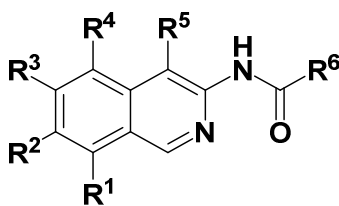


SUMMARY

[004] The present disclosure provides methods and reagents, involving contacting a cell with an agent, such as an isoquinoline compound, in a sufficient amount to antagonize a Wnt activity, e.g., to reverse or control an aberrant growth state or correct a genetic disorder due to mutations in Wnt signaling components.

[005] Some examples disclosed herein include Wnt inhibitors containing an isoquinoline core. Other examples disclosed herein include pharmaceutical compositions and methods of treatment using these compounds.

[006] One example disclosed herein includes a compound having the structure of Formula I:



I

as well as prodrugs and pharmaceutically acceptable salts thereof.

[007] In some examples of Formula (I):

R¹, R², R⁴, and R⁵ are independently selected from the group consisting of H, halide, unsubstituted -(C₁₋₃ haloalkyl), and unsubstituted -(C₁₋₃ alkyl);

R³ is a 5-membered heteroaryl optionally substituted with 1-4 R⁴⁵;

R⁶ is selected from the group consisting of -aryl substituted with 1-5 R³⁶ and a 6-membered heteroaryl optionally substituted with 1-6 R³⁷;

each R³⁶ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -XR⁴², -C(O)N(R⁴⁷)₂, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R⁴³, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R³⁷ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -XR⁴², -C(O)N(R⁴⁷)₂, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R⁴³, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two adjacent R⁴⁵ taken together form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

each R⁴⁶ is independently selected from the group consisting of halide, unsubstituted –(C₁₋₅ alkyl), unsubstituted –(C₂₋₅ alkenyl), unsubstituted –(C₂₋₅ alkynyl), unsubstituted –(C₁₋₅ haloalkyl), and –CN;

each R⁴⁷ is independently selected from the group consisting of unsubstituted –(C₁₋₅ alkyl), unsubstituted –(C₂₋₅ alkenyl), unsubstituted –(C₂₋₅ alkynyl), and unsubstituted –(C₁₋₅ haloalkyl);

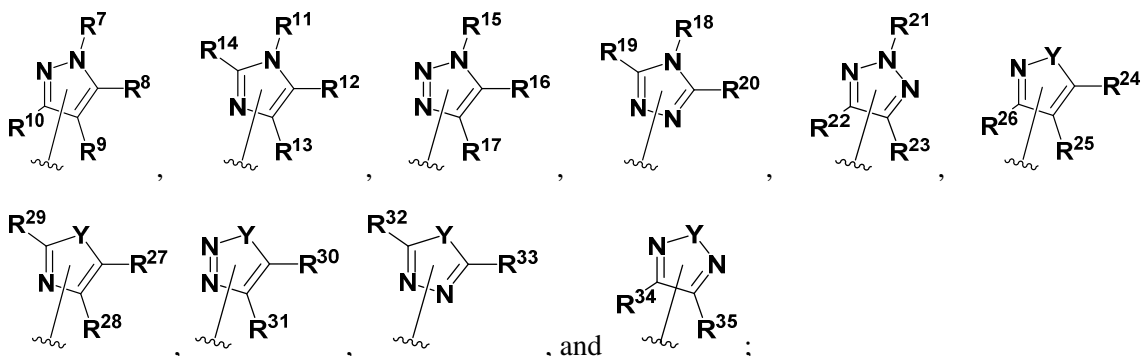
each X is selected from the group consisting of O, S, and NH; and

each p is independently 0 or 1.

[008] In another example of Formula (I):

R¹, R², R⁴, and R⁵ are independently selected from the group consisting of H, halide, unsubstituted –(C₁₋₃ haloalkyl), and unsubstituted –(C₁₋₃ alkyl);

R³ is selected from the group consisting of:



wherein each of R⁷-R³⁵ is, independently, a substituent as defined anywhere herein or a single bond connecting R³ to the isoquinoline ring; wherein only one of R⁷-R¹⁰ (when present) is a bond, only one of R¹¹-R¹⁴ (when present) is a bond, only one of R¹⁵-R¹⁷ (when present) is a bond, only one of R¹⁸-R²⁰ (when present) is a bond, only one of R²¹-R²³ (when present) is a bond, only one of R²⁴-R²⁶ (when present) is a bond, only one of R²⁷-R²⁹ (when present) is a bond, only one of R³⁰-R³¹ (when present) is a bond, only one of R³²-R³³ (when present) is a bond, and only one of R³⁴-R³⁵ (when present) is a bond; for purposes of clarification, any one of the nitrogen atoms attached to R⁷, R¹¹, R¹⁵, R¹⁸, or R²¹ can serve as the point of attachment of R³ to the isoquinoline ring; likewise, any one of the carbon atoms attached to R⁸, R⁹, R¹⁰, R¹², R¹³, R¹⁴, R¹⁶, R¹⁷, R¹⁹, R²⁰,

each R^{44} is selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{46} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{47} is independently selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each X is selected from the group consisting of O, S, and NH;

each Y is selected from the group consisting of O and S; and

each p is independently 0 or 1.

[009] In another example of Formula (I):

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, amino, unsubstituted $-(C_{1-3} \text{ haloalkyl})$, and unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^3 is a 5-membered heteroaryl optionally substituted with 1-4 R^{45} ;

R^6 is selected from the group consisting of $-\text{phenyl}$ substituted with 1-5 R^{36} , $-(C_{1-3} \text{ alkylene})_p\text{pyridinyl}$ optionally substituted with 1-6 R^{37} , and a 6-10 membered heteroaryl optionally substituted with 1-6 R^{37} ; wherein the carbonyl of Formula I is attached to an aromatic ring of the heteroaryl; wherein $-(C_{1-3} \text{ alkylene})$ is optionally substituted with one or more substituents as defined anywhere herein;

each R^{36} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-\text{XR}^{42}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{47})_2$, $-(C_{1-4} \text{ alkylene})_p\text{N}(\text{R}^{50})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{37} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-\text{XR}^{42}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{47})_2$, $-(C_{1-4} \text{ alkylene})_p\text{N}(\text{R}^{50})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R^{38} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$,

each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two adjacent R^{45} taken together form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 R^{40} and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{41} ;

each R^{46} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{47} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{48} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{49} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{50} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-(C_{1-4} \text{ alkylene})N(R^{48})_2$; wherein $-(C_{1-4} \text{ alkylene})$ is optionally substituted with one or more substituents as defined anywhere herein;

each R^{51} is a heteroaryl optionally substituted with 1-6 R^{52} ;

each R^{52} is a $-\text{heterocyclyl}$ optionally substituted with 1-10 R^{46} ;

each X is selected from the group consisting of O, S, and NR^{48} ; and

each p is independently 0 or 1.

[010] In another example of Formula (I):

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, amino, unsubstituted $-(C_{1-3} \text{ haloalkyl})$, and unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^3 is selected from the group consisting of:

each R⁴⁶ is independently selected from the group consisting of halide, unsubstituted –(C₁₋₅ alkyl), unsubstituted –(C₂₋₅ alkenyl), unsubstituted –(C₂₋₅ alkynyl), unsubstituted –(C₁₋₅ haloalkyl), and –CN;

each R⁴⁷ is independently selected from the group consisting of H, unsubstituted –(C₁₋₅ alkyl), unsubstituted –(C₂₋₅ alkenyl), unsubstituted –(C₂₋₅ alkynyl), and unsubstituted –(C₁₋₅ haloalkyl);

each R⁴⁸ is independently selected from the group consisting of H, unsubstituted –(C₁₋₅ alkyl), unsubstituted –(C₂₋₅ alkenyl), unsubstituted –(C₂₋₅ alkynyl), and unsubstituted –(C₁₋₅ haloalkyl);

each R⁴⁹ is independently selected from the group consisting of H, unsubstituted –(C₁₋₅ alkyl), unsubstituted –(C₂₋₅ alkenyl), unsubstituted –(C₂₋₅ alkynyl), and unsubstituted –(C₁₋₅ haloalkyl);

each R⁵⁰ is independently selected from the group consisting of H, unsubstituted –(C₁₋₅ alkyl), unsubstituted –(C₂₋₅ alkenyl), unsubstituted –(C₂₋₅ alkynyl), unsubstituted –(C₁₋₅ haloalkyl), and –(C₁₋₄ alkylene)N(R⁴⁸)₂; wherein –(C₁₋₄ alkylene) is optionally substituted with one or more substituents as defined anywhere herein;

each R⁵¹ is a heteroaryl optionally substituted with 1-6 R⁵²;

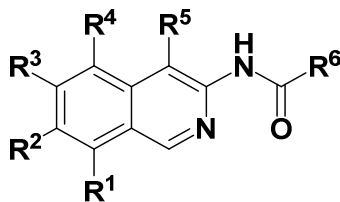
each R⁵² is a –heterocyclyl optionally substituted with 1-10 R⁴⁶;

each X is selected from the group consisting of O, S, and NR⁴⁸;

each Y is selected from the group consisting of O and S; and

each p is independently 0 or 1.

[010a] In one aspect, the present disclosure refers to a compound , or a pharmaceutically acceptable salt thereof, of Formula I:



I

wherein:

R¹, R², R⁴, and R⁵ are independently selected from the group consisting of H, halide, amino, unsubstituted –(C₁₋₃ haloalkyl), and unsubstituted –(C₁₋₃ alkyl);

R^3 is a 5-membered heteroaryl optionally substituted with 1-4 R^{45} ;

R^6 is selected from the group consisting of -phenyl substituted with 1-5 R^{36} , $-(C_{1-3} \text{ alkylene})_p$ pyridinyl optionally substituted with 1-6 R^{37} , and a 6-10 membered heteroaryl optionally substituted with 1-6 R^{37} ; wherein the carbonyl of Formula I is attached to an aromatic ring of the heteroaryl; wherein $-(C_{1-3} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{36} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-XR^{42}$, $-C(=O)N(R^{47})_2$, $-(C_{1-4} \text{ alkylene})_pN(R^{50})_2$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{37} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-XR^{42}$, $-C(=O)N(R^{47})_2$, $-(C_{1-4} \text{ alkylene})_pN(R^{50})_2$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{38} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{39} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{40} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{41} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{42} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p\text{aryl}$ optionally substituted with 1-10 R^{46} , $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-12 R^{43} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{43} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, $-\text{OH}$, $-\text{C}(=\text{O})R^{51}$, $-\text{N}(R^{50})_2$, and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{44} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{45} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pN(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{49}$, $-\text{C}(=\text{O})N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

alternatively, two adjacent R^{45} taken together form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 R^{40} and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{41} ;

each R^{46} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{47} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R⁴⁸ is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R⁴⁹ is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R⁵⁰ is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-(C_{1-4} \text{ alkylene})N(R^{48})_2$; wherein $-(C_{1-4} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

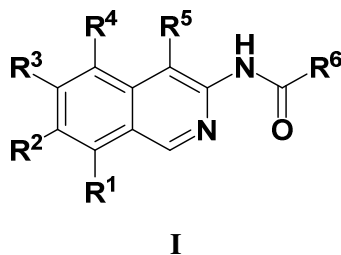
each R⁵¹ is a heteroaryl optionally substituted with 1-6 R⁵²;

each R⁵² is a $-\text{heterocyclyl}$ optionally substituted with 1-10 R⁴⁶;

each X is selected from the group consisting of O, S, and NR⁴⁸; and

each p is independently 0 or 1.

