyl acetate (10 mL x 3), the extracts were combined and washed with brine. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The compound was recrystallized in methanol resulting in light green crystals in a yield of 91% (0.366 g, 1.18 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.30 (td, *J* = 7.6, 1.4 Hz, 1H), 7.27 – 7.24 (m, 1H), 4.26 – 4.15 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.40, 165.77, 138.77, 137.37, 128.66, 128.38, 127.85, 127.71, 127.63, 127.07, 126.32, 40.55.

Synthesis of 2-Chloro-10-(2-chloroethyl)-10H-phenothiazine:

2-Chloro-1-(2-chloro-10*H*-phenothiazin-10-yl)ethan-1-one (0.303 g, 0.98 mmol) and dry THF (5 mL) were added to a dry 25 mL round bottle flask equipped with a magnetic stirring bar. The mixture was flushed with nitrogen and put in an ice water bath and BF_3•Et_2O (0.2 mL, 1.62 mmol) carefully added by syringe while stirring. $NaBH_4$ (0.051 g, 1.35 mmol) was added and the mixture was stirred for a few min. The mixture was then put in an ultrasonic bath for 2 h. The mixture was removed

from the ultrasonic bath and quenched with $NaHCO_3$ and then extracted with ethyl acetate (10 mL x 3). The organic phases were combined and dried over Na_2SO_4, filtered, and solvent was removed under reduced pressure resulting in a light pink solid in a yield of 84% (0.244 g, 0.82 mmol.

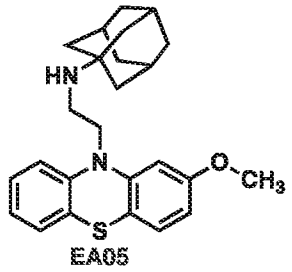
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 – 7.03 (m, 2H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.74 (s, 1H), 4.09 (t, *J* = 7.2 Hz, 2H), 3.68 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.76, 143.70, 133.50, 128.30, 127.90, 127.76, 125.30, 124.04, 123.64, 123.05, 115.74, 115.60, 77.16, 49.36, 39.85.

Synthesis of N-(2-(2-Chloro-10H-phenothiazin-10-yl)ethyl)adamantan-1-amine EA04:

2-Chloro-10-(2-chloroethyl)-10*H*-phenothiazine (0.505 g, 1.23 mmol), KI (0.365 g, 2.19 mmol), adamantylamine (1.282 g, 8.48 mmol) and DMF (10 mL) were added to a round bottle flask (50 mL) equipped with a magnetic stirrer bar. The mixture was heated at 100°C and stirred for 24 h. An NH_4Cl solution (10 mL) was then added, before it was extracted with (20 mL x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were then filtered, and solvent removed under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acate : hexane = 9:1 and 1% Et_3N) and resulted in a waxy compound in a yield of 32% (0.161 g, 0.39 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (ddd, *J* = 14.7, 7.4, 1.5 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.94 (td, *J* = 7.5, 1.2 Hz, 1H), 6.92 – 6.87 (m, 3H), 3.97 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.00 (s, 3H), 1.62 (d, *J* = 12.2 Hz, 3H), 1.58 – 1.50 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.44, 144.39, 133.30, 127.94, 127.57, 127.47, 125.29, 124.03, 123.13, 122.51, 116.12, 50.51, 48.38, 42.54, 37.22, 36.63, 29.51.

Example 4 - Synthesis of *N*-(2-(2-Methoxy-10*H*-phenothiazin-10-yl)ethyl) adamantan-1-amine (Compound EA05)



EA05

Synthesis of 2-Chloro-1-(2-methoxy-10H-phenothiazin-10-yl)ethan-1-one:

2-Methoxy-10*H*-phenothiazine (0.608 g, 2.65 mmol) and chlorobenzene (10 mL) were added to a microwave vial (20 mL) together with a magnetic stirring bar. Chloroacetic chloride (0.55 mL, 6.91 mmol) was carefully added while stirring. After the addition of chloroacetic chloride the mixture was capped and put in the microwave for 30 min at 120°C (in addition to 5 min of pre-stirring). When the reaction in the microwave was completed 10 mL of water was added. The mixture as extracted with ethyl acetate (20 mL x 3), the extracts were combined and washed with brine. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The compound was recrystallized in methanol resulting in light yellow crystals with a yield of 87% (0.706 g, 2.30 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.34 (t, *J* = 8.5 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.19 (d, *J* = 2.7 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.20 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.52, 159.34, 139.15, 137.90, 128.58, 128.15, 127.40, 127.18, 114.08, 55.77, 41.83.

Synthesis of 10-(2-Chloroethyl)-2-methoxy-10H-phenothiazine:

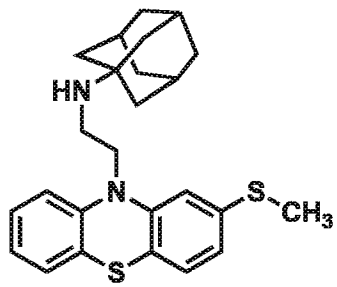
2-Chloro-1-(2-methoxy-10*H*-phenothiazin-10-yl)ethan-1-one (0.688 g, 2.24 mmol) and dry THF (16 mL) were added to a dry round bottle flask (50 mL) equipped with a magnetic stirrer bar. The mixture was flushed with nitrogen and put on an ice water bath and BF_3•Et_2O (0.50 mL, 4.05 mmol) carefully added by syringe while stirring. $NaBH_4$ (0.109 g, 2.88 mmol) was added and the mixture was stirred for a 1 h. The mixture was then split into two round bottle flasks (25 mL) and placed in an ultrasonic bath for 4 h. After removing the mixtures from the ultrasonic bath, they were quenched with $NaHCO_3$ and combined. The combined mixtures were extracted with ethyl acetate (20 mL x 3). The organic phases were combined and

dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure resulting in a dark thick oil with a yield of 69% (0.448 g, 1.54 mmol).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (ddd, *J* = 7.3, 6.0, 1.6 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.81 (td, *J* = 7.4, 1.2 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 4.07 – 4.03 (m, 2H), 3.68 – 3.63 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.92, 145.75, 144.16, 128.01, 127.69, 127.37, 125.92, 123.13, 116.18, 115.31, 103.22, 55.58, 49.30, 39.99.

Synthesis of N-(2-(2-Methoxy-10H-phenothiazin-10-yl)ethyl)adamantan-1-amine EA05:

10-(2-Chloroethyl)-2-methoxy-10*H*-phenothiazine (0.448 g, 1.53 mmol), KI (0.263 g, 1.58 mmol), adamantylamine (1.171 g, 7.74 mmol) and DMF (8 mL) were added to a round bottle flask (50 mL) equipped with a magnetic stirrer bar. The mixture was heated at 100°C and stirred for 24 h. An NH_4Cl solution (10 mL) was then added, before it was extracted with (20 mL x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were then filtered and dried under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate: hexane = 9:1 and 1% Et_3N) obtaining a waxy blue compound with a yield of 15% (0.092 g, 0.22 mmol).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.10 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.91 (t, *J* = 7.1 Hz, 2H), 6.53 – 6.47 (m, 2H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.76 (s, 3H), 2.97 (t, *J* = 6.4 Hz, 2H), 2.00 (s, 3H), 1.61 (d, *J* = 12.0 Hz, 4H), 1.53 (d, *J* = 19.4 Hz, 9H).

Example 5 - Synthesis of *N*-(2-(2-(Methylthio)-10*H*-phenothiazin-10-yl)ethyl) adamantan-1-amine (Compound EA03)



EA03

Synthesis of 2-Chloro-1-(2-(methylthio)-10H-phenothiazin-10-yl)ethan-1-one:
2-(Methylthio)-10*H*-phenothiazine (0.315 g, 1.28 mmol) and chlorobenzene (5 mL) were added to a microwave vial (20 mL) together with a magnetic stirrer bar. Chloroacetic chloride (0.25 mL, 3.14 mmol) was carefully added while stirring. After addition of chloroacetic chloride the mixture was capped and put in the microwave for 30 min at 120°C (in addition to 10 min of pre-stirring), whereupon the mixture was cooled and water added (5 mL). The mixture was extracted with ethyl acetate (10 mL x 3), the extracts were combined and washed with brine. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The compound was recrystallized in methanol resulting in light yellow crystals in a yield of 72% (0.297 g, 0.92 mmol).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.40 (s, 1H), 7.37 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.20 – 7.16 (m, 1H), 7.06 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.10 (d, *J* = 6.3 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.64, 138.68, 138.44, 137.69, 129.21, 128.21, 128.12, 127.55, 127.39, 126.53, 125.65, 124.18, 41.78, 15.97.

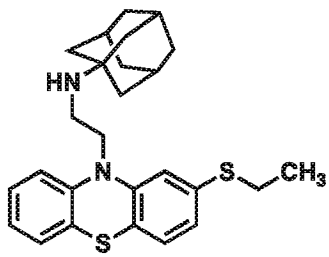
Synthesis of 10-(2-Chloroethyl)-2-(methylthio)-10H-phenothiazine:
2-Chloro-1-(2-(methylthio)-10*H*-phenothiazin-10-yl)ethan-1-one (0.317 g, 0.98 mmol) and dry THF (5 ml) were added to a dry round bottle flask (25 mL) equipped with a magnetic stirring bar. The mixture was flushed with nitrogen and put in an ice water bath and $BF_3 \cdot Et_2O$ (0.20 mL, 1.62 mmol) carefully added by syringe while stirring. $NaBH_4$ (0.045 g, 1.19 mmol) was added and the mixture was stirred for 1 h. The mixture was then placed in an ultrasonic bath for 2 h. After removing the mixture from the ultrasonic bath, it was quenched with $NaHCO_3$ and then extracted with ethyl acetate (10 mL x 3). The organic phases were combined and dried over Na_2SO_4, filtered and solvent was removed under reduced pressure to obtain a thick oil in a yield of 90% (0.272 g, 0.88 mmol).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.12 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.94 (td, *J* = 7.5, 1.2 Hz, 1H), 6.87 – 6.82 (m, 2H), 6.77 (d, *J* = 1.8 Hz, 1H), 4.22 – 4.18 (m, 2H), 3.79 – 3.75 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.86, 144.02, 138.00, 127.82, 127.75, 127.50, 125.54, 123.26, 122.29, 121.36, 115.43, 114.21, 49.32, 39.94, 16.43.

