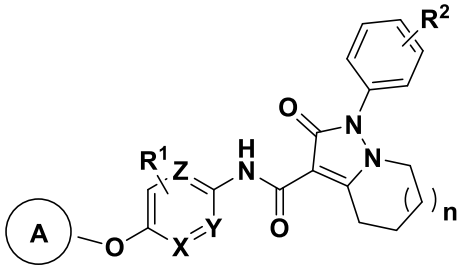
Claims

1. A fused-cyclic pyrazolone formamide compound having the structure of formula I, or its racemate, R-isomer, S-isomer, pharmaceutically acceptable salt or the mixture thereof:



I

wherein:

n is an integer of 0-2~~, preferably 0 or 1~~;

X, Y and Z are CH or N;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, deuterium, tritium, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 alkoxy, substituted or unsubstituted C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, cyano, nitro, amino, hydroxy, hydroxymethyl, carboxy, and $-O[(CH_2)_qO]_rR^3$; wherein the "substituted" refers to one or more hydrogen atoms on the group replaced by a substituent selected from the group consisting of halogen, C_1-C_6 alkyl, halogen-substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen-substituted C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkyl, halogen-substituted C_3-C_8 cycloalkyl, cyano, nitro, amino, hydroxyl, hydroxymethyl, carboxyl, mercapto, sulfonyl, C_6-C_{10} aryl and 3-12 membered heterocyclic group;

R^3 is selected from hydrogen, C_1-C_6 alkyl, halogen-substituted C_1-C_6 alkyl, and hydroxymethyl;

q is 1, 2, 3, or 4;

r is 0, 1, 2, 3 or 4;

or two R^1 and their adjacent carbon atoms together form a group selected from the group consisting of benzene ring, 5-8 membered heteroaromatic ring;

or two R^2 and their adjacent carbon atoms together form a group selected from the group consisting of benzene ring, 5-8 membered heteroaromatic ring;

Ⓐ ring is selected from the group consisting of substituted or unsubstituted 7-20 membered polycyclic heterocyclic ring, substituted or unsubstituted 7-20 membered polycyclic aromatic ring, substituted or unsubstituted 7-20 membered polycyclic aromatic heterocyclic ring, wherein the "substituted" refers to the hydrogen atom on the

group is replaced by 1, 2, 3 or 4 substituents selected from the group consisting of deuterium (D), tritium (T), halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 alkoxy, $-O[(CH_2)_qO]_rR^3$, $-NH[(CH_2)_qO]_rR^3$, $-NH(C=O)[(CH_2)_qO]_rR^3$, $-NH(SO_2)[(CH_2)_qO]_rR^3$, $-O(CH_2)_sAr$, substituted or unsubstituted C_3-C_8 cycloalkoxy, substituted or unsubstituted C_3-C_8 cycloalkylamino, substituted or unsubstituted C_3-C_8 epoxy alkyl, substituted or unsubstituted C_3-C_8 cycloaminoalkyl, cyano, nitro, amino, ~~amino (preferably~~ C_1-C_6 amino~~)~~, hydroxyl, hydroxymethyl, carboxyl, C_6-C_{10} aryl, C_6-C_{10} aryloxy, substituted or unsubstituted 3-12 membered heterocyclic group, substituted or unsubstituted 3-12 membered heterocyclyloxy and substituted or unsubstituted 3-12 membered heterocyclylamino; wherein, the aromatic heterocyclic group, heterocyclic group each independently contains 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen; or two adjacent substituents and their adjacent carbon atoms together form a structure selected from substituted or unsubstituted 6-20 membered heterocyclic ring, while the heterocyclic ring may optionally include 1, 2, 3 or 4 heteroatoms selected from N, O or S;

s is selected from the group consisting of 0, 1, 2, 3 and 4;

Ar is selected from the group consisting of substituted or unsubstituted C_6-C_{12} aryl, substituted or unsubstituted 5-12 membered heteroaryl;

