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— 包括国际检索报告(条约第 21 条(3))。

— 包括经修改的权利要求及声明(条约第 19 条(1))。

WO 2010/135972 A1

(54) **Title**: PREPARATION METHODS AND USES OF 1-(SUBSTITUTED ARYL)-5-TRIFLUOROMETHYL-2-(1H)-PYRIDONE COMPOUNDS AND THEIR SALTS

(54) **发明名称** : 1-(取代芳基)-5-三氟甲基-2-（1H）吡啶酮化合物及其盐的制备方法及其用途

(57) **Abstract**: A 1-(substituted aryl)-5-trifluoromethyl-2-(1H)-pyridone compounds and pharmaceutical acceptable salts, preparation methods and uses for preparing the drugs for treating fibrosis thereof.

(57) **摘要**:

一种 1-取代芳基-5-三氟甲基-2-(1H)-吡啶酮类化合物及其药学上可用的盐，以及所述化合物及其盐的制备方法和它们在制备治疗纤维化药物中的用途。

Preparation of 1-(substituted aryl)-5-trifluoromethyl-2-(1H)pyridone compounds and salts thereof and their applications

TECHNICAL FIELD

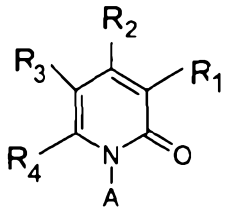
The invention relates to 1-(substituted aryl)-5-trifluoromethyl-2-(1H)pyridone compounds, preparation methods and medical applications for the same.

BACKGROUND OF THE INVENTION

In a variety of organs or tissues, fibrosis causes reduction of parenchyma cells therein and an increase of fibrous connective tissues, eventually damaging tissue structures, causing tissue dysfunction or even organ failure.The mechanism of fibrosis, and diagnostic methods and prevention measures for fibrosis of organs or tissues have been widely studied. In prior art, considerable progress has been made in some aspects, but some key unresolved issues still exist.

US patents US3839346A, US4052509A, US4042699 disclose 29 pyridone compounds having formula I as follows,

Formula I



and disclose functions of the pyridone compounds of resisting inflammation, allaying fever, reducing the level of serum uric acid, relieving pain or the like, wherein 5-methyl-1-phenyl-2(1H)-pyridone (Pirfenidone) has the best activity and lower toxicity.

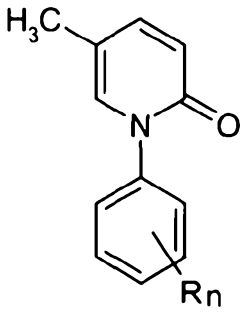
US patent US5,310,562 discloses 5-methyl-1-phenyl-2(1H)-pyridone for the first time in 1994, that is Pirfenidone (PFD), having an anti-fibrosis biological activity; subsequently US patents US5,518,729 and US5,716,632 disclose N-substituted-2-(1H)pyridone described as the structural formula I and N-substituted-3-(1H)pyridone having the same anti-fibrosis function. Forty-four compounds are specified, most of which are known compounds derived from US patent US4052509; and in the compounds, R1, R2, R3, and R4 are defined as methyl groups

or ethyl groups.

Pirfenidone (PFD) is proven to have effectiveness in fibrosis prevention through in vitro and animal experiments. Pirfenidone has functions of stopping or even converting ECM accumulation and preventing or reversing fibrosis and scar formation in experiments using animals with renal fibrosis and pulmonary fibrosis and in the clinical treatment of patients with idiopathic pulmonary fibrosis. (Shimizu T, Fukagawa M, Kuroda T, et al. Pirfenidone prevents collagen accumulation in the remnant kidney in rats with partial nephrectomy. Kidney Int, 1997,52 (Suppl 63): S239-243; Raghu G, Johnson WC, Lockhart D, et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone. Am J Respir Crit Care Med, 1999,159 : 1061-1069).

The applicant proposes a CN patent ZL02114190.8 and provides a class of pyridone compounds of the formula II.

Formula II



In the structural formula II, if n=1, the substituent R is F, Br, or I;

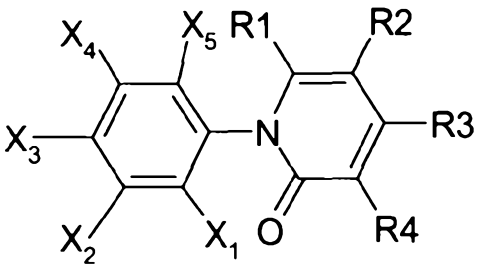
if n=2, the substituents R are F, Cl, Br, I, a saturated linear alkyl group, an oxo-saturated linear alkyl group, or a halo-saturated linear alkyl group.

The substituent R is at any of the ortho-position, meta-position, and para-position on a benzene ring.

Pirfenidone came into the market in Japan in 2008 for treating indications for pulmonary fibrosis. However, Pirfenidone and its derivatives do not have high enough strength. The clinical dose of Pirfenidone achieves 2400mg/day.

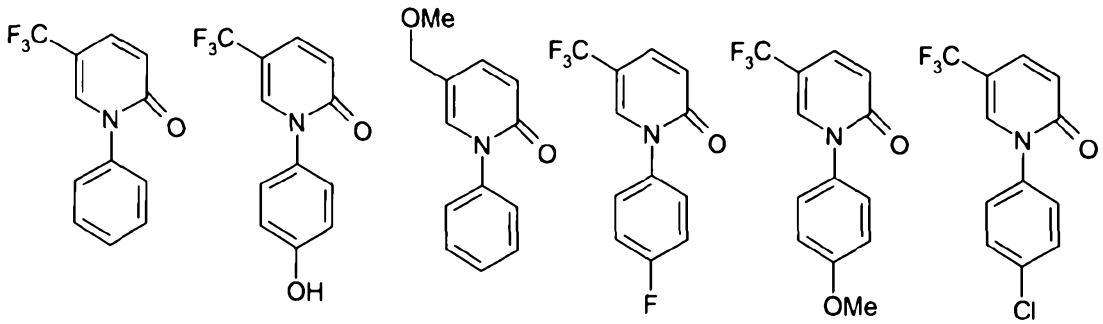
Patent publications WO2007053685 and WO2006122154 disclose compounds having functions of inhibiting p38 kinase, applied to treatment of fibrosis diseases and disclose the formula III;

Formula III



wherein, R1-R4 each are H, an alkyl group, a substituted alkyl group, an alkenyl group, a haloalkyl group, a nitro alkyl group, a hydroxyalkyl group, an alkoxyl group, a phenyl group, a substituted phenyl group, halogen, a hydroxyl group, an alkoxyalkyl group, a carboxyl group, an alkoxycarbonyl group, etc.; X1-X5 each are H, halogen, an alkoxyl group, or a hydroxyl group.

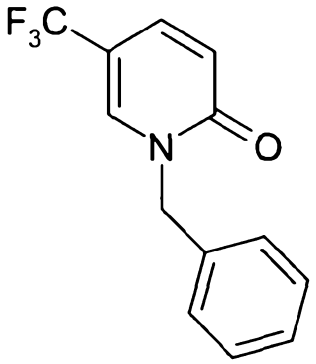
WO2007062167 also discloses compounds having functions of inhibiting p38 kinase and applied to treatment of various fibrosis diseases, wherein some structures are shown as follows:



Some simple substituents are provided on the benzene rings of the compounds.

CN patent 200710034357 discloses some similar compounds having the above structures with anti-fibrosis activity and a compound with the anti-fibrosis activity shown in the formula IV.

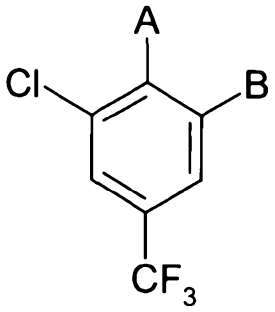
Formula IV



Those compounds are provided with TFM at the 5-position of the pyridone ring, thereby overcoming the disadvantages of inferior action of Pirfenidone, but the strength of those compounds is still not powerful enough.

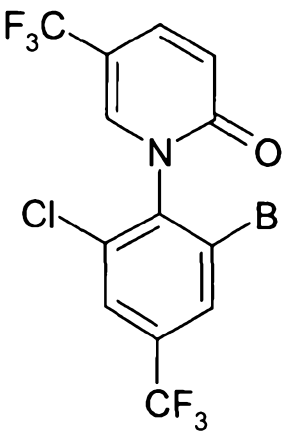
DE patent DE4343528 reports a class of compounds having insecticidal actionsfor agricultural use, with the formula V as follows.

Formula V



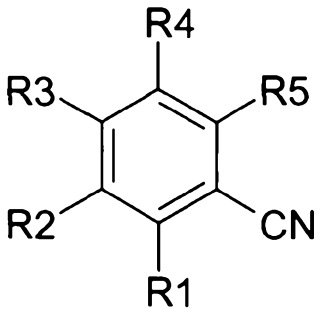
In structural formula V, A and B are substituted by various heterocyclic rings, such as furan, imidazole, pyridine and pyridone; wherein a class of compounds with the formula VI is included.

Formula VI



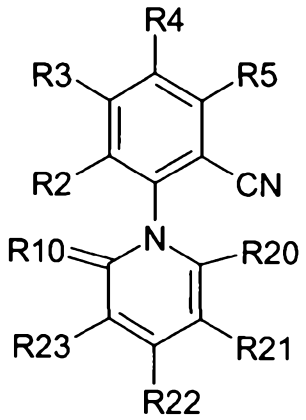
EP patents EP259048, EP367410 and EP398499 report a class of compounds having insecticidal actions for use in agriculture, with the formula VII as follows:

Formula VII



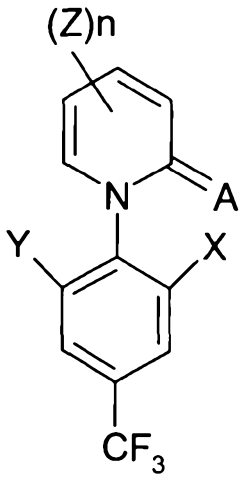
wherein a class of compounds having the formula VIII, in which R1 is pyridone and R10 is O or S, is included.