Synthesis of N-(2-(2-(Methylthio)-10H-phenothiazin-10-yl)ethyl)adamantan-1-amine EA03:

10-(2-Chloroethyl)-2-(methylthio)-10*H*-phenothiazine (0.202 g, 0.66 mmol), KI (0.138, g, 0.83 mmol), adamantylamine (0.493 g, 3.25 mmol), and DMF (5 mL) were added to a round bottle flask (50 mL) equipped with a magnetic stirrer bar. The mixture was heated at 100°C and stirred for 24 h. An NH_4Cl solution (5 mL) was added and then extracted with (10 mL x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were then filtered, and solvent was removed under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate : hexane = 9:1 and 1% Et_3N) resulting in a pink waxy compound in a yield of 53% (0.148 g, 0.35 mmol). R_f = 0.21 (ethyl acetate: hexane = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.12 (m, 2H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.94 – 6.89 (m, 2H), 6.86 – 6.82 (m, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 6.4 Hz, 2H), 2.46 (s, 3H), 2.01 (s, 3H), 1.62 (d, *J* = 11.9 Hz, 3H), 1.53 (d, *J* = 2.9 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.68, 144.73, 137.71, 127.57, 127.52, 127.31, 125.71, 122.86, 122.58, 121.19, 116.05, 114.93, 50.80, 48.04, 42.37, 37.31, 36.59, 29.49, 16.51.

Example 6 – Synthesis of *N*-(2-(2-(Ethylthio)-10*H*-phenothiazin-10-yl)ethyl) adamantan-1-amine (Compound EA06)



EA06

Synthesis of 2-Chloro-1-(2-(ethylthio)-10H-phenothiazin-10-yl)ethan-1-one:

2-(Ethylthio)-10*H*-phenothiazine (0.305 g, 1.18 mmol) and 5 ml of chlorobenzene were added to a microwave vial (20 mL) together with a magnetic stirring bar. Chloroacetic chloride (0.25 mL, 3.14 mmol) was carefully added while stirring. After addition of chloroacetic chloride, the vial was sealed and placed in the microwave

oven cavity for 30 min at 120°C (in addition to 10 min of pre-stirring), whereupon water (5 mL) was added. The mixture was extracted with ethyl acetate (10 mL x 3), the extracts were combined and washed with brine. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The compound was recrystallized in methanol resulting in light yellow crystals in a yield of 86% (0.339 g, 1.01 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.18 (d, *J* = 9.7 Hz, 2H), 3.05 – 2.88 (m, 2H), 1.34 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.48, 138.35, 137.73, 136.79, 128.20, 128.09, 127.82, 127.53, 127.40, 126.51, 41.77, 27.81, 14.24.

Synthesis of 10-(2-Chloroethyl)-2-(ethylthio)-10H-phenothiazine:

2-Chloro-1-(2-(ethylthio)-10*H*-phenothiazin-10-yl)ethan-1-one (0.244 g, 0.73 mmol) and dry THF (5 mL) were added to a dry round bottle flask (25 mL) equipped with a magnetic stirring bar. The mixture was flushed with nitrogen and put in an ice water bath and $BF_3 \cdot Et_2O$ (0.15 mL, 1.22 mmol) carefully added by syringe while stirring. $NaBH_4$ (0.039 g, 1.03 mmol) was added and the mixture was stirred for 1 h. The mixture was then placed on an ultrasonic bath for 2 h. After removing the mixture from the ultrasonic bath, it was quenched with $NaHCO_3$ and then extracted with ethyl acetate (20 mL x 3). The organic phases were combined and dried over Na_2SO_4, filtered and solvent was removed under reduced pressure resulting in a thick oil in a yield of 86% (0.202 g, 0.63 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.88 – 6.83 (m, 2H), 4.24 – 4.18 (m, 2H), 3.80 – 3.75 (m, 2H), 2.92 (q, *J* = 7.4 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.81, 144.04, 135.98, 127.77, 127.75, 127.52, 125.43, 123.89, 123.25, 116.54, 115.40, 49.29, 39.89, 28.26, 14.43.

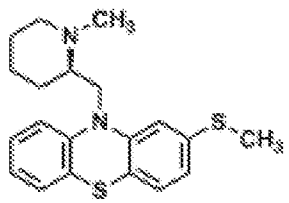
Synthesis of N-(2-(2-(Ethylthio)-10H-phenothiazin-10-yl)ethyl)adamantan-1-amine EA06:

10-(2-Chloroethyl)-2-(ethylthio)-10*H*-phenothiazine (0.194 g, 0.63 mmol) KI (0.140 g, 0.84), adamantylamine (0.456 g, 3.02 mmol) and DMF (5 mL) were added to a round bottle flask (50 mL) equipped with a magnetic stirrer bar. The mixture was heated to 100°C and stirred for 24 h. An NH_4Cl solution (5 mL) was added, before

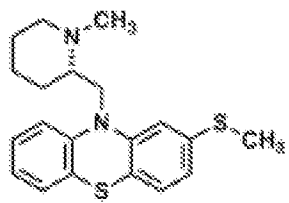
it was extracted with (10 mL x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were then filtered and dried under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate: hexane = 9:1 and 1% Et_3N) obtaining a waxy compound in a yield of 14% (0.039 g, 0.09 mmol). R_f = 0.35 (ethyl acetate: hexane = 9:1).

^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.87 – 6.81 (m, 4H), 3.91 (t, *J* = 6.4 Hz, 2H), 2.88 (t, *J* = 6.4 Hz, 2H), 2.82 (q, *J* = 7.3 Hz, 2H), 1.92 (s, 3H), 1.58 – 1.50 (m, 3H), 1.45 (dd, *J* = 22.8, 2.9 Hz, 9H), 1.21 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.58, 144.85, 135.52, 127.51, 127.31, 125.59, 123.78, 123.61, 122.81, 117.46, 116.03, 50.33, 48.29, 42.59, 37.28, 36.66, 29.53, 28.37, 14.52.

Example 7 - Synthesis of 10-((1-methylpiperidin-2-yl)methyl)-2-(methylthio)-10*H*-phenothiazine (Compounds EA07, EA08)



EA07



EA08

Synthesis of 2-(chloromethyl)-1-methylpiperidine:

To a solution of (1-methylpiperidin-2-yl)methanol (0.53 g, 4.08 mmol) in dichloromethane (5 mL) was added 0.59 mL (0.96 g, 8.07 mmol, 2.0 eq) thionyl chloride. After heating under reflux overnight the solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic phase was dried over $NaSO_4$ and the solvent removed under reduced pressure. The product was obtained as a brown liquid in a yield of 90% (0.540 g, 3.66 mmol).

^1H NMR (300 MHz, $CDCl_3$) *δ* [ppm] - 3.67 (dd,^2J = 11.6 Hz,^3J = 5.1 Hz, 1H), 3.56 (dd,^2J = 11.6 Hz, ^3J = 2.5 Hz, 1H), 2.88 (tdd, ^3J = 11.6 Hz, ^3J = 2.5 Hz, ^3J = 3.5 Hz, 1H), 2.31 (s, 3H), 2.14-2.09 (m, 2H), 1.80-1.58(m, 5H), 1.35-1.27(m, 1H).

Synthesis of 10-((1-methylpiperidin-2-yl)methyl)-2-(methylthio)-10H-phenothiazine (EA07, EA08):

2-(methylthio)-10*H*-phenothiazine (0.36 g, 1.50 mmol) was dissolved in DMSO (2 mL). The flask was flushed with argon before the addition of KOH (0.25 g, 4.50 mmol). The solution was stirred at 80°C for 4h. KI (spatula tip) and 2-(chloromethyl)-1-methylpiperidine (0.22 g, 1.55 mmol) were added and the solution was stirred overnight at 110°C. After extracting three times with ethyl acetate, washing with brine and drying over $NaSO_4$, the crude product was purified by column chromatography with hexane : ethyl acetate = 1:20. Two fractions were identified to be products – fraction 1 was a red solid in a yield of 6% (0.030 g, 0.08 mmol) while fraction 2 was a red solid in a yield of 11% (0.260 g, 0.17 mmol).

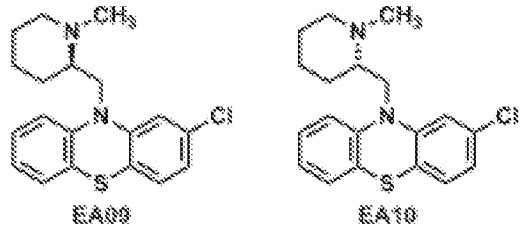
Fraction 1 (EA07, R): ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] - 7.15-6.80 (m, 7H), 4.28 (sex, 1H), 3.14 (dd, ^{2}J = 13.3 Hz, ^{3}J = 6.2 Hz, 1H), 3.04 (dd,^{2}J = 13.3 Hz,^{3}J = 4.8 Hz, 1H), 2.72-2.68 (m, 1H), 2.60-2.56 (m,1H), 2.49 (s, 3H), 2.44 (s, 3H), 2.01-1.95 (m, 1H), 1.84-1.73 (m, 3H), 1.68-1.61 (m, 1H).

Fraction 2 (EA08, S): ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] - 7.16-7.13 (m, 2H), 7.05-7.03(d, 1H), 6.94-6.90 (dt, 1H), 6.87-6.85 (d, 1H), 6.83-6.80 (d, 1H), 6.79-6.78 (d, 1H), 4.24 (dd, ^{2}J = 13.9 Hz, ^{3}J = 4.5 Hz, 1H), 3.72 (dd,^{2}J = 13.8 Hz, ^{3}J = 6.3 Hz, 1H), 2.82-2.78 (m, 1H), 2.45 (s, 3H), 2.43 (s, 3H) 2.38-2.33 (m, 1H), 2.12-2.09 (m, 1H), 1.70-1.67(m, 1H), 1.60-1.51 (m, 2H), 1.35-1.27 (m, 1H), 1.22-1.18 (m, 1H).

Fraction 1 (EA07, R): ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] - 127.4 (C-arom.), 127.4 (C-arom.), 127.2 (C-arom.), 122.5 (C-arom.), 120.9 (C-arom.), 117.0 (C-arom.), 116.0 (C-arom.), 62.7 (CH2), 61.7 (CH), 61.3 (CH_2), 48.1 (CH_3), 30.5 (CH_2), 28.8 (CH_2), 25.0 (CH_2), 16.2 (CH_3).

Fraction 2 (EA08, S): ^{13}C NMR (126 MHz, CDCl3) δ [ppm] - 127.7 (C-arom.), 127.7 (C-arom.), 127.3 (C-arom.), 122.8 (C-arom.), 121.0 (C-arom.), 116.0 (C-arom.), 114.5 (C-arom.), 60.6 (CH), 57.1 (CH_2), 51.1 (CH_2), 43.6 (CH_3), 30.5 (CH_2), 25.8 (CH_2), 23.9 (CH_2), 16.4 (CH_3).

