

Pyrazolyquinoline Compounds and Preparation Methods and Pharmaceutical Compositions Thereof

FIELD OF THE INVENTION

[0001] The present invention is related to a pyrazolyquinoline compound and the preparation method and pharmaceutical composition thereof, and in particular, a pyrazolyquinoline compound against dengue virus and the preparation method and pharmaceutical composition thereof.

BACKGROUND OF THE INVENTION

[0002] Dengue virus (DENV) belongs to the family Flaviviridae and is closely related to West Nile virus (WNV), Yellow Fever virus (YFV) and Hepatitis C virus (HCV). DENV is transmitted by mosquitoes of the species *Aedes aegypti* or *Aedes albopictus*, and people who are infected with DENV will get dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

[0003] Each year, there are about fifty to one hundred million people infected with DENV in the world, and 0.5 million people suffer from DHF causing approximately twenty thousand fatalities. At present, dengue fever is endemic in 112 countries around the world, particularly in tropical and subtropical Asia, Latin America and Caribbean, and there are about 2.5 billion people at the risk of infection. There is a growing number of dengue cases occurring in Taiwan (which is situated in the subtropics) each year, and the epidemic issue of dengue has become a serious public health problem.

[0004] However, there is no effective drug for treating diseases caused by dengue virus infection, and most patients can only receive symptomatic

therapy or supportive medical care. The development of safe and effective medicine is therefore urgently needed.

SUMMARY OF THE INVENTION

[0005] The first aspect of the present invention is to provide a pyrazolyquinoline compound, including: a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R_1 being a halide; a pyrazol; a first benzyl; and a second benzyl, wherein: a C2 position of the quinolinyl binds to a C3 or a C5 position of the pyrazol; on a first condition that the C2 position of the quinolinyl binds to the C3 position of the pyrazol, the C5 position of the pyrazol binds to a C4 position of the first benzyl; on a second condition that the C2 position of the quinolinyl binds to the C5 position of the pyrazol, the C3 position of the pyrazol binds to the C4 position of the first benzyl; and an N1 position of the pyrazol binds to a C4 position of the second benzyl.

[0006] The second aspect of the present invention is to provide a pyrazolyquinoline compound, including: a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R_1 being a halide; a pyrazol; a first benzyl; and a second benzyl, wherein: a C2 position of the quinolinyl binds to a carbon of the pyrazol, another carbon of the pyrazol binds to a C4 position of the second benzyl, and an N1 position of the pyrazol binds to a C4 position of the first benzyl.

[0007] The third aspect of the present invention is to provide a method for preparing a pyrazolyquinoline compound, including steps of: providing 6-fluoro-2-methylquinoline; oxidizing the 6-fluoro-2-methylquinoline with selenium dioxide to form 6-fluoro-2-formylquinoline; condensing the 6-fluoro-2-formylquinoline with an acetophenone derivative to form a carbonyl product; and treating the carbonyl product with a phenylhydrazine derivative

to form the pyrazolyquinoline compound.

[0008] The fourth aspect of the present invention is to provide a pharmaceutical composition, including: a therapeutically effective amount of a pharmaceutical component of the pyrazolyquinoline compound as described above or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier of the pharmaceutical component.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Fig. 1 depicts the synthetic example 1 of the present invention, wherein the quinoliny chalcone compounds **3a-c** are prepared.

[0010] Fig. 2 depicts the synthetic example 2, wherein the pyrazolyquinoline compounds **4a-5c** are prepared, and the synthetic example 3, wherein the pyrazolyquinoline compounds **6a-8c** are prepared, of the present invention.

[0011] Fig. 3 depicts the experiment 1 of the present invention, wherein the structures of 6-fluoro-2-[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline (compound **4c**) and 6-fluoro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **5c**) are determined.

[0012] Fig. 4 depicts the reverse transcriptase-real time polymerase chain reaction (RT-qPCR) in the experiment 6 of the present invention.

[0013] Fig. 5 depicts the western blotting in the experiment 6 of the present invention.

[0014] Figs. 6(a), 6(b) and 6(c) depict the anti-DENV-2 activity assay *in vivo* of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] The technical contents, features and effects related to the present invention are clearly illustrated by the following preferred embodiments.

[0016] The first embodiment of the present invention is to provide a pyrazolyquinoline compound, including: a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R₁ being a halide, the halide can be, but is not limited to, fluorine, chloride, bromide and iodine; a pyrazol; a first benzyl; and a second benzyl, wherein: a C2 position of the quinolinyl binds to a C3 or a C5 position of the pyrazol; on a first condition that the C2 position of the quinolinyl binds to the C3 position of the pyrazol, the C5 position of the pyrazol binds to a C4 position of the first benzyl; on a second condition that the C2 position of the quinolinyl binds to the C5 position of the pyrazol, the C3 position of the pyrazol binds to the C4 position of the first benzyl; and an N1 position of the pyrazol binds to a C4 position of the second benzyl.

[0017] In the pyrazolyquinoline compound of the present embodiment, a C1 position of the first benzyl binds to a substituent R₂ being a hydrogen, a halide, or an alkoxy, wherein the halide can be, but is not limited to, fluorine, chloride, bromide and iodine, and the alkoxy can be, but is not limited to, methoxy, ethoxy, propoxy and butoxy; and a C1 position of the second benzyl binds to a substituent R₃ being a hydrogen, a halide, an alkoxy, or a sulfonamide group, wherein the halide can be, but is not limited to, fluorine, chloride, bromide and iodine, and the alkoxy can be, but is not limited to, methoxy, ethoxy, propoxy and butoxy.

[0018] The pyrazolyquinoline compound of the present embodiment can be selected from the group consisting of:

- 6-fluoro-2-(1,5-diphenyl-1*H*-pyrazol-3-yl)quinoline,
- 6-fluoro-2-[5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
- 6-fluoro-2-[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
- 6-fluoro-2-(1,3-diphenyl-1*H*-pyrazol-5-yl)-quinoline,

6-fluoro-2-[3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1,3-bis(4-fluorophenyl)-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-(1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)quinoline,
 6-fluoro-2-[1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[3-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1,3-bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline,
 4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,
 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and
 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

[0019] The pyrazolyquinoline compound of the present embodiment preferably can be selected from the group consisting of:

4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,
 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and
 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

[0020] The pyrazolyquinoline compound of the present embodiment at best is 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

[0021] The second embodiment of the present invention is to provide a pyrazolyquinoline compound, including: a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R₁ being a halide, and the halide can be fluorine; a pyrazol; a first benzyl; and a second benzyl, wherein: a C2 position of the quinolinyl binds to a carbon of the pyrazol, another carbon of the pyrazol binds to a C4 position of the second benzyl, and an N1 position of the pyrazol binds to a C4 position of the first benzyl.

[0022] In the pyrazolyquinoline compound of the present embodiment, a C1 position of the first benzyl binds to a substituent R₂ being a hydrogen, a halide, or an alkoxy, wherein the halide can be, but is not limited to, fluorine, chloride, bromide and iodine, and the alkoxy can be, but is not limited to, methoxy, ethoxy, propoxy and butoxy; and a C1 position of the second benzyl binds to a substituent R₃ being a hydrogen, a halide, an alkoxy, or a sulfonamide group, wherein the halide can be, but is not limited to, fluorine, chloride, bromide and iodine, and the alkoxy can be, but is not limited to, methoxy, ethoxy, propoxy and butoxy.

[0023] The pyrazolyquinoline compound of the present embodiment can be selected from the group consisting of:

- 6-fluoro-2-(1,5-diphenyl-1*H*-pyrazol-3-yl)quinoline,
- 6-fluoro-2-[5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
- 6-fluoro-2-[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
- 6-fluoro-2-(1,3-diphenyl-1*H*-pyrazol-5-yl)-quinoline,
- 6-fluoro-2-[3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,

6-fluoro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1,3-bis(4-fluorophenyl)-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-(1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)quinoline,
 6-fluoro-2-[1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[3-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1,3-bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline,
 4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,
 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and
 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide) ◦

[0024] The pyrazolyquinoline compound of the present embodiment preferably can be selected from the group consisting of:

4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,
 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and
 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

[0025] The pyrazolyquinoline compound of the present embodiment at best is 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

[0026] The third embodiment of the present invention is to provide a method for preparing a pyrazolyquinoline compound, including steps of: providing 6-fluoro-2-methylquinoline; oxidizing the 6-fluoro-2-methylquinoline with selenium dioxide to form 6-fluoro-2-formylquinoline; condensing the 6-fluoro-2-formylquinoline with an acetophenone derivative to form a carbonyl product; and treating the carbonyl product with a phenylhydrazine derivative to form the pyrazolyquinoline compound.

[0027] In the method of the present embodiment, the acetophenone derivative can be, but is not limited to, acetophenone, 4-fluoroacetophenone, or 4-methoxyacetophenone.

[0028] In the method of the present embodiment, the phenylhydrazine derivative can be, but is not limited to, phenylhydrazine, 4-fluorophenylhydrazine, 4-methoxyphenylhydrazine, or 4-hydrazinobenzenesulfonamide.