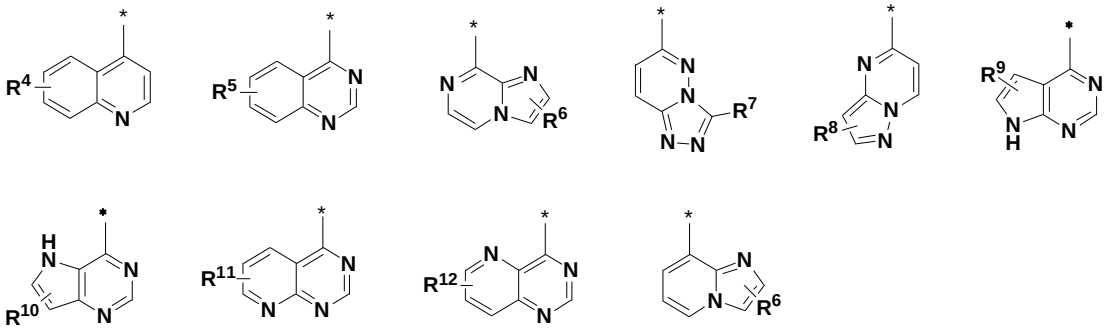
unless otherwise specified, the "substituted" refers to one or more hydrogen atoms on the group replaced by a substituent selected from the group consisting of halogen, C_1-C_6 alkyl, halogen-substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, halogen-substituted C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, cyano, nitro, amino, hydroxyl, hydroxymethyl, carboxyl.

2. The fused-cyclic pyrazolone formamide compound of formula I of claim 1, or its racemate, R-isomer, S-isomer, pharmaceutically acceptable salt or mixture thereof, wherein n is 0 or 1.

~~2~~3. The fused-cyclic pyrazolone formamide compound of formula I of claim 1, or its racemate, R-isomer, S-isomer, pharmaceutically acceptable salt or mixture thereof, wherein, R^1 and R^2 are each independently selected from group consisting of hydrogen, deuterium, tritium, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 alkoxy, cyano, hydroxyl, carboxyl; wherein, the "substituted" refers to one or more hydrogen atoms replaced by a substituent selected from group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, cyano, amino, hydroxyl, hydroxymethyl, carboxyl; or two R^1 and their adjacent carbon atoms together form a group selected from group consisting of benzene ring, 5-8 membered heteroaromatic ring.

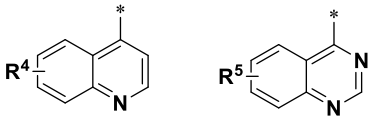
~~3~~4. The fused-cyclic pyrazolone formamide compound of formula I of claim 1, or its racemate, R-isomer, S-isomer, pharmaceutically acceptable salt or mixture thereof,

wherein the Ⓐ ring is selected from the group consisting of:



wherein, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} are 1-4 substituents selected from group consisting of H, D, T, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 alkoxy, $-O[(CH_2)_qO]_rR^3$, $-NH[(CH_2)_qO]_rR^3$, $-NH(C=O)[(CH_2)_qO]_rR^3$, $-NH(SO_2)[(CH_2)_qO]_rR^3$, $-O(CH_2)_sAr$, substituted or unsubstituted C_3-C_8 cycloalkoxy, substituted or unsubstituted C_3-C_8 cycloalkylamino, substituted or unsubstituted C_3-C_8 epoxy alkyl, substituted or unsubstituted C_3-C_8 cycloamine alkyl, cyano, nitro, amino, ~~amino (preferably~~ C_1-C_6 amino~~)~~, hydroxyl, hydroxymethyl, carboxy, C_6-C_{10} aryl, C_6-C_{10} aryloxy , substituted or unsubstituted 3-12 membered heterocyclic group, substituted or unsubstituted 3-12 membered heterocyclyloxy and substituted or unsubstituted 3-12 membered heterocyclic amino; or two adjacent groups mentioned above and their connected atoms t may together form a structure selected from substituted or unsubstituted 6-20 membered heterocycle, wherein the heterocycle may optionally include 1, 2, 3 or 4 heteroatoms selected from N, O or S.