Formula VIII



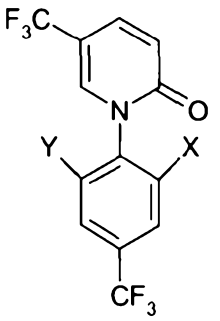
EP patent EP216541 reports a class of compounds having insecticidal actions for use in agriculture, with the formula IX as follows:

Formula IX



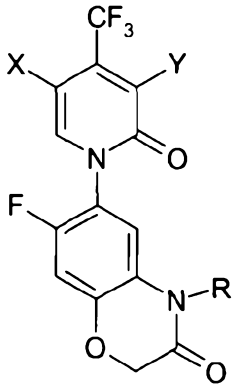
wherein a class of compounds with the formula X is included.

Formula X



EP patent EP488220 reports a class of compounds having insecticidal actions, with the formula XI as follows:

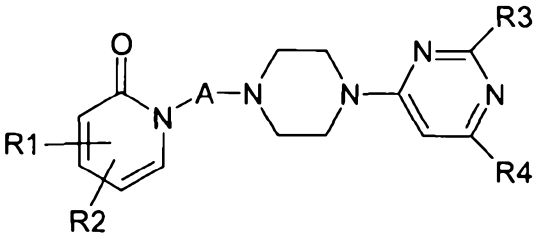
Formula XI



In structures of the above-mentioned compounds, the pyridine ring and the benzene ring at the 1-position of the pyridine ring have a plurality of substituents; the compounds with complicated structures have not been reported to have the anti-fibrosis function.

DE102004027359 discloses a class of compounds capable of modulating dopamine-3 receptor and applied to treatment of Parkinson's disease and schizophrenosis;

Formula XII



wherein, A is a hydrocarbon chain with 4-6 atoms, having 1-2 substituted methyl groups thereon; or 1-2 carbon atoms in the carbon chain are substituted by O, C=O, S and other

atoms; R1 and R2 are H, CN, NO_2, halogen atom, OR^5, NR^6R^7, C(O) NR^6R^7, O-C(O)NR^6R^7; a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, etc.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

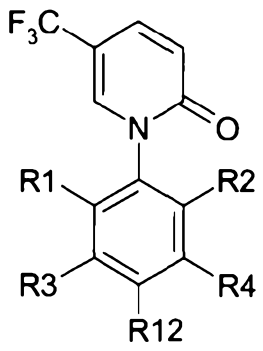
It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

It is an object of a preferred form of the invention to provide compounds exhibiting anti-fibrosis activities which are water-soluble.

SUMMARY OF THE INVENTION

According to a first aspect the present invention provides a 1-(substituted phenyl)-5-trifluoromethyl-2(1H)pyridone compound, having a formula (XIII),

Formula XIII

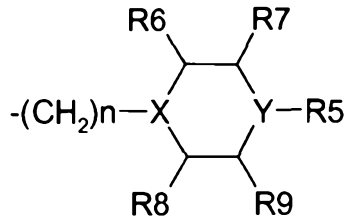


wherein, R1-R4, and R12 are selected from: H, CN, NO_2, a hydroxyl group, an amino group, a halogen atom, a C_1-C_6 alkoxyl group, $NR^{10}R^{11}$, $C(O)R^{14}$,$O\text{-}C(O)R^{14}$, a C1-C6 alkyl group, a C_1-C_6 haloalkyl group, a C_2-C_6 alkenyl group, a carboxyl group and a carboxylic ether; wherein R^{14} is a C_1-C_6 alkyl group, R^{10} and R^{11} are selected from H, a C_1-C_6 alkyl group, a C_1-C_6 hydroxyalkyl group, an esterified C_1-C_6 hydroxyalkyl group, a C_1-C_6 alkoxyalkyl group, or formula XIV;

and at least one of R1-R4, and R12 is $NR^{10}R^{11}$; and at least one of R^{10} and R^{11} is of the

formula XIV.

Formula XIV



and in formula XIV, R5 is selected from H, a C_1-C_6 alkyl group, a C_1-C_6 hydroxyalkyl group, an esterified C_1-C_6 hydroxyalkyl group and a C_2-C_6 alkenyl group; R6-R9 are selected from H, a C_1-C_6 alkoxyl group, =O, a C_1-C_4 alkyl group, a C_1-C_4 haloalkyl group, a C_1-C_4 hydroxyalkyl group, and a C_2-C_4 alkenyl group; X is selected from N, or CH; Y is selected from N, O or C; with the proviso that, when Y is O, R^5 is absent; n is 1-6;
or pharmaceutically acceptable salts thereof.

According to a second aspect the present invention provides an anti-fibrosis medicament comprising a compound defined in the first aspect and a pharmaceutically acceptable excipient.

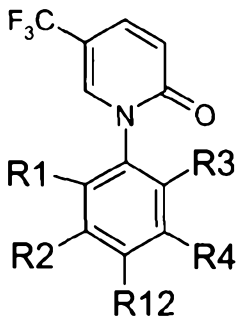
According to a third aspect the present invention provides a method of treating fibrosis comprising the steps of administering to a patient in need of said treatment a compound according to the first aspect.

According to a fourth aspect the present invention provides the use of a compound according to the first aspect for the manufacture of a medicament for the treatment of fibrosis.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

In a related aspect, the invention provides 1-(substituted phenyl)-5-trifluoromethyl-2-(1H)pyridine compounds shown in formula XIII,

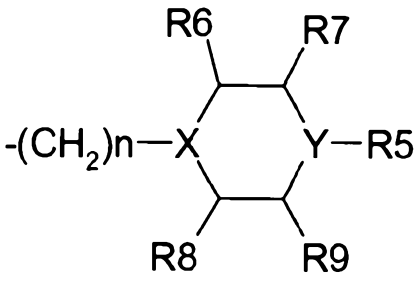
Formula XIII



wherein R1-R4, R12 are selected from H, CN, NO_2, a hydroxyl group, an amino group, a halogen atom, a C_1-C_6 alkoxyl group, $NR^{10}R^{11}$, OR^{13}, $C(O)R^{14}$, $O\text{-}C(O)R^{14}R^{15}$, a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_2-C_6 alkenyl group, a carboxyl group and carboxylic ether; wherein R^{14} and R^{15} are a C_1-C_6 alkyl group, R^{10} and R^{11} are selected from H, a C_1-C_6 hydroxyalkyl group, an esterified C_1-C_6 hydroxyalkyl group, a C_1-C_6 alkoxyalkyl group, or formula XIV;

and at least one of R1-R4 and R12 is $NR^{10}R^{11}$ or OR^{13}; in OR^{13}, R^{13} is a C_1-C_6 hydroxyalkyl group or a C_1-C_6 alkoxyalkyl group; and R^{10} and R^{11} are not simultaneously H;

Formula XIV



in formula XIV, R5 is selected from H, a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 hydroxyalkyl group, an esterified C_1-C_6 hydroxyalkyl group, and a C_2-C_6 alkenyl group; R6-R9 are selected from H, a C_1-C_6 alkoxyl group, =O, a C_1-C_4 alkyl group, a C_1-C_4 haloalkyl group, a C_1-C_4 hydroxyalkyl group, and a C_2-C_4 alkenyl group; X is selected from N and CH; Y is selected from N, O, and C (with the proviso that, when Y is O, R5 is absent; and n is 1-6;

and pharmaceutically available salts thereof.

More preferably, R12 is $NR^{10}R^{11}$ or OR^{13}.

According to embodiments of the invention, more preferably, one of R1-R4 is a halogen atom and others are H if R12 is $NR^{10}R^{11}$ or OR^{13}.

According to embodiments of the invention, the following compounds are preferred:

1-(2-chloro-4-((3-(4-methylpiperazin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 1);

1-(2-chloro-4-((3-morpholinylpropyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 2);

1-(2-chloro-4-((3-piperidin-1-yl)propylamino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 3);

1-(4-((3-butoxypropyl) amino)-2-chlorophenyl)-5-(trifluoromethyl) pyridin-2(1H)-one (compound 4);

1-(2-chloro-4-((2-hydroxyethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 5);

1-(4-(N,N-(2-hydroxyethyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 6);

1-(2-chloro-4-(((3-piperidin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one hydrochloride (compound 7);

1-(2-chloro-4-((2-(2-hydroxyethoxy)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 8);

1-((4-((piperazin-1-yl)ethyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 9);

1-(2-chloro-4-((2-(piperidyl-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 10);

1-(2-chloro-4-((2–morpholinylethyl)amino)-phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 11);