[0029] In the method of the present embodiment, the acetophenone derivative can be 4-methoxyacetophenone, the carbonyl product is (*E*)-3-(6-fluoroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one, and the phenylhydrazine derivative can be, but is not limited to, 4-fluorophenylhydrazine, 4-methoxyphenylhydrazine, or 4-hydrazinobenzenesulfonamide.

[0030] In the method of the present embodiment, the phenylhydrazine derivative is phenylhydrazine, and a 2,3-dichloro-5,6-dicyanobenzoquinone

(DDQ) oxidation is performed after the carbonyl product is treated with the phenylhydrazine derivative.

[0031] The fourth embodiment of the present invention is to provide a pharmaceutical composition, including: a therapeutically effective amount of a pharmaceutical component of the pyrazolyquinoline compound as described in the first embodiment or the second embodiment of the present invention or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier of the pharmaceutical component.

[0032] Synthetic example 1: The preparation of quinolinyl chalcone compounds **3a-c**

[0033] Please refer to Fig. 1, oxidation of 6-fluoro-2-methylquinoline (compound **1**) with selenium dioxide gave 6-fluoro-2-formylquinoline (compound **2**), and the method is described as follows. Compound **1** (0.48 g, 3.0 mmol) and selenium dioxide (SeO₂) (0.66 g, 6.0 mmol) in 1,4-dioxane (50 mL) was heated at 100°C for 2 hours (thin layer chromatography (TLC) monitoring). After cooling, the mixture was treated with 5% sodium bicarbonate (NaHCO₃) aqueous solution (80 mL), extracted with dichloromethane (CH₂Cl₂) (50 mL × 3), the organic layer was collected, dried over magnesium sulfate (MgSO₄), and evaporated. The crude product was crystallized with ethanol (EtOH) to give compound **2** (0.43 g, 81%) as a white solid. Compound **2** was condensed with acetophenone to afford exclusively a trans-conjugated carbonyl product, (*E*)-3-(6-fluoroquinolin-2-yl)-1-phenylprop-2-en-1-one (compound **3a**), and the method is described as follows. Compound **2** (0.36 g, 2.0 mmol) and acetophenone (2.0 mmol) were stirred at 0°C for 15 minutes. Aqueous solution of potassium hydroxide (KOH) (6 equiv.) was added and the mixture was stirred at room temperature

for 12 hours (TLC monitoring). After the reaction reached completion, the resulting mixture was added 1 M hydrogen chloride (HCl) until pH 3 resulted and extracted with ethyl acetate (50 mL $\times$ 3). The organic layer was collected, dried over MgSO₄ and concentrated in vacuo. The crude product was purified and crystallized with EtOH to give a quinoliny chalcone compound **3a**. Similarly, compound **2** reacted with 4-flouroacetophenone and 4-methoxyacetophenone respectively at the same reaction conditions to afford (*E*)-1-(4-fluorophenyl)-3-(6-fluoroquinolin-2-yl)prop-2-en-1-one (compound **3b**) and (*E*)-3-(6-fluoroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (compound **3c**).

[0034] Analytic example 1: (*E*)-3-(6-fluoroquinolin-2-yl)-1-phenylprop-2-en-1-one (compound **3a**)

[0035] Yield: 50% as a yellow solid. Mp.: 156.7-157.7°C. UV λ_{max} nm (log ϵ): 327 (4.23), 264 (4.67), 218 (4.69) in MeOH. ¹H NMR (400 MHz, CDCl₃): 7.45 (dd, 1H, *J* = 8.4, 2.8 Hz, Ar-H), 7.51-7.56 (m, 3H, Ar-H), 7.60-7.64 (m, 1H, Ar-H), 7.68 (d, 1H, *J* = 8.4 Hz), 7.93 (d, 1H, *J* = 15.6 Hz), 8.10-8.17 (m, 5H, Ar-H). ¹³C NMR (100 MHz, CDCl₃): 110.61 (d, *J* = 22.0 Hz), 120.50 (d, *J* = 25.8 Hz), 122.20, 127.02, 128.71 (2C), 128.77 (2C), 128.83 (d, *J* = 9.7 Hz), 132.43 (d, *J* = 9.1 Hz), 133.12, 136.14 (d, *J* = 5.3 Hz), 137.78, 143.18, 145.50, 152.87 (d, *J* = 3.0 Hz), 160.95 (d, *J* = 248.7 Hz), 190.58. ESIMS [M+H]⁺: 278. Anal. calcd for C₁₈H₁₂FNO·0.5 H₂O: C 75.51, H 4.58, N 4.89; found C 75.50, H 4.38, N 4.65.

[0036] Analytic example 2: (*E*)-1-(4-fluorophenyl)-3-(6-fluoroquinolin-2-yl)prop-2-en-1-one (compound **3b**)

[0037] Yield: 69% as a yellow solid. Mp.: 194.7-195.4°C. UV λ_{max} nm (log ϵ): 327 (4.07), 263 (4.65), 218 (4.70) in MeOH. ¹H NMR (400 MHz,

CDCl₃): 7.18-7.24 (m, 2H, Ar-H), 7.45 (dd, 1H, *J* = 8.4, 2.8 Hz, Ar-H), 7.54 (ddd, 1H, *J* = 9.2, 8.4, 2.8 Hz, Ar-H), 7.67 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.93 (d, 1H, *J* = 15.6 Hz, CH=), 8.12-8.18 (m, 5H, Ar-H). ¹³C NMR (100 MHz, CDCl₃): 110.66 (d, *J* = 21.9 Hz), 115.86 (2C, d, *J* = 21.3 Hz), 120.58 (d, *J* = 25.7 Hz), 122.37, 126.49, 128.91 (d, *J* = 9.8 Hz), 131.41 (2C, d, *J* = 9.8 Hz), 132.42 (d, *J* = 9.1 Hz), 134.12 (d, *J* = 2.8 Hz), 136.20 (d, *J* = 6.1 Hz), 143.28, 145.49, 152.66 (d, *J* = 3.1 Hz), 160.97 (d, *J* = 248.6 Hz), 165.82 (d, *J* = 253.1 Hz), 188.84. ESIMS [M+H]⁺: 296. Anal. calcd for C₁₈H₁₁F₂NO·0.4 H₂O: C 71.47, H 3.93, N 4.63; found C 71.57, H 3.96, N 4.65.

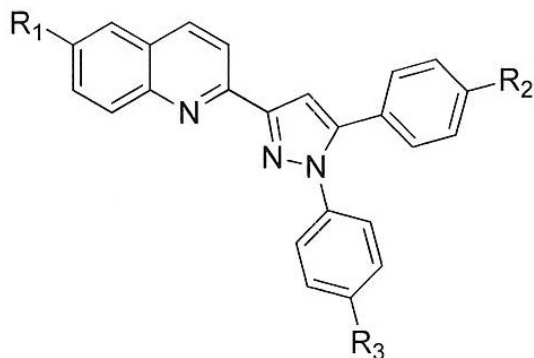
[0038] Analytic example 3: (*E*)-3-(6-fluoroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (compound **3c**):

[0039] Yield: 79% as a yellow solid. Mp.: 157.7-158.6°C. UV λ_{max} nm (logε): 333 (4.43), 264 (4.71), 218 (4.74) in MeOH. ¹H NMR (400 MHz, CDCl₃): 3.91 (s, 3H, OCH₃), 7.01 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.44 (dd, 1H, *J* = 8.8, 2.8 Hz, Ar-H), 7.52 (ddd, 1H, *J* = 9.2, 8.4, 2.8 Hz, Ar-H), 7.67 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.92 (d, 1H, *J* = 15.6 Hz, CH=), 8.12-8.19 (m, 5H, Ar-H). ¹³C NMR (100 MHz, CDCl₃): 55.51, 110.62 (d, *J* = 21.9 Hz), 113.92 (2C), 120.43 (d, *J* = 25.7 Hz), 122.29, 126.92, 128.80 (d, *J* = 9.8 Hz), 130.76, 131.14 (2C), 132.37 (d, *J* = 9.1 Hz), 136.09 (d, *J* = 5.3 Hz), 142.30, 145.48, 153.05 (d, *J* = 3.0 Hz), 160.87 (d, *J* = 248.7 Hz), 163.70, 188.66. ESIMS [M+H]⁺: 308. Anal. calcd for C₁₉H₁₄FNO₂·0.5 H₂O: C 72.14, H 4.78, N 4.43; found C 72.15, H 4.51, N 4.18.

