

NOVEL USE OF MULTI-KINASE INHIBITOR

TECHNICAL FIELD

[0001] The present invention belongs to the technical field of medicines, and particularly relates to a multi-kinase inhibitor compound or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof for use in the treatment of biliary tract cancer, a pharmaceutical composition comprising the multi-kinase inhibitor compound or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof, a method for treating biliary tract cancer by using the multi-kinase inhibitor compound or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof, use of the multi-kinase inhibitor compound or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof in the treatment of biliary tract cancer, and use of the multi-kinase inhibitor compound or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof in the preparation of a medicament for treating biliary tract cancer.

BACKGROUND

[0002] Biliary tract cancer (BTC) is a malignant tumor derived from biliary epithelial cells, and is relatively rare clinically and has a low incidence rate, but in recent years, it tends to increase gradually. As its early clinical symptoms lack specificity, most diagnosed patients are at the advanced stage. It can be classified into cholangiocarcinoma (CCA) and gallbladder carcinoma (GBC) according to anatomical location.

[0003] Cholangiocarcinoma is a highly heterogeneous malignant tumor that develops in the biliary tract, accounting for approximately 3% of all digestive system tumors. Cholangiocarcinoma can be classified into three types according to the anatomical site of a lesion, including intrahepatic cholangiocarcinoma (iCC), perihilar cholangiocarcinoma (pCC), and distal cholangiocarcinoma (dCC). Intrahepatic cholangiocarcinoma is located in the liver parenchyma and accounts for approximately 10%–20% of cholangiocarcinoma, and perihilar cholangiocarcinoma and distal cholangiocarcinoma are both extrahepatic cholangiocarcinoma and accounts for approximately 80% of cholangiocarcinoma (Rizvi, S., & Gores, G.J. (2013), Pathogenesis, Diagnosis, and Management of Cholangiocarcinoma. Gastroenterology, 145(6), 1215–1229). The prognosis of cholangiocarcinoma is poor, wherein patients have no obvious clinical symptoms in the early stage, and metastasis usually

occurs when diagnosis is confirmed. Because of the significant resistance of cholangiocarcinoma to chemotherapy, chemotherapy is often used in palliative treatments, the generally effective treatment being surgical resection and/or liver transplantation. Surgery is the primary treatment for resectable cholangiocarcinoma, and the post-operative survival rate depends mainly on tumor margin negativity, no vascular infiltration and lymphatic metastasis, and sufficient residual liver to be functional. Since most diagnosed patients are at the advanced stage, recurrence is common, with a recurrence rate of approximately 49%–64% within 2–3 years after surgical resection. The survival rate of patients after surgical resection for five years is also poor, with the survival rate of intrahepatic cholangiocarcinoma being 22%–44%, the survival rate of perihilar cholangiocarcinoma being 11%–41%, and the survival rate of distal cholangiocarcinoma being 27%–37%. Only less than 1/3 of patients have the opportunity to receive surgical resection due to local tumor infiltration, peritoneal or distant metastasis, lack of biliary reconstruction protocols, and prediction of insufficient residual liver after surgery. For cholangiocarcinoma patients who are unable to undergo surgical resection, another treatment option is liver transplantation. However, liver transplantation has very strict selection criteria and limited availability for patients, and even among patients who can receive liver transplantation, prognosis is still poor, the recurrence rate is high, and the survival rate is only 10%–25%. Currently, the preferred choice for treatment of patients with unresectable or metastatic tumors includes: 1) clinical trials; 2) fluorouracil-based or gemcitabine-based chemotherapy; or 3) optimal supportive treatment.

[0004] The incidence rate and mortality rate of cholangiocarcinoma is on an increasing trend year by year. Current research conditions suggest that the development and treatment of cholangiocarcinoma may be associated with multiple targets.

[0005] Fibroblast growth factor receptor (FGFR) can regulate the survival and proliferation of cells, and a plurality of researches suggest that FGFR aberration is a potential therapeutic target of a plurality of tumors. FGFR2 fusion is one of the important inducing factors of cholangiocarcinoma, and the gene is commonly found in intrahepatic cholangiocarcinoma and accounts for approximately 15% of intrahepatic cholangiocarcinoma. In addition to FGFR fusion aberration, cholangiocarcinoma has also been found to be drug resistant to a range of FGFR aberrations, such as FGFR2 N549H, FGFR2 V564F, FGFR3 K650E, and FGFR3 R248C (Shiao MS, Chiablaem K, Charoensawan V, et al. Emergence of Intrahepatic Cholangiocarcinoma: How

High-Throughput Technologies Expedite the Solutions for a Rare Cancer Type. *Frontiers in Genetics*. 2018;9:309).

[0006] The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway may be involved in cancer cell proliferation and regulation of the tumor microenvironment via IL6 (Labib PL, Goodchild G, Pereira SP. *Molecular Pathogenesis of Cholangiocarcinoma*. *BMC Cancer*. 2019;19(1):185). Constitutive phosphorylation of STAT3 has been reported in a panel of 7 different genetic profiles of human cholangiocarcinoma cell lines, demonstrating that the negative feedback loop of the IL-6/JAK/STAT3 pathway is epigenetically silenced in cholangiocarcinoma cells, resulting in sustained signaling (Isomoto H, Mott JL, Kobayashi S, et al. *Sustained IL-6/STAT-3 signaling in cholangiocarcinoma cells due to SOCS-3 epigenetic silencing*. *Gastroenterology*. 2007;132(1):384–396).

[0007] The expression of Aurora A kinase (Aurora A) is also likely to be up-regulated in cholangiocarcinoma and is associated with poor progression-free survival and overall survival (Ding X, Huang T, Ahn KS, et al. *Su1459 – Aurora Kinase A Sustains Cholangiocarcinoma Proliferation and Represents a New Therapeutic Target*. *Gastroenterology*. 2018;154(6):S-1153). WO2018108079A1 discloses a class of multi-kinase inhibitor compounds capable of inhibiting, modulating and/or regulating the activity of one or more protein kinases such as Aurora kinase and VEGFR kinase, thereby having an anti-tumor effect.

[0008] In summary, the optimal adjuvant therapy strategy after cholangiocarcinoma surgery is uncertain, and the clinical outcome in support of standard adjuvant therapy protocols is very limited. Currently, targeted inhibitors for cholangiocarcinoma are researched clinically, but there are still many cholangiocarcinoma patients who do not carry FGFR aberrations and also urgently need effective targeted therapy, so that huge unmet needs exist clinically for cholangiocarcinoma with FGFR aberration, non-FGFR aberration and wild type FGFR, and the research and development of effective targeted formulations for cholangiocarcinoma are urgently needed clinically.

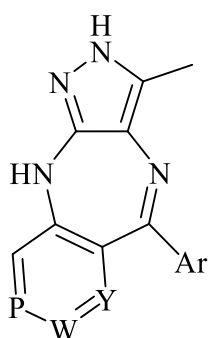
SUMMARY

[0009] 1. Brief Description of the Invention

[0010] The present invention researches novel use of a multi-kinase inhibitor compound of the following general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof in the field of cancers. Researches find that the multi-kinase inhibitor compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof has a treatment effect on biliary tract cancer, and particularly has a remarkable treatment effect on cholangiocarcinoma.

[0011] Therefore, the present invention aims to provide novel use of a multi-kinase inhibitor compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof in the treatment of biliary tract cancer.

[0012] Therefore, in a first aspect of the present invention, provided is use of a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof in the preparation of a medicament for treating biliary tract cancer:



(I)

[0013] wherein Ar is phenyl optionally substituted with 1–3 R_6 , each R_6 is independently selected from hydrogen, amino, cyano, halogen, C_{1-4} alkyl and trifluoromethyl;

[0014] Y is CR_3 ;

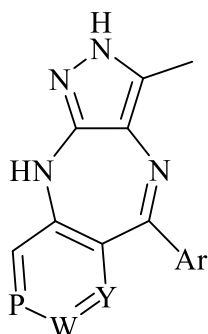
[0015] P is CR_4 ;

[0016] W is N;

[0017] R_3 is selected from hydrogen and C_{1-4} alkyl;

[0018] R_4 is $-(CH_2)_n$ -(5-11) membered heterocyclyl, wherein $n = 0-6$, a ring-forming S atom in the heterocyclyl is optionally oxidized to $S(O)$ or $S(O)_2$, a ring-forming C atom in the heterocyclyl is optionally oxidized to $C(O)$, and the heterocyclyl is optionally substituted with one to more substituents independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl.

[0019] In a second aspect of the present invention, provided is use of a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof in the treatment of biliary tract cancer:

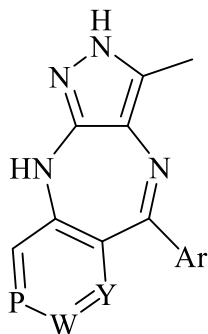


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(I)

[0020] wherein the variables in the above general formula (I) are as defined above.

[0021] In a third aspect of the present invention, provided is a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof for use in the treatment of biliary tract cancer:



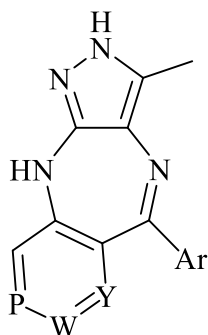
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(I)

[0022] wherein the variables in the above general formula (I) are as defined above.

[0023] In a fourth aspect of the present invention, provided is a method for treating biliary tract cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof:

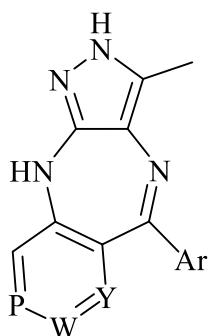
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(I)

[0024] wherein the variables in the above general formula (I) are as defined above.

[0025] In a fifth aspect of the present invention, provided is a pharmaceutical
 5 composition for use in the treatment of biliary tract cancer, comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof, and optionally comprising a pharmaceutically acceptable carrier:

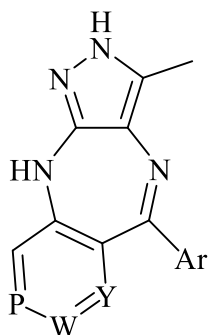


(I)

[0026] wherein the variables in the above general formula (I) are as defined above.

[0027] 2. Detailed Description of the Invention

[0028] As described above, in the first aspect of the present invention, provided is use
 of a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer
 15 and a crystal form thereof in the preparation of a medicament for treating biliary tract cancer:



(I)

[0029] wherein the variables in the above general formula (I) are as defined above.

[0030] In one embodiment, Ar is phenyl optionally substituted with 1–3 R_6 , and each
5 R_6 is independently selected from hydrogen and halogen;

[0031] Y is CR_3 ;

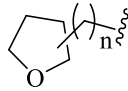
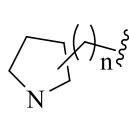
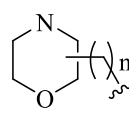
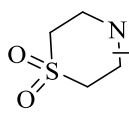
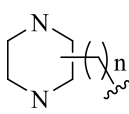
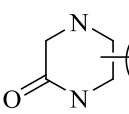
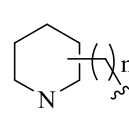
[0032] P is CR_4 ;

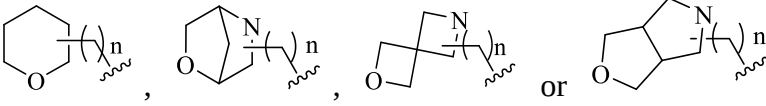
[0033] W is N;

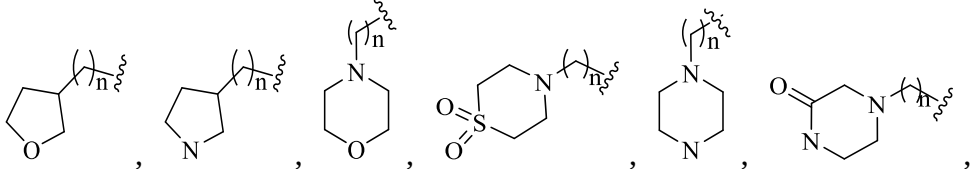
[0034] R_3 is hydrogen;

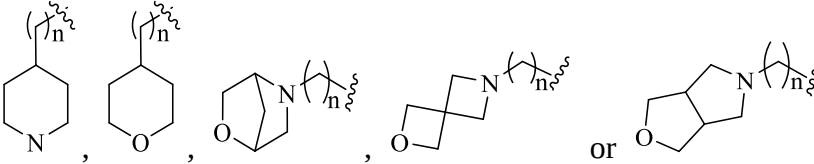
10 **[0035]** R_4 is selected from $-(CH_2)_n$ -(5-6) membered monocyclic heterocyclyl and $-(CH_2)_n$ -(7-11) membered fused heterocyclyl, wherein $n = 0-6$, a ring-forming S atom in the heterocyclyl is optionally oxidized to S(O) or S(O)₂, a ring-forming C atom is optionally oxidized to C(O), and the heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

15 **[0036]** In a further embodiment, the (5-6) membered monocyclic heterocyclyl is (5-6) membered saturated monocyclic heterocyclyl, and the (7-11) membered fused heterocyclyl is (7-11) membered saturated fused heterocyclyl. In a preferred embodiment, the (7-11) membered fused heterocyclyl is (7-11) membered saturated ortho-fused heterocyclyl, (7-11) membered saturated spiro-heterocyclyl or (7-11) membered saturated bridged heterocyclyl.