~~4~~5. The fused-cyclic pyrazolone formamide compound of formula I of claim ~~2~~3, or its racemate, R-isomer, S-isomer, pharmaceutically acceptable salt or mixture thereof, wherein the Ⓐ ring is selected from the group consisting of:



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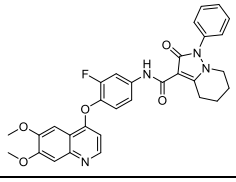
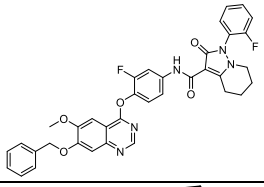
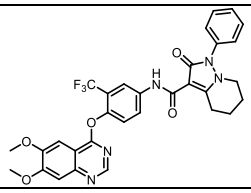
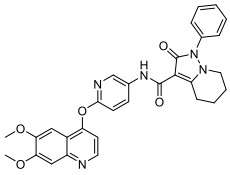
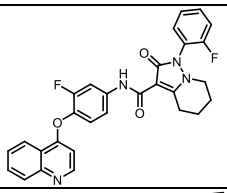
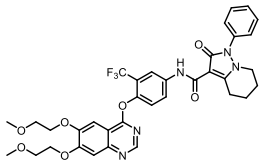
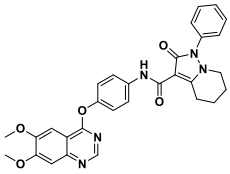
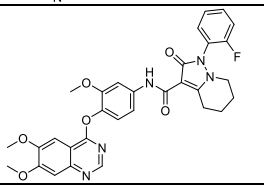
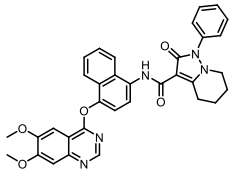
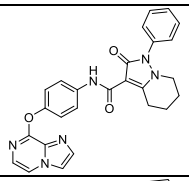
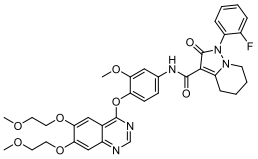
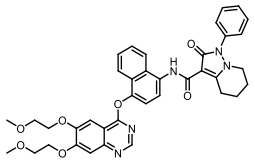
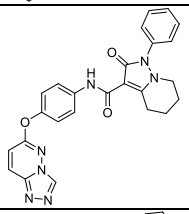
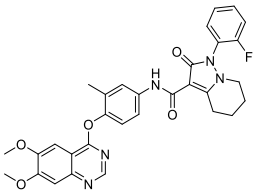
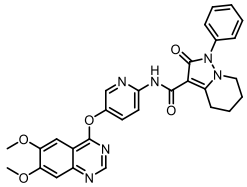
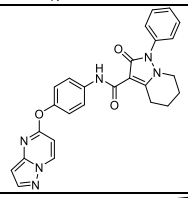
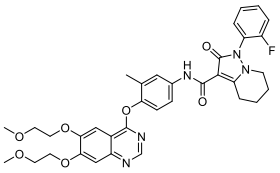
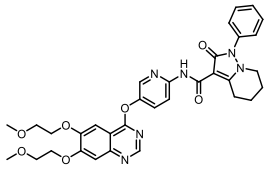
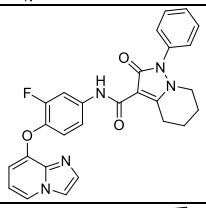
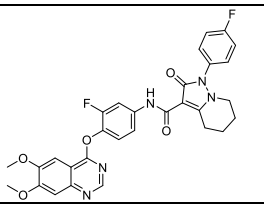
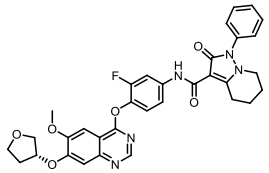
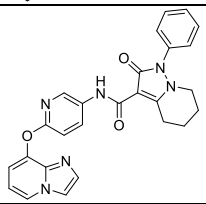
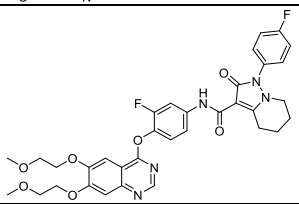
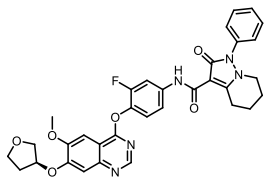
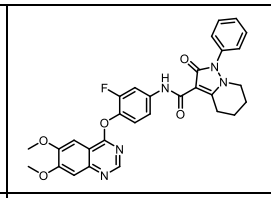
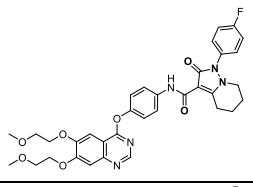
