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(54) Title: ISOQUINOLIN-3-YL CARBOXAMIDES AND PREPARATION AND USE THEREOF

(57) **Abrégé/Abstract:**

Isoquinoline compounds for treating various diseases and pathologies are disclosed. More particularly, the present disclosure concerns the use of an isoquinoline compound or analogs thereof, in the treatment of disorders characterized by the activation of Wnt pathway signaling (e.g., cancer, abnormal cellular proliferation, angiogenesis, Alzheimer's disease, lung disease, inflammation, auto-immune diseases and osteoarthritis), the modulation of cellular events mediated by Wnt pathway signaling, as well as neurological conditions/disorders/diseases linked to overexpression of DYRK1A.

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- (54) Title: ISOQUINOLIN-3-YL CARBOXAMIDES AND PREPARATION AND USE THEREOF
- (57) Abstract: Isoquinoline compounds for treating various diseases and pathologies are disclosed. More particularly, the present disclosure concerns the use of an isoquinoline compound or analogs thereof, in the treatment of disorders characterized by the activation of Wnt pathway signaling (e.g., cancer, abnormal cellular proliferation, angiogenesis, Alzheimer's disease, lung disease, inflammation, auto-immune diseases and osteoarthritis), the modulation of cellular events mediated by Wnt pathway signaling, as well as neurological conditions/disorders/diseases linked to overexpression of DYRK1A.
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ISOQUINOLIN-3-YL CARBOXAMIDES AND PREPARATION AND USE THEREOF

RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application No. 62/328,210, filed April 27, 2016, which is incorporated herein by reference in its entirety.

BACKGROUND

Technical Field

[002] This disclosure relates to inhibitors of one or more proteins in the Wnt pathway, including inhibitors of one or more Wnt proteins, and compositions comprising the same. More particularly, it concerns the use of an isoquinoline compound or salts or analogs thereof, in the treatment of disorders characterized by the activation of Wnt pathway signaling (e.g., cancer, abnormal cellular proliferation, angiogenesis, Alzheimer's disease, lung disease, inflammation, auto-immune diseases fibrotic disorders, cartilage (chondral) defects, and osteoarthritis), the modulation of cellular events mediated by Wnt pathway signaling, as well as genetic diseases and neurological conditions/disorders/diseases due to mutations or dysregulation of the Wnt pathway and/or of one or more of Wnt signaling components. Also provided are methods for treating Wnt-related disease states, as well as neurological conditions/disorders/diseases linked to overexpression of DYRK1A.

Background

[003] The Wnt growth factor family includes more than 10 genes identified in the mouse and at least 19 genes identified in the human. Members of the Wnt family of signaling molecules mediate many short-and long-range patterning processes during invertebrate and vertebrate development. The Wnt signaling pathway is known for its role in the inductive interactions that regulate growth and differentiation, and it also plays roles in the homeostatic maintenance of post-embryonic tissue integrity. Wnt stabilizes cytoplasmic β -catenin, which stimulates the expression of genes including c-myc, c jun, fra-1, and cyclin D1. In addition, misregulation of Wnt signaling can cause developmental defects and is implicated in the genesis of several human cancers. The Wnt pathway has also been implicated in the maintenance of stem or progenitor cells in a growing list of adult tissues including skin, blood, gut, prostate, muscle, and the nervous system.

[004] Dual specificity tyrosine-phosphorylation-regulated kinase 1A is an enzyme that in humans is encoded by the DYRK1A gene. DYRK1A is a member of the dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family. DYRK1A contains a nuclear targeting signal sequence, a protein kinase domain, a leucine zipper motif, and a highly conservative 13-consecutive-histidine repeat. It catalyzes its autophosphorylation on serine/threonine and tyrosine residues. It may play a significant role in a signaling pathway regulating cell proliferation and may be involved in brain development. DYRK1A is localized in the Down syndrome critical region of chromosome 21, and is considered to be a candidate gene for learning defects associated with Down syndrome. DYRK1A is also expressed in adult brain neurons, indicating that DYRK1A may play a role in the mature central nervous system. Thus, several lines of evidence point to some synaptic functions of DYRK1A. For instance, it has been found that DYRK1A phosphorylates and modulates the interaction of several components of the endocytic protein complex machinery (Dynamin 1, Amphiphysin, and Synaptojanin), suggesting a role in synaptic vesicle recycling. In addition, a polymorphism (SNP) in DYRK1A was found to be associated with HIV-1 replication in monocyte-derived macrophages, as well as with progression to AIDS in two independent cohorts of HIV-1-infected individuals.

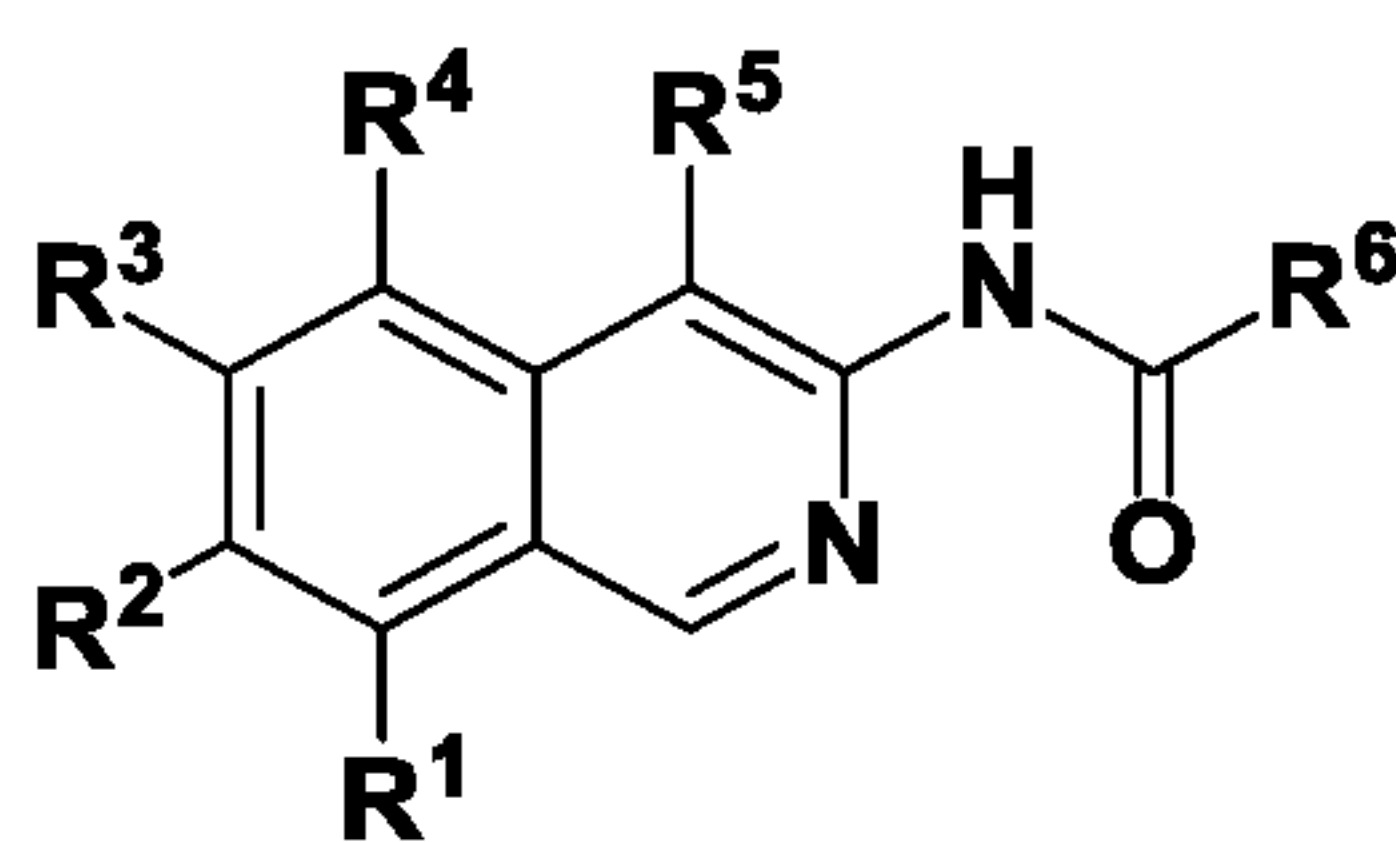
SUMMARY

[005] 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.

[006] The present disclosure also provides methods and reagents, involving contacting a cell with an agent, such as an isoquinoline compound, in a sufficient amount to antagonize DYRK1A activity, e.g., i) to normalize prenatal and early postnatal brain development; ii) to improve cognitive function in youth and adulthood; and/or iii) to attenuate Alzheimer's-type neurodegeneration.

[007] Some embodiments disclosed herein include Wnt and/or DYRK1A inhibitors containing an isoquinoline core. Other embodiments disclosed herein include pharmaceutical compositions and methods of treatment using these compounds.

[008] One embodiment disclosed herein includes a compound having the structure of Formula I:



I

as well as prodrugs and pharmaceutically acceptable salts thereof.

[009] In some embodiments of Formula (I):

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, 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 $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{36} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{37} , $-(C_{1-4} \text{ alkylene})N(R^{46})(R^{47})$, and $-CF(C_{1-9} \text{ alkyl})_2$; wherein each alkyl of $-CF(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more halides; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 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 $-(C_{1-5} \text{ haloalkyl})$, $-CN$, 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 one or more substituents as defined anywhere herein;

each R^{39} independently 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 $-(C_{1-5} \text{ haloalkyl})$, $-CN$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} ; wherein each $-(C_{1-4}$

alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

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 $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ 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^{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 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 $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ 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^{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 $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, 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^{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 H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 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} ;

R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

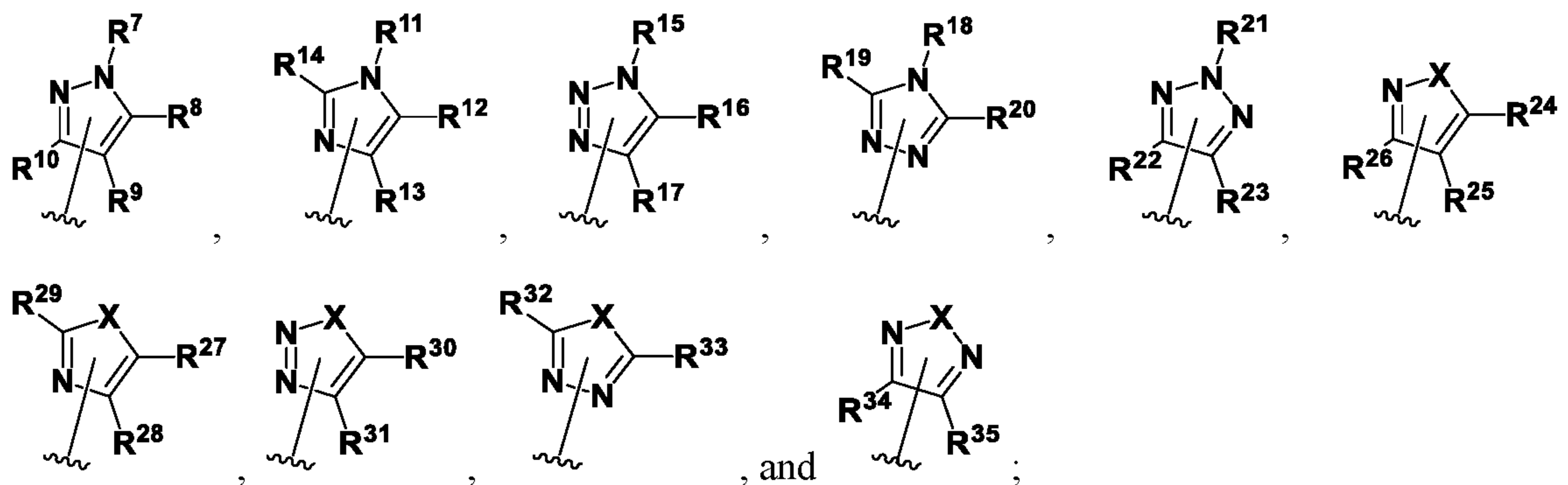
R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl 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 one or more substituents as defined anywhere herein;

each p is independently 0 or 1.

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

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, 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; for purposes of clarification, 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; likewise, 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; so 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 nitrogen atom to which R^{18} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{18} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{19} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{19} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{20} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{20} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{21} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{21} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{22} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{22} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{23} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{23} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{24} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{24} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{25} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{25} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{26} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{26} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{27} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{27} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{28} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{28} 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 $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{36} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{37} , $-(C_{1-4} \text{ alkylene})N(R^{46})(R^{47})$, and $-CF(C_{1-9} \text{ alkyl})_2$; wherein each alkyl of $-CF(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more halides; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{38} ,

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, one of R⁷ and R⁸, R⁸ and R⁹, or R⁹ and R¹⁰ 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;

R¹¹ 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)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted with 1-12 R³⁹; wherein –(C₁₋₄ alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

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

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)_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, 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)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl optionally substituted

with 1-12 R³⁹; wherein -(C₁₋₄ alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

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

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)_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, 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)_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, 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)_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, 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)_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, 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)_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;

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)_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, 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), –(C₁₋₄ alkylene)_pOR⁴², –(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), –(C₁₋₄ alkylene)_pOR⁴², –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R⁴³, and –(C₁₋

₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R³⁸ independently 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 $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R³⁹ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴⁰ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴¹ 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 R⁴² is independently selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴³ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴⁴ 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 $-\text{CN}$;

R⁴⁶ is attached to the nitrogen and is selected from the group consisting of H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9}$

haloalkyl), $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

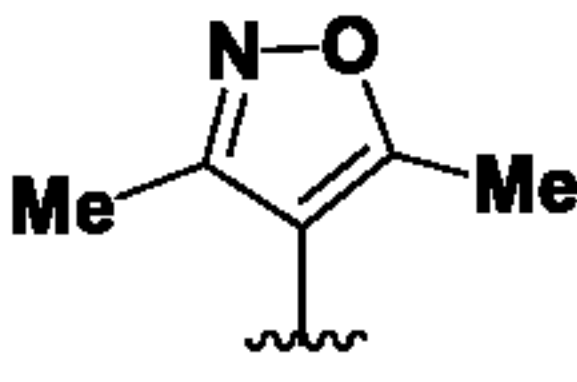
each X is O or S; and

each p is independently 0 or 1.

[011] In another embodiment of Formula (I):

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, 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} ;

with the proviso that R^3 is not  ;

R^6 is selected from the group consisting of $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{36} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{37} , $-(C_{1-4} \text{ alkylene})N(R^{46})(R^{47})$, $-N(R^{48})(R^{49})$, $-\text{CF}(C_{1-9} \text{ alkyl})_2$, $-(C_{1-4} \text{ alkylene})_pO(C_{3-9} \text{ alkyl})$, and $-(C_{2-9} \text{ alkynyl})$ optionally substituted with one or more halides; wherein each alkyl of $-\text{CF}(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more halides; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

with the proviso that R^6 is not unsubstituted $-(CH_2)$ tetrahydropyranyl;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{43} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} , $-\text{C}(=\text{O})(R^{50})$, $-(C_{1-4} \text{ alkylene})C(=\text{O})OR^{51}$, $-(C_{1-4} \text{ alkylene})\text{aryl}$ optionally substituted with one or more halides, $-(C_{1-4} \text{ alkylene})_p$ heteroaryl optionally substituted with one or more halides, and $-\text{SO}_2(R^{52})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two R^{36} attached to the same carbon atom can together represent $=\text{O}$ to form a carbonyl group;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-N(R^{53})_2$, $-C(=O)(R^{50})$, $-C(=O)OR^{51}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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} independently 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 $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, 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 one or more substituents as defined anywhere herein;

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 one or more substituents as defined anywhere herein;

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 $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ 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^{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 $-(C_{1-5} \text{ haloalkyl})$, 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^{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 $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, 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^{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 H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_p\text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, two adjacent R^{45} 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^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

R^{48} is attached to the nitrogen and 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 $-(C_{1-5} \text{ haloalkyl})$;

R^{49} is attached to the nitrogen and is selected from the group consisting of $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{50} is selected from the group consisting of H, unsubstituted $-(C_{3-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{aryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heteroaryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with one or more halides or one or more

unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

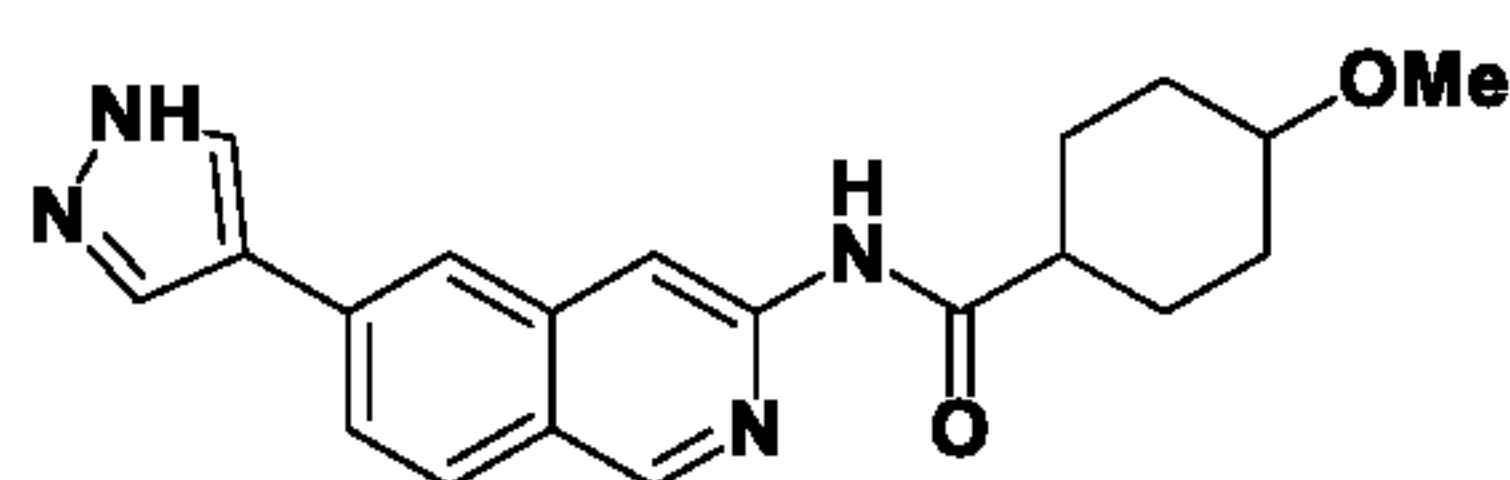
R^{51} is selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{aryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heteroaryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{52} is selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{aryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heteroaryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

each R^{53} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, and unsubstituted $-(C_{2-5} \text{ alkynyl})$;

each p is independently 0 or 1; and

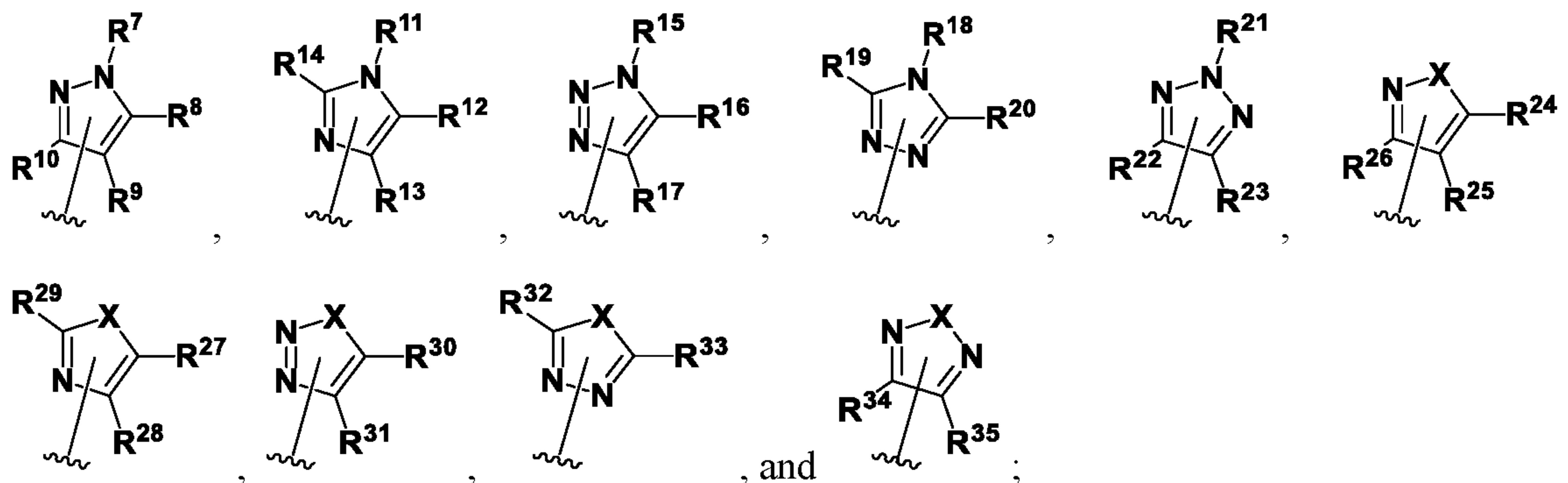
with the proviso that Formula I is not a structure selected from the group consisting of:



[012] In another embodiment of Formula (I):

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, 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; for purposes of clarification, 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; likewise, 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; so 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 nitrogen atom to which R^{18} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{18} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{19} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{19} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{20} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{20} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{21} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{21} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{22} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{22} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{23} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{23} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{24} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{24} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{25} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{25} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{26} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{26} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{27} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{27} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{28} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{28} 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 $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{36} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{37} , $-(C_{1-4} \text{ alkylene})N(R^{46})(R^{47})$, $-N(R^{48})(R^{49})$, $-CF(C_{1-9} \text{ alkyl})_2$, $-(C_{1-4} \text{ alkylene})_pO(C_{3-9} \text{ alkyl})$, and $-(C_{2-9} \text{ alkynyl})$ optionally substituted with one or more halides; wherein each alkyl of $-CF(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more halides; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

with the proviso that R^6 is not unsubstituted $-(CH_2)$ tetrahydropyranyl;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

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)OR⁴², –(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 one or more substituents as defined anywhere herein;

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), –N(R⁵³)₂, –(C₁₋₄ alkylene)_pOR⁴², –(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 one or more substituents as defined anywhere herein;

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)OR⁴², –(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 one or more substituents as defined anywhere herein;

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), –N(R⁵³)₂, –(C₁₋₄ alkylene)_pOR⁴², –(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 one or more substituents as defined anywhere herein;

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)OR⁴², –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁸, and –carbocyclyl

optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

R^{22} and R^{23} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, R^{22} and R^{23} 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^{24} , R^{25} , and R^{26} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

with the proviso that when R^{25} is a single bond connecting R^3 to the isoquinoline ring, R^{24} and R^{26} are not methyls;

alternatively, one of R^{24} and R^{25} or R^{25} and R^{26} 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^{27} , R^{28} , and R^{29} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, R^{27} and R^{28} 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^{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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$

optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

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 –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), $-N(R^{53})_2$, –(C₁₋₄ alkylene)_pOR⁴², –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{34} and R^{35} 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), $-N(R^{53})_2$, –(C₁₋₄ alkylene)_pOR⁴², –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

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 –(C₁₋₉ alkyl), unsubstituted –(C₂₋₉ alkenyl), unsubstituted –(C₂₋₉ alkynyl), unsubstituted –(C₁₋₉ haloalkyl), –(C₁₋₄ alkylene)_pOR⁴², –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R^{43} , –(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R^{44} , $-C(=O)(R^{50})$, –(C₁₋₄ alkylene)C(=O)OR⁵¹, –(C₁₋₄ alkylene)aryl optionally substituted with one or more halides, –(C₁₋₄ alkylene)_pheteroaryl optionally substituted with one or more halides, and $-SO_2(R^{52})$; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two R^{36} attached to the same carbon atom can together represent $=O$ to form a carbonyl group;

each R^{37} 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)_pOR⁴², $-N(R^{53})_2$, $-C(=O)(R^{50})$, $-C(=O)OR^{51}$, –(C₁₋₄ alkylene)_pheterocyclyl

optionally substituted with 1-10 R⁴³, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R³⁸ independently 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 $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R³⁹ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴⁰ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴¹ 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 R⁴² is independently selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴³ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴⁴ 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 $-\text{CN}$;

R⁴⁶ is attached to the nitrogen and is selected from the group consisting of H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R³⁸, and $-\text{carbocyclyl}$ optionally substituted with 1-12 R³⁹; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

R⁴⁷ is attached to the nitrogen and is selected from the group consisting of unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R³⁸, and $-\text{carbocyclyl}$ optionally substituted with 1-12 R³⁹; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

R⁴⁸ is attached to the nitrogen and 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 $-(C_{1-5} \text{ haloalkyl})$;

R⁴⁹ is attached to the nitrogen and is selected from the group consisting of $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R³⁸, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R³⁹; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R⁵⁰ is selected from the group consisting of H, unsubstituted $-(C_{3-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ aryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heteroaryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R⁵¹ is 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 $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ aryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heteroaryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R⁵² is selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ aryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4}$

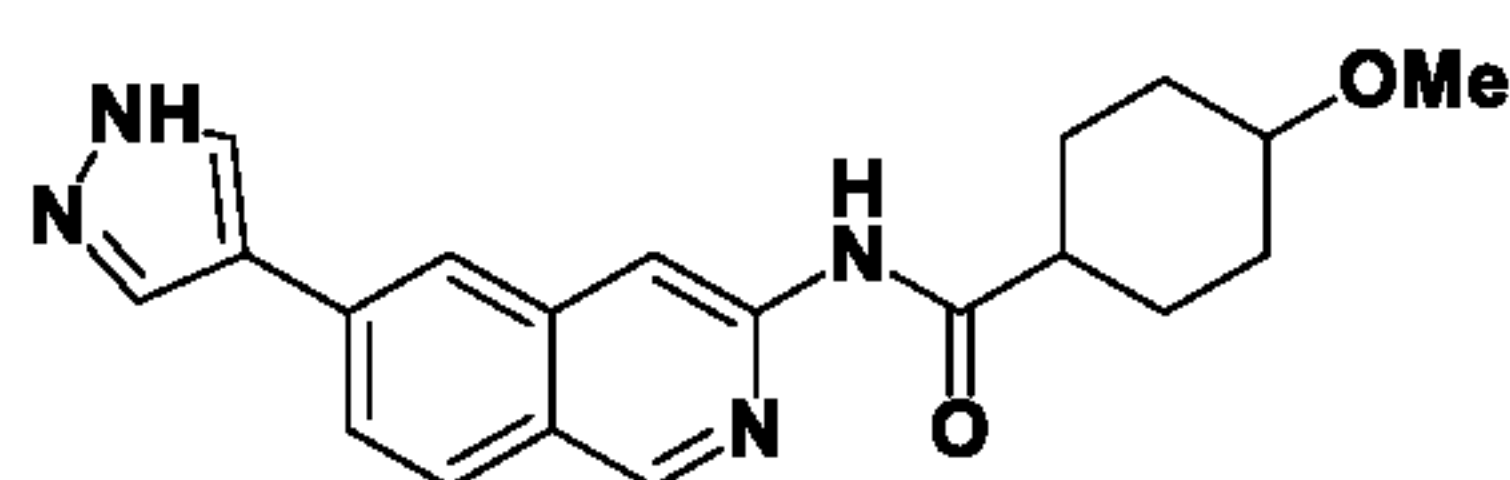
alkylene)_pheteroaryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

each R^{53} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, and unsubstituted $-(C_{2-5} \text{ alkynyl})$;

each X is O or S; and

each p is independently 0 or 1; and

with the proviso that Formula I is not a structure selected from the group consisting of:



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

[014] Some embodiments include pro-drugs of a compound of Formula (I).

[015] Some embodiments of the present disclosure include pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier, diluent, or excipient.

[016] Other embodiments 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.

[017] Other embodiments disclosed herein include methods of inhibiting DYRK1A by administering to a patient affected by a disorder or disease in which DYRK1A overexpression is implicated, such as Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson's Disease, Pick's Disease, and additional diseases with pronounced neurodegeneration such as Autism, Dementia, Epilepsy, Huntington's Disease, Multiple Sclerosis; diseases and disorders

associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor and Stroke.

[018] 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, onycho-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.

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

[020] 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 disclosure, as claimed.

DETAILED DESCRIPTION

[021] Provided herein are compositions and methods for inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins. Other Wnt inhibitors and methods for using the same are disclosed in U.S. Application Ser. Nos. 13/614,296; 14/019,229; and 14/664,517, all of which are incorporated by reference in their entirety herein.

[022] Provided herein are compositions and methods for inhibiting DYRK1A. Other DYRK1A inhibitors and methods for using the same are disclosed in U.S. Application Ser. No. 14/664,517, which is incorporated by reference in its entirety herein.

[023] Some embodiments provided herein relate to a method for treating a disease including, but not limited to, neurological diseases or disorders, cancers, chronic inflammation, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, bone and cartilage diseases, lung disease,

osteoarthritis, 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-Awadi/Raas-Rothschild/Schinzal phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, 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's syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease, and Rett syndrome.

[024] In some embodiments, non-limiting examples of bone and cartilage diseases which can be treated with the compounds and compositions provided herein include bone spur (osteophytes), craniosynostosis, fibrodysplasia ossificans progressive, fibrous dysplasia, giant cell tumor of bone, hip labral tear, meniscal tears, osteoarthritis, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), osteochondritis dissecans, osteochondroma (bone tumor), osteopetrosis, relapsing polychondritis, and Salter-Harris fractures.

[025] In some embodiments, non-limiting examples of a neurological disease or disorder associated with tau protein, amyloid or alpha-synuclein pathology which can be treated with the compounds and compositions provided herein include, but are not limited to, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson's Disease, Pick's Disease, and additional diseases with pronounced neurodegeneration such as Autism, Dementia, Epilepsy, Huntington's Disease, Multiple Sclerosis; diseases and disorders associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor, and Stroke.

[026] In some embodiments, non-limiting examples of diseases in which chronic inflammation is involved which can be treated with the compounds and compositions provided herein include eye disorders, joint pain, arthritis (rheumatoid, osteo, psoriatic gout), cancers (colon, breast, lung, pancreas, and others), gastrointestinal disorders (ulcerative colitis and inflammatory bowel diseases), pulmonary disorders (chronic obstructive pulmonary disorder and asthma), allergies, skin disorders (atopic dermatitis and psoriasis), diabetes, pancreatitis, tendonitis, hepatitis, heart disease, myocarditis, stroke, lupus, and neurological disorders such as multiple sclerosis, Parkinson's and dementia including Alzheimer's disease.

[027] In some embodiments, non-limiting examples of cancers which can be treated with the compounds and compositions provided herein include colon, ovarian, pancreatic, breast, liver, prostate, and hematologic cancers.

[028] In some embodiments, pharmaceutical compositions are provided that are effective for treatment of a disease of an animal, e.g., a mammal, caused by either the pathological activation or mutations of the Wnt pathway or DYRK1A overexpression. The composition includes a pharmaceutically acceptable carrier and a compound as described herein.

Definitions

[029] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[030] As used herein, "alkyl" means a branched, or straight chain chemical group containing only carbon and hydrogen, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, sec-pentyl and neo-pentyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents. In some embodiments, alkyl groups include 1 to 9 carbon atoms (for example, 1 to 6 carbon atoms, 1 to 4 carbon atoms, or 1 to 2 carbon atoms).

[031] As used herein, "alkenyl" means a straight or branched chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond, such as ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. In various embodiments, alkenyl groups can either be unsubstituted or substituted with one or more substituents. Typically, alkenyl groups will comprise 2 to 9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

[032] As used herein, "alkynyl" means a straight or branched chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon triple bond, such as ethynyl, 1-propynyl, 1-butyne, 2-butyne, and the like. In various embodiments, alkynyl groups can either be unsubstituted or substituted with one or more substituents. Typically, alkynyl groups will comprise 2 to 9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

[033] As used herein, "alkylene" means a bivalent branched, or straight chain chemical group containing only carbon and hydrogen, such as methylene, ethylene, n-propylene,

iso-propylene, n-butylene, iso-butylene, sec-butylene, tert-butylene, n-pentylene, iso-pentylene, sec-pentylene and neo-pentylene. Alkylene groups can either be unsubstituted or substituted with one or more substituents. In some embodiments, alkylene groups include 1 to 9 carbon atoms (for example, 1 to 6 carbon atoms, 1 to 4 carbon atoms, or 1 to 2 carbon atoms).

[034] As used herein, “alkenylene” means a bivalent branched, or straight chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond, such as ethenylene, 1-propenylene, 2-propenylene, 2-methyl-1-propenylene, 1-butenylene, 2-butenylene, and the like. In various embodiments, alkenylene groups can either be unsubstituted or substituted with one or more substituents. Typically, alkenylene groups will comprise 2 to 9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

[035] As used herein, “alkynylene” means a bivalent branched, or straight chain chemical group containing only carbon and hydrogen and containing at least one carbon-carbon triple bond, such as ethynylene, 1-propynylene, 1-butyne, 2-butyne, and the like. In various embodiments, alkynylene groups can either be unsubstituted or substituted with one or more substituents. Typically, alkynylene groups will comprise 2 to 9 carbon atoms (for example, 2 to 6 carbon atoms, 2 to 4 carbon atoms, or 2 carbon atoms).

[036] As used herein, “alkoxy” means an alkyl-O— group in which the alkyl group is as described herein. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, pentoxy, hexoxy and heptoxy, and also the linear or branched positional isomers thereof.

[037] As used herein, “haloalkoxy” means a haloalkyl-O— group in which the haloalkyl group is as described herein. Exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and also the linear or branched positional isomers thereof.

[038] As used herein, “carbocyclyl” means a cyclic ring system containing only carbon atoms in the ring system backbone, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl. Carbocyclyls may include multiple fused rings. Carbocyclyls may have any degree of saturation provided that none of the rings in the ring system are aromatic. Carbocyclyl groups can either be unsubstituted or substituted with one or more substituents. In some embodiments, carbocyclyl groups include 3 to 10 carbon atoms, for example, 3 to 6 carbon atoms.

[039] As used herein, “aryl” means a mono-, bi-, tri- or polycyclic group with only carbon atoms present in the ring backbone having 5 to 14 ring atoms, alternatively 5, 6, 9, or 10 ring atoms; and having 6, 10, or 14 pi electrons shared in a cyclic array; wherein at least one ring

in the system is aromatic. Aryl groups can either be unsubstituted or substituted with one or more substituents. Examples of aryl include phenyl, naphthyl, tetrahydronaphthyl, 2,3-dihydro-1H-indenyl, and others. In some embodiments, the aryl is phenyl.

[040] As used herein, “arylalkylene” means an aryl-alkylene- group in which the aryl and alkylene moieties are as previously described. In some embodiments, arylalkylene groups contain a C₁₋₄alkylene moiety. Exemplary arylalkylene groups include benzyl and 2-phenethyl.

[041] As used herein, the term “heteroaryl” means a mono-, bi-, tri- or polycyclic group having 5 to 14 ring atoms, alternatively 5, 6, 9, or 10 ring atoms; and having 6, 10, or 14 pi electrons shared in a cyclic array; wherein at least one ring in the system is aromatic, and at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, and S. Heteroaryl groups can either be unsubstituted or substituted with one or more substituents. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnoliny, indazolyl, indolyl, isoquinoliny, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinoliny, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridine, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromane, 2,3-dihydrobenzo[*b*][1,4]dioxine, benzo[*d*][1,3]dioxole, 2,3-dihydrobenzofuran, tetrahydroquinoline, 2,3-dihydrobenzo[*b*][1,4]oxathiine, isoindoline, and others. In some embodiments, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindoliny, pyranyl, pyrazinyl, and pyrimidinyl.

[042] As used herein, “halo”, “halide” or “halogen” is a chloro, bromo, fluoro, or iodo atom radical. In some embodiments, a halo is a chloro, bromo or fluoro. For example, a halide can be fluoro.

[043] As used herein, “haloalkyl” means a hydrocarbon substituent, which is a linear or branched, alkyl, alkenyl or alkynyl substituted with one or more chloro, bromo, fluoro, and/or iodo atom(s). In some embodiments, a haloalkyl is a fluoroalkyls, wherein one or more of the hydrogen atoms have been substituted by fluoro. In some embodiments, haloalkyls are of 1 to about 3 carbons in length (e.g., 1 to about 2 carbons in length or 1 carbon in length). The term “haloalkylene” means a diradical variant of haloalkyl, and such diradicals may act as spacers between radicals, other atoms, or between a ring and another functional group.

[044] As used herein, “heterocyclyl” means a nonaromatic cyclic ring system comprising at least one heteroatom in the ring system backbone. Heterocyclyls may include

multiple fused rings. Heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, heterocycles have 3-11 members. In six membered monocyclic heterocycles, the heteroatom(s) are selected from one to three of O, N or S, and wherein when the heterocycle is five membered, it can have one or two heteroatoms selected from O, N, or S. Examples of heterocyclyl include aziriny, aziridiny, azetidiny, oxetany, thietany, 1,4,2-dithiazoly, dihydropyridiny, 1,3-dioxany, 1,4-dioxany, 1,3-dioxolany, morpholiny, thiomorpholiny, piperaziny, pyran, pyrrolidiny, tetrahydrofury, tetrahydropyridiny, oxaziny, thiaziny, thiiny, thiazolidiny, isothiazolidiny, oxazolidiny, isoxazolidiny, piperidiny, pyrazolidiny, imidazolidiny, thiomorpholiny, and others. In some embodiments, the heterocyclyl is selected from azetidiny, morpholiny, piperaziny, pyrrolidiny, and tetrahydropyridiny.

[045] As used herein, “monocyclic heterocyclyl” means a single nonaromatic cyclic ring comprising at least one heteroatom in the ring system backbone. Heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, heterocycles have 3-7 members. In six membered monocyclic heterocycles, the heteroatom(s) are selected from one to three of O, N or S, and wherein when the heterocycle is five membered, it can have one or two heteroatoms selected from O, N, or S. Examples of heterocyclyls include aziriny, aziridiny, azetidiny, oxetany, thietany, 1,4,2-dithiazoly, dihydropyridiny, 1,3-dioxany, 1,4-dioxany, 1,3-dioxolany, morpholiny, thiomorpholiny, piperaziny, pyran, pyrrolidiny, tetrahydrofury, tetrahydropyridiny, oxaziny, thiaziny, thiiny, thiazolidiny, isothiazolidiny, oxazolidiny, isoxazolidiny, piperidiny, pyrazolidiny, imidazolidiny, thiomorpholiny, and others.

[046] As used herein, “bicyclic heterocyclyl” means a nonaromatic bicyclic ring system comprising at least one heteroatom in the ring system backbone. Bicyclic heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, bicyclic heterocycles have 4-11 members with the heteroatom(s) being selected from one to five of O, N or S. Examples of bicyclic heterocyclyls include 2-azabicyclo[1.1.0]butane, 2-azabicyclo[2.1.0]pentane, 2-azabicyclo[1.1.1]pentane, 3-azabicyclo[3.1.0]hexane, 5-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.2.0]heptane, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[4.1.0]heptane, 7-azabicyclo[2.2.1]heptane, 6-azabicyclo[3.1.1]heptane, 7-azabicyclo[4.2.0]octane, 2-azabicyclo[2.2.2]octane, and the like.

[047] As used herein, “spirocyclic heterocyclyl” means a nonaromatic bicyclic ring system comprising at least one heteroatom in the ring system backbone and with the rings connected through just one atom. Spirocyclic heterocyclyls may be substituted or unsubstituted with one or more substituents. In some embodiments, spirocyclic heterocycles have 5-11 members with the heteroatom(s) being selected from one to five of O, N or S. Examples of spirocyclic

heterocyclyls include 2-azaspiro[2.2]pentane, 4-azaspiro[2.5]octane, 1-azaspiro[3.5]nonane, 2-azaspiro[3.5]nonane, 7-azaspiro[3.5]nonane, 2-azaspiro[4.4]nonane, 6-azaspiro[2.6]nonane, 1,7-diazaspiro[4.5]decane, 2,5-diazaspiro[3.6]decane, and the like.

[048] The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more non-hydrogen atoms of the molecule. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. Substituents can include, for example, $-(C_{1-9} \text{ alkyl})$ optionally substituted with one or more of hydroxyl, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, and $-N(C_{1-3} \text{ alkyl})_2$; $-(C_{1-9} \text{ haloalkyl})$; a halide; a hydroxyl; a carbonyl [such as $-C(O)OR$, and $-C(O)R$]; a thiocarbonyl [such as $-C(S)OR$, $-C(O)SR$, and $-C(S)R$]; $-(C_{1-9} \text{ alkoxy})$ optionally substituted with one or more of halide, hydroxyl, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, and $-N(C_{1-3} \text{ alkyl})_2$; $-OPO(OH)_2$; a phosphonate [such as $-PO(OH)_2$ and $-PO(OR')_2$]; $-OPO(OR')R''$; $-NRR'$; $-C(O)NRR'$; $-C(NR)NR'R''$; $-C(NR')R''$; a cyano; a nitro; an azido; $-SH$; $-S-R$; $-OSO_2(OR)$; a sulfonate [such as $-SO_2(OH)$ and $-SO_2(OR)$]; $-SO_2NR'R''$; and $-SO_2R$; in which each occurrence of R , R' and R'' are independently selected from H ; $-(C_{1-9} \text{ alkyl})$; C_{6-10} aryl optionally substituted with from 1-3 R''' ; 5-10 membered heteroaryl having from 1-4 heteroatoms independently selected from N , O , and S and optionally substituted with from 1-3 R''' ; C_{3-7} carbocyclyl optionally substituted with from 1-3 R''' ; and 3-8 membered heterocyclyl having from 1-4 heteroatoms independently selected from N , O , and S and optionally substituted with from 1-3 R''' ; wherein each R''' is independently selected from $-(C_{1-6} \text{ alkyl})$, $-(C_{1-6} \text{ haloalkyl})$, a halide (e.g., F), a hydroxyl, $-C(O)OR$, $-C(O)R$, $-(C_{1-6} \text{ alkoxy})$, $-NRR'$, $-C(O)NRR'$, and a cyano, in which each occurrence of R and R' is independently selected from H and $-(C_{1-6} \text{ alkyl})$. In some embodiments, the substituent is selected from $-(C_{1-6} \text{ alkyl})$, $-(C_{1-6} \text{ haloalkyl})$, a halide (e.g., F), a hydroxyl, $-C(O)OR$, $-C(O)R$, $-(C_{1-6} \text{ alkoxy})$, $-NRR'$, $-C(O)NRR'$, and a cyano, in which each occurrence of R and R' is independently selected from H and $-(C_{1-6} \text{ alkyl})$.

[049] As used herein, when two groups are indicated to be “linked” or “bonded” to form a “ring”, it is to be understood that a bond is formed between the two groups and may involve replacement of a hydrogen atom on one or both groups with the bond, thereby forming a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring. The skilled artisan will recognize that such rings can and are readily formed by routine chemical reactions. In some embodiments, such rings have from 3-7 members, for example, 5 or 6 members.

[050] The skilled artisan will recognize that some chemical structures described herein may be represented on paper by one or more other resonance forms; or may exist in one or more other tautomeric forms, even when kinetically, the artisan recognizes that such tautomeric forms represent only a very small portion of a sample of such compound(s). Such compounds are clearly contemplated within the scope of this disclosure, though such resonance forms or tautomers are not explicitly represented herein.

[051] The compounds provided herein may encompass various stereochemical forms. The compounds also encompass diastereomers as well as optical isomers, e.g., mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

[052] The present disclosure includes all pharmaceutically acceptable isotopically labeled compounds of Formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature. Examples of isotopes suitable for inclusion in the compounds of the disclosure include, but are not limited to, isotopes of hydrogen, such as ^2H (deuterium) and ^3H (tritium), carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S .

[053] The term “administration” or “administering” refers to a method of providing a dosage of a compound or pharmaceutical composition to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian, where the method is, e.g., orally, subcutaneously, intravenously, intralymphatic, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, ontologically, neuro-otologically, intraocularly, subconjunctivally, via anterior eye chamber injection, intravitreally, intraperitoneally, intrathecally, intracystically, intrapleurally, via wound irrigation, intrabuccally, intra-abdominally, intra-articularly, intra-aurally, intrabronchially, intracapsularly, intrameningeally, via inhalation, via endotracheal or endobronchial instillation, via direct instillation into pulmonary cavities, intraspinally, intrasynovially, intrathoracically, via thoracostomy irrigation, epidurally, intratympanically, intracisternally, intravascularly, intraventricularly, intraosseously, via irrigation

of infected bone, or via application as part of any admixture with a prosthetic device. The method of administration can vary depending on various factors, e.g., the components of the pharmaceutical composition, the site of the disease, the disease involved, and the severity of the disease.

[054] A “diagnostic” as used herein is a compound, method, system, or device that assists in the identification or characterization of a health or disease state. The diagnostic can be used in standard assays as is known in the art.

[055] The term “mammal” is used in its usual biological sense. Thus, it specifically includes humans, cattle, horses, monkeys, dogs, cats, mice, rats, cows, sheep, pigs, goats, and non-human primates, but also includes many other species.

[056] The term “pharmaceutically acceptable carrier”, “pharmaceutically acceptable diluent” or “pharmaceutically acceptable excipient” includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings, isotonic and absorption delaying agents and the like which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman *et al.* (Eds.) (2010); Goodman and Gilman’s: The Pharmacological Basis of Therapeutics, 12th Ed., The McGraw-Hill Companies.

[057] The term “pharmaceutically acceptable salt” refers to salts that retain the biological effectiveness and properties of the compounds provided herein and, which are not biologically or otherwise undesirable. In many cases, the compounds provided herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Many such salts are known in the art, for example, as described in WO 87/05297. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived

include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine.

[058] “Patient” as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate, or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate. In some embodiments, the patient is a human.

[059] A “therapeutically effective amount” of a compound as provided herein is one which is sufficient to achieve the desired physiological effect and may vary according to the nature and severity of the disease condition, and the potency of the compound. “Therapeutically effective amount” is also intended to include one or more of the compounds of Formula I in combination with one or more other agents that are effective to treat the diseases and/or conditions described herein. The combination of compounds can be a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Advances in Enzyme Regulation* (1984), 22, 27-55, occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. It will be appreciated that different concentrations may be employed for prophylaxis than for treatment of an active disease. This amount can further depend upon the patient’s height, weight, sex, age and medical history.

[060] A therapeutic effect relieves, to some extent, one or more of the symptoms of the disease.

[061] “Treat,” “treatment,” or “treating,” as used herein refers to administering a compound or pharmaceutical composition as provided herein for therapeutic purposes. The term “therapeutic treatment” refers to administering treatment to a patient already suffering from a disease thus causing a therapeutically beneficial effect, such as ameliorating existing symptoms, ameliorating the underlying metabolic causes of symptoms, postponing or preventing the further development of a disorder, and/or reducing the severity of symptoms that will or are expected to develop.

[062] “Drug-eluting” and/or controlled release as used herein refers to any and all mechanisms, e.g., diffusion, migration, permeation, and/or desorption by which the drug(s) incorporated in the drug-eluting material pass therefrom over time into the surrounding body tissue.

[063] “Drug-eluting material” and/or controlled release material as used herein refers to any natural, synthetic or semi-synthetic material capable of acquiring and retaining a desired shape or configuration and into which one or more drugs can be incorporated and from which incorporated drug(s) are capable of eluting over time.

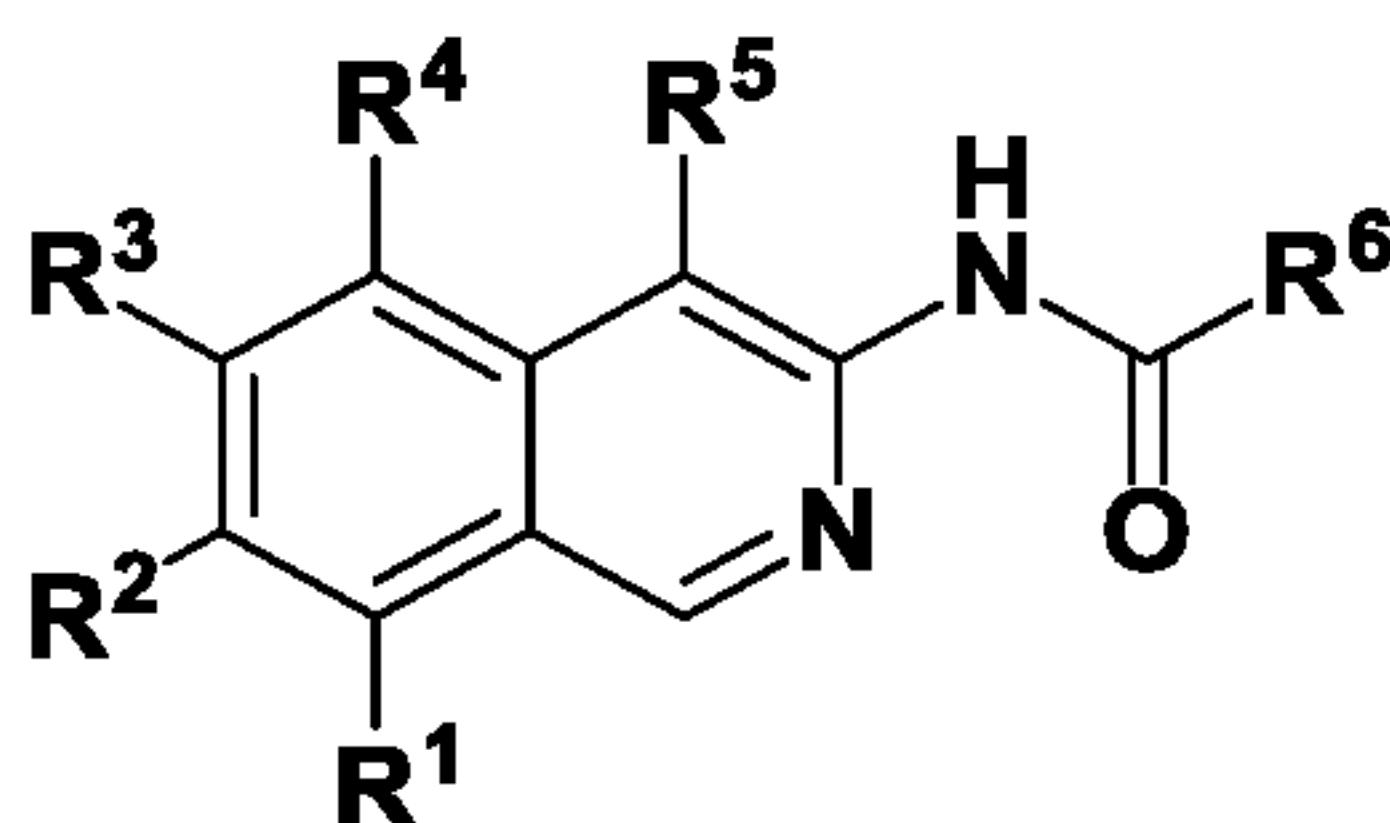
[064] “Elutable drug” as used herein refers to any drug or combination of drugs having the ability to pass over time from the drug-eluting material in which it is incorporated into the surrounding areas of the body.

Compounds

[065] The compounds and compositions described herein can be used as anti-proliferative agents, e.g., anti-cancer and anti-angiogenesis agents, and/or as inhibitors of the Wnt signaling pathway, e.g., for treating diseases or disorders associated with aberrant Wnt signaling. In addition, the compounds can be used as inhibitors of one or more kinases, kinase receptors, or kinase complexes. Such compounds and compositions are also useful for controlling cellular proliferation, differentiation, and/or apoptosis.

[066] The compounds and compositions described herein can be used to inhibit DYRK1A for treating a disorder or disease in which DYRK1A overexpression is implicated, such as Alzheimer’s Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson’s Disease, Pick’s Disease, and additional diseases with pronounced neurodegeneration such as Autism, Dementia, Epilepsy, Huntington’s Disease, Multiple Sclerosis; diseases and disorders associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor, and Stroke.

[067] Some embodiments of the present disclosure include compounds of Formula I:



I

or salts, pharmaceutically acceptable salts, or prodrugs thereof.

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

[069] In some embodiments, R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H and halide.

[070] In some embodiments, R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H and F.

[071] In some embodiments, R^1 , R^2 , R^4 , and R^5 are all H.

[072] In some embodiments, R^1 is F, and R^2 , R^4 , and R^5 are all H.

[073] In some embodiments, R^2 is F, and R^1 , R^4 , and R^5 are all H.

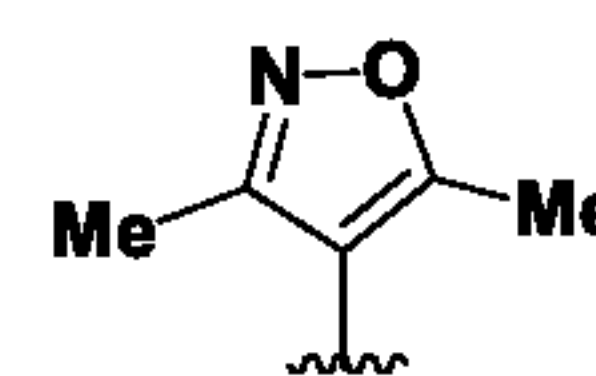
[074] In some embodiments, R^4 is F, and R^1 , R^2 , and R^5 are all H.

[075] In some embodiments, R^5 is F, and R^1 , R^2 , and R^4 are all H.

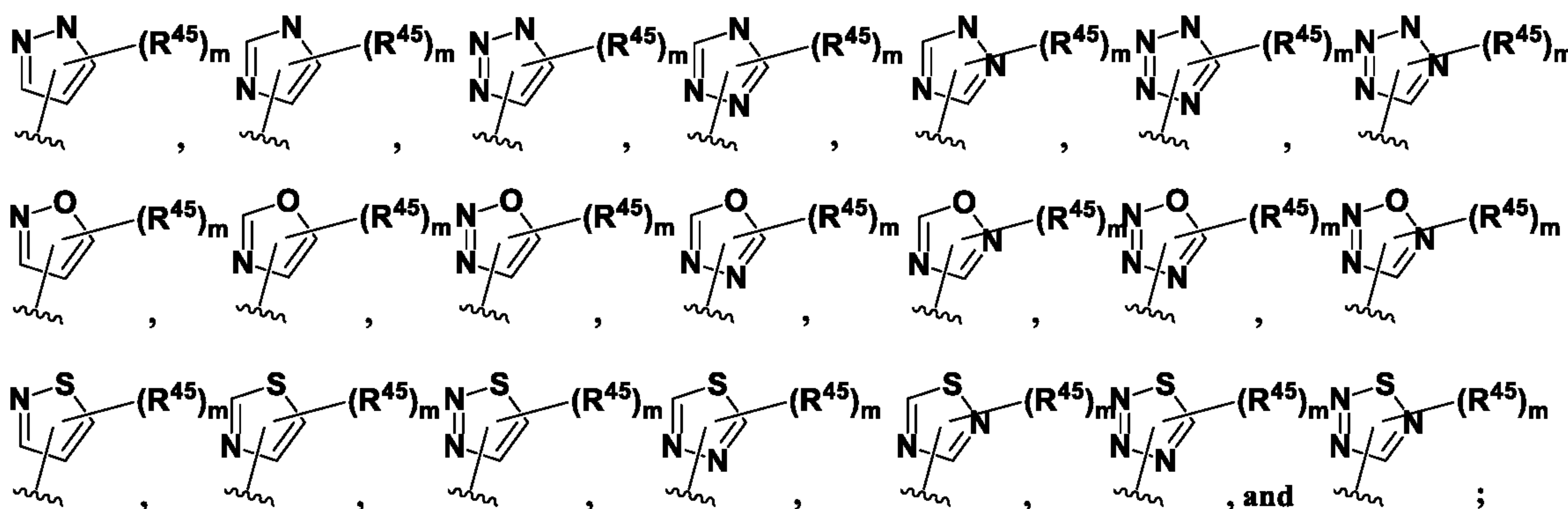
[076] In some embodiments, R^3 is a 5-membered heteroaryl ring optionally substituted as defined anywhere herein.

[077] In some embodiments, R^3 is 5-membered heteroaryl ring optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45} ;

[078] In some embodiments, there is the proviso that R^3 is not

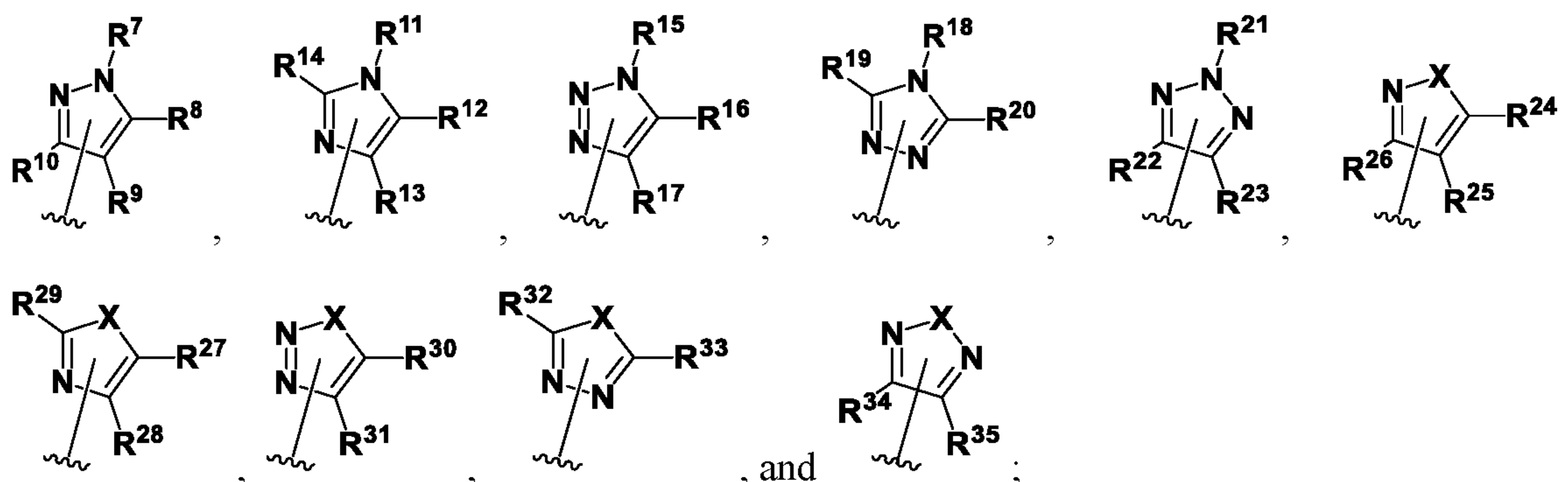


[079] In some embodiments, R^3 is selected from the group consisting of: furanyl optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45} , thiophenyl optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45} , pyrrolyl optionally substituted with 1-4 (e.g., 1-3, 1-2, 1) R^{45} ,



wherein each m is independently 1 to 4 (e.g., 1-3, 1-2, 1).

[080] In some embodiments, R^3 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, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, or R³⁵ can serve as the point of attachment of R³ to the isoquinoline ring.

[081] In some embodiments, R⁶ is selected from the group consisting of -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁶, -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁷, -(C₁₋₄ alkylene)N(R⁴⁶)(R⁴⁷), and -CF(C₁₋₉ alkyl)₂; wherein each alkyl of -CF(C₁₋₉ alkyl)₂ is, independently, optionally substituted with one or more halides; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[082] In some embodiments, R⁶ is selected from the group consisting of -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R³⁶, -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R³⁷, -(C₁₋₄ alkylene)N(R⁴⁶)(R⁴⁷), -N(R⁴⁸)(R⁴⁹), -CF(C₁₋₉ alkyl)₂, -(C₁₋₄ alkylene)_pO(C₃₋₉ alkyl), and -(C₂₋₉ alkynyl) optionally substituted with one or more halides; wherein each alkyl of -CF(C₁₋₉ alkyl)₂ is, independently, optionally substituted with one or more halides; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[083] In some embodiments, there is the proviso that R⁶ is not unsubstituted -(CH₂)₄tetrahydropyranyl.

[084] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[085] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein.

[086] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[087] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein.

[088] In some embodiments, 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 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41} .

[089] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein.

[090] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein.

[091] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[092] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein.

[093] In some embodiments, one of R^{11} and R^{12} , R^{12} and R^{13} , or R^{14} and R^{11} are taken together to form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41} .

[094] In some embodiments, R^{15} is selected from the group consisting of H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein.

[095] In some embodiments, R^{15} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein.

[096] In some embodiments, R^{16} and R^{17} are independently selected from the group consisting of H, halide, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[097] In some embodiments, R^{16} and R^{17} 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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_p\text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein.

[098] In some embodiments, one of R^{15} and R^{16} or R^{16} and R^{17} are taken together to form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41} .

[099] In some embodiments, R^{18} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein.

[0100] In some embodiments, R^{18} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})\text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein.

[0101] In some embodiments, R^{19} and R^{20} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ;

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

[0102] In some embodiments, R^{19} and R^{20} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein

[0103] In some embodiments, one of R^{18} and R^{19} or R^{18} and R^{20} are taken together to form a heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} .

[0104] In some embodiments, R^{21} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein.

[0105] In some embodiments, R^{21} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein.

[0106] In some embodiments, R^{22} and R^{23} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0107] In some embodiments, R^{22} and R^{23} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally

substituted with 1-12 R³⁹; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0108] In some embodiments, R²² and R²³ are taken together to form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴⁰ and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴¹.

[0109] In some embodiments, R²⁴, R²⁵, and R²⁶ 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p \text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁸, and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁹; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0110] In some embodiments, R²⁴, R²⁵, and R²⁶ 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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(\text{R}^{53})_2$, $-(C_{1-4} \text{ alkylene})_p \text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p \text{heterocyclyl}$ optionally substituted with 1-10 R³⁸, and $-\text{carbocyclyl}$ optionally substituted with 1-12 R³⁹; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0111] In some embodiments, there is the proviso that when R²⁵ is a single bond connecting R³ to the isoquinoline ring, R²⁴ and R²⁶ are not methyls.

[0112] In some embodiments, there is the proviso that when R²⁵ is a single bond connecting R³ to the isoquinoline ring, R²⁴ and R²⁶ are not both methyls.

[0113] In some embodiments, there is the proviso that when R²⁵ is a single bond connecting R³ to the isoquinoline ring, R²⁴ and R²⁶ are not selected from the group consisting of a single bond, H, halide, unsubstituted $-(C_{1-2} \text{ alkyl})$, unsubstituted $-(C_2 \text{ alkenyl})$, unsubstituted $-(C_2 \text{ alkynyl})$, unsubstituted $-(C_{1-2} \text{ haloalkyl})$.

[0114] In some embodiments, one of R²⁴ and R²⁵ or R²⁵ and R²⁶ are taken together to form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴⁰ and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴¹.

[0115] In some embodiments, R²⁷, R²⁸, and R²⁹ 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4}$

alkylene)_pheterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁸, and –carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0116] In some embodiments, 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), –N(R⁵³)₂, –(C₁₋₄ alkylene)_pOR⁴², –(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 one or more substituents as defined anywhere herein.

[0117] In some embodiments, R²⁷ and R²⁸ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴⁰ and –carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴¹.

[0118] In some embodiments, 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)_pheterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁸, and –carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁹; wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0119] In some embodiments, 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), –N(R⁵³)₂, –(C₁₋₄ alkylene)_pOR⁴², –(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 one or more substituents as defined anywhere herein.

[0120] In some embodiments, R³⁰ and R³¹ are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴⁰ and –carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴¹.

[0121] In some embodiments, 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)_pheterocyclyl

optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and –carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0122] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein.

[0123] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and –carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0124] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein.

[0125] In some embodiments, 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 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and –carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41} .

[0126] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{43} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0127] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{43} , $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{44} , $-C(=O)(R^{50})$, $-(C_{1-4} \text{ alkylene})C(=O)OR^{51}$, $-(C_{1-4} \text{ alkylene})\text{aryl}$ optionally substituted with one or more halides, $-(C_{1-4} \text{ alkylene})_p\text{heteroaryl}$ optionally substituted with one or more halides (e.g. F, Cl, Br, I), and $-SO_2(R^{52})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0128] In some embodiments, two R^{36} that are attached to the same carbon atom can together represent $=O$ to form a carbonyl group.

[0129] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{43} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0130] In some embodiments, 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-N(R^{53})_2$, $-C(=O)(R^{50})$, $-C(=O)OR^{51}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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.

[0131] In some embodiments, 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 $-(C_{1-5} \text{ haloalkyl})$, $-CN$, and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0132] In some embodiments, 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 $-(C_{1-5} \text{ haloalkyl})$, $-CN$, and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{44} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0133] In some embodiments, 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 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0134] In some embodiments, 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.

[0135] In some embodiments, each R⁴² is independently selected from the group consisting of unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0136] In some embodiments, 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, and -(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R⁴⁴; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0137] In some embodiments, 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.

[0138] In some embodiments, each R⁴⁵ is independently selected from the group consisting of H, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉ alkynyl), unsubstituted -(C₁₋₉ haloalkyl), -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁸, and -carbocyclyl optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R³⁹; wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0139] In some embodiments, each R⁴⁵ is independently selected from the group consisting of H, unsubstituted -(C₁₋₉ alkyl), unsubstituted -(C₂₋₉ alkenyl), unsubstituted -(C₂₋₉

alkynyl), unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein.

[0140] In some embodiments, two adjacent R^{45} groups are taken together to form a ring which is selected from the group consisting of $-\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{40} and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{41} .

[0141] In some embodiments, R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein.

[0142] In some embodiments, R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 (e.g., 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 (e.g., 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1) R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein.

[0143] In some embodiments, R^{48} is attached to the nitrogen and 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 $-(C_{1-5} \text{ haloalkyl})$.

[0144] In some embodiments, R^{49} is attached to the nitrogen and is selected from the group consisting of $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

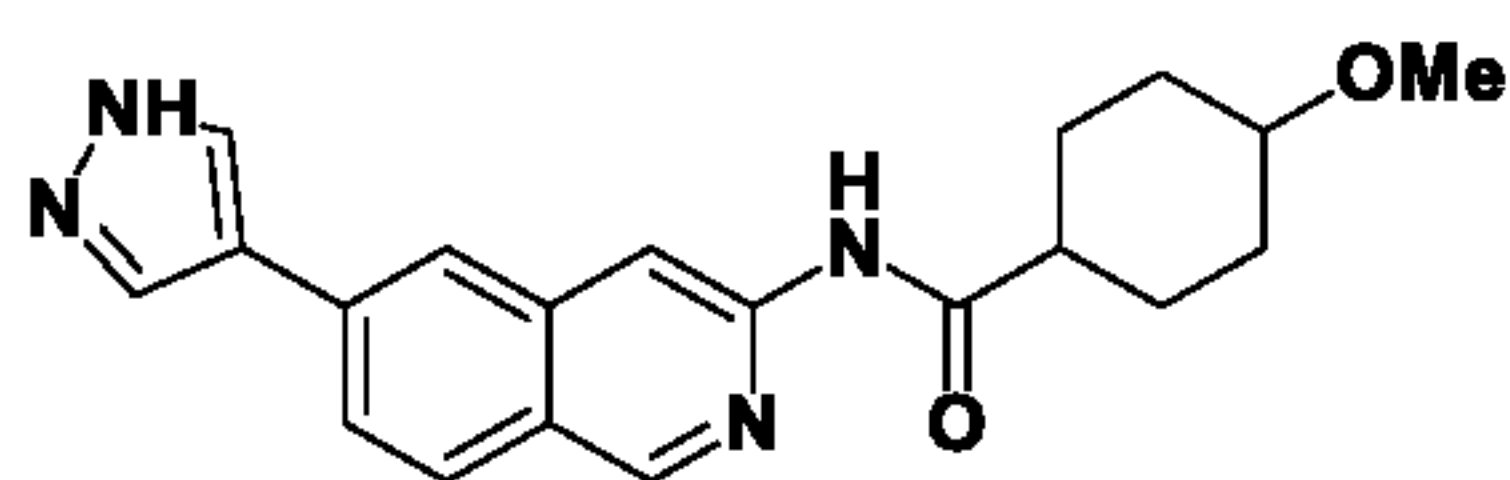
[0145] In some embodiments, R^{50} is selected from the group consisting of H, unsubstituted $-(C_{3-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{aryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heteroaryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0146] In some embodiments, R^{51} is 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 $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{aryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heteroaryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein.

[0147] In some embodiments, R^{52} is selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{aryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heteroaryl}$ optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein.

[0148] In some embodiments, each R^{53} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, and unsubstituted $-(C_{2-5} \text{ alkynyl})$.

[0149] In some embodiments, there is the proviso that Formula I is not a structure selected from the group consisting of:



[0150] In some embodiments, the carbocyclyl of $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ is optionally substituted with 1-12 R^{37} .

[0151] In some embodiments, the $-(C_{1-4} \text{ alkylene})$ of $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ is optionally substituted with 1-12 R^{37} .

[0152] In some embodiments, the heterocyclyl of $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ is optionally substituted with 1-10 R^{38} .

[0153] In some embodiments, the $-(C_{1-4} \text{ alkylene})$ of $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ is optionally substituted with 1-10 R^{38} .

[0154] In some embodiments, the carbocyclyl of $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ is optionally substituted with 1-12 R^{44} .

[0155] In some embodiments, the $-(C_{1-4} \text{ alkylene})$ of $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ is optionally substituted with 1-12 R^{44} .

[0156] In some embodiments, the heterocyclyl of $-(C_{1-4} \text{ alkylene})_p \text{heterocyclyl}$ is optionally substituted with 1-10 R^{43} .

[0157] In some embodiments, the $-(C_{1-4} \text{ alkylene})$ of $-(C_{1-4} \text{ alkylene})_p \text{heterocyclyl}$ is optionally substituted with 1-10 R^{43} .

[0158] In some embodiments, $-(C_{1-4} \text{ alkylene})$ is optionally substituted with 1-5 halide or 1-5 unsubstituted $-(C_{1-3} \text{ alkyl})$.

[0159] In some embodiments, $-(C_{1-4} \text{ alkylene})$ is substituted with 1-2 fluorines.

[0160] In some embodiments, $-(C_{1-4} \text{ alkylene})$ is substituted with 1-2 methyls.

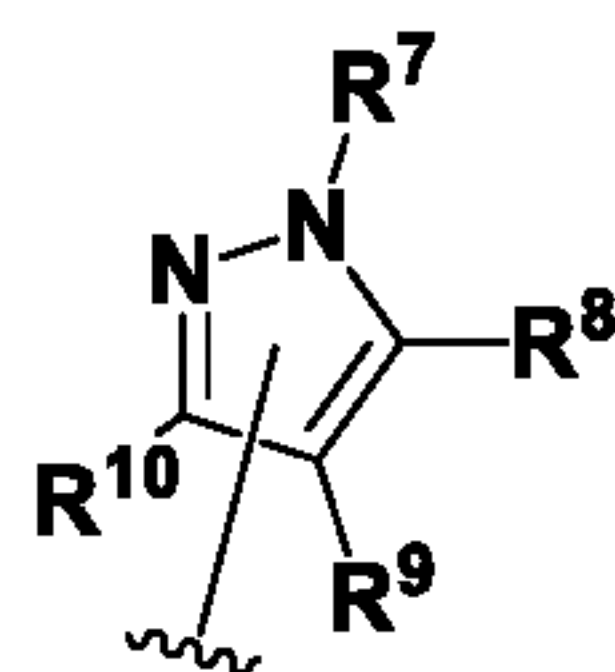
[0161] In some embodiments, each X is O or S.

[0162] In some embodiments, each m is independently 1 to 4 (e.g., 1-3, 1-2, 1).

[0163] In some embodiments, each n is independently 0 to 3 (e.g., 0-2, 0-1, 0).

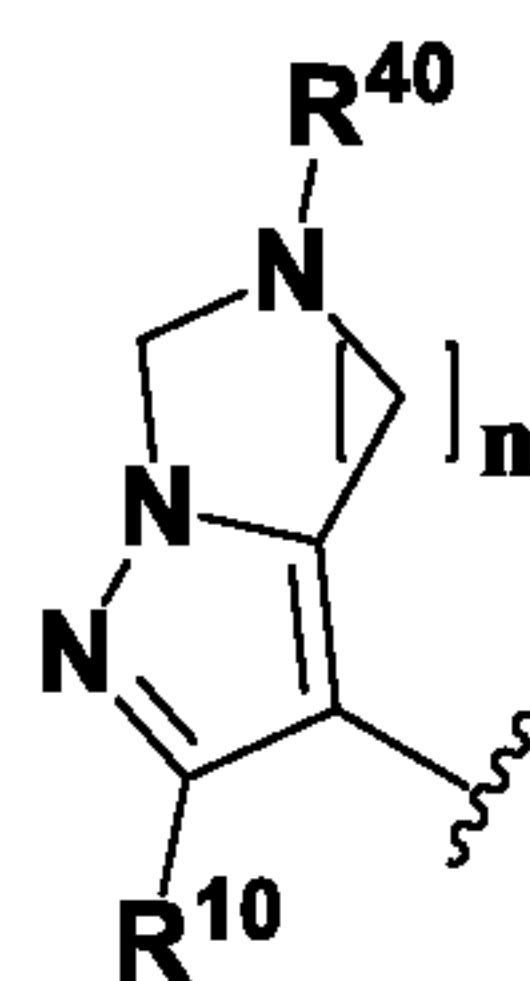
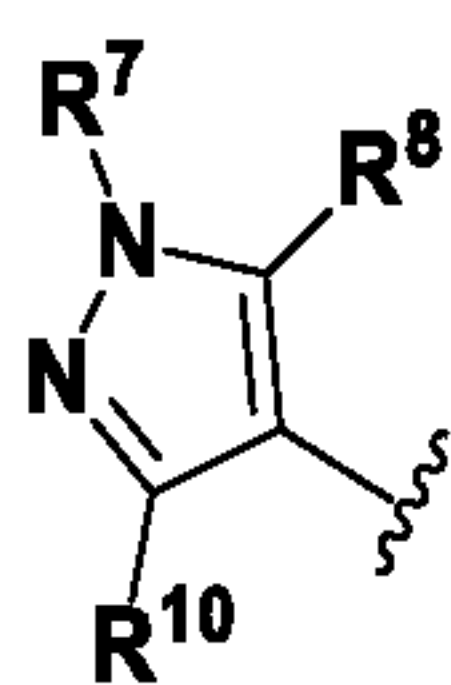
[0164] In some embodiments, each p is independently 0 or 1.

[0165] In some embodiments, each q is independently 0 to 12 (e.g., 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0).



[0166] In some embodiments, R^3 is

[0167] In certain embodiments, R^9 is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



[0168] In some embodiments, R^3 is and n is 1 to 3.

[0169] In some embodiments, R^7 is selected from the group consisting of H, unsubstituted $-(C_{1-3} \text{ alkyl})$, unsubstituted $-(C_{1-2} \text{ haloalkyl})$, and $-(C_{3-4} \text{ carbocyclyl})$ optionally substituted with 1-2 R^{39} .

[0170] In some embodiments, R^7 is selected from the group consisting of H, methyl, $-\text{CF}_3$, and cyclopropyl optionally substituted with 1-2 R^{39} .

[0171] In some embodiments, R^7 is selected from the group consisting of H and methyl.

[0172] In some embodiments, R^7 is methyl.

[0173] In some embodiments, R^7 is $-CD_3$.

[0174] In some embodiments, R^8 is selected from the group consisting of H, halide, unsubstituted $-(C_{1-2} \text{ alkyl})$, unsubstituted $-(C_{1-2} \text{ haloalkyl})$, and $-(C_{1-2} \text{ alkylene})OR^{42}$.

[0175] In some embodiments, R^8 is selected from the group consisting of H, F, methyl, $-CF_3$, $-(CH_2)OH$, and $-(CH_2)OMe$.

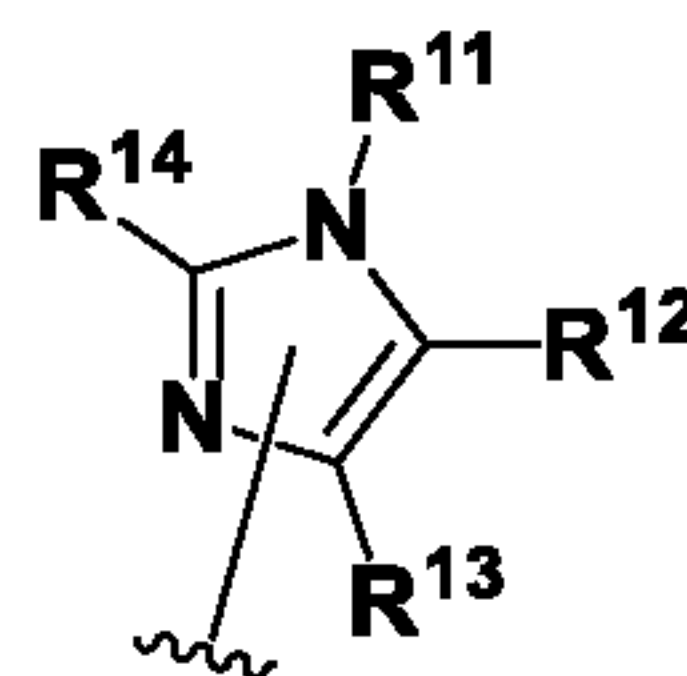
[0176] In some embodiments, R^8 is selected from the group consisting of H, F, and methyl.

[0177] In some embodiments, R^8 is H.

[0178] In some embodiments, R^{10} is selected from the group consisting of H and halide.

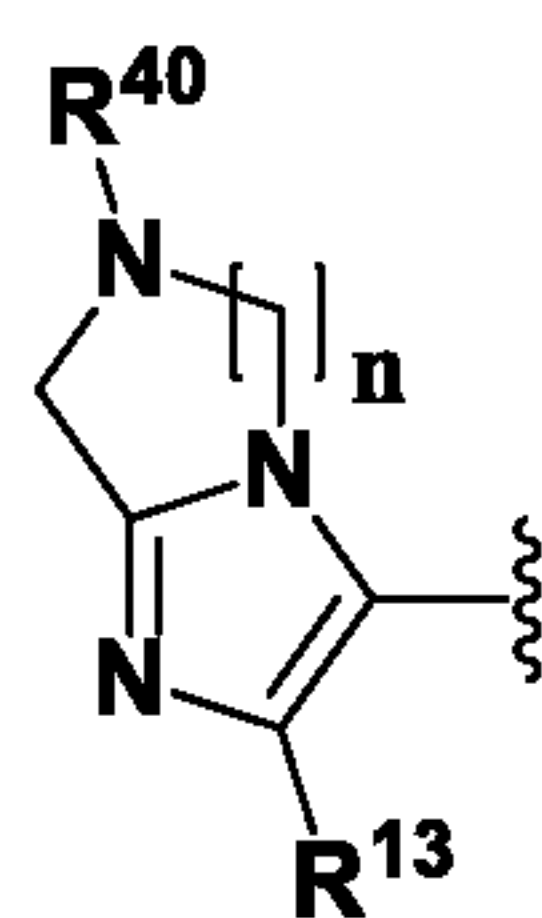
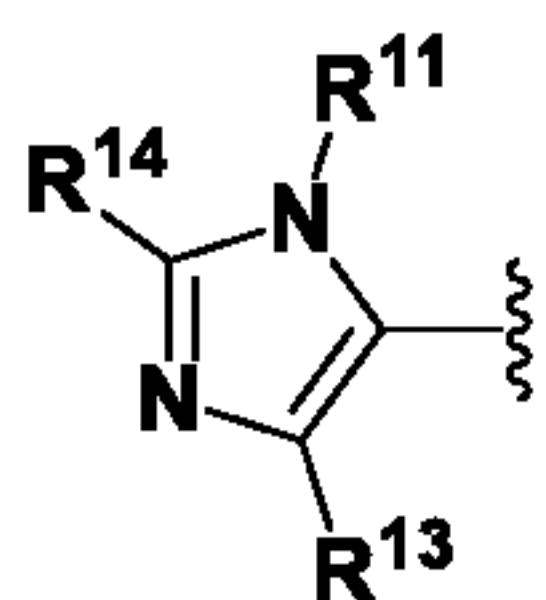
[0179] In some embodiments, R^{10} is selected from the group consisting of H and F.

[0180] In some embodiments, R^{10} is H.



[0181] In some embodiments, R^3 is

[0182] In certain embodiments, R^{12} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



[0183] In some embodiments, R^3 is and n is 1 to 3.

[0184] In some embodiments, R^{11} is selected from the group consisting of H, unsubstituted $-(C_{1-3} \text{ alkyl})$, unsubstituted $-(C_{1-2} \text{ haloalkyl})$, and $-(C_{3-4} \text{ carbocyclyl})$ optionally substituted with 1-2 R^{39} .

[0185] In some embodiments, R^{11} is selected from the group consisting of H, methyl, $-CF_3$, and cyclopropyl optionally substituted with 1-2 R^{39} .

[0186] In some embodiments, R^{11} is selected from the group consisting of H and methyl.

[0187] In some embodiments, R^{11} is methyl.

[0188] In some embodiments, R^{11} is $-CD_3$.

[0189] In some embodiments, R^{13} is selected from the group consisting of H and halide.

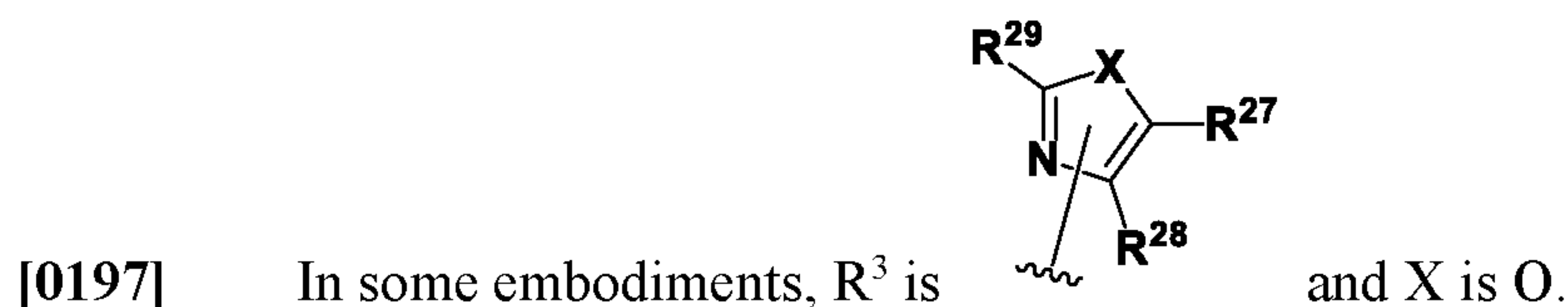
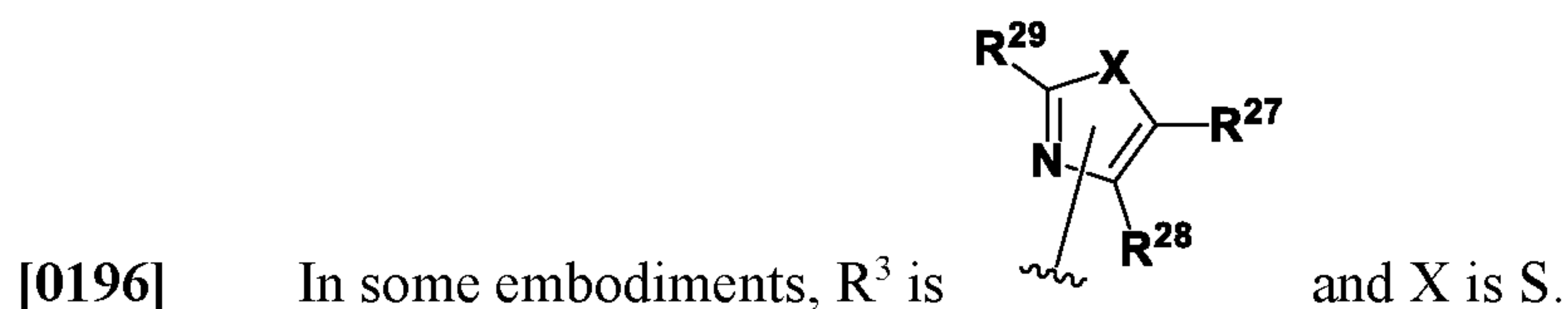
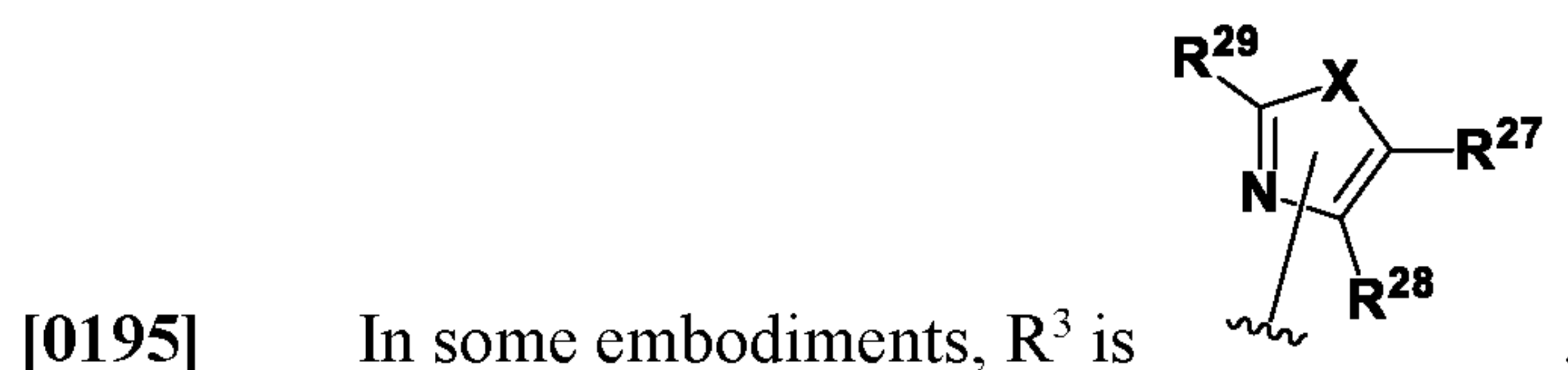
[0190] In some embodiments, R^{13} is selected from the group consisting of H and F.

[0191] In some embodiments, R^{14} is selected from the group consisting of H, halide, unsubstituted $-(C_{1-2} \text{ alkyl})$, and unsubstituted $-(C_{1-2} \text{ haloalkyl})$.

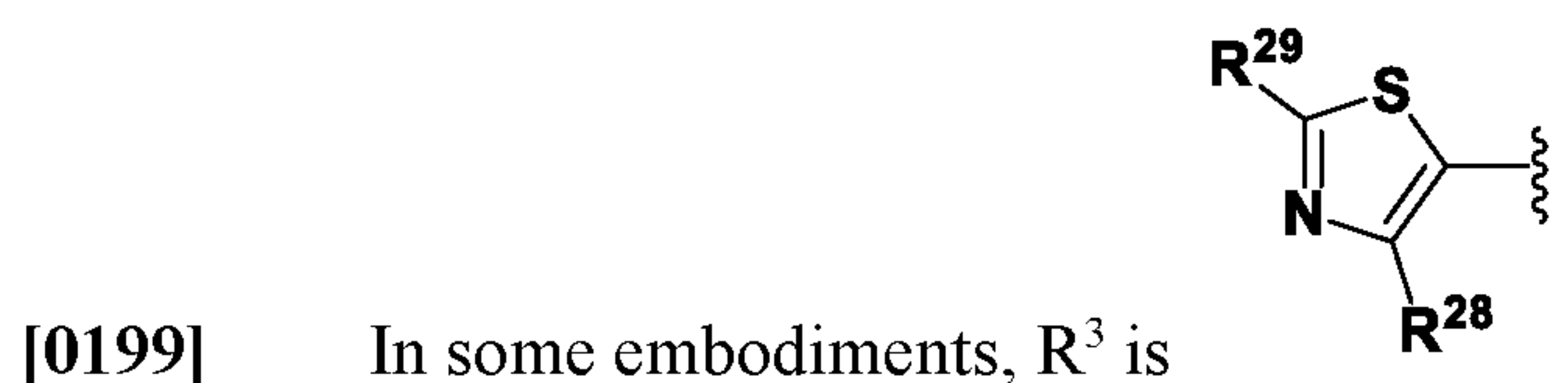
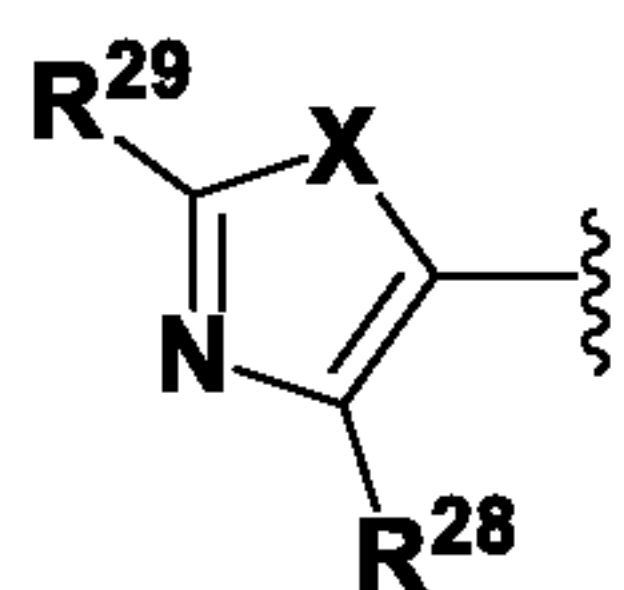
[0192] In some embodiments, R^{14} is selected from the group consisting of H, F, methyl, and $-CF_3$.

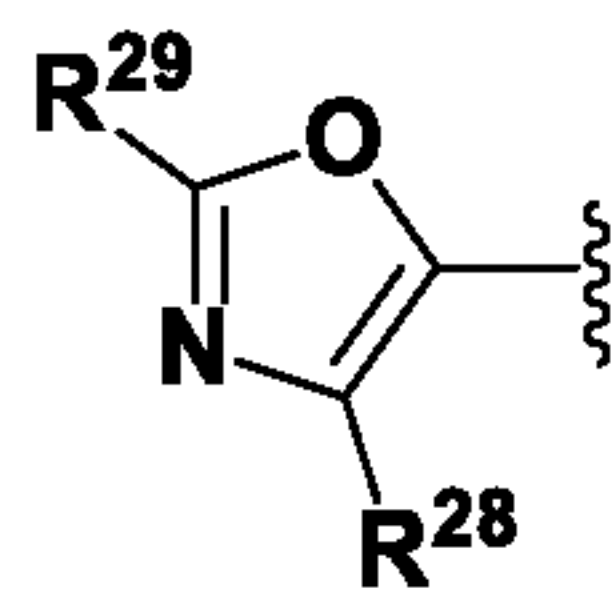
[0193] In some embodiments, R^{14} is selected from the group consisting of H and methyl.

[0194] In some embodiments, R^{11} and R^{14} are both methyl.



[0198] In certain embodiments, R^{27} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:





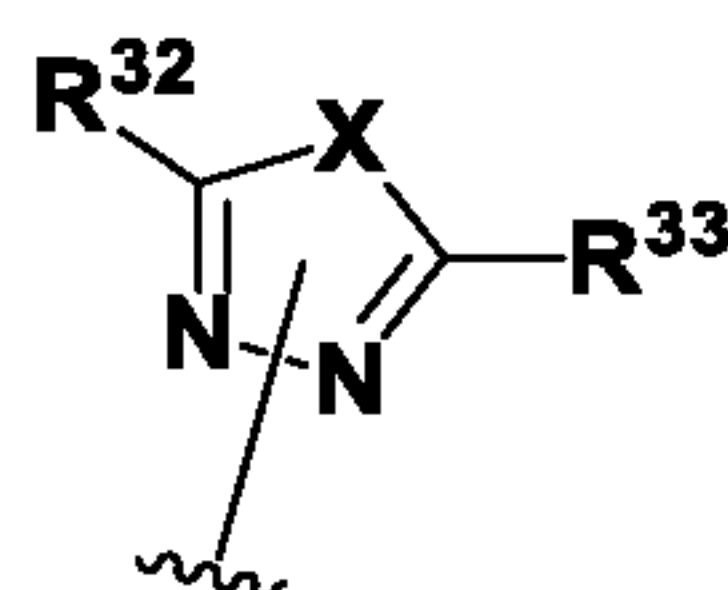
[0200] In some embodiments, R^3 is

[0201] In some embodiments, R^{28} is selected from the group consisting of H and halide.

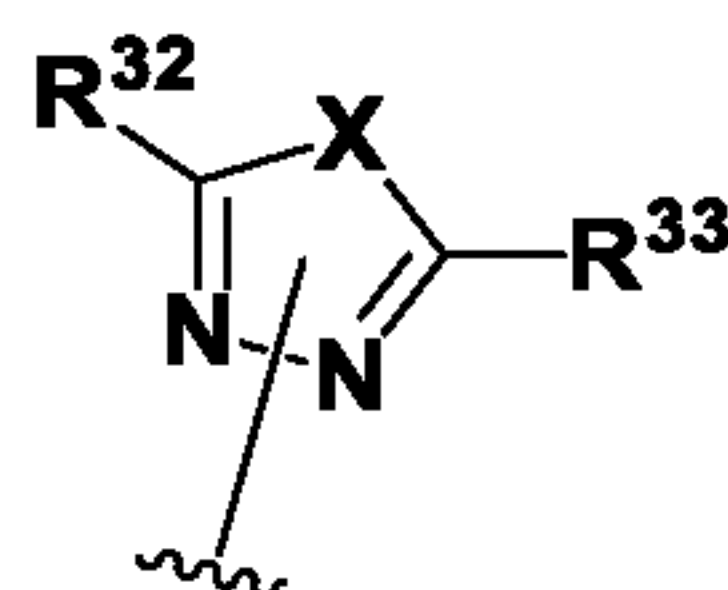
[0202] In some embodiments, R^{28} is selected from the group consisting of H and F.

[0203] In some embodiments, R^{29} is selected from the group consisting of H, halide, unsubstituted $-(C_{1-2} \text{ alkyl})$, and unsubstituted $-(C_{1-2} \text{ haloalkyl})$.

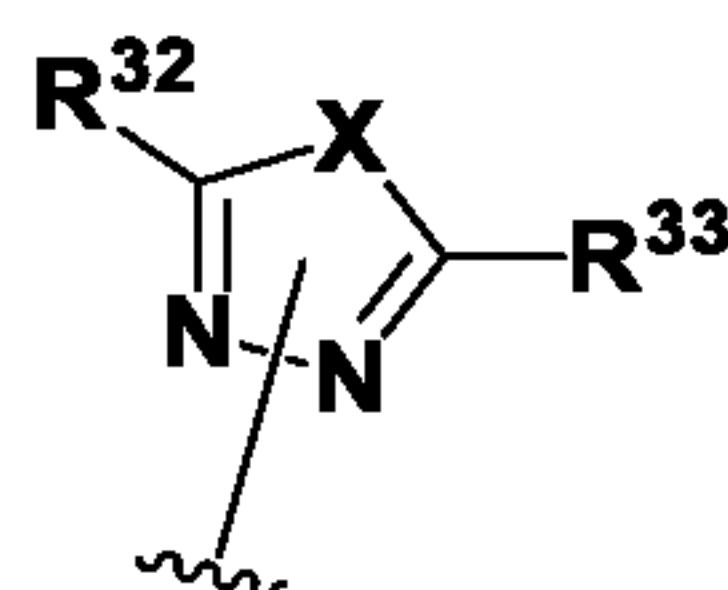
[0204] In some embodiments, R^{29} is selected from the group consisting of H, F, methyl, and $-CF_3$.



[0205] In some embodiments, R^3 is

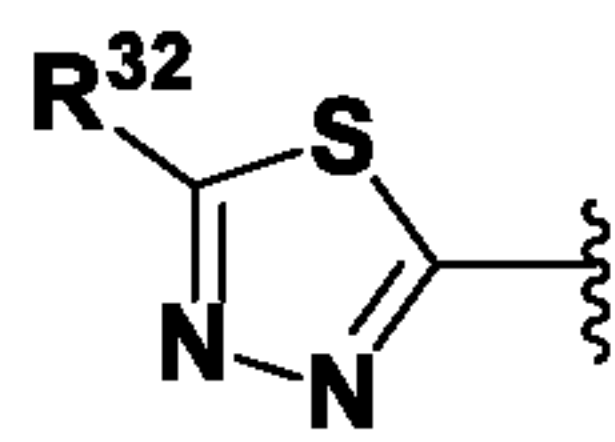
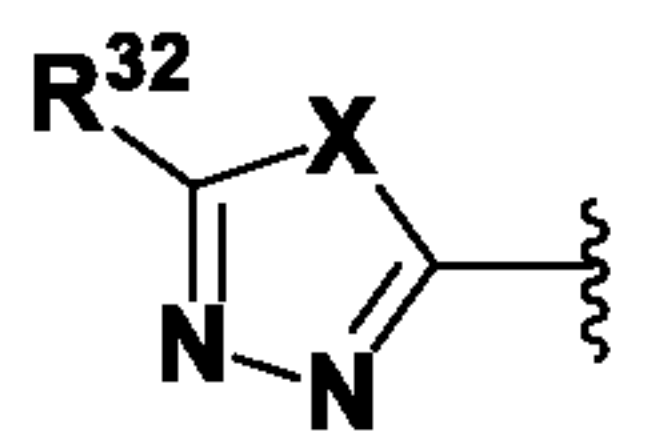


[0206] In some embodiments, R^3 is and X is S.

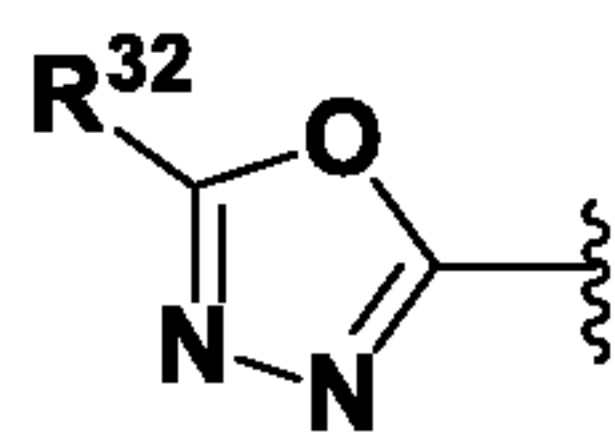


[0207] In some embodiments, R^3 is and X is O.

[0208] In certain embodiments, R^{33} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



[0209] In some embodiments, R^3 is



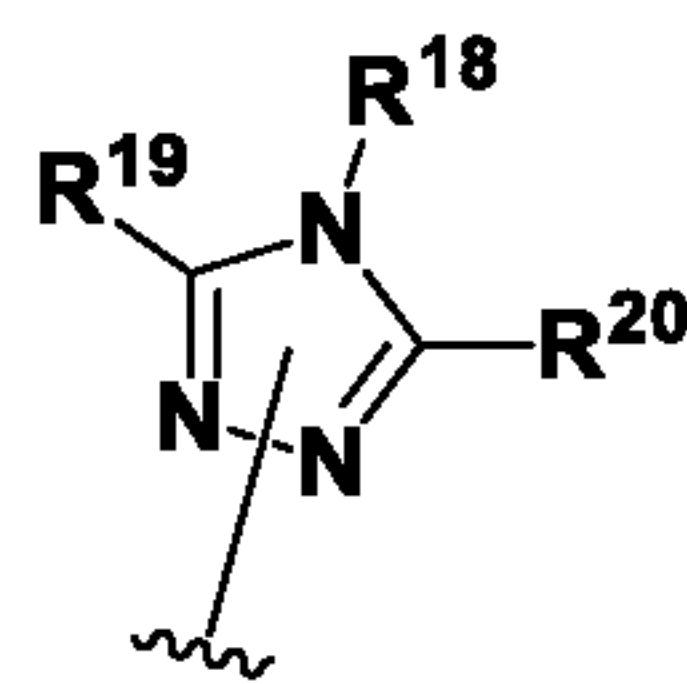
[0210] In some embodiments, R^3 is

[0211] In some embodiments, R^{32} is selected from the group consisting of H, halide, unsubstituted $-(C_{1-2} \text{ alkyl})$, unsubstituted $-(C_{1-2} \text{ haloalkyl})$, and $-N(R^{53})_2$.

[0212] In some embodiments, R^{32} is selected from the group consisting of H, F, methyl, $-\text{CF}_3$, $-\text{NHMe}$, and $-\text{NMe}_2$.

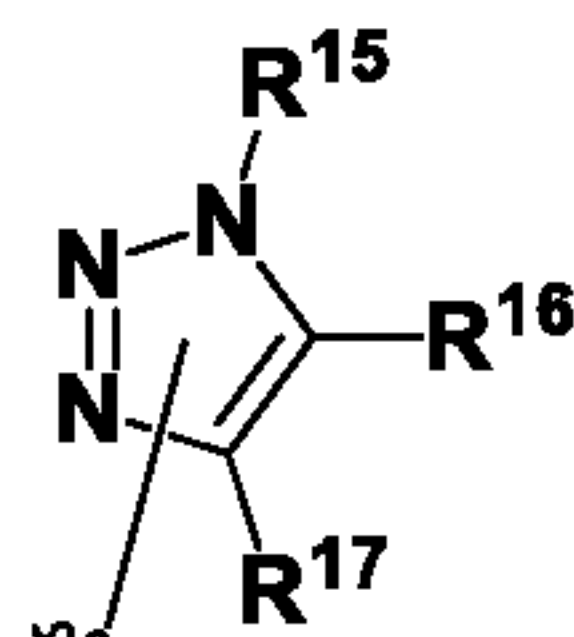
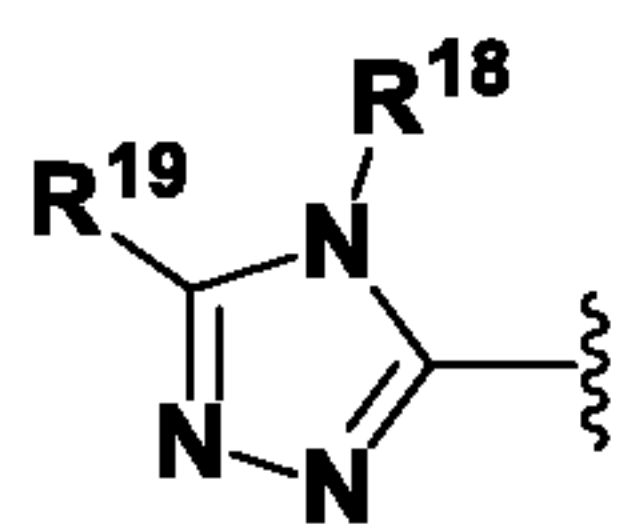
[0213] In some embodiments, R^{32} is selected from the group consisting of H and methyl.

[0214] In some embodiments, R^{32} is methyl.



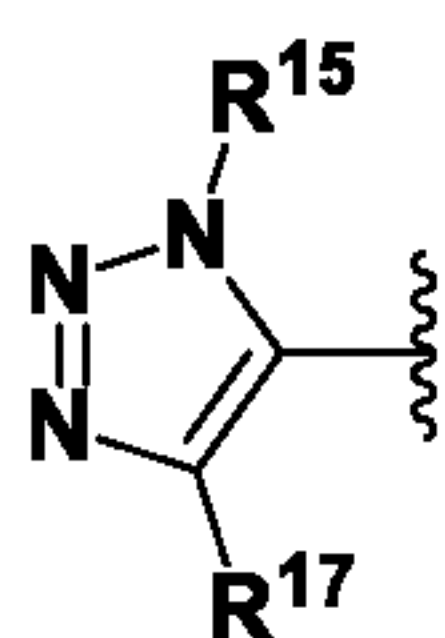
[0215] In some embodiments, R^3 is .

[0216] In certain embodiments, R^{20} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:

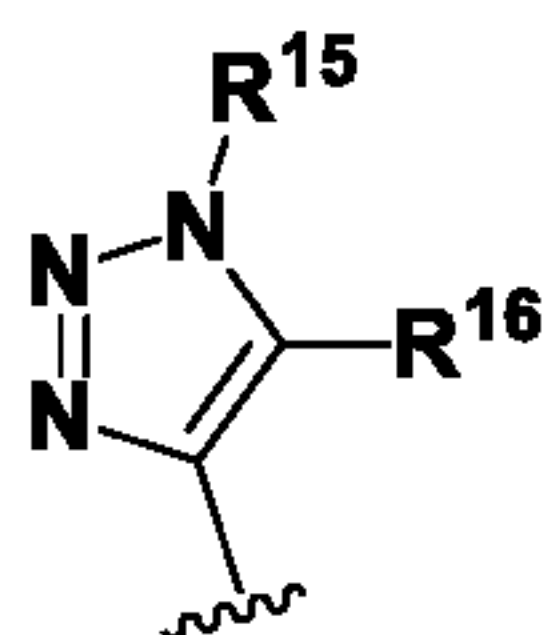


[0217] In some embodiments, R^3 is .

[0218] In certain embodiments, R^{16} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:



[0219] In certain embodiments, R^{17} is a single bond connecting R^3 to the isoquinoline ring, i.e., R^3 has the following formula:

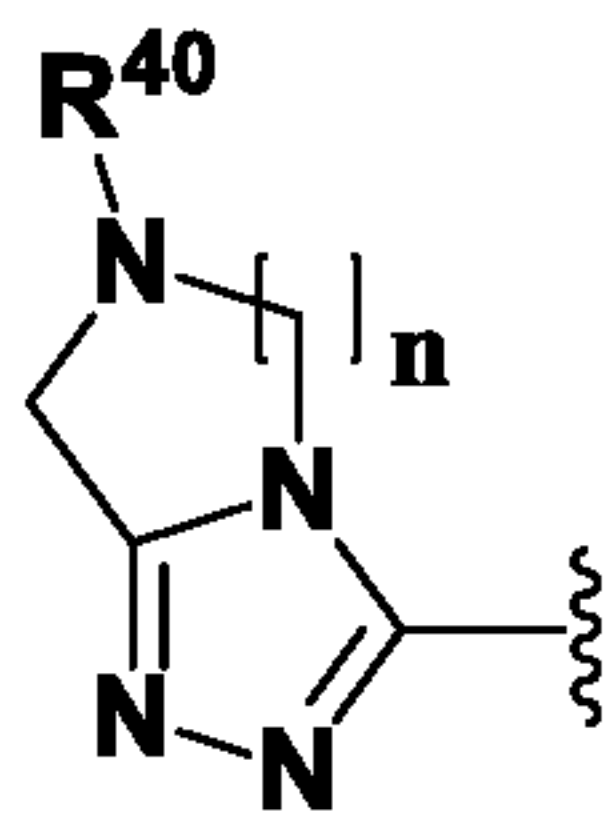


[0220] In some embodiments, R^{15} is selected from the group consisting of H and unsubstituted $-(\text{C}_{1-2} \text{ alkyl})$.

[0221] In some embodiments, R^{15} is selected from the group consisting of H and methyl.

[0222] In some embodiments, R^{15} is methyl.

[0223] In some embodiments, R^{15} is $-CD_3$.



[0224] In some embodiments, R^3 is and n is 1 to 3.

[0225] In some embodiments, R^{18} is selected from the group consisting of H, unsubstituted $-(C_{1-3} \text{ alkyl})$, unsubstituted $-(C_{1-2} \text{ haloalkyl})$, and $-(C_{3-4} \text{ carbocycl})$ optionally substituted with 1-2 R^{39} .

[0226] In some embodiments, R^{18} is selected from the group consisting of H, methyl, $-CF_3$, and cyclopropyl optionally substituted with 1-2 R^{39} .

[0227] In some embodiments, R^{18} is selected from the group consisting of H and methyl.

[0228] In some embodiments, R^{19} is selected from the group consisting of H, halide, unsubstituted $-(C_{1-2} \text{ alkyl})$, and unsubstituted $-(C_{1-2} \text{ haloalkyl})$.

[0229] In some embodiments, R^{19} is selected from the group consisting of H, F, methyl, and $-CF_3$.

[0230] In some embodiments, R^{39} is selected from the group consisting of halide, unsubstituted $-(C_{1-3} \text{ alkyl})$, and unsubstituted $-(C_{1-2} \text{ haloalkyl})$.

[0231] In some embodiments, R^{39} is selected from the group consisting of F, methyl, and $-CF_3$.

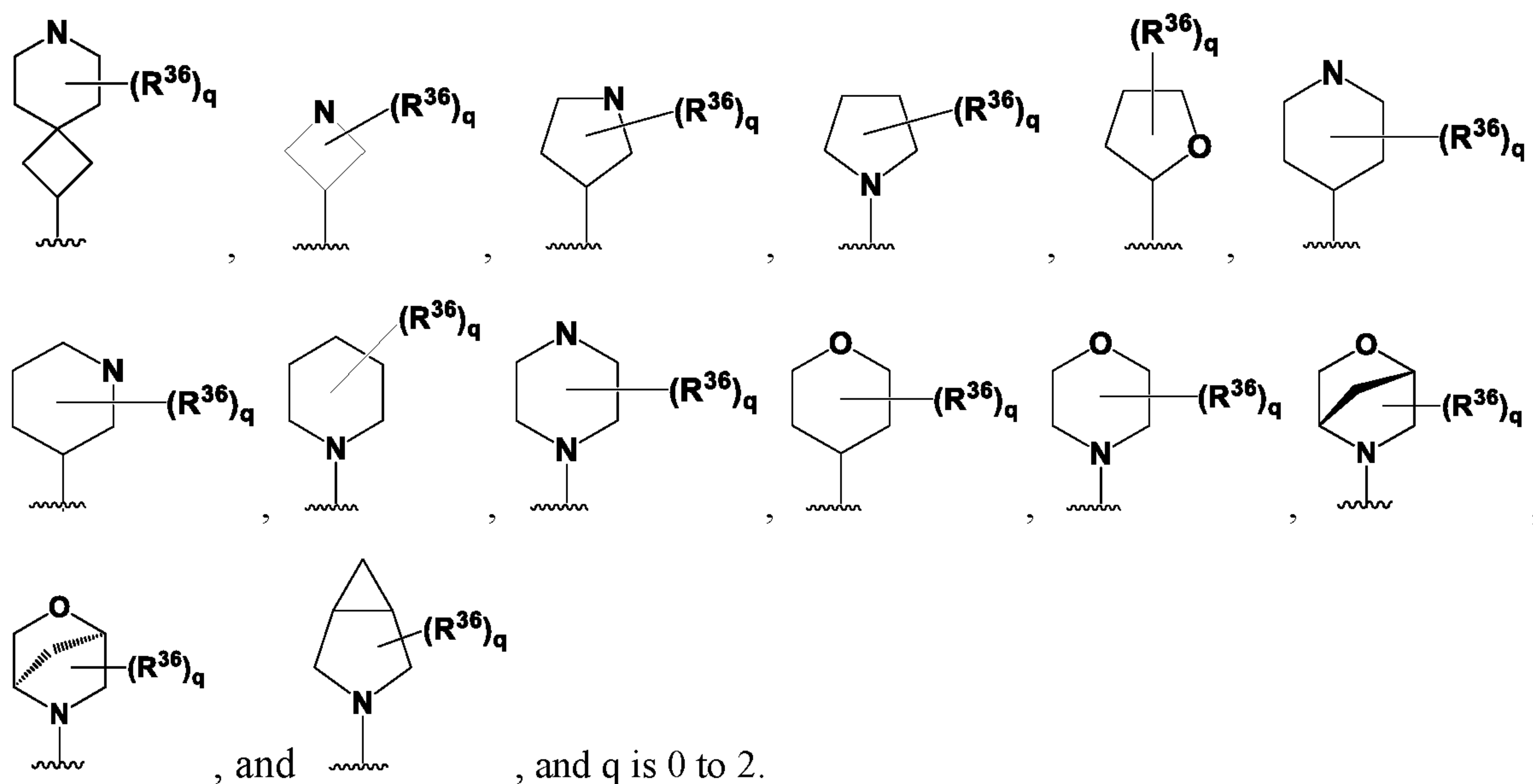
[0232] In some embodiments, R^{40} is selected from the group consisting of H and unsubstituted $-(C_{1-2} \text{ alkyl})$.

[0233] In some embodiments, R^{40} is selected from the group consisting of H and methyl.

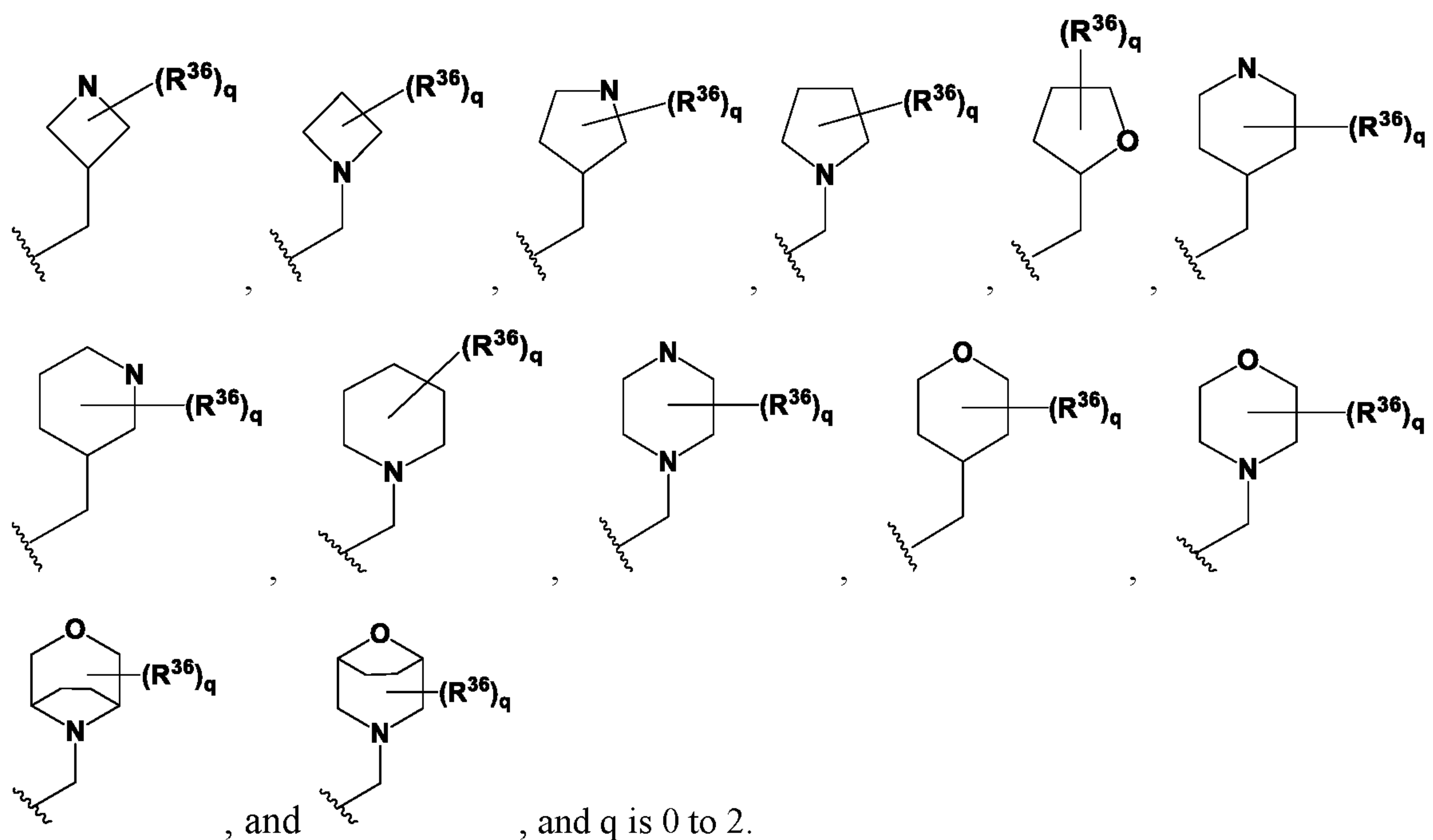
[0234] In some embodiments, R^6 is selected from the group consisting of $-(C_{1-4} \text{ alkylene})_p$ heterocycl optional substituted with 1-10 R^{36} , and $-(C_{1-4} \text{ alkylene})_p$ carbocycl optional substituted with 1-12 R^{37} .

[0235] In some embodiments, R^6 is a $-$ heterocycl optional substituted with 1-2 R^{36} .

[0236] In some embodiments, R^6 is selected from the group consisting of:



[0237] In some embodiments, R^6 is selected from the group consisting of:



[0238] In some embodiments, R^6 is a --carbocyclyl optionally substituted with 1-2 R^{37} .

[0239] In some embodiments, R^6 is a $\text{--(CH}_2\text{)carbocyclyl}$ optionally substituted with 1-2 R^{37} .

[0240] In some embodiments, R^6 is a $\text{--(C}_{1-4}\text{ alkylene)N(R}^{46}\text{)(R}^{47}\text{)}$.

[0241] In some embodiments, R^6 is a $\text{--(CH}_2\text{)N(R}^{46}\text{)(R}^{47}\text{)}$.

[0242] In some embodiments, R^6 is a $\text{--(CH}_2\text{)NH(C}_{1-5}\text{ alkyl)}$.

[0243] In some embodiments, R^6 is a $\text{--(CH}_2\text{)NH(C}_{1-4}\text{ alkyl)}$.

- [0244] In some embodiments, R^6 is a $-(CH_2)NH(C_{1-3} \text{ alkyl})$.
- [0245] In some embodiments, R^6 is a $-(CH_2)NHEt$.
- [0246] In some embodiments, R^6 is a $-(CH_2)NHMe$.
- [0247] In some embodiments, R^6 is a $-(CH_2)NH\text{carbocyclyl}$.
- [0248] In some embodiments, R^6 is a $-(CH_2)NH(CH_2)\text{carbocyclyl}$.
- [0249] In some embodiments, R^6 is a $-(CH_2)N(C_{1-5} \text{ alkyl})_2$.
- [0250] In some embodiments, R^6 is a $-(CH_2)N(C_{1-4} \text{ alkyl})_2$.
- [0251] In some embodiments, R^6 is a $-(CH_2)N(C_{1-3} \text{ alkyl})_2$.
- [0252] In some embodiments, R^6 is a $-(CH_2)N(C_{1-2} \text{ alkyl})_2$.
- [0253] In some embodiments, R^6 is a $-(CH_2)NMe_2$.
- [0254] In some embodiments, R^6 is a $-(CH_2)N(C_{1-5} \text{ alkyl})\text{carbocyclyl}$.
- [0255] In some embodiments, R^6 is a $-(CH_2)N(C_{1-5} \text{ alkyl})(CH_2)\text{carbocyclyl}$.
- [0256] In some embodiments, R^6 is a $-(CH_2)N(C_{1-4} \text{ alkyl})\text{carbocyclyl}$.
- [0257] In some embodiments, R^6 is a $-(CH_2)N(C_{1-4} \text{ alkyl})(CH_2)\text{carbocyclyl}$.
- [0258] In some embodiments, R^6 is a $-(CH_2)N(C_{1-3} \text{ alkyl})\text{carbocyclyl}$.
- [0259] In some embodiments, R^6 is a $-(CH_2)N(C_{1-3} \text{ alkyl})(CH_2)\text{carbocyclyl}$.
- [0260] In some embodiments, R^6 is a $-(CH_2)N(C_{1-2} \text{ alkyl})\text{carbocyclyl}$.
- [0261] In some embodiments, R^6 is a $-(CH_2)N(C_{1-2} \text{ alkyl})(CH_2)\text{carbocyclyl}$.
- [0262] In some embodiments, R^6 is a $-(CH_2)N(Me)\text{carbocyclyl}$.
- [0263] In some embodiments, R^6 is a $-(CH_2)NMe(CH_2)\text{carbocyclyl}$.
- [0264] In some embodiments, R^6 is $-CF(C_{1-9} \text{ alkyl})_2$; wherein each alkyl of $-CF(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more halides.
- [0265] In some embodiments, R^6 is $-CF(C_{1-9} \text{ alkyl})_2$; wherein each alkyl of $-CF(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more fluorines.
- [0266] In some embodiments, R^6 is $-CF(C_{1-7} \text{ alkyl})_2$.
- [0267] In some embodiments, R^6 is $-CF(C_{1-5} \text{ alkyl})_2$.
- [0268] In some embodiments, R^6 is $-CF(C_{1-4} \text{ alkyl})_2$.
- [0269] In some embodiments, R^6 is $-CF(C_{1-3} \text{ alkyl})_2$.
- [0270] In some embodiments, R^6 is $-CF(C_{1-2} \text{ alkyl})_2$.
- [0271] In some embodiments, R^6 is $-CFMe_2$.
- [0272] In some embodiments, R^6 is $-CF(Me)(Et)$.
- [0273] In some embodiments, R^6 is $-CFEt_2$.
- [0274] In some embodiments, R^6 is $-CF(Et)(^nPr)$.
- [0275] In some embodiments, R^6 is $-CF^nPr_2$.

[0276] In some embodiments, R^6 is $-\text{CF}(\text{Me})(^n\text{Pr})$.

[0277] In some embodiments, R^6 is $-\text{CF}^i\text{Pr}_2$.

[0278] In some embodiments, R^6 is $-\text{CF}(\text{Et})(^i\text{Pr})$.

[0279] In some embodiments, R^6 is $-\text{CF}(\text{Me})(^i\text{Pr})$.

[0280] In some embodiments, R^{36} is selected from the group consisting of halide, unsubstituted $-(\text{C}_{1-5} \text{ alkyl})$, unsubstituted $-(\text{C}_{1-5} \text{ haloalkyl})$, $-(\text{CH}_2\text{CH}_2)\text{OR}^{42}$, $-\text{heterocyclyl}$ optionally substituted with 1-2 R^{43} , $-(\text{CH}_2)\text{heterocyclyl}$ optionally substituted with 1-2 R^{43} , $-(\text{C}_{3-4} \text{ carbocyclyl})$ optionally substituted with 1-2 R^{44} , and $-(\text{CH}_2)(\text{C}_{3-4} \text{ carbocyclyl})$ optionally substituted with 1-2 R^{44} .

[0281] In some embodiments, R^{37} is selected from the group consisting of halide, unsubstituted $-(\text{C}_{1-5} \text{ alkyl})$, unsubstituted $-(\text{C}_{1-5} \text{ haloalkyl})$, $-\text{OR}^{42}$, $-\text{heterocyclyl}$ optionally substituted with 1-2 R^{43} , and $-(\text{CH}_2)\text{heterocyclyl}$ optionally substituted with 1-2 R^{43} .

[0282] In some embodiments, the heterocyclyl is selected from the group consisting of azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, morpholinyl, and tetrahydropyranyl.

[0283] In some embodiments, R^{42} is selected from the group consisting of unsubstituted $-(\text{C}_{1-3} \text{ alkyl})$, and unsubstituted $-(\text{C}_{1-3} \text{ haloalkyl})$.

[0284] In some embodiments, R^{42} is selected from the group consisting of methyl, ethyl, propyl, isopropyl, $-\text{CF}_3$.

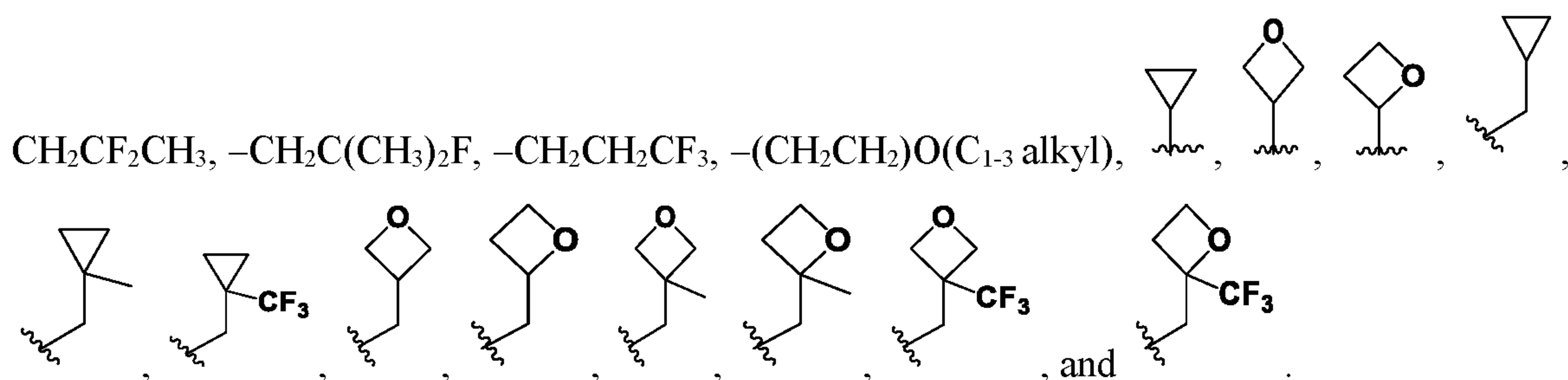
[0285] In some embodiments, R^{43} is selected from the group consisting of halide, unsubstituted $-(\text{C}_{1-2} \text{ alkyl})$, and unsubstituted $-(\text{C}_{1-2} \text{ haloalkyl})$.

[0286] In some embodiments, R^{43} is selected from the group consisting of F, methyl, ethyl, $-\text{CF}_3$.

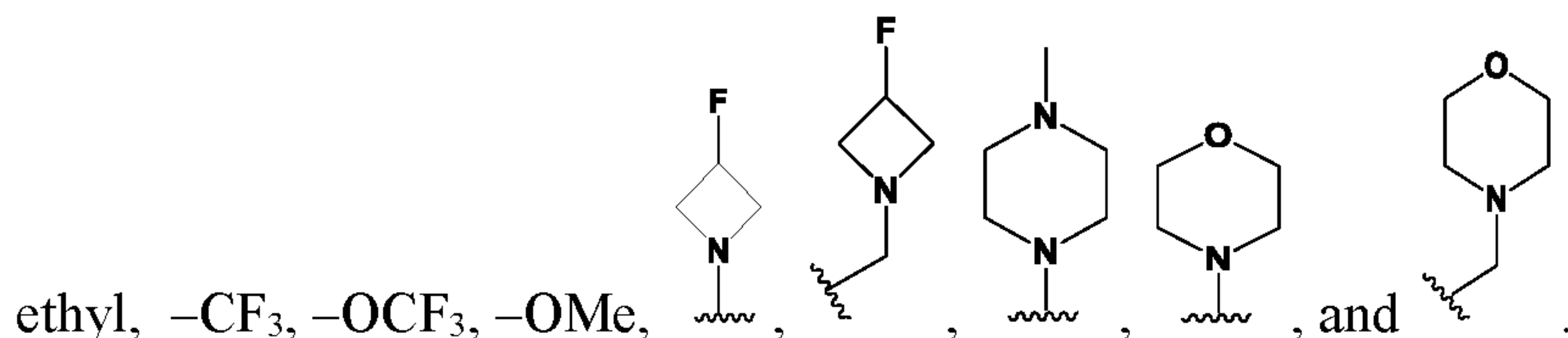
[0287] In some embodiments, R^{44} is selected from the group consisting of halide, unsubstituted $-(\text{C}_{1-2} \text{ alkyl})$, and unsubstituted $-(\text{C}_{1-2} \text{ haloalkyl})$.

[0288] In some embodiments, R^{44} is selected from the group consisting of F, methyl, ethyl, $-\text{CF}_3$.

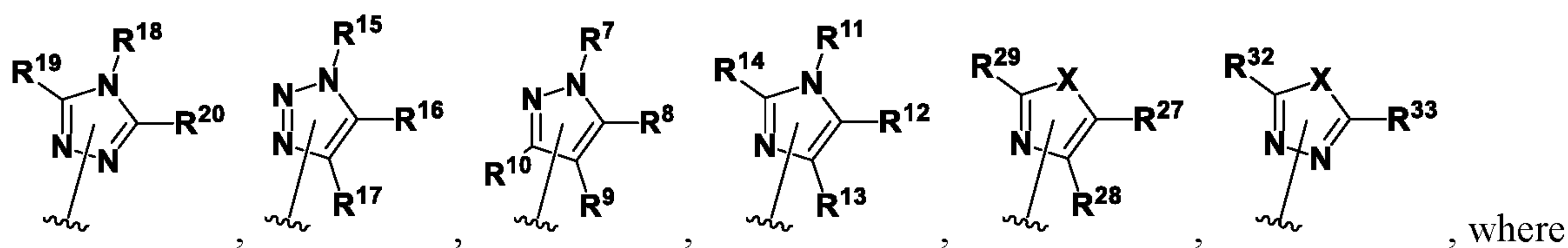
[0289] In some embodiments, R^{36} is selected from the group consisting of F, methyl, ethyl, n-propyl, isopropyl, isobutyl, *tert*-butyl, neopentyl, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-$



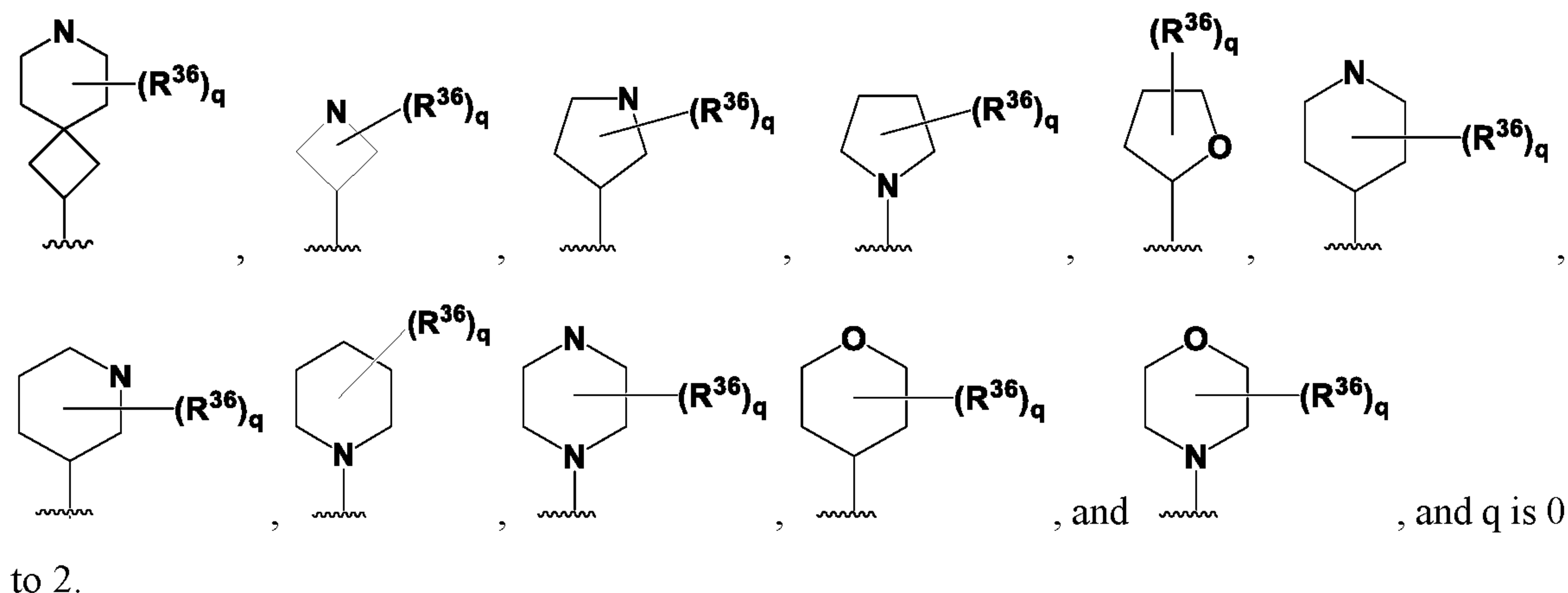
[0290] In some embodiments, R³⁷ is selected from the group consisting of F, methyl,



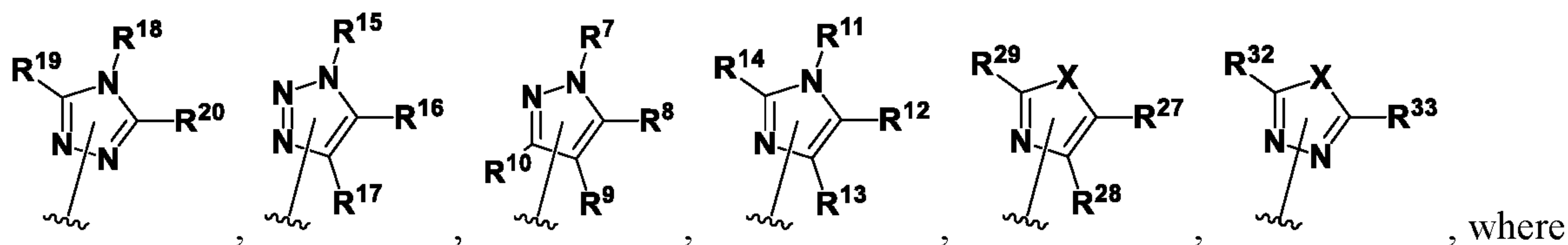
[0291] In some embodiments, R³ is selected from the group consisting of:



in X is S or O and R⁶ is selected from the group consisting of:

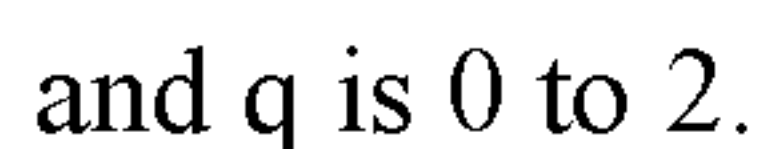


[0292] In some embodiments, R³ is selected from the group consisting of:

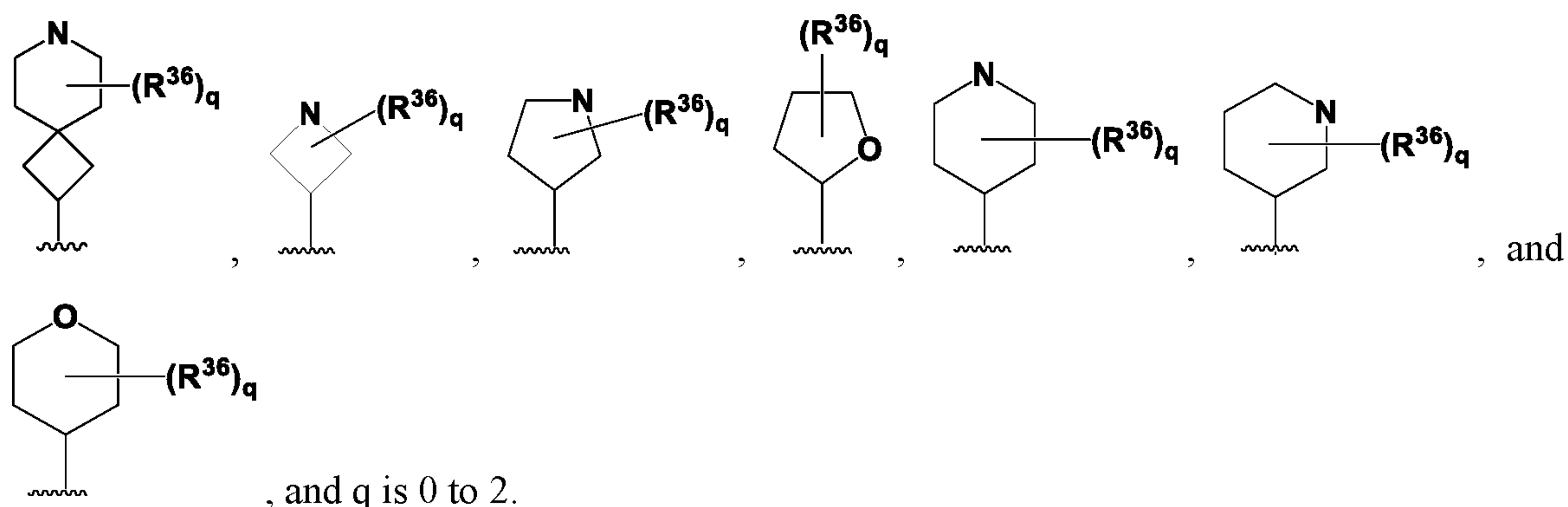


in X is S or O and R⁶ is selected from the group consisting of -carbocyclyl optionally substituted with 1-2 R³⁷ and -(CH₂)carbocyclyl optionally substituted with 1-2 R³⁷.