20 **[0037]** In one embodiment, the (5-11) membered heterocyclyl is , , , , , , ,


, and $n = 0-3$, wherein the heterocyclyl is optionally substituted with one to more substituents independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl. In a preferred embodiment, the (5-11) membered

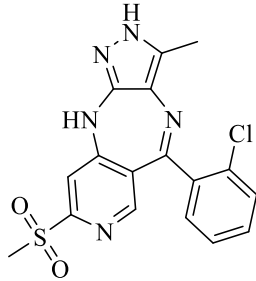
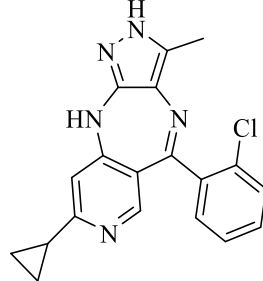
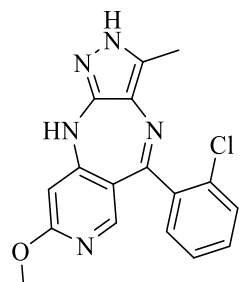
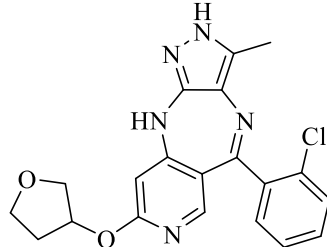
heterocyclyl is
 
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, and $n = 0-3$, wherein the heterocyclyl is optionally substituted with one to more substituents independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl.

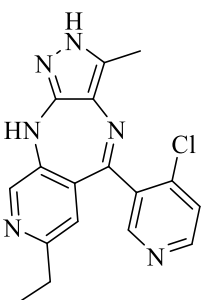
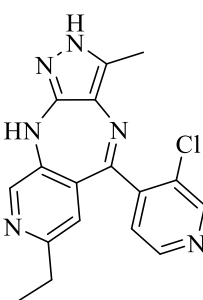
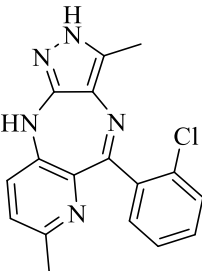
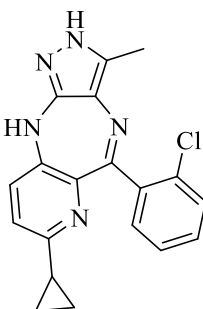
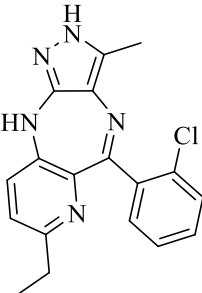
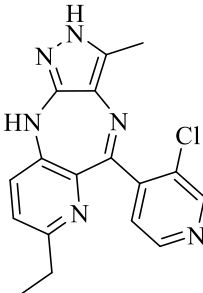
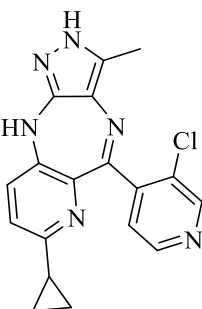
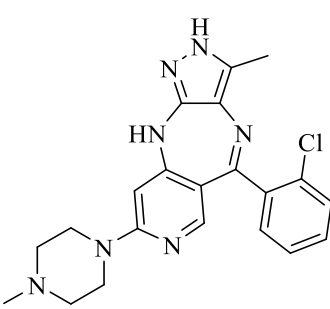
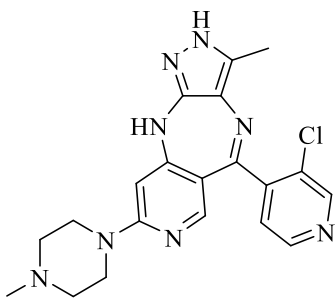
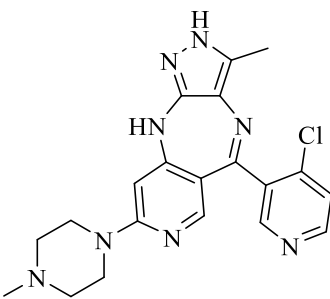
[0038] In one embodiment, the compound of general formula (I) is a compound shown in Table 1 or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

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Table 1. Compounds of the present invention

No.	Structure	No.	Structure
1		2	
3		4	

No.	Structure	No.	Structure
5		6	
7		8	
9		10	
11		12	
13		14	

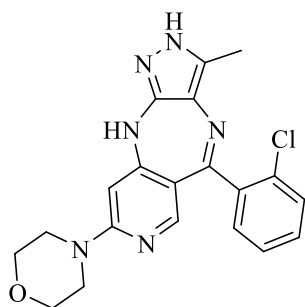
No.	Structure	No.	Structure
15		16	
17		18	
19		20	
21		22	
23		24	

No.	Structure	No.	Structure
25		26	
27		28	
29		30	
31		32	
33		34	

No.	Structure	No.	Structure
35		36	
37		38	
39		40	
41		42	
43		44	

No.	Structure	No.	Structure
45		46	
47		48	
49		50	
51			

[0039] In a preferred embodiment, the compound of general formula (I) is



or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

[0040] In one embodiment, the biliary tract cancer refers to cholangiocarcinoma.

5 **[0041]** In a further embodiment, the cholangiocarcinoma refers to an FGFR-mediated cholangiocarcinoma. In a preferred embodiment, the FGFR-mediated cholangiocarcinoma refers to cholangiocarcinoma mediated by any one of FGFR1, FGFR2 and FGFR3 or any combination thereof.

10 **[0042]** In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with non-FGFR aberration. In a preferred embodiment, the cholangiocarcinoma with non-FGFR aberration refers to cholangiocarcinoma with non-FGFR2 aberration.

15 **[0043]** In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with FGFR aberration. In a preferred embodiment, the cholangiocarcinoma with FGFR aberration refers to a cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

20 **[0044]** In still further embodiments, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR fusion, FGFR mutation and FGFR overexpression or any combination thereof. Wherein the FGFR mutation comprises an FGFR point mutation and an FGFR insertion/deletion mutation.

25 **[0045]** In a preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR2 fusion, FGFR2 and/or FGFR3 mutation and FGFR overexpression or any combination thereof. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 fusion. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 and/or FGFR3 mutation. In another preferred embodiment, the cholangiocarcinoma refers to

cholangiocarcinoma with any one of FGFR2 N549H, FGFR2 V564F and FGFR3 K650E or any combination thereof.

[0046] In another further embodiment, the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma that is positive for FGFR aberration but not responsive to an FGFR inhibitor, or drug-resistant cholangiocarcinoma after administration of an FGFR inhibitor. In a preferred embodiment, the cholangiocarcinoma refers to a drug-resistant cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0047] In another further embodiment, the cholangiocarcinoma refers to any one of intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and distal cholangiocarcinoma or any combination thereof. In a preferred embodiment, the cholangiocarcinoma refers to perihilar cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to distal cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to intrahepatic cholangiocarcinoma. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 aberration. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 fusion. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with non-FGFR aberration.

[0048] In one embodiment, the cholangiocarcinoma further comprises cholangiocarcinoma mediated by other mechanisms, including Aurora-kinase-mediated cholangiocarcinoma and cholangiocarcinoma caused by abnormal IL-6-mediated JAK-STAT signaling pathway.

[0049] In one embodiment, the medicament for treating biliary tract cancer may further comprise a pharmaceutically acceptable carrier in addition to the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof.

[0050] In one embodiment, the medicament may comprise one or more pharmaceutically acceptable carriers, and may be administered to a patient or subject in need of such treatment by oral, parenteral, rectal, or transpulmonary administration, and the like. For oral administration, the pharmaceutical composition can be prepared into a conventional solid formulation, such as tablets, capsules, pills and granules; or can be prepared into an oral liquid formulation, such as oral solutions, oral suspensions and syrups. In the preparation of

an oral formulation, an appropriate filler, binder, disintegrant, lubricant and the like may be added. For parenteral administration, the pharmaceutical composition can be prepared into an injection, including a solution injection, a sterile powder for injection and a concentrated solution for injection. The injection can be produced by a conventional method existing in the pharmaceutical field, and during the preparation process, no additive may be added, or an appropriate additive may be added according to the property of the medicament. For rectal administration, the pharmaceutical composition can be prepared into a suppository and the like. For transpulmonary administration, the pharmaceutical composition can be prepared into an inhalant, a spray or the like.

[0051] In one embodiment, the medicament for treating biliary tract cancer further comprises one or more second therapeutically active agents in addition to the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof.

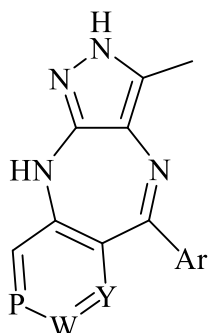
[0052] In a further embodiment, the second therapeutically active agent is an antimetabolite, a growth factor inhibitor, a mitotic inhibitor, an anti-tumor hormone, an alkylating agent, metallic platinum, a topoisomerase inhibitor, a hormonal drug, an immunomodulator, a tumor suppressor gene, a cancer vaccine, or an immune checkpoint inhibitor.

[0053] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment in combination.

[0054] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment sequentially, simultaneously or in a combined formulation.

[0055] In a further embodiment, the patient or subject is a mammal. In a preferred embodiment, the patient or subject is a human.

[0056] In a second aspect of the present invention, provided is a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof for use in the treatment of biliary tract cancer,



(I)

[0057] wherein the variables in the above general formula (I) are as defined above.

[0058] In one embodiment, Ar is phenyl optionally substituted with 1–3 R_6 , and each
5 R_6 is independently selected from hydrogen and halogen;

[0059] Y is CR_3 ;

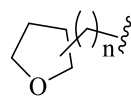
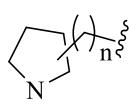
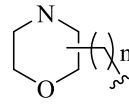
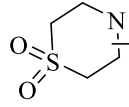
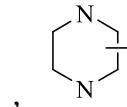
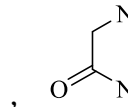
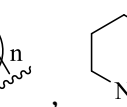
[0060] P is CR_4 ;

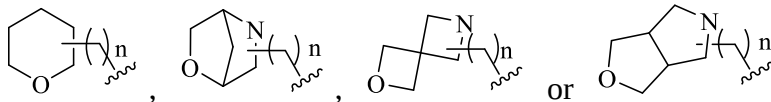
[0061] W is N;

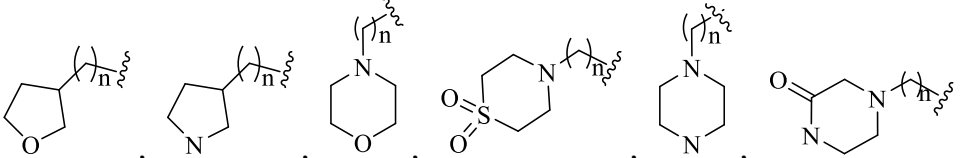
[0062] R_3 is hydrogen;

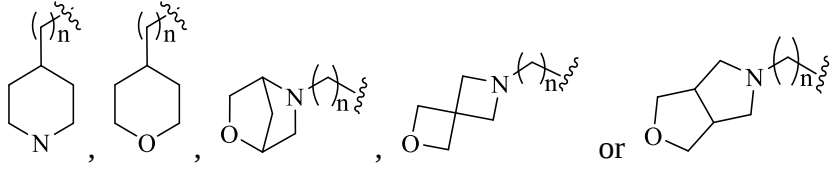
10 [0063] R_4 is selected from $-(CH_2)_n$ -(5-6) membered monocyclic heterocyclyl and $-(CH_2)_n$ -(7-11) membered fused heterocyclyl, wherein $n = 0-6$, a ring-forming S atom in the heterocyclyl is optionally oxidized to S(O) or S(O)₂, a ring-forming C atom is optionally oxidized to C(O), and the heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

15 [0064] In a further embodiment, the (5-6) membered monocyclic heterocyclyl is (5-6) membered saturated monocyclic heterocyclyl, and the (7-11) membered fused heterocyclyl is (7-11) membered saturated fused heterocyclyl. In a preferred embodiment, the (7-11) membered fused heterocyclyl is (7-11) membered saturated ortho-fused heterocyclyl, (7-11) membered saturated spiro-heterocyclyl or (7-11) membered saturated bridged heterocyclyl.

20 [0065] In one embodiment, the (5-11) membered heterocyclyl is , , , , , , 

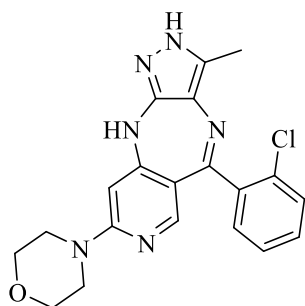

, and $n = 0-3$, wherein the heterocyclyl is optionally substituted with one to more substituents independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl. In a preferred embodiment, the (5-11) membered

heterocyclyl is
 
,

5
 
, and $n = 0-3$, wherein the heterocyclyl is optionally substituted with one to more substituents independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl.

