[0005] Inflammatory responses are notably associated with the influx of leukocytes and/or leukocyte chemotaxis. Inflammatory responses may result from infection with pathogenic organisms and viruses, noninfectious means such as trauma or reperfusion following myocardial infarction or stroke, immune responses to foreign antigens, and autoimmune diseases. Leukocytes provide a first line of immune defense against many common microorganisms.

[0006] Lee, *et al.*, *FASEB J.* (2006) 20:455-465 describes evidence that inhibition of PI3Kδ attenuates allergic airway inflammation and hyperresponsiveness in murine asthma models, demonstrating that selective inhibitors of PI3Kδ are useful to treat asthma and allergic reactions as well as immune disorders.

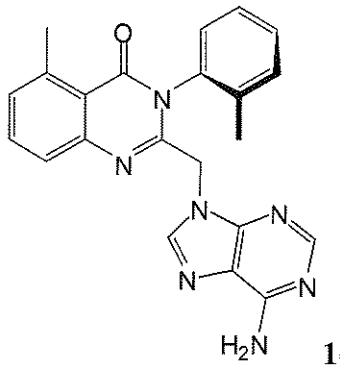
[0007] With regards to cancer, compounds that express relatively high levels of p110δ may be useful for treating mainly hematologic cancers. The p110β isoform of PI3K may also play a role in PI3K-mediated signaling in certain cancers, such as solid tumors.

[0008] There is a need for a treatment of PI3K-mediated disorders relating to cancers and inflammatory conditions. The present invention provides a specific isomer of one quinazolinone compound that is particularly useful for the treatment of inflammatory conditions and cancer.

Summary~~Disclosure~~ of the Invention

[0009] The invention relates to selective PI3Kδ inhibitors and methods to treat inflammatory conditions and cancers with compounds that are selective PI3Kδ inhibitors. In particular, compounds of the invention exist as separable atropisomers and the invention provides separated atropisomers having unexpected advantages over mixtures of atropisomers for use in treatment of inflammation. The compounds, compositions, and methods of the invention are therapeutically beneficial in treating inflammatory conditions.

[0009a] In a first aspect, the present invention refers to an optically active compound comprising an atropisomer of formula **1(S)**

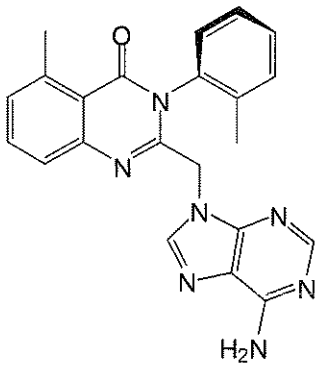


1(S)

or a pharmaceutically acceptable salt or solvate thereof;

wherein the atropisomer of formula **1(S)** or a pharmaceutically acceptable salt thereof, is present in excess of its corresponding enantiomer or a pharmaceutically acceptable salt thereof.

[0009b] In a second aspect, the present invention refers to an optically active compound comprising an atropisomer of formula **1(R)**

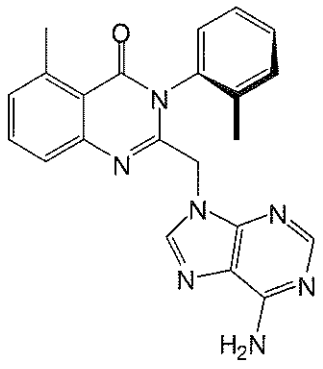


1(R)

or a pharmaceutically acceptable salt or solvate thereof;

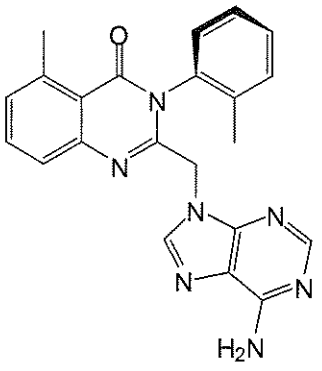
wherein the atropisomer of formula **1(R)** or a pharmaceutically acceptable salt thereof, is present in excess of its corresponding enantiomer or a pharmaceutically acceptable salt thereof.