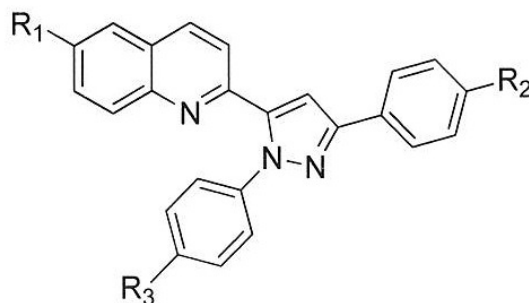
[0040] Synthetic example 2: The preparation of pyrazolyquinoline compounds **4a-5c** via cyclocondensation of quinolinyl chalcone compounds **3a-c** and phenylhydrazines

[0041] Please refer to Fig. 2, treatment of (*E*)-3-(6-fluoroquinolin-2-yl)-1-phenylprop-2-en-1-one (compound **3a**) with phenylhydrazine followed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation gave 6-fluoro-2-(1,5-diphenyl-1*H*-pyrazol-3-yl)quinoline (compound **4a**) and 6-fluoro-2-(1,3-diphenyl-1*H*-pyrazol-5-yl)-quinoline (compound **5a**) in 21% and 20% yields respectively, and the method is described as follows. To a solution of quinolinyl chalcone compound **3a** (2.1 mmol) in EtOH (10 mL) was added phenylhydrazine (2.1 mmol). The resulting solution was refluxed until the reaction was completed as monitored by TLC (ca. 18 hours). The solvent was evaporated in vacuo, and then added DDQ in 1,4-dioxane (10 mL). The reaction mixture was refluxed for 12 hours (TLC monitoring) and then concentrated in vacuo. The residue was extracted with CH₂Cl₂ (50 mL × 3). The organic layer was collected, dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, using CH₂Cl₂/methanol (MeOH) (20:1) as eluant and recrystallized with MeOH to afford the pyrazolyquinoline compounds **4a** and **5a**. Similarly, at the same reaction conditions, (*E*)-1-(4-fluorophenyl)-3-(6-fluoroquinolin-2-yl)prop-2-en-1-one (compound **3b**) reacted with phenylhydrazine to afford a mixture of 6-fluoro-2-[5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline (compound **4b**) and 6-fluoro-2-[3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **5b**), and (*E*)-3-(6-fluoroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (compound **3c**) reacted with phenylhydrazine to afford a mixture of 6-fluoro-2-[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline (compound **4c**) and 6-fluoro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **5c**). Compounds **4a**, **4b** and **4c**

have a general formula of Ia, and compounds **5a**, **5b** and **5c** have a general formula of Ib.



Ia



Ib

[0042] Analytic example 4: 6-fluoro-2-(1,5-diphenyl-1*H*-pyrazol-3-yl)quinoline (compound **4a**)

[0043] Compound **4a** was obtained in 21% yield (0.16 g) as a yellow solid. Mp.: 153.4-154.4°C. UV λ_{max} nm (log ϵ): 331 (4.10), 260 (4.78), 218 (4.78) in MeOH. ^1H NMR (400 MHz, CDCl_3): 7.33-7.51 (m, 13H, Ar-H), 8.14-8.17 (m, 2H, Ar-H), 8.30 (d, 1H, $J = 8.8$ Hz, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 106.83, 110.68 (d, $J = 21.2$ Hz), 119.55 (d, $J = 25.0$ Hz), 119.56, 125.41 (2C), 127.75, 128.34 (d, $J = 10.6$ Hz), 128.39, 128.48 (2C), 128.77 (2C), 128.98 (2C), 130.33, 131.88 (d, $J = 9.1$ Hz), 135.77 (d, $J = 5.3$ Hz), 140.07, 144.87, 145.20, 151.62, 152.30, 160.30 (d, $J = 246.3$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 366. Anal. calcd for $\text{C}_{24}\text{H}_{16}\text{FN}_3 \cdot 0.1 \text{ H}_2\text{O}$: C 78.50, H 4.45, N 11.44; found C 78.37, H 4.52, N 11.45.

[0044] Analytic example 5: 6-fluoro-2-(1,3-diphenyl-1*H*-pyrazol-5-yl)quinoline (compound **5a**)

[0045] Compound **5a** was obtained in 20% yield (0.15 g) as a pink solid. Mp.: 114.5-115.2°C. UV λ_{max} nm (log ϵ): 258 (4.78), 219 (4.78) in MeOH. ^1H

NMR (400 MHz, CDCl₃): 7.25-7.30 (m, 2H, Ar-H), 7.34-7.51 (m, 10H, Ar-H), 7.96-8.01 (m, 4H, Ar-H). ¹³C NMR (100 MHz, CDCl₃): 106.62, 110.57 (d, *J* = 22.0 Hz), 120.26 (d, *J* = 25.8 Hz), 121.87, 125.54 (2C), 125.88 (2C), 127.68 (d, *J* = 9.8 Hz), 127.80, 128.11, 128.65 (2C), 128.93 (2C), 133.14 (d, *J* = 9.1 Hz), 132.82, 135.55 (d, *J* = 5.3 Hz), 140.48, 143.56, 144.99, 148.81 (d, *J* = 3.0 Hz), 152.23, 160.77 (d, *J* = 247.8 Hz). ESIMS [M+H]⁺: 366. Anal. calcd for C₂₄H₁₆FN₃·0.1 H₂O: C 78.50, H 4.45, N 11.44; found C 78.22, H 4.54, N 11.37.

[0046] Analytic example 6: 6-fluoro-2-[5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline (compound **4b**)

[0047] Compound **4b** was obtained in 22% yield (0.17 g) as a yellow solid. Mp.: 178.0-178.9°C. UV λ_{max} nm (logε): 330 (4.12), 259 (4.80), 219 (4.81) in MeOH. ¹H NMR (400 MHz, CDCl₃): 7.01-7.06 (m, 2H, Ar-H), 7.27-7.51 (m, 10H, Ar-H), 8.13-8.17 (m, 2H, Ar-H), 8.29 (d, 1H, *J* = 9.2 Hz, Ar-H). ¹³C NMR (100 MHz, CDCl₃): 106.81, 110.69 (d, *J* = 22.0 Hz), 115.65 (2C, d, *J* = 21.2 Hz), 119.50, 119.60 (d, *J* = 25.0 Hz), 125.41 (2C), 126.45 (d, *J* = 2.8 Hz), 127.89, 128.36 (d, *J* = 9.8 Hz), 129.07 (2C), 130.59 (2C, d, *J* = 7.6 Hz), 131.86 (d, *J* = 9.1 Hz), 135.80 (d, *J* = 5.3 Hz), 139.87, 143.84, 145.18, 151.47 (d, *J* = 3.0 Hz), 152.34, 160.26 (d, *J* = 234.0 Hz), 162.33 (d, *J* = 234.1 Hz). ESIMS [M+H]⁺: 384. Anal. calcd for C₂₄H₁₅F₂N₃·0.1 H₂O: C 74.83, H 3.98, N 10.91; found C 74.68, H 4.16, N 10.87.

[0048] Analytic example 7: 6-fluoro-2-[3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **5b**)

[0049] Compound **5b** was obtained in 25% yield (0.19 g) as a yellow solid. Mp.: 68.8-69.8°C. UV λ_{max} nm (logε): 323 (4.07), 260 (4.81), 219 (4.81) in MeOH. ¹H NMR (400 MHz, CDCl₃): 7.11-7.15 (m, 2H, Ar-H), 7.20 (s, 1H),

7.34-7.52 (m, 8H, Ar-H), 7.92-8.01 (m, 4H, Ar-H), 8.00 (d, 2H, $J = 8.4$ Hz, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 106.38, 110.59 (d, $J = 22.0$ Hz), 115.59 (2C, d, $J = 21.2$ Hz), 120.33 (d, $J = 25.0$ Hz), 121.82, 125.51 (2C), 127.57 (d, $J = 9.8$ Hz), 127.70 (2C, d, $J = 9.9$ Hz), 127.89, 128.98 (2C), 132.13 (d, $J = 9.1$ Hz), 135.59 (d, $J = 6.0$ Hz), 135.82 (d, $J = 2.8$ Hz), 140.36, 143.69, 144.99, 148.69 (d, $J = 2.8$ Hz), 151.36, 160.78 (d, $J = 247.8$ Hz), 162.82 (d, $J = 244.7$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 384. Anal. calcd for $\text{C}_{24}\text{H}_{15}\text{F}_2\text{N}_3 \cdot 0.1 \text{H}_2\text{O}$: C 74.83, H 3.98, N 10.91; found C 74.99, H 4.33, N 10.61.

[0050] Analytic example 8: 6-fluoro-2-[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline (compound **4c**):

[0051] Compound **4c** was obtained in 23% yield (0.18 g) as a white solid. Mp.: 175.3-176.0°C. UV λ_{max} nm (log ϵ): 331 (4.12), 261 (4.81), 219 (4.81) in MeOH. ^1H NMR (400 MHz, CDCl_3): 3.82 (s, 3H, OCH_3), 6.86 (d, 2H, $J = 8.8$ Hz, ArH), 7.25 (d, 2H, $J = 8.8$ Hz, Ar-H), 7.30 (s, 1H), 7.32-7.51 (m, 7H, Ar-H), 8.13-8.17 (m, 2H, Ar-H), 8.29 (d, 1H, $J = 8.4$ Hz, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 55.25, 106.28, 110.67 (d, $J = 22.0$ Hz), 113.93 (2C), 119.52 (d, $J = 25.7$ Hz), 119.57, 122.73, 125.41 (2C), 127.66, 128.32 (d, $J = 9.1$ Hz), 128.96 (2C), 130.07 (2C), 131.86 (d, $J = 9.1$ Hz), 135.73 (d, $J = 5.3$ Hz), 140.18, 144.73, 145.19, 151.71 (d, $J = 2.3$ Hz), 152.19, 159.63, 160.28 (d, $J = 246.2$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 396. Anal. calcd for $\text{C}_{25}\text{H}_{18}\text{FN}_3\text{O}$: C 75.93, H 4.59, N 10.63; found C 75.63, H 4.61, N 10.96.