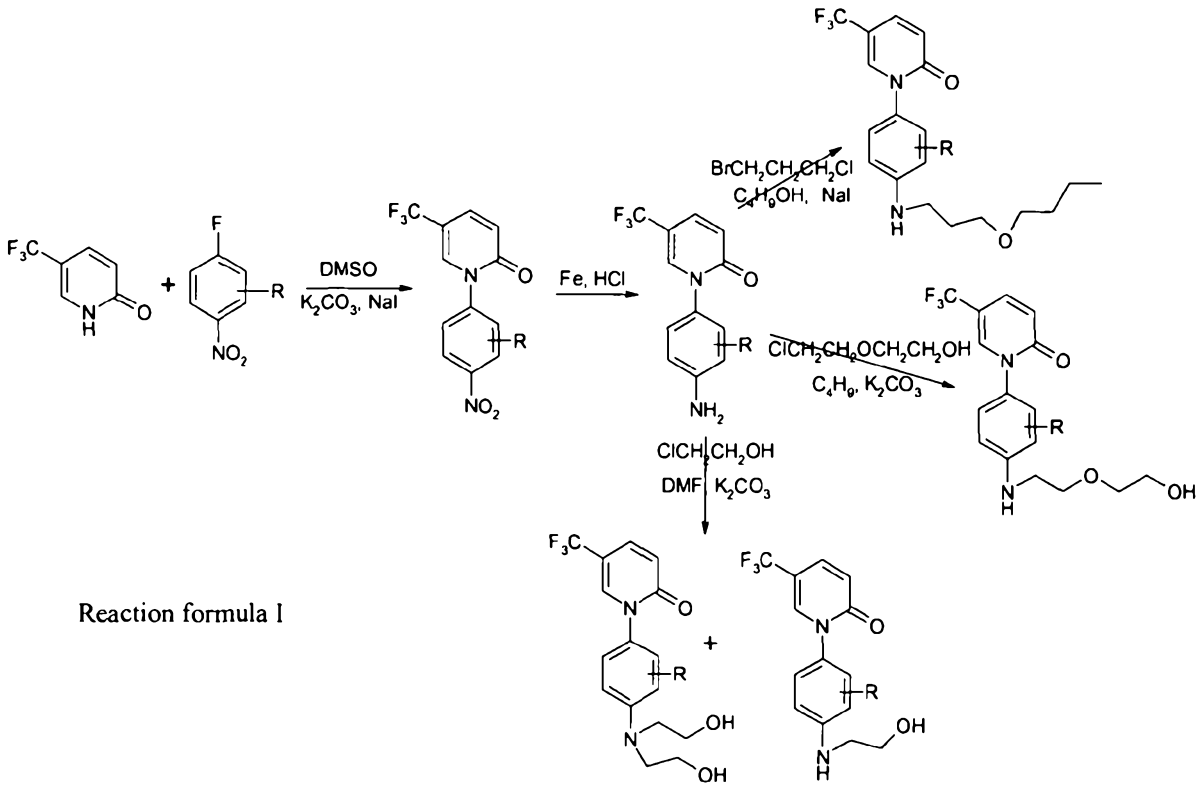
1-(2-chloro-4-((2-(4-methylpiperazin-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 12);

1-(2-chloro-4-((2-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)amino)-phenyl)-5-

(trifluoromethyl)pyridin-2(1H)-one (compound 13),

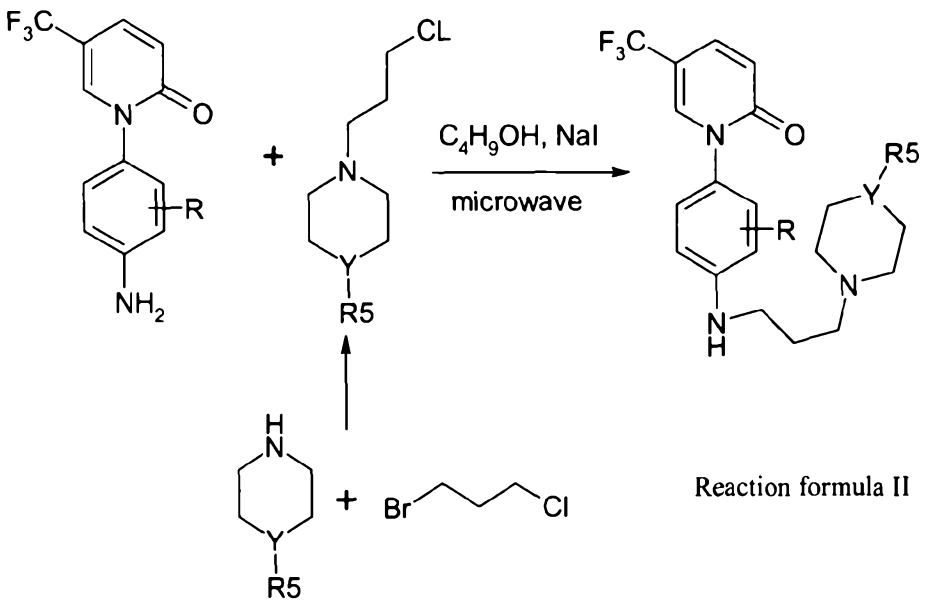
and pharmaceutically acceptable salts, including hydrochlorate, sulfate, phosphate, perchlorate, methanesulfonate, trifluoromethanesulfonate, formate, acetate, propionate, butyrate, maleate, succinate, trifluoroacetate, succinate, salicylate, DL-aspartate, D-aspartate, L-aspartate, DL-glutamate, D-glutamate, L-glutamate, glycerate, succinate, stearate, DL-tartrate, D-tartrate, L-tartrate, (+/-)-mandelate, (R)-(-)-mandelate, (S)-(+)-mandelate, citrate, mucate, maleate, malonate, benzoate, DL-malate, D-malate, L-malate, hemimalate, 1-adamantane acetate, 1-adamantane carboxylate, flavianate, sulfoacetate, (+/-)-lactate, L-(+)-lactate, D-(-)-lactate, pamoate, D-α-galacturonic acid salt, glycerate, DL-cystine salt, D-cystine salt, L-cystine salt, DL-homocystine salt, D-homocystine salt, L-homocystine salt, DL-cysteine salt, D-cysteine salt, L-cysteine salt, (4S)-hydroxy-L-proline, cyclopropane-1,1-dicarboxylate, 2,2-methyl malonate, tyrosine salt, proline salt, fumarate, 1-hydroxy-2-naphthoate, phosphonoacetate, carbonate, bicarbonate, 3-phosphonopropionate, DL-pyroglutamate, D-pyroglutamate, L-pyroglutamate, toluenesulfonate, benzenesulfonate, esilate, (+/-)-camsilate, naphthalenesulfenesulfonate, 1R-(-)-camsilate, 1S-(+)-camsilate, 1,5-napadisilate, 1,2-ethanedisulphonate, 1,3-propanedisulphonate, 3-(N-morpholino) propane sulphonate, biphenyl sulphonate, isethionate, 1-hydroxy-2–naphthalenesulfenesulfonate, dihydric phosphate, potassium hydrogen phosphate, dipotassium phosphate, potassium phosphate, sodium hydrogen phosphate, disodium phosphate, sodium phosphate, sodium dihydrogen phosphate, calcium phosphate, tertiary calcium phosphate, hexafluoro phosphate, ethenyl phosphate, 2-carboxylethyl phosphate and phenyl phosphate.

The invention also provides a synthetic method for a compound of formula XIII, including: reacting 5-trifluoromethyl-2(1H)pyridone with nitro-substituted fluorobenzene, with DMSO as solvent, potassium carbonate as an acid-binding agent and sodium iodide as a catalyst so as to form a nitro substituent; reducing the nitro substituent by iron powder in the presence of hydrochloric acid to prepare a simple amino-substituted compound; and preparing target products according to different compounds, shown in reaction formula I.



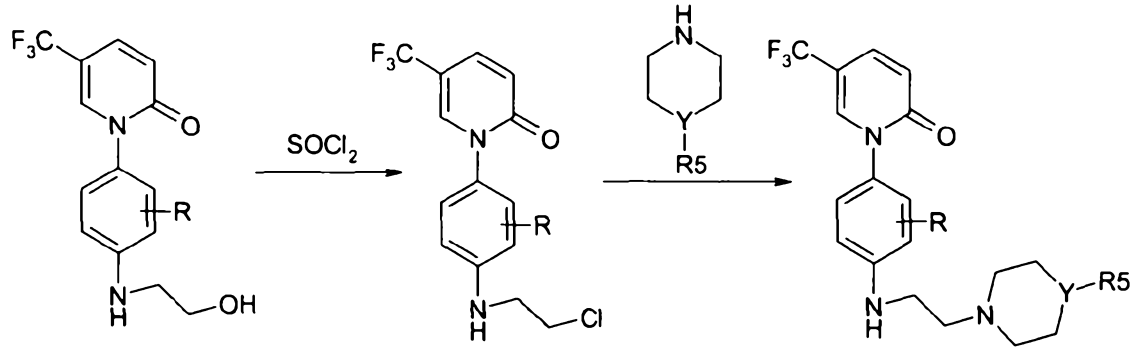
Reaction formula I

A compound, in which an amino group is bonded to a heterocyclic ring through an aliphatic side chain, is prepared by first reacting bromochloropropane with a heterocyclic compound to produce the chloroalkyl heterocyclic compound; and then reacting with the amino substituted compound prepared according to reaction formula I to obtain the target product, catalyzed by microwave irradiation, with normal butanol as solvent and sodium iodide as a catalyst, shown in the reaction formula II.



Reaction formula II

or, the target product is prepared by reacting a hydroxyethyl amino substituted compound prepared according to reaction formula I with thionyl chloride to produce the chloroethyl amino substituted compound; and then reacting with the heterocyclic compound, shown in reaction formula III.



Reaction formula III

The synthetic starting product trifluoromethyl pyridone is a commercial material.

The above-mentioned compound is used for preparing a broad-spectrum medicament for fibrosis.

In the invention, based on the prior art, a substituted amino group is introduced onto the benzene ring at the 1-position of pyridone; a hydrophilic group such as a hydroxyl group and

heterocyclic ring are introduced onto the amino group through an alkyl chain, thus obtaining a class of new pyridone compounds and salts thereof. The activity of the compounds is greatly enhanced.

The applicant finds that the produced compounds have relatively higher effects than the conventional pyridone compound by modifying the phenyl group by the substituted amino group on the basis of 1-phenyl-5-trifluoromethyl-pyridone; simultaneously the compounds including heterocyclic rings could be produced into various salts which are beneficial for being prepared into various liquid formulations.

The applicant learns through experiment that the compounds provided by the invention have the anti-fibrosis pharmacological action as good as the pyridone compound in the prior art, but have significantly stronger effect, over 60-fold, than the pirfenidone in the prior art. Therefore, the invention also provides applications of compounds represented by formula XIII in preparation of an anti-fibrosis medicament.