[0066] In one embodiment, the compound of general formula (I) is a compound shown in Table 1 or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

10 **[0067]** In a preferred embodiment, the compound of general formula (I) is



or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

[0068] In one embodiment, the biliary tract cancer refers to cholangiocarcinoma.

15 **[0069]** In a further embodiment, the cholangiocarcinoma refers to an FGFR-mediated cholangiocarcinoma. In a preferred embodiment, the FGFR-mediated cholangiocarcinoma refers to cholangiocarcinoma mediated by any one of FGFR1, FGFR2 and FGFR3 or any combination thereof.

[0070] In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with non-FGFR aberration. In a preferred embodiment, the

cholangiocarcinoma with non-FGFR aberration refers to cholangiocarcinoma with non-FGFR2 aberration.

[0071] In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with FGFR aberration. In a preferred embodiment, the
5 cholangiocarcinoma with FGFR aberration refers to a cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0072] In still further embodiments, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR fusion, FGFR mutation and FGFR overexpression or any combination thereof. Wherein the FGFR mutation comprises an FGFR
10 point mutation and an FGFR insertion/deletion mutation.

[0073] In a preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR2 fusion, FGFR2 and/or FGFR3 mutation and FGFR overexpression or any combination thereof. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 fusion. In another preferred
15 embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 and/or FGFR3 mutation. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR2 N549H, FGFR2 V564F and FGFR3 K650E or any combination thereof.

[0074] In another further embodiment, the cholangiocarcinoma refers to drug-resistant
20 cholangiocarcinoma that is positive for FGFR aberration but not responsive to an FGFR inhibitor, or drug-resistant cholangiocarcinoma after administration of an FGFR inhibitor. In a preferred embodiment, the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0075] In another further embodiment, the cholangiocarcinoma refers to any one of
25 intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and distal cholangiocarcinoma or any combination thereof. In a preferred embodiment, the cholangiocarcinoma refers to perihilar cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to distal cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to intrahepatic cholangiocarcinoma. In another preferred
30 embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 aberration . In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 fusion. In

another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with non-FGFR aberration.

5 [0076] In one embodiment, the cholangiocarcinoma further comprises cholangiocarcinoma mediated by other mechanisms, including Aurora-kinase-mediated cholangiocarcinoma and cholangiocarcinoma caused by abnormal IL-6-mediated JAK-STAT signaling pathway.

[0077] In one embodiment, the use comprises administering to a patient or subject in need thereof a therapeutically effective amount of a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

10 [0078] In one embodiment, a therapeutically effective amount of the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof may be further prepared with one or more pharmaceutically acceptable carriers into any pharmaceutically acceptable pharmaceutical formulation.

15 [0079] In one embodiment, the pharmaceutical formulation may comprise one or more pharmaceutically acceptable carriers, and may be administered to a patient or subject in need of such treatment by oral, parenteral, rectal, or transpulmonary administration, and the like. For oral administration, the pharmaceutical composition can be prepared into a conventional solid formulation, such as tablets, capsules, pills and granules; or can be prepared into an oral liquid formulation, such as oral solutions, oral suspensions and syrups. In the preparation of
20 an oral formulation, an appropriate filler, binder, disintegrant, lubricant and the like may be added. For parenteral administration, the pharmaceutical composition can be prepared into an injection, including a solution injection, a sterile powder for injection and a concentrated solution for injection. The injection can be produced by a conventional method existing in the pharmaceutical field, and during the preparation process, no additive may be added, or an
25 appropriate additive may be added according to the property of the medicament. For rectal administration, the pharmaceutical composition can be prepared into a suppository and the like. For transpulmonary administration, the pharmaceutical composition can be prepared into an inhalant, a spray or the like.

30 [0080] In one embodiment, the use further comprises administering to a patient or subject in need thereof a therapeutically effective amount of a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof and one or more second therapeutically active agents.

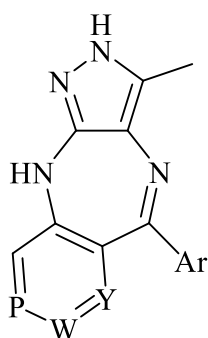
[0081] In a further embodiment, the second therapeutically active agent is an antimetabolite, a growth factor inhibitor, a mitotic inhibitor, an anti-tumor hormone, an alkylating agent, metallic platinum, a topoisomerase inhibitor, a hormonal drug, an immunomodulator, a tumor suppressor gene, a cancer vaccine, or an immune checkpoint inhibitor.

[0082] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment in combination.

[0083] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment sequentially, simultaneously or in a combined formulation.

[0084] In a further embodiment, the patient or subject is a mammal. In a preferred embodiment, the patient or subject is a human.

[0085] In a third aspect of the present invention, provided is a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof for use in the treatment of biliary tract cancer:



(I)

[0086] wherein the variables in the above general formula (I) are as defined above.

[0087] In one embodiment, Ar is phenyl optionally substituted with 1–3 R₆, and each R₆ is independently selected from hydrogen and halogen;

[0088] Y is CR₃;

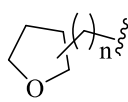
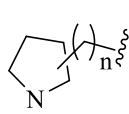
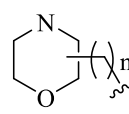
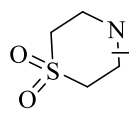
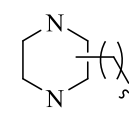
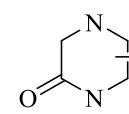
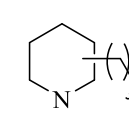
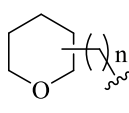
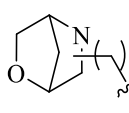
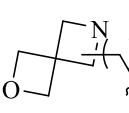
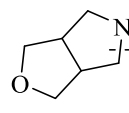
[0089] P is CR₄;

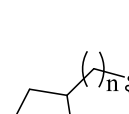
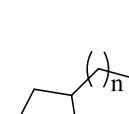
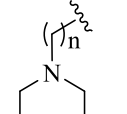
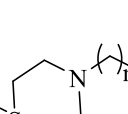
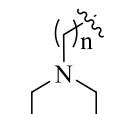
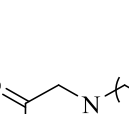
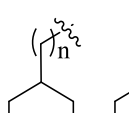
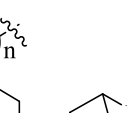
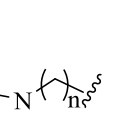
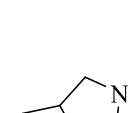
[0090] W is N;

[0091] R₃ is hydrogen;

[0092] R₄ is selected from -(CH₂)_n-(5-6) membered monocyclic heterocyclyl and -(CH₂)_n-(7-11) membered fused heterocyclyl, wherein n = 0–6, a ring-forming S atom in the
5 heterocyclyl is optionally oxidized to S(O) or S(O)₂, a ring-forming C atom is optionally oxidized to C(O), and the heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

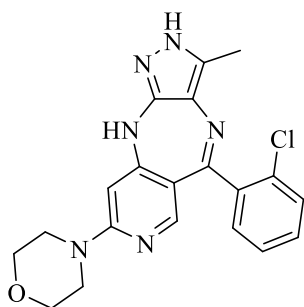
[0093] In a further embodiment, the (5-6) membered monocyclic heterocyclyl is (5-6) membered saturated monocyclic heterocyclyl, and the (7-11) membered fused heterocyclyl is
10 (7-11) membered saturated fused heterocyclyl. In a preferred embodiment, the (7-11) membered fused heterocyclyl is (7-11) membered saturated ortho-fused heterocyclyl, (7-11) membered saturated spiro-heterocyclyl or (7-11) membered saturated bridged heterocyclyl.

[0094] In one embodiment, the (5-11) membered heterocyclyl is ,
, , , , , ,
15 , ,  or , and n = 0–3, wherein the heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl. In a preferred embodiment, the (5-11) membered

heterocyclyl is , , , , , ,
, , ,  or , and n = 0–3, wherein the
20 heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

[0095] In one embodiment, the compound of general formula (I) is a compound shown in Table 1 or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

[0096] In a preferred embodiment, the compound of general formula (I) is



or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

[0097] In one embodiment, the biliary tract cancer refers to cholangiocarcinoma.

5 **[0098]** In a further embodiment, the cholangiocarcinoma refers to an FGFR-mediated cholangiocarcinoma. In a preferred embodiment, the FGFR-mediated cholangiocarcinoma refers to cholangiocarcinoma mediated by any one of FGFR1, FGFR2 and FGFR3 or any combination thereof.

10 **[0099]** In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with non-FGFR aberration. In a preferred embodiment, the cholangiocarcinoma with non-FGFR aberration refers to a cholangiocarcinoma with non-FGFR2 aberration.

15 **[0100]** In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with FGFR aberration. In a preferred embodiment, the cholangiocarcinoma with FGFR aberration refers to a cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

20 **[0101]** In still further embodiments, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR fusion, FGFR mutation and FGFR overexpression or any combination thereof. Wherein the FGFR mutation comprises an FGFR point mutation and an FGFR insertion/deletion mutation.

25 **[0102]** In a preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR2 fusion, FGFR2 and/or FGFR3 mutation and FGFR overexpression or any combination thereof. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 fusion. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 and/or FGFR3 mutation. In another preferred embodiment, the cholangiocarcinoma refers to

cholangiocarcinoma with any one of FGFR2 N549H, FGFR2 V564F and FGFR3 K650E or any combination thereof.

[0103] In another further embodiment, the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma that is positive for FGFR aberration but not responsive to an FGFR inhibitor, or drug-resistant cholangiocarcinoma after administration of an FGFR inhibitor. In a preferred embodiment, the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0104] In another further embodiment, the cholangiocarcinoma refers to any one of intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and distal cholangiocarcinoma or any combination thereof. In a preferred embodiment, the cholangiocarcinoma refers to perihilar cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to distal cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to intrahepatic cholangiocarcinoma. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 aberration. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 fusion. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with non-FGFR aberration.

[0105] In one embodiment, the cholangiocarcinoma further comprises cholangiocarcinoma mediated by other mechanisms, including Aurora-kinase-mediated cholangiocarcinoma and cholangiocarcinoma caused by abnormal IL-6-mediated JAK-STAT signaling pathway.

[0106] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof is administered in a therapeutically effective amount to a patient or subject in need thereof.

[0107] In one embodiment, a therapeutically effective amount of the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof may be further prepared with one or more pharmaceutically acceptable carriers into any pharmaceutically acceptable pharmaceutical formulation.

[0108] In one embodiment, the pharmaceutical formulation may comprise one or more pharmaceutically acceptable carriers, and may be administered to a patient or subject in need

of such treatment by oral, parenteral, rectal, or transpulmonary administration, and the like. For oral administration, the pharmaceutical composition can be prepared into a conventional solid formulation, such as tablets, capsules, pills and granules; or can be prepared into an oral liquid formulation, such as oral solutions, oral suspensions and syrups. In the preparation of an oral formulation, an appropriate filler, binder, disintegrant, lubricant and the like may be added. For parenteral administration, the pharmaceutical composition can be prepared into an injection, including a solution injection, a sterile powder for injection and a concentrated solution for injection. The injection can be produced by a conventional method existing in the pharmaceutical field, and during the preparation process, no additive may be added, or an appropriate additive may be added according to the property of the medicament. For rectal administration, the pharmaceutical composition can be prepared into a suppository and the like. For transpulmonary administration, the pharmaceutical composition can be prepared into an inhalant, a spray or the like.

[0109] In one embodiment, a therapeutically effective amount of a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof can further be administered in combination with one or more second therapeutically active agents to a patient or subject in need thereof.

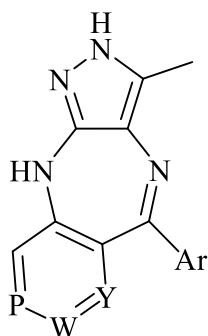
[0110] In a further embodiment, the second therapeutically active agent is an antimetabolite, a growth factor inhibitor, a mitotic inhibitor, an anti-tumor hormone, an alkylating agent, metallic platinum, a topoisomerase inhibitor, a hormonal drug, an immunomodulator, a tumor suppressor gene, a cancer vaccine, or an immune checkpoint inhibitor.

[0111] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment in combination.

[0112] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment sequentially, simultaneously or in a combined formulation.

[0113] In a further embodiment, the patient or subject is a mammal. In a preferred embodiment, the patient or subject is a human.

[0114] In a fourth aspect of the present invention, provided is a method for treating biliary tract cancer, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof,



(I)

[0115] wherein the variables in the above general formula (I) are as defined above.