[0052] Analytic example 9: 6-fluoro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **5c**)

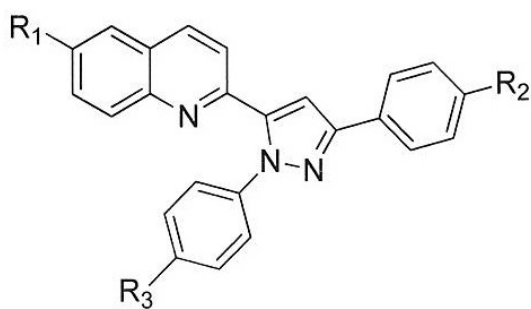
[0053] Compound **5c** was obtained in 40% yield (0.32 g) as a white solid. Mp.: 142.8-143.5°C. UV λ_{max} nm (log ϵ): 260 (4.81), 219 (4.82) in MeOH. ^1H NMR (400 MHz, CDCl_3): 3.86 (s, 3H, OCH_3), 6.98 (d, 2H, $J = 8.8$ Hz, Ar-H),

7.18 (s, 1H), 7.27 (d, 1H, $J = 9.2$ Hz, Ar-H), 7.33-7.51 (m, 7H, Ar-H), 7.89 (d, 2H, $J = 8.8$ Hz, Ar-H), 7.98-8.01 (m, 2H, ArH). ^{13}C NMR (100 MHz, CDCl_3): 55.31, 106.22, 110.57 (d, $J = 21.9$ Hz), 114.06 (2C), 120.24 (d, $J = 25.7$ Hz), 121.90, 125.51 (2C), 125.59, 127.16 (2C), 127.61, 127.70, 128.92 (2C), 132.13 (d, $J = 9.1$ Hz), 135.51 (d, $J = 5.3$ Hz), 140.49, 143.46, 144.99, 148.90 (d, $J = 3.1$ Hz), 152.08, 159.67, 160.74 (d, $J = 247.8$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 396. Anal. calcd for $\text{C}_{25}\text{H}_{18}\text{FN}_3\text{O}$: C 75.93, H 4.59, N 10.63; found C 75.95, H 4.61, N 10.83.

[0054] Synthetic example 3: The preparation of pyrazolyquinoline compounds **6a-8c** via cyclocondensation of quinoliny chalcone compounds **3a-c** and 4-substituted phenylhydrazines

[0055] Please refer to Fig. 2, reflux of (*E*)-3-(6-fluoroquinolin-2-yl)-1-phenylprop-2-en-1-one (compound **3a**) with 4-fluorophenylhydrazine gave exclusively 6-fluoro-2-[1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **6a**) as a sole product, and the method is described as follows. To a solution of quinoliny chalcone compound **3a** (2 mmol) in EtOH (10 mL) was added 4-fluorophenylhydrazine (2.1 mmol). The resulting solution was refluxed until the reaction was completed as monitored by TLC (ca. 12 hours). The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography on silica gel, using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (20:1) as eluant and recrystallized with MeOH to afford the pyrazolyquinoline compound **6a**. Similarly, at the same reaction conditions, (*E*)-1-(4-fluorophenyl)-3-(6-fluoroquinolin-2-yl)prop-2-en-1-one (compound **3b**) and (*E*)-3-(6-fluoroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (compound **3c**) respectively reacted with 4-fluorophenylhydrazine to afford 6-fluoro-2-[1,3-bis(4-fluorophenyl)-1*H*-pyrazol-5-yl]quinoline (compound **6b**)

or 6-fluoro-2-(1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)quinoline (compound **6c**). Reflux of compound **3a** with 4-methoxyphenylhydrazine gave exclusively 6-fluoro-2-[1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **7a**) as a sole product. At the same reaction conditions, compounds **3b** and **3c** respectively reacted with 4-methoxyphenylhydrazine gave 6-fluoro-2-[3-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline (compound **7b**) and 6-fluoro-2-[1,3-bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline (compound **7c**). Reflux of compound **3a** with 4-hydrazinobenzenesulfonamide gave exclusively 4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide (compound **8a**). At the same reaction conditions, compounds **3b** and **3c** respectively reacted with 4-hydrazinobenzenesulfonamide gave 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide (compound **8b**) and 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (compound **8c**). Compounds **6a-8c** have a general formula of Ib.



Ib

[0056] Analytic example 10: 6-fluoro-2-[1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **6a**)

[0057] Yield: 29% as a yellow solid. Mp.: 151.2-152.8°C. UV λ_{max} nm (log ϵ): 323 (4.17), 246 (4.59), 222 (4.52) in MeOH. ^1H NMR (400 MHz, CDCl_3): 7.05-7.10 (m, 2H, Ar-H), 7.23 (s, 1H), 7.35-7.51 (m, 8H, Ar-H), 7.92-7.96 (m, 3H, Ar-H), 8.04 (d, 1H, $J = 8.4\text{ Hz}$, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 106.45, 110.60 (d, $J = 22.0\text{ Hz}$), 115.73 (2C, d, $J = 22.7\text{ Hz}$), 120.39 (d, $J = 25.8\text{ Hz}$), 121.66, 125.88 (2C), 127.47 (d, $J = 8.3\text{ Hz}$), 127.69 (d, $J = 9.9\text{ Hz}$), 128.21, 128.70 (2C), 132.12 (2C, d, $J = 9.1\text{ Hz}$), 132.69, 135.76, 136.87, 143.56, 144.92, 148.48, 152.26, 160.83 (d, $J = 247.9\text{ Hz}$), 161.92 (d, $J = 245.7\text{ Hz}$). ESIMS $[\text{M}+\text{H}]^+$: 384. Anal. calcd for $\text{C}_{24}\text{H}_{15}\text{F}_2\text{N}_3$: C 75.19, H 3.94, N 10.96; found C 75.30, H 3.63, N 10.87.

[0058] Analytic example 11: 6-fluoro-2-[1,3-bis(4-fluorophenyl)-1*H*-pyrazol-5-yl]-6-fluoroquinoline (compound **6b**)

[0059] Yield: 28% as a yellow solid. Mp.: 188.2-189.8°C. UV λ_{max} nm (log ϵ): 326 (4.08), 262 (4.61), 220 (4.51) in MeOH. ^1H NMR (400 MHz, CDCl_3): 7.06-7.16 (m, 4H, ArH), 7.18 (s, 1H), 7.35 (d, 1H, $J = 8.8\text{ Hz}$, ArH), 7.40-7.52 (m, 4H, ArH), 7.90-7.96 (m, 3H, Ar-H), 8.04 (d, 1H, $J = 8.8\text{ Hz}$, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 106.23, 110.61 (d, $J = 21.9\text{ Hz}$), 115.64 (2C, d, $J = 21.3\text{ Hz}$), 115.78 (2C, d, $J = 22.7\text{ Hz}$), 120.45 (d, $J = 25.7\text{ Hz}$), 121.61, 127.39 (2C, d, $J = 9.1\text{ Hz}$), 127.55 (2C, d, $J = 8.4\text{ Hz}$), 127.69 (d, $J = 10.6\text{ Hz}$), 128.87 (d, $J = 3.1\text{ Hz}$), 132.08 (d, $J = 9.1\text{ Hz}$), 135.83 (d, $J = 5.3\text{ Hz}$), 136.67 (d, $J = 3.0\text{ Hz}$), 143.65, 144.88, 148.29 (d, $J = 3.1\text{ Hz}$), 151.35, 160.82 (d, $J = 247.8\text{ Hz}$), 161.91 (d, $J = 246.3\text{ Hz}$), 162.84 (d, $J = 245.6\text{ Hz}$). ESIMS $[\text{M}+\text{H}]^+$: 402. Anal. calcd for $\text{C}_{24}\text{H}_{14}\text{F}_3\text{N}_3$: C 71.82, H 3.52, N 10.47; found C 71.98, H 3.21, N 10.40.