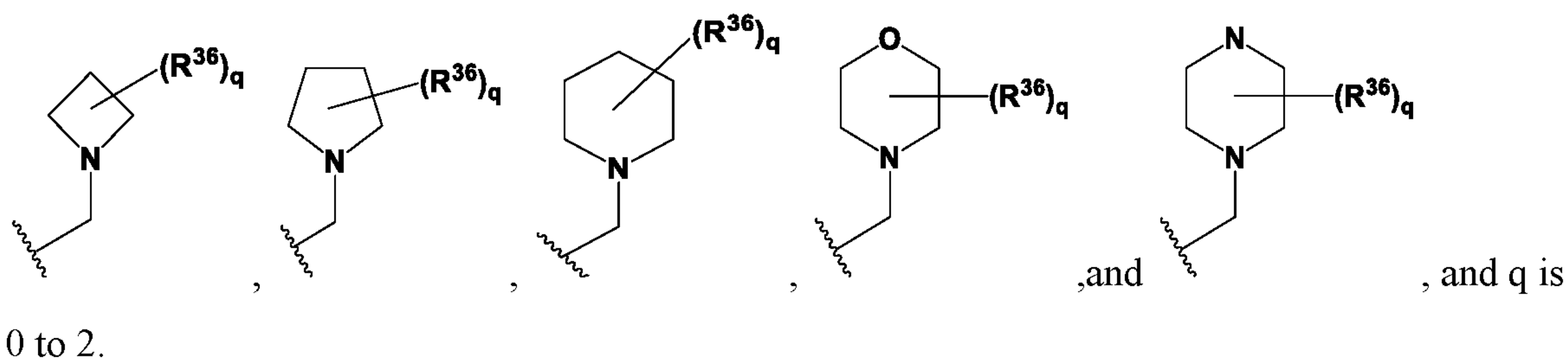
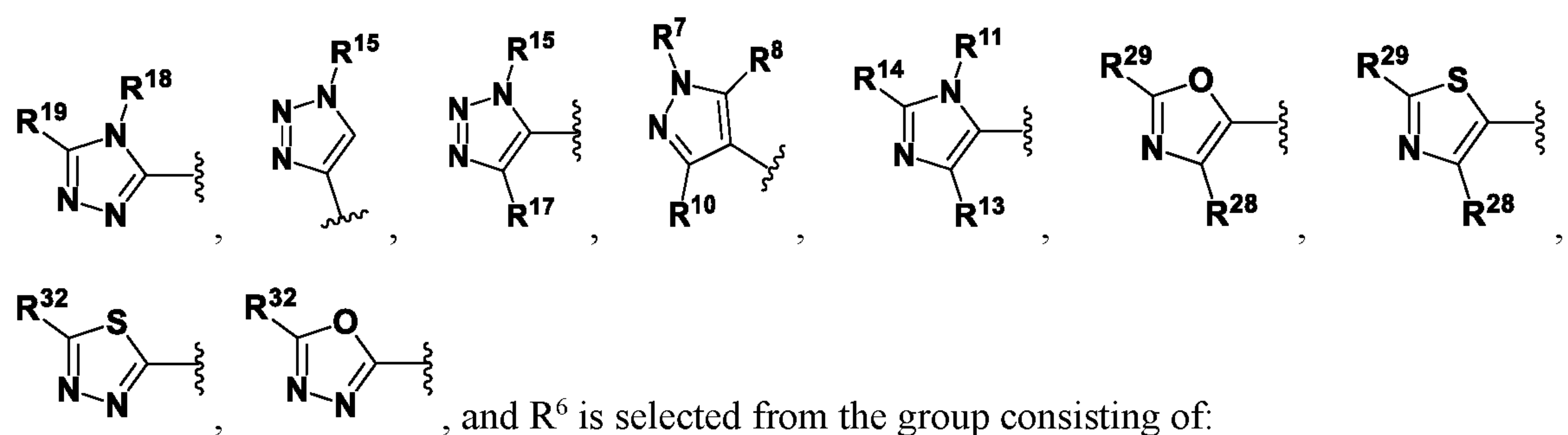
in X is S or O and R⁶ is -CF(C₁₋₉ alkyl)₂; wherein the alkyl of -CF(C₁₋₉ alkyl)₂ is optionally substituted with one or more halides.



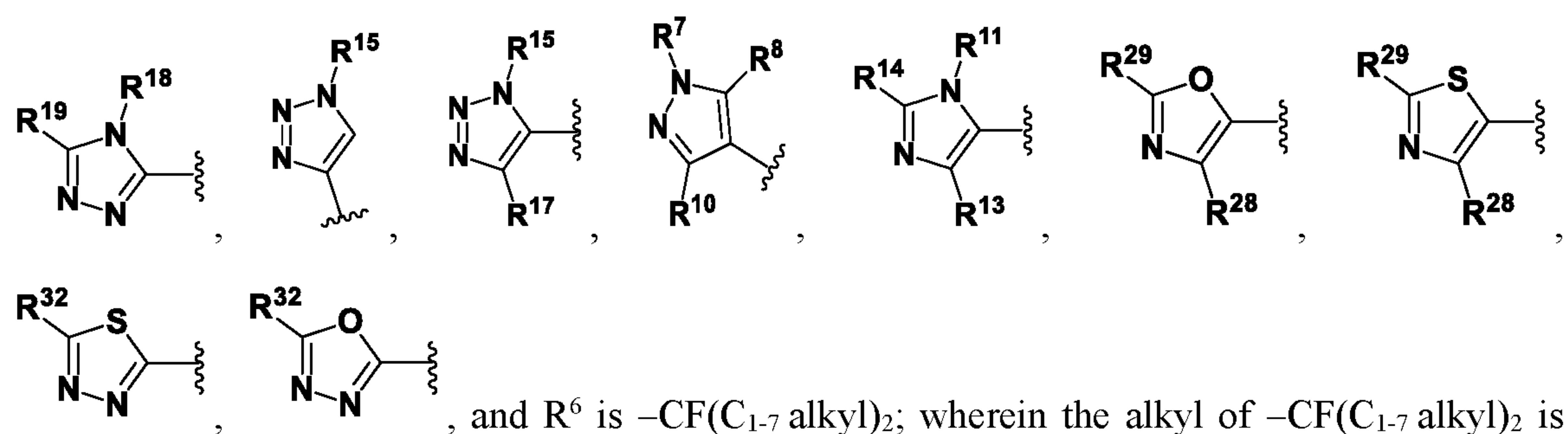
and R^6 is selected from the group consisting of:



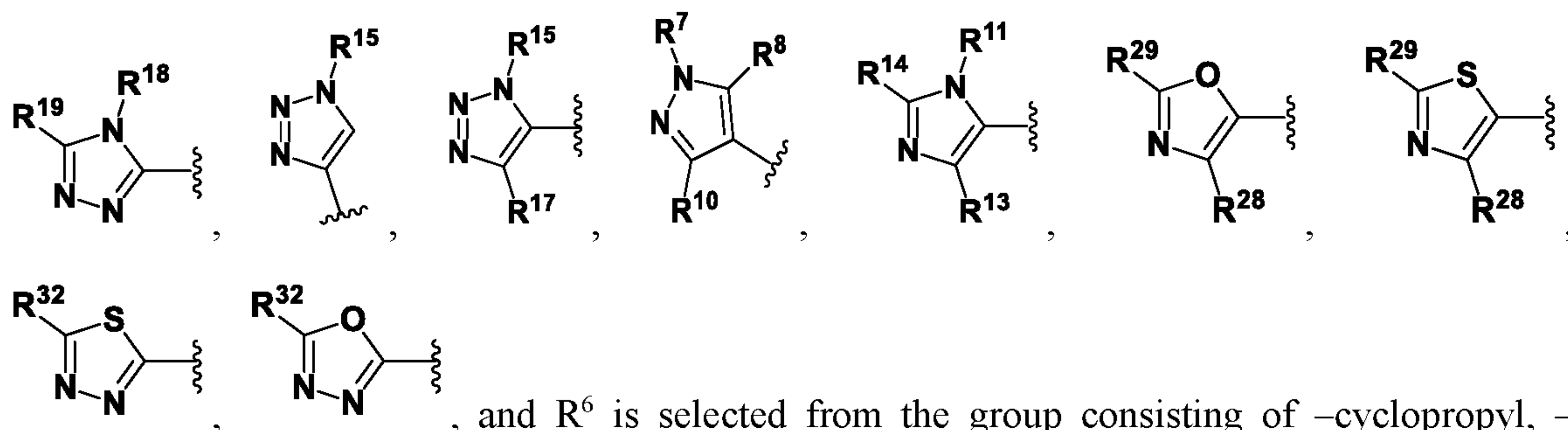
[0296] In some embodiments, R^3 is selected from the group consisting of:



[0297] In some embodiments, R^3 is selected from the group consisting of:

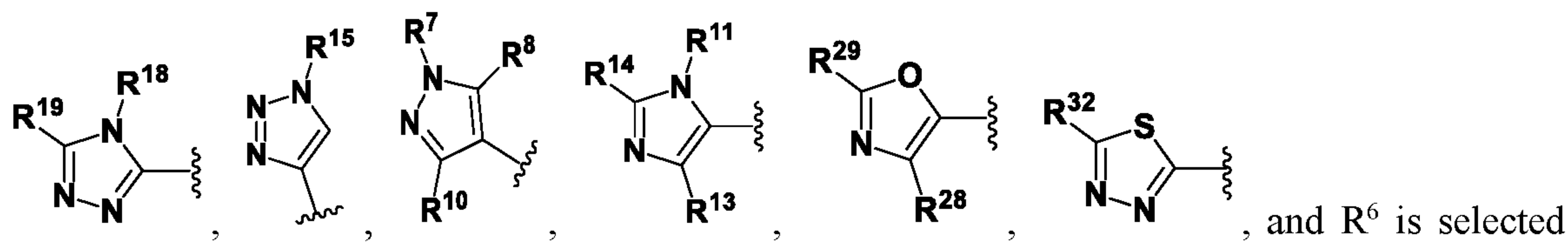


[0298] In some embodiments, R^3 is selected from the group consisting of:

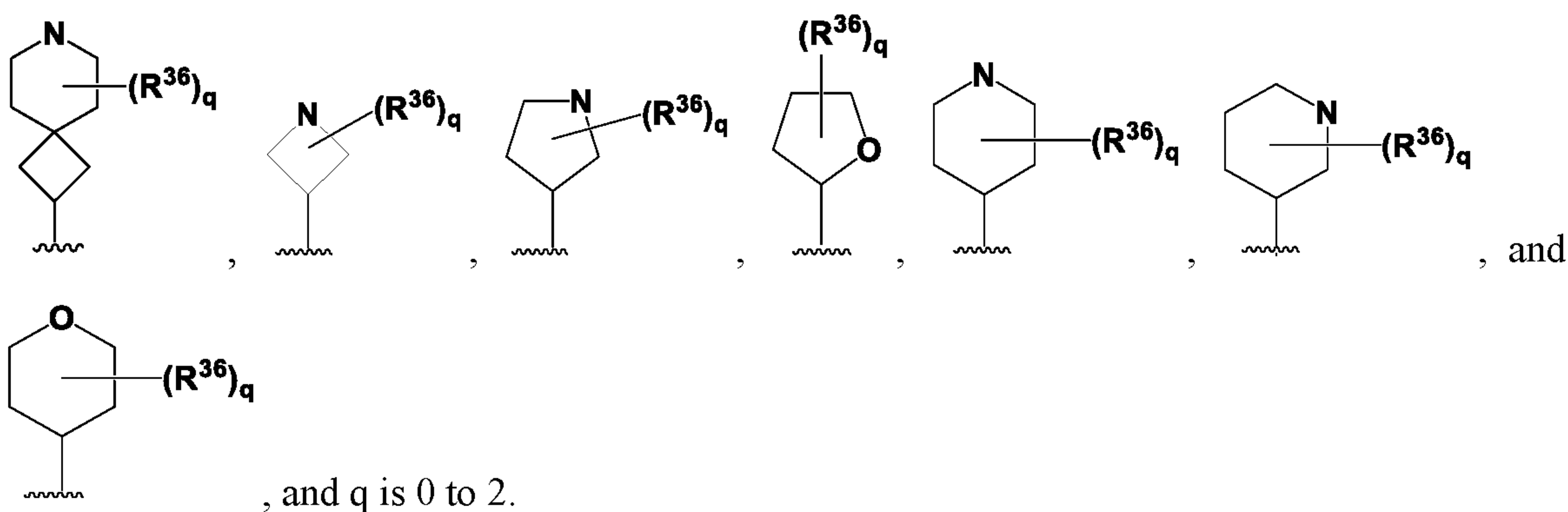


, and R^6 is selected from the group consisting of –cyclopropyl, –cyclobutyl, –cyclopentyl, –cyclohexyl each independently optionally substituted with 1-2 R^{37} and –(CH₂)cyclopropyl, –(CH₂)cyclobutyl, –(CH₂)cyclopentyl, and –(CH₂)cyclohexyl, each independently optionally substituted with 1-2 R^{37} .

[0299] In some embodiments, R^3 is selected from the group consisting of:

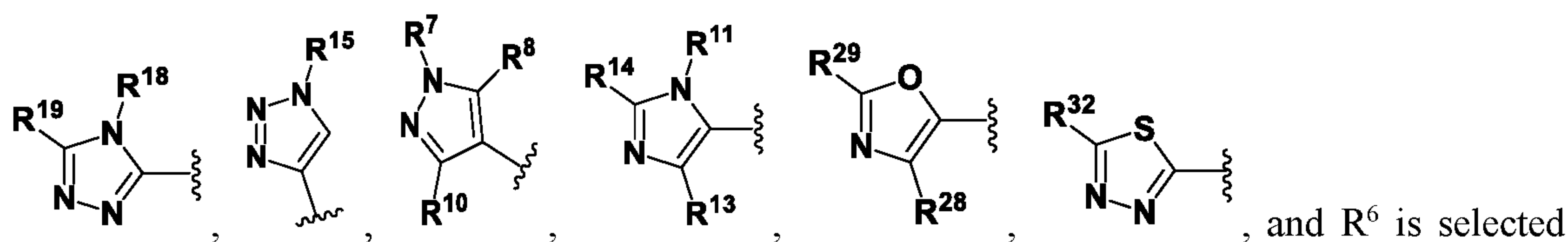


, and R^6 is selected from the group consisting of:

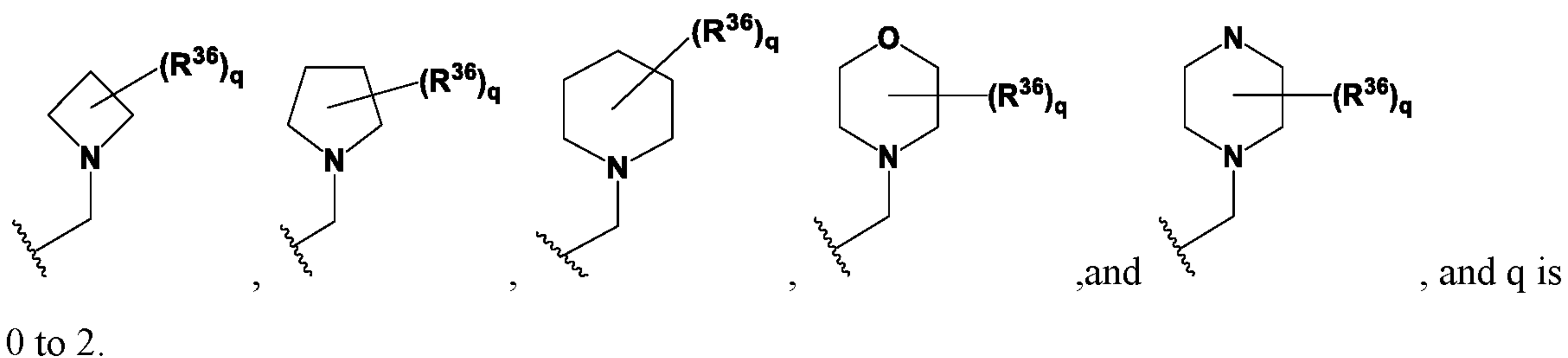


, and q is 0 to 2.

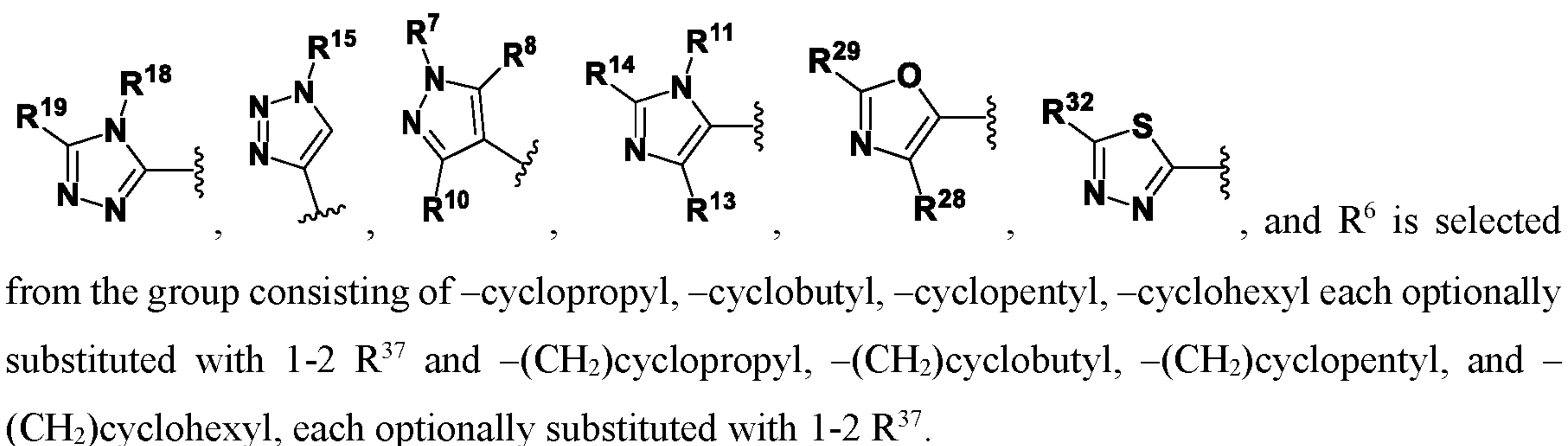
[0300] In some embodiments, R^3 is selected from the group consisting of:



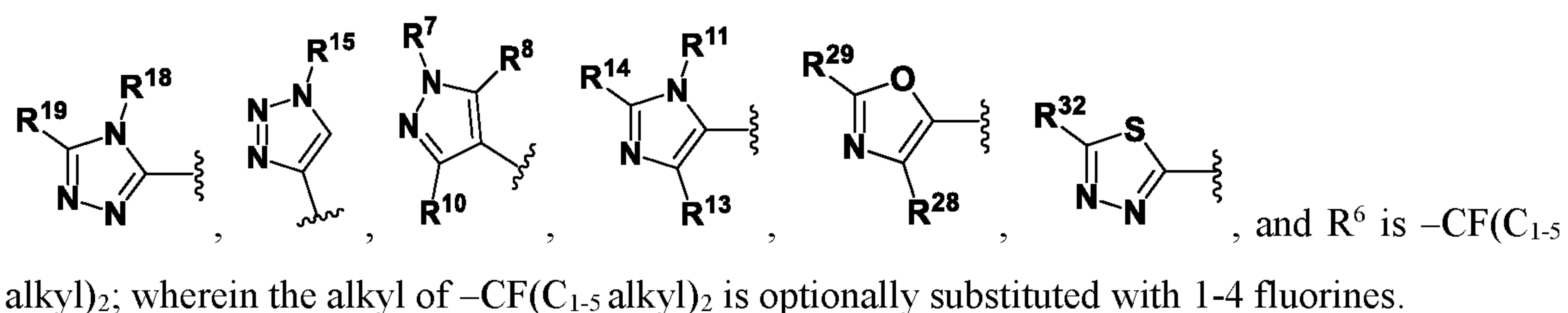
, and R^6 is selected from the group consisting of:



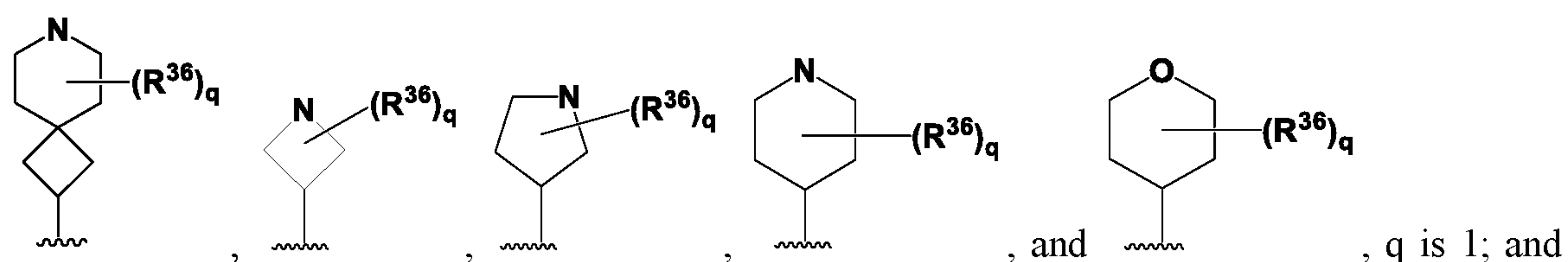
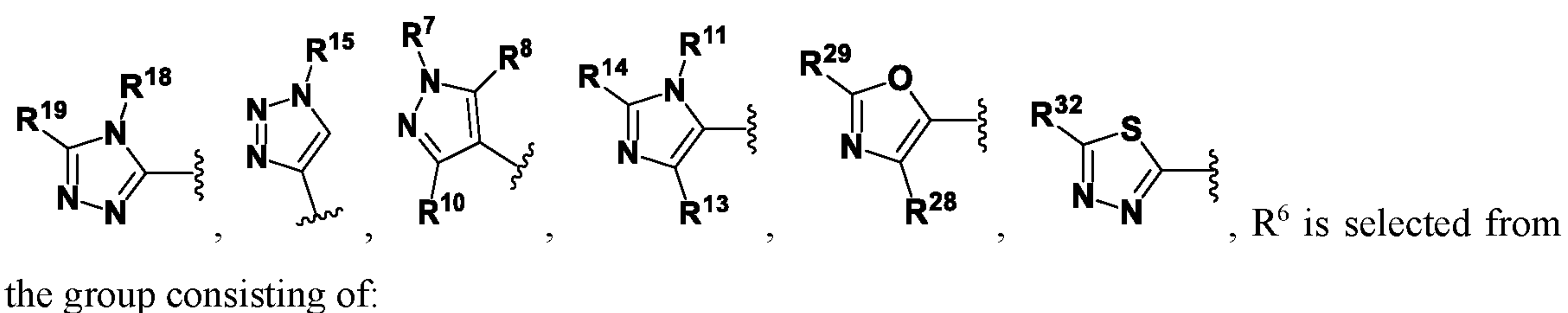
[0301] In some embodiments, R^3 is selected from the group consisting of:



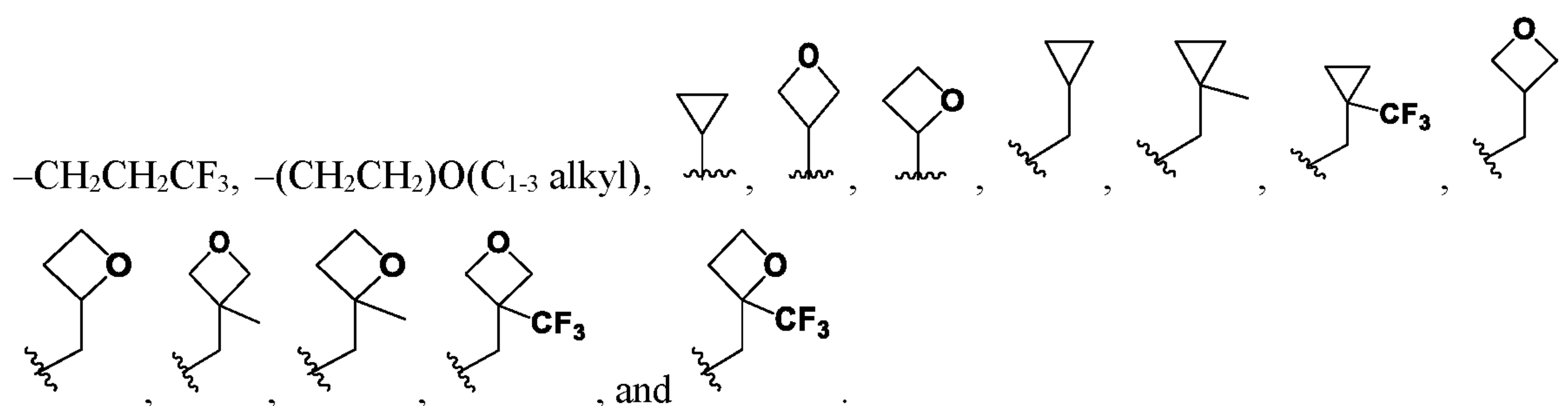
[0302] In some embodiments, R^3 is selected from the group consisting of:



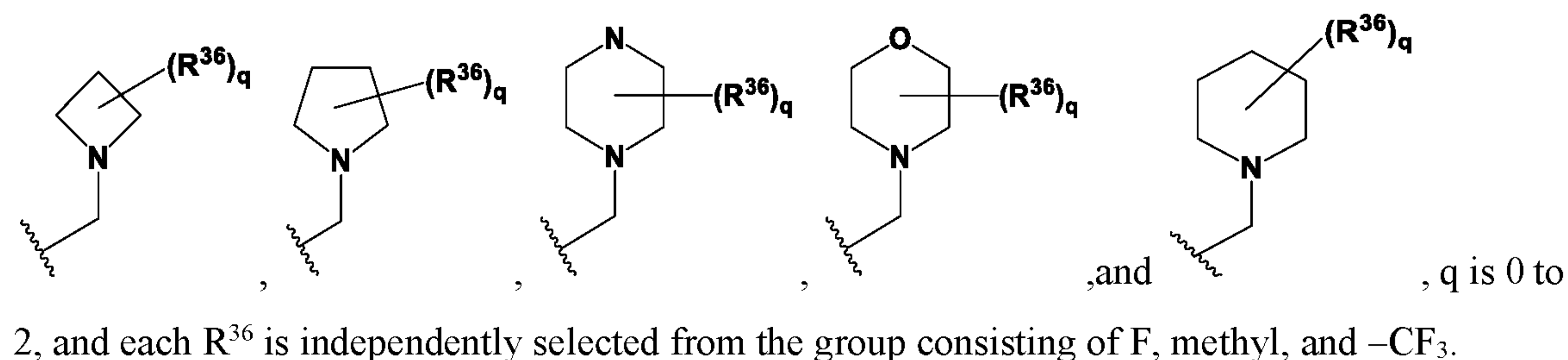
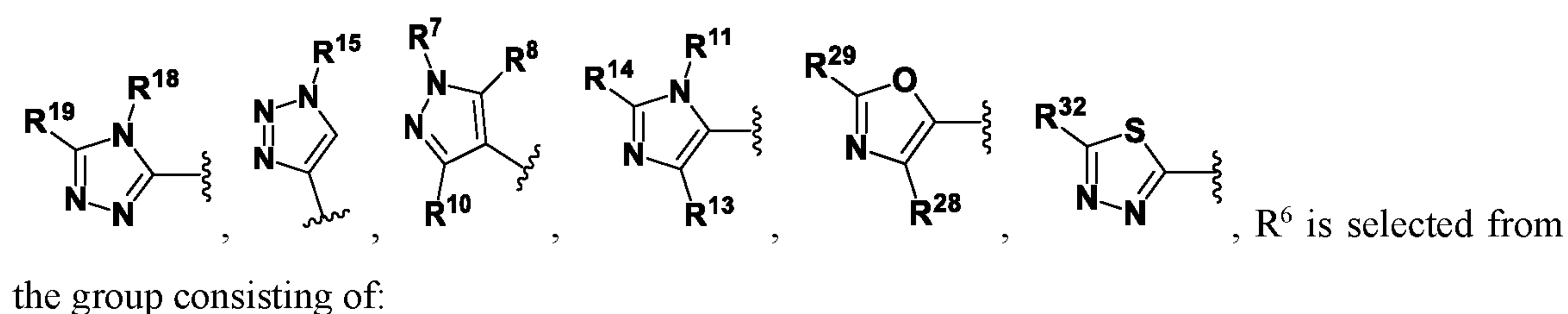
[0303] In some embodiments, R^3 is selected from the group consisting of:



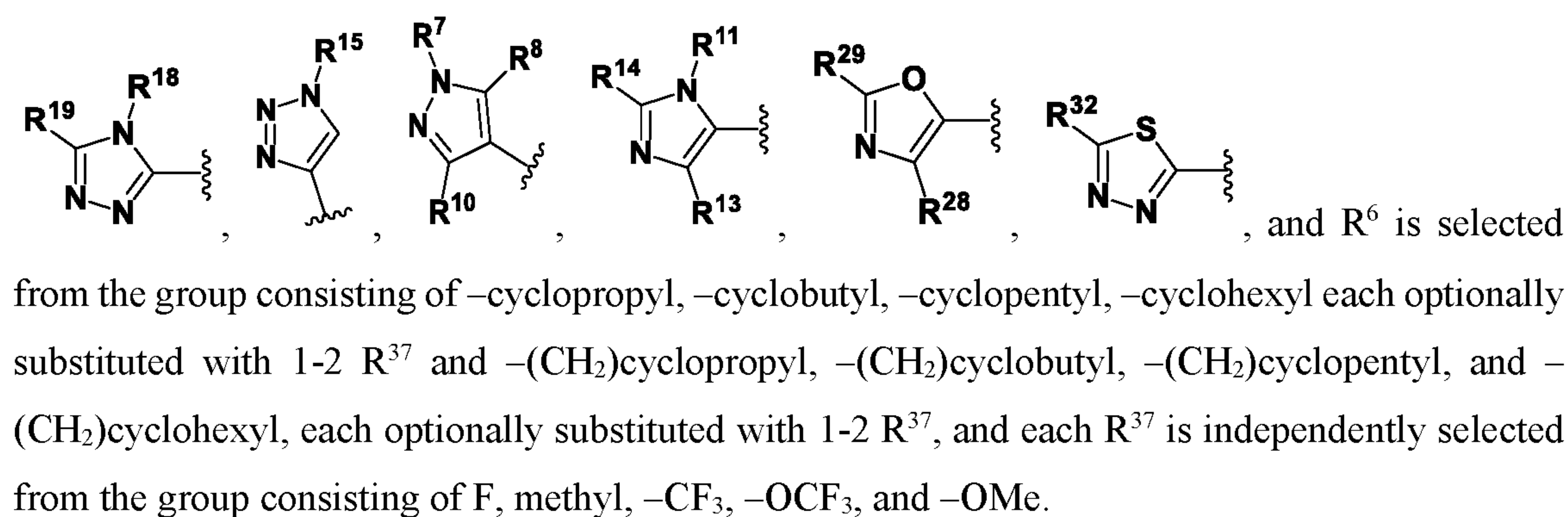
R^{36} is selected from the group consisting of F, methyl, ethyl, n-propyl, isopropyl, isobutyl, *tert*-butyl, neopentyl, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2C(CH_3)_2F$,



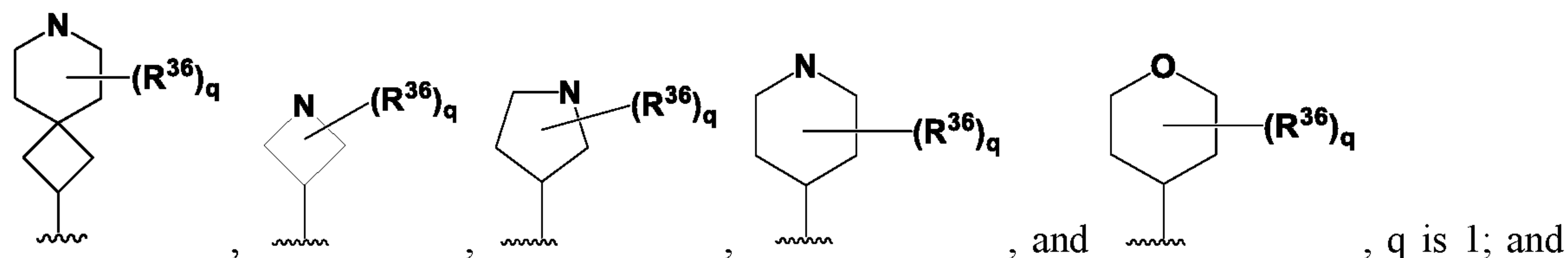
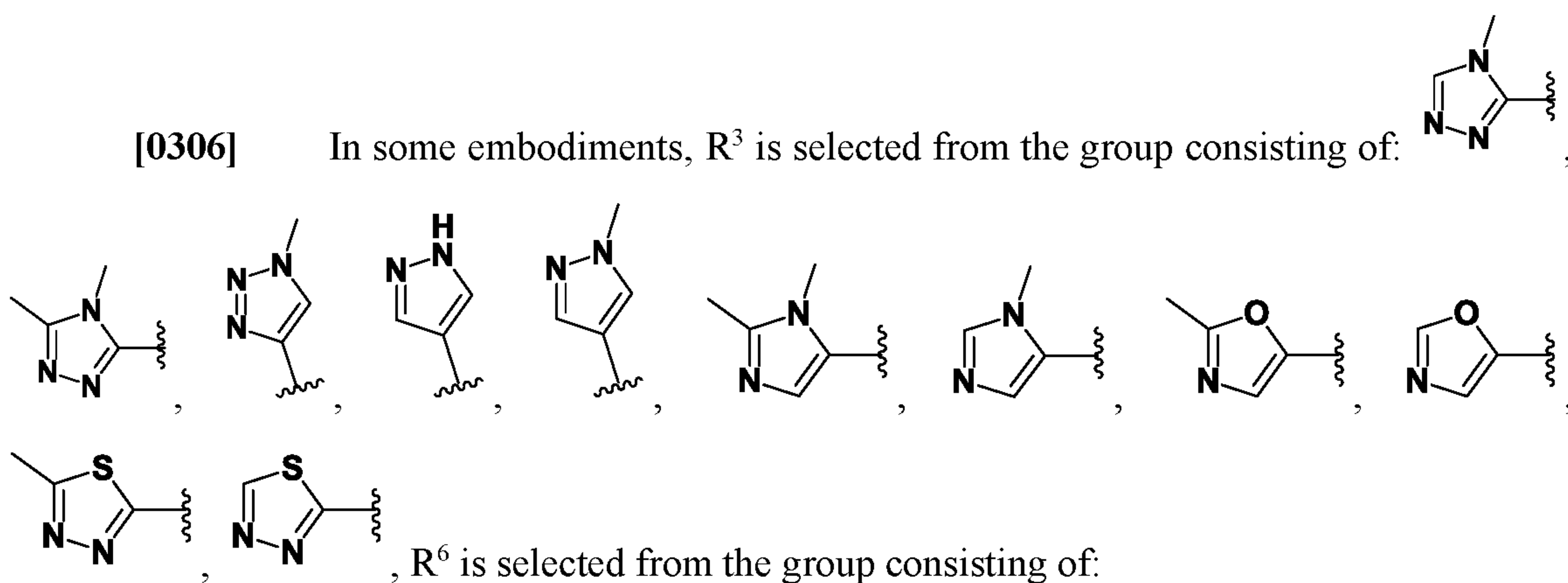
[0304] In some embodiments, R^3 is selected from the group consisting of:



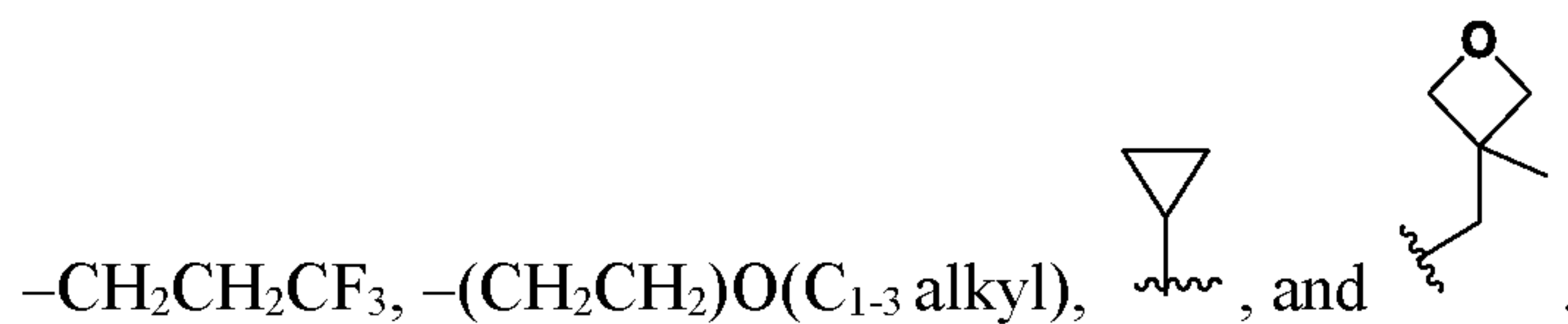
[0305] In some embodiments, R^3 is selected from the group consisting of:



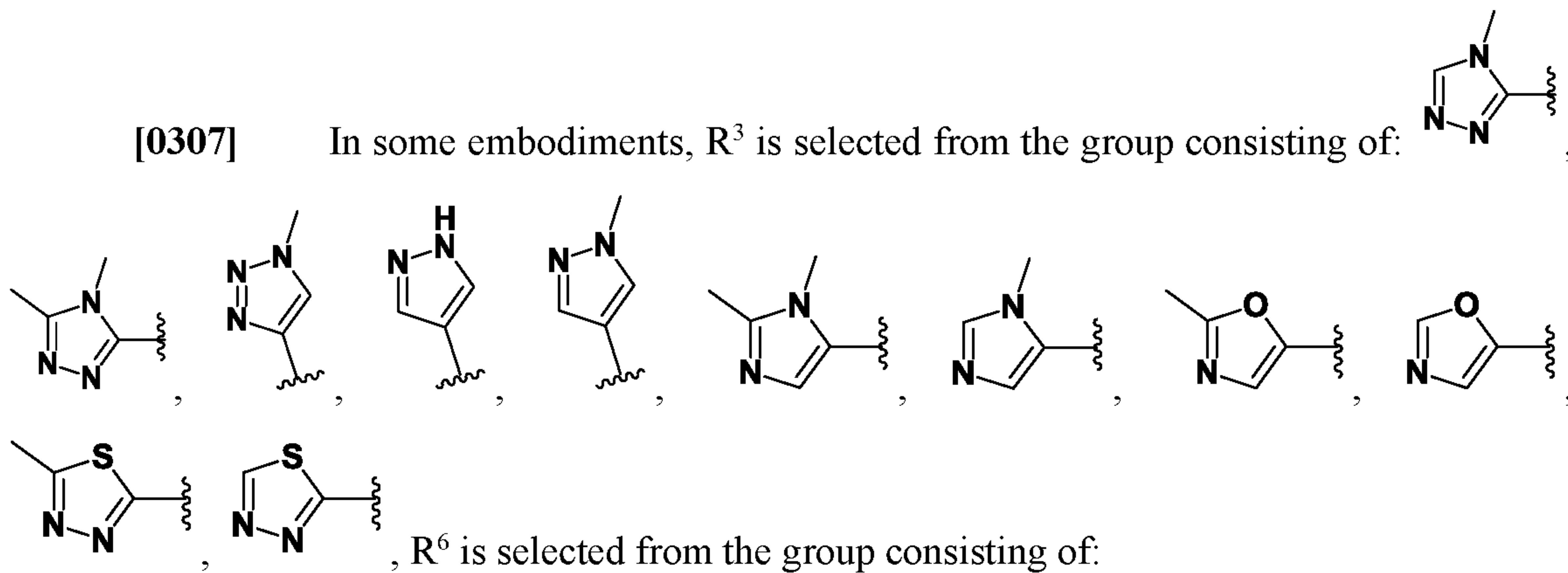
[0306] In some embodiments, R^3 is selected from the group consisting of:

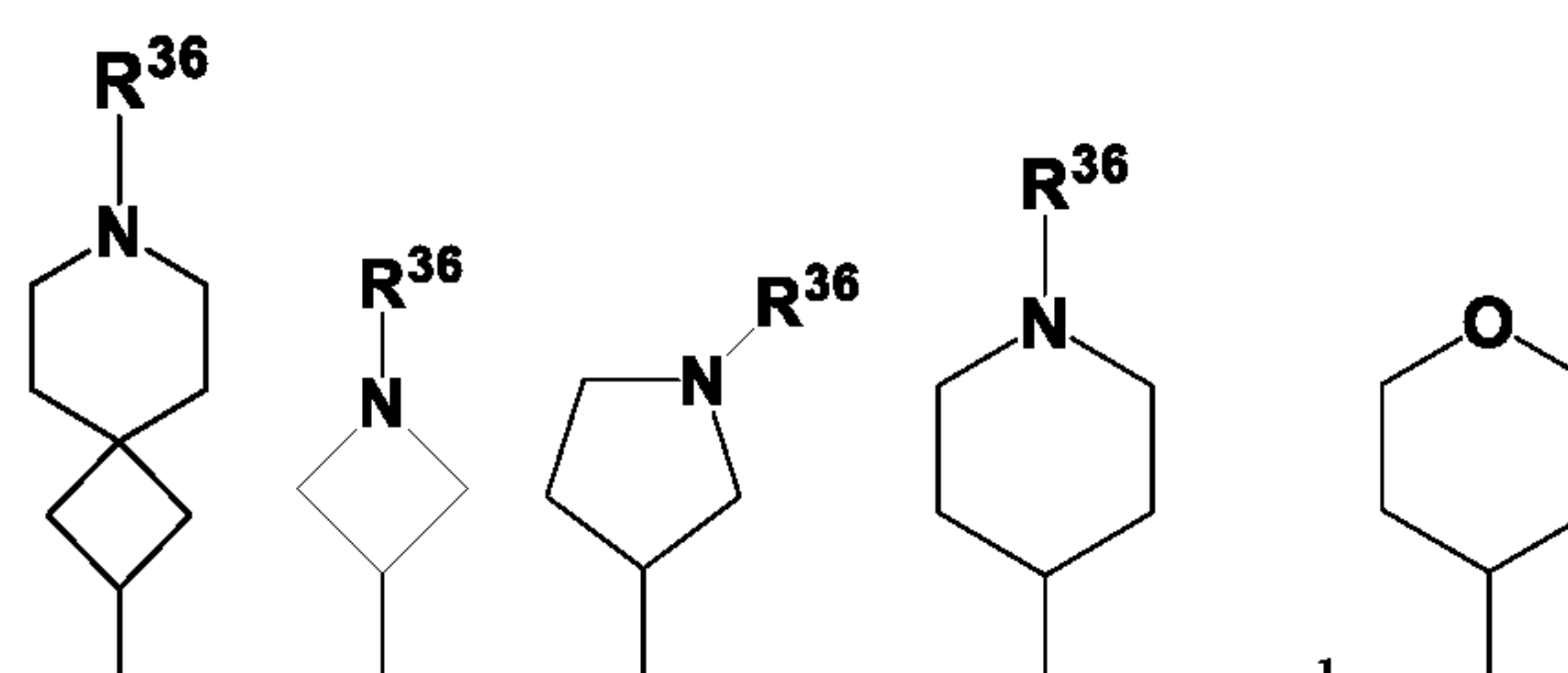
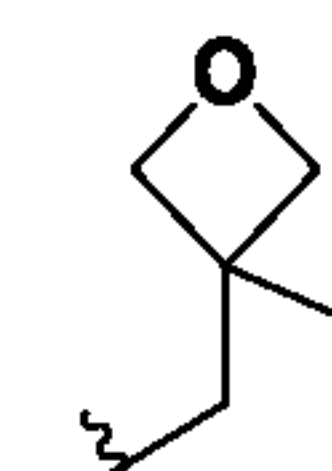


R^{36} is selected from the group consisting of F, methyl, ethyl, n-propyl, isopropyl, isobutyl, *tert*-butyl, neopentyl, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CF}_2\text{CH}_3$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{F}$,

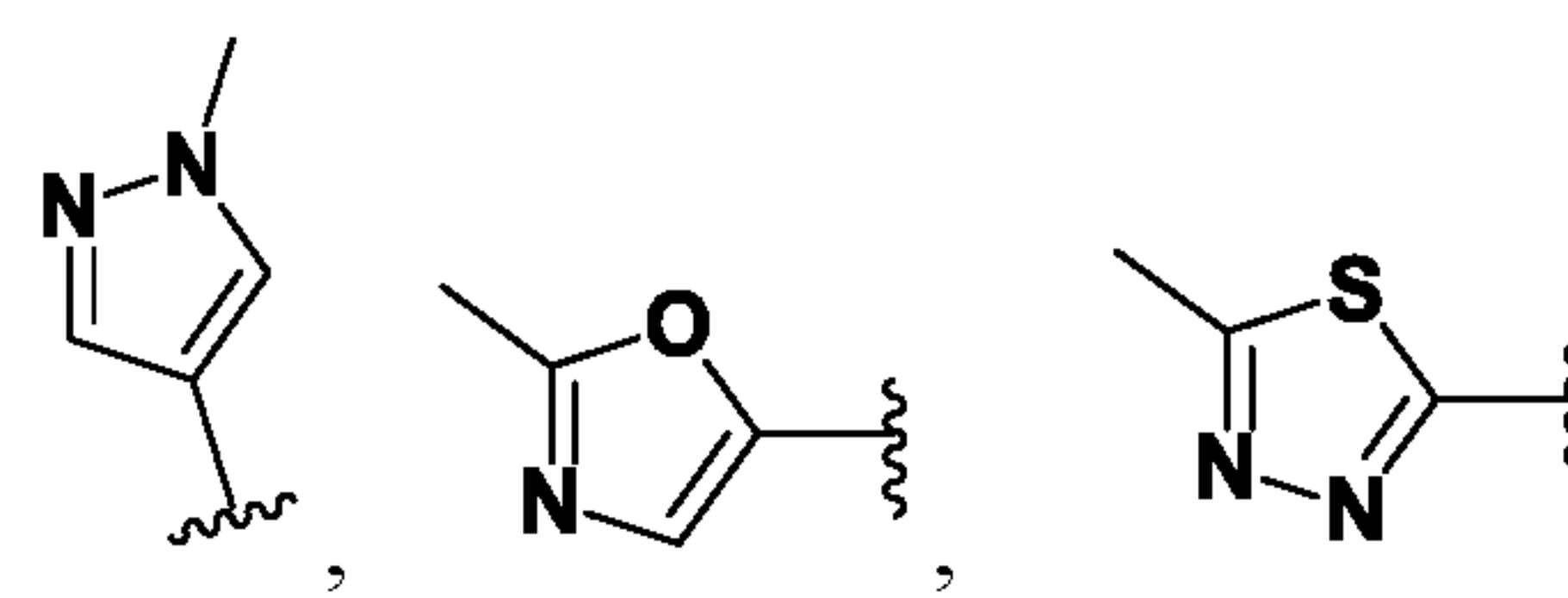


[0307] In some embodiments, R^3 is selected from the group consisting of:

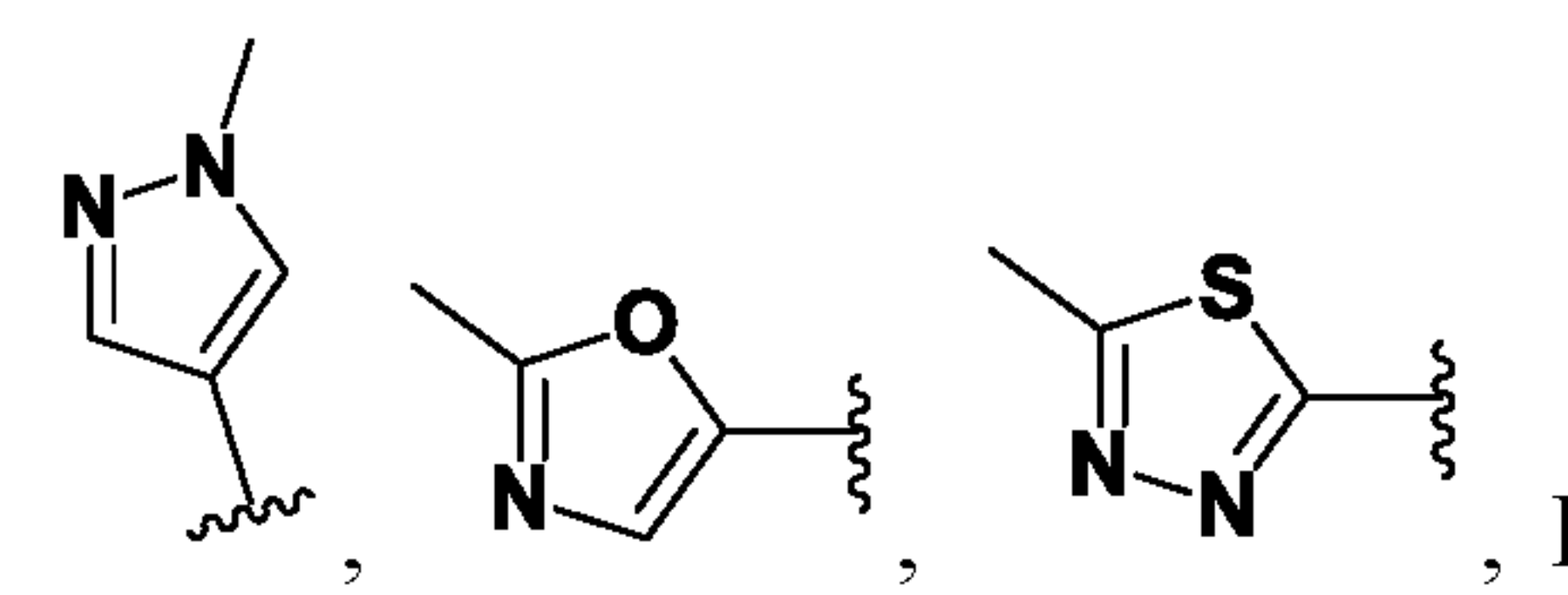


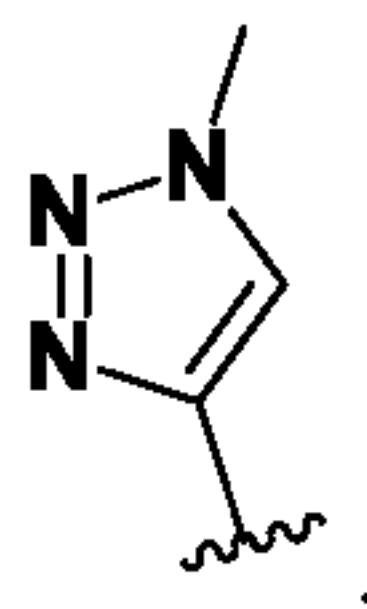

, and R^{36} is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CF}_2\text{CH}_3$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{F}$, $-\text{CH}_2\text{CH}_2\text{CF}_3$, $-(\text{CH}_2\text{CH}_2)\text{OMe}$, $-(\text{CH}_2\text{CH}_2)\text{OiPr}$, , and .

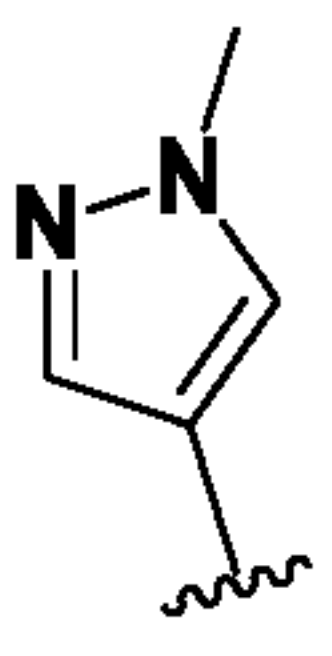
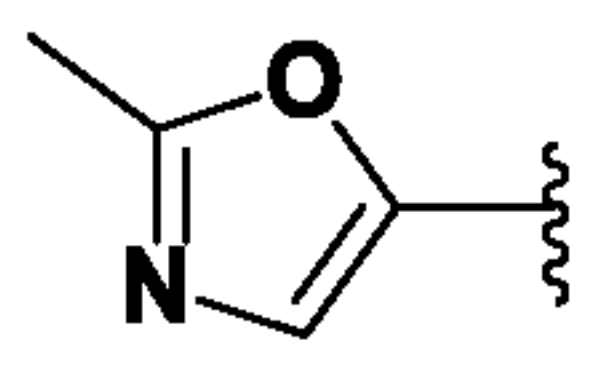
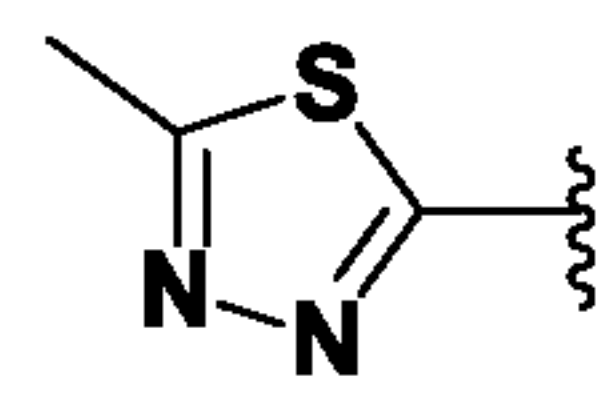
[0308] In some embodiments, R^3 is selected from the group consisting of:

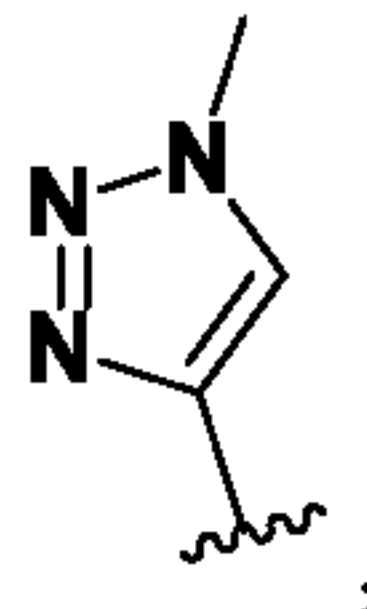

, R^6 is selected from the group consisting of $-(\text{C}_{1-4}$ alkylene)_pheterocyclyl optionally substituted with 1-10 R^{36} and $-(\text{C}_{1-4}$ alkylene)_pcarbocyclyl optionally substituted with 1-12 R^{37} .

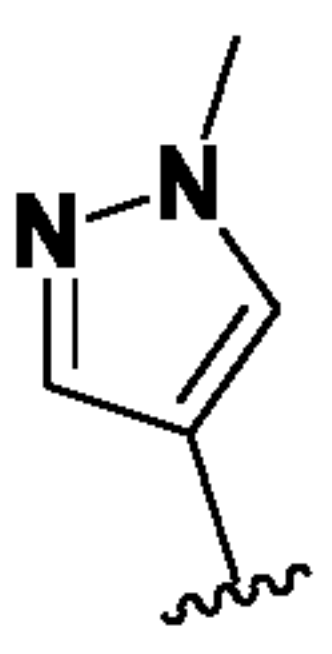
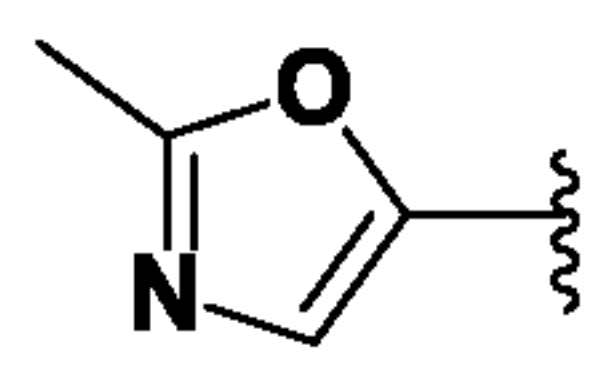
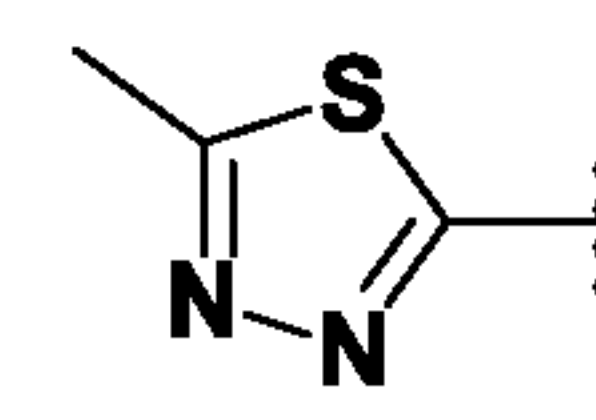
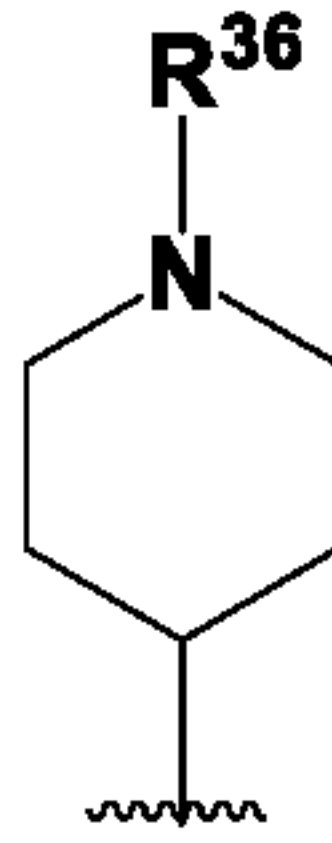
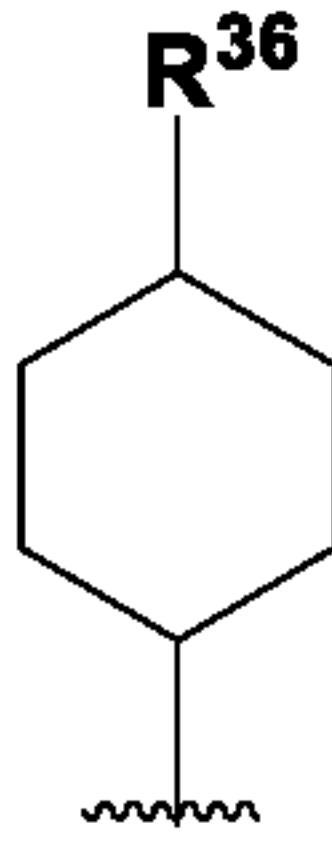
[0309] In some embodiments, R^3 is selected from the group consisting of:

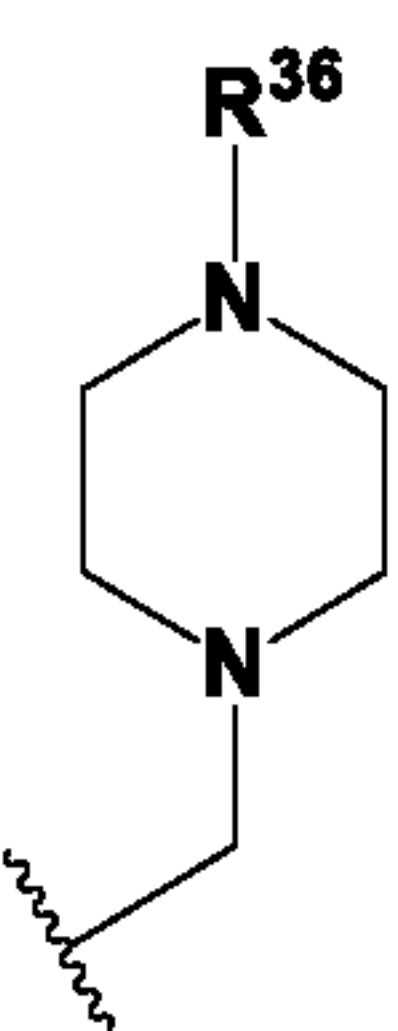
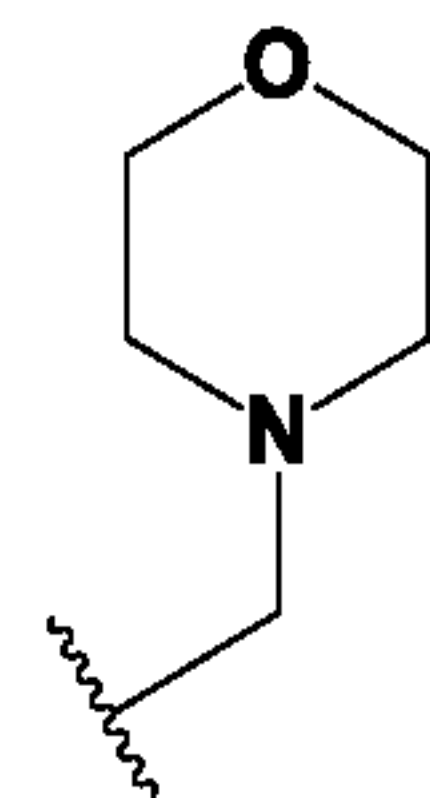
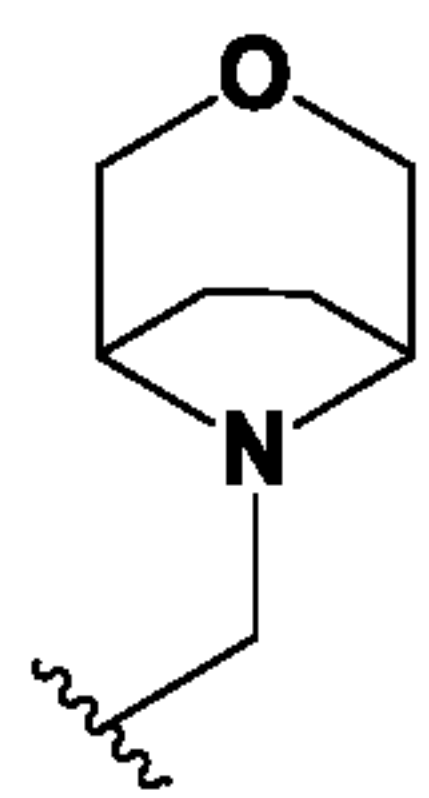
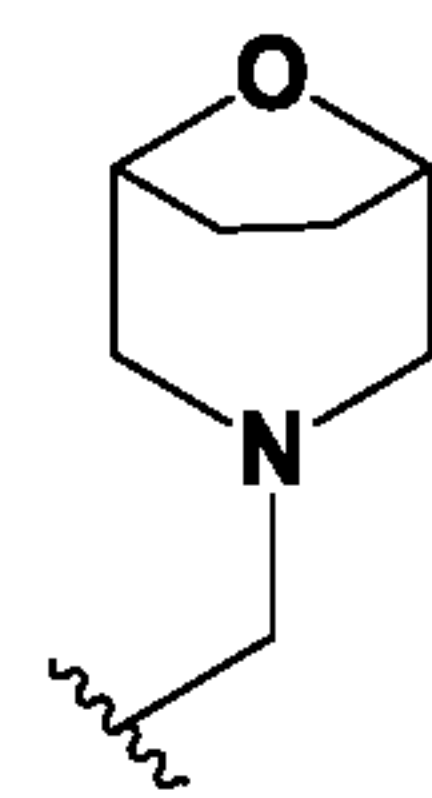
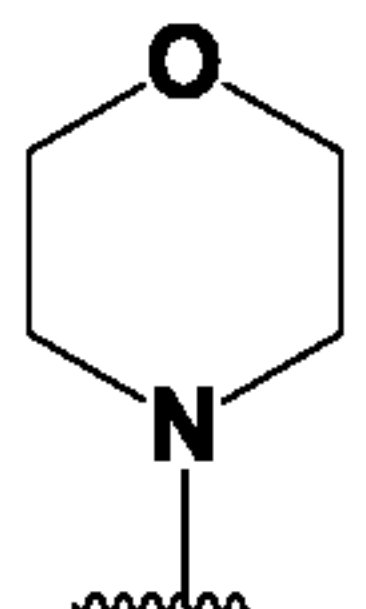

, R^6 is selected from the group consisting of $-(\text{CH}_2)$ heterocyclyl optionally substituted with 1-2 R^{36} , heterocyclyl optionally substituted with 1-2 R^{36} , and carbocyclyl optionally substituted with 1-2 R^{37} , and R^{36} is selected from the group consisting of halide and unsubstituted $-(\text{C}_{1-9}$ alkyl), and R^{37} is selected from the group consisting of halide and unsubstituted $-(\text{C}_{1-9}$ alkyl), $-\text{N}(\text{R}^{53})_2$, and heterocyclyl optionally substituted with 1-2 R^{43} .

[0310] In some embodiments, R^3 is selected from the group consisting of: ,

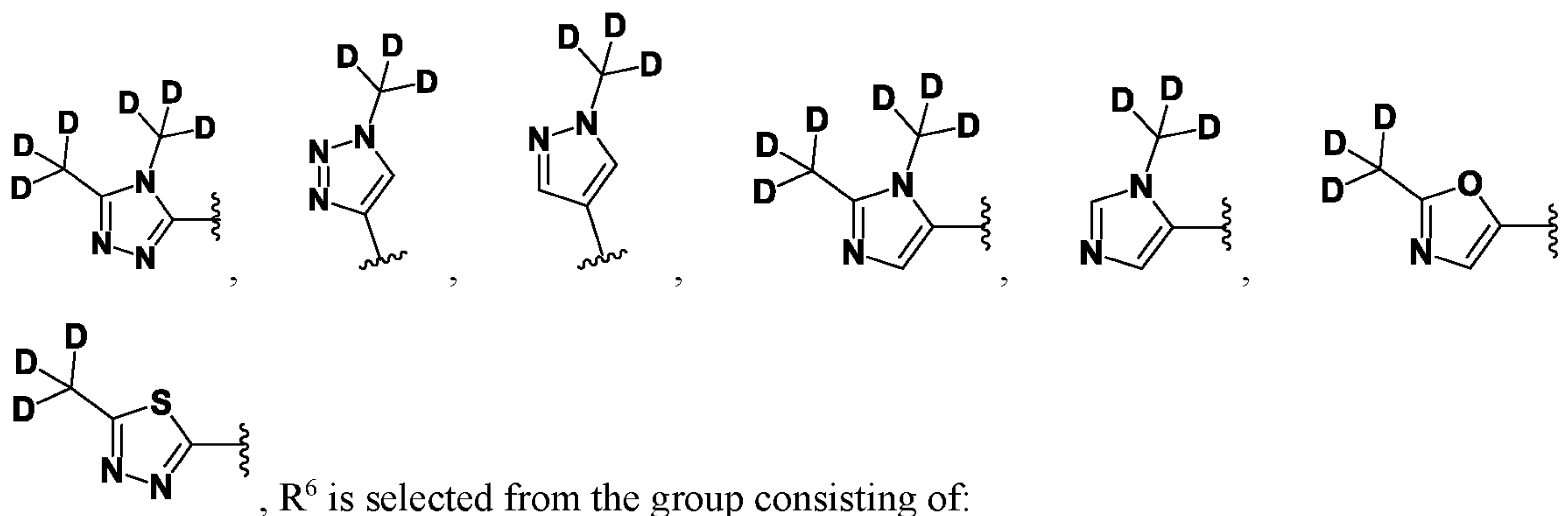
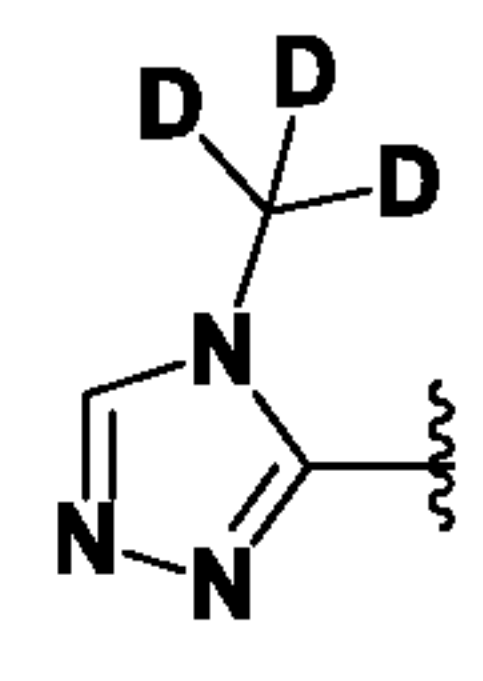
, , , R^6 is selected from the group consisting of $-(CH_2)_{\text{heterocycl}}l$ optionally substituted with 1 R^{36} –heterocyclyl optionally substituted with 1 R^{36} , and –carbocyclyl substituted with 1 R^{37} , and R^{36} is unsubstituted $-(C_{1-5} \text{ alkyl})$, and R^{37} is selected from the group consisting of $-N(C_{1-3} \text{ alkyl})_2$, and an unsubstituted –heterocyclyl.

[0311] In some embodiments, R^3 is selected from the group consisting of: ,

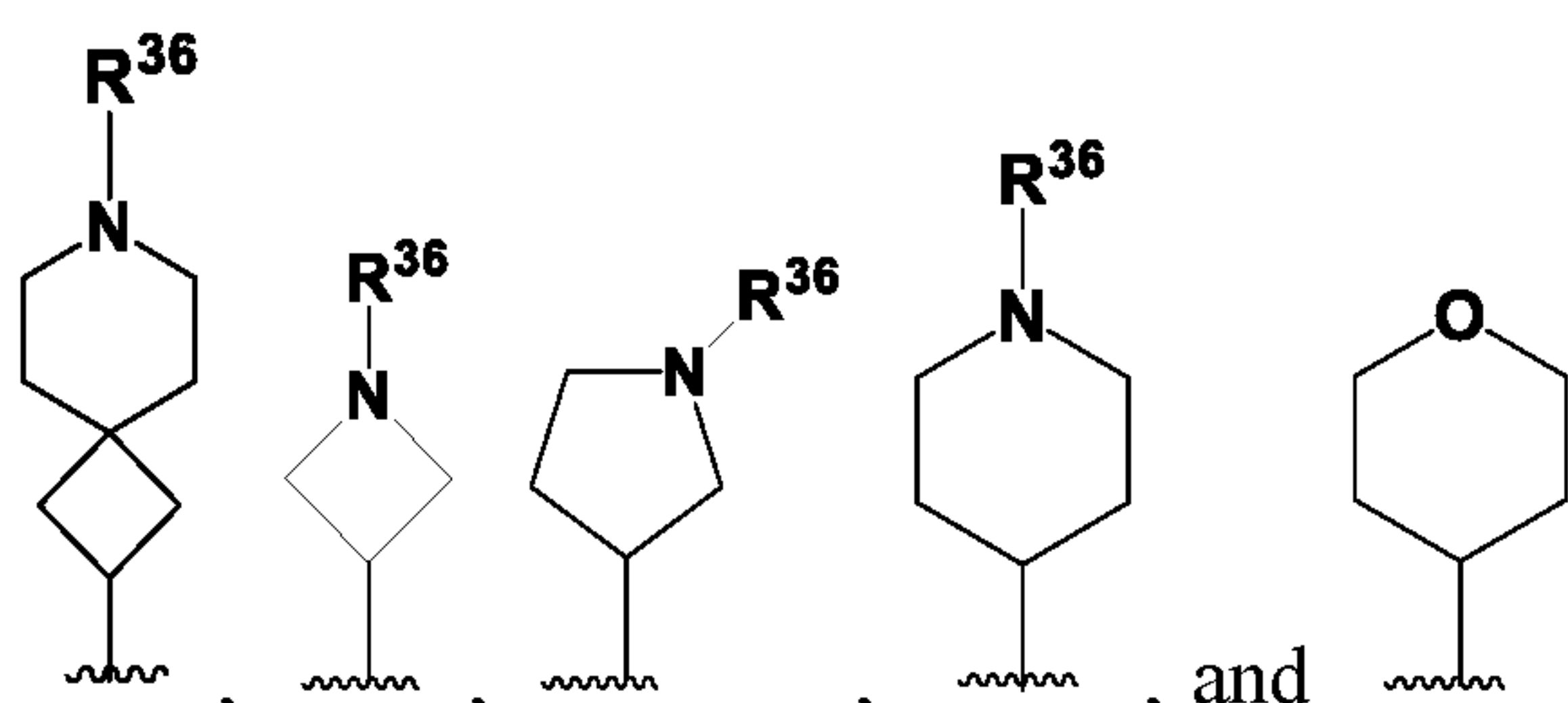
, , , R^6 is selected from the group consisting of: , ,

, , , and , and R^{36} is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, $-NMe_2$, and .

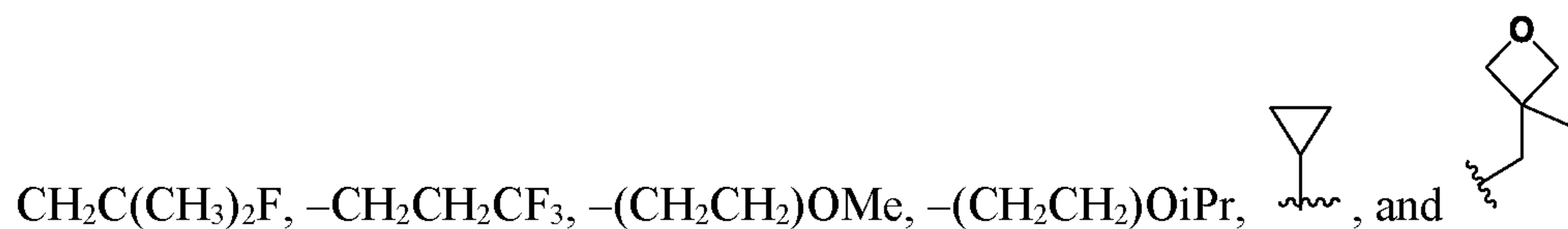
[0312] In some embodiments, R^3 is selected from the group consisting of:



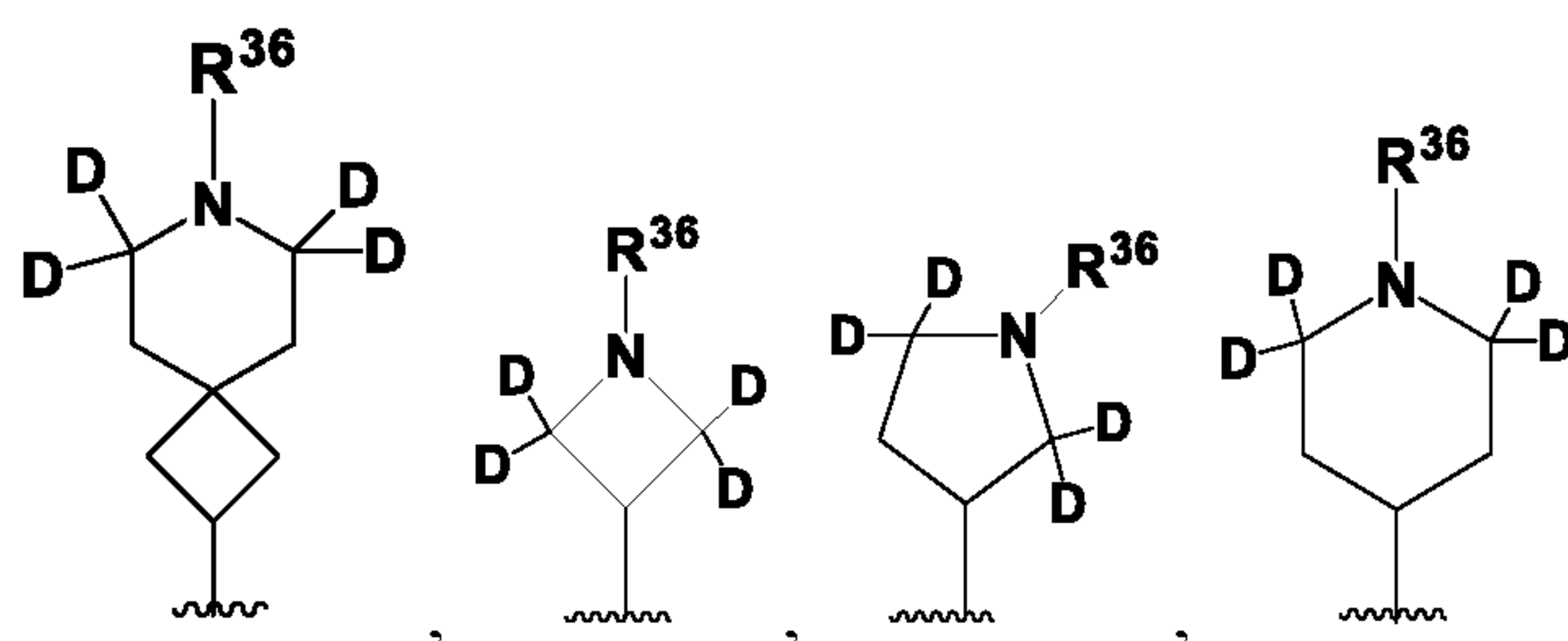
, R^6 is selected from the group consisting of:



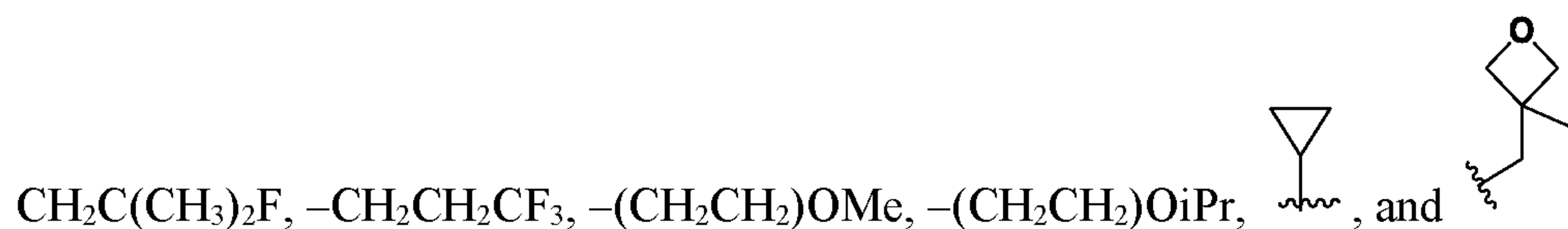
, , , , and , and R³⁶ is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CH₂CF₂CH₃, -

 $\text{CH}_2\text{C}(\text{CH}_3)_2\text{F}$, $-\text{CH}_2\text{CH}_2\text{CF}_3$, $-(\text{CH}_2\text{CH}_2)\text{OMe}$, $-(\text{CH}_2\text{CH}_2)\text{OiPr}$, , and .

[0313] In some embodiments, R^6 is selected from the group consisting of:

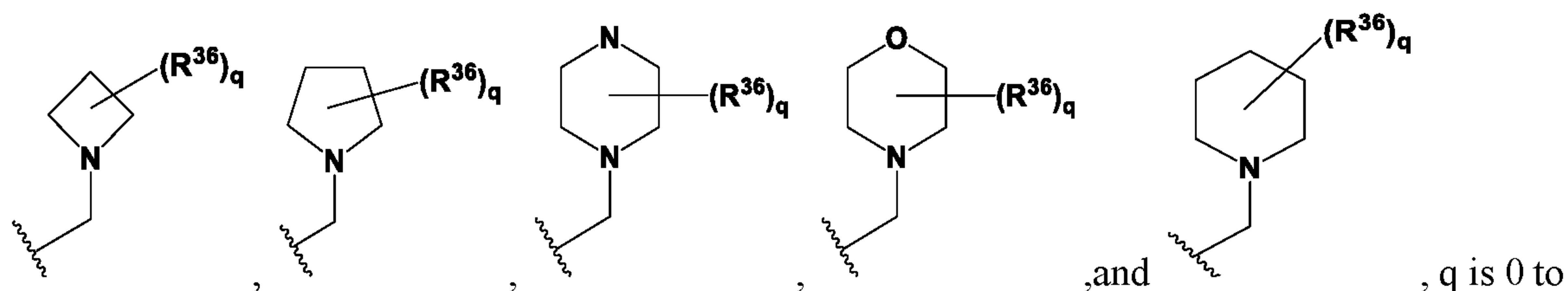
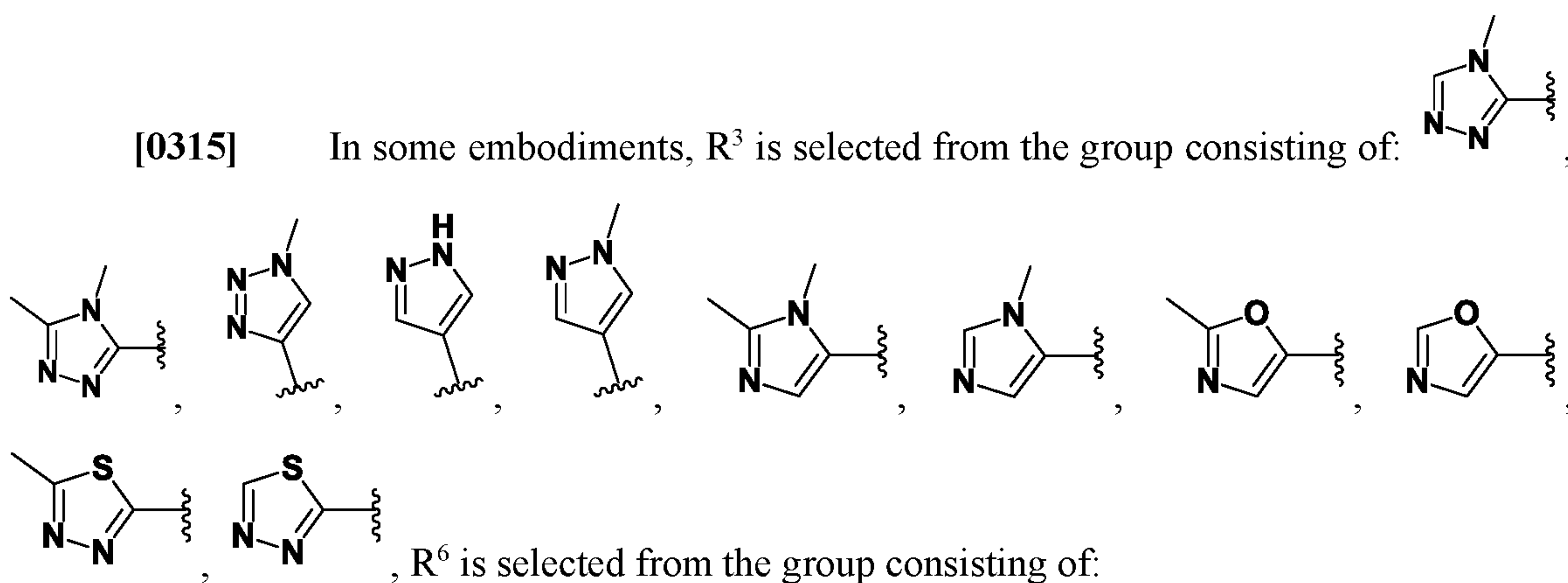


, , , , and R³⁶ is selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CH₂CF₂CH₃, -

 $\text{CH}_2\text{C}(\text{CH}_3)_2\text{F}$, $-\text{CH}_2\text{CH}_2\text{CF}_3$, $-(\text{CH}_2\text{CH}_2)\text{OMe}$, $-(\text{CH}_2\text{CH}_2)\text{OiPr}$, , and .

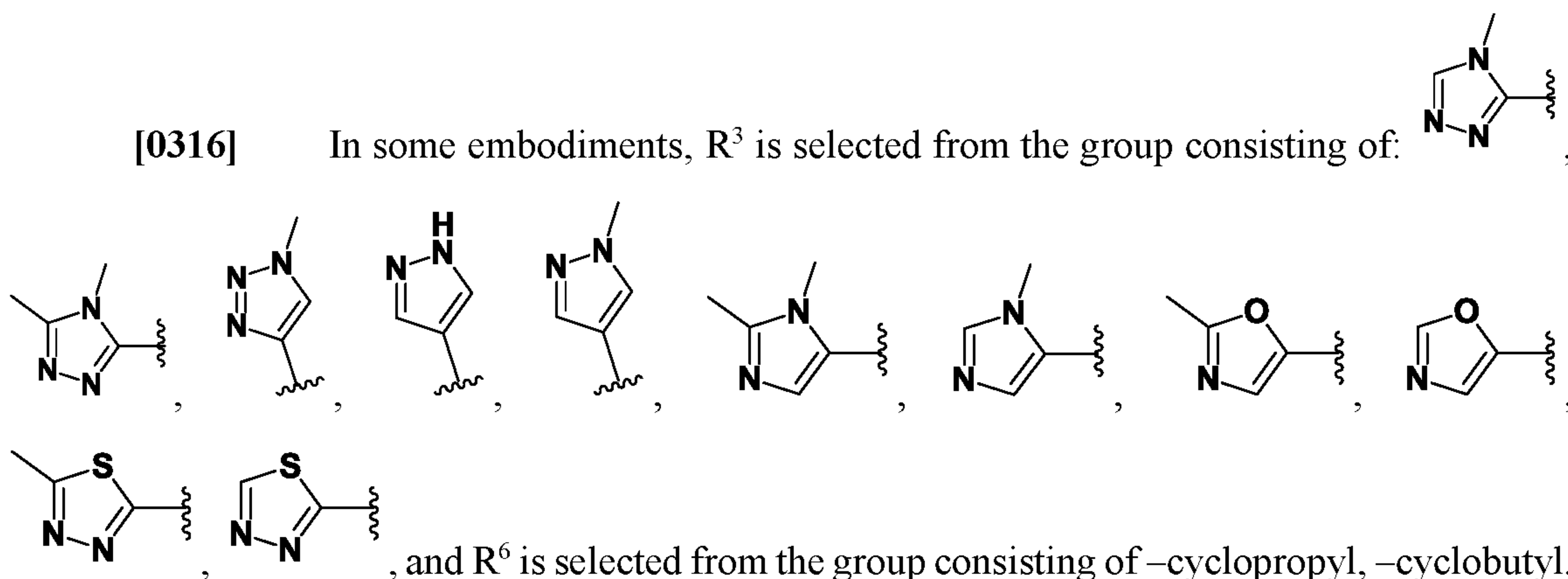
[0314]

[0315] In some embodiments, R^3 is selected from the group consisting of:

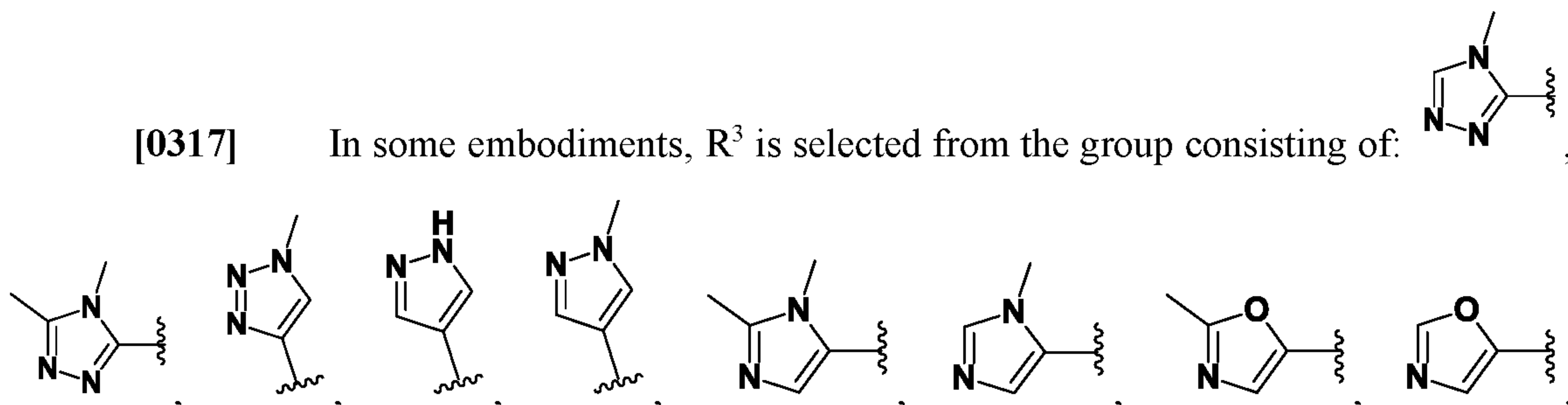


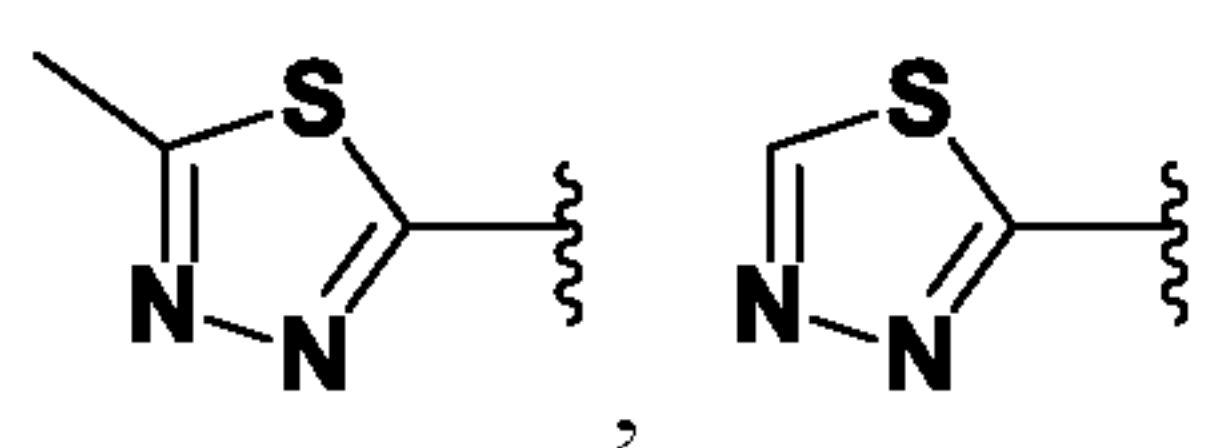
2, and each R^{36} is independently selected from the group consisting of F, methyl, and $-CF_3$.

[0316] In some embodiments, R^3 is selected from the group consisting of:



[0317] In some embodiments, R^3 is selected from the group consisting of:



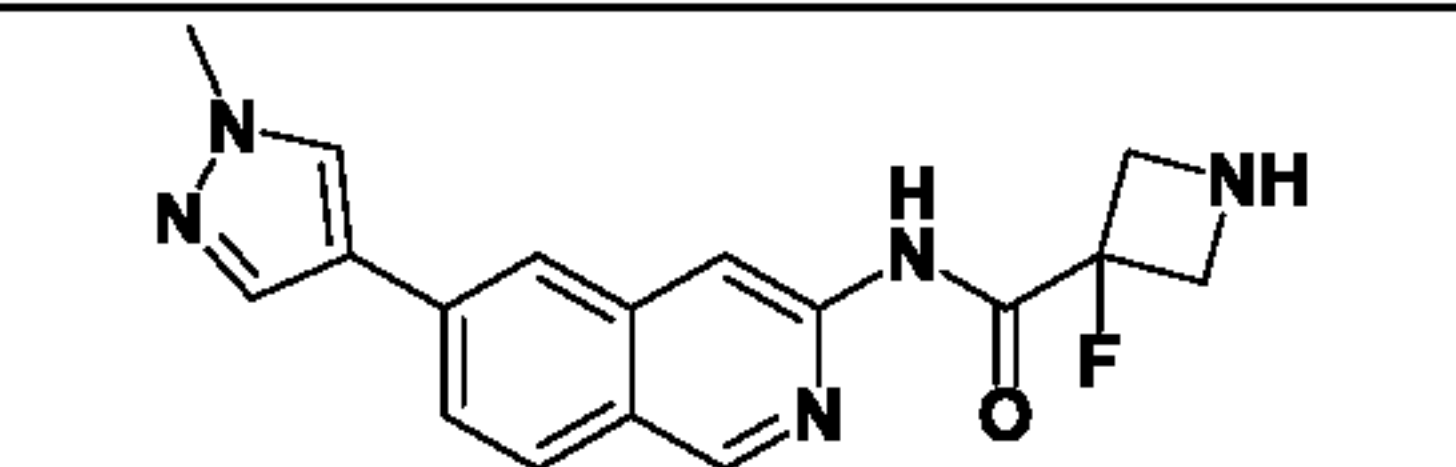
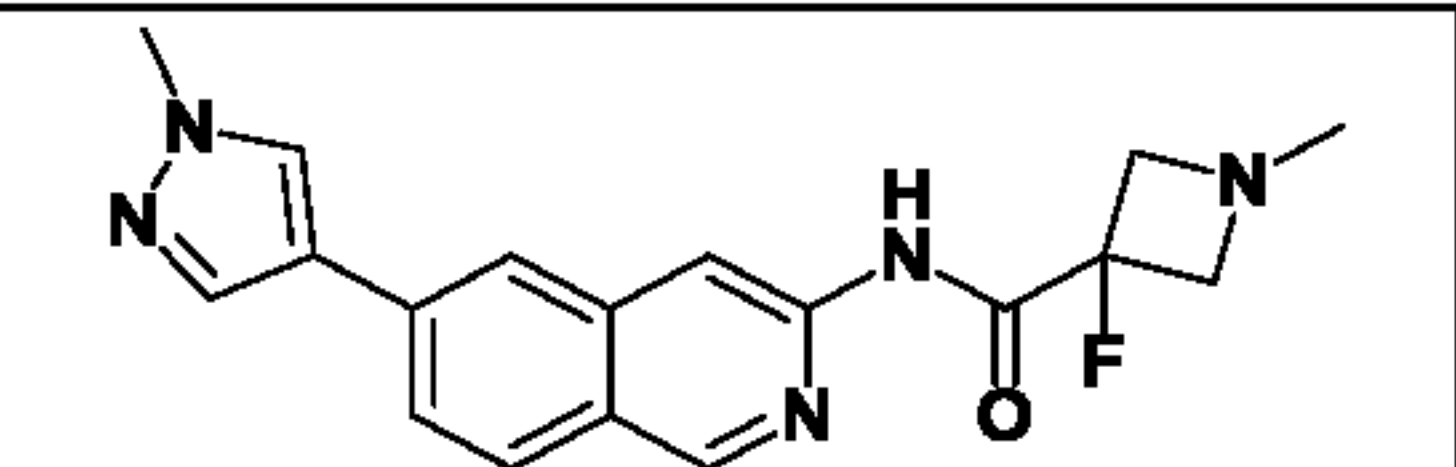
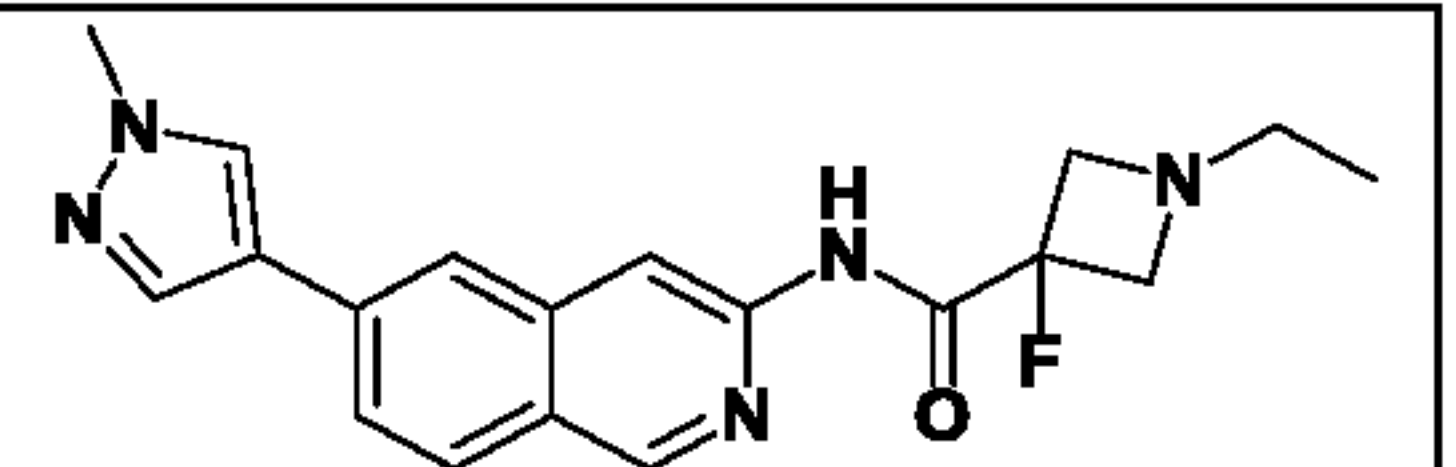
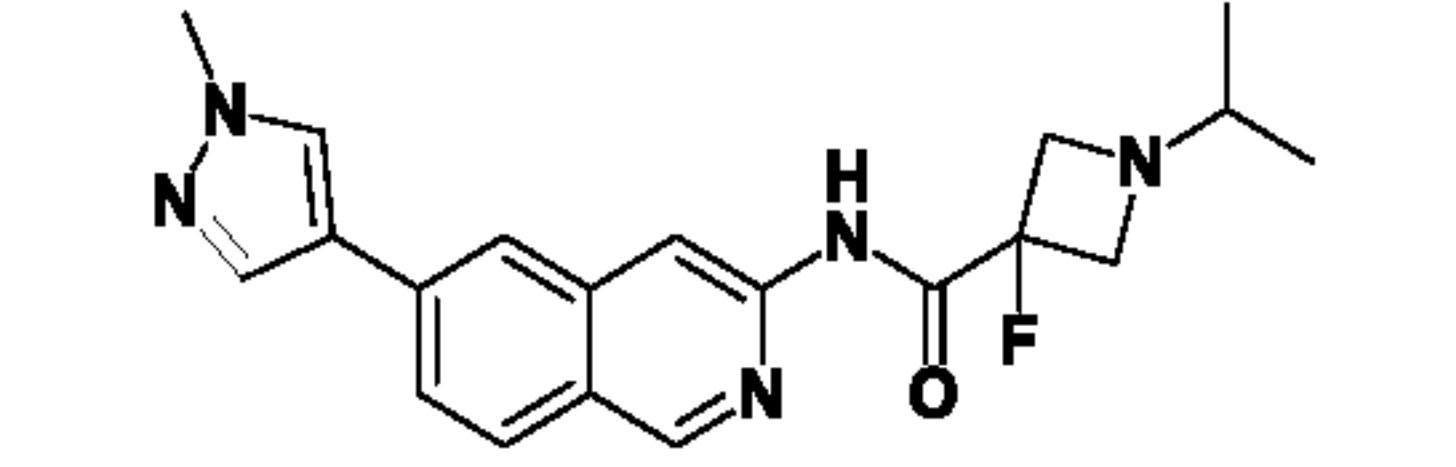
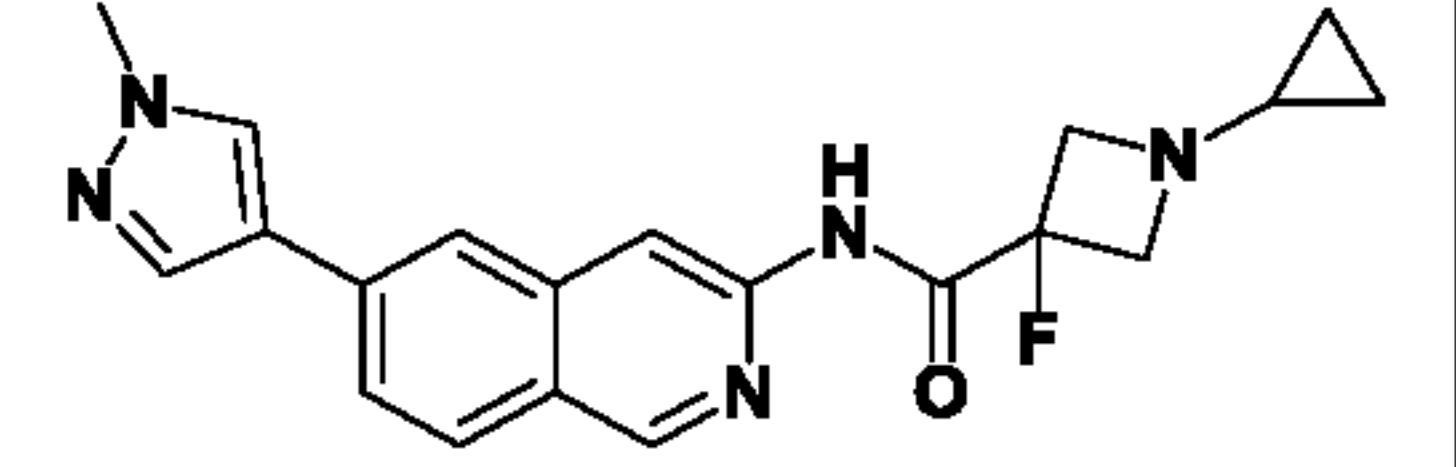
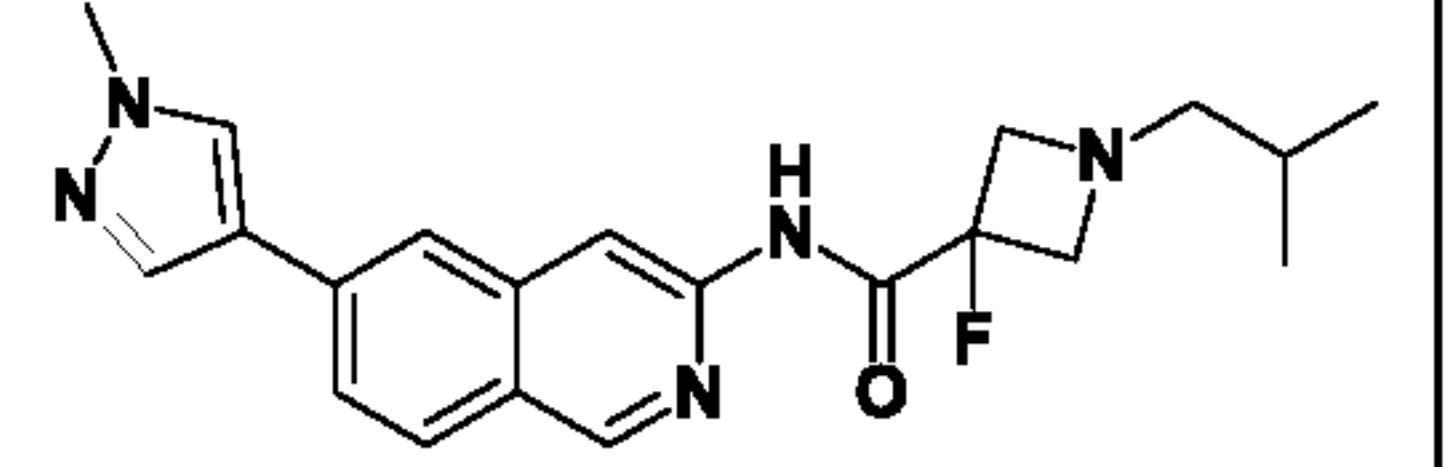
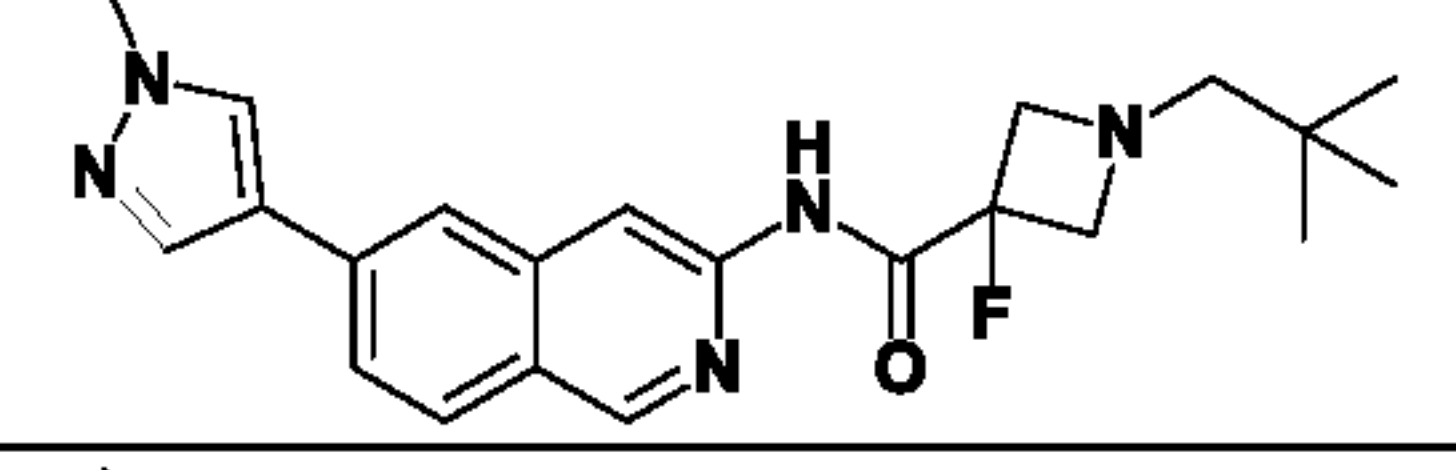
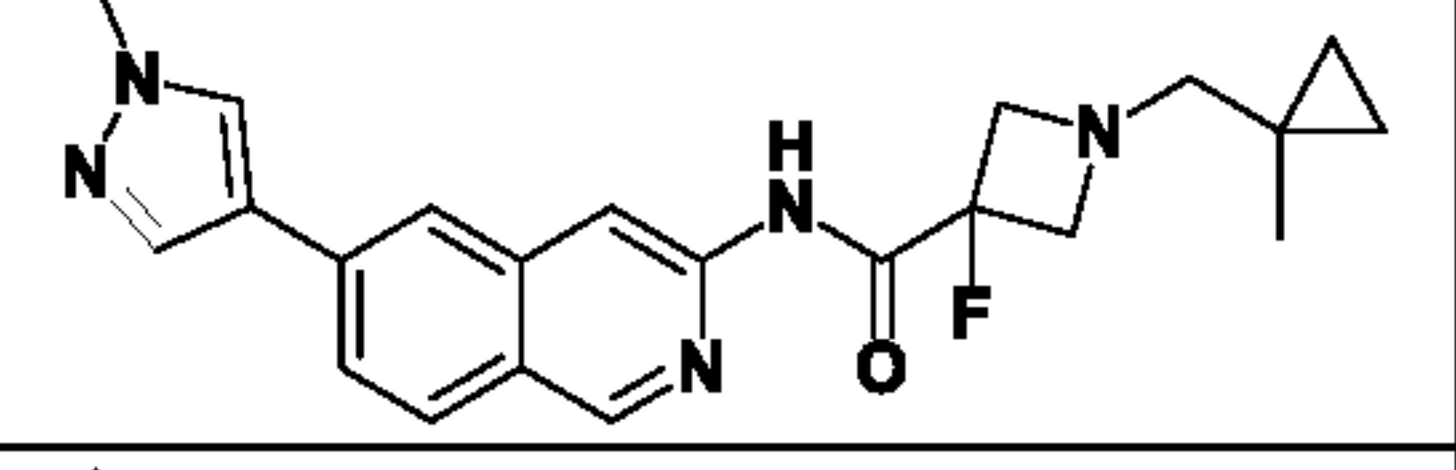
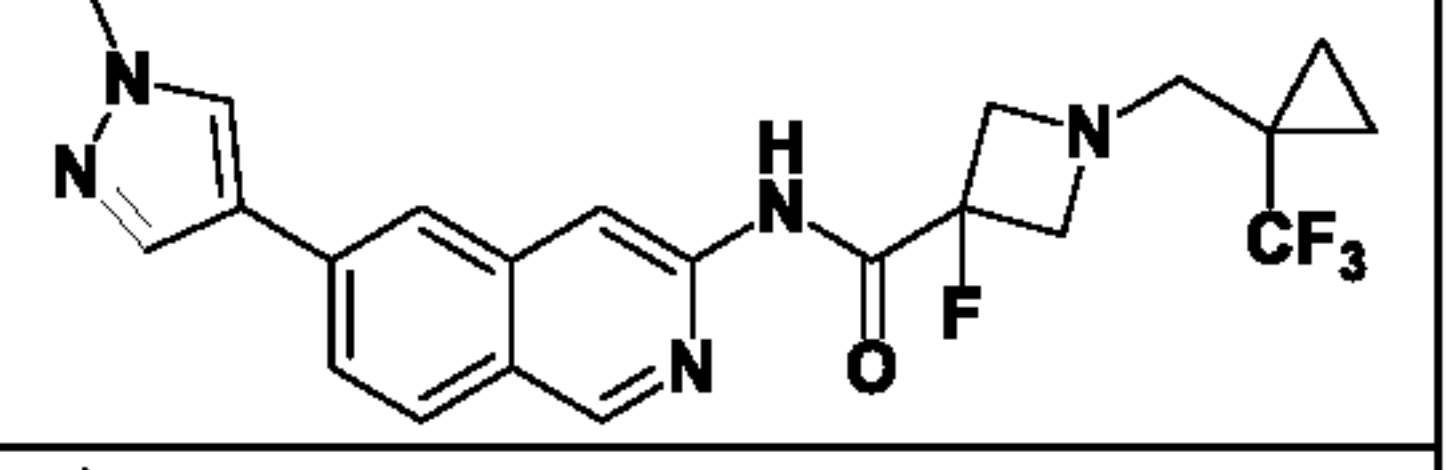
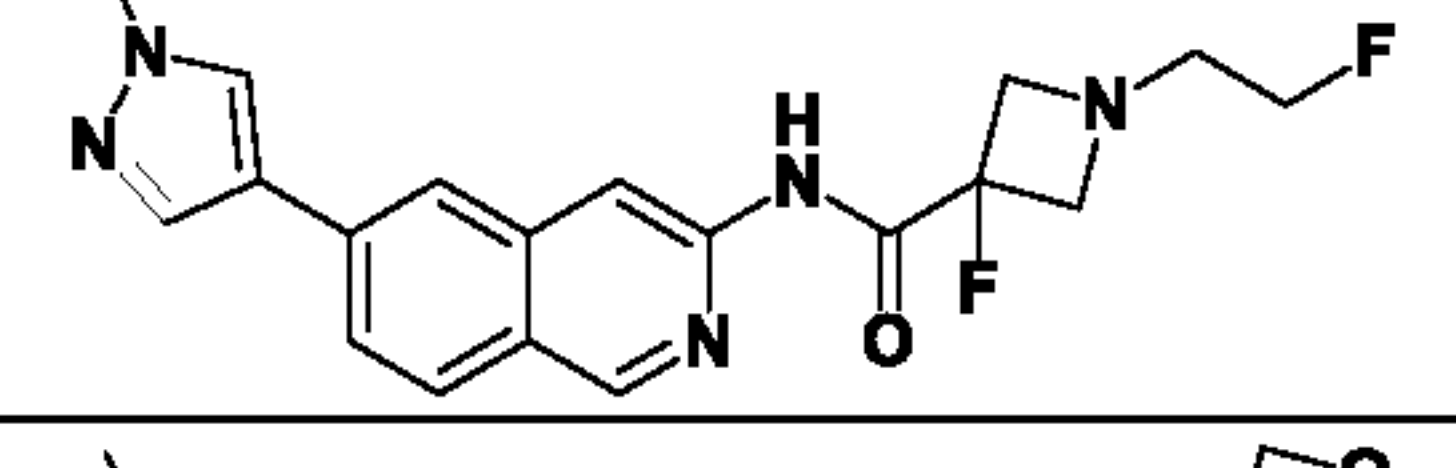
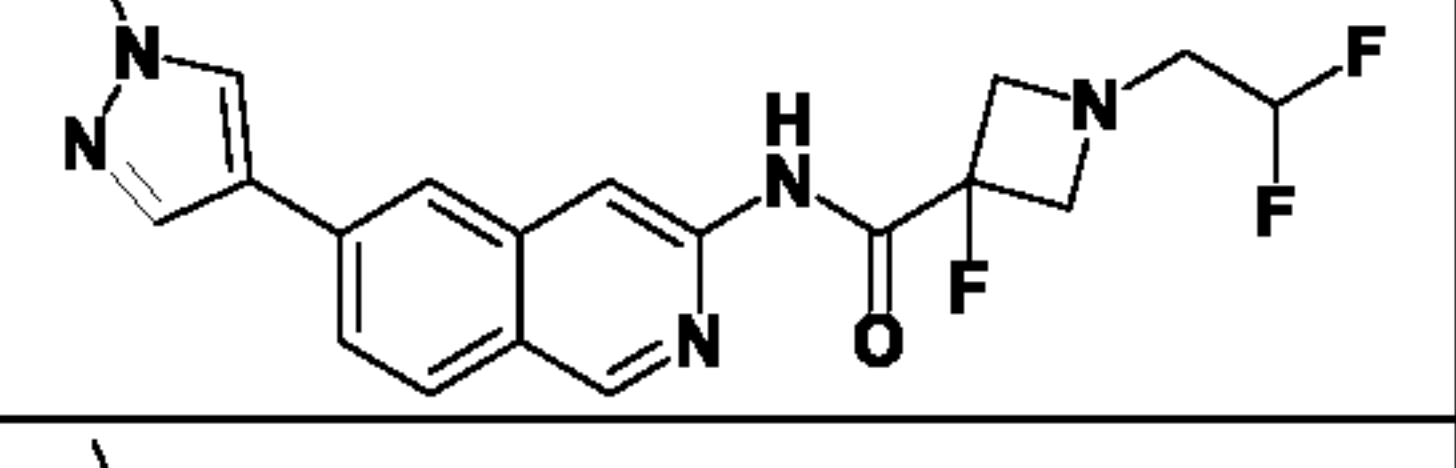
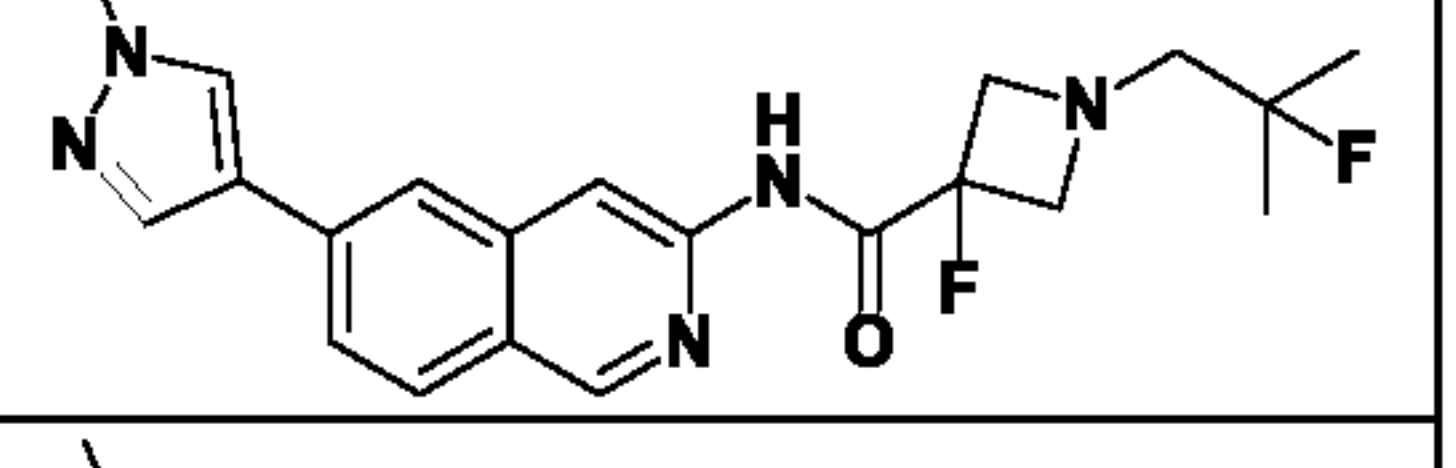
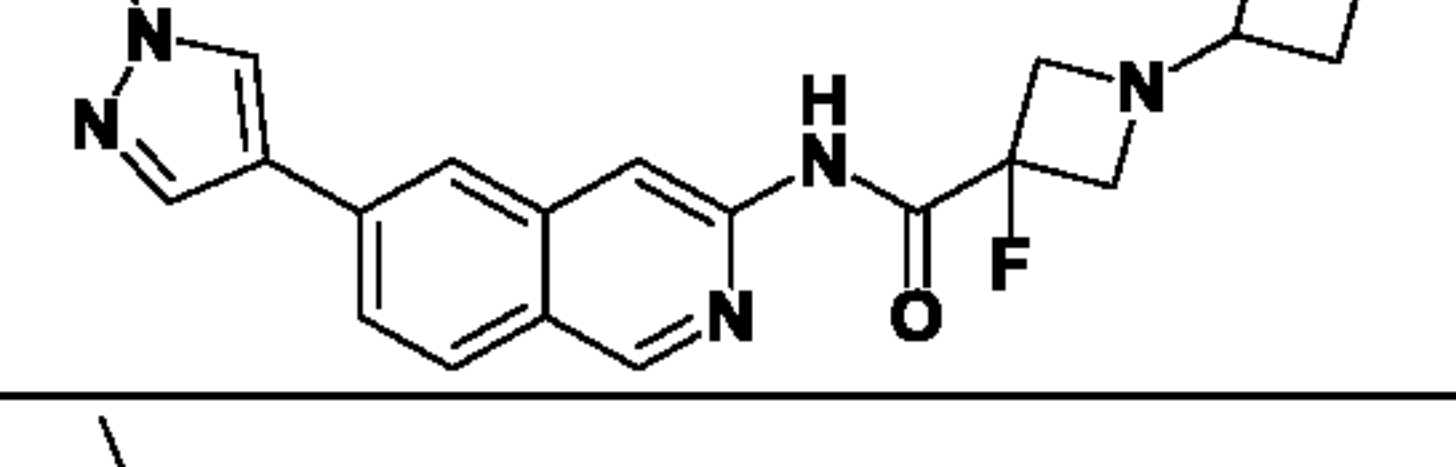
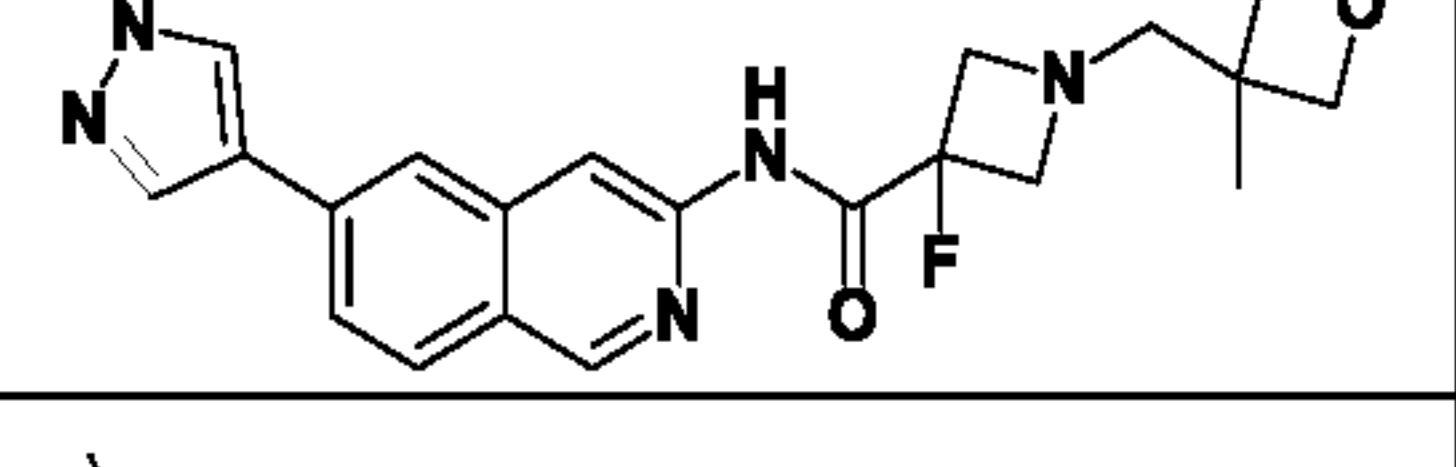
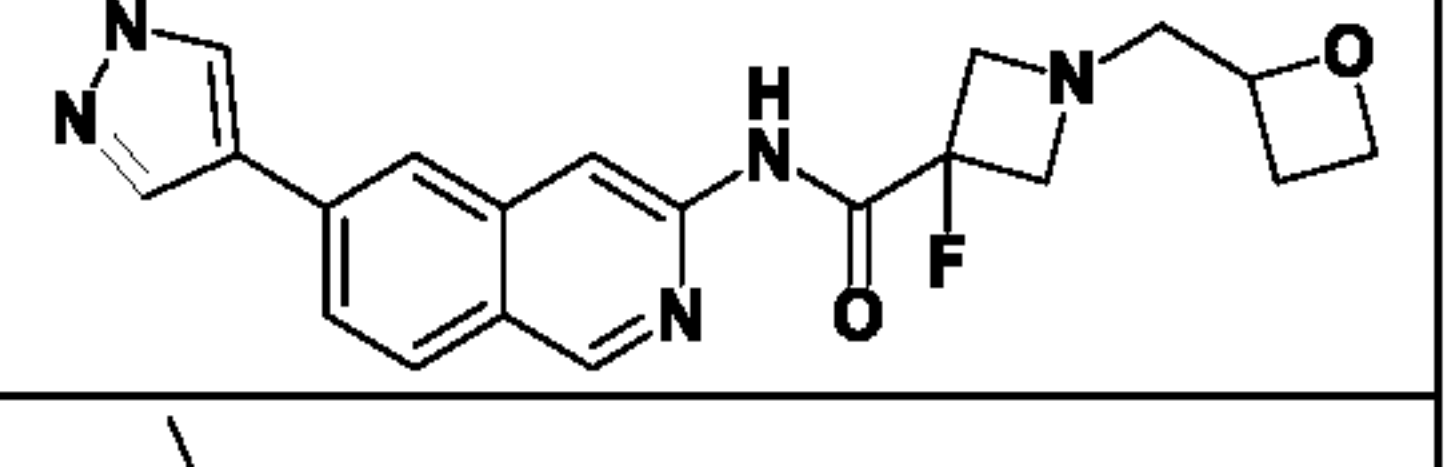
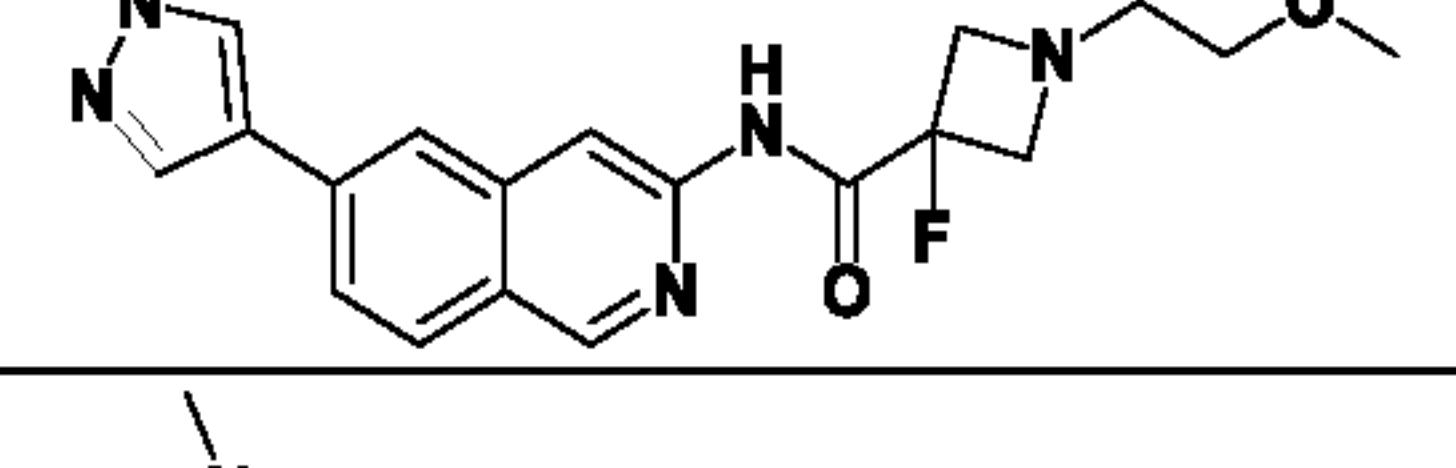
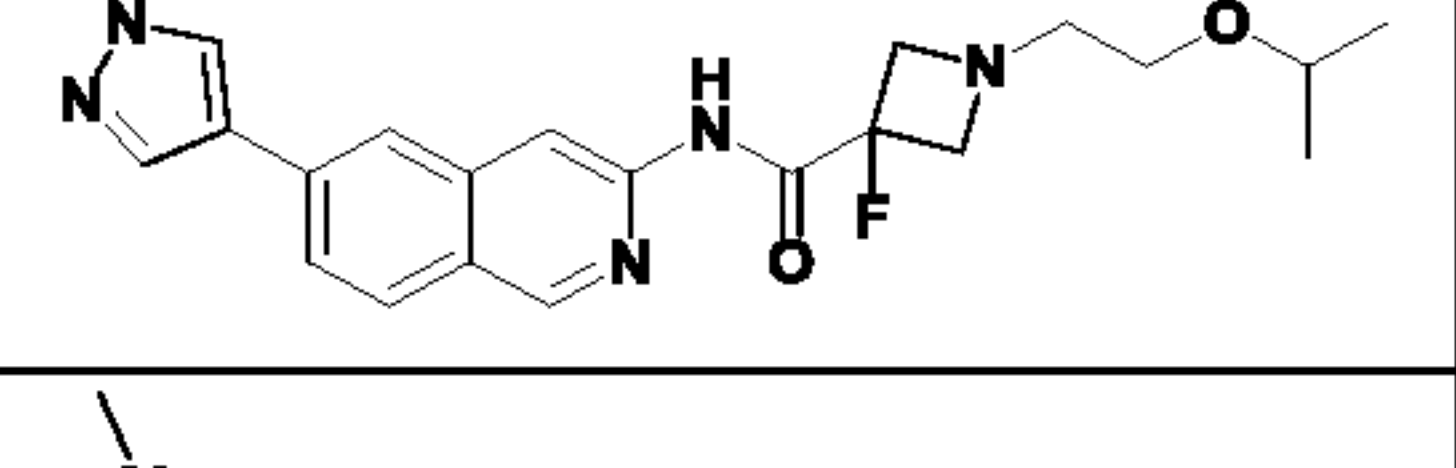
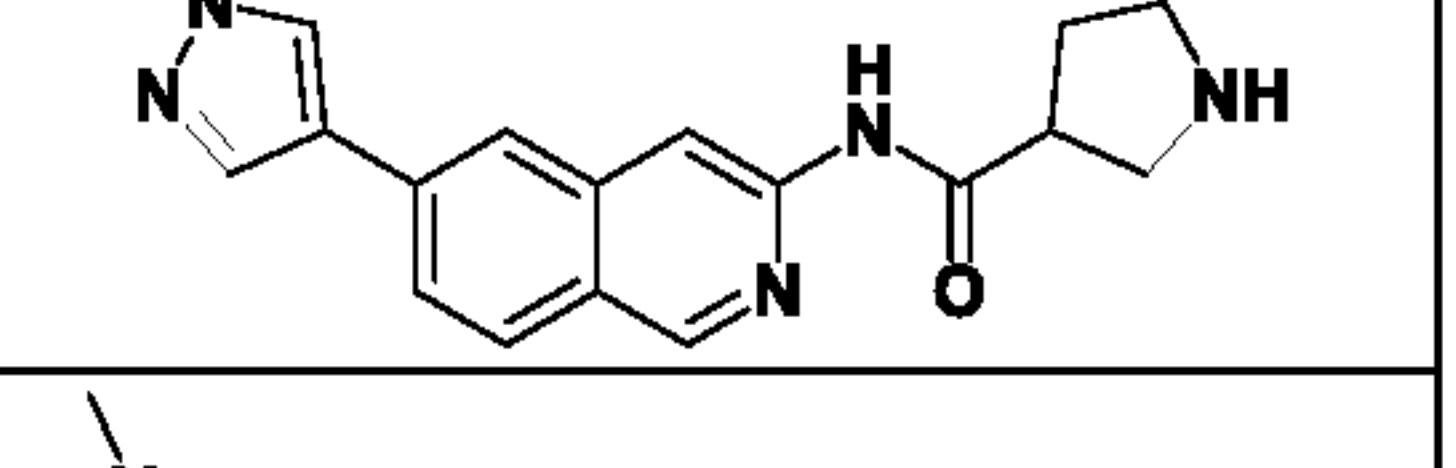
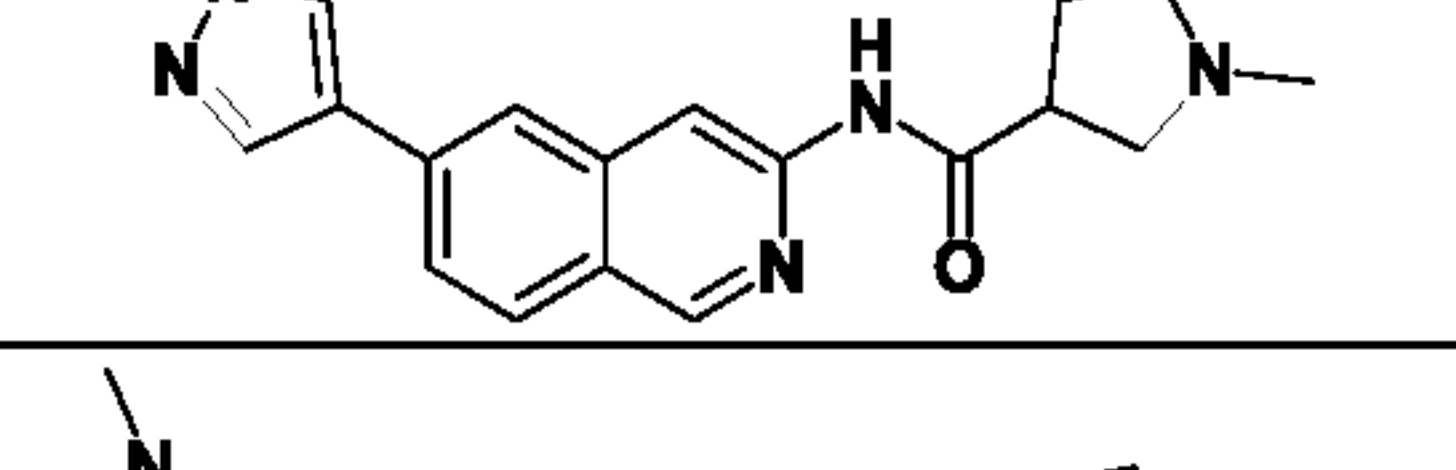
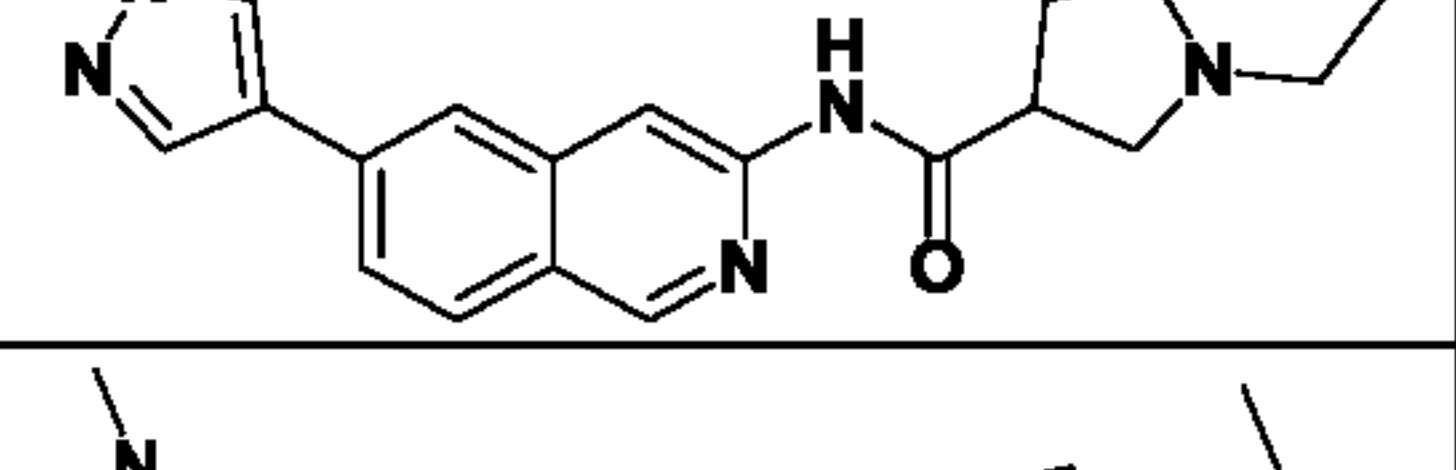
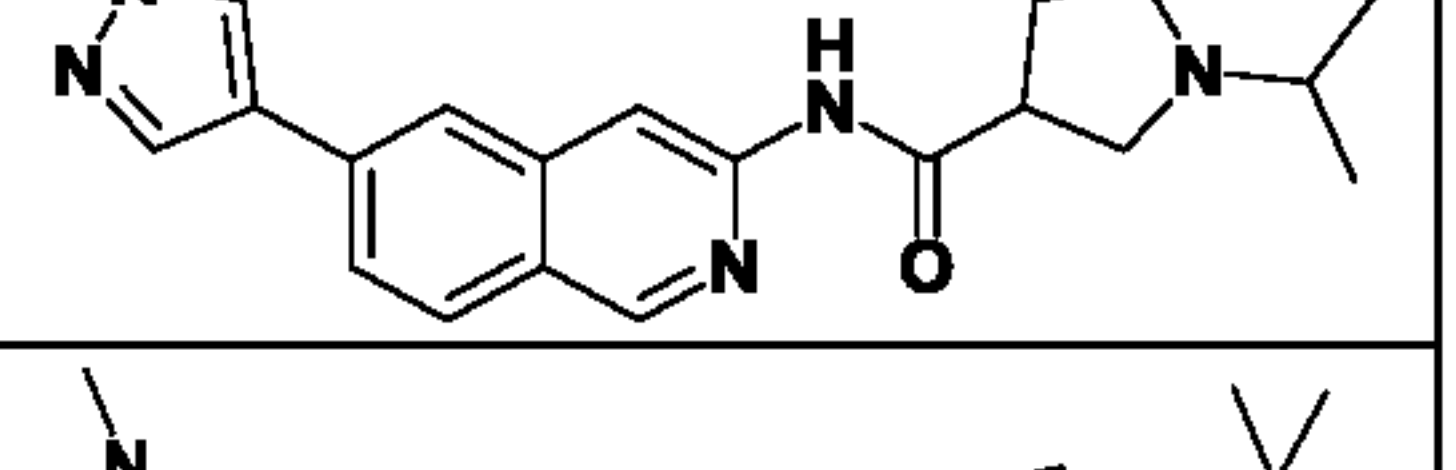
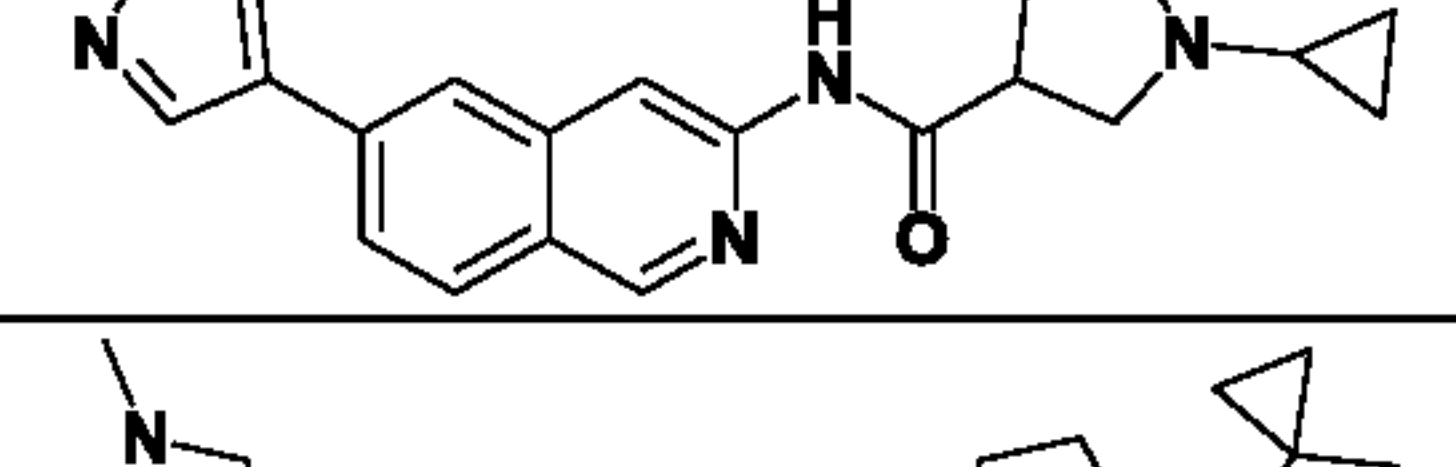
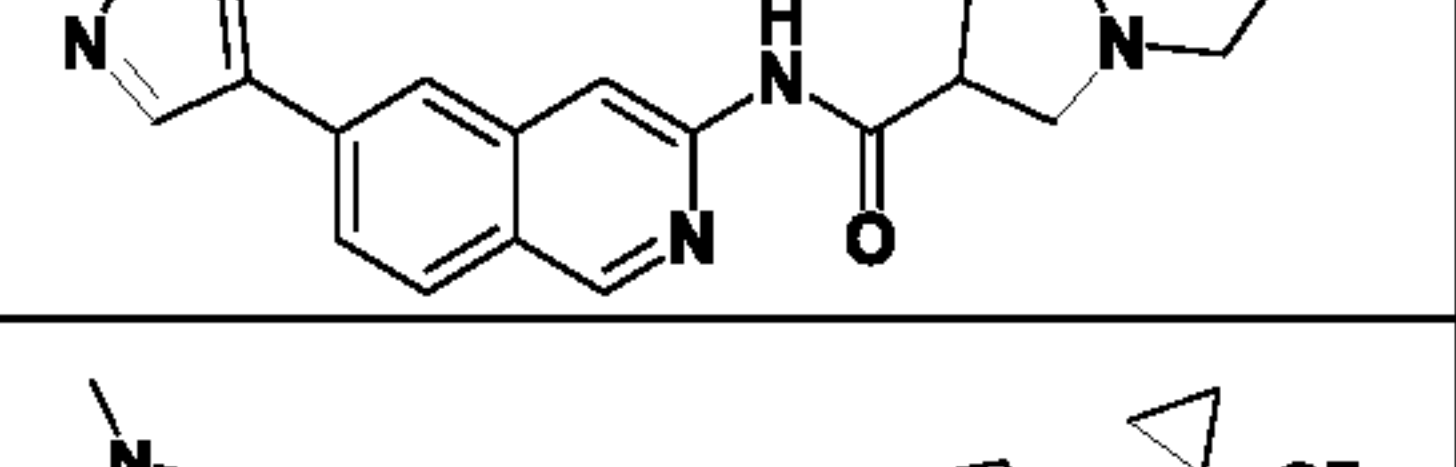
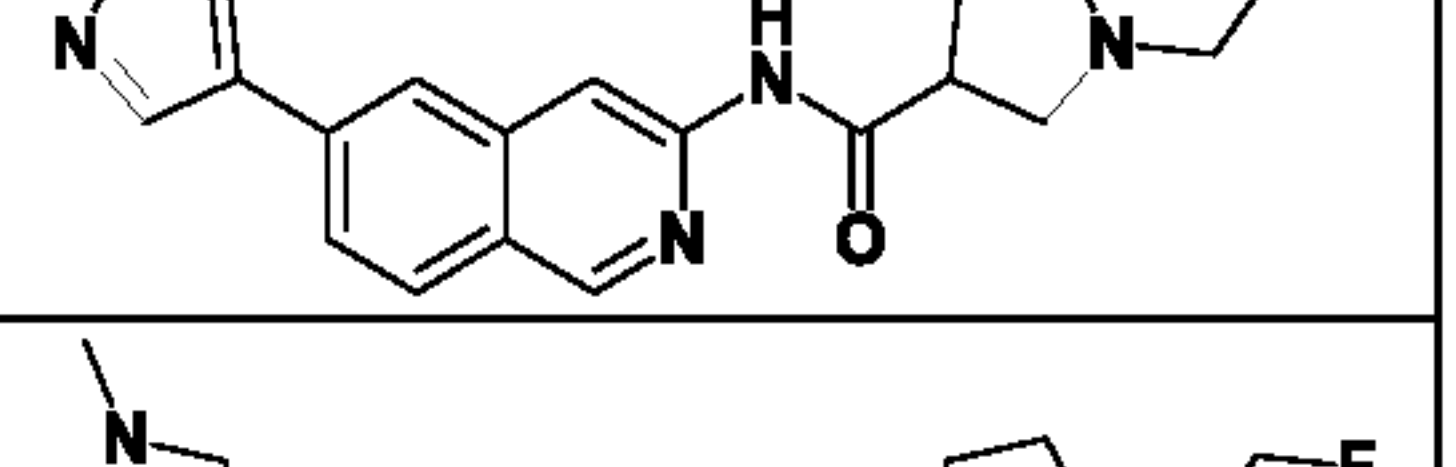
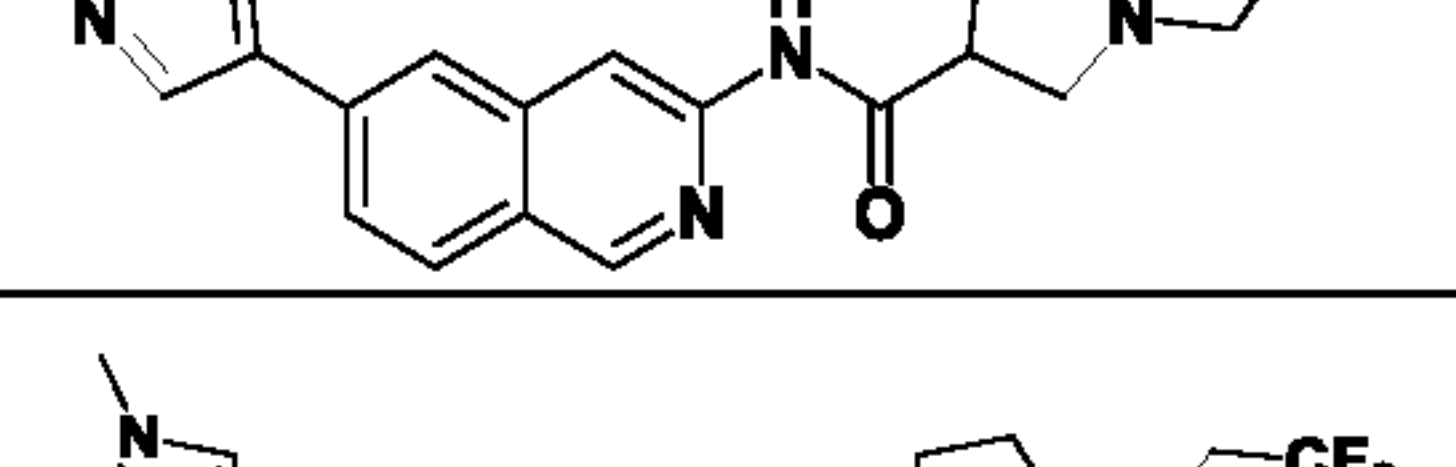
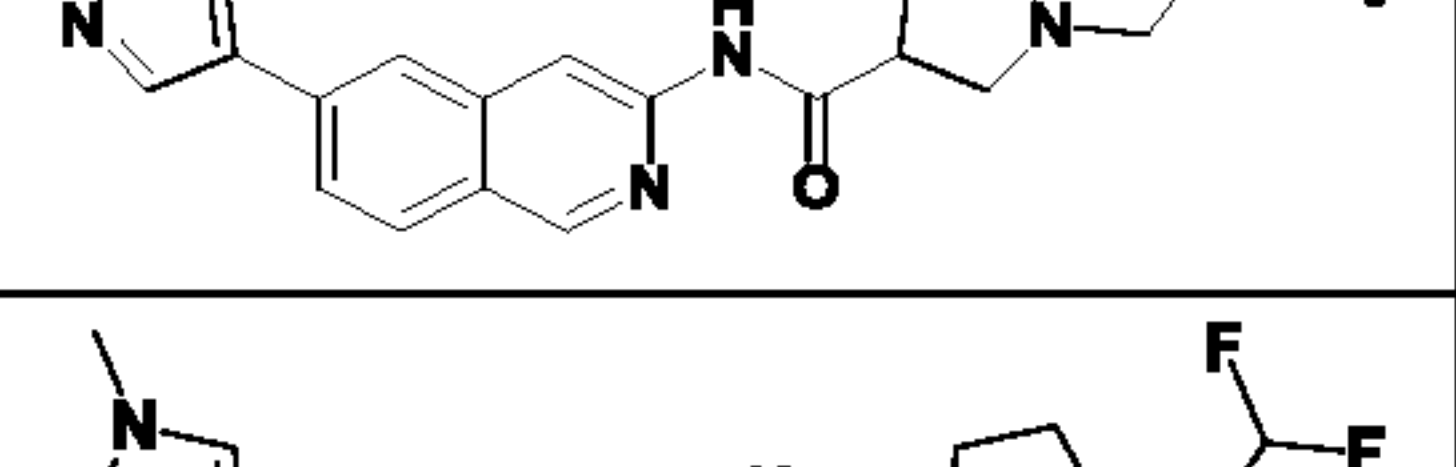
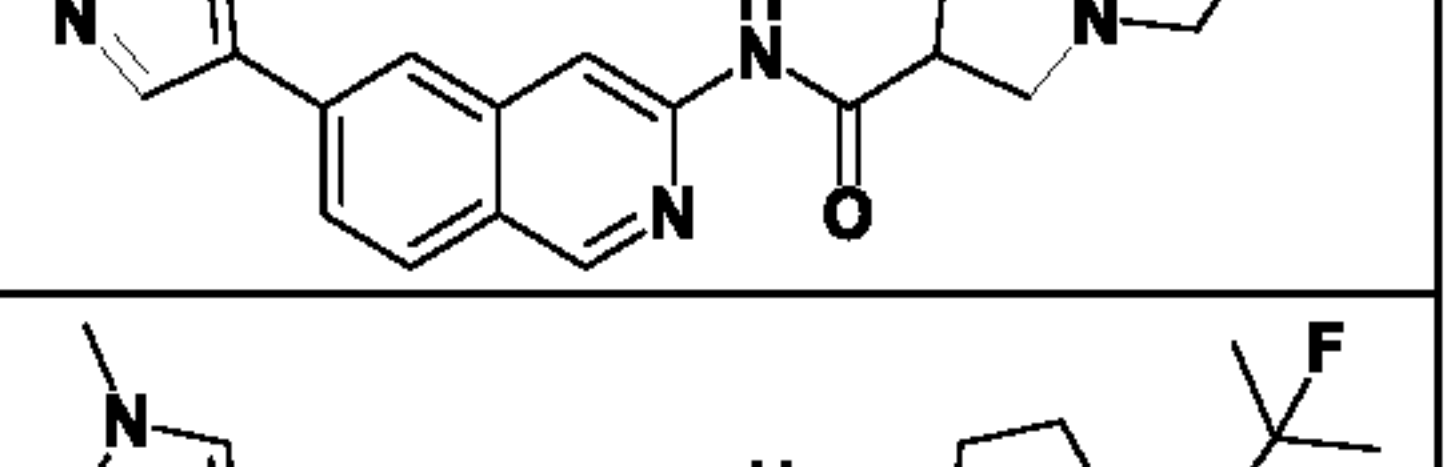
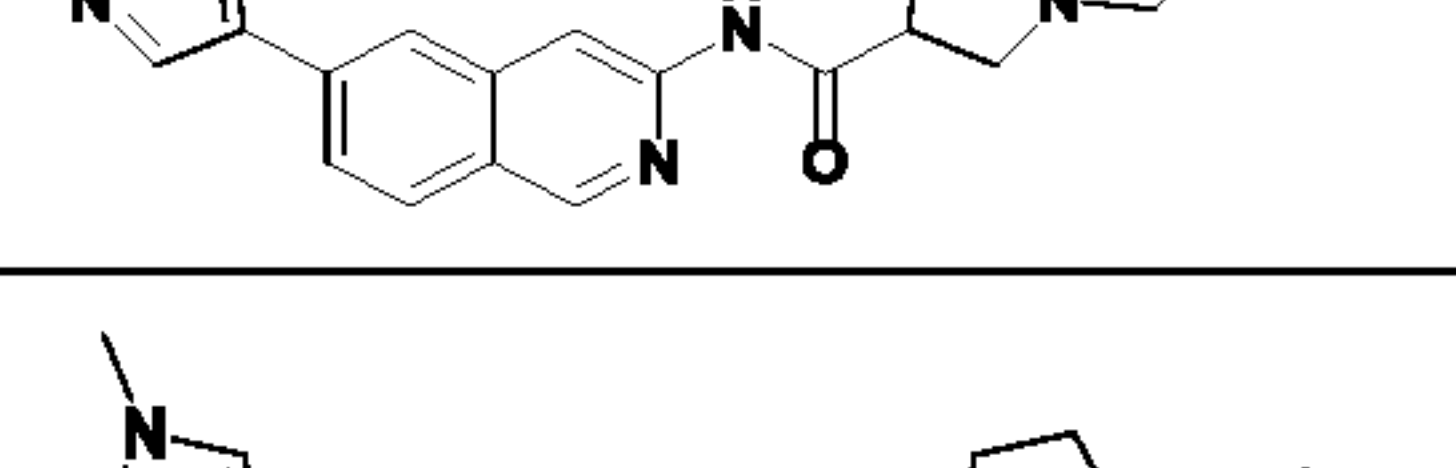
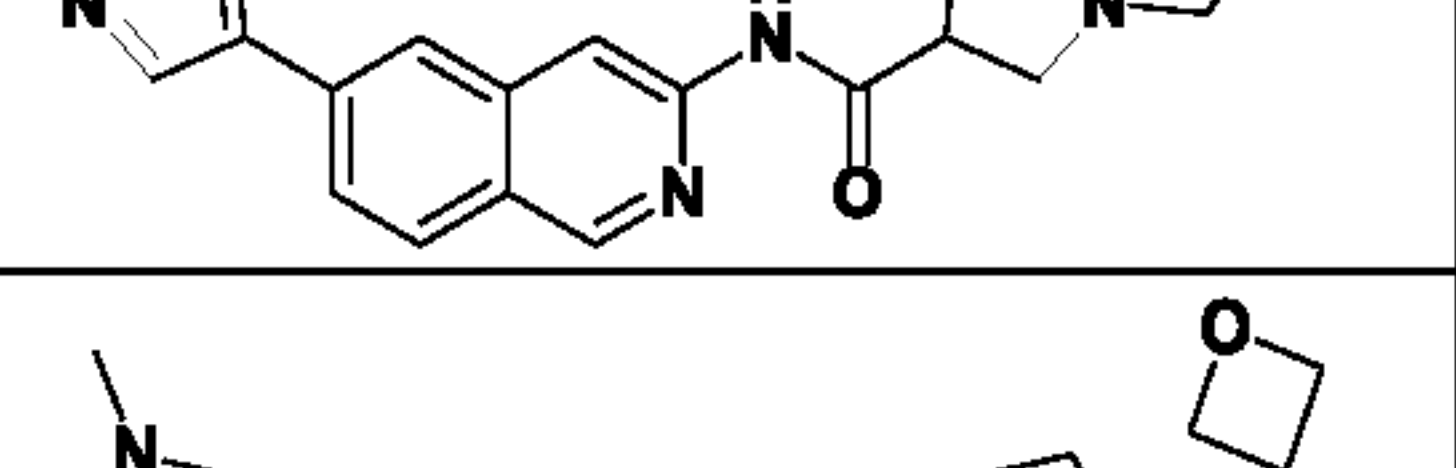
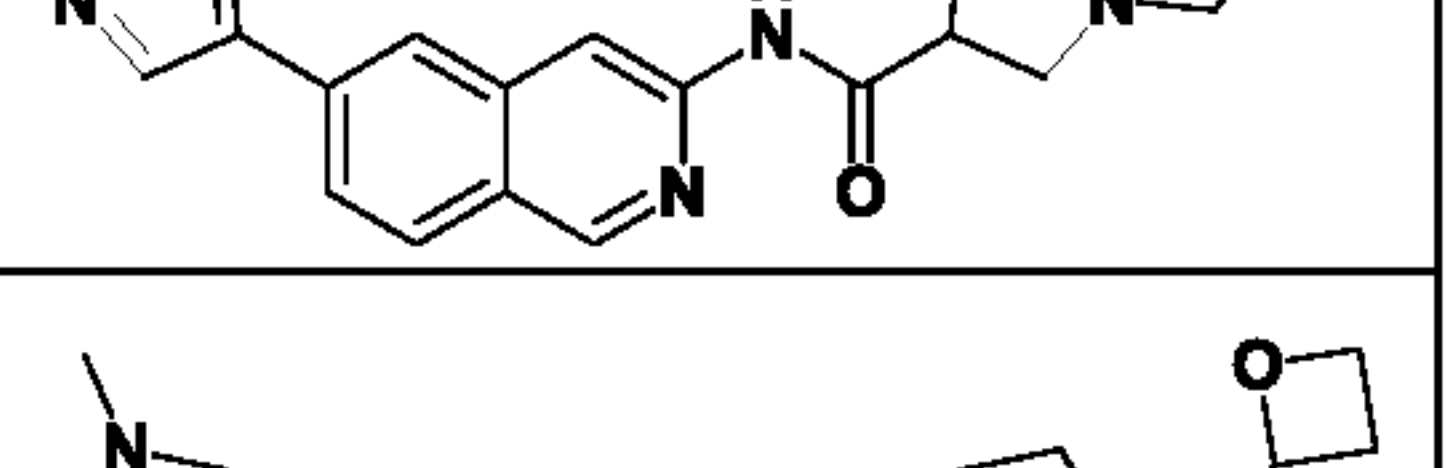
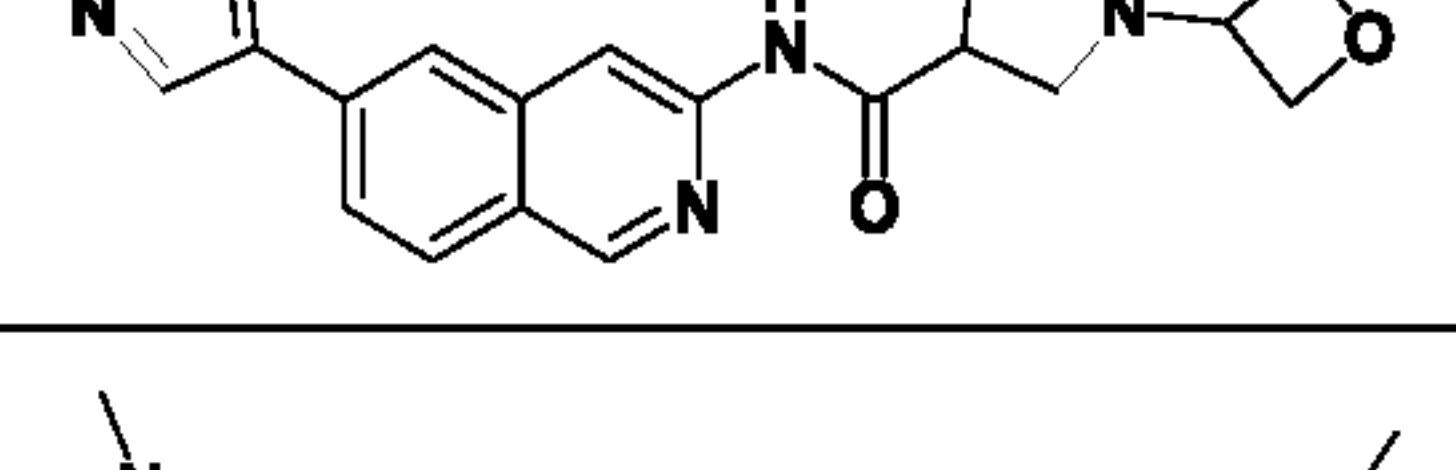
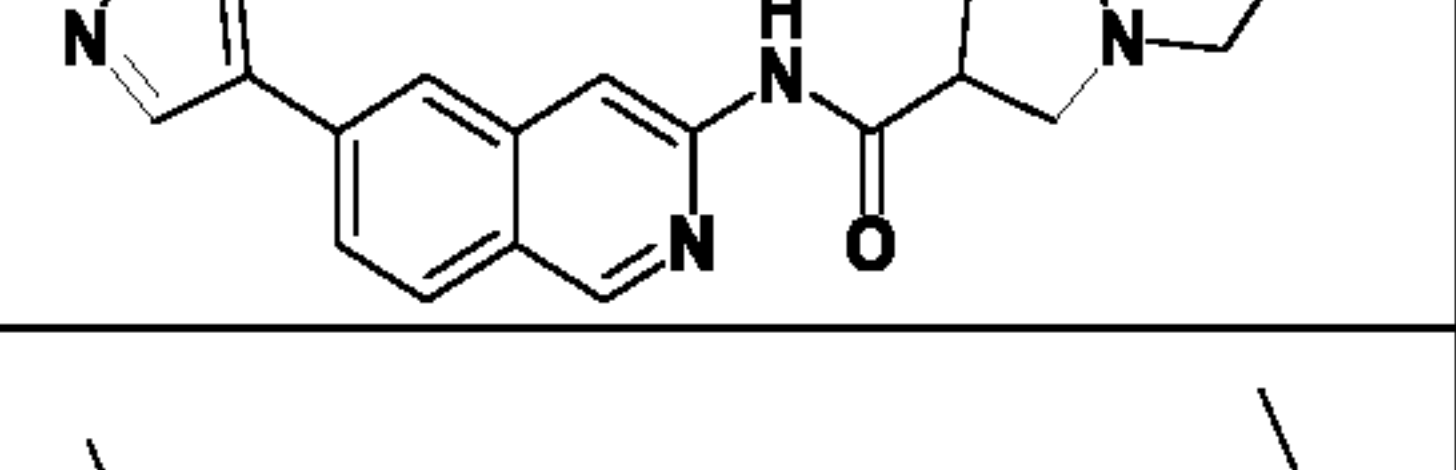
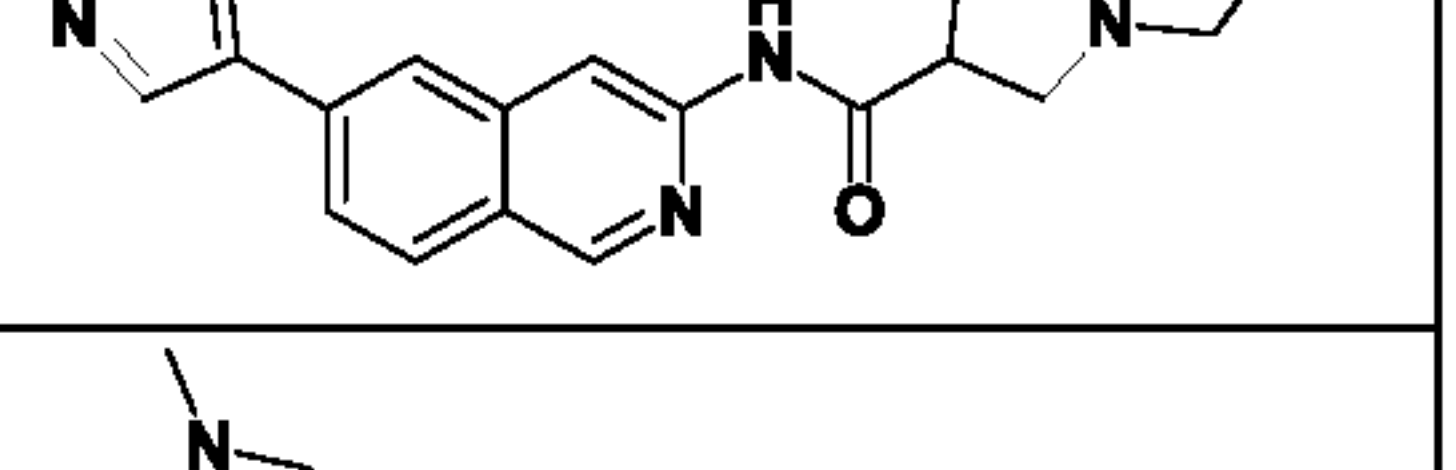
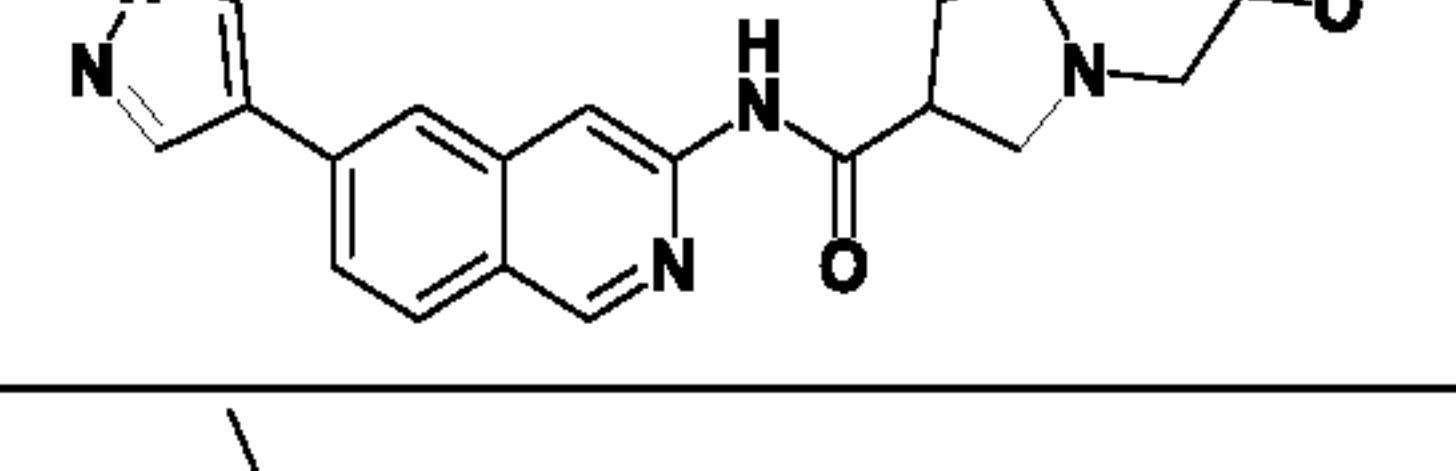
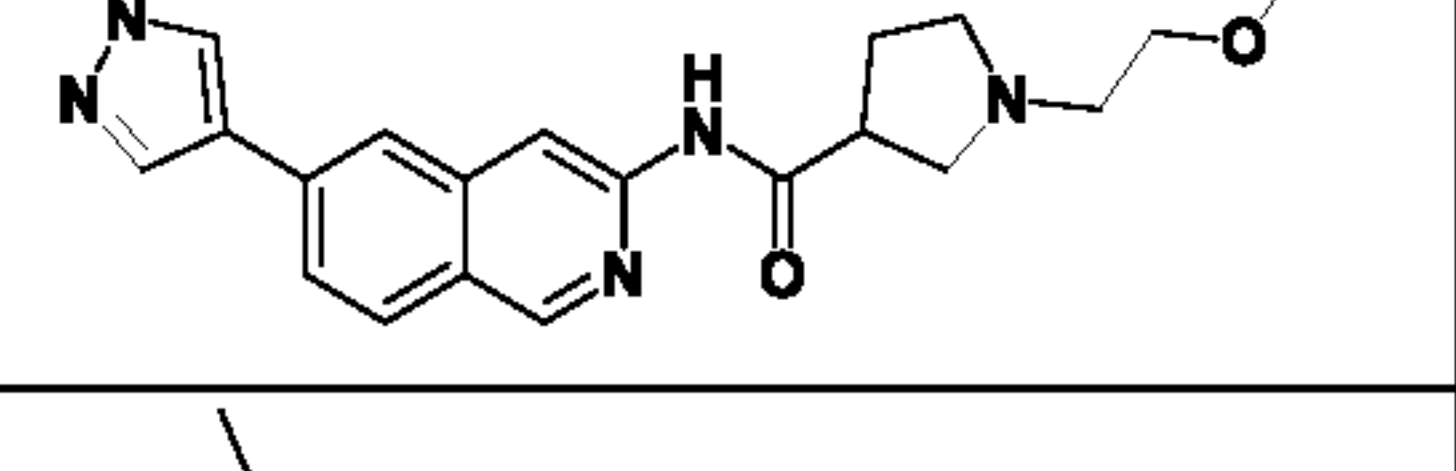
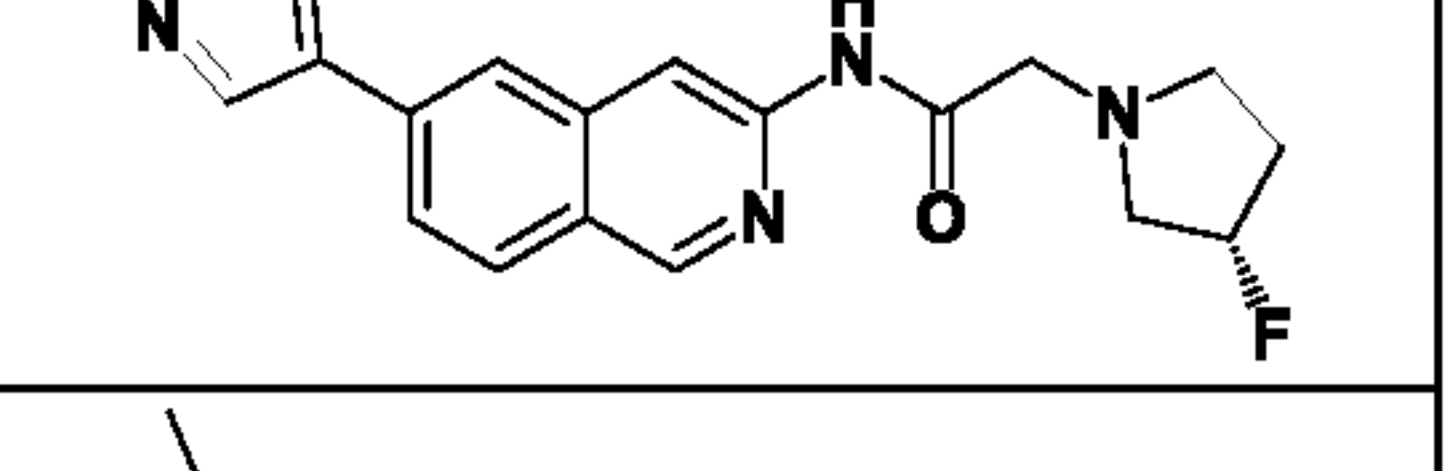
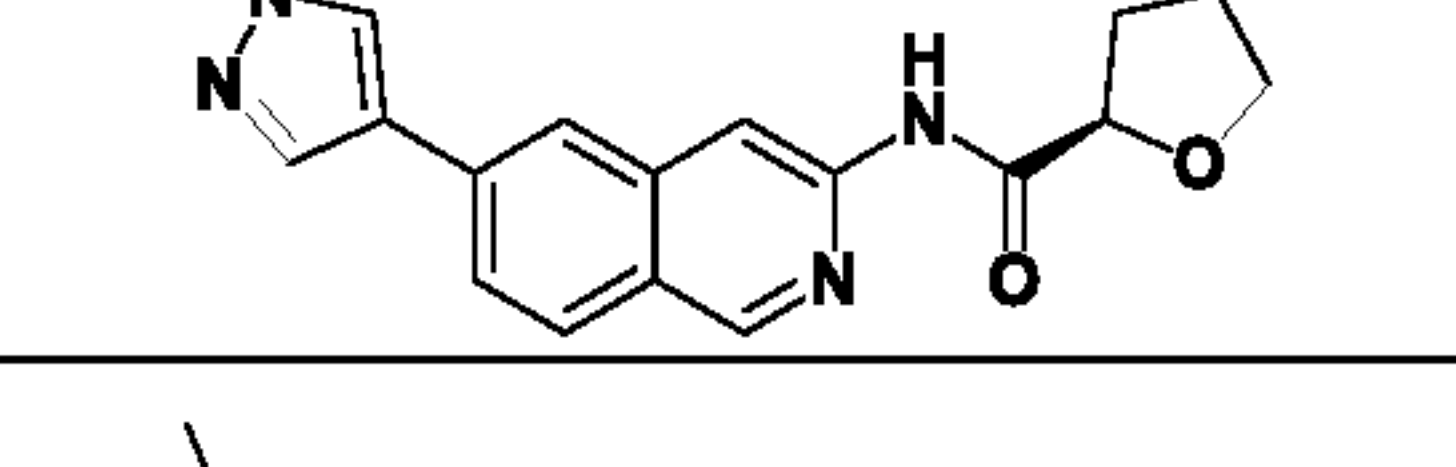
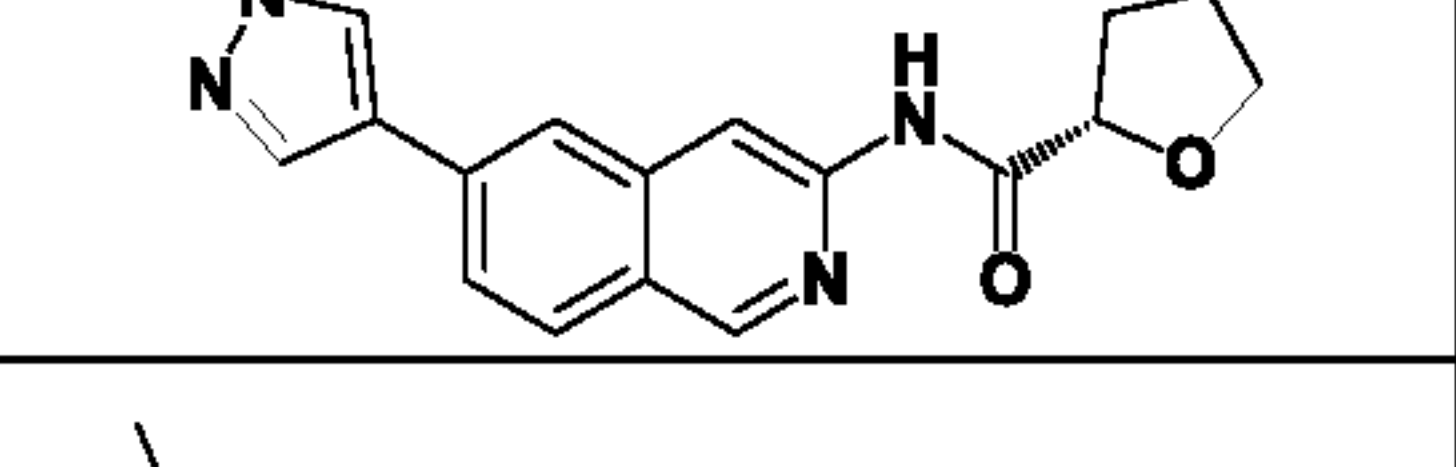
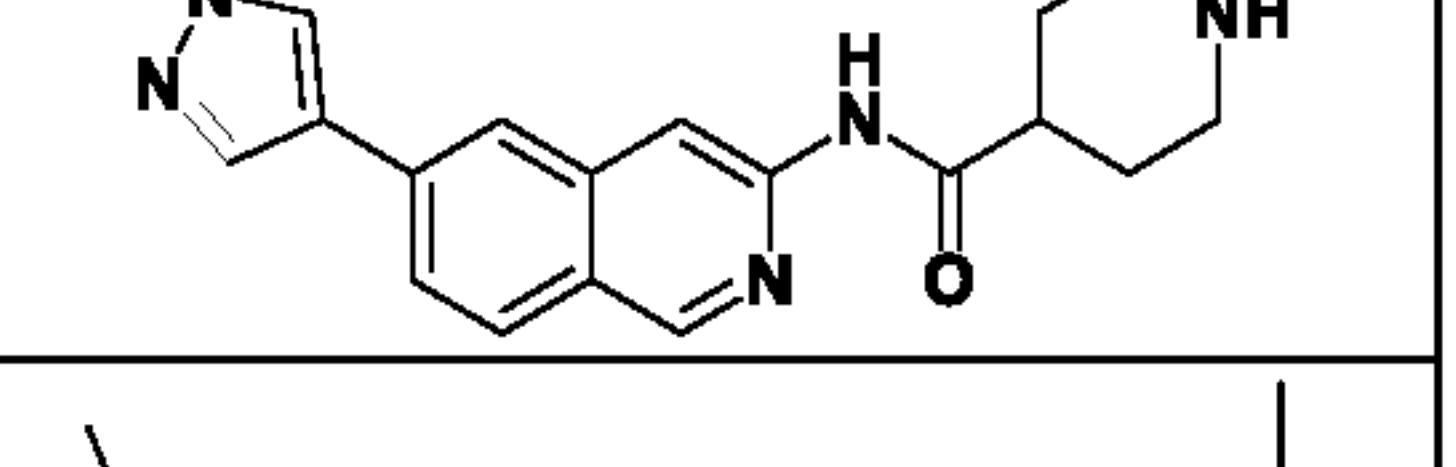
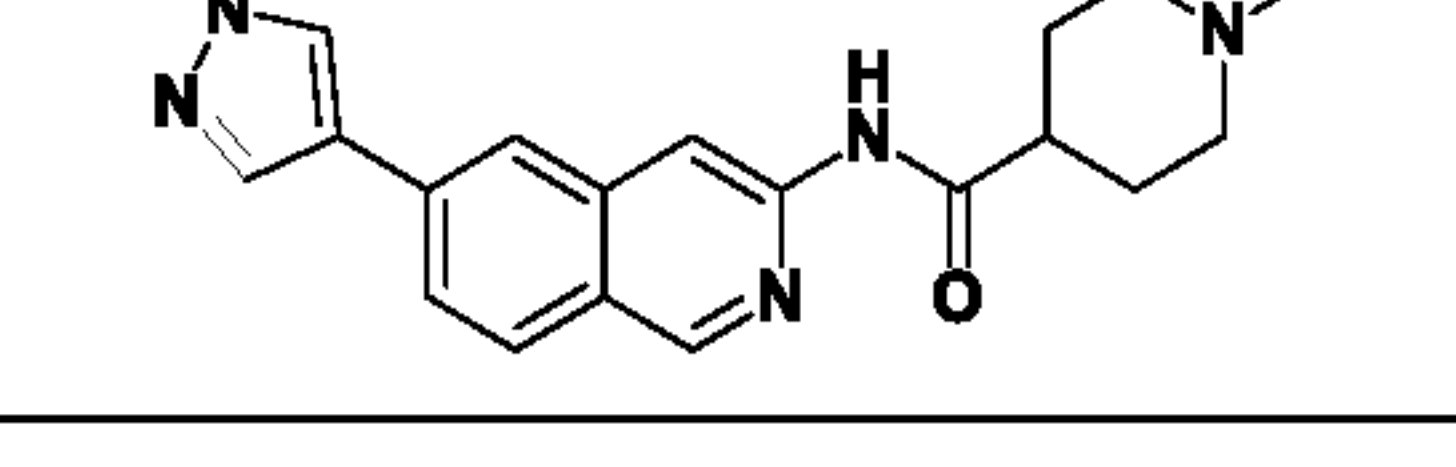
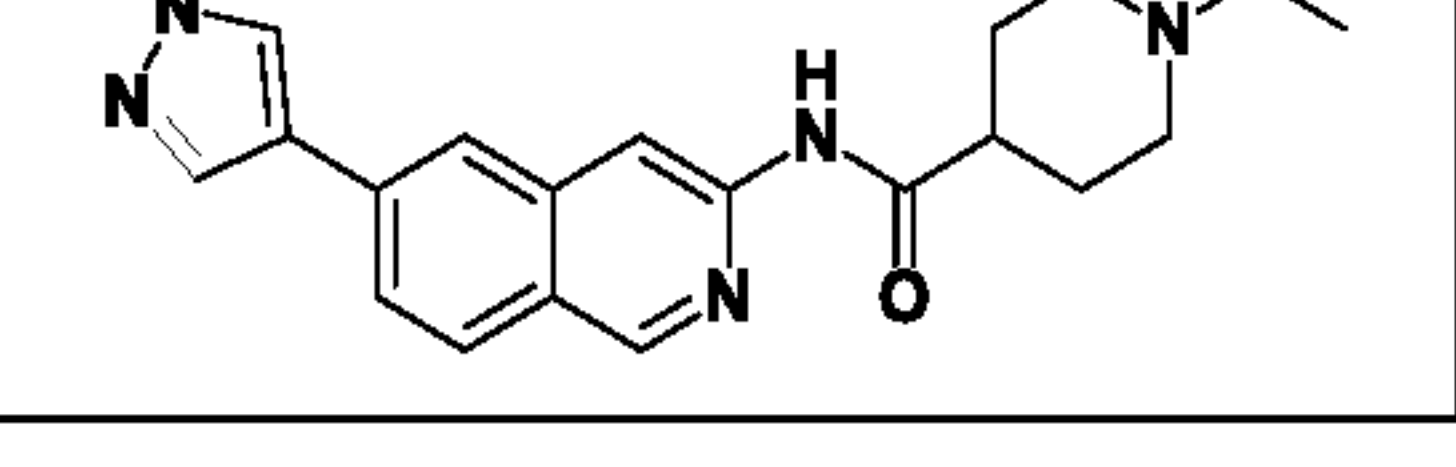
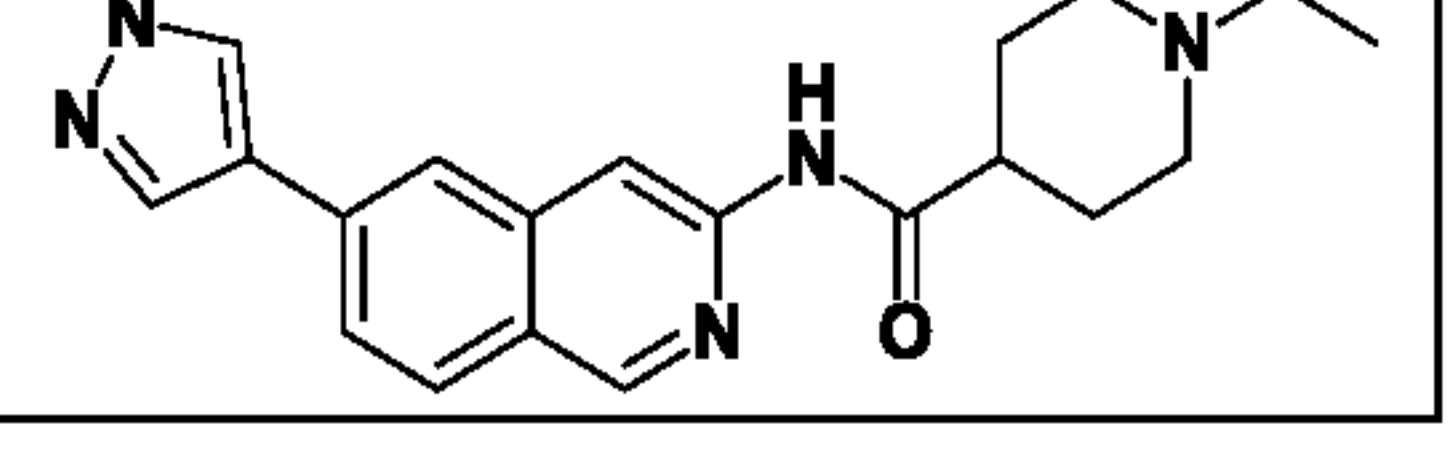