[0010] In one ~~aspect~~example, the invention ~~provides~~describes an optically active compound comprising an atropisomer of formula **1(S)**



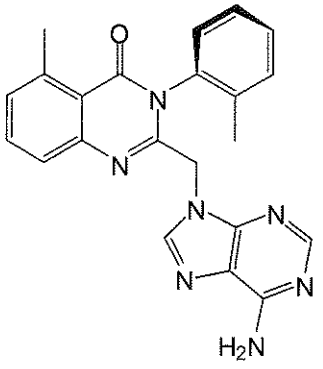
1(S)

or a pharmaceutically acceptable salt or solvate thereof; wherein the atropisomer of formula **1(S)** is present in excess of its corresponding enantiomer of formula **1(R)**



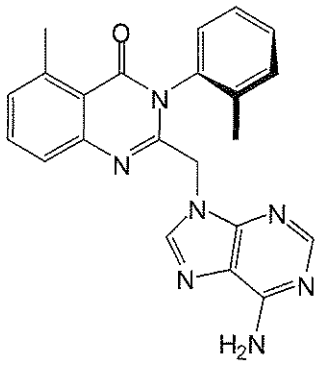
1(R).

[0011] In another ~~aspect~~example, the invention ~~provides~~describes an optically active compound comprising an atropisomer of formula **1(R)**



1(R)

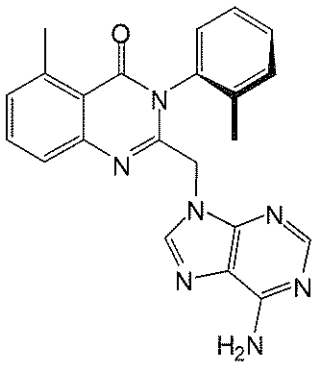
or a pharmaceutically acceptable salt or solvate thereof; and wherein the atropisomer of formula **1(R)** is present in excess of its corresponding enantiomer of formula **1(S)**



1(S).

[0012] In another ~~aspect~~example, the invention ~~provides~~describes a composition comprising an optically active compound described herein, and a pharmaceutically acceptable carrier. In another ~~aspect~~example, the invention ~~provides~~describes a method of treating a condition in a mammal, wherein the condition is characterized by inflammation. In some ~~embodiments~~examples, the condition is selected from the group consisting of chronic inflammatory diseases, tissue or organ transplant rejections, graft versus host disease (GVHD), multiple organ injury syndromes, acute glomerulonephritis, reactive arthritis, hereditary emphysema, chronic obstructive pulmonary disease (COPD), cystic fibrosis, adult respiratory distress syndrome (ARDS), ischemic-reperfusion injury, stroke, rheumatoid arthritis (RA), osteoarthritis (OA), asthma, allergic rhinitis, lupus nephritis, Crohn's disease, ulcerative colitis, necrotizing enterocolitis, pancreatitis, *Pneumocystis carinii* pneumonia (PCP), inflammatory bowel disease (IBD), severe acute respiratory syndrome (SARS), sepsis, community acquired pneumonia (CAP), multiple sclerosis (MS), myocardial infarction, respiratory syncytial virus (RSV) infection, dermatitis, acute purulent meningitis, thermal injury, granulocyte transfusion associated syndromes, cytokine-induced toxicity, and spinal cord injury; which comprises administering to said mammal a therapeutically effective amount of an optically active atropisomer described herein. In certain ~~embodiments~~examples, the optically active compound is represented by formula **1(S)**. In other ~~embodiments~~examples, the optically active compound is represented by formula **1(R)**.