Example 8 - Synthesis of 2-Chloro-10-((1-methylpiperidin-2-yl)methyl)-10*H*-phenothiazine (Compounds EA09, EA10)



2-(Chloromethyl)-1-methylpiperidine (150 mg, 1.02 mmol) was dissolved in DMSO (4 mL), 2-chloro-10*H*-phenothiazine (240 mg, 1.02 mmol), KOH (170 mg, 3.05 mmol) and KI (a spatula tip) were added. The mixture was heated under reflux overnight. Water (10 mL) was added, extracted with ethyl acetate (3 × 5 mL), the aqueous phase was acidified with HCl (3 M) to pH 3 and extracted again with ethyl acetate (3 × 5 mL). The organic phase was washed with brine and dried over $NaSO_4$. The purification was performed with column chromatography with hexane/ethyl acetate-gradient (40:1-10:1). Two fractions were identified to be products. Fraction 1 was a pink solid in a yield of 7% (0.026 g, 0.08 mmol). Fraction 2 was a green solid in a yield of 31% (0.110 g, 0.32 mmol).

Fraction 1 (EA09, R): ^{1}H NMR(300 MHz,, $CDCl_3$) δ [ppm] - 7.17-7.06 (m, 4H), 7.00(d, 1H), 6.92 (dt, 1H), 6.87 (d, 1H), 4.25 (sex, 1H), 3.10 (dd,^{2}J = 13.2 Hz, ^{3}J = 6.3 Hz, 1H), 3.01 (dd, ^{2}J = 13.2 Hz, ^{3}J = 4.8 Hz, 1H), 2.72-2.68 (m, 1H),2.60-2.55 (m, 1H), 2.50-2.43 (m, 3H+1H), 2.00-1.93 (m, 1H), 1.84-1.73 (m, 3H), 1.67-1.61 (m, 1H).

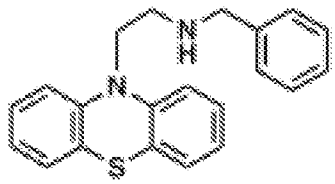
Fraction 2: (EA10, S): ^{1}H NMR(300 MHz, $CDCl_3$) δ [ppm] - 7.18-7.13 (m, 2H), 7.03 (d, 1H), 6.95 (t,1H), 6.90-6.84 (m, 3H), 4.19 (dd,^{2}J = 13.9 Hz, ^{3}J = 4.9 Hz, 1H), 3.69 (dd, ^{2}J = 13.9 Hz, ^{3}J = 6.3 Hz, 1H), 2.80 (m, 1H), 2.42 (s, 3H), 2.34 (m, 1H) 2.09 (td, 1H), 1.97 (m, 1H), 1.69 (m, 1H), 1.40-1.19 (m, 1H).

Fraction 1: (EA09, R): ^{13}C NMR (126 MHz, CDCl3) δ [ppm] - 127.8 (C-arom.), 127.5 (C-arom.), 127.4 (C-arom.), 122.8 (C-arom.), 122.2 (C-arom.), 117.6 (C-arom.), 117.3 (C-arom.), 62.3 (CH2), 61.9 (CH), 61.2 (CH_2), 48.0 (CH_3), 30.3 (CH_2), 28.7 (CH_2), 25.0 (CH_2).

Fraction 2: (EA10, S): ^{13}C NMR (126 MHz, CDCl3) δ [ppm] - 128.1 (C-arom.), 127.8 (C-arom.), 127.5 (C-arom.), 123.1 (C-arom.), 122.5 (C-arom.), 116.2 (C-arom.),

116.0 (C-arom.), 60.4 (CH), 57.1 (CH_2), 51.2 (CH_2), 43.6 (CH3), 30.4 (CH_2), 25.8 (CH_2), 23.8 (CH_2), 16.4 (CH_3).

Example 9 - Synthesis of *N*-benzyl-2-(10*H*-phenothiazin-10-yl)ethan-1-amine (Compound EA16)

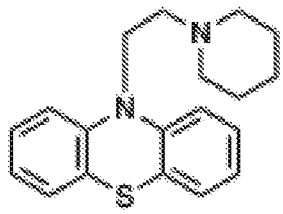


EA16

10-(2-Chloroethyl)-10*H*-phenothiazine (0.219 g, 0.83 mmol) KI (0.159 g, 0.95 mmol), benzylamine (0.42 ml, 3.80 mmol) and DMF (5 mL) were added to a 50 mL round bottle flask equipped with a magnetic stirrer. The mixture was heated to 100°C and stirred overnight. An NH_4Cl solution (5 mL) was added, before it was extracted with (10 mL x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were then filtered and dried under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate: hexane = 3:7 and then increasing the amount of ethyl acetate) obtaining a waxy blue compound with a yield of 6% (0.016 g, 0.048 mmol). R_f = 0.11 (ethyl acetate: hexane = 3:7).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 5H), 7.10 – 7.01 (m, 4H), 6.89 – 6.78 (m, 4H), 4.01 (t, *J* = 6.1 Hz, 2H), 3.71 (s, 2H), 2.93 (t, *J* = 6.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.09, 128.42, 128.09, 127.58, 127.33, 127.06, 125.75, 122.77, 115.80, 53.18, 46.85, 45.06.

Example 10 - Synthesis of 10-(2-(Piperidin-1-yl)ethyl)-10*H*-phenothiazine (Compound EA17)

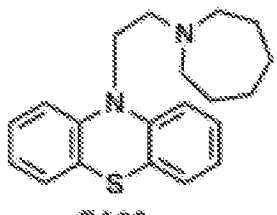


EA17

10-(2-Chloroethyl)-10*H*-phenothiazine (0.165 g, 0.63 mmol) KI (0.222 g, 1.32 mmol), piperidine (0.28 ml, 2.85 mmol) and DMF (5 mL) were added to a 50 mL round bottle flask equipped with a magnetic stirrer. The mixture was heated to 100°C and stirred overnight. An NH_4Cl solution (5 mL) was added and then extracted with ethyl acetate (10 mL x 3). The organic extracts were combined, washed with brine, and dried over $NaSO_4$. The organic extracts were then filtered and dried under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate:hexane = 9:1) initially. The compound was flushed out with MeOH obtaining a waxy compound in a yield of 75% (0.147 g, 0.47 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 – 7.04 (m, 4H), 6.91 – 6.83 (m, 4H), 4.14 (t, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 2.65 (s, 4H), 1.65 (p, *J* = 5.7 Hz, 4H), 1.41 (s, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 144.78, 127.65, 127.54, 125.33, 122.92, 115.59, 55.15, 54.26, 44.03, 24.59, 23.32.

Example 11 - Synthesis of 10-(2-(Azepan-1-yl)ethyl)-10*H*-phenothiazine (Compound EA20)



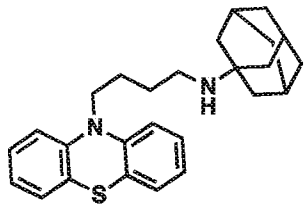
EA20

10-(2-Chloroethyl)-10*H*-phenothiazine (0.206, 0.78 mmol), azepane (0.43 ml, 3.82 mmol), K_2CO_3 (0.600 g, 4.34 mmol), KI (0.128, 0.77 mmol) and THF (20 mL) were added to a round bottle flask (100 mL) equipped with a condenser and a magnetic

stirrer bar. The mixture was heated to reflux and stirred overnight. After stirring the mixture was cooled to room temperature and water added (20 mL), before it was extracted with ethyl acetate (3 × 20 mL). The organic extracts were dried over Na_2SO_4, filtered before the solvent was removed under reduced pressure to obtain a blue solid. The compound was purified using flash column chromatography (ethyl acetate: hexane = 9:1) obtaining a waxy compound in a yield of 13% (0.034 g, 0.10 mmol). R_f = 0.11 (ethyl acetate: hexane = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 – 7.02 (m, 4H), 6.88 (dd, *J* = 8.2, 1.2 Hz, 2H), 6.82 (td, *J* = 7.5, 1.2 Hz, 2H), 3.96 – 3.88 (m, 2H), 2.87 – 2.80 (m, 2H), 2.69 – 2.62 (m, 4H), 1.63 – 1.49 (m, 8H).^{13}C NMR (126 MHz, $CDCl_3$) δ 127.41, 124.62, 122.48, 115.48, 56.71, 54.46, 46.69, 28.56, 27.03.

Example 12 - Synthesis of *N*-(4-(10*H*-phenothiazin-10-yl)butyl)adamantan-1-amine (Compound EA22)



EA22

Synthesis of 10-(4-chlorobutyl)-10H-phenothiazine:

Phenothiazine (1.436 g, 7.21 mmol), anhydrous DMF (10 mL) and NaH (0.260 g, 10.8 mmol) were added to a dry round bottle flask (50 mL) equipped with a magnetic stirring bar. The flask was placed in an ice-water bath and 1-bromo-4-chlorobutane (0.82 ml, 7.11 mmol) was added to the flask. The mixture was capped and stirred for 1 h in an ice water bath and stirred for 18 h at 20°C. Water (50 mL) was added to the flask and the organic phase was extracted using ethyl acetate (50 mL × 3). The organic phases were combined and dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure using a rotary evaporator. The compound was then purified using flash chromatography (hexane : ethyl acetate = 85:15) resulting in a solid product in a yield of 26% (0.532 g, 1.84 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.11 (m, 4H), 6.96 (m, 1H), 6.91 (td, *J* = 7.5, 1.2 Hz, 2H), 6.85 (m, 1H), 3.88 (t, *J* = 6.6 Hz, 2H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.00 –

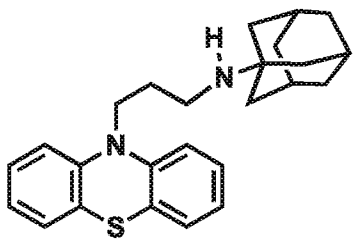
1.83 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.19, 127.62, 127.30, 125.47, 122.63, 115.57, 46.32, 44.75, 29.76, 24.11.

Synthesis of N-(4-(10H-phenothiazin-10-yl)butyl)adamantan-1-amine:

10-(4-chlorobutyl)-10*H*-phenothiazine (0.532 g, 1.84 mmol), KI (0.304 g, 1.84 mmol), adamantylamine (1.382 g, 9.14 mmol) and DMF (5 mL) were added to a round bottle flask (25 mL) equipped with a magnetic stirring bar. The mixture was heated at 100°C and stirred for another 18 h. The mixture was then lowered to 20°C whereupon saturated aqueous solution of NH_4Cl (5 mL) was added. The organic phase was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure using a rotary evaporator. The crude product was purified using flash chromatography (hexane : ethyl acetate = 30:70) R_f = 0.06. A solid blue crystal was isolated (0.562 g, 1.39 mmol) in a yield of 75%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.09 (m, 4H), 6.94 – 6.83 (m, 4H), 3.87 (t, *J* = 7.1 Hz, 2H), 2.65 – 2.60 (t, J = 7.5 Hz, 2H), 1.85 (p, *J* = 7.6 Hz, 4H), 1.68 – 1.55 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.21, 127.45, 127.24, 124.97, 122.41, 115.45, 51.19, 47.12, 42.38, 39.94, 36.64, 29.54, 28.22, 24.80.