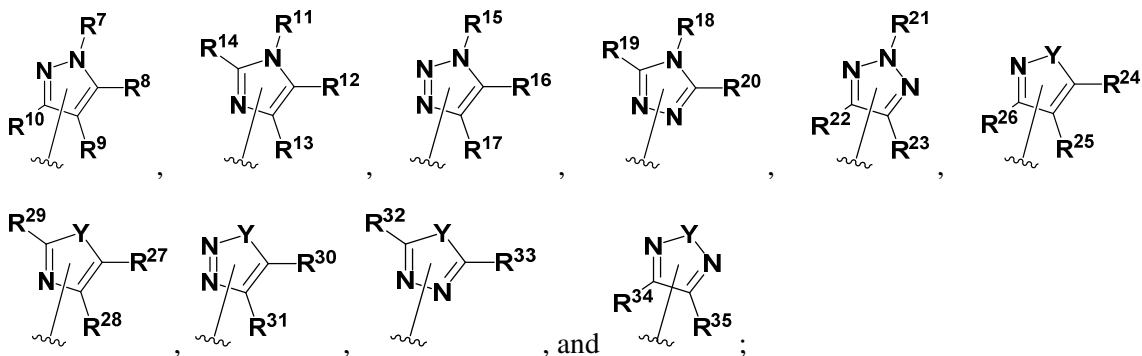
[010b] In one aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof, of Formula I:



wherein:

R¹, R², R⁴, and R⁵ are independently selected from the group consisting of H, halide, amino, unsubstituted $-(C_{1-3} \text{ haloalkyl})$, and unsubstituted $-(C_{1-3} \text{ alkyl})$;

R³ is selected from the group consisting of:



wherein each of R^7 - R^{35} is, independently, a substituent as defined anywhere herein or a single bond connecting R^3 to the isoquinoline ring; wherein only one of R^7 - R^{10} (when present) is a bond, only one of R^{11} - R^{14} (when present) is a bond, only one of R^{15} - R^{17} (when present) is a bond, only one of R^{18} - R^{20} (when present) is a bond, only one of R^{21} - R^{23} (when present) is a bond, only one of R^{24} - R^{26} (when present) is a bond, only one of R^{27} - R^{29} (when present) is a bond, only one of R^{30} - R^{31} (when present) is a bond, only one of R^{32} - R^{33} (when present) is a bond, and only one of R^{34} - R^{35} (when present) is a bond; wherein any one of the nitrogen atoms attached to R^7 , R^{11} , R^{15} , R^{18} , or R^{21} can serve as the point of attachment of R^3 to the isoquinoline ring; wherein any one of the carbon atoms attached to R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{16} , R^{17} , R^{19} , R^{20} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , or R^{35} can serve as the point of attachment of R^3 to the isoquinoline ring; as that:

when the nitrogen atom to which R^7 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^7 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^8 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^8 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^9 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^9 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{10} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{10} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{11} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{11} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{12} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{12} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{13} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{13} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{14} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{14} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{15} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{15} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{16} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{16} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{17} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{17} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{35} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{35} is a single bond connecting R^3 to the isoquinoline ring;

R^6 is selected from the group consisting of $-\text{phenyl}$ substituted with 1-5 R^{36} , $-(C_{1-3} \text{ alkylene})_p\text{pyridinyl}$ optionally substituted with 1-6 R^{37} , and a 6-10 membered heteroaryl optionally substituted with 1-6 R^{37} ; wherein the carbonyl of Formula I is attached to an aromatic ring of the heteroaryl; wherein $-(C_{1-3} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^7 is selected from the group consisting of a single bond, H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^8 , R^9 , and R^{10} are independently selected from the group consisting of a single bond, H, halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pN(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

alternatively, one of R^7 and R^8 , R^8 and R^9 , or R^9 and R^{10} are taken together to form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 R^{40} and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{41} ;

R^{11} is selected from the group consisting of a single bond, H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^{12} , R^{13} , and R^{14} are independently selected from the group consisting of a single bond, H, halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pN(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

alternatively, one of R¹¹ and R¹², R¹² and R¹³, or R¹⁴ and R¹¹ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R¹⁵ is selected from the group consisting of a single bond, H, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)N(R⁴⁸)₂, –(C₁₋₄ alkylene)OR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

R¹⁶ and R¹⁷ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, one of R¹⁵ and R¹⁶ or R¹⁶ and R¹⁷ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R¹⁸ is selected from the group consisting of a single bond, H, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)N(R⁴⁸)₂, –(C₁₋₄ alkylene)OR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

R¹⁹ and R²⁰ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, one of R¹⁸ and R¹⁹ or R¹⁸ and R²⁰ are taken together to form a heterocyclyl optionally substituted with 1-10 R⁴⁰;

R²¹ is selected from the group consisting of a single bond, H, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)N(R⁴⁸)₂, –(C₁₋₄ alkylene)OR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally

substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

R²² and R²³ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, R²² and R²³ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R²⁴, R²⁵, and R²⁶ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, one of R²⁴ and R²⁵ or R²⁵ and R²⁶ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R²⁷, R²⁸, and R²⁹ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, R²⁷ and R²⁸ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R³⁰ and R³¹ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally

substituted with 1-12 R³⁹; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

alternatively, R³⁰ and R³¹ are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R⁴⁰ and -carbocyclyl optionally substituted with 1-12 R⁴¹;

R³² and R³³ are independently selected from the group consisting of a single bond, H, halide, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -(C₁₋₄ alkylene)_pN(R⁴⁸)₂, -(C₁₋₄ alkylene)_pOR⁴⁹, -C(=O)N(R⁴⁸)₂, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and -carbocyclyl optionally substituted with 1-12 R³⁹; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

R³⁴ and R³⁵ are independently selected from the group consisting of a single bond, H, halide, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -(C₁₋₄ alkylene)_pN(R⁴⁸)₂, -(C₁₋₄ alkylene)_pOR⁴⁹, -C(=O)N(R⁴⁸)₂, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and -carbocyclyl optionally substituted with 1-12 R³⁹; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

alternatively, R³⁴ and R³⁵ are taken together to form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R⁴⁰ and -carbocyclyl optionally substituted with 1-12 R⁴¹;

each R³⁶ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -XR⁴², -C(=O)N(R⁴⁷)₂, -(C₁₋₄ alkylene)_pN(R⁵⁰)₂, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R⁴³, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R³⁷ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -XR⁴², -C(=O)N(R⁴⁷)₂, -(C₁₋₄ alkylene)_pN(R⁵⁰)₂, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R⁴³, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R³⁸ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅

haloalkyl), -CN, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R³⁹ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -CN, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴⁰ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -CN, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴¹ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), and -CN;

each R⁴² is independently selected from the group consisting of H, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -(C₁₋₄ alkylene)N(R⁴⁸)₂, -(C₁₋₄ alkylene)_paryl optionally substituted with 1-10 R⁴⁶, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-12 R⁴³, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴³ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -CN, -OH, -C(=O)R⁵¹, -N(R⁵⁰)₂, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴⁴ is selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), and -CN;

each R⁴⁶ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), and -CN;

each R⁴⁷ is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R⁴⁸ is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R⁴⁹ is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R⁵⁰ is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-(C_{1-4} \text{ alkylene})N(R^{48})_2$; wherein $-(C_{1-4} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R⁵¹ is a heteroaryl optionally substituted with 1-6 R⁵²;

each R⁵² is a -heterocyclyl optionally substituted with 1-10 R⁴⁶;

each X is selected from the group consisting of O, S, and NR⁴⁸;

each Y is selected from the group consisting of O and S; and

each p is independently 0 or 1.

[011] Some examples include stereoisomers and pharmaceutically acceptable salts of a compound of Formula (I). Some examples include pharmaceutically acceptable salts of a compound of Formula (I).

[012] Some examples include pro-drugs of a compound of Formula (I).

[013] Some examples of the present disclosure include pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier, diluent, or excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[014] Other examples disclosed herein include methods of inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins by administering to a patient affected by a disorder or disease in which aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, cell cycling and mutations in Wnt signaling components, a compound according to Formula (I). Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit

angiogenesis, to reduce or inhibit cellular proliferation and correct a genetic disorder due to mutations in Wnt signaling components.

[014a] In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the preparation of a pharmaceutical composition for treating a disorder or disease in a patient, wherein the patient is human and the disorder or disease is selected from the group consisting of: cancer, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), degenerative disc disease, bone/osteoporotic fractures, a bone or cartilage disease, osteoarthritis, lung disease, and a fibrotic disorder.

[015] Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, osteochondrodysplasia, Alzheimer's disease, lung disease, bone/osteoporotic (wrist, spine, shoulder and hip) fractures, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-oncho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease, and Rett syndrome.

[016] Some examples of the present disclosure include methods to prepare compounds of Formula (I).

[017] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

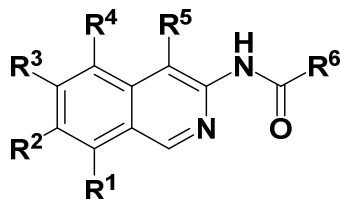
DETAILED DESCRIPTION

[018] Provided herein are compositions and methods for inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins.

[019] Some embodiments provided herein relate to a method for treating a disease or disorder including, but not limited to, cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, bone and cartilage diseases, Alzheimer's disease, lung disease, osteoarthritis, bone/osteoporotic (wrist, spine, shoulder and hip) fractures, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-

WHAT IS CLAIMED IS:

1. A compound, or a pharmaceutically acceptable salt thereof, of Formula I:



wherein:

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, amino, unsubstituted $-(C_{1-3} \text{ haloalkyl})$, and unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^3 is a 5-membered heteroaryl optionally substituted with 1-4 R^{45} ;

R^6 is selected from the group consisting of $-\text{phenyl}$ substituted with 1-5 R^{36} , $-(C_{1-3} \text{ alkylene})_p\text{pyridinyl}$ optionally substituted with 1-6 R^{37} , and a 6-10 membered heteroaryl optionally substituted with 1-6 R^{37} ; wherein the carbonyl of Formula I is attached to an aromatic ring of the heteroaryl; wherein $-(C_{1-3} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{36} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-\text{XR}^{42}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{47})_2$, $-(C_{1-4} \text{ alkylene})_p\text{N}(\text{R}^{50})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{37} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-\text{XR}^{42}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{47})_2$, $-(C_{1-4} \text{ alkylene})_p\text{N}(\text{R}^{50})_2$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{38} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{39} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴⁰ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -CN, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴¹ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), and -CN;

each R⁴² is independently selected from the group consisting of H, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -(C₁₋₄ alkylene)N(R⁴⁸)₂, -(C₁₋₄ alkylene)_paryl optionally substituted with 1-10 R⁴⁶, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-12 R⁴³, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴³ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -CN, -OH, -C(=O)R⁵¹, -N(R⁵⁰)₂, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

each R⁴⁴ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), and -CN;

each R⁴⁵ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -(C₁₋₄ alkylene)_pN(R⁴⁸)₂, -(C₁₋₄ alkylene)_pOR⁴⁹, -C(=O)N(R⁴⁸)₂, -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and -carbocyclyl optionally substituted with 1-12 R³⁹; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted -(C₁₋₃ alkyl);

alternatively, two adjacent R⁴⁵ taken together form a ring which is selected from the group consisting of -heterocyclyl optionally substituted with 1-10 R⁴⁰ and -carbocyclyl optionally substituted with 1-12 R⁴¹;

each R⁴⁶ is independently selected from the group consisting of halide, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), and -CN;

each R⁴⁷ is independently selected from the group consisting of H, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), and unsubstituted -(C₁₋₅ haloalkyl);

each R^{48} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{49} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{50} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-(C_{1-4} \text{ alkylene})N(R^{48})_2$; wherein $-(C_{1-4} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

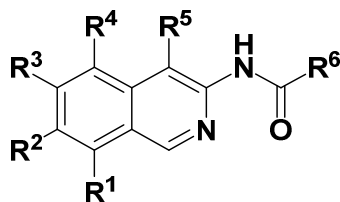
each R^{51} is a heteroaryl optionally substituted with 1-6 R^{52} ;

each R^{52} is a heterocyclyl optionally substituted with 1-10 R^{46} ;

each X is selected from the group consisting of O, S, and NR^{48} ; and

each p is independently 0 or 1.