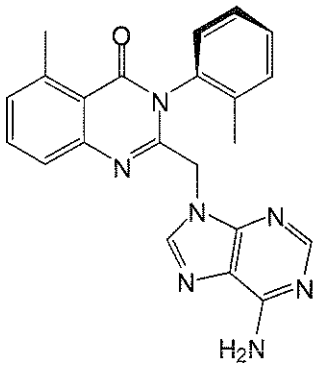
[0012a] In a third aspect, the present invention refers to a pharmaceutical composition comprising an optically active compound of formula **1(S)**,



1(S),

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

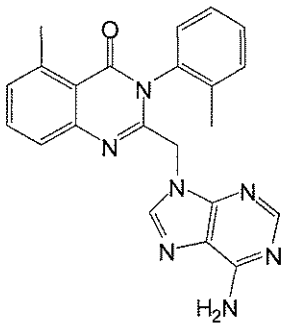
[0012b] In a fourth aspect, the present invention refers to a pharmaceutical composition comprising an optically active compound of formula 1(R),



1(R)

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

[0012c] In a fifth aspect, the present invention refers to an optically active compound obtained by separation of a racemic mixture of formula **1**



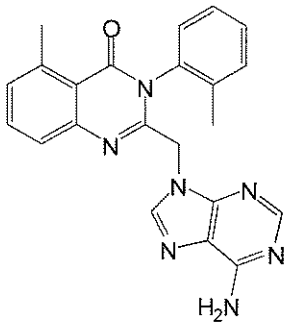
(1);

or a pharmaceutically acceptable salt thereof;

wherein the optically active compound comprises an atropisomer of formula 1 or a pharmaceutically acceptable salt thereof, in excess of its enantiomer or a pharmaceutically acceptable salt thereof, and

wherein the optically active compound is characterized by a shorter retention time on a normal phase chiral column compared to its enantiomer or a pharmaceutically acceptable salt thereof.

[0012d] In a sixth aspect, the present invention refers to an optically active compound obtained by separation of a racemic mixture of formula **1**



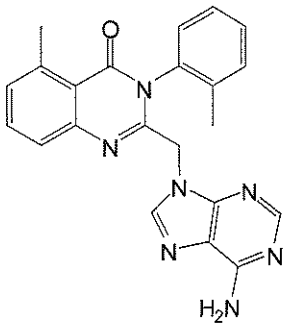
(**1**);

or a pharmaceutically acceptable salt or solvate thereof;

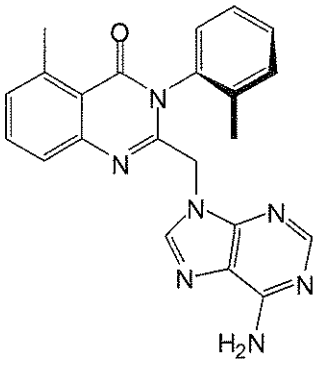
wherein the optically active compound comprises an atropisomer of formula 1 or a pharmaceutically acceptable salt thereof, in excess of its enantiomer or pharmaceutically acceptable salt thereof, and

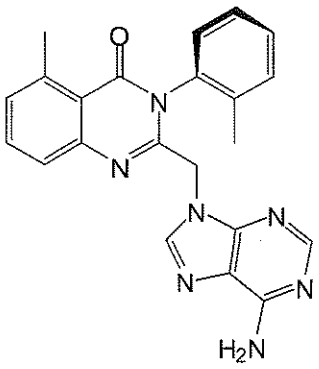
wherein the optically active compound is characterized by a longer retention time on a normal phase chiral column compared to its enantiomer or a pharmaceutically acceptable salt thereof.

[0013] In another ~~aspect~~example, the invention ~~provides~~describes an optically active atropisomer obtained by chiral chromatographic separation of a racemic mixture, of formula **1**

 (**1**);

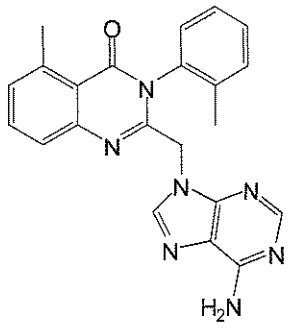
or a pharmaceutically acceptable salt or solvate thereof; wherein a racemic of formula **1** is separated using a normal phase chiral column, and two peaks, A and B, are resolved, wherein peak A and peak B represent the atropisomers, **1(S)** and **1(R)**, respectively,