Example 13 - Synthesis of *N*-(3-(10*H*-phenothiazin-10-yl)propyl)adamantan-1-amine (Compound EA23)



EA23

Synthesis of 3-chloro-1-(10H-phenothiazin-10-yl)propan-1-one:

10*H*-phenothiazine (5.00 g, 25.09 mmol) and 80 ml toluene were added to a round bottle flask (500 mL) equipped with a magnetic stirring bar. The mixture was immersed into an ice-water bath and stirred before 3-chloropropanoyl chloride (3.60 mL, 37.64 mmol) was carefully added by syringe. The mixture was heated at 80°C and stirred for 20 h. The mixture was then cooled to 20°C and the solvent was removed under reduced pressure. The compound was then purified by

recrystallisation in methanol, resulting in white crystals in a yield of 87% (6.346 g, 21.90 mmol).

^{1}H NMR (500 MHz, CDCl3) δ 7.45 (d, J = 7.9 Hz, 2H), 7.39 (dd, J = 7.8, 1.5 Hz, 2H), 7.27 (td, J = 7.7, 1.5 Hz, 2H), 7.18 (td, J = 7.6, 1.4 Hz, 2H), 3.73 (t, J = 6.9 Hz, 2H), 3.00-2.75 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 168.84, 138.22, 128.14, 127.14, 39.63, 37.34.

Synthesis of 10-(3-chloropropyl)-10H-phenothiazine:

3-chloro-1-(10*H*-phenothiazin-10-yl)propan-1-one (2.002 g, 6.90 mmol) and dry THF (45 mL) were transferred to a dry round bottle flask (250 mL) equipped with a magnetic stirring bar. The mixture was flushed with nitrogen and immersed into an ice-water bath. Then, under gentle stirring, $BF_3 \cdot Et_2O$ (1.4 mL, 11.32 mmol) was carefully added by means of a syringe. $NaBH_4$ (0.330 g, 8.70 mmol) was added to the mixture then heated at reflux and stirred for 24 h. The post-reaction mixture was cooled to 20°C and quenched with saturated aqueous solution of $NaHCO_3$. Then the mixture was extracted with ethyl acetate (3 x 50 mL). The organic phases were combined and dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The compound was purified using flash column chromatography (ethyl acetate : hexane = 1:9) to obtain a brown waxy compound in a yield of 37% (0.697 g, 2.53 mmol).

^{1}H NMR (600 MHz, CDCl3) δ 7.03 (td, J = 7.2, 1.5 Hz, 4H), 6.80 (td, J = 7.4, 1.2 Hz, 2H), 6.76 (dd, J = 8.6, 1.3 Hz, 2H), 3.92 (t, J = 6.6 Hz, 2H), 3.51 (t, J = 6.2 Hz, 2H), 2.08 (p, J = 6.4 Hz, 2H). ^{13}C NMR (151 MHz, CDCl3) δ 145.11, 127.71, 127.42, 125.72, 122.83, 115.67, 44.01, 42.56.

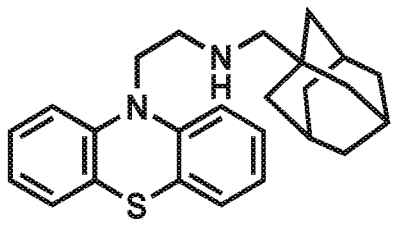
Synthesis of N-(3-(10H-phenothiazin-10-yl)propyl)adamantan-1-amine EA23:

10-(3-chloropropyl)-10H-phenothiazine (0.697 g, 2.53 mmol), KI (0.418 g, 2.53 mmol) adamantyl-amine (1.152 g, 7.58 mmol) and DMF (10 mL) were added to a round bottle flask (50 mL) equipped with a magnetic stirrer bar. The mixture was heated to 100°C and stirred for 24 h. 15 ml of a saturated aqueous solution of NH_4Cl were added, in addition to 50 ml water before it was extracted with (50 ml x 3) ethyl acetate. The organic extracts were combined, washed with brine and dried over $NaSO_4$. The organic extracts were filtered, and solvent removed *in vacuo*, to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate: hexane 9:1 and 1% Et_3N), to obtain a brown

waxy compound in a yield of 41% (0.401 g, 1.03 mmol). R_f = 0.17 (ethyl acetate: hexane 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15-7.10 (m, 4H), 6.91 – 6.86 (m, 4H), 3.93 (t, *J* = 6.7 Hz, 2H), 2.70 (t, *J* = 6.9 Hz, 2H), 2.02-1.98 (m, 3H), 1.90 (p, *J* = 6.8 Hz, 2H), 1.66 – 1.59 (m, 3H), 1.57-1.50 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.29, 127.40, 125.21, 122.40, 115.65, 50.37, 45.41, 44.21, 42.74, 41.84, 37.94, 36.77, 36.25, 35.87, 30.94, 29.59, 29.29, 28.52.

Example 14 - Synthesis of *N*-(adamantan-1-yl)methyl)-2-(10*H*-phenothiazin-10-yl)ethan-1-amine (Compound EA24)



EA24

10-(2-Chloroethyl)-10*H*-phenothiazine (0.507 g, 1.94 mmol), KI (0.324 g, 1.95 mmol) 1-adamantanemethylamine (0.5 mL, 2.82 mmol) and DMF (10 ml) were added to a round bottle flask (50 mL) equipped with a magnetic stirrer bar. The mixture was then heated at 100°C and stirred for 24 h. A saturated aqueous solution of NH_4Cl (15 mL) and water (50 mL) was added before the mixture was extracted with (3 × 50 mL) ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous $NaSO_4$, filtered, and finally the organic solvent was removed under reduced pressure to obtain a dark coloured sticky compound. The compound was purified using flash column chromatography (ethyl acetate : hexane = 9:1 and 1% Et_3N) that delivered a brown waxy compound in a yield of 52% (0.397 g, 1.02 mmol). R_f = 0.25 (ethyl acetate : hexane = 9:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 – 7.04 (m, 4H), 6.88 – 6.82 (m, 4H), 3.96 (t, *J* = 6.1 Hz, 2H), 2.90 (t, *J* = 6.0 Hz, 2H), 2.09 (s, 2H), 1.86-1.80 (m, 3H), 1.63-1.56 (m, 3H), 1.55-1.48 (m, 3H), 1.37-1.32 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.19, 127.51, 127.26, 125.77, 122.68, 115.89, 62.48, 47.39, 46.92, 40.69, 37.17, 33.43, 30.94, 28.43.

Example 15 - *In vitro* activity in cell lines

Method:

Cells from various cell lines (LN18, T98G, U87-MG, U251, NHA, SV80, P3XX) were seeded 20-24 h before the treatment in a 96-well plate to approximately 30% confluency and kept at 37°C in a humidified 5% CO_2 atmosphere. The live cell IncuCyte Zoom imaging system (Essen BioScience) was used to assess the proliferation of the different cell lines in response to the compounds EA01 and EA02 in different concentrations. Brightfield microscopy images were captured at 2 h intervals over the whole treatment period of 72 h and the percentage of confluency was analyzed with the IncuCyte Zoom Software.

Results:

Figure 1 shows the monitored confluency in 96 wells after a treatment for 72 h with 4 µM EA01 in three different cell lines using the IncuCyte Zoom. The glioblastoma cell lines U87-MG and U251 (see B and C) show reduced cell viability and proliferation assessed via percentage of confluency when treated with 4 µM EA01 compared to cells grown in media only (DMEM alt). The control cell line NHA (see Figure 1A) is not affected by treatment with 4 µM EA01.

Figure 2 shows the measured confluency percentage means normalised to the confluency percentage of time point 0 h (= change fold of confluency) for various treatment conditions of U87-MG, p44-46 (n=3) over 72 h (Figure 2A) and to the endpoint 72 h (B) with and without Temozolomide in combination with EA01 and EA02. Temozolomide is not adding to the treatment effect of EA01 and EA02. Both compounds lead to reduced proliferation and cell death for the tested glioblastoma cell lines U87-MG and U251 in lower concentrations compared to normal human astrocytes (NHA) as control cell line.

Example 16 - Cell Viability Assay

Method:

The effect of the compounds EA01-EA10, EA16, EA17, EA20 and EA22 on the viability of various cell lines (LN18, T98G, U87-MG, U251, NHA, SV80, P3XX) was assessed using the WST-1 Assay (Roche, 11644807001). Cells were seeded at a

concentration of 5000 cells × well^{-1} (or 10000 cells × well^{-1} for P3XX) in 96-well plates 20-24 h prior to treatment and kept at 37°C in a humidified 5% CO_2 atmosphere. The cells were treated with various concentrations of the compounds for 72 h before the WST-1 reagent was added in a 1:10 ratio dependent on the well media volume. A 30 second-shaking period on a linear shaker was followed by an incubation for 3 hours at 37°C. The proliferation rate was determined by measuring the absorbance at 450 nm with a microplate photometer (Multiskan FC, ThermoFisher Scientific). LC_{50} values were determined for the different cell lines using the WST1 assay. Log P data was also calculated.

Results:

LC_{50} values in µM for EA01 and EA02 are shown in Table 1 for different glioblastoma and control cell lines.

Table 1

cmp#	MW	log *P*	*LC*$_{50}$						
			LN18	T98G	U87-MG	U251	NHA	SV80	P3XX
EA00	370.6	5.06	—	—	—	—	—	—	—
EA01	376.6	5.25	5.21	10.18	6.27	4.87	8.45	4.74	5.00
EA02	444.6	6.17	8.15	12.23	9.61	7.57	9.15	7.53	5.04
EA03	422.7	5.69	6.23	8.83	8.61	6.17	9.99	6.17	4.02
EA04	411.0	5.81	6.29	10.30	5.44	10.03	11.28	9.53	7.44
EA05	406.6	5.13	7.04	13.64	9.38	6.84	12.89	10.31	7.35
EA06	436.7	6.03	6.58	13.00	6.58	7.03	10.15	9.34	4.72
EA07	356.6	4.96	>30	>30	>30	>30	>30	>30	>30
EA08	356.6	4.96	13.01	20.87	19.30	17.93	24.38	23.09	20.08
EA09	344.9	5.07	>30	>30	>30	>30	>30	>30	>30
EA10	344.9	5.07	22.41	27.69	26.26	19.11	28.97	22.78	19.97
EA16	332.5	5.16	>30	>30	>30	>30	>30	>30	>30
EA17	310.6	4.54	>30	>30	>30	>30	>30	>30	>30
EA20	324.5	4.95	16.19	30.33	23.85	21.71	27.98	20.09	18.41
EA22	404.6	5.81	3.06	5.96	3.66	3.93	5.25	2.54	3.09

EA00=Thioridazine.

NHA (normal human astrocytes) used as reference.