2. The compound of claim 1, wherein R^1 , R^2 , R^4 , and R^5 are H.
3. The compound according to any of claims 1-2, wherein R^3 is a pyrazolyl optionally substituted with 1-4 R^{45} .
4. The compound according to any of claims 1-3, wherein R^3 is an unsubstituted pyrazolyl.
5. The compound according to any of claims 1-3, wherein R^3 is a pyrazolyl substituted with one $-(C_{1-3} \text{ alkyl})$.
6. The compound according to any of claims 1-2, wherein R^3 is an imidazolyl optionally substituted with 1-4 R^{45} .
7. The compound according to any of claims 1-2 and 6, wherein R^3 is a imidazolyl substituted with one $-(C_{1-3} \text{ alkyl})$.
8. The compound according to any of claims 1-2, wherein R^3 is a triazolyl optionally substituted with 1-4 R^{45} .
9. The compound according to any of claims 1-2 and 8, wherein R^3 is an unsubstituted triazolyl.
10. The compound according to any of claims 1-2 and 8, wherein R^3 is a triazolyl substituted with one $-(C_{1-3} \text{ alkyl})$.
11. A compound, or a pharmaceutically acceptable salt thereof, of Formula I:

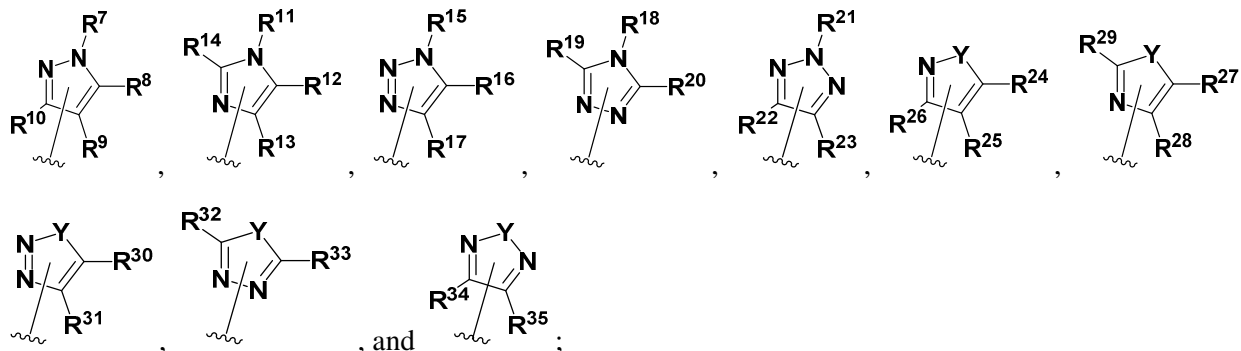


I

wherein:

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, amino, unsubstituted $-(C_{1-3} \text{ haloalkyl})$, and unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^3 is selected from the group consisting of:



wherein each of R^7 - R^{35} is, independently, a substituent as defined anywhere herein or a single bond connecting R^3 to the isoquinoline ring; wherein only one of R^7 - R^{10} (when present) is a bond, only one of R^{11} - R^{14} (when present) is a bond, only one of R^{15} - R^{17} (when present) is a bond, only one of R^{18} - R^{20} (when present) is a bond, only one of R^{21} - R^{23} (when present) is a bond, only one of R^{24} - R^{26} (when present) is a bond, only one of R^{27} - R^{29} (when present) is a bond, only one of R^{30} - R^{31} (when present) is a bond, only one of R^{32} - R^{33} (when present) is a bond, and only one of R^{34} - R^{35} (when present) is a bond; wherein any one of the nitrogen atoms attached to R^7 , R^{11} , R^{15} , R^{18} , or R^{21} can serve as the point of attachment of R^3 to the isoquinoline ring; wherein any one of the carbon atoms attached to R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{16} , R^{17} , R^{19} , R^{20} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , or R^{35} can serve as the point of attachment of R^3 to the isoquinoline ring; as that:

when the nitrogen atom to which R^7 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^7 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^8 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^8 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^9 is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^9 is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{10} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{10} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{11} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{11} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{12} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{12} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{29} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{29} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{30} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{30} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{31} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{31} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{32} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{32} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{33} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{33} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{34} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{34} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{35} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{35} is a single bond connecting R^3 to the isoquinoline ring;

R^6 is selected from the group consisting of $-phenyl$ substituted with 1-5 R^{36} , $-(C_{1-3} alkylene)_p pyridinyl$ optionally substituted with 1-6 R^{37} , and a 6-10 membered heteroaryl optionally substituted with 1-6 R^{37} ; wherein the carbonyl of Formula I is attached to an aromatic ring of the heteroaryl; wherein $-(C_{1-3} alkylene)$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} alkyl)$;

R^7 is selected from the group consisting of a single bond, H, unsubstituted $-(C_{1-9} alkyl)$, unsubstituted $-(C_{2-9} alkenyl)$, unsubstituted $-(C_{2-9} alkynyl)$, unsubstituted $-(C_{1-9} haloalkyl)$, $-(C_{1-4} alkylene)N(R^{48})_2$, $-(C_{1-4} alkylene)OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} alkylene)_p heterocyclyl$ optionally substituted with 1-10 R^{38} , and $-carbocyclyl$ optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4} alkylene)$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} alkyl)$;

R^8 , R^9 , and R^{10} are independently selected from the group consisting of a single bond, H, halide, unsubstituted $-(C_{1-9} alkyl)$, unsubstituted $-(C_{2-9} alkenyl)$, unsubstituted $-(C_{2-9} alkynyl)$, unsubstituted $-(C_{1-9} haloalkyl)$, $-(C_{1-4} alkylene)_p N(R^{48})_2$, $-(C_{1-4} alkylene)_p OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} alkylene)_p heterocyclyl$ optionally substituted with 1-10 R^{38} , and $-carbocyclyl$ optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} alkylene)$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} alkyl)$;

alternatively, one of R^7 and R^8 , R^8 and R^9 , or R^9 and R^{10} are taken together to form a ring which is selected from the group consisting of $-heterocyclyl$ optionally substituted with 1-10 R^{40} and $-carbocyclyl$ optionally substituted with 1-12 R^{41} ;

R^{11} is selected from the group consisting of a single bond, H, unsubstituted $-(C_{1-9} alkyl)$, unsubstituted $-(C_{2-9} alkenyl)$, unsubstituted $-(C_{2-9} alkynyl)$, unsubstituted $-(C_{1-9} haloalkyl)$, $-(C_{1-4} alkylene)N(R^{48})_2$, $-(C_{1-4} alkylene)OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} alkylene)_p heterocyclyl$ optionally

substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

R¹², R¹³, and R¹⁴ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, one of R¹¹ and R¹², R¹² and R¹³, or R¹⁴ and R¹¹ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R¹⁵ is selected from the group consisting of a single bond, H, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)N(R⁴⁸)₂, –(C₁₋₄ alkylene)OR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

R¹⁶ and R¹⁷ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, one of R¹⁵ and R¹⁶ or R¹⁶ and R¹⁷ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R¹⁸ is selected from the group consisting of a single bond, H, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)N(R⁴⁸)₂, –(C₁₋₄ alkylene)OR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

R¹⁹ and R²⁰ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each

–(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, one of R¹⁸ and R¹⁹ or R¹⁸ and R²⁰ are taken together to form a heterocyclyl optionally substituted with 1-10 R⁴⁰;

R²¹ is selected from the group consisting of a single bond, H, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)N(R⁴⁸)₂, –(C₁₋₄ alkylene)OR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

R²² and R²³ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, R²² and R²³ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R²⁴, R²⁵, and R²⁶ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, one of R²⁴ and R²⁵ or R²⁵ and R²⁶ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R⁴⁰ and –carbocyclyl optionally substituted with 1-12 R⁴¹;

R²⁷, R²⁸, and R²⁹ are independently selected from the group consisting of a single bond, H, halide, unsubstituted –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pN(R⁴⁸)₂, –(C₁₋₄ alkylene)_pOR⁴⁹, –C(=O)N(R⁴⁸)₂, –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted –(C₁₋₃ alkyl);

alternatively, R^{27} and R^{28} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{40} and –carbocyclyl optionally substituted with 1-12 R^{41} ;

R^{30} and R^{31} are independently selected from the group consisting of a single bond, H, halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

alternatively, R^{30} and R^{31} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{40} and –carbocyclyl optionally substituted with 1-12 R^{41} ;

R^{32} and R^{33} are independently selected from the group consisting of a single bond, H, halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

R^{34} and R^{35} are independently selected from the group consisting of a single bond, H, halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p OR^{49}$, $-C(=O)N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

alternatively, R^{34} and R^{35} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{40} and –carbocyclyl optionally substituted with 1-12 R^{41} ;

each R^{36} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-XR^{42}$, $-C(=O)N(R^{47})_2$, $-(C_{1-4} \text{ alkylene})_p N(R^{50})_2$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{37} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-XR^{42}$, –

$C(=O)N(R^{47})_2$, $-(C_{1-4} \text{ alkylene})_p N(R^{50})_2$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{43} , and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{38} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{39} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{40} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{41} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{42} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})N(R^{48})_2$, $-(C_{1-4} \text{ alkylene})_p$ aryl optionally substituted with 1-10 R^{46} , $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-12 R^{43} , and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{43} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, $-\text{OH}$, $-\text{C}(=\text{O})R^{51}$, $-\text{N}(R^{50})_2$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{44} is selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{46} is independently selected from the group consisting of halide, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-\text{CN}$;

each R^{47} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{48} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{49} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, and unsubstituted $-(C_{1-5} \text{ haloalkyl})$;

each R^{50} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-(C_{1-4} \text{ alkylene})N(R^{48})_2$; wherein $-(C_{1-4} \text{ alkylene})$ is optionally substituted with 1-5 halide and/or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$;

each R^{51} is a heteroaryl optionally substituted with 1-6 R^{52} ;

each R^{52} is a -heterocyclyl optionally substituted with 1-10 R^{46} ;

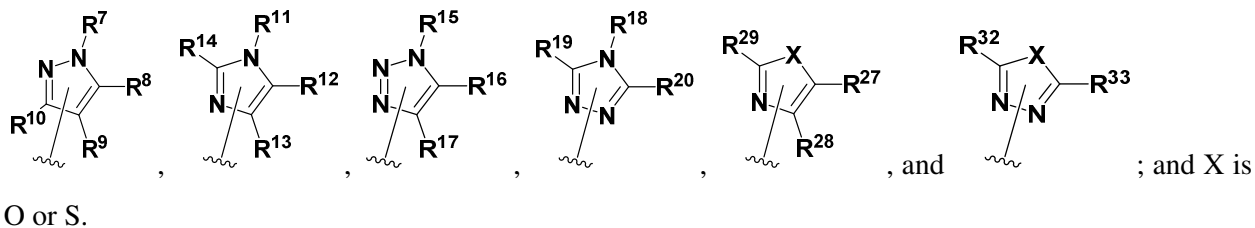
each X is selected from the group consisting of O, S, and NR^{48} ;

each Y is selected from the group consisting of O and S; and

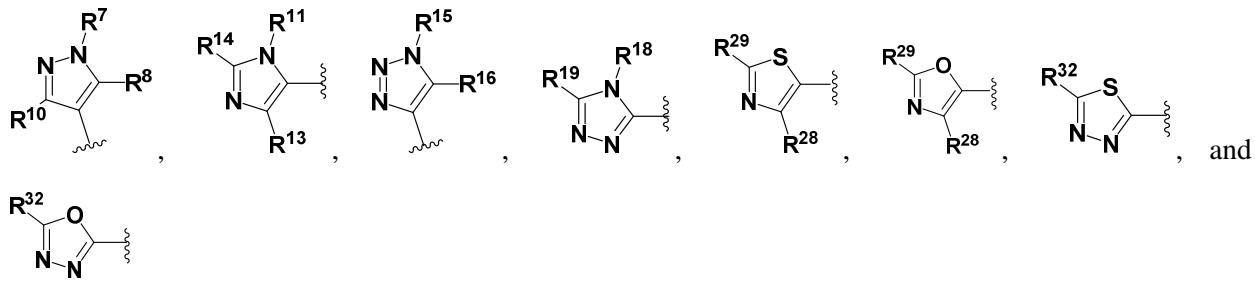
each p is independently 0 or 1.