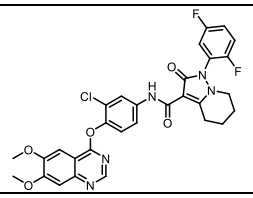
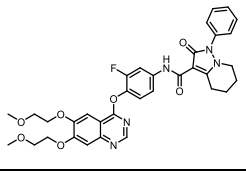
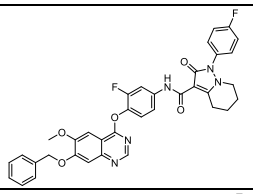
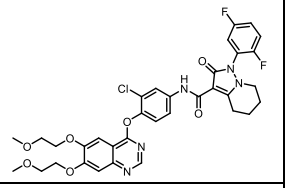
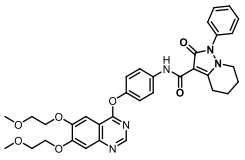
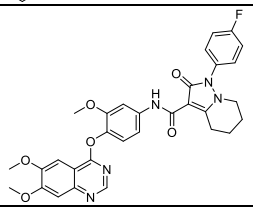
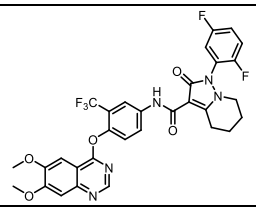
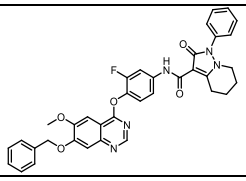
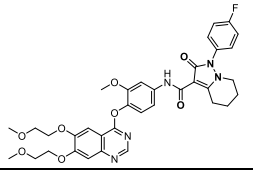
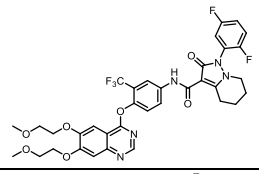
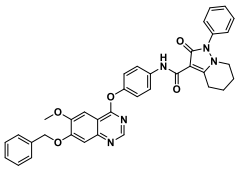
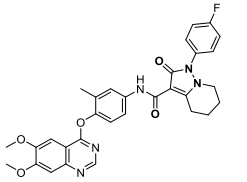
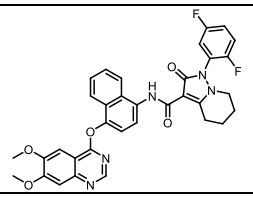
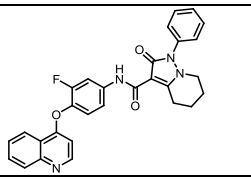
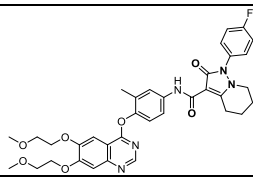
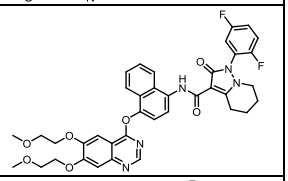
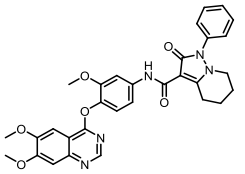
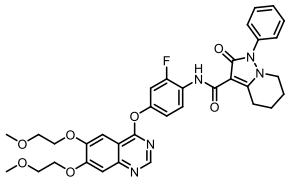
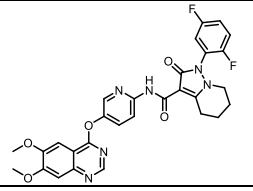
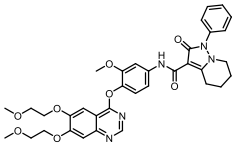
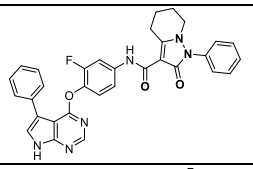
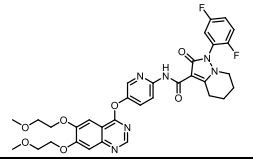
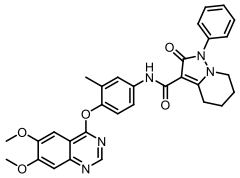
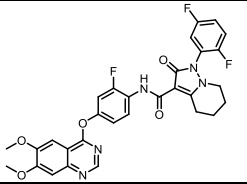
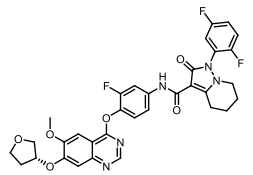
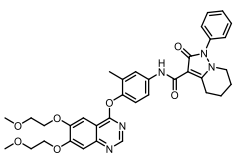
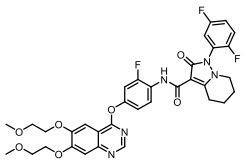
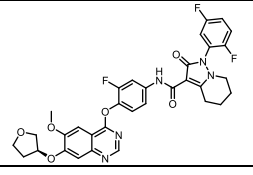
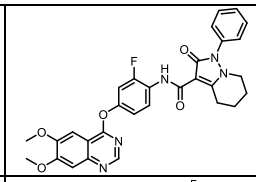
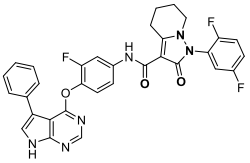
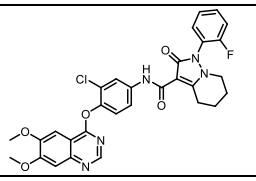
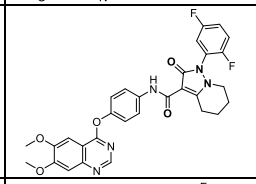
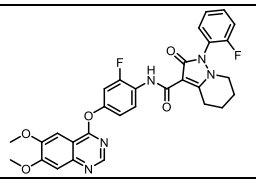
