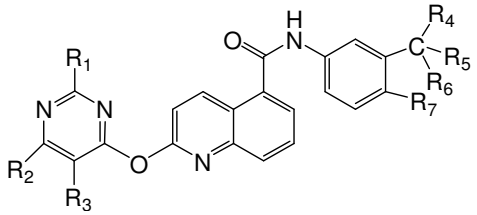
which are closely associated with cancers. For example, the abnormal activation of FGFR2 has been found in endometrial cancer, cervical cancer, breast cancer, lung cancer and stomach cancer. SRC kinase family comprises proteins having tyrosine protein kinase activity. SRC kinase family, as an oncegene protein, is initially found in Rous Sarcoma Virus. It has been found that the inhibition of SRC has some treatment and improvement effect on cancers or other diseases. p38 Mitogen-Activated Protein Kinase (MAPK) Pathway is intracellular stress response signal pathway, which is closely associated with inflammatory response.

Therefore, there is still a need to develop new protein kinase inhibitors.

Summary of the Invention

The object of the present invention is to provide a new compound as angiogenesis inhibitor and/or protein kinase inhibitor, intermediate compound for preparing it, and use thereof.

The present invention provides a compound as represented by formula I, or a pharmaceutically acceptable salt thereof, wherein the structural formula is as follows:



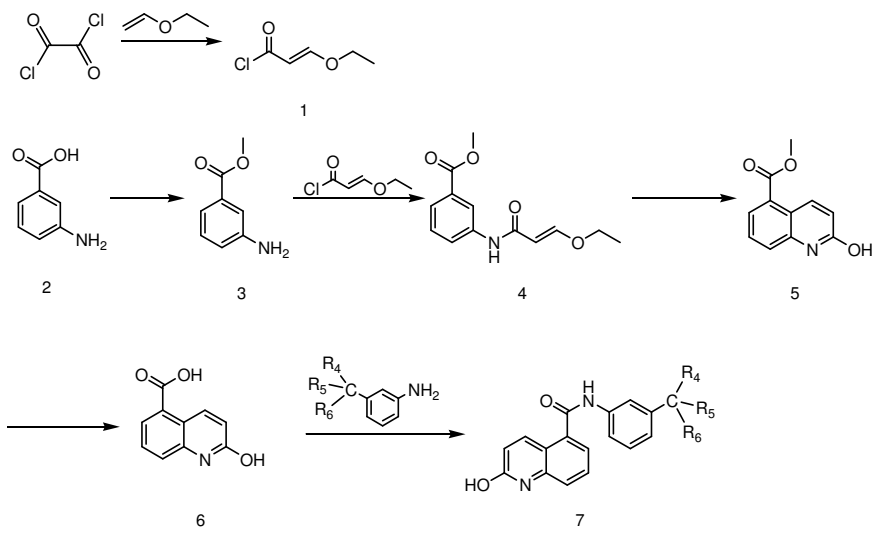
Formula I

wherein, R_1 is selected from H, amino, hydroxy or sulfydryl; R_2 is selected from H, amino, hydroxy, sulfydryl or $-(CH_2)_nNHR_8$, wherein n=1-5, R_8 is H or C1-3 alkyl; R_3 is selected from H or C1-6 alkyl; R_4, R_5 and R_6 are each independently selected from H, halogen, C1-6 alkyl or halogen substituted alkyl; and R_7 is selected from H, C1-6 alkyl or halogen;

or, R_2 and R_3 together with the carbon atom connecting them form substituted or unsubstituted 5- or 6-membered ring having 1 to 2 heteroatoms, wherein the heteroatoms are N, O or S, and the substituent is C1-6 alkyl.

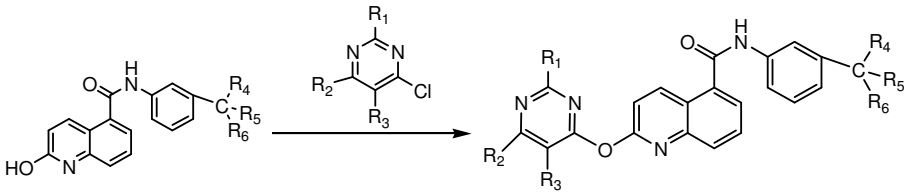
In one embodiment, R_2 is selected from H, amino or $-(CH_2)_nNHR_8$, wherein n=1-3, R_8 is H or C1-2 alkyl; R_3 is selected from H or C1-2 alkyl; R_4, R_5 and R_6 are each independently selected from halogen, C1-2 alkyl or halogen substituted alkyl; and R_7 is selected from H or halogen;

or, R_2 and R_3 together with the carbon atom connecting them form substituted or unsubstituted 5-



wherein R_4, R_5 and R_6 have the same definition as above;

(2) synthesis of the target compound:



wherein R_1, R_2 and R_3 have the same definition as above.

The present invention further provides the use of the above compound, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for inhibiting the abnormal proliferation of angiogenesis.

In one embodiment, the medicament for inhibiting the abnormal proliferation of angiogenesis is vascular endothelial cell growth factor receptor 2 (VEGFR2) inhibitor.

