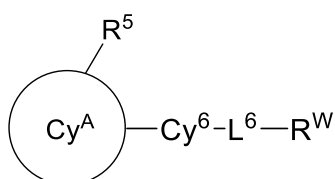


duration of responses suggest they were limited by toxicities. Thus, there is a need for FGFR2-selective inhibitor compounds and methods for treating cancers and other disorders with these compounds. (For reviews of pan-FGFR1-3 inhibitors and clinical responses, see I. S. Babina and N.C. Turner, *Nat. Rev. Cancer* 2017, 17:318-332; M. Katoh, *Nat. Rev. Clin. Oncol.* 2019, 16:105-122; and references cited therein.).

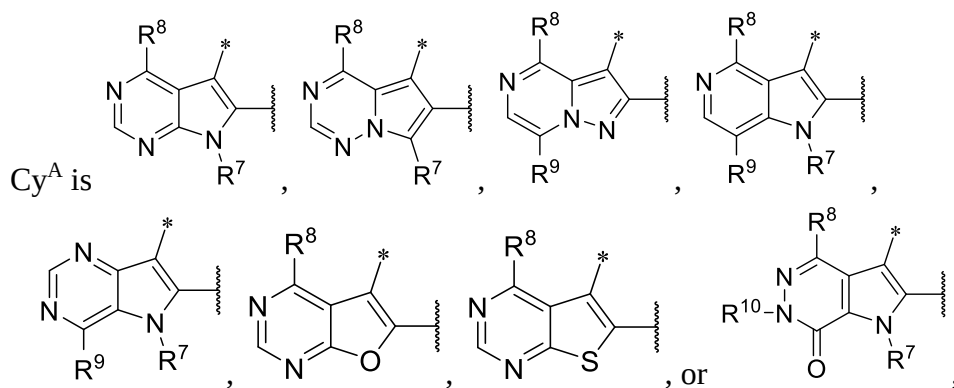
SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a compound of formula I-1:



I-1

or a pharmaceutically acceptable salt thereof, wherein:

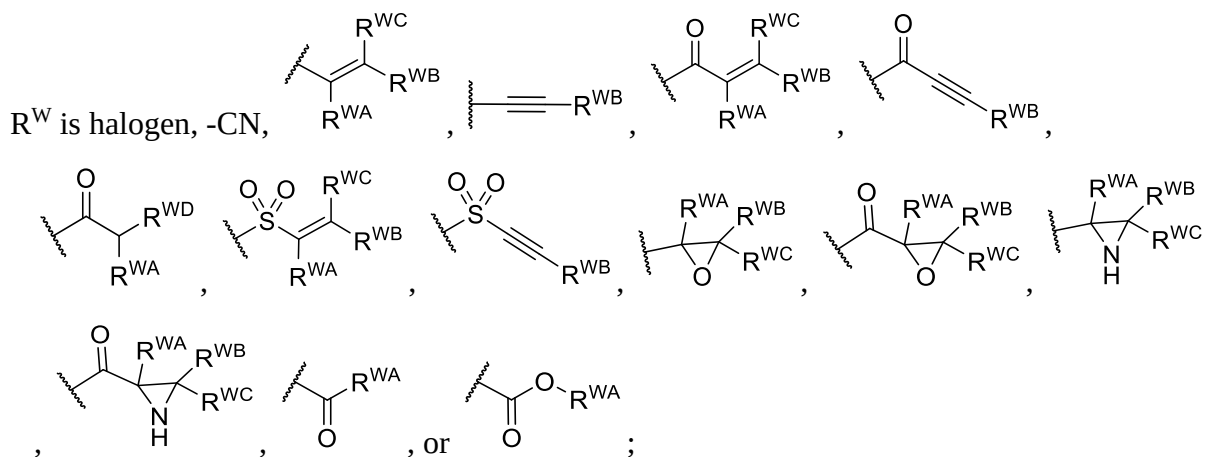


wherein represents a bond to R⁵ and represents a bond to Cy⁶;
R⁵ is -R^{5A}-L⁵-R^{5B};

R^{5A} is a bivalent radical of R^B, wherein R^{5A} is substituted with m instances of R^{5C} in addition to -L⁵-R^{5B};

R^{5B} is hydrogen or R^B, wherein R^{5B} is substituted with n instances of R^{5D};

Cy⁶ is phenylene; a bivalent saturated or partially unsaturated 3-14 membered carbocyclic ring; a bivalent saturated or partially unsaturated 3-14 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-14 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein Cy⁶ is substituted with p instances of R⁶ in addition to -L⁶-R^W;



or

two instances of R⁶, an instance of R⁶ and an instance of R^L, an instance of R⁶ and an instance of R^{WA}, or an instance of R⁶ and an instance of R^{7a} are taken together with their intervening atoms to form a 4-8 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with r instances of R^C;

R⁷ is H or R^B, wherein R⁷ is substituted with t instances of R^{7A};

R⁸ is H, -NR₂, halogen, -OH, or C₁₋₆ aliphatic optionally substituted with 1-3 halogens;

R⁹ is H, -NR₂, halogen, or C₁₋₆ aliphatic optionally substituted with 1-3 halogens;