Log P estimated by means of "Chemical properties" of ChemDraw Professional

Example 17 - Effect of compounds on tumor spheroids

Method:

The effect of the compounds EA01 and EA02 was tested on the viability of 21-day old fetal rat brain organoids (FRBO) and on 5-day old tumor spheroids. FRBO were prepared according to a modified protocol as described in Bjerkvig et al., Cancer

Res. 1986, 46(8), 4071-4079. Tumor spheroids of the stem-cell like cell lines P3, P3-GFP, BG5, BG5-GFP, BG7 and BG7-GFP were obtained by seeding 5000 cells per well in U-bottom 96-well plates. After centrifugation at 2000 rpm and 37°C for 90 min, cells were incubated at standard conditions. FRBO and tumor spheroids were treated with various concentrations of the compounds for 72 h before the WST-1 protocol was performed.

Results:

LC_{50} values for treatment of the different primary glioblastoma cell lines derived from patient material are displayed in Table 2, with and without GFP-labelling. EA01 has a higher toxicity than EA02 in all studied stem-cell like cell lines. The FRBO as a model for the adult human brain is not affected at these LC_{50} concentrations and tolerates a higher concentration of both EA01 and EA02 with an LC_{50} of approximately 18 µM for both compounds (see Figures 3A and 3B).

Table 2

Cell Line (Spheroids), n≥3	LC_{50} EA01 [µM]	LC_{50} EA02 [µM]
P3 wt	6.97	7.62
P3-GFP	7.50	8.77
BG5 wt	4.93	7.94
BG5 GFP	4.93	8.59
BG7 wt	4.10	6.05
BG7-GFP	3.64	5.66

Example 18 - Co-culture Model

Method:

Old FRBO (21 day) and old tumor spheroids (5-day) of the sorted stem-cell like cell lines P3-GFP, BG5-GFP and BG7-GFP were confronted in U-bottom 96-well plates and treated with different concentrations of compound EA01 and EA02. After 24 h these co-cultures were then transferred to a µ-Slide 8 well glass chamber under continued treatment. Invasion of the tumor cells into the FRBO was observed using confocal microscopy (Andor Dragonfly 505) in time intervals of 24, 48 and 72 h. The co-cultures were quantified using Photoshop.

Results:

Figure 4 shows brightfield and fluorescence confocal microscopy images of P3-GFP (Figure 4A) and BG5-GFP (Figure 4B) confronted with FRBO generation 33 after 72 h of treatment with EA01 and EA02. Consistent with the LC_{50} determination for both tumor spheroids and FRBO, advanced toxicity of both compounds for the tumor spheroids but not the FRBO was detected for the indicated concentrations of EA01 and EA02.

Example 19 - Colony formation assay

Method:

LN18, U251 and NHA cells (125 cells per well) were seeded in 6-well culture plates in triplicate and incubated at 37°C in a humidified chamber of 5% CO_2 for up 14 days. Colonies were washed with PBS, fixed in methanol for 10 min and stained with crystal violet for 10 min at room temperature. Colonies were counted when they were formed by more than 50 cells.

Results:

As shown in Figure 5, the control cell line NHA tolerated higher concentrations of EA01 compared to the glioblastoma cell lines (LN18, LN229, U251).

Example 20 - *In vivo* toxicity screen in mice

A first *in vivo* toxicity screen was performed in C57BL/6 male mice. EA01 and EA02 were dissolved in DMSO and diluted to the final concentrations. After randomization, the animals were stratified into a control group (DMSO, n=5) and the following treatment groups: EA01 7 mg × kg^{-1} (n=5), EA01 14 mg × kg^{-1} (n=5), EA01 21 mg × kg^{-1} (n=5), EA02 7 mg × kg^{-1} (n=5), EA02 14 mg × kg^{-1} (n=5), and EA02 21 mg × kg^{-1} (n=5). Treatment was administered once via intraperitoneal injection and the animals were observed closely. Euthanization and explantation of the organs (brain, heart, liver and kidney) was performed after 24, 48, 72 h (n=1 per group respectively) and 120 h (n=2 per group). Organs were formalin fixed and hematoxylin and eosin (H&E) stains were performed on the sections. All mice treated with EA01 and EA02 developed transient symptoms of drowsiness and recovered fully 15 min. after injection.

Example 21 - Cell viability assay in melanoma cell lines

Method:

The effect of the compounds EA01, EA02 and EA10 on various melanoma cell lines (H1, H3 and H10) was tested using the same protocol as in Example 14.

Results:

IC_{50} values are provided in Table 3:

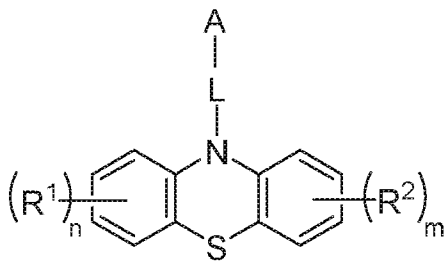
Table 3

	IC_{50} - Melanoma cell lines*		
Compound	**H1**	**H3**	**H10**
EA01	8.3	7.5	7.5
EA02	10.7	11.9	9.1
EA10	7.2	6.8	6.7

* mean value of three replicates

Claims:

1. A compound of formula (Ib), a stereoisomer, or a pharmaceutically acceptable salt thereof, for use in the treatment of glioblastoma:



(Ib)

wherein:

A is an optionally substituted amine or an optionally substituted carbocyclic or heterocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{2-6} alkenyl (preferably C_{2-4} alkenyl),

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),

-OH,

-SH,

halogen (e.g. F, Cl or Br), and

an optionally substituted aryl group (e.g. optionally substituted phenyl);

each R^2 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),

C_{2-6} alkenyl (preferably C_{2-4} alkenyl),

C_{2-6} alkynyl (preferably C_{2-4} alkynyl),

C_{1-6} haloalkyl (e.g. $-CF_3$),

$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),

-S-C_{1-6} alkyl (preferably -S-C_{1-3} alkyl, e.g. -SCH_3),
-OH,
-SH,
halogen (e.g. F, Cl or Br), and
an optionally substituted aryl group (e.g. optionally substituted phenyl);
n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2; and
m is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2.

2. A compound for use as claimed in claim 1, wherein A is an optionally substituted carbocyclic or heterocyclic ring system.

3. A compound for use as claimed in claim 2, wherein A is an optionally substituted carbocyclic ring system.

4. A compound for use as claimed in claim 3, wherein A is an optionally substituted cycloalkyl or cycloalkenyl group, preferably an optionally substituted cycloalkyl group containing two or three rings which are fused or bridged.

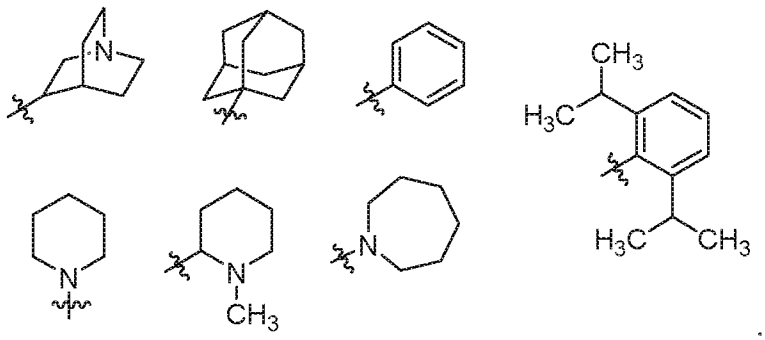
5. A compound for use as claimed in claim 2, wherein A is an optionally substituted heterocyclic group.

6. A compound for use as claimed in claim 2, wherein A is selected from substituted or unsubstituted adamantyl, phenyl, quinuclidinyl, piperidinyl and azepanyl.

7. A compound for use as claimed in claim 6, wherein A is substituted or unsubstituted adamantyl, preferably unsubstituted adamantyl.

8. A compound for use as claimed in any one of the preceding claims, wherein A is substituted by one or more groups independently selected from -OH, C_{1-6} alkyl, -O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen atoms (e.g. F, Cl or Br).

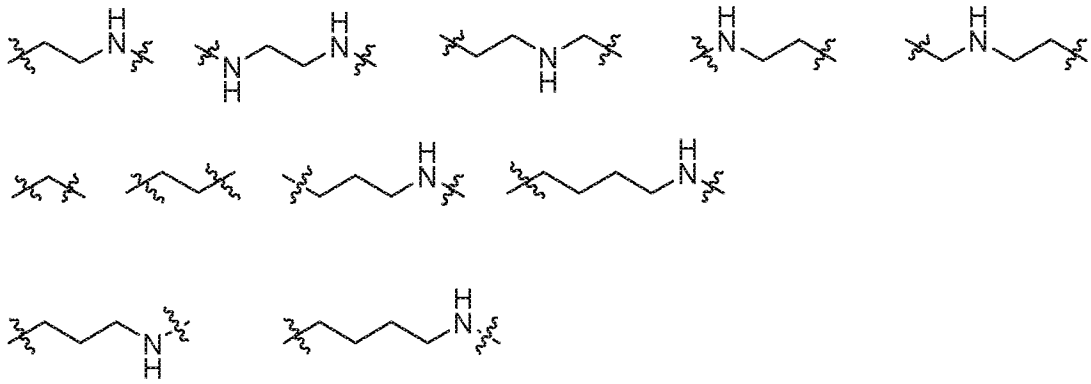
9. A compound for use as claimed in any one of the preceding claims, wherein A is selected from the following:



10. A compound for use as claimed in any one of the preceding claims, wherein L is an optionally substituted, straight-chained or branched C_{1-6} alkylene group.

11. A compound for use as claimed in any one of claims 1 to 9, wherein L is an optionally substituted C_{1-6} alkylene group, preferably C_{2-6} alkylene group, in which one or more $-CH_2-$ groups of the alkylene chain are replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl).