BRIEF DESCRIPTION OF DRAWINGS

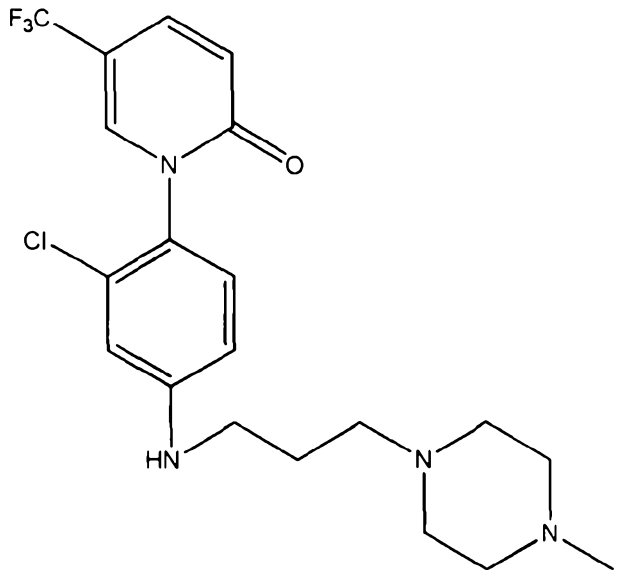
Figure 1 HE staining for renal pathology in embodiment 15 (×200)

Figure 2 Masson staining for renal pathology in embodiment 15 (×200)

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Example 1

Preparation of 1-(2-chloro-4-((3-(4-methylpiperazin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



(Compound 1)

A. Preparation of 1-(2-chloro-4-nitrophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one

The preparation of 1-(2-chloro-4-nitrophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: adding 8.2g (0.050mol) of 5-(trifluoromethyl)pyridin-2(1H)-one in 100 ml of DMSO for dissolving; adding 13.1g (0.075mol) of 3-chloro-4-fluoronitrobenzene, 11.0g (0.080mol) of potassium carbonate and 1.4g of sodium iodide and allowing the resulting system to react at 130 °C for 4 hours under stirring; after reaction, cooling to 40 °C; adding 100ml of 12% ammonia solution; separating out a great amount of precipitate; filtering; dissolving the filter residue with ethyl acetate; decolorizing by active carbon; filtering; drying the filtrate by anhydrous sodium sulfate; filtering out sodium sulfate; reclaiming solvent; filtering to obtain the product of 1-(2-chloro-4-nitrophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one. The product is 12.0g of brown solid; m.p.: 217.7-218.3°C. MS(m/z): 318(M^+). ^{1}H-NMR($CDCl_3$,300MHz)δppm: 6.769~6.800(d,1H,Ar-H, J=3.3Hz), 7.579~7.570(t,3H,Ar-H), 8.296~8.333(dd,1H,J=3.3Hz,8.7Hz, Ar-H),8.492(s,1H,Ar-H).

B. Preparation of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one

The preparation of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: heating 12.0g (0.035mol) of 1-(2-chloro-4-nitrophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one, 200mL of 50% ethanol and 5.8g (0.105mol) of reductive iron powder to reflux; slowly adding 0.42mL (0.004mol) of

concentrated HCl dropwise (dropping after dilution by 5mL of 50% ethanol); refluxing for 5 hours under stirring; after reaction, regulating pH value to 10 by 15% KOH ethanol solution; filtering; washing the filter residues by 95% ethanol (2 x 10 mL); extracting by ethyl acetate (50 mL x 3) after evaporating ethanol from the filtrate; drying the organic phase by anhydrous sodium sulfate overnight; filtering; and evaporating filtrate to obtain the product of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one. The product is 12.0g of khaki solid powder. m.p. : 136-138 °C. EI-MS(m/z) : 288$[M]^+$. NMR(CDCl3,300MHz)δppm : 3.559(br,2H,-NH2),6.633~6.670(dd,1H,J=2.7 Hz,8.7HzAr-H),6.708~6.740(d,1H, J=9.6Hz,Ar-H),6.820~6.828(d,1H,2.4Hz,Ar-H),7.089~7.117(d,1H,J=2.4Hz,Ar-H),7.503~7.544(dd,1H,2.7Hz,9.6Hz,Ar-H),7.595(s,1H,Ar-H).

C. Preparation of 1-(3-chloropropyl)-4-methylpiperazine

The preparation of 1-(3-chloropropyl)-4-methylpiperazine includes steps of: chilling 0.1mol of piperidine on ice, chilling 100mL of acetone and 0.125mol of sodium hydrate (25%) below 5 °C; slowly adding 0.1mol of 1-chloro-3-bromopropane dropwise; reacting for 48 hours at room temperature 25 °C; vacuum-evaporating solvent to dryness; adding 50mL of water; extracting by methylene dichloride (3 x 50 mL); combining organic phases; drying by sodium sulphate overnight; filtering; vacuum-evaporating to get an oily product; adding concentrated hydrochloric acid dropwise to regulate pH value to 1-2; adding methylene dichloride and stirring to remove 1-chloro-3-bromopropane; dissolving the filter residue by adding an amount of water; regulating pH value to 12 by 25% sodium hydroxide; extracting by methylene dichloride (20ml x 3); drying by sodium sulphate; filtering and vacuum-evaporating to obtain a yellow oily product with a yield of 14.2%.

^{1}H-NMR($CDCl_3$,300MHz)δ:

1.930~1.999(m,2H,-CH2-),2.301(s,3H,-CH3),2.470~2.517(m,10H,-CH2-),3.575~3.619(t,2H,-CH2).

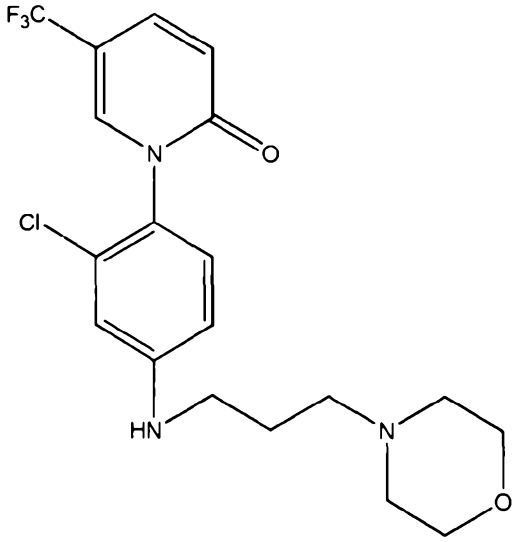
D. Preparation of 1-(2-chloro-4-((3-(4-methylpiperazin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one

The preparation of

1-(2-chloro-4-((3-(4-methylpiperazin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: adding 15mL of normal butanol to dissolve 2.59g (0.003mol) of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one; adding 0.528g(0.001mol) of 1-(3-chloro)propyl-4-methylpiperazine and uniformly mixing; and adding a catalytic amount of potassium iodide; carrying out microwave reaction at 170 °C; filtering; removing solvent from the filtrate through evaporating; and separating residue by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 (1% triethylamine) to obtain 0.15g of yellow solid. m.p.: 129-132 °C. ESI- MS(m/z): 429$[M+H]^+$. ^{1}H-NMR($CDCl_3$,300MHz)δppm: 1.805~1.845(m,2H,-CH2-),2.369(s,3H,-CH3),2.534~2.575(t,10H,-CH2-),3.201(br,2H,-CH2-), 5.501(br,1H,-NH-),6.516~6.553(dd,1H,*J*=2.4Hz,8.7Hz,Ar-H),6.678~6.734(dd,1H,*J*=2.4Hz,7.2Hz,Ar-H),7.071~7.100（d,1H,*J*=8.7Hz,Ar-H）, 7.491~7.532(dd,1H,*J*=2.7Hz,9.6Hz,Ar-H), 7.604(s,1H,Ar-H).

Example 2

Preparation of 1-(2-chloro-4-((3-morpholinylpropyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



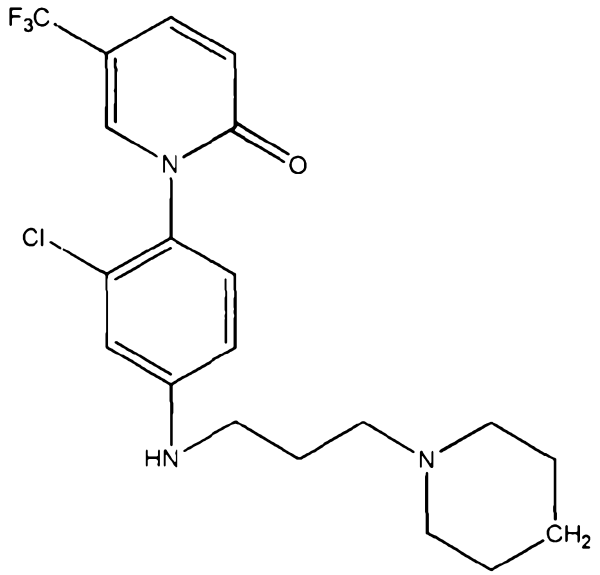
(Compound 2)

The preparation of 1-(2-chloro-4-((3-morpholinylpropyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: adding 5mL of normal butanol to dissolve 0.54g (0.003mol) of

1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one; adding 0.528g(0.001mol) of 1-(3-chloro)propyl-morpholine and a catalytic amount of potassium iodide and uniformly mixing; carrying out microwave reaction at 180 °C; filtering, evaporating filtrate to dryness; and separating residues by chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 (1% triethylamine) to obtain 0.16g of a yellow solid. m.p.: 95-97 °C, ESI-MS(m/z): 416[M+H]$^+$. ^{1}H-NMR($CDCl_3$,300MHz)δppm: 1.836~1.856(m,2H,-CH2-), 2.527(br,6H,-CH2-),3.202~3.258(t,2H,-CH2-),3.777(br,4H,-CH2-),5.403(br,1H,-NH-),6.523~6.559(dd,1H,*J*=2.4Hz,8.7Hz,Ar-H),6.689~6.698(d,1H,*J*=2.7Hz,Ar-H),6.737(s,1H,Ar-H),7.078~7.138d,1H,*J*=8.7Hz,Ar-H），7.493~7.534(dd,1H,*J*=2.7Hz,9.9Hz,Ar-H),7.604(s,1H,Ar-H).