R¹⁰ is H or C₁₋₆ aliphatic optionally substituted with 1-3 halogens;

each of L⁵ and L⁶ is independently a covalent bond, or a C₁₋₄ bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -CH(R^L)-, -C(R^L)₂-, C₃₋₆ cycloalkylene, 3-6 membered heterocycloalkylene, 5-6 membered heteroarylene, -NH-, -N(R^L)-, -NHC(O)-, -N(R^L)C(O)-, -C(O)NH-, -C(O)N(R^L)-, -NHS(O)₂-, -N(R^L)S(O)₂-, -S(O)₂NH-, -S(O)₂N(R^L)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)-, or -S(O)₂-; wherein each of said C₃₋₆ cycloalkylene, 3-6 membered heterocycloalkylene, and 5-6 membered heteroarylene is optionally substituted with one instance of R^A or C₁₋₆ aliphatic;

each of R^{WA}, R^{WB}, and R^{WC} is independently hydrogen, deuterium, halogen, -CN, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^{WA} and R^{WB} , R^{WB} and R^{WC} , R^{WA} and an instance of R^L , or R^{WC} and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with w instances of R^C ;

R^{WD} is halogen or $-OS(O)_2R$;

each instance of R^{5C} , R^{5D} , R^{7A} , and R^L is independently R^A or R^B , and is substituted by u instances of R^C ; or

two instances of R^{5C} , one instance of R^{5C} and one instance of R^{5D} , or two instances of R^{5D} are taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with v instances of R^C ;

each instance of R^A is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $-N(R)S(O)_2R$;

each instance of R^B is independently C_{1-6} aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^C is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-S(O)_2F$, $-OS(O)_2F$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

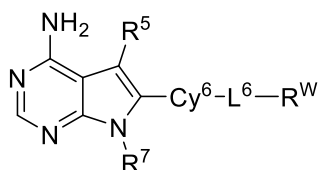
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6

membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each of m, n, p, q, r, t, u, v, and w is independently 0, 1, 2, 3, or 4.

[0003b] In another aspect of the present disclosure, there is provided a compound of formula I:



I

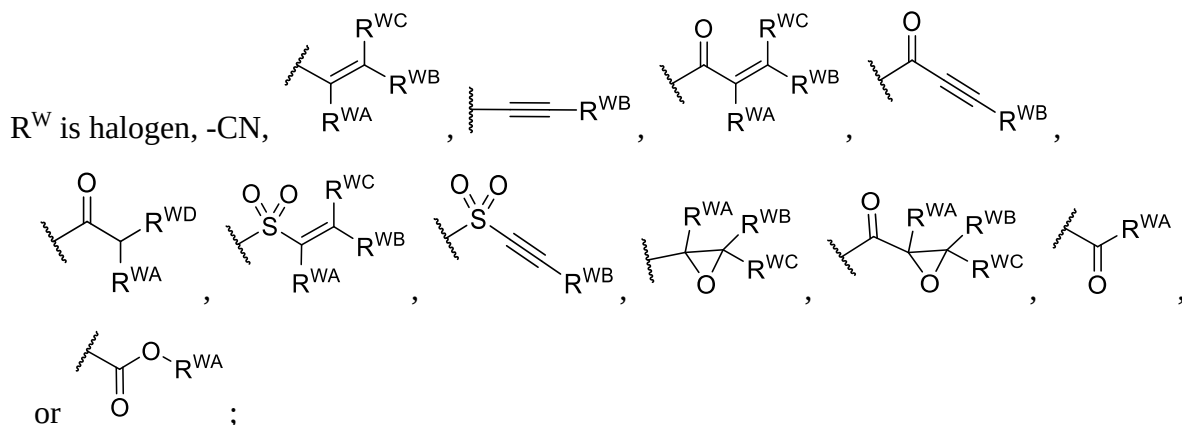
or a pharmaceutically acceptable salt thereof, wherein:

R^5 is $-R^{5A}-L^5-R^{5B}$;

R^{5A} is a bivalent radical of R^B , wherein R^{5A} is substituted with m instances of R^{5C} in addition to $-L^5-R^{5B}$;

R^{5B} is hydrogen or R^B , wherein R^{5B} is substituted with n instances of R^{5D} ;

Cy^6 is phenylene or a 6-membered heteroarylene having 1-3 nitrogen atoms, wherein Cy^6 is substituted with p instances of R^6 in addition to $-L^6-R^W$;



each instance of R^6 is independently R^A or R^B , wherein R^6 is substituted by q instances of R^C ;

or

two instances of R^6 , or an instance of R^6 and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with r instances of R^C ;

R^7 is H or R^B , wherein R^7 is substituted with t instances of R^{7A} ;

each of L^5 and L^6 is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-5} cycloalkylene, 3-5 membered heterocycloalkylene, 5-6 membered heteroarylene, $-NH-$, $-N(R^L)-$, $-NHC(O)-$, $-N(R^L)C(O)-$, $-C(O)NH-$, $-C(O)N(R^L)-$, $-NHS(O)_2-$, $-N(R^L)S(O)_2-$, $-S(O)_2NH-$, $-S(O)_2N(R^L)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

each of R^{WA} , R^{WB} , and R^{WC} is independently hydrogen, halogen, $-CN$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^{WA} and R^{WB} , R^{WB} and R^{WC} , R^{WA} and an instance of R^L , or R^{WC} and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{WD} is halogen or $-OS(O)_2R$;

each instance of R^{5C} , R^{5D} , R^{7A} , and R^L is independently R^A or R^B , and is substituted by u instances of R^C ;

each instance of R^A is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $-N(R)S(O)_2R$;

each instance of R^B is independently C_{1-6} aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