12. A compound for use as claimed in any one of the preceding claims, wherein L is selected from the following:



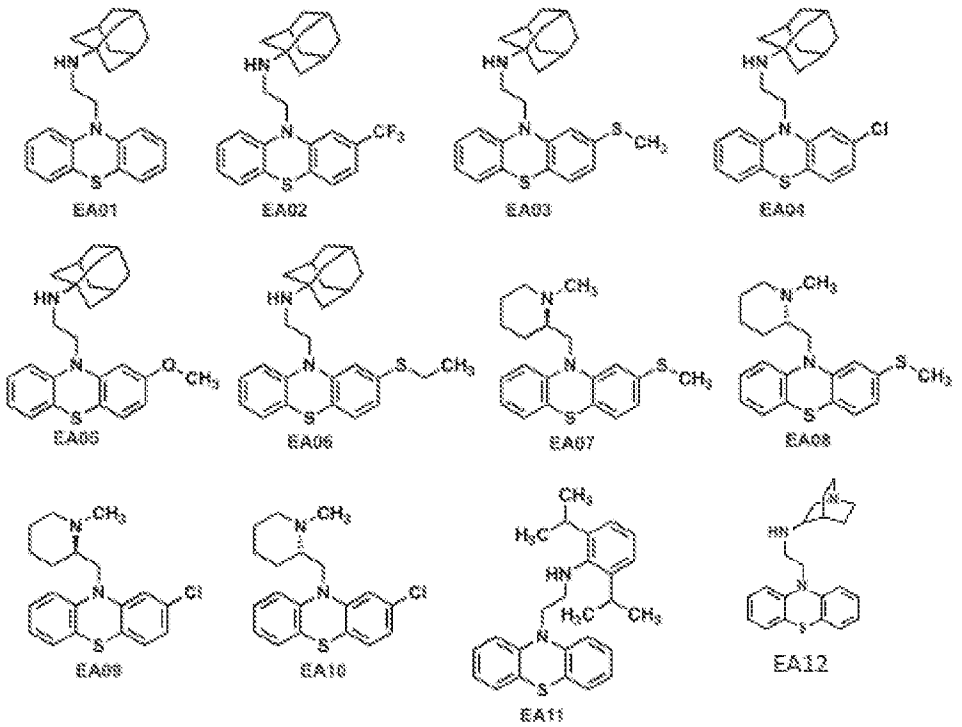
13. A compound for use as claimed in any one of the preceding claims, wherein each R^1 is independently selected from C_{1-3} alkyl (e.g. $-CH_3$), $-CF_3$, $-O-C_{1-3}$ alkyl (e.g. $-OCH_3$ or $-OCH_2CH_3$), $-S-C_{1-3}$ alkyl (e.g. $-SCH_3$ or $-SCH_2CH_3$), F, Cl, Br and phenyl.

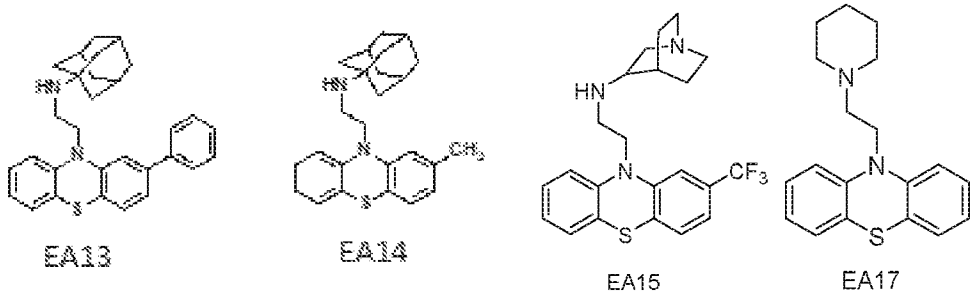
14. A compound for use as claimed in any one of the preceding claims, wherein n is 0, 1 or 2, preferably 0 or 1.

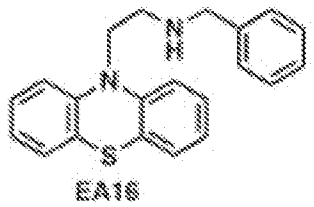
15. A compound for use as claimed in any one of the preceding claims, wherein each R^2 is independently selected from C_{1-3} alkyl (e.g. $-CH_3$), $-CF_3$, $-O-C_{1-3}$ alkyl (e.g. $-OCH_3$ or $-OCH_2CH_3$), $-S-C_{1-3}$ alkyl (e.g. $-SCH_3$ or $-SCH_2CH_3$), F, Cl, Br and phenyl.

16. A compound for use as claimed in any one of the preceding claims, wherein m is 0, 1 or 2, preferably 0 or 1.

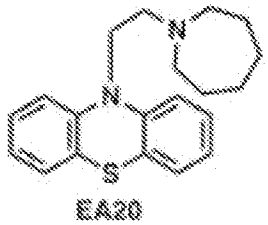
17. A compound for use as claimed in claim 1 which is selected from the following compounds, their stereoisomers, and their pharmaceutically acceptable salts:



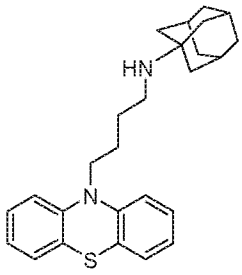




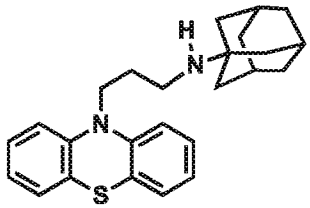
EA16



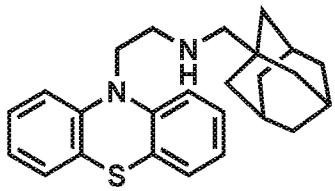
EA20



EA22



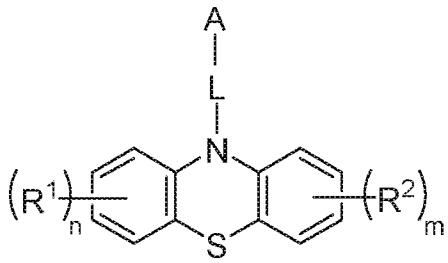
EA23



EA24

18. A compound for use as claimed in any one of the preceding claims in the treatment of an astrocytoma, oligodendroglioma or ependymoma.

19. A compound of formula II, a stereoisomer or a pharmaceutically acceptable salt thereof:



(II)

wherein:

A is an optionally substituted carbocyclic ring system;

L is a linking group which is an optionally substituted C_{1-6} alkylene group in which one or more $-CH_2-$ groups of the alkylene chain may be replaced by a group independently selected from -O-, -S- and -NR'- (where R' is H or C_{1-3} alkyl, e.g. methyl);

each R^1 and R^2 is independently selected from:

C_{1-6} alkyl (preferably C_{1-3} alkyl, e.g. $-CH_3$),
C_{2-6} alkenyl (preferably C_{2-4} alkenyl),
C_{2-6} alkynyl (preferably C_{2-4} alkynyl),
C_{1-6} haloalkyl (e.g. $-CF_3$),
$-O-C_{1-6}$ alkyl (preferably $-O-C_{1-3}$ alkyl, e.g. $-OCH_3$),
$-S-C_{1-6}$ alkyl (preferably $-S-C_{1-3}$ alkyl, e.g. $-SCH_3$),
-OH,
-SH,
halogen (e.g. F, Cl or Br), and
an optionally substituted aryl group (e.g. optionally substituted phenyl);
n is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2; and
m is an integer from 0 to 4, preferably 0 to 2, e.g. 0, 1, or 2.

20. A compound as claimed in claim 19, wherein A is an optionally substituted cycloalkyl group, preferably an optionally substituted cycloalkyl group containing two or three rings which are fused or bridged.

21. A compound as claimed in claim 19, wherein A is substituted or unsubstituted adamantyl.

22. A compound as claimed in claim 19 having the formula EA01, EA02, EA03, EA04, EA05, EA06, EA13, EA14, EA22, EA23 or EA24 as defined in claim 17, or a stereoisomer or pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a compound of formula (II), a stereoisomer, or a pharmaceutically acceptable salt thereof as claimed in any one of claims 19 to 22, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

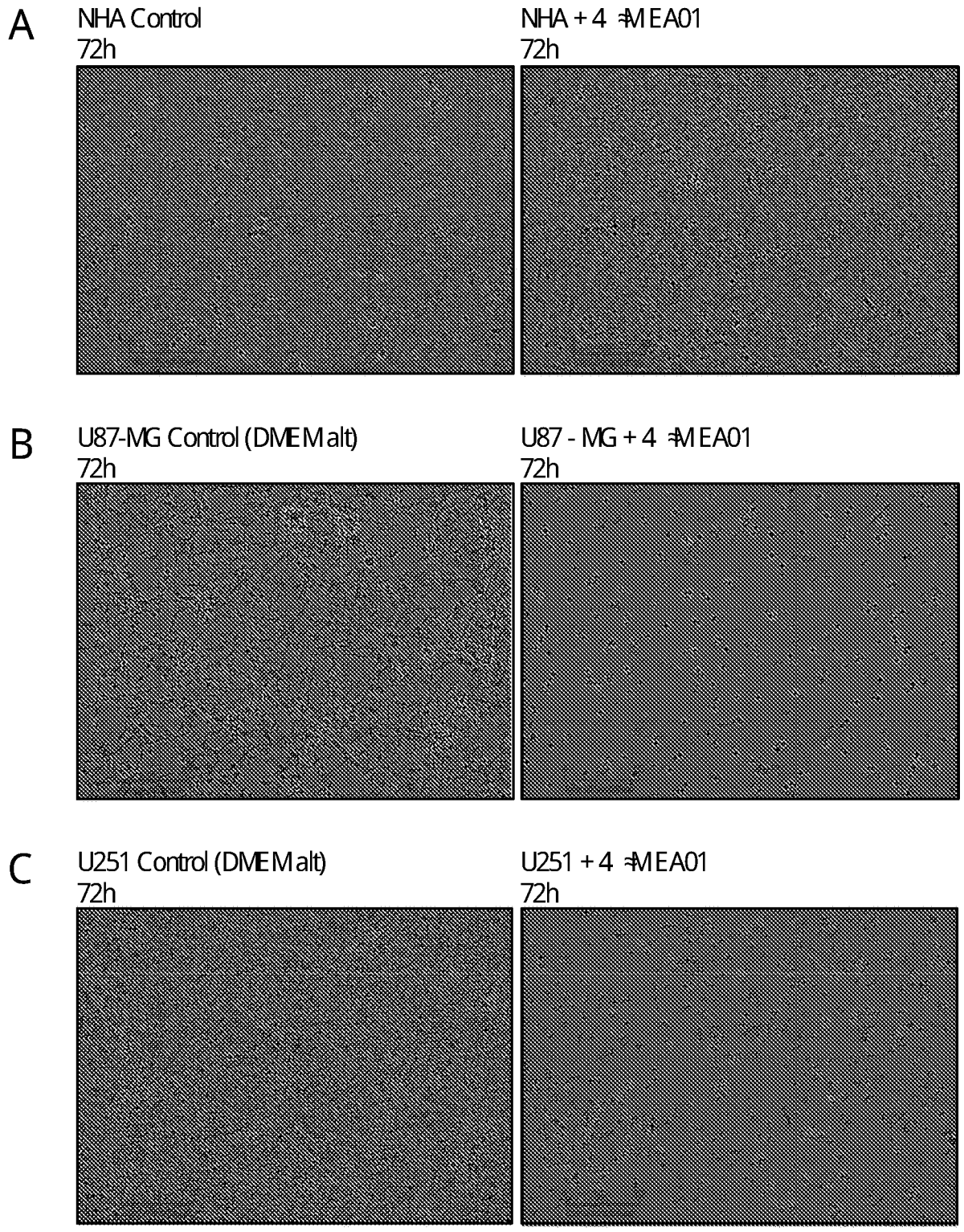

A
NHA Control
72h
NHA + 4 nM EA01
72h
B
U87-MG Control (DMEM alt)
72h
U87 - MG + 4 nM EA01
72h
C
U251 Control (DMEM alt)
72h
U251 + 4 nM EA01
72h