, and R^6 is $-\text{CF}(\text{C}_{1-3} \text{ alkyl})_2$; wherein the alkyl of $-\text{CF}(\text{C}_{1-3} \text{ alkyl})_2$ is optionally substituted with 1-2 fluorines.

[0318] Illustrative compounds of Formula (I) are shown in Table 1.

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Administration and Pharmaceutical Compositions

[0319] Some embodiments include pharmaceutical compositions comprising: (a) a therapeutically effective amount of a compound provided herein, or its corresponding enantiomer, diastereoisomer or tautomer, or pharmaceutically acceptable salt; and (b) a pharmaceutically acceptable carrier.

[0320] The compounds provided herein may also be useful in combination (administered together or sequentially) with other known agents.

[0321] Non-limiting examples of diseases which can be treated with a combination of a compound of Formula (I) and other another active agent are colorectal cancer, ovarian cancer, chronic inflammation, diabetic retinopathy, pulmonary fibrosis, and osteoarthritis. For example, a compound of Formula (I) can be combined with one or more chemotherapeutic compounds.

[0322] In some embodiments, colorectal cancer can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: 5-Fluorouracil (5-FU), which can be administered with the vitamin-like drug leucovorin (also called folinic acid); capecitabine (XELODA[®]), irinotecan (CAMPOSTAR[®]), oxaliplatin (ELOXATIN[®]). Examples of combinations of these drugs which could be further combined with a compound of Formula (I) are FOLFOX (5-FU, leucovorin, and oxaliplatin), FOLFIRI (5-FU, leucovorin, and irinotecan), FOLFOXIRI (leucovorin, 5-FU, oxaliplatin, and irinotecan) and CapeOx (Capecitabine and oxaliplatin). For rectal cancer, chemo with 5-FU or capecitabine combined with radiation may be given before surgery (neoadjuvant treatment).

[0323] In some embodiments, ovarian cancer can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: Topotecan, Liposomal doxorubicin (DOXIL[®]), Gemcitabine (GEMZAR[®]), Cyclophosphamide (CYTOXAN[®]), Vinorelbine (NAVELBINE[®]), Ifosfamide (IFEX[®]), Etoposide (VP-16), Altretamine (HEXALEN[®]), Capecitabine (XELODA[®]), Irinotecan (CPT-11, CAMPTOSAR[®]), Melphalan, Pemetrexed (ALIMTA[®]) and Albumin bound paclitaxel (nab-paclitaxel, ABRAXANE[®]). Examples of combinations of these drugs which could be further combined with a compound of Formula (I) are TIP (paclitaxel [Taxol], ifosfamide, and cisplatin), VeIP (vinblastine, ifosfamide, and cisplatin) and VIP (etoposide [VP-16], ifosfamide, and cisplatin).

[0324] In some embodiments, a compound of Formula (I) can be used to treat cancer in combination with any of the following methods: (a) Hormone therapy such as aromatase inhibitors, LHRH [luteinizing hormone-releasing hormone] analogs and inhibitors, and others; (b) Ablation or embolization procedures such as radiofrequency ablation (RFA), ethanol (alcohol) ablation, microwave thermotherapy and cryosurgery (cryotherapy); (c) Chemotherapy using

alkylating agents such as cisplatin and carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil and ifosfamide; (d) Chemotherapy using anti-metabolites such as azathioprine and mercaptopurine; (e) Chemotherapy using plant alkaloids and terpenoids such as vinca alkaloids (i.e. Vincristine, Vinblastine, Vinorelbine and Vindesine) and taxanes; (f) Chemotherapy using podophyllotoxin, etoposide, teniposide and docetaxel; (g) Chemotherapy using topoisomerase inhibitors such as irinotecan, topotecan, amsacrine, etoposide, etoposide phosphate, and teniposide; (h) Chemotherapy using cytotoxic antibiotics such as actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and mitomycin; (i) Chemotherapy using tyrosine-kinase inhibitors such as Imatinib mesylate (GLEEVEC[®], also known as STI-571), Gefitinib (Iressa, also known as ZD1839), Erlotinib (marketed as TARCEVA[®]), Bortezomib (VELCADE[®]), tamoxifen, tofacitinib, crizotinib, Bcl-2 inhibitors (e.g. obatoclax in clinical trials, ABT-263, and Gossypol), PARP inhibitors (e.g. Iniparib, Olaparib in clinical trials), PI3K inhibitors (e.g. perifosine in a phase III trial), VEGF Receptor 2 inhibitors (e.g. Apatinib), AN-152, (AEZS-108), Braf inhibitors (e.g. vemurafenib, dabrafenib and LGX818), MEK inhibitors (e.g. trametinib and MEK162), CDK inhibitors, (e.g. PD-0332991), salinomycin and Sorafenib; (j) Chemotherapy using monoclonal antibodies such as Rituximab (marketed as MABTHERA[®] or RITUXAN[®]), Trastuzumab (Herceptin also known as ErbB2), Cetuximab (marketed as ERBITUX[®]), and Bevacizumab (marketed as AVASTIN[®]); and (k) radiation therapy.

[0325] In some embodiments, diabetic retinopathy can be treated with a combination of a compound of Formula (I) and one or more of the following natural supplements: Bilberry, Butcher's broom, Ginkgo, Grape seed extract, and Pycnogenol (Pine bark).

[0326] In some embodiments, idiopathic pulmonary fibrosis/pulmonary fibrosis can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: pirfenidone (pirfenidone was approved for use in 2011 in Europe under the brand name Esbriet[®]), prednisone, azathioprine, N-acetylcysteine, interferon- γ 1b, bosentan (bosentan is currently being studied in patients with IPF, [*The American Journal of Respiratory and Critical Care Medicine* (2011), 184(1), 92-9]), Nintedanib (BIBF 1120 and Vargatef), QAX576 [*British Journal of Pharmacology* (2011), 163(1), 141-172], and anti-inflammatory agents such as corticosteroids.

[0327] In some embodiments, a compound of Formula (I) can be used to treat idiopathic pulmonary fibrosis/pulmonary fibrosis in combination with any of the following methods: oxygen therapy, pulmonary rehabilitation and surgery.

[0328] In some embodiments, a compound of Formula (I) can be used to treat osteoarthritis in combination with any of the following methods: (a) Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, aspirin and acetaminophen; (b) physical therapy; (c) injections of corticosteroid medications; (d) injections of hyaluronic acid derivatives (e.g. Hyalgan, Synvisc); (e) narcotics, like codeine; (f) in combination with braces and/or shoe inserts or any device that can immobilize or support your joint to help you keep pressure off it (e.g., splints, braces, shoe inserts or other medical devices); (g) realigning bones (osteotomy); (h) joint replacement (arthroplasty); and (i) in combination with a chronic pain class.

[0329] In some embodiments, macular degeneration can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: Bevacizumab (Avastin[®]), Ranibizumab (Lucentis[®]), Pegaptanib (Macugen), Aflibercept (Eylea[®]), verteporfin (Visudyne[®]) in combination with photodynamic therapy (PDT) or with any of the following methods: (a) in combination with laser to destroy abnormal blood vessels (photocoagulation); and (b) in combination with increased vitamin intake of antioxidant vitamins and zinc.

[0330] In some embodiments, retinitis pigmentosa can be treated with a combination of a compound of Formula (I) and one or more of the following drugs: UF-021 (Ocuseva[™]), vitamin A palmitate and pikachurin or with any of the following methods: (a) with the Argus[®] II retinal implant; and (b) with stem cell and/or gene therapy.

[0331] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration, including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, ontologically, neuro-otologically, intraocularly, subconjunctivally, via anterior eye chamber injection, intravitreally, intraperitoneally, intrathecally, intracistically, intrapleurally, via wound irrigation, intrabuccally, intra-abdominally, intra-articularly, intra-aurally, intrabronchially, intracapsularly, intrameningeally, via inhalation, via endotracheal or endobronchial instillation, via direct instillation into pulmonary cavities, intraspinally, intrasynovially, intrathoracically, via thoracostomy irrigation, epidurally, intratympanically, intracisternally, intravascularly, intraventricularly, intraosseously, via irrigation of infected bone, or via application as part of any admixture with a prosthetic devices. In some embodiments, the administration method includes oral or parenteral administration.

[0332] Compounds provided herein intended for pharmaceutical use may be administered as crystalline or amorphous products. Pharmaceutically acceptable compositions may include solid, semi-solid, liquid, solutions, colloidal, liposomes, emulsions, suspensions,

complexes, coacervates and aerosols. Dosage forms, such as, *e.g.*, tablets, capsules, powders, liquids, suspensions, suppositories, aerosols, implants, controlled release or the like. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, milling, grinding, supercritical fluid processing, coacervation, complex coacervation, encapsulation, emulsification, complexation, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose. The compounds can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills (tablets and or capsules), transdermal (including electrotransport) patches, implants and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

[0333] The compounds can be administered either alone or in combination with a conventional pharmaceutical carrier, excipient or the like. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- α -tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α -, β -, and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a compound as described herein in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. The contemplated compositions may contain 0.001%-100% of a compound provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

[0334] In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a compound provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as

magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, granule, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more compounds provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

[0335] Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. a compound provided herein and optional pharmaceutical adjuvants in a carrier (*e.g.*, water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution, colloid, liposome, emulsion, complexes, coacervate or suspension. If desired, the pharmaceutical composition can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, co-solvents, solubilizing agents, pH buffering agents and the like (*e.g.*, sodium acetate, sodium citrate, cyclodextrin derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, and the like).

[0336] In some embodiments, the unit dosage of compounds of Formula (I) is about 0.25 mg/Kg to about 50 mg/Kg in humans.

[0337] In some embodiments, the unit dosage of compounds of Formula (I) is about 0.25 mg/Kg to about 20 mg/Kg in humans.

[0338] In some embodiments, the unit dosage of compounds of Formula (I) is about 0.50 mg/Kg to about 19 mg/Kg in humans.

[0339] In some embodiments, the unit dosage of compounds of Formula (I) is about 0.75 mg/Kg to about 18 mg/Kg in humans.

[0340] In some embodiments, the unit dosage of compounds of Formula (I) is about 1.0 mg/Kg to about 17 mg/Kg in humans.

[0341] In some embodiments, the unit dosage of compounds of Formula (I) is about 1.25 mg/Kg to about 16 mg/Kg in humans.

[0342] In some embodiments, the unit dosage of compounds of Formula (I) is about 1.50 mg/Kg to about 15 mg/Kg in humans.

[0343] In some embodiments, the unit dosage of compounds of Formula (I) is about 1.75 mg/Kg to about 14 mg/Kg in humans.

[0344] In some embodiments, the unit dosage of compounds of Formula (I) is about 2.0 mg/Kg to about 13 mg/Kg in humans.

[0345] In some embodiments, the unit dosage of compounds of Formula (I) is about 3.0 mg/Kg to about 12 mg/Kg in humans.

[0346] In some embodiments, the unit dosage of compounds of Formula (I) is about 4.0 mg/Kg to about 11 mg/Kg in humans.

[0347] In some embodiments, the unit dosage of compounds of Formula (I) is about 5.0 mg/Kg to about 10 mg/Kg in humans.

[0348] In some embodiments, the compositions are provided in unit dosage forms suitable for single administration.

[0349] In some embodiments, the compositions are provided in unit dosage forms suitable for twice a day administration.

[0350] In some embodiments, the compositions are provided in unit dosage forms suitable for three times a day administration.

[0351] Injectables can be prepared in conventional forms, either as liquid solutions, colloid, liposomes, complexes, coacervate or suspensions, as emulsions, or in solid forms suitable for reconstitution in liquid prior to injection. The percentage of a compound provided herein contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the patient. However, percentages of active ingredient of 0.01% to 10% in solution are employable, and could be higher if the composition is a solid or suspension, which could be subsequently diluted to the above percentages.

[0352] In some embodiments, the composition will comprise about 0.1-10% of the active agent in solution.

[0353] In some embodiments, the composition will comprise about 0.1-5% of the active agent in solution.

[0354] In some embodiments, the composition will comprise about 0.1-4% of the active agent in solution.

[0355] In some embodiments, the composition will comprise about 0.15-3% of the active agent in solution.

[0356] In some embodiments, the composition will comprise about 0.2-2% of the active agent in solution.

[0357] In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-96 hours.

[0358] In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-72 hours.

[0359] In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-48 hours.

[0360] In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-24 hours.

[0361] In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-12 hours.

[0362] In some embodiments, the compositions are provided in dosage forms suitable for continuous dosage by intravenous infusion over a period of about 1-6 hours.

[0363] In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 5 mg/m² to about 300 mg/m².

[0364] In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 5 mg/m² to about 200 mg/m².

[0365] In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 5 mg/m² to about 100 mg/m².

[0366] In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 10 mg/m² to about 50 mg/m².

[0367] In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 50 mg/m² to about 200 mg/m².

[0368] In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 75 mg/m² to about 175 mg/m².

[0369] In some embodiments, these compositions can be administered by intravenous infusion to humans at doses of about 100 mg/m² to about 150 mg/m².

[0370] It is to be noted that concentrations and dosage values may also vary depending on the specific compound and the severity of the condition to be alleviated. It is to be further understood that for any particular patient, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[0371] In one embodiment, the compositions can be administered to the respiratory tract (including nasal and pulmonary) e.g., through a nebulizer, metered-dose inhalers, atomizer, mister, aerosol, dry powder inhaler, insufflator, liquid instillation or other suitable device or technique.

[0372] In some embodiments, aerosols intended for delivery to the nasal mucosa are provided for inhalation through the nose. For optimal delivery to the nasal cavities, inhaled particle sizes of about 5 to about 100 microns are useful, with particle sizes of about 10 to about 60 microns being preferred. For nasal delivery, a larger inhaled particle size may be desired to maximize impaction on the nasal mucosa and to minimize or prevent pulmonary deposition of the administered formulation. In some embodiments, aerosols intended for delivery to the lung are provided for inhalation through the nose or the mouth. For delivery to the lung, inhaled aerodynamic particle sizes of about less than 10 μm are useful (e.g., about 1 to about 10 microns). Inhaled particles may be defined as liquid droplets containing dissolved drug, liquid droplets containing suspended drug particles (in cases where the drug is insoluble in the suspending medium), dry particles of pure drug substance, drug substance incorporated with excipients, liposomes, emulsions, colloidal systems, coacervates, aggregates of drug nanoparticles, or dry particles of a diluent which contain embedded drug nanoparticles.

[0373] In some embodiments, compounds of Formula (I) disclosed herein intended for respiratory delivery (either systemic or local) can be administered as aqueous formulations, as non-aqueous solutions or suspensions, as suspensions or solutions in halogenated hydrocarbon propellants with or without alcohol, as a colloidal system, as emulsions, coacervates, or as dry powders. Aqueous formulations may be aerosolized by liquid nebulizers employing either hydraulic or ultrasonic atomization or by modified micropump systems (like the soft mist inhalers, the Aerodose[®] or the AERx[®] systems). Propellant-based systems may use suitable pressurized metered-dose inhalers (pMDIs). Dry powders may use dry powder inhaler devices (DPIs), which are capable of dispersing the drug substance effectively. A desired particle size and distribution may be obtained by choosing an appropriate device.

[0374] In some embodiments, the compositions of Formula (I) disclosed herein can be administered to the ear by various methods. For example, a round window catheter (e.g., U.S. Pat. Nos. 6,440,102 and 6,648,873) can be used.

[0375] Alternatively, formulations can be incorporated into a wick for use between the outer and middle ear (e.g., U.S. Pat. No. 6,120,484) or absorbed to collagen sponge or other solid support (e.g., U.S. Pat. No. 4,164,559).

[0376] If desired, formulations of the disclosure can be incorporated into a gel formulation (e.g., U.S. Pat. Nos. 4,474,752 and 6,911,211).

[0377] In some embodiments, compounds of Formula (I) disclosed herein intended for delivery to the ear can be administered via an implanted pump and delivery system through a needle directly into the middle or inner ear (cochlea) or through a cochlear implant stylet electrode

channel or alternative prepared drug delivery channel such as but not limited to a needle through temporal bone into the cochlea.

[0378] Other options include delivery via a pump through a thin film coated onto a multichannel electrode or electrode with a specially imbedded drug delivery channel (pathways) carved into the thin film for this purpose. In other embodiments the acidic or basic solid compound of Formula (I) can be delivered from the reservoir of an external or internal implanted pumping system.

[0379] Formulations of the disclosure also can be administered to the ear by intratympanic injection into the middle ear, inner ear, or cochlea (e.g., U.S. Pat. No. 6,377,849 and Ser. No. 11/337,815).

[0380] Intratympanic injection of therapeutic agents is the technique of injecting a therapeutic agent behind the tympanic membrane into the middle and/or inner ear. In one embodiment, the formulations described herein are administered directly onto the round window membrane via transtympanic injection. In another embodiment, the ion channel modulating agent auris-acceptable formulations described herein are administered onto the round window membrane via a non-transtympanic approach to the inner ear. In additional embodiments, the formulation described herein is administered onto the round window membrane via a surgical approach to the round window membrane comprising modification of the crista fenestrae cochleae.

[0381] In some embodiments, the compounds of Formula (I) are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), and the like.

[0382] Suppositories for rectal administration of the drug (either as a solution, colloid, suspension or a complex) can be prepared by mixing a compound provided herein with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt or erode/dissolve in the rectum and release the compound. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter, is first melted.

[0383] Solid compositions can be provided in various different types of dosage forms, depending on the physicochemical properties of the compound provided herein, the desired dissolution rate, cost considerations, and other criteria. In one of the embodiments, the solid

composition is a single unit. This implies that one unit dose of the compound is comprised in a single, physically shaped solid form or article. In other words, the solid composition is coherent, which is in contrast to a multiple unit dosage form, in which the units are incoherent.

[0384] Examples of single units which may be used as dosage forms for the solid composition include tablets, such as compressed tablets, film-like units, foil-like units, wafers, lyophilized matrix units, and the like. In one embodiment, the solid composition is a highly porous lyophilized form. Such lyophilizates, sometimes also called wafers or lyophilized tablets, are particularly useful for their rapid disintegration, which also enables the rapid dissolution of the compound.

[0385] On the other hand, for some applications the solid composition may also be formed as a multiple unit dosage form as defined above. Examples of multiple units are powders, granules, microparticles, pellets, mini-tablets, beads, lyophilized powders, and the like. In one embodiment, the solid composition is a lyophilized powder. Such a dispersed lyophilized system comprises a multitude of powder particles, and due to the lyophilization process used in the formation of the powder, each particle has an irregular, porous microstructure through which the powder is capable of absorbing water very rapidly, resulting in quick dissolution. Effervescent compositions are also contemplated to aid the quick dispersion and absorption of the compound.

[0386] Another type of multiparticulate system which is also capable of achieving rapid drug dissolution is that of powders, granules, or pellets from water-soluble excipients which are coated with a compound provided herein so that the compound is located at the outer surface of the individual particles. In this type of system, the water-soluble low molecular weight excipient may be useful for preparing the cores of such coated particles, which can be subsequently coated with a coating composition comprising the compound and, for example, one or more additional excipients, such as a binder, a pore former, a saccharide, a sugar alcohol, a film-forming polymer, a plasticizer, or other excipients used in pharmaceutical coating compositions.

[0387] Also provided herein are kits. Typically, a kit includes one or more compounds or compositions as described herein. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering a compound as provided herein, and directions for use of the kit (e.g., instructions for treating a patient). In another embodiment, the kit can include a compound or composition as described herein and a label that indicates that the contents are to be administered to a patient with cancer. In another embodiment, the kit can include a compound or composition as described herein and a label that indicates that the contents are to be administered to a patient with one or more of hepatocellular carcinoma, colon cancer, leukemia, lymphoma, sarcoma, ovarian cancer, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis,

ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, bone and cartilage diseases, 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, 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-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, 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.

Methods of Treatment

[0388] The compounds and compositions provided herein can be used as inhibitors and/or modulators of one or more components of the Wnt pathway, which may include one or more Wnt proteins, and thus can be used to treat a variety of disorders and diseases in which aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, and cell cycling. Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation, to correct a genetic disorder, and/or to treat a neurological condition/disorder/disease due to mutations or dysregulation of the Wnt pathway and/or of one or more of Wnt signaling components. 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, scleroderma, mycotic and viral infections, bone and cartilage diseases, neurological conditions/diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), motor neuron disease, multiple sclerosis or autism, lung disease, bone/osteoporotic (wrist, spine, shoulder and hip) fractures, 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-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, 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.

[0389] With respect to cancer, the Wnt pathway is known to be constitutively activated in a variety of cancers including, for example, colon cancer, hepatocellular carcinoma, lung cancer, ovarian cancer, prostate cancer, pancreatic cancer and leukemias such as CML, CLL and T-ALL. Accordingly, the compounds and compositions described herein may be used to treat these cancers in which the Wnt pathway is constitutively activated. In certain embodiments, the cancer is chosen from hepatocellular carcinoma, colon cancer, leukemia, lymphoma, sarcoma and ovarian cancer.

[0390] Other cancers can also be treated with the compounds and compositions described herein.

[0391] More particularly, cancers that may be treated by the compounds, compositions and methods described herein include, but are not limited to, the following:

[0392] 1) Breast cancers, including, for example ER⁺ breast cancer, ER⁻ breast cancer, her2⁻ breast cancer, her2⁺ breast cancer, stromal tumors such as fibroadenomas, phyllodes tumors, and sarcomas, and epithelial tumors such as large duct papillomas; carcinomas of the breast including *in situ* (noninvasive) carcinoma that includes ductal carcinoma *in situ* (including Paget's disease) and lobular carcinoma *in situ*, and invasive (infiltrating) carcinoma including, but not limited to, invasive ductal carcinoma, invasive lobular carcinoma, medullary carcinoma, colloid (mucinous) carcinoma, tubular carcinoma, and invasive papillary carcinoma; and miscellaneous malignant neoplasms. Further examples of breast cancers can include luminal A, luminal B, basal A, basal B, and triple negative breast cancer, which is estrogen receptor negative (ER⁻), progesterone receptor negative, and her2 negative (her2⁻). In some embodiments, the breast cancer may have a high risk Oncotype score.

[0393] 2) Cardiac cancers, including, for example sarcoma, e.g., angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma; myxoma; rhabdomyoma; fibroma; lipoma and teratoma.

[0394] 3) Lung cancers, including, for example, bronchogenic carcinoma, e.g., squamous cell, undifferentiated small cell, undifferentiated large cell, and adenocarcinoma; alveolar and bronchiolar carcinoma; bronchial adenoma; sarcoma; lymphoma; chondromatous hamartoma; and mesothelioma.

[0395] 4) Gastrointestinal cancer, including, for example, cancers of the esophagus, e.g., squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, and lymphoma; cancers of the stomach, e.g., carcinoma, lymphoma, and leiomyosarcoma; cancers of the pancreas, e.g., ductal

adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, and vipoma; cancers of the small bowel, e.g., adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, and fibroma; cancers of the large bowel, e.g., adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, and leiomyoma.

[0396] 5) Genitourinary tract cancers, including, for example, cancers of the kidney, e.g., adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, and leukemia; cancers of the bladder and urethra, e.g., squamous cell carcinoma, transitional cell carcinoma, and adenocarcinoma; cancers of the prostate, e.g., adenocarcinoma, and sarcoma; cancer of the testis, e.g., seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, and lipoma.

[0397] 6) Liver cancers, including, for example, hepatoma, e.g., hepatocellular carcinoma; cholangiocarcinoma; hepatoblastoma; angiosarcoma; hepatocellular adenoma; and hemangioma.

[0398] 7) Bone cancers, including, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondilagenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors.

[0399] 8) Nervous system cancers, including, for example, cancers of the skull, e.g., osteoma, hemangioma, granuloma, xanthoma, and osteitis deformans; cancers of the meninges, e.g., meningioma, meningiosarcoma, and gliomatosis; cancers of the brain, e.g., astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, oligodendrocytoma, schwannoma, retinoblastoma, and congenital tumors; and cancers of the spinal cord, e.g., neurofibroma, meningioma, glioma, and sarcoma.

[0400] 9) Gynecological cancers, including, for example, cancers of the uterus, e.g., endometrial carcinoma; cancers of the cervix, e.g., cervical carcinoma, and pre tumor cervical dysplasia; cancers of the ovaries, e.g., ovarian carcinoma, including serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa theca cell tumors, Sertoli Leydig cell tumors, dysgerminoma, and malignant teratoma; cancers of the vulva, e.g., squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, and melanoma; cancers of the vagina, e.g., clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma, and embryonal rhabdomyosarcoma; and cancers of the fallopian tubes, e.g., carcinoma.

[0401] 10) Hematologic cancers, including, for example, cancers of the blood, e.g., acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic

lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, and myelodysplastic syndrome, Hodgkin's lymphoma, non-Hodgkin's lymphoma (malignant lymphoma) and Waldenström's macroglobulinemia.

[0402] 11) Skin cancers and skin disorders, including, for example, malignant melanoma and metastatic melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, and scleroderma.

[0403] 12) Adrenal gland cancers, including, for example, neuroblastoma.

[0404] More particularly, tumors of the central nervous system that may be treated by the compounds, compositions and methods described herein include:

[0405] 1) Astrocytic tumors, e.g., diffuse astrocytoma (fibrillary, protoplasmic, gemistocytic, mixed), anaplastic (malignant) astrocytoma, glioblastoma multiforme (giant cell glioblastoma and gliosarcoma), pilocytic astrocytoma (pilomyxoid astrocytoma), pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, and gliomatosis cerebri.

[0406] 2) Oligodendroglial tumors, e.g., oligodendroglioma and anaplastic oligodendroglioma.

[0407] 3) Oligoastrocytic tumors, e.g., oligoastrocytoma and anaplastic oligoastrocytoma.

[0408] 4) Ependymal tumors, e.g., subependymoma, myxopapillary ependymoma, ependymoma, (cellular, papillary, clear cell, tanycytic), and anaplastic (malignant) ependymoma.

[0409] 5) Choroid plexus tumors, e.g., choroid plexus papilloma, atypical choroid plexus papilloma, and choroid plexus carcinoma.

[0410] 6) Neuronal and mixed neuronal-glial tumors, e.g., gangliocytoma, ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), desmoplastic infantile astrocytoma/ganglioglioma, central neurocytoma, anaplastic ganglioglioma, extraventricular neurocytoma, cerebellar liponeurocytoma, Papillary glioneuronal tumor, Rosette-forming glioneuronal tumor of the fourth ventricle, and paraganglioma of the filum terminale.

[0411] 7) Pineal tumors, e.g., pineocytoma, pineoblastoma, papillary tumors of the pineal region, and pineal parenchymal tumor of intermediate differentiation.

[0412] 8) Embryonal tumors, e.g., medulloblastoma (medulloblastoma with extensive nodularity, anaplastic medulloblastoma, desmoplastic, large cell, melanotic, medulloblastoma), medulloepithelioma, supratentorial primitive neuroectodermal tumors, and

primitive neuroectodermal tumors (PNETs) such as neuroblastoma, ganglioneuroblastoma, ependymoblastoma, and atypical teratoid/rhabdoid tumor.

[0413] 9) Neuroblastic tumors, e.g., olfactory (esthesioneuroblastoma), olfactory neuroepithelioma, and neuroblastomas of the adrenal gland and sympathetic nervous system.

[0414] 10) Glial tumors, e.g., astroblastoma, chordoid glioma of the third ventricle, and angiocentric glioma.

[0415] 11) Tumors of cranial and paraspinal nerves, e.g., schwannoma, neurofibroma Perineurioma, and malignant peripheral nerve sheath tumor.

[0416] 12) Tumors of the meninges such as tumors of meningothelial cells, e.g., meningioma (atypical meningioma and anaplastic meningioma); mesenchymal tumors, e.g., lipoma, angiolipoma, hibernoma, liposarcoma, solitary fibrous tumor, fibrosarcoma, malignant fibrous histiocyoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, chondroma, chondrosarcoma, osteoma, osteosarcoma, osteochondroma, haemangioma, epithelioid hemangioendothelioma, haemangiopericytoma, anaplastic haemangiopericytoma, angiosarcoma, Kaposi Sarcoma, and Ewing Sarcoma; primary melanocytic lesions, e.g., diffuse melanocytosis, melanocytoma, malignant melanoma, meningeal melanomatosis; and hemangioblastomas.

[0417] 13) Tumors of the hematopoietic system, e.g., malignant Lymphomas, plasmocytoma, and granulocytic sarcoma.

[0418] 14) Germ cell tumors, e.g., germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, and mixed germ cell tumors.

[0419] 15) Tumors of the sellar region, e.g., craniopharyngioma, granular cell tumor, pituicytoma, and spindle cell oncocytoma of the adenohypophysis.

[0420] Cancers may be solid tumors that may or may not be metastatic. Cancers may also occur, as in leukemia, as a diffuse tissue. Thus, the term “tumor cell,” as provided herein, includes a cell afflicted by any one of the above identified disorders.

[0421] A method of treating cancer using a compound or composition as described herein may be combined with existing methods of treating cancers, for example by chemotherapy, irradiation, or surgery (e.g., oophorectomy). In some embodiments, a compound or composition can be administered before, during, or after another anticancer agent or treatment.

[0422] The compounds and compositions described herein can be used as anti-angiogenesis agents and as agents for modulating and/or inhibiting the activity of protein kinases, thus providing treatments for cancer and other diseases associated with cellular proliferation mediated by protein kinases. For example, the compounds described herein can inhibit the activity

of one or more kinases. Accordingly, provided herein is a method of treating cancer or preventing or reducing angiogenesis through kinase inhibition.

[0423] In addition, and including treatment of cancer, the compounds and compositions described herein can function as cell-cycle control agents for treating proliferative disorders in a patient. Disorders associated with excessive proliferation include, for example, cancers, scleroderma, immunological disorders involving undesired proliferation of leukocytes, and restenosis and other smooth muscle disorders. Furthermore, such compounds may be used to prevent de-differentiation of post-mitotic tissue and/or cells.

[0424] Diseases or disorders associated with uncontrolled or abnormal cellular proliferation include, but are not limited to, the following:

- a variety of cancers, including, but not limited to, carcinoma, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system and other tumors including melanoma, seminoma and Kaposi's sarcoma.
- a disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neurofibromatosis, atherosclerosis, arthritis, glomerulonephritis, restenosis following angioplasty or vascular surgery, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections. Fibrotic disorders such as 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; fatty liver disease (FLD); adhesions, such as those occurring in the abdomen, pelvis, spine or tendons; chronic obstructive pulmonary disease; fibrosis following myocardial infarction; pulmonary fibrosis; fibrosis and scarring associated with diffuse/interstitial lung disease; central nervous system fibrosis, such as fibrosis following stroke; fibrosis associated with neuro-degenerative disorders such as Alzheimer's Disease or multiple sclerosis; fibrosis associated with proliferative vitreoretinopathy (PVR); restenosis; endometriosis; ischemic disease and radiation fibrosis.
- defective apoptosis-associated conditions, such as cancers (including but not limited to those types mentioned herein), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus erythematosus, rheumatoid arthritis, sepsis,

ankylosing spondylitis, psoriasis, scleroderma, autoimmune mediated glomerulonephritis, inflammatory bowel disease and autoimmune diabetes mellitus), neuro-degenerative disorders (including but not limited to Alzheimer's disease, lung disease, amyotrophic lateral sclerosis, retinitis pigmentosa, Parkinson's disease, AIDS-related dementia, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis), tendinopathies such as tendinitis and tendinosis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

- genetic diseases due to mutations in Wnt signaling components, such as 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-Awadi/Raas-Rothschild/Schinzal phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, 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.

[0425] The compounds and compositions provided herein have been found to possess immunomodulatory activities and are expected to control the innate and adaptive immune system (e.g. macrophages, microglia, dendritic cells, B and T cells) and suppress pro-inflammatory cytokine release (e.g. TNF, IL-6, IL-1, IFN γ) which is well known to be involved in chronic inflammation in a wide variety of disease areas. Therefore compounds and compositions provided herein can be used to treat chronic inflammation associated with disorders and diseases including but not limited to eye disorders, joint pain, arthritis (rheumatoid, osteo, psoriatic gout), cancers (colon, breast, lung, pancreas, and others), gastrointestinal disorders (ulcerative colitis and inflammatory bowel diseases), pulmonary disorders (chronic obstructive pulmonary disorder and asthma), allergies, skin disorders (atopic dermatitis and psoriasis), diabetes, pancreatitis, tendonitis,

hepatitis, heart disease, myocarditis, stroke, lupus, and neurological disorders such as multiple sclerosis, Parkinson's and dementia including Alzheimer's disease.

[0426] The compounds and compositions provided herein can be used as inhibitors and/or modulators of the enzyme DYRK1A, and thus can be used to treat a variety of disorders and diseases associated with tau protein, amyloid, alpha-synuclein, TDP-43 or FUS pathology including, but not limited to, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), down syndrome, frontotemporal dementia (FTD) including FTD with Parkinsonism-17 (FTDP-17), behavioural variant frontotemporal dementia (bvFTD), FTD in patients with motor neuron disease (MND) (typically amyotrophic lateral sclerosis, also called FTD-ALS), corticobasal degeneration (CBD) (also called corticobasal ganglionic degeneration), progressive supranuclear palsy, primary progressive aphasia (PPA), globular glial tauopathy (GGT), myotonic dystrophy type 1 (DM1) (also called Steinert disease), myotonic dystrophy type 2 (DM2) (also called proximal myotonic myopathy), Guam complex, argyrophilic grain disease, dementia pugilistica, post-encephalitic parkinsonism, Lewy body dementia, Parkinson's disease, Pick's disease, and additional diseases with pronounced neurodegeneration such as autism, dementia, epilepsy, Huntington's disease, multiple sclerosis; diseases and disorders associated with acquired brain injury such as chronic traumatic encephalopathy, traumatic brain injury, tumor, and stroke.

[0427] Non-limiting examples of neurological disorders (e.g., neurological conditions and neurological diseases) which can be treated with the compounds and compositions provided herein include Alzheimer's disease, aphasia, apraxia, arachnoiditis, ataxia telangiectasia, attention deficit hyperactivity disorder, auditory processing disorder, autism, alcoholism, Bell's palsy, bipolar disorder, brachial plexus injury, Canavan disease, carpal tunnel syndrome, causalgia, central pain syndrome, central pontine myelinolysis, centronuclear myopathy, cephalic disorder, cerebral aneurysm, cerebral arteriosclerosis, cerebral atrophy, cerebral gigantism, cerebral palsy, cerebral vasculitis, cervical spinal stenosis, Charcot-Marie-Tooth disease, Chiari malformation, chronic fatigue syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic pain, Coffin-Lowry syndrome, complex regional pain syndrome, compression neuropathy, congenital facial diplegia, corticobasal degeneration, cranial arteritis, craniosynostosis, Creutzfeldt-Jakob disease, cumulative trauma disorder, Cushing's syndrome, cytomegalic inclusion body disease (CIBD), Dandy-Walker syndrome, Dawson disease, De Morsier's syndrome, Dejerine-Klumpke palsy, Dejerine-Sottas disease, delayed sleep phase syndrome, dementia, dermatomyositis, developmental dyspraxia, diabetic neuropathy, diffuse sclerosis, Dravet syndrome, dysautonomia, dyscalculia, dysgraphia, dyslexia, dystonia, empty sella syndrome, encephalitis, encephalocele, encephalotrigeminal angiomatosis, encopresis, epilepsy, Erb's palsy,

erythromelalgia, essential tremor, Fabry's disease, Fahr's syndrome, familial spastic paralysis, febrile seizure, Fisher syndrome, Friedreich's ataxia, fibromyalgia, Foville's syndrome, Gaucher's disease, Gerstmann's syndrome, giant cell arteritis, giant cell inclusion disease, globoid cell leukodystrophy, gray matter heterotopia, Guillain-Barré syndrome, HTLV-1 associated myelopathy, Hallervorden-Spatz disease, hemifacial spasm, hereditary spastic paraplegia, heredopathia atactica polyneuritiformis, herpes zoster oticus, herpes zoster, Hirayama syndrome, holoprosencephaly, Huntington's disease, hydranencephaly, hydrocephalus, hypercortisolism, hypoxia, immune-mediated encephalomyelitis, inclusion body myositis, incontinentia pigmenti, infantile phytanic acid storage disease, infantile Refsum disease, infantile spasms, inflammatory myopathy, intracranial cyst, intracranial hypertension, Joubert syndrome, Karak syndrome, Kearns-Sayre syndrome, Kennedy disease, Kinsbourne syndrome, Klippel Feil syndrome, Krabbe disease, Kugelberg-Welander disease, kuru, Lafora disease, Lambert-Eaton myasthenic syndrome, Landau-Kleffner syndrome, lateral medullary (Wallenberg) syndrome, Leigh's disease, Lennox-Gastaut syndrome, Lesch-Nyhan syndrome, leukodystrophy, Lewy body dementia, lissencephaly, locked-in syndrome, Lou Gehrig's disease, lumbar disc disease, lumbar spinal stenosis, Lyme disease, Machado-Joseph disease (Spinocerebellar ataxia type 3), macrencephaly, macropsia, megalencephaly, Melkersson-Rosenthal syndrome, Meniere's disease, meningitis, Menkes disease, metachromatic leukodystrophy, microcephaly, micropsia, Miller Fisher syndrome, misophonia, mitochondrial myopathy, Mobius syndrome, monomelic amyotrophy, motor neuron disease, motor skills disorder, Moyamoya disease, mucopolysaccharidoses, multi-infarct dementia, multifocal motor neuropathy, multiple sclerosis, multiple system atrophy, muscular dystrophy, myalgic encephalomyelitis, myasthenia gravis, myelinoclastic diffuse sclerosis, myoclonic Encephalopathy of infants, myoclonus, myopathy, myotubular myopathy, myotonia congenital, narcolepsy, neurofibromatosis, neuroleptic malignant syndrome, lupus erythematosus, neuromyotonia, neuronal ceroid lipofuscinosis, Niemann-Pick disease, O'Sullivan-McLeod syndrome, occipital Neuralgia, occult Spinal Dysraphism Sequence, Ohtahara syndrome, olivopontocerebellar atrophy, opsoclonus myoclonus syndrome, optic neuritis, orthostatic hypotension, palinopsia, paresthesia, Parkinson's disease, paramyotonia Congenita, paraneoplastic diseases, paroxysmal attacks, Parry-Romberg syndrome, Pelizaeus-Merzbacher disease, periodic paralyses, peripheral neuropathy, photic sneeze reflex, phytanic acid storage disease, Pick's disease, polymicrogyria (PMG), polymyositis, porencephaly, post-polio syndrome, postherpetic neuralgia (PHN), postural hypotension, Prader-Willi syndrome, primary lateral sclerosis, prion diseases, progressive hemifacial atrophy, progressive multifocal leukoencephalopathy, progressive supranuclear palsy, pseudotumor cerebri, Ramsay Hunt syndrome type I, Ramsay Hunt syndrome type II, Ramsay Hunt

syndrome type III, Rasmussen's encephalitis, reflex neurovascular dystrophy, Refsum disease, restless legs syndrome, retrovirus-associated myelopathy, Rett syndrome, Reye's syndrome, rhythmic movement disorder, Romberg syndrome, Saint Vitus dance, Sandhoff disease, schizophrenia, Schilder's disease, schizencephaly, sensory integration dysfunction, septo-optic dysplasia, Shy-Drager syndrome, Sjögren's syndrome, snatiation, Sotos syndrome, spasticity, spina bifida, spinal cord tumors, spinal muscular atrophy, spinocerebellar ataxia, Steele-Richardson-Olszewski syndrome, Stiff-person syndrome, stroke, Sturge-Weber syndrome, subacute sclerosing panencephalitis, subcortical arteriosclerotic encephalopathy, superficial siderosis, Sydenham's chorea, syncope, synesthesia, syringomyelia, tarsal tunnel syndrome, tardive dyskinesia, tardive dysphrenia, Tarlov cyst, Tay-Sachs disease, temporal arteritis, tetanus, tethered spinal cord syndrome, Thomsen disease, thoracic outlet syndrome, tic douloureux, Todd's paralysis, Tourette syndrome, toxic encephalopathy, transient ischemic attack, transmissible spongiform encephalopathies, transverse myelitis, tremor, trigeminal neuralgia, tropical spastic paraparesis, trypanosomiasis, tuberous sclerosis, ubisiosis, Von Hippel-Lindau disease (VHL), Viliuisk Encephalomyelitis (VE), Wallenberg's syndrome, Werdnig, Hoffman disease, west syndrome, Williams syndrome, Wilson's disease, and Zellweger syndrome.

[0428] The compounds and compositions may also be useful in the inhibition of the development of invasive cancer, tumor angiogenesis and metastasis.

[0429] In some embodiments, the disclosure provides a method for treating a disease or disorder associated with aberrant cellular proliferation by administering to a patient in need of such treatment an effective amount of one or more of the compounds of Formula (I), in combination (simultaneously or sequentially) with at least one other agent.

[0430] In some embodiments, the disclosure provides a method of treating or ameliorating in a patient a disorder or disease selected from the group consisting of: cancer, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), degenerative disc disease, bone/osteoporotic fractures, bone or cartilage disease, and osteoarthritis, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

[0431] In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0432] In some embodiments, the method of treats a disorder or disease in which aberrant Wnt signaling is implicated in a patient, the method comprises administering to the patient

a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0433] In some embodiments, the disorder or disease is the pain and inflammation associated with cancer.

[0434] In some embodiments, the disorder or disease is the pain and inflammation associated with a joint.

[0435] In some embodiments, the disorder or disease is the pain and inflammation associated with the knee.

[0436] In some embodiments, the disorder or disease is the pain and inflammation associated with the hip.

[0437] In some embodiments, the disorder or disease is the pain and inflammation associated with the shoulder.

[0438] In some embodiments, the disorder or disease is the pain and inflammation associated with arthritis.

[0439] In some embodiments, the disorder or disease is the pain and inflammation associated with gastrointestinal disorders.

[0440] In some embodiments, the disorder or disease is the pain and inflammation associated with pulmonary disorders.

[0441] In some embodiments, the disorder or disease is the pain and inflammation associated with allergies.

[0442] In some embodiments, the disorder or disease is the pain and inflammation associated with skin disorders.

[0443] In some embodiments, the disorder or disease is the pain and inflammation associated with diabetes.

[0444] In some embodiments, the disorder or disease is the pain and inflammation associated with pancreatitis.

[0445] In some embodiments, the disorder or disease is the pain and inflammation associated with tendonitis.

[0446] In some embodiments, the disorder or disease is the pain and inflammation associated with heart disease.

[0447] In some embodiments, the disorder or disease is the pain and inflammation associated with lupus.

[0448] In some embodiments, the disorder or disease is the pain and inflammation associated with a neurological disorder.

[0449] In some embodiments, the disorder or disease is the pain and inflammation associated with multiple sclerosis.

[0450] In some embodiments, the disorder or disease is the pain and inflammation associated with Parkinson's.

[0451] In some embodiments, the disorder or disease is cancer.

[0452] In some embodiments, the disorder or disease is systemic inflammation.

[0453] In some embodiments, the disorder or disease is metastatic melanoma.

[0454] In some embodiments, the disorder or disease is fatty liver disease.

[0455] In some embodiments, the disorder or disease is liver fibrosis.

[0456] In some embodiments, the disorder or disease is tendon regeneration.

[0457] In some embodiments, the disorder or disease is diabetes.

[0458] In some embodiments, the disorder or disease is degenerative disc disease.

[0459] In some embodiments, the disorder or disease is osteoarthritis.

[0460] In some embodiments, the disorder or disease is diabetic retinopathy.

[0461] In some embodiments, the disorder or disease is pulmonary fibrosis.

[0462] In some embodiments, the disorder or disease is idiopathic pulmonary fibrosis (IPF).

[0463] In some embodiments, the disorder or disease is degenerative disc disease.

[0464] In some embodiments, the disorder or disease is rheumatoid arthritis.

[0465] In some embodiments, the disorder or disease is scleroderma.

[0466] In some embodiments, the disorder or disease is a mycotic or viral infection.

[0467] In some embodiments, the disorder or disease is a bone or cartilage disease.

[0468] In some embodiments, the disorder or disease is a neurological disorder.

[0469] In some embodiments, the disorder or disease is Alzheimer's disease.

[0470] In some embodiments, the disorder or disease is osteoarthritis.

[0471] In some embodiments, the disorder or disease is lung disease.

[0472] In some embodiments, the disorder or disease is a genetic disease caused by mutations in Wnt signaling components, wherein the genetic disease is selected from: 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/Schinzal 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.

[0473] In some embodiments, the patient is a human.

[0474] In some embodiments, the cancer is chosen from: 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.

[0475] In some embodiments, the cancer is chosen from: 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 (gastric) 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.

[0476] In some embodiments, the cancer is hepatocellular carcinoma.

[0477] In some embodiments, the cancer is colon cancer.

[0478] In some embodiments, the cancer is colorectal cancer.

[0479] In some embodiments, the cancer is breast cancer.

[0480] In some embodiments, the cancer is pancreatic cancer.

[0481] In some embodiments, the cancer is chronic myeloid leukemia (CML).

[0482] In some embodiments, the cancer is chronic myelomonocytic leukemia.

[0483] In some embodiments, the cancer is chronic lymphocytic leukemia (CLL).

[0484] In some embodiments, the cancer is acute myeloid leukemia.

[0485] In some embodiments, the cancer is acute lymphocytic leukemia.

[0486] In some embodiments, the cancer is Hodgkin lymphoma.

[0487] In some embodiments, the cancer is lymphoma.

[0488] In some embodiments, the cancer is sarcoma.

[0489] In some embodiments, the cancer is ovarian cancer.

[0490] In some embodiments, the cancer is lung cancer - non-small cell.

[0491] In some embodiments, the cancer is lung cancer - small cell.

[0492] In some embodiments, the cancer is multiple myeloma.

- [0493] In some embodiments, the cancer is nasopharyngeal cancer.
- [0494] In some embodiments, the cancer is neuroblastoma.
- [0495] In some embodiments, the cancer is osteosarcoma.
- [0496] In some embodiments, the cancer is penile cancer.
- [0497] In some embodiments, the cancer is pituitary tumors.
- [0498] In some embodiments, the cancer is prostate cancer.
- [0499] In some embodiments, the cancer is retinoblastoma.
- [0500] In some embodiments, the cancer is rhabdomyosarcoma.
- [0501] In some embodiments, the cancer is salivary gland cancer.
- [0502] In some embodiments, the cancer is skin cancer - basal and squamous cell.
- [0503] In some embodiments, the cancer is skin cancer – melanoma.
- [0504] In some embodiments, the cancer is small intestine cancer.
- [0505] In some embodiments, the cancer is stomach (gastric) cancers.
- [0506] In some embodiments, the cancer is testicular cancer.
- [0507] In some embodiments, the cancer is thymus cancer.
- [0508] In some embodiments, the cancer is thyroid cancer.
- [0509] In some embodiments, the cancer is uterine sarcoma.
- [0510] In some embodiments, the cancer is vaginal cancer.
- [0511] In some embodiments, the cancer is vulvar cancer.
- [0512] In some embodiments, the cancer is Wilms tumor.
- [0513] In some embodiments, the cancer is laryngeal or hypopharyngeal cancer.
- [0514] In some embodiments, the cancer is kidney cancer.
- [0515] In some embodiments, the cancer is Kaposi sarcoma.
- [0516] In some embodiments, the cancer is gestational trophoblastic disease.
- [0517] In some embodiments, the cancer is gastrointestinal stromal tumor.
- [0518] In some embodiments, the cancer is gastrointestinal carcinoid tumor.
- [0519] In some embodiments, the cancer is gallbladder cancer.
- [0520] In some embodiments, the cancer is eye cancer (melanoma and lymphoma).
- [0521] In some embodiments, the cancer is Ewing tumor.
- [0522] In some embodiments, the cancer is esophagus cancer.
- [0523] In some embodiments, the cancer is endometrial cancer.
- [0524] In some embodiments, the cancer is colorectal cancer.
- [0525] In some embodiments, the cancer is cervical cancer.
- [0526] In some embodiments, the cancer is brain or spinal cord tumor.

[0527] In some embodiments, the cancer is bone metastasis.

[0528] In some embodiments, the cancer is bone cancer.

[0529] In some embodiments, the cancer is bladder cancer.

[0530] In some embodiments, the cancer is bile duct cancer.

[0531] In some embodiments, the cancer is anal cancer.

[0532] In some embodiments, the cancer is adrenal cortical cancer.

[0533] In some embodiments, the disorder or disease is a neurological condition, disorder or disease, wherein the neurological condition/disorder/disease is selected from: Alzheimer's disease, frontotemporal dementias, dementia with Lewy bodies, prion diseases, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, amyotrophic lateral sclerosis (ALS), inclusion body myositis, autism, degenerative myopathies, diabetic neuropathy, other metabolic neuropathies, endocrine neuropathies, orthostatic hypotension, multiple sclerosis and Charcot-Marie-Tooth disease.

[0534] In some embodiments, the disorder or disease is a neurological disease or disorder associated with tau protein, amyloid, alpha-synuclein pathology, Tar DNA-binding Protein of 43KDa (TDP-43), Prion protein PrP or fused in sarcoma (FUS).

[0535] In some embodiments, the disorder or disease is selected from the group consisting of: Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Down Syndrome, Frontotemporal Dementia with Parkinsonism-17 (FTDP-17), Lewy body dementia, Parkinson's Disease, Pick's Disease, and additional diseases with pronounced neurodegeneration such as Autism, Dementia, Epilepsy, Huntington's Disease, Multiple Sclerosis; diseases and disorders associated with acquired brain injury such as Chronic Traumatic Encephalopathy, Traumatic Brain Injury, Tumor, and Stroke.

[0536] In some embodiments, a compound of Formula (I) inhibits DYRK1A.

[0537] In some embodiments, a compound of Formula (I) inhibits GSK3.

[0538] In some embodiments, a compound of Formula (I) inhibits GSK3 β .

[0539] In some embodiments, a compound of Formula (I) inhibits DYRK1A and GSK3 β .

[0540] In some embodiments, the compound of Formula (I) inhibits one or more proteins in the Wnt pathway.

[0541] In some embodiments, the compound of Formula (I) inhibits signaling induced by one or more Wnt proteins.

[0542] In some embodiments, the Wnt proteins are chosen from: WNT1, WNT2, WNT2B, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, and WNT16.

[0543] In some embodiments, the compound of Formula (I) inhibits a kinase activity.

[0544] In some embodiments, the method treats a disease or disorder mediated by the Wnt pathway in a patient, the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

[0545] In some embodiments, the compound of Formula (I) inhibits one or more Wnt proteins.

[0546] In some embodiments, the method treats a disease or disorder mediated by kinase activity in a patient, the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

[0547] In some embodiments, the disease or disorder comprises tumor growth, cell proliferation, or angiogenesis.

[0548] In some embodiments, the method inhibits the activity of a protein kinase receptor, the method comprises contacting the receptor with an effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

[0549] In some embodiments, the method treats a disease or disorder associated with aberrant cellular proliferation in a patient; the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

[0550] In some embodiments, the method prevents or reduces angiogenesis in a patient; the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

[0551] In some embodiments, the method prevents or reduces abnormal cellular proliferation in a patient; the method comprises administering to the patient a therapeutically effective amount of a compound (or compounds) of Formula (I), or a pharmaceutically acceptable salt thereof.

[0552] In some embodiments, the method treats a disease or disorder associated with aberrant cellular proliferation in a patient, the method comprises administering to the patient a pharmaceutical composition comprising one or more of the compounds of claim 1 in combination with a pharmaceutically acceptable carrier and one or more other agents.

[0553] Moreover, the compounds and compositions, for example, as inhibitors of the cyclin-dependent kinases (CDKs), can modulate the level of cellular RNA and DNA synthesis and therefore are expected to be useful in the treatment of viral infections such as HIV, human papilloma virus, herpes virus, Epstein-Barr virus, adenovirus, Sindbis virus, pox virus and the like.

[0554] Compounds and compositions described herein can inhibit the kinase activity of, for example, CDK/cyclin complexes, such as those active in the G₀ or G₁ stage of the cell cycle, e.g., CDK2, CDK4, and/or CDK6 complexes.

Evaluation of Biological Activity

[0555] The biological activity of the compounds described herein can be tested using any suitable assay known to those of skill in the art, see, e.g., WO 2001/053268 and WO 2005/009997. For example, the activity of a compound may be tested using one or more of the test methods outlined below.

[0556] In one example, tumor cells may be screened for Wnt independent growth. In such a method, tumor cells of interest are contacted with a compound (i.e. inhibitor) of interest, and the proliferation of the cells, e.g. by uptake of tritiated thymidine, is monitored. In some embodiments, tumor cells may be isolated from a candidate patient who has been screened for the presence of a cancer that is associated with a mutation in the Wnt signaling pathway. Candidate cancers include, without limitation, those listed above.

[0557] In another example, one may utilize *in vitro* assays for Wnt biological activity, e.g. stabilization of β -catenin and promoting growth of stem cells. Assays for biological activity of Wnt include stabilization of β -catenin, which can be measured, for example, by serial dilutions of a candidate inhibitor composition. An exemplary assay for Wnt biological activity contacts a candidate inhibitor with cells containing constitutively active Wnt/ β -catenin signaling. The cells are cultured for a period of time sufficient to stabilize β -catenin, usually at least about 1 hour, and lysed. The cell lysate is resolved by SDS PAGE, then transferred to nitrocellulose and probed with antibodies specific for β -catenin.

[0558] In a further example, the activity of a candidate compound can be measured in a *Xenopus* secondary axis bioassay (Leyns, L. *et al. Cell* (1997), 88(6), 747-756).

[0559] In another example, *in vitro* assays for DYRK1A biological activity may be used, e.g. regulation of microtubule-associated protein tau (MAPT/Tau) phosphorylation in neuronal cell line such as the human SH-SY5Y neuroblastoma cell line. Assays for DYRK1A-regulated level of phosphorylation can include monitoring levels of basal pSer396 Tau, which can be measured, for example, by serial dilutions of a candidate inhibitor composition using a ten

micromolar top concentration and detected by ELISA or Western Blotting. An exemplary assay for DYRK-1A-regulated phosphorylation uses the SH-SY5Y cells cultured in a 96 well plate format for a period of time sufficient to stabilize microtubules and Tau phosphorylation, usually at least 2 days, then treated with a 1/3 serial dilution of compounds overnight and lysed. The cell lysate is resolved by SDS PAGE, then transferred to nitrocellulose and probed with an antibody specific for pSer396 Tau. The chemiluminescence signal for HRP-linked antibodies used in western blotting is detected using a Carestream Image Station and blot densitometry for pSer396 and beta-actin are analyzed using ImageJ (NIH).

[0560] In a further example, the activity of a candidate compound can be measured by ELISA by adding the lysate mentioned above onto total Tau-coated plates and detected with a specific pSer396 antibody. Colorimetric detection of ELISA signal is performed by Cytation3 plate reader (Biotek).

[0561] To further illustrate this disclosure, the following examples are included. The examples should not, of course, be construed as specifically limiting the disclosure. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the disclosure as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the disclosure without exhaustive examples.

EXAMPLES

Compound preparation

[0562] The starting materials used in preparing the compounds of the disclosure are known, made by known methods, or are commercially available. It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the compounds.

[0563] It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations are discussed in standard texts such as *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 7th Ed., John Wiley & Sons (2013), Carey and Sundberg, *Advanced Organic Chemistry* 5th Ed., Springer (2007), *Comprehensive Organic Transformations*:

A Guide to Functional Group Transformations, 2nd Ed., John Wiley & Sons (1999) (incorporated herein by reference in its entirety) and the like.

[0564] The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in P. Wuts *Greene's Protective Groups in Organic Synthesis*, 5th Ed., John Wiley & Sons (2014), incorporated herein by reference in its entirety.

[0565] Trademarks used herein are examples only and reflect illustrative materials used at the time of the disclosure. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the disclosure.

[0566] (¹H) nuclear magnetic resonance spectra (NMR) were measured in the indicated solvents on a Bruker NMR spectrometer (Avance TM DRX300, 300 MHz for ¹H or Avance TM DRX500, 500 MHz for ¹H) or Varian NMR spectrometer (Mercury 400BB, 400 MHz for ¹H). Peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak multiplicities are denoted as follows, s, singlet; d, doublet; t, triplet; q, quartet; ABq, AB quartet; quin, quintet; sex, sextet; sep, septet; non, nonet; dd, doublet of doublets; ddd, doublet of doublets of doublets; d/ABq, doublet of AB quartet; dt, doublet of triplets; td, triplet of doublets; dq, doublet of quartets; m, multiplet.

[0567] The following abbreviations have the indicated meanings:

brine = saturated aqueous sodium chloride

CDCl₃ = deuterated chloroform

DCE = dichloroethane

DCM = dichloromethane

DIPEA = N,N-diisopropylethylamine

DMAP = 4-dimethylaminopyridine

DMF = N,N-dimethylformamide

DMSO-*d*₆ = deuterated dimethylsulfoxide

ESIMS = electron spray mass spectrometry

EtOAc = ethyl acetate

HATU = 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

HCl = hydrochloric acid

HOAc = acetic acid

ISCO = Teledyne ISCO, Inc brand CombiFlash[®] Rf 200

KOAc = potassium acetate

LAH = Lithium aluminium hydride

LC/MS = Liquid chromatography–mass spectrometry

MeCN = acetonitrile

MeOH = methanol

MgSO₄ = magnesium sulfate

MsCl = mesyl chloride or methanesulfonyl chloride

MTBE = methyl tert-butyl ether

MW = microwave irradiation

NaBH₃CN = sodium cyanoborohydride

NaHCO₃ = sodium bicarbonate

Na(OAc)₃BH = Sodium triacetoxyborohydride

NMR = nuclear magnetic resonance

ON = overnight

Pd(dppf)Cl₂ = 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride

Pd(PPh₃)₄ = tetrakis(triphenylphosphine)palladium(0)

r.t. = room temperature

SPhos Pd G3 = [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'- triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1' -biphenyl)]palladium(II) methanesulfonate methanesulfonate

SPhos Pd G4 = Methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II)

TBAF = Tetra-n-butylammonium fluoride,

TEA = triethylamine

TFA = trifluoroacetic acid

THF = tetrahydrofuran

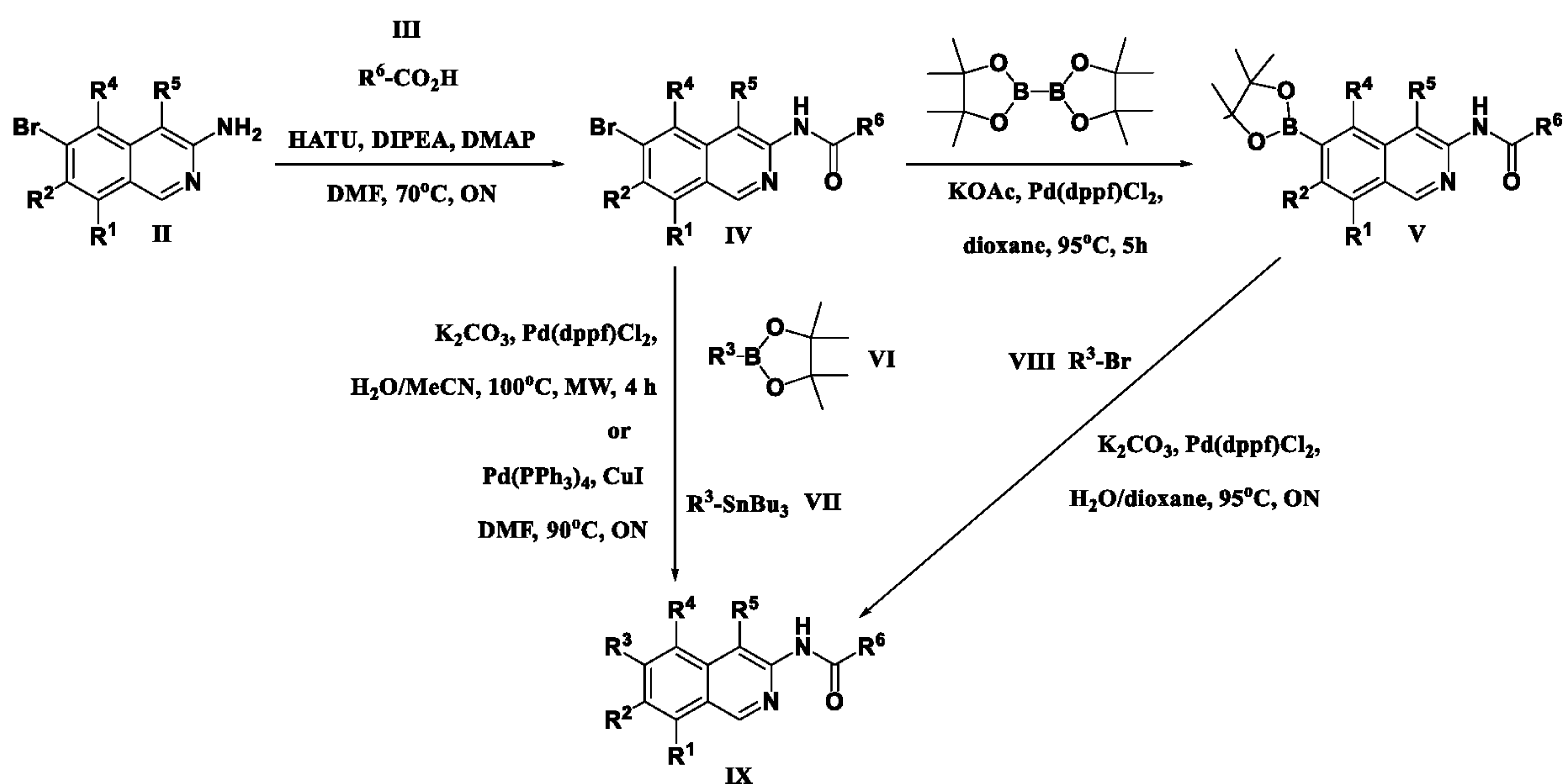
TLC = thin layer chromatography

[0568] The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compounds provided herein.

Furthermore, other methods for preparing compounds of the disclosure will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure. The compound numberings used in the synthetic schemes depicted below are meant for those specific schemes only, and should not be construed as or confused with same numberings in other sections of the application. Unless otherwise indicated, all variables are as defined above.

General procedures

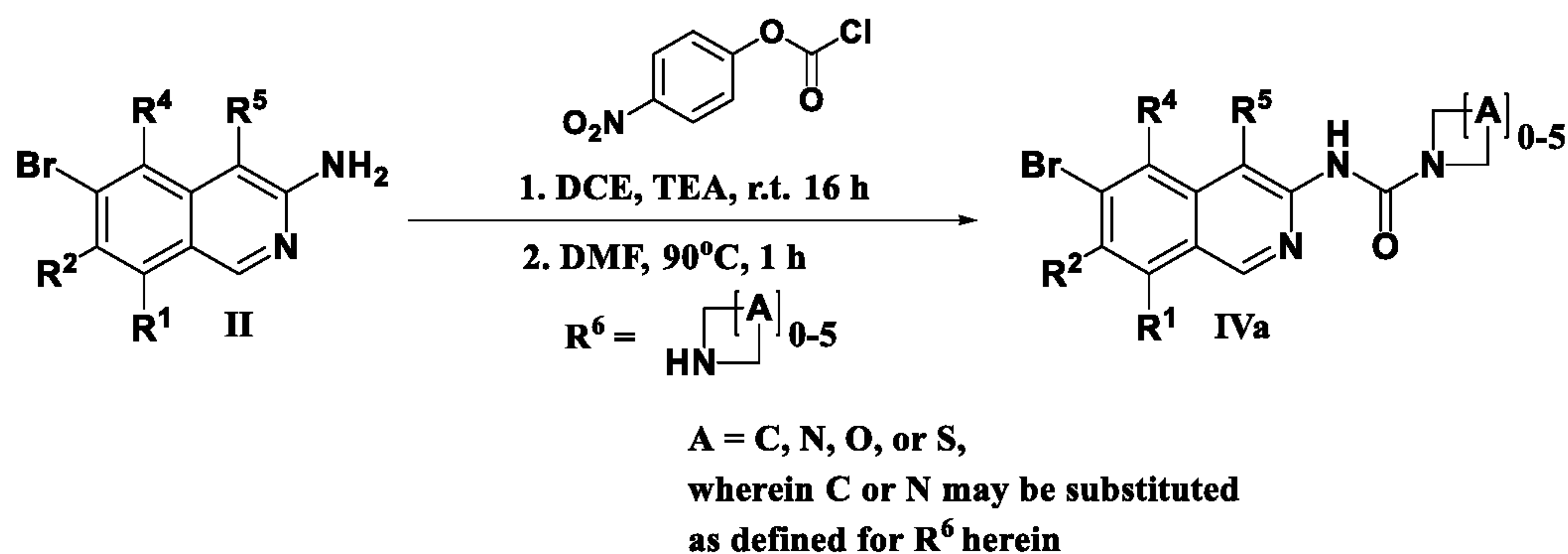
[0569] Compounds of Formula I of the present disclosure can be prepared as depicted in Scheme 1.



Scheme 1

[0570] Scheme 1 describes a method for preparation of isoquinoline-3-carboxamide derivatives (IX) by first coupling the amine with a variety of acids (III) to produce amide IV. The bromo derivative IV is then reacted with bis(pinacolato)diboron to give the pinacol ester (V). Suzuki coupling with a variety of 5-membered heteroaryl bromides (VIII) yields the desired R³ substituted isoquinoline IX. Alternatively, the bromo derivative IV is Suzuki coupled with a variety of 5-membered heteroaryl pinacol esters (VI) or coupled to a variety of 5-membered heteroaryl stannanes (VII) to produce the final R³ substituted isoquinoline IX.

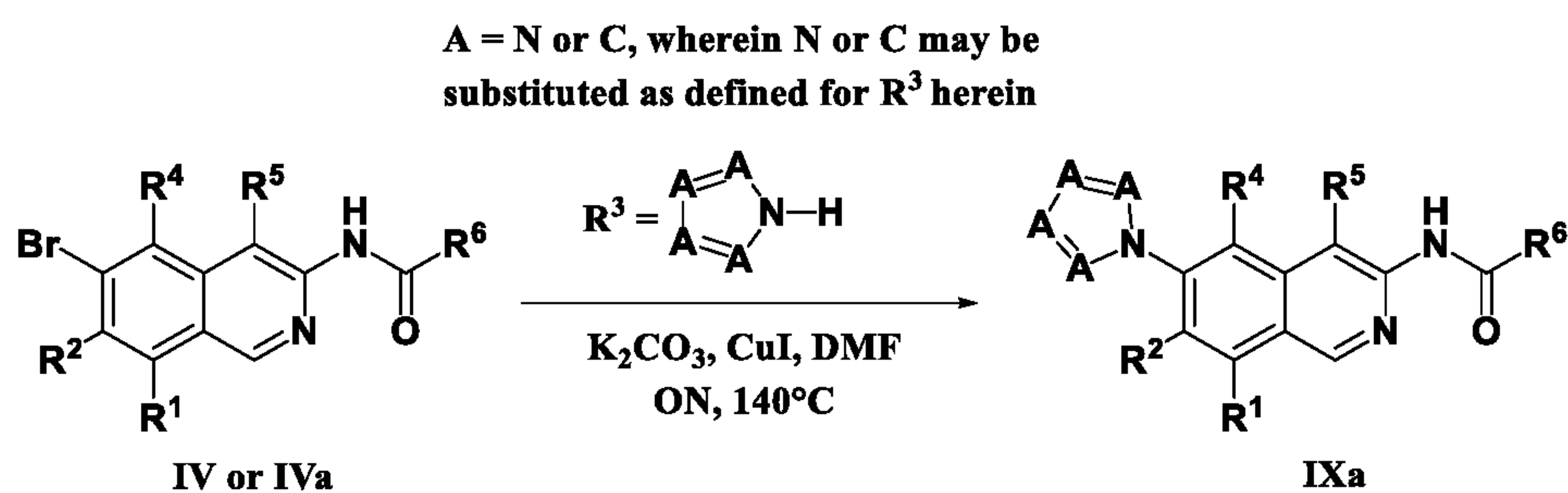
[0571] In some embodiments, compounds of Formula I of the present disclosure can be prepared as depicted in Scheme 2.



Scheme 2

[0572] Scheme 2 describes a method for preparation of isoquinoline-3-carboxamide intermediate (IVa) by first coupling the amine 4-nitrophenyl carbonochloridate followed by coupling with a variety of R⁶ NH heterocyclyls. Intermediate IVa could then be used in place of IV in Scheme 1 or 3.

[0573] In other embodiments, compounds of Formula I of the present disclosure can be prepared as depicted in Scheme 3.

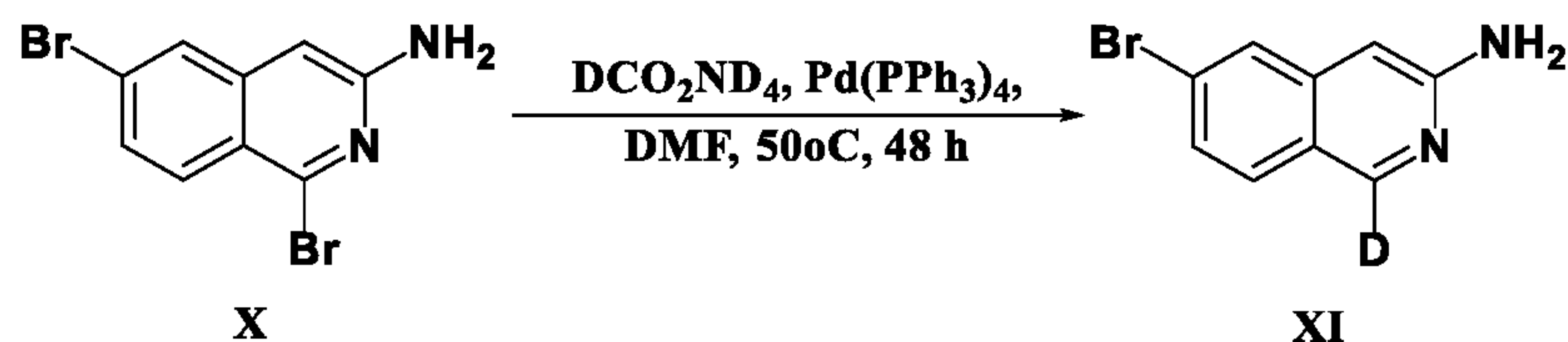


Scheme 3

[0574] Scheme 3 describes a method for preparation of isoquinoline-3-carboxamide derivatives (IXa) starting with bromo intermediate IV or IVa and couple with the nitrogen of a variety of R³ NH heteroaryls to produce the final R³ substituted isoquinoline IXa.

Illustrative Compound Examples

[0575] Preparation of intermediate 6-bromoisoquinolin-1-*d*-3-amine (XI) is depicted below in Scheme 4.

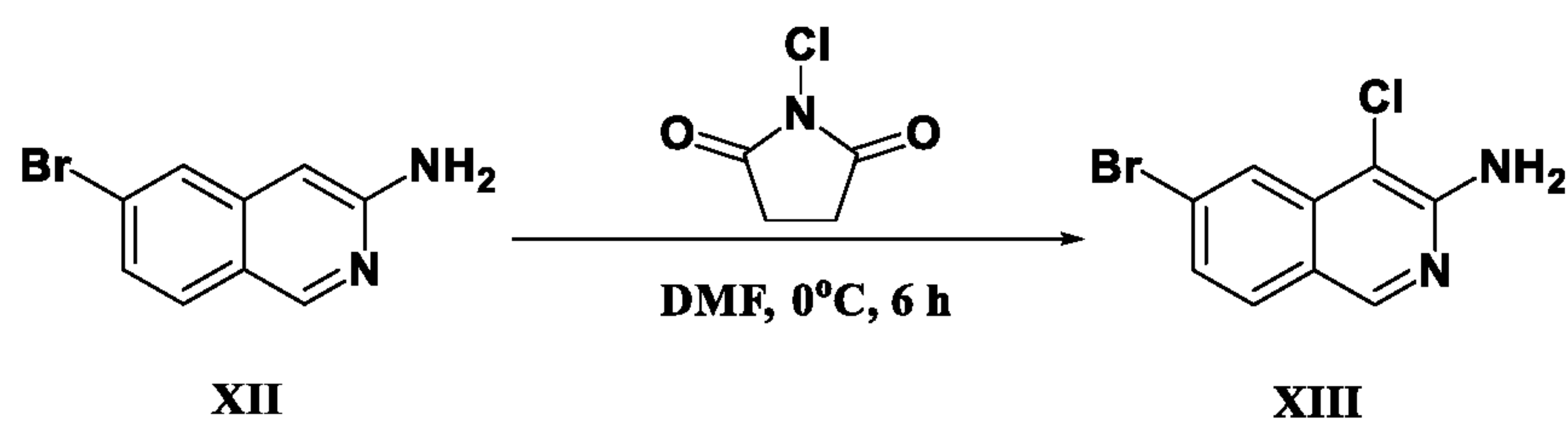


Scheme 4

Step 1

[0576] To a mixture of 1,6-dibromoisoquinolin-3-amine (X) (0.5 g, 1.66 mmol), ammonium formate-*d*₅ (0.56 g, 8.28 mmol) and Pd(PPh₃)₄ (191.3 mg, 0.170 mmol) in DMF (5 mL) was heated to 50°C for 48 h. The solvents were concentrated and the residue was suspended in chloroform. The solid was collected by filtration and washed with water and EtOAc. The solid were dried under high vacuo to obtain 6-bromo-1-deuterio-isoquinolin-3-amine (XI) (115 mg, 0.513 mmol, 31.0% yield) as a pale yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.11 (2 H, s), 6.55 (1 H, s), 7.22 (1 H, dd, *J*=8.78, 1.92 Hz), 7.73 (1 H, d, *J*=8.51 Hz), 7.79 (1 H, d, *J*=1.92 Hz); ESIMS found for C₉H₆DBrN₂ *m/z* 224.0 (⁷⁹BrM+H).

[0577] Preparation of intermediate 6-bromo-4-chloroisoquinolin-3-amine (XIII) is depicted below in Scheme 5.

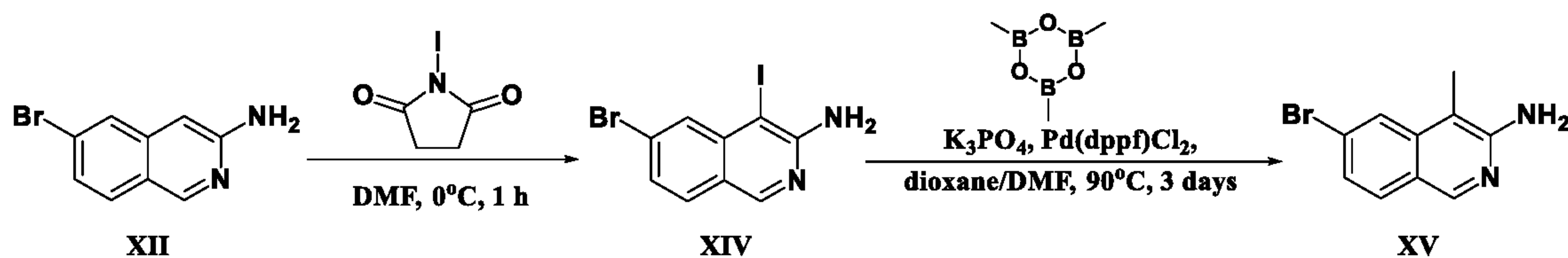


Scheme 5

Step 1

[0578] To a stirred suspension of 6-bromoisoquinolin-3-amine (**XII**) (1.0 g, 4.48 mmol) in DMF (15 mL) at 0°C was added 1-chloropyrrolidine-2,5-dione (598.6 mg, 4.48 mmol) portionwise. The mixture was stirred at 0°C for 6 h. The reaction mixture was added to water (150 mL), stirred for 1 h and the resulting solids were collected by filtration and air dried overnight to obtain 6-bromo-4-chloro-isoquinolin-3-amine (**XIII**) (922 mg, 3.58 mmol, 79.9% yield) as a beige solid which was used for next step without purification. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 6.55 (2 H, s), 7.40 (1 H, dd, *J*=8.64, 1.78 Hz), 7.88 (1 H, d, *J*=8.51 Hz), 7.90 (1 H, d, *J*=1.10 Hz), 8.86 (1 H, s); ESIMS found for C₉H₆BrClN₂ *m/z* 256.9 (⁷⁹BrM+H).

[0579] Preparation of intermediate 6-bromo-4-methylisoquinolin-3-amine (**XV**) is depicted below in Scheme 6.



Scheme 6

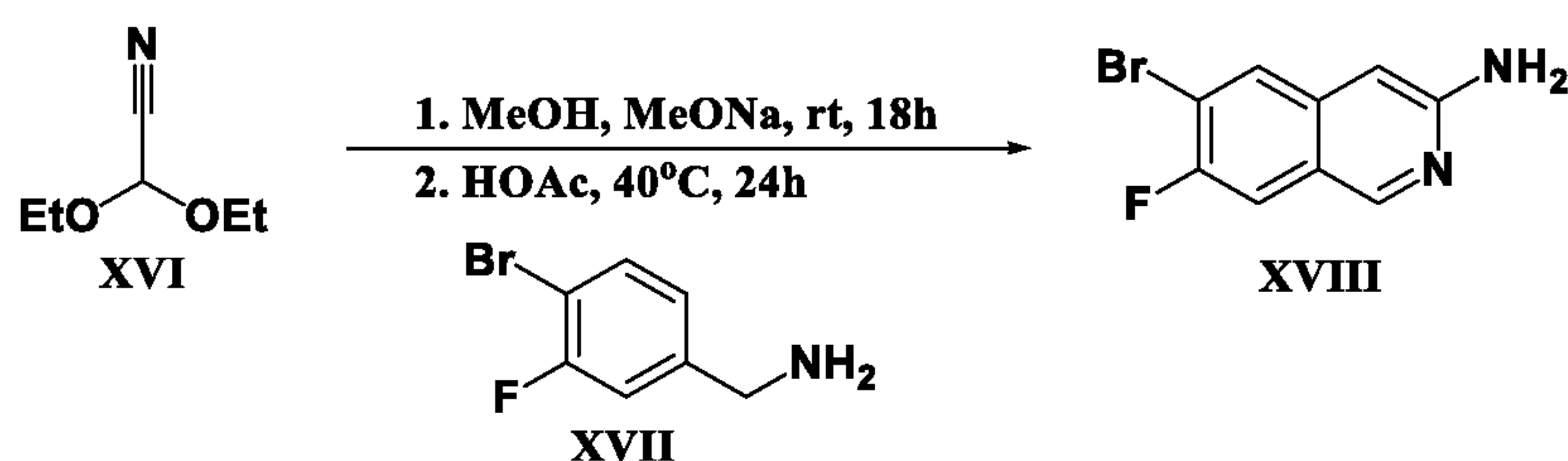
Step 1

[0580] To a stirred suspension of 6-bromoisoquinolin-3-amine (**XII**) (2.g, 8.97mmol) in DMF (25.1 mL) at 0°C was added 1-iodopyrrolidine-2,5-dione (2.02 g, 8.97 mmol) portionwise, The mixture was stirred at 0°C for 1 hr. LC-MS of the mixture showed completion of the reaction and the desired product. The solvent was removed under vacuum, the residue was purified by C18 Silica gel (240g) [0→100% H₂O/MeCN (0.1%Formic acid)] to produce 6-bromo-4-iodo-isoquinolin-3-amine (**XIV**) (1.95 g, 5.58 mmol, 62.2% yield) as a brown solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 6.41 (2 H, br s), 7.40 (1 H, dd, *J*=8.64, 1.78 Hz), 7.76 - 7.81 (1 H, m), 7.82 (1 H, d, *J*=8.51 Hz), 8.81 (1 H, s); ESIMS found for C₉H₆BrIN₂ *m/z* 348.9 (⁷⁹BrM+H).

Step 2

[0581] A stirred solution of 6-bromo-4-iodo-isoquinolin-3-amine (**XIV**) (1.0 g, 2.87 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.72 g, 2.87 mmol), Pd(dppf)Cl₂ (0.23 g, 0.29 mmol), and K₃PO₄ (5.73 mL, 5.73 mmol) in 1,4-dioxane (10 mL) was heated to 90°C for 3 days. The solvent was removed under high vacuum and the residue was purified by C18 silica gel (240g) [0→20% H₂O/MeCN (0.1%Formic acid)] to produce 6-bromo-4-methyl-isoquinolin-3-amine (**XV**) (74 mg, 0.312 mmol, 10.9% yield) as an off-white solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.23 (3 H, br s), 5.91 (2 H, br s), 7.27 (1 H, br d, *J*=2.20 Hz), 7.71 - 7.82 (1 H, m), 7.92 (1 H, br s), 8.72 (1 H, br s); ESIMS found for C₁₀H₉BrN₂ *m/z* 239.0 (⁸¹BrM+H).

[0582] Preparation of intermediate 6-bromo-7-fluoroisoquinolin-3-amine (**XVIII**) is depicted below in Scheme 7.

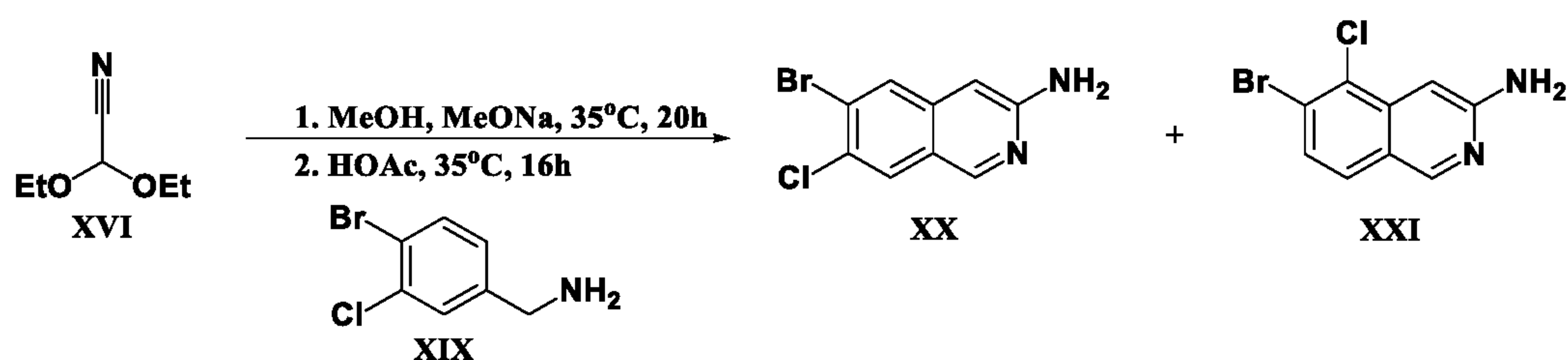


Scheme 7

Step 1

[0583] To a vial was added 2,2-diethoxyacetonitrile (**XVI**) (1.0 g, 7.74 mmol) dissolved MeOH (7.74 mL) followed by addition of MeONa/MeOH (0.18 mL, 0.77 mmol) dropwise. The reaction was stirred at room temperature for 20 h. HOAc (44.3 μ L, 0.77 mmol) was added until pH=7-8 (using pH strips). (4-Bromo-3-fluoro-phenyl)methanamine hydrochloride (**XVII**) (1.86 g, 7.74 mmol) was added and stirred at 40°C for 4 h. The solvent was removed under vacuum. Sulfuric acid (12.6 mL, 232.3 mmol) was added and stirred at 40°C for 16 h. NH_4OH (30.8 mL, 240.0 mmol) was added dropwise at 0°C. The solvent was removed under vacuum and the residue was purified by C18 silica gel (240g) [0 $\rightarrow$ 50% $\text{H}_2\text{O}/\text{MeCN}$ (0.1%Formic acid)] to produce 6-bromo-7-fluoro-isoquinolin-3-amine (**XVIII**) (1.33 g, 5.50 mmol, 71.1% yield) as an off-white solid. ^1H NMR (499 MHz, $\text{DMSO}-d_6$) δ ppm 6.07 (2 H, s), 6.61 (1 H, s), 7.76 (1 H, d, $J=9.33$ Hz), 8.01 (1 H, d, $J=6.86$ Hz), 8.80 (1 H, s); ESIMS found for $\text{C}_9\text{H}_6\text{BrFN}_2$ m/z 242.9 ($^{81}\text{BrM}+\text{H}$).

[0584] Preparation of intermediates 6-bromo-7-chloroisoquinolin-3-amine (**XX**) and 6-bromo-5-chloroisoquinolin-3-amine (**XXI**) is depicted below in Scheme 8.

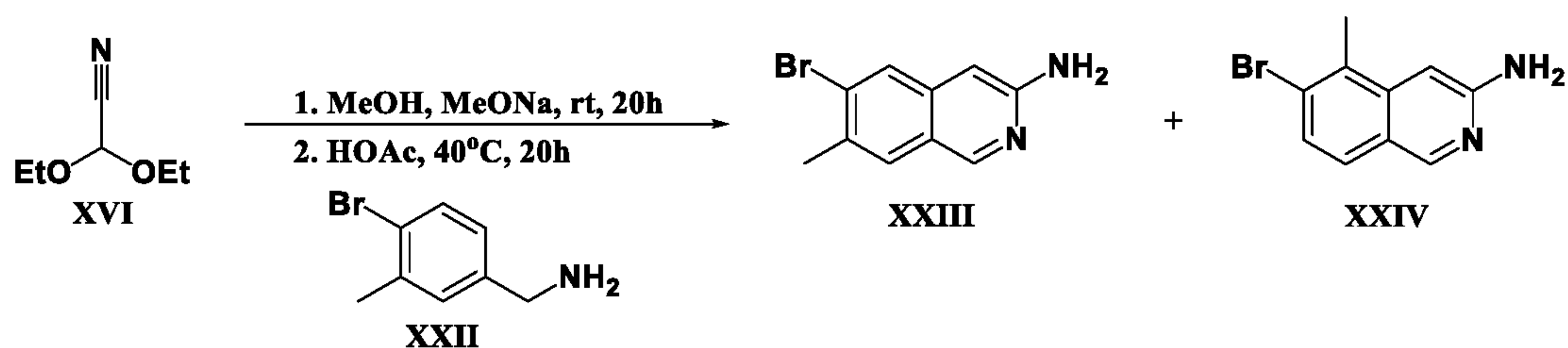


Scheme 8

Step 1

[0585] To a stirred solution of 2,2-diethoxyacetonitrile (**XVI**) (0.59 g, 4.57 mmol) in a vial containing MeOH (4.57 mL) was added MeONa (0.1 mL, 0.46 mmol) dropwise. The reaction was stirred at 35°C for 20 h. HOAc was added (26.1 μ L, 0.46 mmol) (checked that the pH is 7-8 using pH strips) followed by (4-bromo-3-chloro-phenyl)methanamine (**XIX**) (1.01 g, 4.57 mmol). The mixture was stirred at 35°C for 40 h. The solvent was removed under vacuum. Sulfuric Acid (7.43 mL, 137.0 mmol) was then added and stirred at 35°C for 16 h. NH₄OH (60.6 mL, 141.6 mmol) was added at 0°C. The reaction was filtered through Celite and purified by C18 silica gel (240g) [0 $\rightarrow$ 30% H₂O/MeCN (0.1% Formic acid)] to produce a 1:1 mixture (by nmr) of 6-bromo-7-chloro-isoquinolin-3-amine (**XX**) and 6-bromo-5-chloroisoquinolin-3-amine (**XXI**) (633.7 mg, 2.46 mmol, 53.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 6.23 (2 H, s), 6.46 (2 H, s), 6.57 (1 H, s), 6.83 (1 H, s), 7.40 (1 H, d, *J*=8.51 Hz), 7.74 (1 H, d, *J*=8.51 Hz), 8.05 (1 H, s), 8.09 (1 H, s), 8.81 (1 H, s), 8.88 (1 H, s); ESIMS found for C₉H₆BrClN₂ *m/z* 256.9 (⁷⁹BrM+H).

[0586] Preparation of intermediates 6-bromo-7-methylisoquinolin-3-amine (**XXIII**) and 6-bromo-5-methylisoquinolin-3-amine (**XXIV**) is depicted below in Scheme 9.

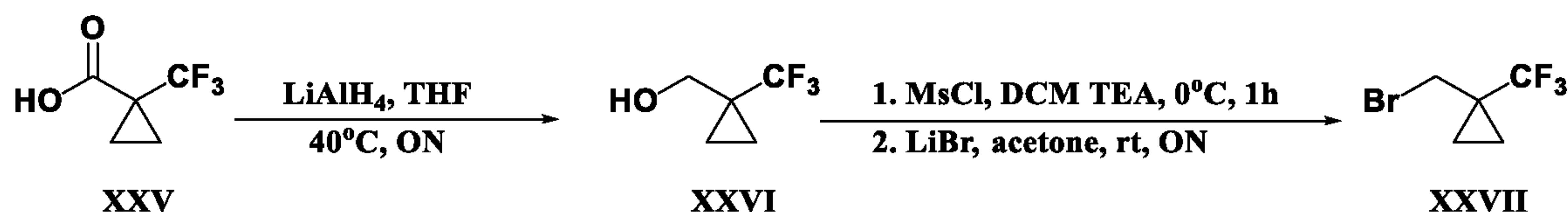


Scheme 9

Step 1

[0587] To a stirred solution of 2,2-diethoxyacetonitrile (**XVI**) (0.33 g, 2.52 mmol) in a vial containing MeOH (2.52 mL) was added MeONa (0.23 mL, 0.25 mmol) dropwise. The reaction was stirred at 22°C for 20 h. HOAc was added (14.4 μ L, 0.25 mmol) (checked that the pH is 7-8 using pH strips) followed by (4-bromo-3-methyl-phenyl)methanamine (**XXII**) (0.5 g, 2.52 mmol). The mixture was stirred at 40°C for 40 h. The solvent was removed under vacuum. Sulfuric Acid (4.09 mL, 75.49 mmol) was then added and stirred at 40°C for 16 h. NH₄OH (33.4 mL, 78 mmol) was added at 0°C. The reaction was filtered through Celite and purified by C18 silica gel (240g) [0 $\rightarrow$ 30% H₂O/MeCN (0.1%Formic acid)] to produce a 1:1 mixture (by nmr) of 6-bromo-7-methylisoquinolin-3-amine (**XXIII**) and 6-bromo-5-methylisoquinolin-3-amine (**XXIV**) (378 mg, 1.59 mmol, 63.4% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.40 (3 H, s), 2.52 (3 H, s), 5.96 (2 H, s), 6.12 (1 H, s), 6.54 (1 H, s), 6.71 (1 H, s), 7.27 (1 H, d, *J*=8.78 Hz), 7.58 (1 H, d, *J*=8.78 Hz), 7.73 (1 H, s), 7.86 (1 H, s), 8.74 (1 H, s), 8.79 (1 H, s); ESIMS found for C₁₀H₉BrN₂ *m/z* 237.0 (⁷⁹BrM+H).

[0588] Preparation of intermediate 1-(bromomethyl)-1-(trifluoromethyl)cyclopropane (**XXVII**) is depicted below in Scheme 10.