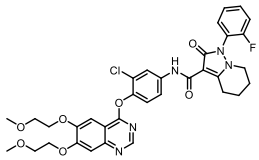
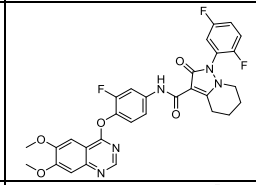
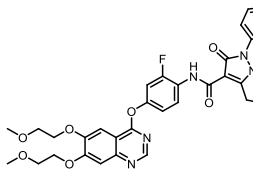
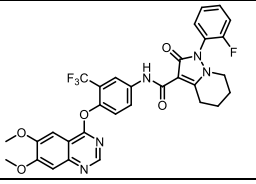
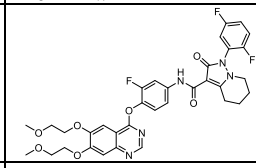
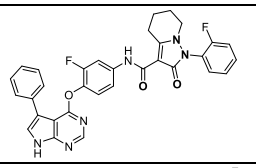
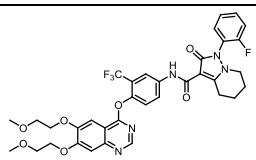
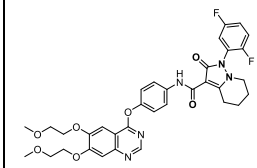
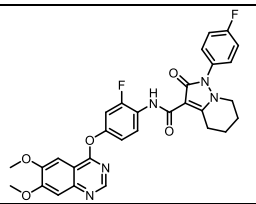
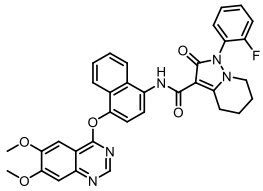
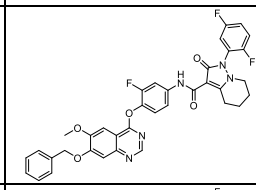
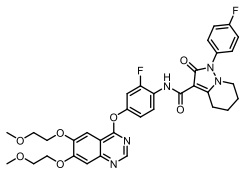
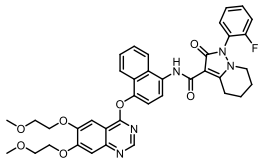
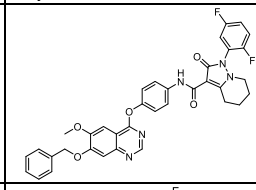
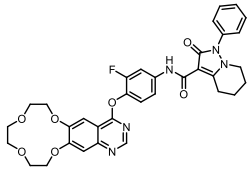
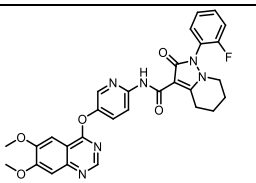
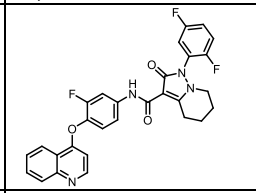
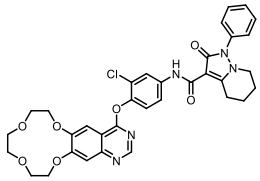
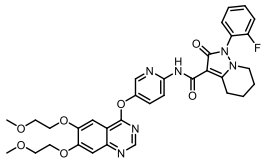
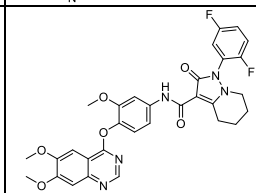
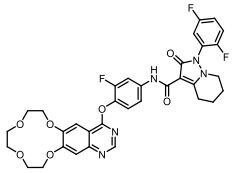
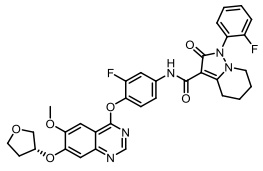
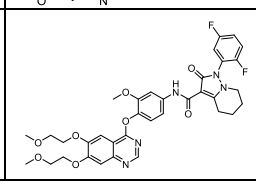
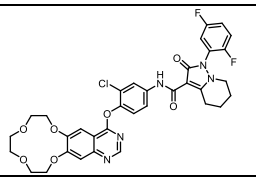
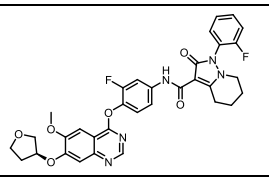
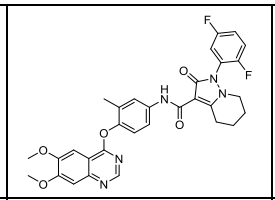
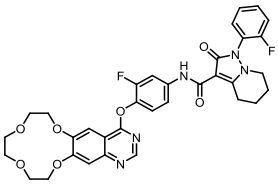
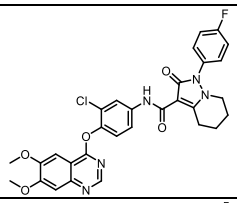
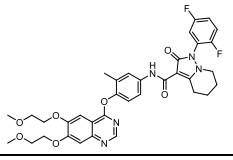
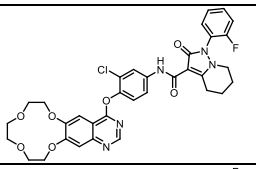
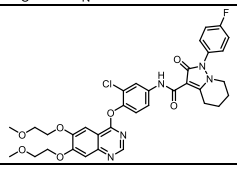
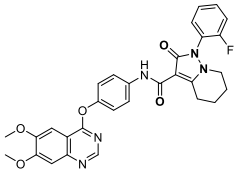
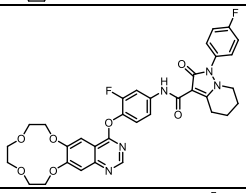