12. The compound of claim 11, wherein R^1 , R^2 , R^4 , and R^5 are H.

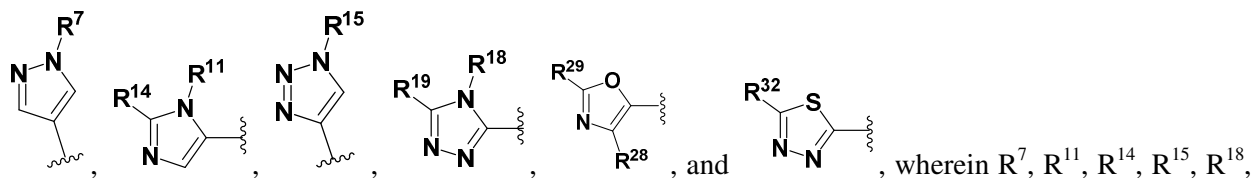
13. The compound according to any one of claims 11-12, wherein R^3 is selected from the group consisting of:



14. The compound according to any one of claims 11-13, wherein R^3 is selected from the group consisting of:



15. The compound according to any one of claims 11-14, wherein R^3 is selected from the group consisting of:



and R¹⁹ are independently selected from the group consisting of H and $-(C_{1-3} \text{ alkyl})$.

16. The compound according to any one of claims 1-15, wherein R⁶ is $-\text{aryl}$ substituted with 1-5 R³⁶.

17. The compound according to any one of claims 1-16, wherein R⁶ is $-\text{phenyl}$ substituted with 1-5 R³⁶.

18. The compound according to any one of claims 1-17, wherein R⁶ is $-\text{phenyl}$ substituted with one R³⁶.

19. The compound according to any one of claims 1-18, wherein R³⁶ is selected from the group consisting of halide, $-\text{heterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{CH}_2\text{heterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{Oheterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{NHheterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{O}(C_{1-4} \text{ alkyl})$, and $-\text{O}(C_{1-4} \text{ haloalkyl})$.

20. The compound according to any one of claims 1-15, wherein R⁶ is a 6-membered heteroaryl optionally substituted with 1-6 R³⁷.

21. The compound according to any one of claims 1-15 and 20, wherein R⁶ is $-\text{pyridinyl}$ optionally substituted with 1-6 R³⁷.

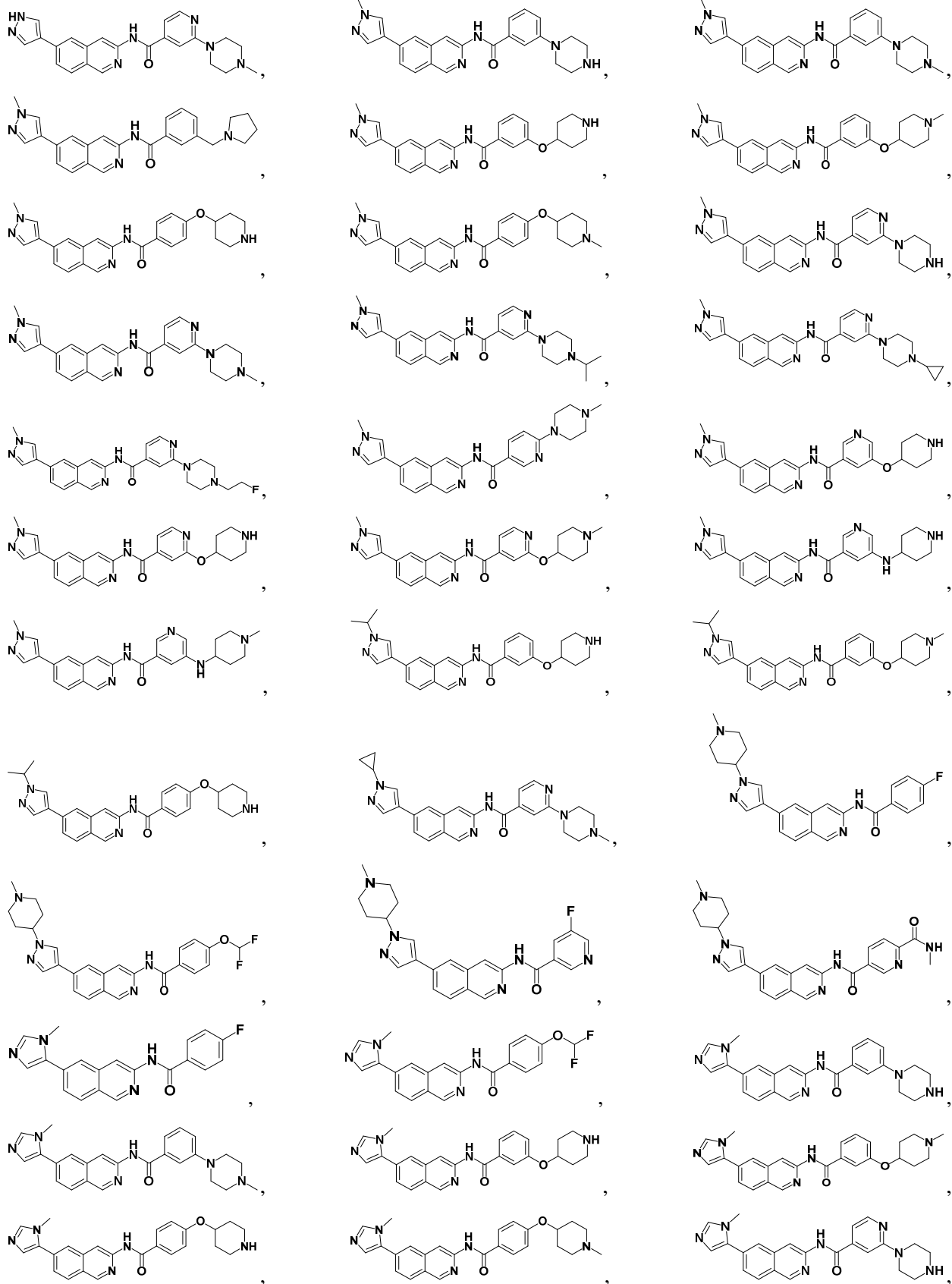
22. The compound according to any one of claims 1-15 and 20-21, wherein R⁶ is $-\text{pyridin-3-yl}$ optionally substituted with one R³⁷.

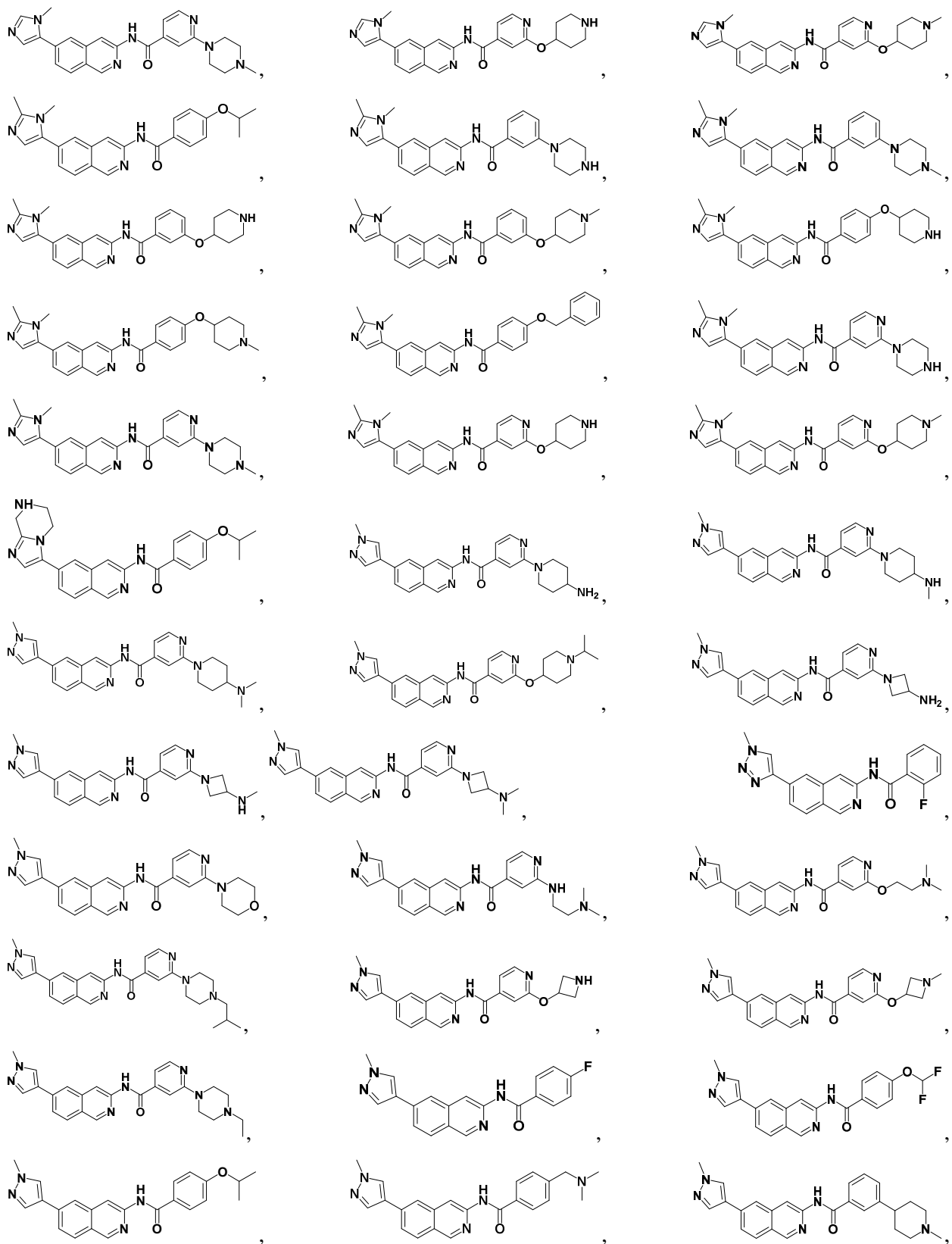
23. The compound according to any one of claims 1-15 and 20-21, wherein R⁶ is $-\text{pyridin-4-yl}$ optionally substituted with one R³⁷.