FIG. 1

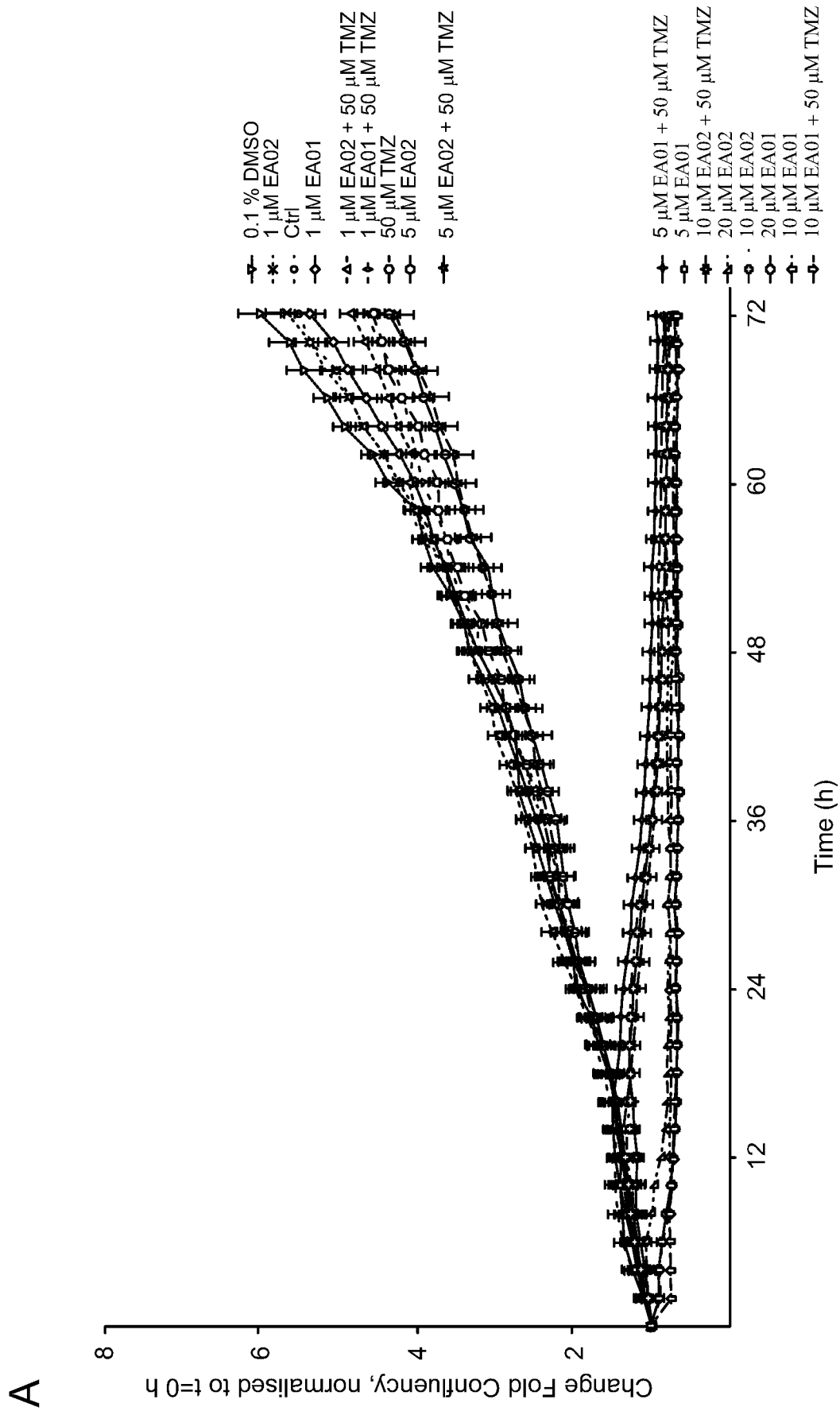

A
Change Fold Confluency, normalised to t=0 h
2
4
6
8
12
24
36
48
60
72
Time (h)
0.1 % DMSO
1 µM EA02
Ctrl
1 µM EA01
1 µM EA02 + 50 µM TMZ
1 µM EA01 + 50 µM TMZ
50 µM TMZ
5 µM EA02
5 µM EA02 + 50 µM TMZ
5 µM EA01 + 50 µM TMZ
5 µM EA01
10 µM EA02 + 50 µM TMZ
20 µM EA02
10 µM EA02
20 µM EA01
10 µM EA01
10 µM EA01 + 50 µM TMZ

FIG. 2

B

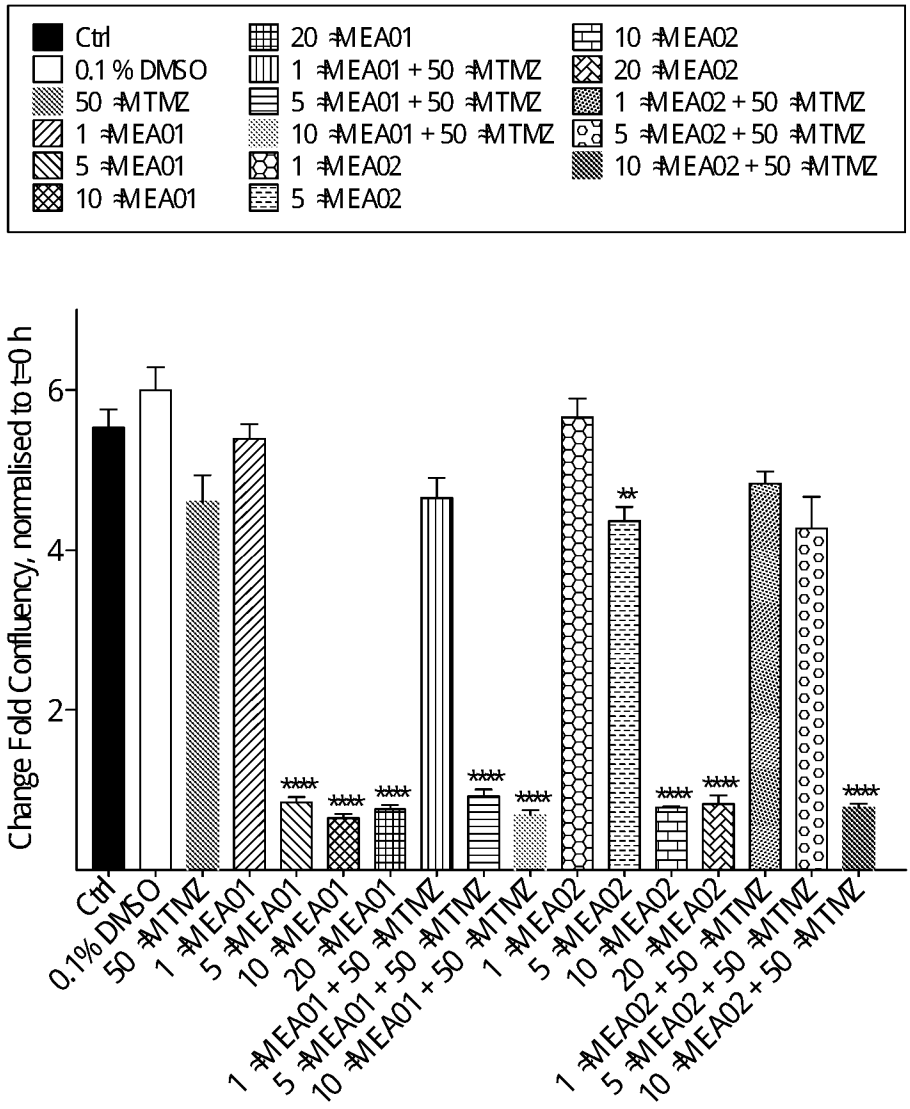


FIG. 2 (continued)

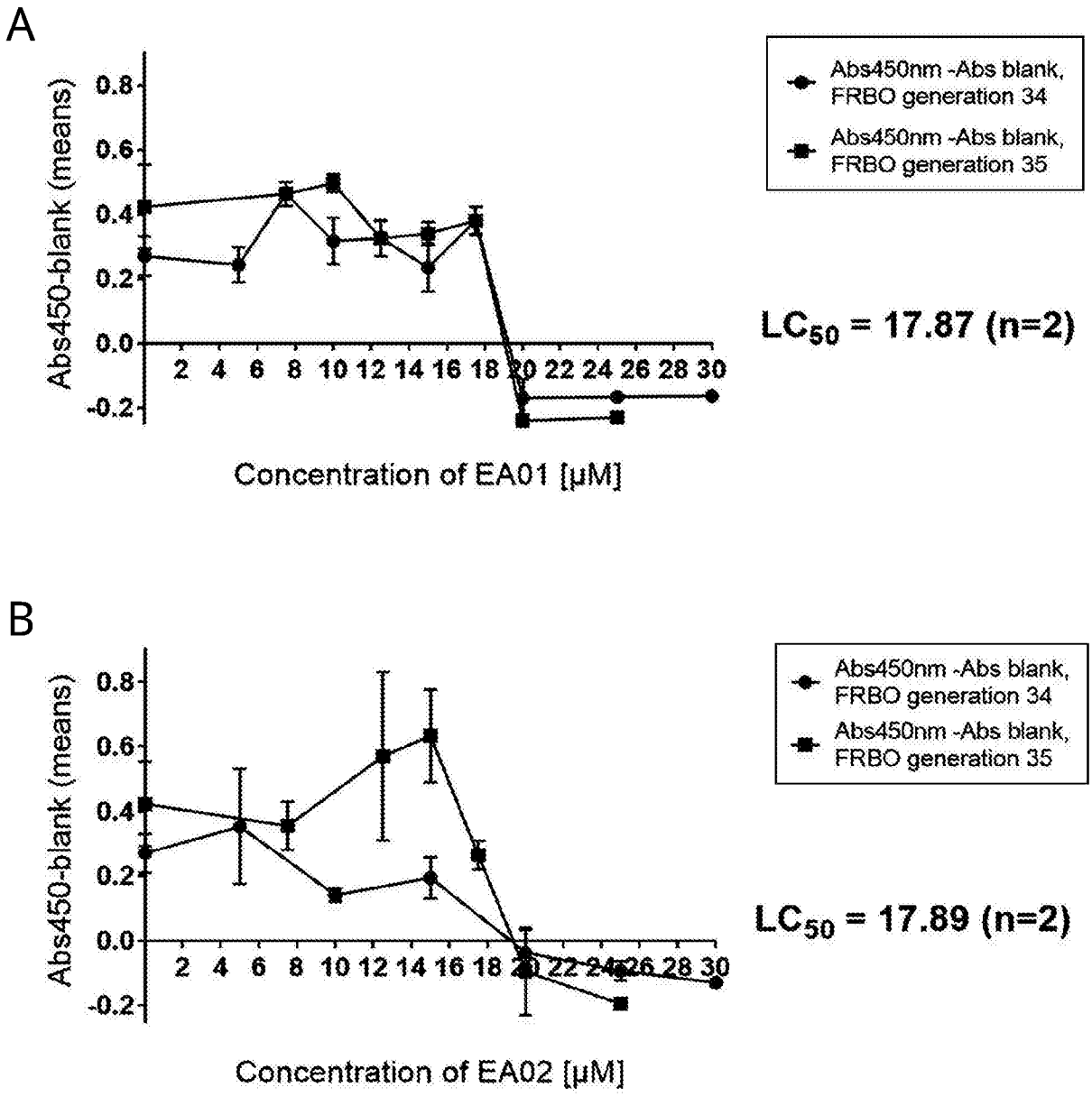

A
Abs450-blank (means)
0.8
0.6
0.4
0.2
0.0
-0.2
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Concentration of EA01 [µM]
Abs450nm -Abs blank, FRBO generation 34
Abs450nm -Abs blank, FRBO generation 35
LC50 = 17.87 (n=2)
B
Abs450-blank (means)
0.8
0.6
0.4
0.2
0.0
-0.2
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Concentration of EA02 [µM]
Abs450nm -Abs blank, FRBO generation 34
Abs450nm -Abs blank, FRBO generation 35
LC50 = 17.89 (n=2)