In another embodiment, the medicament for inhibiting the abnormal proliferation of angiogenesis is a medicament against ocular angiogenesis.

In another embodiment, the medicament for inhibiting the abnormal proliferation of angiogenesis is choroidal angiogenesis inhibitor.

In another embodiment, the medicament for inhibiting the abnormal proliferation of angiogenesis is a medicament for treating or preventing wet macular degeneration, diabetic retinopathy or neovascular glaucoma.

In another embodiment, the medicament preferably is an ophthalmic preparation.

In another embodiment, the ophthalmic preparation is an eye drop, an eye ointment or an

Preferably, suitable organic acids include, but not limited to, carboxylic acid, phosphoric acid, sulfonic acid or aminocarboxylicacid, for example, acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, hydroxyacetic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acid, e.g., glutamic acid or aspartic acid, maleic acid, hydroxy acid, methyl maleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-amino salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane or ethane sulfonic acid, 2-oxyethylsulfonic acid, ethane-1,2-disulfonic acid, phenylsulfonic acid, 2-naphthalene sulfonic acid, 1,5-naphthalene disulfonic acid, 2-toluene sulfonic acid, p-toluene sulfonic acid, ethylsulfuric acid, dodecyl sulfuric acid, N-cyclohexyl amino acetic acid, N-methyl-N-ethyl-N-propyl-sulfamic acid, or other organic acids, e.g., ascorbic acid.

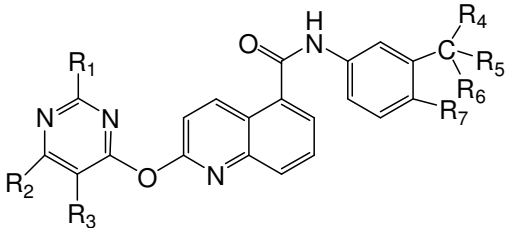
Additionally, the salt can also be pharmaceutically unacceptable salt used in separation or purification, for example, picrate or perchlorate. However, the salt used for therapeutic use can only be pharmaceutically acceptable salt or free compound, in the form of suitable pharmaceutical preparation.

In one embodiment, the present invention further provides isotope labelled compound of the above compound, or a pharmaceutically acceptable salt thereof, wherein the isotope labelled compound refers to the same compound as that of present invention, but one or more atoms therein are replaced by another atom, which has different atomic mass or mass number in comparison with those common in nature. The isotopes that can be introduced into the compound comprise H, C, N, O, S, i.e., 2H, 3H, 13C, 14C, 15N, 17O, 18O, and 35S. Compounds comprising the above isotopic and/or other isotopic atoms, and stereoisomers thereof, as well as pharmaceutical salts of the compounds and stereoisomers, should be within the scope of the present invention.

In the present invention, the separation and purification of the critical intermediate and compound are conducted by common separation and purification methods in organic chemistry,

CLAIMS

1. A compound as represented by formula I, or a pharmaceutically acceptable salt thereof,



Formula I

wherein, R_1 is selected from H, amino, hydroxy or sulfydryl, R_2 is selected from H, amino, hydroxy, sulfydryl or $-(CH_2)_nNHR_8$, wherein n=1-5, R_8 is H or C1-3 alkyl; R_3 is selected from H or C1-6 alkyl; R_4, R_5 and R_6 are each independently selected from H, halogen, C1-6 alkyl or halogen substituted alkyl; and R_7 is selected from H, C1-6 alkyl or halogen;

or, R_2 and R_3 together with the carbon atom connecting them form substituted or unsubstituted 5- or 6-membered ring having 1 to 2 heteroatoms, wherein the heteroatoms are N, O or S, and the substituent is C1-6 alkyl.

2. The compound or the pharmaceutically acceptable salt thereof according to claim 1, wherein R_2 is selected from H, amino or $-(CH_2)_nNHR_8$, wherein n=1-3, R_8 is H or C1-2 alkyl; R_3 is selected from H or C1-2 alkyl; R_4, R_5 and R_6 are each independently selected from halogen, C1-2 alkyl or halogen substituted alkyl; and R_7 is selected from H or halogen;

or, R_2 and R_3 together with the carbon atom connecting them form substituted or unsubstituted 5- or 6-membered ring having 1 nitrogen atom, wherein the substituent is C1-3 alkyl.

3. The compound or the pharmaceutically acceptable salt thereof according to claim 1, wherein R_2 is selected from H, amino or $-(CH_2)_nNHR_8$, wherein n=1-3, R_8 is H or C1-2 alkyl; R_3 is selected from H or C1-2 alkyl; R_4, R_5 and R_6 are each independently selected from halogen, C1-2 alkyl or halogen substituted alkyl; and R_7 is selected from H or halogen;

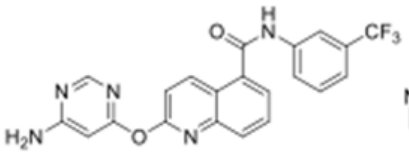
or, R_2 and R_3 together with the carbon atom connecting them form substituted or unsubstituted 5- or 6-membered ring having 1 nitrogen atom, wherein the substituent is C1-3 alkyl,

the halogen is F or Cl.