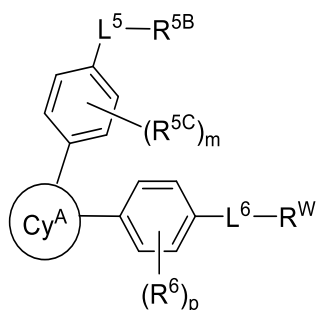
each instance of R^C is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-S(O)_2F$, $-OS(O)_2F$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$,

-C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

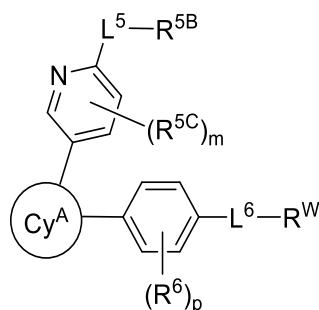
each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and each of m, n, p, q, r, t, and u is independently 0, 1, 2, 3, or 4.

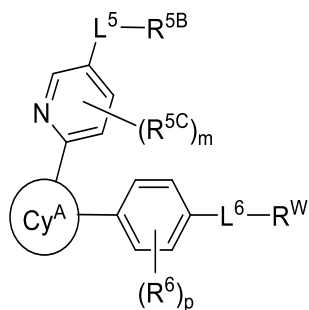
[0003c] In a further aspect of the present disclosure, there is provided a compound of formula X-1, XI-1, XII-1, or XIII-1:



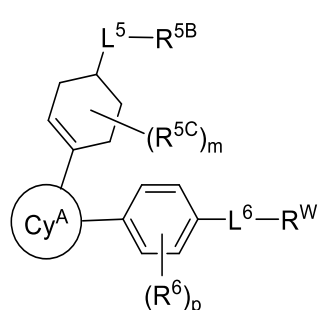
X-1



XI-1



XII-1



XIII-1

or a pharmaceutically acceptable salt thereof, wherein:

each of L^5 and L^6 is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-5} cycloalkylene, 3-5 membered heterocycloalkylene, 5-6 membered heteroarylene, $-NH-$, $-N(R^L)-$, $-NHC(O)-$, $-N(R^L)C(O)-$, $-C(O)NH-$, $-C(O)N(R^L)-$, $-NHS(O)_2-$, $-N(R^L)S(O)_2-$, $-S(O)_2NH-$, $-S(O)_2N(R^L)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

each of R^{WA} , R^{WB} , and R^{WC} is independently hydrogen, deuterium, halogen, $-CN$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^{WA} and R^{WB} , R^{WB} and R^{WC} , R^{WA} and an instance of R^L , or R^{WC} and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{WD} is halogen or $-OS(O)_2R$;

each instance of R^{5C} , R^{5D} , R^{7A} , and R^L is independently R^A or R^B , and is substituted by u instances of R^C ;

each instance of R^A is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $-N(R)S(O)_2R$;

each instance of R^B is independently C_{1-6} aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^C is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-S(O)_2F$, $-OS(O)_2F$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$,

$-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and each of m, n, p, q, r, t, and u is independently 0, 1, 2, 3, or 4.

[0003d] In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound disclosed herein, and a pharmaceutically acceptable carrier.

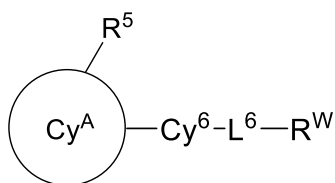
[0003e] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or the pharmaceutical composition disclosed herein, for use in therapy.

[0003f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting FGFR2 signaling activity in a subject.

[0003g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating an FGFR2-mediated disorder in a subject.

[0003h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disorder in a subject, wherein the disorder is bile duct cancer, liver cancer, breast cancer, prostate cancer, lung cancer, thyroid cancer, gastric cancer, ovarian cancer, rectal cancer, endometrial cancer, or urothelial cancer.

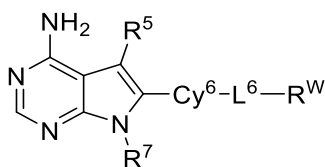
[0004] In some examples, the present disclosure provides a compound of formula I-1:



I-1

or a pharmaceutically acceptable salt thereof, wherein each of Cy^A , Cy^6 , L^6 , R^5 , and R^W is as defined in examples and classes and subclasses herein.

[0005] In some examples, the present disclosure provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein each of Cy^6 , L^6 , R^5 , R^7 , and R^W is as defined in examples and classes and subclasses herein.

[0006] In some examples, the present disclosure provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent. In some examples, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, for example, a compound of formula I-1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

[0007] In some examples, the present disclosure provides a method of treating a FGFR-mediated disorder comprising administering to a patient in need thereof a compound of formula I, or composition comprising said compound. In some examples, the present

disclosure provides a method of treating a FGFR-mediated disorder comprising administering to a patient in need thereof a compound of the present disclosure, for example, a compound of formula I-1, or composition comprising said compound.