Example 3

Preparation of 1-(2-chloro-4-((3-piperidin-1-yl)propylamino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



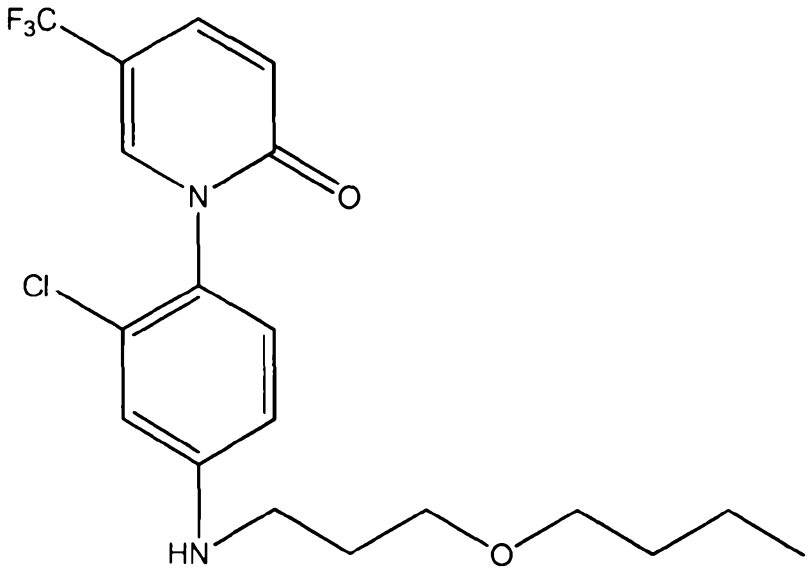
(Compound 3)

The preparation of 1-(2-chloro-4-((3-piperidin-1-yl)propylamino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one incudes steps of: adding 15mL of normal butanol to dissolve 3.50g(0.012mol) of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one; adding 0.528g(0.004mol) of 1-(3-chloro)propylpiperidine and uniformly mixing; and adding a catalytic amount of potassium iodide; carrying out microwave reaction at 180 °C; filtering; evaporating filtrate to

dryness; and separating residue by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 (1% triethylamine) to obtain 0.21g of light brown solid . m.p.: 112-115°C, EI-MS(m/z): 413[M]$^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm: 1.482~1.489 (m,2H) ,1.607~1.642(m.4H),1.736~1.843(m,2H),2.425~2.491(m,6H),3.185(br,2H),6.011(br,1H-NH-),6.499~6.537(dd,1H,*J*=2.7Hz,8.7Hz,Ar-H),6.654~6.662(d,1H,*J*=2.4Hz,Ar-H),6.698~7.731(d,1H,*J*=9.9Hz,Ar-H),7.059~7.088(d,1H,*J*=8.7Hz,Ar-H),7.483~7.524(dd,1H,*J*=2.7Hz, 9.9Hz,Ar-H), 7.607(s,1H,Ar-H).

Example 4

Preparation of 1-(4-((3-butoxypropyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



(Compound 4)

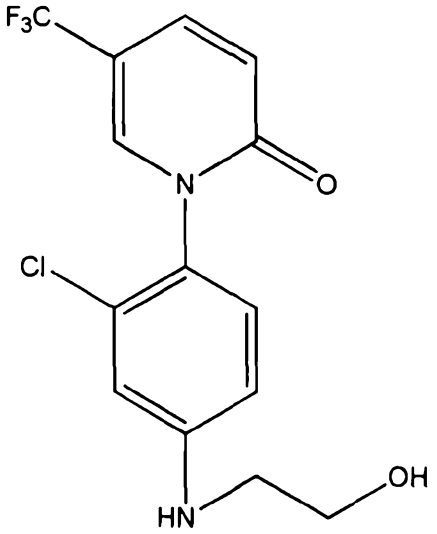
The preparation of 1-(4-((3-butoxypropyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one incudes steps of: adding 15mL of normal butanol to dissolve 2.88g(0.01mol) of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one; adding 3.14g(0.02mol) of 1-chloro-3-bromopropane for uniformly mixing; and feeding a catalytic amount of potassium iodide; carrying out microwave reaction at 180 DEG C; filtering; evaporating filtrate to

dryness; and separating residue by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 3:1 (1% triethylamine) to obtain 0.20g of off-white solid. m.p.: 83.0-85.0 °C. ESI-MS(m/z): 425[M+Na]$^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm: 0.921~0.970 (t, 3H, -CH3), 1.364~1.439(m,2H,-CH2-),1.563~1.612(m,2H,-CH2-),1.880~1.919 (m,2H,-CH2-),3.213~3.255(t,H,-CH2-),3.415~3.458(t,2H,-CH2-),3.542~3.579(t,2H,-CH2-),4.696(br,1H,-NH-),6.508~6.545(dd,1H,*J*=2.4 Hz,2.4Hz,Ar-H),6.680~6.689(d,1H,*J*=2.7Hz,Ar-H),.704~6.736(d,1H,*J*=9.6Hz,Ar-H),7.070~7.099(d,1H,*J*=8.7Hz,Ar-H),7.491~7.532(dd,1H,*J*=2.7Hz,2.4Hz,Ar-H),7.606(s,1H,Ar-H).

Example 5

Preparation of

1-(2-chloro-4-((2-hydroxyethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



(Compound 5)

The preparation of 1-(2-chloro-4-((2-hydroxyethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: adding 12mL of chloroethanol and 12mL of DMF to dissolve 0.57g(0.002mol) of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one; adding 0.56g(0.004mol) of potassium carbonate; mixing for reaction for 12 hours at 130 °C; filtering; evaporating filtrate to dryness; and separating residue by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 to obtain 0.080g of brown solid.

m.p.: 161.0-164.0°C, EI-MS(m/z): 332[M]$^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm:

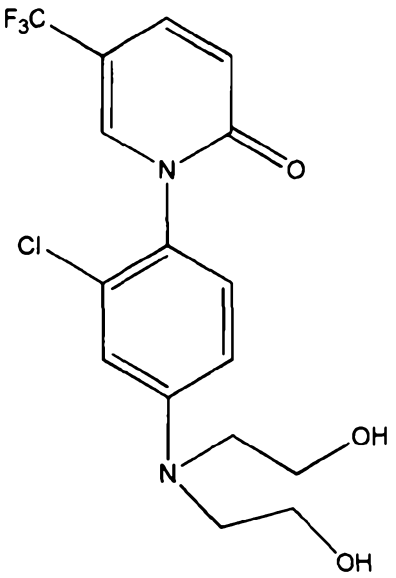
3.504~3.543(t,2H,-CH2-),3.658~3.709(t,2H-CH2-),4.412(br,1H,-NH-),6.590~6.627(dd,1H,J=2.7Hz,2.4Hz,Ar-H),

710~6.742(d,1H,*J*=9.6Hz,Ar-H),6.754~6.762(d,1H,*J*=2.4Hz,Ar-H),7.128~7.157(d,1H,J=8.7Hz,Ar-H),7.500~7.542(dd,1H,*J*=2.7Hz,9.6Hz,Ar-H),7.597(s,1H,Ar-H).

Example 6

Preparation of

1-(4-(N,N-(2-hydroxyethyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



(Compound 6)

The preparation of

1-(4-(N,N-(2-hydroxyethyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: adding 12mL of chloroethanol and 12mL of DMF to dissolve 0.57g(0.002mol) of 1-(4-amino-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one; adding 0.56g(0.004mol) of potassium carbonate; mixing for reaction for 12 hours at 130 DEG C; filtering; evaporating filtrate to dryness; and separating residue by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 to obtain 0.070g of red brown solid. m.p.: 169.0~172.0°C, EI-MS (m/z): 376[M]$^+$,

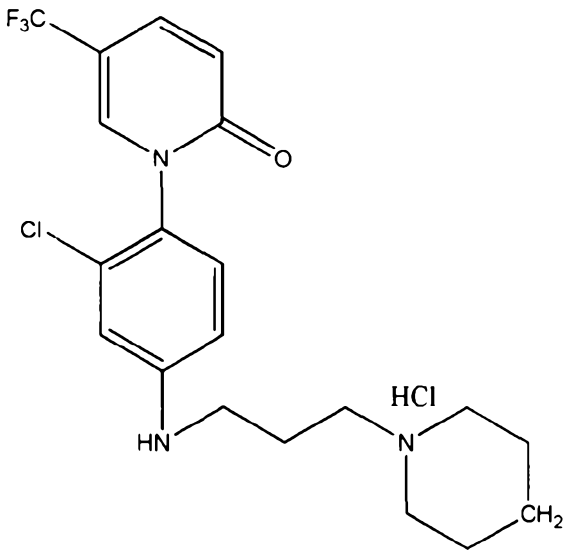
^{1}H-NMR($CDCl_3$,300MHz)δppm:

3.213~3.245(t,4H,-CH2-),3.661~3,754(t,4H-CH2-),6.714~6.746(d,1H,*J*=9.6Hz,Ar-H),6.864~6.903(dd,1H,*J*=2.7 Hz,9.6Hz,Ar-H),

7.018~7.027(d,1H,*J*=2.7Hz,Ar-H),7.214~7.244(d,1H,*J*=9.0Hz,Ar-H),7.505~7.514(dd,1H,*J*=2.7Hz,Ar-H).