[0116] In one embodiment, Ar is phenyl optionally substituted with 1–3 R_6 , and each R_6 is independently selected from hydrogen and halogen;

10 **[0117]** Y is CR_3 ;

[0118] P is CR_4 ;

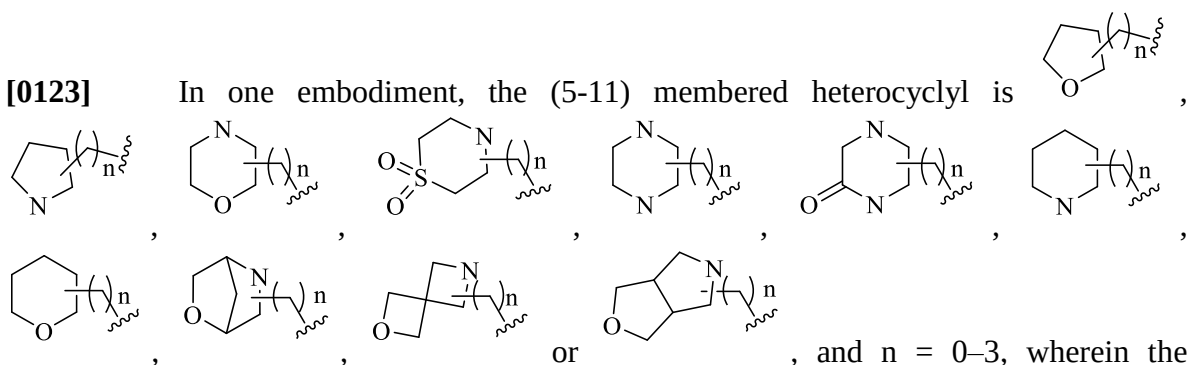
[0119] W is N;

[0120] R_3 is hydrogen;

15 **[0121]** R_4 is selected from $-(CH_2)_n$ -(5-6) membered monocyclic heterocyclyl and $-(CH_2)_n$ -(7-11) membered fused heterocyclyl, wherein $n = 0-6$, a ring-forming S atom in the heterocyclyl is optionally oxidized to S(O) or S(O)₂, a ring-forming C atom is optionally oxidized to C(O), and the heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

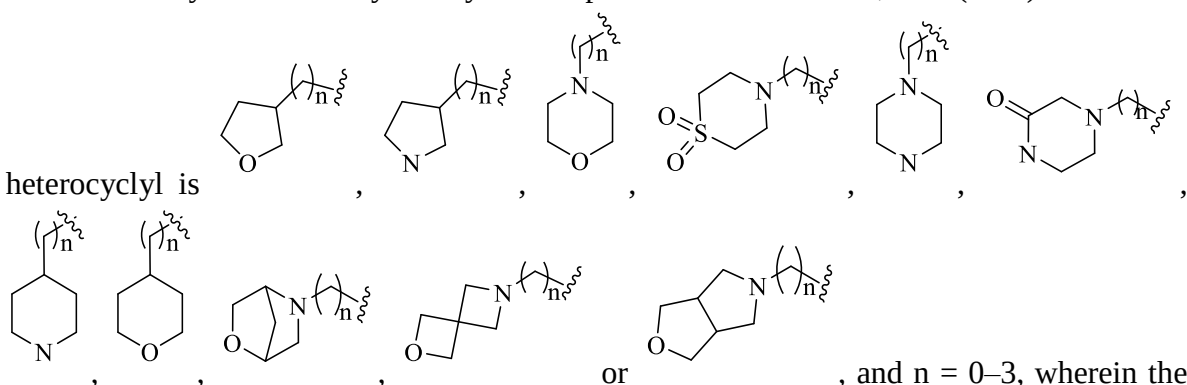
20 **[0122]** In a further embodiment, the (5-6) membered monocyclic heterocyclyl is (5-6) membered saturated monocyclic heterocyclyl, and the (7-11) membered fused heterocyclyl is (7-11) membered saturated fused heterocyclyl. In a preferred embodiment, the (7-11) membered fused heterocyclyl is (7-11) membered saturated ortho-fused heterocyclyl, (7-11) membered saturated spiro-heterocyclyl or (7-11) membered saturated bridged heterocyclyl.

In one embodiment, the (5-11) membered heterocyclyl is



heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl. In a preferred embodiment, the (5-11) membered

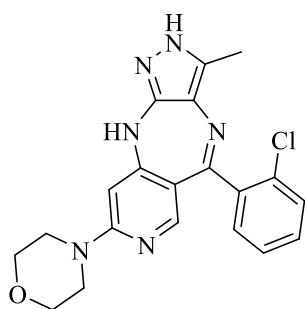
heterocyclyl is



heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

10 **[0124]** In one embodiment, the compound of general formula (I) is a compound shown in Table 1 or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

[0125] In a preferred embodiment, the compound of general formula (I) is



or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

15 **[0126]** In one embodiment, the biliary tract cancer refers to cholangiocarcinoma.

[0127] In a further embodiment, the cholangiocarcinoma refers to an FGFR-mediated cholangiocarcinoma. In a preferred embodiment, the FGFR-mediated cholangiocarcinoma

refers to cholangiocarcinoma mediated by any one of FGFR1, FGFR2 and FGFR3 or any combination thereof.

[0128] In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with non-FGFR aberration. In a preferred embodiment, the
5 cholangiocarcinoma with non-FGFR aberration refers to cholangiocarcinoma with non-FGFR2 aberration.

[0129] In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with FGFR aberration. In a preferred embodiment, the
10 cholangiocarcinoma with FGFR aberration refers to a cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0130] In still further embodiments, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR fusion, FGFR mutation and FGFR overexpression or any combination thereof. Wherein the FGFR mutation comprises an FGFR point mutation and an FGFR insertion/deletion mutation.

[0131] In a preferred embodiment, the cholangiocarcinoma refers to
15 cholangiocarcinoma with any one of FGFR2 fusion, FGFR2 and/or FGFR3 mutation and FGFR overexpression or any combination thereof. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 fusion. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 and/or
20 FGFR3 mutation. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR2 N549H, FGFR2 V564F and FGFR3 K650E or any combination thereof.

[0132] In another further embodiment, the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma that is positive for FGFR aberration but not responsive to an FGFR
25 inhibitor, or drug-resistant cholangiocarcinoma after administration of an FGFR inhibitor. In a preferred embodiment, the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0133] In another further embodiment, the cholangiocarcinoma refers to any one of intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and distal
30 cholangiocarcinoma or any combination thereof. In a preferred embodiment, the cholangiocarcinoma refers to perihilar cholangiocarcinoma. In a preferred embodiment, the

cholangiocarcinoma refers to distal cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to intrahepatic cholangiocarcinoma. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 aberration . In another preferred embodiment, the intrahepatic
5 cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 fusion. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with non-FGFR aberration.

[0134] In one embodiment, the cholangiocarcinoma further comprises cholangiocarcinoma mediated by other mechanisms, including Aurora-kinase-mediated
10 cholangiocarcinoma and cholangiocarcinoma caused by abnormal IL-6-mediated JAK-STAT signaling pathway.

[0135] In one embodiment, the therapeutically effective amount of the compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof may be further prepared with one or more pharmaceutically acceptable carriers into
15 any pharmaceutically acceptable pharmaceutical formulation.

[0136] In one embodiment, the pharmaceutical formulation may comprise one or more pharmaceutically acceptable carriers, and may be administered to a patient or subject in need of such treatment by oral, parenteral, rectal, or transpulmonary administration, and the like. For oral administration, the pharmaceutical composition can be prepared into a conventional
20 solid formulation, such as tablets, capsules, pills and granules; or can be prepared into an oral liquid formulation, such as oral solutions, oral suspensions and syrups. In the preparation of an oral formulation, an appropriate filler, binder, disintegrant, lubricant and the like may be added. For parenteral administration, the pharmaceutical composition can be prepared into an injection, including a solution injection, a sterile powder for injection and a concentrated
25 solution for injection. The injection can be produced by a conventional method existing in the pharmaceutical field, and during the preparation process, no additive may be added, or an appropriate additive may be added according to the property of the medicament. For rectal administration, the pharmaceutical composition can be prepared into a suppository and the like. For transpulmonary administration, the pharmaceutical composition can be prepared
30 into an inhalant, a spray or the like.

[0137] In one embodiment, the method further comprises administering to a patient or subject in need thereof a therapeutically effective amount of a compound of general formula

(I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof and one or more second therapeutically active agents.

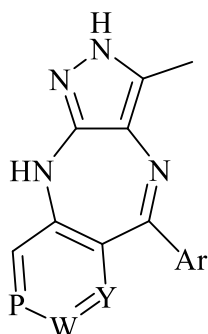
[0138] In a further embodiment, the second therapeutically active agent is an antimetabolite, a growth factor inhibitor, a mitotic inhibitor, an anti-tumor hormone, an alkylating agent, metallic platinum, a topoisomerase inhibitor, a hormonal drug, an immunomodulator, a tumor suppressor gene, a cancer vaccine, or an immune checkpoint inhibitor.

[0139] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment in combination.

[0140] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment sequentially, simultaneously or in a combined formulation.

[0141] In a further embodiment, the patient or subject is a mammal. In a preferred embodiment, the patient or subject is a human.

[0142] In a fifth aspect of the present invention, provided is a pharmaceutical composition for use in the treatment of biliary tract cancer, comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof, and optionally comprising a pharmaceutically acceptable carrier:



(I)

[0143] wherein the variables in the above general formula (I) are as defined above.

[0144] In one embodiment, Ar is phenyl optionally substituted with 1–3 R₆, and each R₆ is independently selected from hydrogen and halogen;

[0145] Y is CR₃;

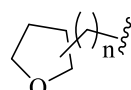
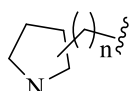
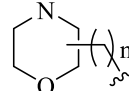
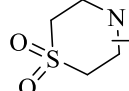
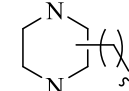
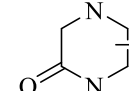
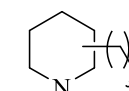
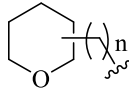
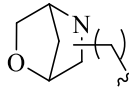
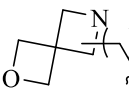
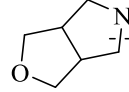
[0146] P is CR₄;

5 **[0147]** W is N;

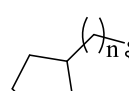
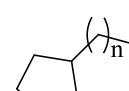
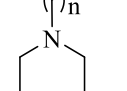
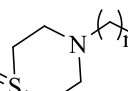
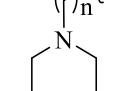
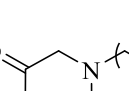
[0148] R₃ is hydrogen;

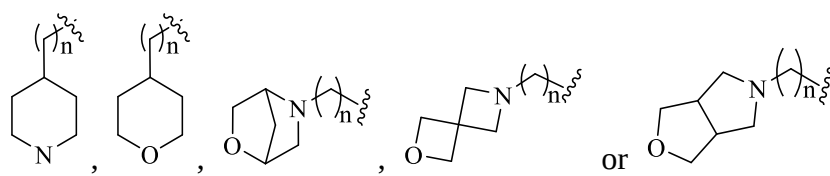
[0149] R₄ is selected from -(CH₂)_n-(5-6) membered monocyclic heterocyclyl and -(CH₂)_n-(7-11) membered fused heterocyclyl, wherein n = 0–6, a ring-forming S atom in the heterocyclyl is optionally oxidized to S(O) or S(O)₂, a ring-forming C atom is optionally
10 oxidized to C(O), and the heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

[0150] In a further embodiment, the (5-6) membered monocyclic heterocyclyl is (5-6) membered saturated monocyclic heterocyclyl, and the (7-11) membered fused heterocyclyl is (7-11) membered saturated fused heterocyclyl. In a preferred embodiment, the (7-11)
15 membered fused heterocyclyl is (7-11) membered saturated ortho-fused heterocyclyl, (7-11) membered saturated spiro-heterocyclyl or (7-11) membered saturated bridged heterocyclyl.

[0151] In one embodiment, the (5-11) membered heterocyclyl is ,
, , , , , ,
, ,  or , and n = 0–3, wherein the

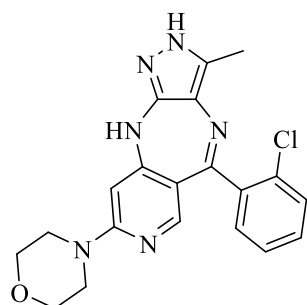
20 heterocyclyl is optionally substituted with one to more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl. In a preferred embodiment, the (5-11) membered

heterocyclyl is , , , , , ,


, and $n = 0-3$, wherein the heterocyclyl is optionally substituted with one to more substituents independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl.

[0152] In one embodiment, the compound of general formula (I) is a compound shown in Table 1 or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

[0153] In a preferred embodiment, the compound of general formula (I) is



or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof.

[0154] In one embodiment, the biliary tract cancer refers to cholangiocarcinoma.

[0155] In a further embodiment, the cholangiocarcinoma refers to an FGFR-mediated cholangiocarcinoma. In a preferred embodiment, the FGFR-mediated cholangiocarcinoma refers to cholangiocarcinoma mediated by any one of FGFR1, FGFR2 and FGFR3 or any combination thereof.

[0156] In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with non-FGFR aberration. In a preferred embodiment, the cholangiocarcinoma with non-FGFR aberration refers to cholangiocarcinoma with non-FGFR2 aberration.

[0157] In another further embodiment, the cholangiocarcinoma refers to a cholangiocarcinoma with FGFR aberration. In a preferred embodiment, the cholangiocarcinoma with FGFR aberration refers to a cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0158] In still further embodiments, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR fusion, FGFR mutation and FGFR

overexpression or any combination thereof. Wherein the FGFR mutation comprises an FGFR point mutation and an FGFR insertion/deletion mutation.