 **1(S)**

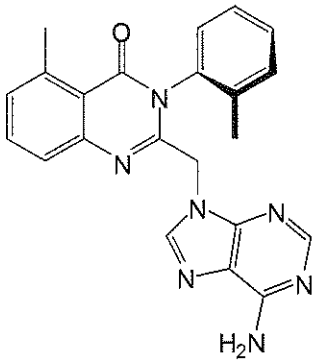
 **1(R)**; and

wherein the optically active atropisomer obtained consists predominantly of the first isomer to elute from the column. In certain ~~embodiments~~examples, the optically active atropisomer obtained consists of the compound of formula **1(S)** substantially free of the compound of formula **1(R)**. In another ~~embodiment~~example, the optically active atropisomer obtained consists of the compound of formula **1(R)** substantially free of the compound of formula **1(S)**.

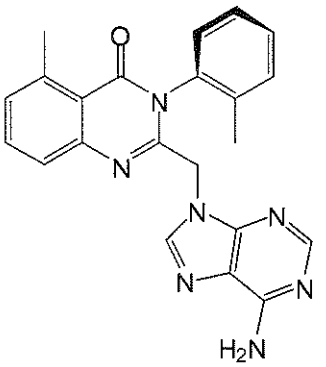
[0014] In yet another ~~aspect~~example, the invention ~~provides~~describes an optically active atropisomer obtained by chiral chromatographic separation of a racemic of formula **1**

 (**1**);

or a pharmaceutically acceptable salt or solvate thereof; wherein a racemic mixture of formula **1** is separated using a normal phase chiral column, and two peaks, A and B, are resolved, wherein peak A and peak B represent the atropisomers, **1(S)** and **1(R)**, respectively,



1(S)



1(R); and

wherein the optically active atropisomer obtained consists predominantly of the second isomer to elute from the column.

[0015] In another ~~aspect~~example, the invention ~~provides~~describes pharmaceutical compositions comprising any of the optically active compounds described herein, and at least one pharmaceutically acceptable excipient.

Brief Description of the Drawings

[0016] Figure 1 shows a synthetic scheme of the preparation of racemic compound **1**.

[0017] Figure 2 shows HPLC traces of injected compound, **1**, containing resolved atropisomers on normal phase (Fig. 2A) or reverse phase (Fig. 2B) chiral columns.

[0018] Figure 3 shows HPLC traces of resolved injected compound, **1**, prior to preparatory chromatographic separation (Fig. 3A), and isolated atropisomers peak 1 (Fig. 3B), **1(S)**, and peak 2 (Fig. 3C), **1(R)**, after separation using a normal phase column method.

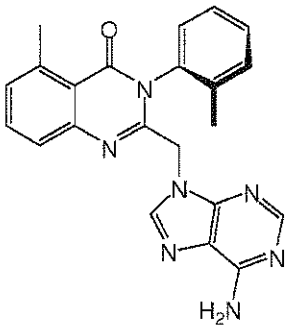
[0019] Figure 4 shows solubility data of compound **1** and the resolved atropisomers, **1(S)** and **1(R)**, in a series of aqueous solvents.

[0020] Figure 5 shows the differences in p110 activity of different isoforms between racemic compound **1** and the atropisomers **1(S)** and **1(R)** in biochemical (Fig. 5A) and cell-based assays (Fig. 5B).

[0021] Figure 6 shows the plasma concentration of atropisomers **1(S)** and **1(R)** in rats after oral dosing with racemic compound **1**.

Claims

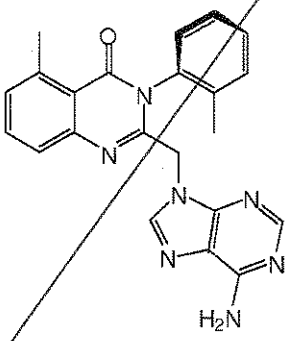
1. An optically active compound comprising an atropisomer of formula **1(S)**



1(S)

or a pharmaceutically acceptable salt or solvate thereof;

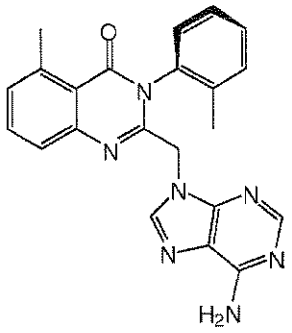
wherein the atropisomer of formula **1(S)** is present in excess of its corresponding enantiomer of formula **1(R)**



1(R).