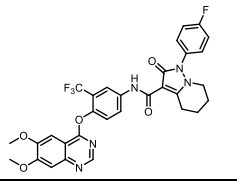
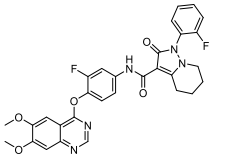
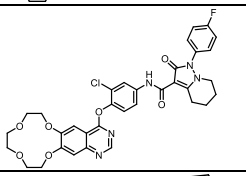
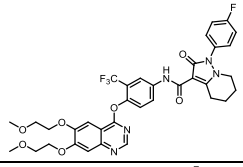
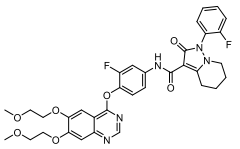
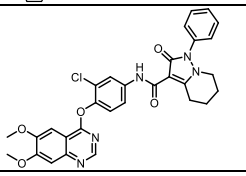
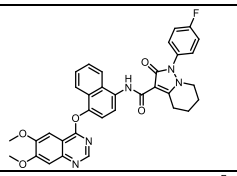
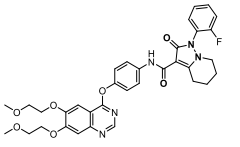
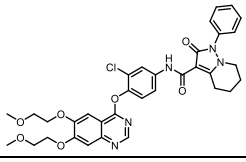
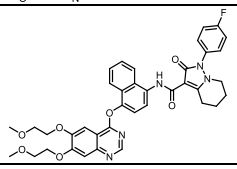
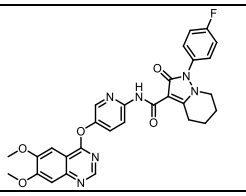
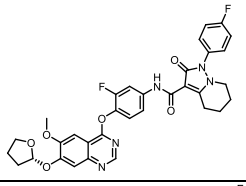
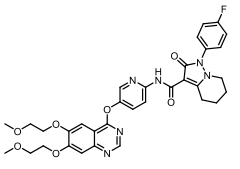
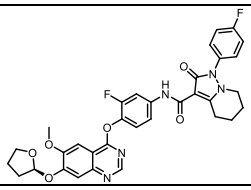
~~5~~6. The fused-cyclic pyrazolone formamide compound of formula I of claim ~~4~~5, or its racemate, R-isomer, S-isomer, pharmaceutically acceptable salt or mixture thereof, wherein R^4 and R^5 are respectively 1-4 substituents selected from the group consisting of substituted or unsubstituted C_1-C_6 alkoxy, $-O[(CH_2)_qO]_rR^3$, $-NH[(CH_2)_qO]_rR^3$, $-NH(C=O)[(CH_2)_qO]_rR^3$, $-NH(SO_2)[(CH_2)_qO]_rR^3$, $-O(CH_2)_sAr$, substituted or unsubstituted 3-12 membered heterocyclyloxy and substituted or unsubstituted 3-12 membered heterocyclylamino; or two adjacent groups and their connected atoms together form a structure selected from substituted or unsubstituted 6-20 membered heterocycle, wherein the heterocycle may optionally include 1, 2, 3, or 4 heteroatoms selected from N, O or S.