Scheme 10

Step 1

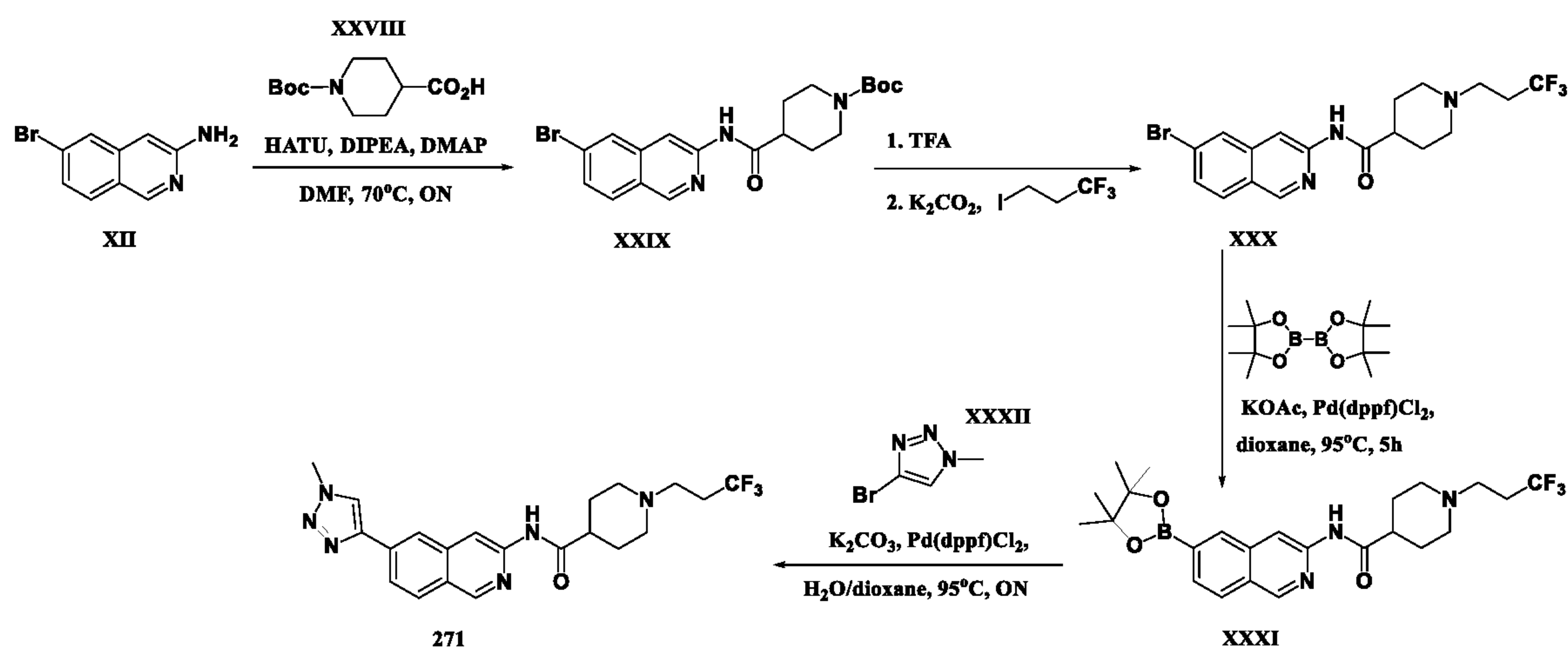
[0589] 1-(Trifluoromethyl)cyclopropane-1-carboxylic acid (**XXV**) (3.7334 g, 24.23 mmol) was dissolved in THF (162 mL) and cooled to 0°C. LAH (1.1614 g, 29.07 mmol) was then added and the reaction heated to 40°C overnight. The reaction was cooled to 0°C. Water (2 mL) was added to quench the reaction followed by 2 N NaOH (0.3 mL). The reaction was stirred forming a precipitate which was filtered off and washed with ether. The aqueous phase was removed and the organic phase was washed with brine, dried, and carefully concentrated to give (1-(trifluoromethyl)cyclopropyl)methanol (**XXVI**) (1.5376 g, 10.98 mmol, 45.3% yield) as a clear, volatile liquid.

Step 2

[0590] To a solution of (1-(Trifluoromethyl)cyclopropyl)methanol (**XXVI**) (1.6 g, 11.42 mmol) in DCM (23 mL) was added Et₃N (1.9 mL, 13.7 mmol). The reaction was cooled to 0°C and MsCl was added dropwise. The reaction was stirred at 0°C for 1 h. The reaction was poured into water, and extracted with DCM. The organic phase was separated, washed with brine, dried, and concentrated. The crude mesylate was then dissolved in acetone (22 mL). LiBr (4.96 g, 57.1 mmol) was added, and the reaction stirred at room temperature overnight. The acetone was carefully removed, and the residue was partitioned between water and ether. The aqueous phase was separated and reextracted with ether. The organic phases were combined, washed with brine, dried, and carefully concentrated to give 1-(bromomethyl)-1-(trifluoromethyl)cyclopropane (**XXVII**) (1.2867 g, 6.34 mmol, 55.5% yield) as a gold liquid with residual amounts of acetone. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.04 (2 H, tquin, *J*=5.17, 5.17, 1.74, 1.74, 1.74, 1.74 Hz), 1.23 - 1.27 (2 H, m), 3.77 (2 H, s).

Example 1.

[0591] Preparation of N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide (**271**) is depicted below in Scheme 11.



Scheme 11

Step 1

[0592] To a stirred solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (XXVIII) (1.542 g, 6.72 mmol) and HATU (2.56 g, 6.72 mmol) was added DIPEA (2.349 mL, 13.45 mmol). After 10 min, 6-bromoisoquinolin-3-amine (XII) (1 g, 4.48 mmol) was added followed by the addition of DMAP (0.110 g, 0.897 mmol) and the mixture was heated to 70°C overnight. The LC/MS of mixture showed complete conversion of the amine to the product. The solvents were concentrated in vacuo, the residue taken into EtOAc, washed with water, sat. aq. NaHCO₃ and brine solution. The organic layer was dried over anhydrous Na₂SO₄, solvents removed in vacuo and the residue was dried under high vacuo to obtain crude *tert*-butyl 4-((6-bromoisoquinolin-3-yl)carbamoyl)piperidine-1-carboxylate (XXIX) as a brown gummy solid (2.29 g, 5.27 mmol, 11.8% yield). Used for next step without purification.

Step 2

[0593] To a stirred solution of *tert*-butyl 4-((6-bromoisoquinolin-3-yl)carbamoyl)piperidine-1-carboxylate (XXIX) (1.0 g, 2.302 mmol) in DCM (4.0 mL) was added TFA (4.0 mL, 51.9 mmol) dropwise and the mixture was stirred at room temperature for 2 h. The solvent were evaporated in vacuo, the residue was neutralized with 7 N NH₃/MeOH, concentrated and dried under high vacuo to obtain N-(6-bromoisoquinolin-3-yl)piperidine-4-carboxamide as a dark brown solid (0.769 g, 2.302 mmol, 100% yield). Used for next step without purification. ESIMS found for C₁₅H₁₆BrN₃O *m/z* 336.1 (⁸¹BrM+H).

Step 3

[0594] To a stirred suspension of N-(6-bromoisoquinolin-3-yl)piperidine-4-carboxamide (0.769 g, 2.30 mmol) and potassium carbonate (1.271 g, 9.20 mmol) in MeCN (10 ml) was added 1,1,1-trifluoro-3-iodopropane (0.270 mL, 2.300 mmol). The mixture was then heated to 90°C overnight. Another equivalents of 1,1,1-trifluoro-3-iodopropane (0.270 mL, 2.300 mmol) was added and heating continued at 90°C over a 2nd night. The reaction mixture was absorbed on silica and was purified by ISCO using EtOAc/hexanes (0→100%) and then with CHCl₃/MeOH (0→100% to recover unreacted starting material). The pure fractions were combined, concentrated, the residue suspended in diethylether, sonicated and the solid were collected by filtration and dried under high vacuo to obtain N-(6-bromoisoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide (**XXX**) as an off-white solid (0.31 g, 0.720 mmol, 31.3% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.57 - 1.71 (m, 2 H), 1.79 (br d, *J*=11.80 Hz, 2 H), 1.89 - 2.01 (m, 2 H), 2.41 - 2.60 (m, 5 H), 2.88 - 2.98 (m, 2 H), 7.63 (dd, *J*=8.78, 1.92 Hz, 1 H), 8.00 (d, *J*=8.78 Hz, 1 H), 8.18 (d, *J*=1.37 Hz, 1 H), 8.45 (s, 1 H), 9.14 (s, 1 H), 10.61 (s, 1 H); ESIMS found for C₁₈H₁₉BrF₃N₃O *m/z* 432.3 (⁸¹BrM+H).

Step 4

[0595] To a solution of N-(6-bromoisoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide (**XXX**) (0.170 g, 0.395 mmol), bis(pinacolato)diboron (0.150 g, 0.593 mmol), potassium acetate (0.116 g, 1.185 mmol) and Pd(dppf)Cl₂-CH₂Cl₂ adduct (0.032 g, 0.040 mmol) was taken in dioxane (2.5 mL). N₂ gas was bubbled into the mixture for 10 min and then the mixture was heated to 95°C for 5 h to produce N-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide (**XXXI**). ESIMS found for C₂₄H₃₁BF₃N₃O₃ *m/z* 478.1 (M+1). Use for next step without work up or further purification.

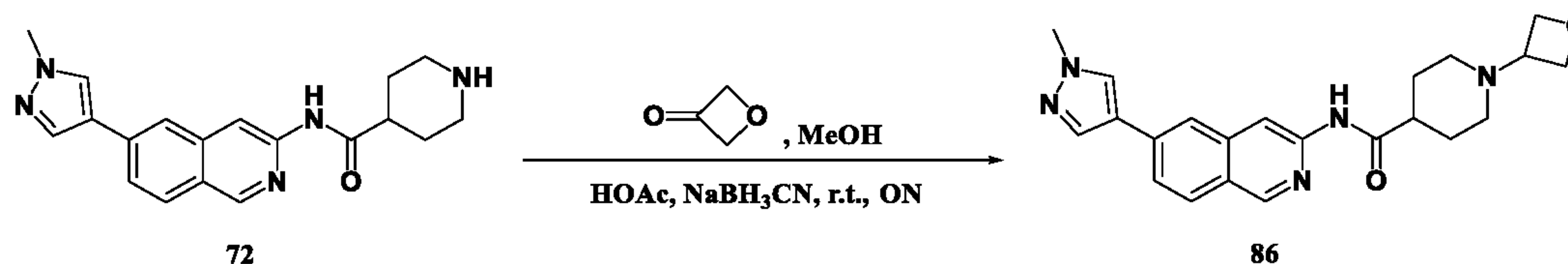
Step 5

[0596] To the above solution was added 4-bromo-1-methyl-1H-1,2,3-triazole (**XXXII**) (0.064 g, 0.395 mmol), Pd(dppf)Cl₂-CH₂Cl₂ adduct (0.032 g, 0.040 mmol) and 2 M aqueous solution of potassium carbonate (0.395 mL, 0.790 mmol). The reaction mixture was heated overnight at 95°C. The reaction mixture was absorbed on silica and purified by ISCO using CHCl₃/7N NH₃ in MeOH (0→5%) followed by preparative TLC to obtain N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide (**271**) as a beige solid (0.011 g, 0.025 mmol, 6.44% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.60 - 1.73 (m, 2 H), 1.76 - 1.84 (m, 2 H), 1.92 - 2.01 (m, 2 H), 2.41 - 2.60 (m, 5 H), 2.94 (br d, *J*=11.25 Hz, 2

H), 4.14 (s, 3 H), 8.01 (dd, $J=8.51, 1.37$ Hz, 1 H), 8.11 (d, $J=8.51$ Hz, 1 H), 8.28 (s, 1 H), 8.50 (s, 1 H), 8.73 (s, 1 H), 9.11 (s, 1 H), 10.55 (s, 1 H); ESIMS found for $C_{21}H_{23}F_3N_6O$ m/z 433.2 (M+1).

Example 2.

[0597] Preparation of N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl) piperidine-4-carboxamide (**86**) is depicted below in Scheme 12.



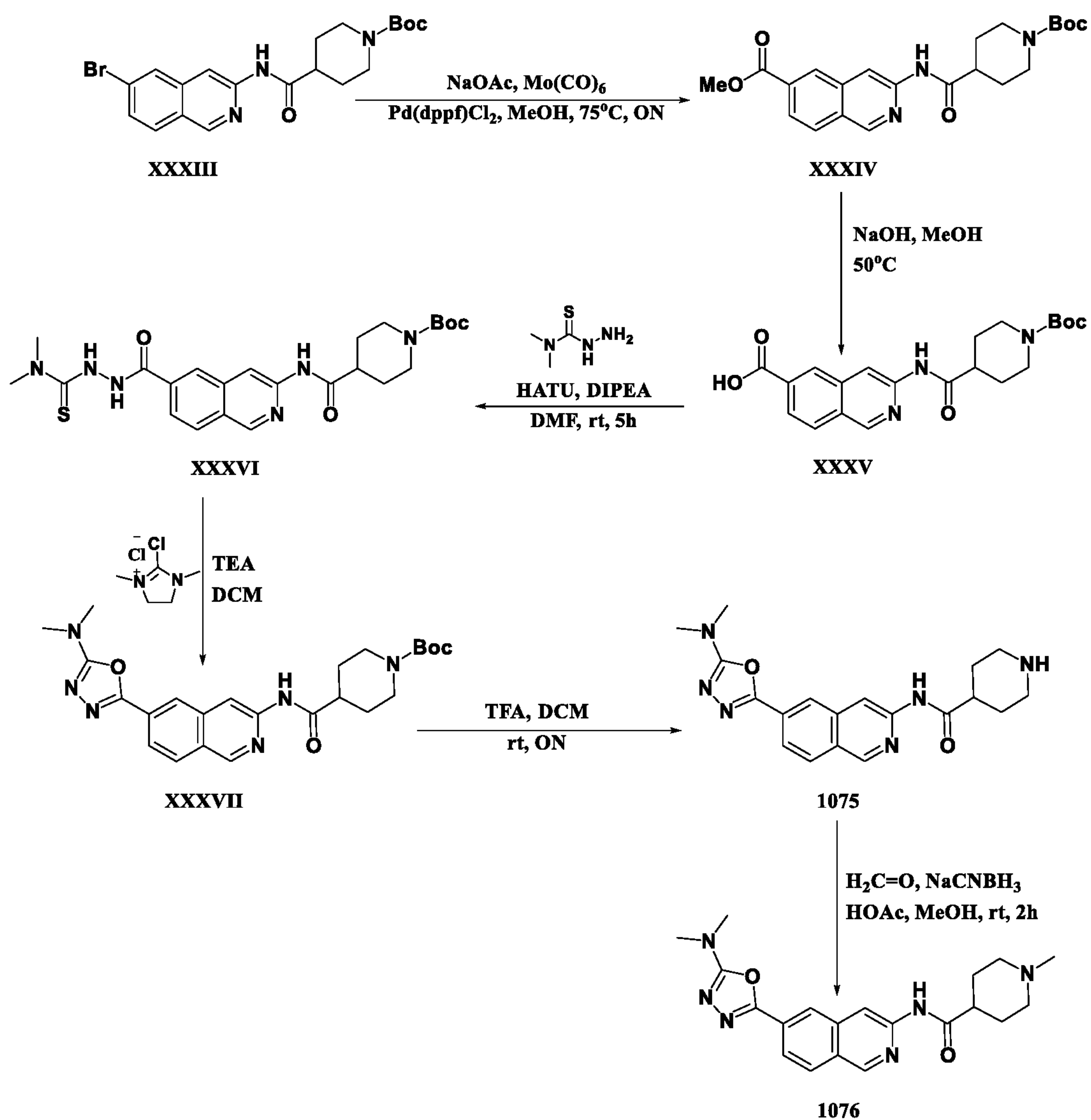
Scheme 12

Step 1

[0598] To a solution of N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide (**72**) (0.095 g, 0.283 mmol) in MeOH (1.5 mL) was added oxetan-3-one (0.027 mL, 0.425 mmol) followed by the addition of HOAc (0.081 mL, 1.416 mmol). The mixture was stirred for 20 min, then, sodium cyanoborohydride (0.027 g, 0.425 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, the residue partitioned between EtOAc/sat. aq. $NaHCO_3$, the organic layer separated, washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 , solvents removed in vacuo and the crude product was purified by ISCO (0→5% $CHCl_3$ /7 N NH_3 in MeOH). The pure fractions were combined, concentrated, the residue suspended in DCM, sonicated and the solids were collected by filtration to obtain N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide (**86**) off-white solid (62.0 mg, 0.158 mmol, 56.0% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.62 - 1.73 (m, 2 H), 1.74 - 1.86 (m, 4 H), 2.52 - 2.60 (m, 1 H), 2.71 - 2.80 (m, 2 H), 3.38 (quin, $J=6.45$ Hz, 1 H), 3.90 (s, 3 H), 4.43 (t, $J=6.17$ Hz, 2 H), 4.53 (t, $J=6.59$ Hz, 2 H), 7.74 (dd, $J=8.51, 1.37$ Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.45 (s, 1 H), 9.02 (s, 1 H), 10.48 (s, 1 H); ESIMS found for $C_{22}H_{25}N_5O_2$ m/z 392.2 (M+1).

Example 3.

[0599] Preparation of N-(6-(5-(Dimethylamino)-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide (**1075**) and N-(6-(5-(dimethylamino)-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide (**1076**) is depicted below in Scheme 13.



Scheme 13

Step 1

[0600] To a mixture of *tert*-butyl 4-[(6-bromo-3-isoquinolyl)carbamoyl]piperidine-1-carboxylate (XXXIII) (1 g, 2.3 mmol), NaOAc (566.6 mg, 6.91 mmol), molybdenumhexacarbonyl (953 mg, 3.45 mmol) and Pd(dppf)Cl₂ (376 mg, 0.46 mmol) in MeOH (20 mL) was heated to 75°C overnight. The reaction mixture was absorbed on silica gel and was purified by column chromatography using (25%→100% EtOAc/hexanes) to obtain methyl 3-[(1-*tert*-butoxycarbonylpiperidine-4-carbonyl)amino]isoquinoline-6-carboxylate (XXXIV) (950 mg, 2.30 mmol, 99.8% yield) as a grey solid. ESIMS found for C₂₂H₂₇N₃O₅ *m/z* 414.2 (M+1).

Step 2

[0601] To a stirred solution of methyl 3-[(1-*tert*-butoxycarbonylpiperidine-4-carbonyl)amino]isoquinoline-6-carboxylate (XXXIV) (950 mg, 2.3 mmol) in MeOH (15 mL) was added 2N aqueous solution of NaOH (2.3 mL, 4.6 mmol) and the mixture was heated to 50°C. The reaction mixture was concentrated, the residue taken up in water and acidified with 1N HCl and the resulting solid was collected by filtration, washed with water and dried under high vacuo to obtain 3-[(1-*tert*-butoxycarbonylpiperidine-4-carbonyl)amino]isoquinoline-6-carboxylic acid (XXXV) (900 mg, 2.25 mmol, 98.1% yield) as a brown solid. ESIMS found for C₂₁H₂₅N₃O₅ *m/z* 400.2 (M+1).

Step 3

[0602] To a mixture of 3-[(1-*tert*-butoxycarbonylpiperidine-4-carbonyl)amino]isoquinoline-6-carboxylic acid (XXXV) (0.5 g, 1.26 mmol), HATU (0.48 g, 1.26 mmol) and N-ethyl-N-isopropyl-propan-2-amine (0.66 mL, 3.77 mmol) in DMF (10 mL) was stirred for 10 min. Then 3-amino-1,1-dimethylthiourea (0.18 g, 1.51 mmol) was added and the mixture was stirred at room temperature for 5h. The reaction mixture was concentrated, the residue taken in CHCl₃, washed with sat. NaHCO₃, H₂O and brine. The organic layer was separated and dried (MgSO₄) before concentration to dryness to obtain *tert*-butyl 4-[[6-[(dimethylcarbamothioylamino)carbamoyl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (XXXVI) (600 mg, 1.20 mmol, 95.4% yield) as a brown solid which was used for next step without purification. ESIMS found for C₂₄H₃₂N₆O₄S *m/z* 501.2 (M+1).

Step 4

[0603] To a mixture of *tert*-butyl 4-[[6-[(dimethylcarbamothioylamino)carbamoyl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (XXXVI) (600 mg, 1.2 mmol), 2-chloro-1,3-dimethyl-4,5-dihydroimidazol-1-ium chloride (405.2 mg, 2.4 mmol) and N,N-diethylethanamine (0.5 mL, 3.6 mmol) in DCM (10 mL) was stirred overnight at room temperature. Reaction mixture was concentrated and the residue was purified by column chromatography (0→10% 7N-NH₃-MeOH/CHCl₃) to obtain *tert*-butyl 4-[[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (XXXVII) (60 mg, 0.129 mmol, 10.7% yield) as a brown solid. ESIMS found for C₂₄H₃₀N₆O₄ *m/z* 467.2 (M+1).

Step 5

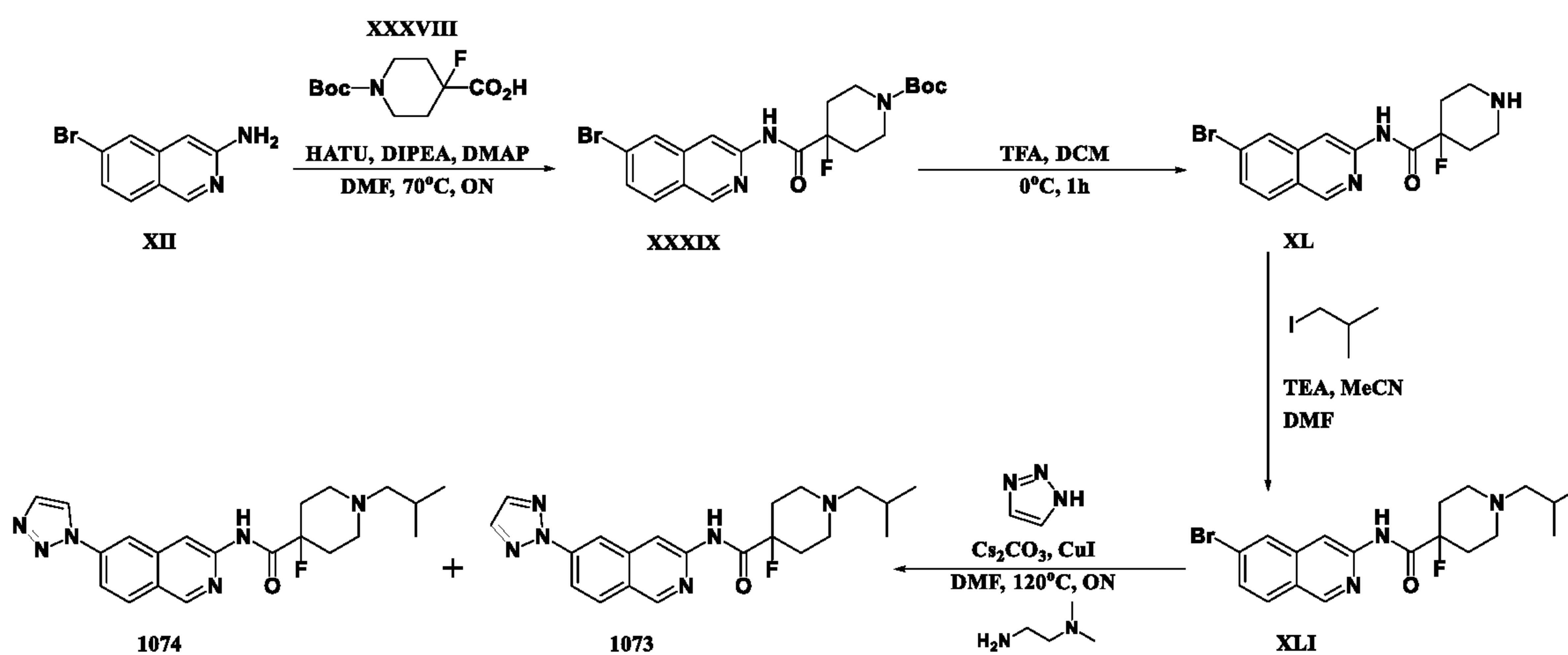
[0604] To a stirred solution of *tert*-butyl 4-[[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (**XXXVII**) (60 mg, 0.130 mmol) in DCM (2 mL) was added TFA (0.2 mL, 2.57 mmol) and the mixture was stirred at room temperature for 5h. Reaction mixture was concentrated and the residue was absorbed on silica gel, purified by flash column chromatography (0-10% 7N-NH₃-MeOH/CHCl₃) to obtain N-[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]piperidine-4-carboxamide (**1075**) (32 mg, 0.087 mmol, 67.9% yield) as a white solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.54 (2 H, qd, *J*=12.17, 4.12 Hz), 1.71 (2 H, br d, *J*=10.43 Hz), 2.44 - 2.49 (2 H, m), 2.65 (1 H, tt, *J*=11.49, 3.60 Hz), 2.98 (2 H, br d, *J*=12.08 Hz), 3.13 (6 H, s), 7.96 (1 H, dd, *J*=8.51, 1.65 Hz), 8.15 (1 H, d, *J*=8.51 Hz), 8.35 (1 H, s), 8.59 (1 H, s), 9.17 (1 H, s), 10.55 (1 H, s); ESIMS found for C₁₉H₂₂N₆O₂ *m/z* 367.2 (M+1).

Step 6

[0605] To a mixture of N-[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]piperidine-4-carboxamide (**1075**) (27 mg, 0.070 mmol), NaBH₃CN (14.03 mg, 0.070 mmol) and catalytic HOAc in MeOH (2 mL) was stirred for 30 min, formaldehyde (2.21 mg, 0.070 mmol) was added and the stirring was continued 2h. The reaction mixture was quenched with minimum amount of aq. saturated NH₄Cl, concentrated on under vacuum and the residue was adsorbed on silica gel, purified by chromatography (0→20% 7N.NH₃-MeOH/CHCl₃) to obtain N-[6-[5-(dimethylamino)-1,3,4-oxadiazol-2-yl]-3-isoquinolyl]-1-methyl-piperidine-4-carboxamide (**1076**) (25 mg, 0.066 mmol, 89.2% yield) as a white solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.74 (2 H, m), 1.74 - 1.81 (2 H, m), 1.87 (2 H, td, *J*=11.66, 2.20 Hz), 2.16 (3 H, s), 2.51 - 2.56 (1 H, m), 2.77 - 2.85 (2 H, m), 3.13 (6 H, s), 7.96 (1 H, dd, *J*=8.51, 1.65 Hz), 8.15 (1 H, d, *J*=8.51 Hz), 8.35 (1 H, s), 8.59 (1 H, s), 9.18 (1 H, s), 10.61 (1 H, s); ESIMS found for C₂₀H₂₄N₆O₂ *m/z* 381.2 (M+1).

Example 4.

[0606] Preparation of N-(6-(1H-1,2,3-triazol-1-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (**1074**) and N-(6-(2H-1,2,3-triazol-2-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (**1075**) is depicted below in Scheme 14.



Scheme 14

Step 1

[0607] To a mixture of 1-*tert*-butoxycarbonyl-4-fluoropiperidine-4-carboxylic acid (XXXVIII) (1.07 mL, 13.99 mmol), HATU (7.09 g, 18.65 mmol) and DIPEA (4.87 mL, 27.97 mmol) in DMF (40 mL) was stirred for 10 min. Then, 6-bromoisoquinolin-3-amine (XII) (2.08 g, 9.32 mmol) and DMAP (0.23 g, 1.86 mmol) was added then the mixture was heated to 80°C overnight. The reaction mixture was concentrated, the residue partitioned between EtOAc/sat.NaHCO₃, organic layer separated, washed with water and brine. The organics were then separated and dried (MgSO₄) before concentration to dryness. The crude was then purified by flash column chromatography (0→40% EtOAc/hexanes). The desired fractions were concentrated to dryness en vacuo and recrystallized with hexanes to obtain *tert*-butyl 4-[(6-bromo-3-isoquinolyl)carbamoyl]-4-fluoropiperidine-1-carboxylate (XXXIX) (2.94 g, 6.50 mmol, 69.7% yield) as a white solid. ESIMS found for C₂₀H₂₃BrFN₃O₃ *m/z* 452.1 (⁷⁹BrM+1).

Step 2

[0608] To a suspension of *tert*-butyl 4-[(6-bromo-3-isoquinolyl)carbamoyl]-4-fluoropiperidine-1-carboxylate (XXXIX) (1.92 g, 4.24 mmol) in DCM (8 mL) was added TFA (8 mL, 103.84 mmol) at 0°C and the mixture was stirred for 1 h. The solvents were concentrated, triturated with CHCl₃ (3X) and the resulting solids were dried under high vacuo to obtain N-(6-bromo-3-isoquinolyl)-4-fluoropiperidine-4-carboxamide (XL) (1.979 g, 4.24 mmol, 100% yield) as an off-white solid which was used for next step without further purification. ESIMS found for C₁₅H₁₅BrFN₃O *m/z* 352.0 (⁷⁹BrM+1).

Step 3

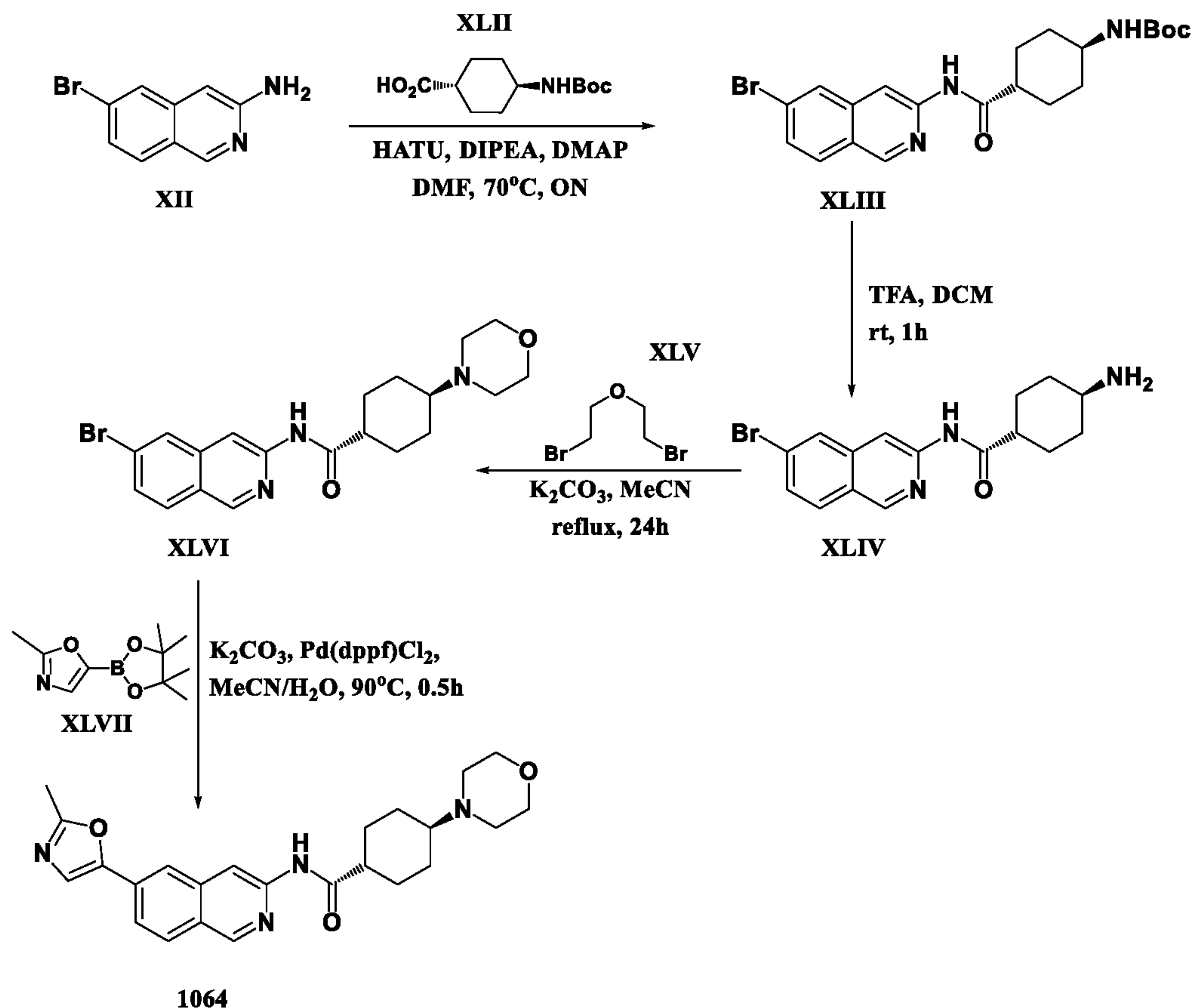
[0609] To a suspension of N-(6-bromo-3-isoquinolyl)-4-fluoro-piperidine-4-carboxamide (**XL**) (1.98 g, 4.24 mmol) in MeCN (20 mL) was added 1-iodo-2-methyl-propane (0.98 mL, 8.48 mmol) and the mixture was stirred for 30 min. The solvents were concentrated, treated with 7N NH₃/MeOH, absorbed on silica gel and purified by column chromatography (0→30% CHCl₃/10% 7N NH₃ MeOH) to obtain N-(6-bromo-3-isoquinolyl)-4-fluoro-1-isobutyl-piperidine-4-carboxamide (**XLI**) (1.4 g, 3.43 mmol, 80.9% yield) as a beige solid. ESIMS found for C₁₉H₂₃BrFN₃O *m/z* 408.1 (⁷⁹BrM+1).

Step 4

[0610] To a mixture of N-(6-bromo-3-isoquinolyl)-4-fluoro-1-isobutyl-piperidine-4-carboxamide (**XLI**) (150 mg, 0.370 mmol), 1H-triazole (0.04 mL, 0.730 mmol), Cs₂CO₃ (239 mg, 0.730 mmol), N,N-dimethylethylenediamine (6.48 mg, 0.070 mmol) and CuI (0.04 mL, 0.040 mmol) in DMF (2 mL) was purged with N₂ gas for 10 min. The mixture was then heated to 120°C overnight. The reaction mixture was filtered through Celite and to the filtrates, water was added and extracted with EtOAc. The organics were separated, washed with brine, dried over anhydrous Na₂SO₄, and evaporated under vacuo. The crude products were purified by RP-HPLC. The pure fractions were combined and dried under vacuum to obtain N-(6-(2H-1,2,3-triazol-2-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (**1073**) (3.5 mg, 0.008 mmol, 2.2% yield) as an off-white solid; ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.88 (6 H, d, *J*=6.59 Hz), 1.79 (1 H, dq_{uin}, *J*=13.55, 6.84, 6.84, 6.84, 6.84 Hz), 1.92 - 2.02 (2 H, m), 2.05 - 2.21 (6 H, m), 2.75 - 2.82 (2 H, m), 8.25 (2 H, s), 8.26 - 8.29 (1 H, m), 8.29 - 8.33 (1 H, m), 8.52 (1 H, d, *J*=1.37 Hz), 8.56 (1 H, s), 9.25 (1 H, s), 10.02 (1 H, br d, *J*=3.29 Hz); ESIMS found for C₂₁H₂₅FN₆O *m/z* 397.0 (M+1) and N-(6-(1H-1,2,3-triazol-1-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide (**1074**) (2 mg, 0.005 mmol, 1.2% yield) as an off-white solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.88 (6 H, d, *J*=6.59 Hz), 1.79 (1 H, dq_{uin}, *J*=13.46, 6.79, 6.79, 6.79, 6.79 Hz), 1.92 - 2.02 (2 H, m), 2.06 - 2.12 (2 H, m), 2.12 - 2.21 (4 H, m), 2.73 - 2.83 (2 H, m), 8.06 (1 H, d, *J*=1.10 Hz), 8.19 (1 H, dd, *J*=8.92, 2.06 Hz), 8.34 (1 H, d, *J*=9.06 Hz), 8.53 (1 H, d, *J*=1.92 Hz), 8.58 (1 H, s), 9.03 (1 H, d, *J*=1.10 Hz), 9.28 (1 H, s), 10.07 (1 H, br d, *J*=3.84 Hz); ESIMS found for C₂₁H₂₅FN₆O *m/z* 397.0 (M+1).

Example 5.

[0611] Preparation of *trans*-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide (**1064**) is depicted below in Scheme 15.



Scheme 15

Step 1

[0612] To a mixture of *trans*-4-(*tert*-butoxycarbonylamino)cyclohexanecarboxylic acid (**XLII**) (1.15 mL, 56.04 mmol), HATU (21.31 g, 56.04 mmol), 6-bromoisoquinolin-3-amine (**XII**) (10. g, 44.83 mmol), and DMAP (1.1 g, 8.97 mmol) in DMF (100 mL) was added DIPEA (23.4 mL, 134.49 mmol). The mixture was stirred at 70°C overnight. The reaction mixture was cooled before water (800 mL) was added and stirred for ~2h. The solid was collected by filtration and sequentially washed with aq. sat. NH_4Cl , water and aq. sat. NaHCO_3 . The solid was dried under high vacuo to obtain *tert*-butyl *trans*-N-[4-[(6-bromo-3-isoquinolyl)carbamoyl]cyclohexyl] carbamate (**XLIII**) (17.87 g, 39.86 mmol, 88.9% yield) as a grey solid which was used for next step without further purification. ESIMS found for $\text{C}_{21}\text{H}_{26}\text{BrN}_3\text{O}_3$ m/z 448.1 ($^{79}\text{BrM}+1$).

Step 2

[0613] To a stirred solution of *tert*-butyl *trans*-N-[4-[(6-bromo-3-isoquinolyl)carbamoyl]cyclohexyl]carbamate (**XLIII**) (5.5 g, 11.15 mmol) in DCM (20 mL) was added TFA (10 mL, 129.8 mmol). The mixture was stirred for 1 h at 25°C. The solvent was concentrated and the residue was treated with 7N NH₃/MeOH. The crude product was purified by column chromatography (25→100% CHCl₃/10% 7N NH₃ MeOH in CHCl₃). The pure fractions were combined, concentrated, the residue suspended in EtOAc, sonicated and the solid was collected by filtration, washed with diethyl ether and dried under high vacuo to obtain *trans*-4-amino-N-(6-bromo-3-isoquinolyl)cyclohexanecarboxamide (**XLIV**) (3 g, 8.61 mmol, 77.2% yield) as a beige solid. ESIMS found for C₁₆H₁₈BrN₃O *m/z* 348.1 (⁷⁹BrM+1).

Step 3

[0614] To a mixture of *trans*-4-amino-N-(6-bromo-3-isoquinolyl)cyclohexanecarboxamide (**XLIV**) (550 mg, 1.58 mmol), 1-bromo-2-(2-bromoethoxy)ethane (**XLV**) (439.53 mg, 1.9 mmol) and K₂CO₃ (654.8 mg, 4.74 mmol) in MeCN (8 mL) was heated to reflux for 24 h. The reaction mixture was concentrated and the residue was taken into DCM, washed with water and brine. The organic layer was then separated and dried (MgSO₄) before concentration to dryness. The crude was dissolved in EtOAc, sonicated and the solid was collected by filtration and dried under high vacuo to obtain the desired product *trans*-N-(6-bromo-3-isoquinolyl)-4-morpholino-cyclohexanecarboxamide (**XLVI**) (320 mg, 0.765 mmol, 48.4% yield) as an off-white solid. ESIMS found for C₂₀H₂₄BrN₃O₂ *m/z* 418.1 (⁷⁹BrM+1).

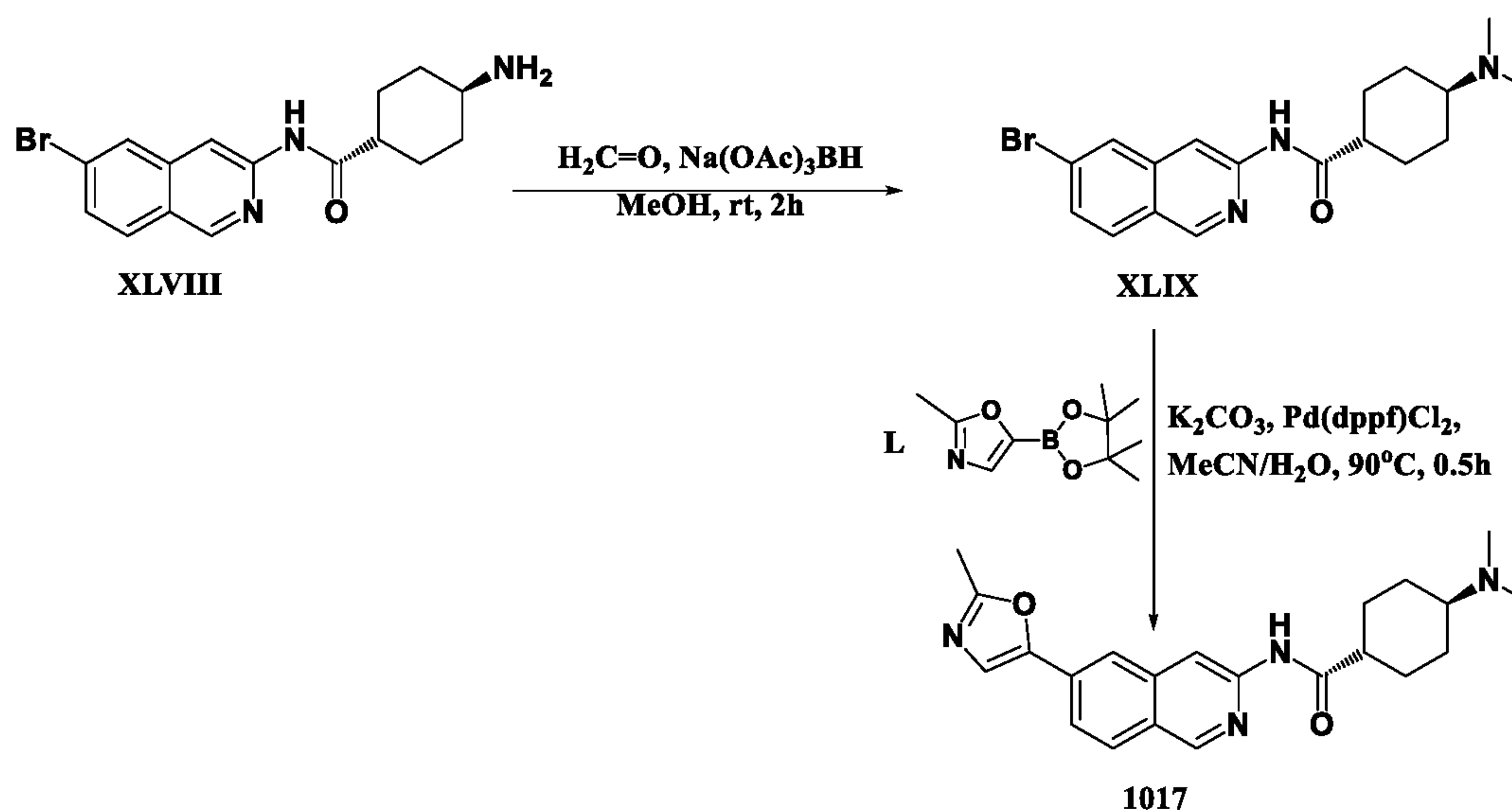
Step 4

[0615] To a mixture of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (**XLVII**) (62.5 mg, 0.300 mmol), Pd(dppf)Cl₂-CH₂Cl₂ adduct (9.76 mg, 0.010 mmol) and *trans*-N-(6-bromo-3-isoquinolyl)-4-morpholino-cyclohexanecarboxamide (**XLVI**) (100 mg, 0.240 mmol) in MeCN (1 mL) was added a 2 M aqueous solution of K₂CO₃ (0.3 mL, 0.600 mmol). N₂ gas was bubbled into the mixture for 10 min and then the solution was heated to 90°C for 0.5 h. The organic layer was carefully separated, absorbed on silica gel and purified by flash column chromatography (0→40% CHCl₃/10% 7N NH₃ in MeOH) followed by preparative TLC. The purified product was suspended in EtOAc, sonicated and the solid was collected by filtration and dried under high vacuo to obtain *trans*-N-[6-(2-methyloxazol-5-yl)-3-isoquinolyl]-4-morpholino-cyclohexanecarboxamide (**1064**) (18 mg, 0.043 mmol, 17.9% yield) as an off-white solid. ¹H NMR

(499 MHz, DMSO- d_6) δ ppm 1.16 - 1.27 (2 H, m), 1.42 - 1.56 (2 H, m), 1.91 (4 H, br t, $J=11.80$ Hz), 2.17 - 2.27 (1 H, m), 2.44 - 2.49 (4 H, m), 2.53 (3 H, s), 3.26 - 3.30 (1 H, m), 3.54 - 3.58 (4 H, m), 7.78 (1 H, s), 7.79 - 7.83 (1 H, m), 8.09 (2 H, dd, $J=4.80$, 3.98 Hz), 8.50 (1 H, s), 9.10 (1 H, s), 10.51 (1 H, s); ESIMS found for $C_{24}H_{28}N_4O_3$ m/z 421.2 (M+1).

Example 6.

[0616] Preparation of *trans*-4-(dimethylamino)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide (**1017**) is depicted below in Scheme 16.



Scheme 16

Step 1

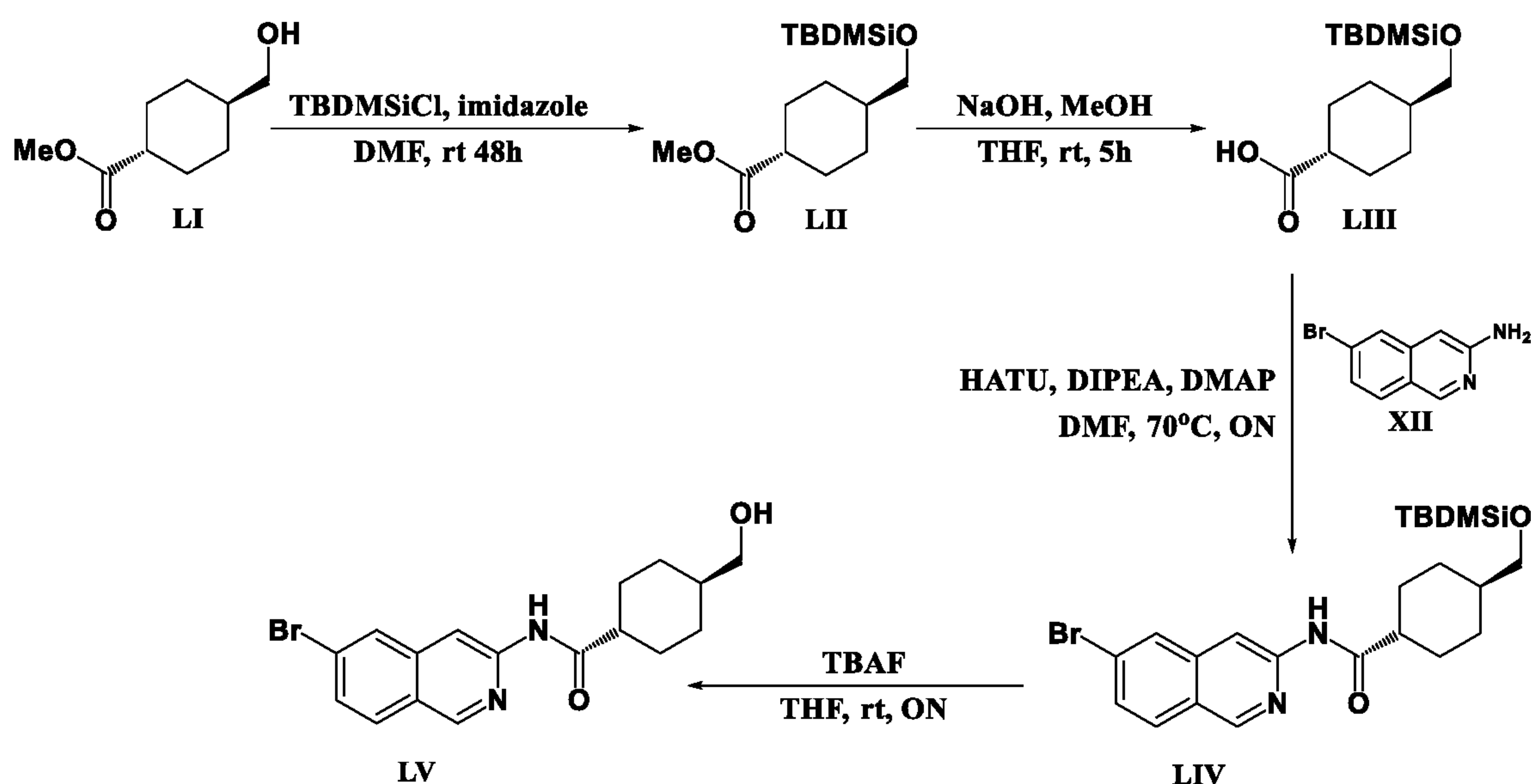
[0617] To a stirred solution of *trans*-4-amino-N-(6-bromo-3-isoquinolyl)cyclohexanecarboxamide (**XLVIII**) (3 g, 8.61 mmol) in MeOH (50 mL) was added formaldehyde (8.64 mL, 42.93 mmol). After 15 min, $\text{Na(OAc)}_3\text{BH}$ (9.1 g, 42.93 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvents were removed in vacuo, the residue taken in water, basified with 1N NaOH solution and extracted with CHCl_3 . The organic layer was separated, washed with water and brine, and dried over anhydrous Na_2SO_4 . The solvent was concentrated and the crude was suspended in diethyl ether, sonicated and the solid was collected by filtration and dried under high vacuo to obtain the desired product *trans*-N-(6-bromo-3-isoquinolyl)-4-(dimethylamino)cyclohexanecarboxamide (**XLIX**) (2.28 g, 6.06 mmol, 70.3% yield) as a beige solid. ESIMS found for $C_{18}H_{22}\text{BrN}_3\text{O}$ m/z 376.1 ($^{79}\text{BrM}+1$).

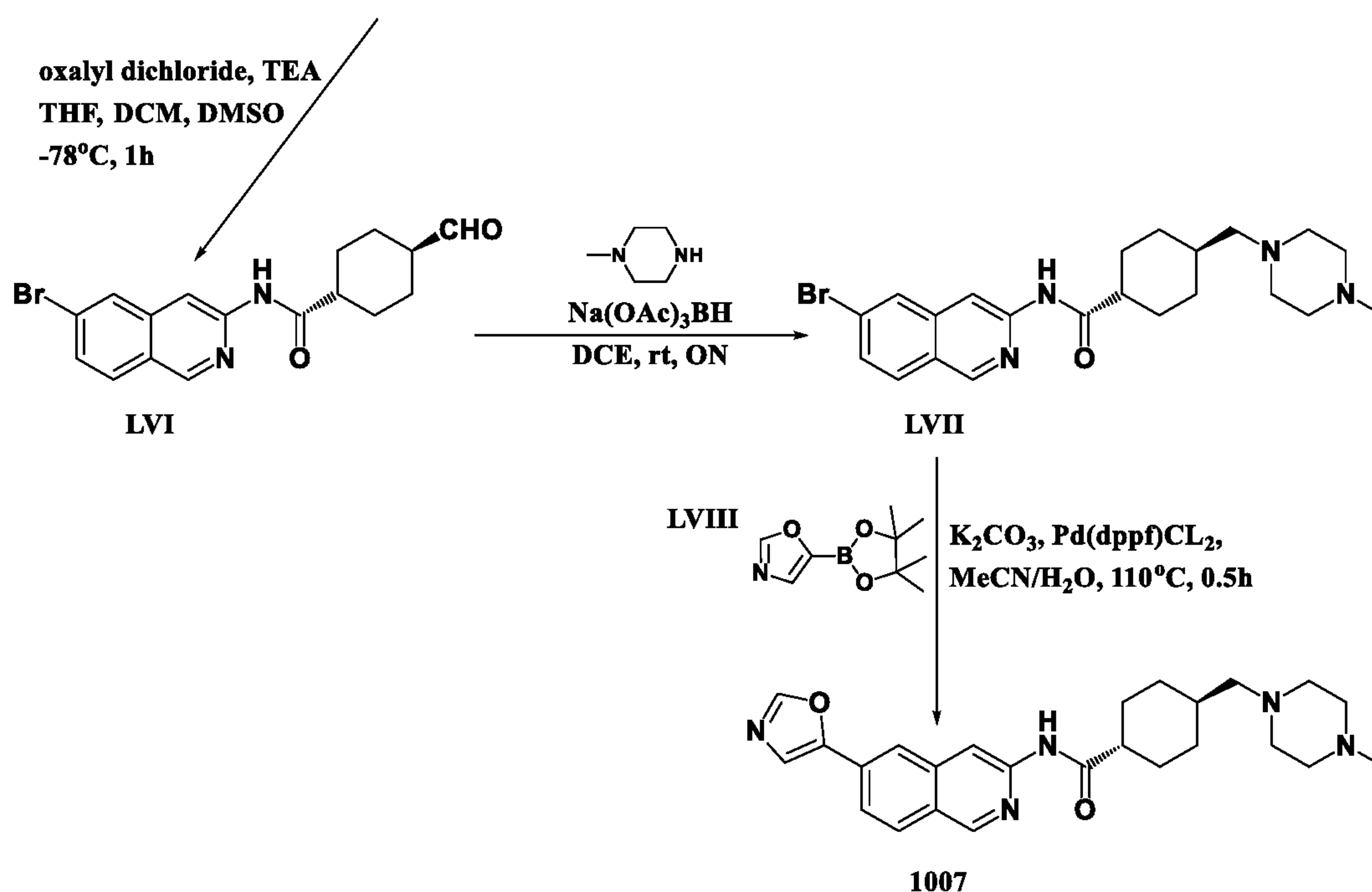
Step 2

[0618] To a mixture of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (L) (138.9 mg, 0.660 mmol), Pd(dppf)Cl₂-CH₂Cl₂ adduct (43.4 mg, 0.050 mmol), a 2 M aqueous solution of K₂CO₃ (0.66 mL, 1.33 mmol) and *trans*-N-(6-bromo-3-isoquinolyl)-4-(dimethylamino)cyclohexanecarboxamide (XLIX) (200 mg, 0.530 mmol) in MeCN (2.5 mL). N₂ gas was bubbled into the mixture for 10 min and then the solution was heated to 110°C for 30 min in a microwave. The organic layer was carefully separated, absorbed on silica gel and purified by column chromatography (0→50% CHCl₃/10 %7N NH₃ MeOH in CHCl₃). The pure fractions were combined, concentrated and the product was suspended in EtOAc, sonicated and the solid was collected by filtration, washed with diethyl ether and dried under high vacuo to obtain *trans*-4-(dimethylamino)-N-[6-(2-methyloxazol-5-yl)-3-isoquinolyl]cyclohexanecarboxamide (1017) (92 mg, 0.243 mmol, 45.7% yield) as a beige solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.14 - 1.23 (2 H, m), 1.43 - 1.54 (2 H, m), 1.83 - 1.95 (4 H, m), 2.10 - 2.16 (1 H, m), 2.18 (6 H, s), 2.44 - 2.49 (1 H, m), 2.53 (3 H, s), 7.78 (1 H, s), 7.79 - 7.84 (1 H, m), 8.06 - 8.13 (2 H, m), 8.50 (1 H, s), 9.10 (1 H, s), 10.49 (1 H, s); ESIMS found for C₂₂H₂₆N₄O₂ *m/z* 379.2 (M+1).

Example 7.

[0619] Preparation of *trans*-4-((4-methylpiperazin-1-yl)methyl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide (1007) is depicted below in Scheme 17.





Scheme 17

Step 1

[0620] To a mixture of methyl *trans*-4-(hydroxymethyl)cyclohexanecarboxylate (**LI**) (5.0 g, 29.03 mmol) imidazole (3.95 g, 58.07 mmol) and *tert*-butyl-chloro-dimethyl-silane (4.81 g, 31.94 mmol) in DMF (50 mL) was stirred at room temperature for 48 h. The solvents were concentrated to 1/2 volume, water (200 mL) was added and extracted with MTBE. The organic layer was separated and washed with 1 N HCl, H₂O and brine. The organics were dried over anhydrous Na₂SO₄ and the solvent was concentrated to dryness to obtain methyl *trans*-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxylate (**LII**) (8.09 g, 28.24 mmol, 97.3% yield) as a colorless oil. ESIMS found for C₁₅H₃₀O₃Si *m/z* 287.1 (M+1).

Step 2

[0621] To a stirred solution of methyl *trans*-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxylate (**LII**) (8.05 g, 28.1 mmol) in a mixture of THF (20mL) and MeOH (20mL) was added 2 M solution of NaOH (28.1 mL, 56.2 mmol). The mixture was stirred at room temperature for 5 h. The solvent was reduced to 1/3 volume, acidified with 1 N HCl and the resulting solid was filtered, washed with water and dried under high vacuo to obtain 5 grams of the desired product. The filtrates were extracted with EtOAc (2x), washed with water, brine, dried over anhydrous Na₂SO₄, concentrated, and dried in vacuo to obtain another 1.1 g of *trans*-4-[[*tert*-

butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxylic acid (**LIII**) (Total 6.1 g, 22.39 mmol, 79.7% yield) as a white solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.01 (6 H, s), 0.83 - 0.87 (8 H, m), 0.88 - 0.96 (2 H, m), 1.19 - 1.32 (2 H, m), 1.32 - 1.43 (1 H, m), 1.74 (2 H, br dd, *J*=13.31, 3.16 Hz), 1.84 - 1.94 (2 H, m), 2.09 (1 H, tt, *J*=12.18, 3.46 Hz), 3.38 (2 H, d, *J*=6.31 Hz), 11.98 (1 H, br s); ESIMS found for C₁₄H₂₈O₃Si *m/z* 273.1 (*M*+1).

Step 3

[0622] A mixture of DIPEA (5.86 mL, 33.62 mmol), DMAP (0.27 g, 2.24 mmol) and HATU (5.11 g, 13.45 mmol) in DMF (30mL) was stirred for 10 min. 6-Bromoisquinolin-3-amine (**XII**) (2.5 g, 11.21 mmol) was then added followed by the addition of *trans*-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxylic acid (**LIII**) (3.66 g, 13.45 mmol). The mixture was heated to 70°C overnight. An additional 0.5 equiv. of HATU were added and the mixture was continued for additional 6 h. The solvent was concentrated, the residue taken up in EtOAc, washed with sat. NaHCO₃ and brine. The organic layer was then concentrated and the crude product was purified by column chromatography (0→30% EtOAc/hexanes). The pure fractions were combine and concentrated to obtain *trans*-N-(6-bromo-3-isoquinolyl)-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxamide (**LIV**) (2.25 g, 4.71 mmol, 42.0% yield) as a crystalline off-white solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.03 (6 H, s), 0.87 (9 H, s), 0.98 (2 H, qd, *J*=12.72, 3.29 Hz), 1.38 - 1.51 (3 H, m), 1.73 - 1.82 (2 H, m), 1.85 - 1.92 (2 H, m), 2.46 - 2.55 (1 H, m), 3.41 (2 H, d, *J*=6.04 Hz), 7.62 (1 H, dd, *J*=8.64, 1.78 Hz), 7.99 (1 H, d, *J*=8.78 Hz), 8.16 (1 H, d, *J*=1.65 Hz), 8.44 (1 H, s), 9.13 (1 H, s), 10.53 (1 H, s); ESIMS found for C₂₃H₃₃BrN₂O₂Si *m/z* 477.2 (⁷⁹Br*M*+1).

Step 4

[0623] To a stirred solution of *trans*-N-(6-bromo-3-isoquinolyl)-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]cyclohexanecarboxamide (**LIV**) (2.24 g, 4.69 mmol) in THF (10 mL) was added 1 M solution of TBAF (7.04 mL, 7.04 mmol) in THF. The mixture was stirred at room temperature overnight (monitored by LCMS). Water was added to the reaction mixture and extracted with EtOAc (2x). The organic layer was separated, washed with brine, and dried over anhydrous Na₂SO₄. The solvent was concentrated and the crude product was suspended in EtOAc, sonicated and the solid was collected by filtration and dried under high vacuo to obtain *trans*-N-(6-bromo-3-isoquinolyl)-4-(hydroxymethyl)cyclohexanecarboxamide (**LV**) (1.437 g, 3.96 mmol, 84.3% yield) as a light beige solid. ESIMS found for C₁₇H₁₉BrN₂O₂ *m/z* 363.1 (⁷⁹Br*M*+1).

Step 5

[0624] To a stirred solution of DMSO (0.59 mL, 8.26 mmol) in DCM (3 mL) at -78°C was added dropwise under Ar, oxalyl dichloride (0.36 mL, 4.13 mmol) in DCM (1 mL). After 15 min, *trans*-N-(6-bromo-3-isoquinolyl)-4-(hydroxymethyl)cyclohexanecarboxamide (LV) (1.0 g, 2.75 mmol) in a mixture of THF (12 mL) and DMSO (0.5 mL) was added and the mixture was stirred at -78°C for 1 h. Then, TEA (1.15 mL, 8.26 mmol) was added and the mixture was continued to stir for 1 h and warmed to room temperature for 1 h. The reaction mixture was diluted with H₂O and DCM and the organic layer separated, washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo to obtain *trans*-4-formyl-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]cyclohexanecarboxamide (LVI) (215 mg, 0.593 mmol, 108.1% yield) as a white solid which was used for next step without further purification. ESIMS found for C₁₇H₁₇BrN₂O₂ *m/z* 361.05 (⁷⁹BrM+1).

Step 6

[0625] To a mixture of 1-methylpiperazine (0.23 mL, 2.03 mmol), *trans*-N-(6-bromo-3-isoquinolyl)-4-formyl-cyclohexanecarboxamide (LVI) (490 mg, 1.36 mmol) and in DCE (6 mL) was stirred for 20 min. Then, Na(OAc)₃BH (431.2 mg, 2.03 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, washed with sat. NaHCO₃, H₂O and brine. The organic layer was then separated and dried (MgSO₄) before concentration to dryness to obtain *trans*-N-(6-bromo-3-isoquinolyl)-4-[(4-methylpiperazin-1-yl)methyl]cyclohexanecarboxamide (LVII) (610 mg, 1.37 mmol, 100% yield) as a beige solid. ESIMS found for C₂₂H₂₉BrN₄O *m/z* 445.1 (⁷⁹BrM+1).

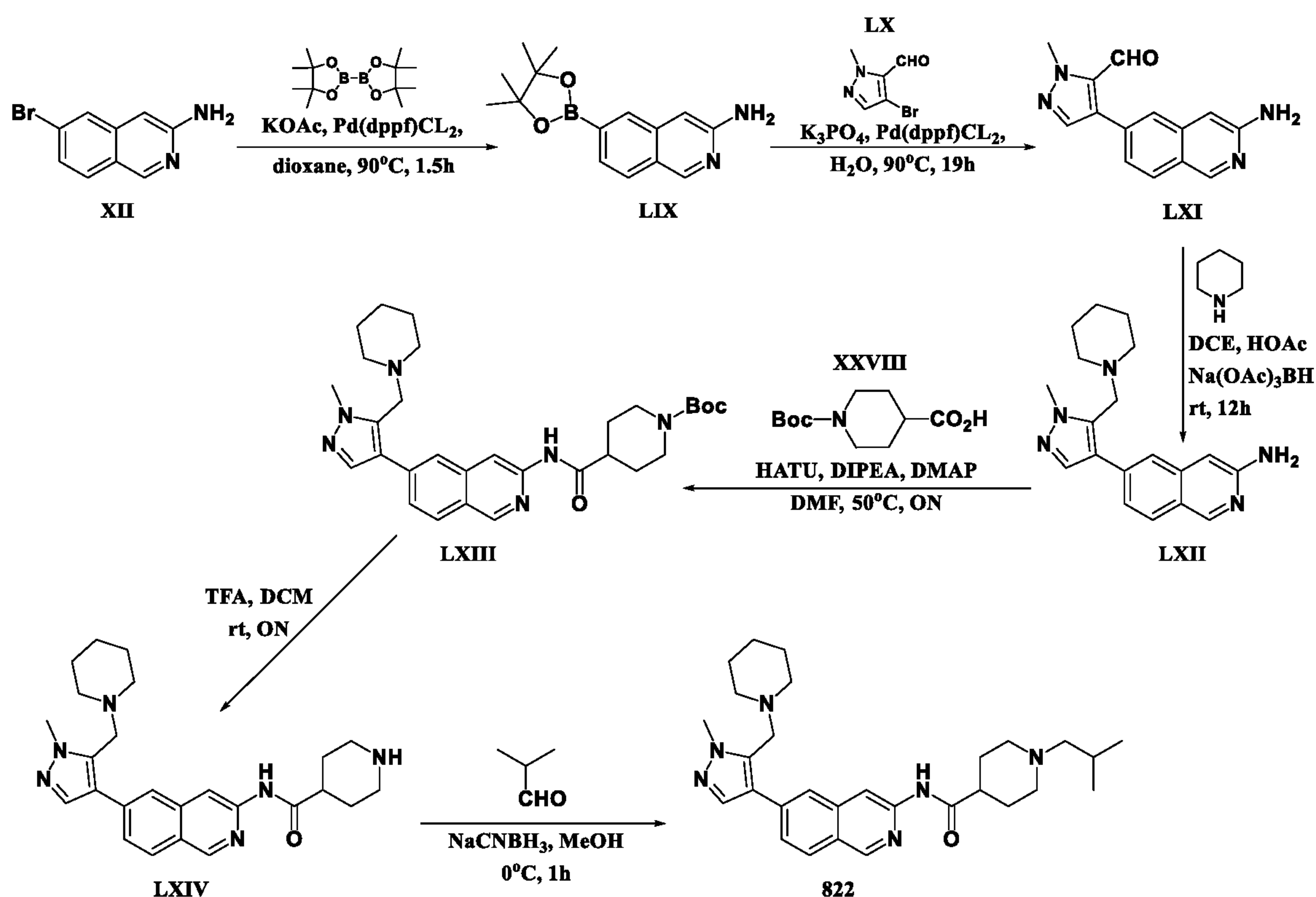
Step 7

[0626] To a mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (LVIII) (54.7 mg, 0.280 mmol), Pd(dppf)Cl₂-CH₂Cl₂ adduct (18.3 mg, 0.020 mmol), and *trans*-N-(6-bromo-3-isoquinolyl)-4-[(4-methylpiperazin-1-yl)methyl]cyclohexanecarboxamide (LVII) (100 mg, 0.220 mmol) was taken in MeCN (1 mL) and was added a 2 M aqueous solution of K₂CO₃ (0.28 mL, 0.560 mmol). N₂ gas was bubbled into the mixture for 10 min and then was heated to 110°C for 0.5 h. The organic layer was separated, absorbed on silica gel and was purified by column chromatography (10→80% CHCl₃/10%7N NH₃ MeOH in CHCl₃). The pure fractions were combined, concentrated, the residue suspended in a mixture EtOAc/diethyl ether, sonicated

and the resulting solid was collected by filtration and dried under vacuo to obtain *trans*-4-[(4-methylpiperazin-1-yl)methyl]-N-(6-oxazol-5-yl-3-isoquinolyl)cyclohexanecarboxamide (**1007**) (25 mg, 0.058 mmol, 25.7% yield) as a light brown solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.83 - 0.96 (2 H, m), 1.41 - 1.54 (3 H, m), 1.79 - 1.92 (4 H, m), 2.08 (2 H, d, *J*=7.41 Hz), 2.14 (3 H, s), 2.31 (8 H, br s), 2.52 - 2.56 (1 H, m), 7.86 (1 H, dd, *J*=8.51, 1.65 Hz), 7.94 (1 H, s), 8.12 (1 H, d, *J*=8.51 Hz), 8.18 (1 H, s), 8.53 (1 H, s), 8.57 (1 H, s), 9.12 (1 H, s), 10.50 (1 H, s); ESIMS found for C₂₅H₃₁N₅O₂ *m/z* 434.2 (M+1).

Example 8.

[0627] Preparation of 1-isobutyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide (**822**) is depicted below in Scheme 18.



Scheme 18

Steps 1-2

[0628] To a mixture of 6-bromoisoquinolin-3-amine (**XII**) (4.0 g, 17.93 mmol), Pd(dppf)Cl₂-CH₂Cl₂ adduct (1.03 g, 1.26 mmol), KOAc (4.39 g, 44.83 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.01 g, 19.72 mmol) in 1,4-dioxane (50 mL) was bubbled with N₂ for 2 min. The reaction mixture was sealed

and heated at 90°C for 1.5 h. The reaction was cooled to room temperature, filtered and washed with EtOAc. The filtrate was concentrated and the residue taken in dioxane (50 mL). To the suspension was added 4-bromo-2-methyl-pyrazole-3-carbaldehyde (**LX**) (3.39 g, 17.93 mmol) followed by K₃PO₄ (9.52 g, 44.83 mmol), Pd(dppf)Cl₂-CH₂Cl₂ adduct (1.03 g, 1.26 mmol) and water (15 mL). The mixture was purged with N₂ for a min, sealed and heated again at 90°C for 19 h. The mixture was cooled to room temperature and concentrated to about 20 mL. The concentrate was diluted with EtOAc and filtered through a pad of Celite. The filtrate was diluted with water and the organic layer separated. The organic layer was washed with brine; dried, filtered and concentrated. The residue was triturated in ether and the resulting solid filtered to afford 4-(3-amino-6-isoquinolyl)-2-methyl-pyrazole-3-carbaldehyde (**LXI**) (4.1 g, 16.2 mmol, 90.6% yield) as a brown solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.01 (6 H, s), 0.86 (9 H, s), 0.88 - 1.00 (2 H, m), 1.23 - 1.35 (2 H, m), 1.35 - 1.46 (1 H, m), 1.69 - 1.79 (2 H, m), 1.85 - 1.95 (2 H, m), 2.21 (1 H, tt, *J*=12.21, 3.57 Hz), 3.38 (2 H, d, *J*=6.31 Hz), 3.57 (3 H, s) ESIMS found for C₁₄H₁₂N₄O *m/z* 252.95 (M+1).

Step 3

[0629] To a mixture of 4-(3-amino-6-isoquinolyl)-2-methyl-pyrazole-3-carbaldehyde (**LXI**) (1.07 g, 4.25 mmol), piperidine (0.84 mL, 8.51 mmol) and catalytic HOAc in DCE (10 mL) was stirred for 30 min. Na(OAc)₃BH (1.8 g, 8.51 mmol) was added and stirring was continued for 12 h at room temperature. The reaction mixture was quenched with minimum amount of aq. saturated ammonium chloride solution, and concentrated under vacuum. The residue was adsorbed on silica gel and purified by chromatography (0→20% 7N NH₃-MeOH/CHCl₃) to obtain 6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]isoquinolin-3-amine (**LXII**) (800 mg, 2.49 mmol, 58.5% yield) as a white solid. ESIMS found for C₁₉H₂₃N₅ *m/z* 322.2 (M+1).

Step 4

[0630] To a mixture of 1-*tert*-butoxycarbonylpiperidine-4-carboxylic acid (**XXVIII**) (1.15mL, 1.63mmol), HATU (703.87 mg, 1.85 mmol) and DIPEA (0.57 mL, 3.27 mmol) in DMF (5mL) was stirred for 10 min. To this mixture was added 6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]isoquinolin-3-amine (**LXII**) (350 mg, 1.09 mmol) and DMAP (26.61 mg, 0.220 mmol) and the mixture was stirred at 50°C overnight. The solvent was concentrated and the residue was taken up in EtOAc, washed with sat. NaHCO₃, water and brine. The organic layer was then separated and dried (MgSO₄) before concentrating to dryness. The crude product was purified by column chromatography (25%→100% EtOAc/hexanes). The pure fractions were combined,

concentrated, the residue triturated with diethyl ether, sonicated and the solid were collected by filtration and dried under high vacuo to obtain *tert*-butyl 4-[[6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (**LXIII**) (550 mg, 1.03 mmol, 94.8% yield) as a dark beige solid. ESIMS found for $C_{30}H_{40}N_6O_3$ m/z 533.3 (M+1).

Step 5

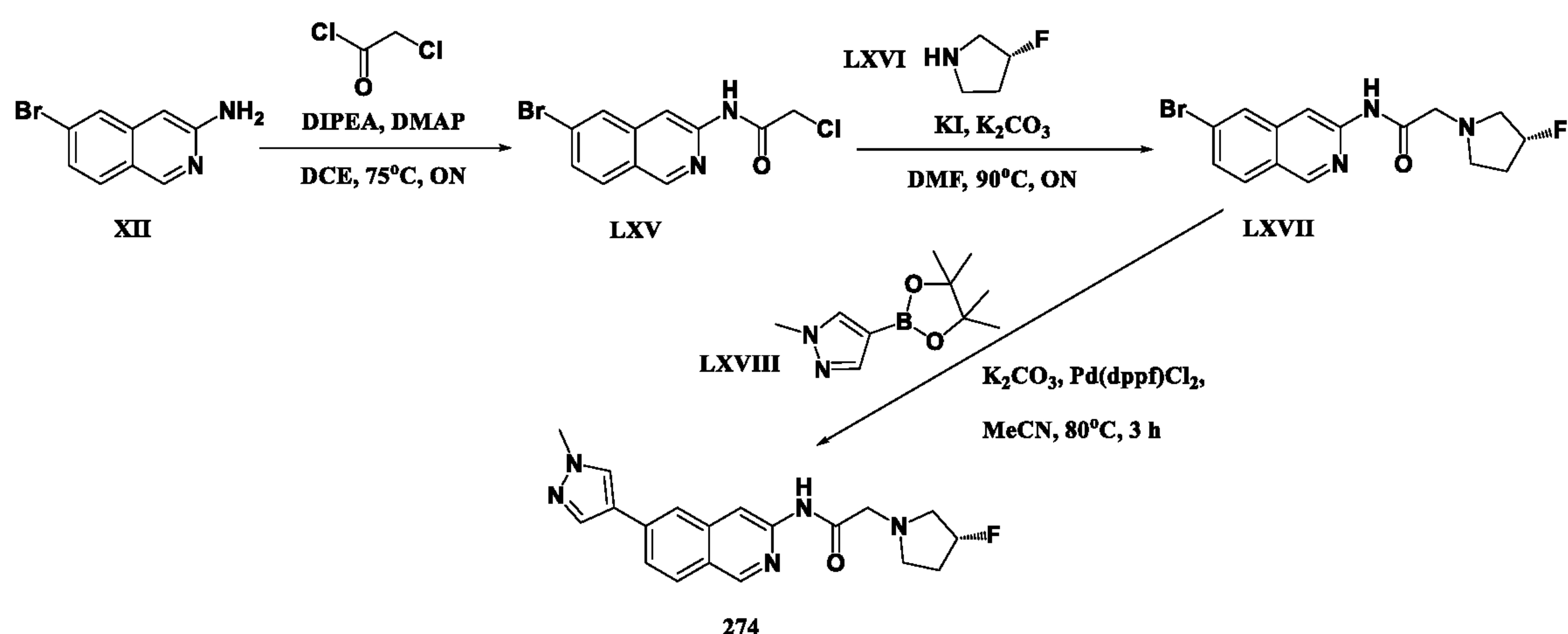
[0631] To a stirred solution of *tert*-butyl 4-[[6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]-3-isoquinolyl]carbamoyl]piperidine-1-carboxylate (**LXIII**) (300 mg, 0.560 mmol) in DCM (5 mL) was added TFA (1.23 mL, 15.91 mmol). The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was adsorbed on silica gel, purified by column chromatography (0-10% 7N.NH₄-MeOH/CHCl₃), pure fractions were concentrated and the solid were triturated with MeOH, filtered and dried to obtain N-[6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]-3-isoquinolyl]piperidine-4-carboxamide (**LXIV**) (191 mg, 0.441 mmol, 78.4% yield) as a white solid. ESIMS found for $C_{25}H_{32}N_6O$ m/z 433.3 (M+1).

Step 6

[0632] To stirred mixture of N-[6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]-3-isoquinolyl]piperidine-4-carboxamide (**LXIV**) (95 mg, 0.220 mmol) and 2-methylpropanal (0.06 mL, 0.660 mmol) in MeOH (2 mL) was added NaCNBH₃ (27.6 mg, 0.440 mmol) at 0°C. The mixture was stirred for 30 min→1h at room temperature. Reaction mixture was quenched with minimum amount of aq. saturated ammonium chloride solution, concentrated under vacuum and the residue was adsorbed on silica gel, purified by chromatography (0→10% 7N.NH₃-MeOH/CHCl₃) to obtain 1-isobutyl-N-[6-[1-methyl-5-(1-piperidylmethyl)pyrazol-4-yl]-3-isoquinolyl]piperidine-4-carboxamide (**822**) (30 mg, 0.061 mmol, 28.0% yield) as a beige solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.86 (6 H, d, J =6.59 Hz), 1.33 - 1.42 (2 H, m), 1.45 - 1.53 (4 H, m), 1.61 - 1.72 (2 H, m), 1.72 - 1.81 (3 H, m), 1.86 (2 H, td, J =11.60, 1.78 Hz), 2.02 (2 H, d, J =7.41 Hz), 2.36 (4 H, br s), 2.52 - 2.59 (1 H, m), 2.86 (2 H, br d, J =11.53 Hz), 3.65 (2 H, s), 3.91 (3 H, s), 7.68 (1 H, dd, J =8.37, 1.51 Hz), 7.79 (1 H, s), 8.02 (1 H, d, J =9.33 Hz), 8.03 (1 H, s), 8.46 (1 H, s), 9.07 (1 H, s), 10.46 (1 H, s); ESIMS found for $C_{29}H_{40}N_6O$ m/z 489.3 (M+1).

Example 9.

[0633] Preparation of 2-[(3R)-3-fluoropyrrolidin-1-yl]-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]acetamide (**274**) is depicted below in Scheme 19.



Scheme 19

Step 1

[0634] To a stirred suspension of 6-bromoisoquinolin-3-amine (**XII**) (1.0 g, 4.48 mmol) and DMAP (109.5 mg, 0.90 mmol) in DCE (35 mL) was added DIPEA (3.12 mL, 17.93 mmol) followed by the addition of 2-chloroacetyl chloride (1.07 mL, 13.45 mmol). The mixture was heated to 75°C overnight. The reaction mixture was then cooled to room temperature, diluted with DCM, washed with H₂O and brine, the organic layer were then separated and dried over MgSO₄ before concentrating to dryness. The crude product was then purified by flash column chromatography using EtOAc/hexanes (0→100%) to obtain N-(6-bromo-3-isoquinolyl)-2-chloroacetamide (**LXV**) as a light yellow solid (350 mg, 1.16 mmol, 26.1% yield). ESIMS found for C₁₁H₈BrClN₂O *m/z* 298.9 (⁷⁹BrM+H).

Step 2

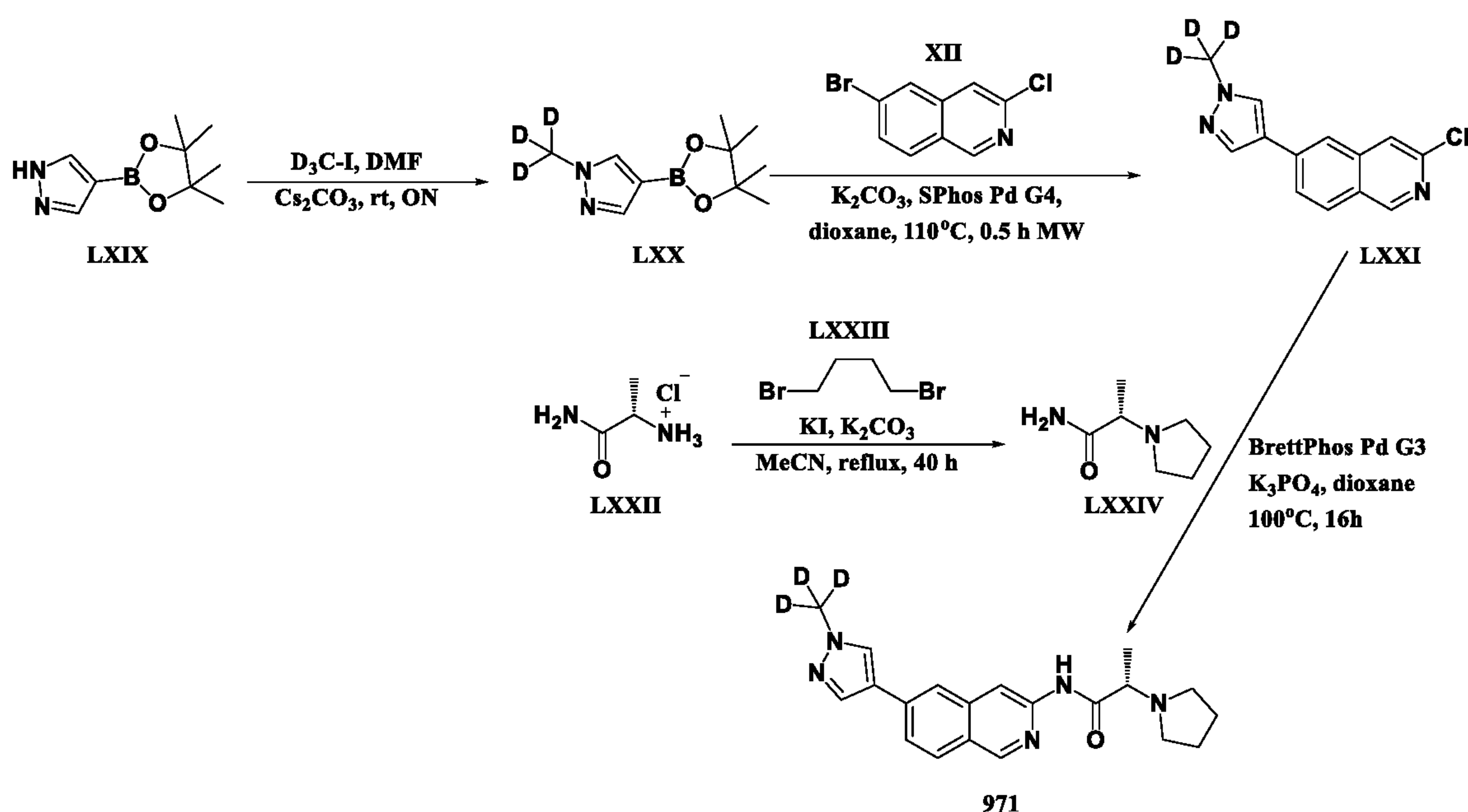
[0635] To a solution of N-(6-bromo-3-isoquinolyl)-2-chloroacetamide (**LXV**) (100 mg, 0.33 mmol), (3*R*)-3-fluoropyrrolidine hydrochloride (**LXVI**) (209.6 mg, 1.67 mmol), KI (0.02 mL, 0.33 mmol) and K₂CO₃ (461.4 mg, 3.34 mmol) in DMF (2 mL) was heated to 90°C overnight. The reaction was then concentrated to dryness and the residue was taken up in EtOAc and the organic layer was washed with water then brine. The organic layer was then separated and dried over MgSO₄ before concentration to dryness to obtain N-(6-bromo-3-isoquinolyl)-2-[(3*R*)-3-fluoropyrrolidin-1-yl]acetamide (**LXVII**) as a dark brown thick gum (110 mg, 0.312 mmol, 94.6% yield). Used for next step without purification. ESIMS found for C₁₅H₁₅BrFN₃O *m/z* 352.2 (⁷⁹BrM+H).

Step 3

[0636] To a solution of N-(6-bromo-3-isoquinolyl)-2-[(3R)-3-fluoropyrrolidin-1-yl]acetamide (LXVII) (116.2 mg, 0.33 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo (LXVIII) (103 mg, 0.50 mmol), Pd(dppf)Cl₂ (27 mg, 0.03 mmol) in MeCN (1.5 mL) was added a 2 M aqueous solution of K₂CO₃ (0.5 mL, 0.99 mmol). N₂ gas was bubbled into the mixture for 10 min and then heated to 80°C for 3 h. The organic layer was carefully separated, absorbed on silica gel and purified by flash column chromatography (0→30% CHCl₃/10% 7 N NH₃ in MeOH). The pure fractions were concentrated, the residue suspended in minimum EtOAc, sonicated and the resulting solid was collected by filtration, washed with diethyl ether and dried to obtain 2-[(3R)-3-fluoropyrrolidin-1-yl]-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]acetamide (274) as a white solid (58.0 mg, 0.164 mmol, 49.7% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.88 - 2.03 (m, 1 H), 2.12 - 2.28 (m, 1 H), 2.53 - 2.61 (m, 1 H), 2.86 (ddd, *J*=32.40, 11.80, 4.95 Hz, 1 H), 2.95 - 3.04 (m, 2 H), 3.41 (s, 2 H), 3.90 (s, 3 H), 5.26 (ddd, *J*=55.80, 6.05, 4.95 Hz, 1 H), 7.77 (dd, *J*=8.51, 1.37 Hz, 1 H), 8.02 (d, *J*=8.78 Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.44 (s, 1 H), 9.03 (s, 1 H), 10.02 (s, 1 H); ESIMS found for C₁₉H₂₀FN₅O *m/z* 354.1 (M+1).

Example 10.

[0637] Preparation of (S)-N-(6-(1-(methyl-*d*₃)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide (971) is depicted below in Scheme 20.



Scheme 20

Step 1

[0638] To a stirred suspension of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (LXIX) (1.435 g, 7.4 mmol) and Cs_2CO_3 (2.89 g, 8.87 mmol) in DMF (15 mL) was added trideuterio(iodo)methane (0.51 mL, 8.13 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was filtered and the filtrates were concentrated and dried under high vacuo to obtain 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trideuteriomethyl)pyrazole (LXX) (3.9 g, 18.48 mmol, 249.8% yield) as a white solid which was used for next step without purification. ESIMS found for $\text{C}_{10}\text{H}_{14}[\text{}^2\text{H}_3]\text{BN}_2\text{O}_2$ m/z 212. (M+1).

Step 2

[0639] To a mixture of 6-bromo-3-chloro-isoquinoline (XII) (0.5g, 2.06mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trideuteriomethyl)pyrazole (LXX) (1.305 g, 6.19 mmol) and SPhos Pd G4 (81.9 mg, 0.100 mmol) in 1,4-dioxane (10 mL) and was added a 2 M aqueous solution of K_2CO_3 (3.88 mL, 7.77 mmol). N_2 gas was bubbled into the mixture for 10 min and then the mixture was heated to 110°C for 0.5 h in a microwave. The organic layer was carefully separated, absorbed on silica gel and purified by column chromatography (0→100% hexanes/EtOAc) to obtain 3-chloro-6-[1-(trideuteriomethyl)pyrazol-4-yl]isoquinoline (LXXI) (400 mg, 1.62 mmol, 78.6% yield) as an off-white solid. ESIMS found for $\text{C}_{13}\text{H}_7[\text{}^2\text{H}_3]\text{ClN}_3$ m/z 246.9 (M+1).

Step 3

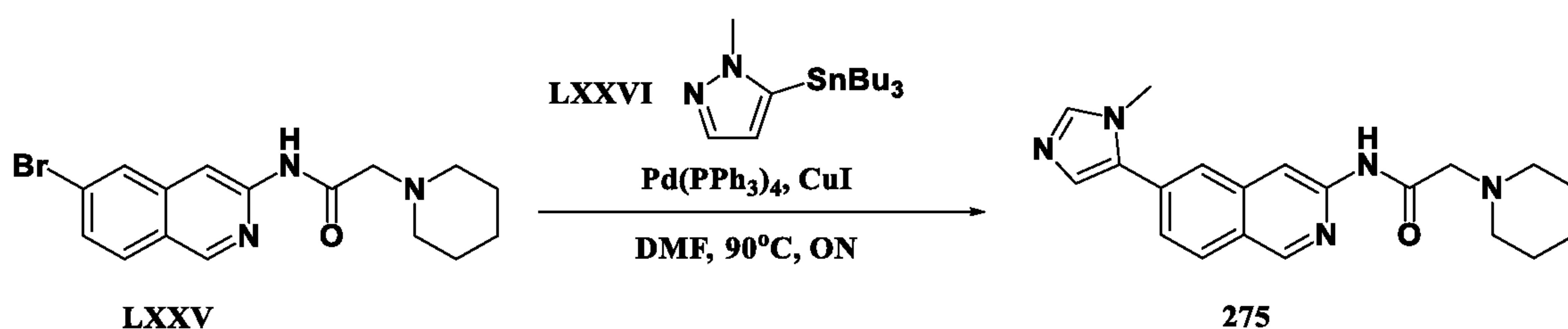
[0640] To a mixture of (S)-2-aminopropanamide HCl (**LXXII**) (100 mg, 0.330 mmol), 1,4-dibromobutane (**LXXIII**) (1.9 mL, 16.06 mmol), K₂CO₃ (4.437 g, 32.11 mmol) and KI (266.5 mg, 1.61 mmol) in MeCN (80 mL) was heated to reflux for 40 h. 1 N hydrochloric acid (100 mL) and DCM (100 mL) were added to the reaction mixture. The organic phase is separated off and discarded. The aqueous phase is made basic with a NaOH solution and extracted with CHCl₃ (3x80 ml). The organic layers were combined and dried under high vacuo to obtain (2S)-2-pyrrolidin-1-ylpropanamide (**LXXIV**) (1.10 g, 7.45 mmol, 46.4% yield) as a white solid which was used for next step without purification. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.15 (3 H, d, *J*=6.86 Hz), 1.63 - 1.72 (4 H, m), 2.44 - 2.49 (4 H, m), 2.72 (1 H, q, *J*=6.68 Hz), 6.88 (1 H, br s), 7.07 (1 H, br s) ESIMS found for C₇H₁₄N₂O *m/z* 143.1 (M+1).

Step 4

[0641] To a mixture of (2S)-2-pyrrolidin-1-ylpropanamide (**LXXIV**) (420.1 mg, 2.95 mmol) BrettPhos Pd G3 (223.2 mg, 0.250 mmol), 3-chloro-6-[1-(trideuteriomethyl)pyrazol-4-yl]isoquinoline (**LXXI**) (200 mg, 0.810 mmol) and K₃PO₄ (1.045 g, 4.92 mmol) was taken in 1,4-dioxane (5 mL). N₂ gas was bubbled into the mixture for 10 min and then the mixture was heated to 100°C for 16 h. The reaction mixture was filtered through Celite, washed with EtOAc, the filtrates concentrated and the crude product was purified by flash chromatography followed by preparative TLC (50% CHCl₃/10% 7N NH₃ in MeOH) to obtain (2S)-2-pyrrolidin-1-yl-N-[6-[1-(trideuteriomethyl)pyrazol-4-yl]-3-isoquinolyl]propanamide (**971**) (150.0 mg, 0.426 mmol, 50.6% yield) as a beige solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.30 (3 H, d, *J*=6.86 Hz), 1.75 (4 H, br s), 2.59 - 2.69 (4 H, m), 3.29 - 3.32 (1 H, m), 7.76 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.08 (2 H, s), 8.35 (1 H, s), 8.43 (1 H, s), 9.03 (1 H, s), 9.91 (1 H, s); ESIMS found for C₂₀H₂₀[²H₃]N₅O *m/z* 353.0 (M+1).

Example 11.

[0642] Preparation of N-[6-(3-methylimidazol-4-yl)-3-isoquinolyl]-2-(1-piperidyl)acetamide (**275**) is depicted below in Scheme 21.



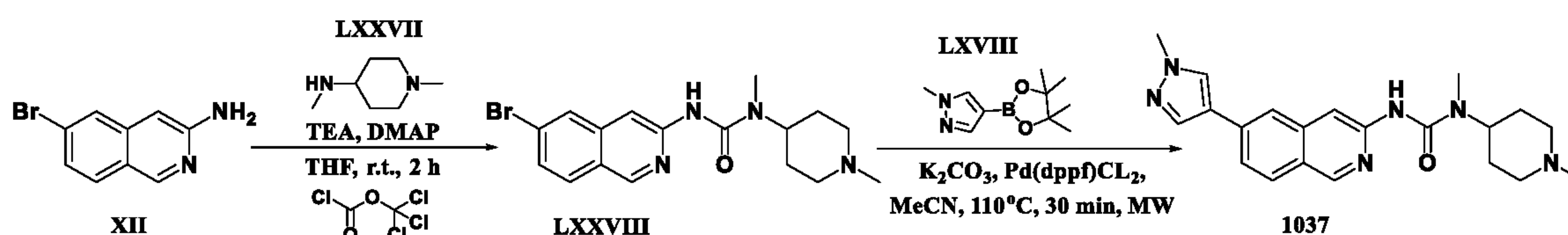
Scheme 21

Step 1

[0643] To a stirred mixture of N-(6-bromo-3-isoquinolyl)-2-(1-piperidyl)acetamide (**LXXV**) (100 mg, 0.29 mmol) tributyl-(3-methylimidazol-4-yl)stannane (**LXXVI**) (117.24 mg, 0.32 mmol) $\text{Pd(PPh}_3)_4$ (33.2 mg, 0.03 mmol) and cuprous iodide (5.47 mg, 0.03 mmol) in DMF (2 mL) was bubbled N_2 gas for 10 min and then heated to 90°C overnight. The reaction mixture was concentrated, absorbed on silica gel and purified by flash column chromatography using $\text{CHCl}_3/10\% \text{ 7 N NH}_3$ in MeOH (0→40%). The pure fractions were concentrated, the residue suspended in diethyl ether, sonicated and the resulting solids were collected by filtration, and dried to obtain N-[6-(3-methylimidazol-4-yl)-3-isoquinolyl]-2-(1-piperidyl)acetamide (**275**) as a white solid (53.0 mg, 0.152 mmol, 52.3% yield). $^1\text{H NMR}$ ($\text{DMSO-}d_6$, 500 MHz) δ ppm 1.43 (br d, $J=4.94$ Hz, 2 H), 1.59 (quin, $J=5.63$ Hz, 4 H), 2.52 (br d, $J=5.21$ Hz, 4 H), 3.18 (s, 2 H), 3.84 (s, 3 H), 7.33 (br s, 1 H), 7.70 (dd, $J=8.51, 1.65$ Hz, 1 H), 7.81 (br s, 1 H), 8.06 (s, 1 H), 8.11 (d, $J=8.51$ Hz, 1 H), 8.53 (s, 1 H), 9.14 (s, 1 H), 9.98 (s, 1 H); ESIMS found for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}$ m/z 350.2 ($\text{M}+1$).

Example 12.

[0644] Preparation of 1-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(1-methylpiperidin-4-yl)urea (**1037**) is depicted below in Scheme 22.



Scheme 22

Step 1

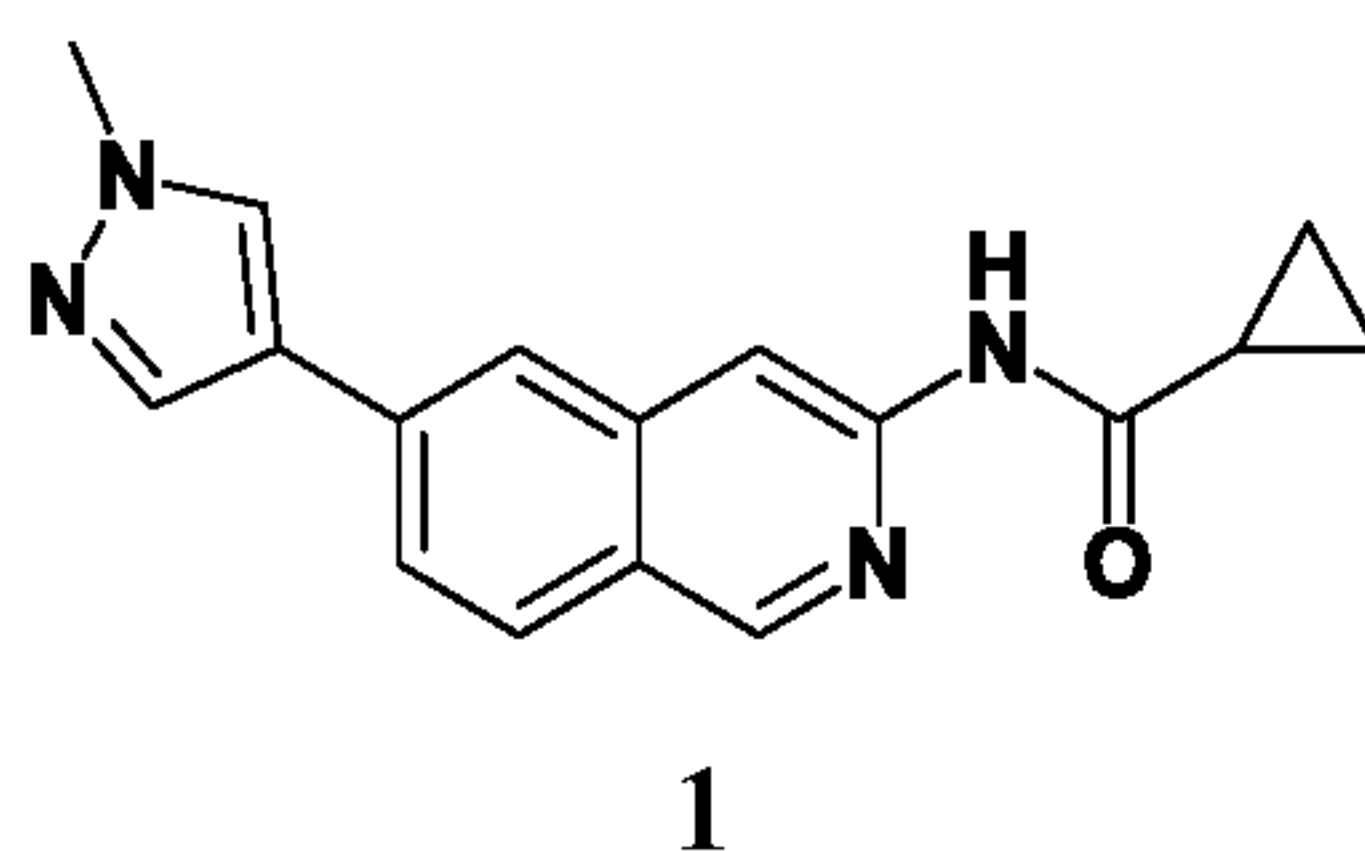
[0645] To a stirred suspension of 6-bromoisoquinolin-3-amine (**XII**) (200 mg, 0.900 mmol), DMAP (11 mg, 0.090 mmol) and TEA (0.5 mL, 3.59 mmol) in THF (40 mL) was added trichloromethyl carbonochloridate (0.11 mL, 0.900 mmol) and the mixture was stirred for 1 h at

room temperature. N,1-dimethylpiperidin-4-amine (**LXXVII**) (115 mg, 0.900 mmol) was then added and the mixture was stirred for 2 h at room temperature. The reaction was concentrated and the residue taken in DCM, washed with water, sat. NaHCO₃ and brine. The organic layer was dried over anhydrous Na₂SO₄, solvents removed in vacuo and the crude was purified by column chromatography (0→10% CHCl₃/7N NH₃ in MeOH) to obtain 3-(6-bromo-3-isoquinolyl)-1-methyl-1-(1-methyl-4-piperidyl)urea (**LXXVIII**) (98 mg, 0.260 mmol, 29.0% yield) as a beige solid. ESIMS found for C₁₇H₂₁BrN₄O *m/z* 377.1 (⁷⁹BrM+H).

Step 2

[0646] To a mixture of Pd(dppf)Cl₂-CH₂Cl₂ adduct (19.6 mg, 0.020 mmol), 1-(6-bromo-3-isoquinolyl)-3-(1-methyl-4-piperidyl)urea (**LXXVIII**) (87 mg, 0.240 mmol), and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (**LXVIII**) (59.8 mg, 0.290 mmol) in MeCN (5 mL) was added a 2 M aqueous solution of K₂CO₃ (0.24 mL, 0.480 mmol). N₂ gas was bubbled into the mixture for 10 min and then heated at 110°C for 30 min in a microwave. The organic layer was carefully separated, absorbed on silica gel and purified by flash column chromatography (0→10% 7N NH₃ in MeOH/CHCl₃). The pure fractions were combined, concentrated and the residue was triturated from DCM/hexanes. The solid was collected by filtration and dried under high vacuum to obtain 1-(1-methyl-4-piperidyl)-3-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]urea (**1037**) (35 mg, 0.096 mmol, 40.1% yield) as a beige solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.52 (2 H, br d, *J*=10.15 Hz), 1.74 (2 H, qd, *J*=12.12, 3.70 Hz), 1.93 - 2.02 (2 H, m), 2.17 (3 H, s), 2.82 (2 H, br d, *J*=11.25 Hz), 2.88 (3 H, s), 3.90 (3 H, s), 4.09 (1 H, tt, *J*=12.01, 3.91 Hz), 7.65 - 7.72 (1 H, m), 7.93 - 7.99 (2 H, m), 8.06 (1 H, s), 8.15 (1 H, s), 8.33 (1 H, s), 8.76 (1 H, s), 8.97 (1 H, s); ESIMS found for C₂₁H₂₆N₆O *m/z* 379.2 (M+1).

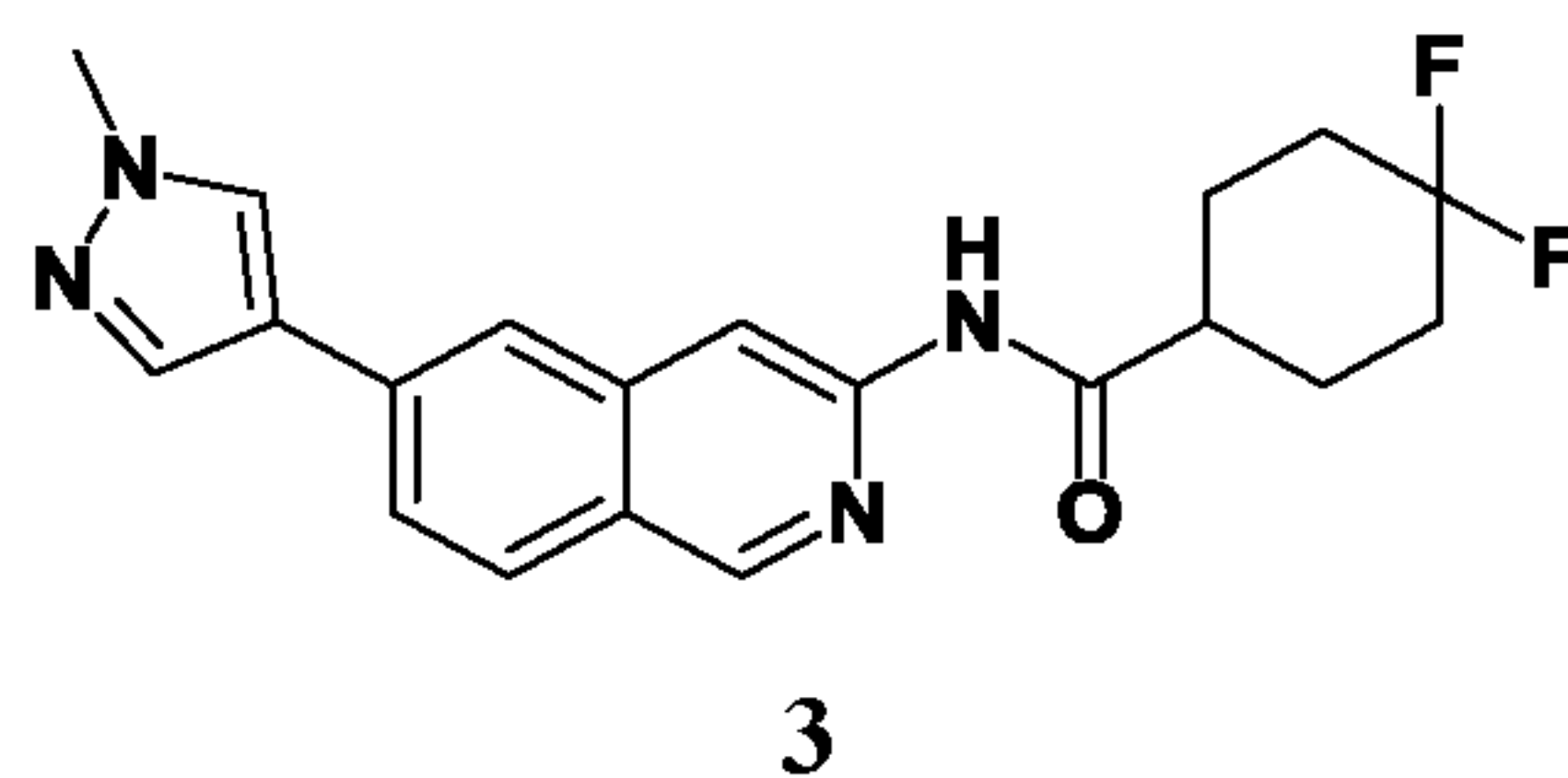
[0647] The following compounds were prepared in accordance with the procedures described in the above Examples 1-12.



[0648] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclopropanecarboxamide **1**.

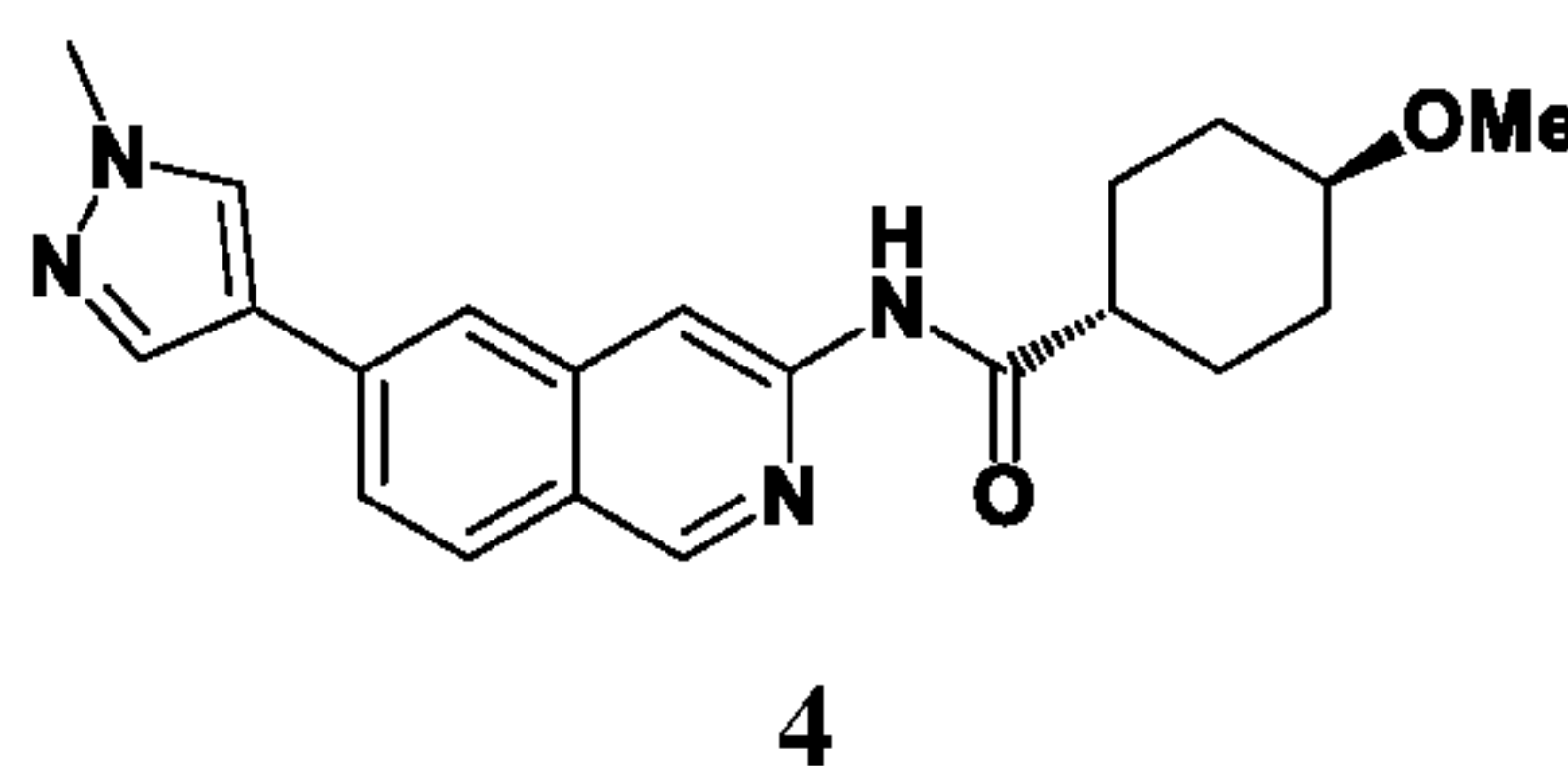
[0649] Beige solid (32.0 mg, 0.109 mmol, 31.9% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.77 - 0.90 (m, 4 H), 2.03 - 2.12 (m, 1 H), 3.90 (s, 3 H), 7.74 (dd, *J*=8.51, 1.65 Hz, 1

H), 7.96 – 8.03 (m, 2 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.40 (s, 1 H), 9.03 (s, 1 H), 10.83 (s, 1 H); ESIMS found for $C_{17}H_{16}N_4O$ m/z 293.1 (M+1).



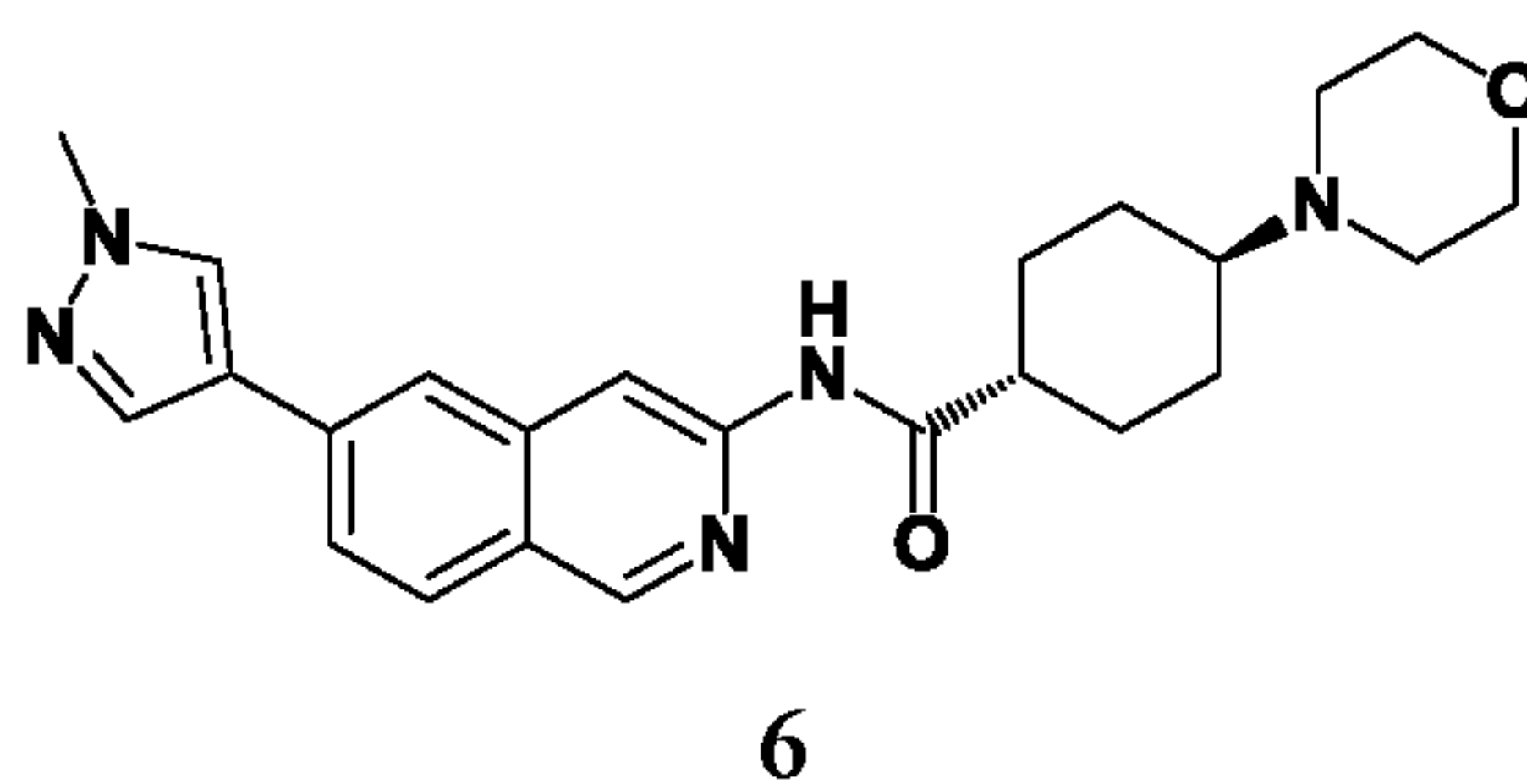
[0650] 4,4-Difluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexanecarboxamide 3.

[0651] Beige solid (41.6 mg, 0.112 mmol, 56.2% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.66 - 1.90 (m, 4 H), 1.91 - 2.00 (m, 2 H), 2.06 - 2.18 (m, 2 H), 2.66 - 2.76 (m, 1 H), 3.90 (s, 3 H), 7.75 (dd, $J=8.64$, 1.51 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.43 (s, 1 H), 9.03 (s, 1 H), 10.57 (s, 1 H); ESIMS found for $C_{20}H_{20}F_2N_4O$ m/z 371.2 (M+1).



[0652] *trans*-4-Methoxy-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide 4.

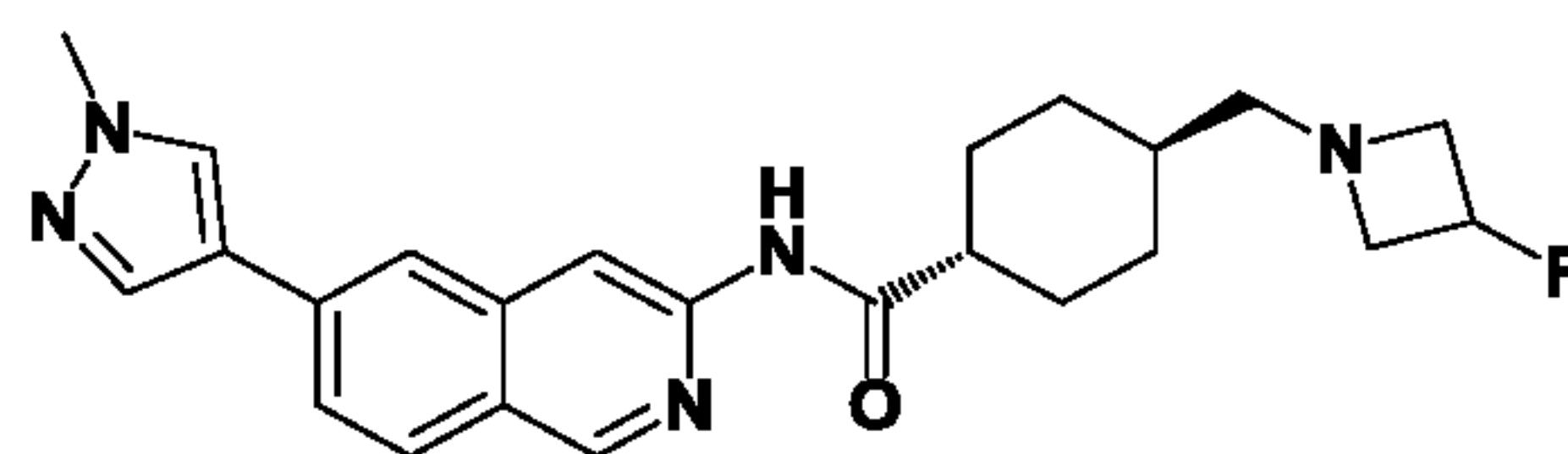
[0653] White solid (101 mg, 0.277 mmol, 62.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.07 - 1.17 (2 H, m), 1.43 - 1.56 (2 H, m), 1.84 - 1.95 (2 H, m), 2.03 - 2.11 (2 H, m), 2.51 - 2.57 (1 H, m), 3.12 (1 H, tt, $J=10.67$, 4.15 Hz), 3.25 (3 H, s), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.42 (1 H, s), 9.02 (1 H, s), 10.42 (1 H, s); ESIMS found for $C_{21}H_{24}N_4O_2$ m/z 365.2 (M+1).



[0654] *trans*-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide 6.

[0655] White solid (36 mg, 0.086 mmol, 30.0% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.15 - 1.30 (2 H, m), 1.41 - 1.56 (2 H, m), 1.91 (4 H, br t, $J=11.11$ Hz), 2.17 - 2.28 (1 H, m), 3.28 (4 H, br s), 3.50 - 3.60 (4 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H,

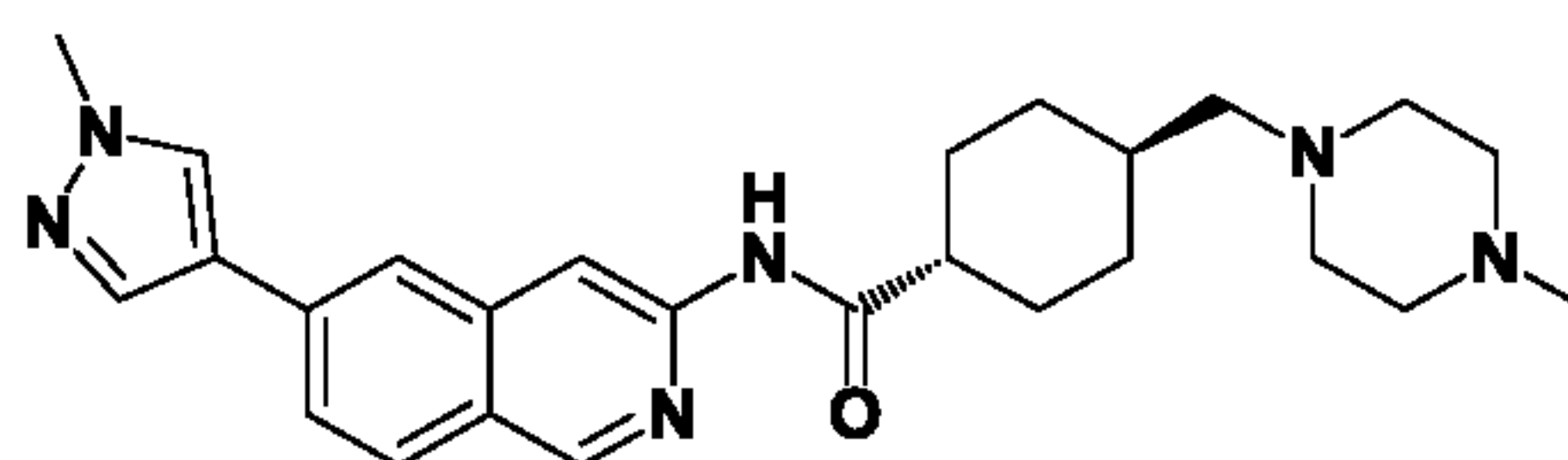
d, $J=8.51$ Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.35 (1 H, s), 8.42 (1 H, s), 9.02 (1 H, s), 10.41 (1 H, s); ESIMS found for $C_{24}H_{29}N_5O_2$ m/z 420.2 (M+1).



10

[0656] *trans*-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **10**.

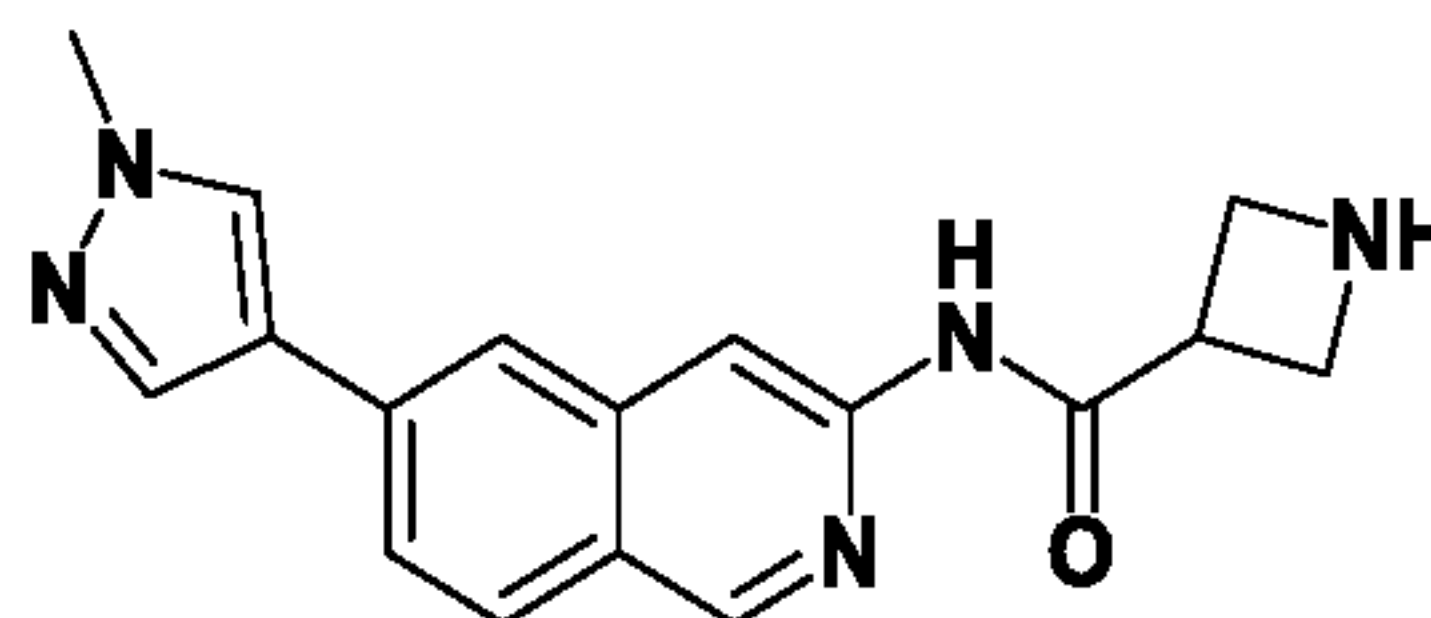
[0657] White solid (42.0 mg, 0.100 mmol, 36.1% yield). ^1H NMR (500 MHz, $DMSO-d_6$) δ ppm 0.91 (2 H, qd, $J=12.67$, 3.16 Hz), 1.20 - 1.33 (1 H, m), 1.37 - 1.51 (2 H, m), 1.51 - 1.61 (1 H, m), 1.75 - 1.90 (4 H, m), 2.29 (2 H, d, $J=6.86$ Hz), 2.96 - 3.08 (2 H, m), 3.48 - 3.60 (2 H, m), 3.90 (3 H, s), 5.02 - 5.22 (1 H, m), 7.73 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.42 (1 H, s), 9.01 (1 H, s), 10.38 (1 H, s); ESIMS found for $C_{24}H_{28}FN_5O$ m/z 422.0 (M+1).



14

[0658] *trans*-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide **14**.

[0659] White solid (35.0 mg, 0.078 mmol, 28.4% yield). ^1H NMR (499 MHz, $DMSO-d_6$) δ ppm 0.82 - 0.95 (2 H, m), 1.40 - 1.54 (4 H, m), 1.79 - 1.91 (4 H, m), 2.08 (2 H, d, $J=7.14$ Hz), 2.14 (3 H, s), 2.23 - 2.41 (8 H, m), 3.90 (3 H, s), 7.73 (1 H, dd, $J=8.51$, 1.37 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.43 (1 H, s), 9.01 (1 H, s), 10.37 (1 H, s); ESIMS found for $C_{26}H_{34}N_6O$ m/z 447.0 (M+1).

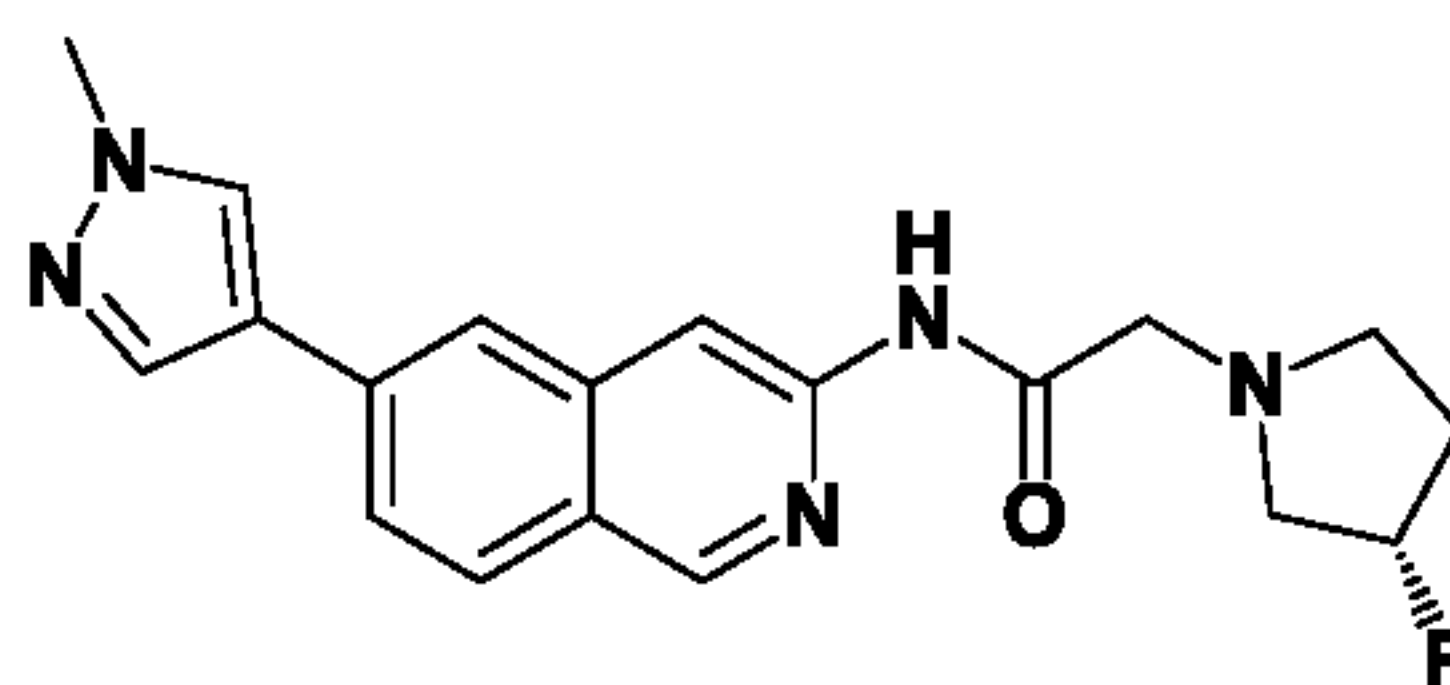


16

[0660] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide **16**.

[0661] Yellow solid (10.8 mg, 0.035 mmol, 62.4% yield). ^1H NMR ($DMSO-d_6$, 500 MHz) δ ppm 3.50 (br s, 2 H), 3.76 (br s, 3 H), 3.90 (s, 3 H), 7.75 (dd, $J=8.51$, 1.37 Hz, 1 H), 8.00

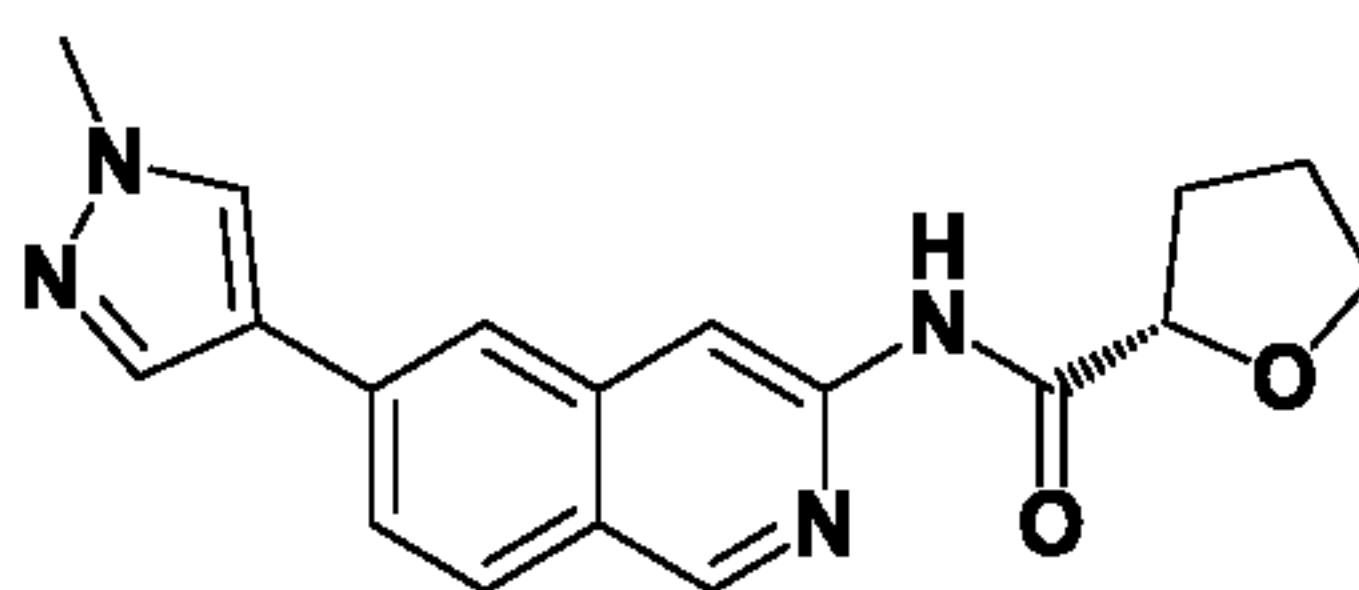
(d, $J=8.51$ Hz, 1 H), 8.06 (s, 1 H), 8.09 (s, 1 H), 8.36 (s, 1 H), 8.47 (s, 1 H), 9.02 (s, 1 H), 10.45 (s, 1 H); ESIMS found for $C_{17}H_{17}N_5O$ m/z 308.1 (M+1).



69

[0662] (S)-2-(3-Fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **69**.

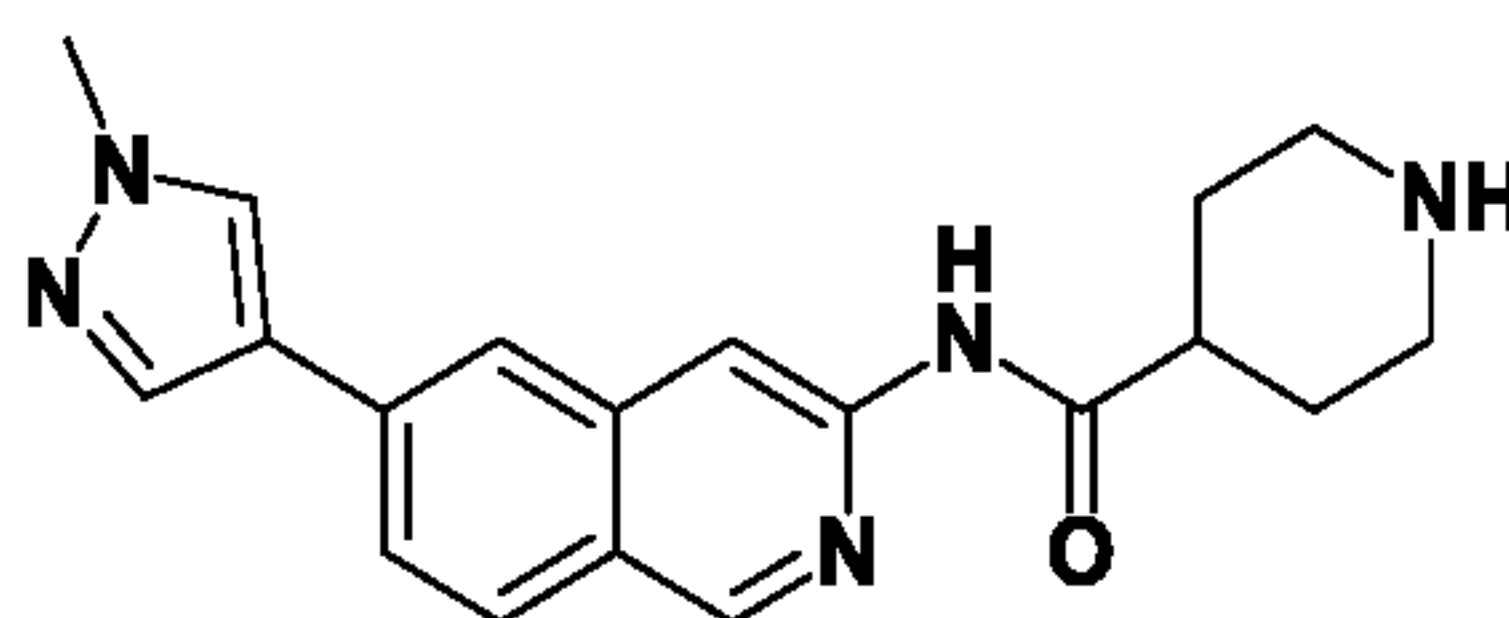
[0663] Off-white solid (70.0 mg, 0.198 mmol, 41.0% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.87 - 2.04 (m, 1 H), 2.12 - 2.29 (m, 1 H), 2.55 - 2.62 (m, 1 H), 2.81 - 2.94 (m, 1 H), 2.96 - 3.06 (m, 2 H), 3.42 (s, 2 H), 5.17 - 5.35 (m, 1 H), 7.77 (dd, $J=8.64$, 1.51 Hz, 1 H), 8.02 (d, $J=8.78$ Hz, 1 H), 8.10 (d, $J=0.82$ Hz, 2 H), 8.36 (s, 1 H), 8.44 (s, 1 H), 9.03 (s, 1 H), 10.02 (s, 1 H); ESIMS found for $C_{19}H_{20}FN_5O$ m/z 354.2 (M+1).



71

[0664] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide **71**.

[0665] Off-white solid (30.0 mg, 0.093 mmol, 59.8% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.83 - 1.96 (m, 2 H), 1.97 - 2.07 (m, 1 H), 2.19 - 2.30 (m, 1 H), 3.83 - 3.88 (m, 1 H), 3.90 (s, 3 H), 3.99 - 4.07 (m, 1 H), 4.53 (dd, $J=8.23$, 5.76 Hz, 1 H), 7.78 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.03 (d, $J=8.51$ Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.42 (s, 1 H), 9.05 (s, 1 H), 9.75 (s, 1 H); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.2 (M+1).

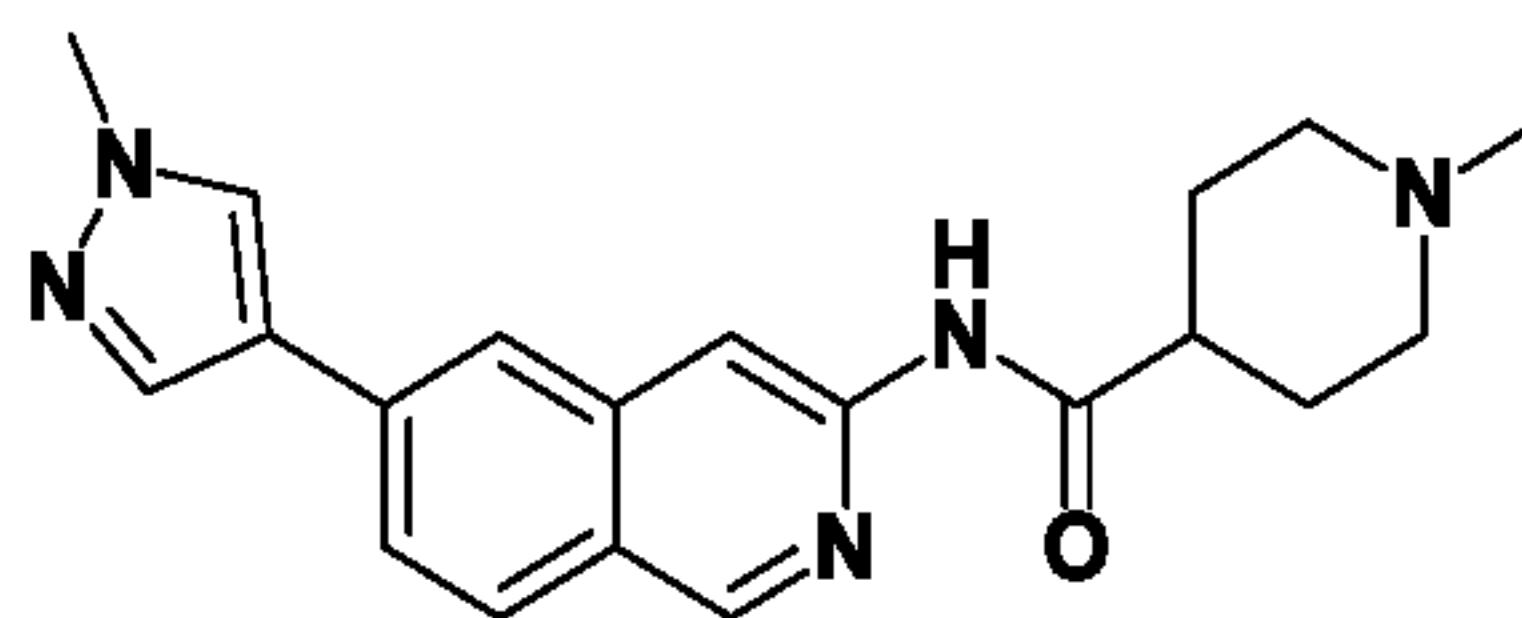


72

[0666] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **72**.