2. The optically active compound according to claim 1, substantially free of its corresponding atropisomer of formula **1(R)**.

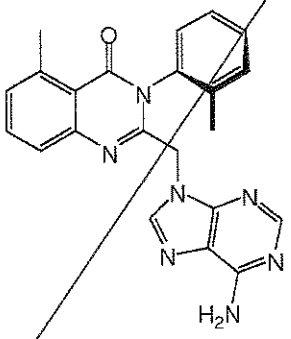
3. An optically active compound comprising an atropisomer of formula **1(R)**



1(R)

or a pharmaceutically acceptable salt or solvate thereof;

wherein the atropisomer of formula **1(R)** is present in excess of its corresponding enantiomer of formula **1(S)**



1(S).

4. The optically active compound according to claim 3, substantially free of its corresponding atropisomer of formula **1(S)**.

5. A pharmaceutical composition comprising the optically active compound according to claim 1, and a pharmaceutically acceptable carrier.

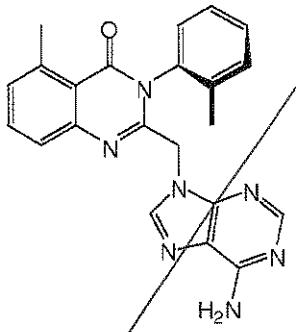
6. A pharmaceutical composition comprising the optically active compound according to claim 3, and a pharmaceutically acceptable carrier.

7. A method of treating a condition in a mammal, wherein the condition is selected from the group consisting of allergic rhinitis, asthma, atopic dermatitis, chronic obstructive pulmonary disease (COPD), multiple sclerosis (MS), rheumatoid arthritis (RA), and diabetes,

which comprises administering to a mammal in need thereof a therapeutically effective amount of the optically active compound according to claim 1.

8. A method of treating a condition in a human, wherein the condition is selected from the group consisting of allergic rhinitis, asthma, atopic dermatitis, chronic obstructive pulmonary disease (COPD), multiple sclerosis (MS), rheumatoid arthritis (RA), and diabetes,

which comprises administering to a human in need thereof a therapeutically effective amount of an optically active atropisomer having the formula

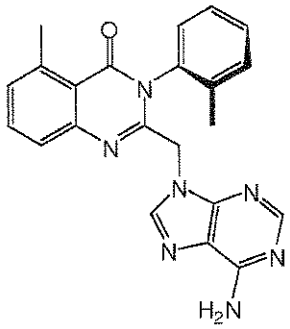


1(S)

or a pharmaceutically acceptable salt thereof.

9. A method of treating cancer in a mammal, wherein the cancer is leukemia, lymphoma or multiple myeloma, which comprises administering to a mammal in need thereof a therapeutically effective amount of the optically active compound according to claim 1.

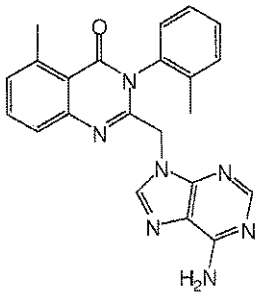
10. A method of treating cancer in a human, wherein the cancer is leukemia, lymphoma, or multiple myeloma, which comprises administering to a human in need thereof a therapeutically effective amount of an optically active atropisomer having the formula



1(S)

or a pharmaceutically acceptable salt thereof.

11. An optically active atropisomer obtained by separation of a racemic mixture of formula **1**

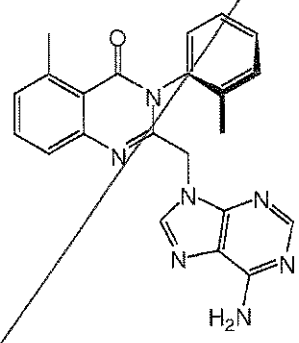


(1);

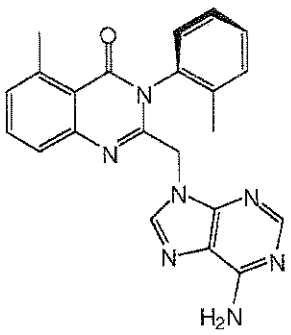
or a pharmaceutically acceptable salt or solvate thereof;

wherein the optically active atropisomer is characterized by a shorter retention time on a normal phase chiral column when compared to its enantiomer.