Example 7

Preparation of 1-(2-chloro-4-(((3–piperidin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one hydrochloride



(Compound 7)

The preparation of 1-(2-chloro-4-(((3–piperidin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one hydrochloride includes steps of: dissolving 2.9mmol of 1-(4-(((3-piperidin-1-yl)propyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one by an amount of ethanol; adding 2mmol of hydrochloric acid; mixing for reaction for 2 hours; evaporating solvent to dryness to obtain 0.12g of 1-(2-chloro-4-(((3-piperidin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one hydrochloride as an off-white solid. M.P.: 192~195°C, EI-MS(m/z): 414$[M+H]^+$,

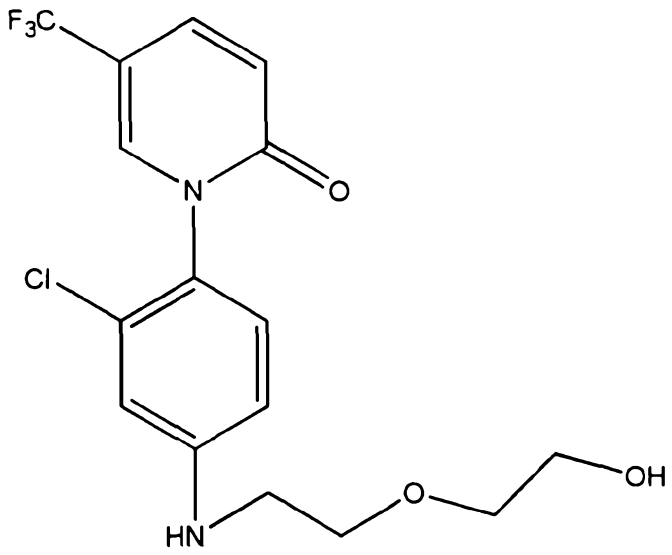
^{1}H-NMR(D_2O)δppm:

1.343~1.718(m,6H,-CH2-),1.857~1.905(2H,-H),1.956~2.055(m,2H,-CH2-),2.829~2.905(t,2H,-CH2-),3.122~3.116(t,2H,-CH2-),3.221~3.284(2H-CH2-),3.445~3.487(2H-CH2-),6.764~6.8

12(2H,Ar-H),6.965~6.972(1H,Ar-H),7.199~7.228(1H,Ar-H),7.785~7.907(1H,Ar-H),8.075(1H,Ar-H).

Example 8

Preparation of 1-(2-chloro-4-((2-(2-hydroxyethoxy)ethyl)amino)-phenyl)-5-(trifluoromethyl) pyridin-2(1H)-one



(Compound 8)

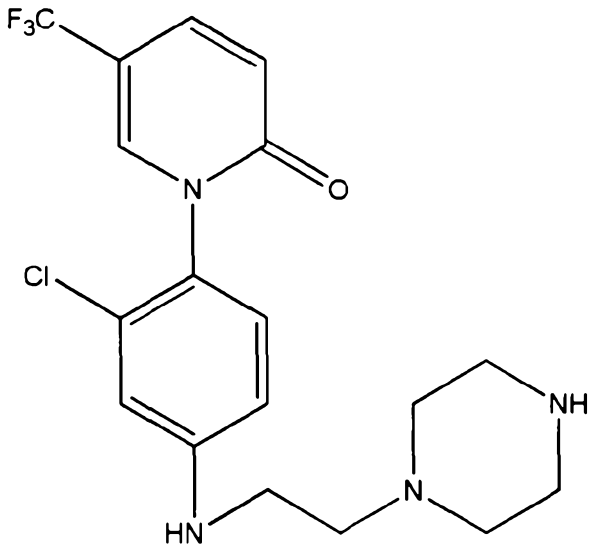
The preparation of 1-(2-chloro-4-((2-(2-hydroxyethoxy)ethyl)amino)-phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: dissolving 1-(4-amino-2-chloro)phenyl-5-(trifluoromethyl)pyridin-2(1H)-one and 28mmol of chloroethoxy ethanol in 50mL of normal butanol; adding 1.9mmol of potassium carbonate; carrying out refluxing reaction for 72 hours; filtering; evaporating filtrate to dryness; and separating by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 to obtain 0.33g of a yellow oily product. EI-MS(m/z): 376$[M]^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm:

3.320~3.355(t,2H,-CH2-),3.607~3,637(t,2H,-CH2-),3.714~6.748((t,2H,-CH2-),3.768~3.798((t,2H,-CH2-),6.609~6.646(dd,1H,J=2.4Hz,8.4Hz,Ar-H),6.710-6.742(d,1H,J=9.6Hz,Ar-H),6.775~6.783(d,1H,J=2.4Hz,Ar-H),7.107~7.136(d,1H,J=8.7Hz,Ar-H),7.501~7.542(dd,1H,J=2.7Hz,

9.6Hz,Ar-H),7.603(s,1H,Ar-H).

Example 9

Preparation of 1-((4-((piperazin-1-yl)ethyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



(Compound 9)

A. Preparation of 1-(2-chloro-4-((2-chloroethyl)amino)-phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one

The preparation of 1-(2-chloro-4-((2-chloroethyl)amino)-phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: mixing 3mmol of 1-(2-chloro-4-((2-hydroxyethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one, 120mL of methylene dichloride, 4.5mmol of thionyl chloride and 4.5mmol of triethylamine for reaction for 28 hours at room temperature; and separating by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 3:1 to obtain 0.5g of straw yellow solid. M.P.: 160.0~162.0°C, EI-MS(m/z): 350[M]$^+$, ^{1}H-NMR($CDCl_3$,300MHz) δppm: 3.502~3.541(t,2H,-CH2-),3.713~3.752(t,2H,-CH2-),6.909~6.647(dd,1H,J=2.7Hz,8.7Hz,Ar-H),6.716~6.777(2H,Ar-H),7.135~7.164(d,1H,J=8.7Hz,Ar-H),7.508~7.550(dd,1H,J=2.7Hz,9.6Hz,Ar-H),7.600(s,1H,Ar-H).

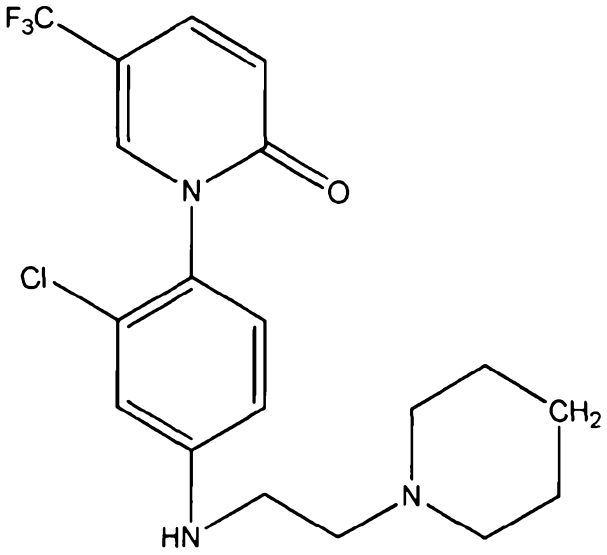
B. Preparation of

1-(2-chloro-4-((2-piperazin-1-yl)ethyl)amino)-phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one dissolving 1.3mmol of 1-(2-chloro-4-((2-chloroethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one and 7.8mmol of anhydrous piperazine in 50mL of acetonitrile; adding an amount of sodium iodide; carrying out refluxing reaction for 12 hours; filtering; evaporating filtrate to dryness; and separating by column chromatography with eluent of ethyl acetate and methanol with proportion of 5:1 (2% triethylamine) to obtain 0.32g of yellow colloid substance.

EI-MS(m/z): 400[M]$^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm: 2.442(s,4H,-CH2-),2.628(s,2H,-CH2-),2.904(s,4H,-CH2-),3.144~3.158(d,2H,-CH2-),4.776(s,1H,-NH-),6.572~6.60(d,1H,J=8.4Hz,Ar-H),6.707~6.736(d,1H,J=8.7Hz,Ar-H),7.094~7.122(d,1H,J=8.4Hz,Ar-H),7.500~7.530(d,1H,J=9.0Hz,Ar-H),7.609(s,1H,Ar-H).

Example 10

Preparation of 1-(2-chloro-4-((2-(piperidyl-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



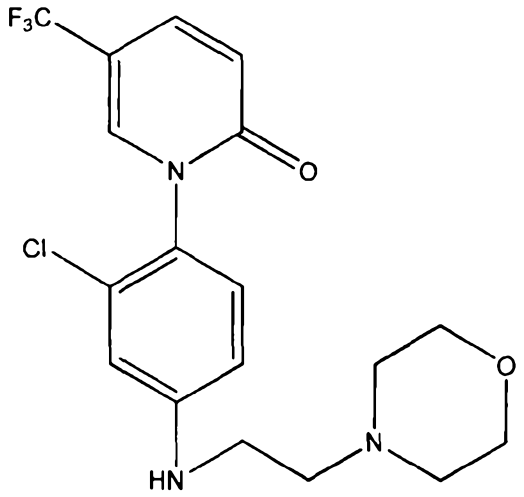
(Compound 10)

The preparation of 1-(2-chloro-4-((2-(piperidyl-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: dissolving 1.7mmol of

1-(2-chloro-4-((2-chloroethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one and 10.3mmol of piperazine in 50mL of acetonitrile; adding an amount of sodium iodide; carrying out refluxing reaction for 17 hours; filtering; evaporating filtrate to dryness; and separating by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 to obtain 0.34g of yellow colloid substance. EI-MS(m/z) : 399$[M]^+$, ^{1}H-NMR(CDCl3,300MHz)δppm : 1.470~1.487(d,2H,J=5.1,-CH2-),1.576~1.647(m,4H,-CH2-),2.436(s,4H,-CH2-),2.604~2.644(t,2H,-CH2-),3.152~3.165(d,2H,-CH2-),4.941(s,1H,-NH-),6.568~6.605(dd,1H,J=2.4Hz,8.7Hz, Ar-H),6.708~6.734(t,1H,Ar-H),7.088~7.117(d,1H, J=8.7Hz,Ar-H),7.493~7.502(d,1H,J=2.7Hz,Ar-H),7.525~7.534(d,-H,J=2.7Hz,Ar-H).