[0667] White solid (75.0 mg, 0.224 mmol, 92.2% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.65 (qd, $J=12.30$, 3.70 Hz, 2 H), 1.81 (br d, $J=10.70$ Hz, 2 H), 2.64 (td, $J=12.28$, 2.33 Hz, 2 H), 2.71 (ddt, $J=11.32$, 7.62, 3.84, 3.84 Hz, 1 H), 3.12 (br d, $J=12.35$ Hz, 2 H), 3.90 (s,

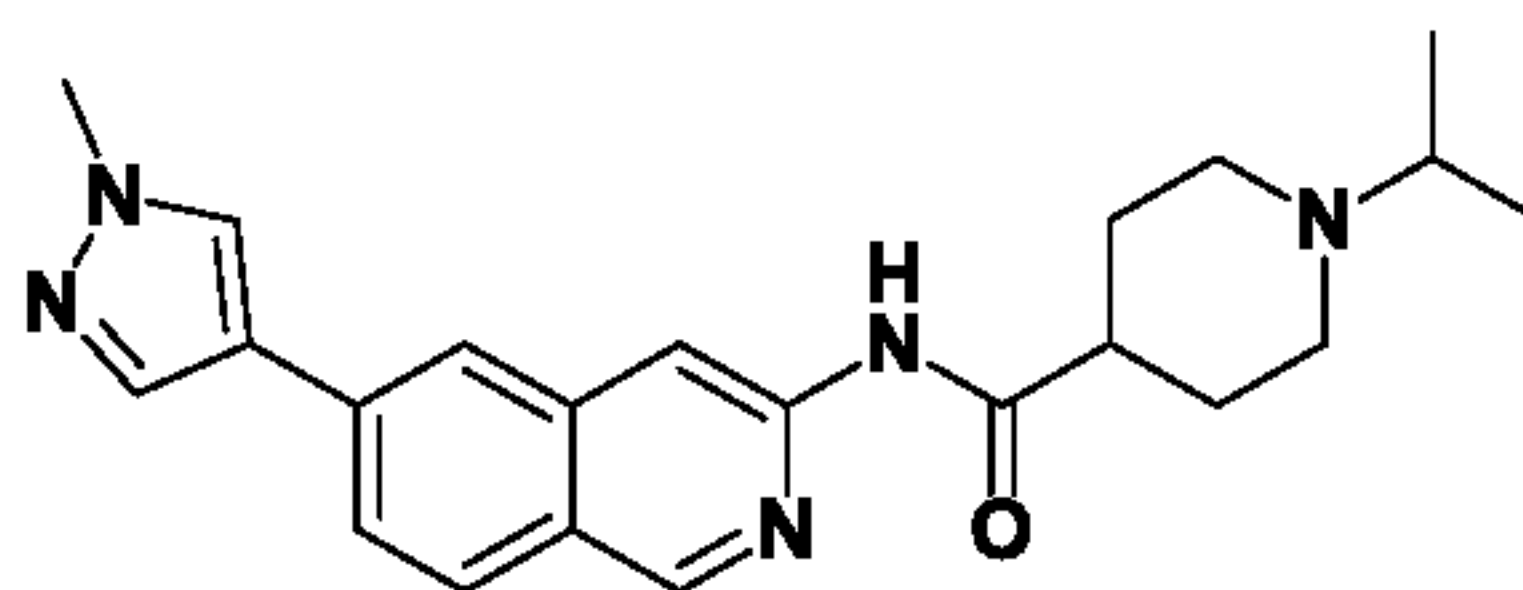
3 H), 7.75 (dd, $J=8.51, 1.37$ Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.43 (s, 1 H), 9.03 (s, 1 H), 10.50 (s, 1 H); ESIMS found for $C_{19}H_{21}N_5O$ m/z 336.1 (M+1).



73

[0668] 1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 73.

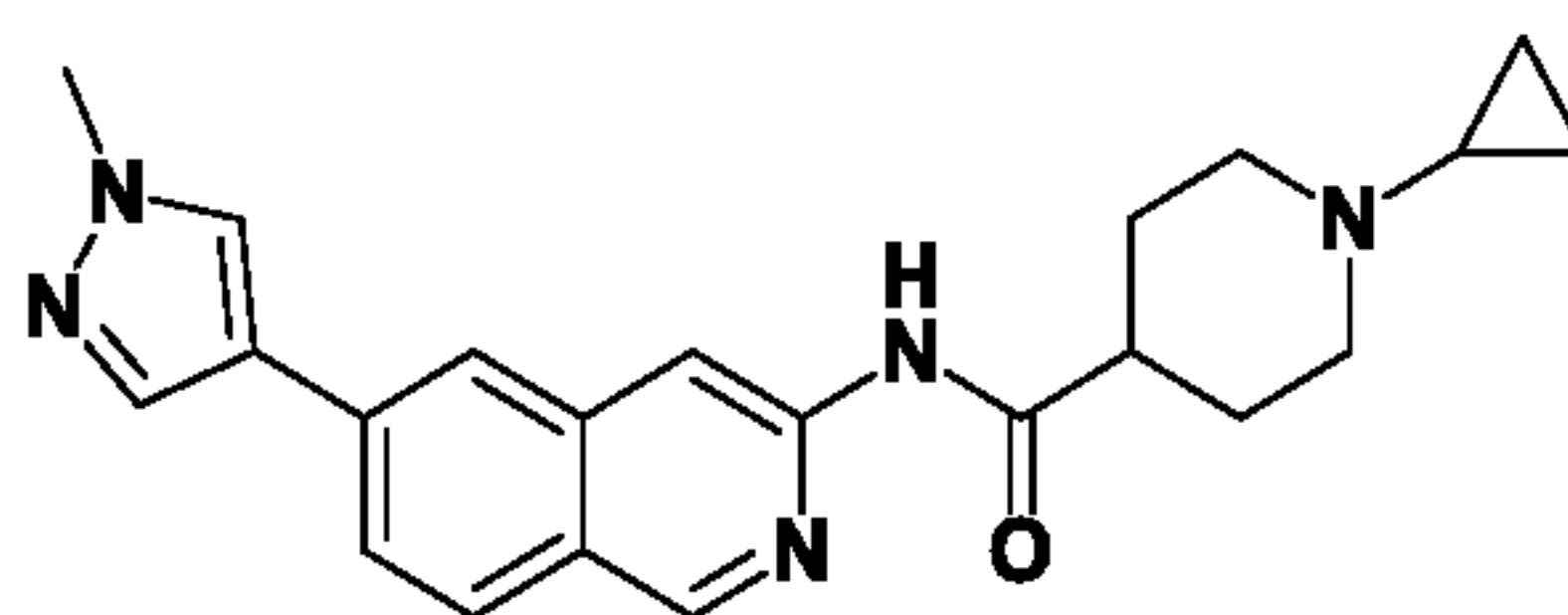
[0669] White solid (114.0 mg, 0.326 mmol, 42.1% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.60 - 1.73 (m, 2 H), 1.73 - 1.80 (m, 2 H), 1.86 (td, $J=11.66, 2.20$ Hz, 2 H), 2.16 (s, 3 H), 2.45 - 2.55 (m, 1 H), 2.81 (br d, $J=11.53$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51, 1.65$ Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.02 (s, 1 H), 8.07 (s, 1 H), 8.35 (s, 1 H), 8.43 (s, 1 H), 9.02 (s, 1 H), 10.46 (s, 1 H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).



75

[0670] 1-Isopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 75.

[0671] Off-white solid (43.0 mg, 0.114 mmol, 40.22% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 0.97 (d, $J=6.31$ Hz, 6 H), 1.63 (qd, $J=11.98, 3.57$ Hz, 2 H), 1.78 (br d, $J=10.15$ Hz, 2 H), 2.11 (br t, $J=11.11$ Hz, 2 H), 2.45 - 2.55 (m, 1 H), 2.62 - 2.73 (m, 1 H), 2.83 (br d, $J=10.98$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51, 1.65$ Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.08 (d, $J=0.82$ Hz, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.44 (s, 1 H); ESIMS found for $C_{22}H_{27}N_5O$ m/z 378.3 (M+1).

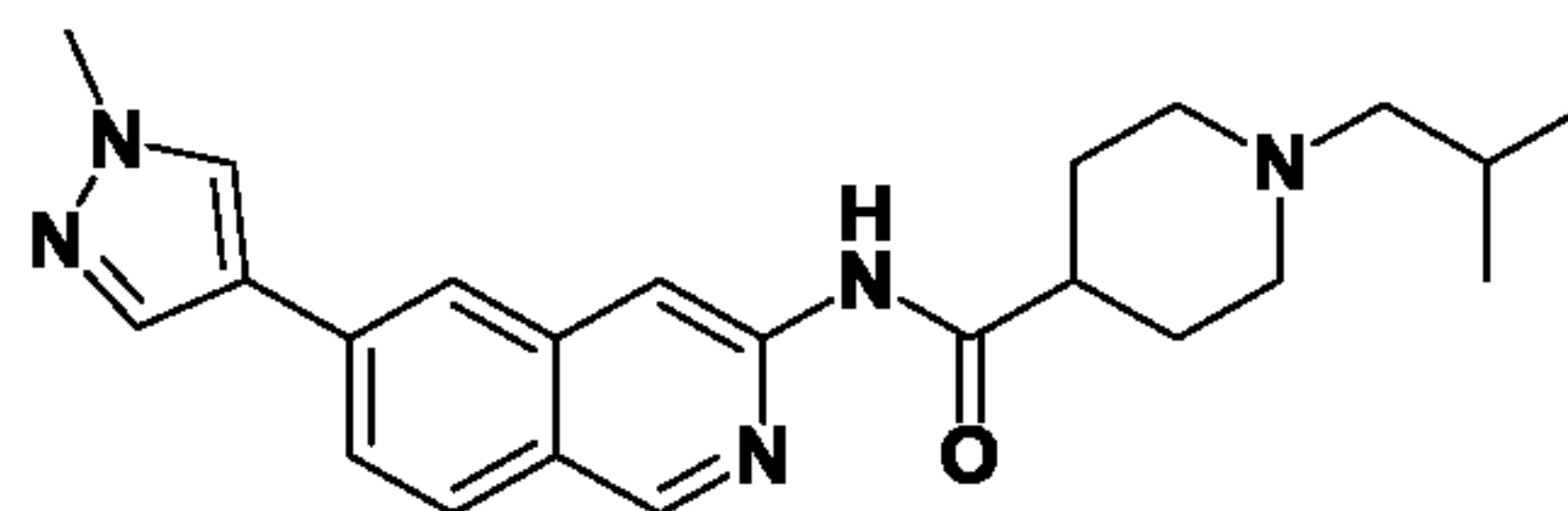


76

[0672] 1-Cyclopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide 76.

[0673] White solid (42.0 mg, 0.112 mmol, 24.6% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 0.25 - 0.33 (m, 2 H), 0.38 - 0.46 (m, 2 H), 1.53 - 1.65 (m, 3 H), 1.76 (br d, $J=10.98$

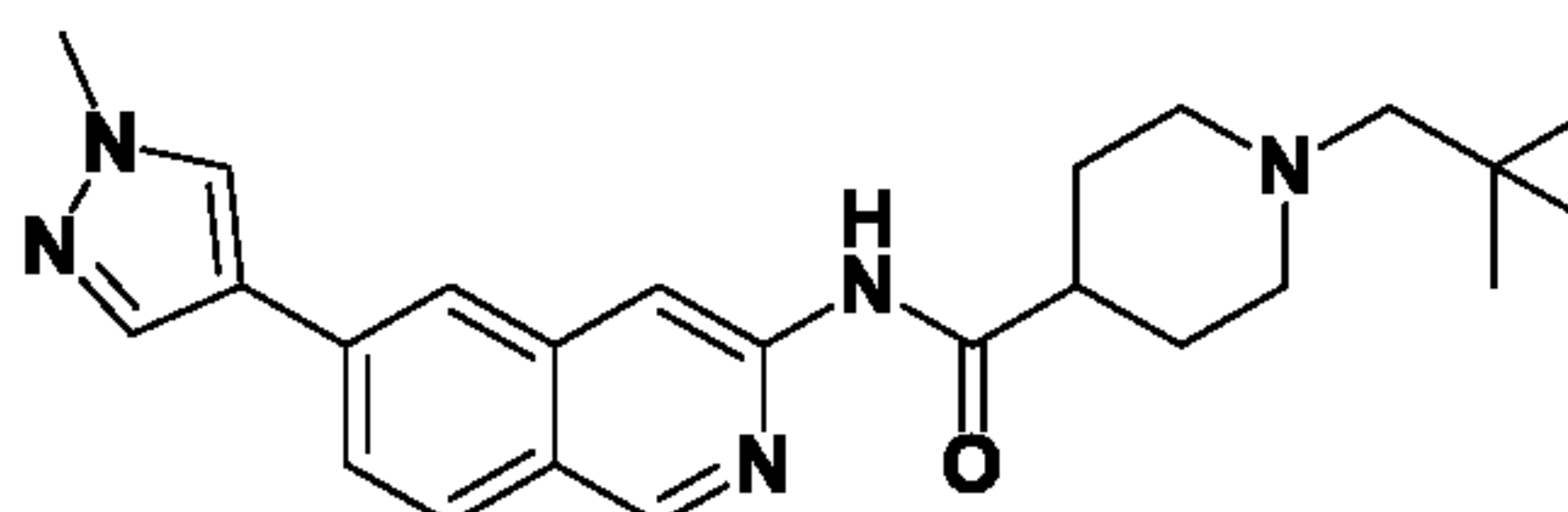
Hz, 2 H), 2.11 - 2.22 (m, 2 H), 2.51 - 2.60 (m, 1 H), 2.98 (br d, $J=11.25$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 7.99 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.07 (s, 1 H), 8.34 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.47 (s, 1 H); ESIMS found for $C_{22}H_{25}N_5O$ m/z 376.2 (M+1).



77

[0674] 1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **77**.

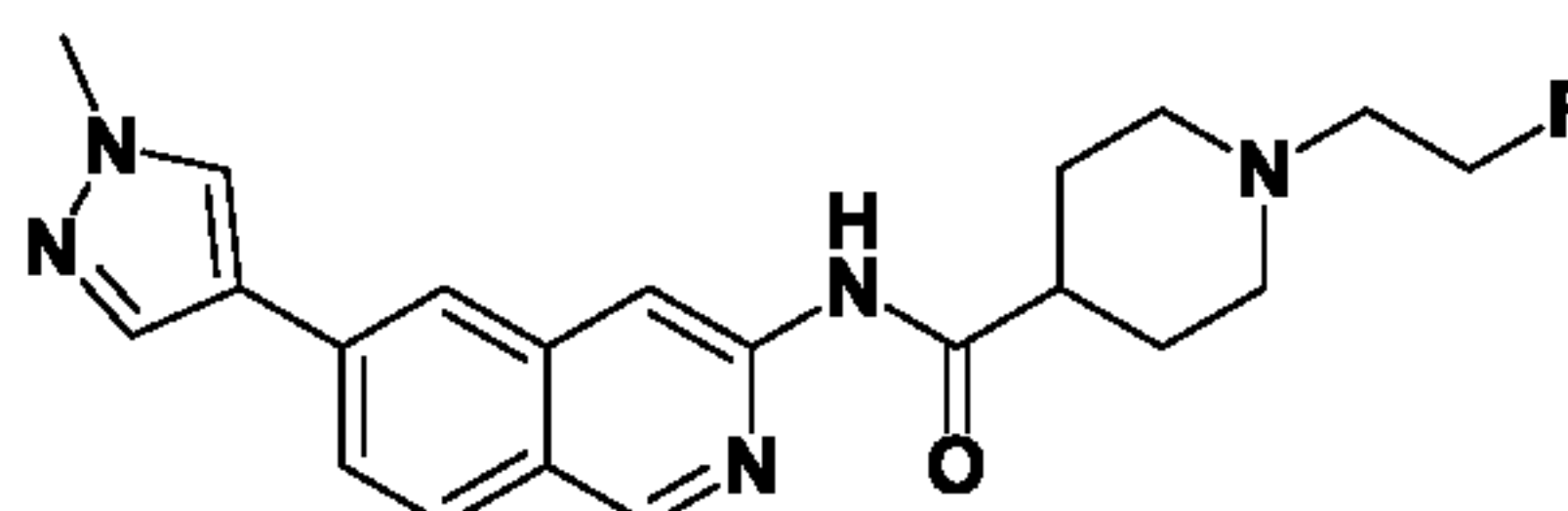
[0675] White solid (128.0 mg, 0.327 mmol, 60.3% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 0.85 (d, $J=6.59$ Hz, 6 H), 1.60 - 1.73 (m, 2 H), 1.73 - 1.80 (m, 3 H), 1.82 - 1.90 (m, 2 H), 2.01 (d, $J=7.41$ Hz, 2 H), 2.51 - 2.57 (m, 1 H), 2.86 (br d, $J=11.53$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51$, 1.37 Hz, 1 H), 7.99 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.46 (s, 1 H); ESIMS found for $C_{23}H_{29}N_5O$ m/z 392.2 (M+1).



78

[0676] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide **78**.

[0677] White solid (16.5 mg, 0.041 mmol, 13.7% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 0.85 (s, 9 H), 1.67 - 1.76 (m, 4 H), 2.04 (s, 2 H), 2.16 - 2.26 (m, 2 H), 2.81 (br d, $J=11.25$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 7.99 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.45 (s, 1 H); ESIMS found for $C_{24}H_{31}N_5O$ m/z 406.3 (M+1).

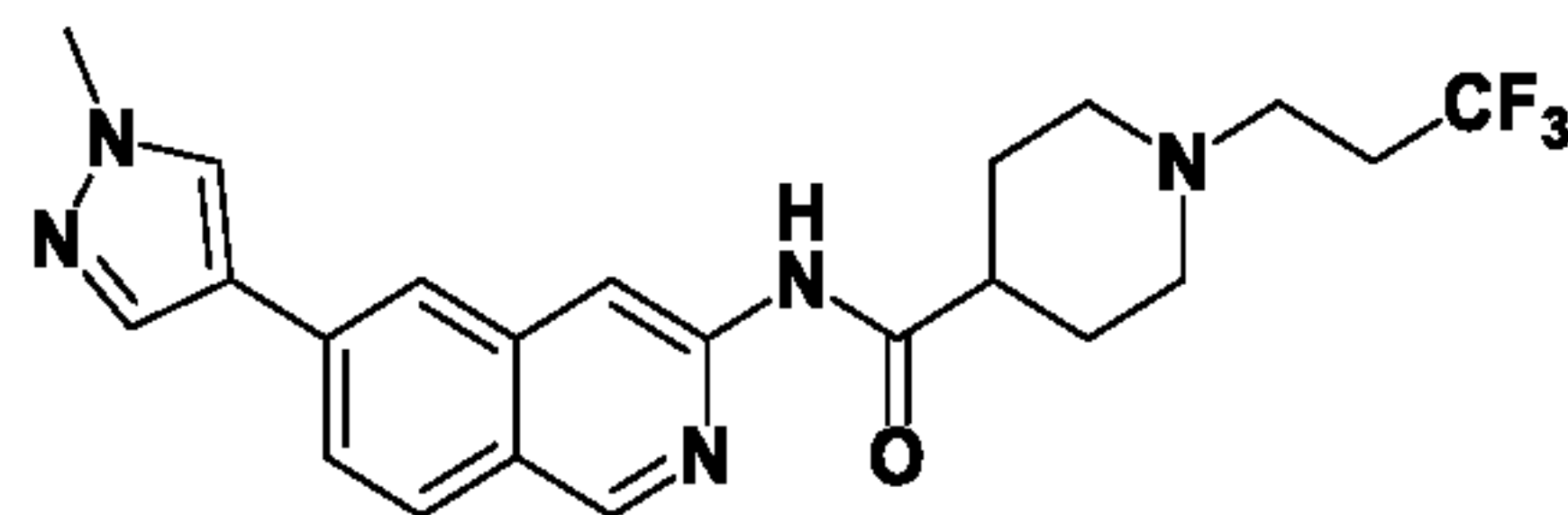


81

[0678] 1-(2-Fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **81**.

[0679] White solid (257.0 mg, 0.674 mmol, 62.1% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.68 (qd, $J=12.12$, 3.70 Hz, 2 H), 1.75 - 1.83 (m, 2 H), 2.03 (td, $J=11.66$, 2.20 Hz, 2 H), 2.51 - 2.56 (m, 1 H), 2.61 (dt, $J=28.30$, 4.90 Hz, 2 H), 2.91 - 2.99 (m, 2 H), 3.90 (s, 3 H), 4.53

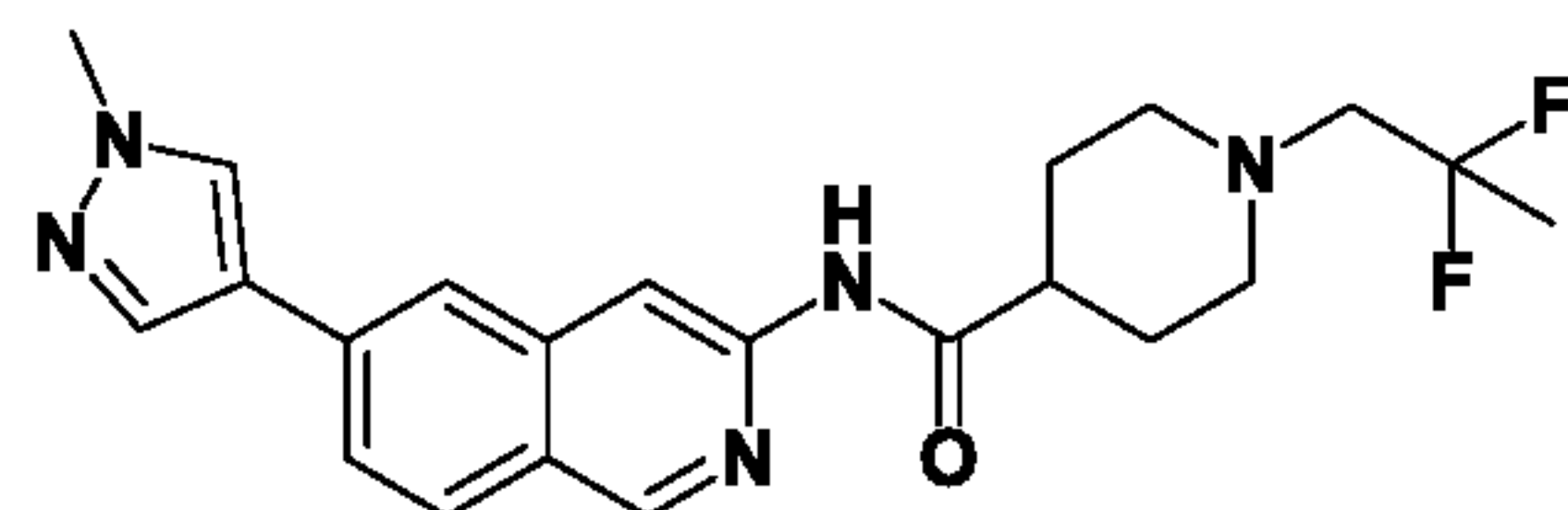
(dt, $J=47.75$, 4.95 Hz, 2 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.07 (s, 1 H), 8.34 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.46 (s, 1 H); ESIMS found for $C_{21}H_{24}FN_5O$ m/z 382.2 (M+1).



82

[0680] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **82**.

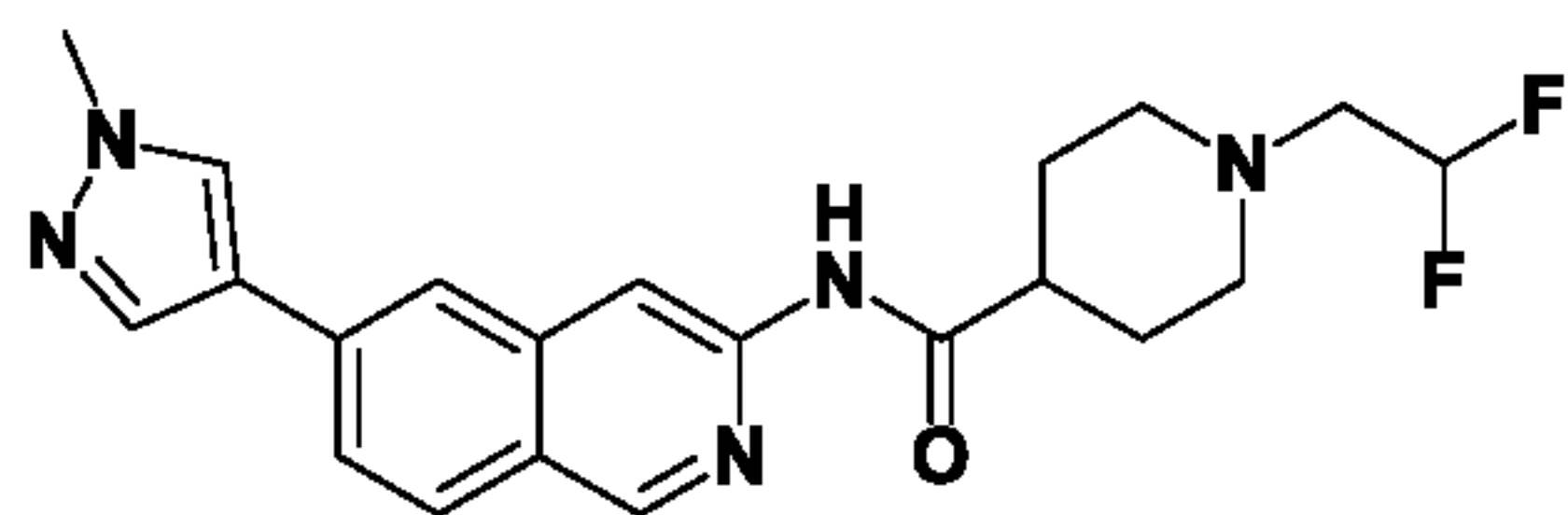
[0681] White solid (137.0 mg, 0.318 mmol, 54.9% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.58 - 1.74 (m, 2 H), 1.79 (br d, $J=10.70$ Hz, 2 H), 1.92 - 2.02 (m, 2 H), 2.40 - 2.60 (m, 5 H), 2.93 (br d, $J=11.25$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51$, 1.37 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.48 (s, 1 H); ESIMS found for $C_{22}H_{24}F_3N_5O$ m/z 432.2 (M+1).



83

[0682] 1-(2,2-Difluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **83**.

[0683] Off-white solid (29.0 mg, 0.070 mmol, 23.5% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.62 (t, $J=19.21$ Hz, 3 H), 1.66 - 1.73 (m, 2 H), 1.73 - 1.81 (m, 2 H), 2.21 (td, $J=11.66$, 2.47 Hz, 2 H), 2.50 - 2.57 (m, 1 H), 2.70 (t, $J=14.00$ Hz, 2 H), 2.94 (br d, $J=11.53$ Hz, 2 H), 3.89 (s, 3 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 7.99 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.07 (d, $J=0.82$ Hz, 1 H), 8.34 (s, 1 H), 8.43 (s, 1 H), 9.01 (s, 1 H), 10.48 (s, 1 H); ESIMS found for $C_{22}H_{25}F_2N_5O$ m/z 414.2 (M+1).

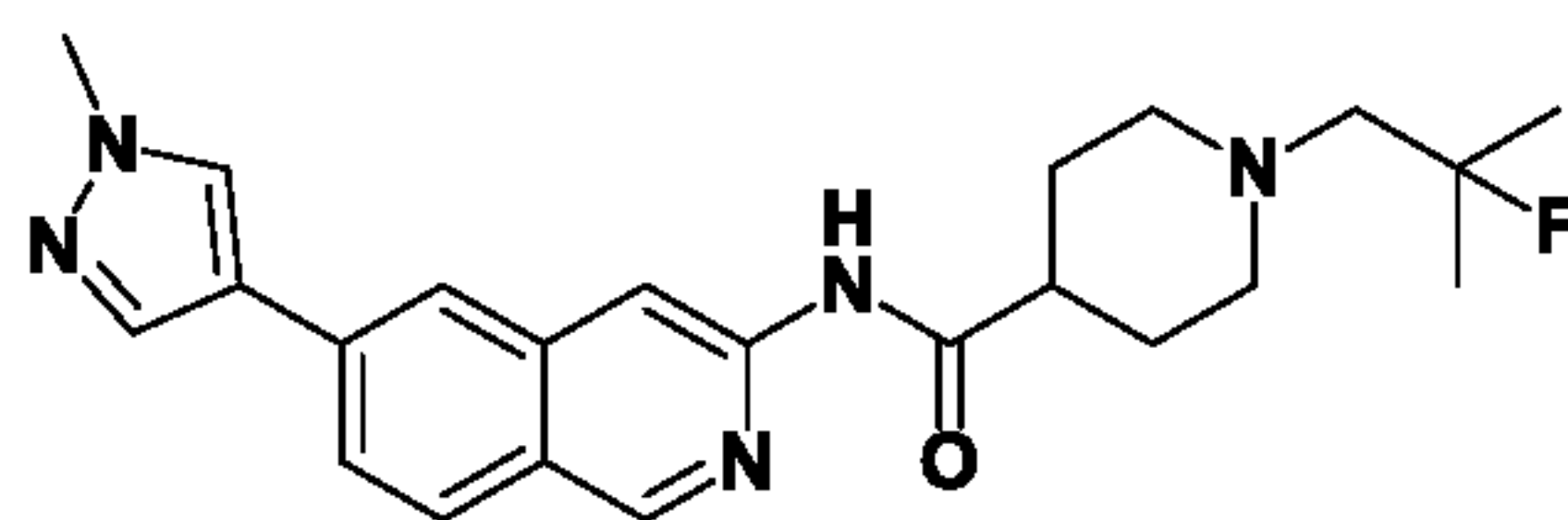


84

[0684] 1-(2,2-Difluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **84**.

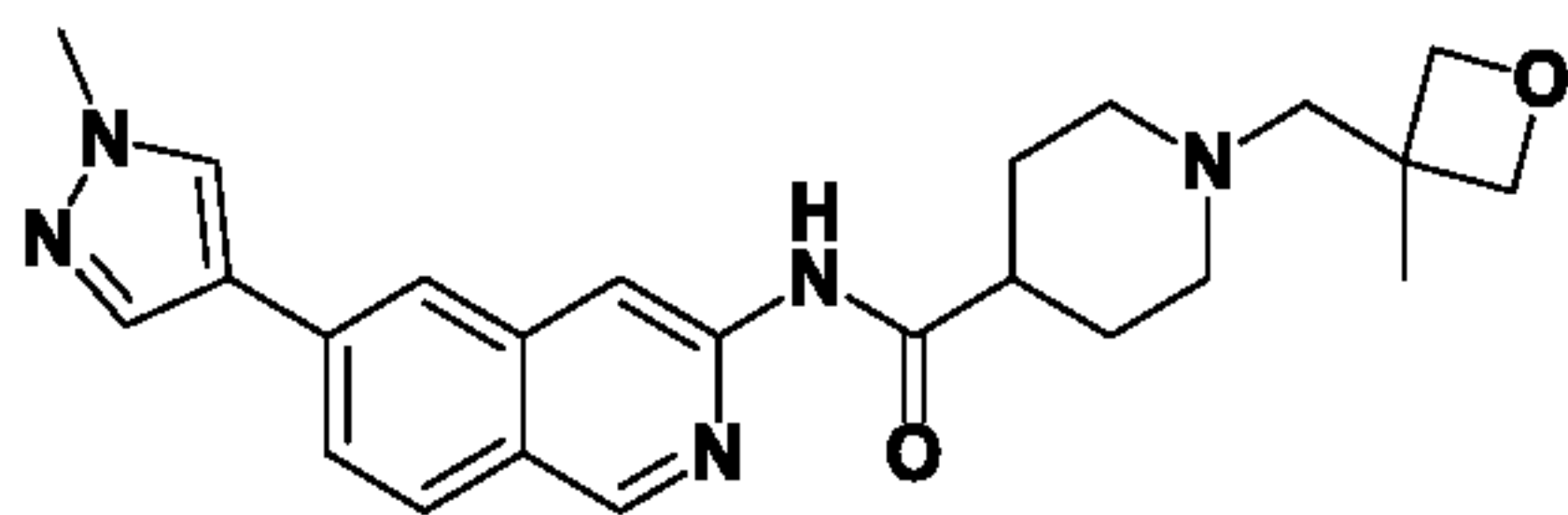
[0685] White solid (147.0 mg, 0.368 mmol, 7.71% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.68 (qd, $J=12.12$, 3.70 Hz, 2 H), 1.74 - 1.83 (m, 2 H), 2.14 - 2.23 (m, 2 H), 2.52 -

2.59 (m, 1 H), 2.72 (td, $J=15.57$, 4.25 Hz, 2 H), 2.96 (br d, $J=11.53$ Hz, 2 H), 3.90 (s, 3 H), 6.13 (tt, $J=55.75$, 4.15 Hz, 1 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.07 (s, 1 H), 8.34 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.47 (s, 1 H); ESIMS found for $C_{21}H_{23}F_2N_5O$ m/z 400.2 (M+1).

**85**

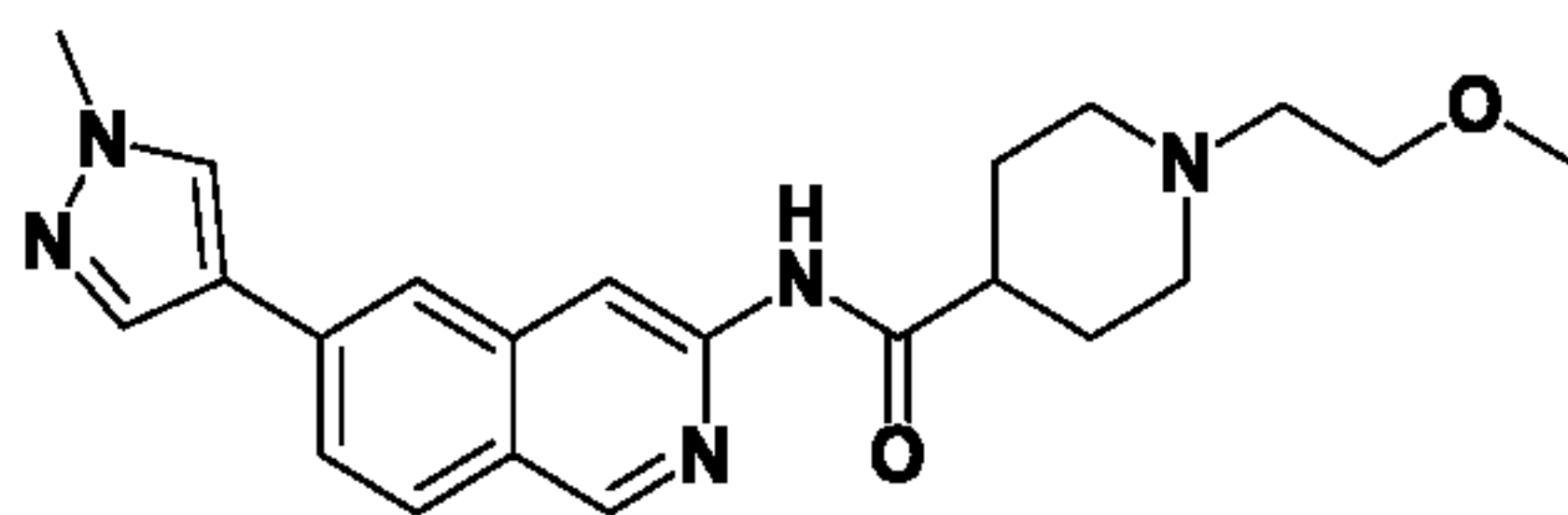
[0686] 1-(2-Fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **85**.

[0687] Off-white solid (110.0 mg, 0.269 mmol, 47.4% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.31 (d, $J=21.45$ Hz, 6 H), 1.64 - 1.81 (m, 4 H), 2.10 (td, $J=11.53$, 2.74 Hz, 2 H), 2.45 (t, $J=22.85$ Hz, 2 H), 2.51 - 2.57 (m, 1 H), 2.95 (br d, $J=11.53$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51$, 1.37 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.46 (s, 1 H); ESIMS found for $C_{23}H_{28}FN_5O$ m/z 410.2 (M+1).

**87**

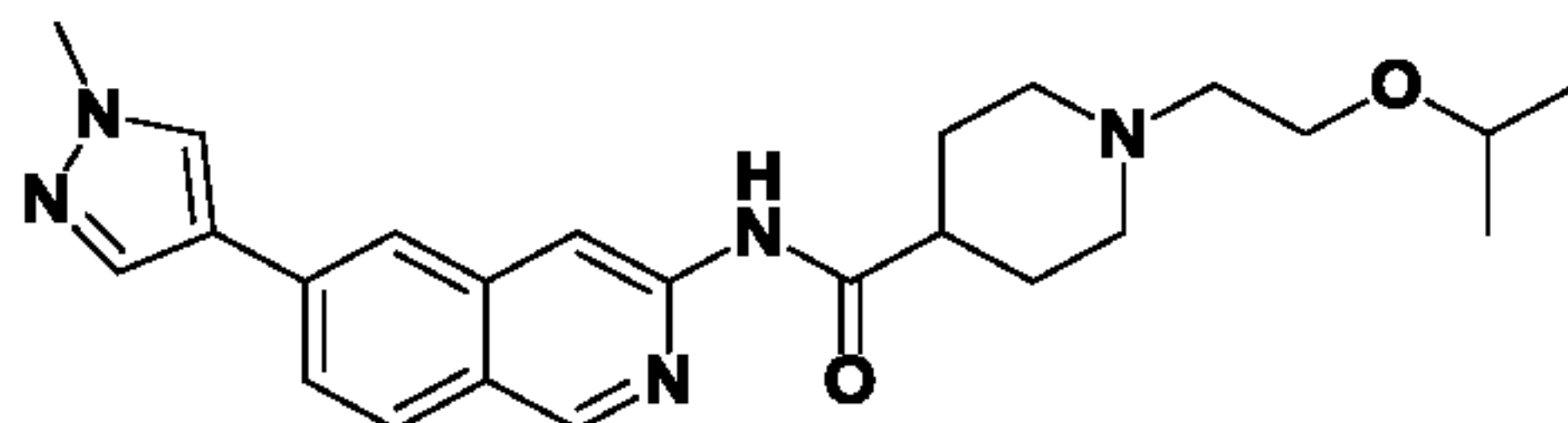
[0688] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide **87**.

[0689] White solid (58.0 mg, 0.138 mmol, 57.8% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.31 (s, 3 H), 1.59 - 1.70 (m, 2 H), 1.71 - 1.79 (m, 2 H), 1.97 (td, $J=11.53$, 2.47 Hz, 2 H), 2.48 (s, 2 H), 2.51 - 2.57 (m, 1 H), 2.62 (br d, $J=11.25$ Hz, 2 H), 3.90 (s, 3 H), 4.19 (d, $J=5.49$ Hz, 2 H), 4.36 (d, $J=5.76$ Hz, 2 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.47 (s, 1 H); ESIMS found for $C_{24}H_{29}N_5O_2$ m/z 420.3 (M+1).

**89**

[0690] 1-(2-Methoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **89**.

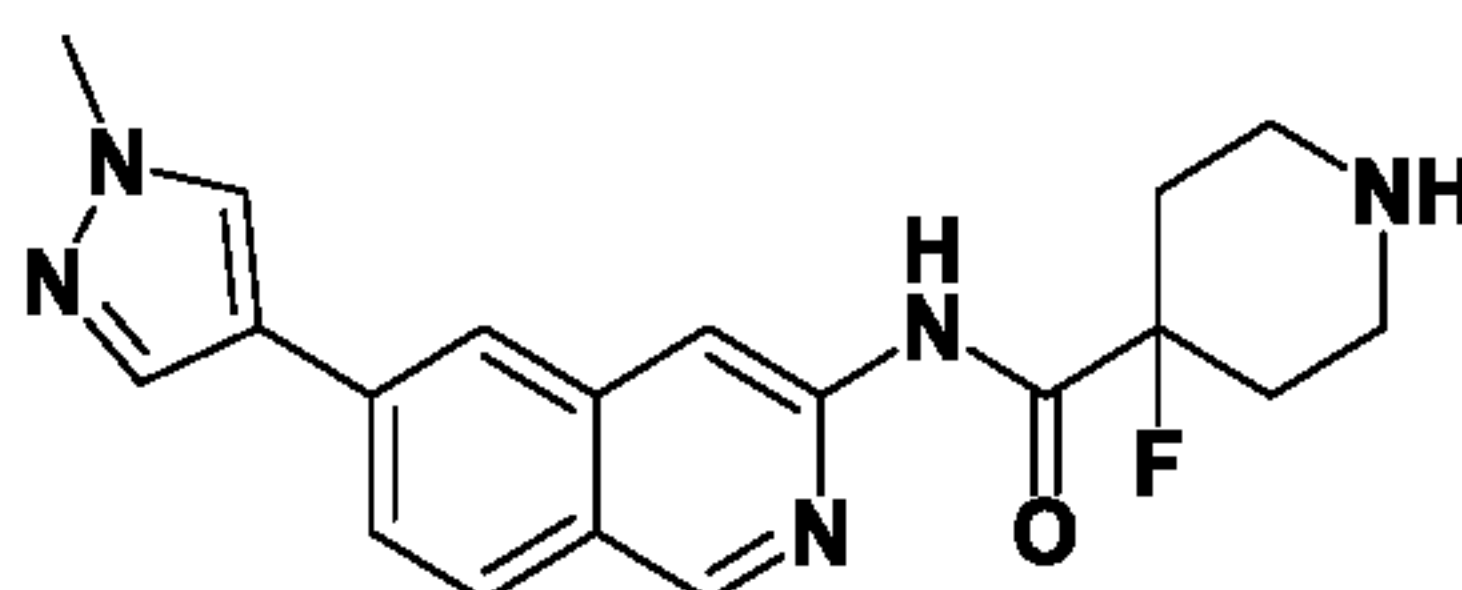
[0691] White solid (32.0 mg, 0.081 mmol, 28.7% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.59 - 1.71 (m, 2 H), 1.73 - 1.81 (m, 2 H), 1.92 - 2.04 (m, 2 H), 2.46 (t, $J=5.90$ Hz, 2 H), 2.51 - 2.58 (m, 1 H), 2.92 (br d, $J=11.25$ Hz, 2 H), 3.24 (s, 3 H), 3.43 (t, $J=6.04$ Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.08 (d, $J=0.82$ Hz, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.46 (s, 1 H); ESIMS found for $\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_2$ m/z 394.2 (M+1).



90

[0692] 1-(2-Isopropoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **90**.

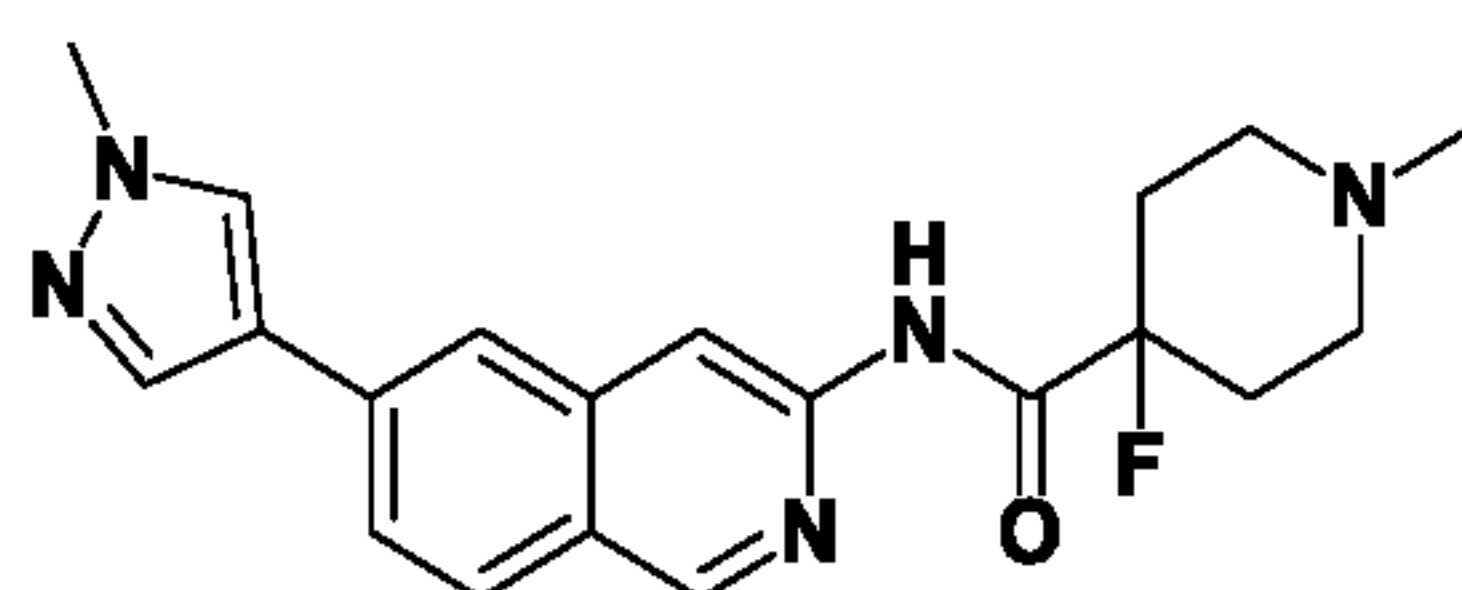
[0693] Off-white solid (71.0 mg, 0.168 mmol, 56.5% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.08 (d, $J=6.04$ Hz, 7 H), 1.59 - 1.71 (m, 2 H), 1.73 - 1.82 (m, 2 H), 1.98 (td, $J=11.60$, 2.06 Hz, 2 H), 2.44 (t, $J=6.17$ Hz, 2 H), 2.51 - 2.58 (m, 1 H), 2.92 (br d, $J=11.53$ Hz, 2 H), 3.46 (t, $J=6.31$ Hz, 2 H), 3.53 (dt, $J=12.14$, 6.14 Hz, 1 H), 3.90 (s, 3 H), 7.74 (dd, $J=8.64$, 1.51 Hz, 1 H), 7.99 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.45 (s, 1 H); ESIMS found for $\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_2$ m/z 422.2 (M+1).



91

[0694] 4-Fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **91**.

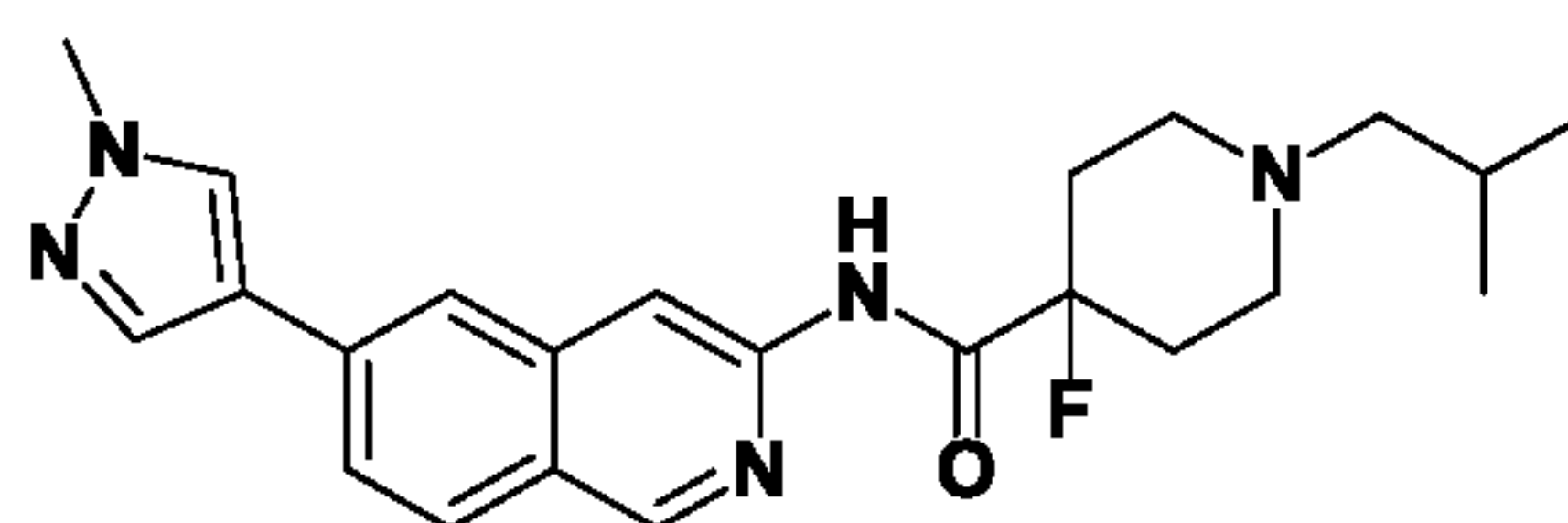
[0695] White solid (54.0 mg, 0.153 mmol). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.79 - 1.90 (m, 2 H), 1.93 - 2.12 (m, 2 H), 2.74 (td, $J=12.28$, 2.33 Hz, 2 H), 2.86 - 2.94 (m, 2 H), 3.90 (s, 3 H), 7.81 (dd, $J=8.64$, 1.51 Hz, 1 H), 8.05 (d, $J=8.51$ Hz, 1 H), 8.09 (s, 1 H), 8.12 (s, 1 H), 8.36 (s, 1 H), 8.40 (s, 1 H), 9.08 (s, 1 H), 9.78 (d, $J=4.39$ Hz, 1 H); ESIMS found for $\text{C}_{19}\text{H}_{20}\text{FN}_5\text{O}$ m/z 354.2 (M+1).



92

[0696] 4-Fluoro-1-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide **92**.

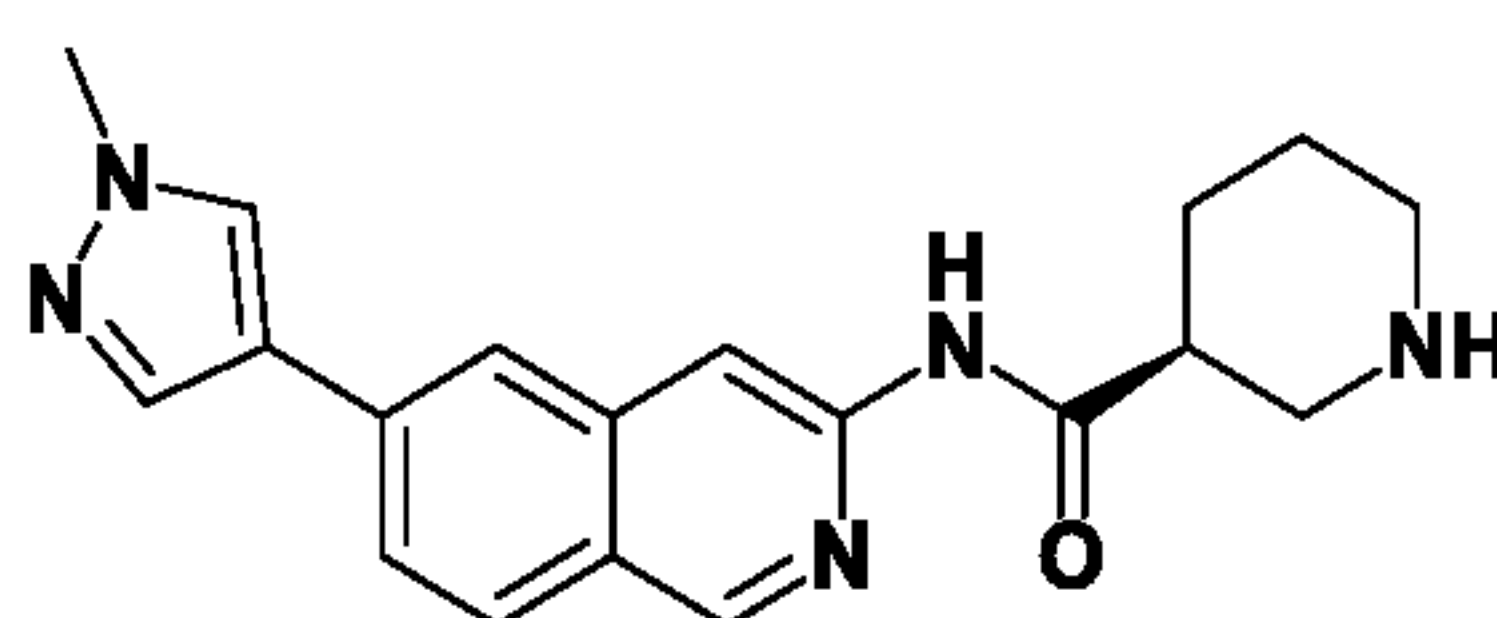
[0697] White solid (57.0 mg, 0.155 mmol, 68.5% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.89 - 2.01 (m, 2 H), 2.05 - 2.20 (m, 4 H), 2.22 (s, 3 H), 2.69 - 2.77 (m, 2 H), 3.91 (s, 3 H), 7.81 (dd, *J*=8.51, 1.37 Hz, 1 H), 8.05 (d, *J*=8.78 Hz, 1 H), 8.09 (s, 1 H), 8.11 (s, 1 H), 8.36 (s, 1 H), 8.40 (s, 1 H), 9.08 (s, 1 H), 9.87 (d, *J*=4.12 Hz, 1 H); ESIMS found for C₂₀H₂₂FN₅O *m/z* 368.2 (M+1).



96

[0698] 4-Fluoro-1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide **96**.

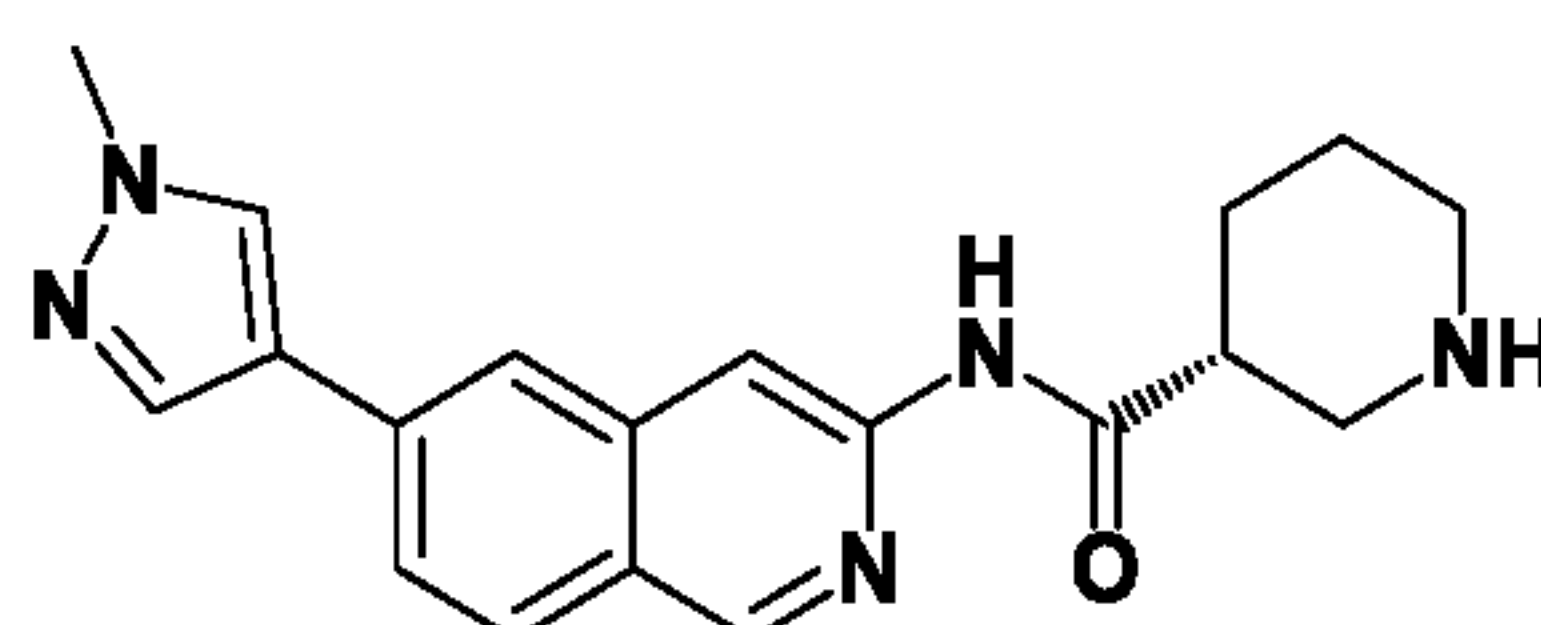
[0699] White solid (37.0 mg, 0.090 mmol, 39.9% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.88 (d, *J*=6.59 Hz, 6 H), 1.74 - 1.85 (m, 1 H), 1.91 - 2.01 (m, 2 H), 2.09 (d, *J*=7.41 Hz, 2 H), 2.11 - 2.21 (m, 4 H), 2.78 (br d, *J*=8.23 Hz, 2 H), 3.90 (s, 3 H), 7.81 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.05 (d, *J*=8.51 Hz, 1 H), 8.10 (s, 1 H), 8.12 (s, 1 H), 8.37 (s, 1 H), 8.40 (s, 1 H), 9.08 (s, 1 H), 9.86 (d, *J*=4.39 Hz, 1 H); ESIMS found for C₂₃H₂₈FN₅O *m/z* 410.2 (M+1).



110

[0700] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide **110**.

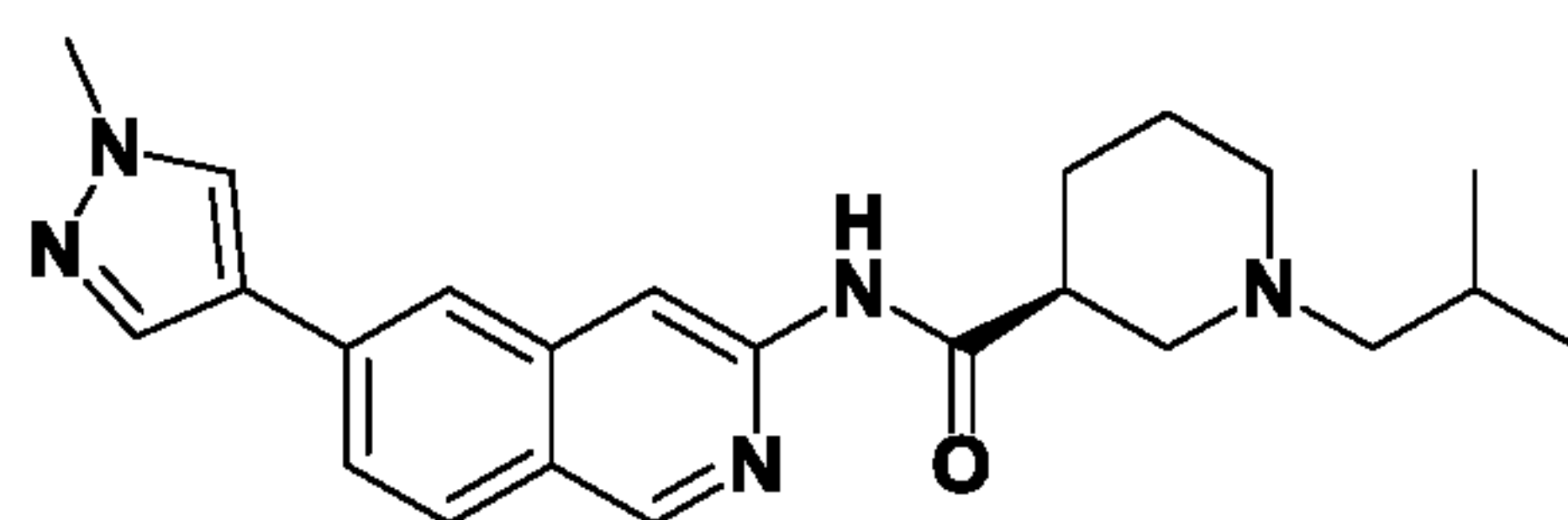
[0701] White solid (37.7 mg, 0.112 mmol, 47.0% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.34 - 1.48 (m, 1 H), 1.55 - 1.64 (m, 1 H), 1.64 - 1.73 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.52 - 2.67 (m, 2 H), 2.71 - 2.85 (m, 2 H), 2.98 (dd, *J*=11.94, 3.16 Hz, 1 H), 3.90 (s, 3 H), 7.74 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.00 (d, *J*=8.51 Hz, 1 H), 8.03 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.42 (s, 1 H), 9.01 (s, 1 H), 10.75 (s, 1 H); ESIMS found for C₁₉H₂₁N₅O *m/z* 336.1 (M+1).



111

[0702] (R)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide 111.

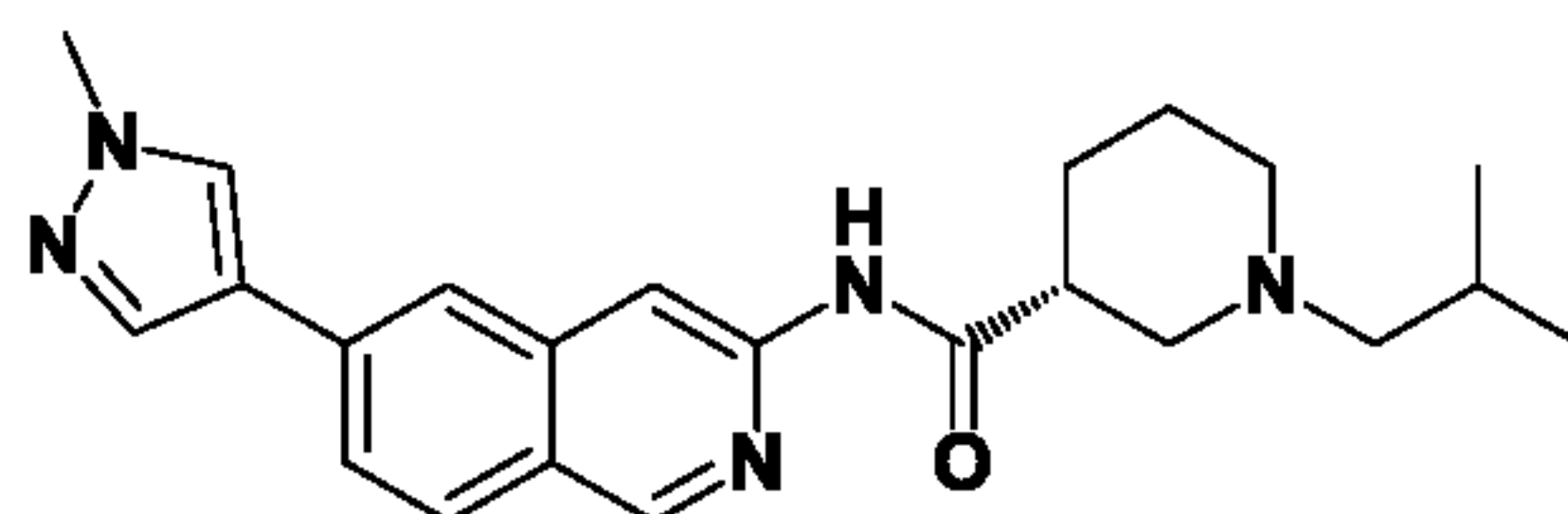
[0703] White solid (6.5 mg, 0.019 mmol, 44.8% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.33 - 1.49 (m, 1 H), 1.55 - 1.64 (m, 1 H), 1.64 - 1.74 (m, 1 H), 1.81 - 1.93 (m, 1 H), 2.52 - 2.66 (m, 2 H), 2.71 - 2.86 (m, 2 H), 2.98 (dd, *J*=11.80, 2.74 Hz, 1 H), 3.90 (s, 3 H), 7.74 (dd, *J*=8.64, 1.51 Hz, 1 H), 8.00 (d, *J*=8.51 Hz, 1 H), 8.03 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.42 (s, 1 H), 9.01 (s, 1 H), 10.75 (s, 1 H); ESIMS found for C₁₉H₂₁N₅O *m/z* 336.2 (M+1).



112

[0704] (S)-1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide 112.

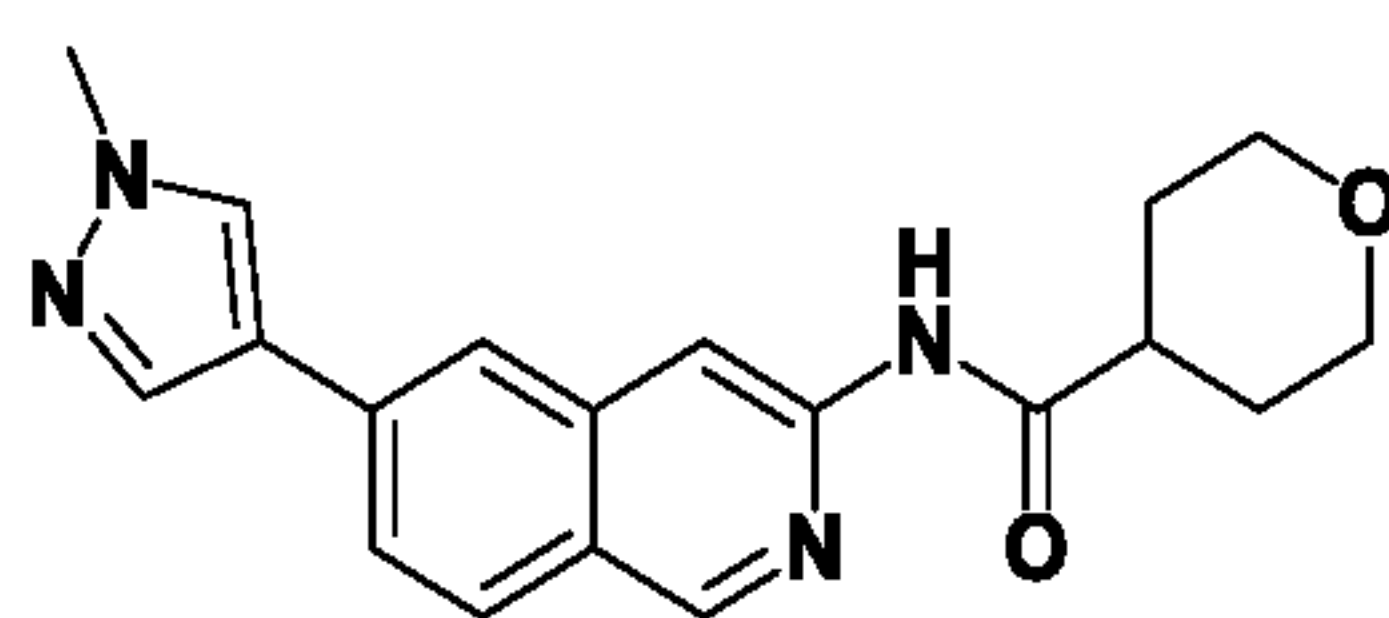
[0705] Beige solid (17.8 mg, 0.045 mmol, 4.7% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.88 (d, *J*=6.59 Hz, 3 H), 0.90 (d, *J*=6.59 Hz, 3 H), 1.48 - 1.60 (m, 2 H), 1.64 - 1.73 (m, 1 H), 1.77 - 1.86 (m, 2 H), 2.07 (d, *J*=7.41 Hz, 2 H), 2.10 (br dd, *J*=4.25, 3.16 Hz, 1 H), 2.30 (br d, *J*=7.14 Hz, 1 H), 2.55 - 2.63 (m, 1 H), 2.76 (br d, *J*=7.68 Hz, 2 H), 3.90 (s, 3 H), 7.74 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.00 (d, *J*=8.78 Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.42 (s, 1 H), 9.01 (s, 1 H), 10.68 (s, 1 H); ESIMS found for C₂₃H₂₉N₅O *m/z* 392.2 (M+1).



113

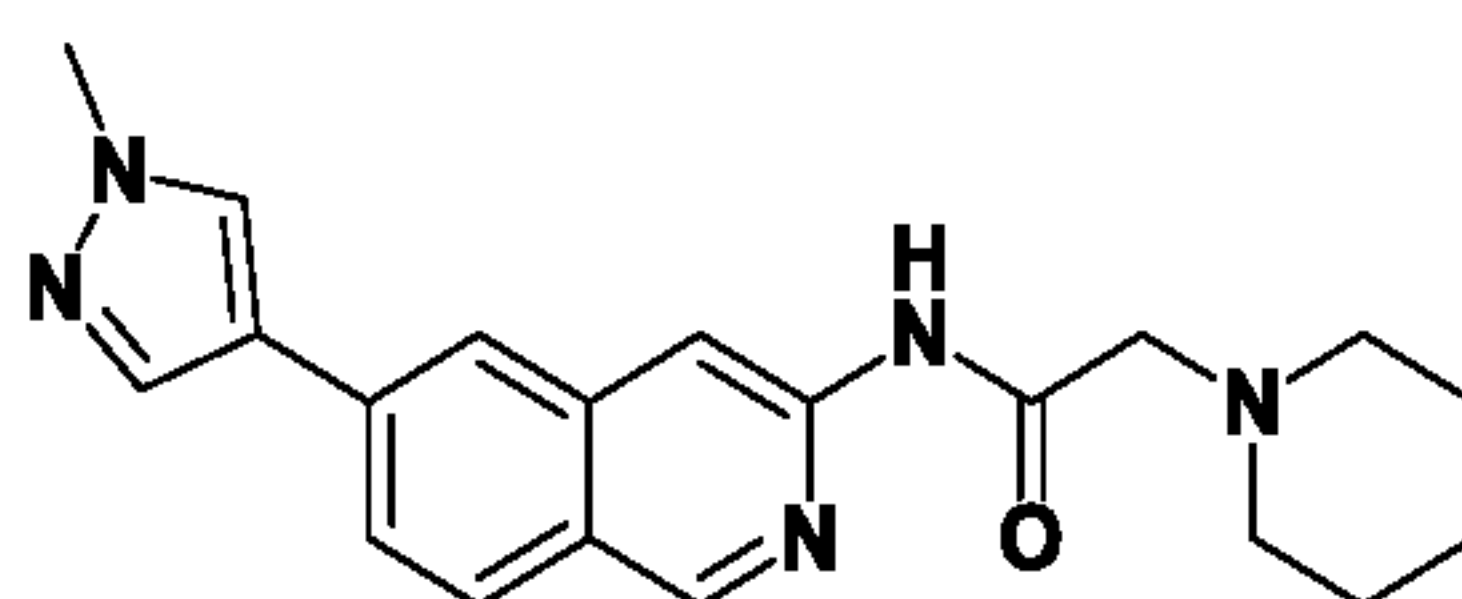
[0706] (R)-1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide 113.

[0707] Beige solid (110 mg, 0.281 mmol, 26.8% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.88 (3 H, d, *J*=6.59 Hz), 0.90 (3 H, d, *J*=6.59 Hz), 1.49 - 1.59 (2 H, m), 1.68 (1 H, br dd, *J*=8.23, 3.29 Hz), 1.76 - 1.88 (2 H, m), 2.07 (2 H, d, *J*=7.41 Hz), 2.10 (1 H, br s), 2.30 (1 H, br d, *J*=6.59 Hz), 2.55 - 2.62 (1 H, m), 2.76 (2 H, br d, *J*=7.68 Hz), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.37 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.42 (1 H, s), 9.01 (1 H, s), 10.68 (1 H, s); ESIMS found for C₂₃H₂₉N₅O *m/z* 392.2 (M+1).

**114**

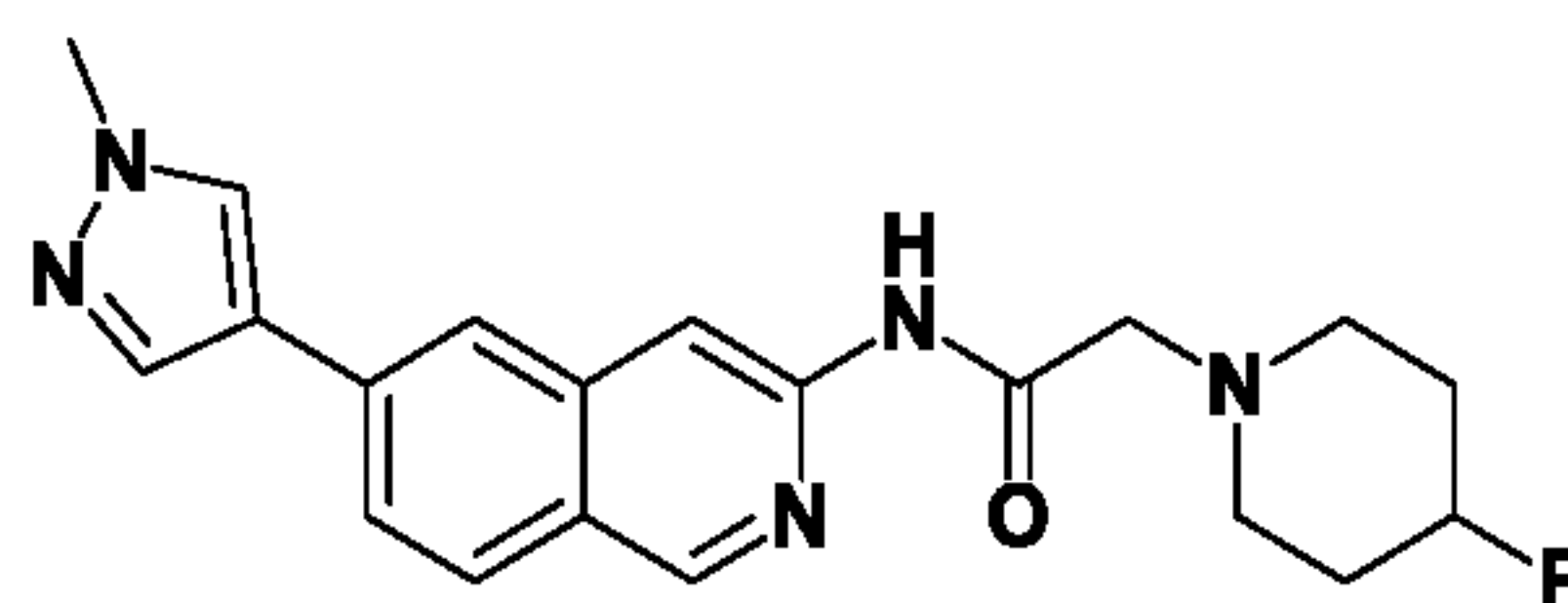
[0708] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide **114**.

[0709] White solid (95.0 mg, 0.282 mmol, 63.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.62 - 1.80 (m, 4 H), 2.76 - 2.87 (m, 1 H), 3.32 - 3.38 (m, 2 H), 3.90 (s, 3 H), 3.91 - 3.95 (m, 2 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.03 (s, 1 H), 10.49 (s, 1 H); ESIMS found for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2$ m/z 337.15 (M+1).

**115**

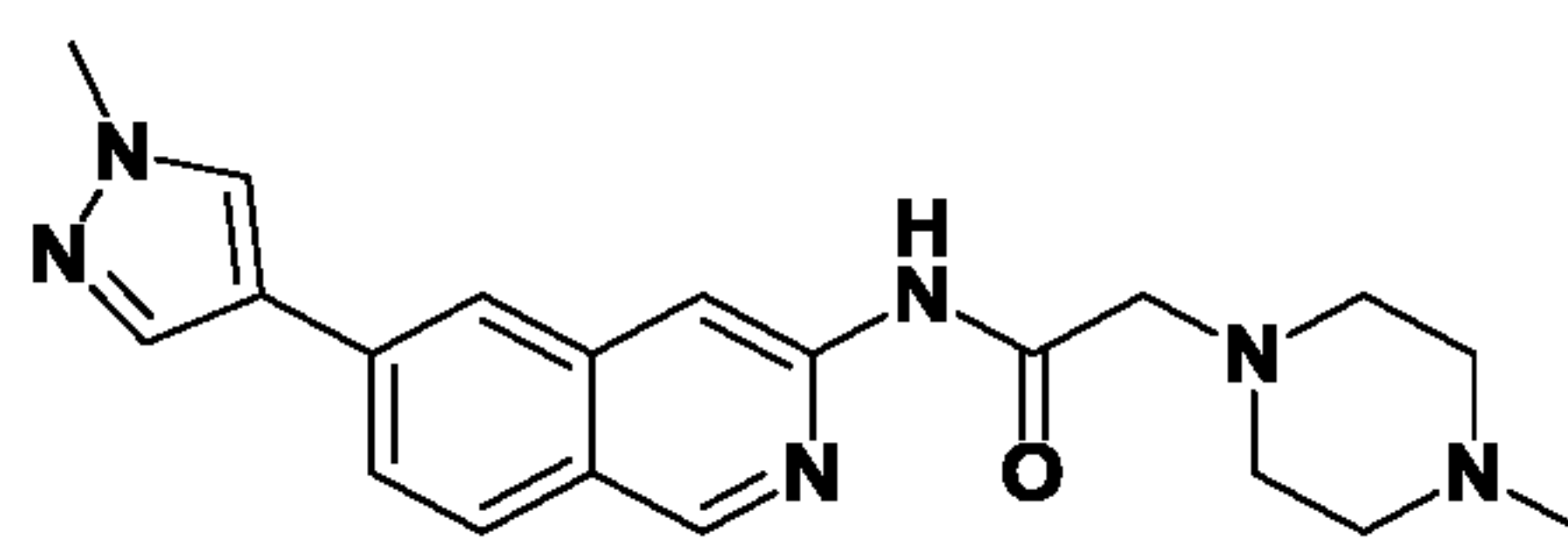
[0710] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide **115**.

[0711] Off-white solid (23.0 mg, 0.066 mmol, 16.5% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.43 (2 H, br d, $J=4.39$ Hz), 1.59 (4 H, quin, $J=5.56$ Hz), 2.52 (4 H, br s), 3.17 (2 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, $J=8.51$, 1.37 Hz), 8.02 (1 H, d, $J=8.51$ Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.91 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}$ m/z 350.2 (M+1).

**116**

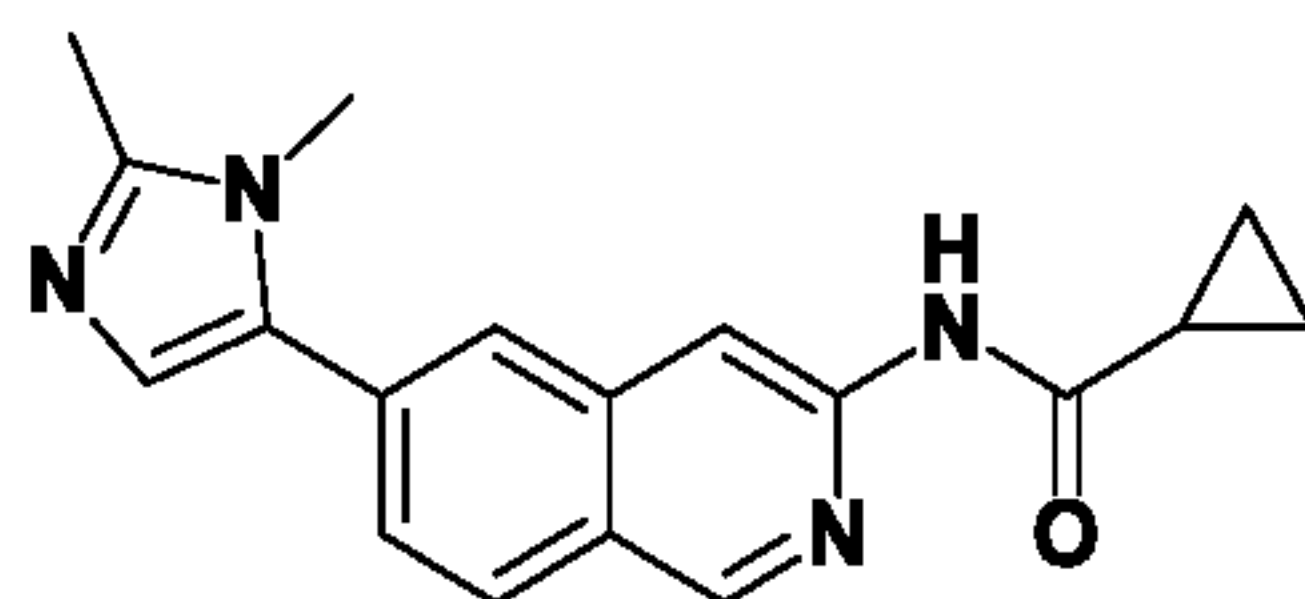
[0712] 2-(4-Fluoropiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **116**.

[0713] Off-white solid (80.0 mg, 0.218 mmol, 44.3% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.73 - 1.86 (2 H, m), 1.87 - 2.01 (2 H, m), 2.54 (2 H, ddd, $J=11.39$, 7.41, 3.70 Hz), 2.67 - 2.76 (2 H, m), 3.24 (2 H, s), 4.66 - 4.83 (1 H, m), 7.77 (1 H, dd, $J=8.51$, 1.65 Hz), 8.02 (1 H, d, $J=8.51$ Hz), 8.10 (2 H, s), 8.36 (1 H, s), 8.44 (1 H, s), 9.04 (1 H, s), 9.98 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{22}\text{FN}_5\text{O}$ m/z 368.2 (M+1).

**118**

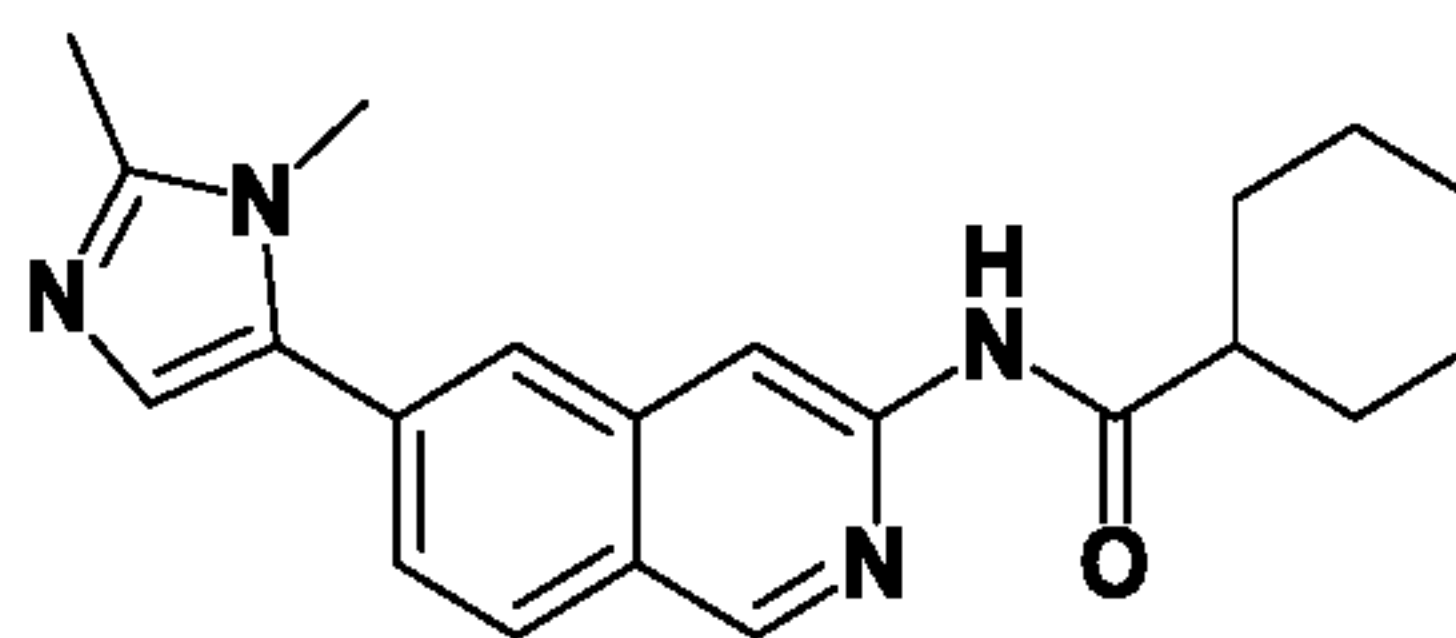
[0714] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **118**.

[0715] Beige solid (18.0 mg, 0.049 mmol, 59.8% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 2.19 (3 H, s), 2.33 - 2.46 (4 H, m), 2.58 (4 H, br s), 3.22 (2 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.93 (1 H, s); ESIMS found for C₂₀H₂₄N₆O *m/z* 365.2 (M+1).

**119**

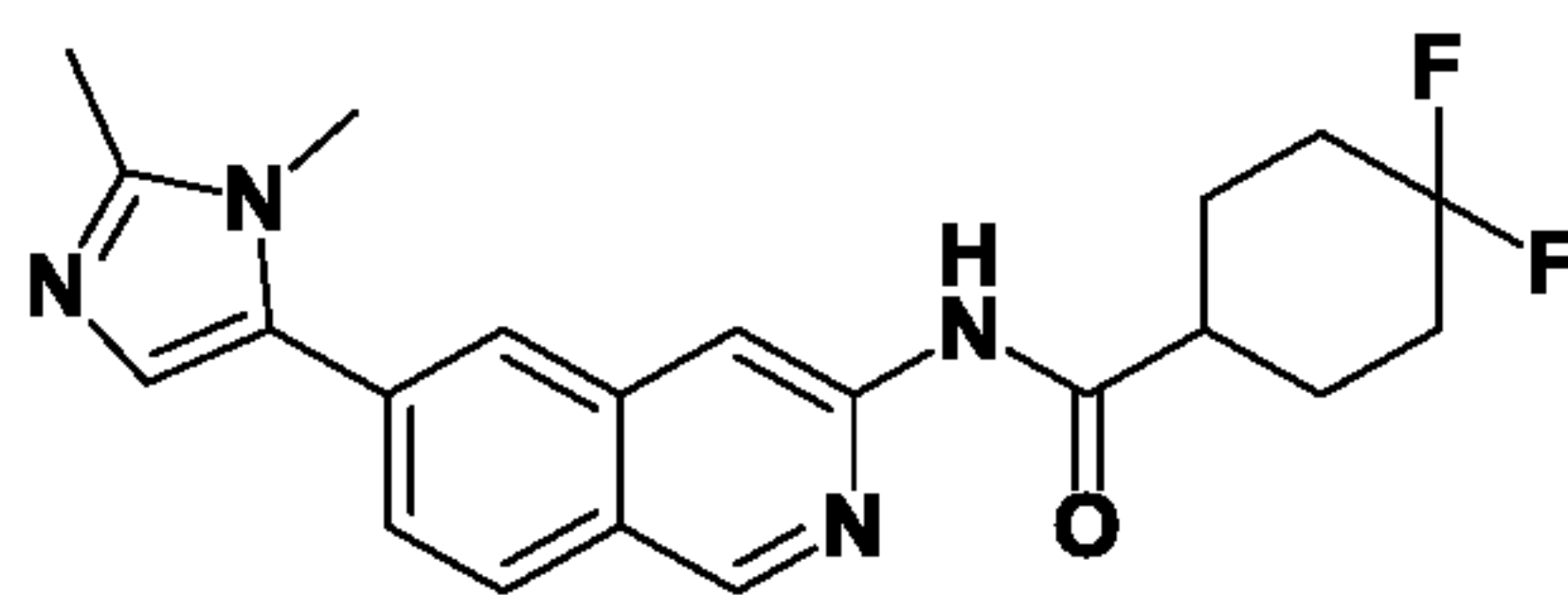
[0716] N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide **119**.

[0717] Beige solid (70.0 mg, 0.228 mmol, 28.9% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.78 - 0.91 (4 H, m), 2.02 - 2.13 (1 H, m), 2.39 (3 H, s), 3.65 (3 H, s), 7.11 (1 H, s), 7.59 (1 H, dd, *J*=8.51, 1.37 Hz), 7.88 (1 H, s), 8.07 (1 H, d, *J*=8.51 Hz), 8.49 (1 H, s), 9.12 (1 H, s), 10.89 (1 H, s); ESIMS found for C₁₈H₁₈N₄O *m/z* 307.1 (M+1).

**120**

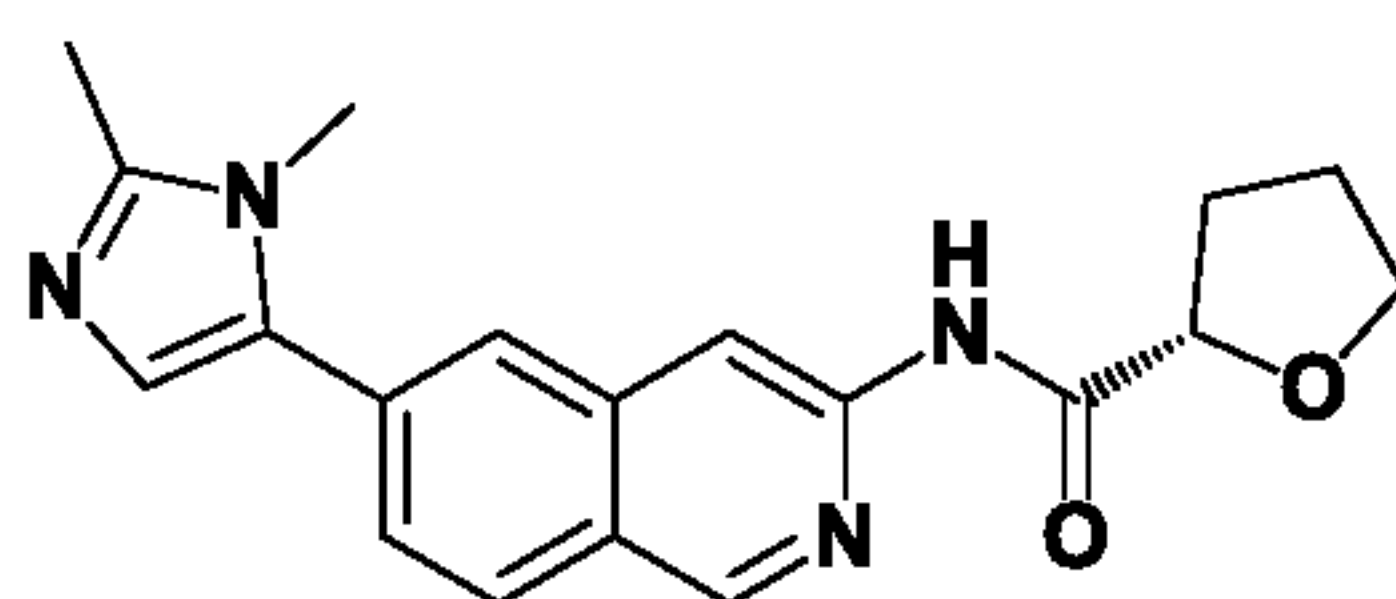
[0718] N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexanecarboxamide **120**.

[0719] Beige solid (20.0 mg, 0.056 mmol, 18.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.17 - 1.34 (3 H, m), 1.44 (2 H, qd, *J*=12.21, 2.61 Hz), 1.66 (1 H, br d, *J*=11.53 Hz), 1.71 - 1.79 (2 H, m), 1.83 (2 H, br d, *J*=13.17 Hz), 2.39 (3 H, br s), 2.52 - 2.62 (1 H, m), 3.66 (3 H, s), 7.13 (1 H, br s), 7.58 (1 H, dd, *J*=8.51, 1.37 Hz), 7.89 (1 H, s), 8.07 (1 H, d, *J*=8.51 Hz), 8.51 (1 H, s), 9.11 (1 H, s), 10.43 (1 H, s); ESIMS found for C₂₁H₂₄N₄O *m/z* 349.0 (M+1).

**121**

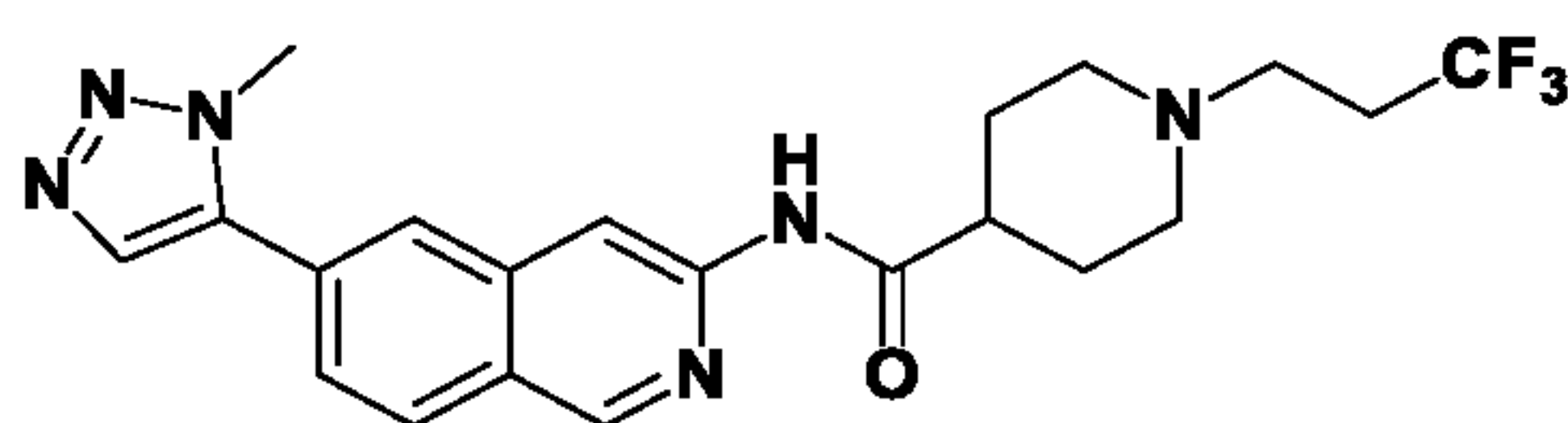
[0720] N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4,4-difluorocyclohexanecarboxamide **121**.

[0721] Off-white solid (40.0 mg, 0.104 mmol, 38.4% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.66 - 1.76 (2 H, m), 1.77 - 1.91 (2 H, m), 1.92 - 2.01 (2 H, m), 2.08 - 2.21 (2 H, m), 2.39 (3 H, s), 2.71 (1 H, br t, *J*=10.43 Hz), 3.66 (3 H, s), 7.12 (1 H, br s), 7.61 (1 H, dd, *J*=8.51, 1.37 Hz), 7.91 (1 H, s), 8.08 (1 H, d, *J*=8.51 Hz), 8.51 (1 H, s), 9.12 (1 H, s), 10.63 (1 H, s); ESIMS found for C₂₁H₂₂F₂N₄O *m/z* 385.2 (M+1).

**188**

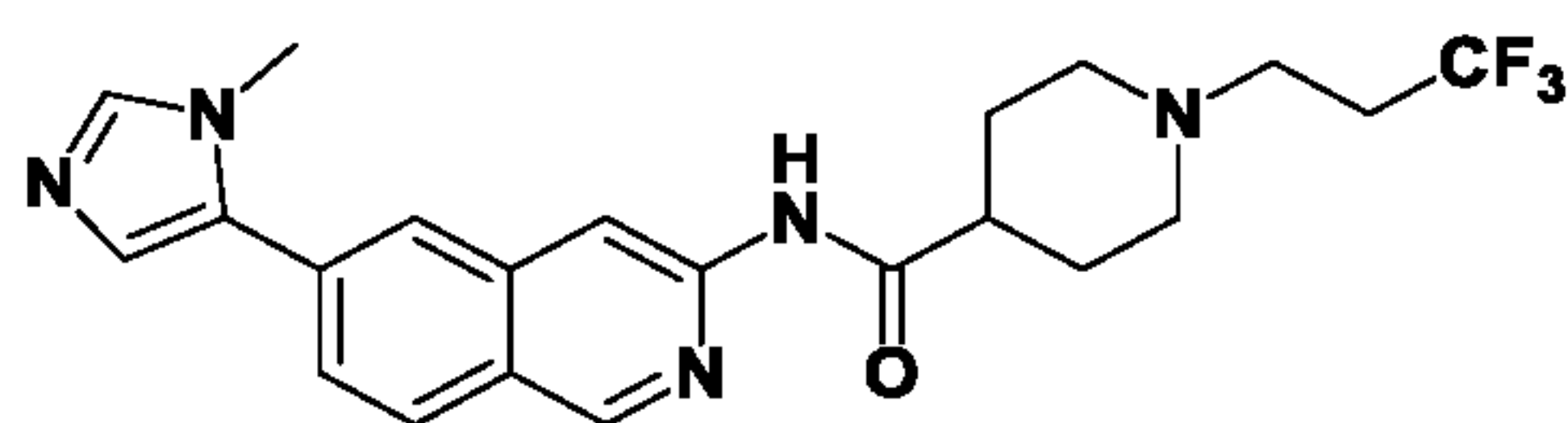
[0722] (S)-N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide **188**.

[0723] Light yellow solid (60.0 mg, 0.178 mmol, 57.3% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.83 - 1.95 (2 H, m), 1.97 - 2.07 (1 H, m), 2.19 - 2.30 (1 H, m), 2.39 (3 H, s), 3.67 (3 H, s), 3.82 - 3.91 (1 H, m), 3.98 - 4.07 (1 H, m), 4.54 (1 H, dd, *J*=8.23, 5.49 Hz), 7.13 (1 H, s), 7.64 (1 H, dd, *J*=8.51, 1.65 Hz), 7.96 (1 H, s), 8.11 (1 H, d, *J*=8.51 Hz), 8.50 (1 H, s), 9.14 (1 H, s), 9.85 (1 H, s); ESIMS found for C₁₉H₂₀N₄O₂ *m/z* 337.1 (M+1).

**248**

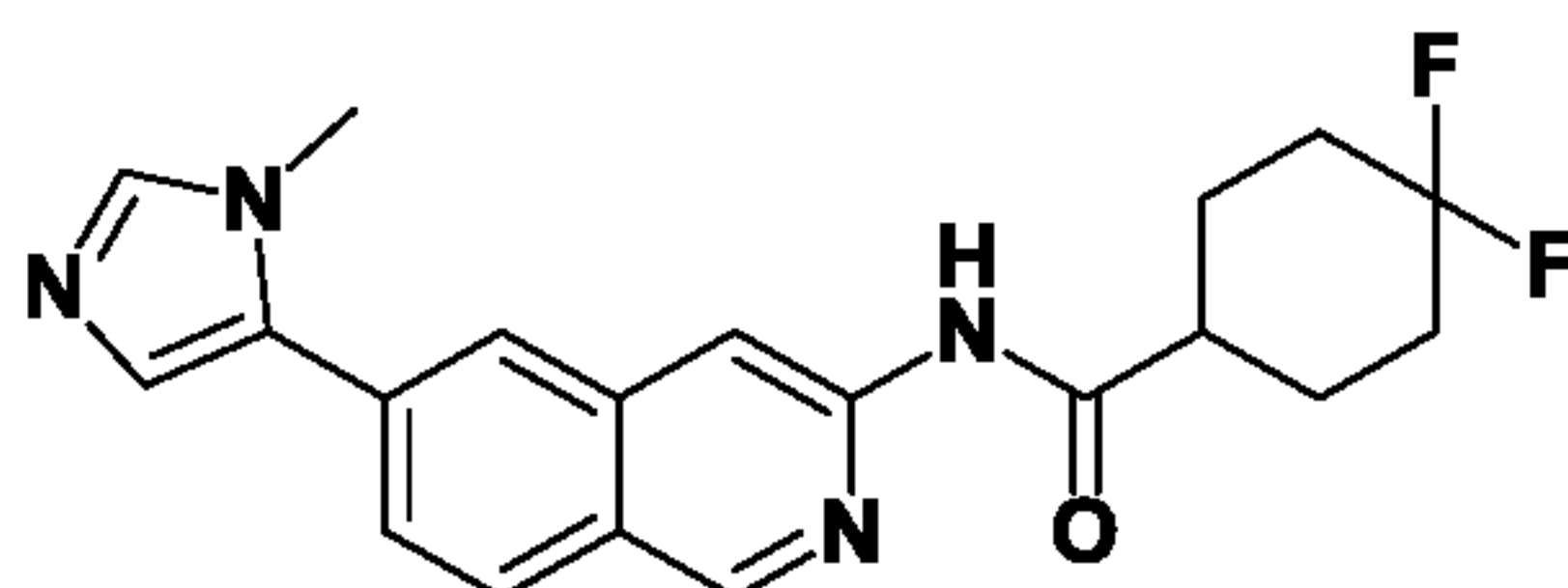
[0724] N-(6-(1-Methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **248**.

[0725] Off-white solid (99.0 mg, 0.229 mmol, 50.3% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.61 - 1.74 (m, 2 H), 1.80 (br d, *J*=10.70 Hz, 2 H), 1.97 (br t, *J*=11.11 Hz, 2 H), 2.40 - 2.61 (m, 5 H), 2.89 - 3.00 (m, 2 H), 4.20 (s, 3 H), 7.68 - 7.77 (m, 1 H), 8.10 (s, 1 H), 8.17 - 8.21 (m, 2 H), 8.60 (s, 1 H), 9.21 (s, 1 H), 10.62 (br s, 1 H); ESIMS found for C₂₁H₂₃F₃N₆O *m/z* 433.2 (M+1).

**262**

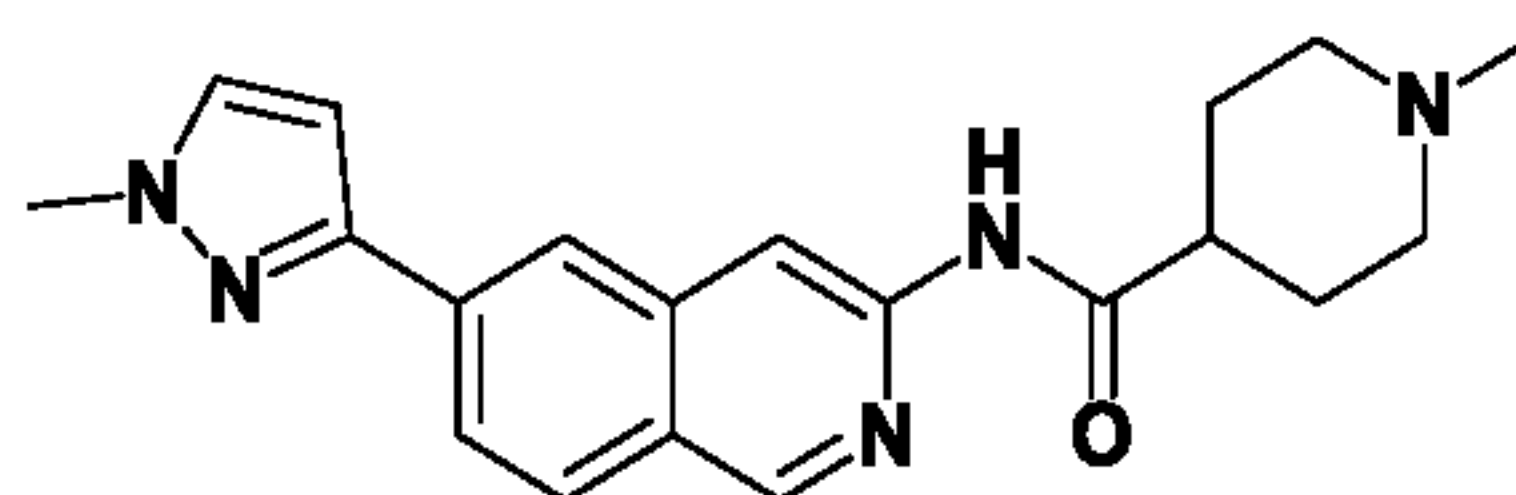
[0726] N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **262**.

[0727] White solid (82.5 mg, 0.191 mmol, 82.4% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.68 (qd, *J*=12.17, 3.57 Hz, 2 H), 1.81 (br d, *J*=11.25 Hz, 2 H), 1.97 - 2.11 (m, 2 H), 2.50 (dt, *J*=3.64, 1.89 Hz, 2 H), 2.52 - 2.62 (m, 3 H), 2.97 (br d, *J*=10.43 Hz, 2 H), 3.83 (s, 3 H), 7.30 (d, *J*=0.82 Hz, 1 H), 7.67 (dd, *J*=8.51, 1.65 Hz, 1 H), 7.80 (s, 1 H), 8.00 (s, 1 H), 8.08 (d, *J*=8.51 Hz, 1 H), 8.54 (s, 1 H), 9.12 (s, 1 H), 10.55 (s, 1 H); ESIMS found for C₂₂H₂₄F₃N₅O *m/z* 432.2 (M+1).

**263**

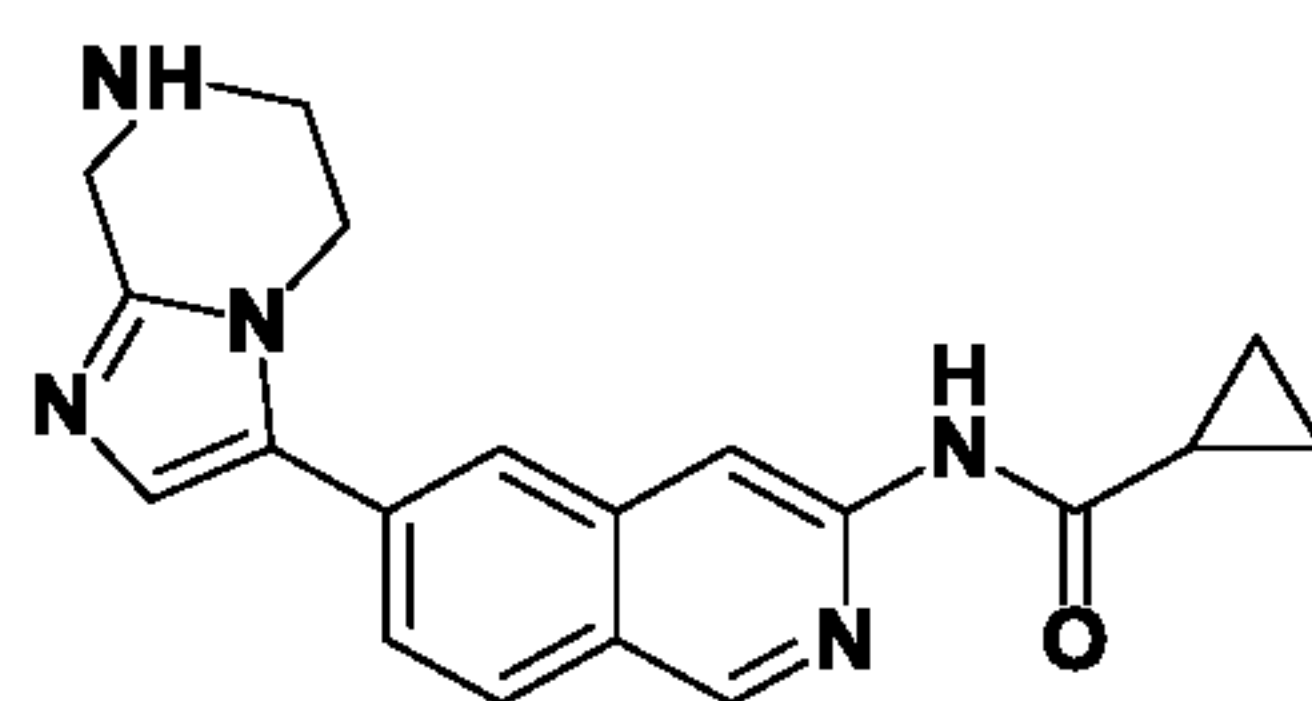
[0728] 4,4-Difluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexanecarboxamide **263**.

[0729] White solid (60.0 mg, 0.162 mmol, 46.0% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.63 - 1.76 (m, 2 H), 1.76 - 1.91 (m, 2 H), 1.95 (br d, *J*=12.90 Hz, 2 H), 2.06 - 2.20 (m, 2 H), 2.71 (br t, *J*=10.84 Hz, 1 H), 3.83 (s, 3 H), 7.30 (d, *J*=0.82 Hz, 1 H), 7.67 (dd, *J*=8.37, 1.78 Hz, 1 H), 7.79 (s, 1 H), 8.01 (d, *J*=0.82 Hz, 1 H), 8.09 (d, *J*=8.78 Hz, 1 H), 8.53 (s, 1 H), 9.13 (s, 1 H), 10.64 (s, 1 H); ESIMS found for C₂₀H₂₀F₂N₄O *m/z* 371.2 (M+1).

**264**

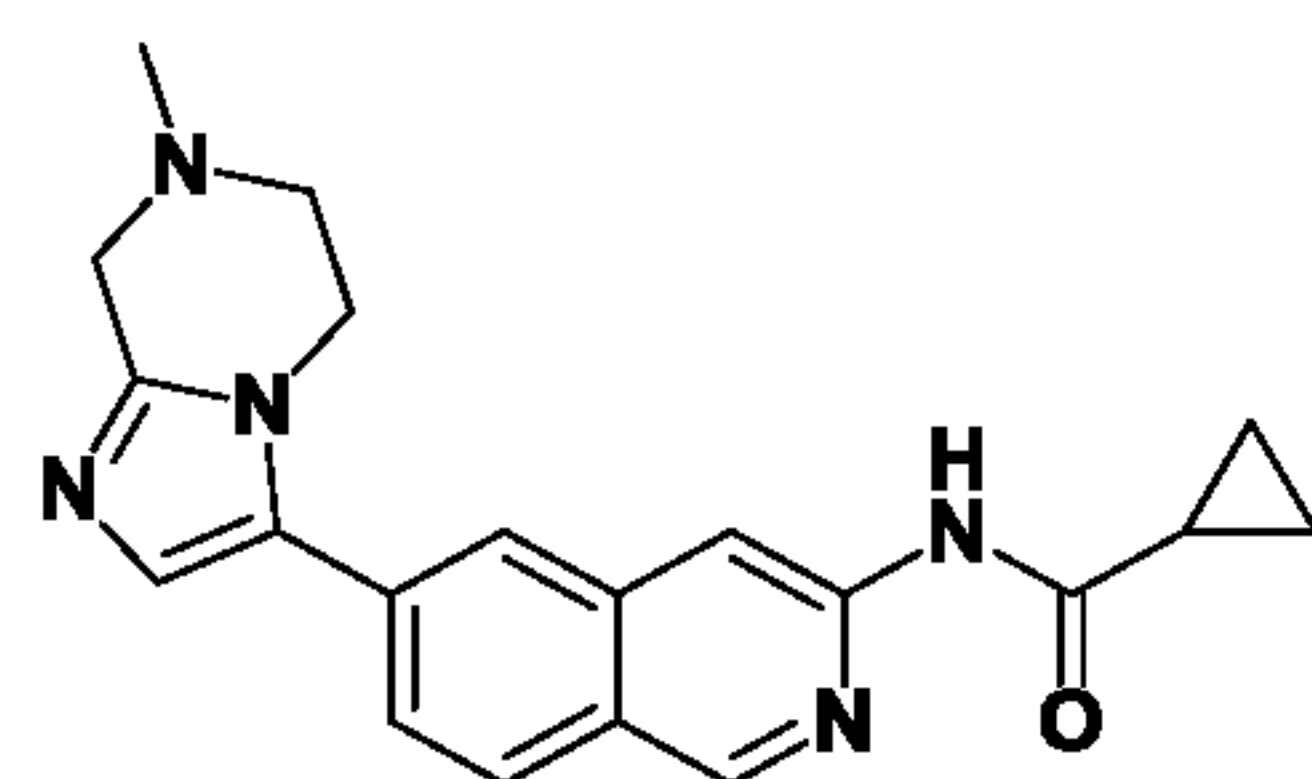
[0730] 1-Methyl-N-(6-(1-methyl-1H-pyrazol-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide **264**.

[0731] White solid (36.5 mg, 0.104 mmol, 48.5% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.60 - 1.72 (m, 2 H), 1.74 - 1.80 (m, 2 H), 1.86 (td, *J*=11.60, 2.06 Hz, 2 H), 2.16 (s, 3 H), 2.45 - 2.56 (m, 1 H), 2.81 (br d, *J*=11.25 Hz, 2 H), 3.93 (s, 3 H), 6.93 (d, *J*=2.20 Hz, 1 H), 7.81 (d, *J*=2.20 Hz, 1 H), 7.95 - 8.01 (m, 1 H), 8.01 - 8.08 (m, 1 H), 8.20 (s, 1 H), 8.49 (s, 1 H), 9.07 (s, 1 H), 10.49 (s, 1 H); ESIMS found for C₂₀H₂₃N₅O *m/z* 350.2 (M+1).

**265**

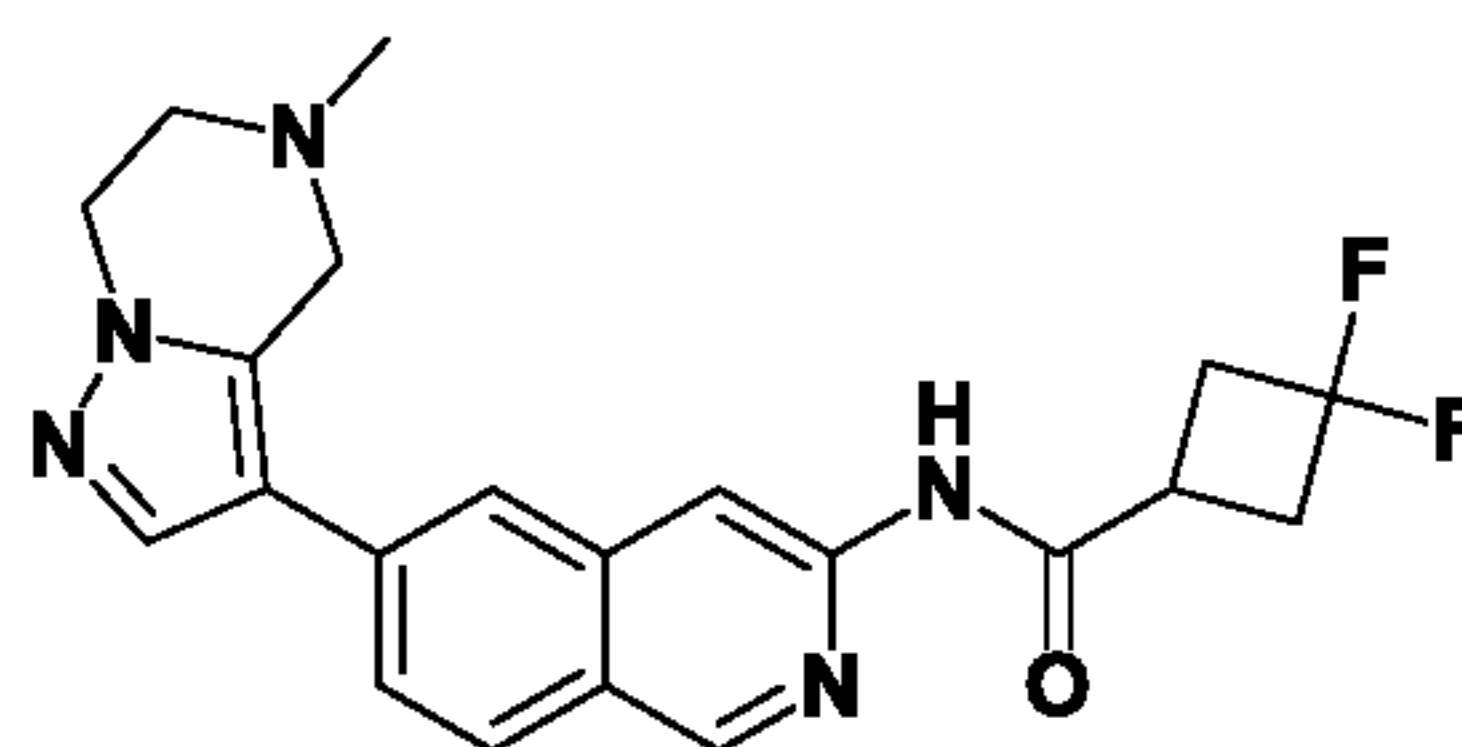
[0732] N-(6-(5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)isoquinolin-3-yl)cyclopropanecarboxamide **265**.

[0733] Off-white solid (168.0 mg, 0.504 mmol, 87.3% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.78 - 0.90 (m, 4 H), 2.03 - 2.13 (m, 1 H), 2.77 (br s, 1 H), 3.07 (t, *J*=5.35 Hz, 2 H), 3.95 (s, 2 H), 4.10 (t, *J*=5.35 Hz, 2 H), 7.28 (s, 1 H), 7.65 (dd, *J*=8.51, 1.65 Hz, 1 H), 7.91 (s, 1 H), 8.06 (d, *J*=8.51 Hz, 1 H), 8.49 (s, 1 H), 9.10 (s, 1 H), 10.87 (s, 1 H); ESIMS found for C₁₉H₁₉N₅O *m/z* 334.1 (M+1).

**266**

[0734] N-(6-(7-Methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)isoquinolin-3-yl)cyclopropanecarboxamide **266**.

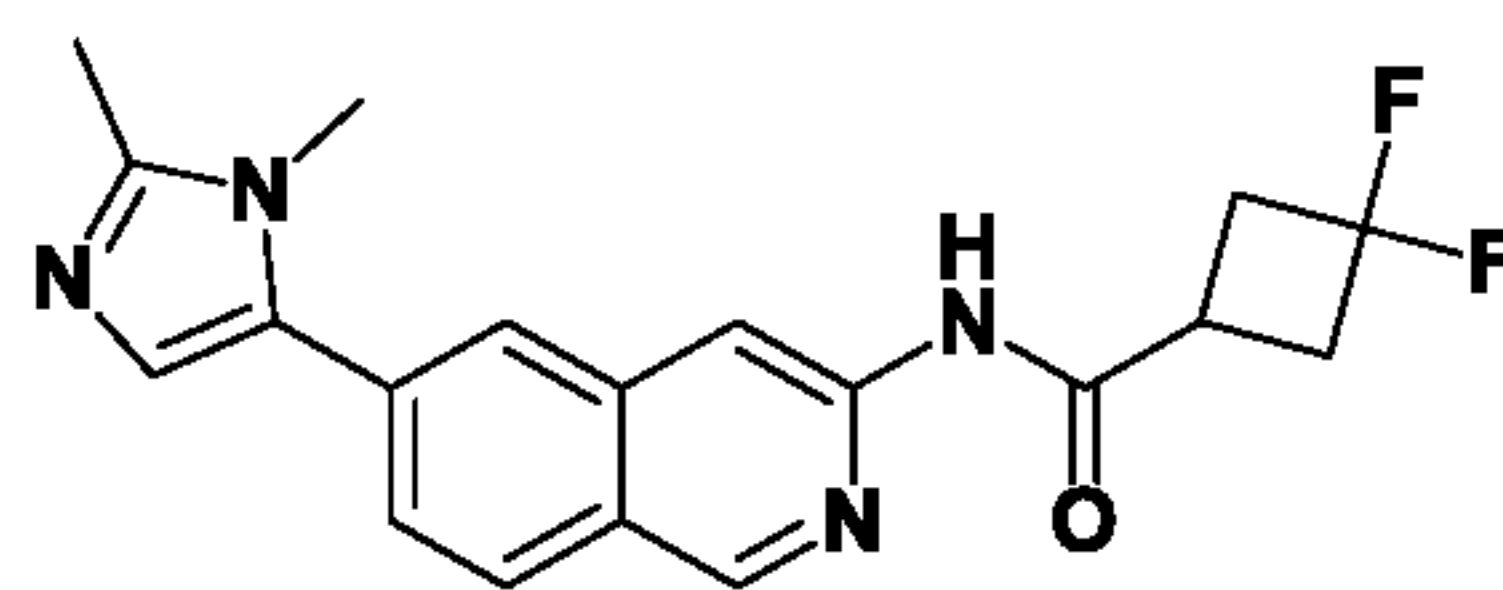
[0735] White solid (75.0 mg, 0.216 mmol, 69.9% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.77 - 0.90 (m, 4 H), 2.01 - 2.13 (m, 1 H), 2.42 (s, 3 H), 2.80 (t, *J*=5.35 Hz, 2 H), 3.63 (s, 2 H), 4.21 (t, *J*=5.35 Hz, 2 H), 7.29 (s, 1 H), 7.66 (dd, *J*=8.51, 1.65 Hz, 1 H), 7.95 (s, 1 H), 8.06 (d, *J*=8.51 Hz, 1 H), 8.49 (s, 1 H), 9.10 (s, 1 H), 10.87 (s, 1 H); ESIMS found for C₂₀H₂₁N₅O *m/z* 348.2 (M+1).

**267**

[0736] 3,3-Difluoro-N-(6-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-3-yl)isoquinolin-3-yl)cyclobutanecarboxamide **267**.

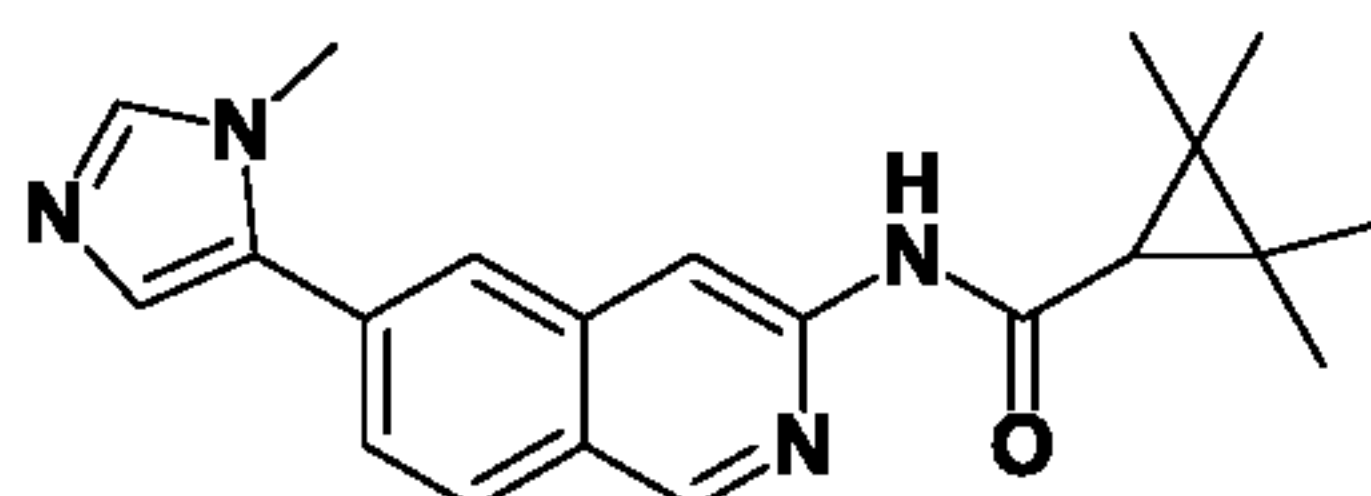
[0737] Beige solid (65.0 mg, 0.164 mmol, 28.5% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 2.55 (br s, 2 H), 2.75 - 2.88 (m, 4 H), 2.93 - 3.10 (m, 1 H), 3.94 - 4.10 (m, 1 H), 4.21

(br s, 2 H), 7.66 (dd, $J=8.51$, 1.65 Hz, 1 H), 7.79 (s, 1 H), 8.02 (s, 1 H), 8.05 (d, $J=8.51$ Hz, 1 H), 8.52 (s, 1 H), 9.08 (s, 1 H), 10.76 (s, 1 H); ESIMS found for $C_{21}H_{21}F_2N_5O$ m/z 398.2 (M+1).

**268**

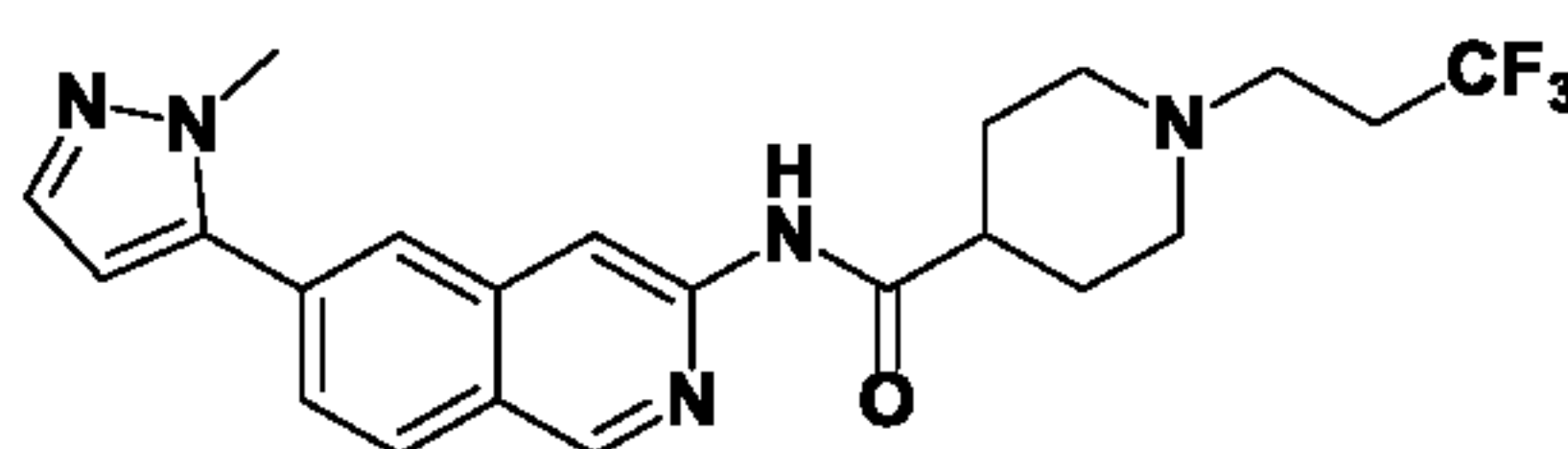
[0738] N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3,3-difluorocyclobutanecarboxamide **268**.

[0739] White solid (67.0 mg, 0.188 mmol, 49.3% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 2.39 (s, 3 H), 2.76 - 2.92 (m, 4 H), 3.27 - 3.36 (m, 1 H), 3.67 (s, 3 H), 7.12 (s, 1 H), 7.62 (dd, $J=8.51$, 1.65 Hz, 1 H), 7.93 (s, 1 H), 8.09 (d, $J=8.51$ Hz, 1 H), 8.55 (s, 1 H), 9.13 (s, 1 H), 10.80 (s, 1 H); ESIMS found for $C_{19}H_{18}F_2N_4O$ m/z 357.1 (M+1).

**269**

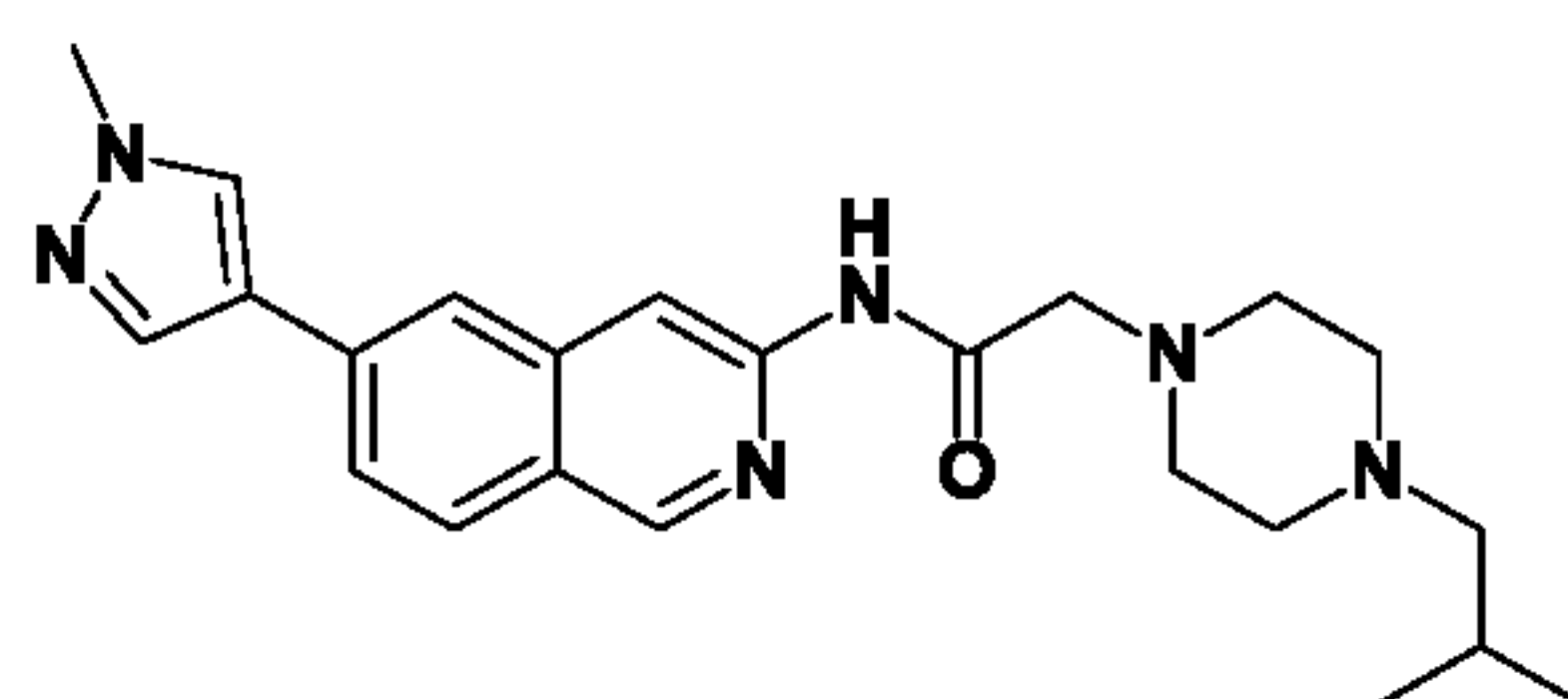
[0740] 2,2,3,3-Tetramethyl-N-[6-(3-methylimidazol-4-yl)-3-isoquinolyl]cyclopropanecarboxamide **269**.

[0741] Light yellow solid (132.0 mg, 0.379 mmol, 65.3% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.19 (s, 6 H), 1.28 (s, 6 H), 1.63 (s, 1 H), 3.83 (s, 3 H), 7.26 - 7.40 (m, 1 H), 7.64 (dd, $J=8.51$, 1.37 Hz, 1 H), 7.75 - 7.87 (m, 1 H), 8.00 (s, 1 H), 8.06 (d, $J=8.51$ Hz, 1 H), 8.52 (s, 1 H), 9.09 (s, 1 H), 10.51 (s, 1 H); ESIMS found for $C_{21}H_{24}N_4O$ m/z 349.2 (M+1).

**270**

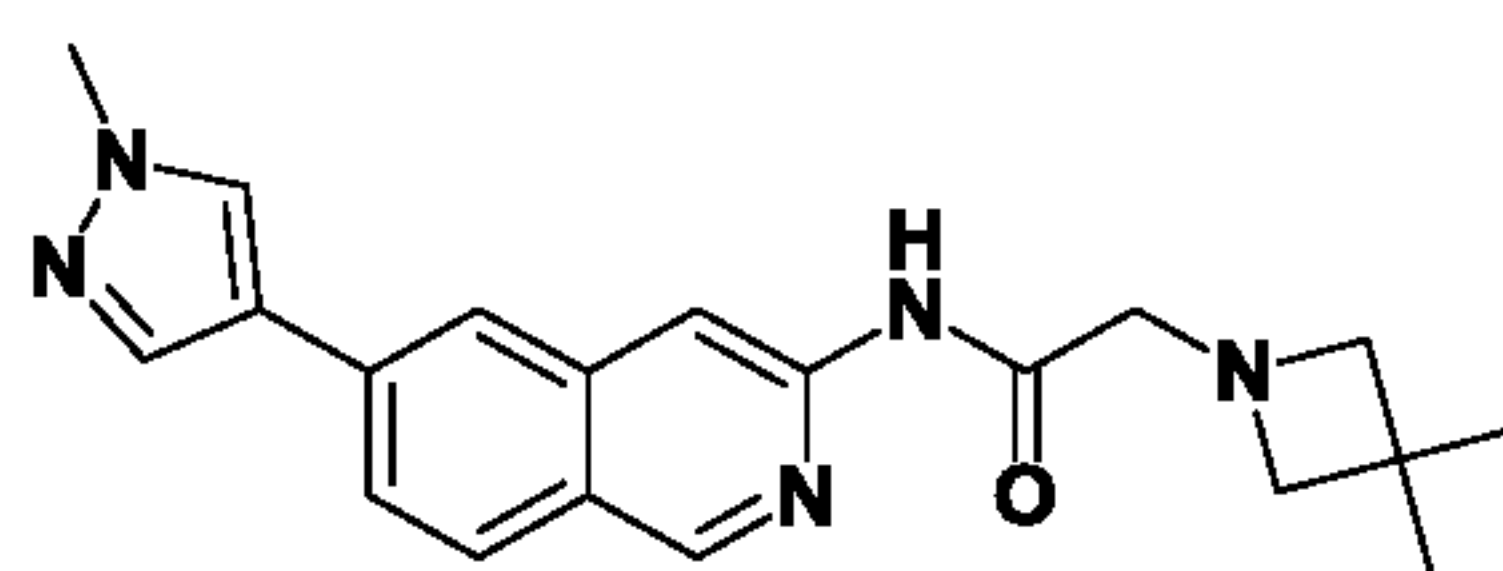
[0742] N-(6-(1-Methyl-1H-pyrazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **270**.

[0743] Off-white solid (45.0 mg, 0.104 mmol, 44.9% yield). ^1H NMR (DMSO- d_6 , 500 MHz) δ ppm 1.61 - 1.75 (m, 2 H), 1.75 - 1.86 (m, 2 H), 1.98 (br d, $J=1.92$ Hz, 2 H), 2.42 - 2.63 (m, 5 H), 2.95 (br d, $J=1.10$ Hz, 2 H), 3.97 (s, 3 H), 6.60 (d, $J=1.92$ Hz, 1 H), 7.54 (d, $J=1.92$ Hz, 1 H), 7.66 (dd, $J=8.37$, 1.51 Hz, 1 H), 8.07 (s, 1 H), 8.14 (d, $J=8.51$ Hz, 1 H), 8.58 (s, 1 H), 9.18 (s, 1 H), 10.60 (s, 1 H); ESIMS found for $C_{22}H_{24}F_3N_5O$ m/z 432.2 (M+1).

**272**

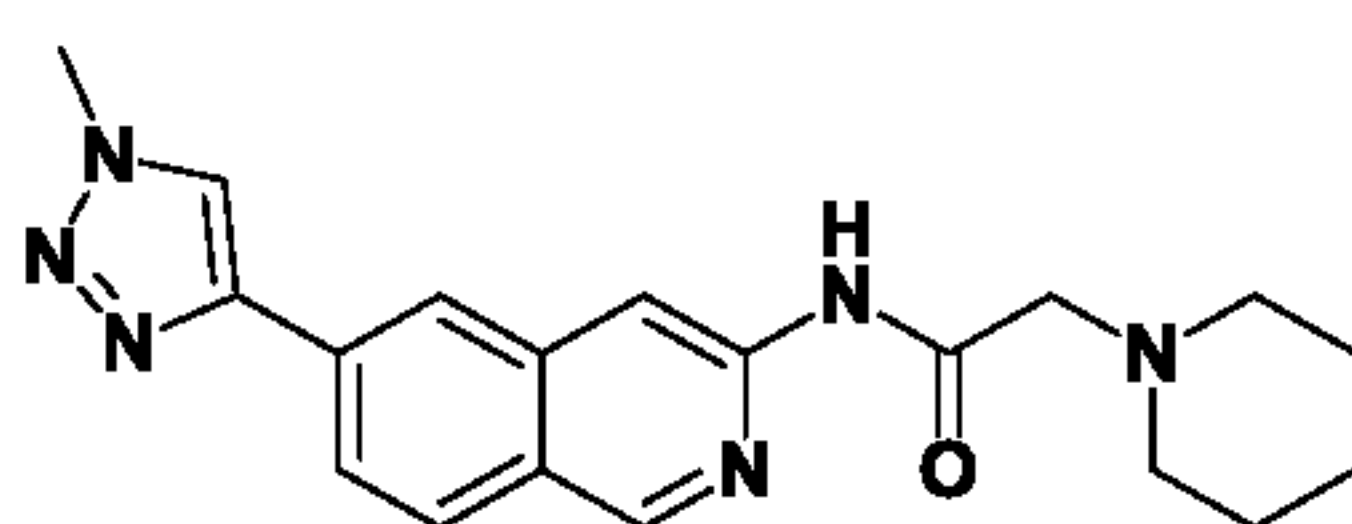
[0744] 2-(4-Isobutylpiperazin-1-yl)-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]acetamide **272**.