12. The atropisomer according to claim 11, wherein the optically active atropisomer obtained consists mostly of the compound of formula **1(S)** substantially free of the compound of formula **1(R)**, wherein **1(S)** and **1(R)** are depicted below:

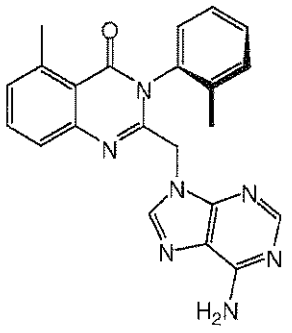


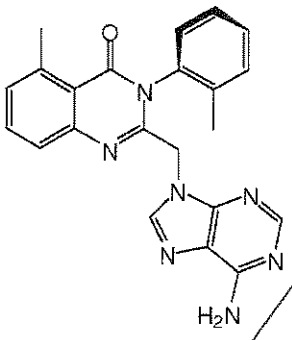
1(S)



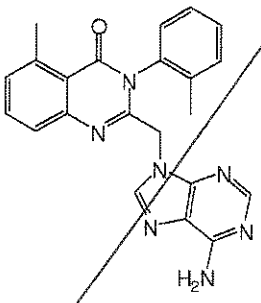
1(R).

13. The atropisomer according to claim 11, wherein the optically active atropisomer obtained consists mostly of the compound of formula **1(R)** substantially free of the compound of formula **1(S)**, wherein **1(S)** and **1(R)** are depicted below:


1(S)


1(R).

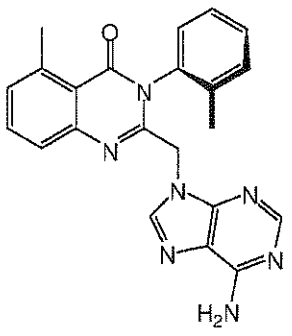
14. An optically active atropisomer obtained by separation of a racemic mixture of formula **1**


(**1**);

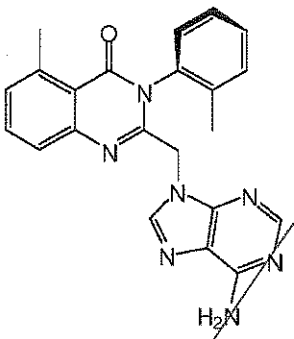
or a pharmaceutically acceptable salt or solvate thereof;

wherein the optically active atropisomer is characterized by a longer retention time on a normal phase chiral column when compared to its enantiomer.

15. The atropisomer according to claim 14, wherein the optically active atropisomer obtained consists mostly of the compound of formula **1(S)** substantially free of the compound of formula **1(R)**, wherein **1(S)** and **1(R)** are depicted below:

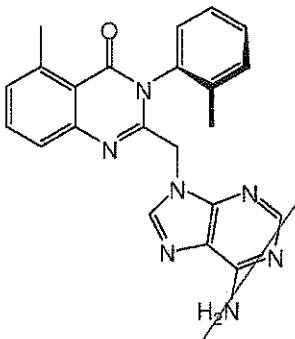


1(S)

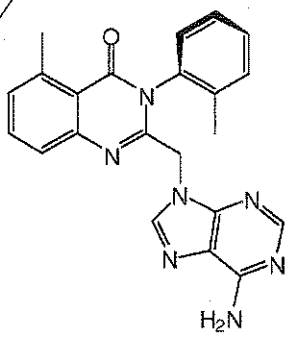


1(R).