Example 11

Preparation of 1-(2-chloro-4-((2-morpholinylethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



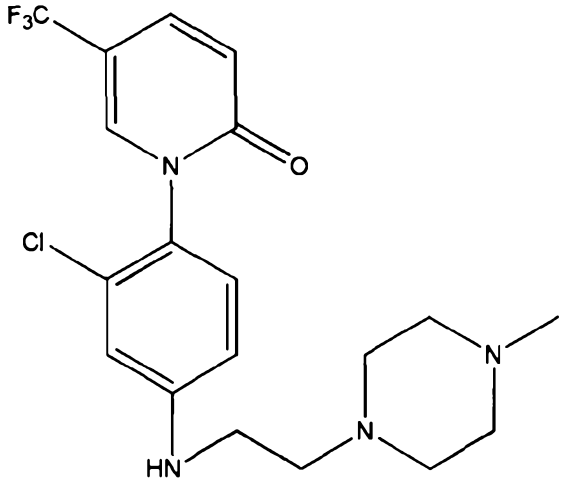
(Compound 11)

The preparation of 1-(2-chloro-4-((2-morpholinylethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: dissolving 1.7mmol of 1-(2-chloro-4-((2-chloroethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one and 10.9mmol of morpholine in 50mL of acetonitrile; adding an amount of sodium iodide; carrying out refluxing reaction for 24 hours; filtering; evaporating filtrate to dryness; and separating by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1

to obtain 0.67g of yellow colloid substance. EI-MS(m/z): 401[M]$^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm: 2.500(s,4H,-CH2-),2.650~2.688(t,2H,-CH2-),3.150~3.204(m,2H,-CH2-),3.728~3.758(t,4H,-CH2-),4.781(s,1H),6.573~6.610(dd,1H,J=2.4Hz,6.0Hz,Ar-H),6.703~6.743(t,2H,Ar-H),7.098~7.127(d,1H,J=8.7Hz,Ar-H),7.494~7.535(dd,1H,J=2.7Hz,9.6Hz,Ar-H),7.603(s,1H,Ar-H).

Example 12

Preparation of 1-(2-chloro-4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one



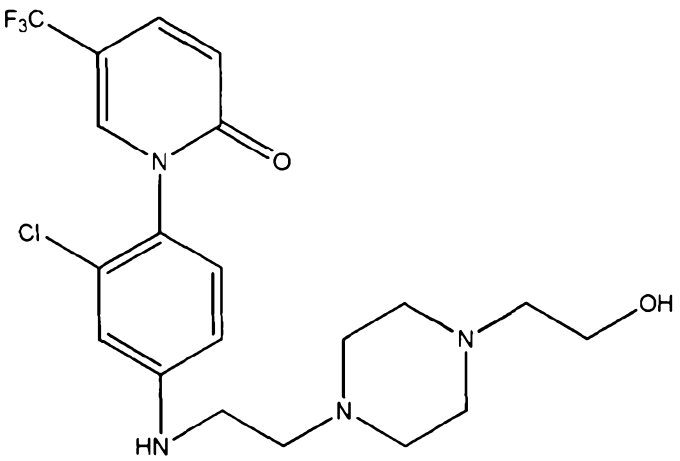
(Compound 12)

The preparation of 1-(2-chloro-4-((2-(4-methylpiperazin-1-yl)ethyl)amino)-phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one includes steps of: dissolving 1.7mmol of 1-(2-chloro-4-((2-chloroethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one and 10.9mmol of N-methyl piperazine in 50mL of acetonitrile; adding an amount of sodium iodide; carrying out refluxing reaction for 22 hours; filtering; evaporating filtrate to dryness; and separating by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 to obtain 0.70g of yellow solid. m.p.: 113.1~115.2,EI-MS(m/z): 414[M]$^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm: 2.321(s,3H,-CH3),2.511(br,8H,-CH2-),2.639~2.678(t,2H,-CH2-),3.126~3.181(q,2H,-CH2-),4.736~4.765(t,1H,-NH-),6.566~6.603(dd,1H,J=2.4Hz,8.7Hz,Ar-H),6.708~6.740(t,2H,Ar-H),7.096~7.125(d,1H, J=9.6Hz,Ar-H),7.496~7.537(dd,1H,J=2.7Hz,9.6Hz,Ar-H),7.609(s,1H,Ar-H).

Example 13

Preparation of

1-(2-chloro-4-((2-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl) pyridin-2(1H)-one



(Compound 13)

The preparation of

1-(2-chloro-4-((2-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl) pyridin-2(1H)-one includes steps of: dissolving 1.7mmol of 1-(2-chloro-4-((2-chloroethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one and 10.9mmol of hydroxyethyl piperazine in 50mL of acetonitrile; adding an amount of sodium iodide; carrying out refluxing reaction for 24 hours; filtering; evaporating filtrate to dryness; and separating by column chromatography with eluent of petroleum ether and ethyl acetate with proportion of 1:1 to obtain 0.51g of yellow colloid substance. EI-MS(m/z): 444$[M]^+$, ^{1}H-NMR($CDCl_3$,300MHz)δppm: 2.567~2.691(m,12H, -CH2-),3.139~3,192(t,2H,-CH2-),3.632~3.667(t,2H,-CH2-),4.737(br,1H,-NH-),6.563~6.600(dd,1H,J=2.4Hz,8.7Hz,Ar-H),6.702~6.738(t,2H,Ar-H),7.094~7.123(d,1H,J=8.7Hz,Ar-H),7.49 2~7.533(dd,1H, J=2.7Hz,9.0Hz,Ar-H),7.603(s,1H,Ar-H).

Example 14

Inhibition test of compounds on NIH3T3 fibroblasts

An MTT method is used and comprises steps of: culturing cells in DMEM culture medium including 5% calf serum and preparing the cells into cell suspension of $3x10^4$/ml; inoculating in 96-well plate according to 100μl/well; transferring new culture medium including compounds with different concentration, fluorofenidone and 1% calf serum after cells are adhered, wherein three repeated wells are provided for each concentration; respectively adding 100 μl of MTT solution in each well after 48 hours and 72 hours of administrating (the culture medium is prepared into 5mg/ml and kept in dark after filtering), sucking out MTT after 4 hours; adding 150μl of DMSO which is the dissolving liquid of MTT; after 10min and MTT is completely dissolved, measuring OD value by ELISA reader; calculating IC50 values of fluorofenidone and measured compounds according to inhibition ratio; calculating multiple of activities of measured compounds and fluorofenidone according to IC50 values of fluorofenidone and measured compounds; and obtaining relative IC50 value of measured compounds according to multiple and IC50 value of fluorofenidone on a certain plate.

Inhibition activity of measured compounds to NIH3T3 fibroblasts

Measured compounds	48 hours		72 hours	
	Relative IC50 (mM)	Multiple	Relative IC50 (mM)	Multiple
Fluorofenidone	4.43		3.52	
Compound 1	0.286	**15.50**	0.163	**21.60**
Compound 2	0.241	**18.36**	0.161	**21.87**
Compound 3	0.238	**18.60**	0.065	**54.0**
Compound 4	0.702	**6.31**	0.311	**11.31**
Compound 5	1.380	**3.21**	0.632	**5.57**
Compound 6	0.641	**6.91**	0.587	**6.00**
Compound 7	0.259	**17.09**	0.049	**71.17**
Compound 8	0.487	**9.09**	0.332	**10.59**
Compound 10	0.214	**20.73**	0.062	**56.50**
Compound 11	0.174	**25.50**	0.056	**62.50**
Compound 12	0.330	**13.42**	0.106	**33.33**
Compound 13	0.100	**44.14**	0.062	**57.20**

Notes: multiple is IC50 value of compounds to IC50 value of fluorofenidone

5

Example 15

Observation of treatment effect of compound 13 in a rat unilateral ureteral obstruction renal fibrosis model

Materials and methods

1. Experimental chemicals

The compound 13 is prepared according to the method provided by the invention.

2. Experimental animals

Nine male SD rats of 188-213g, coming from Hunan Slac Laboratory Animals Co., Ltd., are illuminated for 12 hours every day; feed is provided by Shanghai Slac Laboratory Animals Co., Ltd.; and drinking water is provided by Department of Laboratory Animal Science of Central South University.

3. Experimental methods

(1) **Randomization**: nine rats are divided into three groups at random, namely a normal group (n=3); a model group (n=3) and a treatment group (n=3) treated by compound 13 of 15mg/kg; three rats are in a hutch; and the experimental animals are adaptively fed for two days.

(2) Unilateral ureteral obstruction modeling:

The unilateral ureteral obstruction modeling comprises steps of: lumbar-injecting each rat with 10% chloral hydrate according to 0.35ml/100g for anesthesia, fixing on a rat fixing plate; wetting the back skin by water, tightening the skin; unhairing by elbowed surgical scissors in a way closely attaching the skin; sterilizing drape in a conventional way; making an incision of 1.0cm in longitudinal direction at a junction of a position 1.0cm below left costal margin and 0.8cm next to median line of vertebral column; separating successive layers to expose left kidney and left ureter; tying off left ureter against lower pole of left kidney by a thread of 4.0 and another portion 1.0cm therebelow; isolating ureter between those two points; flushing abdominal cavity by gentamicin physiological saline solution; and stitching successive layers of retroperitoneal space and back skins after no leakage and hemorrhage.

(3) Pharmacological intervention: intragastric administration is carried out the day before modeling operation according to one time per day for 12 days; the method is detailed as follows:

a) preparing 0.5% CMCNa solution by adding an amount of 0.9% physiological saline into CMCNa powder and preparing following samples with 0.5% CMCNa solution as solvent.

b) lavaging the normal group with 6ml/kg.d 0.5% CMCNa for one time per day.

c) lavaging the model group with 6ml/kg.d 0.5% CMCNa for one time per day.

d) lavaging the treatment group treated by compound 13 at 15mg/kg with 6ml/kg.d 0.5%

CMCNa for one time per day.