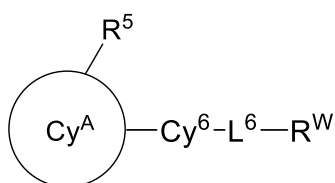
[0008] In some examples, the present disclosure provides a process for providing a compound of formula I, or synthetic intermediates thereof. In some examples, the present disclosure provides a process for providing a compound of the present disclosure, for example, a compound of formula I-1, or synthetic intermediates thereof.

[0009] In some examples, the present disclosure provides a process for providing pharmaceutical compositions comprising compounds of formula I. In some examples, the present disclosure provides a process for providing pharmaceutical compositions comprising compounds of the present disclosure, for example, a compound of formula I-1.

DETAILED DESCRIPTION

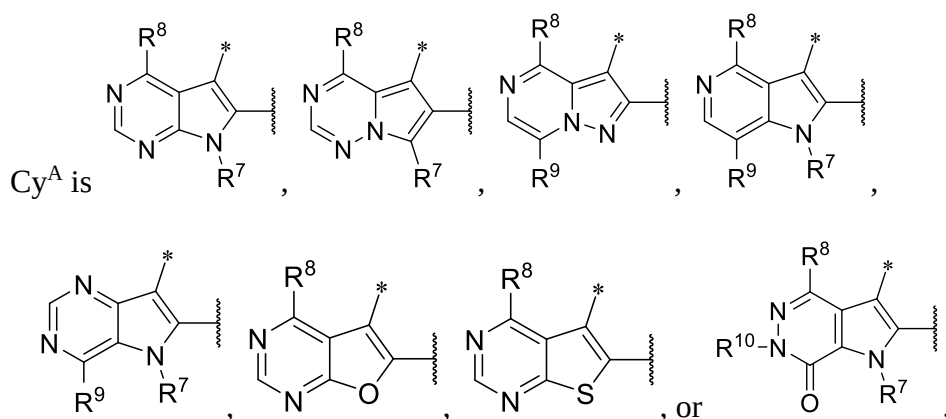
1. General Description of Certain Embodiments of the Invention

[0010] Compounds of the present invention, and pharmaceutical compositions thereof, are useful as inhibitors of FGFR2. In some embodiments, the present invention provides a compound of formula I-1:



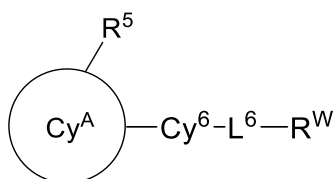
I-1

or a pharmaceutically acceptable salt thereof, wherein:



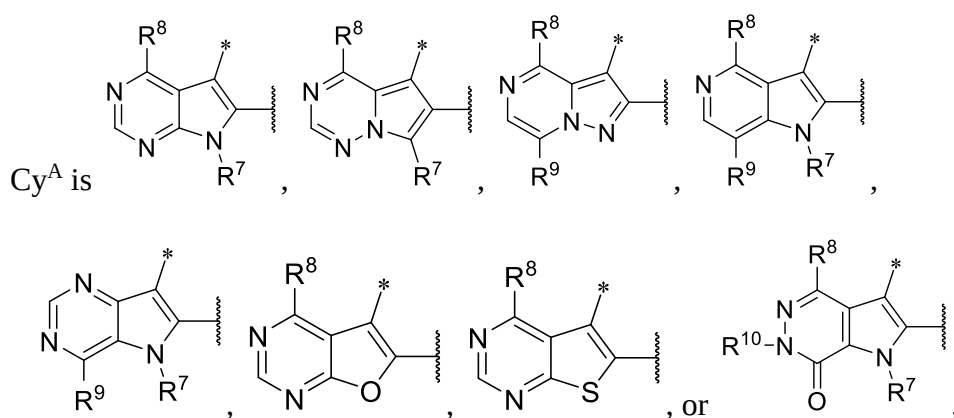
What is claimed is:

1. A compound of formula I-1:



I-1

or a pharmaceutically acceptable salt thereof, wherein:



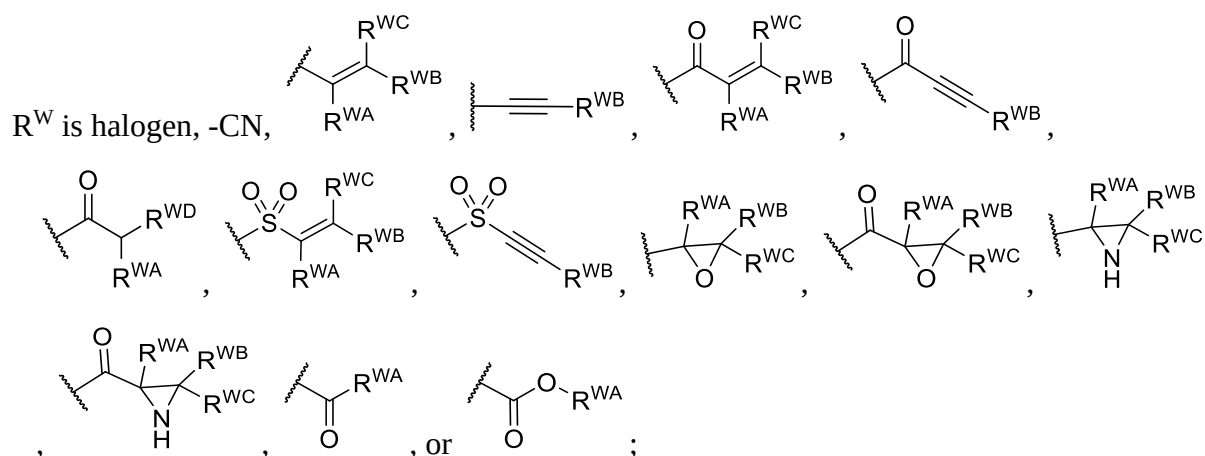
wherein represents a bond to R⁵ and represents a bond to Cy⁶;