16. The atropisomer according to claim 14, wherein the optically active atropisomer obtained consists mostly of the compound of formula **1(R)** substantially free of the compound of formula **1(S)**, wherein **1(S)** and **1(R)** are depicted below:



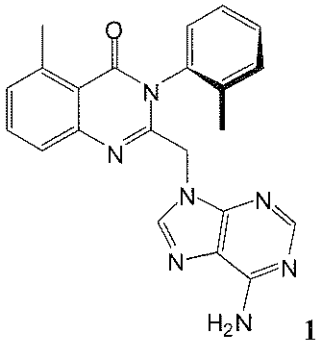
1(S)



1(R).

Claims

1. An optically active compound comprising an atropisomer of formula **1(S)**



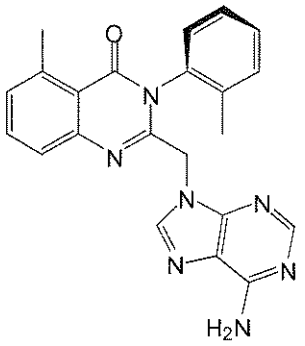
1(S)

or a pharmaceutically acceptable salt or solvate thereof;

wherein the atropisomer of formula **1(S)** or a pharmaceutically acceptable salt thereof, is present in excess of its corresponding enantiomer or a pharmaceutically acceptable salt thereof.

2. The optically active compound according to claim 1, substantially free of the corresponding enantiomer or a pharmaceutically acceptable salt thereof.

3. An optically active compound comprising an atropisomer of formula **1(R)**



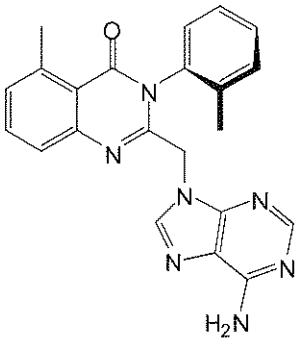
1(R)

or a pharmaceutically acceptable salt or solvate thereof;

wherein the atropisomer of formula **1(R)** or a pharmaceutically acceptable salt thereof, is present in excess of its corresponding enantiomer or a pharmaceutically acceptable salt thereof.

4. The optically active compound according to claim 3, substantially free of the corresponding enantiomer or a pharmaceutically acceptable salt thereof.

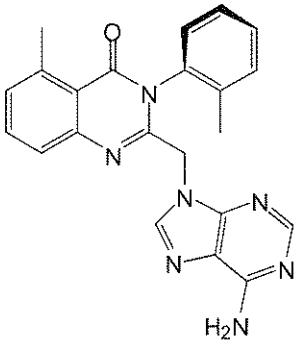
5. A pharmaceutical composition comprising an optically active compound of formula **1(S)**,



1(S),

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

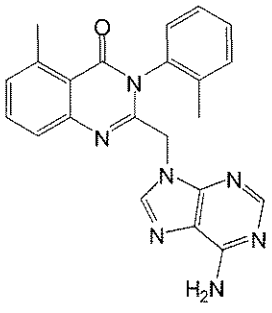
6. A pharmaceutical composition comprising an optically active compound of formula 1(R),



1(R)

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

7. An optically active compound obtained by separation of a racemic mixture of formula **1**



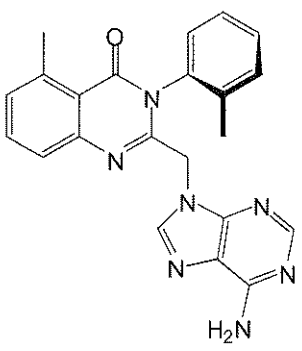
(1);

or a pharmaceutically acceptable salt thereof;

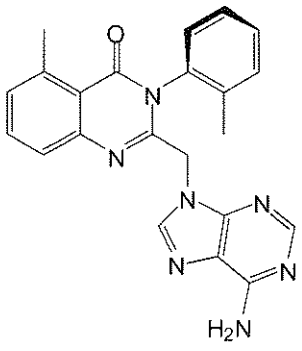
wherein the optically active compound comprises an atropisomer of formula 1 or a pharmaceutically acceptable salt thereof, in excess of its enantiomer or a pharmaceutically acceptable salt thereof, and

wherein the optically active compound is characterized by a shorter retention time on a normal phase chiral column compared to its enantiomer or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 7, consisting of the compound of formula **1(S)** or a pharmaceutically acceptable salt thereof, substantially free of the compound of formula **1(R)**, or a pharmaceutically acceptable salt thereof, wherein **1(S)** and **1(R)** are depicted below:

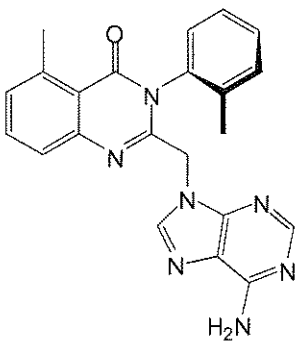


1(S)

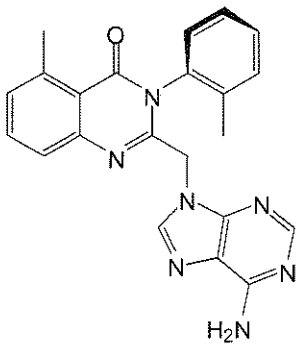


1(R).

9. The compound according to claim 7, consisting of the compound of formula **1(R)** or a pharmaceutically acceptable salt thereof, substantially free of the compound of formula **1(S)**, or a pharmaceutically acceptable salt thereof, wherein **1(S)** and **1(R)** are depicted below:

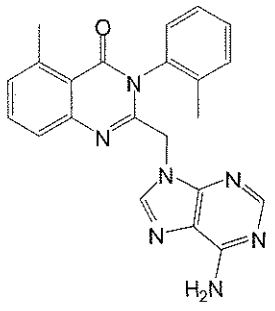


1(S)



1(R).

10. An optically active compound obtained by separation of a racemic mixture of formula **1**



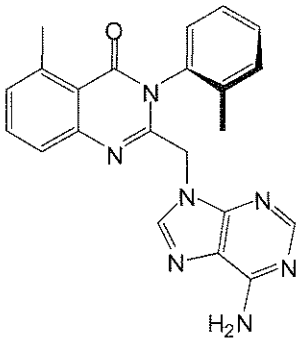
(1);

or a pharmaceutically acceptable salt or solvate thereof;

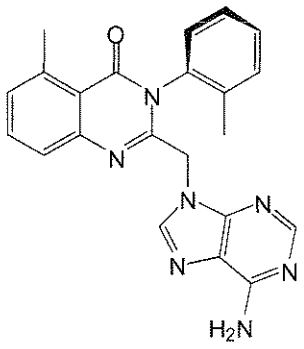
wherein the optically active compound comprises an atropisomer of formula 1 or a pharmaceutically acceptable salt thereof, in excess of its enantiomer or pharmaceutically acceptable salt thereof, and

wherein the optically active compound is characterized by a longer retention time on a normal phase chiral column compared to its enantiomer or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10 consisting of the compound of formula **1(S)** or pharmaceutically acceptable salt thereof, substantially free of the compound of formula **1(R),** or a pharmaceutically acceptable salt thereof, wherein **1(S)** and **1(R)** are depicted below:



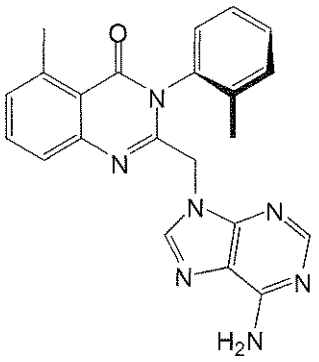
1(S)



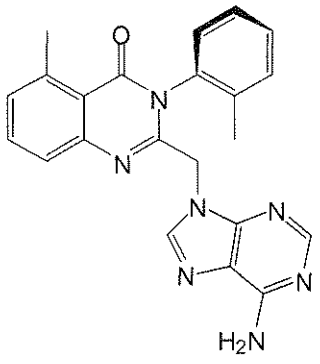
1(R).

12. The compound according to claim 10, consisting of the compound of formula **1(R)** or a pharmaceutically acceptable salt thereof, substantially free of the compound of

formula **1(S)** or a pharmaceutically acceptable salt thereof, wherein **1(S)** and **1(R)** are depicted below:



1(S)



1(R).