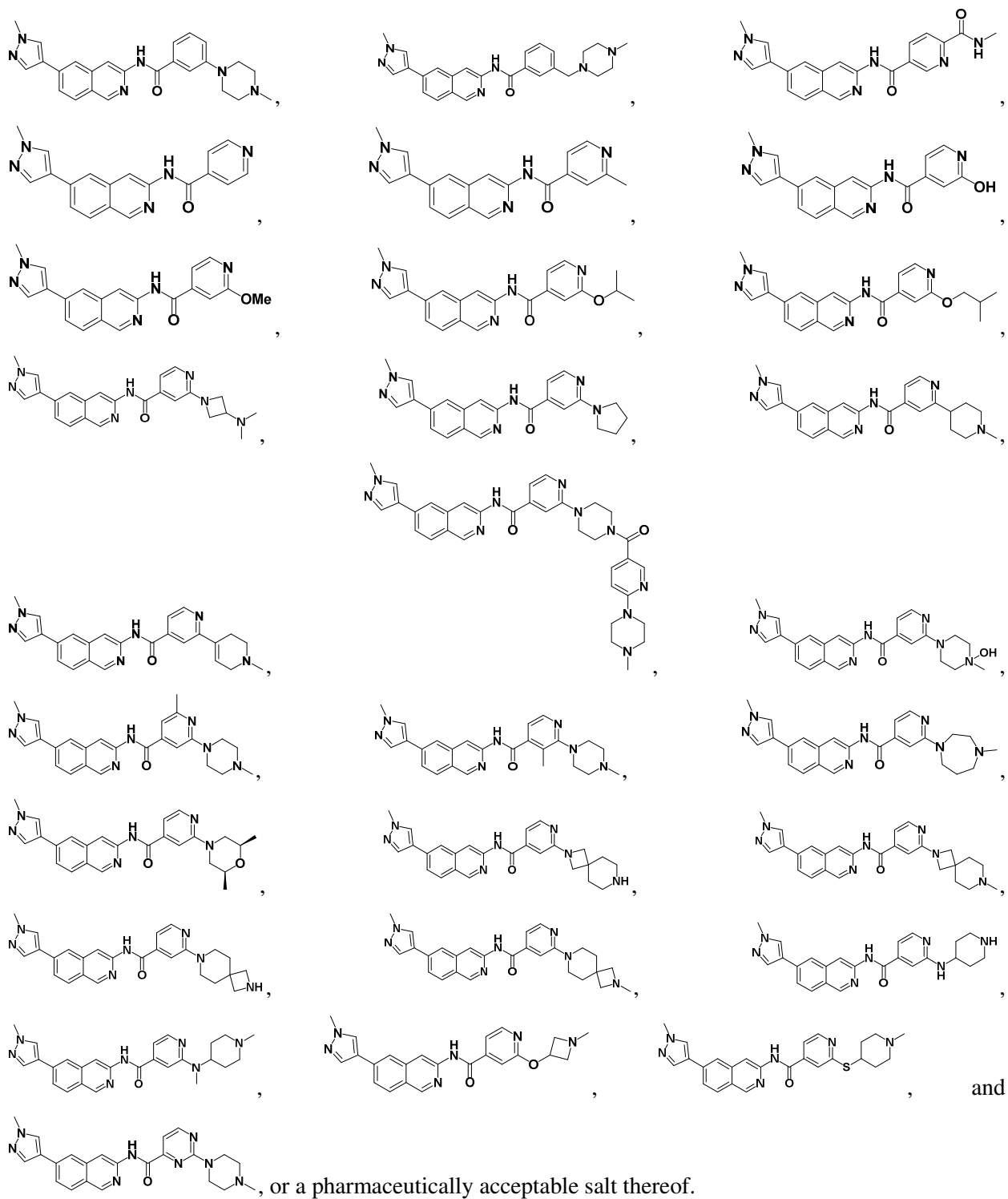
24. The compound according to any one of claims 1-15 and 20-23, wherein R³⁷ is selected from the group consisting of halide, $-(C_{1-3} \text{ alkyl})$, $-\text{heterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{CH}_2\text{heterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{Oheterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{NHheterocyclyl}$ optionally substituted with 1-2 R⁴³, $-\text{O}(C_{1-4} \text{ alkyl})$, and $-\text{O}(C_{1-4} \text{ haloalkyl})$.

25. The compound according to any one of claims 1-24, wherein R⁴³ is selected from the group consisting of unsubstituted $-(C_{1-3} \text{ alkyl})$, unsubstituted $-(C_{1-3} \text{ haloalkyl})$, and $-\text{carbocyclyl}$ optionally substituted with 1-12 R⁴⁴.

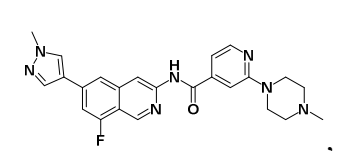
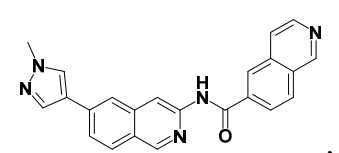
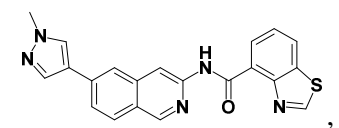
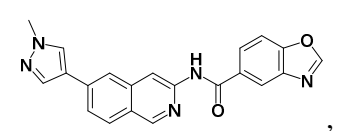
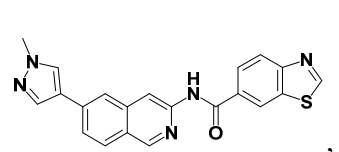
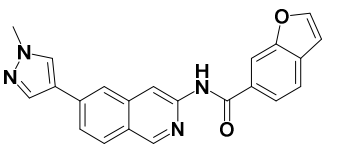
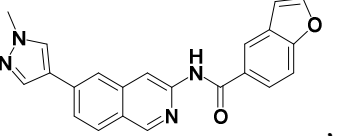
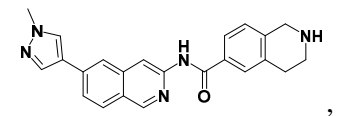
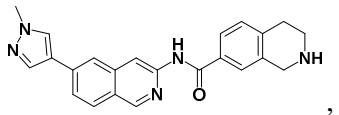
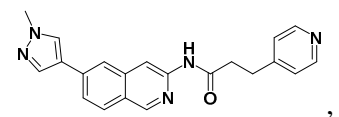
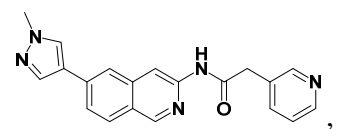
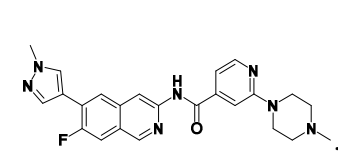
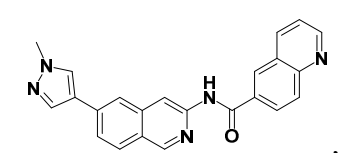
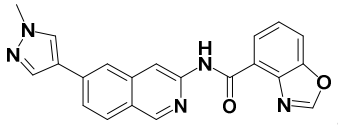
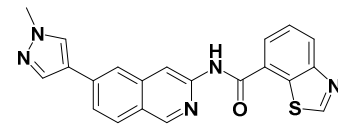
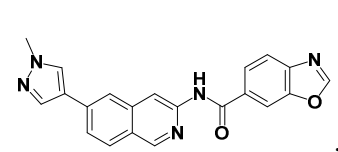
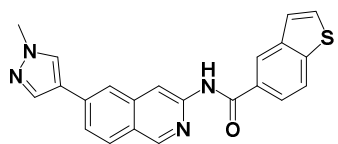
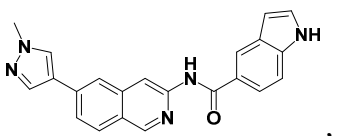
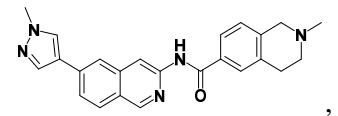
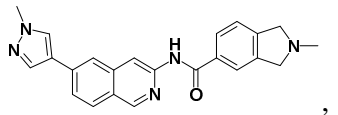
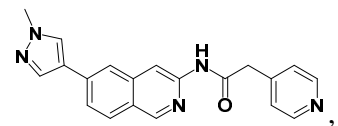
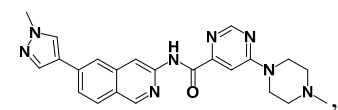
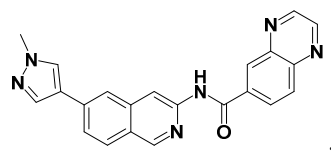
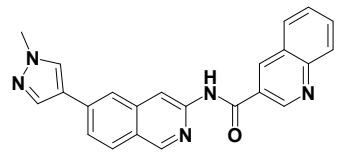
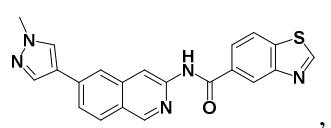
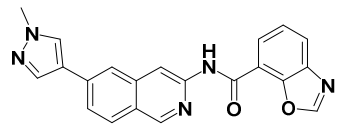
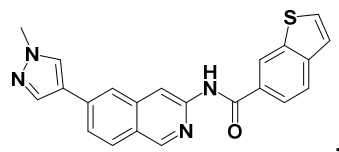
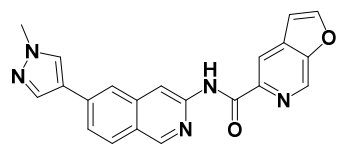
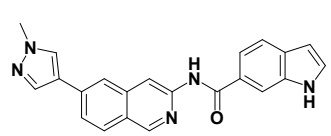
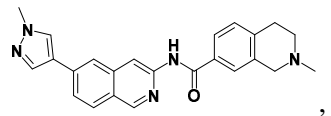
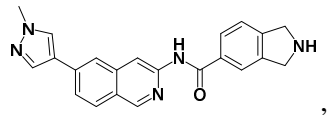
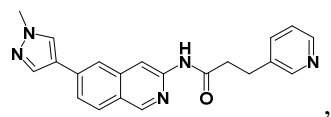
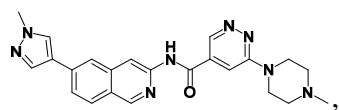
26. The compound of claim 1, wherein the compound of Formula **I** is selected from the group consisting of:

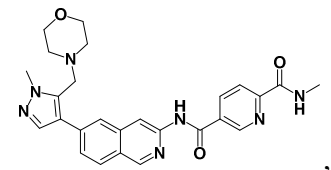
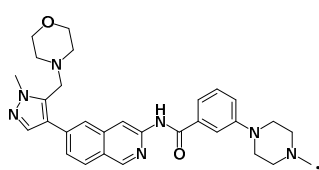
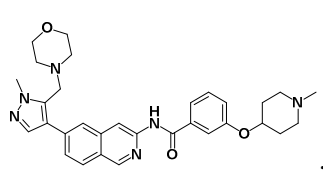
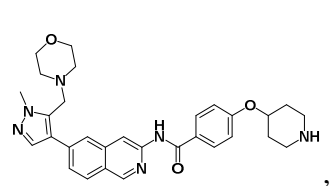
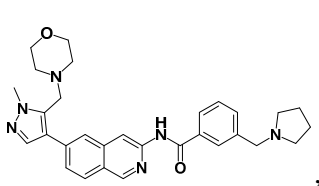
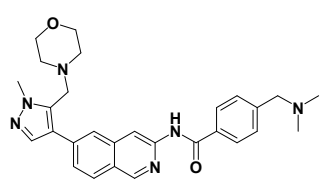
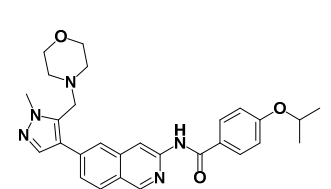
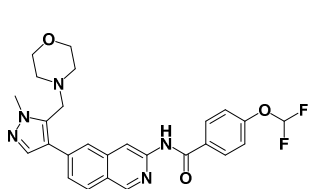
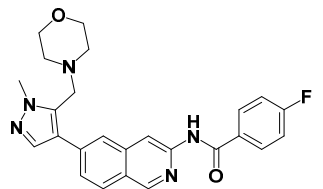
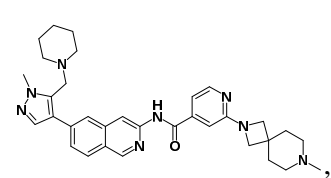
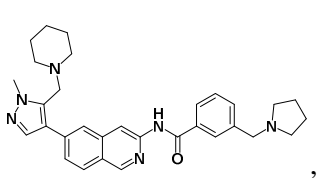
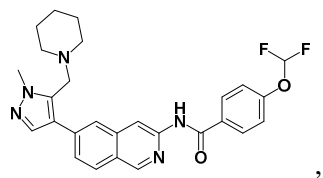
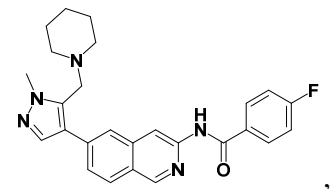
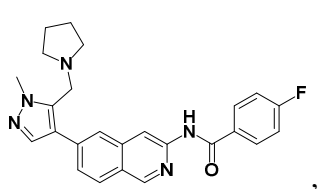
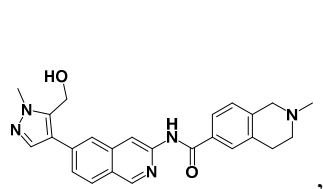
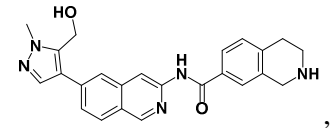
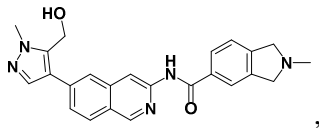
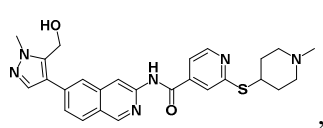
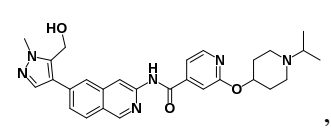
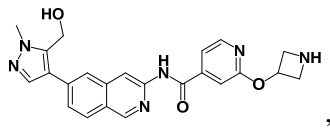
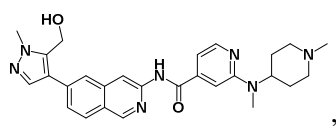
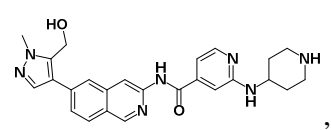
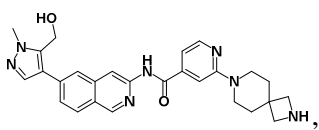
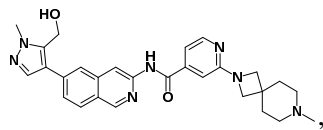
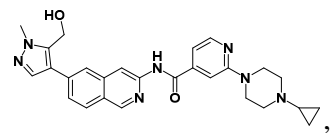
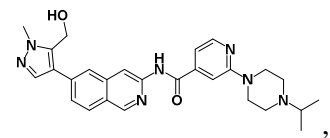
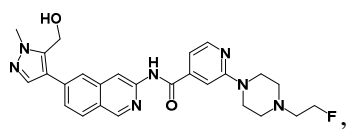