[0060] Analytic example 12: 6-fluoro-2-(1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)quinoline (compound **6c**)

[0061] Yield: 29% as a yellow solid. Mp.: 180.4-181.6°C. UV λ_{max} nm (log ϵ): 326 (4.17), 262 (4.62), 221 (4.51) in MeOH. ^1H NMR (400 MHz, CDCl_3): 3.86 (s, 3H, OCH_3), 6.96-7.10 (m, 4H, Ar-H), 7.16 (s, 1H), 7.35 (d, 1H, $J = 8.8$ Hz, Ar-H), 7.39-7.51 (m, 4H, Ar-H), 7.86-7.89 (m, 2H, Ar-H), 7.94 (dd, 1H, $J = 9.2, 5.2$ Hz, Ar-H), 8.03 (d, 1H, $J = 8.4$ Hz, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 55.31, 106.05, 110.59 (d, $J = 21.2$ Hz), 114.07 (2C), 115.72 (2C, d, $J = 22.7$ Hz), 120.36 (d, $J = 25.9$ Hz), 121.68, 125.39, 127.13 (2C), 127.39 (2C, d, $J = 9.1$ Hz), 127.65 (d, $J = 9.9$ Hz), 132.08 (d, $J = 9.1$ Hz), 135.74 (d, $J = 5.3$ Hz), 136.80 (d, $J = 3.1$ Hz), 143.44, 144.88, 148.51 (d, $J = 3.0$ Hz), 152.07, 159.71, 160.77 (d, $J = 247.8$ Hz), 161.82 (d, $J = 246.3$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 414. Anal. calcd for $\text{C}_{25}\text{H}_{17}\text{F}_2\text{N}_3\text{O}$: C 72.63, H 4.14, N 10.16; found C 72.86, H 4.23, N 9.94.

[0062] Analytic example 13: 6-fluoro-2-[1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline (compound **7a**)

[0063] Yield: 18% as a brown solid. Mp.: 203.6-204.5°C. UV λ_{max} nm (log ϵ): 258 (4.72), 215 (4.81) in MeOH. ^1H NMR (400 MHz, CDCl_3): 3.83 (s, 3H, OCH_3), 6.88-6.91 (m, 2H, Ar-H), 7.25-7.27 (m, 2H, Ar-H), 7.33-7.53 (m, 7H, Ar-H), 7.95-8.05 (m, 4H, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 55.52, 106.17, 110.55 (d, $J = 21.9$ Hz), 114.11 (2C), 120.24 (d, $J = 25.0$ Hz), 121.80, 125.84 (2C), 126.95 (2C), 127.63 (d, $J = 9.9$ Hz), 128.01, 128.63 (2C), 132.12 (d, $J = 9.1$ Hz), 132.89, 133.67, 135.51 (d, $J = 5.3$ Hz), 143.56, 144.98, 148.83 (d, $J = 3.0$ Hz), 151.91, 159.15, 160.73 (d, $J = 247.8$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 396. Anal. calcd for $\text{C}_{25}\text{H}_{18}\text{FN}_3\text{O} \cdot 0.1 \text{H}_2\text{O}$: C 75.59, H 4.62, N 10.58; found: C 75.49, H 4.47, N 10.54.

[0064] Analytic example 14: 6-fluoro-2-[3-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline (compound **7b**)

[0065] Yield: 19% as a brown solid. Mp.: 167.5-168.3°C. UV λ_{max} nm (log ϵ): 259 (4.84), 219 (4.84) in MeOH. ^1H NMR (400 MHz, CDCl_3): 3.83 (s, 3H, OCH_3), 6.88-6.92 (m, 2H, Ar-H), 7.10-7.15 (m, 2H, Ar-H), 7.19 (s, 1H, Ar-H), 7.24 (d, 1H, $J = 8.8$ Hz, Ar-H), 7.33-7.36 (m, 2H, Ar-H), 7.40 (dd, 1H, $J = 8.8, 2.8$ Hz, Ar-H), 7.47-7.52 (m, 1H, Ar-H), 7.90-7.94 (m, 2H, Ar-H), 7.98 (d, 1H, $J = 8.8$ Hz, Ar-H), 8.03 (dd, 1H, $J = 9.2, 5.6$ Hz, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 55.53, 105.91 (d, $J = 22.0$ Hz), 114.15 (2C), 114.19, 115.55 (d, $J = 22.0$ Hz), 120.28 (d, $J = 25.7$ Hz), 121.74, 126.91 (2C), 127.52 (2C, d, $J = 8.4$ Hz), 127.65 (d, $J = 9.9$ Hz), 129.13 (d, $J = 3.0$ Hz), 132.13 (d, $J = 9.1$ Hz), 133.55, 135.53 (d, $J = 5.3$ Hz), 143.72, 144.99, 148.71 (d, $J = 3.0$ Hz), 151.03, 159.20, 160.75 (d, $J = 247.8$ Hz), 162.76 (d, $J = 245.5$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 414. Anal. calcd for $\text{C}_{25}\text{H}_{17}\text{F}_2\text{N}_3\text{O}\cdot 0.2 \text{H}_2\text{O}$: C 72.00, H 4.21, N 10.08; found C 71.90, H 4.33, N 9.79.

[0066] Analytic example 15: 6-fluoro-2-[1,3-bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline (compound **7c**)

[0067] Yield: 22% as a brown solid. Mp.: 63.5-63.9°C. UV λ_{max} nm (log ϵ): 261 (4.85), 218 (4.86) in MeOH. ^1H NMR (400 MHz, CDCl_3): 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.88-6.90 (m, 2H, Ar-H), 6.96-6.99 (m, 2H, Ar-H), 7.17 (s, 1H, Ar-H), 7.25 (d, 1H, $J = 8.8$ Hz, Ar-H), 7.334-7.37 (m, 2H, Ar-H), 7.40 (dd, 1H, $J = 8.8, 2.8$ Hz, Ar-H), 7.47-7.52 (m, 1H, Ar-H), 7.88-7.90 (m, 2H, Ar-H), 7.98 (d, 1H, $J = 8.8$ Hz, Ar-H), 8.03 (dd, 1H, $J = 8.8, 5.2$ Hz, Ar-H). ^{13}C NMR (100 MHz, CDCl_3): 55.30, 55.53, 105.71, 110.54 (d, $J = 22.0$ Hz), 114.04 (2C), 114.11 (2C), 120.19 (d, $J = 25.0$ Hz), 121.82, 125.71, 126.94 (2C), 127.12 (2C), 127.58 (d, $J = 9.8$ Hz), 132.15 (d, $J = 9.1$ Hz), 133.75, 135.45 (d, $J = 5.3$ Hz), 143.53, 145.03, 148.96, 151.78, 159.10, 159.60, 160.72 (d, $J = 247.9$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 426. Anal. calcd for $\text{C}_{26}\text{H}_{20}\text{FN}_3\text{O}_2$:

C 73.40, H 4.74, N 9.88; found C 73.29, H 4.95, N 9.84.

[0068] Analytic example 16: 4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide (compound **8a**)

[0069] Yield: 25% as a brown solid. Mp.: 244.5-245.3°C. UV λ_{max} nm (log ϵ): 260 (4.86), 219 (4.86) in MeOH. ^1H NMR (400 MHz, DMSO- d_6): 7.39-7.44 (m, 1H, Ar-H), 7.49-7.52 (m, 4H, Ar-H), 7.61-7.75 (m, 5H, Ar-H), 7.82-7.89 (m, 4H, Ar-H), 7.99-8.01 (m, 2H, Ar-H), 8.46 (d, 1H, $J = 8.4$ Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO- d_6): 107.58, 111.11 (d, $J = 22.0$ Hz), 120.37 (d, $J = 25.8$ Hz), 121.94, 125.53 (2C), 125.70 (2C), 126.27 (2C), 127.67 (d, $J = 9.8$ Hz), 128.45, 128.88 (2C), 131.62 (d, $J = 9.1$ Hz), 132.12, 136.74 (d, $J = 5.3$ Hz), 142.90, 142.95, 143.29, 144.02, 147.97 (d, $J = 2.3$ Hz), 151.65, 160.24 (d, $J = 244.8$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 445. Anal. calcd for $\text{C}_{24}\text{H}_{17}\text{FN}_4\text{O}_2\text{S}$: C 64.85, H 3.86, N 12.60; found C 64.60, H 3.94, N 12.45.

[0070] Analytic example 17: 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide (compound **8b**)

[0071] Yield: 28% as a green solid. Mp.: 236.5-237.7°C. UV λ_{max} nm (log ϵ): 332 (4.10), 260 (4.61), 224 (4.52) in MeOH. ^1H NMR (400 MHz, DMSO- d_6): 7.32-7.37 (m, 2H, Ar-H), 7.49 (s, 2H, NH_2), 7.60-7.75 (m, 5H, Ar-H), 7.82-7.88 (m, 4H, Ar-H), 8.02-8.05 (m, 2H, Ar-H), 8.46 (d, 1H, $J = 8.8$ Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO- d_6): 107.50, 111.10 (d, $J = 22.0$ Hz), 115.79 (2C, d, $J = 21.3$ Hz), 120.38 (d, $J = 25.8$ Hz), 121.90, 125.68 (2C), 126.27 (2C), 127.59 (2C, d, $J = 8.3$ Hz), 127.67 (d, $J = 9.1$ Hz), 128.70 (d, $J = 3.0$ Hz), 131.61 (d, $J = 9.8$ Hz), 136.74 (d, $J = 5.3$ Hz), 142.87, 142.93, 143.37, 144.01, 147.92, 150.76, 160.04 (d, $J = 244.8$ Hz), 162.25 (d, $J = 244.0$ Hz). ESIMS $[\text{M}+\text{H}]^+$: 463. Anal. calcd for $\text{C}_{24}\text{H}_{16}\text{F}_2\text{N}_4\text{O}_2\text{S} \cdot 0.5 \text{H}_2\text{O}$: C 61.14, H 3.63, N 11.88; found C 61.43, H 3.40, N 11.76.