~~6~~7. The fused-cyclic pyrazolone formamide compound of formula I of claim 1, or its racemate, R-isomer, S-isomer, pharmaceutically acceptable salt or mixture thereof, wherein the fused cyclic pyrazolone carboxamide compound is selected from the group consisting of:

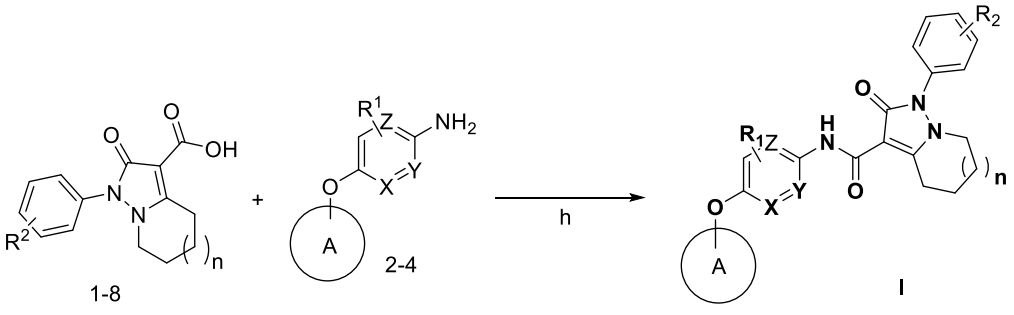
No.	Structure	No.	Structure	No.	Structure
DC621 001		DC621 037		DC621 071	
DC621 002		DC621 038		DC621 072	
DC621 004		DC621 039		DC621 073	
DC621 006		DC621 040		DC621 074	
DC621 007		DC621 041		DC621 075	
DC621 008		DC621 042		DC621 076	
DC621 009		DC621 043		DC621 077	
DC621 010		DC621 044		DC621 078	