[0159] In a preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR2 fusion, FGFR2 and/or FGFR3 mutation and
5 FGFR overexpression or any combination thereof. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 fusion. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with FGFR2 and/or FGFR3 mutation. In another preferred embodiment, the cholangiocarcinoma refers to cholangiocarcinoma with any one of FGFR2 N549H, FGFR2 V564F and FGFR3 K650E or
10 any combination thereof.

[0160] In another further embodiment, the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma that is positive for FGFR aberration but not responsive to an FGFR inhibitor, or drug-resistant cholangiocarcinoma after administration of an FGFR inhibitor. In a preferred embodiment, the cholangiocarcinoma refers to drug-resistant
15 cholangiocarcinoma with FGFR2 and/or FGFR3 aberration.

[0161] In another further embodiment, the cholangiocarcinoma refers to any one of intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and distal cholangiocarcinoma or any combination thereof. In a preferred embodiment, the cholangiocarcinoma refers to perihilar cholangiocarcinoma. In a preferred embodiment, the
20 cholangiocarcinoma refers to distal cholangiocarcinoma. In a preferred embodiment, the cholangiocarcinoma refers to intrahepatic cholangiocarcinoma. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 aberration. In another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with FGFR2 fusion. In
25 another preferred embodiment, the intrahepatic cholangiocarcinoma refers to intrahepatic cholangiocarcinoma with non-FGFR aberration.

[0162] In one embodiment, the cholangiocarcinoma further comprises cholangiocarcinoma mediated by other mechanisms, including Aurora-kinase-mediated cholangiocarcinoma and cholangiocarcinoma caused by abnormal IL-6-mediated
30 JAK-STAT signaling pathway.

[0163] In one embodiment, the compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof can be further prepared with one or

more pharmaceutically acceptable carriers into any pharmaceutically acceptable pharmaceutical formulation.

[0164] In one embodiment, the pharmaceutical formulation may comprise one or more pharmaceutically acceptable carriers, and may be administered to a patient or subject in need of such treatment by oral, parenteral, rectal, or transpulmonary administration, and the like. For oral administration, the pharmaceutical composition can be prepared into a conventional solid formulation, such as tablets, capsules, pills and granules; or can be prepared into an oral liquid formulation, such as oral solutions, oral suspensions and syrups. In the preparation of an oral formulation, an appropriate filler, binder, disintegrant, lubricant and the like may be added. For parenteral administration, the pharmaceutical composition can be prepared into an injection, including a solution injection, a sterile powder for injection and a concentrated solution for injection. The injection can be produced by a conventional method existing in the pharmaceutical field, and during the preparation process, no additive may be added, or an appropriate additive may be added according to the property of the medicament. For rectal administration, the pharmaceutical composition can be prepared into a suppository and the like. For transpulmonary administration, the pharmaceutical composition can be prepared into an inhalant, spray or the like.

[0165] In one embodiment, the pharmaceutical composition further comprises one or more second therapeutically active agents.

[0166] In a further embodiment, the second therapeutically active agent is an antimetabolite, a growth factor inhibitor, a mitotic inhibitor, an anti-tumor hormone, an alkylating agent, metallic platinum, a topoisomerase inhibitor, a hormonal drug, an immunomodulator, a tumor suppressor gene, a cancer vaccine, or an immune checkpoint inhibitor.

[0167] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment in combination.

[0168] In one embodiment, the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agent are administered to a patient or subject in need of treatment sequentially, simultaneously or in a combined formulation.

[0169] In a further embodiment, the patient or subject is a mammal. In a preferred embodiment, the patient or subject is a human.

[0170] **3. Definition**

[0171] The "halogen" described herein refers to fluorine, chlorine, bromine, iodine and
5 the like, and preferably fluorine and chlorine.

[0172] The "halogenated" described herein means that any hydrogen atom in a substituent can be substituted with one or more identical or different halogen. "Halogen" is defined as above.

[0173] The "cyano" described herein referred to the -CN group.

10 [0174] The "amino" described herein refers to the -NH₂ group.

[0175] As described herein, "C₁₋₄ alkyl" refers to a linear or branched alkyl derived from a hydrocarbon moiety having 1 to 4 carbon atoms by removing one hydrogen atom, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl. The "C₁₋₃ alkyl" refers to the above alkyl having 1 to 3 carbon atoms.

15 [0176] The "C₃₋₆ cycloalkyl" described herein refers to a monocyclic cycloalkyl or bicyclic cycloalkyl system or a polycyclic cycloalkyl system having 3 to 6 carbon atoms. These groups are saturated but not aromatic, including monocyclic and fused ring structures which can be formed, unless otherwise specified. Examples thereof include, but are not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.2]hexane, and
20 bicyclo[3.2.1]hexane.

[0177] The "5-11 membered heterocyclyl" described herein refers to a non-aromatic cyclic group having 5 to 11 ring carbon atoms, wherein at least one ring carbon atom is substituted with one or more heteroatoms selected from O, S and N, and preferably 1 to 3 heteroatoms, and ring-forming atoms including carbon atoms, nitrogen atoms and sulfur
25 atoms may be oxidized.

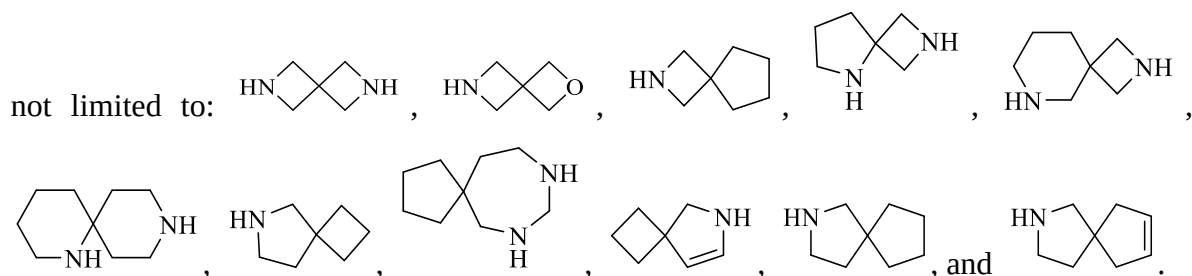
[0178] The "heterocyclyl" refers to a monocyclic heterocyclyl or bicyclic heterocyclyl system or a polycyclic heterocyclyl system, including saturated and partially saturated heterocyclyl, but not including aromatic rings. Unless otherwise specified, the "5-11 membered heterocyclyl" described herein includes monocyclic and fused ring structures
30 which can be formed.

[0179] The monocyclic heterocyclyl may be 5-7 membered heterocyclyl, 5-6 membered heterocyclyl, 5-6 membered oxygen-containing heterocyclyl, 5-6 membered nitrogen-containing heterocyclyl, 5-6 membered saturated heterocyclyl and the like. Examples of 5-6 membered monocyclic heterocyclyl described herein include, but are not limited to, tetrahydrofuranyl, tetrahydropyrrolyl, tetrahydrothienyl, imidazolidinyl, pyrazolidinyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, 1,2-thiazolidinyl, 1,3-thiazolidinyl, tetrahydro-2*H*-pyranyl, tetrahydro-2*H*-thiopyranyl, piperidinyl, piperazinyl, morpholiny, 1,4-dioxanyl, 1,4-oxathianyl, 4,5-dihydroisoxazolyl, 4,5-dihydrooxazolyl, 2,5-dihydrooxazolyl, 2,3-dihydrooxazolyl, 3,4-dihydro-2*H*-pyrrolyl, 2,3-dihydro-1*H*-pyrrolyl, 2,5-dihydro-1*H*-imidazolyl, 4,5-dihydro-1*H*-imidazolyl, 4,5-dihydro-1*H*-pyrazolyl, 4,5-dihydro-3*H*-pyrazolyl, 4,5-dihydrothiazolyl, 2,5-dihydrothiazolyl, 2*H*-pyranyl, 4*H*-pyranyl, 2*H*-thiopyranyl, 4*H*-thiopyranyl, 2,3,4,5-tetrahydropyridyl, 1,2-isoxazolyl, 1,4-isoxazolyl, 6*H*-1,3-oxazinyl, or the like.

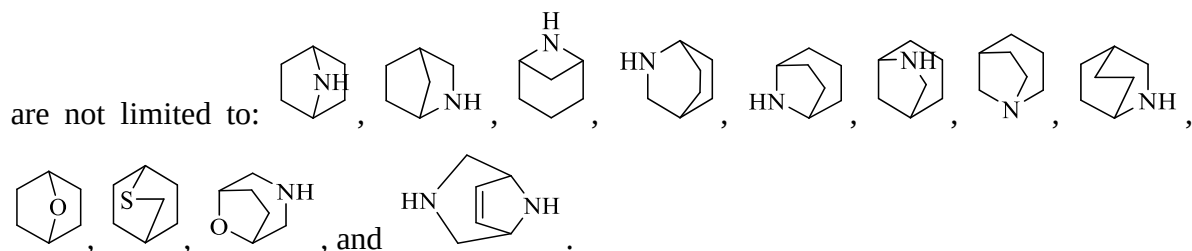
[0180] The fused heterocyclyl includes ortho-fused heterocyclyl, spiro-heterocyclyl and bridged heterocyclyl, which may be saturated, partially saturated or unsaturated, but non-aromatic. Unless otherwise specified, the 7-11 membered fused heterocyclyl described herein includes ortho-fused, spiro and bridged structures which can be formed.

[0181] The ortho-fused heterocyclyl may be 7-11 membered ortho-fused cyclyl, and preferably 7-11 membered saturated ortho-fused cyclyl; examples of which include, but are not limited to: 3,6-diazabicyclo[3.2.0]heptyl, 3,8-diazabicyclo[4.2.0]octyl, 3,7-diazabicyclo[4.2.0]octyl, octahydropyrrolo[3,4-*c*]pyrroly, octahydropyrrolo[3,4-*b*]pyrroly, octahydropyrrolo[3,4-*b*][1,4]oxazinyl, octahydro-1*H*-pyrrolo[3,4-*c*]pyridinyl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, indolin-1-yl, indolin-2-yl, indolin 3-yl, 2,3-dihydrobenzothien-2-yl, octahydro-1*H*-indolyl, and octahydrobenzofuranyl.

[0182] The spiro-heterocyclyl may be 7-11 membered spiro-heterocyclyl, and preferably 7-11 membered saturated spiro-heterocyclyl; examples of which include, but are



[0183] The bridged heterocyclyl may be 7-11 membered bridged heterocyclyl, and preferably 7-11 membered saturated bridged heterocyclyl; examples of which include, but



- 5 **[0184]** The "pharmaceutically acceptable salt" described herein refers to both pharmaceutically acceptable acid and base addition salts and solvates. Such pharmaceutically acceptable salts include salts of the following acids: hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid, sulfurous acid, formic acid, toluenesulfonic acid, methanesulfonic acid, nitric acid, benzoic acid, citric acid, tartaric acid, maleic acid, hydroiodic acid, alkanolic acid (such as acetic acid, $\text{HOOC}-(\text{CH}_2)_n\text{-COOH}$ (wherein n is 0–4)), and the like. Such pharmaceutically acceptable salts further include salts of the following bases: sodium, potassium, calcium, ammonium, and the like. Those skilled in the art know a variety of pharmaceutically acceptable non-toxic addition salts.

- 15 **[0185]** All numerical ranges described herein include both endpoints of the ranges, all integers within the range and subranges formed by these integers. For example, "5-11 membered" includes 5, 6, 7, 8, 9, 10 or 11 membered, "5-6 membered" includes 5 or 6 membered, and "7-11 membered" includes 7, 8, 9, 10 or 11 membered and so on.

- 20 **[0186]** The "one to more" as described herein with respect to a substituent refers to the number of substituents with which all positions can be chemically substituted in the substituted group, preferably 1 to 6, more preferably 1 to 5, more preferably 1 to 3, and more preferably 1 to 2.

[0187] The "crystal form" described herein may be prepared from the compound of general formula (I) by conventional methods for preparing crystal forms used in the art.

- 25 **[0188]** The "stereoisomer" of the compound of general formula (I) described herein means that an enantiomer can be formed when asymmetric carbon atoms are present in the compound of general formula (I); a cis-trans isomer can be formed when a carbon-carbon double bond or a ring structure is present in the compound; a tautomer can be formed when a ketone or oxime is present in the compound. All enantiomers, diastereomers, racemates,

cis-trans isomers, tautomers, geometric isomers and epimers of the compound of general formula (I) as well as mixtures thereof are included in the scope of the present invention.

[0189] The preparation of the compound of general formula (I) described herein can be found in the detailed description of WO2018108079A1.

5 **[0190]** The "therapeutically effective amount" described herein refers to an amount of the aforementioned compound or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and/or the pharmaceutical formulation that, when administered to a patient, is at least capable of alleviating symptoms of the patient's condition. An actual amount comprising the "therapeutically effective amount" will vary depending on a variety of circumstances, including, but not limited to, the particular condition being treated, the severity of the condition, the physique and health of the patient, and the route of administration. The appropriate amount can be readily determined by skilled medical practitioners using methods known in the medical field.