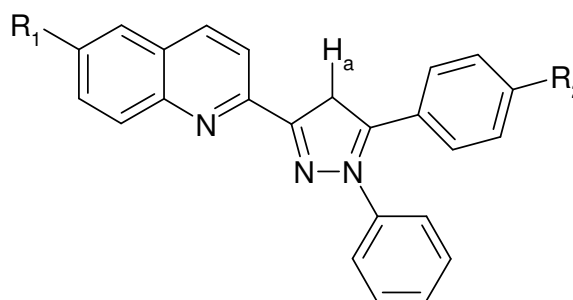
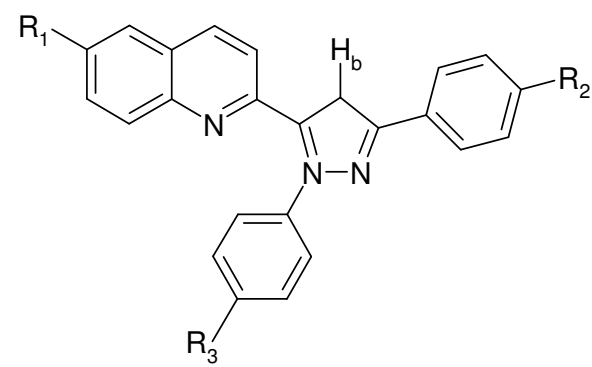
[0072] Analytic example 18: 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (compound **8c**)

[0073] Yield: 23% as a yellow solid. Mp.: 233.1-234°C. UV λ_{max} nm (log ϵ): 262(4.89), 219 (4.89) in MeOH. ^1H NMR (400 MHz, DMSO- d_6): 3.37 (s, 3H, OCH₃), 7.05-7.07 (m, 2H, Ar-H), 7.49 (s, 2H, NH₂), 7.58-7.76 (m, 5H, Ar-H), 7.82-7.93 (m, 6H, Ar-H), 8.46 (d, 1H, $J = 8.8\text{ Hz}$, Ar-H). ^{13}C NMR (100 MHz, DMSO- d_6): 55.20, 107.21, 111.11 (d, $J = 22.0\text{ Hz}$), 114.27 (2C), 120.36 (d, $J = 25.7\text{ Hz}$), 121.95, 124.70, 125.58 (2C), 126.27 (2C), 126.92 (2C), 127.66 (d, $J = 11.3\text{ Hz}$), 131.63 (d, $J = 9.9\text{ Hz}$), 136.71 (d, $J = 5.3\text{ Hz}$), 142.73, 143.00, 143.18, 144.05, 148.09 (d, $J = 3.0\text{ Hz}$), 151.59, 159.52, 160.04 (d, $J = 244.8\text{ Hz}$). ESIMS $[\text{M}+\text{H}]^+$: 475. Anal. calcd for C₂₅H₁₉FN₄O₃S·0.5 H₂O: C 62.10, H 4.17, N 11.59; found C 61.72, H 3.85, N 11.51.

[0074] In the analytic examples of the present invention, melting points were determined on an Electrothermal IA9100 melting point apparatus. Infrared (IR) spectra were measured using a Perkin Elmer System-2000 spectrometer. Ultraviolet (UV) spectra (λ_{max} in nm) were recorded in spectroscopic grade MeOH on a Shimadzu UV-160A UV-vis spectrophptometer. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian Gemini 200 spectrometer or Varian-Unity-400 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co. Mass spectra were recorded on Bruker APEX II (ESI) mass spectrometer. The elemental analyses were performed in the Instrument Center of National Science Council at National Cheng-Kung University, Tainan, Taiwan and National Taiwan University, Taipei, Taiwan using Heraeus CHN-O Rapid EA,

and all values are within $\pm 0.4\%$ of the theoretical compositions.

Table 1. Comparative studies on the chemical shifts (δ 7.16-7.68 ppm) for ^1H NMR signals of the pyrazoyl part of the pyrazolylquinoline compounds

Compound	H _a Chemical shift	H _b Chemical shift
4a ¹	7.37	--
5a ¹	--	7.25
4b ¹	7.34	--
5b ¹	--	7.20
4c ¹	7.30	--
5c ¹	--	7.18
6a ¹	--	7.25
6b ¹	--	7.20
6c ¹	--	7.17
7a ²	--	7.68
7b ²	--	7.67
7c ²	--	7.61
8a ¹	--	7.23
8b ¹	--	7.18

8c ¹	--	7.16
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¹CDCl₃; ²DMSO-*d*₆

[0075] In the experiments of the present invention, compounds were dissolved in DMSO at 10 mM and then diluted in culture medium. Human hepatoma Huh-7 cells were purchased from Bioresources Collection and Research Center, Taiwan. Huh-7-DV-Fluc cells and C6/36 cells were kindly provided by Dr. Huey Nan Wu, Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan, R.O.C. The DENV-2 strain 16681 was isolated from a patient with dengue hemorrhage fever (DHF) from Thailand, and was amplified in C6/36 mosquito cells.

[0076] Experiment 1:

[0077] Please refer to Fig. 3, structures of compounds **4c** and **5c** were determined by X-ray crystallographical analysis. The structure was solved and refined by direct methods Shelx 97⁴² suite of programs. White single crystal of compound **4c** was obtained by slow evaporation from MeOH/CH₂Cl₂ (30/70) solution: triclinic, space group P-1, *a* = 6.262(3) Å, *b* = 11.961(5) Å, *c* = 13.502(6) Å, α = 68.380 (11)°, β = 87.617(13)°, γ = 83.998(12)°, *V* = 935.0(8) Å³, *Z* = 2, δ (calcd) = 1.405 Mg.m⁻³, FW = 395.42 for C₂₅H₁₈FN₃O, *F*(000) = 412. Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC 1054761 for compound **4c**. White single crystal of compound **5c** was obtained by slow evaporation from MeOH/CH₂Cl₂ (30/70) solution: monoclinic, space group P2₁/c, *a* = 12.8551(14) Å, *b* = 14.1552(15) Å, *c* = 10.8351(13) Å, α = 90°, β = 98.879(2)°, γ = 90°, *V* = 1948.0(4) Å³, *Z* = 4, δ (calcd) = 1.348 Mg.m⁻³, FW = 395.42 for C₂₅H₁₈FN₃O, *F*(000) = 824. Complete crystallographic data for the

structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC 1054760 for compound **5c**. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk).

[0078] Experiment 2: Cytotoxicity assays

[0079] Please refer to Table 2, for cytotoxicity assays, plates at an initial density of 5×10^3 Huh-7 cells/well in the maintenance medium are cultured without or with serial dilutions (20 and 200 μ M) of compounds **4a-8c**. Cell viability was determined after 3 days at 37°C in a humidified CO₂ (5%) atmosphere by the 2,3-bis[2-methoxy-4-nitro-5-sulphophenyl]-2*H*-tetrazolium-5-carboxanilide (XTT) method. The results showed that compounds **6c**, **7c** and **8c** exhibited low cytotoxicity, with greater than 50% viability at a concentration of 200 μ M.

[0080] Experiment 3: Analysis of anti-DENV-2 virus

[0081] Please refer to Table 2, Huh-7-DV-Fluc cells were seeded in 24-well plates at a density of 2×10^4 cells/well, and treated with the compounds **4a-8c** at two concentrations (1 and 10 μ M), 0.1% DMSO as a negative control, and ribavirin as a positive control. After 3 days of incubation, the luciferase activity assay was performed using the Bright-Glo Luciferase assay system (Promega) according to the manufacturer's instructions.

[0082] Compounds which exhibited >32% inhibition of DENV-2 at a concentration of 10 μ M were considered as active. Results from Table 2 indicated that compound **4a**, which exhibited 15% inhibition of DENV-2 at a concentration of 10 μ M, was more active than its fluoro-substituted counterpart **4b** and methoxy-substituted counterpart **4c**. Compound **4a** was

also more active than its positional isomer **5a**. However, compound **5b**, which exhibited 25% inhibition of DENV-2 at a concentration of 10 μ M, was more active than its positional isomer **4b**. Introduction of 4-methoxy or 4-sulfonamide group at *N*-1 phenyl ring improved anti-DENV-2 activity in which compounds **7a** and **8a** were more active than compound **5a** while compounds **7c** and **8c** were more active than compound **5c**. However, compound **5b** was exceptionally active against DENV-2 and more active than that of compounds **7a** and **8a**. Among these compounds, compounds **6c**, **7c** and **8c** are the most active which exhibited 55%, 66% and 85% inhibition of DENV-2 replication in the Huh-7-DV-Fluc cells at a concentration of 10 μ M compared to 33% inhibition exhibited by the positive control, ribavirin.