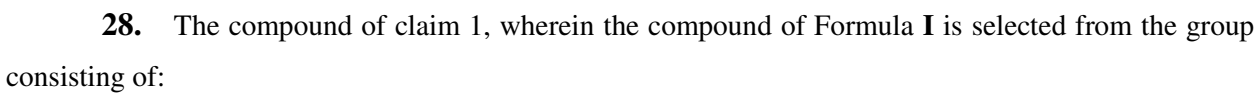


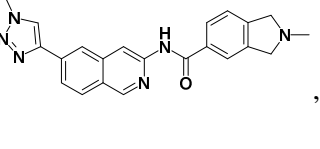
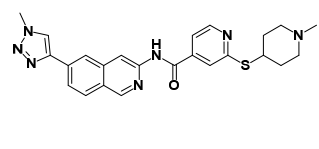
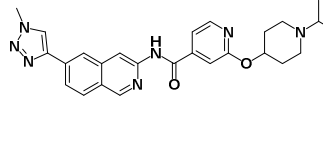
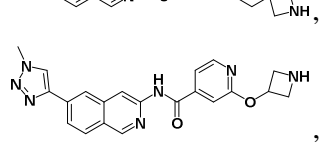
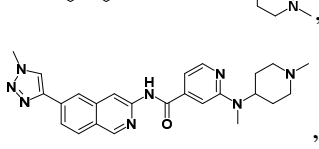
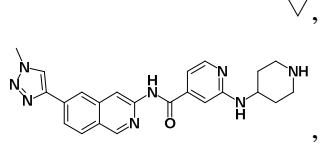
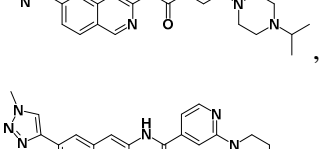
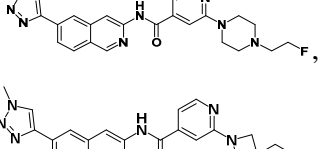
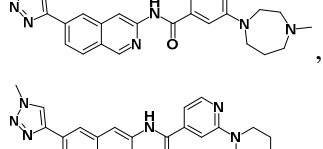
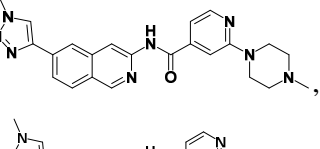
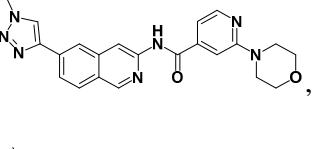
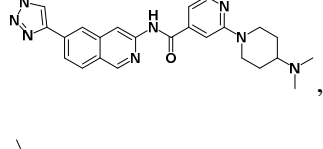
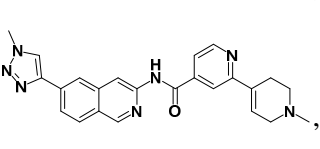
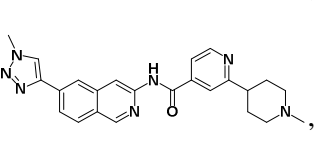
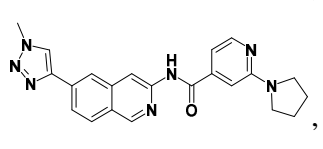
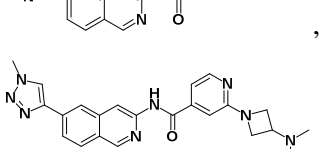
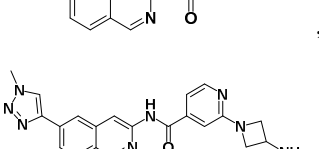
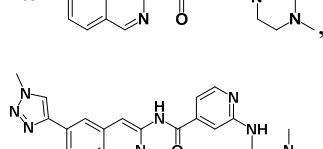
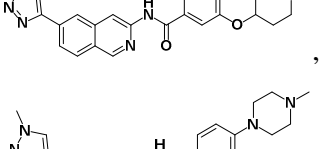
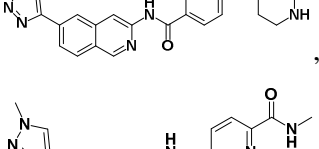
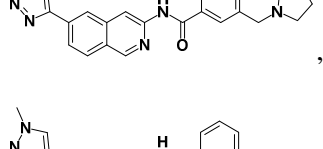
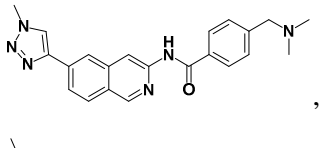
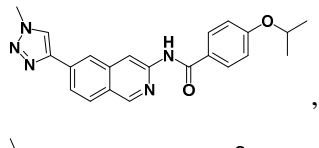
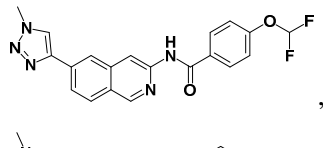
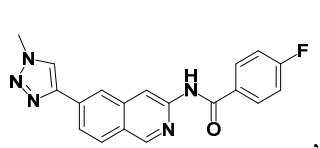
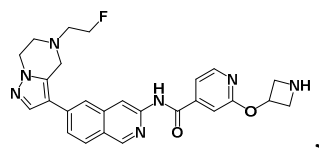
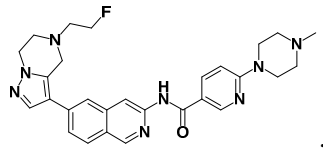
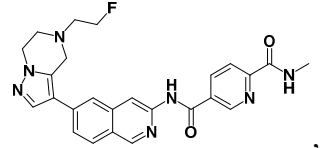
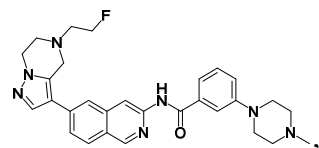
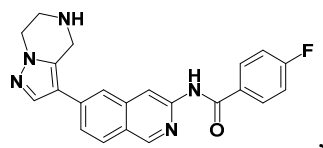


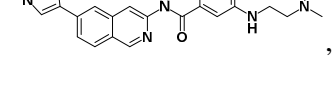
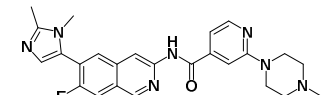
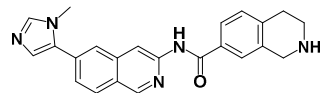
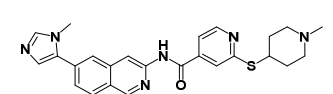
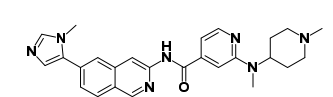
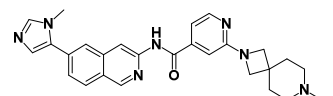
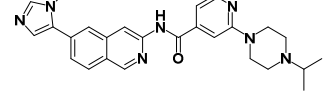
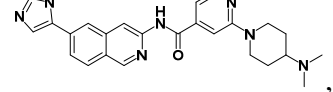
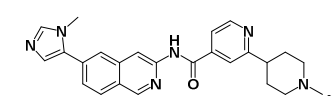
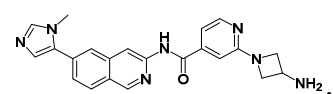
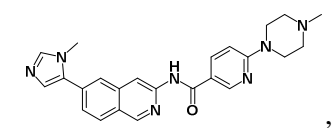
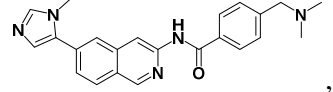
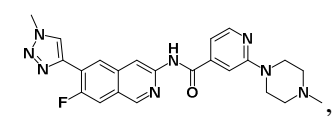
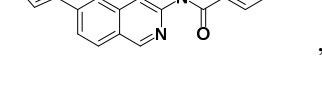
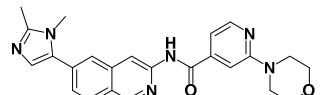
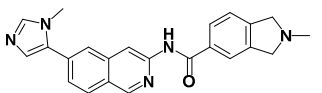
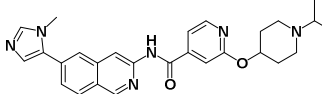
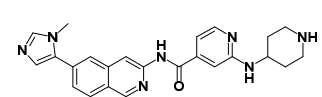
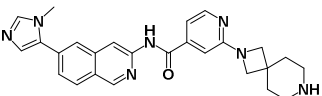
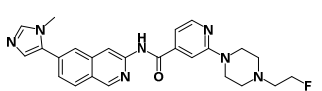
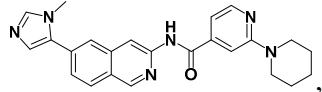
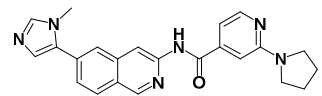
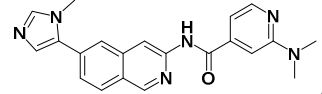
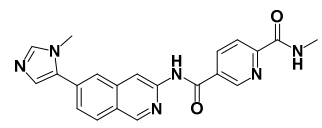
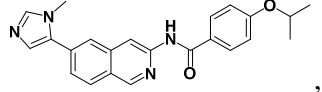
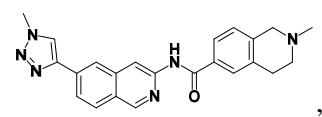
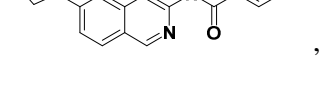
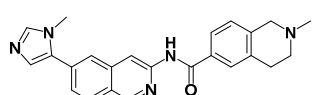
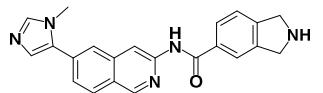
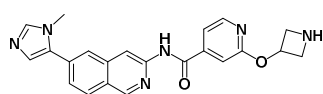
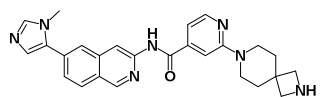
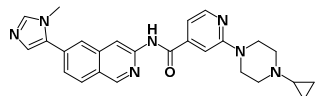
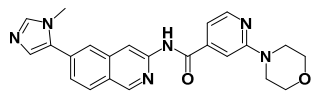
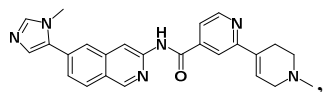
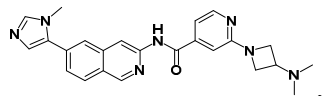
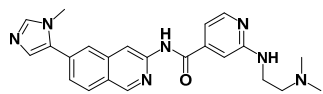
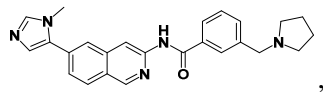
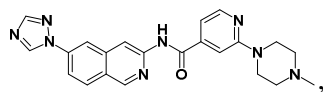
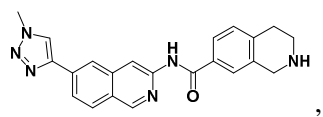
27. The compound of claim 1, wherein the compound of Formula **I** is selected from the group consisting of:

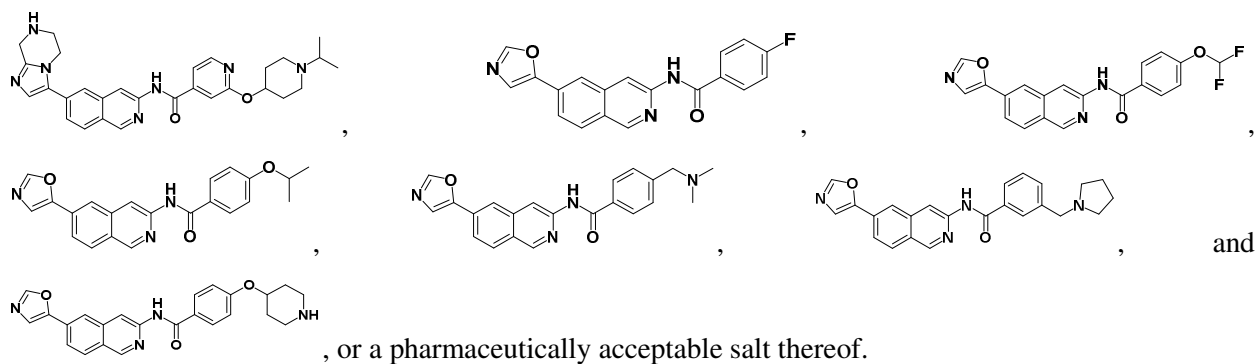




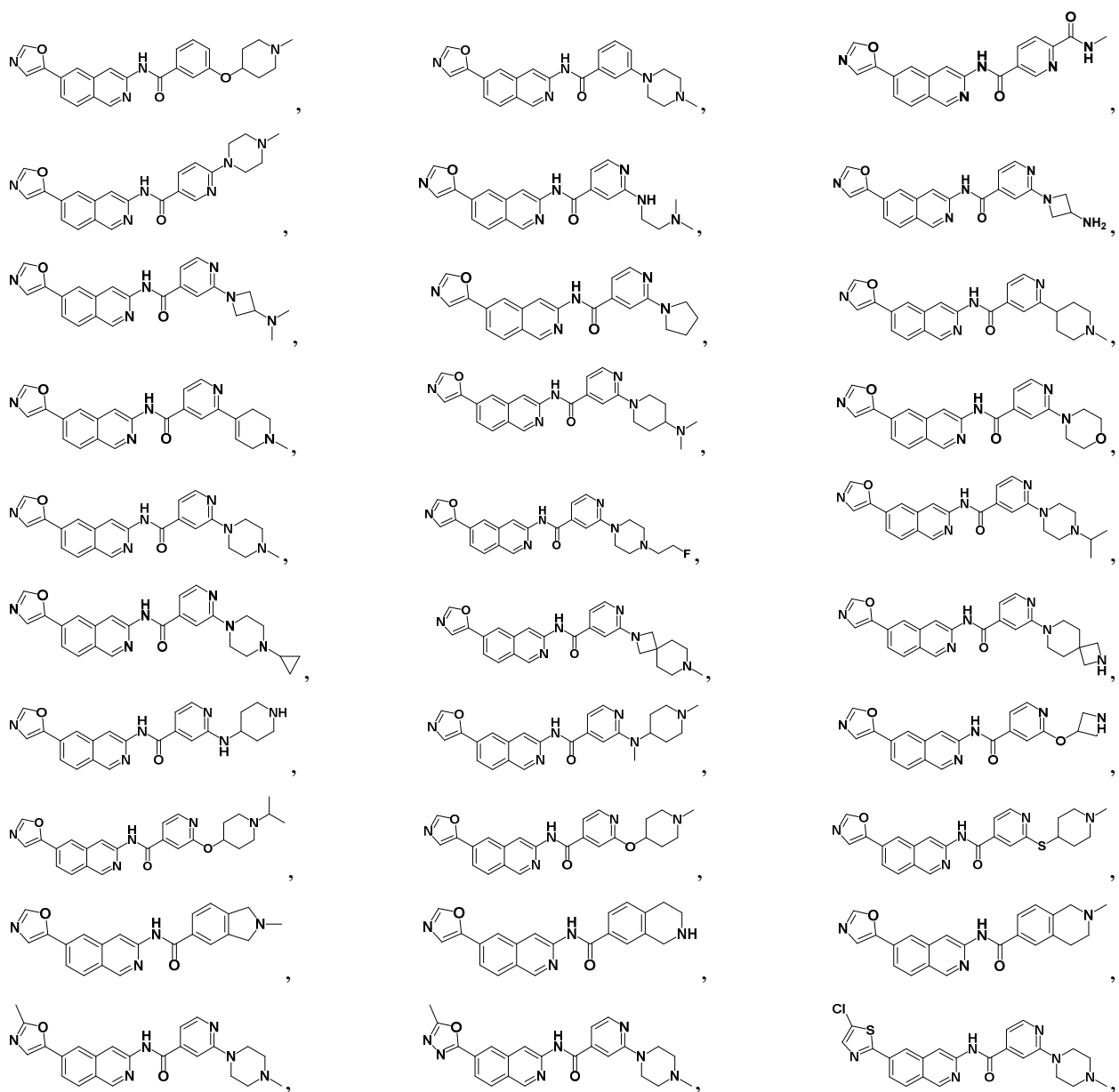


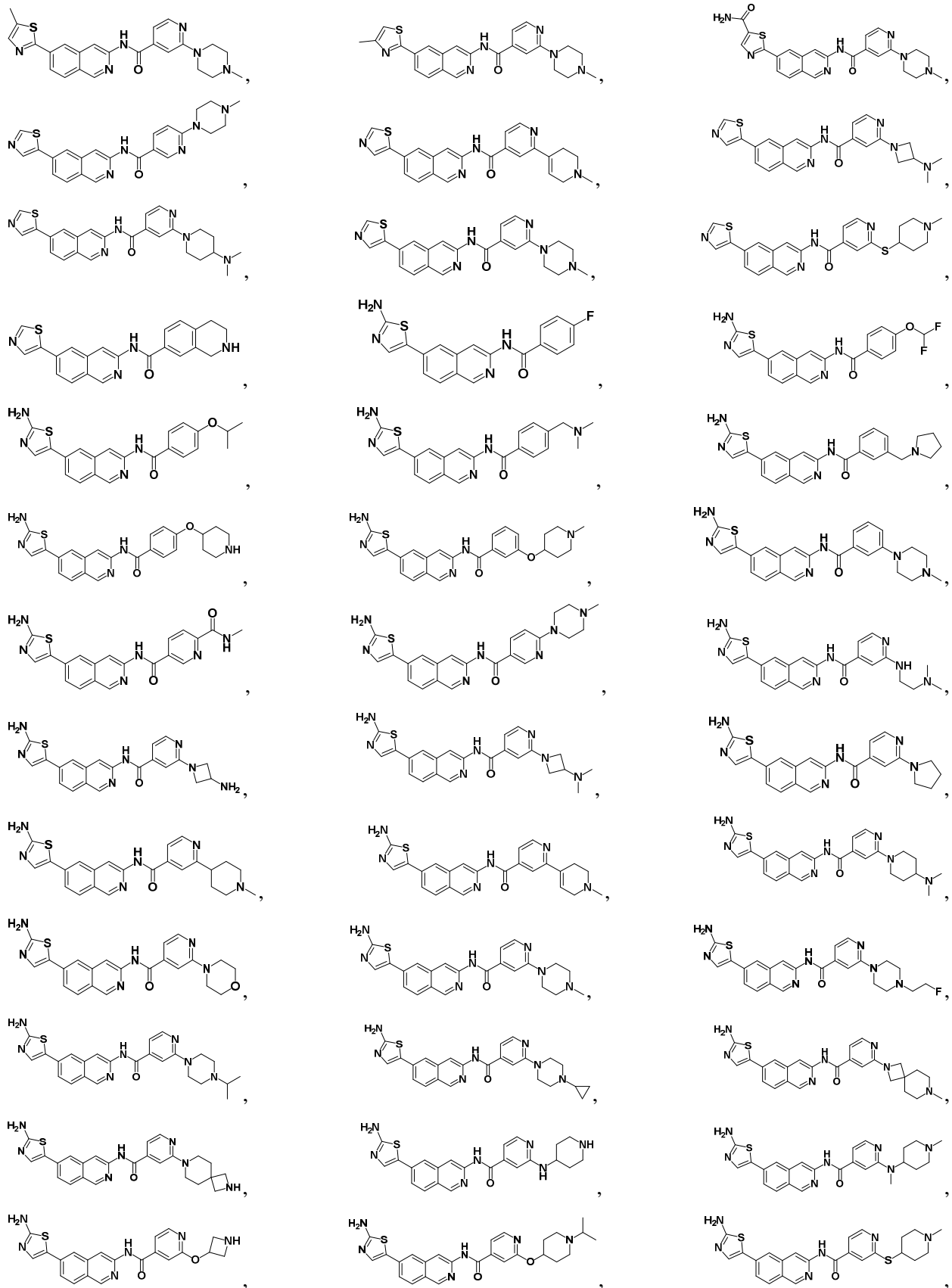


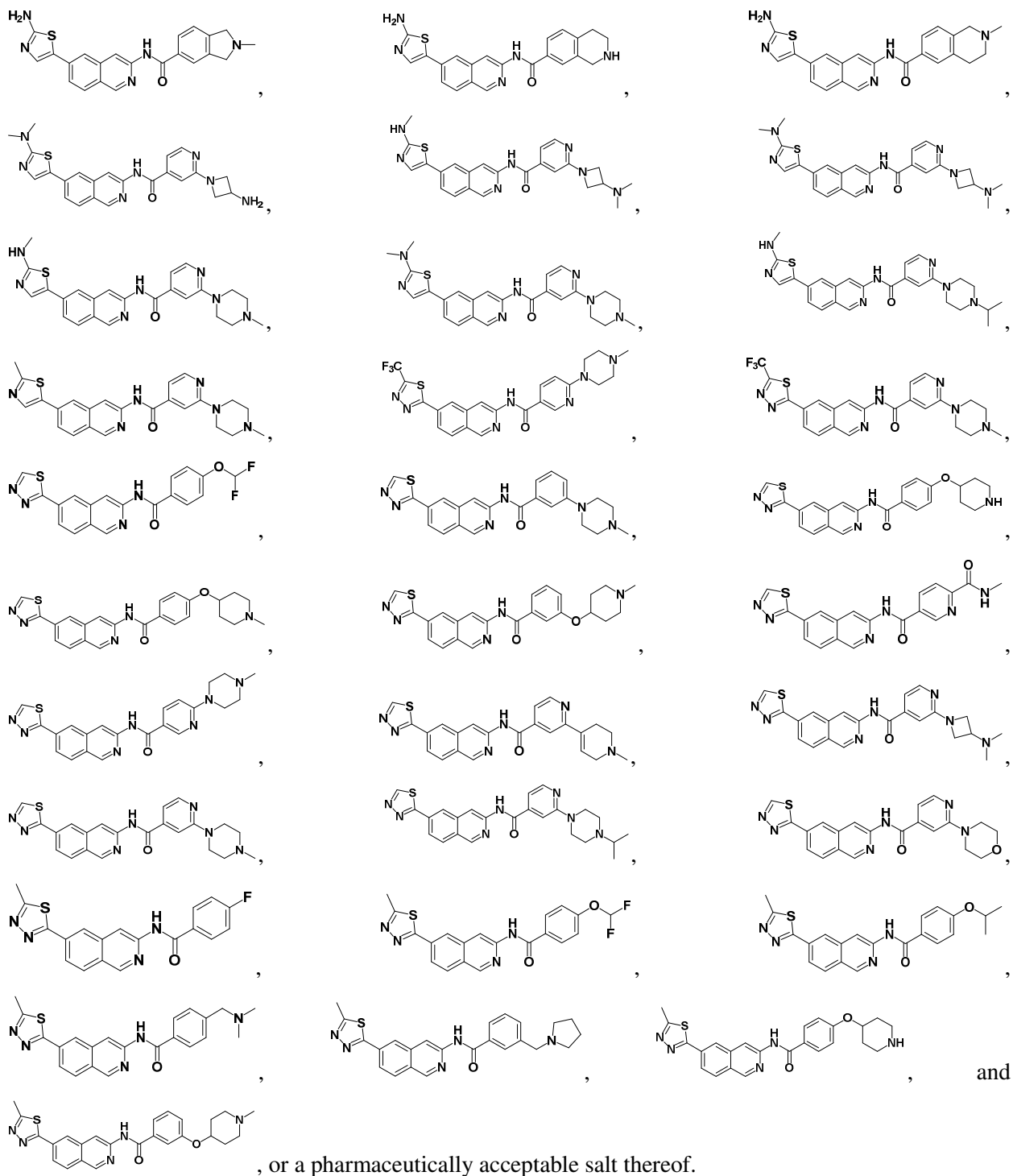




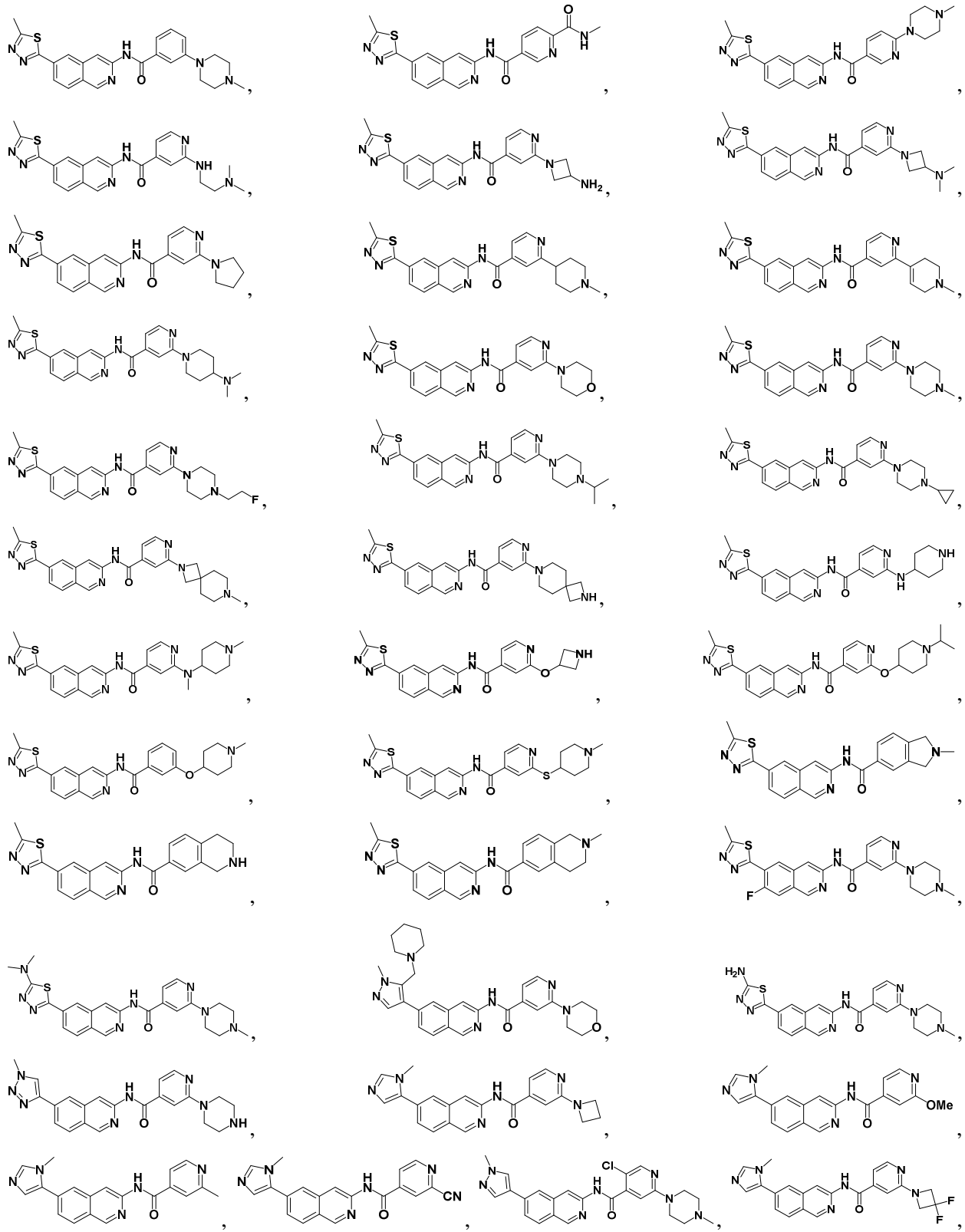
29. The compound of claim 1, wherein the compound of Formula I is selected from the group consisting of:

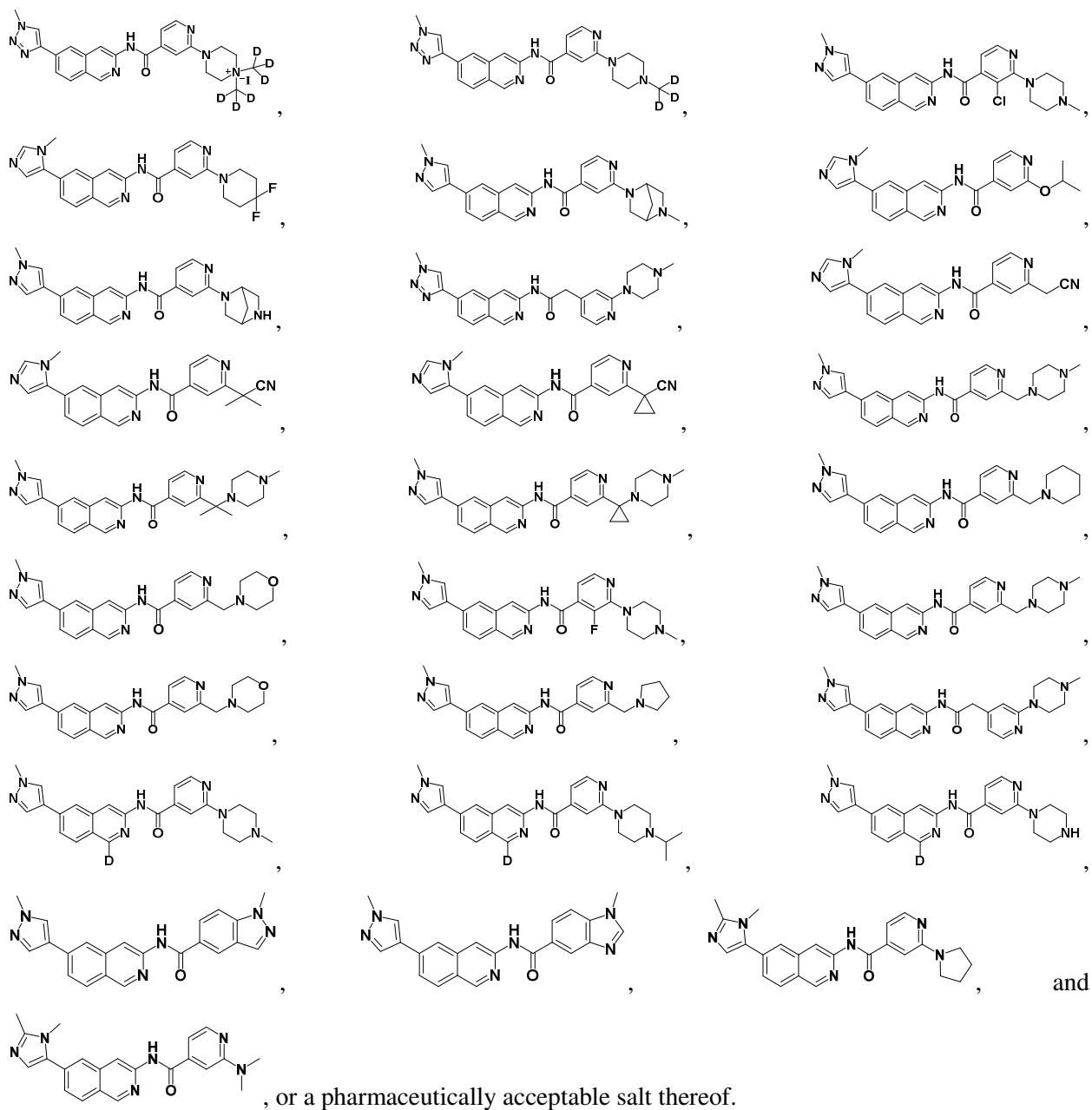






30. The compound of claim 1, wherein the compound of Formula I is selected from the group consisting of:





31. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

32. Use of a compound according to any one of claims 1-30, or a pharmaceutically acceptable salt thereof, in the preparation of a pharmaceutical composition for treating a disorder or disease in a patient, wherein the patient is human and the disorder or disease is selected from the group consisting of: cancer, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), degenerative disc disease,

bone/osteoporotic fractures, a bone or cartilage disease, osteoarthritis, lung disease, and a fibrotic disorder.

33. The use according to claim 32, wherein the disorder or disease is cancer.

34. The use according to claim 32, wherein the disorder or disease is pulmonary fibrosis.

35. The use according to claim 32, wherein the disorder or disease is idiopathic pulmonary fibrosis (IPF).

36. The use according to claim 32, wherein the disorder or disease is lung disease.

37. The use according to claim 32, wherein the disorder or disease is degenerative disc disease.

38. The use according to claim 32, wherein the disorder or disease is a bone/osteoporotic fracture.

39. The use according to claim 32, wherein the disorder or disease is a bone or cartilage disease.

40. The use according to claim 32, wherein the disorder or disease is osteoarthritis.