15 **[0191]** The "mammal" described herein refers to a group of animals of the class mammalia of the subphylum vertebrates, which are lactated by the mammary glands to suckle young children. It can be divided into human mammals and non-human mammals. Examples of non-human mammals include, but are not limited to, tigers, leopards, wolves, deer, giraffes, minks, monkeys, orangutans, tapirs, foxes, sloths, bears, koala bears, polar bears, elephants, musk-oxen, rhinoceros, sea cattle, lions, red pandas, pandas, warthogs, antelopes, koalas, lynxes, pangolins, anteaters, otters, dolphins, walruses, seals, whales, platypuses, hedgehogs, kangaroos, hippopotamus, weasels, badgers, leopard cats, horses, cattle, sheep, mules, donkeys, dogs, mice, cats, and rabbits.

25 **[0192]** The "pharmaceutically acceptable carrier" described herein includes, but is not limited to, solid carriers and liquid carriers. Suitable solid carriers include, but are not limited to, cellulose, glucose, lactose, mannitol, magnesium stearate, magnesium carbonate, sodium carbonate, sodium saccharin, sucrose, dextrin, talc, starch, pectin, gelatin, tragacanth, arabic gum, sodium alginate, *p*-hydroxylbenzoate, methylcellulose, sodium carboxymethyl cellulose, low-melting wax, cocoa butter, and the like. Suitable liquid carriers include, but are not limited to, water, ethanol, polyol (such as glycerin, propylene glycol and liquid polyethylene glycol), vegetable oil, glyceride and mixtures thereof.

30 **[0193]** The "FGFR inhibitor" described herein is a small-molecule inhibitor drug which is available on the market or is in clinical research or preclinical research and is proved

to be capable of targeting FGFR kinase to play a role in treating cancer, and in particular to a drug for treating cholangiocarcinoma, such as: Erdafitinib, BGJ-398, TAS-120 and INCB-054828.

BENEFICIAL EFFECTS OF PRESENT INVENTION

5 [0194] The compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof can effectively treat biliary tract cancer, and particularly has a remarkable treatment effect on cholangiocarcinoma. Researches show that the compound has a good treatment effect on cholangiocarcinoma with non-FGFR aberration, cholangiocarcinoma with FGFR aberration, various FGFR drug-resistant
10 cholangiocarcinomas and cholangiocarcinoma of various anatomical sites.

DETAILED DESCRIPTION

[0195] In order to make the objective, technical solutions and advantages of the present invention more apparent, the present invention is further described in detail below. It should be apparent that the examples described herein are only some examples of the present
15 invention, but not all examples. Based on the examples of the present invention, all other examples obtained by those of ordinary skill in the art without creative work shall fall within the protection scope of the present invention.

[0196] The abbreviations and English expressions used in the present invention have the following meanings:

20 Table 2. Abbreviations and English expressions

Abbreviation/English	Meaning
DMSO	Dimethyl sulfoxide
MOPS	3-morpholinopropanesulfonic acid
EDTA	Ethylenediaminetetraacetic acid
MnCl ₂	Manganese chloride
MC	Methylcellulose
ATP	Adenosine triphosphate
Glu	Glutamic acid
Tyr	Tyrosine
PEG	Polyethylene glycol
Qd	Administration once daily

Qw

Administration once a week

BiW

Administration twice a week

[0197] Experimental Example 1: Assay on Inhibitory Activity of Compounds of the Present Invention Against FGFR Wild-Type Enzyme

[0198] Test samples: the compounds of the present invention, which have structures shown in Table 1 and are prepared as described in the embodiments of WO2018108079A1.

5 **[0199]** Experiment method

[0200] (1) Preparation of the compound plate

[0201] The compounds were each dissolved in DMSO to prepare stock solutions with a maximum concentration of 500 μ M. The compound stock solutions were diluted with DMSO to final concentrations of 500, 150, 50, 15, 5, 1.5, 0.5, 0.15, 0.05 μ M to obtain compound
10 working solutions (50 $\times$).

[0202] (2) Experimental procedures

[0203] a) Preparation of different reaction systems

[0204] FGFR1(h) was dissolved in 8 mM MOPS (pH 7.0), 0.2 mM EDTA and 250 μ M KKKSPGEYVNIEFG;

15 **[0205]** FGFR2(h) was dissolved in 8 mM MOPS (pH 7.0), 0.2 mM EDTA, 2.5 mM MnCl₂ and 0.1 mg/mL poly (Glu, Tyr) (4:1);

[0206] FGFR3(h) was dissolved in 8 mM MOPS (pH 7.0), 0.2 mM EDTA, 10 mM MnCl₂ and 0.1 mg/mL poly (Glu, Tyr) (4: 1);

[0207] b) Enzymatic reaction

20 **[0208]** The reaction was initiated by the addition of 10 mM magnesium acetate and 10 μ M [γ -³³P]-ATP. After incubation at room temperature for 40 min, the reaction was stopped by using a 3% (v/v) phosphoric acid solution. 10 μ L of the reaction solution was pipetted onto P30 filter paper, washed 3 times with 75 mM phosphoric acid solution for 5 min each time, dried and counted by scintillation. 2% (v/v) DMSO was taken as a positive control (Max)
25 instead of the compound solutions; high concentration positive control inhibitor (10 μ M Staurosporine) was taken as a negative control (Min) instead of the compound solutions.

[0209] Test results:

Table 3. Inhibitory activity of compounds of the present invention against wild-type FGFRs (IC₅₀)

Test samples	FGFR1 (nM)	FGFR2 (nM)	FGFR3 (nM)
Compound 29	2	3	5

[0210] It can be seen from the experimental results in Table 3 that the compounds of the present invention can target FGFR1–3, have a good inhibitory activity against FGFR1–3, and have good clinical application potential in the aspect of treating diseases mediated by FGFR1–3.

[0211] Experimental Example 2: Assay on Inhibitory Activity of Compounds of the Present Invention Against Wild-Type and Mutant FGFR

[0212] Test samples: the compounds of the present invention, which have structures shown in Table 1 and are prepared as described in the embodiments of WO2018108079A1.

Table 4. Names and sources of enzymes/reagents

Abbreviations	Name	Source
FGFR2 WT	Wild-type FGFR2 enzyme	Invitrogen
FGFR2 N549H	N549H gene mutant FGFR2 enzyme	Signalchem
FGFR2 V564F	V564F gene mutant FGFR2 enzyme	Signalchem
FGFR3 WT	Wild-type FGFR3 enzyme	Invitrogen
FGFR3 K650E	K650E gene mutant FGFR3 enzyme	Signalchem
HTRF KinEASE-TK kit	Homogeneous time-resolved fluorescence method kit	Cisbio
BIBF 1120	Nintedanib	ChemExpress

[0213] Experiment method

[0214] (1) Preparation of the compound plate

[0215] The compounds were dissolved in DMSO and 3-fold diluted with DMSO to obtain 10 serially diluted stock solutions. The stock solutions were added into a 384-well plate to obtain a 3-fold diluted series of 10 concentrations of the compound starting from 10 μM.

[0216] (2) Experimental procedures

[0217] Different enzyme solutions (2×) were prepared, transferred into the 384-well plate, incubated with the compound solutions with different concentrations for 10 min at room temperature, and a mixed solution (2×) of biotinylated tyrosine kinase substrate/ATP

was added to activate the reaction. After incubation for 50 min at room temperature, an HTRF detection reagent and a corresponding kinase antibody cryptate were added, and after incubation for 1 h at room temperature, fluorescence readings at 615 nm (cryptate) and 665 nm (HTRF detection reagent) were detected by using an Envision 2104 multifunctional microplate reader. 10 μ M BIBF-1120 was taken as a compound positive control (PC) instead of the compound solutions, and 0.1% (v/v) DMSO was taken as a solvent negative control (VC) instead of the compound solutions.

[0218] (3) Data processing

[0219] The fluorescence ratio of 665/615 nm was calculated, and the enzyme activity inhibition rate (%) was calculated according to the following formula:

$$\text{Inhibition rate \%} = 100 - \frac{\text{Fluorescence ratio of compounds} - \text{Mean fluorescence ratio of PC}}{\text{Mean fluorescence ratio of VC} - \text{Mean fluorescence ratio of PC}} \times 100$$

[0220] IC₅₀ values were fitted using GraphPad 6.0 based on inhibition rates of compounds with different concentrations.

[0221] Test results:

15 Table 5. Inhibitory Activity of Compounds of the Present Invention Against FGFR enzyme (IC₅₀)

Test samples	Enzymes	IC ₅₀ (nM)
Compound 29	FGFR2 WT	0.5
	FGFR2 N549H	1.9
	FGFR2 V564F	0.7
Compound 29	FGFR3 WT	1.0
	FGFR3 K650E	1.7

[0222] It can be seen from the experimental results in Table 5 that the compounds of the present invention have an obvious inhibitory effect on both wild-type and mutant FGFR2 and FGFR3, which indicates that the compounds of the present invention have better clinical application potential in treating diseases mediated by wild-type and/or mutant FGFR, such as cholangiocarcinoma.

[0223] Experimental Example 3: Cholangiocarcinoma Organoid Experiment of Compounds of the Present Invention

[0224] Test samples: the compounds of the present invention, which have structures shown in Table 1 and are prepared as described in the embodiments of WO2018108079A1.

[0225] Organoid information: Human distal cholangiocarcinoma (dCC) from K2 Oncology Co. Ltd., Beijing, code KOBD-002

5 Table 6. Names and sources of reagents and instruments

Name	Source/model No.
96-channel high-throughput full-automatic liquid workstation	NAYO N96
Microplate reader	BMG FLUOstar
Fetal bovine serum	Gibco
Penicillin/streptomycin double-antibody	Gibco 15140122
Pancreatin	Gibco 12604013
Cell Viability fluorescence detection kit CellTiter-Glo® Luminescent Cell Viability Assay	Promega G7573
GAS-Ad-BD medium	K2 Oncology, K2O-CML-01801
BEZ235	MCE
Gemcitabine	
Cisplatin	MCE
5-fluorouracil	MCE
Matrigel	BD 356231

[0226] Experiment method

[0227] (1) Preparation of the compound plate

[0228] The compounds were dissolved in DMSO, then diluted 3-fold to obtain stock solutions (1000 ×) with 10-concentration gradients, and diluted 100-fold using GAS-Ad-BD medium to obtain working solutions (10 ×).

[0229] (2) Experimental procedures

[0230] After tumor organoids could be passaged, matrigel was melted at 4 °C for later use. Cultured tumor organoids were collected using a Pasteur dropper and added with pancreatin to form a single cell suspension. After cell counting, the cell concentration was adjusted to 8×10^4 cell/mL by using GAS-Ad-BD medium, and 2 mL of the cell suspension was placed on ice for later use. A matrigel mixed solution was prepared by mixing the cell suspension and the matrigel and then placed on ice for later use, 50 uL of the mixed solution was added to a 96-well plate, incubated at 37 °C for 30 min and added with GAS-Ad-BD

medium, and after 2 days of incubation in a 37 °C cell incubator, the formation and growth of tumor organoids were observed.

[0231] After the formation and growth of the tumor organoids were observed, 10 µL of working solutions (10 ×) with 10-concentration gradients prepared on the same day were sequentially added. The solutions were incubated at 37 °C for 96 h with 5% carbon dioxide. The starting concentrations of each compound were as follows: compound 29 at 10 µM, gemcitabine at 40 µM, cisplatin at 60 µM, and 5-fluorouracil at 30 µM. A solvent negative control group (DMSO, 100% survival) and a positive control group (2.5 µM BEZ235, 0% survival) were set.

[0232] After the cultivation was completed, 70 µL of CellTiter-Glo® solution was added, and the fluorescence value was determined after the operation was performed according to the specification.

[0233] (3) Data processing

[0234] The corresponding compound concentration at 50% survival was calculated by using GraphPad Prism 5 software, that is the IC₅₀ value (absolute IC₅₀ value) for the compounds on these cells.

[0235] Test results:

Table 7. Inhibitory Activity of Compounds of the Present Invention Against KOBD-002 Distal Cholangiocarcinoma Organoids

Test samples	IC ₅₀ (µM)
Compound 29	1.27
Gemcitabine	17.97
Cisplatin	18.77
5-fluorouracil	>30

[0236] It can be seen from the experimental results in Table 7 that the compounds of the present invention have a good inhibitory activity against KOBD-002 distal cholangiocarcinoma organoids, and are superior to gemcitabine, cisplatin and 5-fluorouracil, which indicates that the compounds have good clinical application potential in treating cholangiocarcinoma, and especially distal cholangiocarcinoma.

[0237] **Experimental Example 4: *In Vivo* Efficacy Test of Compounds of the Present Invention on HuPrime® Human Cholangiocarcinoma CC6204 Subcutaneous Xenograft Tumor Model**

[0238] Test samples: the compounds of the present invention, which have structures shown in Table 1 and are prepared as described in the embodiments of WO2018108079A1; gemcitabine hydrochloride, commercially available.

[0239] The source of tumor mass: CC6204 was a HuPrime® xenograft model established by a female cholangiocarcinoma patient. The pathological diagnosis was intrahepatic cholangiocarcinoma, with FGFR2-BICC1 fusion aberration.