(4) Animal sacrifice and sample collection

On the 11th day after operation, each group of rats is respectively sacrificed by lumbar injection of 10% chloral hydrate (0.7-0.9ml/100g) to excessive anesthesia, renal tissues on the obstruction side are fixed by 4% formaldehyde, embedded in paraffin and prepared into 4 μm-thick slices for HE staining and Masson staining.

(5) HE staining evaluation standard:

HE stained slices of renal tissues are successively observed in fives fields of view of renal tubulointerstitium on upper left side, upper right side, lower left side, lower right side and middle portion by a low power lens and are evaluated according to eight indexes of renal interstitium lesion: renal tubular epithelial cell vacuolar degeneration, renal tubular ectasia, renal tubular atrophy, red cell cast, protein cast, interstitial edema, interstitial fibrosis and interstitial inflammatory cell infiltration; an average value is calculated as the index of renal tubulointerstitial lesion of the sample; and the evaluation standard is based on the reference of Radford MG Jr, Donadio JV Jr, Bergstralh EJ, et al. Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol, 1997, 8(2):199-207.

(6) Masson staining evaluation standard

Masson staining slices of renal tissues are observed in 20 fields of vision for each sample at random under 400X light microscope; percent of blue-stain collagens in the fields of vision is calculated; an average value is determined after semi-quantitative evaluation: no positive staining, 0; <25%, 1; 25-50%, 2; 50-75%, 3; >75 %, 4; and the evaluation standard is based on references. Lin SL, Chen RH, Chen YM, et al. Pentoxifylline Attenuates Tubulointerstitial Fibrosis by Blocking Smad3/4-Activated Transcription and Profibrogenic Effects of Connective Tissue Growth Factor. J Am Soc Nephrol.2005, 16: 2702–2713。

4. Statistical methods: analytical method of variance of single factor is adopted.

Experimental Results

1. Pathological evaluation results of renal interstitium lesions through HE staining

Table 1 comparison of indexes of renal tubulointerstitial lesions of obstruction kidneys of rats in groups

Group	Number	Score($\overline{X}$±S)
Normal group	3	0.33±0.12
Model group	3	9.00±1.00***
Compound 13 group	3	7.00±0.35****

Notes:

comparison to normal group, $^{\star}p<0.05$, $^{\star\star}p<0.01$; $^{\star\star\star}p<0.001$;

comparison to model group, *p<0.05, ** p<0.01, *** p<0.001;

2. Pathological evaluation results of renal interstitium lesions through MASSON staining

Table 2 evaluation results of renal interstitium collagens of left kidneys of rats in groups through MASSON staining

Group	Number	Score($\overline{X}$±S)
Normal group	3	0.25±0.00
Model group	3	2.45±0.38***
Compound 13 group	3	1.52±0.16****

Notes:

comparison to normal group, $^{\star}p<0.05$, $^{\star\star}p<0.01$; $^{\star\star\star}p<0.001$;

comparison to model group, *p<0.05, ** p<0.01, *** p<0.001;

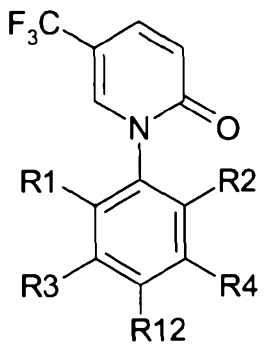
Conclusion:

The compound 13 of 15mg/kg can effectively treat renal fibrosis.

CLAIMS

1. A 1-(substituted phenyl)-5-trifluoromethyl-2(1H)pyridone compound, having a formula (XIII),

Formula XIII

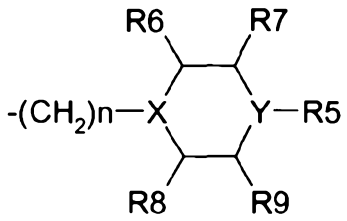


wherein, R1-R4, and R12 are selected from: H, CN, NO_2, a hydroxyl group, an amino group, a halogen atom, a C_1-C_6 alkoxyl group, $NR^{10}R^{11}$, $C(O)R^{14}$,O-$C(O)R^{14}$, a C1-C6 alkyl group, a C_1-C_6 haloalkyl group, a C_2-C_6 alkenyl group, a carboxyl group and a carboxylic ether;

wherein R^{14} is a C_1-C_6 alkyl group, R^{10} and R^{11} are selected from H, a C_1-C_6 alkyl group, a C_1-C_6 hydroxyalkyl group, an esterified C_1-C_6 hydroxyalkyl group, a C_1-C_6 alkoxyalkyl group, or formula XIV;

and at least one of R1-R4, and R12 is $NR^{10}R^{11}$; and at least one of R^{10} and R^{11} is of the formula XIV.

Formula XIV



and in formula XIV, R5 is selected from H, a C_1-C_6 alkyl group, a C_1-C_6 hydroxyalkyl group, an esterified C_1-C_6 hydroxyalkyl group and a C_2-C_6 alkenyl group; R6-R9 are selected from H, a C_1-C_6 alkoxyl group, =O, a C_1-C_4 alkyl group, a C_1-C_4 haloalkyl group, a C_1-C_4 hydroxyalkyl group, and a C_2-C_4 alkenyl group; X is selected from N, or CH; Y is selected from N, O or C; with the proviso that, when Y is O, R^5 is absent; n is 1-6;

or pharmaceutically acceptable salts thereof.

2. The 1-(substituted phenyl)-5-trifluoromethyl-2(1H)pyridone compound according to claim 1, wherein R12 is $NR^{10}R^{11}$.

3. The 1-(substituted phenyl)-5-trifluoromethyl-2(1H)pyridone compound according to claim 1, wherein one of R1-R4 is a halogen atom and others are H if R12 is $NR^{10}R^{11}$.

4. The 1-(substituted phenyl)-5-trifluoromethyl-2(1H)pyridone compound according to claim 1, selected from the group consisting of:

1-(2-chloro-4-((3-(4-methylpiperazin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 1);

1-(2-chloro-4-((3-morpholinylpropyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 2);

1-(2-chloro-4-((3-piperidin-1-yl)propylamino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 3);

1-(4-((3-butoxypropyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 4);

1-(2-chloro-4-((2-hydroxyethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 5);

1-(4-(N,N-(2-hydroxyethyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 6);

1-(2-chloro-4-(((3-piperidin-1-yl)propyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one hydrochloride (compound 7);

1-(2-chloro-4-((2-(2-hydroxyethoxy)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 8);

1-((4-((piperazin-1-yl)ethyl)amino)-2-chlorophenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 9);

1-(2-chloro-4-((2-(piperidyl-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 10);

1-(2-chloro-4-((2-morpholinylethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(1H)-one (compound 11);

1-(2-chloro-4-((2-(4-methylpiperazin-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl)pyridin-2(

1H)-one (compound 12); and

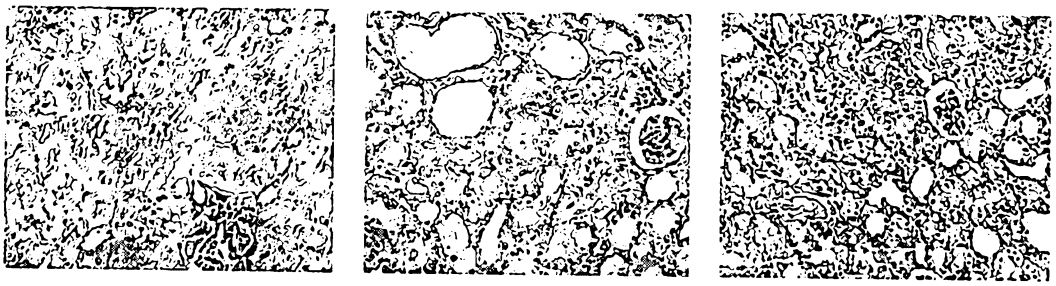
1-(2-chloro-4-((2-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)amino)phenyl)-5-(trifluoromethyl) pyridin-2(1H)-one (compound 13).

5. An anti-fibrosis medicament comprising a compound as defined in any one of claims 1-4 and a pharmaceutically acceptable excipient .

6. A method of treating fibrosis comprising the steps of administering to a patient in need of said treatment a compound according to any one of claims 1-4.

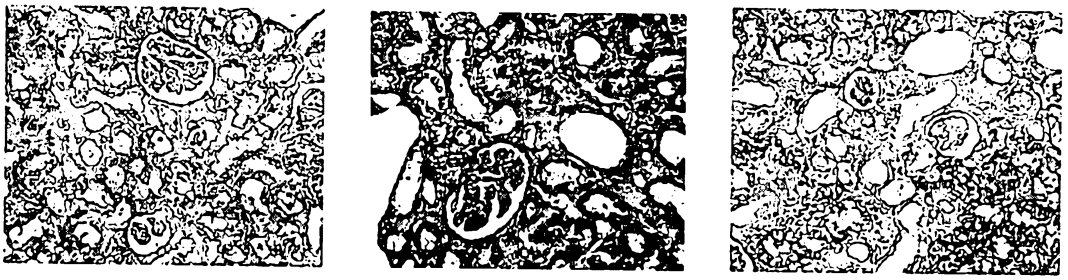
7. The use of a compound according to any one of claims 1 to 4 for the manufacture of a medicament for the treatment of fibrosis.

8. A 1-(substituted phenyl)-5-trifluoromethyl-2(1H)pyridone compound having a structural formula (XIII), an anti-fibrosis medicament, a method of treating fibrosis or the use of a compound substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples but excluding comparative examples.



Normal group　　Model group　　Compound 13 group

Fig 1



Normal group　　Model group　　Compound 13 group

Fig 2