FIG. 3

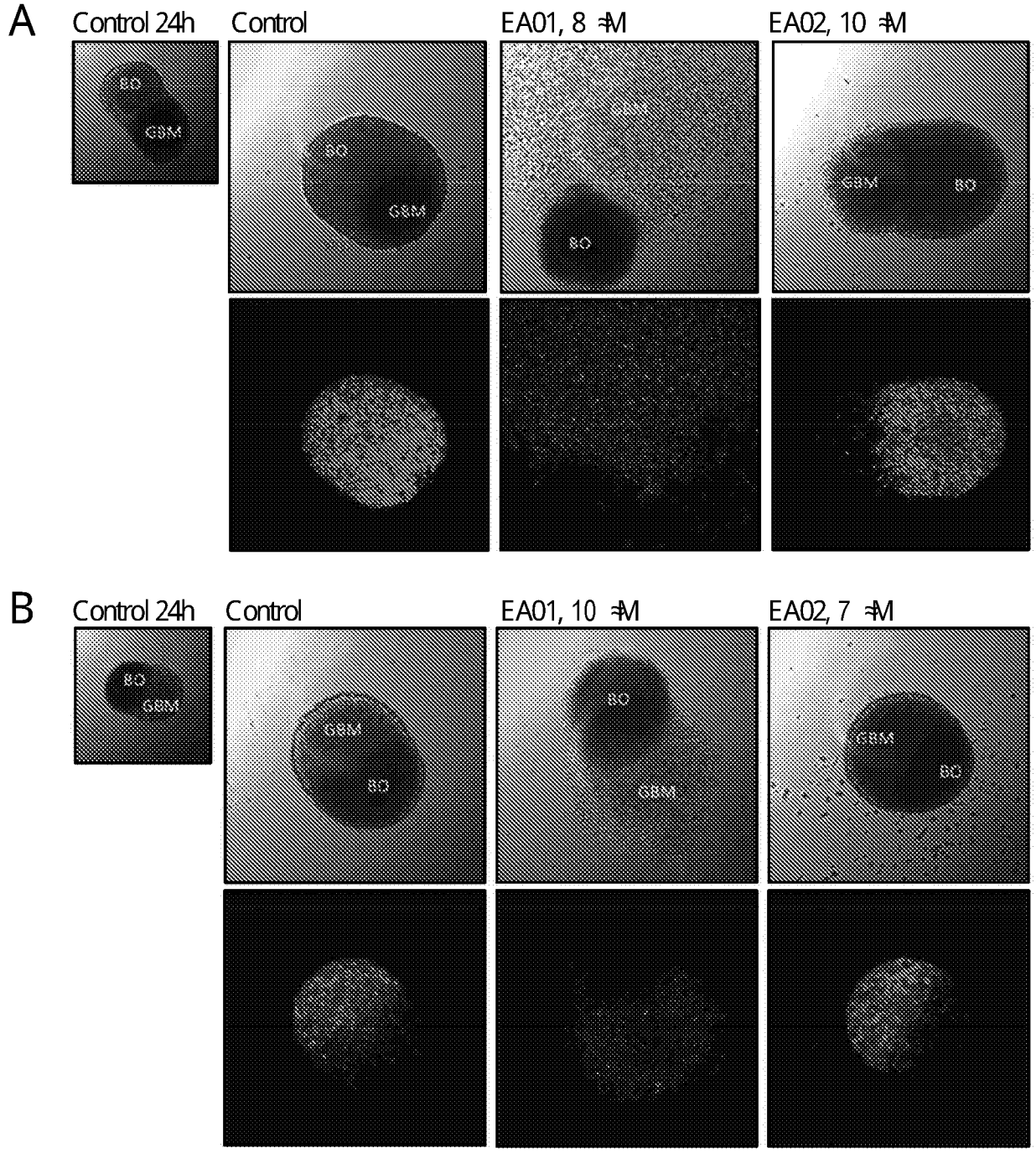

A
Control 24h
Control
EA01, 8 μM
EA02, 10 μM
BO
GBM
B
Control 24h
Control
EA01, 10 μM
EA02, 7 μM
BO
GBM

FIG. 4

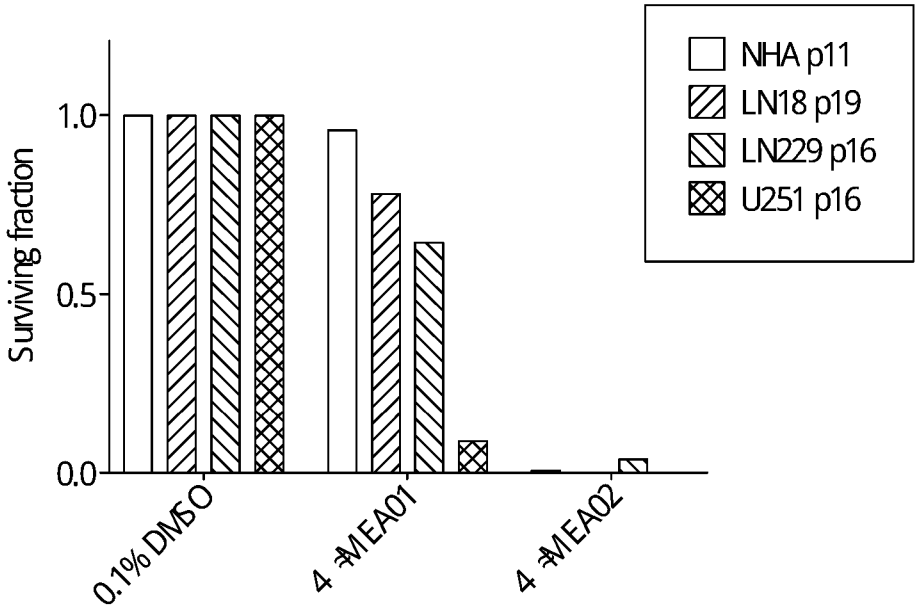

NHA p11
LN18 p19
LN229 p16
U251 p16
Surviving fraction
1.0
0.5
0.0
0.1% DMSO
4-MEA01
4-MEA02

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2022/052006

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5415 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/017185 A1 (ODYSSEY THERA INC [US]) 16 February 2006 (2006-02-16) claims 1,8,14; compound promazine	1-23
X	US 2013/289023 A1 (HUANG CHI-YING [TW] ET AL) 31 October 2013 (2013-10-31) claims 1,4,5; compound thioridazine	1-23

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2022	08/11/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bareyt, Sébastian

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIN SOON YOUNG ET AL: "The antipsychotic agent chlorpromazine induces autophagic cell death by inhibiting the Akt/mTOR pathway in human U-87MG glioma cells", CARCINOGENESIS, vol. 34, no. 9, 1 September 2013 (2013-09-01), pages 2080-2089, XP055956920, GB ISSN: 0143-3334, DOI: 10.1093/carcin/bgt169 Retrieved from the Internet: URL:https://watermark.silverchair.com/bgt169.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAuAwggLcBgkqhkiG9w0BBwagggLNMIICyQIBADCCAsIGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMdqYIe38hwVgVPnmoAgEQgIICk86k_V6wLV1XHQkmRPWsDDi0fKNt7y-MmvcvQMDk2WPHw4kvySTBNzUFrVW1zFiQBA7G9Q61_7PTAHhaYTS6XEMkn2rQG> compound chlorpromazine	1-16
X	DONNIER-MARÉCHAL MARION ET AL: "Carboline- and phenothiazine-derivated heterocycles as potent SIGMA-1 protein ligands", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 89, 18 October 2014 (2014-10-18), pages 198-206, XP029110639, ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2014.10.053 compound 6f	1-23
X	CHENG H-W ET AL: "Identification of thioridazine, an antipsychotic drug, as an antiglioblastoma and anticancer stem cell agent using public gene expression data", CELL DEATH & DISEASE, vol. 6, no. 5, 1 May 2015 (2015-05-01), pages e1753-e1753, XP055969769, DOI: 10.1038/cddis.2015.77 Retrieved from the Internet: URL:http://www.nature.com/articles/cddis201577> compound thioridazine	1-23

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2022/052006

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KANG SEOKMIN ET AL: "Trifluoperazine, a Well-Known Antipsychotic, Inhibits Glioblastoma Invasion by Binding to Calmodulin and Disinhibiting Calcium Release Channel IP3R", MOLECULAR CANCER THERAPEUTICS, vol. 16, no. 1, 1 January 2017 (2017-01-01), pages 217-227, XP055956918, US ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-16-0169-T Retrieved from the Internet: URL:https://watermark.silverchair.com/217.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAtEwggLNBgkqhkiG9w0BBwagggK-MIICugIBADCCArMGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMuJ1giUaJujsUcbY4AgEQgIIChI4Pr45eI6cBcecwLjKfpKiYCzM6GUqALCxmex-9IvhawUk14Wg1QdbuGqVd3UyXxvYv2VuKFLN27MLq4-0PrHBkdMTyFDiR> compound trifluoperazine	1-23
X	WO 2019/229236 A1 (INST NAT SANTE RECH MED [FR] ET AL.) 5 December 2019 (2019-12-05) claim 1; compound trifluoperazine	1-23
X	US 2002/048271 A1 (RASTINEJAD FARZAN [US] ET AL) 25 April 2002 (2002-04-25) paragraph [0160]; claim 24; compound trifluoperazine	1-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2022/052006

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