R⁵ is -R^{5A}-L⁵-R^{5B};

R^{5A} is a bivalent radical of R^B, wherein R^{5A} is substituted with m instances of R^{5C} in addition to -L⁵-R^{5B};

R^{5B} is hydrogen or R^B, wherein R^{5B} is substituted with n instances of R^{5D};

Cy⁶ is phenylene; a bivalent saturated or partially unsaturated 3-14 membered carbocyclic ring; a bivalent saturated or partially unsaturated 3-14 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 5-14 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein Cy⁶ is substituted with p instances of R⁶ in addition to -L⁶-R^W;



each instance of R^6 is independently R^A or R^B , wherein R^6 is substituted by q instances of R^C ;
 or

two instances of R^6 , an instance of R^6 and an instance of R^L , an instance of R^6 and an instance of R^{WA} , or an instance of R^6 and an instance of R^{7a} are taken together with their intervening atoms to form a 4-8 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with r instances of R^C ;

R^7 is H or R^B , wherein R^7 is substituted with t instances of R^{7A} ;

R^8 is H, $-NR_2$, halogen, $-OH$, or C_{1-6} aliphatic optionally substituted with 1-3 halogens;

R^9 is H, $-NR_2$, halogen, or C_{1-6} aliphatic optionally substituted with 1-3 halogens;

R^{10} is H or C_{1-6} aliphatic optionally substituted with 1-3 halogens;

each of L^5 and L^6 is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, 3-6 membered heterocycloalkylene, 5-6 membered heteroarylene, $-NH-$, $-N(R^L)-$, $-NHC(O)-$, $-N(R^L)C(O)-$, $-C(O)NH-$, $-C(O)N(R^L)-$, $-NHS(O)_2-$, $-N(R^L)S(O)_2-$, $-S(O)_2NH-$, $-S(O)_2N(R^L)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$; wherein each of said C_{3-6} cycloalkylene, 3-6 membered heterocycloalkylene, and 5-6 membered heteroarylene is optionally substituted with one instance of R^A or C_{1-6} aliphatic;

each of R^{WA} , R^{WB} , and R^{WC} is independently hydrogen, deuterium, halogen, $-CN$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6

membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^{WA} and R^{WB} , R^{WB} and R^{WC} , R^{WA} and an instance of R^L , or R^{WC} and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with w instances of R^C ;

R^{WD} is halogen or $-OS(O)_2R$;

each instance of R^{5C} , R^{5D} , R^{7A} , and R^L is independently R^A or R^B , and is substituted by u instances of R^C ; or

two instances of R^{5C} , one instance of R^{5C} and one instance of R^{5D} , or two instances of R^{5D} are taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with v instances of R^C ;

each instance of R^A is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $-N(R)S(O)_2R$;

each instance of R^B is independently C_{1-6} aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

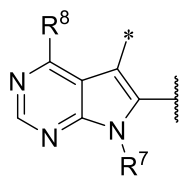
each instance of R^C is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-S(O)_2F$, $-OS(O)_2F$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen,

and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

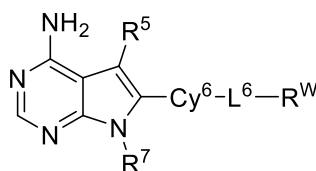
two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each of m, n, p, q, r, t, u, v, and w is independently 0, 1, 2, 3, or 4.



2. The compound of claim 1, wherein Cy^A is

3. A compound of formula I:



I

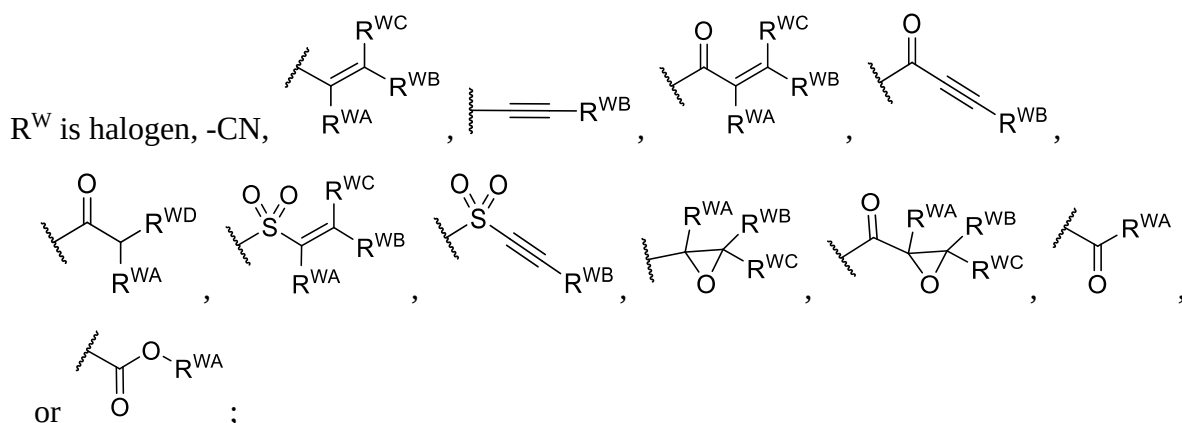
or a pharmaceutically acceptable salt thereof, wherein:

R⁵ is -R^{5A}-L⁵-R^{5B};

R^{5A} is a bivalent radical of R^B, wherein R^{5A} is substituted with m instances of R^{5C} in addition to -L⁵-R^{5B};

R^{5B} is hydrogen or R^B, wherein R^{5B} is substituted with n instances of R^{5D};

Cy⁶ is phenylene or a 6-membered heteroarylene having 1-3 nitrogen atoms, wherein Cy⁶ is substituted with p instances of R⁶ in addition to -L⁶-R^W;



each instance of R^6 is independently R^A or R^B , wherein R^6 is substituted by q instances of R^C ;
 or

two instances of R^6 , or an instance of R^6 and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with r instances of R^C ;

R^7 is H or R^B , wherein R^7 is substituted with t instances of R^{7A} ;

each of L^5 and L^6 is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-5} cycloalkylene, 3-5 membered heterocycloalkylene, 5-6 membered heteroarylene, $-NH-$, $-N(R^L)-$, $-NHC(O)-$, $-N(R^L)C(O)-$, $-C(O)NH-$, $-C(O)N(R^L)-$, $-NHS(O)_2-$, $-N(R^L)S(O)_2-$, $-S(O)_2NH-$, $-S(O)_2N(R^L)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

each of R^{WA} , R^{WB} , and R^{WC} is independently hydrogen, halogen, -CN, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^{WA} and R^{WB} , R^{WB} and R^{WC} , R^{WA} and an instance of R^L , or R^{WC} and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{WD} is halogen or $-OS(O)_2R$;

each instance of R^{5C} , R^{5D} , R^{7A} , and R^L is independently R^A or R^B , and is substituted by u instances of R^C ;

each instance of R^A is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, or $-N(R)S(O)_2R$;

each instance of R^B is independently C_{1-6} aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

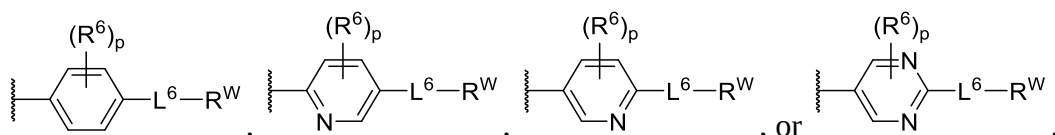
each instance of R^C is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-S(O)_2F$, $-OS(O)_2F$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

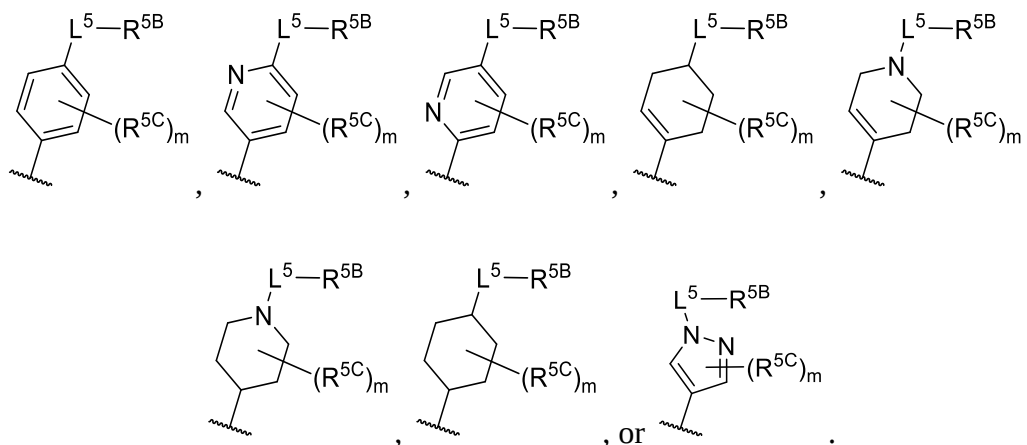
two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of m, n, p, q, r, t, and u is independently 0, 1, 2, 3, or 4.

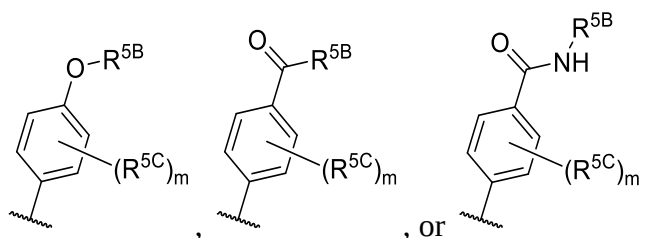
4. The compound of any one of claims 1-3, wherein $-\text{Cy}^6\text{-L}^6\text{-R}^W$ taken together is:



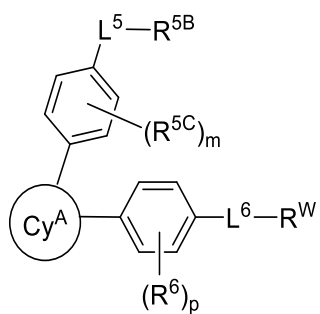
5. The compound of any one of claims 1-4, wherein R^5 is:



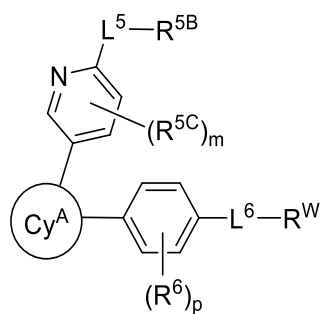
6. The compound of any one of claims 1-4, wherein R^5 is:



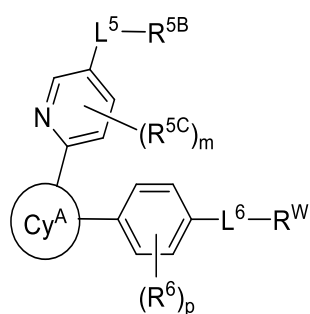
7. A compound of formula X-1, XI-1, XII-1, or XIII-1:



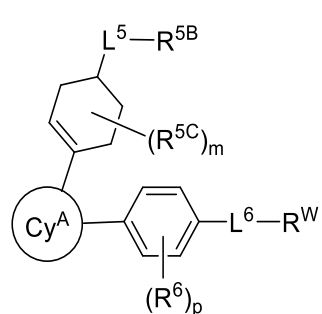
X-1



XI-1

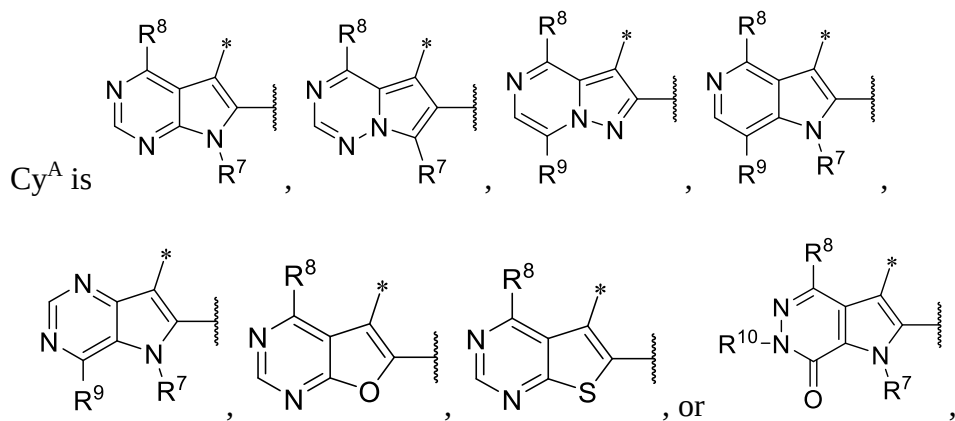


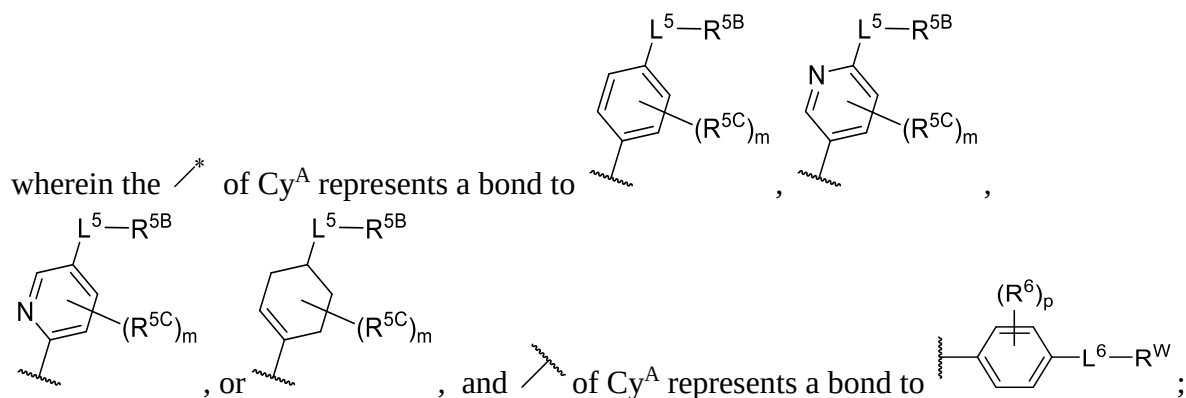
XII-1



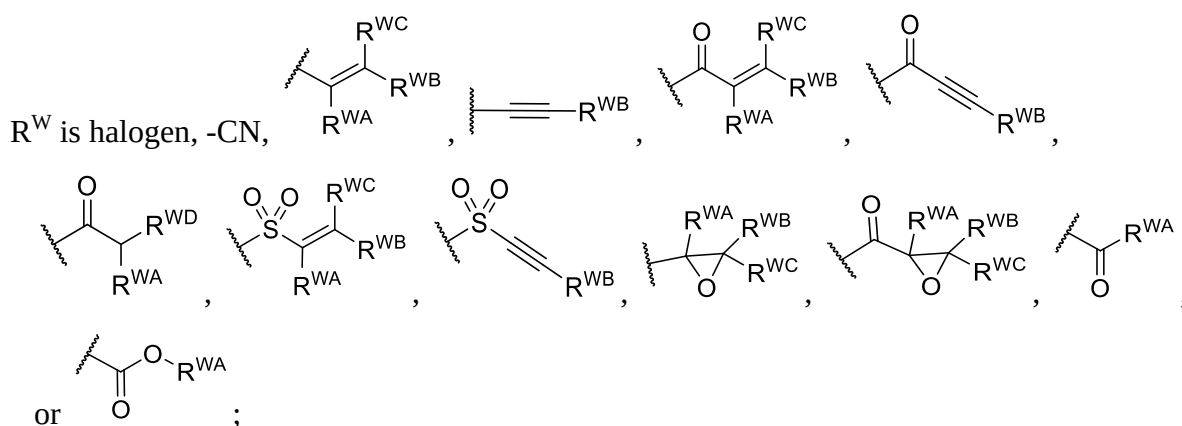
XIII-1

or a pharmaceutically acceptable salt thereof, wherein:





R^{5B} is hydrogen or R^B, wherein R^{5B} is substituted with n instances of R^{5D};



each instance of R⁶ is independently R^A or R^B, wherein R⁶ is substituted by q instances of R^C;

or

two instances of R⁶, or an instance of R⁶ and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with r instances of R^C;

R⁷ is H or R^B, wherein R⁷ is substituted with t instances of R^{7A};

R⁸ is H, -NR₂, halogen, -OH, or C₁₋₆ aliphatic optionally substituted with 1-3 halogens;

R⁹ is H, -NR₂, halogen, or C₁₋₆ aliphatic optionally substituted with 1-3 halogens;

R¹⁰ is H or C₁₋₆ aliphatic optionally substituted with 1-3 halogens;

each of L⁵ and L⁶ is independently a covalent bond, or a C₁₋₄ bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -CH(R^L)-, -C(R^L)₂-, C₃₋₅

cycloalkylene, 3-5 membered heterocycloalkylene, 5-6 membered heteroarylene, -NH-, -N(R^L)-, -NHC(O)-, -N(R^L)C(O)-, -C(O)NH-, -C(O)N(R^L)-, -NHS(O)₂-, -N(R^L)S(O)₂-, -S(O)₂NH-, -S(O)₂N(R^L)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)-, or -S(O)₂-;

each of R^{WA}, R^{WB}, and R^{WC} is independently hydrogen, deuterium, halogen, -CN, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

R^{WA} and R^{WB}, R^{WB} and R^{WC}, R^{WA} and an instance of R^L, or R^{WC} and an instance of R^L are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{WD} is halogen or -OS(O)₂R;

each instance of R^{5C}, R^{5D}, R^{7A}, and R^L is independently R^A or R^B, and is substituted by *u* instances of R^C;

each instance of R^A is independently oxo, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)NR₂, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, or -N(R)S(O)₂R;

each instance of R^B is independently C₁₋₆ aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

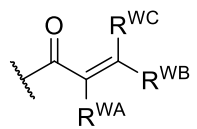
each instance of R^C is independently oxo, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)NR₂, -S(O)₂F, -OS(O)₂F, -C(O)R, -C(O)OR, -C(O)NR₂,

-C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

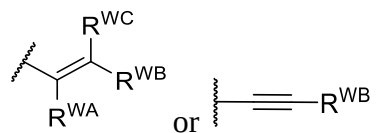
each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of m, n, p, q, r, t, and u is independently 0, 1, 2, 3, or 4.



8. The compound of any one of claims 1-7, wherein R^W is



9. The compound of any one of claims 1-7, wherein R^W is

10. The compound of any one of claims 1-9, wherein L⁶ is -NH-.

11. The compound of any one of claims 1-10, wherein the compound is selected from those depicted in Table 1, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition, comprising a compound of any one of claims 1-11, and a pharmaceutically acceptable carrier.

13. A compound of any one of claims 1-11, or the pharmaceutical composition of claim 12, for use in therapy.

14. Use of a compound of any one of claims 1-11, or the pharmaceutical composition of claim 12, in the manufacture of a medicament for inhibiting FGFR2 signaling activity in a subject.
15. Use of a compound of any one of claims 1-11, or the pharmaceutical composition of claim 12, in the manufacture of a medicament for treating an FGFR2-mediated disorder in a subject.
16. Use of a compound of any one of claims 1-11, or the pharmaceutical composition of claim 12, in the manufacture of a medicament for treating a disorder in a subject, wherein the disorder is bile duct cancer, liver cancer, breast cancer, prostate cancer, lung cancer, thyroid cancer, gastric cancer, ovarian cancer, rectal cancer, endometrial cancer, or urothelial cancer.
17. The use of claim 16, wherein the disorder is bile duct cancer.
18. The use of claim 17, wherein the bile duct cancer is intrahepatic cholangiocarcinoma.
19. The use of claim 16, wherein the disorder is liver cancer.
20. The use of claim 19, wherein the liver cancer is hepatocellular carcinoma.
21. The use of claim 16, wherein the disorder is lung cancer.
22. The use of claim 21, wherein the lung cancer is lung squamous cell carcinoma or non-small cell lung cancer.