[0745] Off-white solid (39.0 mg, 0.096 mmol, 29.1% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 0.85 (d, *J*=6.59 Hz, 6 H), 1.76 (dq, *J*=13.64, 6.81, 6.81, 6.81, 6.81 Hz, 1 H), 2.06 (d, *J*=7.41 Hz, 2 H), 2.41 (br s, 4 H), 2.58 (br s, 4 H), 3.22 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.02 (d, *J*=8.51 Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 9.04 (s, 1 H), 9.92 (s, 1 H); ESIMS found for C₂₃H₃₀N₆O *m/z* 407.2 (M+1).

**273**

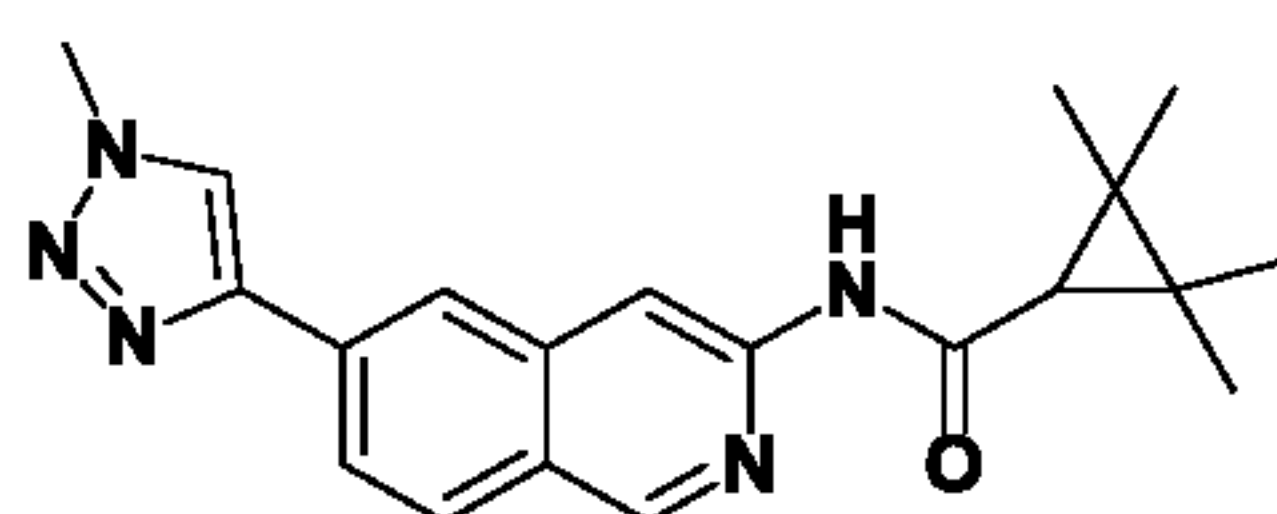
[0746] 2-(3,3-Dimethylazetidin-1-yl)-N-[6-(1-methylpyrazol-4-yl)-3-isoquinolyl]acetamide **273**.

[0747] Off-white solid (51.0 mg, 0.146 mmol, 44.2% yield). ¹H NMR (DMSO-*d*₆, 500 MHz) δ ppm 1.23 (s, 6 H), 3.10 (s, 4 H), 3.31 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.02 (d, *J*=8.51 Hz, 1 H), 8.10 (s, 2 H), 8.36 (s, 1 H), 8.41 (s, 1 H), 9.04 (s, 1 H), 9.88 (s, 1 H); ESIMS found for C₂₀H₂₃N₅O *m/z* 350.2 (M+1).

**276**

[0748] N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide **276**.

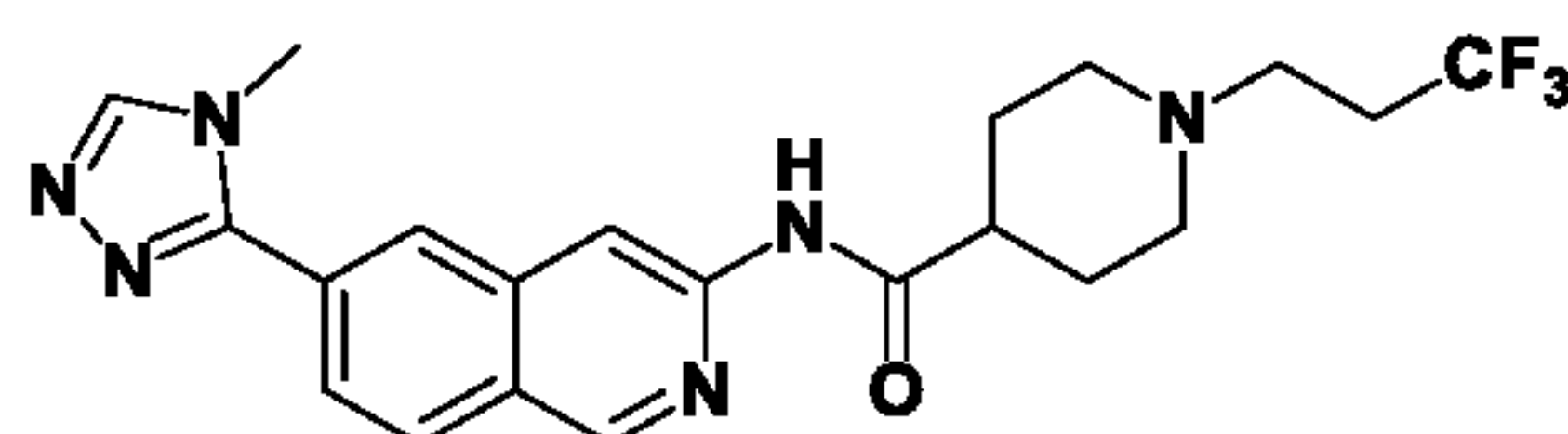
[0749] White solid (61.0 mg, 0.174 mmol, 51.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.44 (br d, *J*=5.21 Hz, 2 H), 1.59 (quin, *J*=5.56 Hz, 4 H), 2.53 (br s, 4 H), 3.18 (s, 2 H), 4.14 (s, 3 H), 8.04 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.13 (d, *J*=8.51 Hz, 1 H), 8.34 (s, 1 H), 8.50 (s, 1 H), 8.74 (s, 1 H), 9.13 (s, 1 H), 9.97 (s, 1 H); ESIMS found for C₁₉H₂₂N₆O *m/z* 351.2 (M+1).

**178**

277

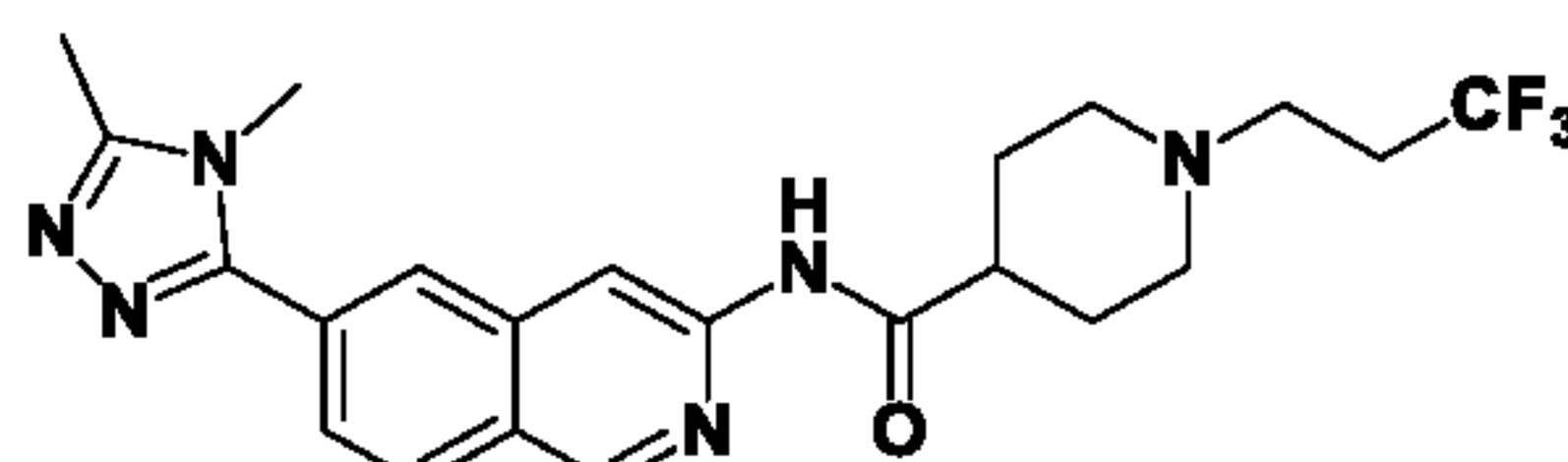
[0750] 2,2,3,3-Tetramethyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide **277**.

[0751] White solid (6.0 mg, 0.017 mmol, 6.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.19 (s, 6 H), 1.29 (s, 6 H), 1.63 (s, 1 H), 4.14 (s, 3 H), 7.99 (dd, *J*=8.51, 1.37 Hz, 1 H), 8.09 (d, *J*=8.51 Hz, 1 H), 8.28 (s, 1 H), 8.47 (s, 1 H), 8.69 (s, 1 H), 9.09 (s, 1 H), 10.50 (s, 1 H); ESIMS found for C₂₀H₂₃N₅O *m/z* 350.2 (M+1).

**278**

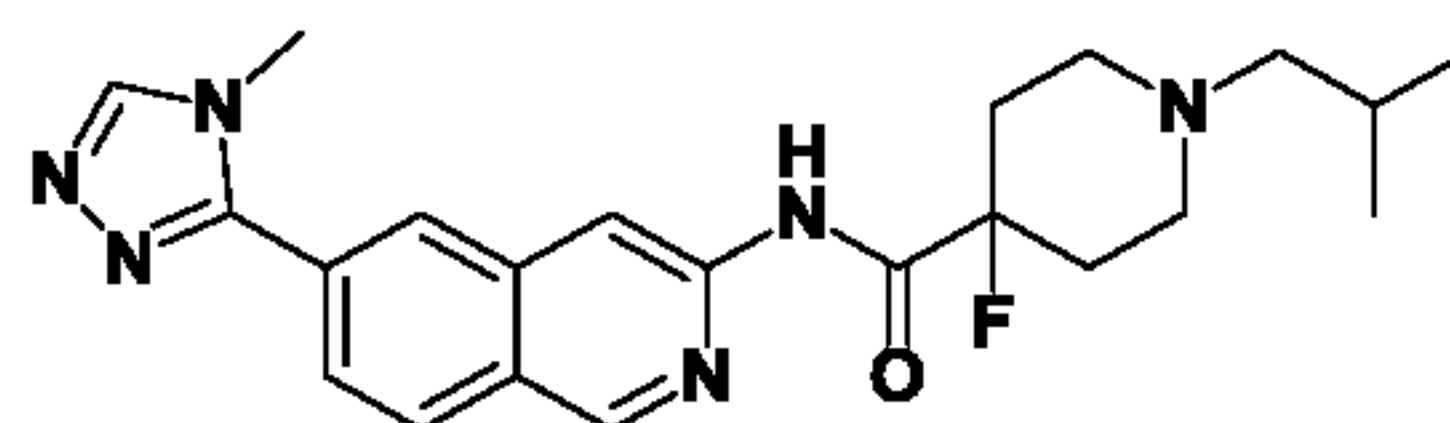
[0752] N-(6-(4-Methyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **278**.

[0753] Off-white solid (30.0 mg, 0.069 mmol, 30.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.60 - 1.74 (m, 2 H), 1.80 (br d, *J*=10.70 Hz, 2 H), 1.92 - 2.03 (m, 2 H), 2.40 - 2.49 (m, 2 H), 2.51 - 2.62 (m, 3 H), 2.94 (br d, *J*=11.25 Hz, 2 H), 3.88 (s, 3 H), 7.90 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.19 (d, *J*=8.51 Hz, 1 H), 8.27 (s, 1 H), 8.63 (s, 1 H), 8.65 (s, 1 H), 9.22 (s, 1 H), 10.63 (s, 1 H); ESIMS found for C₂₁H₂₃F₃N₆O *m/z* 433.2 (M+1).

**279**

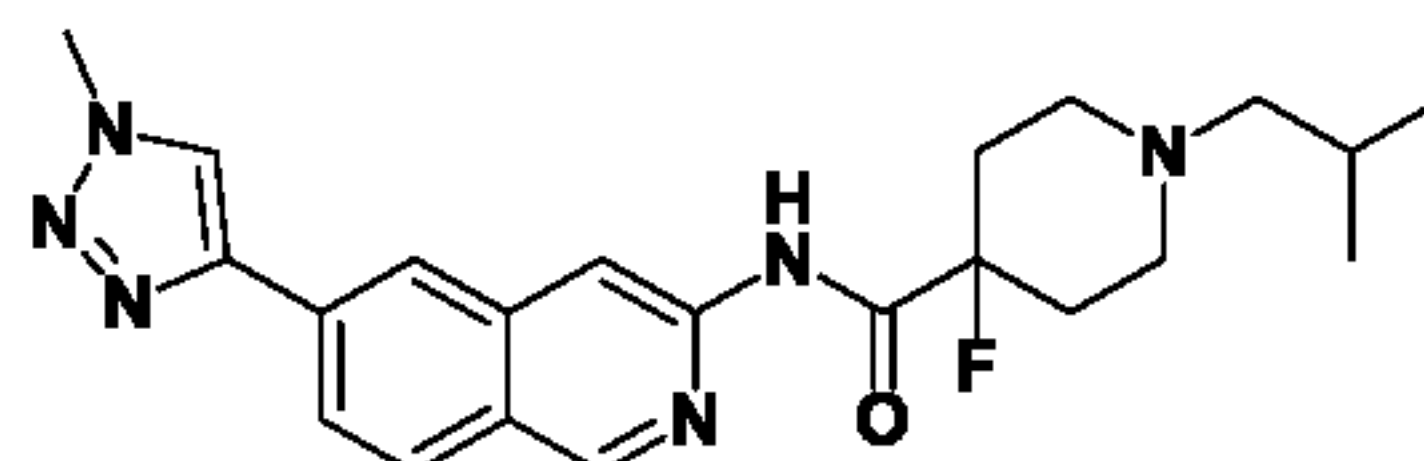
[0754] N-(6-(4,5-Dimethyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **279**.

[0755] Light pink solid (53.0 mg, 0.119 mmol, 51.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.73 (m, 2 H), 1.80 (br d, *J*=11.53 Hz, 2 H), 1.92 - 2.04 (m, 2 H), 2.40 - 2.49 (m, 5 H), 2.51 - 2.61 (m, 3 H), 2.94 (br d, *J*=10.98 Hz, 2 H), 3.70 (s, 3 H), 7.82 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.14 - 8.22 (m, 2 H), 8.62 (s, 1 H), 9.21 (s, 1 H), 10.63 (s, 1 H); ESIMS found for C₂₂H₂₅F₃N₆O *m/z* 447.2 (M+1).

**280**

[0756] 4-Fluoro-1-isobutyl-N-(6-(4-methyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide **280**.

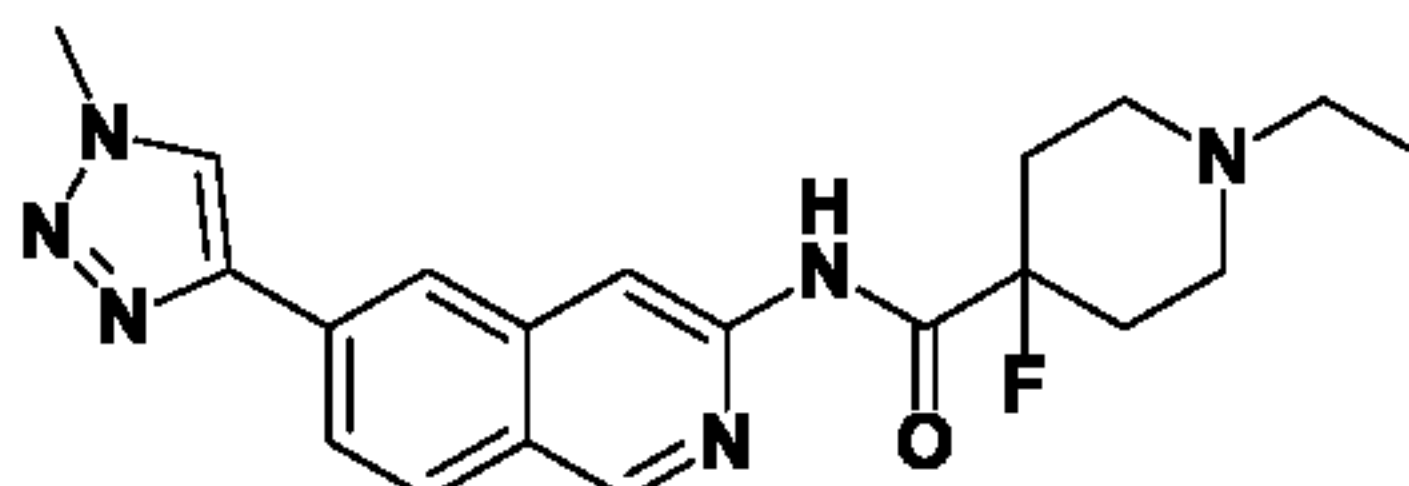
[0757] White solid (38.0 mg, 0.093 mmol, 25.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.88 (d, *J*=6.59 Hz, 6 H), 1.79 (dq, *J*=13.46, 6.79, 6.79, 6.79, 6.79 Hz, 1 H), 1.92 - 2.02 (m, 2 H), 2.09 (d, *J*=7.41 Hz, 3 H), 2.12 - 2.21 (m, 3 H), 2.74 - 2.83 (m, 2 H), 3.89 (s, 3 H), 7.97 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.24 (d, *J*=8.51 Hz, 1 H), 8.36 (s, 1 H), 8.60 (s, 1 H), 8.66 (s, 1 H), 9.28 (s, 1 H), 10.06 (d, *J*=3.84 Hz, 1 H); ESIMS found for C₂₂H₂₇FN₆O *m/z* 411.2 (M+1).



281

[0758] 4-Fluoro-1-isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **281**.

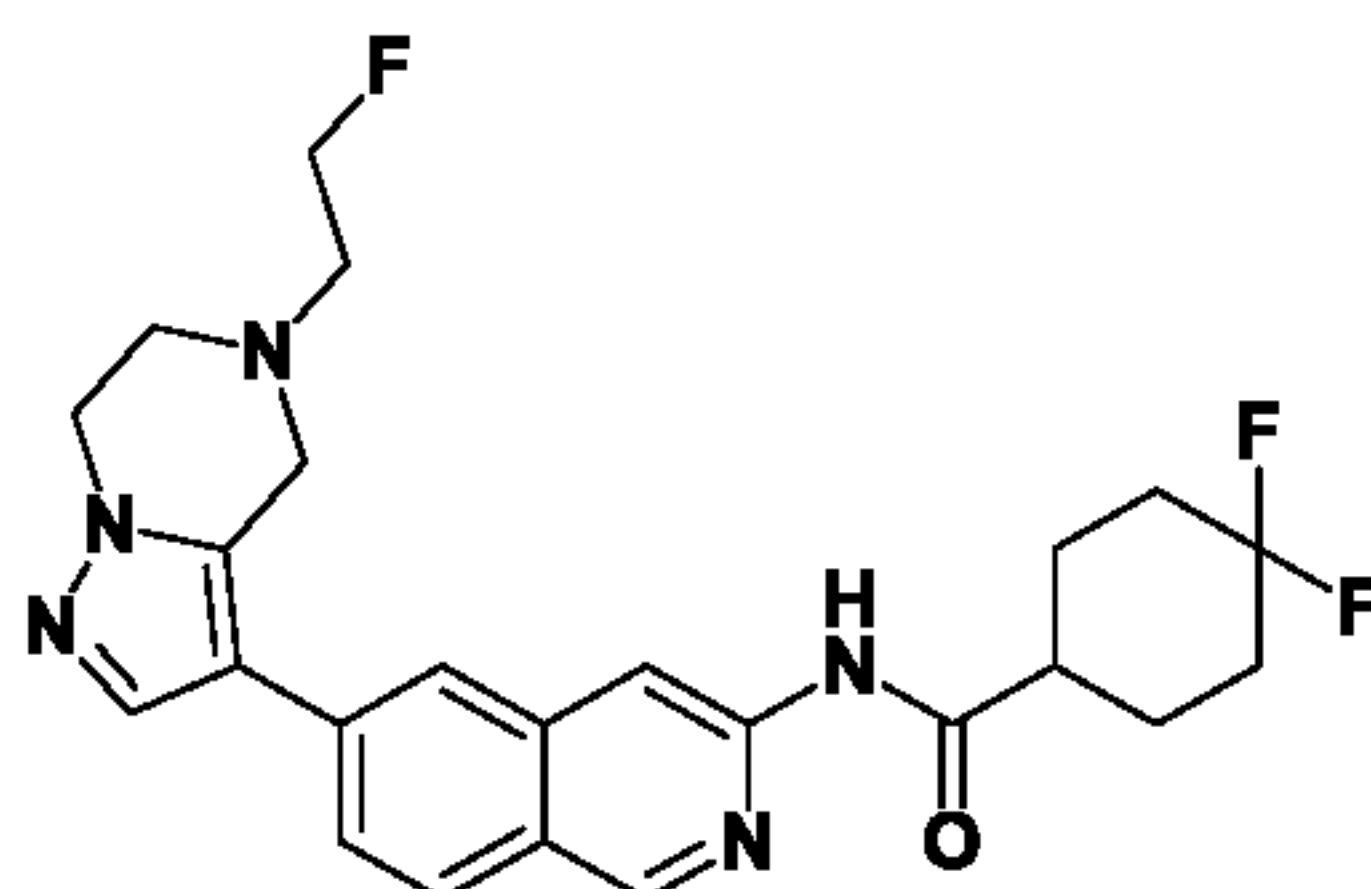
[0759] Off-white solid (31.0 mg, 0.076 mmol, 20.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.88 (d, *J*=6.59 Hz, 6 H), 1.79 (dq, *J*=13.52, 6.71, 6.71, 6.71, 6.71 Hz, 1 H), 1.91 - 2.01 (m, 2 H), 2.06 - 2.22 (m, 6 H), 2.78 (br d, *J*=7.96 Hz, 2 H), 4.15 (s, 3 H), 8.07 (dd, *J*=8.51, 1.65 Hz, 1 H), 8.16 (d, *J*=8.78 Hz, 1 H), 8.37 (s, 1 H), 8.47 (s, 1 H), 8.74 (s, 1 H), 9.17 (s, 1 H), 9.95 (d, *J*=4.12 Hz, 1 H); ESIMS found for C₂₂H₂₇FN₆O *m/z* 411.2 (M+1).



282

[0760] 1-Ethyl-4-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **282**.

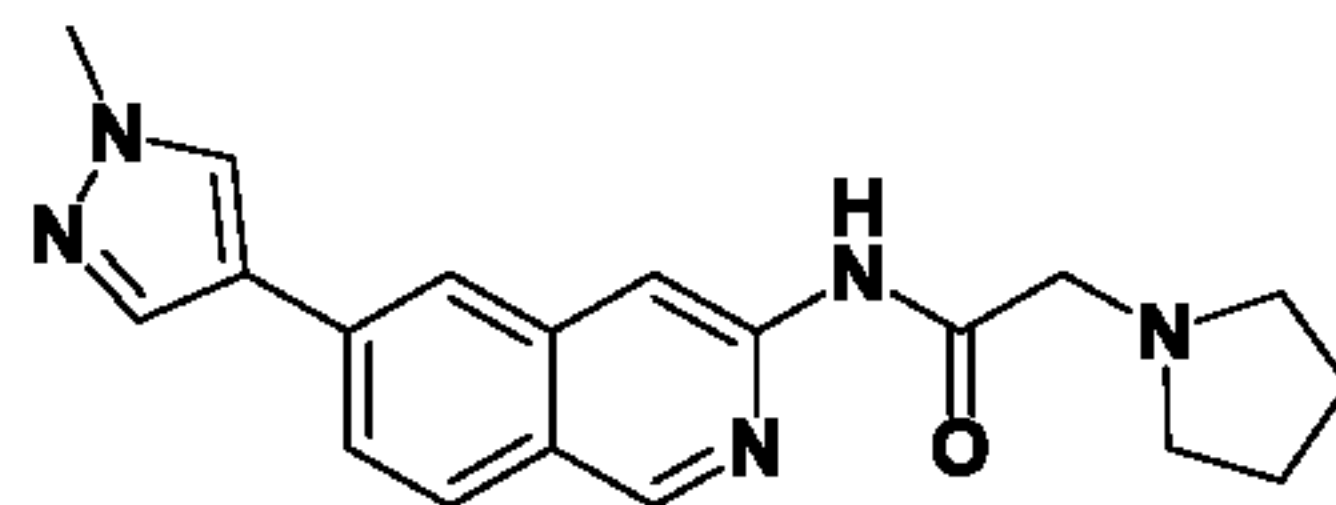
[0761] Beige solid (6.0 mg, 0.016 mmol, 5.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.03 (t, *J*=7.14 Hz, 3 H), 1.93 - 2.02 (m, 2 H), 2.05 - 2.13 (m, 1 H), 2.13 - 2.20 (m, 3 H), 2.39 (q, *J*=7.14 Hz, 2 H), 2.80 - 2.88 (m, 2 H), 4.15 (s, 3 H), 8.03 - 8.10 (m, 1 H), 8.16 (d, *J*=8.51 Hz, 1 H), 8.36 (s, 1 H), 8.47 (s, 1 H), 8.73 (s, 1 H), 9.17 (s, 1 H), 9.94 (d, *J*=4.12 Hz, 1 H); ESIMS found for C₂₀H₂₃FN₆O *m/z* 383.2 (M+1).



283

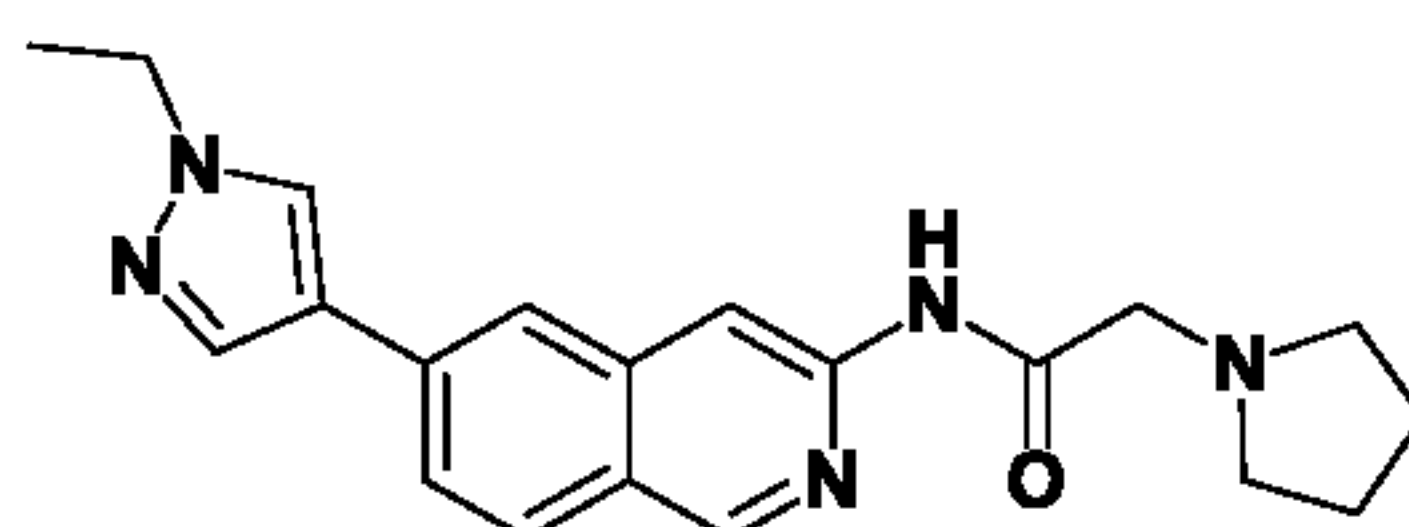
[0762] 4,4-Difluoro-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **283**.

[0763] Beige solid (7.7 mg, 0.017 mmol, 12.4% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.66 - 1.77 (m, 2 H), 1.77 - 1.91 (m, 2 H), 1.92 - 2.01 (m, 2 H), 2.08 - 2.19 (m, 2 H), 2.67 - 2.76 (m, 1 H), 2.96 (t, $J=4.80$ Hz, 1 H), 3.01 (t, $J=4.80$ Hz, 1 H), 3.07 (t, $J=5.35$ Hz, 2 H), 4.08 (s, 2 H), 4.18 (t, $J=5.35$ Hz, 2 H), 4.66 (dt, $J=47.85, 4.95$ Hz, 2 H), 7.64 (dd, $J=8.51, 1.37$ Hz, 1 H), 7.76 (s, 1 H), 8.00 (s, 1 H), 8.03 (d, $J=8.78$ Hz, 1 H), 8.47 (s, 1 H), 9.06 (s, 1 H), 10.58 (s, 1 H); ESIMS found for $\text{C}_{24}\text{H}_{26}\text{F}_3\text{N}_5\text{O}$ m/z 458.2 ($\text{M}+1$).

**284**

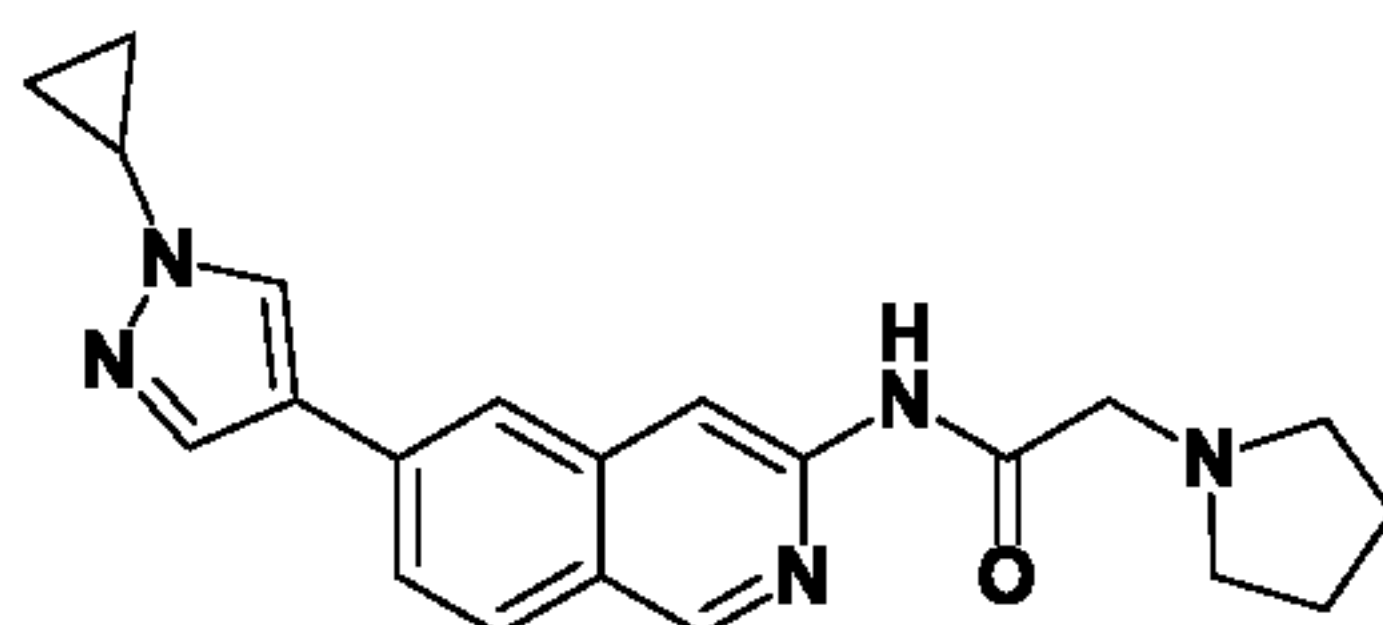
[0764] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **284**.

[0765] White gummy paste (53.0 mg, 0.150 mmol, 45.5% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.78 (dt, $J=6.52, 3.19$ Hz, 4 H), 2.66 (br t, $J=5.90$ Hz, 4 H), 3.35 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.51, 1.65$ Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 9.03 (s, 1 H), 9.92 (s, 1 H); ESIMS found for $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}$ m/z 336.2 ($\text{M}+1$).

**285**

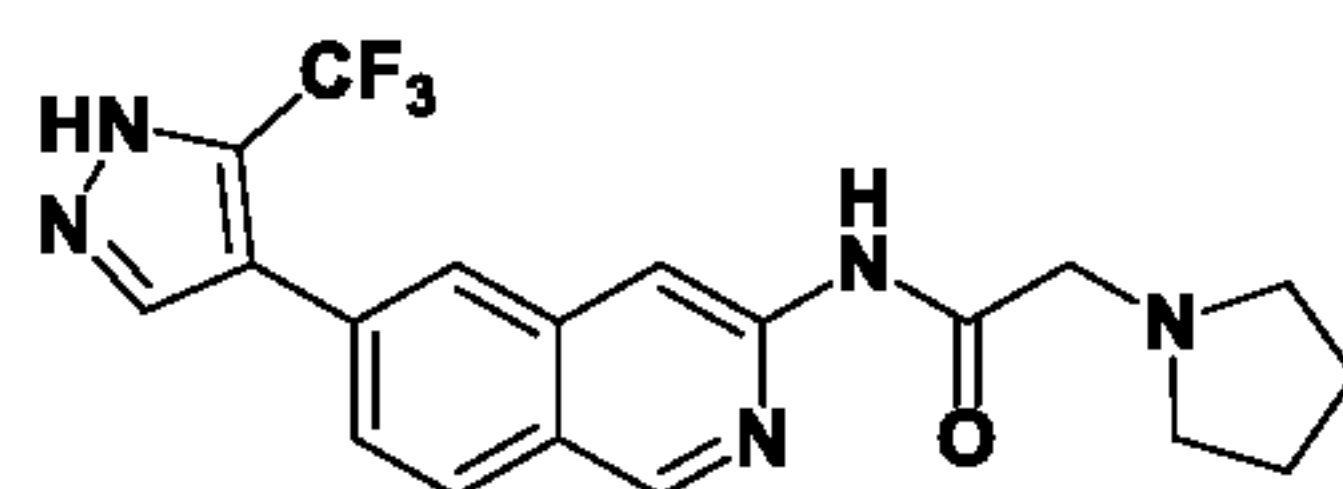
[0766] N-(6-(1-Ethyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **285**.

[0767] Dark pink paste (42.0 mg, 0.114 mmol, 63.6% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.44 (t, $J=7.27$ Hz, 3 H), 1.78 (dt, $J=6.66, 3.12$ Hz, 4 H), 2.62 - 2.69 (m, 4 H), 3.35 (s, 2 H), 4.18 (q, $J=7.41$ Hz, 2 H), 7.78 (dd, $J=8.51, 1.65$ Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.09 - 8.14 (m, 2 H), 8.43 (s, 2 H), 9.03 (s, 1 H), 9.92 (s, 1 H); ESIMS found for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}$ m/z 350.2 ($\text{M}+1$).

**286**

[0768] N-(6-(1-Cyclopropyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **286**.

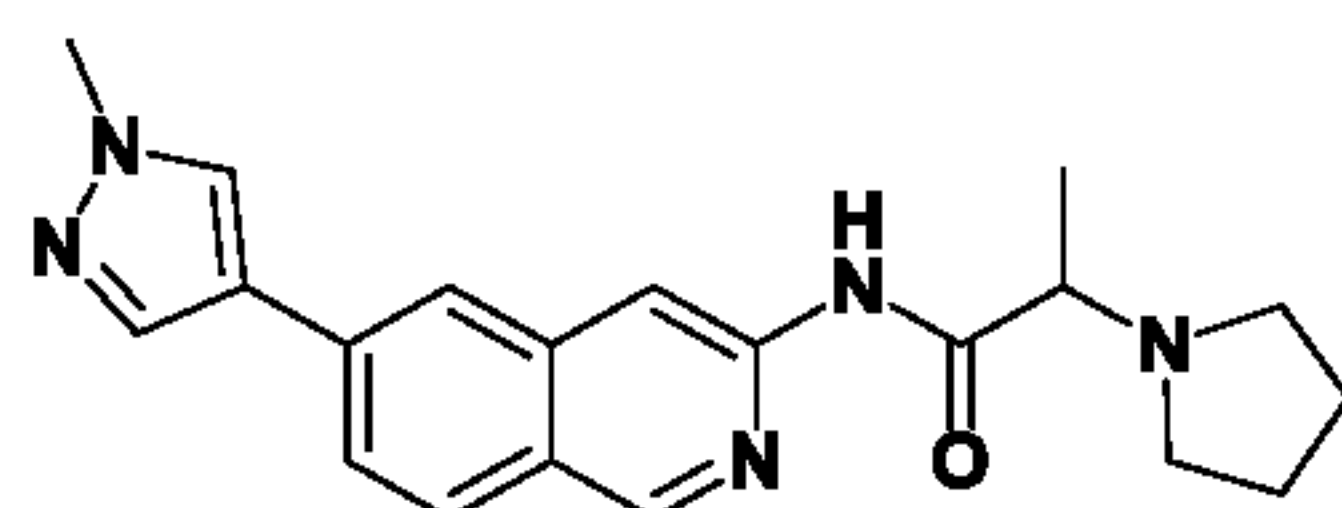
[0769] White paste (68.0 mg, 0.179 mmol, 59.7% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 0.98 - 1.05 (m, 2 H), 1.08 - 1.13 (m, 2 H), 1.78 (dt, $J=6.86$, 3.16 Hz, 4 H), 2.62 - 2.69 (m, 4 H), 3.35 (s, 2 H), 3.78 (tt, $J=7.34$, 3.77 Hz, 1 H), 7.79 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.01 (d, $J=8.78$ Hz, 1 H), 8.08 - 8.15 (m, 2 H), 8.43 (s, 1 H), 8.48 (s, 1 H), 9.03 (s, 1 H), 9.92 (s, 1 H); ESIMS found for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}$ m/z 362.2 (M+1).



287

[0770] 2-(Pyrrolidin-1-yl)-N-(6-(5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **287**.

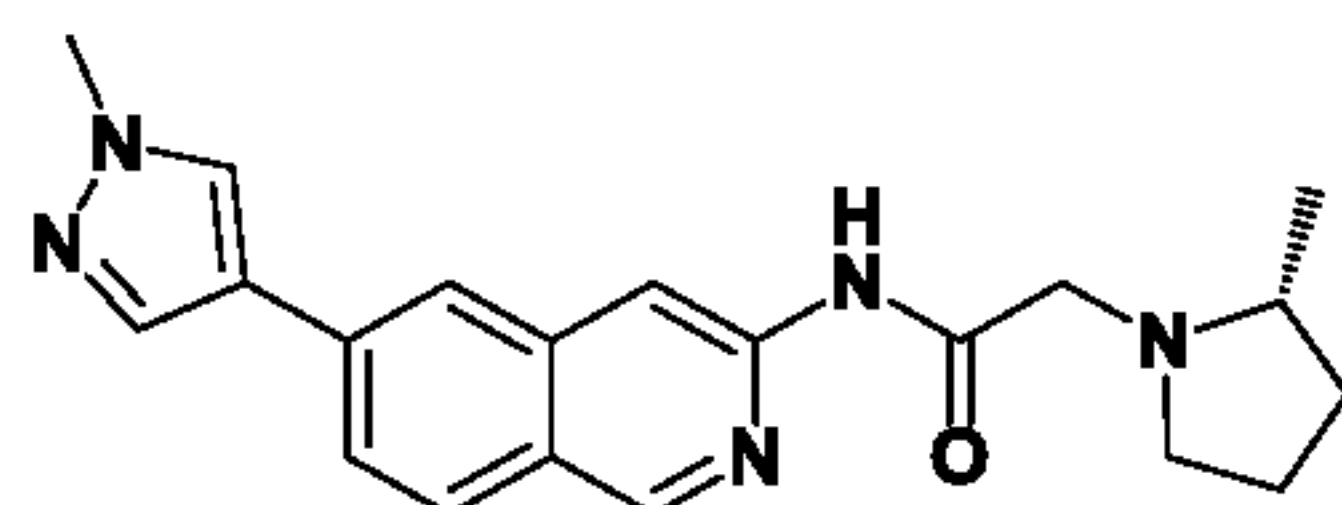
[0771] White solid (83.0 mg, 0.203 mmol, 45.1% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.78 (dt, $J=6.72$, 3.22 Hz, 4 H), 2.61 - 2.70 (m, 4 H), 3.36 (s, 2 H), 7.60 (dd, $J=8.37$, 1.24 Hz, 1 H), 7.93 (s, 1 H), 8.12 (d, $J=8.51$ Hz, 1 H), 8.40 (s, 1 H), 8.46 (s, 1 H), 9.14 (s, 1 H), 10.01 (s, 1 H); ESIMS found for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_5\text{O}$ m/z 390.1 (M+1).



288

[0772] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide **288**.

[0773] White solid (58.8 mg, 0.158 mmol, 50.9% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.30 (d, $J=6.86$ Hz, 3 H), 1.74 (br s, 4 H), 2.57 - 2.69 (m, 4 H), 3.28 (q, $J=6.95$ Hz, 1 H), 3.90 (s, 3 H), 7.76 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.06 - 8.12 (m, 2 H), 8.36 (s, 1 H), 8.43 (s, 1 H), 9.03 (s, 1 H), 9.95 (s, 1 H); ESIMS found for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}$ m/z 350.1 (M+1).

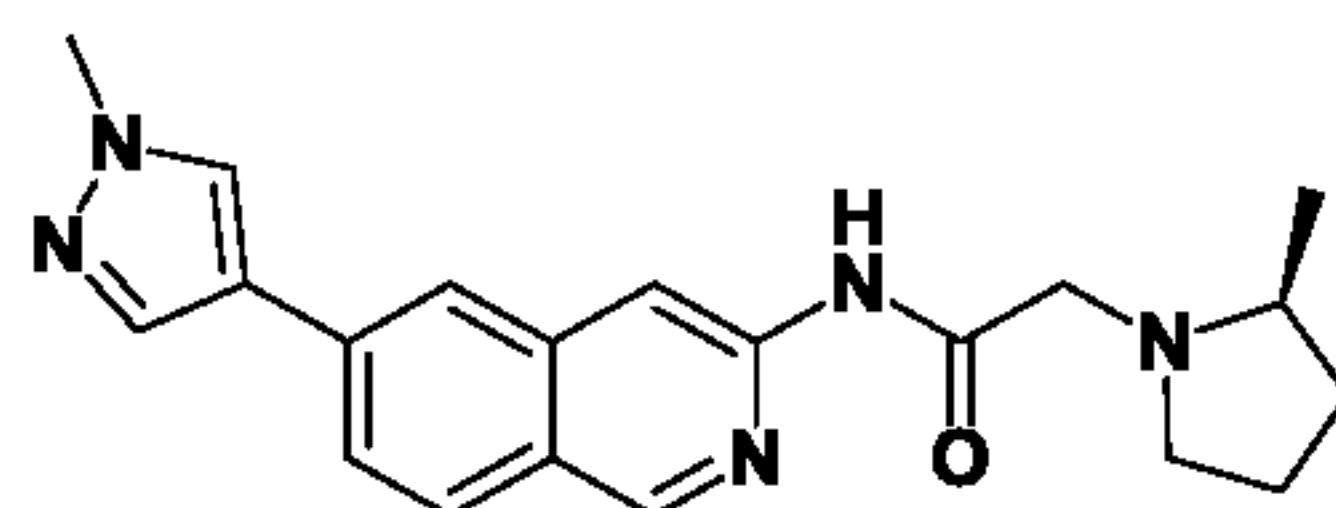


289

[0774] (*R*)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide **289**.

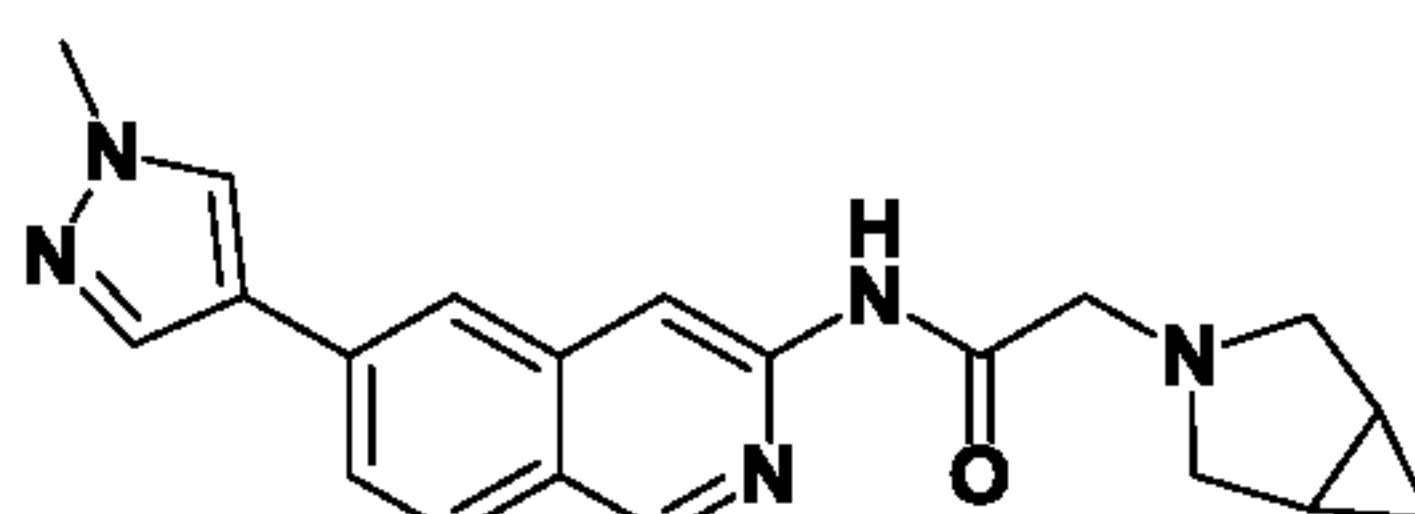
[0775] White paste (79.5 mg, 0.216 mmol, 65.5% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.09 (d, $J=6.04$ Hz, 3 H), 1.42 (dddd, $J=12.25$, 10.33, 8.30, 6.45 Hz, 1 H), 1.66 - 1.83 (m, 2 H), 1.91 - 2.02 (m, 1 H), 2.40 (q, $J=8.78$ Hz, 1 H), 2.56 - 2.66 (m, 1 H), 3.12 (d, $J=16.19$ Hz, 1 H), 3.14 - 3.19 (m, 1 H), 3.54 (d, $J=16.47$ Hz, 1 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.51$, 1.65 Hz, 1

H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.07 - 8.14 (m, 2 H), 8.37 (s, 1 H), 8.44 (s, 1 H), 9.03 (s, 1 H), 9.89 (s, 1 H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

**290**

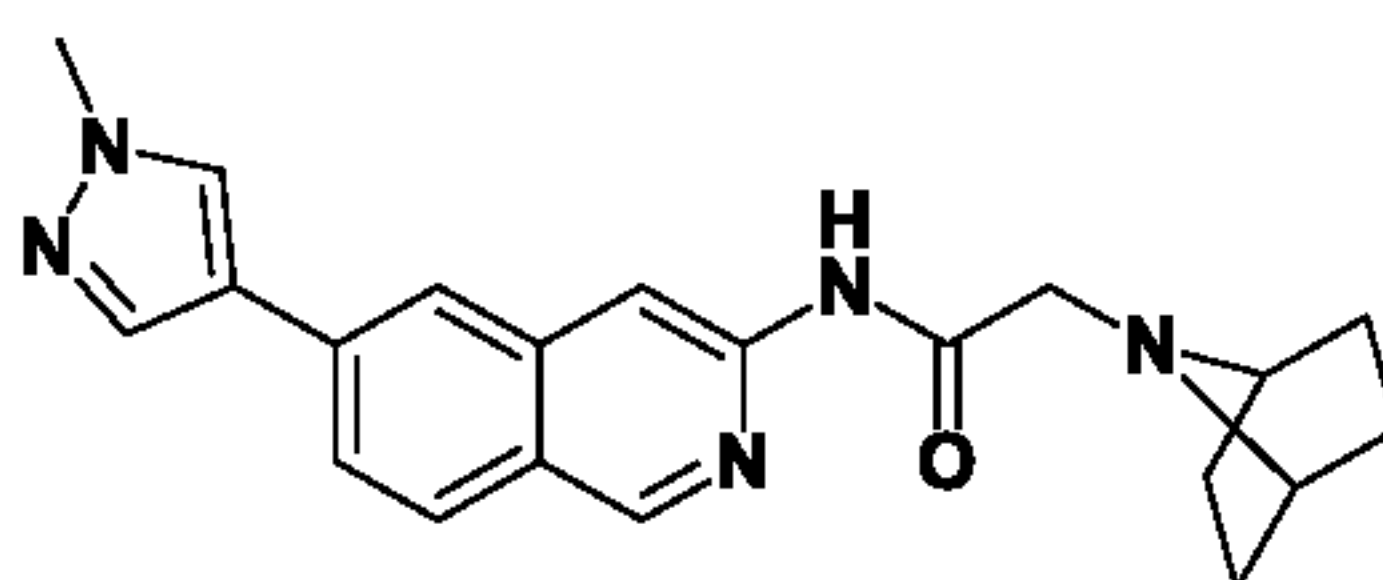
[0776] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide **290**.

[0777] White solid (77.0 mg, 0.209 mmol, 66.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.09 (d, $J=6.04$ Hz, 3 H), 1.42 (dddd, $J=12.32, 10.39, 8.30, 6.31$ Hz, 1 H), 1.66 - 1.84 (m, 2 H), 1.91 - 2.01 (m, 1 H), 2.40 (q, $J=8.78$ Hz, 1 H), 2.57 - 2.66 (m, 1 H), 3.12 (d, $J=16.47$ Hz, 1 H), 3.14 - 3.19 (m, 1 H), 3.54 (d, $J=16.19$ Hz, 1 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.51, 1.37$ Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.08 - 8.13 (m, 2 H), 8.37 (s, 1 H), 8.44 (s, 1 H), 9.03 (s, 1 H), 9.88 (s, 1 H); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

**291**

[0778] 2-(3-Azabicyclo[3.1.0]hexan-3-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **291**.

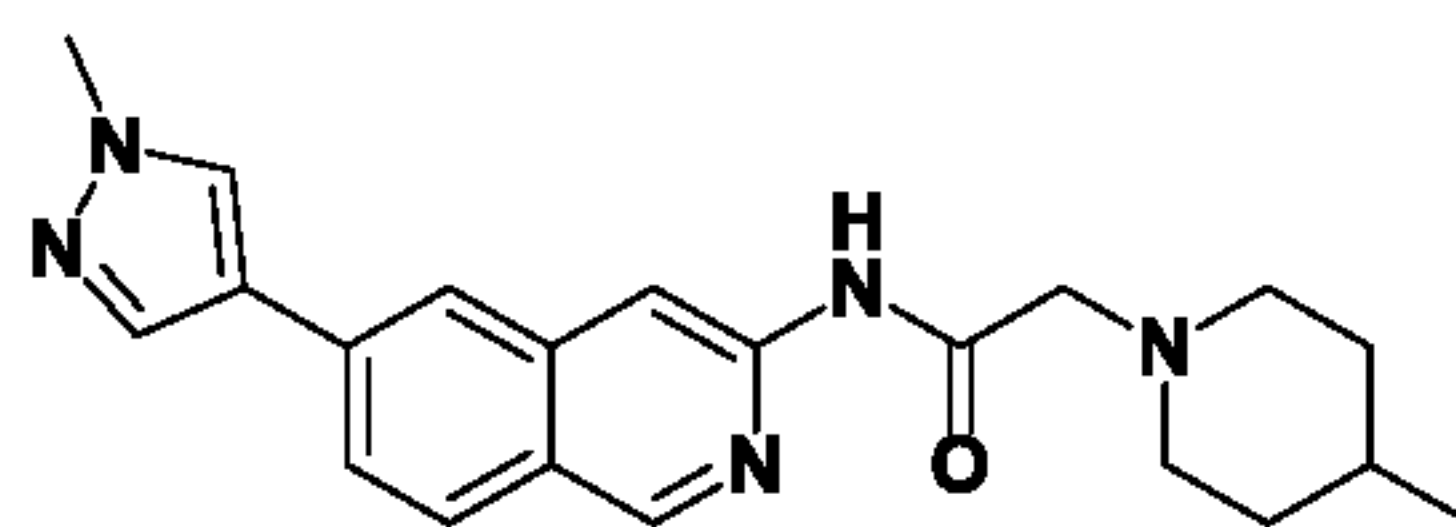
[0779] White solid (72.0 mg, 0.207 mmol, 62.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.44 (td, $J=7.55, 4.12$ Hz, 1 H), 0.70 (q, $J=3.84$ Hz, 1 H), 1.40 - 1.48 (m, 2 H), 2.57 (br d, $J=8.23$ Hz, 2 H), 3.04 (d, $J=8.78$ Hz, 2 H), 3.33 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.51, 1.37$ Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.09 (s, 2 H), 8.36 (s, 1 H), 8.41 (s, 1 H), 9.03 (s, 1 H), 9.77 (s, 1 H); ESIMS found for $C_{20}H_{21}N_5O$ m/z 348.2 (M+1).

**292**

[0780] 2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **292**.

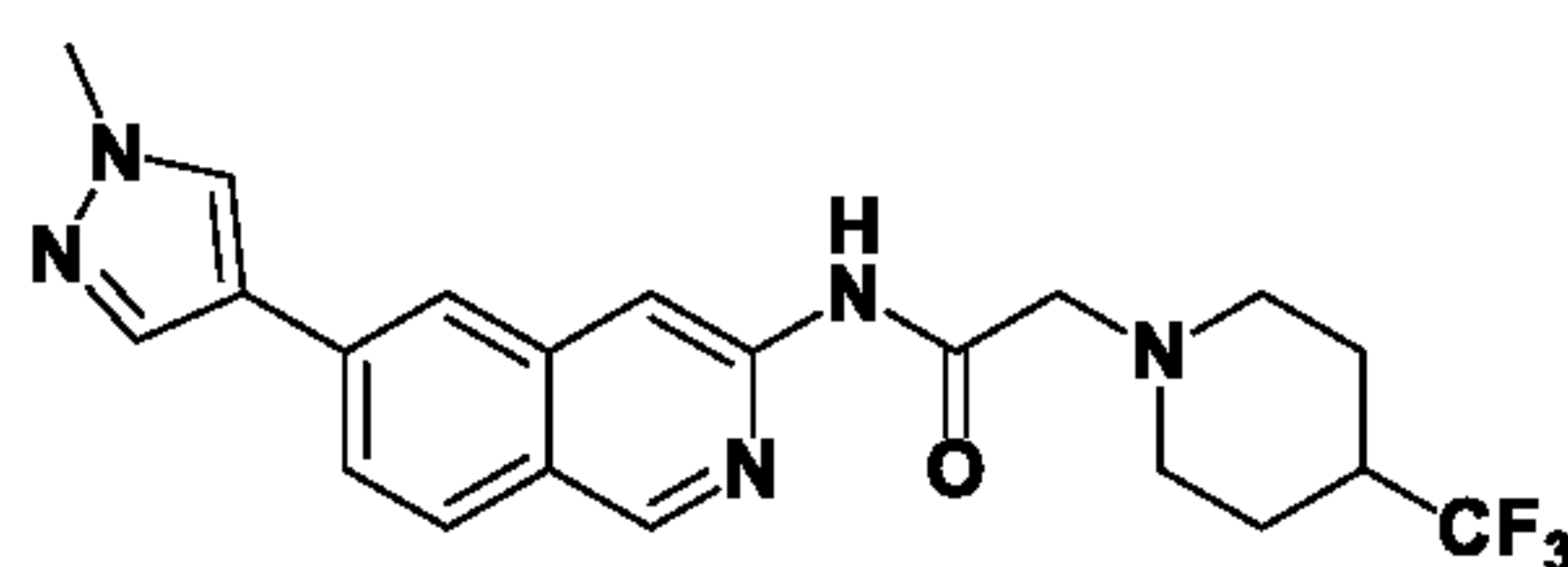
[0781] Beige solid (64.0 mg, 0.177 mmol, 53.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.34 (br d, $J=6.86$ Hz, 4 H), 1.74 (br d, $J=6.59$ Hz, 4 H), 3.19 (s, 2 H), 3.34 - 3.39 (m, 2

H), 3.90 (s, 3 H), 7.74 - 7.83 (m, 1 H), 8.02 (d, $J=8.78$ Hz, 1 H), 8.08 - 8.14 (m, 2 H), 8.37 (s, 1 H), 8.46 (s, 1 H), 9.04 (s, 1 H), 10.08 (s, 1 H); ESIMS found for $C_{21}H_{23}N_5O$ m/z 362.2 (M+1).

**293**

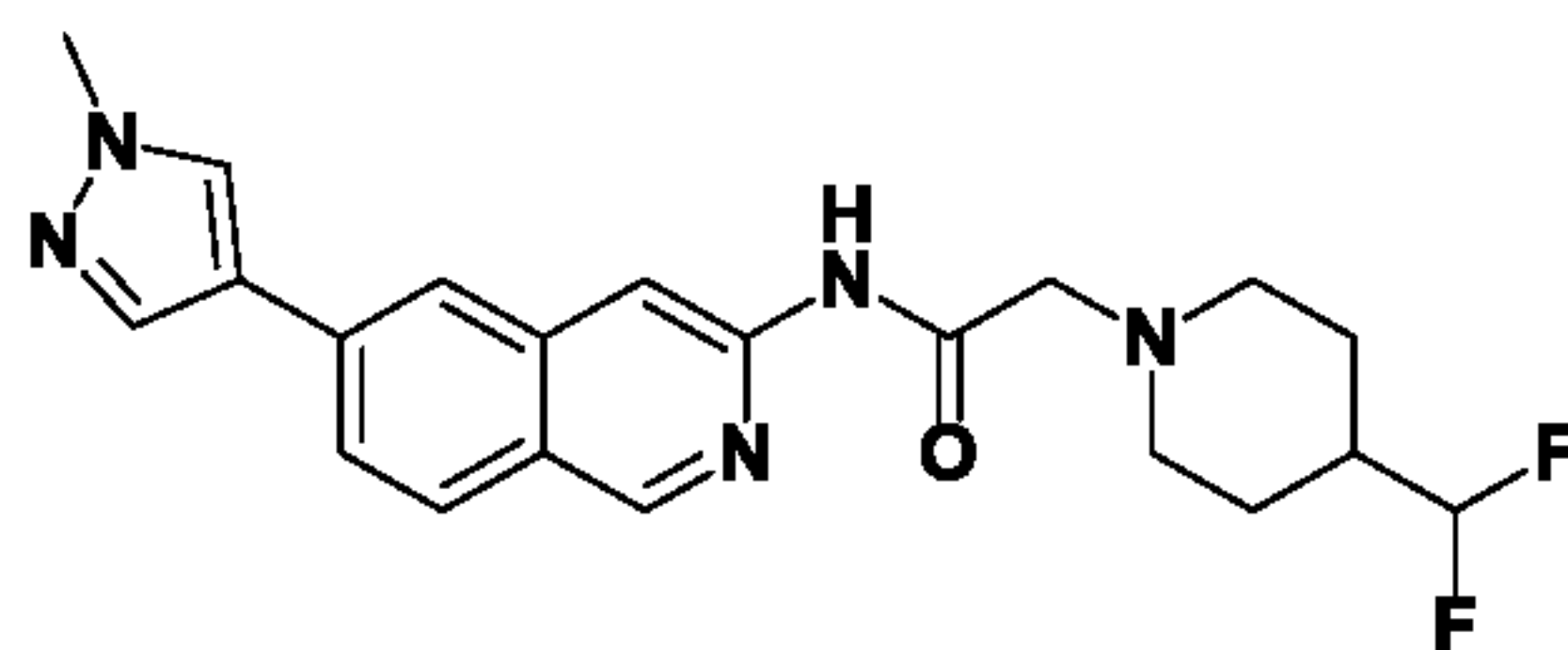
[0782] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide **293**.

[0783] White solid (56.0 mg, 0.146 mmol, 44.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.93 (d, $J=6.59$ Hz, 3 H), 1.18 - 1.29 (m, 2 H), 1.32 - 1.43 (m, 1 H), 1.64 (br d, $J=11.25$ Hz, 2 H), 2.20 (td, $J=11.53$, 1.92 Hz, 2 H), 2.87 (br d, $J=11.53$ Hz, 2 H), 3.18 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.51$, 1.37 Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 9.04 (s, 1 H), 9.90 (s, 1 H); ESIMS found for $C_{21}H_{25}N_5O$ m/z 364.2 (M+1).

**294**

[0784] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)acetamide **294**.

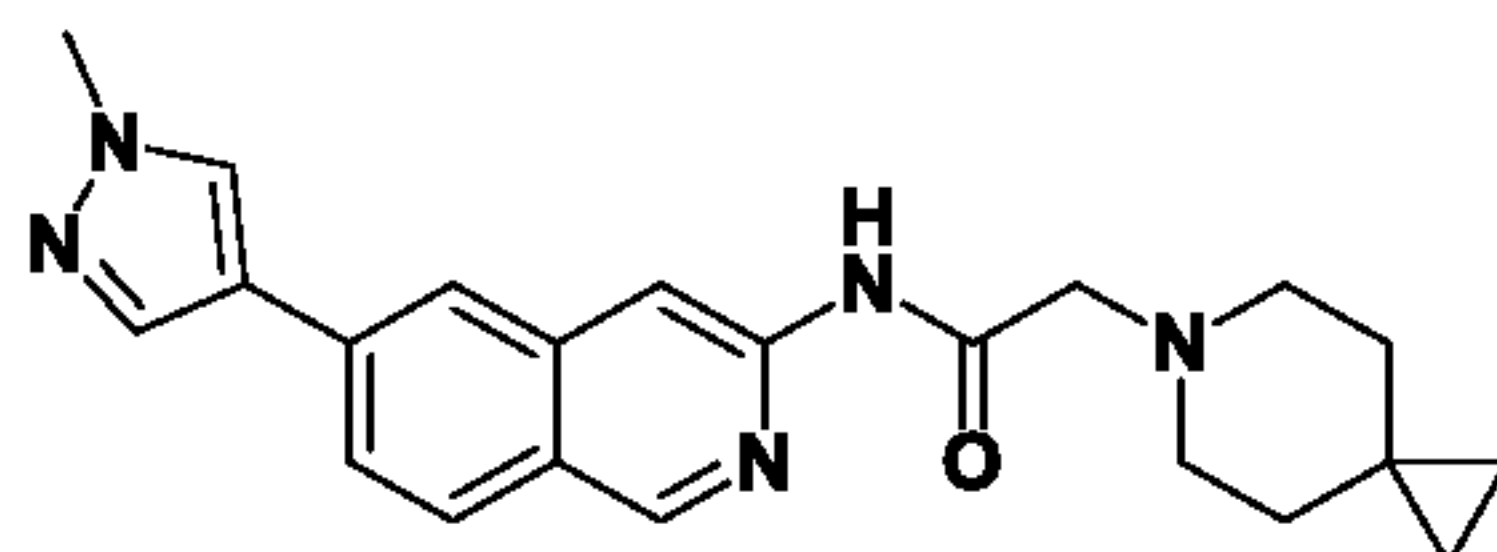
[0785] Off-white solid (92.0 mg, 0.209 mmol, 63.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.56 (qd, $J=12.44$, 3.84 Hz, 2 H), 1.83 (br d, $J=12.62$ Hz, 2 H), 2.28 (td, $J=11.94$, 1.92 Hz, 2 H), 2.30 - 2.39 (m, 1 H), 3.00 (br d, $J=11.53$ Hz, 2 H), 3.25 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.64$, 1.51 Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.44 (s, 1 H), 9.04 (s, 1 H), 9.98 (s, 1 H); ESIMS found for $C_{21}H_{22}F_3N_5O$ m/z 418.2 (M+1).

**295**

[0786] 2-(4-(Difluoromethyl)piperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **295**.

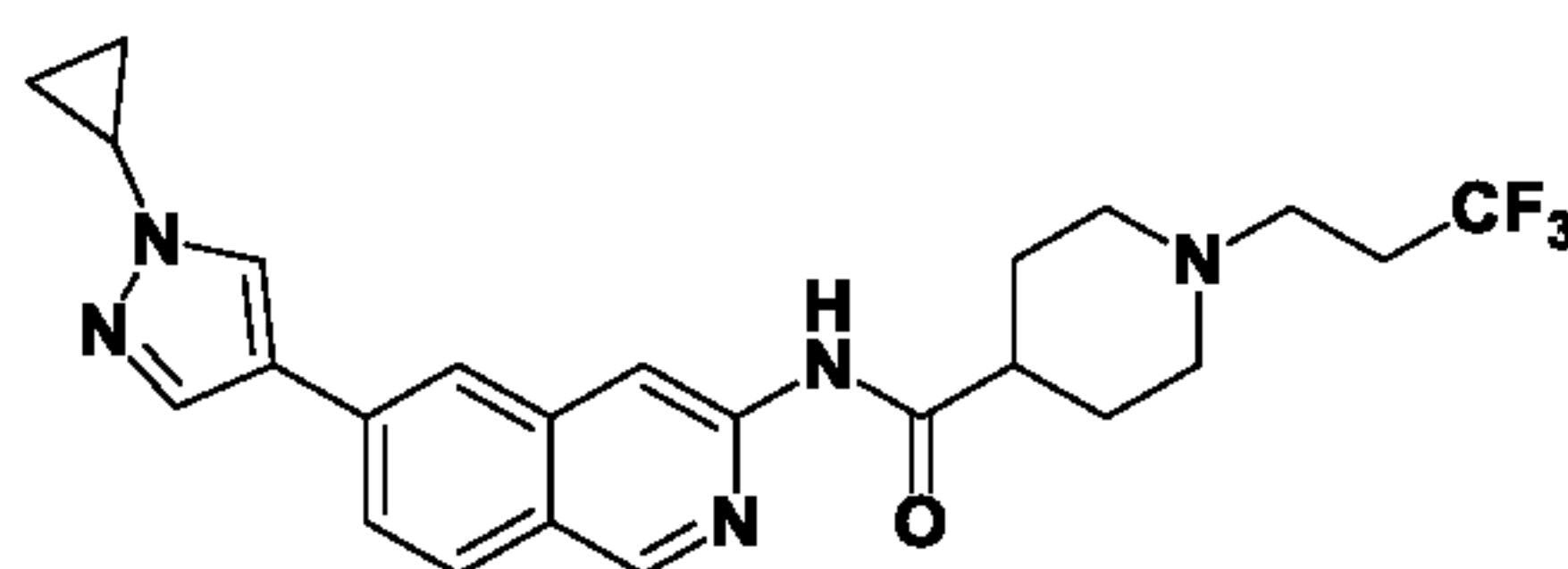
[0787] Beige solid (70.0 mg, 0.167 mmol, 62.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.47 (qd, $J=12.44$, 3.84 Hz, 2 H), 1.71 (br d, $J=12.35$ Hz, 2 H), 1.75 - 1.90 (m, 1 H), 2.23 (td, $J=11.80$, 1.92 Hz, 2 H), 2.97 (br d, $J=11.53$ Hz, 2 H), 3.23 (s, 2 H), 3.90 (s, 3 H), 5.95 (td,

$J=56.90$, 4.40 Hz, 1 H), 7.77 (dd, $J=8.51$, 1.37 Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.44 (s, 1 H), 9.04 (s, 1 H), 9.93 (s, 1 H); ESIMS found for $C_{21}H_{23}F_2N_5O$ m/z 400.2 (M+1).

**296**

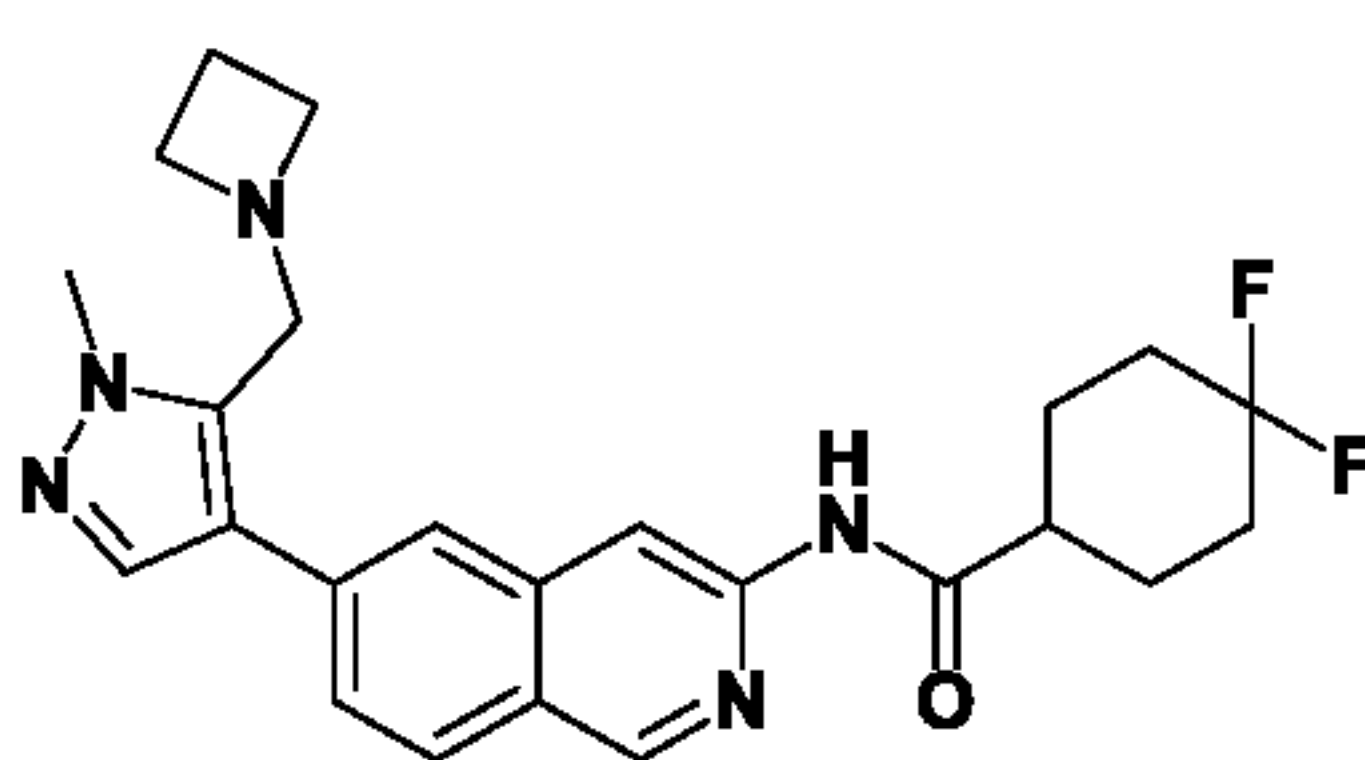
[0788] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide **296**.

[0789] Off-white solid (60.0 mg, 0.152 mmol, 56.9% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.29 (s, 4 H), 1.42 (br s, 4 H), 2.56 - 2.64 (m, 4 H), 3.24 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.64$, 1.51 Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.08 - 8.14 (m, 2 H), 8.37 (s, 1 H), 8.44 (s, 1 H), 9.04 (s, 1 H), 9.96 (s, 1 H); ESIMS found for $C_{22}H_{25}N_5O$ m/z 376.2 (M+1).

**297**

[0790] N-(6-(1-Cyclopropyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **297**.

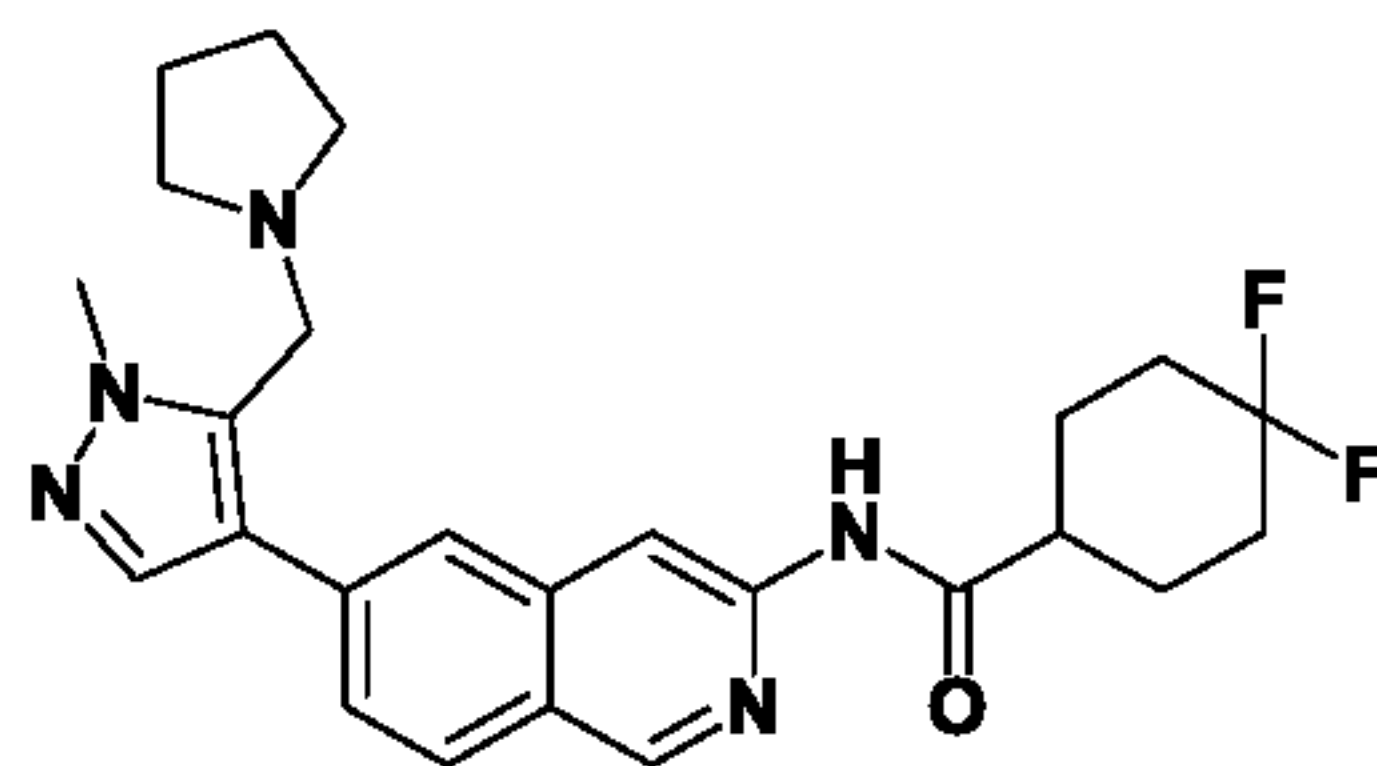
[0791] Off-white solid (21.0 mg, 0.046 mmol, 24.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.97 - 1.06 (m, 2 H), 1.08 - 1.14 (m, 2 H), 1.60 - 1.73 (m, 2 H), 1.79 (br d, $J=10.43$ Hz, 2 H), 1.92 - 2.02 (m, 2 H), 2.40 - 2.60 (m, 5 H), 2.93 (br d, $J=11.25$ Hz, 2 H), 3.78 (tt, $J=7.44$, 3.81 Hz, 1 H), 7.76 (dd, $J=8.51$, 1.37 Hz, 1 H), 7.99 (d, $J=8.51$ Hz, 1 H), 8.04 - 8.11 (m, 2 H), 8.45 (d, $J=9.06$ Hz, 2 H), 9.02 (s, 1 H), 10.47 (s, 1 H); ESIMS found for $C_{24}H_{26}F_3N_5O$ m/z 458.2 (M+1).

**298**

[0792] N-(6-(5-(Azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4,4-difluorocyclohexane-1-carboxamide **298**.

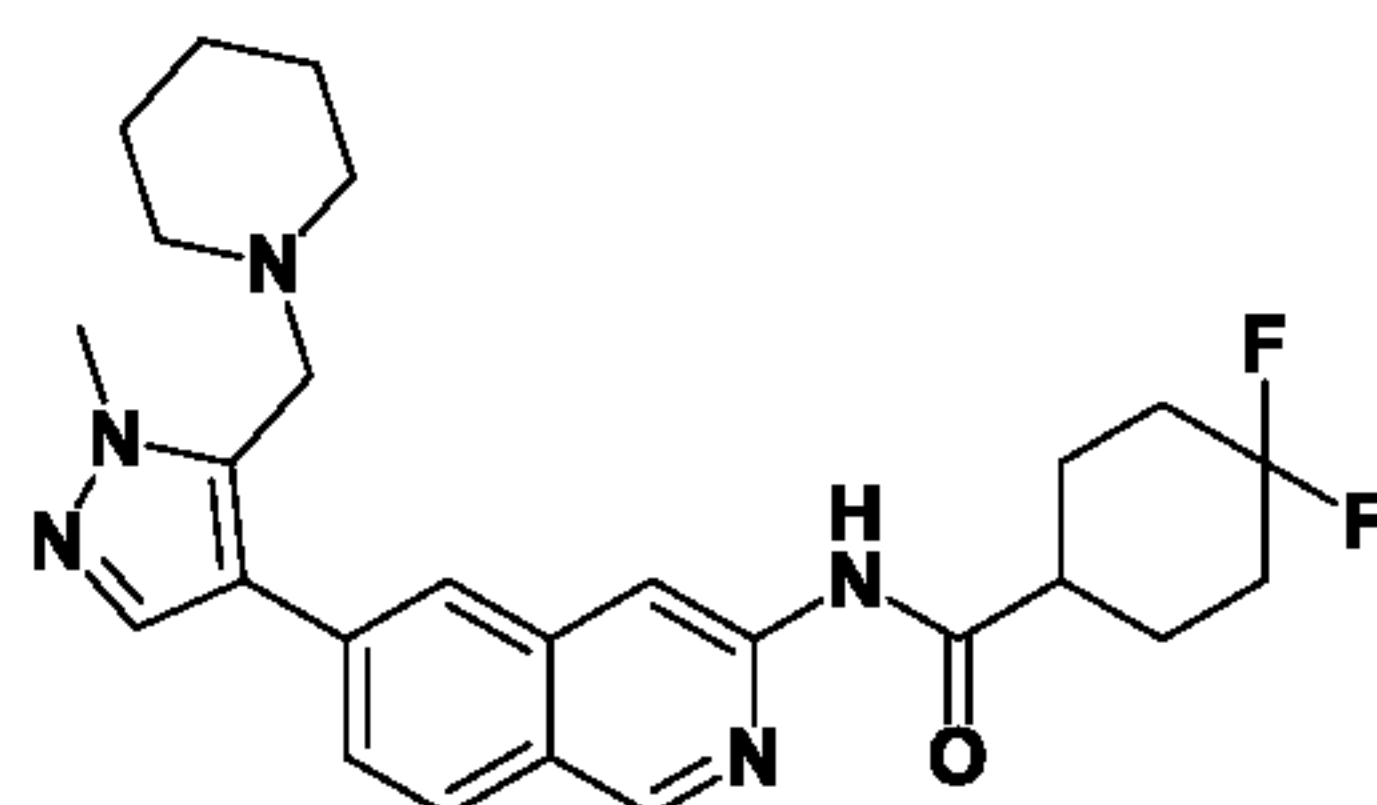
[0793] Beige solid (4.4 mg, 0.010 mmol, 3.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.67 - 2.02 (m, 8 H), 2.07 - 2.19 (m, 2 H), 2.67 - 2.77 (m, 1 H), 3.11 (t, $J=6.86$ Hz, 4 H),

3.77 (s, 2 H), 3.92 (s, 3 H), 7.67 (dd, $J=8.51, 1.37$ Hz, 1 H), 7.75 (s, 1 H), 7.93 (s, 1 H), 8.05 (d, $J=8.51$ Hz, 1 H), 8.46 (s, 1 H), 9.09 (s, 1 H), 10.60 (s, 1 H); ESIMS found for $C_{24}H_{27}F_2N_5O$ m/z 440.2 (M+1).

**299**

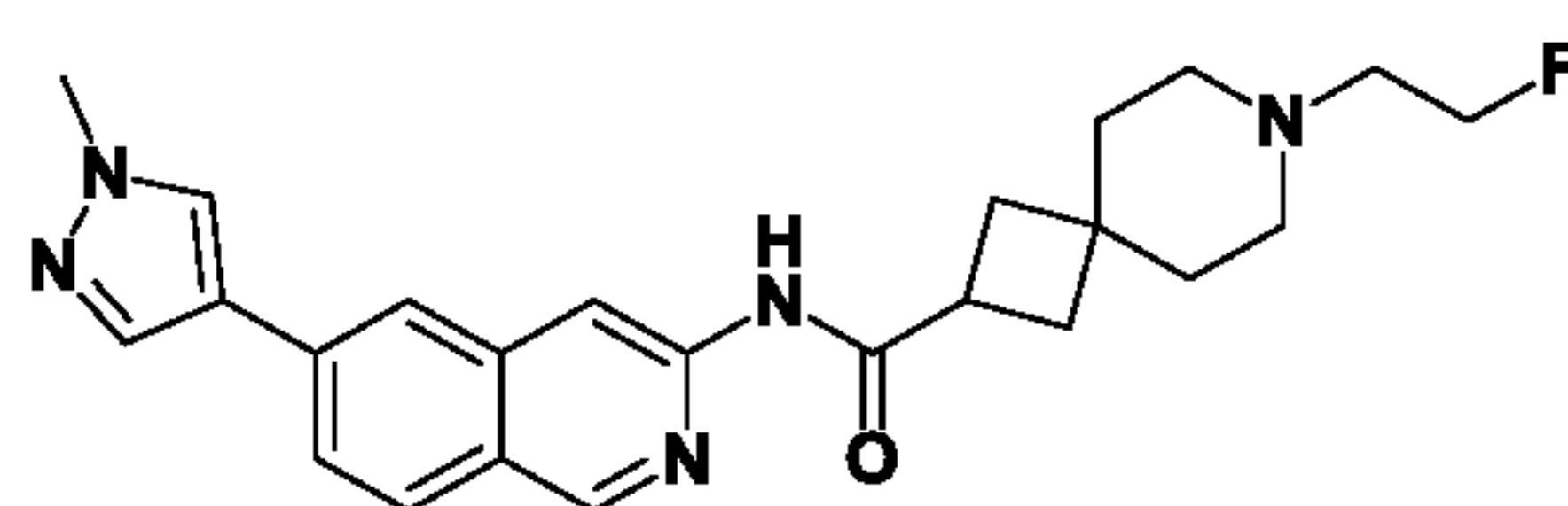
[0794] 4,4-Difluoro-N-(6-(1-methyl-5-(pyrrolidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **299**.

[0795] Beige solid (26.4 mg, 0.058 mmol, 23.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.67 (br s, 4 H), 1.69 - 1.91 (m, 4 H), 1.95 (br d, $J=12.90$ Hz, 2 H), 2.06 - 2.18 (m, 2 H), 2.44 (br s, 4 H), 2.71 (br t, $J=10.84$ Hz, 1 H), 3.83 (s, 2 H), 3.92 (s, 3 H), 7.68 (dd, $J=8.51, 1.65$ Hz, 1 H), 7.78 (s, 1 H), 7.96 (s, 1 H), 8.03 (d, $J=8.51$ Hz, 1 H), 8.44 (s, 1 H), 9.08 (s, 1 H), 10.59 (s, 1 H); ESIMS found for $C_{25}H_{29}F_2N_5O$ m/z 454.2 (M+1).

**300**

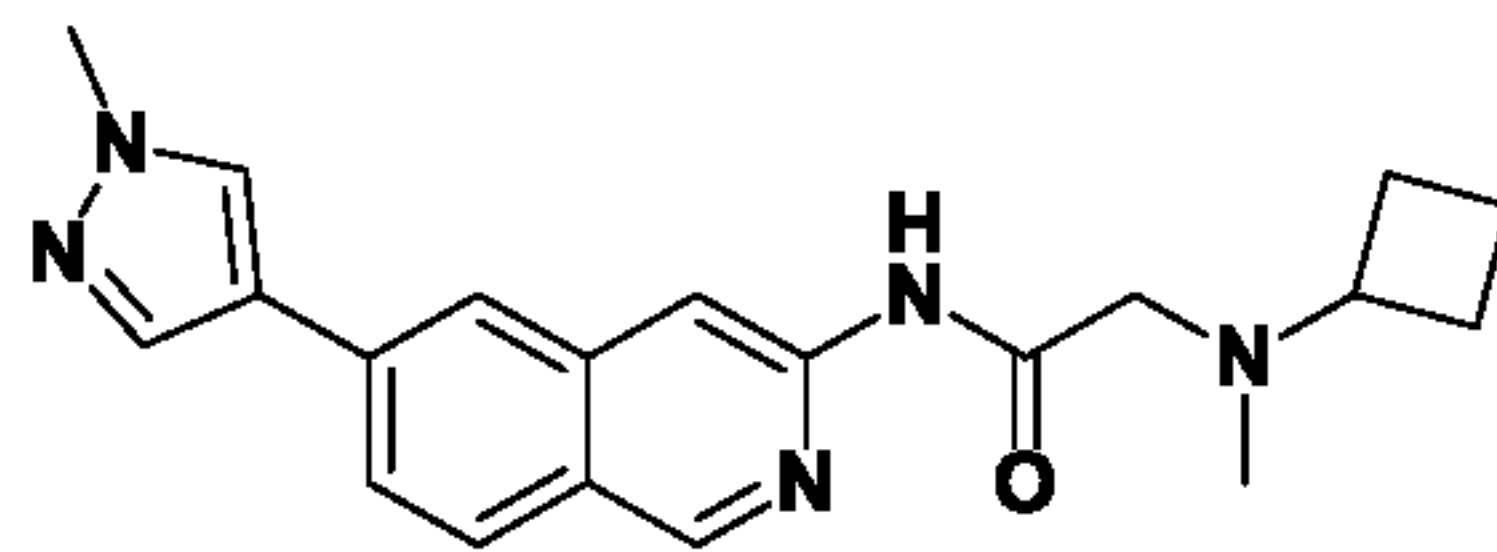
[0796] 4,4-Difluoro-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **300**.

[0797] White solid (10.6 mg, 0.023 mmol, 18.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.38 (br d, $J=4.12$ Hz, 2 H), 1.44 - 1.53 (m, 4 H), 1.66 - 1.90 (m, 4 H), 1.92 - 2.01 (m, 2 H), 2.06 - 2.18 (m, 2 H), 2.36 (br d, $J=1.65$ Hz, 4 H), 2.65 - 2.76 (m, 1 H), 3.65 (s, 2 H), 3.91 (s, 3 H), 7.70 (dd, $J=8.51, 1.65$ Hz, 1 H), 7.80 (s, 1 H), 7.98 - 8.07 (m, 2 H), 8.45 (s, 1 H), 9.08 (s, 1 H), 10.58 (s, 1 H); ESIMS found for $C_{26}H_{31}F_2N_5O$ m/z 468.2 (M+1).

**301**

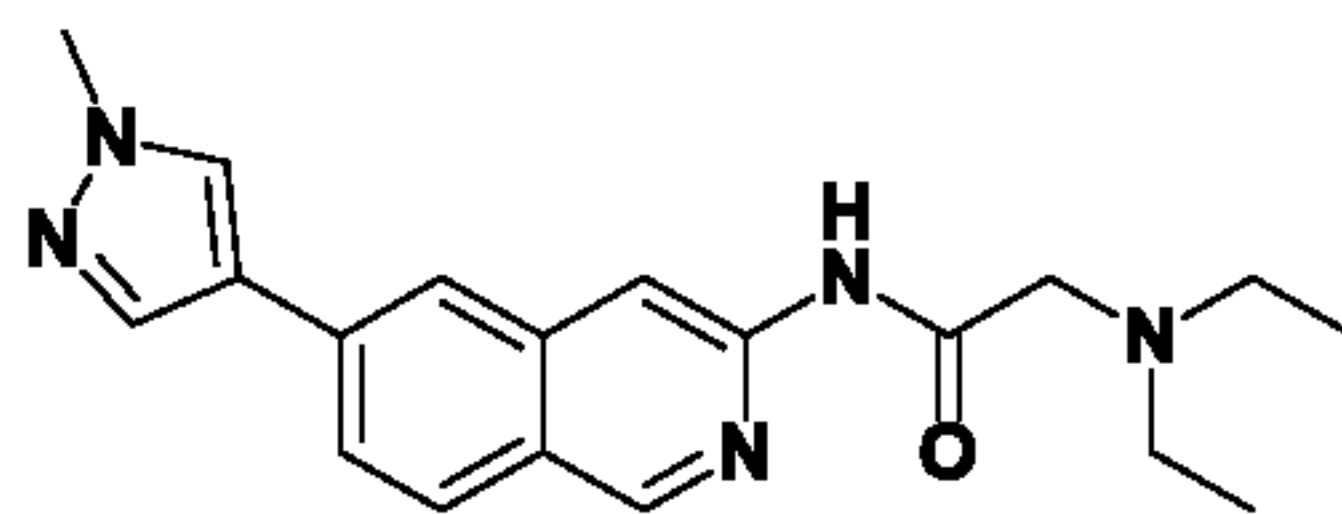
[0798] 7-(2-Fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide **301**.

[0799] Beige solid (50.0 mg, 0.119 mmol, 18.1% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.53 (br t, $J=5.35$ Hz, 2 H), 1.59 (br t, $J=5.35$ Hz, 2 H), 1.97 (d, $J=8.51$ Hz, 4 H), 2.30 (br s, 2 H), 2.33 - 2.44 (m, 2 H), 2.55 (dt, $J=28.30, 5.20$ Hz, 2 H), 3.33 - 3.42 (m, 1 H), 3.90 (s, 3 H), 4.50 (dt, $J=48.10, 5.25$ Hz, 2 H), 7.74 (dd, $J=8.51, 1.65$ Hz, 1 H), 7.99 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.46 (s, 1 H), 9.01 (s, 1 H), 10.34 (s, 1 H); ESIMS found for $\text{C}_{24}\text{H}_{28}\text{FN}_5\text{O}$ m/z 422.2 ($\text{M}+1$).

**302**

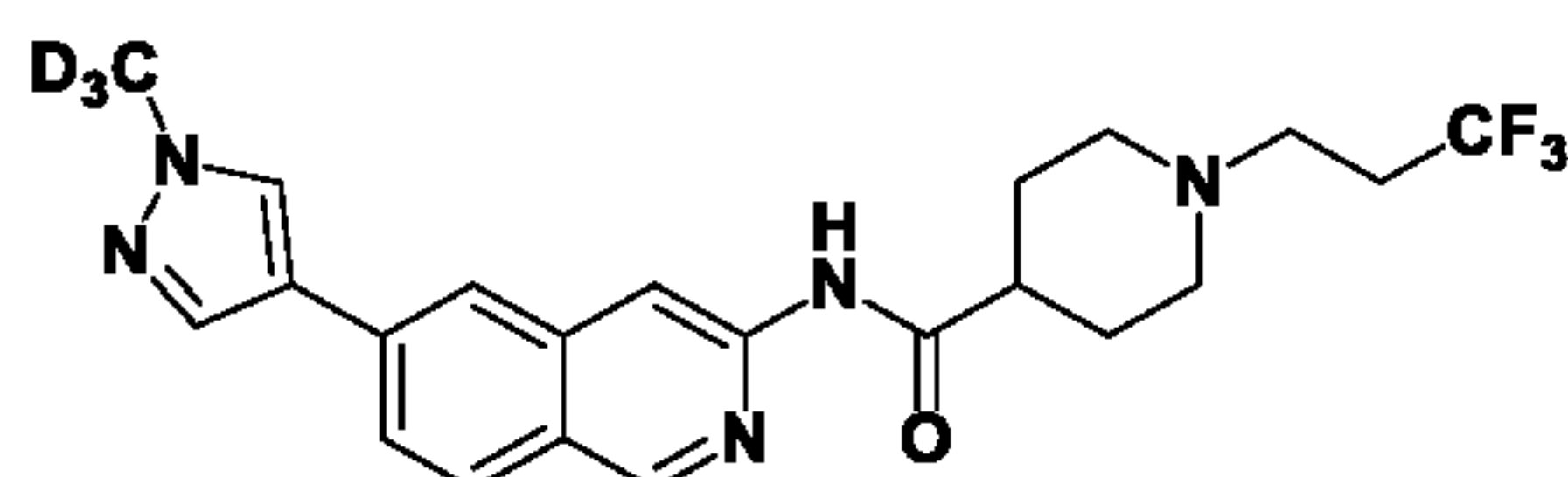
[0800] 2-(Cyclobutyl(methyl)amino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **302**.

[0801] Off-white solid (69.0 mg, 0.198 mmol, 59.8% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.53 - 1.69 (m, 2 H), 1.81 - 1.92 (m, 2 H), 1.97 - 2.07 (m, 2 H), 2.23 (s, 3 H), 3.03 - 3.10 (m, 1 H), 3.11 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.51, 1.37$ Hz, 1 H), 8.03 (d, $J=8.51$ Hz, 1 H), 8.08 - 8.14 (m, 2 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 9.04 (s, 1 H), 9.91 (s, 1 H); ESIMS found for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}$ m/z 350.2 ($\text{M}+1$).

**303**

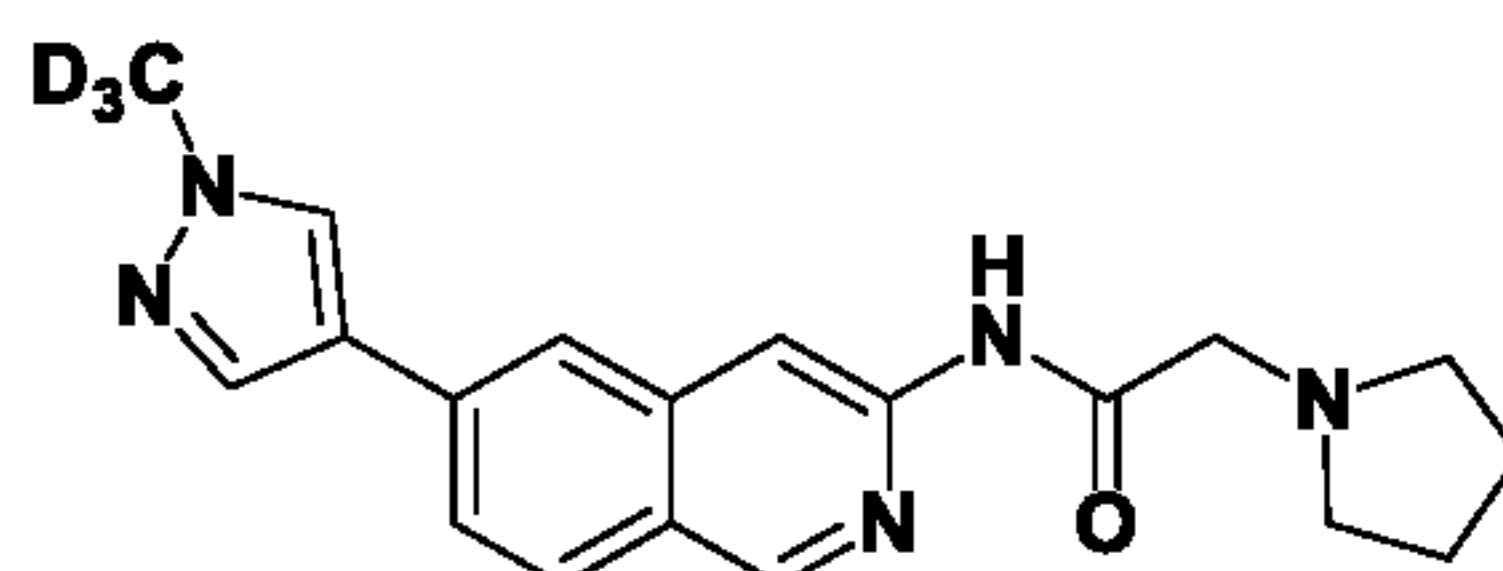
[0802] 2-(Diethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **303**.

[0803] White paste (74.0 mg, 0.219 mmol, 66.5% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.05 (t, $J=7.14$ Hz, 6 H), 2.65 (q, $J=7.14$ Hz, 4 H), 3.24 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.51, 1.37$ Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.08 - 8.14 (m, 2 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 9.03 (s, 1 H), 9.93 (s, 1 H); ESIMS found for $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}$ m/z 338.2 ($\text{M}+1$).

**304**

[0804] N-(6-(1-(Methyl- d_3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **304**.

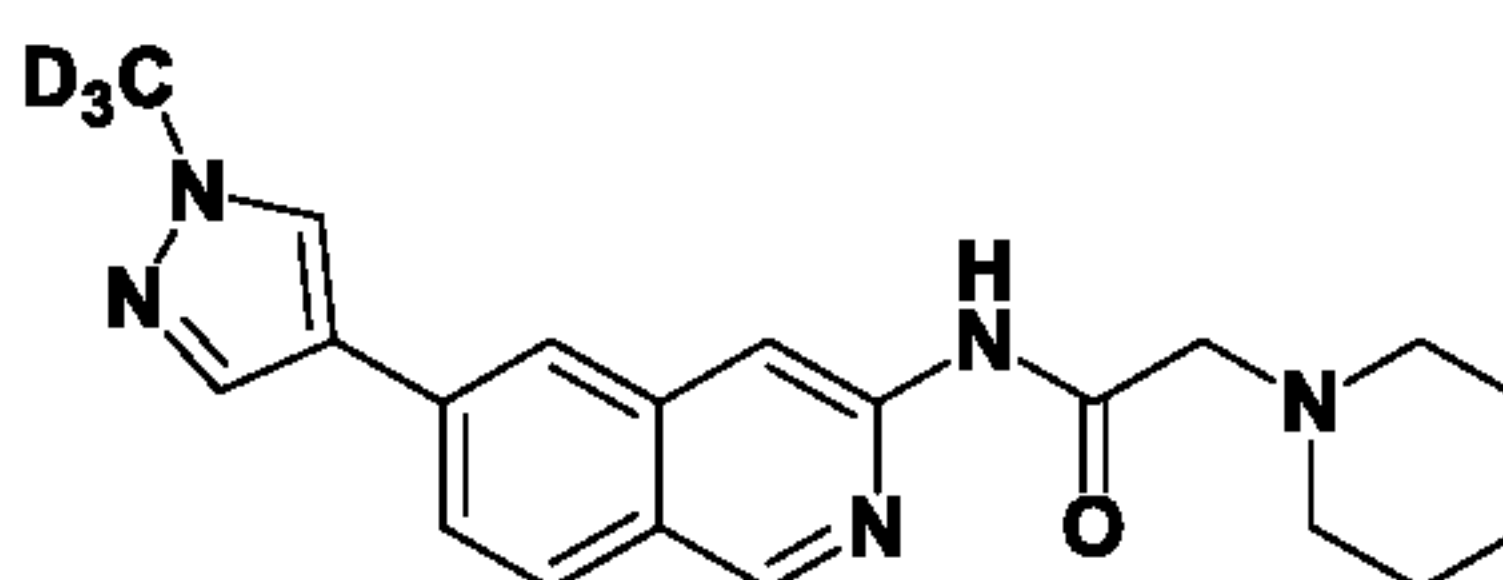
[0805] Off-white solid (54.0 mg, 0.124 mmol, 44.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.60 - 1.72 (m, 2 H), 1.79 (br d, $J=10.15$ Hz, 2 H), 1.91 - 2.02 (m, 2 H), 2.39 - 2.60 (m, 5 H), 2.93 (br d, $J=11.25$ Hz, 2 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H), 8.07 (s, 1 H), 8.34 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.47 (s, 1 H); ESIMS found for $\text{C}_{22}\text{H}_{21}\text{D}_3\text{F}_3\text{N}_5\text{O}$ m/z 435.2 (M+1).



305

[0806] N-(6-(1-(Methyl- d_3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **305**.

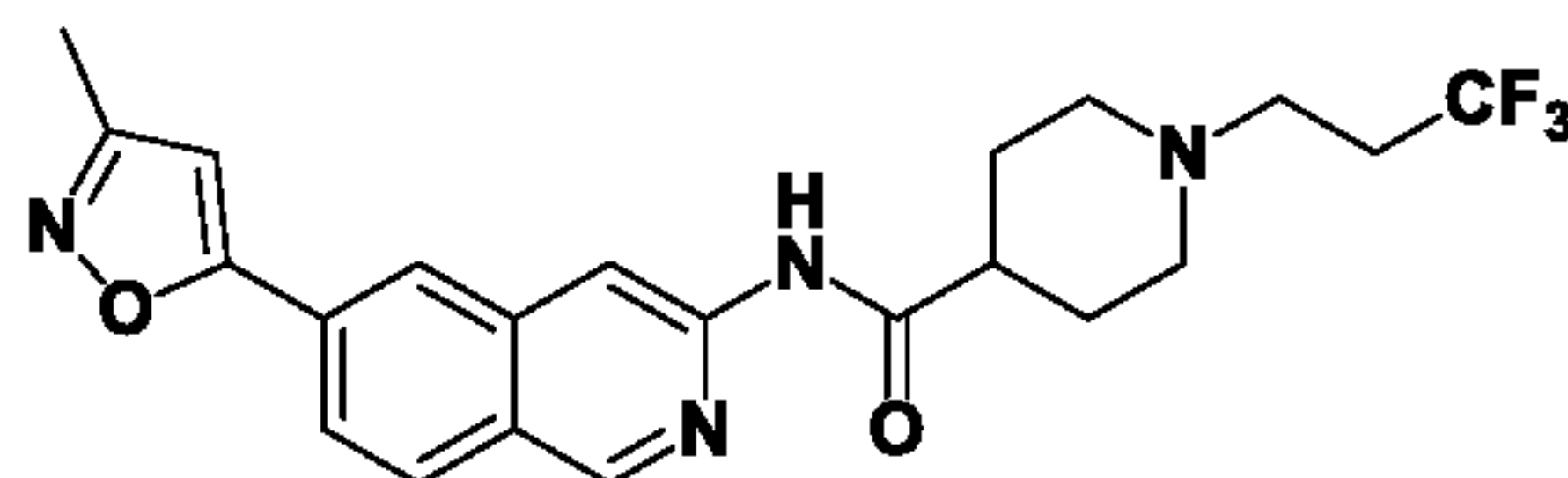
[0807] White paste (80.0 mg, 0.236 mmol, 71.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.78 (dt, $J=6.59$, 3.29 Hz, 4 H), 2.62 - 2.70 (m, 4 H), 3.35 (s, 2 H), 7.77 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.10 (s, 2 H), 8.36 (s, 1 H), 8.43 (s, 1 H), 9.03 (s, 1 H), 9.92 (s, 1 H); ESIMS found for $\text{C}_{19}\text{H}_{18}\text{D}_3\text{N}_5\text{O}$ m/z 339.2 (M+1).



306

[0808] N-(6-(1-(Methyl- d_3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide **306**.

[0809] Beige solid (82.0 mg, 0.233 mmol, 70.5% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.43 (br d, $J=4.94$ Hz, 2 H), 1.59 (quin, $J=5.56$ Hz, 4 H), 2.52 (br d, $J=1.92$ Hz, 4 H), 3.17 (s, 2 H), 7.77 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.02 (d, $J=8.78$ Hz, 1 H), 8.10 (s, 2 H), 8.36 (s, 1 H), 8.43 (s, 1 H), 9.04 (s, 1 H), 9.91 (s, 1 H); ESIMS found for $\text{C}_{20}\text{H}_{20}\text{D}_3\text{N}_5\text{O}$ m/z 353.2 (M+1).

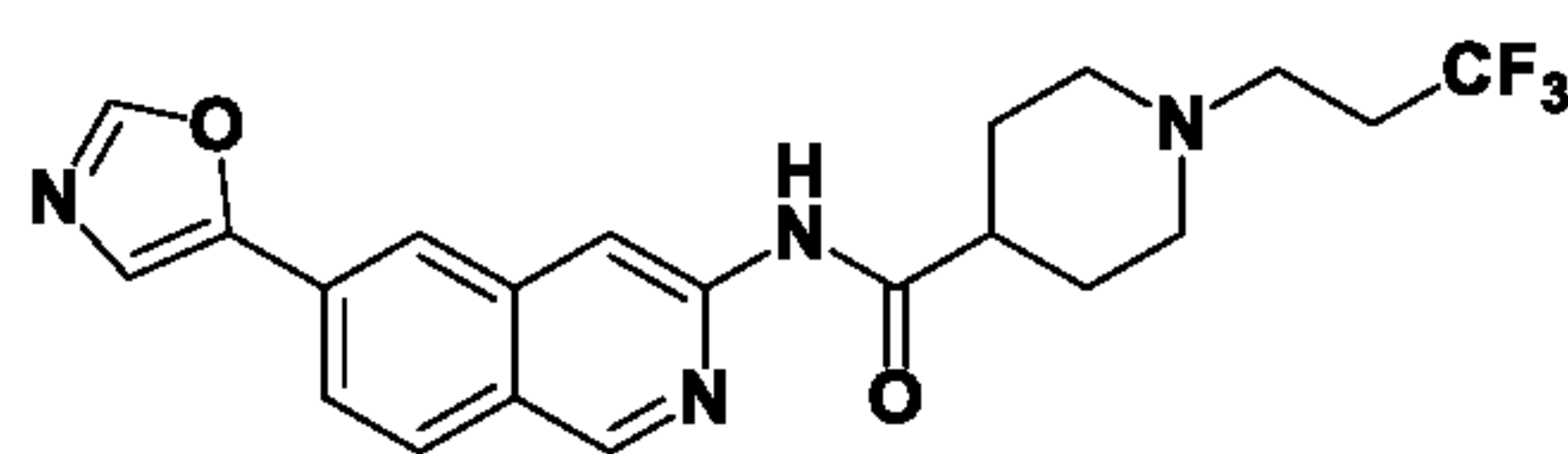


307

[0810] N-(6-(3-Methylisoxazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **307**.

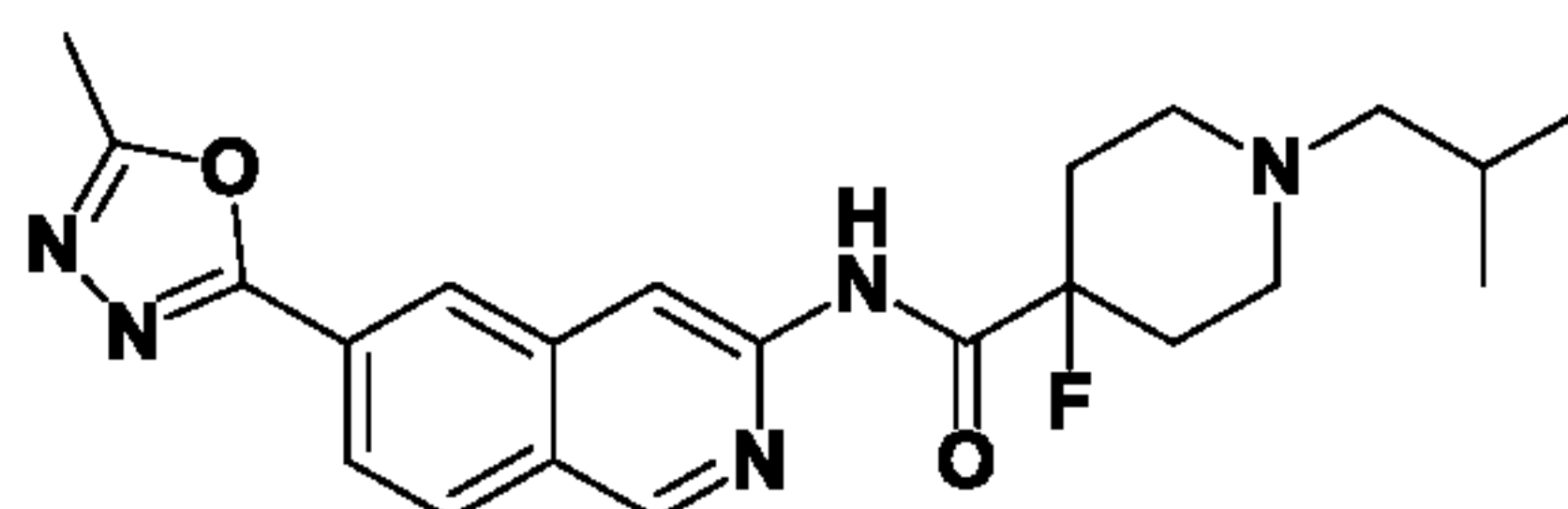
[0811] White solid (3.0 mg, 0.007 mmol, 2.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.61 - 1.73 (m, 2 H), 1.80 (br d, $J=10.43$ Hz, 2 H), 1.92 - 2.02 (m, 2 H), 2.41 - 2.61 (m, 5 H), 2.51 (s, 3 H), 2.93 (br d, $J=11.25$ Hz, 2 H), 7.68 (dd, $J=8.37$, 1.51 Hz, 1 H), 8.04 (s, 1 H),

8.11 (d, $J=8.51$ Hz, 1 H), 8.54 (s, 1 H), 9.13 (s, 1 H), 9.34 (s, 1 H), 10.56 (s, 1 H); ESIMS found for $C_{22}H_{23}F_3N_4O_2$ m/z 433.2 (M+1).

**308**

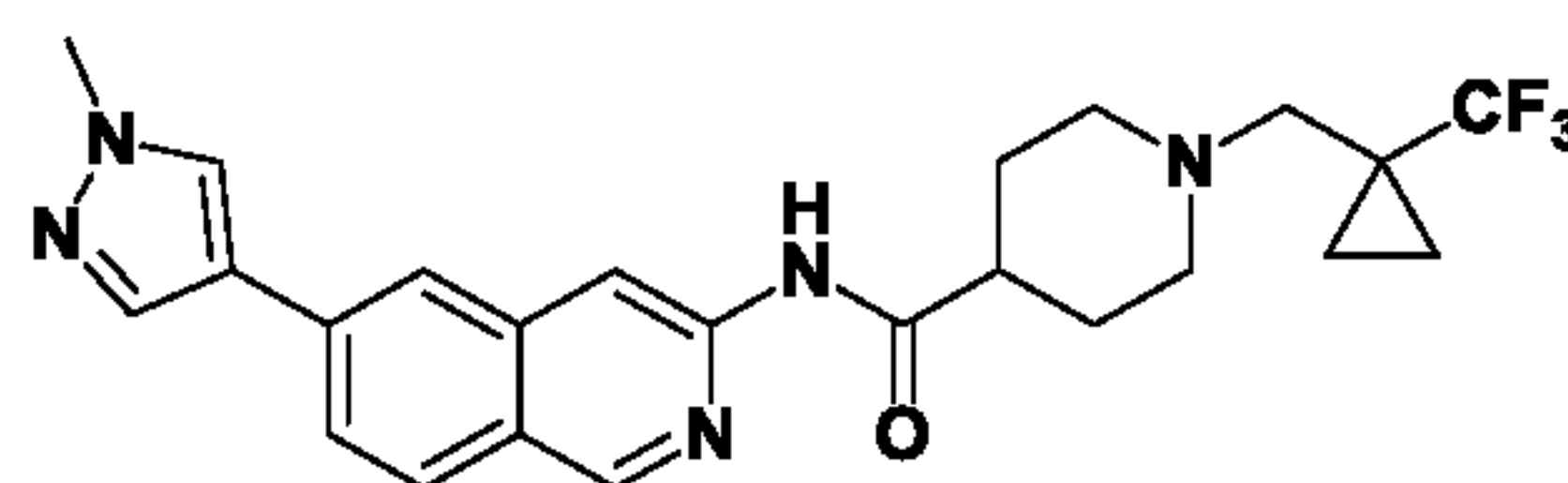
[0812] N-(6-(Oxazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide **308**.

[0813] Off-white solid (16.0 mg, 0.038 mmol, 16.5% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.58 - 1.72 (m, 2 H), 1.80 (br d, $J=10.70$ Hz, 2 H), 1.91 - 2.03 (m, 2 H), 2.40 - 2.61 (m, 5 H), 2.94 (br d, $J=11.25$ Hz, 2 H), 7.87 (dd, $J=8.64$, 1.51 Hz, 1 H), 7.95 (s, 1 H), 8.13 (d, $J=8.51$ Hz, 1 H), 8.20 (s, 1 H), 8.54 (s, 1 H), 8.58 (s, 1 H), 9.13 (s, 1 H), 10.58 (s, 1 H); ESIMS found for $C_{21}H_{21}F_3N_4O_2$ m/z 419.1 (M+1).

**309**

[0814] 4-Fluoro-1-isobutyl-N-(6-(5-methyl-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide **309**.

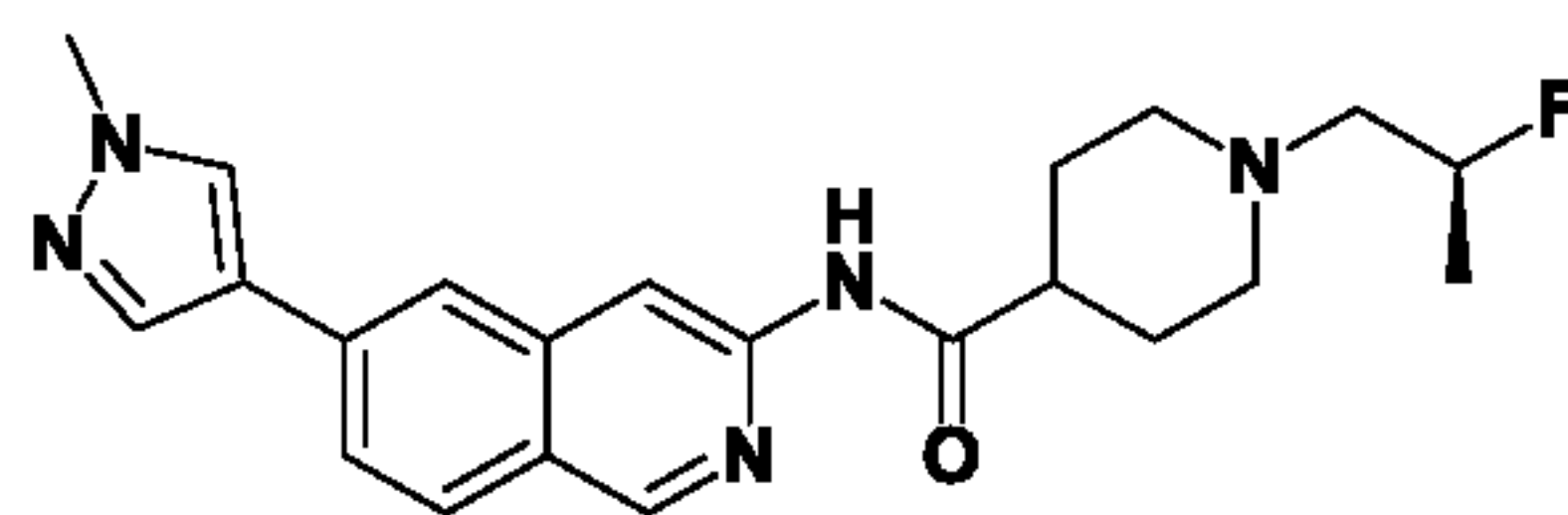
[0815] Off-white solid (20.0 mg, 0.049 mmol, 13.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.88 (d, $J=6.59$ Hz, 6 H), 1.80 (dquin, $J=13.55$, 6.84, 6.84, 6.84, 6.84 Hz, 1 H), 1.92 - 2.02 (m, 2 H), 2.09 (d, $J=7.41$ Hz, 2 H), 2.06 - 2.21 (m, 4 H), 2.64 (s, 3 H), 2.75 - 2.82 (m, 2 H), 8.11 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.29 (d, $J=8.51$ Hz, 1 H), 8.57 (s, 1 H), 8.60 (s, 1 H), 9.30 (s, 1 H), 10.11 (d, $J=3.57$ Hz, 1 H); ESIMS found for $C_{22}H_{26}FN_5O_2$ m/z 412.2 (M+1).

**310**

[0816] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide **310**.

[0817] Off-white solid (70.0 mg, 0.153 mmol, 76.5% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.73 (s, 2 H), 0.93 - 0.99 (m, 2 H), 1.60 - 1.72 (m, 2 H), 1.73 - 1.82 (m, 2 H), 1.89 - 2.00 (m, 2 H), 2.49 (br s, 2 H), 2.52 - 2.58 (m, 1 H), 2.96 (br d, $J=11.25$ Hz, 2 H), 3.90 (s, 3

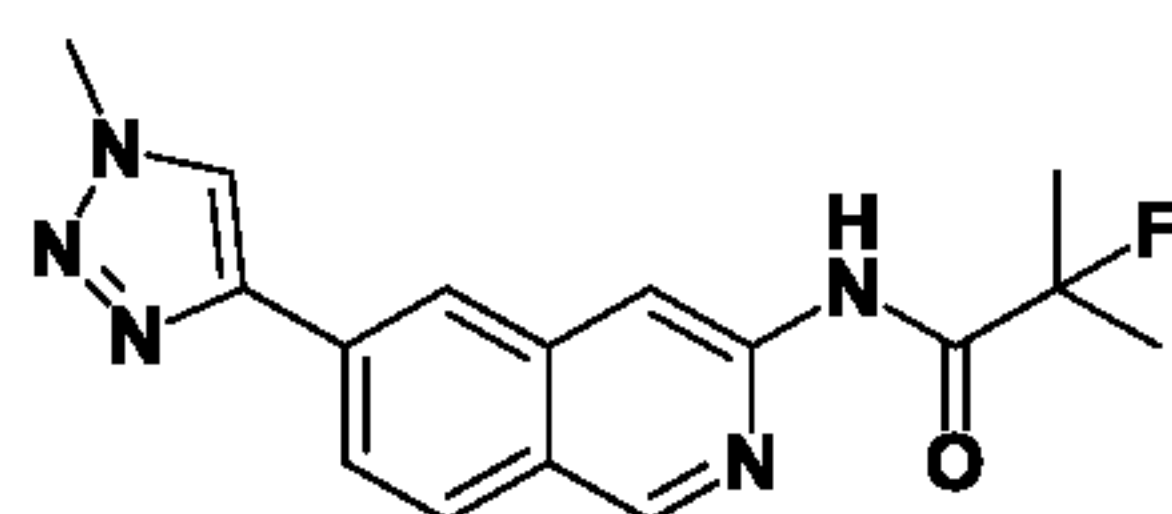
H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.46 (s, 1 H); ESIMS found for $C_{24}H_{26}F_3N_5O$ m/z 458.2 (M+1).



311

[0818] (S)-1-(2-Fluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **311**.

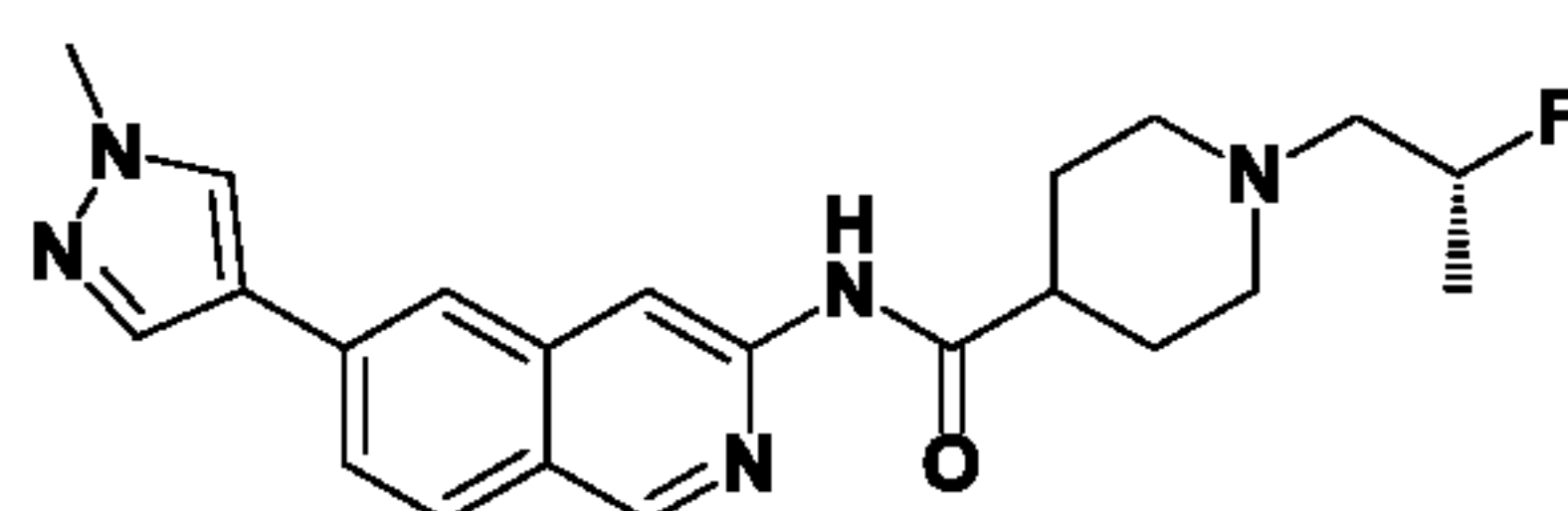
[0819] White solid (71.0 mg, 0.180 mmol, 60.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.26 (dd, $J=23.95$, 6.35 Hz, 3 H), 1.62 - 1.72 (m, 2 H), 1.74 - 1.82 (m, 2 H), 2.00 - 2.12 (m, 2 H), 2.34 - 2.49 (m, 2 H), 2.52 - 2.59 (m, 1 H), 2.93 (br t, $J=11.80$ Hz, 2 H), 3.90 (s, 3 H), 4.75 - 4.94 (m, 1 H), 7.74 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.00 (d, $J=8.78$ Hz, 1 H), 8.04 (s, 1 H), 8.07 (s, 1 H), 8.34 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.45 (s, 1 H); ESIMS found for $C_{22}H_{26}FN_5O$ m/z 396.2 (M+1).



312

[0820] 2-Fluoro-2-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)propanamide **312**.

[0821] Off-white solid (21.0 mg, 0.067 mmol, 10.5% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.64 (d, $J=22.00$ Hz, 6 H), 4.15 (s, 3 H), 8.07 (dd, $J=8.51$, 1.65 Hz, 1 H), 8.16 (d, $J=8.51$ Hz, 1 H), 8.36 (s, 1 H), 8.46 (s, 1 H), 8.74 (s, 1 H), 9.17 (s, 1 H), 9.91 (d, $J=3.57$ Hz, 1 H); ESIMS found for $C_{16}H_{16}FN_5O$ m/z 314.1 (M+1).

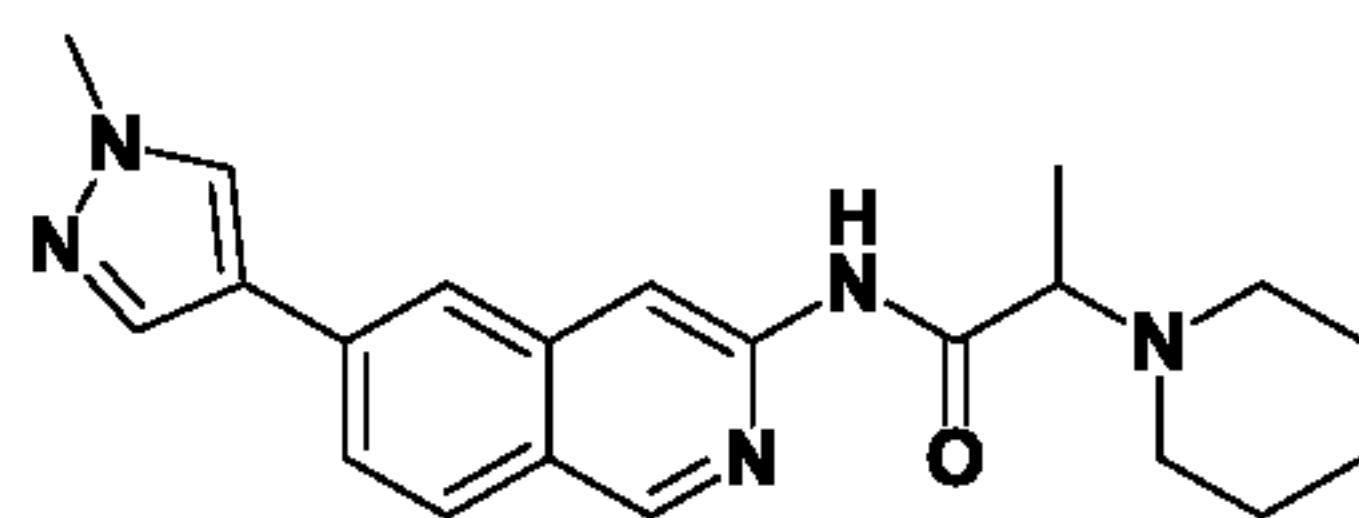


313

[0822] (R)-1-(2-Fluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **313**.

[0823] White solid (30.0 mg, 0.076 mmol, 25.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.26 (dd, $J=23.90$, 6.30 Hz, 3 H), 1.68 (q, $J=11.53$ Hz, 2 H), 1.74 - 1.81 (m, 2 H), 1.99 - 2.09 (m, 2 H), 2.35 - 2.47 (m, 1 H), 2.52 - 2.57 (m, 1 H), 2.93 (br t, $J=11.80$ Hz, 2 H), 3.90 (s, 3 H), 4.74 - 4.94 (m, 1 H), 7.74 (dd, $J=8.51$, 1.37 Hz, 1 H), 8.00 (d, $J=8.51$ Hz, 1 H), 8.03 (s, 1 H),

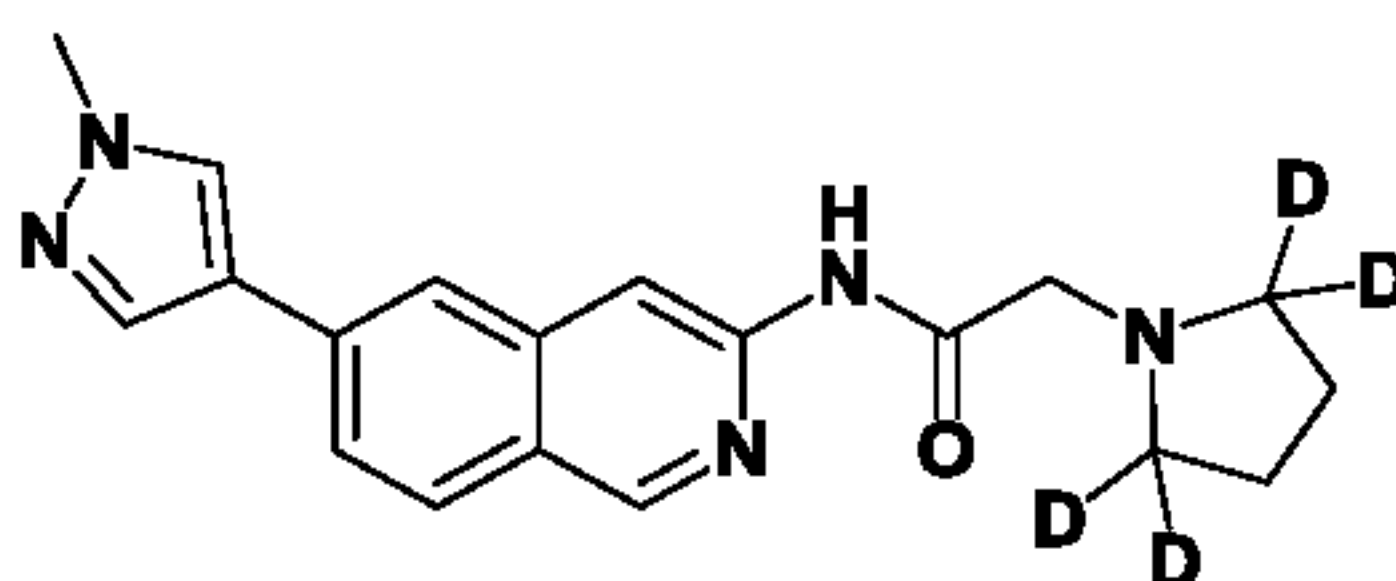
8.07 (s, 1 H), 8.35 (s, 1 H), 8.44 (s, 1 H), 9.02 (s, 1 H), 10.46 (s, 1 H); ESIMS found for $C_{22}H_{26}FN_5O$ m/z 396.2 (M+1).



314

[0824] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)propanamide **314**.

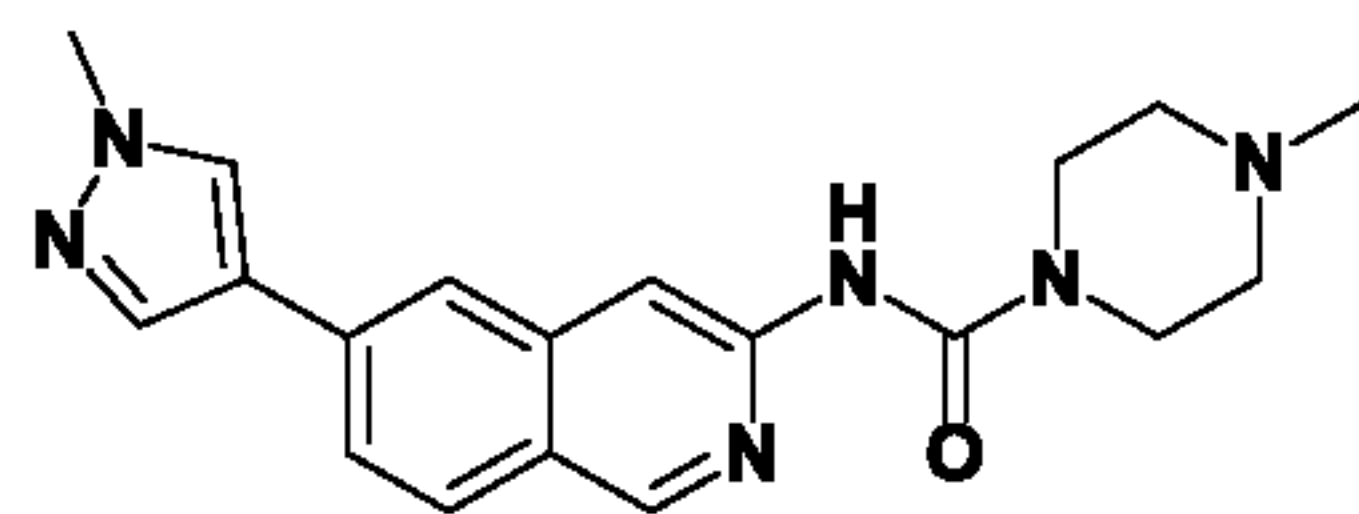
[0825] Off-white solid (57.0 mg, 0.157 mmol, 51.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.20 (d, $J=7.14$ Hz, 3 H), 1.39 - 1.46 (m, 2 H), 1.53 - 1.64 (m, 4 H), 2.52 - 2.58 (m, 2 H), 3.44 (q, $J=6.86$ Hz, 1 H), 3.90 (s, 3 H), 7.76 (dd, $J=8.51, 1.65$ Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.06 - 8.11 (m, 2 H), 8.36 (s, 1 H), 8.44 (s, 1 H), 9.04 (s, 1 H), 10.09 (s, 1 H); ESIMS found for $C_{21}H_{25}N_5O$ m/z 364.2 (M+1).



315

[0826] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl-2,2,5,5- d_4)acetamide **315**.

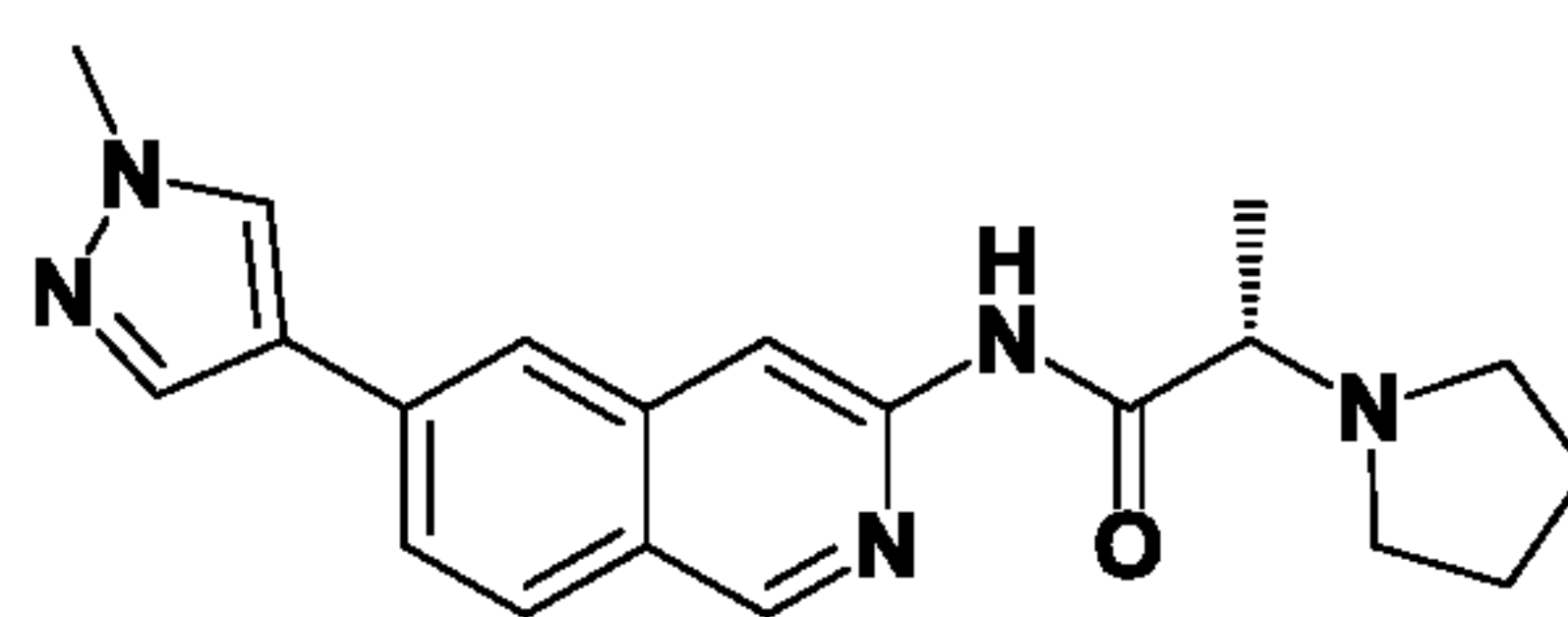
[0827] Beige solid (43.0 mg, 0.127 mmol, 42.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.76 (s, 4 H), 3.36 (s, 2 H), 3.90 (s, 3 H), 7.77 (dd, $J=8.64, 1.51$ Hz, 1 H), 8.02 (d, $J=8.51$ Hz, 1 H), 8.10 (s, 2 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 9.03 (s, 1 H), 9.93 (s, 1 H); ESIMS found for $C_{19}H_{17}D_4N_5O$ m/z 340.2 (M+1).



316

[0828] 4-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperazine-1-carboxamide **316**.