DC621011		DC621045		DC621079	
DC621012		DC621046		DC621080	
DC621013		DC621047		DC621081	
DC621014		DC621048		DC621082	
DC621015		DC621049		DC621083	
DC621016		DC621050		DC621084	
DC621017		DC621051		DC621085	
DC621018		DC621052		DC621086	
DC621019		DC621053		DC621087	
DC621020		DC621054		DC621088	

DC621021		DC621055		DC621089	
DC621022		DC621056		DC621090	
DC621023		DC621057		DC621091	
DC621024		DC621058		DC621092	
DC621025		DC621059		DC621093	
DC621026		DC621060		DC621094	
DC621027		DC621061		DC621095	
DC621028		DC621062		DC621096	
DC621029		DC621063		DC621097	
DC621030		DC621064		DC621098	

DC621031		DC621065		DC621099	
DC621032		DC621066		DC621100	
DC621033		DC621067		DC621101	
DC621034		DC621068		DC621102	
DC621035		DC621069		DC621103	
DC621036		DC621070		DC621104	
DC621105		DC621107			
DC621106		DC621108			.

78. A preparation method of compound of claim 1, wherein comprises the following steps:



in an inert solvent, reacting formula 1-8 compound and formula 2-4 compound to provide formula I compound.

~~8~~9. A pharmaceutical composition, wherein the pharmaceutical composition comprises: a therapeutically effective amount of formula I compound of claim 1, or the pharmaceutically acceptable salt, racemate, R-isomer, S-isomer thereof or the mixture thereof, and optional pharmaceutically acceptable carriers, excipients, adjuvants, accessories, and/or diluting agent.

~~9~~10. A kinase inhibitor which comprises: therapeutically effective amount of one or more of formula I compound of claim 1, or the pharmaceutically acceptable salt, racemate, R-isomer, S-isomer thereof or the mixture thereof; and optional pharmaceutically acceptable carriers, excipients, adjuvants, accessories, and/or diluting agent; and the kinase is selected from the group consisting of AXL, c-Met, or combination thereof.

~~10~~11. The use of the compound of formula I of claim 1~~, wherein one or more uses selected from the group consisting of: (i) treating or preventing diseases related to kinase activity or expression; (ii) inhibiting the activity of kinase, or reducing the expression of kinase; (iii)~~ in preparing pharmaceutical composition for treating or preventing diseases related to kinase activity~~;~~, or ~~(iv)~~ preparing kinase inhibitor;

wherein the kinase is selected from the group consisting of AXL, c-Met, or combination thereof; and the disease is selected from the group consisting of lung cancer, stomach cancer, liver cancer, kidney cancer, breast cancer, pancreatic cancer, colorectal cancer, ovarian cancer, prostate cancer, thyroid cancer, esophageal cancer, head and neck cancer, melanoma, glioma, acute myeloid leukemia.