[0240] Animals: Balb/c nude female mice at 5–6 weeks (weeks of age at time of mice inoculation).

[0241] Test method:

[0242] (1) Construction and grouping of tumor-bearing mice

[0243] Tumor tissues were collected from tumor-bearing mice of HuPrime® cholangiocarcinoma xenograft model CC6204, cut into tumor masses of a diameter of 2–3 mm and then subcutaneously inoculated into the right anterior scapula of the Balb/c nude mice, and the mice were grouped and administered when an average volume of tumors reached 133 mm³. Grouping method: animals were weighed before administration and tumor volumes were measured. Grouping was designed in blocks according to the tumor volume, with 6 mice per group.

[0244] (2) Administration regimen

Table 8. Administration regimen

Group	Vehicle	Dosage (mg/kg)	Dosing volume (mL/kg)	Route of administration	Frequency of administration	Administration period
Vehicle control	0.5% (v/v) MC containing 0.5% (v/v) Tween 80	0	10	Oral intragastric administration	Qd	68 days
Compound 29	0.5%(w/v)MC	15	10	Oral intragastric administration	Qd	68 days
Gemcitabine hydrochloride	Normal saline	120	10	Intraperitoneal	QW ^a	68 days

[0245] Note: ^a gemcitabine hydrochloride was administered once a week for a total of 10.

[0246] (3) Experimental observation index

[0247] Animals were monitored daily for health and mortality, body weight and tumor volume were measured twice a week, and samples were collected after the last administration. The therapeutic effect of tumor volume was evaluated by TGI%, wherein the relative tumor inhibition rate TGI (%): $TGI = 1 - T/C$ (%). T/C% is the relative tumor proliferation rate, i.e., the percentage of the relative tumor volume in the treatment and control groups at a given time point. T and C are relative tumor volumes (RTVs) of the treatment and control groups at a given time point, respectively.

[0248] The calculation formula is as follows: $T/C \% = T_{RTV} / C_{RTV} \times 100\%$ (T_{RTV} : mean RTV for treatment group; C_{RTV} : mean RTV for vehicle control group; $RTV = V_t/V_0$, wherein V_0 is the tumor volume of the animal at the time of grouping, and V_t is the tumor volume of the animal after treatment). The drug is considered to be effective according to the National Institute of Health (NIH) Guidelines that TGI is $\geq 58\%$.

[0249] Test results:

Table 9. Effect of Compounds of the Present Invention on Tumor Growth in Mice of HuPrime[®] Human Cholangiocarcinoma CC6204 subcutaneous xenograft tumor model

Group	Number of animals	Tumor volume ^a (mm ³)	TGI (%) ^b	<i>P</i> ^c
Vehicle control	6	696.52	--	--
Compound 29	6	147.8	80	<0.001
Gemcitabine hydrochloride	6	397.22	43	0.973

[0250] Note: ^a: tumor volumes were statistic data for 21 days of administration. ^b: TGI: relative tumor inhibition rate, statistic data for 21 days of administration. ^c: $P < 0.05$ indicates that there was a statistical difference, $P < 0.01$ indicates that there was a significant statistical difference, and $P < 0.001$ indicates that there was an extremely significant statistical difference.

Table 10. Effect of Compounds of the Present Invention on Survival Rate of Mice of HuPrime[®] Human Cholangiocarcinoma CC6204 subcutaneous xenograft tumor model

Group	Number of animals	Number of surviving animals ^a	Survival rate (%)	<i>P</i> ^b
Vehicle control	6	0	0	--
Compound 29	6	6	100	<0.001
Gemcitabine hydrochloride	6	1	16.7	0.467

[0251] Note: ^a: surviving animals were data statistics after the last administration (day 67). ^b: $P < 0.05$ indicates that there was a statistical difference, $P < 0.01$ indicates that there was a significant statistical difference, and $P < 0.001$ indicates that there was an extremely significant statistical difference.

5 [0252] It can be seen from the experimental results in Table 9 and Table 10 that the compounds of the present invention have a remarkable inhibitory effect on HuPrime[®] human cholangiocarcinoma CC6204 subcutaneous xenograft tumor model, effectively prolong the life cycle of tumor-bearing animals, and are significantly superior to clinical standard treatment of gemcitabine, which indicates that the compounds of the present invention can be
10 used in clinical treatment of intrahepatic cholangiocarcinoma tumors with FGFR2 aberration, and have good clinical application potential.

[0253] **Experimental Example 5: *In Vivo* Efficacy Test of Compounds of the Present Invention on HuPrime[®] Human Cholangiocarcinoma CC6639 Subcutaneous Xenograft Tumor Model**

15 [0254] Test samples: the compounds of the present invention, which have structures shown in Table 1 and are prepared as described in the embodiments of WO2018108079A1.

[0255] The source of tumor mass: CC6639 was a HuPrime[®] xenograft model established by a male cholangiocarcinoma patient. The pathological diagnosis was intrahepatic cholangiocarcinoma, with no FGFR2 aberration.

20 [0256] Animals: Balb/c nude female mice at 4–5 weeks (weeks of age at time of mice inoculation).

[0257] Experiment method

[0258] (1) Construction and grouping of tumor-bearing mice

[0259] Tumor tissues were collected from tumor-bearing mice of HuPrime[®]
25 cholangiocarcinoma xenograft model CC6639, cut into tumor masses of a diameter of 2–3 mm and then subcutaneously inoculated into the right anterior scapula of the Balb/c nude mice, and the mice were grouped and administered when an average volume of tumors reached 202mm³. Grouping method: animals were weighed before administration and tumor volumes were measured. Grouping was designed in blocks according to the tumor volume,
30 with 5 mice per group.

[0260] (2) Administration regimen shown in Table 11

Table 11. Administration regimen

Group	Vehicle	Dosage (mg/kg)	Dosing volume (mL/kg)	Route of administration	Frequency of administration	Administration period
Vehicle control	0.5% (w/v)MC	0	10	Oral intragastric administration	Qd	21 days
Compound 29	0.5% (w/v)MC	15	10	Oral intragastric administration	Qd	21 days

[0261] (3) Experimental observation index

[0262] Animals were monitored daily for health and mortality, body weight and tumor volume were measured twice a week, and samples were collected after the last administration. The therapeutic effect of tumor volume was evaluated by TGI%, wherein the relative tumor inhibition rate TGI (%): $TGI = 1 - T/C$ (%). T/C% is the relative tumor proliferation rate, i.e., the percentage of the relative tumor volume in the treatment and control groups at a given time point. T and C are relative tumor volumes (RTVs) of the treatment and control groups at a given time point, respectively. The calculation formula is as follows: $T/C \% = T_{RTV} / C_{RTV} \times 100\%$ (T_{RTV} : mean RTV for treatment group; C_{RTV} : mean RTV for vehicle control group; $RTV = V_t/V_0$, wherein V_0 is the tumor volume of the animal at the time of grouping, and V_t is the tumor volume of the animal after treatment). The drug is considered to be effective according to the NIH Guidelines that TGI is $\geq 58\%$.

[0263] Test results:

[0264] Table 12. Effect of Compound 29 of the present invention on tumor growth in mice of HuPrime[®] human cholangiocarcinoma CC6639 subcutaneous xenograft tumor model

Group	Number of animals	Tumor volume (mm ³)	TGI (%) ^a	<i>P</i> ^b
Vehicle control	5	2195.88	--	--
Compound 29	5	623.72	72	0.0045

[0264] Note: ^a: statistical data after the last administration; TGI: relative tumor inhibition rate. ^b: $P < 0.05$ indicates that there was a statistical difference, $P < 0.01$ indicates that there was a significant statistical difference, and $P < 0.001$ indicates that there was an extremely significant statistical difference.

[0265] It can be seen from the experimental results in Table 12 that Compound 29 has a remarkable inhibitory effect on HuPrime[®] human cholangiocarcinoma CC6639 subcutaneous xenograft tumor model, which indicates that the compound can be used in

clinical treatment of intrahepatic cholangiocarcinoma tumors with non-FGFR2 aberration and has good clinical application potential.

[0266] Experimental Example 6: *In Vivo* Efficacy Test of Compounds of the Present Invention on Human Perihilar Cholangiocarcinoma PDX Subcutaneous Xenograft Tumor Model

[0267] Test samples: the compounds of the present invention, which have structures shown in Table 1 and are prepared as described in the embodiments of WO2018108079A1.

[0268] The source of tumor mass: the human perihilar cholangiocarcinoma tumor sample was derived from a female patient.

[0269] Animals: NCG male mice at 5–8 weeks.

[0270] Test method:

[0271] (1) Construction and grouping of tumor-bearing mice

[0272] The tumor samples excised in the surgery were inoculated into mice as P0 generation and then passaged as P1 generation for drug efficacy evaluation. The tumor masses were inoculated into the right back of the mice, and the mice were grouped and administered when an average volume of tumors reached approximately 100 mm³. Grouping method: animals were weighed before administration and tumor volumes were measured. Grouping was designed in blocks according to the tumor volume, with 6 mice per group.

[0273] (2) Administration according to administration regimen of Table 13

Table 13. Administration regimen

Group	Vehicle	Dosage (mg/kg)	Dosing volume (mL/kg)	Route of administration	Frequency of administration	Administration period
Vehicle control	0.5%(w/v)MC	0	10	Oral intragastric administration	Qd	25 days
Compound 29	0.5%(w/v)MC	15	10	Oral intragastric administration	Qd	25 days
Gemcitabine hydrochloride + Cisplatin	Normal saline	30 +3	10 +10	Intraperitoneal	BiW Qw	25 days

[0274] (3) Experimental observation index

[0275] Animals were monitored daily for health and mortality, body weight and tumor volume were measured twice a week, and samples were collected after the last administration. The therapeutic effect of tumor volume was evaluated by TGI%, wherein the relative tumor inhibition rate TGI (%): $TGI = 1 - T/C$ (%). T/C% is the relative tumor proliferation rate, i.e., the percentage of the relative tumor volume in the treatment and control groups at a given time point. T and C are relative tumor volumes (RTVs) of the treatment and control groups at a given time point, respectively. The calculation formula is as follows: $T/C \% = T_{RTV} / C_{RTV} \times 100\%$ (T_{RTV} : mean RTV for treatment group; C_{RTV} : mean RTV for vehicle control group; $RTV = V_t/V_0$, wherein V_0 is the tumor volume of the animal at the time of grouping, and V_t is the tumor volume of the animal after treatment). The drug is considered to be effective according to the NIH Guidelines that TGI is $\geq 58\%$.

[0276] Test results:

Table 14. Effect of Compound 29 of the Present Invention on Tumor Growth in Mice of HuPrime[®] Human Cholangiocarcinoma CC6204 subcutaneous xenograft tumor model

Group	Number of animals	Tumor volume ^a (mm ³)	TGI (%) ^b	P ^c
Vehicle control	6	233.9	--	--
Compound 29	6	70.9	70	0.0039
Gemcitabine hydrochloride + Cisplatin	6	157.3	35	0.247

[0277] Note: ^a: tumor volumes were statistical data for 21 days of administration; ^b: TGI: relative tumor inhibition rate, statistic data for 21 days of administration. ^c: $P < 0.05$ indicates that there was a statistical difference, $P < 0.01$ indicates that there was a significant statistical difference, and $P < 0.001$ indicates that there was an extremely significant statistical difference.

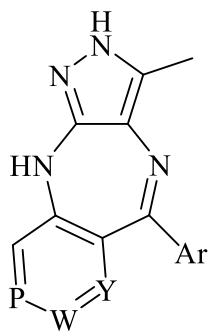
[0278] It can be seen from the experimental results in Table 14 that Compound 29 has a remarkable inhibitory effect on human perihilar cholangiocarcinoma PDX subcutaneous xenograft tumor model, and is significantly superior to the clinical standard treatment of gemcitabine + cisplatin, which indicates that the compound of the present invention can be used in clinical treatment of perihilar cholangiocarcinoma tumors and has good clinical application potential.

[0279] The above description is only for the purpose of illustrating the preferred example of the present invention, and is not intended to limit the scope of the present

invention. Any modifications, equivalents, improvements and the like made without departing from the spirit and principle of the present invention should be included in the protection scope of the present invention.

What is claimed is:

1. Use of a compound of general formula (I) or a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof in the preparation of a medicament for treating biliary tract cancer:



(I)

wherein Ar is phenyl optionally substituted with 1–3 R_6 , each R_6 is independently selected from hydrogen, amino, cyano, halogen, C_{1-4} alkyl and trifluoromethyl;

Y is CR_3 ;

P is CR_4 ;

W is N;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-(CH_2)_n$ -(5-11) membered heterocyclyl, wherein $n = 0-6$, a ring-forming S atom in the heterocyclyl is optionally oxidized to $S(O)$ or $S(O)_2$, a ring-forming C atom in the heterocyclyl is optionally oxidized to $C(O)$, and the heterocyclyl is optionally substituted with one to more substituents independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl.