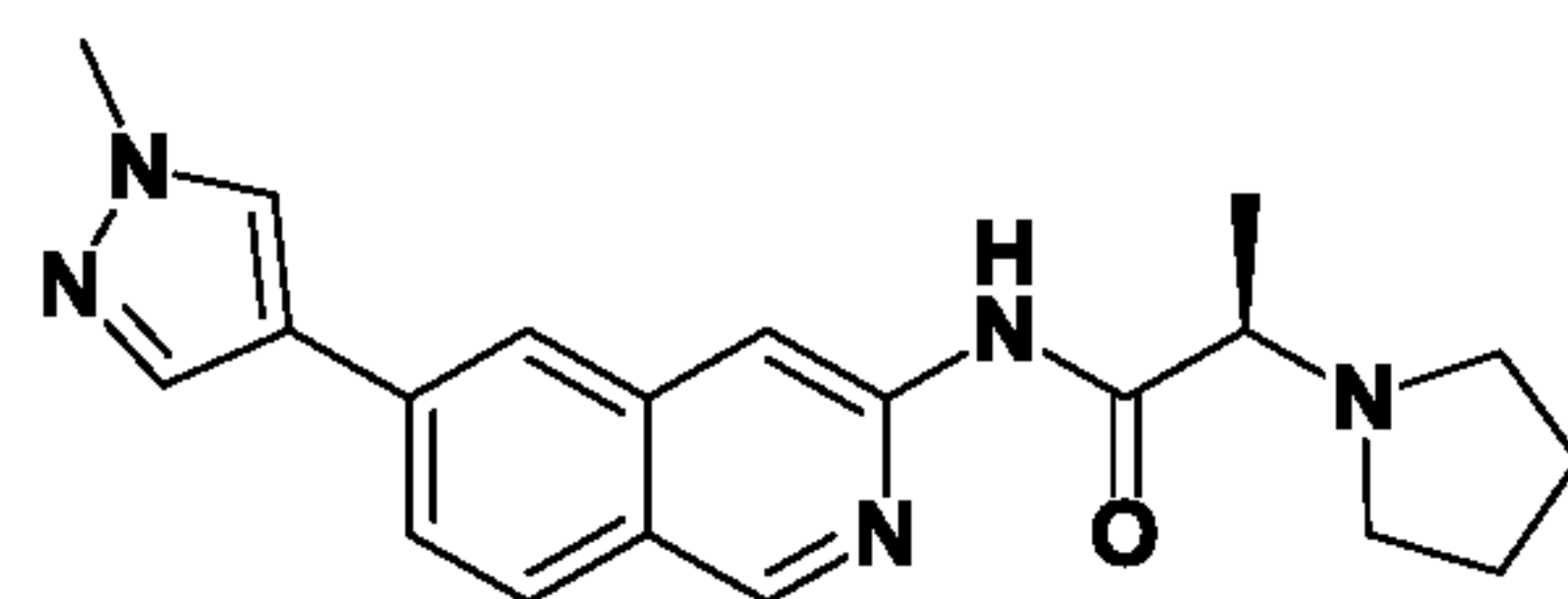
[0829] Off-white solid (14.0 mg, 0.040 mmol, 46.5% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.20 (s, 3 H), 2.29 - 2.35 (m, 4 H), 3.48 - 3.54 (m, 4 H), 3.90 (s, 3 H), 7.68 (dd, $J=8.51, 1.65$ Hz, 1 H), 7.94 - 8.00 (m, 2 H), 8.06 (s, 1 H), 8.14 (s, 1 H), 8.33 (s, 1 H), 8.97 (s, 1 H), 9.13 (s, 1 H); ESIMS found for $C_{19}H_{22}N_6O$ m/z 351.2 (M+1).



317

[0830] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide **317**.

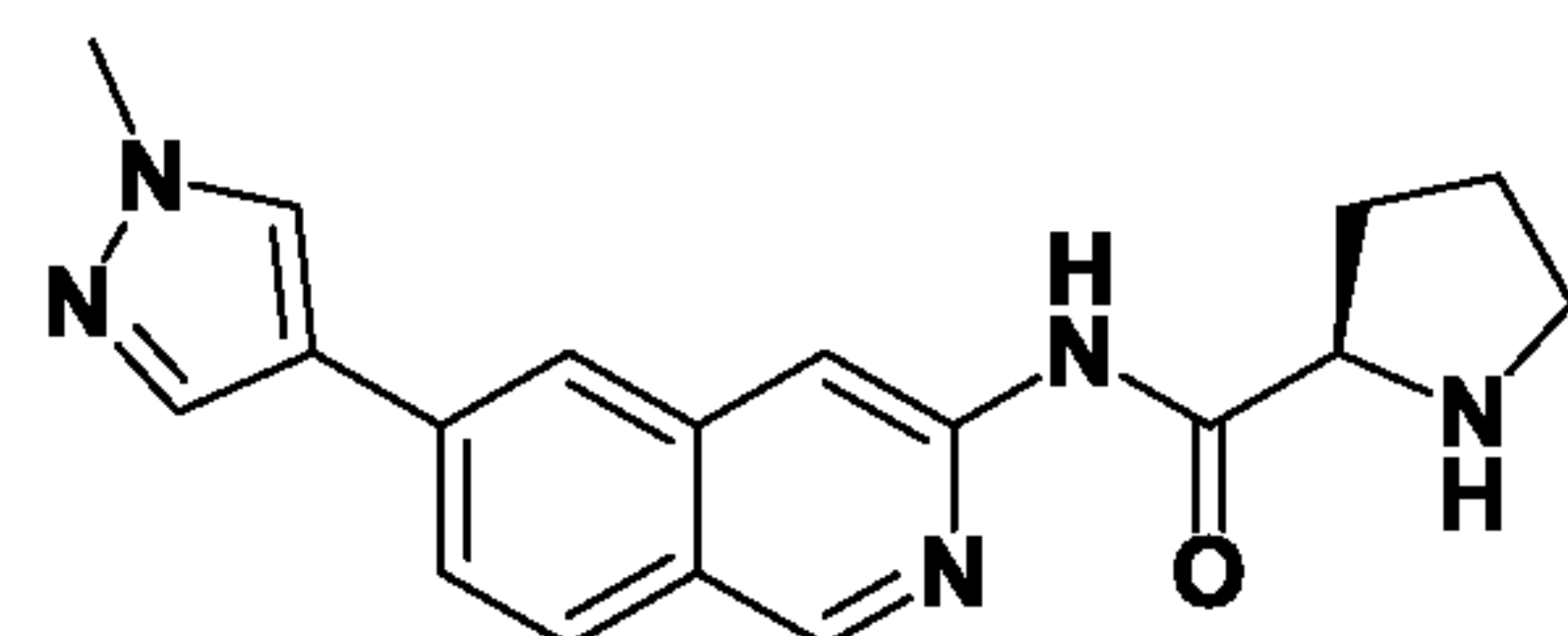
[0831] White solid (75.0 mg, 0.215 mmol, 65.4% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.30 (3 H, d, *J*=6.86 Hz), 1.74 (4 H, br s), 2.57 - 2.68 (4 H, m), 3.25 - 3.30 (1 H, m), 3.90 (3 H, s), 7.76 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.08 (1 H, s), 8.09 (1 H, s), 8.36 (1 H, s), 8.43 (1 H, s), 9.03 (1 H, s), 9.94 (1 H, s); ESIMS found for C₂₀H₂₃N₅O *m/z* 350.2 (M+1).



318

[0832] (R)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide **318**.

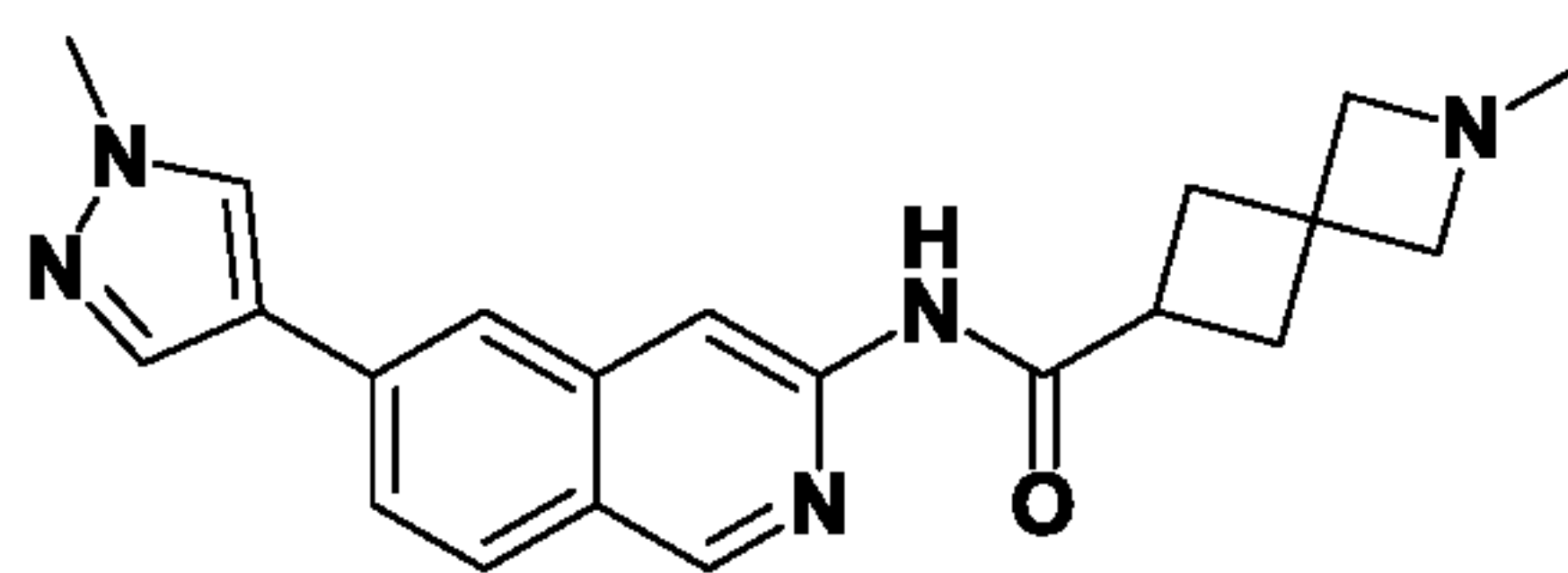
[0833] Light beige solid (89.0 mg, 0.255 mmol, 62.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.30 (3 H, d, *J*=6.86 Hz), 1.74 (4 H, br s), 2.56 - 2.70 (4 H, m), 3.25 - 3.30 (1 H, m), 3.90 (3 H, s), 7.76 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.08 (1 H, s), 8.09 (1 H, s), 8.36 (1 H, s), 8.43 (1 H, s), 9.03 (1 H, s), 9.94 (1 H, s); ESIMS found for C₂₀H₂₃N₅O *m/z* 350.2 (M+1).



320

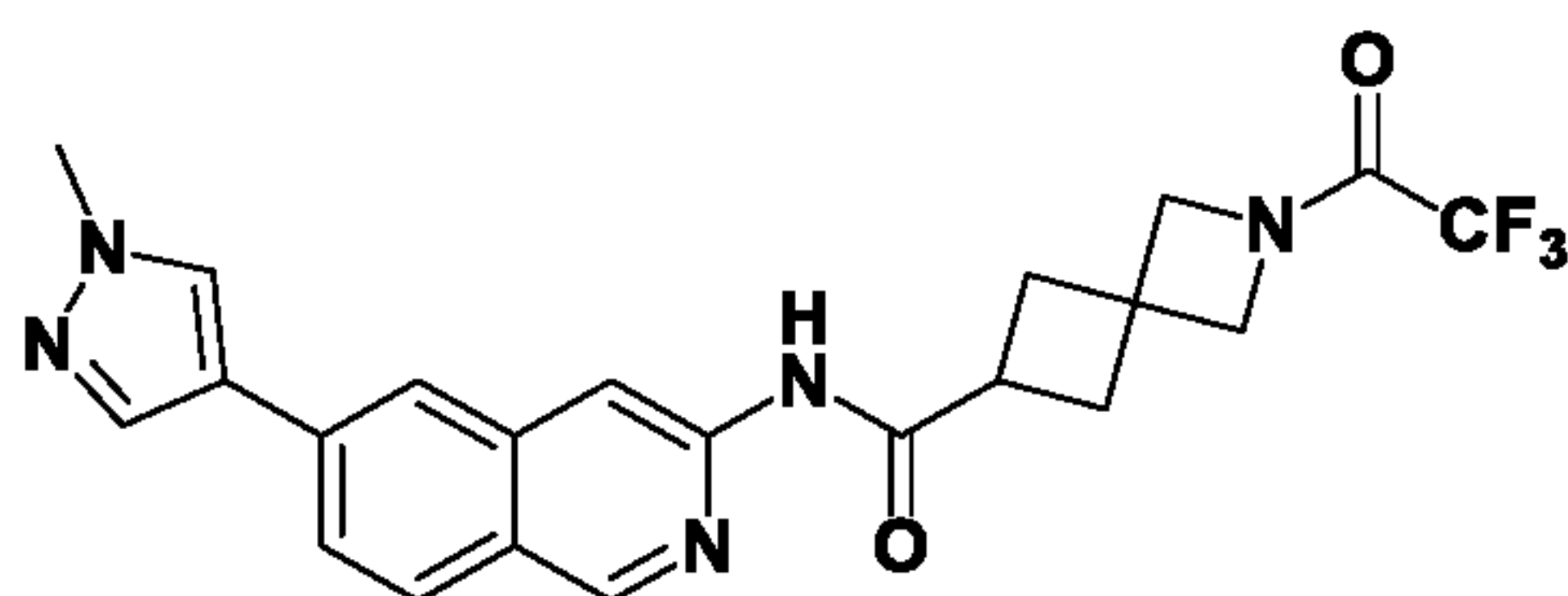
[0834] (R)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide **320**.

[0835] Brown solid (830.0 mg, 2.58 mmol, 78.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.67 (2 H, quin, *J*=6.86 Hz), 1.79 - 1.90 (1 H, m), 2.04 - 2.16 (1 H, m), 2.87 (1 H, dt, *J*=10.15, 6.31 Hz), 2.97 (1 H, dt, *J*=10.15, 6.72 Hz), 3.35 (1 H, br s), 3.80 (1 H, dd, *J*=9.19, 5.35 Hz), 3.90 (3 H, s), 7.76 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.09 (1 H, br s), 8.09 (1 H, s), 8.36 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.34 (1 H, s); ESIMS found for C₁₈H₁₉N₅O *m/z* 322.15 (M+1).

**324**

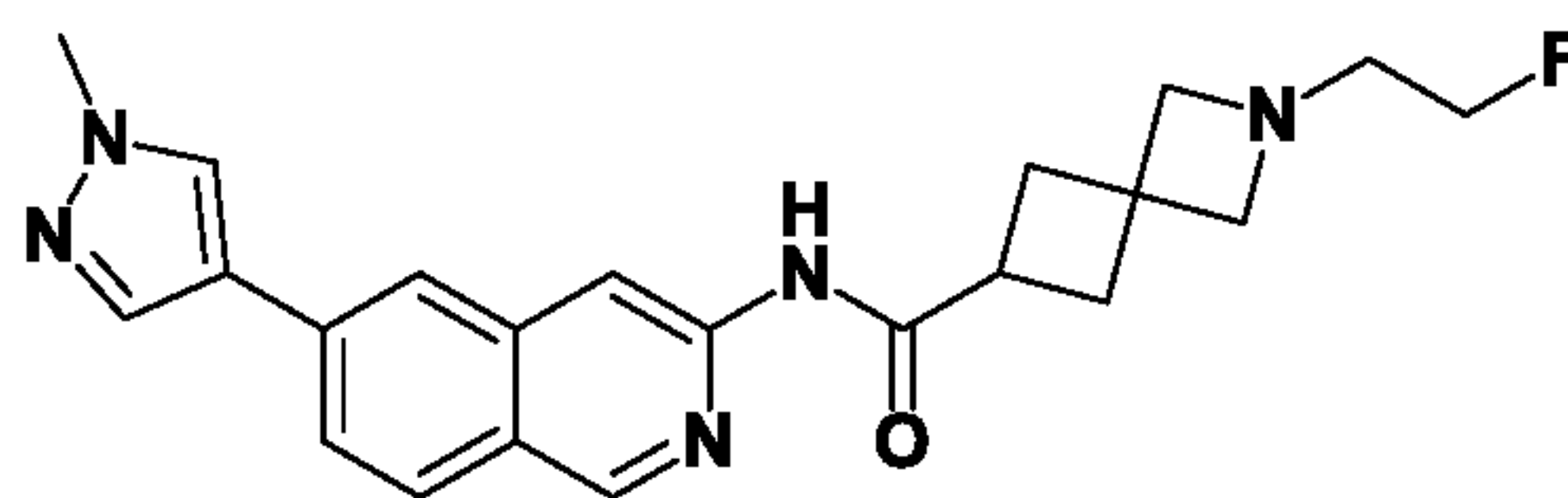
[0836] 2-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide **324**.

[0837] Off-white solid (32.0 mg, 0.089 mmol, 38.4% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.15 (3 H, s), 2.21 - 2.35 (4 H, m), 3.04 (2 H, s), 3.14 (2 H, s), 3.21 - 3.28 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.44 (1 H, s), 9.01 (1 H, s), 10.35 (1 H, s); ESIMS found for C₂₁H₂₃N₅O *m/z* 362.2 (M+1).

**325**

[0838] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide **325**.

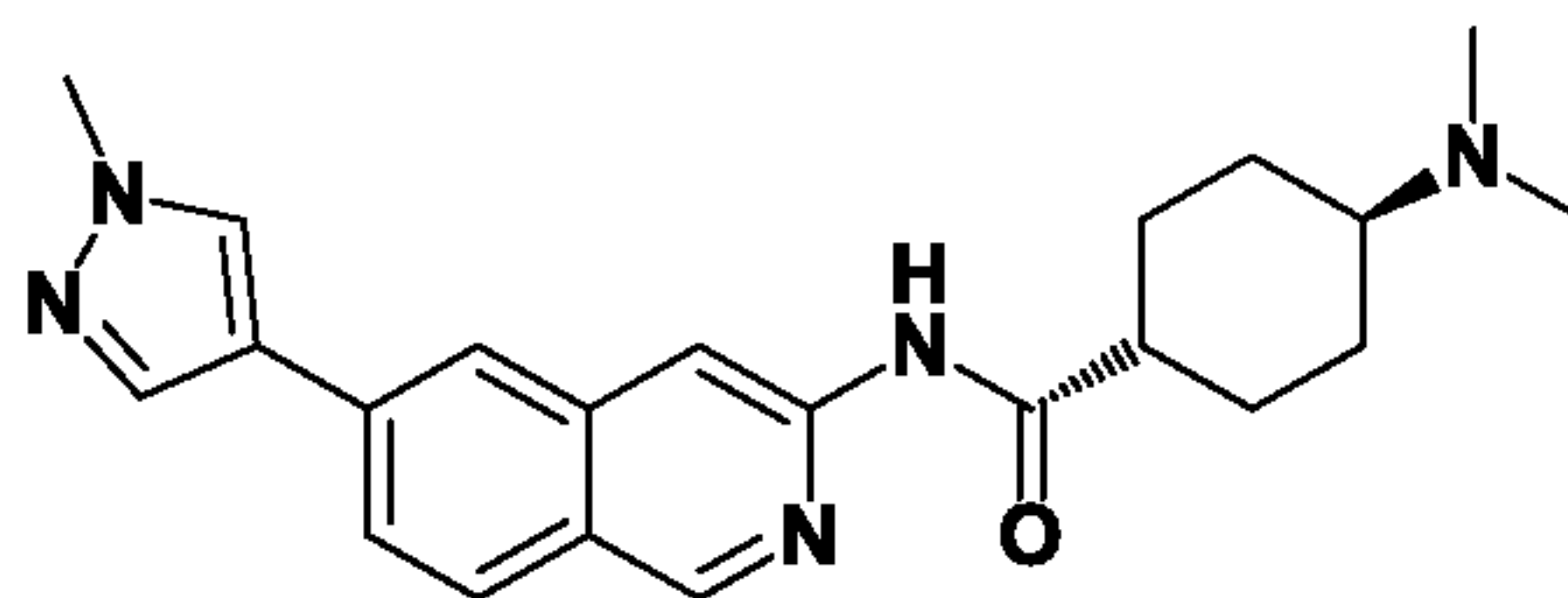
[0839] White solid (26.0 mg, 0.059 mmol, 18.0% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.40 - 2.49 (4 H, m), 3.22 - 3.31 (1 H, m), 4.06 - 4.15 (2 H, m), 4.44 (2 H, br d, *J*=17.56 Hz), 7.75 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.06 (1 H, s), 8.09 (1 H, d, *J*=1.10 Hz), 8.35 (1 H, d, *J*=1.65 Hz), 8.46 (1 H, s), 9.02 (1 H, s), 10.47 (1 H, s); ESIMS found for C₂₂H₂₀F₃N₅O₂ *m/z* 444.15 (M+1).

**326**

[0840] 2-(2-Fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide **326**.

[0841] Beige solid (10.0 mg, 0.025 mmol, 24.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.23 - 2.36 (4 H, m), 2.60 (2 H, dt, *J*=29.00, 5.00 Hz), 3.13 (2 H, s), 3.22 (2 H, s), 3.24 - 3.29 (1 H, m), 4.36 (2 H, dt, *J*=48.00, 5.00 Hz), 7.74 (1 H, dd, *J*=8.51, 1.37 Hz), 7.99 (1 H, d,

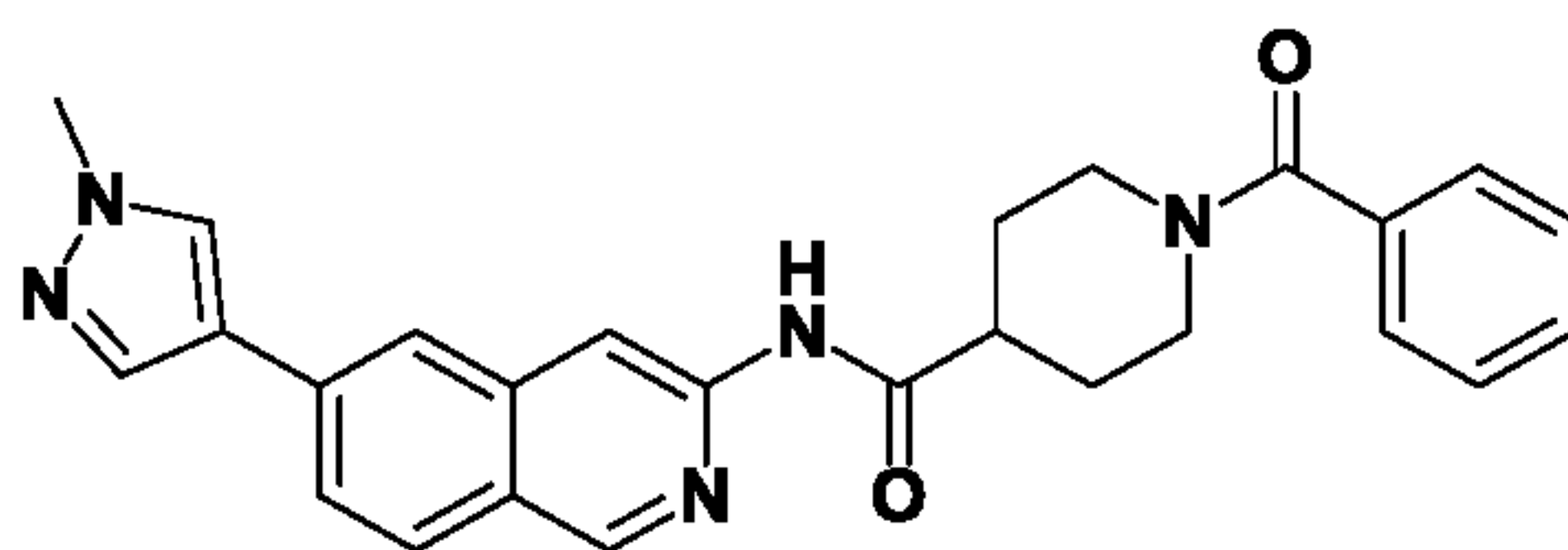
$J=8.51$ Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.44 (1 H, s), 9.01 (1 H, s), 10.36 (1 H, s); ESIMS found for $C_{22}H_{24}FN_5O$ m/z 394.2 (M+1).



327

[0842] *trans*-4-(Dimethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **327**.

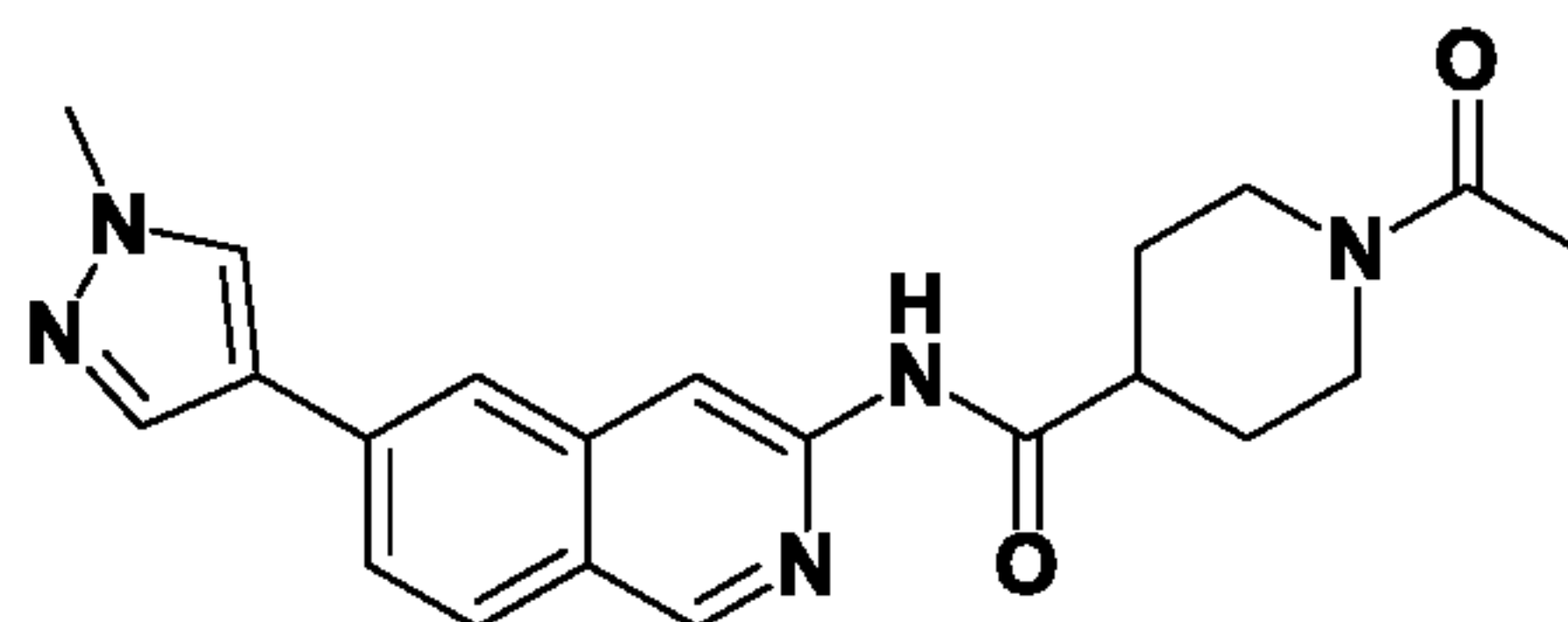
[0843] Beige solid (650.0 mg, 1.72 mmol, 46.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.11 - 1.27 (3 H, m), 1.41 - 1.54 (2 H, m), 1.83 - 1.96 (4 H, m), 2.10 - 2.16 (1 H, m), 2.18 (6 H, s), 2.42 - 2.49 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.37 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.35 (1 H, s), 8.43 (1 H, s), 9.02 (1 H, s), 10.41 (1 H, s); ESIMS found for $C_{22}H_{27}N_5O$ m/z 378.2 (M+1).



328

[0844] 1-Benzoyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **328**.

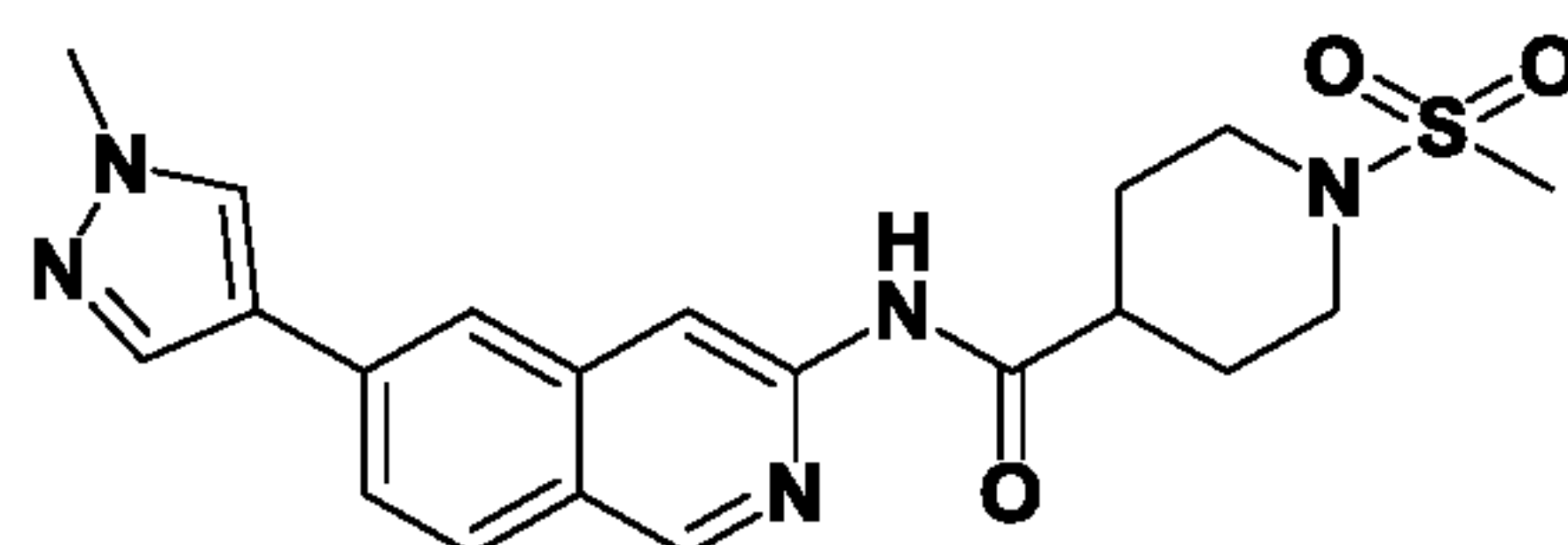
[0845] White solid (65.0 mg, 0.148 mmol, 55.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.57 - 1.72 (2 H, m), 1.75 - 2.00 (2 H, m), 2.86 (2 H, tt, $J=11.18$, 3.77 Hz), 3.04 - 3.19 (1 H, m), 3.57 - 3.75 (1 H, m), 3.90 (3 H, s), 4.43 - 4.63 (1 H, m), 7.38 - 7.43 (2 H, m), 7.43 - 7.49 (3 H, m), 7.75 (1 H, dd, $J=8.51$, 1.37 Hz), 8.00 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.43 (1 H, s), 9.03 (1 H, s), 10.54 (1 H, s); ESIMS found for $C_{26}H_{25}N_5O_2$ m/z 440.0 (M+1).



329

[0846] 1-Acetyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **329**.

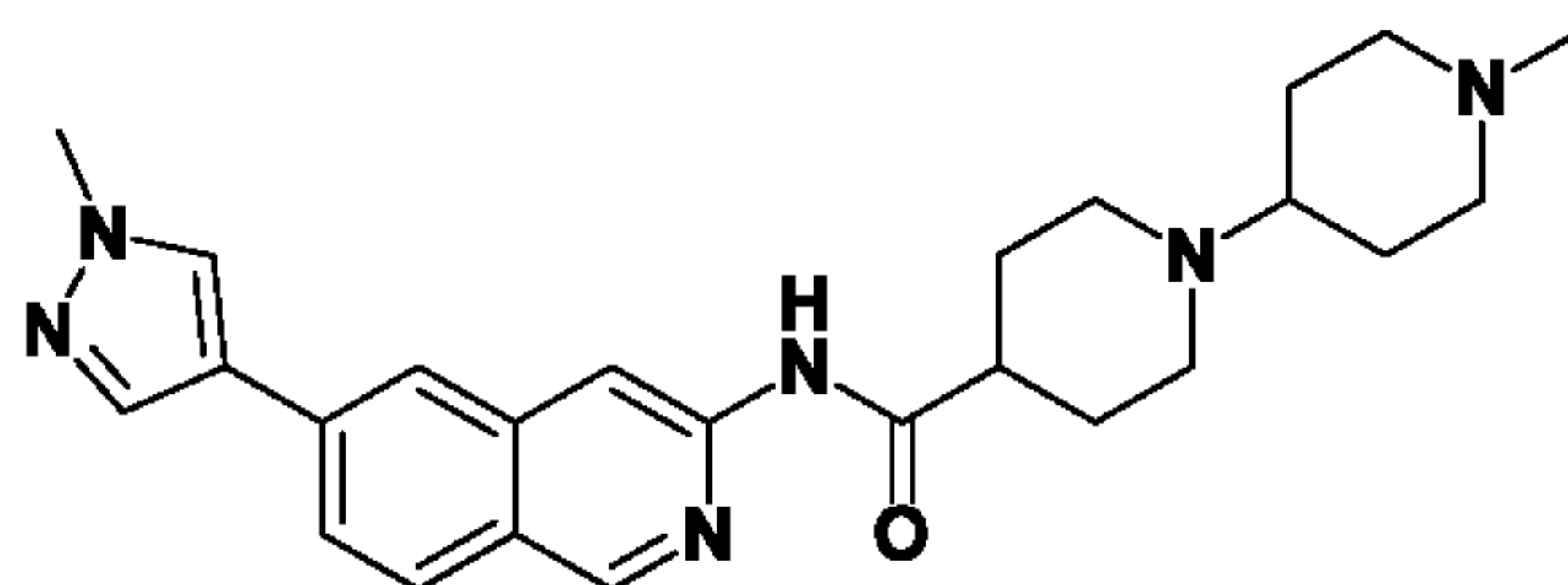
[0847] White solid (60.0 mg, 0.159 mmol, 59.4% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.47 (1 H, qd, *J*=12.26, 4.39 Hz), 1.56 - 1.69 (1 H, m), 1.77 - 1.91 (2 H, m), 2.02 (3 H, s), 2.58 (1 H, td, *J*=12.62, 2.47 Hz), 2.75 - 2.84 (1 H, m), 3.03 - 3.11 (1 H, m), 3.88 (1 H, br d, *J*=13.15 Hz), 3.90 (3 H, s), 4.41 (1 H, br d, *J*=13.17 Hz), 7.75 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.43 (1 H, s), 9.03 (1 H, s), 10.53 (1 H, s); ESIMS found for C₂₁H₂₃N₅O₂ *m/z* 378.0 (M+1).



330

[0848] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide **330**.

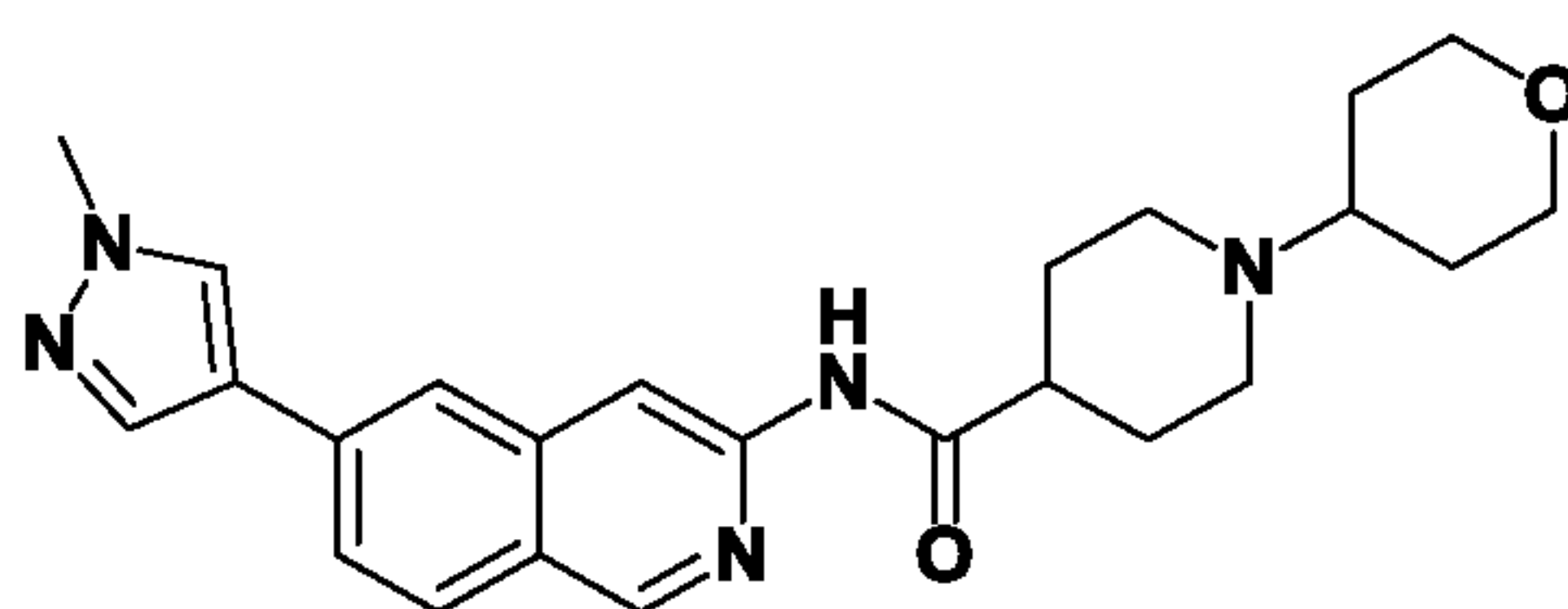
[0849] White solid (60.0 mg, 0.145 mmol, 54.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.65 - 1.77 (2 H, m), 1.95 (2 H, br dd, *J*=13.31, 2.61 Hz), 2.69 (1 H, tt, *J*=11.25, 3.84 Hz), 2.76 (2 H, td, *J*=11.94, 2.20 Hz), 2.89 (3 H, s), 3.59 - 3.67 (2 H, m), 3.90 (3 H, s), 7.75 (1 H, dd, *J*=8.51, 1.65 Hz), 8.01 (1 H, d, *J*=8.51 Hz), 8.05 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.44 (1 H, s), 9.03 (1 H, s), 10.59 (1 H, s); ESIMS found for C₂₀H₂₃N₅O₃S *m/z* 413.9 (M+1).



331

[0850] 1'-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide **331**.

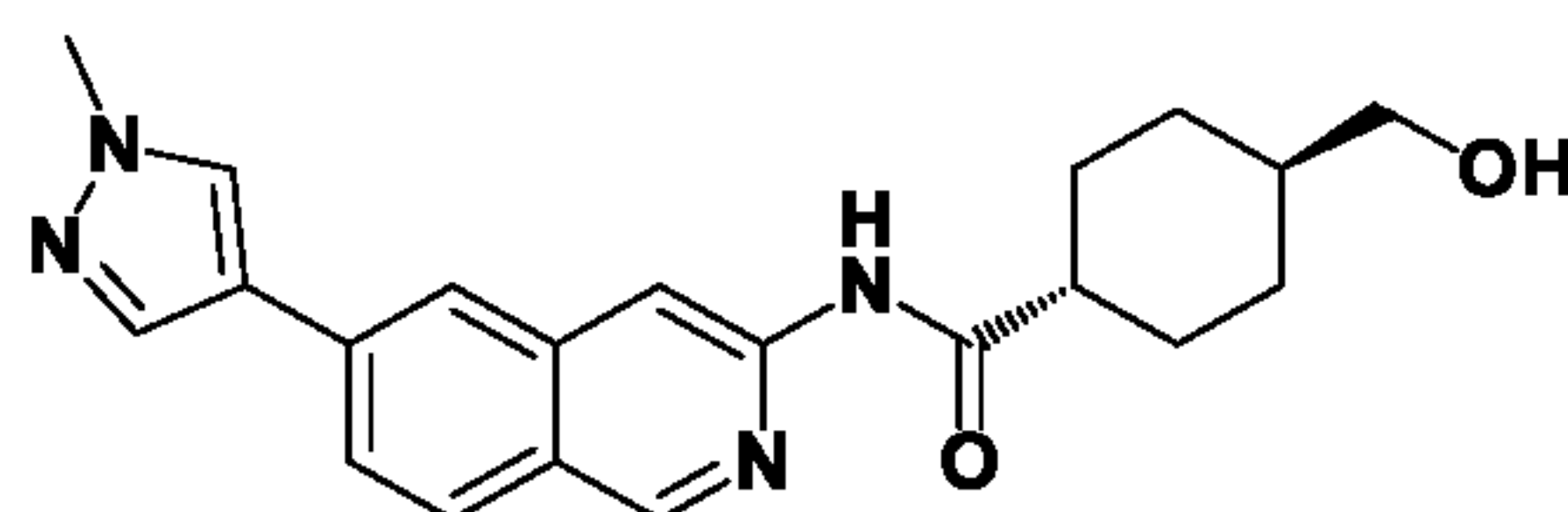
[0851] White solid (4.0 mg, 0.009 mmol, 3.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.44 (2 H, qd, *J*=11.89, 3.57 Hz), 1.58 - 1.71 (4 H, m), 1.73 - 1.87 (4 H, m), 2.06 - 2.20 (4 H, m), 2.12 (3 H, s), 2.78 (2 H, br d, *J*=11.53 Hz), 2.91 (2 H, br d, *J*=11.25 Hz), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.37 Hz), 7.99 (1 H, d, *J*=8.78 Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.42 (1 H, s); ESIMS found for C₂₅H₃₂N₆O *m/z* 433.0 (M+1).



332

[0852] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide **332**.

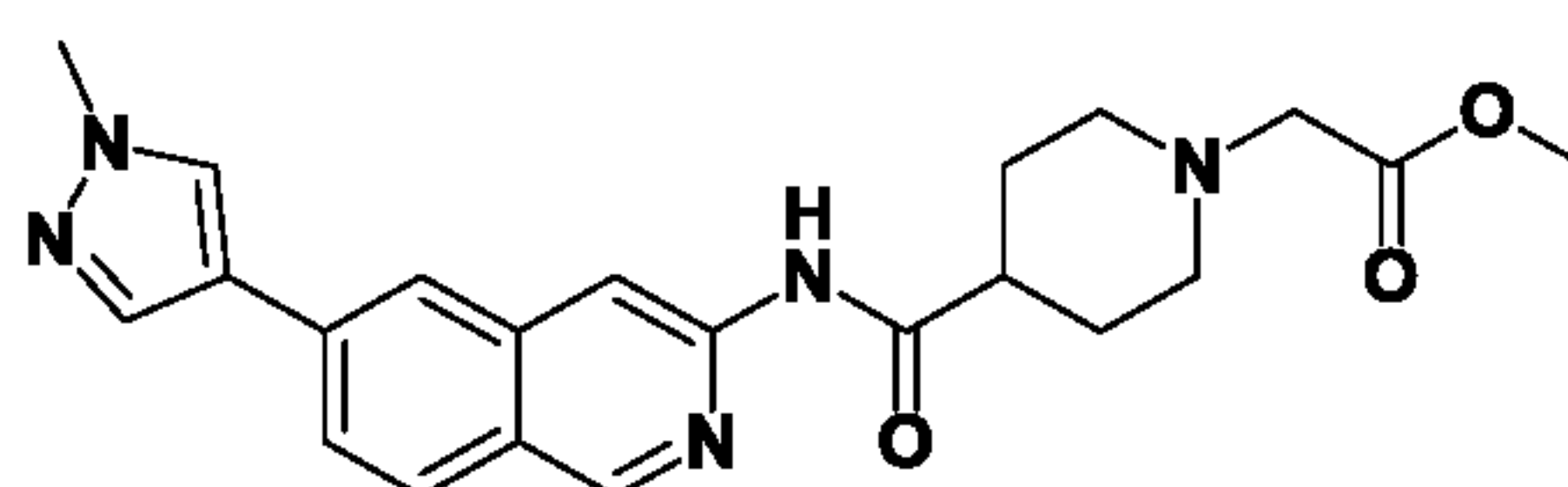
[0853] White solid (11.0 mg, 0.026 mmol, 8.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.43 (2 H, qd, *J*=12.08, 4.39 Hz), 1.59 - 1.69 (4 H, m), 1.79 (2 H, br d, *J*=11.80 Hz), 2.08 - 2.17 (2 H, m), 2.42 (1 H, tt, *J*=11.35, 3.60 Hz), 2.51 - 2.58 (1 H, m), 2.94 (2 H, br d, *J*=11.53 Hz), 3.22 - 3.29 (2 H, m), 3.87 (2 H, br d, *J*=3.57 Hz), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 7.99 (1 H, d, *J*=8.78 Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.43 (1 H, s); ESIMS found for C₂₄H₂₉N₅O₂ *m/z* 420.0 (M+1).



333

[0854] *trans*-4-(Hydroxymethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **333**.

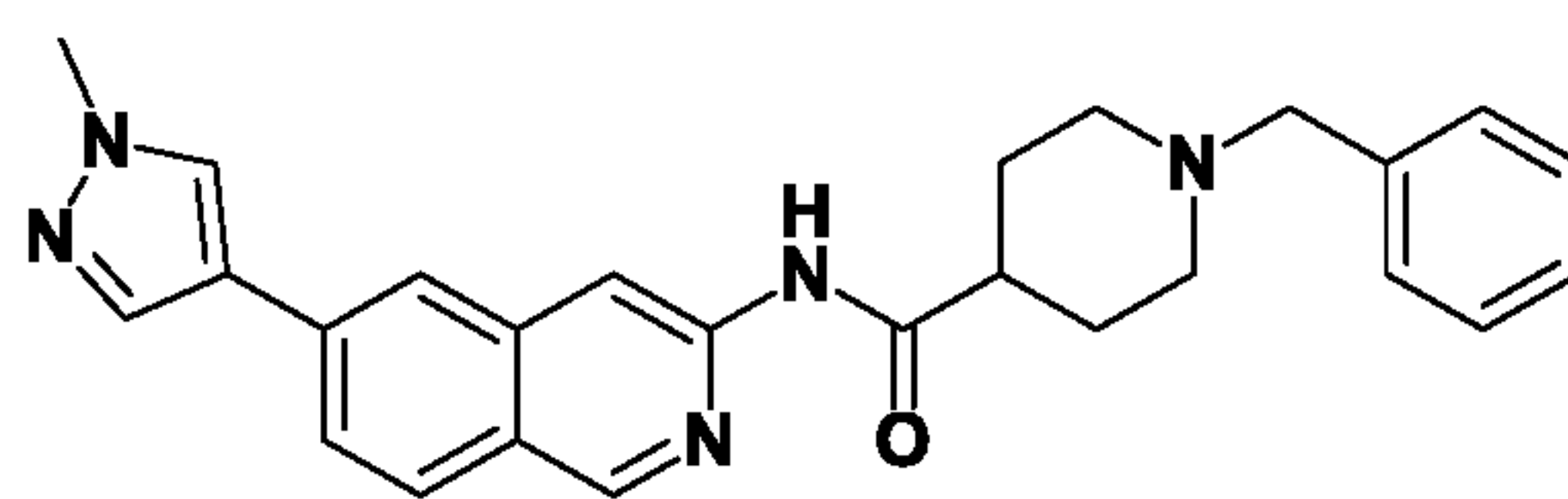
[0855] Light beige solid (215.0 mg, 0.59 mmol, 51.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.95 (2 H, qd, *J*=12.72, 3.29 Hz), 1.31 - 1.39 (1 H, m), 1.45 (2 H, qd, *J*=12.72, 3.02 Hz), 1.80 (2 H, br dd, *J*=13.17, 2.74 Hz), 1.84 - 1.93 (2 H, m), 3.24 (2 H, t, *J*=5.76 Hz), 3.90 (3 H, s), 4.37 (1 H, t, *J*=5.35 Hz), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.43 (1 H, s), 9.02 (1 H, s), 10.38 (1 H, s); ESIMS found for C₂₁H₂₄N₄O₂ *m/z* 365.0 (M+1).



334

[0856] Methyl 2-(4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate **334**.

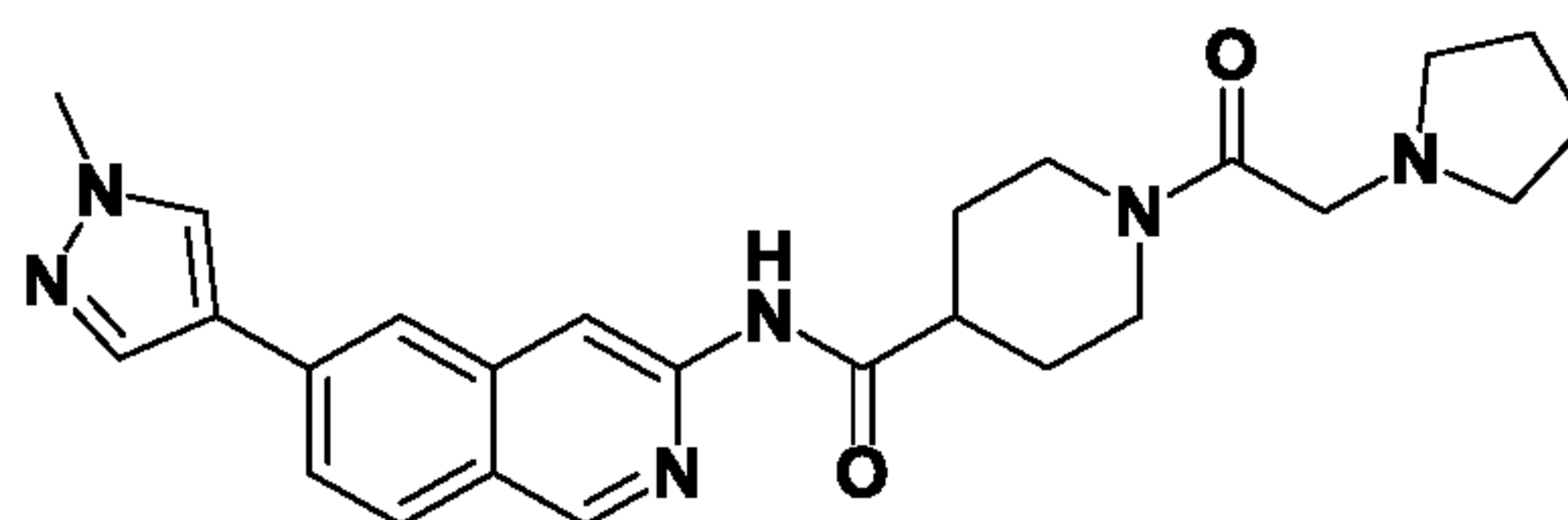
[0857] White solid (20.0 mg, 0.049 mmol, 16.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.73 (2 H, m), 1.74 - 1.82 (2 H, m), 2.22 (2 H, td, *J*=11.53, 2.20 Hz), 2.51 - 2.58 (1 H, m), 2.84 - 2.92 (2 H, m), 3.24 (2 H, s), 3.62 (3 H, s), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.45 (1 H, s); ESIMS found for C₂₂H₂₅N₅O₃ *m/z* 408.0 (M+1).



335

[0858] 1-Benzyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **335**.

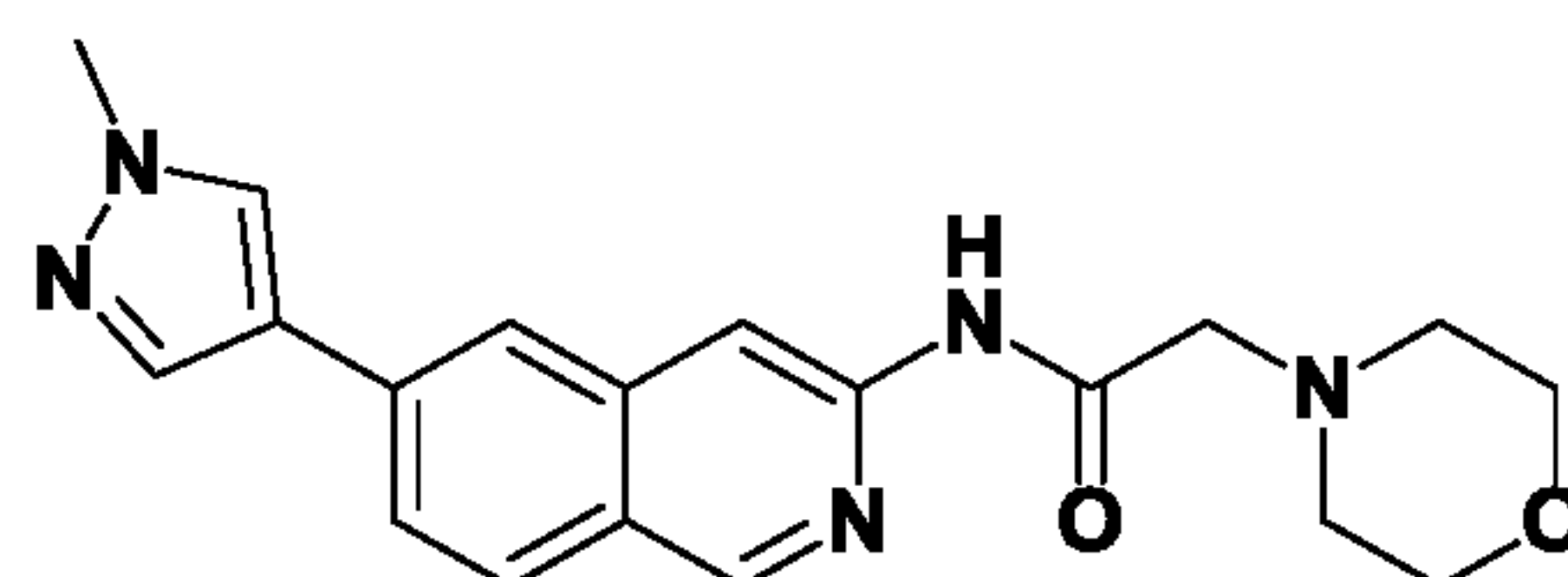
[0859] White solid (22.0 mg, 0.052 mmol, 17.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.60 - 1.72 (2 H, m), 1.73 - 1.81 (2 H, m), 1.98 (2 H, td, *J*=11.60, 2.06 Hz), 2.51 - 2.57 (1 H, m), 2.88 - 2.96 (2 H, m), 3.24 (2 H, s), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 7.99 (1 H, d, *J*=8.78 Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.43 (1 H, s); ESIMS found for C₂₆H₂₇N₅O *m/z* 426.0 (M+1).



336

[0860] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide **336**.

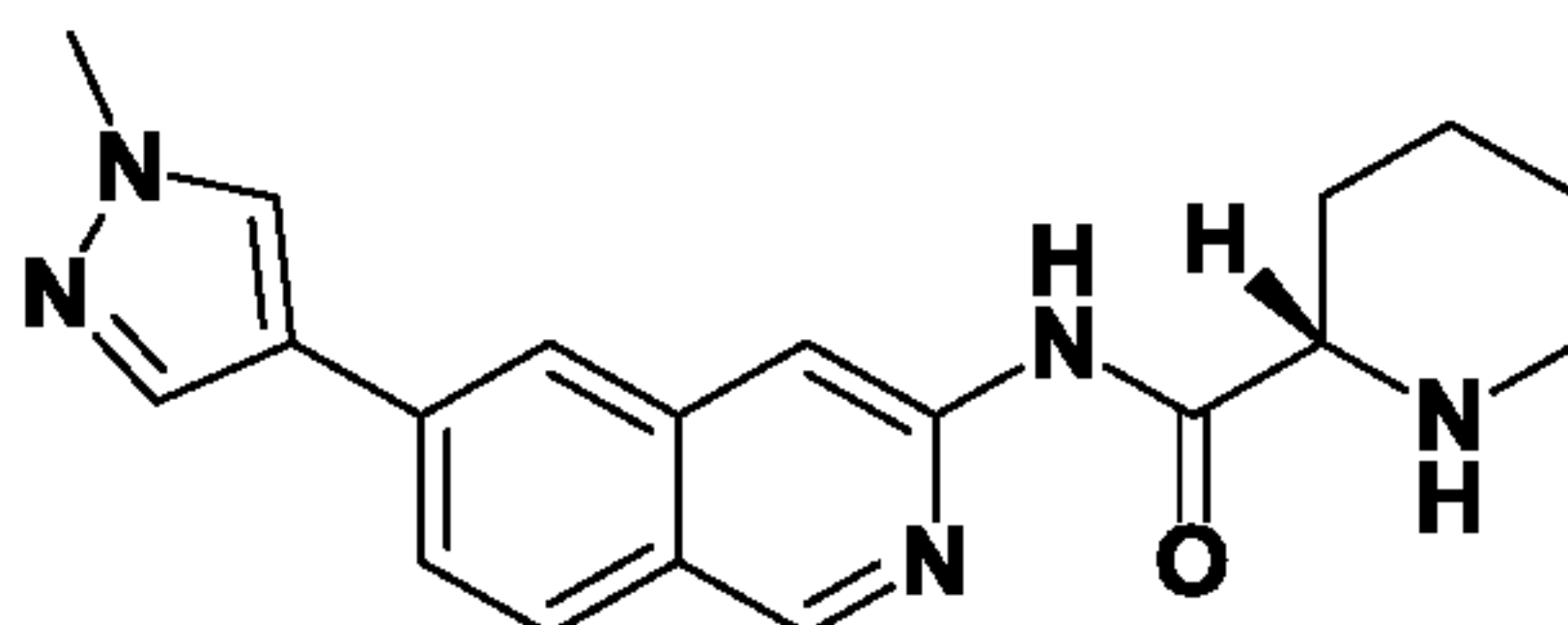
[0861] White solid (21.0 mg, 0.047 mmol, 15.8% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.43 - 1.54 (1 H, m), 1.55 - 1.66 (1 H, m), 1.67 - 1.73 (4 H, m), 1.84 (2 H, br d, *J*=10.98 Hz), 2.48 (4 H, br s), 2.56 - 2.66 (1 H, m), 2.76 - 2.87 (1 H, m), 2.97 - 3.07 (1 H, m), 3.32 (2 H, br s), 3.90 (3 H, s), 4.11 (1 H, br d, *J*=13.17 Hz), 4.40 (1 H, br d, *J*=12.90 Hz), 7.75 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.43 (1 H, s), 9.03 (1 H, s), 10.52 (1 H, s); ESIMS found for C₂₅H₃₀N₆O₂ *m/z* 447.0 (M+1).



338

[0862] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinoacetamide **338**.

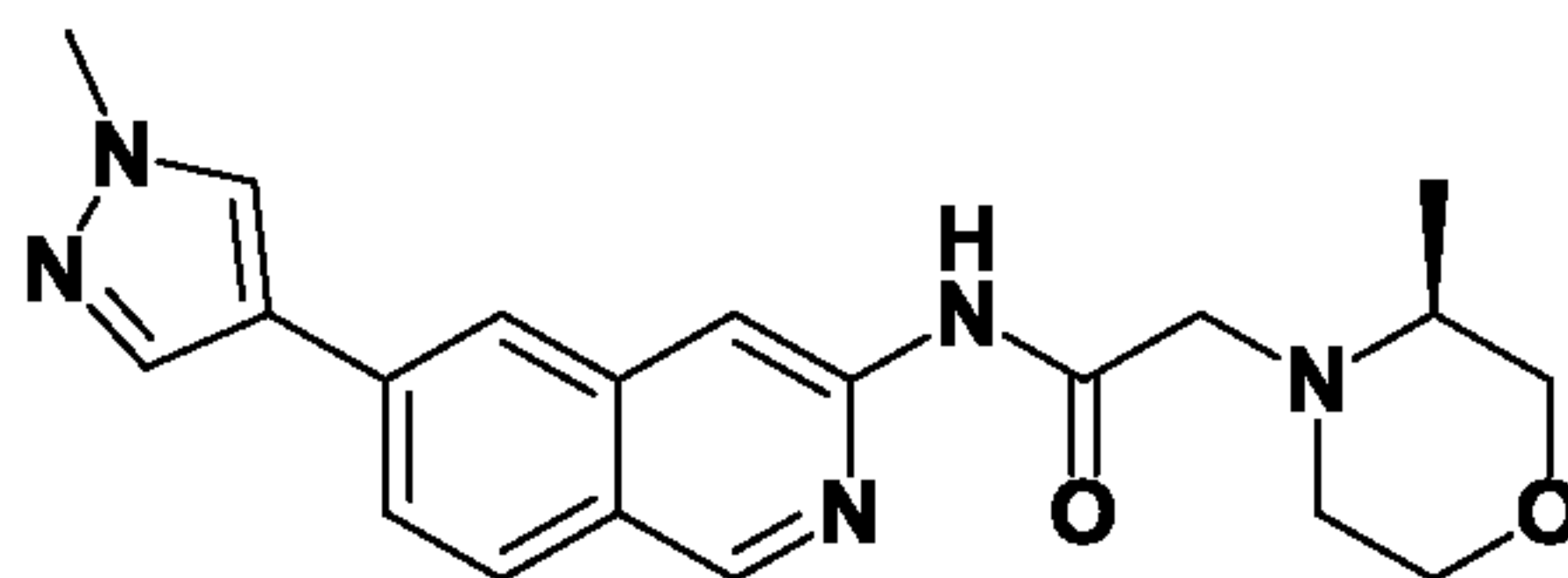
[0863] Beige solid (13.0 mg, 0.037 mmol, 33.6% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 2.55 - 2.60 (3 H, m), 3.24 (2 H, s), 3.62 - 3.70 (4 H, m), 3.90 (3 H, s), 7.77 (1 H, dd, $J=8.51$, 1.65 Hz), 8.02 (1 H, d, $J=8.51$ Hz), 8.09 (2 H, s), 8.35 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.97 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}_2$ m/z 352.0 ($\text{M}+1$).



340

[0864] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-2-carboxamide **340**.

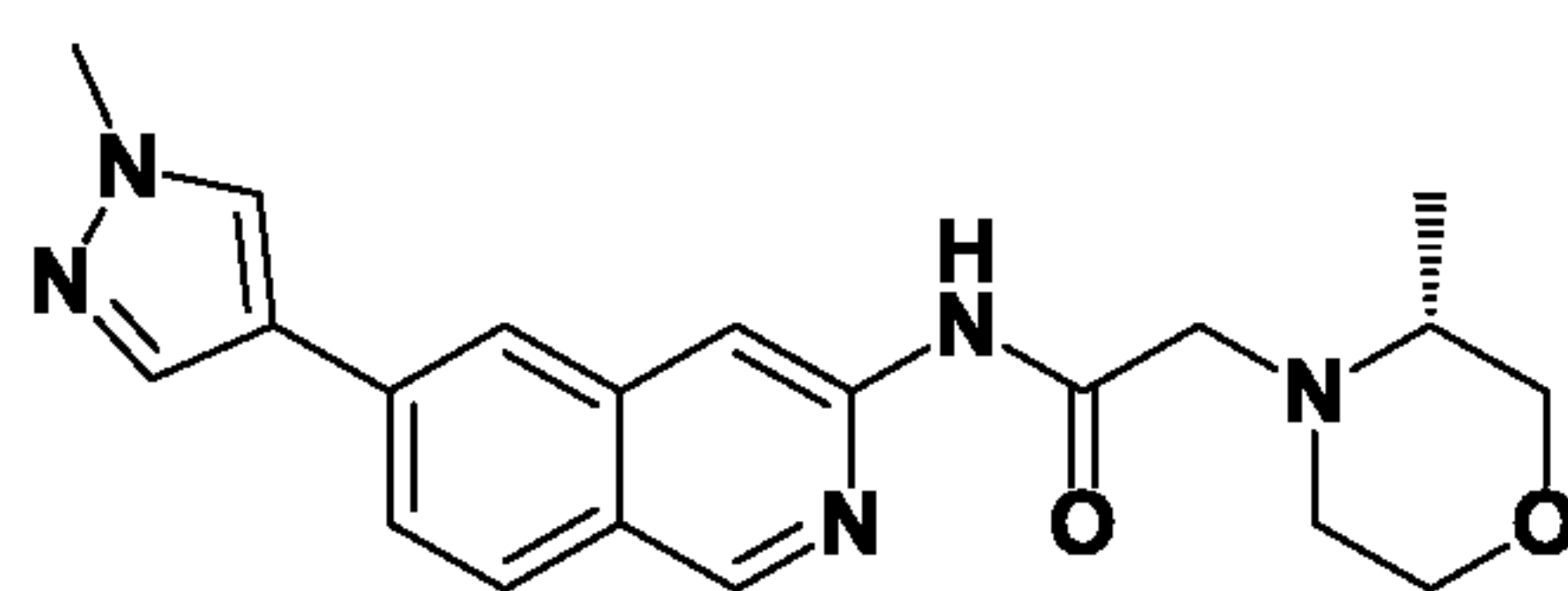
[0865] Light beige solid (35.0 mg, 0.104 mmol, 56.8% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.31 - 1.41 (1 H, m), 1.41 - 1.47 (2 H, m), 1.47 - 1.56 (1 H, m), 1.72 - 1.79 (1 H, m), 1.84 - 1.91 (1 H, m), 2.58 - 2.64 (1 H, m), 2.93 - 3.00 (1 H, m), 3.34 (1 H, br dd, $J=9.19$, 3.16 Hz), 3.90 (3 H, s), 7.76 (1 H, dd, $J=8.51$, 1.65 Hz), 8.01 (1 H, d, $J=8.51$ Hz), 8.07 (1 H, br s), 8.08 (1 H, s), 8.35 (1 H, s), 8.43 (1 H, s), 9.03 (1 H, s), 9.85 (1 H, br s); ESIMS found for $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}$ m/z 336.0 ($\text{M}+1$).



341

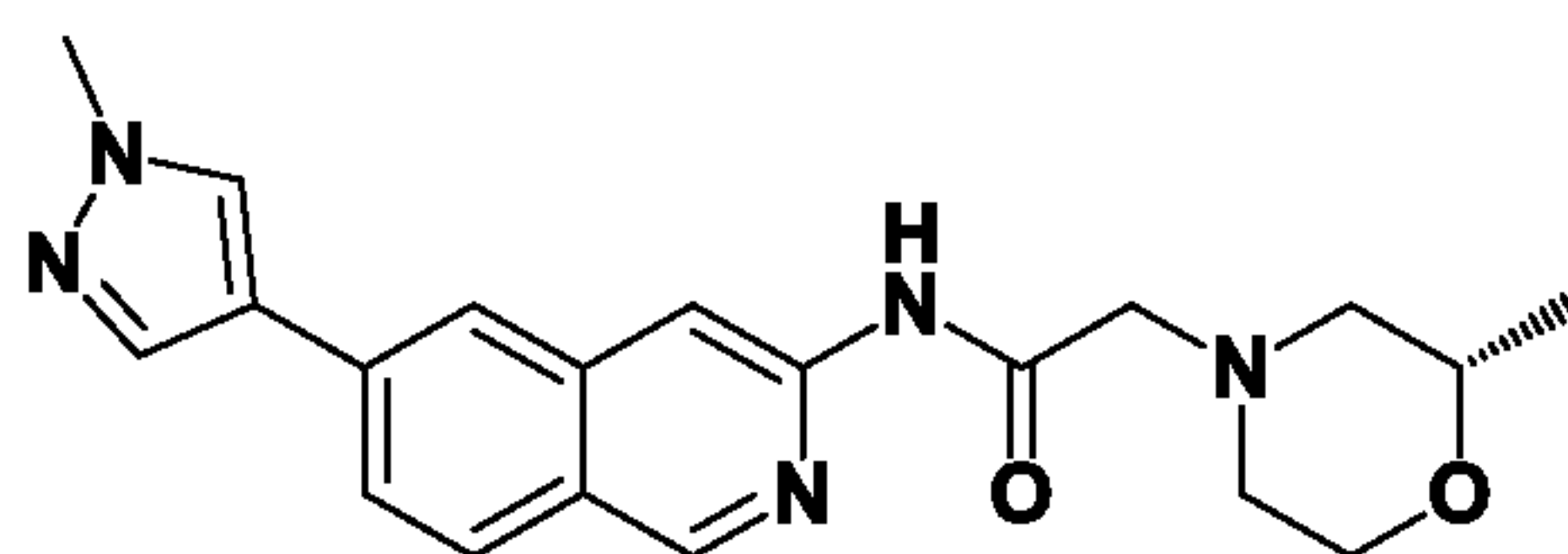
[0866] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide **341**.

[0867] Beige solid (32.5 mg, 0.089 mmol, 34.2% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 0.95 (3 H, d, $J=6.59$ Hz), 2.52 - 2.58 (1 H, m), 2.58 - 2.65 (1 H, m), 2.81 (1 H, dt, $J=11.80$, 2.47 Hz), 3.15 - 3.23 (2 H, m), 3.47 (1 H, d, $J=16.47$ Hz), 3.58 (1 H, td, $J=10.70$, 2.20 Hz), 3.68 (1 H, dd, $J=11.25$, 2.74 Hz), 3.71 - 3.79 (1 H, m), 3.90 (3 H, s), 7.77 (1 H, dd, $J=8.51$, 1.37 Hz), 8.03 (1 H, d, $J=8.51$ Hz), 8.10 (1 H, s), 8.11 (1 H, br s), 8.37 (1 H, s), 8.44 (1 H, s), 9.04 (1 H, s), 9.97 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_2$ m/z 366.2 ($\text{M}+1$).

**342**

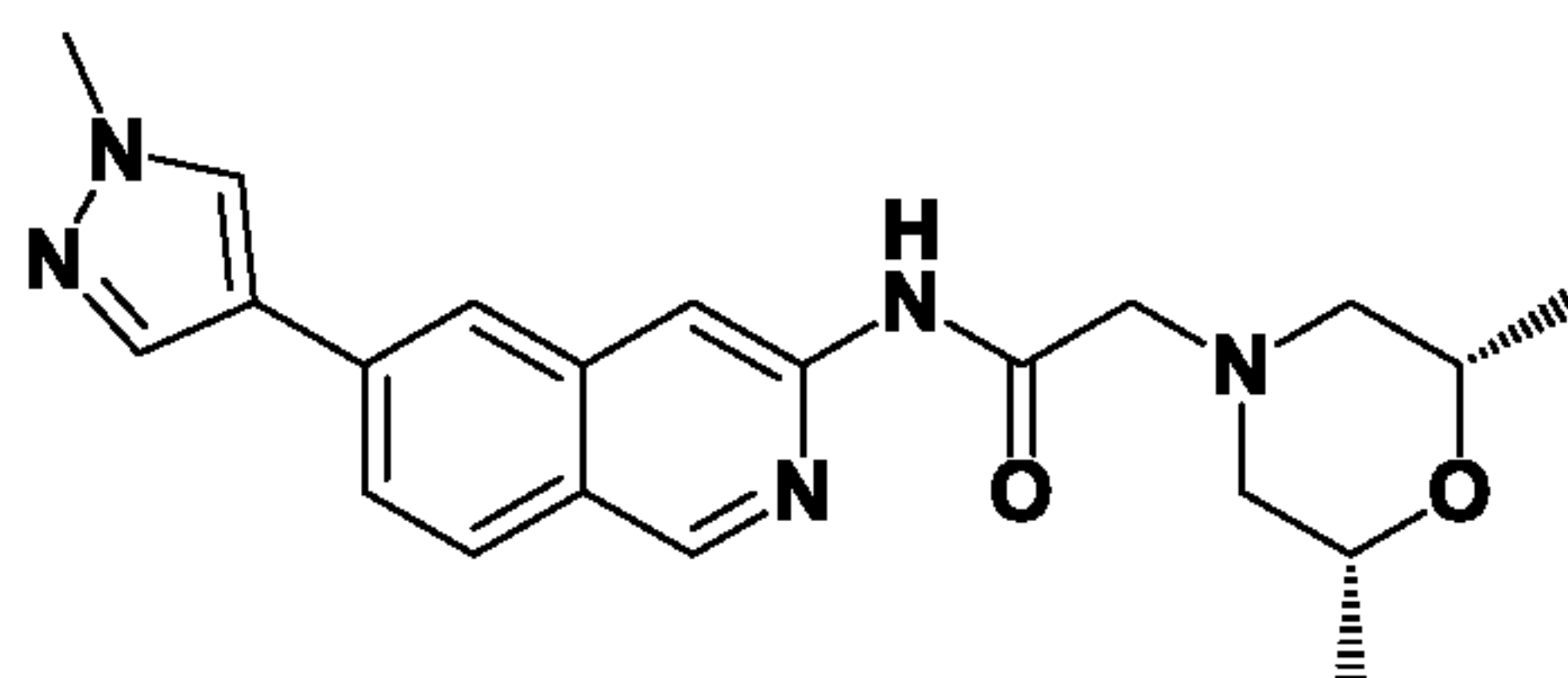
[0868] (R)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide **342**.

[0869] Beige solid (37.0 mg, 0.101 mmol, 38.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.96 (3 H, d, *J*=6.59 Hz), 2.55 (1 H, ddd, *J*=11.80, 10.15, 3.02 Hz), 2.61 (1 H, ddd, *J*=9.13, 6.24, 3.02 Hz), 2.81 (1 H, dt, *J*=11.73, 2.50 Hz), 3.13 - 3.23 (2 H, m), 3.47 (1 H, d, *J*=16.47 Hz), 3.58 (1 H, td, *J*=10.70, 2.20 Hz), 3.68 (1 H, dd, *J*=11.25, 3.02 Hz), 3.74 (1 H, dt, *J*=11.32, 2.71 Hz), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.64, 1.51 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (1 H, s), 8.10 (1 H, br s), 8.36 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.97 (1 H, s); ESIMS found for C₂₀H₂₃N₅O₂ *m/z* 366.2 (M+1).

**343**

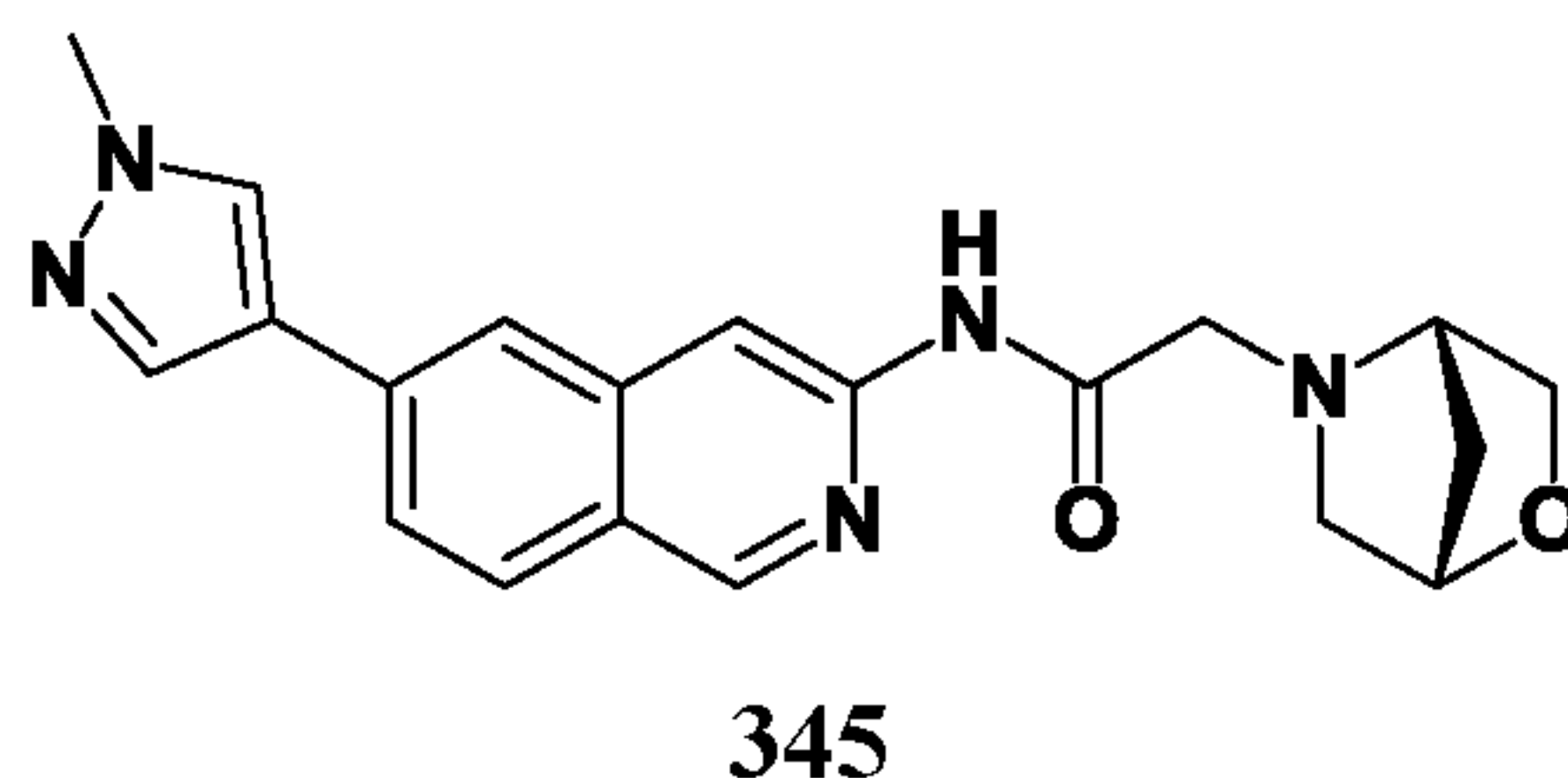
[0870] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide **343**.

[0871] Beige solid (19.0 mg, 0.052 mmol, 15.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.07 (3 H, d, *J*=6.31 Hz), 2.00 (1 H, dd, *J*=10.98, 10.15 Hz), 2.30 (1 H, td, *J*=11.39, 3.02 Hz), 2.73 - 2.79 (1 H, m), 2.83 (1 H, br d, *J*=11.25 Hz), 3.23 (2 H, d, *J*=1.92 Hz), 3.53 - 3.66 (2 H, m), 3.75 - 3.81 (1 H, m), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.64, 1.51 Hz), 8.02 (1 H, d, *J*=8.78 Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.44 (1 H, s), 9.04 (1 H, s), 10.00 (1 H, s); ESIMS found for C₂₀H₂₃N₅O₂ *m/z* 366.2 (M+1).

**344**

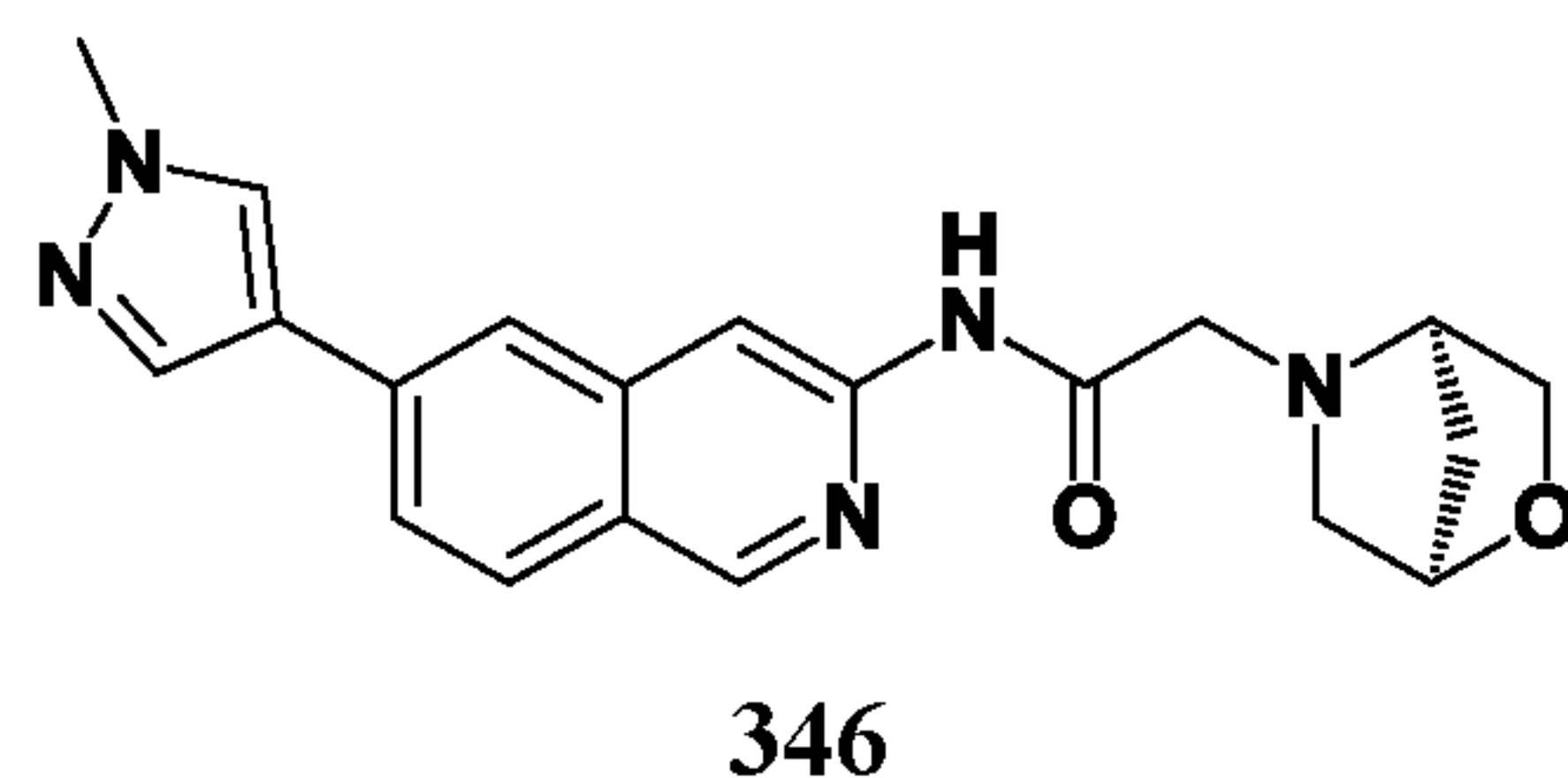
[0872] 2-((2R,6S)-2,6-Dimethylmorpholino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **344**.

[0873] Off-white solid (53.0 mg, 0.140 mmol, 46.6% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.07 (6 H, d, $J=6.31$ Hz), 1.92 (2 H, t, $J=10.84$ Hz), 2.82 (2 H, br d, $J=10.15$ Hz), 3.22 (2 H, s), 3.62 - 3.71 (2 H, m), 3.90 (3 H, s), 7.77 (1 H, dd, $J=8.51$, 1.65 Hz), 8.02 (1 H, d, $J=8.51$ Hz), 8.10 (2 H, s), 8.36 (1 H, s), 8.44 (1 H, s), 9.04 (1 H, s), 9.98 (1 H, s); ESIMS found for $\text{C}_{21}\text{H}_{25}\text{N}_5\text{O}_2$ m/z 380.2 ($\text{M}+1$).



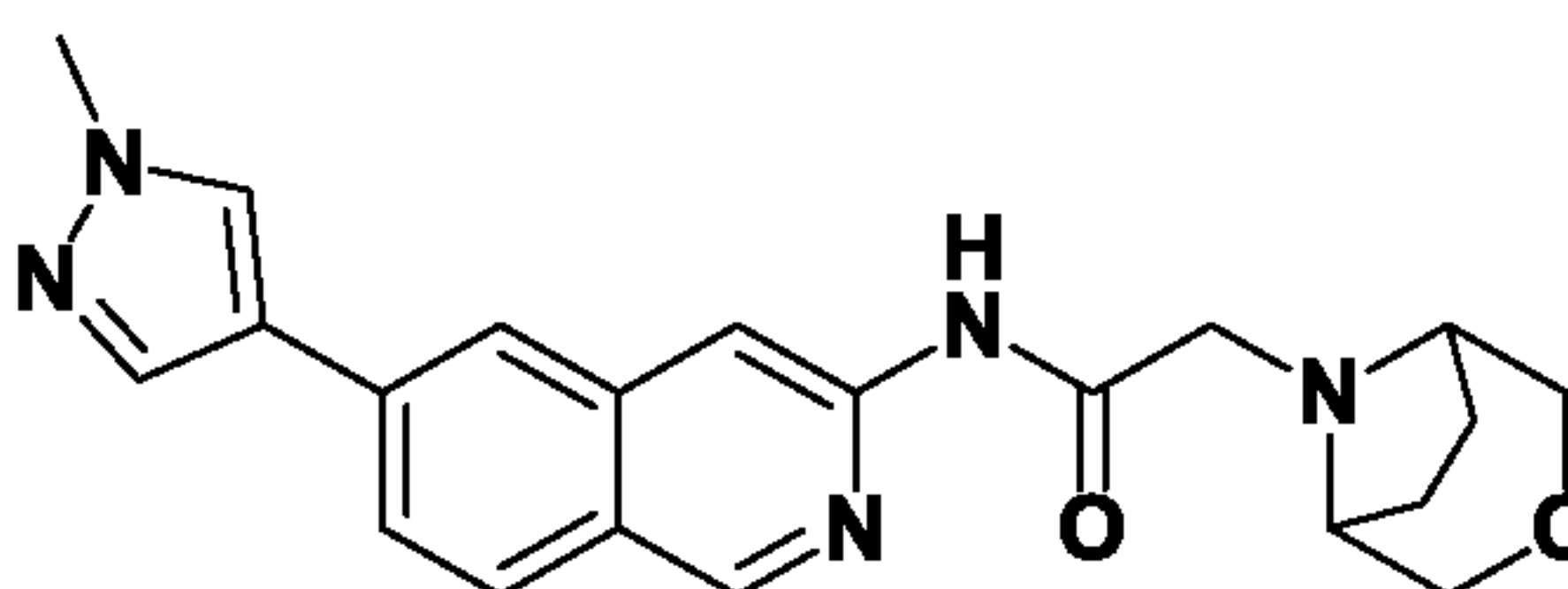
[0874] 2-((1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **345**.

[0875] Ash colored solid (22.0 mg, 0.061 mmol, 18.3% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.67 (1 H, dt, $J=9.61$, 1.10 Hz), 1.87 (1 H, dd, $J=9.74$, 1.78 Hz), 2.62 (1 H, d, $J=10.43$ Hz), 2.95 (1 H, dd, $J=10.02$, 1.51 Hz), 3.45 (2 H, d, $J=5.21$ Hz), 3.59 (1 H, dd, $J=7.82$, 1.78 Hz), 3.63 (1 H, s), 3.88 (1 H, d, $J=7.68$ Hz), 3.90 (3 H, s), 4.41 (1 H, s), 7.77 (1 H, dd, $J=8.64$, 1.51 Hz), 8.03 (1 H, d, $J=8.78$ Hz), 8.10 (1 H, s), 8.11 (1 H, br s), 8.37 (1 H, s), 8.44 (1 H, s), 9.04 (1 H, s), 9.92 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_2$ m/z 364.2 ($\text{M}+1$).



[0876] 2-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **346**.

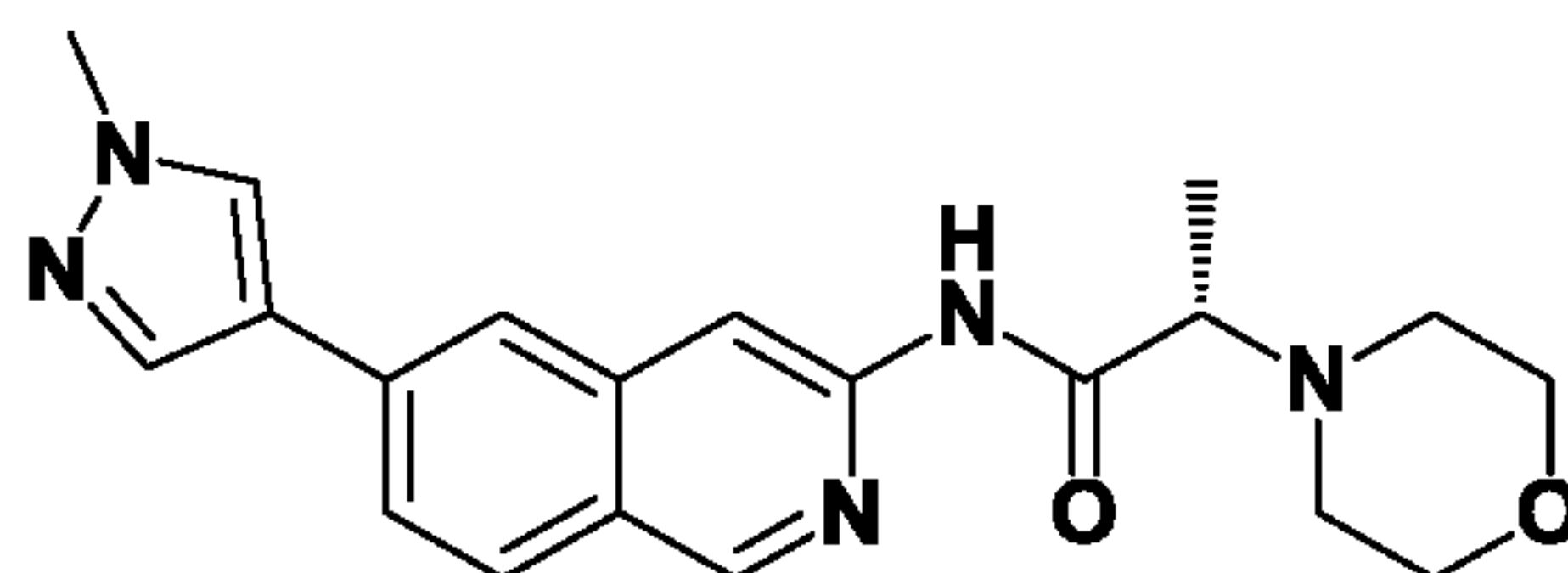
[0877] Ash colored solid (25.0 mg, 0.069 mmol, 18.3% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.63 - 1.70 (1 H, m), 1.87 (1 H, dd, $J=9.74$, 1.78 Hz), 2.62 (1 H, d, $J=10.15$ Hz), 2.95 (1 H, dd, $J=10.02$, 1.51 Hz), 3.45 (2 H, d, $J=4.94$ Hz), 3.59 (1 H, dd, $J=7.68$, 1.92 Hz), 3.63 (1 H, s), 3.88 (1 H, d, $J=7.68$ Hz), 3.90 (3 H, s), 4.41 (1 H, s), 7.77 (1 H, dd, $J=8.51$, 1.65 Hz), 8.03 (1 H, d, $J=8.51$ Hz), 8.10 (1 H, s), 8.11 (1 H, br s), 8.37 (1 H, s), 8.44 (1 H, s), 9.04 (1 H, s), 9.92 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_2$ m/z 364.2 ($\text{M}+1$).



347

[0878] 2-(3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **347**.

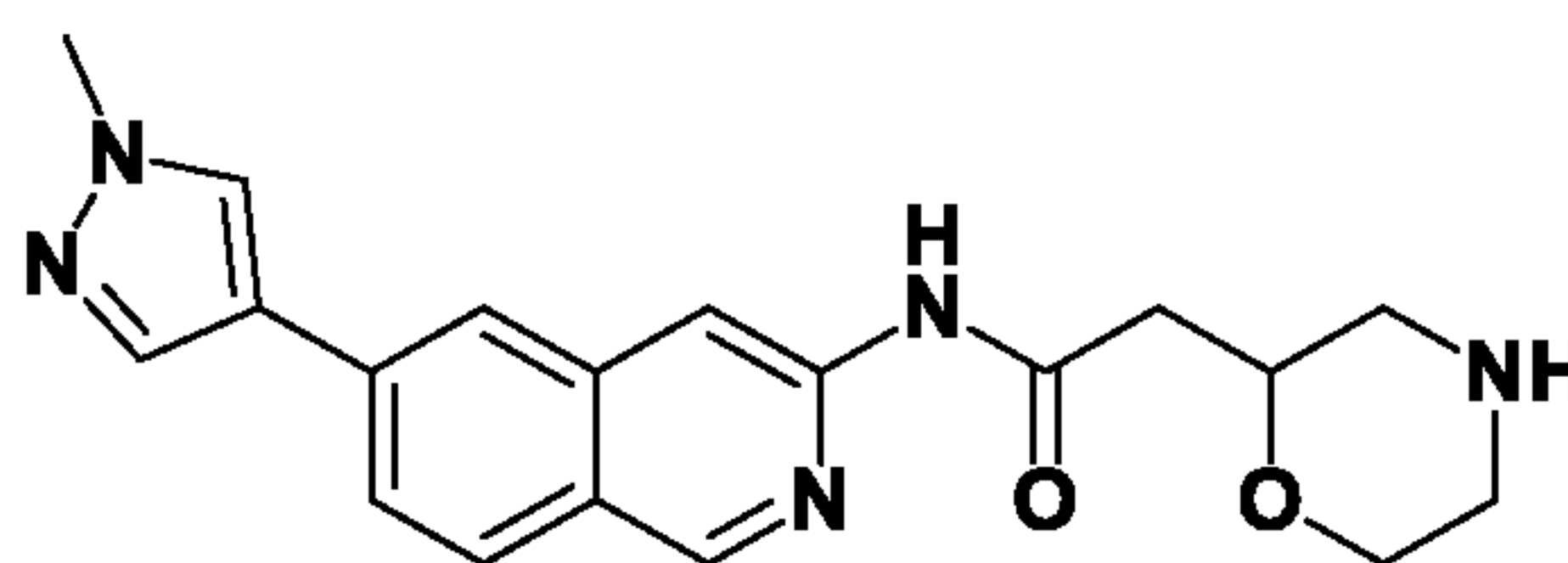
[0879] Off-white solid (8.0 mg, 0.021 mmol, 8.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.75 - 1.82 (2 H, m), 1.86 - 1.94 (2 H, m), 3.14 (2 H, s), 3.17 (2 H, br d, *J*=0.82 Hz), 3.48 - 3.55 (2 H, m), 3.68 (2 H, d, *J*=10.43 Hz), 3.90 (3 H, s), 7.78 (1 H, dd, *J*=8.51, 1.37 Hz), 8.03 (1 H, d, *J*=8.51 Hz), 8.10 (1 H, s), 8.11 (1 H, s), 8.37 (1 H, s), 8.46 (1 H, s), 9.06 (1 H, s), 10.15 (1 H, s); ESIMS found for C₂₁H₂₃N₅O₂ *m/z* 378.2 (M+1).



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[0880] (S)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinopropanamide **348**.

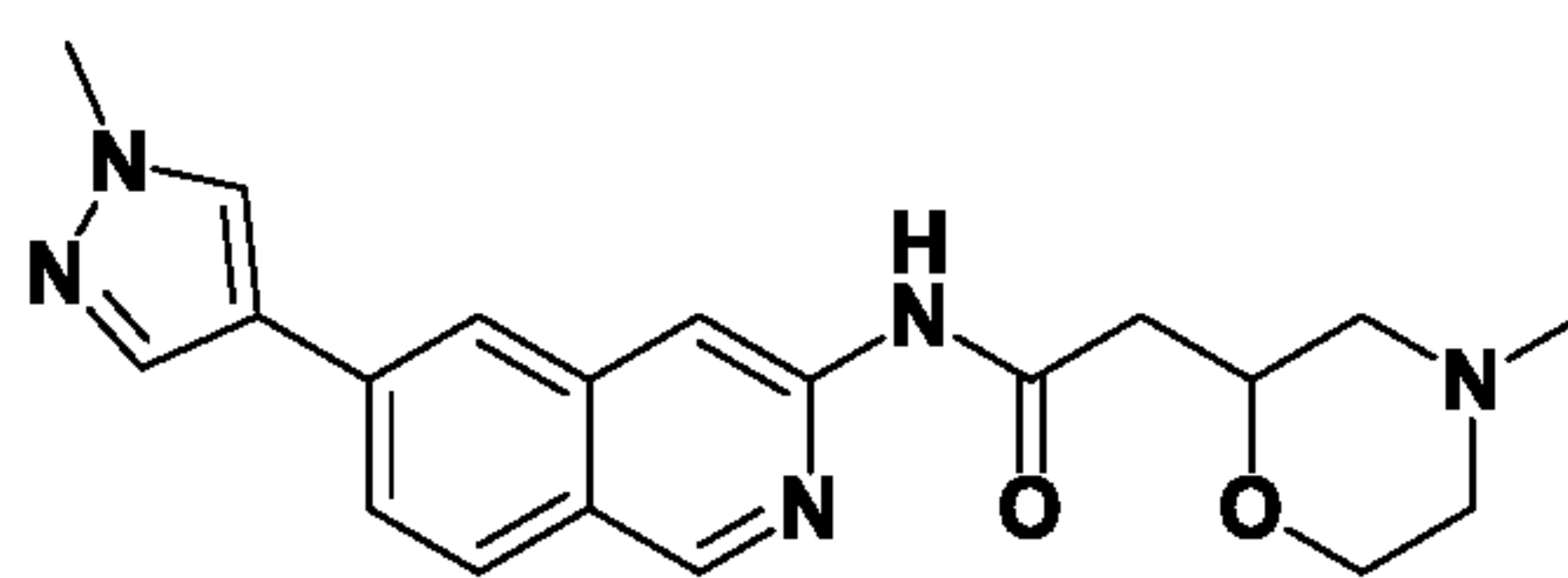
[0881] Light yellow solid (68.0 mg, 0.186 mmol, 45.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.23 (3 H, d, *J*=6.86 Hz), 2.51 - 2.57 (2 H, m), 2.57 - 2.65 (2 H, m), 3.45 (1 H, q, *J*=6.77 Hz), 3.64 (4 H, t, *J*=4.67 Hz), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.37 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.08 (1 H, s), 8.09 (1 H, s), 8.36 (1 H, s), 8.45 (1 H, s), 9.04 (1 H, s), 10.17 (1 H, s); ESIMS found for C₂₀H₂₃N₅O₂ *m/z* 366.2 (M+1).



349

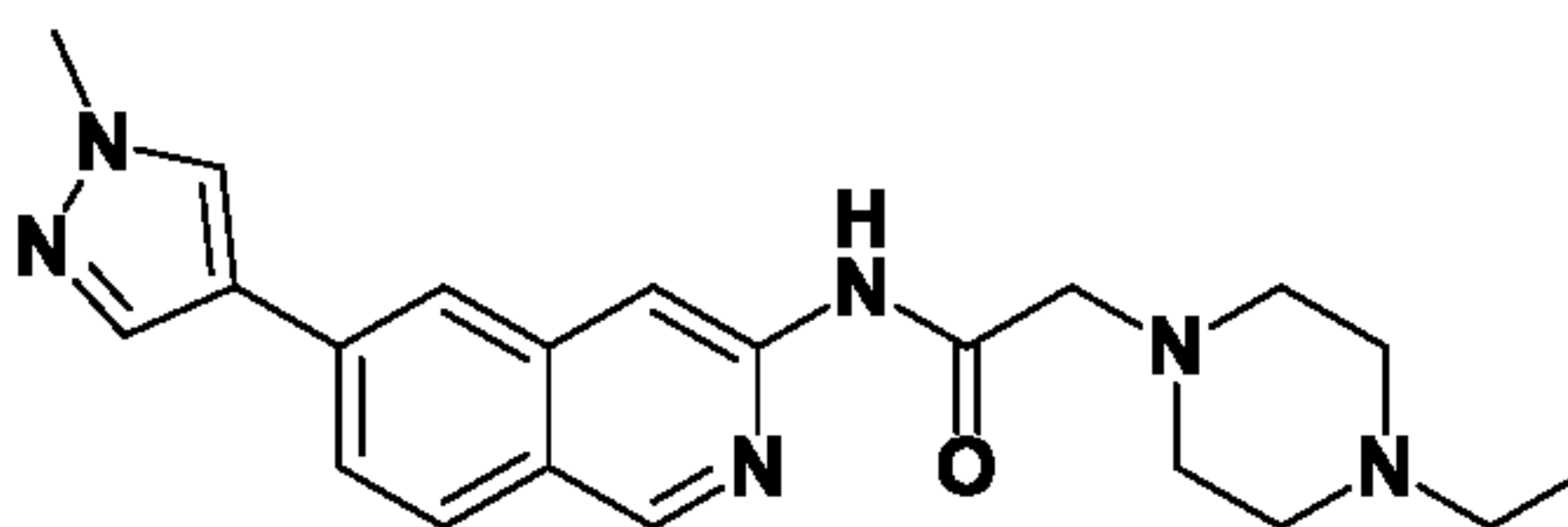
[0882] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide **349**.

[0883] Off-white solid (275.0 mg, 0.783 mmol, 91.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.41 - 2.48 (2 H, m), 2.57 - 2.69 (3 H, m), 2.83 (1 H, br dd, *J*=12.21, 2.06 Hz), 3.43 (1 H, td, *J*=10.63, 3.43 Hz), 3.70 (1 H, br d, *J*=10.70 Hz), 3.78 - 3.85 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.64, 1.51 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.43 (1 H, s), 9.02 (1 H, s), 10.41 (1 H, s); ESIMS found for C₁₉H₂₁N₅O₂ *m/z* 352.0 (M+1).

**350**

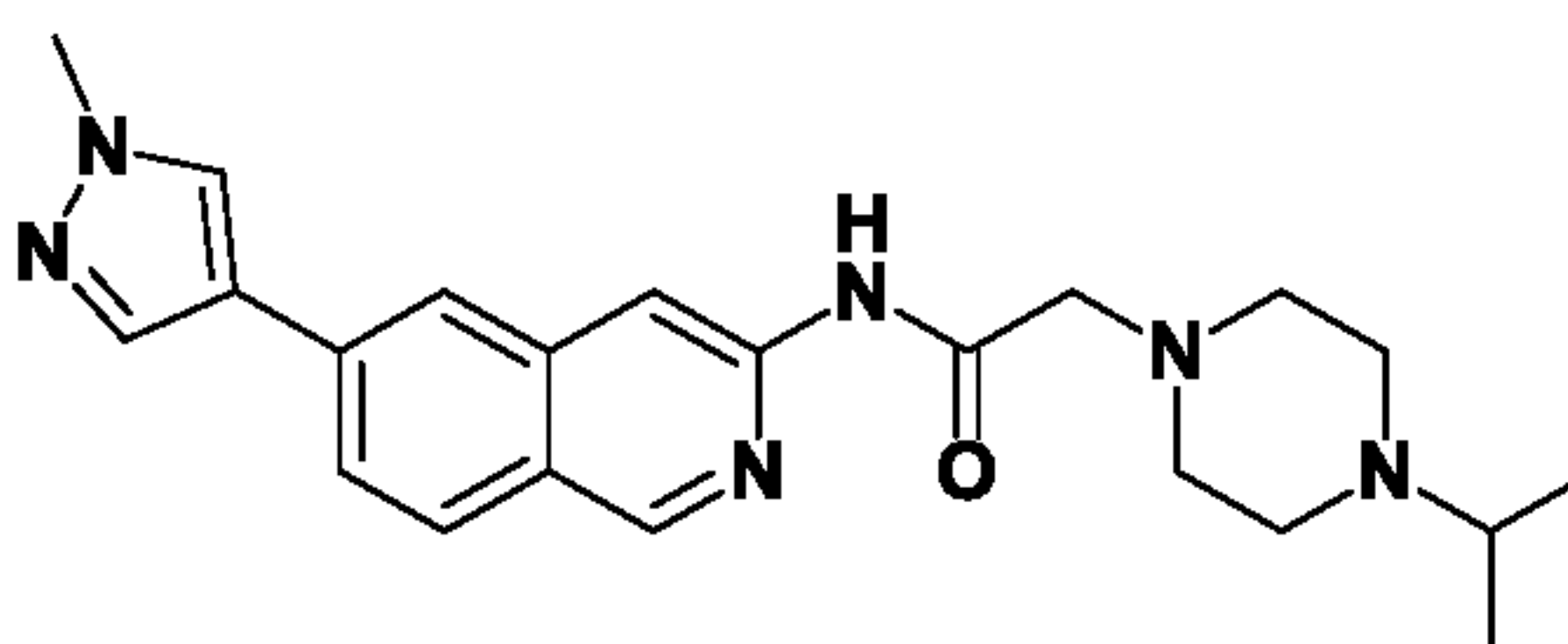
[0884] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide **350**.

[0885] White solid (71.0 mg, 0.194 mmol, 68.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.78 (1 H, t, *J*=11.00 Hz), 1.97 (1 H, td, *J*=11.32, 3.16 Hz), 2.18 (3 H, s), 2.53 (1 H, br d, *J*=5.49 Hz), 2.58 (1 H, br dd, *J*=11.25, 1.37 Hz), 2.66 (1 H, dd, *J*=14.68, 7.82 Hz), 2.74 (1 H, br d, *J*=11.25 Hz), 3.50 (1 H, td, *J*=11.11, 2.47 Hz), 3.72 - 3.80 (1 H, m), 3.86 - 3.96 (1 H, m), 3.90 (3 H, s), 7.75 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.45 (1 H, s); ESIMS found for C₂₀H₂₃N₅O₂ *m/z* 366.0 (M+1).

**351**

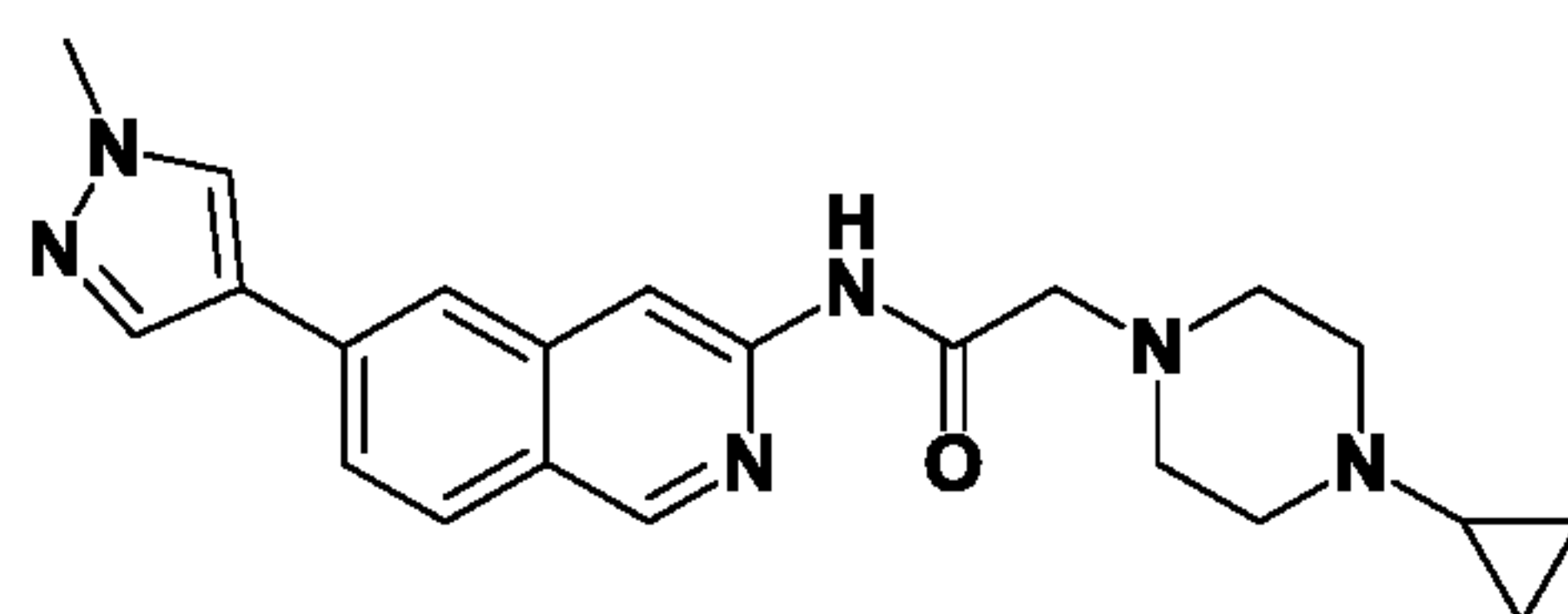
[0886] 2-(4-Ethylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **351**.

[0887] Beige solid (52.0 mg, 0.137 mmol, 52.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.03 (3 H, br s), 2.30 - 2.47 (4 H, m), 2.53 - 2.74 (6 H, m), 3.24 (2 H, br s), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.37 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.96 (1 H, br s); ESIMS found for C₂₁H₂₆N₆O *m/z* 379.2 (M+1).

**352**

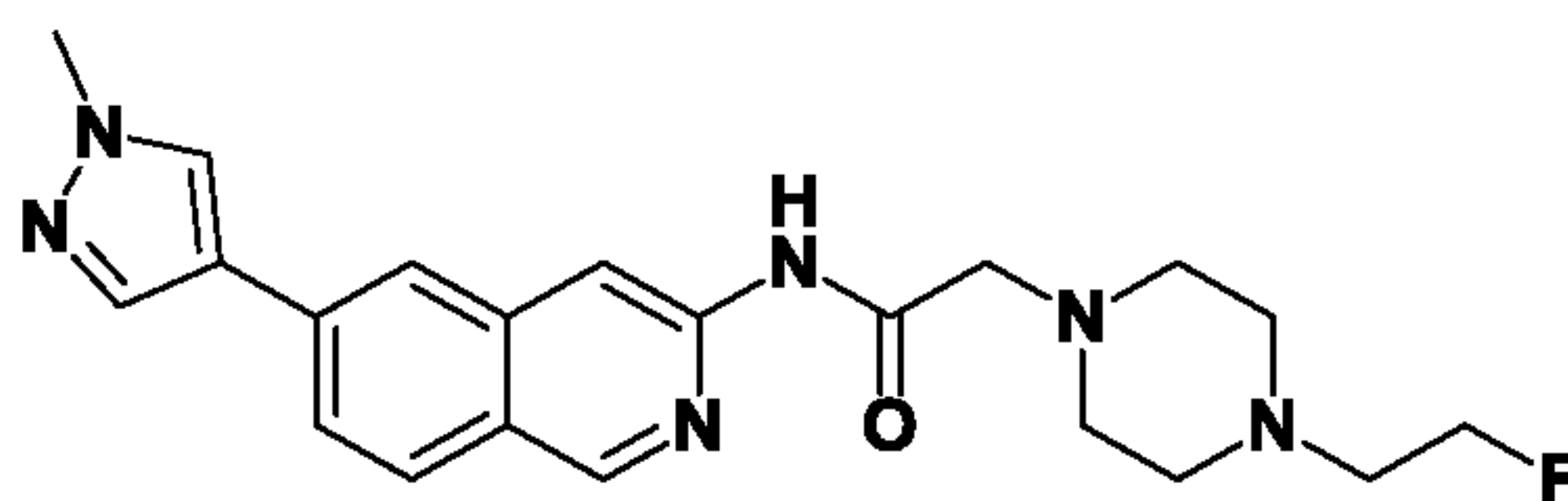
[0888] 2-(4-Isopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **352**.

[0889] Beige solid (66.0 mg, 0.162 mmol, 66.7% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.99 (6 H, d, *J*=6.59 Hz), 2.51 - 2.54 (2 H, m), 2.57 (4 H, br s), 2.61 - 2.69 (1 H, m), 3.20 (2 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.64, 1.51 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (2 H, s), 8.36 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.89 (1 H, s); ESIMS found for C₂₂H₂₈N₆O *m/z* 393.0 (M+1).

**353**

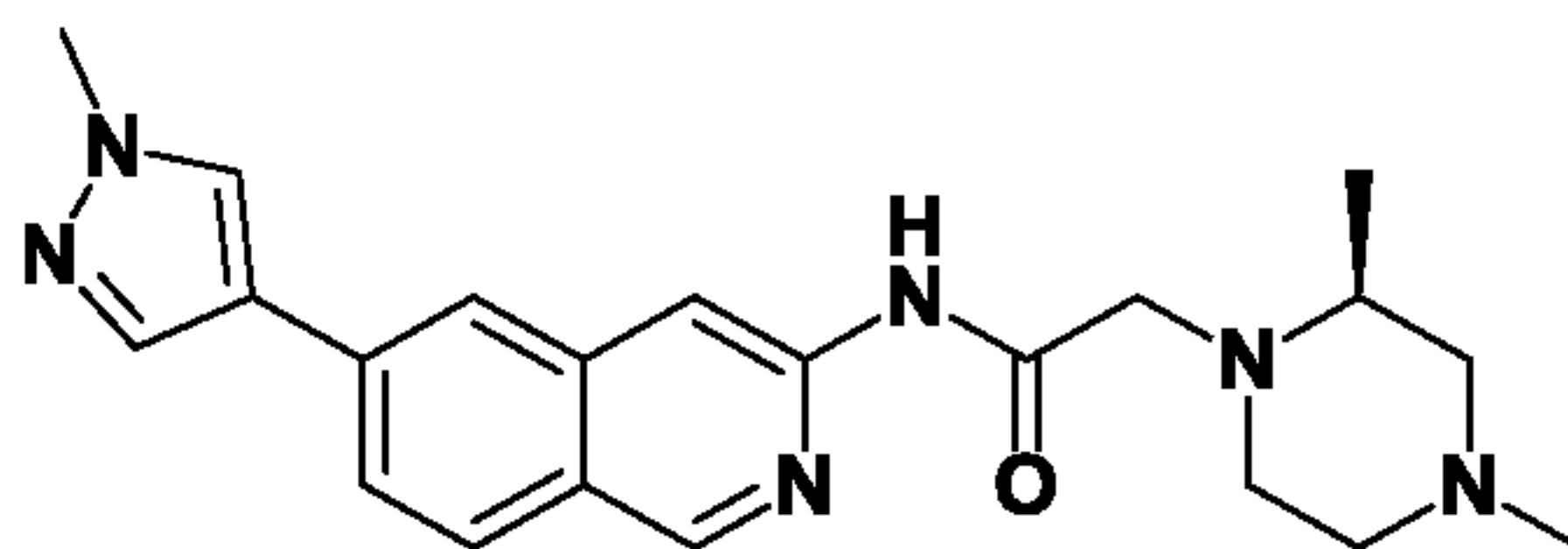
[0890] 2-(4-Cyclopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **353**.

[0891] Beige solid (44.0 mg, 0.109 mmol, 44.7% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.26 - 0.32 (2 H, m), 0.39 - 0.45 (2 H, m), 1.66 (1 H, tt, *J*=6.59, 3.43 Hz), 2.51 - 2.57 (4 H, m), 2.62 (4 H, br s), 3.20 (2 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.78 Hz), 8.09 (2 H, s), 8.36 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.92 (1 H, s); ESIMS found for C₂₂H₂₆N₆O *m/z* 391.0 (M+1).

**354**

[0892] 2-(4-(2-Fluoroethyl)piperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **354**.

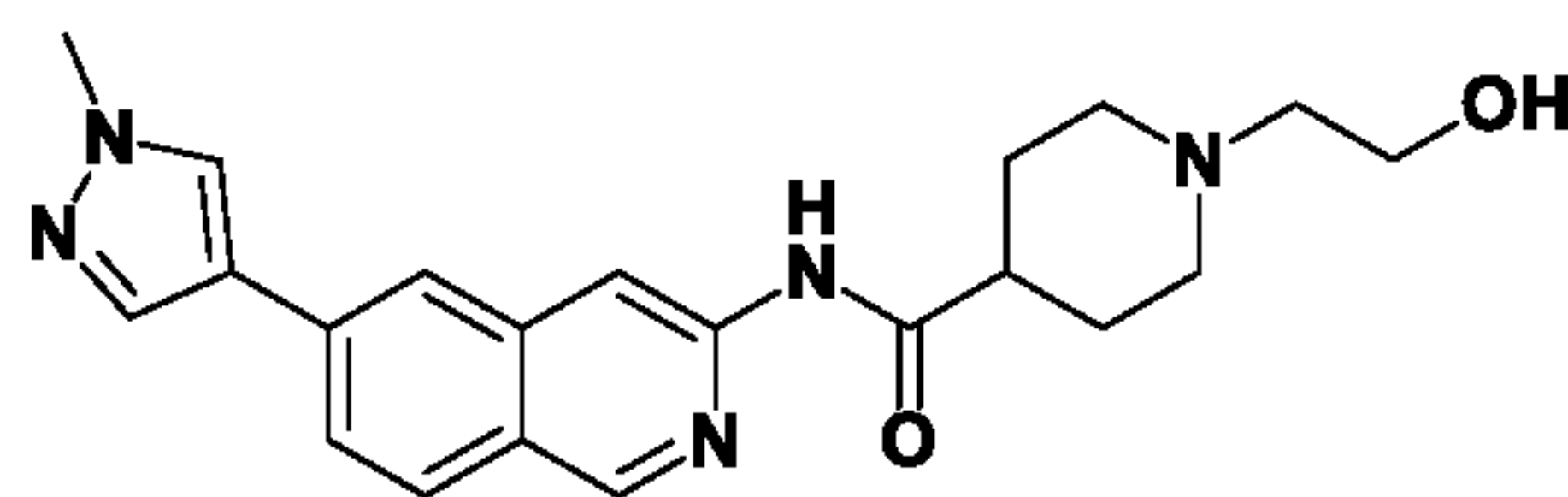
[0893] Off-white solid (33.0 mg, 0.083 mmol, 25.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.54 (4 H, br s), 2.57 - 2.60 (3 H, m), 2.64 (4 H, dt, *J*=28.60, 4.95 Hz), 3.22 (2 H, s), 3.90 (3 H, s), 4.54 (2 H, dt, *J*=47.80, 4.70 Hz), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.93 (1 H, s); ESIMS found for C₂₁H₂₅FN₆O *m/z* 397.2 (M+1).

**355**

[0894] (S)-2-(2,4-Dimethylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **355**.

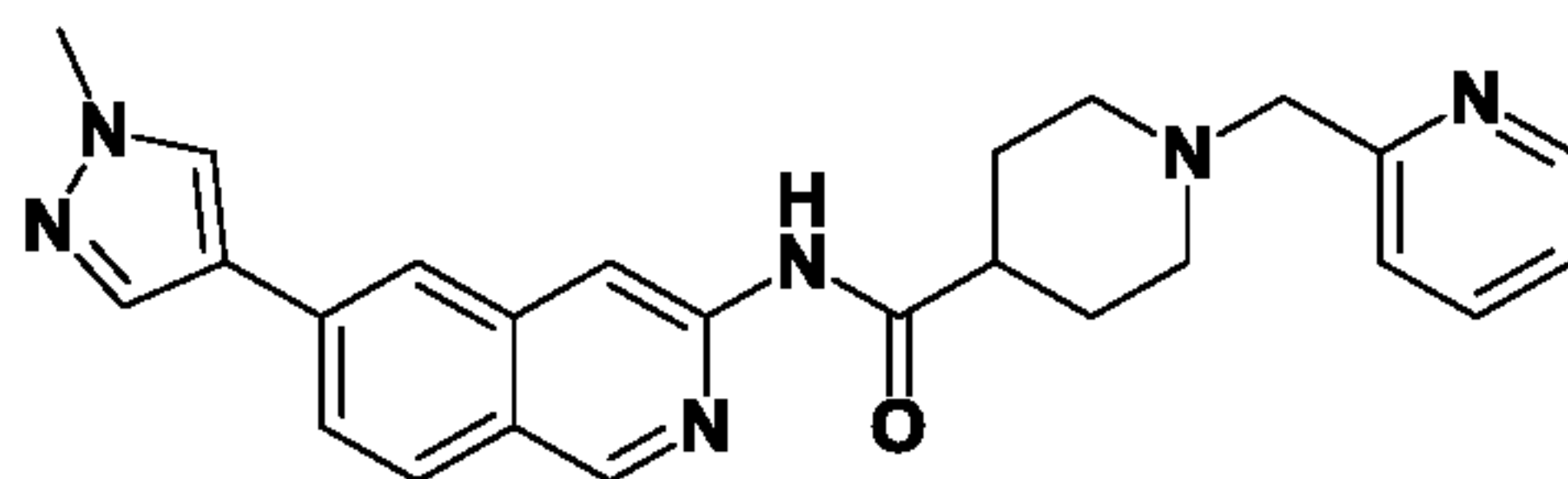
[0895] Beige solid (20.0 mg, 0.053 mmol, 20.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.01 (3 H, d, *J*=6.31 Hz), 1.87 (1 H, br t, *J*=8.51 Hz), 2.11 - 2.19 (1 H, m), 2.17 (3 H, s), 2.51 - 2.57 (1 H, m), 2.57 - 2.67 (3 H, m), 2.83 (1 H, dt, *J*=11.25, 3.02 Hz), 3.13 (1 H, d, *J*=16.47 Hz), 3.43 (1 H, d, *J*=16.74 Hz), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51

Hz), 8.10 (1 H, s), 8.11 (1 H, br s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.92 (1 H, s); ESIMS found for $C_{21}H_{26}N_6O$ m/z 379.2 (M+1).

**358**

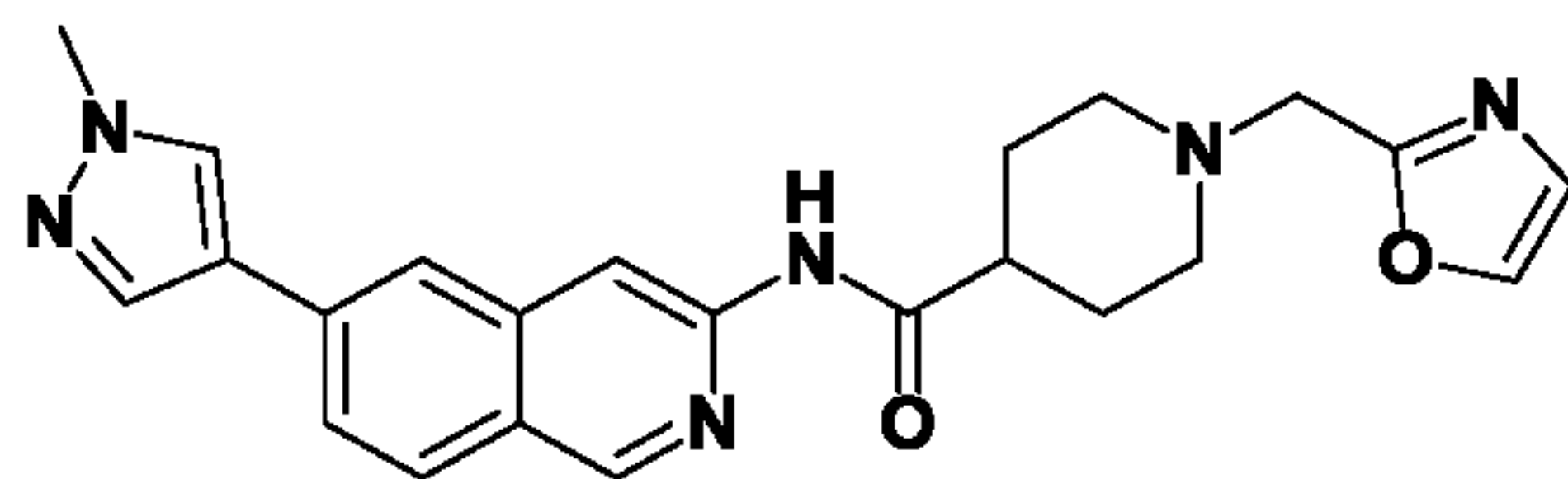
[0896] 1-(2-Hydroxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **358**.

[0897] White solid (41.0 mg, 0.108 mmol, 36.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.62 - 1.73 (2 H, m), 1.73 - 1.81 (2 H, m), 1.98 (2 H, td, $J=11.46$, 2.06 Hz), 2.39 (2 H, t, $J=6.31$ Hz), 2.52 - 2.57 (1 H, m), 2.92 (2 H, br d, $J=11.53$ Hz), 3.50 (2 H, q, $J=6.04$ Hz), 3.90 (3 H, s), 4.30 (1 H, br t, $J=5.35$ Hz), 7.73 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.02 (1 H, s), 8.06 (1 H, s), 8.33 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.39 (1 H, s); ESIMS found for $C_{21}H_{25}N_5O_2$ m/z 380.0 (M+1).

**359**

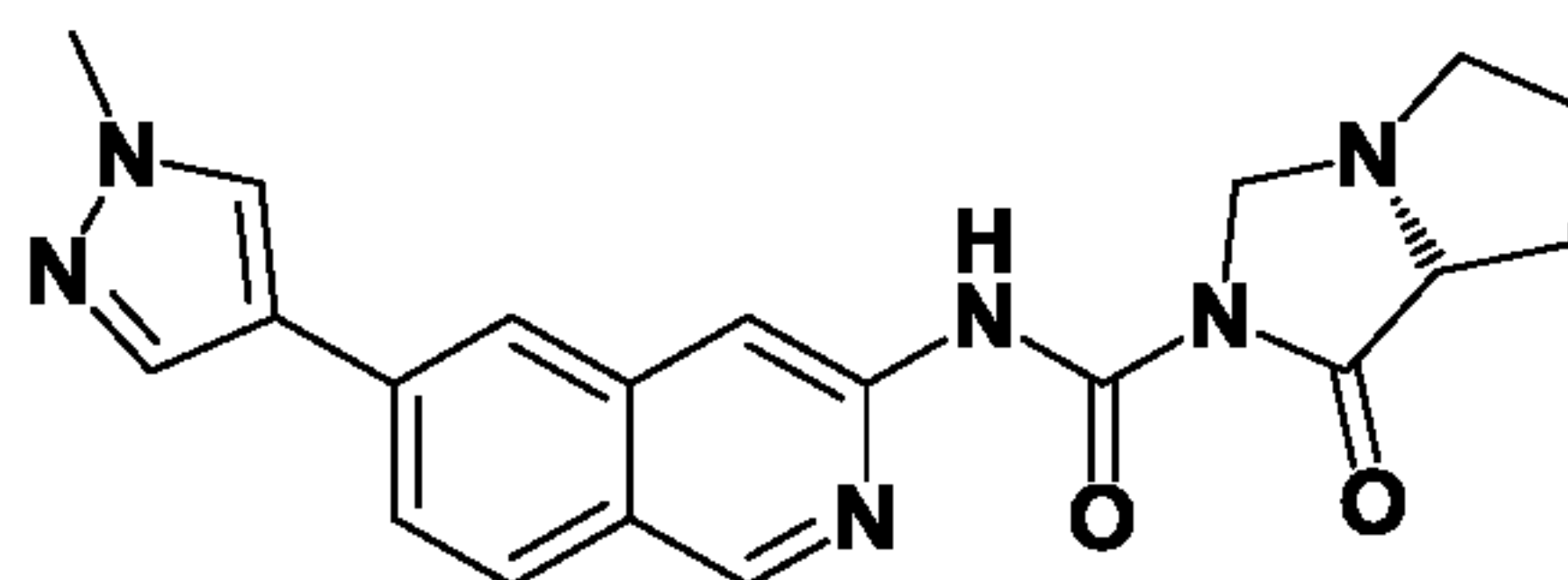
[0898] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide **359**.

[0899] Beige solid (11.0 mg, 0.026 mmol, 8.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.66 - 1.77 (2 H, m), 1.77 - 1.84 (2 H, m), 2.01 - 2.12 (2 H, m), 2.53 - 2.62 (1 H, m), 2.85 - 2.94 (2 H, m), 3.60 (2 H, s), 3.90 (3 H, s), 7.25 (1 H, dd, $J=6.86$, 5.49 Hz), 7.46 (1 H, d, $J=7.96$ Hz), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 7.77 (1 H, td, $J=7.62$, 1.78 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.33 (1 H, s), 8.44 (1 H, s), 8.49 (1 H, br d, $J=4.12$ Hz), 9.02 (1 H, s), 10.41 (1 H, s); ESIMS found for $C_{25}H_{26}N_6O$ m/z 427.0 (M+1).

**360**

[0900] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl)piperidine-4-carboxamide **360**.

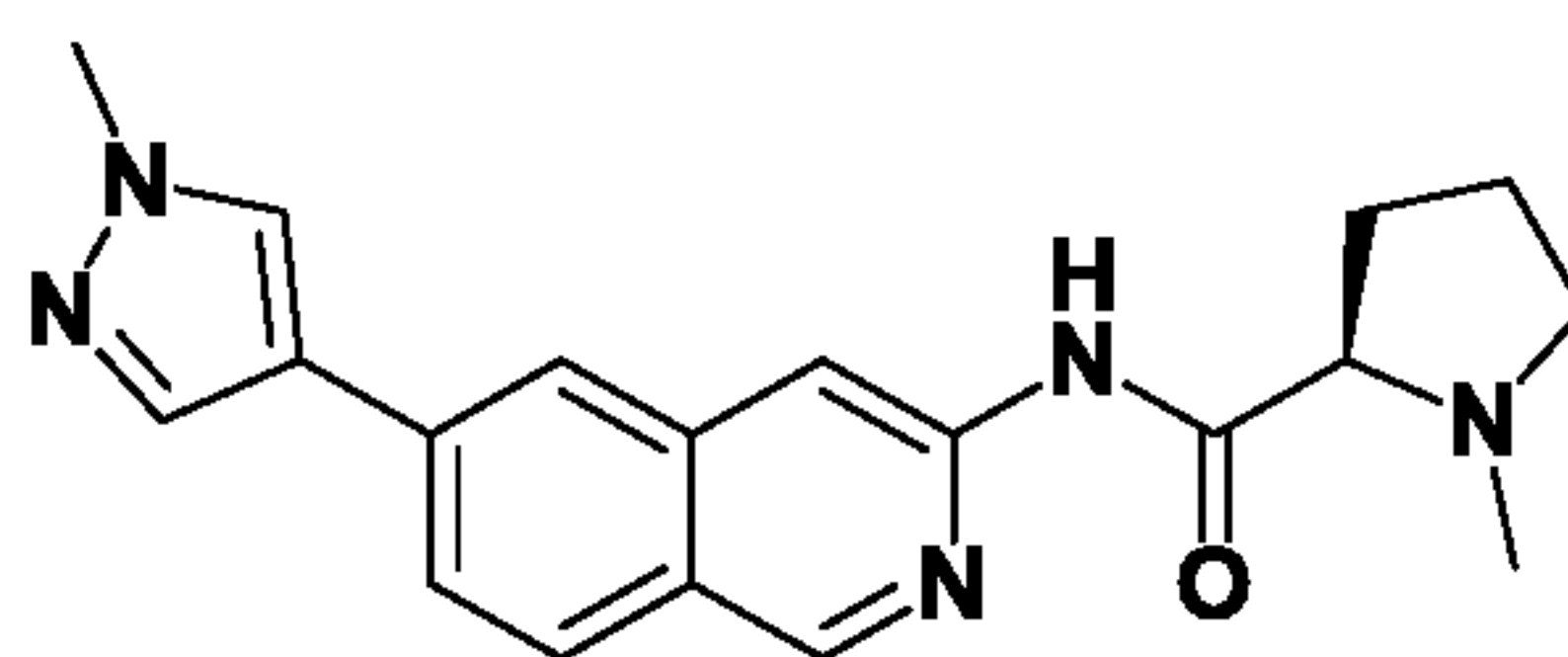
[0901] White solid (65.0 mg, 0.156 mmol, 52.3% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.68 (2 H, qd, $J=12.21, 3.43$ Hz), 1.79 (2 H, br d, $J=10.43$ Hz), 2.07 - 2.18 (2 H, m), 2.51 - 2.57 (1 H, m), 2.85 - 2.94 (2 H, m), 3.67 (2 H, s), 3.90 (3 H, s), 7.17 (1 H, d, $J=0.82$ Hz), 7.73 (1 H, dd, $J=8.64, 1.51$ Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.02 (1 H, s), 8.06 (1 H, s), 8.06 (1 H, d, $J=0.82$ Hz), 8.33 (1 H, s), 8.43 (1 H, s), 9.01 (1 H, s), 10.40 (1 H, s); ESIMS found for $\text{C}_{23}\text{H}_{24}\text{N}_6\text{O}_2$ m/z 416.95 ($\text{M}+1$).



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[0902] (R)-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-oxotetrahydro-1H-pyrrolo[1,2-c]imidazole-2(3H)-carboxamide **362**.

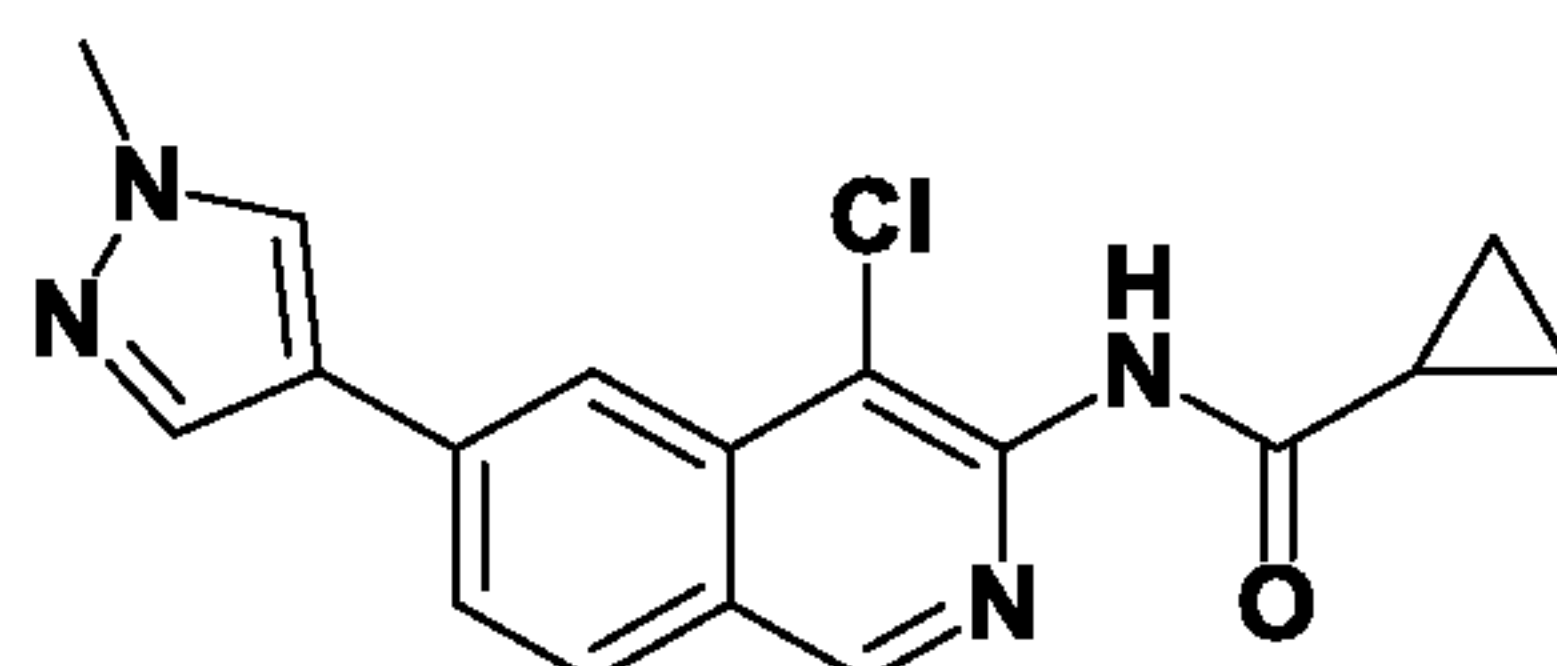
[0903] White solid (120.0 mg, 0.360 mmol, 57.8% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.70 - 1.83 (2 H, m), 2.02 (1 H, dtd, $J=12.49, 8.16, 8.16, 3.84$ Hz), 2.08 - 2.18 (1 H, m), 2.64 (1 H, td, $J=9.33, 6.86$ Hz), 3.17 (1 H, ddd, $J=9.74, 6.17, 4.12$ Hz), 3.90 (3 H, s), 3.96 (1 H, dd, $J=9.06, 4.12$ Hz), 4.99 - 5.10 (2 H, m), 7.80 (1 H, dd, $J=8.51, 1.65$ Hz), 8.04 (1 H, d, $J=8.51$ Hz), 8.11 (1 H, s), 8.13 (1 H, s), 8.38 (1 H, s), 8.60 (1 H, s), 9.09 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}$ m/z 334.1 ($\text{M}+1$).