Table 2. Antiviral activities and cytotoxicities of the pyrazolyquinoline compounds **4a-8c**

Compounds	DENV-2		Huh-7 cell	
	% Inhibition at 1 μ M	% Inhibition at 10 μ M	% viability at 20 μ M	% viability at 200 μ M
4a	5.21 $\pm$ 3.1	15.31 $\pm$ 2.3	124.10 $\pm$ 7.48	115.31 $\pm$ 11.43
4b	3.58 $\pm$ 1.7	6.14 $\pm$ 2.1	88.26 $\pm$ 9.46	89.72 $\pm$ 1.71
4c	4.14 $\pm$ 2.3	7.15 $\pm$ 1.9	95.56 $\pm$ 5.07	93.68 $\pm$ 5.75
5a	3.02 $\pm$ 1.8	5.13 $\pm$ 1.4	125.54 $\pm$ 6.35	98.29 $\pm$ 7.59
5b	11.23 $\pm$ 2.8	25.39 $\pm$ 3.4	88.13 $\pm$ 1.84	87.49 $\pm$ 7.61
5c	5.31 $\pm$ 1.6	8.09 $\pm$ 2.3	103.99 $\pm$ 3.75	98.90 $\pm$ 9.26
6a	4.36 $\pm$ 1.7	8.31 $\pm$ 1.5	97.82 $\pm$ 3.68	91.56 $\pm$ 3.85
6b	8.91 $\pm$ 1.3	22.35 $\pm$ 1.7	95.32 $\pm$ 2.61	86.51 $\pm$ 4.51
6c	41.42 $\pm$ 2.4	55.32 $\pm$ 1.8	98.75 $\pm$ 2.87	95.37 $\pm$ 3.64
7a	7.81 $\pm$ 2.5	20.68 $\pm$ 3.7	115.73 $\pm$ 3.28	97.35 $\pm$ 8.21
7b	6.12 $\pm$ 2.1	15.83 $\pm$ 3.2	89.08 $\pm$ 8.16	52.55 $\pm$ 1.89
7c	46.87 $\pm$ 5.3	65.71 $\pm$ 4.1	95.81 $\pm$ 4.82	98.40 $\pm$ 16.44

8a	4.52 ± 2.7	11.81 ± 1.9	89.22 ± 4.03	83.64 ± 2.68
8b	5.71 ± 1.7	12.75 ± 3.8	91.12 ± 2.04	42.97 ± 2.47
8c	58.96 ± 2.8	85.34 ± 6.7	83.71 ± 2.52	89.53 ± 2.41
Ribavirin	10.14 ± 1.98	32.53 ± 2.3	71.37 ± 1.31	26.78 ± 1.59

[0083] Experiment 4: The 50% inhibitory concentration (IC₅₀) of DENV-2 replication, the 50% cytotoxic concentration (CC₅₀) for cell growth, and the selectivity index (SI, SI = CC₅₀/IC₅₀) of compounds **6c**, **7c** and **8c**

[0084] Please refer to Table 3, which shows the determination of the 50% inhibitory concentration (IC₅₀) of DENV-2 replication, the 50% cytotoxic concentration (CC₅₀) for cell growth, and the selective index (SI, SI = CC₅₀/IC₅₀) of compounds **6c**, **7c** and **8c**. Results indicated that compounds **6c**, **7c** and **8c** exhibited approximately 10-folds more active anti-DENV-2 activity (IC₅₀ of 1.36, 1.09 and 0.81 µM, respectively) than that of ribavirin (IC₅₀ = 12.61 µM). Compounds **6c**, **7c** and **8c** have a good selectivity with the SI value of greater than 147, 183 and 247 respectively which was higher than that of ribavirin (SI = 4.47).

Table 3. Antiviral activities [IC₅₀ (µM)]^a of the pyrazolyquinoline compounds **6c**, **7c** and **8c**

Compounds	IC ₅₀ ^a	CC ₅₀ ^b	SI ^c
6c	1.36 ± 0.13	> 200	> 147.06
7c	1.09 ± 0.15	> 200	> 183.49
8c	0.81 ± 0.07	> 200	> 246.91
Ribavirin	12.61 ± 1.17	56.31 ± 2.32	4.47

^a The IC₅₀ is the concentration of the compound resulting in a 50% inhibition

in virus production.

^b The CC₅₀ is the concentration of the compound causing a 50% growth inhibition of uninfected Huh-7 cells.

^c SI: selectivity index. $SI = CC_{50}/IC_{50}$.

[0085] Experiment 5: DENV infection assay

[0086] Huh-7 cells were seeded at the density of 4×10^4 cells/well in the 24 well culture plate for 16-20 hours and then infected with DENV-2 (16681 strain) at a multiplicity of infection (MOI) of 0.1 for 2 hours at 37°C. Cells were washed with phosphate-buffered saline (PBS) once and then re-filled with DMEM-2% FBS medium containing various indicating concentration of compound **8c**.

[0087] Experiment 6: Compound **8c** reduced DENV-2 replication in DENV-2-infected Huh-7 cells

[0088] To confirm the results of dose-dependent decrease luciferase activity representing the DENV-2 replication in the Huh-7-DV-Fluc cells, the reverse transcriptase-real time polymerase chain reaction (RT-qPCR) and western blotting were performed using specific primers and specific antibody against DENV-2 NS2B protein, respectively, in which cellular glyceraldehydes 3-phosphate dehydrogenase (GAPDH) was served as a loading control.

[0089] In the RT-qPCR, total cellular RNA was extracted after a 3-day treatment for compound **8c** through a Total RNA Miniprep Purification Kit (GMbiolab, Taiwan) according to the manufacturer's instructions. The expression of DENV NS5 mRNA level was determine through quantification real-time RT-PCR with specific primers corresponding to the DENV NS gene, where a forward primer is 5'-AAG GTG AGA AGC AAT GCA GC-3' (SEQ

ID NO: 1), and a reverse primer is 5'-CCA CTC AGG GAG TTC TCT CT-3' (SEQ ID NO: 2). The copy number of NS5 in each sample was normalized to GAPDH, where a forward primer is 5'-GTC TTC ACC ACC ATG GAG AA-3' (SEQ ID NO: 3), and a reverse primer is 5'-ATG GCA TGG ACT GTG GTC AT-3' (SEQ ID NO: 4). The CT value of each sample was determined by the ABI Step One Real-Time PCR-System (ABI Warrington, UK).

[0090] In the western blotting, the membranes were incubated overnight with rabbit polyclonal antibodies against NS2B (1:3000) (Genetex, Irvine, CA, USA) and GAPDH (1:10000) (Genetex, Irvine, CA, USA) serving as loading control.

[0091] Please refer to Fig. 4 and Fig. 5, both results of RT-qPCR and western blotting revealed that compound **8c** reduced the DENV replication in the Huh-7-DV-Fluc cells after the 3-day treatment. Treatment of 0.1% DMSO was served as a mock control on the inhibition of DENV-2 replication.

[0092] Experiment 7: Anti-DENV-2 activity assay *in vivo*

[0093] Please refer to Figs. 6(a), 6(b) and 6(c), to investigate whether compound **8c** exerted protective effects against the DENV infection *in vivo*, six-days-old ICR suckling mice were randomly divided into 3 groups (n = 5/group): Group 1: intracerebrally injected 2.5×10^5 pfu 60°C heat-inactive DENV-2 (iDENV) (serving as a mock control), Group 2: intracerebrally injected 2.5×10^5 pfu DENV-2 + intraperitoneally injected saline (DENV), and Group 3: intracerebrally injected 2.5×10^5 pfu DENV virus + intraperitoneally injected 1, 5, 10 and 20 mg/kg compound **8c**. Mice were injected with DENV-2 intracerebrally and with saline and compound **8c** (1, 5, 10 and 20 mg/kg) intraperitoneally at 1, 3, and 5 days post-infection (dpi). Survival rate, body weight and clinical score were measured every day after

the DENV-2 injection, and a total of 6 days of measurement. Illness symptoms were scored as follow: 0 for no symptom; 1 for slight losing weight and ruffled hair; 2 for slowing of activity; 3 for asthenia; 4 for paralysis and mortally ill; and 5 for death. The results were expressed as means $\pm$ S.D. Differences in mean values between groups were analyzed by a one-way analysis of variance (ANOVA) and Student's t-test. For the septic shock assay, the log-rank test was used. Statistical significance was assessed as $p < 0.05$ [$*p < 0.05$; $**p < 0.01$].