41. The use according to any one of claims 32-33, wherein the cancer is selected from the group consisting of: hepatocellular carcinoma, colon cancer, breast cancer, pancreatic cancer, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic lymphocytic leukemia (CLL), acute myeloid leukemia, acute lymphocytic leukemia, Hodgkin lymphoma, lymphoma, sarcoma, and ovarian cancer.

42. The use according to any one of claims 32-33, wherein the cancer is selected from the group consisting of: lung cancer - non-small cell, lung cancer - small cell, multiple myeloma, nasopharyngeal cancer, neuroblastoma, osteosarcoma, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer - basal and squamous cell, skin cancer – melanoma, small intestine cancer, stomach cancers, testicular cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, laryngeal or hypopharyngeal cancer, kidney cancer, Kaposi sarcoma, gestational trophoblastic disease, gastrointestinal stromal tumor, gastrointestinal carcinoid tumor, gallbladder cancer, eye cancer (melanoma and lymphoma), Ewing tumor, esophagus cancer, endometrial cancer, colorectal cancer, cervical cancer, brain or spinal cord tumor, bone metastasis, bone cancer, bladder cancer, bile duct cancer, anal cancer, and adrenal cortical cancer.

43. The use according to claim 32, wherein the disorder or disease is a fibrotic disorder, wherein the fibrotic disorder is selected from the group consisting of: skin fibrosis; scleroderma; progressive systemic fibrosis; lung fibrosis; muscle fibrosis; kidney fibrosis; glomerulosclerosis; glomerulonephritis; hypertrophic scar formation; uterine fibrosis; renal fibrosis; cirrhosis of the liver, liver fibrosis; adhesions; chronic obstructive pulmonary disease; fibrosis following myocardial infarction;

pulmonary fibrosis; fibrosis and scarring associated with diffuse/interstitial lung disease; central nervous system fibrosis; fibrosis associated with proliferative vitreoretinopathy (PVR); restenosis; endometriosis; ischemic disease, and radiation fibrosis.

- 44.** The use according to claim 41, wherein the disorder or disease is pancreatic cancer .