2. The use according to claim 1,

wherein Ar is phenyl optionally substituted with 1–3 R_6 , and each R_6 is independently selected from hydrogen and halogen;

Y is CR_3 ;

P is CR_4 ;

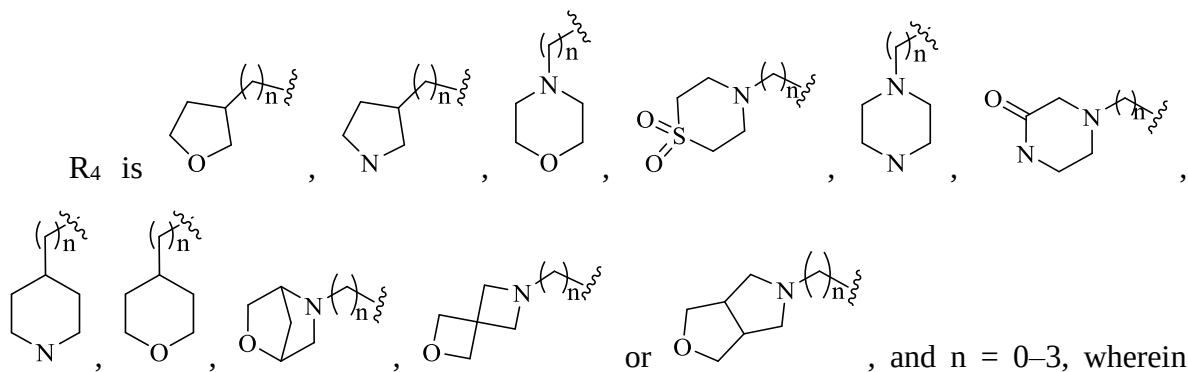
W is N;

R_3 is hydrogen;

R_4 is selected from $-(CH_2)_n$ -(5-6) membered monocyclic heterocyclyl and $-(CH_2)_n$ -(7-11) membered fused heterocyclyl, wherein $n = 0-6$, a ring-forming S atom in the heterocyclyl is optionally oxidized to $S(O)$ or $S(O)_2$, a ring-forming C atom is optionally oxidized to $C(O)$, and the heterocyclyl is optionally substituted with one to more

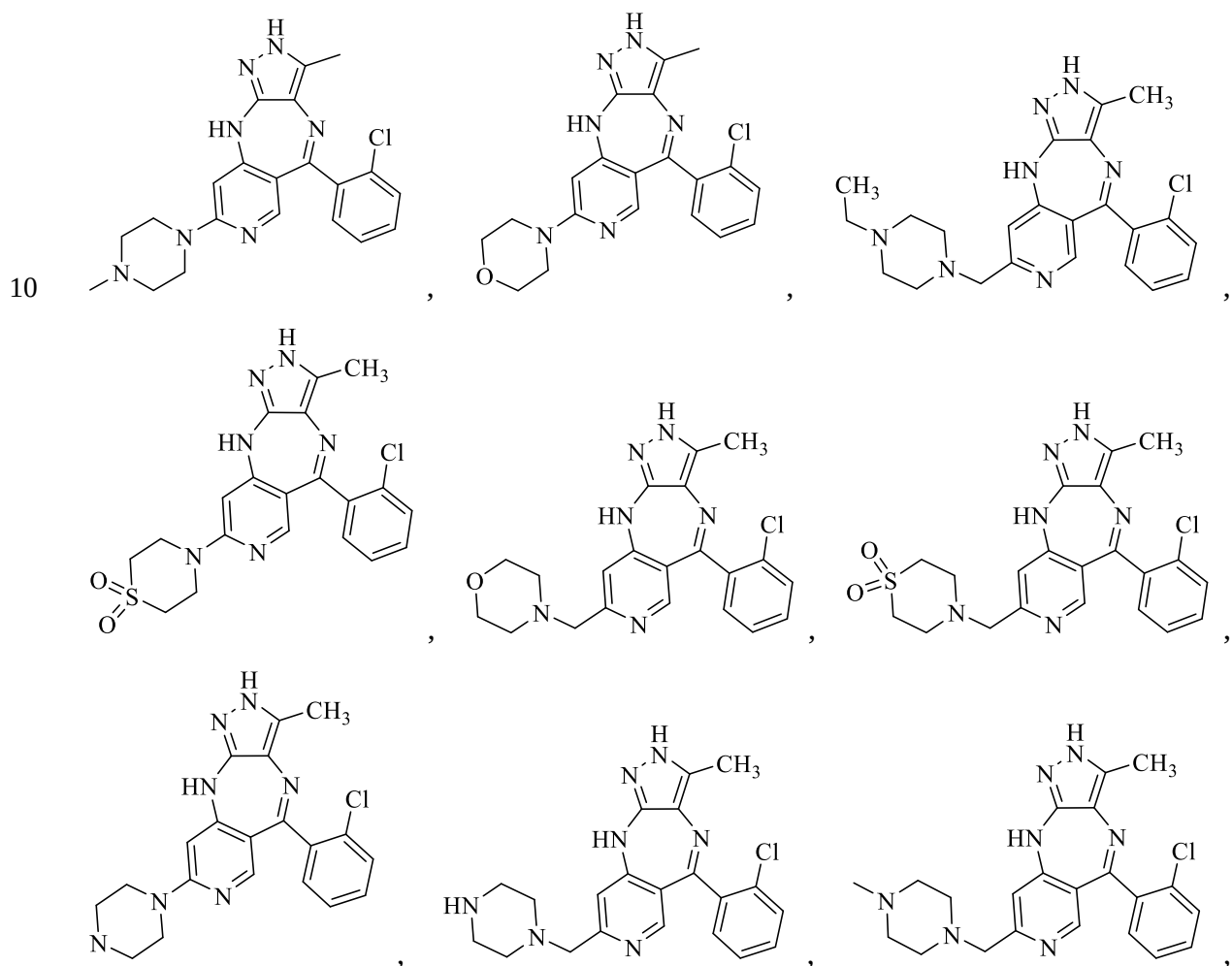
substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

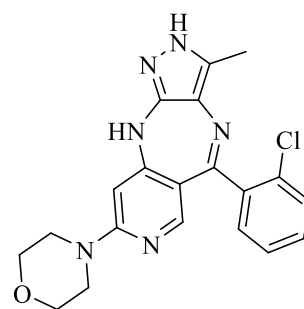
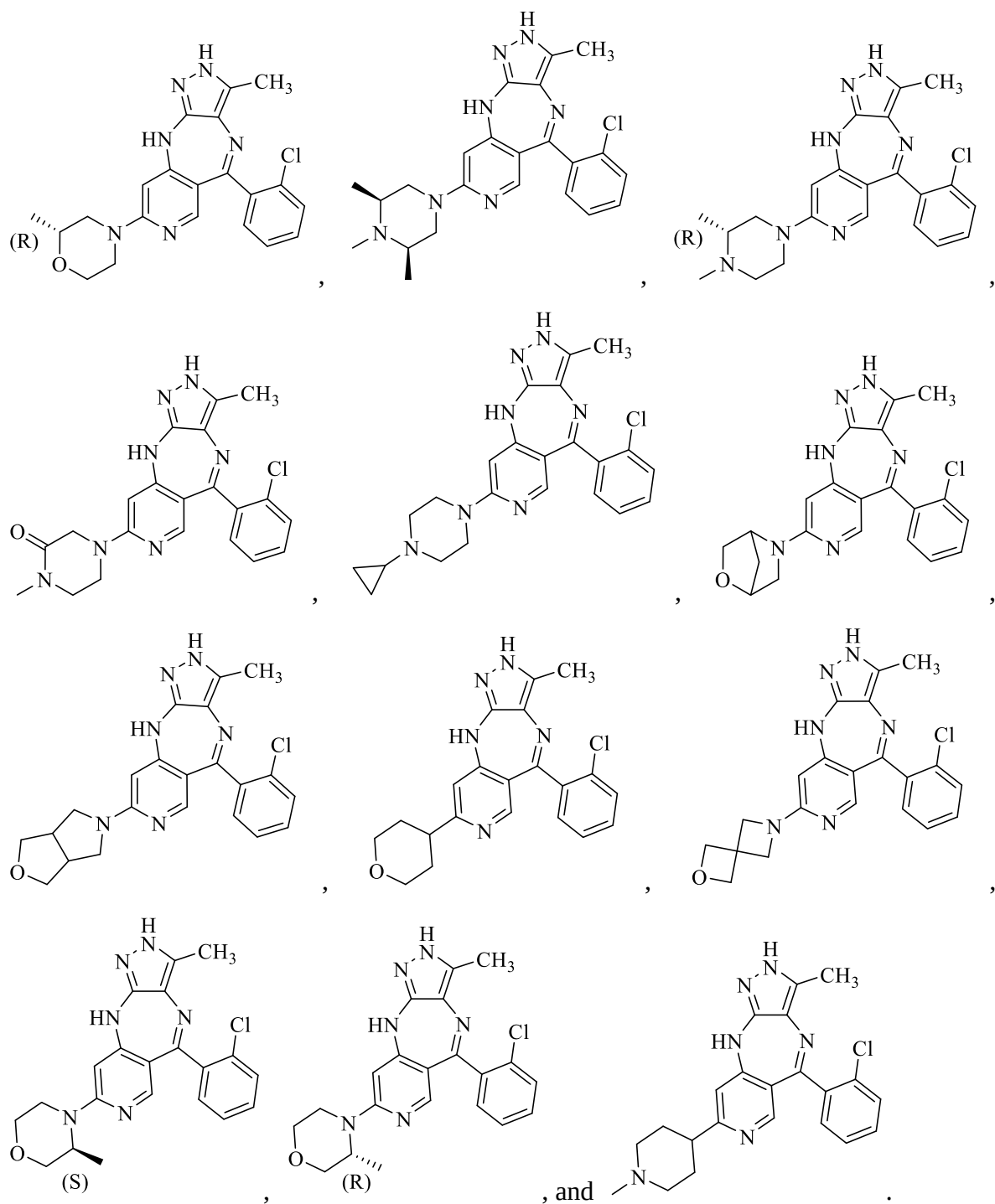
3. The use according to claim 2, wherein

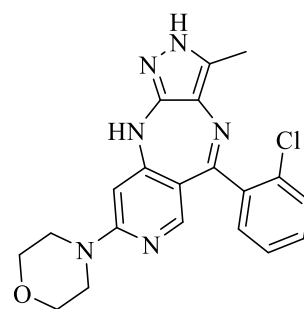


5 the heterocyclyl is optionally substituted with one to more substituents independently
selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

4. The use according to claim 3, wherein the compound is selected from compounds of the following structures, and a pharmaceutically acceptable salt, a stereoisomer and a crystal form thereof:





5 5. The use according to claim 4, wherein the compound is  or a pharmaceutically acceptable salt, a stereoisomer, and a crystal form thereof.

6. The use according to any one of claims 1 to 5, wherein the biliary tract cancer is cholangiocarcinoma, preferably an FGFR-mediated cholangiocarcinoma, and further preferably cholangiocarcinoma mediated by any one of FGFR1, FGFR2 and FGFR3 or any combination thereof.

5 7. The use according to claim 6, wherein the cholangiocarcinoma is a cholangiocarcinoma with non-FGFR aberration.

8. The use according to claim 6, wherein the cholangiocarcinoma is a cholangiocarcinoma with FGFR aberration, and preferably a cholangiocarcinoma with FGFR2 aberration and/or a cholangiocarcinoma with FGFR3 aberration.

10 9. The use according to claim 8, wherein the cholangiocarcinoma is cholangiocarcinoma with any one of FGFR fusion, FGFR mutation and FGFR overexpression or any combination thereof.

10. The use according to claim 9, wherein the cholangiocarcinoma is cholangiocarcinoma with any one of FGFR2 fusion, FGFR2 and/or FGFR3 mutation and
15 FGFR overexpression or any combination thereof.

11. The use according to claim 6, wherein the cholangiocarcinoma refers to drug-resistant cholangiocarcinoma that is positive for FGFR aberration but not responsive to an FGFR inhibitor, or drug-resistant cholangiocarcinoma after administration of an FGFR inhibitor.

20 12. The use according to claim 6, wherein the cholangiocarcinoma is any one of intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and distal cholangiocarcinoma or any combination thereof.

13. The use according to any one of claims 1 to 5, wherein the medicament for treating biliary tract cancer further comprises a pharmaceutically acceptable carrier in addition to
25 the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and a crystal form thereof.

14. The use according to any one of claims 1 to 5, wherein the medicament for treating biliary tract cancer further comprises one or more second therapeutically active agents in addition to the compound of general formula (I) or the pharmaceutically acceptable salt, the
30 stereoisomer and the crystal form thereof, wherein the one or more second therapeutically active agents are any one of an antimetabolite, a growth factor inhibitor, a mitotic inhibitor, an anti-tumor hormone, an alkylating agent, metallic platinum, a topoisomerase inhibitor, a hormonal agent, an immunomodulator, a tumor suppressor gene, a cancer vaccine and an

immune checkpoint inhibitor or any combination thereof.

15. The use according to claim 14, wherein the compound of general formula (I) or the pharmaceutically acceptable salt, the stereoisomer and the crystal form thereof and the second therapeutically active agents are administered to a patient or subject in need of treatment sequentially, simultaneously or in a combined formulation.

16. The use according to claim 15, wherein the patient or subject is a mammal.

17. The use according to claim 16, wherein the patient or subject is a human.