[0094] Please refer to Figs. 6(a), 6(b) and 6(c), DENV-infected mice that were not treated with compound **8c** developed severe sickness leading to death within 4 ~ 6 dpi compared with iDENV-infected control mice. In contrast, compound **8c** at various concentrations shielded the mice from the life-threatening effects of the DENV-2 infection when compared to the non-compound **8c**-treated mice. DENV-infected mice that did not receive compound **8c** developed severe paralysis, anorexia, and asthenia and lost of their body weight compared with iDENV-treated mice at 6 dpi. In contrast, DENV-infected mice treated with compound **8c** showed slight paralysis, anorexia, and asthenia compared with iDENV-infected mice at 6 dpi.

[0095] Embodiments

[0096] 1. A pyrazolyquinoline compound, including: a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R_1 being a halide; a pyrazol; a first benzyl; and a second benzyl, wherein: a C2 position of the quinolinyl binds to a C3 or a C5 position of the pyrazol; on a first condition that the C2 position of the quinolinyl binds to the C3 position of the pyrazol, the C5 position of the pyrazol binds to a C4 position of the first benzyl; on a second condition that the C2 position of the quinolinyl binds to the C5 position

of the pyrazol, the C3 position of the pyrazol binds to the C4 position of the first benzyl; and an N1 position of the pyrazol binds to a C4 position of the second benzyl.

[0097] 2. The pyrazolyquinoline compound according to Embodiment 1, wherein a C1 position of the first benzyl binds to a substituent R₂ being a hydrogen, a halide, or an alkoxy, and a C1 position of the second benzyl binds to a substituent R₃ being a hydrogen, a halide, an alkoxy, or a sulfonamide group.

[0098] 3. The pyrazolyquinoline compound according to Embodiments 1-2, wherein R₁ is a fluorine, R₂ is a hydrogen, a fluorine or a methoxyl, and R₃ is a hydrogen, a fluorine, a methoxyl, or a sulfonamide group.

[0099] 4. The pyrazolyquinoline compound according to Embodiments 1-3, wherein the pyrazolyquinoline compound is one selected from the group consisting of:

- 6-fluoro-2-(1,5-diphenyl-1*H*-pyrazol-3-yl)quinoline,
- 6-fluoro-2-[5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
- 6-fluoro-2-[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
- 6-fluoro-2-(1,3-diphenyl-1*H*-pyrazol-5-yl)-quinoline,
- 6-fluoro-2-[3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,
- 6-fluoro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,
- 6-fluoro-2-[1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
- 6-fluoro-2-[1,3-bis(4-fluorophenyl)-1*H*-pyrazol-5-yl]quinoline,
- 6-fluoro-2-(1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)quinoline,
- 6-fluoro-2-[1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
- 6-fluoro-2-[3-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-

yl]quinoline,

6-fluoro-2-[1,3-bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline,

4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,

4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and

4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

[00100] 5. The pyrazolyquinoline compound according to Embodiments 1-4, wherein the pyrazolyquinoline compound is one selected from the group consisting of:

4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,

4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and

4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

[00101] 6. A pyrazolyquinoline compound, including: a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R₁ being a halide; a pyrazol; a first benzyl; and a second benzyl, wherein:

a C2 position of the quinolinyl binds to a carbon of the pyrazol, another carbon of the pyrazol binds to a C4 position of the second benzyl, and an N1 position of the pyrazol binds to a C4 position of the first benzyl.

[00102] 7. A method for preparing a pyrazolyquinoline compound, including steps of: providing 6-fluoro-2-methylquinoline; oxidizing the 6-fluoro-2-methylquinoline with selenium dioxide to form 6-fluoro-2-

formylquinoline; condensing the 6-fluoro-2-formylquinoline with an acetophenone derivative to form a carbonyl product; and treating the carbonyl product with a phenylhydrazine derivative to form the pyrazolyquinoline compound.

[00103] 8. The method according to Embodiment 7, wherein the acetophenone derivative is acetophenone, 4-fluoroacetophenone, or 4-methoxyacetophenone.

[00104] 9. The method according to Embodiments 7-8, wherein the phenylhydrazine derivative is phenylhydrazine, 4-fluorophenylhydrazine, 4-methoxyphenylhydrazine, or 4-hydrazinobenzenesulfonamide.

[00105] 10. The method according to Embodiments 7-9, wherein the acetophenone derivative is 4-methoxyacetophenone, the carbonyl product is (*E*)-3-(6-fluoroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one, and the phenylhydrazine derivative is 4-fluorophenylhydrazine, 4-methoxyphenylhydrazine, or 4-hydrazinobenzenesulfonamide.

[00106] 11. The method according to Embodiments 7-10, wherein the phenylhydrazine derivative is phenylhydrazine, and a 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation is performed after the carbonyl product is treated with the phenylhydrazine derivative.

[00107] 12. A pharmaceutical composition, including: a therapeutically effective amount of a pharmaceutical component of the pyrazolyquinoline compound in any one of Embodiments 1 to 6 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier of the pharmaceutical component.

Claims

1. A pyrazolyquinoline compound, comprising:

a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R₁ being a halide;

a pyrazol;

a first benzyl; and

a second benzyl, wherein:

a C2 position of the quinolinyl binds to a C3 or a C5 position of the pyrazol;

on a first condition that the C2 position of the quinolinyl binds to the C3 position of the pyrazol, the C5 position of the pyrazol binds to a C4 position of the first benzyl;

on a second condition that the C2 position of the quinolinyl binds to the C5 position of the pyrazol, the C3 position of the pyrazol binds to the C4 position of the first benzyl; and

an N1 position of the pyrazol binds to a C4 position of the second benzyl.

2. The pyrazolyquinoline compound according to Claim 1, wherein a C1 position of the first benzyl binds to a substituent R₂ being a hydrogen, a halide, or an alkoxy, and a C1 position of the second benzyl binds to a substituent R₃ being a hydrogen, a halide, an alkoxy, or a sulfonamide group.
3. The pyrazolyquinoline compound according to Claim 1, wherein R₁ is a fluorine, R₂ is a hydrogen, a fluorine or a methoxyl, and R₃ is a hydrogen, a fluorine, a methoxyl, or a sulfonamide group.
4. The pyrazolyquinoline compound according to Claim 1, wherein the pyrazolyquinoline compound is one selected from the group consisting of:

6-fluoro-2-(1,5-diphenyl-1*H*-pyrazol-3-yl)quinoline,

6-fluoro-2-[5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
 6-fluoro-2-[5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoline,
 6-fluoro-2-(1,3-diphenyl-1*H*-pyrazol-5-yl)-quinoline,
 6-fluoro-2-[3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1,3-bis(4-fluorophenyl)-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-(1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)quinoline,
 6-fluoro-2-[1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[3-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline,
 6-fluoro-2-[1,3-bis(4-methoxyphenyl)-1*H*-pyrazol-5-yl]quinoline,
 4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,
 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and
 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

5. The pyrazolyquinoline compound according to Claim 1, wherein the pyrazolyquinoline compound is one selected from the group consisting of:

4-[5-(6-fluoroquinolin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide,
 4-[3-(4-fluorophenyl)-5-(6-fluoroquinolin-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide, and
 4-[5-(6-fluoroquinolin-2-yl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

yl]benzenesulfonamide.

6. A pyrazolyquinoline compound, comprising:

a quinolinyl, wherein a C6 position of the quinolinyl binds to a substituent R₁ being a halide;

a pyrazol;

a first benzyl; and

a second benzyl, wherein:

a C2 position of the quinolinyl binds to a carbon of the pyrazol, another carbon of the pyrazol binds to a C4 position of the second benzyl, and an N1 position of the pyrazol binds to a C4 position of the first benzyl.

7. A method for preparing a pyrazolyquinoline compound, comprising steps of:

providing 6-fluoro-2-methylquinoline;

oxidizing the 6-fluoro-2-methylquinoline with selenium dioxide to form 6-fluoro-2-formylquinoline;

condensing the 6-fluoro-2-formylquinoline with an acetophenone derivative to form a carbonyl product; and

treating the carbonyl product with a phenylhydrazine derivative to form the pyrazolyquinoline compound.

8. The method according to Claim 7, wherein the acetophenone derivative is acetophenone, 4-fluoroacetophenone, or 4-methoxyacetophenone.

9. The method according to Claim 7, wherein the phenylhydrazine derivative is phenylhydrazine, 4-fluorophenylhydrazine, 4-methoxyphenylhydrazine, or 4-hydrazinobenzenesulfonamide.

10. The method according to Claim 7, wherein the acetophenone derivative is 4-methoxyacetophenone, the carbonyl product is (*E*)-3-(6-fluoroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one, and the phenylhydrazine derivative is

4-fluorophenylhydrazine, 4-methoxyphenylhydrazine, or 4-hydrazinobenzenesulfonamide.

11. The method according to Claim 7, wherein the phenylhydrazine derivative is phenylhydrazine, and a 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation is performed after the carbonyl product is treated with the phenylhydrazine derivative.

12. A pharmaceutical composition, comprising:

a therapeutically effective amount of a pharmaceutical component of the pyrazolyquinoline compound in any one of Claims 1 to 6 or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier of the pharmaceutical component.