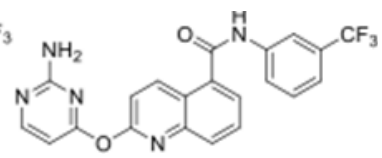
4. The compound or the pharmaceutically acceptable salt thereof according to claim 2 or 3, wherein R_2 is selected from amino or $-(CH_2)_nNHR_8$; or, R_2 and R_3 together with the carbon atom connecting them form substituted or unsubstituted 5- or 6-membered ring having 1 nitrogen atom, wherein the substituent is C1-3 alkyl.

5. The compound or the pharmaceutically acceptable salt thereof according to claim 2 or 3, wherein at least one of R_1, R_2 and R_3 is amino, and the rest are H; R_4, R_5 and R_6 are the same and are selected from F or Cl; and R_7 is H.

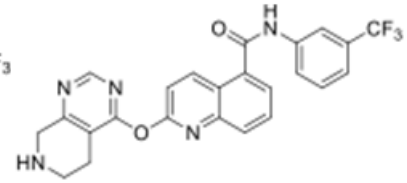
6. The compound or the pharmaceutically acceptable salt thereof according to any one of claims 1-5, wherein the compound is one of the following compounds:



2-1 ,



2-2 ,



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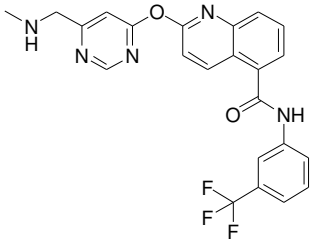
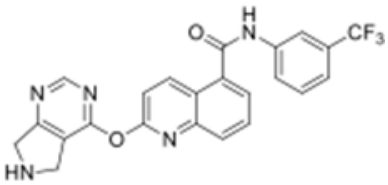


2-4 ,



2-5 .

7. Use of the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1-6 in the preparation of a medicament for inhibiting the abnormal proliferation of angiogenesis or treating diseases associated with the abnormal proliferation of angiogenesis.

8. Use according to claim 7, wherein the medicament for inhibiting the abnormal proliferation of angiogenesis is VEGFR2 inhibitor.

9. Use according to claim 7, wherein the medicament for inhibiting the abnormal proliferation of angiogenesis is a medicament against ocular angiogenesis, and the diseases associated with the abnormal proliferation of angiogenesis are diseases associated with ocular angiogenesis.

10. Use according to claim 7, wherein the medicament for inhibiting the abnormal proliferation of angiogenesis is choroidal angiogenesis inhibitor, and the diseases associated with the abnormal proliferation of angiogenesis are diseases associated with choroidal angiogenesis.

11. Use according to claim 9 or 10, wherein the medicament for inhibiting the abnormal proliferation of angiogenesis is a medicament for treating or preventing wet macular degeneration, diabetic retinopathy or neovascular glaucoma, and the diseases associated with the abnormal proliferation of angiogenesis are wet macular degeneration, diabetic retinopathy or neovascular glaucoma.

12. Use of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-6 in the preparation of a protein kinase inhibitor medicament or in the preparation of a medicament for treating diseases caused by the abnormal protein kinases.

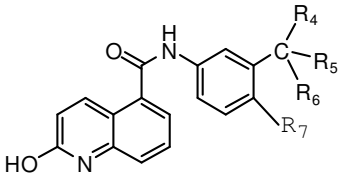
13. Use according to claim 12, wherein the protein kinases are VEGFR2, PDGFR-β, KIT, AURORA-B, FGFR2, SRC, JAK2 or P38-α.

14. Use according to claim 12, wherein the protein kinases are VEGFR2, KIT or PDGFR-β.

15. A pharmaceutical composition, comprising an effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-6.

16. The pharmaceutical composition according to claim 15, wherein the composition is an ophthalmic preparation.

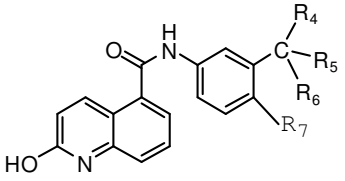
17. An intermediate compound as represented by formula II:



II

wherein R_4, R_5 and R_6 are each independently selected from H, halogen, C1-6 alkyl or halogen substituted alkyl, R_7 is selected from H, C1-6 alkyl or halogen.

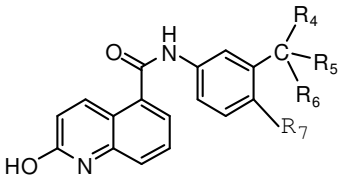
18. An intermediate compound as represented by formula II:



II

wherein R_4, R_5 and R_6 are each independently selected from halogen, C1-2 alkyl or halogen substituted alkyl, R_7 is selected from H or halogen.

19. An intermediate compound as represented by formula II:



II

wherein R_4, R_5 and R_6 are the same, and are selected from F or Cl; and R_7 is H.