363

[0904] (R)-1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide **363**.

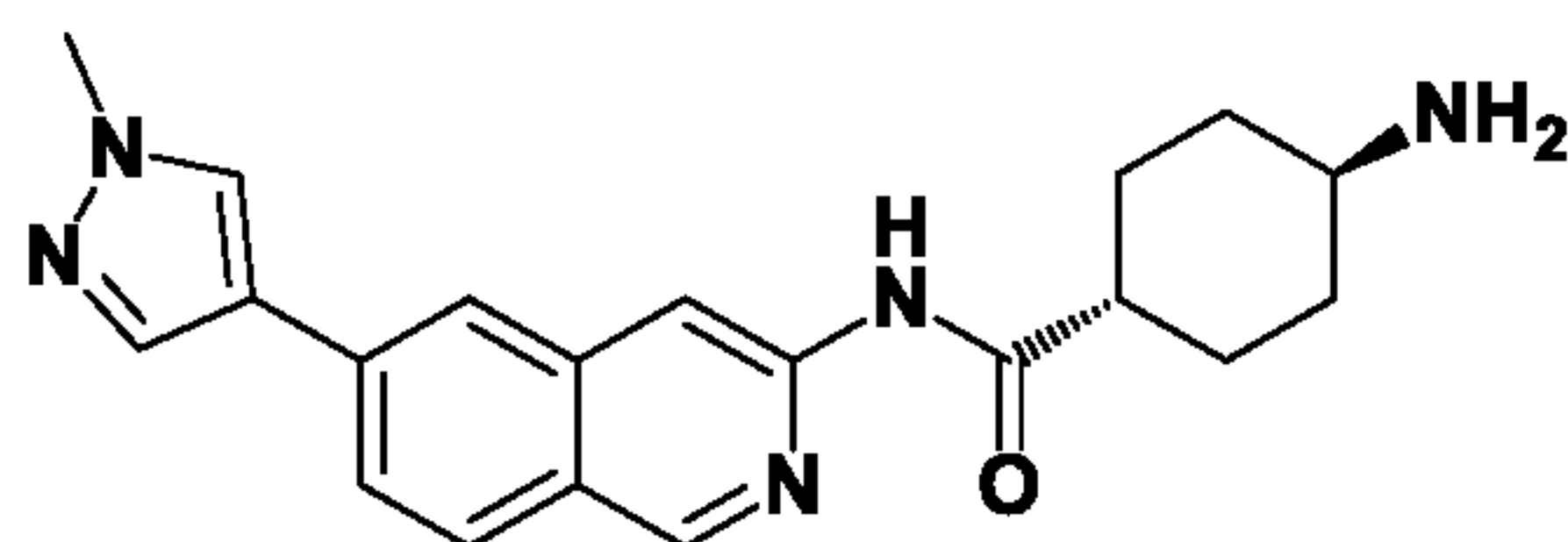
[0905] Off-white solid (65.0 mg, 0.194 mmol, 62.3% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.74 - 1.82 (2 H, m), 1.82 - 1.90 (1 H, m), 2.17 - 2.28 (1 H, m), 2.37 - 2.44 (1 H, m), 2.42 (3 H, s), 3.07 (1 H, dd, $J=9.88, 5.49$ Hz), 3.17 (1 H, ddd, $J=8.92, 6.04, 3.16$ Hz), 3.90 (3 H, s), 7.77 (1 H, dd, $J=8.51, 1.65$ Hz), 8.03 (1 H, d, $J=8.51$ Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.44 (1 H, s), 9.03 (1 H, s), 9.92 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}$ m/z 336.2 ($\text{M}+1$).



364

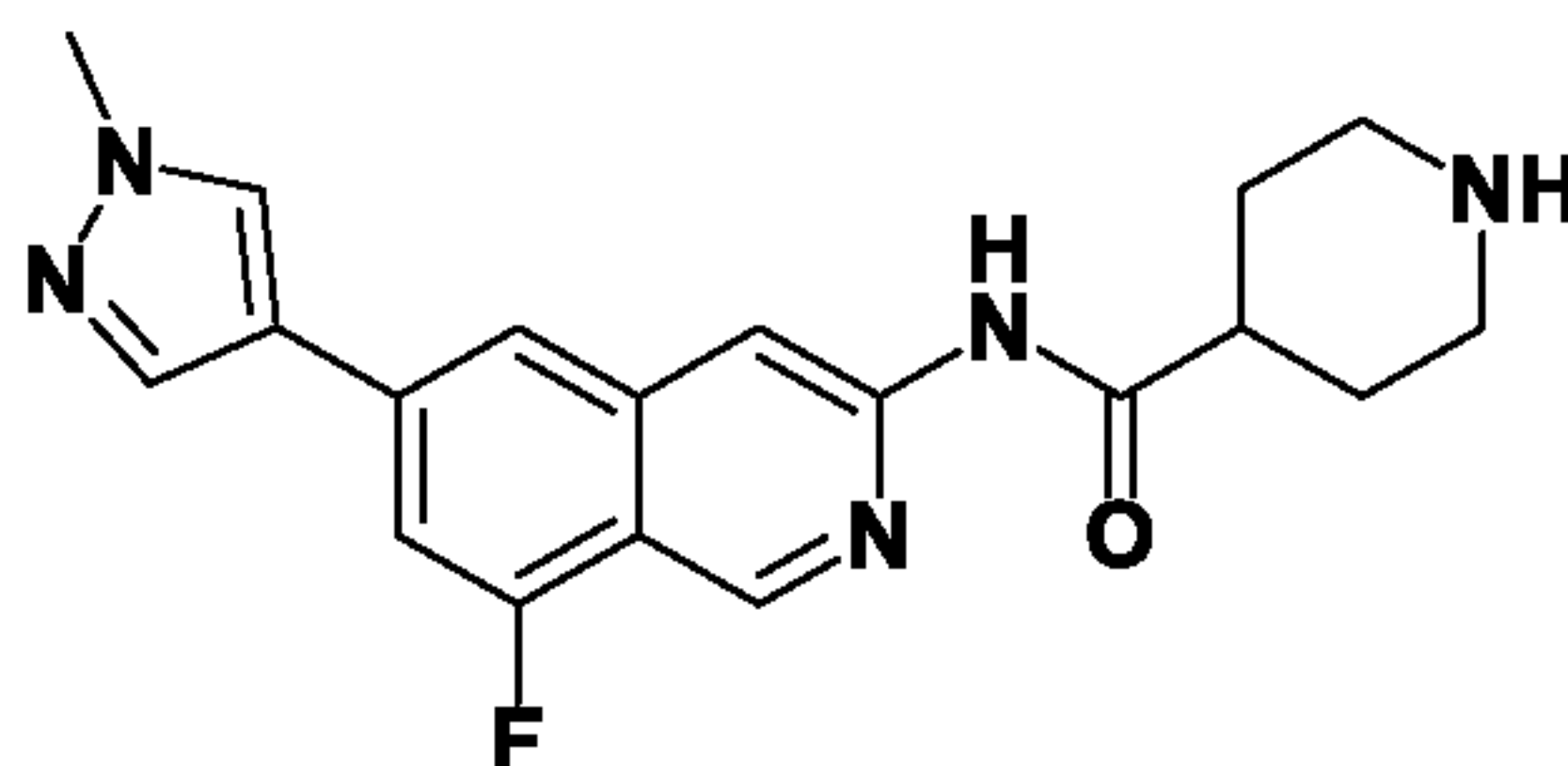
[0906] N-(4-Chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) cyclopropanecarboxamide **364**.

[0907] Beige solid (240.0 mg, 0.734 mmol, 95.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.80 - 0.86 (4 H, m), 1.91 (1 H, quin, *J*=6.24 Hz), 3.92 (3 H, s), 7.99 (1 H, dd, *J*=8.51, 1.37 Hz), 8.14 (1 H, s), 8.19 (1 H, d, *J*=8.78 Hz), 8.22 (1 H, d, *J*=0.82 Hz), 8.49 (1 H, s), 9.10 (1 H, s), 10.48 (1 H, s); ESIMS found for C₁₇H₁₅ClN₄O *m/z* 327.1 (M+1).

**365**

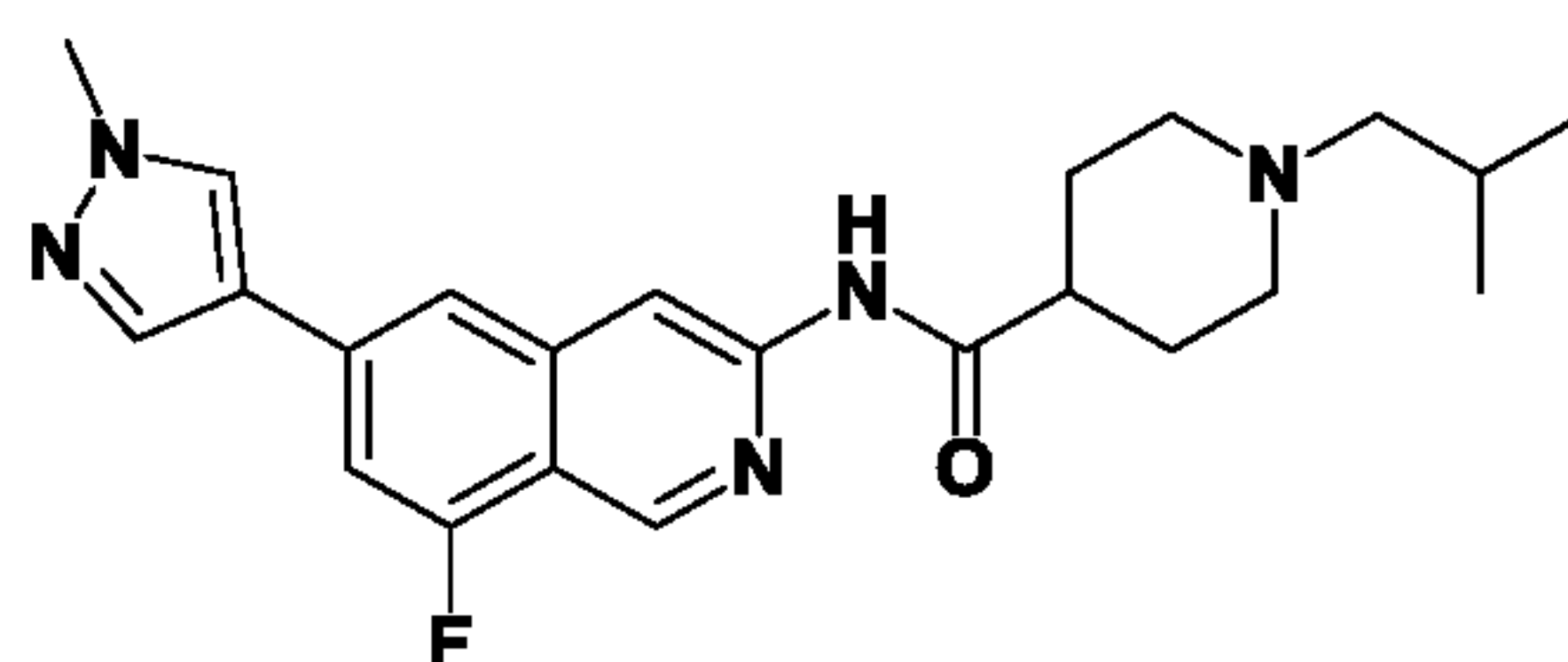
[0908] *trans*-4-Amino-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) cyclohexane-1-carboxamide **365**.

[0909] Beige solid (350.0 mg, 1.00 mmol, 90.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.99 - 1.11 (2 H, m), 1.42 - 1.64 (4 H, m), 1.82 (4 H, br d, *J*=11.80 Hz), 2.42 - 2.49 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.35 (1 H, s), 8.42 (1 H, s), 9.02 (1 H, s), 10.40 (1 H, s); ESIMS found for C₂₀H₂₃N₅O *m/z* 350.2 (M+1).

**366**

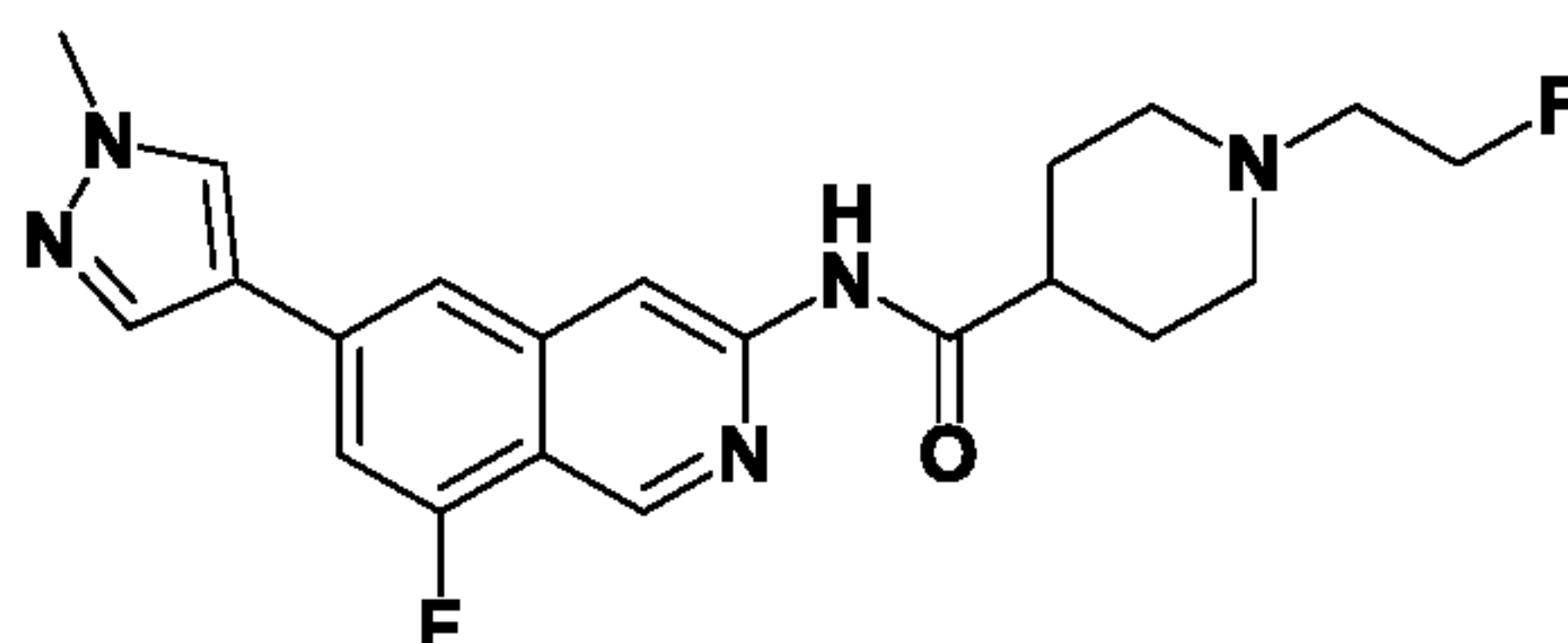
[0910] N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **366**.

[0911] White solid (260.0 mg, 0.736 mmol, 73.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.53 (2 H, qd, *J*=12.21, 3.98 Hz), 1.70 (2 H, br d, *J*=10.98 Hz), 2.42 - 2.49 (2 H, m), 2.60 - 2.70 (1 H, m), 2.97 (2 H, br d, *J*=14.00 Hz), 3.90 (3 H, s), 7.58 (1 H, dd, *J*=12.08, 1.10 Hz), 7.92 (1 H, s), 8.11 (1 H, s), 8.39 (1 H, s), 8.49 (1 H, s), 9.14 (1 H, s), 10.56 (1 H, s); ESIMS found for C₁₉H₂₀FN₅O *m/z* 354.15 (M+1).

**367**

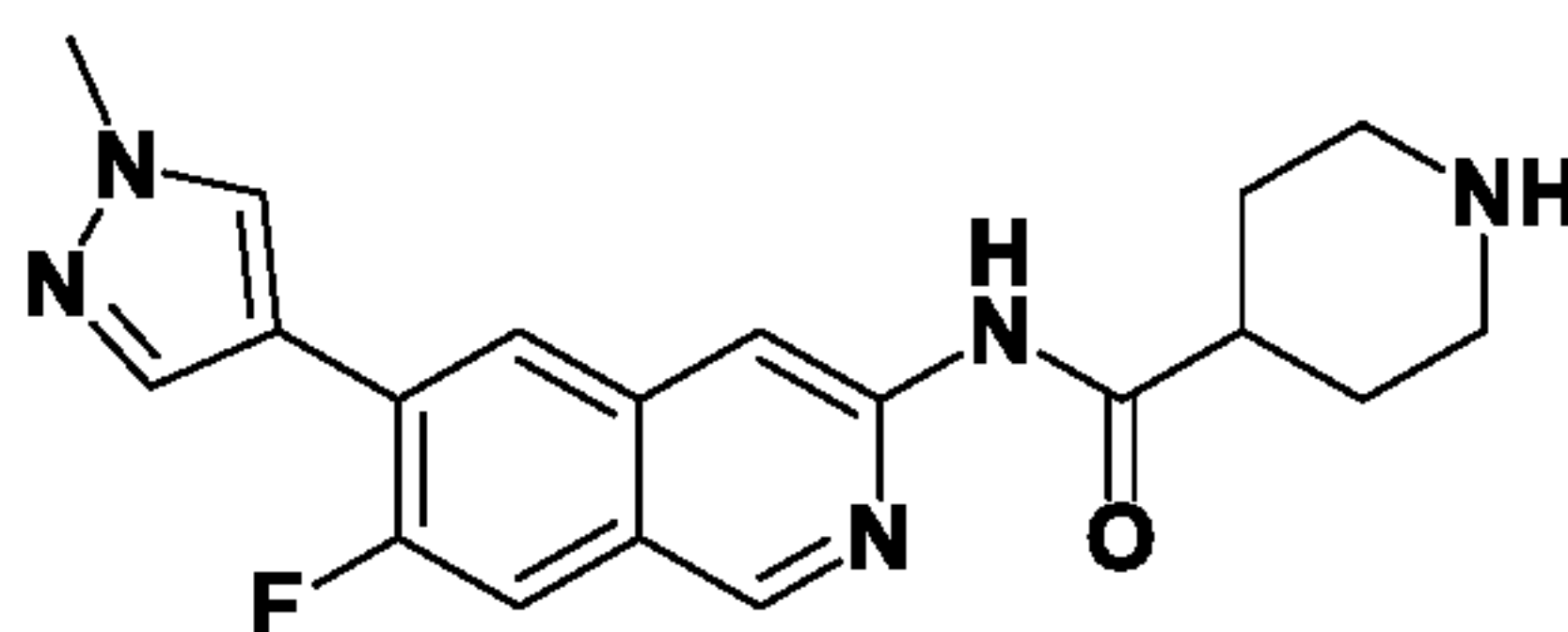
[0912] N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide **367**.

[0913] Beige solid (15.0 mg, 0.037 mmol, 16.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.86 (6 H, d, $J=6.59$ Hz), 1.61 - 1.72 (2 H, m), 1.73 - 1.81 (3 H, m), 1.83 - 1.92 (2 H, m), 2.02 (2 H, d, $J=7.41$ Hz), 2.51 - 2.59 (1 H, m), 2.82 - 2.91 (2 H, m), 3.90 (3 H, s), 7.58 (1 H, dd, $J=12.08, 1.10$ Hz), 7.92 (1 H, s), 8.11 (1 H, s), 8.39 (1 H, s), 8.49 (1 H, s), 9.15 (1 H, s), 10.61 (1 H, s); ESIMS found for $\text{C}_{23}\text{H}_{28}\text{FN}_5\text{O}$ m/z 410.2 ($M+1$).

**368**

[0914] N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)piperidine-4-carboxamide **368**.

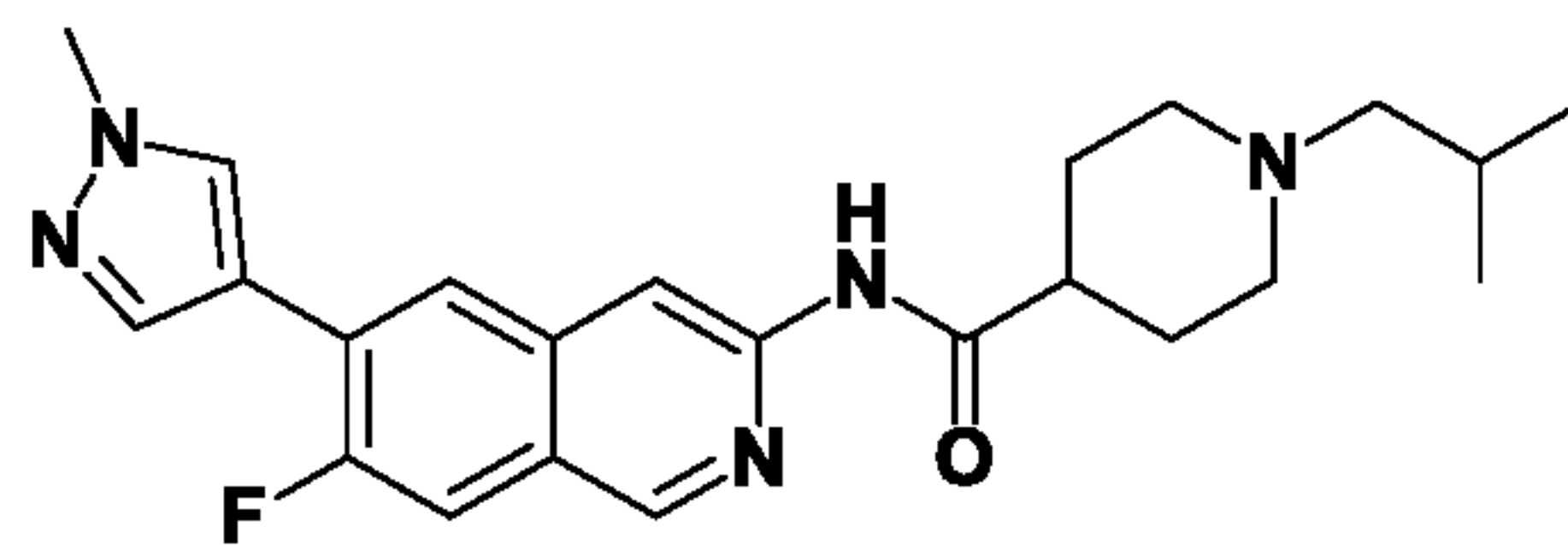
[0915] Off-white solid (26.0 mg, 0.065 mmol, 28.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.68 (2 H, qd, $J=12.21, 3.70$ Hz), 1.75 - 1.83 (2 H, m), 2.00 - 2.07 (2 H, m), 2.52 - 2.57 (1 H, m), 2.61 (2 H, dt, $J=28.30, 4.95$ Hz), 2.94 (2 H, br d, $J=11.53$ Hz), 3.90 (3 H, s), 4.53 (2 H, dt, $J=48.10, 5.25$ Hz), 7.59 (1 H, dd, $J=12.08, 1.37$ Hz), 7.92 (1 H, s), 8.11 (1 H, d, $J=0.82$ Hz), 8.39 (1 H, s), 8.50 (1 H, s), 9.15 (1 H, s), 10.62 (1 H, s); ESIMS found for $\text{C}_{21}\text{H}_{23}\text{F}_2\text{N}_5\text{O}$ m/z 400.2 ($M+1$).

**369**

[0916] N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **369**.

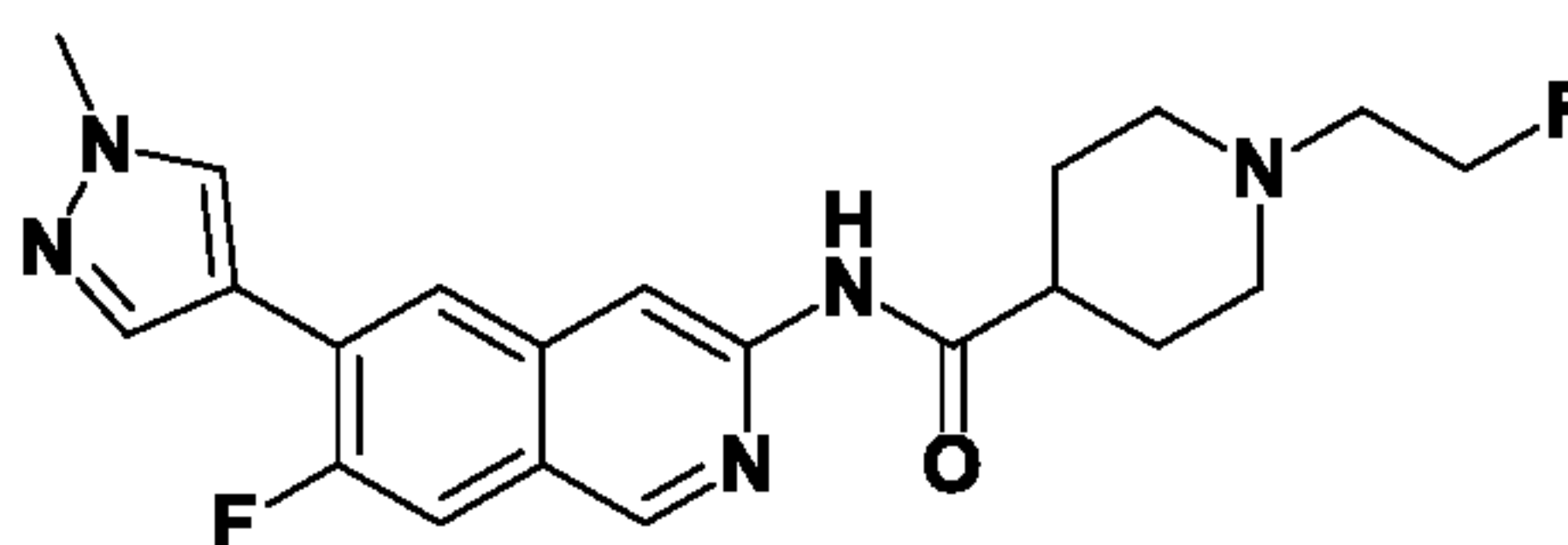
[0917] Off-white solid (135.0 mg, 0.382 mmol, 74.0% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.53 (2 H, qd, $J=12.17, 3.84$ Hz), 1.70 (2 H, br dd, $J=12.08, 1.65$ Hz), 2.43 - 2.49

(2 H, m), 2.63 (1 H, tt, $J=11.63, 3.74$ Hz), 2.97 (2 H, br d, $J=12.08$ Hz), 3.93 (3 H, s), 7.89 (1 H, d, $J=11.80$ Hz), 8.10 (1 H, s), 8.26 (1 H, d, $J=7.41$ Hz), 8.30 (1 H, d, $J=2.74$ Hz), 8.49 (1 H, s), 9.03 (1 H, s), 10.44 (1 H, s); ESIMS found for $C_{19}H_{20}FN_5O$ m/z 354.15 (M+1).

**370**

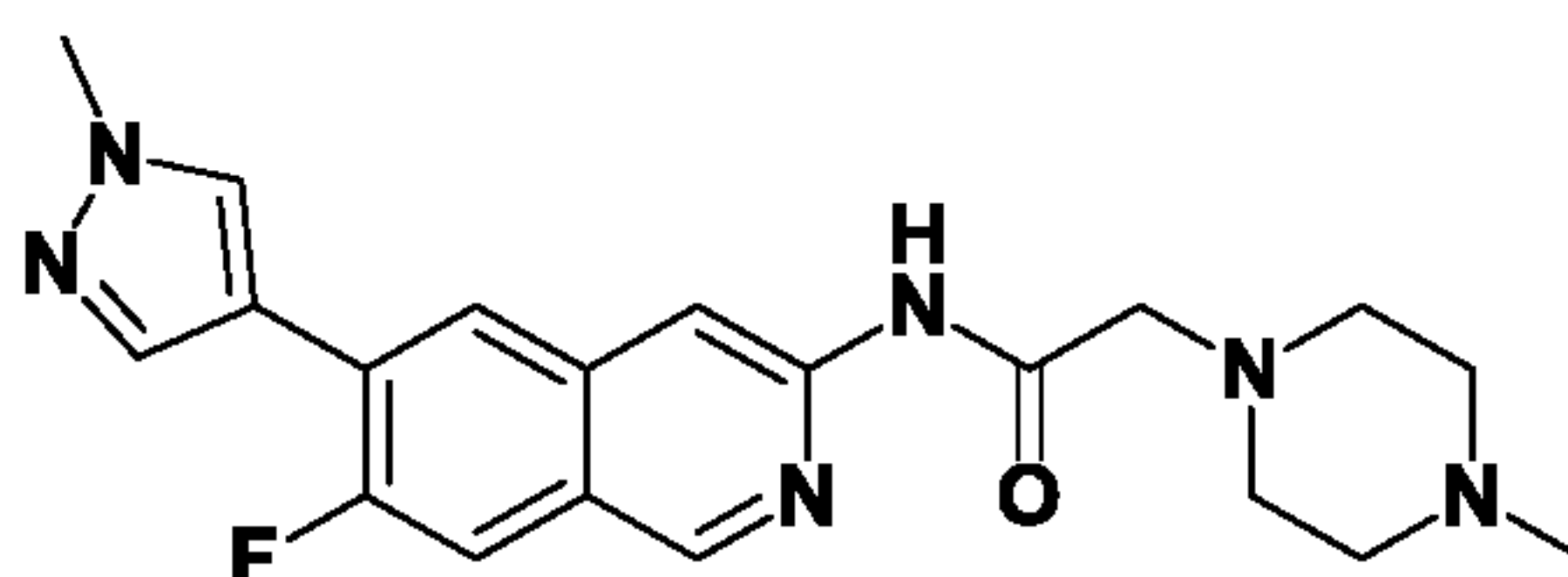
[0918] N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide **370**.

[0919] Off-white solid (45.0 mg, 0.106 mmol, 53.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.86 (6 H, d, $J=6.59$ Hz), 1.61 - 1.72 (2 H, m), 1.73 - 1.81 (3 H, m), 1.83 - 1.92 (2 H, m), 2.02 (2 H, d, $J=7.41$ Hz), 2.51 - 2.58 (1 H, m), 2.86 (2 H, br d, $J=11.25$ Hz), 3.93 (3 H, s), 7.89 (1 H, d, $J=11.53$ Hz), 8.10 (1 H, d, $J=0.82$ Hz), 8.27 (1 H, d, $J=7.41$ Hz), 8.30 (1 H, d, $J=2.74$ Hz), 8.50 (1 H, s), 9.03 (1 H, s), 10.49 (1 H, s); ESIMS found for $C_{23}H_{28}FN_5O$ m/z 410.2 (M+1).

**371**

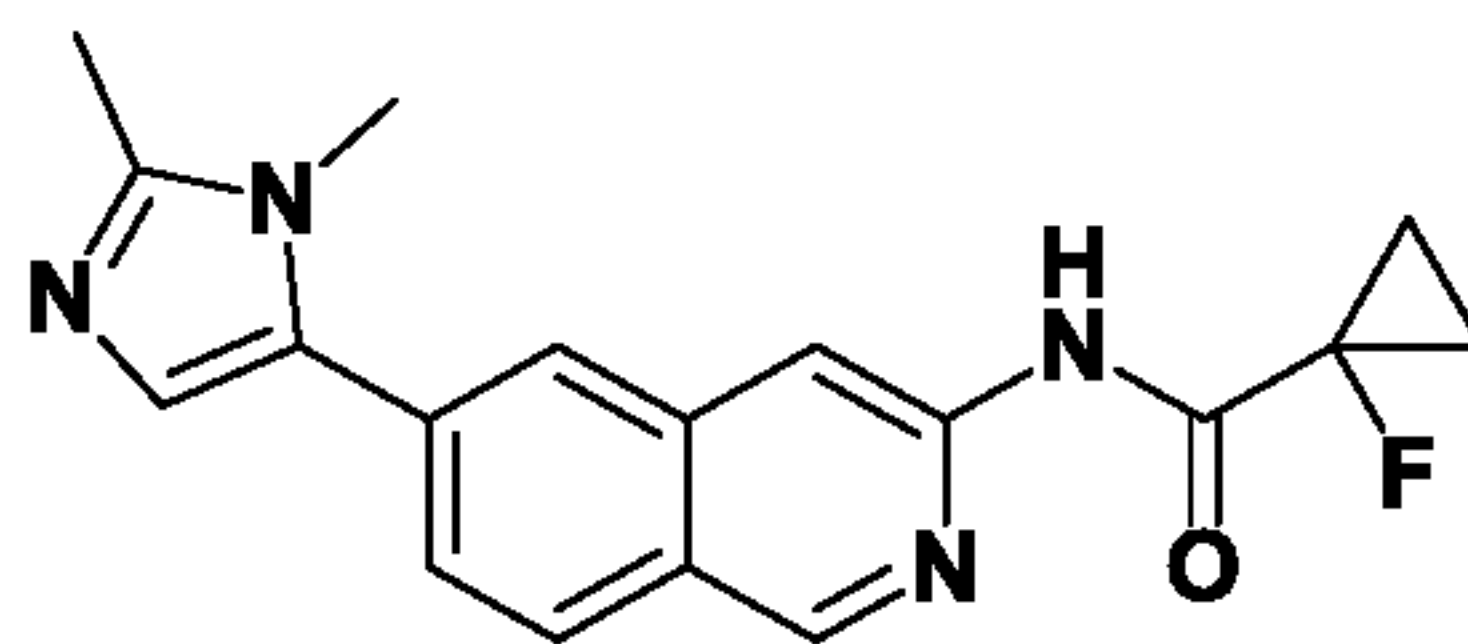
[0920] N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)piperidine-4-carboxamide **371**.

[0921] White solid (30.0 mg, 0.072 mmol, 51.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.68 (2 H, qd, $J=12.21, 3.70$ Hz), 1.76 - 1.83 (2 H, m), 2.04 (2 H, td, $J=11.80, 2.20$ Hz), 2.54 (1 H, td, $J=7.62, 3.98$ Hz), 2.61 (2 H, dt, $J=28.35, 4.95$ Hz), 2.94 (2 H, br d, $J=11.53$ Hz), 3.93 (3 H, s), 4.53 (2 H, dt, $J=47.80, 4.95$ Hz), 7.89 (1 H, d, $J=11.53$ Hz), 8.10 (1 H, s), 8.27 (1 H, d, $J=7.68$ Hz), 8.30 (1 H, d, $J=2.74$ Hz), 8.50 (1 H, s), 9.04 (1 H, s), 10.49 (1 H, s); ESIMS found for $C_{21}H_{23}F_2N_5O$ m/z 400.2 (M+1).

**372**

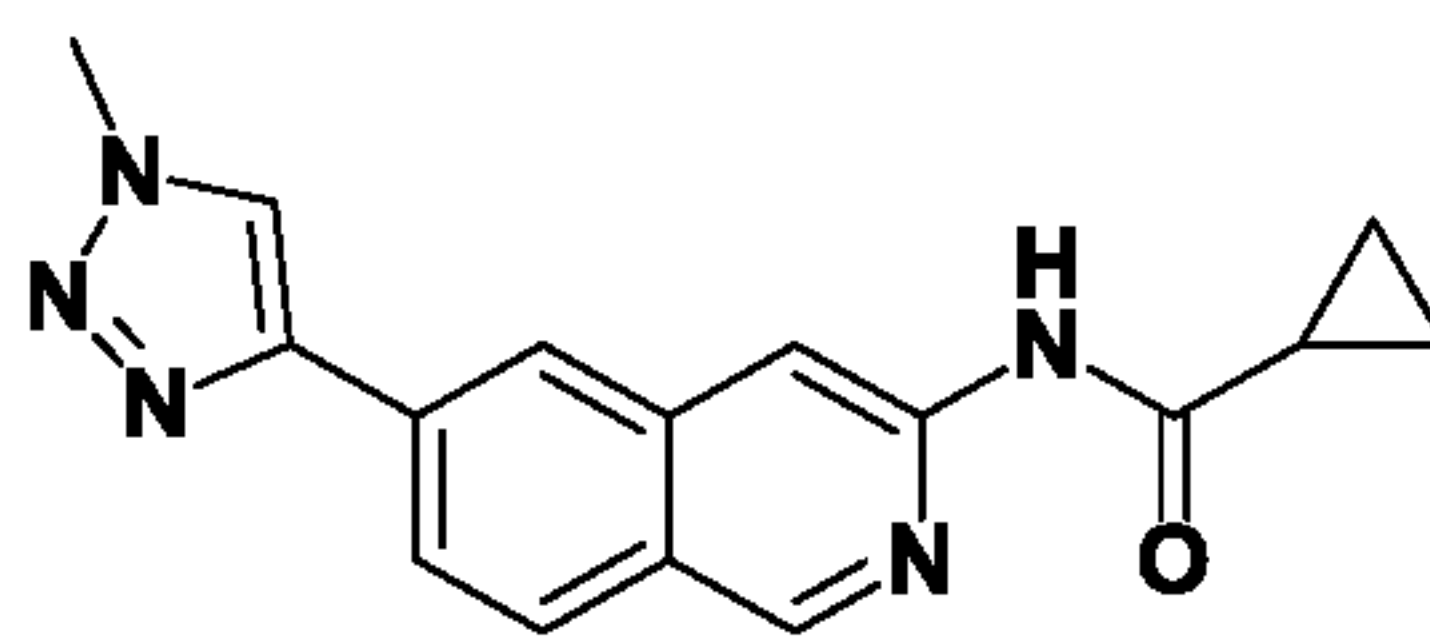
[0922] N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **372**.

[0923] Off-white solid (16.0 mg, 0.042 mmol, 13.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.19 (3 H, s), 2.40 (4 H, br s), 2.58 (4 H, br s), 3.22 (2 H, s), 3.93 (3 H, s), 7.92 (1 H, d, *J*=11.53 Hz), 8.13 (1 H, s), 8.32 (1 H, d, *J*=3.02 Hz), 8.34 (1 H, d, *J*=7.41 Hz), 8.49 (1 H, s), 9.05 (1 H, s), 9.95 (1 H, s); ESIMS found for C₂₀H₂₃FN₆O *m/z* 383.2 (M+1).

**376**

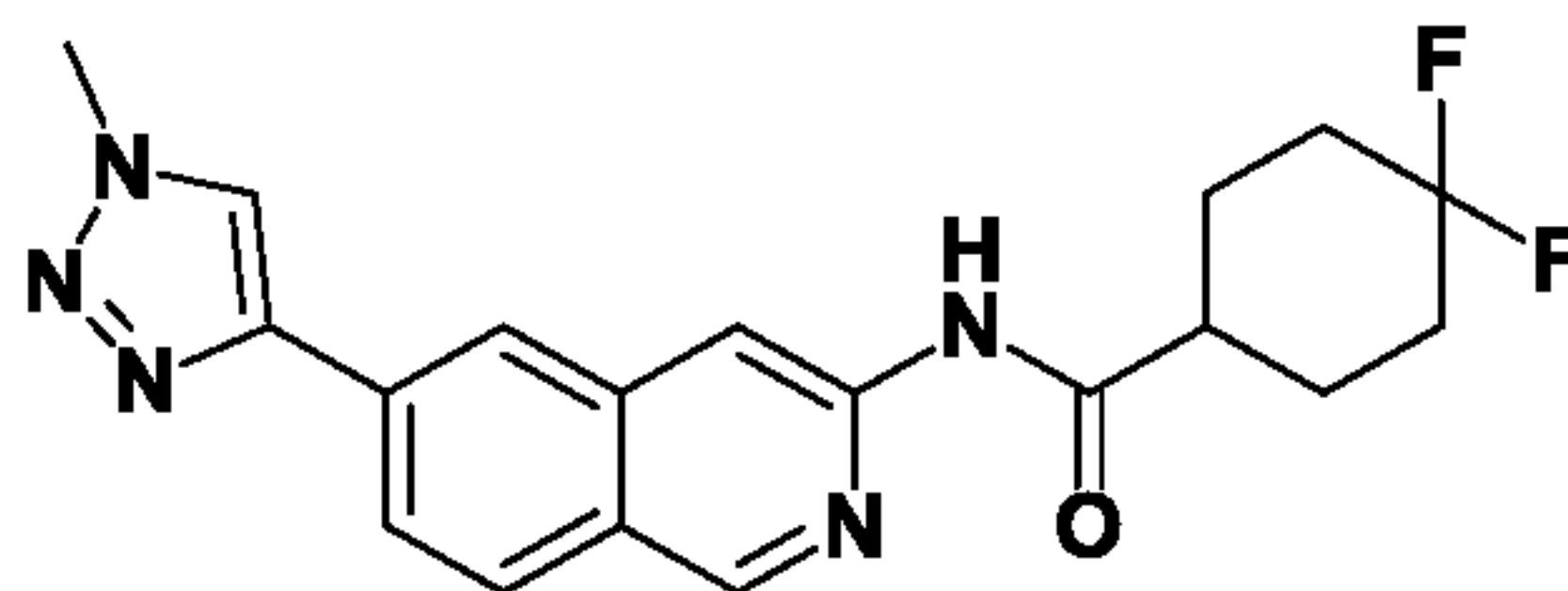
[0924] N-(6-(1,2-Dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-fluorocyclopropane-1-carboxamide **376**.

[0925] Beige solid (32.0 mg, 0.094 mmol, 19.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.33 - 1.42 (2 H, m), 1.43 - 1.53 (2 H, m), 2.39 (3 H, s), 3.67 (3 H, s), 7.13 (1 H, s), 7.67 (1 H, dd, *J*=8.51, 1.65 Hz), 7.97 (1 H, s), 8.13 (1 H, d, *J*=8.51 Hz), 8.46 (1 H, s), 9.18 (1 H, s), 10.28 (1 H, s); ESIMS found for C₁₈H₁₇FN₄O *m/z* 325.1 (M+1).

**433**

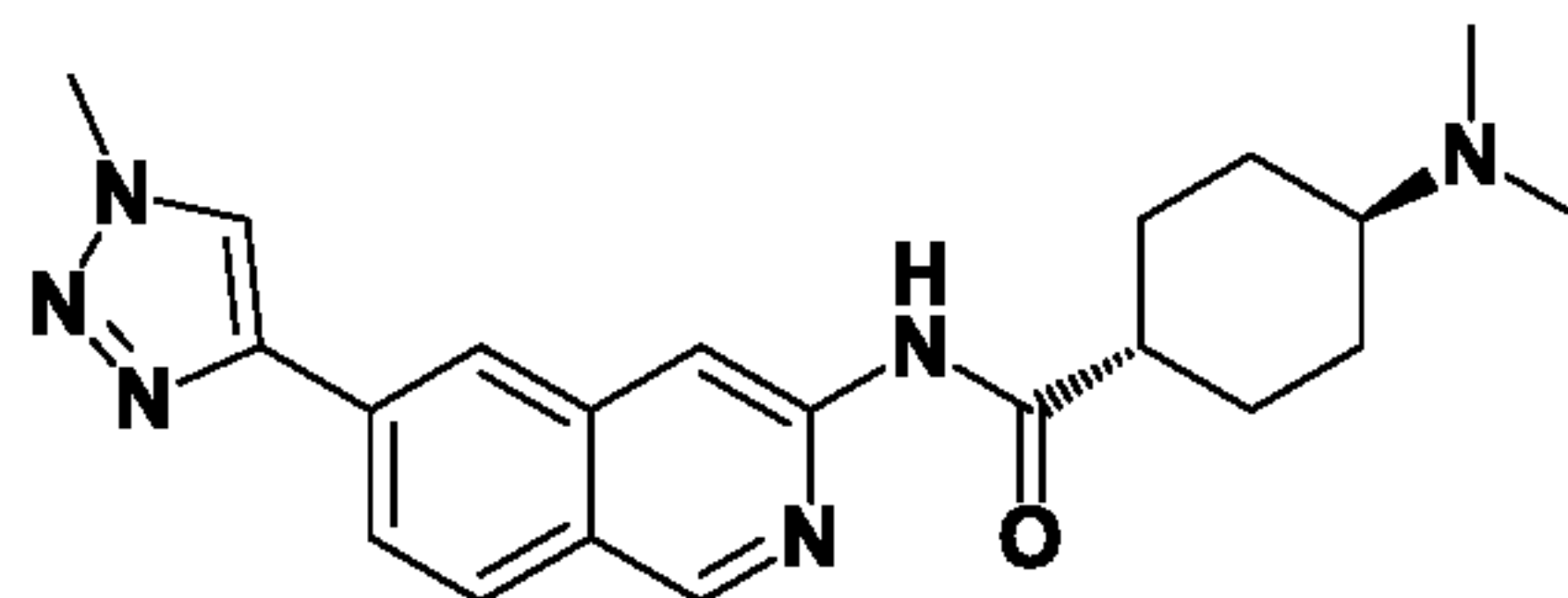
[0926] N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclopropanecarboxamide **433**.

[0927] Beige solid (14.0 mg, 0.048 mmol, 10.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.79 - 0.91 (4 H, m), 2.03 - 2.12 (1 H, m), 4.14 (3 H, s), 8.01 (1 H, dd, *J*=8.51, 1.65 Hz), 8.11 (1 H, d, *J*=8.78 Hz), 8.26 (1 H, s), 8.47 (1 H, s), 8.72 (1 H, s), 9.12 (1 H, s), 10.90 (1 H, s); ESIMS found for C₁₆H₁₅N₅O *m/z* 294.1 (M+1).

**441**

[0928] 4,4-Difluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **441**.

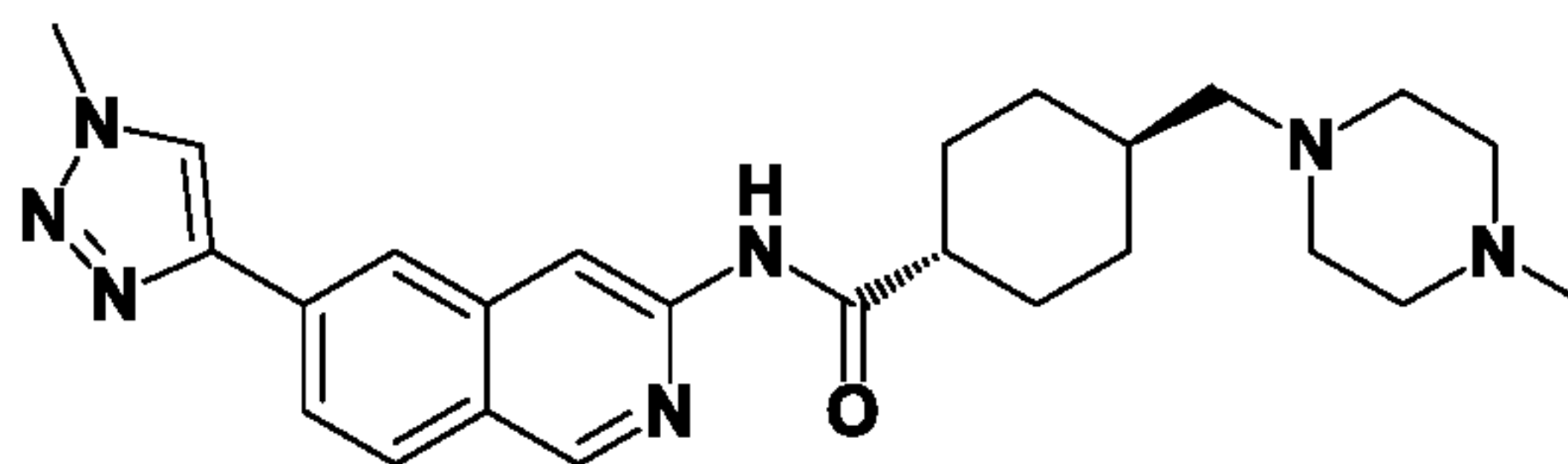
[0929] White solid (57.8 mg, 0.156 mmol, 43.2% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.67 - 1.91 (4 H, m), 1.96 (2 H, br d, $J=12.90$ Hz), 2.08 - 2.18 (2 H, m), 2.69 - 2.75 (1 H, m), 4.14 (3 H, s), 8.02 (1 H, dd, $J=8.51$, 1.37 Hz), 8.11 (1 H, d, $J=8.51$ Hz), 8.29 (1 H, s), 8.50 (1 H, s), 8.73 (1 H, s), 9.12 (1 H, s), 10.63 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{19}\text{F}_2\text{N}_5\text{O}$ m/z 372.2 ($\text{M}+1$).



443

[0930] *trans*-4-(Dimethylamino)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **443**.

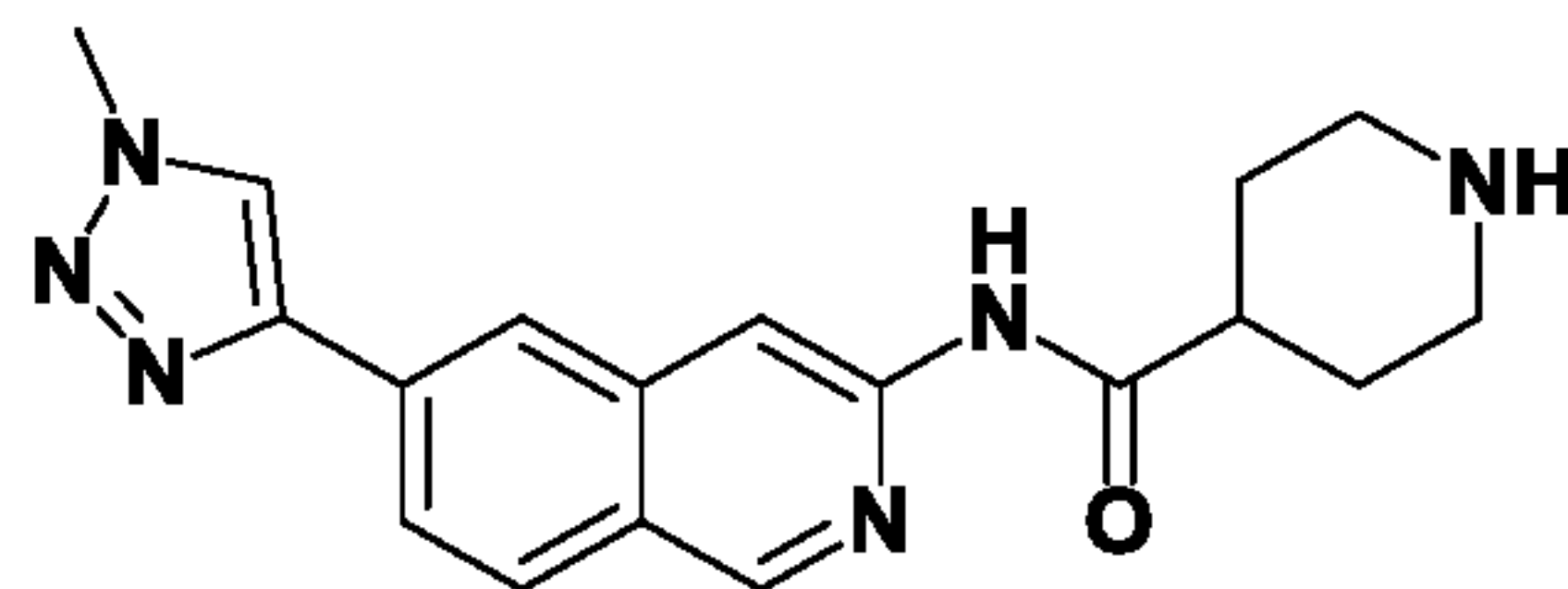
[0931] White solid (8.0 mg, 0.021 mmol, 10.9% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.13 - 1.23 (2 H, m), 1.43 - 1.55 (2 H, m), 1.83 - 1.96 (4 H, m), 2.11 - 2.16 (1 H, m), 2.18 (6 H, s), 2.44 - 2.48 (1 H, m), 4.14 (3 H, s), 8.01 (1 H, dd, $J=8.51$, 1.65 Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.27 (1 H, s), 8.49 (1 H, s), 8.72 (1 H, s), 9.11 (1 H, s), 10.47 (1 H, s); ESIMS found for $\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}$ m/z 379.2 ($\text{M}+1$).



448

[0932] *trans*-N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide **448**.

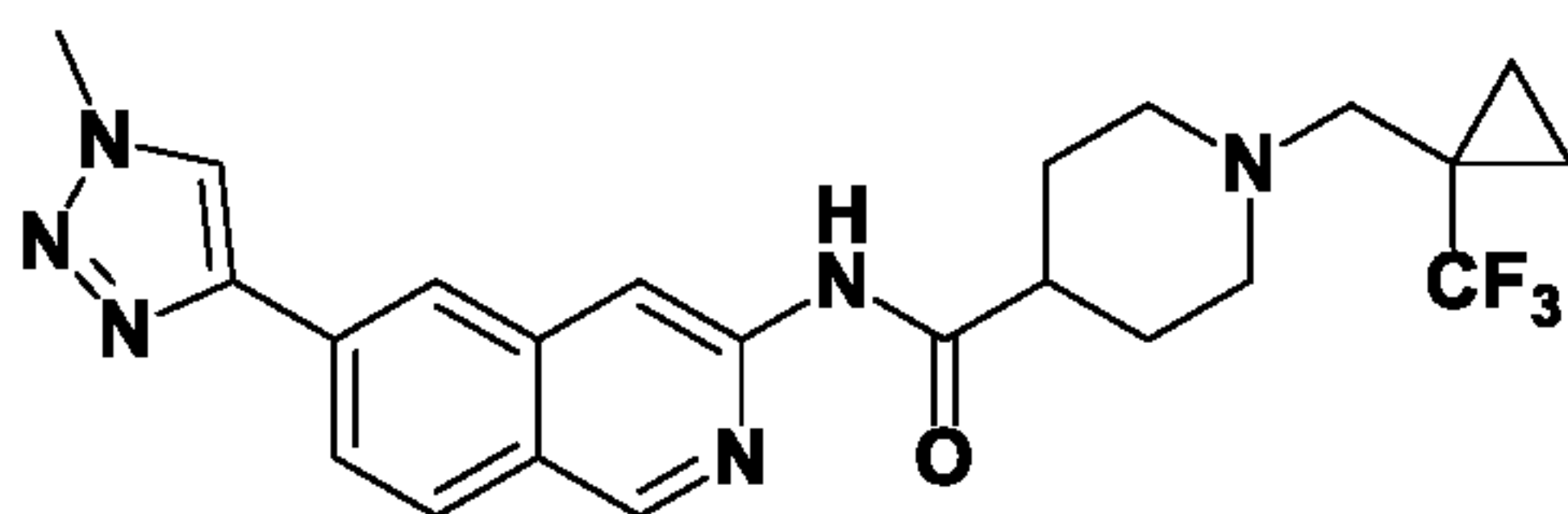
[0933] Off-white solid (22.0 mg, 0.049 mmol, 14.6% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 0.82 - 0.95 (2 H, m), 1.41 - 1.52 (3 H, m), 1.79 - 1.91 (4 H, m), 2.08 (2 H, d, $J=7.14$ Hz), 2.14 (3 H, s), 2.31 (8 H, br s), 2.51 - 2.55 (1 H, m), 4.14 (3 H, s), 8.00 (1 H, dd, $J=8.51$, 1.37 Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.27 (1 H, s), 8.50 (1 H, s), 8.72 (1 H, s), 9.10 (1 H, s), 10.47 (1 H, s); ESIMS found for $\text{C}_{25}\text{H}_{33}\text{N}_7\text{O}$ m/z 448.3 ($\text{M}+1$).



452

[0934] N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **452**.

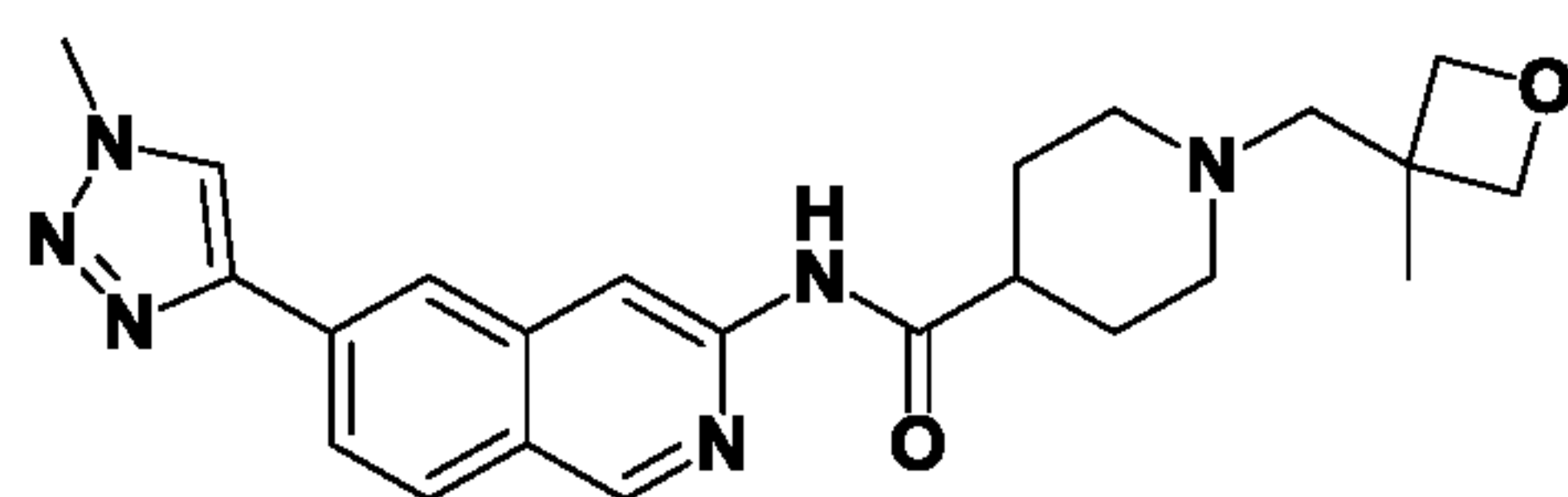
[0935] White solid (119.4 mg, 0.355 mmol, 77.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.54 (2 H, qd, *J*=12.17, 3.84 Hz), 1.71 (2 H, br d, *J*=11.25 Hz), 2.45 - 2.49 (2 H, m), 2.65 (1 H, tt, *J*=11.70, 3.67 Hz), 2.98 (2 H, br d, *J*=12.08 Hz), 4.14 (3 H, s), 8.01 (1 H, dd, *J*=8.51, 1.37 Hz), 8.11 (1 H, d, *J*=8.51 Hz), 8.28 (1 H, s), 8.50 (1 H, s), 8.73 (1 H, s), 9.11 (1 H, s), 10.48 (1 H, s); ESIMS found for C₁₈H₂₀N₆O *m/z* 337.2 (M+1).



470

[0936] N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide **470**.

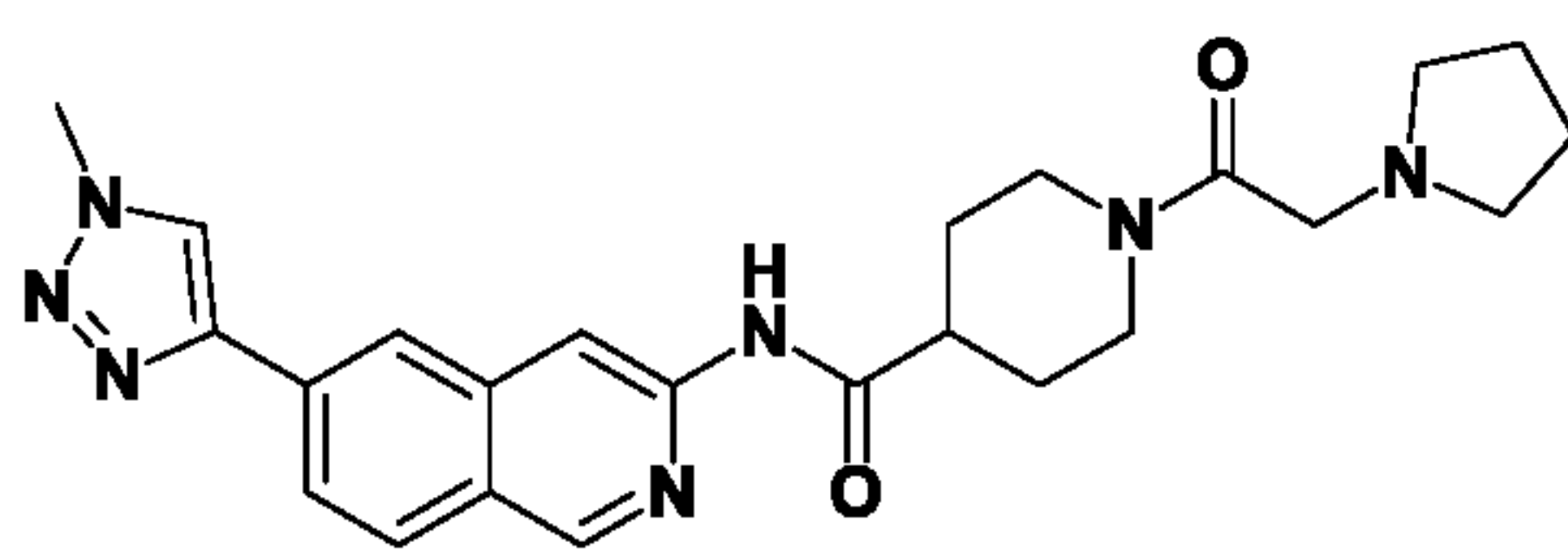
[0937] White solid (75.9 mg, 0.166 mmol, 79.4% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.73 (2 H, br s), 0.93 - 1.00 (2 H, m), 1.63 - 1.74 (2 H, m), 1.78 (2 H, br d, *J*=10.70 Hz), 1.95 (2 H, br t, *J*=10.57 Hz), 2.52 - 2.60 (1 H, m), 2.97 (2 H, br d, *J*=10.98 Hz), 3.28 (2 H, s), 4.14 (3 H, s), 8.01 (1 H, dd, *J*=8.51, 1.37 Hz), 8.11 (1 H, d, *J*=8.51 Hz), 8.28 (1 H, s), 8.50 (1 H, s), 8.72 (1 H, s), 9.11 (1 H, s), 10.52 (1 H, s); ESIMS found for C₂₃H₂₅F₃N₆O *m/z* 459.2 (M+1).



472

[0938] N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide **472**.

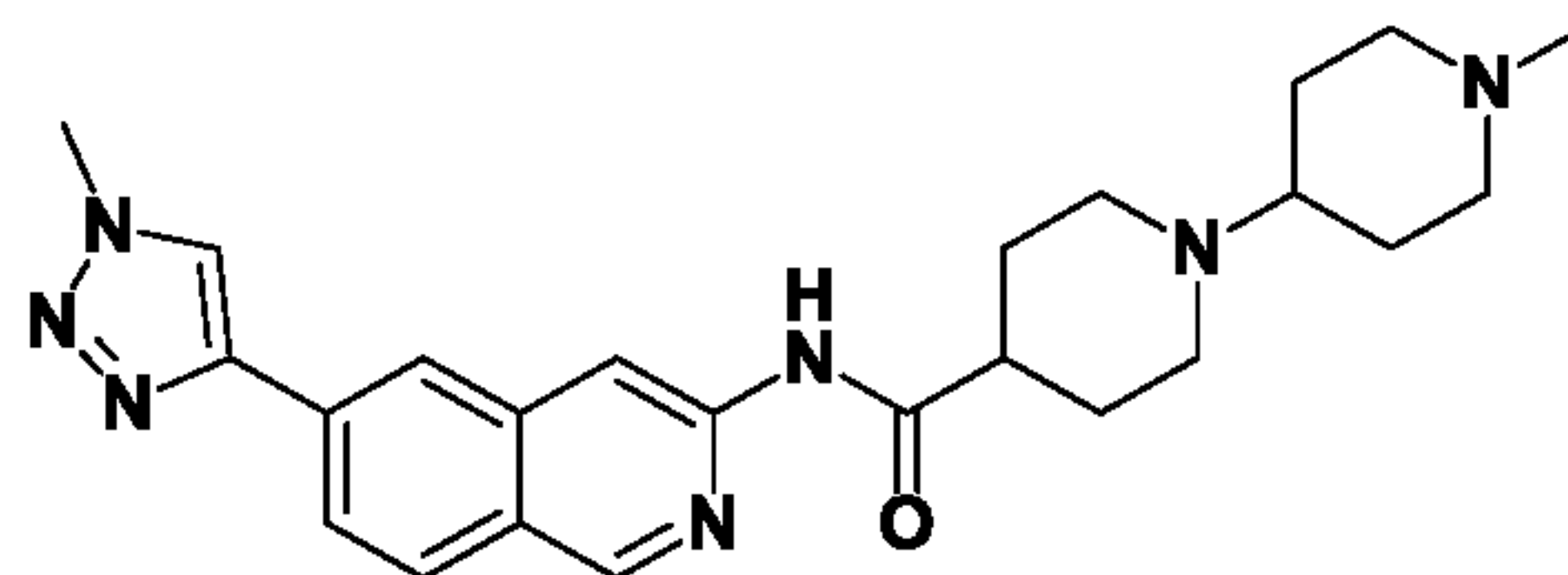
[0939] Beige solid (32.0 mg, 0.076 mmol, 21.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.31 (3 H, s), 1.60 - 1.71 (2 H, m), 1.72 - 1.80 (2 H, m), 1.93 - 2.02 (2 H, m), 2.48 (2 H, br s), 2.52 - 2.59 (1 H, m), 2.59 - 2.67 (2 H, m), 4.14 (3 H, s), 4.19 (2 H, d, *J*=5.49 Hz), 4.36 (2 H, d, *J*=5.76 Hz), 8.01 (1 H, dd, *J*=8.51, 1.37 Hz), 8.11 (1 H, d, *J*=8.51 Hz), 8.28 (1 H, s), 8.50 (1 H, s), 8.73 (1 H, s), 9.11 (1 H, s), 10.54 (1 H, s); ESIMS found for C₂₃H₂₈N₆O₂ *m/z* 421.2 (M+1).



475

[0940] N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide **475**.

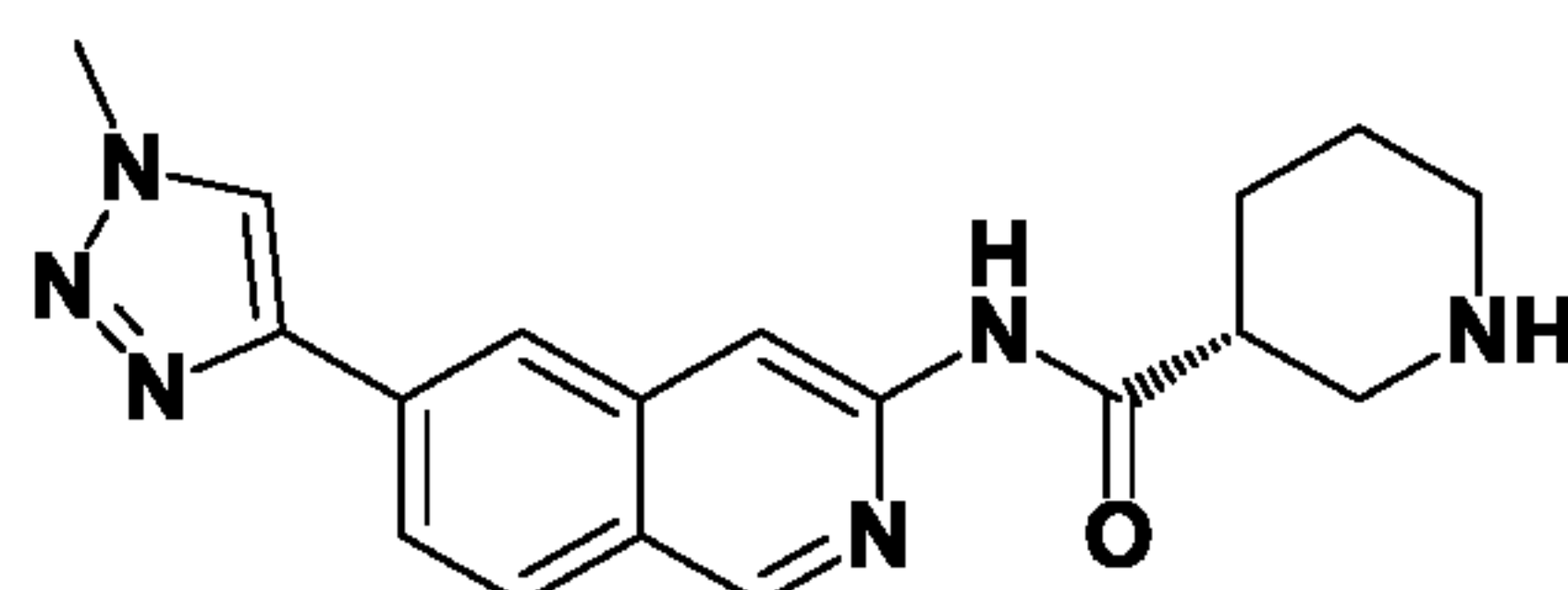
[0941] White solid (7.8 mg, 0.017 mmol, 20.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.44 - 1.55 (2 H, m), 1.57 - 1.66 (2 H, m), 1.67 - 1.73 (4 H, m), 1.85 (2 H, br d, *J*=10.43 Hz), 2.58 - 2.65 (1 H, m), 2.82 (1 H, ddd, *J*=11.32, 7.34, 4.39 Hz), 2.99 - 3.06 (1 H, m), 3.16 - 3.21 (2 H, m), 3.30 - 3.38 (2 H, m), 4.10 (1 H, br d, *J*=1.10 Hz), 4.14 (3 H, s), 4.36 - 4.44 (1 H, m), 8.01 (1 H, dd, *J*=8.51, 1.37 Hz), 8.11 (1 H, d, *J*=8.78 Hz), 8.28 (1 H, s), 8.49 (1 H, s), 8.71 (1 H, s), 9.11 (1 H, s), 10.56 (1 H, s); ESIMS found for C₂₄H₂₉N₇O₂ *m/z* 448.0 (M+1).



477

[0942] 1'-Methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide **477**.

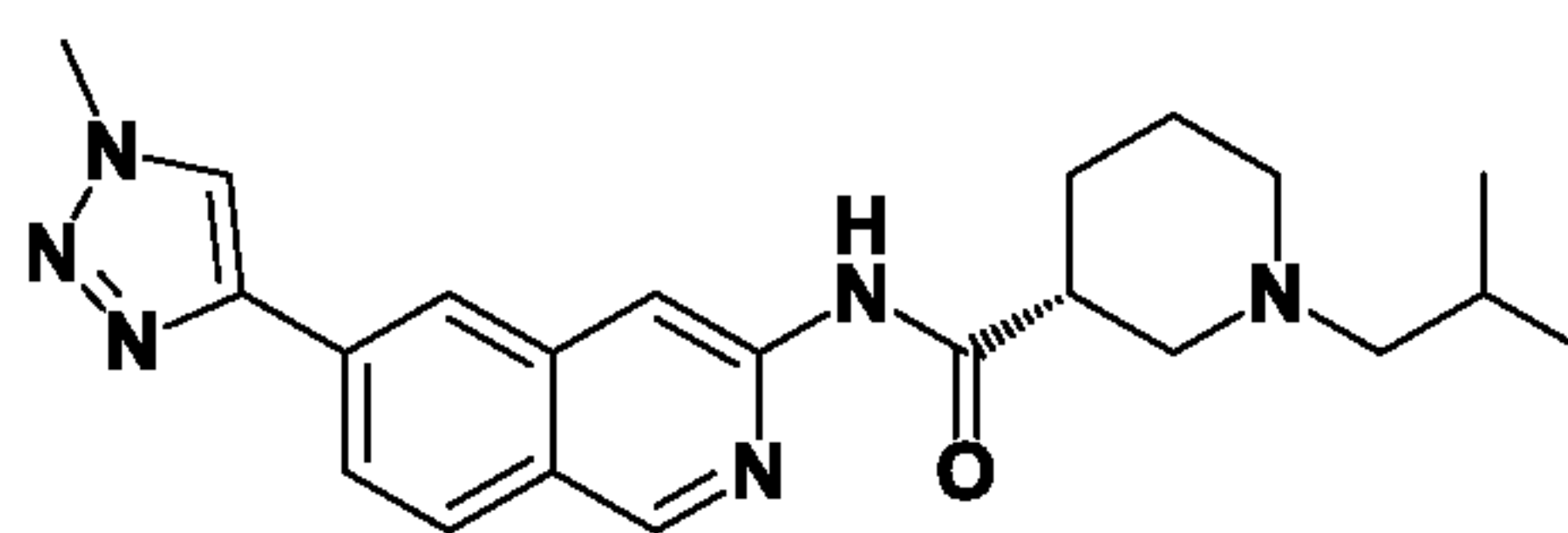
[0943] Off-white solid (65.0 mg, 0.150 mmol, 37.6% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.43 (2 H, qd, *J*=11.94, 3.70 Hz), 1.57 - 1.70 (4 H, m), 1.75 - 1.86 (4 H, m), 2.08 - 2.19 (1 H, m), 2.12 (3 H, s), 2.51 - 2.57 (1 H, m), 2.77 (2 H, br d, *J*=11.53 Hz), 2.90 (2 H, br d, *J*=11.25 Hz), 3.17 (2 H, d, *J*=2.20 Hz), 4.14 (3 H, s), 8.01 (1 H, dd, *J*=8.51, 1.65 Hz), 8.10 (1 H, d, *J*=8.51 Hz), 8.28 (1 H, s), 8.51 (1 H, s), 8.72 (1 H, s), 9.10 (1 H, s), 10.51 (1 H, s); ESIMS found for C₂₄H₃₁N₇O *m/z* 434.25 (M+1).



481

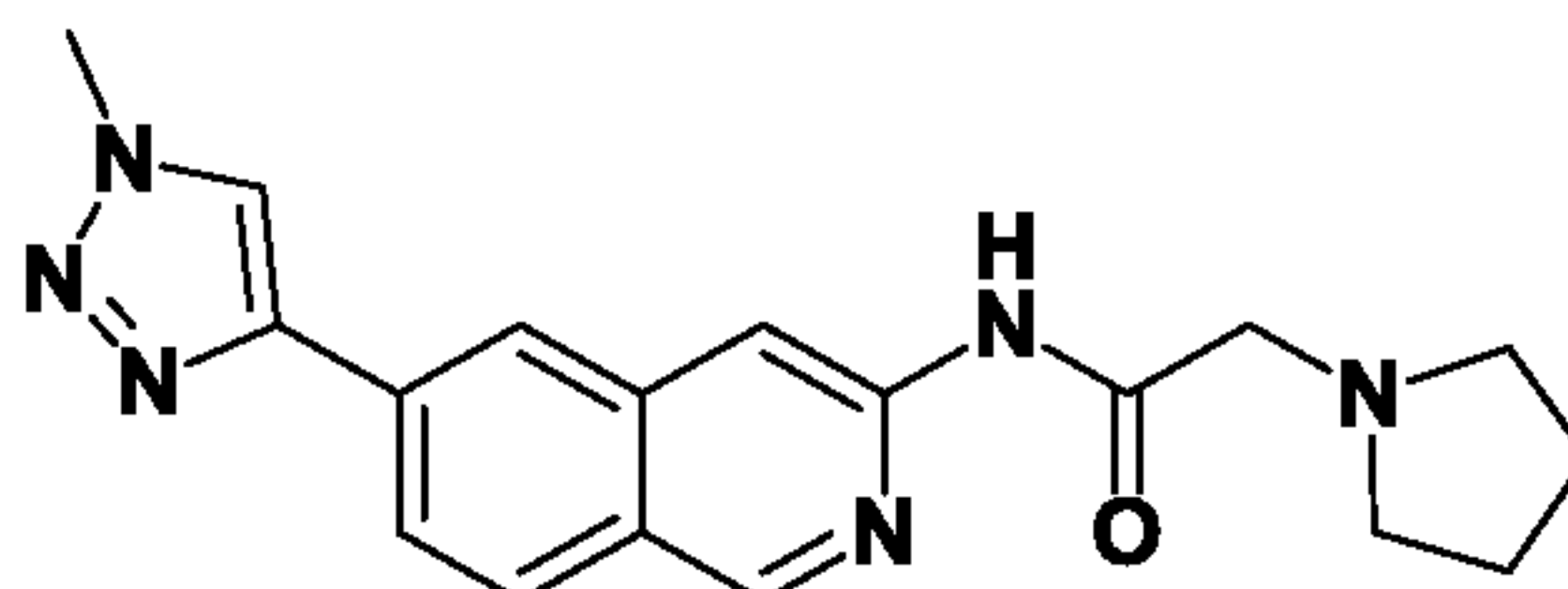
[0944] (R)-N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide **481**.

[0945] White solid (80.4 mg, 0.239 mmol, 87.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.36 - 1.46 (1 H, m), 1.56 - 1.64 (1 H, m), 1.64 - 1.72 (1 H, m), 1.84 - 1.92 (1 H, m), 2.53 - 2.60 (1 H, m), 2.63 (1 H, dq, *J*=8.71, 4.41 Hz), 2.75 (1 H, dd, *J*=11.94, 8.92 Hz), 2.81 (1 H, dt, *J*=12.14, 3.95 Hz), 3.00 (1 H, dd, *J*=11.94, 3.16 Hz), 4.14 (3 H, s), 8.01 (1 H, dd, *J*=8.51, 1.65 Hz), 8.11 (1 H, d, *J*=8.51 Hz), 8.28 (1 H, s), 8.49 (1 H, s), 8.73 (1 H, s), 9.10 (1 H, s), 10.81 (1 H, s); ESIMS found for C₁₈H₂₀N₆O *m/z* 337.2 (M+1).

**483**

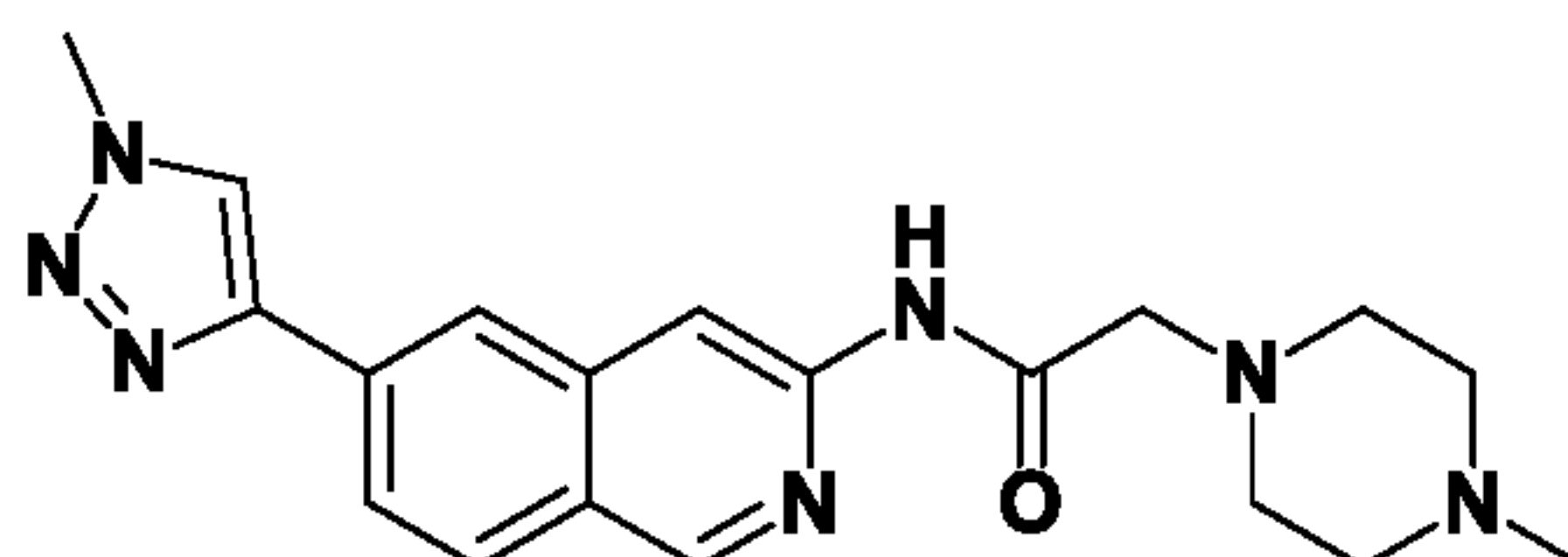
[0946] (R)-1-Isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide **483**.

[0947] White solid (45.9 mg, 0.117 mmol, 82.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.88 (3 H, d, *J*=6.59 Hz), 0.91 (3 H, d, *J*=6.59 Hz), 1.50 - 1.61 (2 H, m), 1.65 - 1.73 (1 H, m), 1.78 - 1.86 (2 H, m), 2.08 (2 H, br d, *J*=7.41 Hz), 2.10 - 2.16 (1 H, m), 2.25 - 2.33 (1 H, m), 2.55 - 2.62 (1 H, m), 2.77 (2 H, br d, *J*=7.68 Hz), 4.14 (3 H, s), 8.01 (1 H, dd, *J*=8.51, 1.65 Hz), 8.11 (1 H, d, *J*=8.78 Hz), 8.28 (1 H, s), 8.49 (1 H, s), 8.73 (1 H, s), 9.10 (1 H, s), 10.73 (1 H, s); ESIMS found for C₂₂H₂₈N₆O *m/z* 393.2 (M+1).

**487**

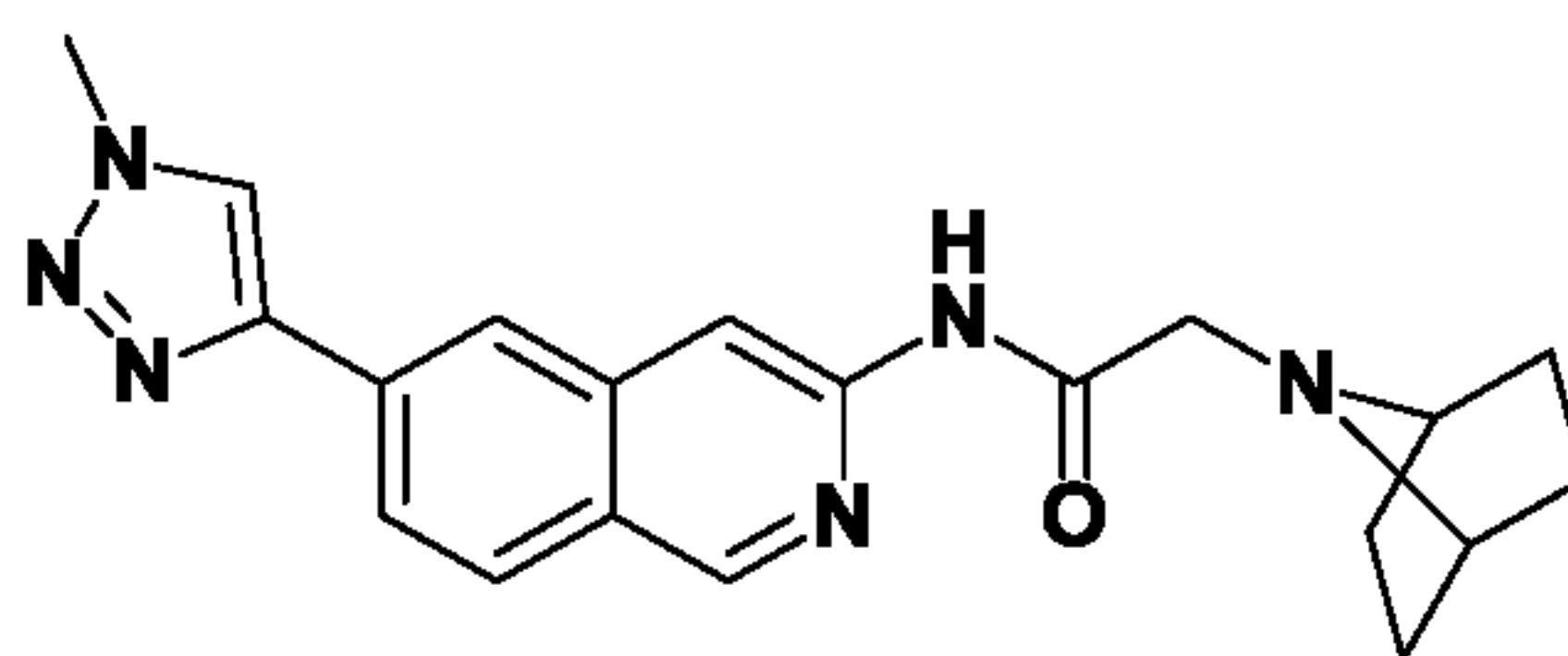
[0948] N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **487**.

[0949] Off-white solid (18.2 mg, 0.054 mmol, 16.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.78 (4 H, dt, *J*=6.52, 3.19 Hz), 2.62 - 2.70 (4 H, m), 3.36 (2 H, s), 4.14 (3 H, s), 8.04 (1 H, dd, *J*=8.51, 1.37 Hz), 8.13 (1 H, d, *J*=8.51 Hz), 8.34 (1 H, s), 8.50 (1 H, s), 8.74 (1 H, s), 9.12 (1 H, s), 9.98 (1 H, s); ESIMS found for C₁₈H₂₀N₆O *m/z* 337.15 (M+1).

**500**

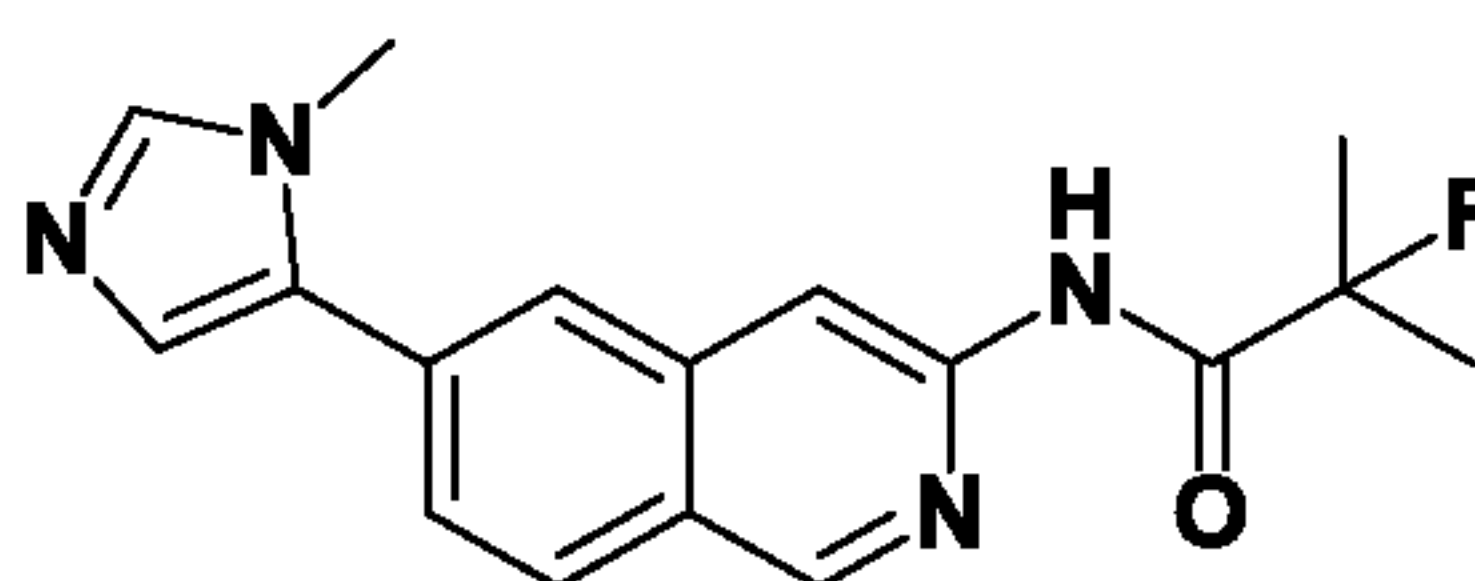
[0950] N-(6-(1-Methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **500**.

[0951] Beige solid (5.0 mg, 0.014 mmol, 4.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.19 (3 H, s), 2.34 - 2.46 (4 H, m), 2.58 (4 H, br s), 3.23 (2 H, s), 4.14 (3 H, s), 8.04 (1 H, dd, *J*=8.51, 1.65 Hz), 8.14 (1 H, d, *J*=8.51 Hz), 8.34 (1 H, s), 8.50 (1 H, s), 8.74 (1 H, s), 9.13 (1 H, s), 10.00 (1 H, s); ESIMS found for C₁₉H₂₃N₇O *m/z* 366.2 (M+1).

**513**

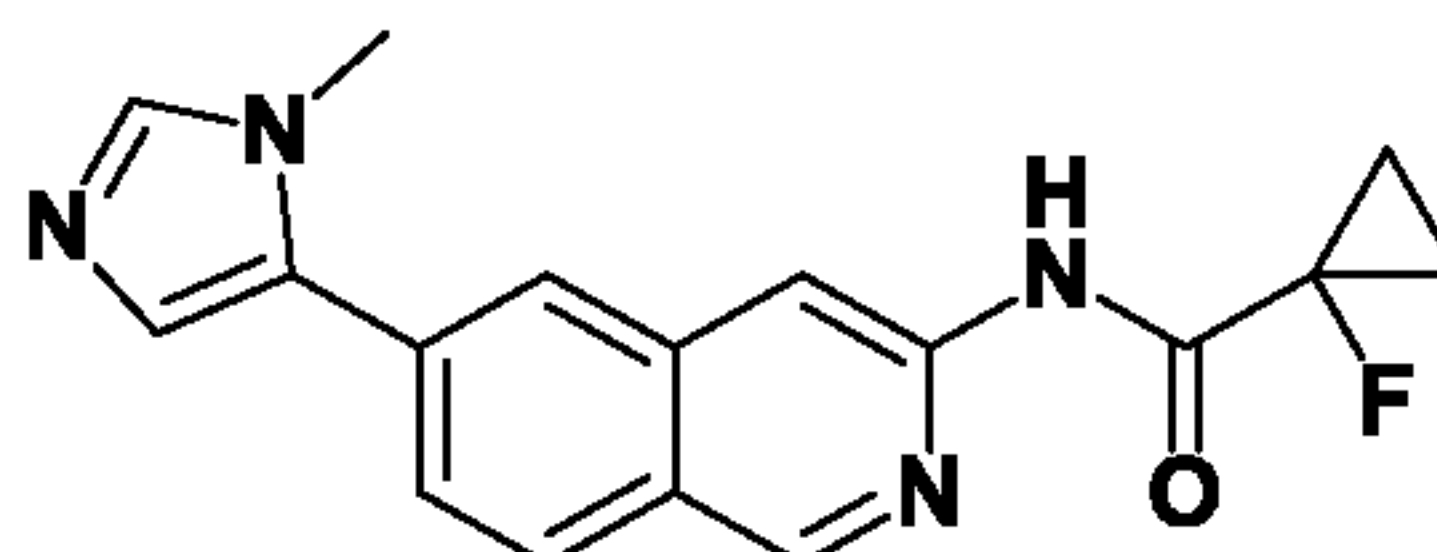
[0952] 2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide **513**.

[0953] White solid (12.2 mg, 0.034 mmol, 17.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.34 (4 H, br d, *J*=7.14 Hz), 1.75 (4 H, br d, *J*=6.86 Hz), 3.20 (2 H, s), 3.37 (2 H, br s), 4.14 (3 H, s), 8.05 (1 H, dd, *J*=8.51, 1.37 Hz), 8.14 (1 H, d, *J*=8.51 Hz), 8.35 (1 H, s), 8.52 (1 H, s), 8.74 (1 H, s), 9.12 (1 H, s), 10.14 (1 H, s); ESIMS found for C₂₀H₂₂N₆O *m/z* 363.2 (M+1).

**517**

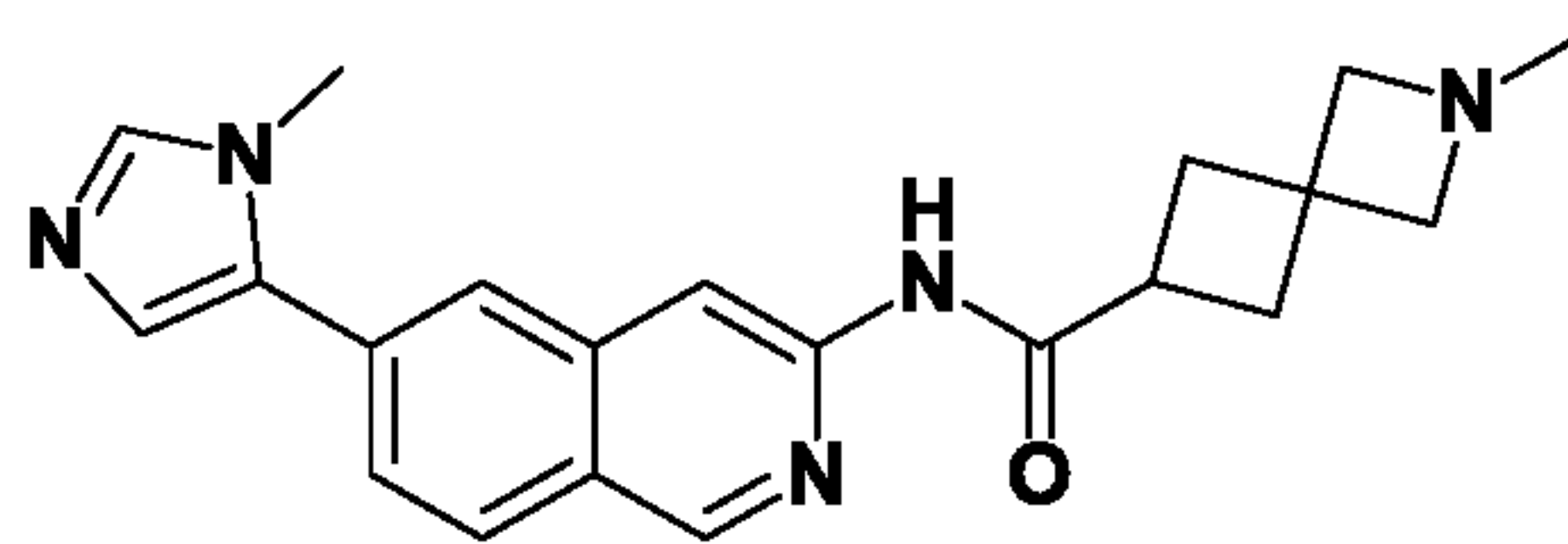
[0954] 2-Fluoro-2-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)propanamide **517**.

[0955] Off-white solid (70.0 mg, 0.224 mmol, 50.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.64 (6 H, d, *J*=21.70 Hz), 3.83 (3 H, s), 7.32 (1 H, d, *J*=1.10 Hz), 7.73 (1 H, dd, *J*=8.51, 1.65 Hz), 7.79 (1 H, s), 8.07 (1 H, s), 8.14 (1 H, d, *J*=8.51 Hz), 8.49 (1 H, s), 9.18 (1 H, s), 9.85 (1 H, br d, *J*=3.57 Hz); ESIMS found for C₁₇H₁₇FN₄O *m/z* 313.0 (M+1).

**521**

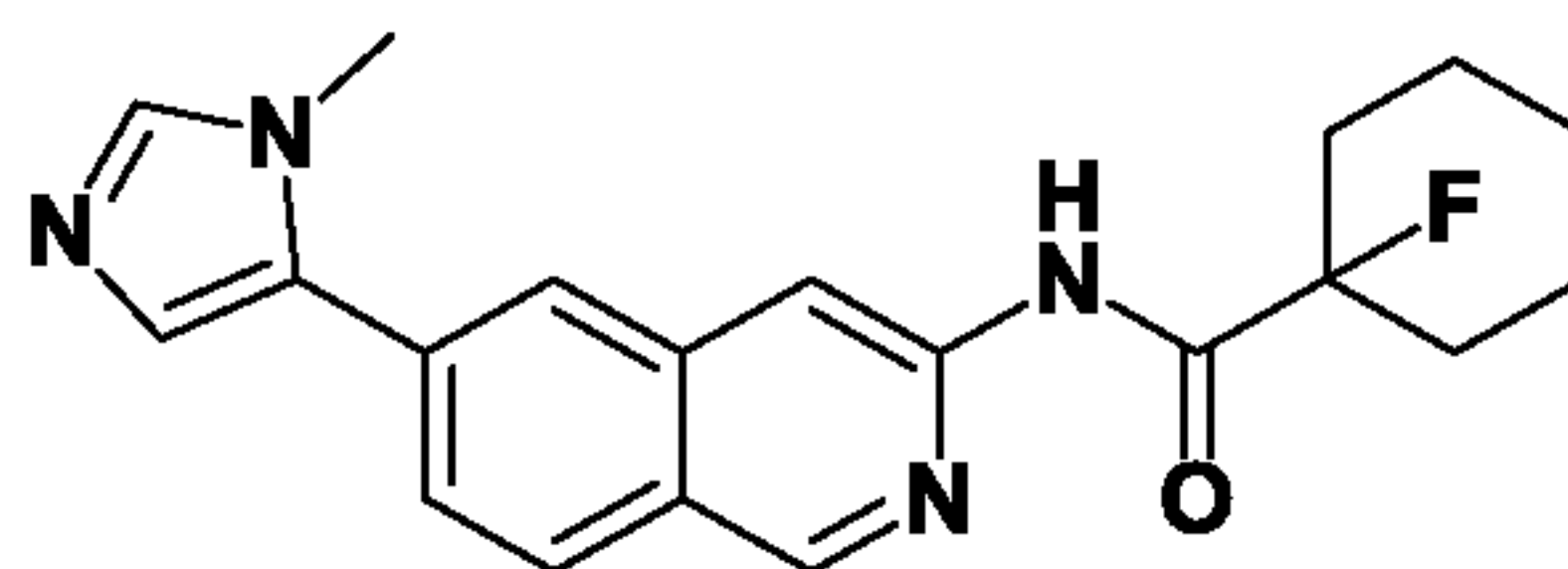
[0956] 1-Fluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide **521**.

[0957] White solid (100.0 mg, 0.306 mmol, 63.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.34 - 1.42 (2 H, m), 1.42 - 1.52 (2 H, m), 3.83 (3 H, s), 7.38 (1 H, br s), 7.73 (1 H, br d, *J*=8.51 Hz), 7.86 (1 H, br s), 8.06 (1 H, s), 8.14 (1 H, d, *J*=8.51 Hz), 8.47 (1 H, s), 9.19 (1 H, s), 10.29 (1 H, s); ESIMS found for C₁₇H₁₅FN₄O *m/z* 311.1 (M+1).

**523**

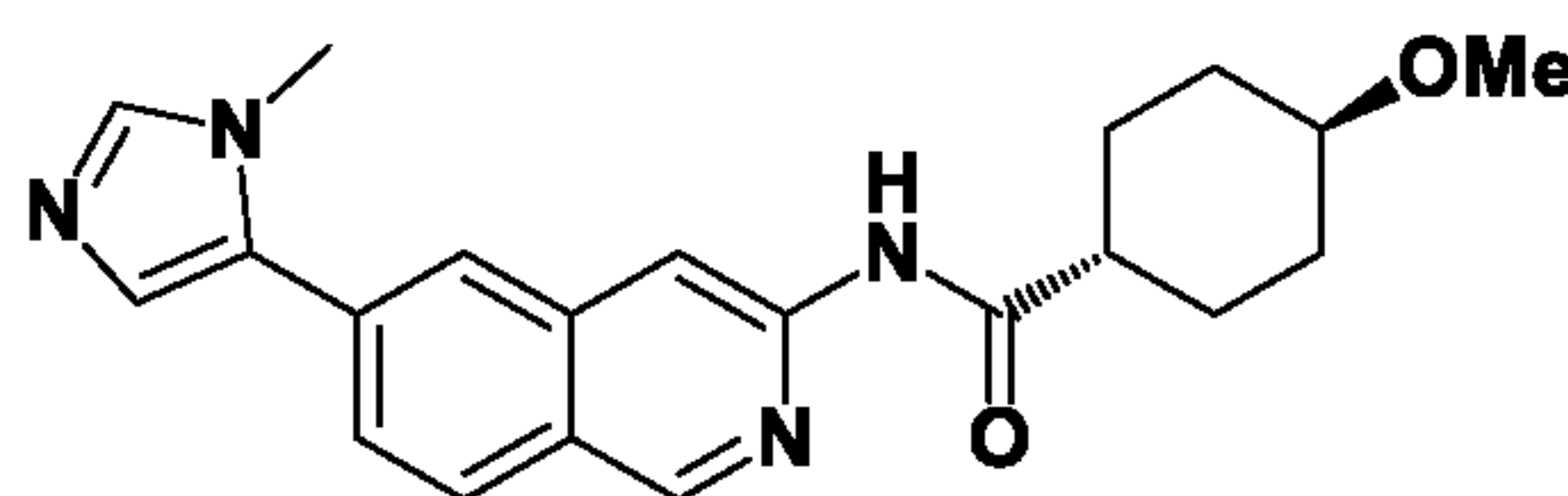
[0958] 2-Methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide **523**.

[0959] White solid (5.0 mg, 0.014 mmol, 7.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.15 (3 H, s), 2.22 - 2.36 (4 H, m), 3.04 (2 H, s), 3.14 (2 H, s), 3.22 - 3.29 (1 H, m), 3.83 (3 H, s), 7.30 (1 H, d, *J*=1.10 Hz), 7.66 (1 H, dd, *J*=8.51, 1.65 Hz), 7.79 (1 H, s), 8.00 (1 H, s), 8.08 (1 H, d, *J*=8.51 Hz), 8.54 (1 H, s), 9.11 (1 H, s), 10.42 (1 H, s); ESIMS found for C₂₁H₂₃N₅O *m/z* 362.2 (M+1).

**527**

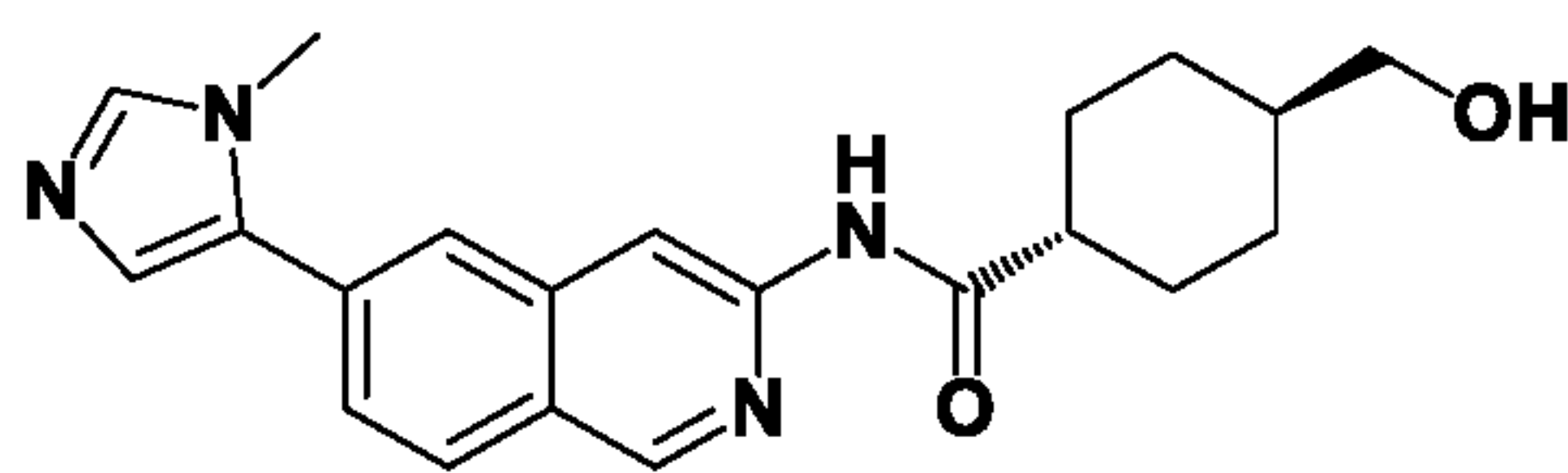
[0960] 1-Fluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **527**.

[0961] White solid (16.0 mg, 0.043 mmol, 10.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.30 - 1.42 (1 H, m), 1.50 - 1.63 (2 H, m), 1.68 (3 H, br d, *J*=9.61 Hz), 1.85 - 2.02 (4 H, m), 3.84 (3 H, s), 7.32 (1 H, d, *J*=1.10 Hz), 7.73 (1 H, dd, *J*=8.51, 1.92 Hz), 7.80 (1 H, s), 8.07 (1 H, s), 8.13 (1 H, d, *J*=8.51 Hz), 8.50 (1 H, s), 9.17 (1 H, s), 9.83 (1 H, d, *J*=4.12 Hz); ESIMS found for C₂₀H₂₁FN₄O *m/z* 353.15 (M+1).

**528**

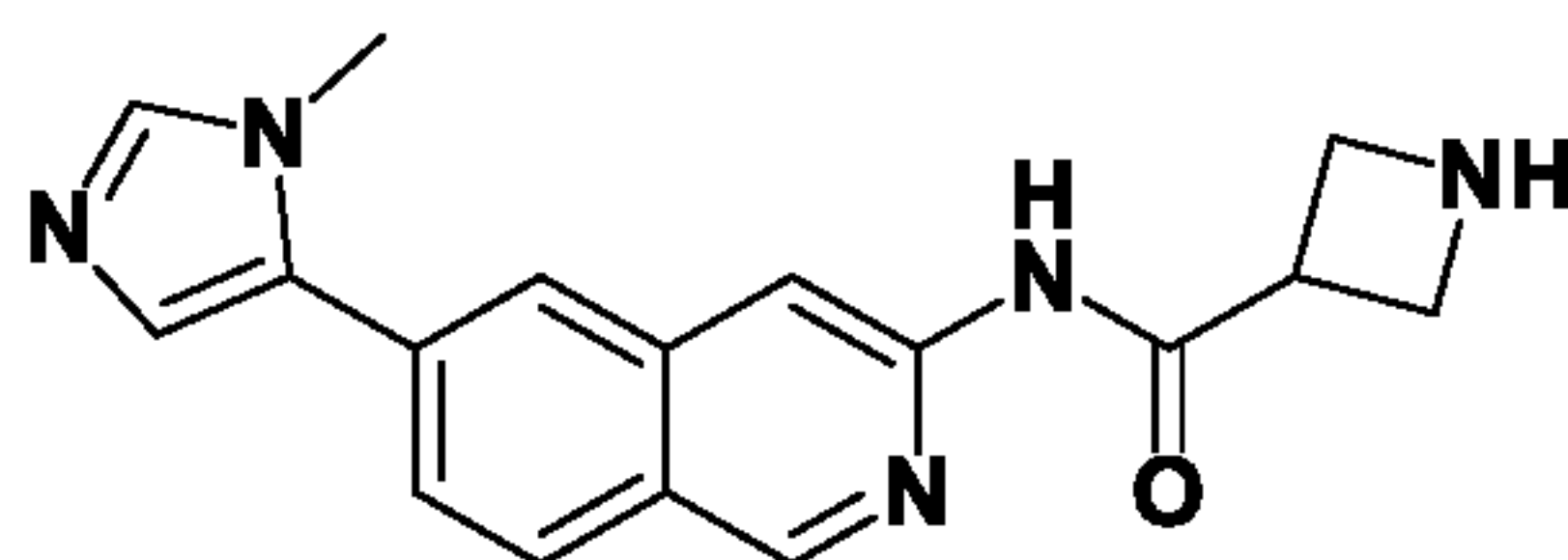
[0962] *trans*-4-Methoxy-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **528**.

[0963] White solid (96.6 mg, 0.265 mmol, 39.6% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.06 - 1.18 (2 H, m), 1.44 - 1.56 (2 H, m), 1.86 - 1.95 (2 H, m), 2.04 - 2.12 (2 H, m), 2.52 - 2.58 (1 H, m), 3.07 - 3.16 (1 H, m), 3.25 (3 H, s), 3.82 (3 H, s), 7.30 (1 H, s), 7.66 (1 H, dd, *J*=8.51, 1.65 Hz), 7.79 (1 H, s), 7.99 (1 H, s), 8.08 (1 H, d, *J*=8.51 Hz), 8.52 (1 H, s), 9.12 (1 H, s), 10.50 (1 H, s); ESIMS found for C₂₁H₂₄N₄O₂ *m/z* 365.2 (M+1).

**531**

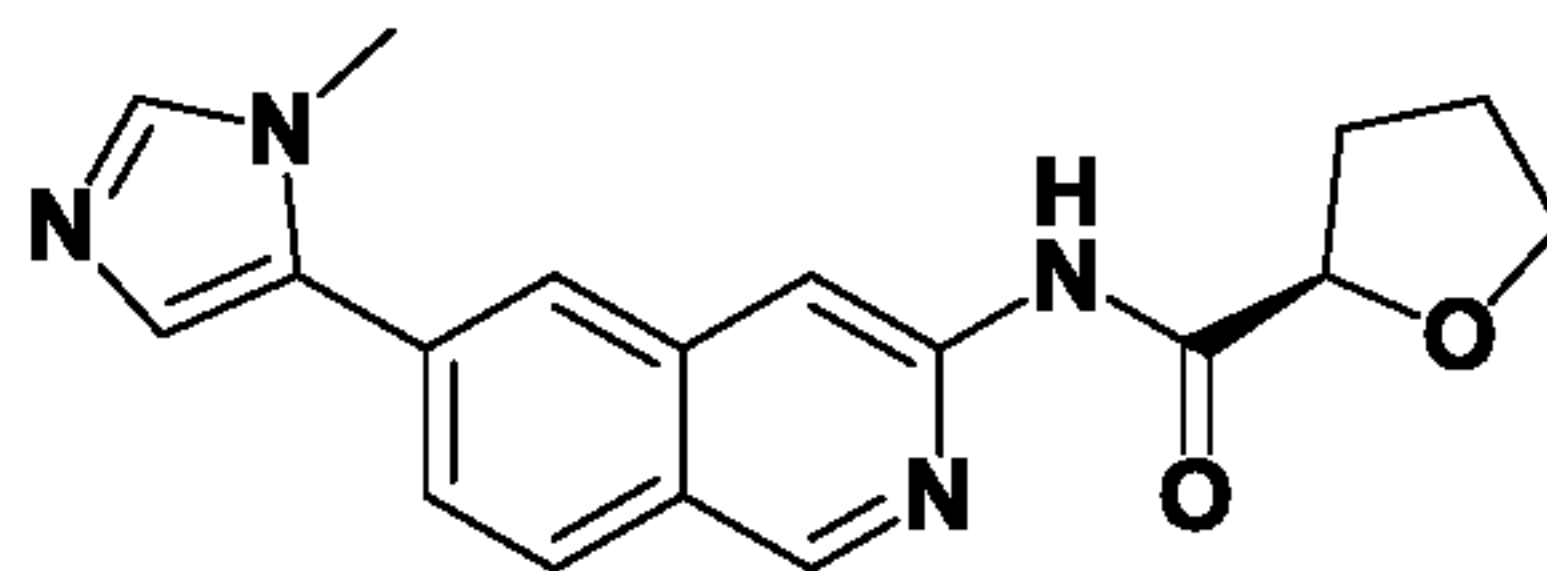
[0964] *trans*-4-(Hydroxymethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **531**.

[0965] Off-white solid (17.0 mg, 0.047 mmol, 7.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.95 (2 H, qd, *J*=12.81, 3.29 Hz), 1.36 (1 H, dtt, *J*=14.75, 5.90, 5.90, 3.05, 3.05 Hz), 1.45 (2 H, qd, *J*=12.76, 3.16 Hz), 1.80 (2 H, br dd, *J*=13.04, 2.61 Hz), 1.84 - 1.93 (2 H, m), 2.51 - 2.54 (1 H, m), 3.24 (2 H, t, *J*=5.76 Hz), 3.82 (3 H, s), 4.38 (1 H, t, *J*=5.35 Hz), 7.30 (1 H, d, *J*=1.10 Hz), 7.66 (1 H, dd, *J*=8.51, 1.65 Hz), 7.79 (1 H, s), 7.98 (1 H, d, *J*=0.82 Hz), 8.08 (1 H, d, *J*=8.51 Hz), 8.53 (1 H, s), 9.12 (1 H, s), 10.47 (1 H, s); ESIMS found for C₂₁H₂₄N₄O₂ *m/z* 365.2 (M+1).

**535**

[0966] N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide **535**.

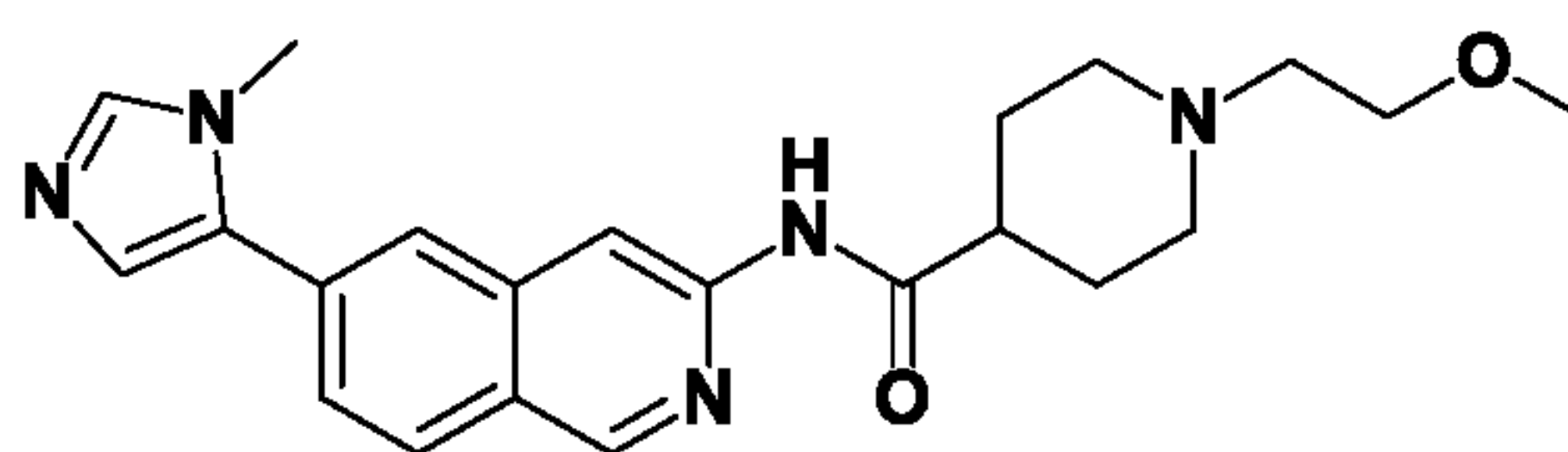
[0967] Orange solid (4.0 mg, 0.013 mmol, 3.5% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.23 - 3.32 (1 H, m), 3.70 - 3.78 (2 H, m), 3.83 (3 H, s), 3.90 - 3.98 (2 H, m), 7.31 (1 H, d, *J*=1.10 Hz), 7.69 (1 H, dd, *J*=8.51, 1.65 Hz), 7.80 (1 H, s), 8.03 (1 H, s), 8.10 (1 H, d, *J*=8.51 Hz), 8.57 (1 H, s), 9.13 (1 H, s), 10.65 (1 H, br s) ESIMS found for C₁₇H₁₇N₅O *m/z* 308.15 (M+1).

**537**

[0968] (R)-N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide **537**.

[0969] Off-white solid (100.0 mg, 0.310 mmol, 69.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.84 - 1.97 (2 H, m), 1.98 - 2.08 (1 H, m), 2.20 - 2.31 (1 H, m), 3.83 (3 H, s), 3.84 - 3.90 (1 H, m), 4.00 - 4.07 (1 H, m), 4.54 (1 H, dd, *J*=8.23, 5.76 Hz), 7.31 (1 H, d, *J*=0.82

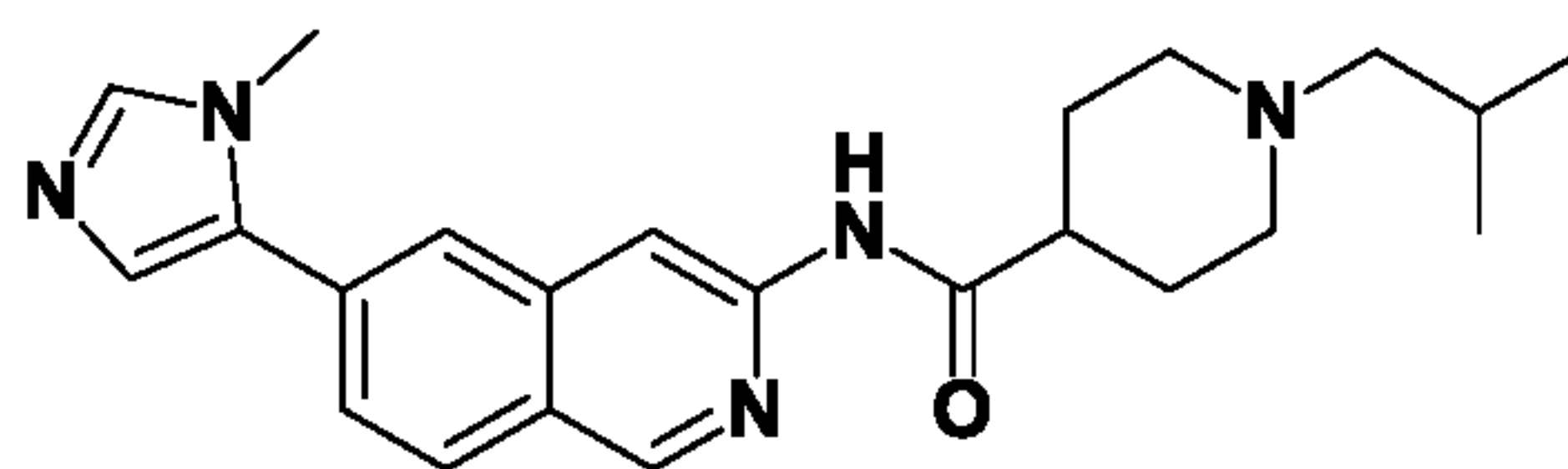
Hz), 7.70 (1 H, dd, $J=8.51$, 1.65 Hz), 7.79 (1 H, s), 8.05 (1 H, s), 8.11 (1 H, d, $J=8.51$ Hz), 8.52 (1 H, s), 9.14 (1 H, s), 9.79 (1 H, s); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.0 (M+1).



547

[0970] 1-(2-Methoxyethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **547**.

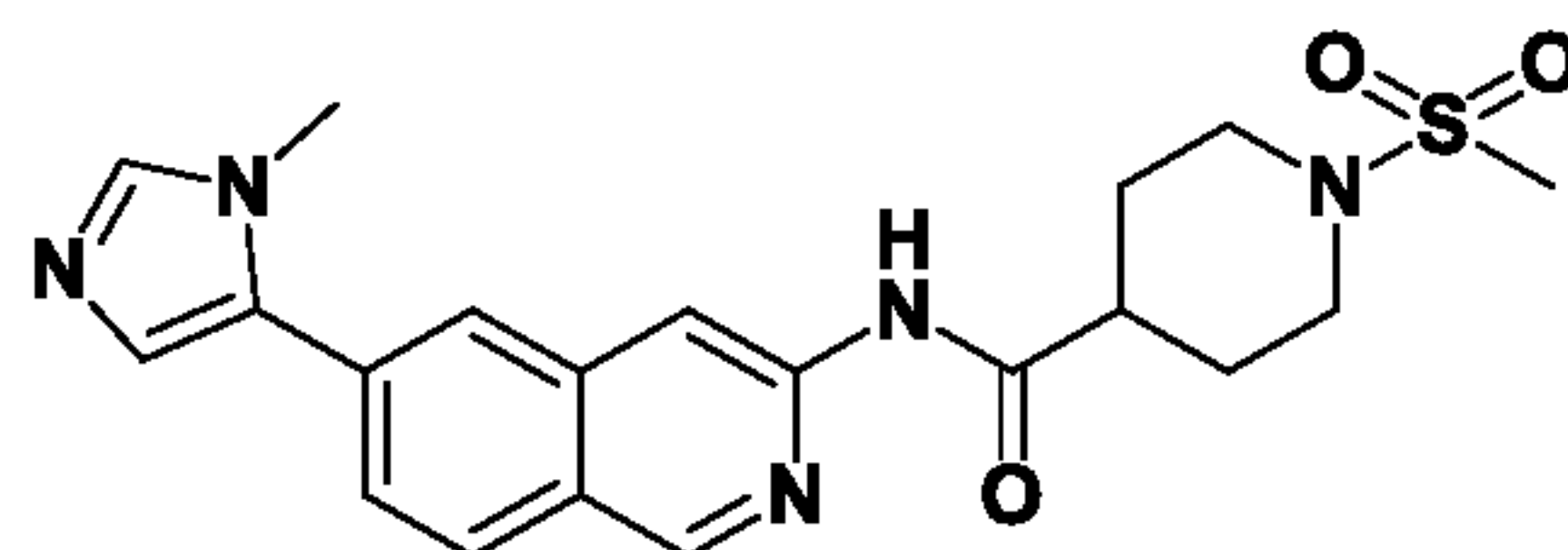
[0971] Yellow-white solid (5.0 mg, 0.013 mmol, 8.5% yield). ^1H NMR (499 MHz, METHANOL- d_4) δ ppm 1.88 - 1.98 (4 H, m), 2.25 (2 H, dt, $J=11.05$, 7.51 Hz), 2.56 (1 H, dt, $J=15.51$, 7.62 Hz), 2.66 (2 H, t, $J=5.63$ Hz), 3.12 (2 H, br d, $J=11.80$ Hz), 3.36 (3 H, s), 3.57 (2 H, t, $J=5.63$ Hz), 3.85 (3 H, s), 7.28 (1 H, s), 7.64 (1 H, dd, $J=8.51$, 1.65 Hz), 7.85 (1 H, s), 7.94 (1 H, s), 8.07 (1 H, d, $J=8.51$ Hz), 8.51 (1 H, s), 9.06 (1 H, s); ESIMS found for $C_{22}H_{27}N_5O_2$ m/z 394.2 (M+1).



554

[0972] 1-Isobutyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **554**.

[0973] White solid (50.0 mg, 0.121 mmol, 31.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.85 (6 H, d, $J=6.59$ Hz), 1.60 - 1.73 (2 H, m), 1.74 - 1.81 (3 H, m), 1.83 - 1.91 (2 H, m), 2.02 (2 H, d, $J=7.41$ Hz), 2.52 - 2.60 (1 H, m), 2.86 (2 H, br d, $J=11.25$ Hz), 3.83 (3 H, s), 7.30 (1 H, d, $J=1.10$ Hz), 7.66 (1 H, dd, $J=8.51$, 1.65 Hz), 7.79 (1 H, s), 8.00 (1 H, s), 8.08 (1 H, d, $J=8.78$ Hz), 8.54 (1 H, s), 9.12 (1 H, s), 10.52 (1 H, s); ESIMS found for $C_{23}H_{29}N_5O$ m/z 392.2 (M+1).

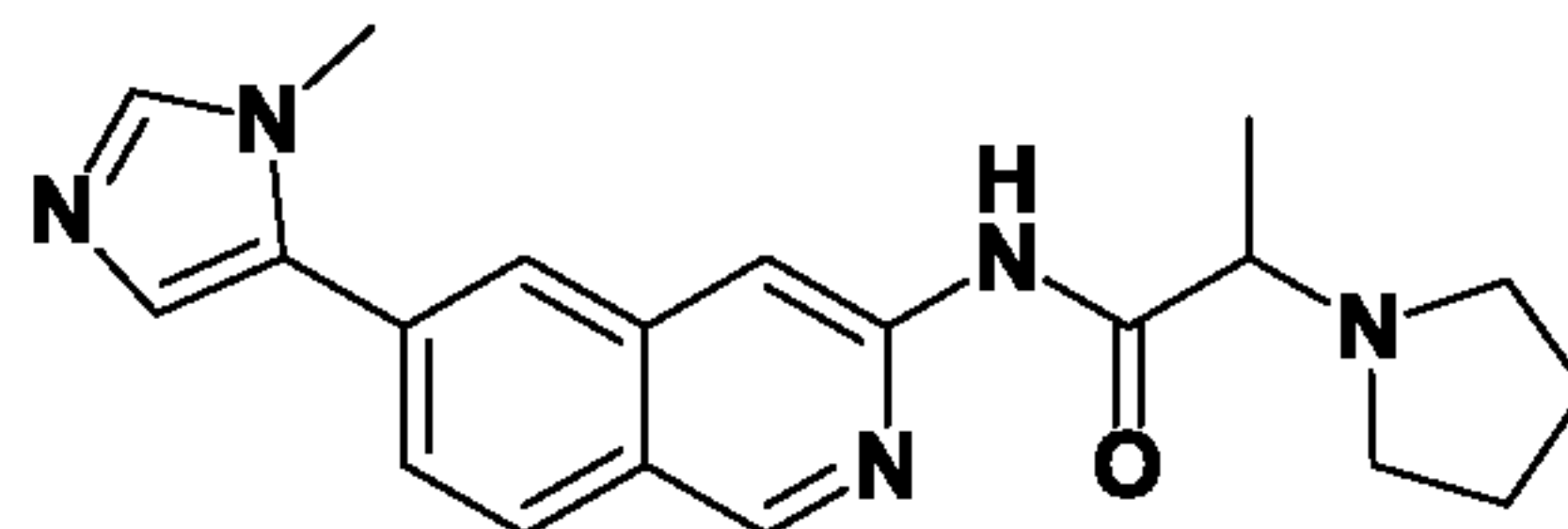


561

[0974] N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide **561**.

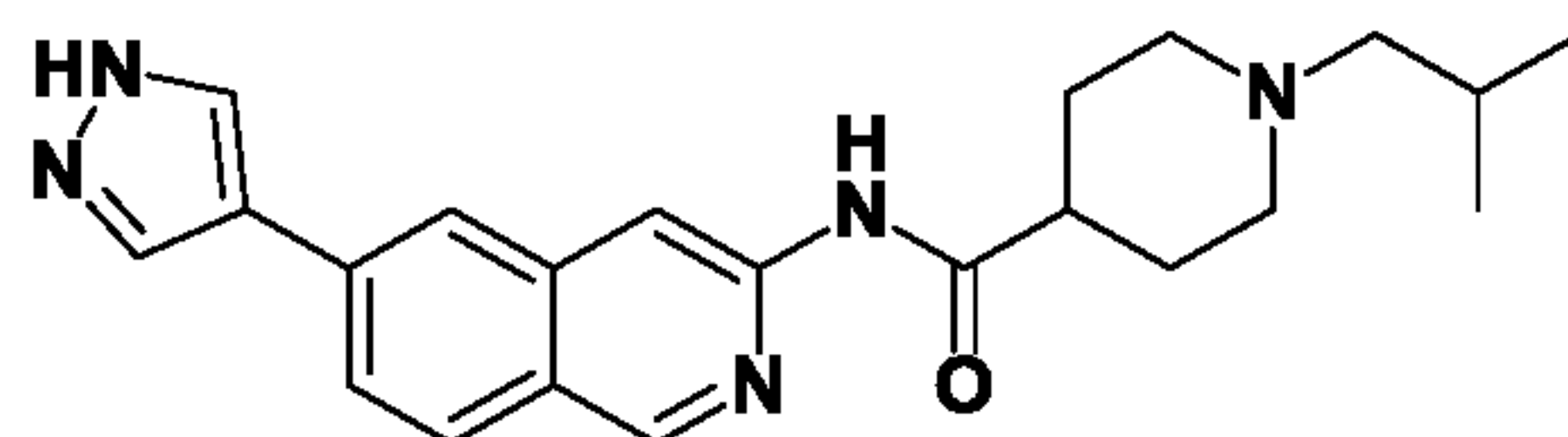
[0975] Beige solid (15.0 mg, 0.036 mmol, 21.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.64 - 1.77 (2 H, m), 1.91 - 1.98 (2 H, m), 2.65 - 2.73 (1 H, m), 2.77 (2 H, td, $J=11.94$,

2.20 Hz), 2.89 (3 H, s), 3.59 - 3.67 (2 H, m), 3.83 (3 H, s), 7.30 (1 H, d, $J=1.10$ Hz), 7.67 (1 H, dd, $J=8.64$, 1.51 Hz), 7.78 (1 H, s), 8.01 (1 H, s), 8.09 (1 H, d, $J=8.51$ Hz), 8.54 (1 H, s), 9.13 (1 H, s), 10.62 (1 H, s); ESIMS found for $C_{20}H_{23}N_5O_3S$ m/z 413.9 (M+1).

**579**

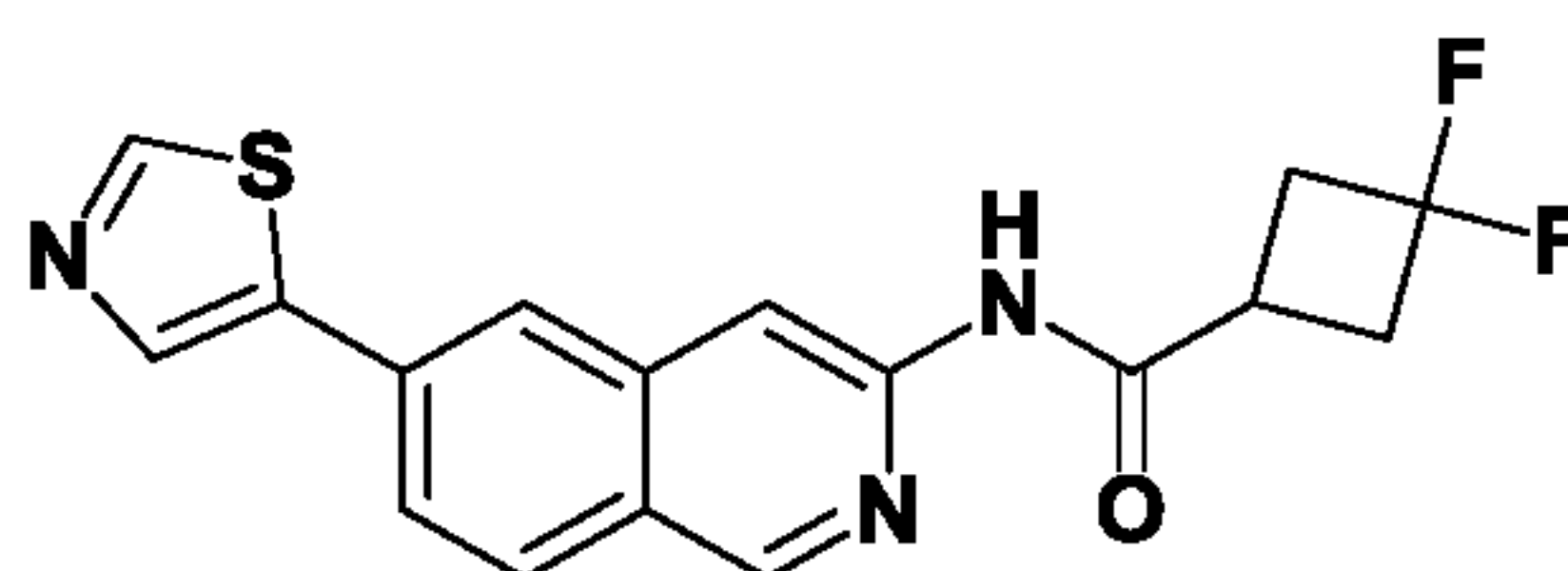
[0976] N-(6-(1-Methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide **579**.

[0977] White solid (15.0 mg, 0.043 mmol, 10.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.30 (3 H, d, $J=6.86$ Hz), 1.74 (4 H, br s), 2.56 - 2.69 (4 H, m), 3.28 - 3.31 (1 H, m), 3.83 (3 H, s), 7.31 (1 H, s), 7.69 (1 H, dd, $J=8.51$, 1.65 Hz), 7.80 (1 H, s), 8.04 (1 H, s), 8.10 (1 H, d, $J=8.51$ Hz), 8.53 (1 H, s), 9.13 (1 H, s), 10.02 (1 H, s); ESIMS found for $C_{20}H_{23}N_5O$ m/z 350.2 (M+1).

**643**

[0978] N-(6-(1H-Pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide **643**.

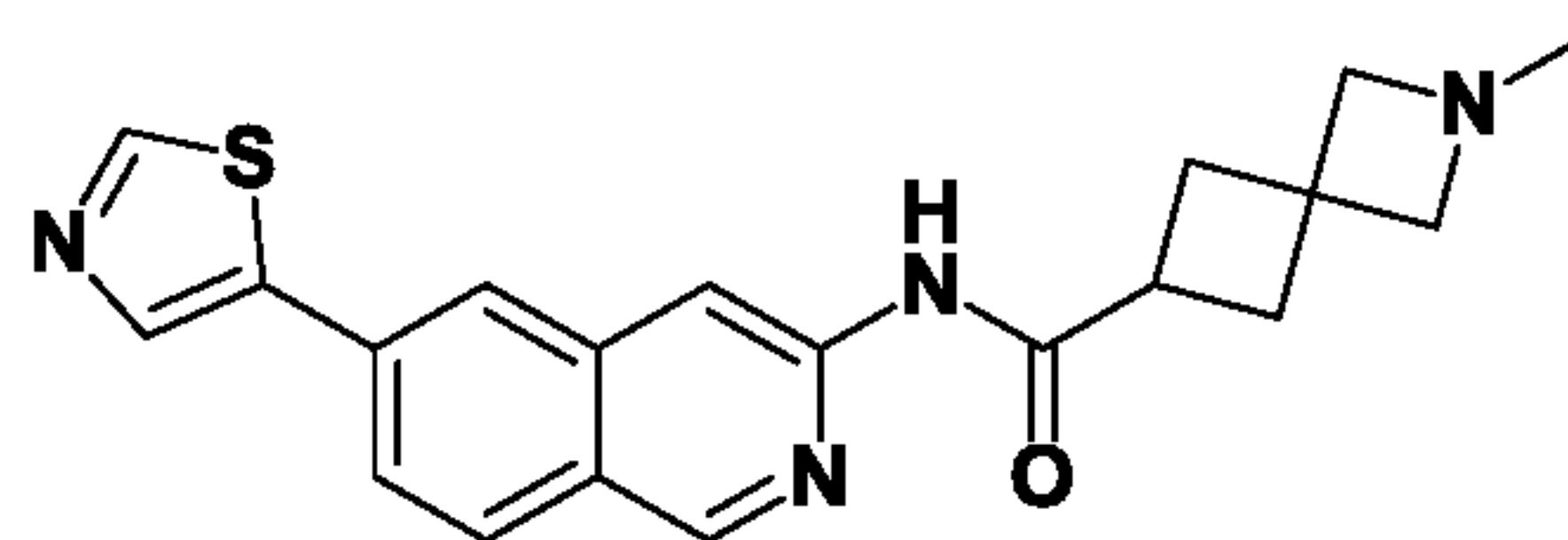
[0979] Brown solid (31.0 mg, 0.082 mmol, 32.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.86 (6 H, d, $J=6.59$ Hz), 1.62 - 1.73 (2 H, m), 1.73 - 1.80 (3 H, m), 1.82 - 1.91 (2 H, m), 2.02 (2 H, d, $J=7.41$ Hz), 2.51 - 2.59 (1 H, m), 2.86 (2 H, br d, $J=11.25$ Hz), 7.80 (1 H, dd, $J=8.64$, 1.51 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.09 (1 H, s), 8.14 (1 H, br s), 8.42 (1 H, br s), 8.45 (1 H, s), 9.02 (1 H, s), 10.44 (1 H, s), 13.09 (1 H, br s); ESIMS found for $C_{22}H_{27}N_5O$ m/z 378.2 (M+1).

**699**

[0980] 3,3-Difluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide **699**.

[0981] Beige solid (8.0 mg, 0.023 mmol, 8.5% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.75 - 2.90 (5 H, m), 7.89 (1 H, dd, $J=8.64$, 1.78 Hz), 8.12 (1 H, d, $J=8.51$ Hz), 8.24 (1

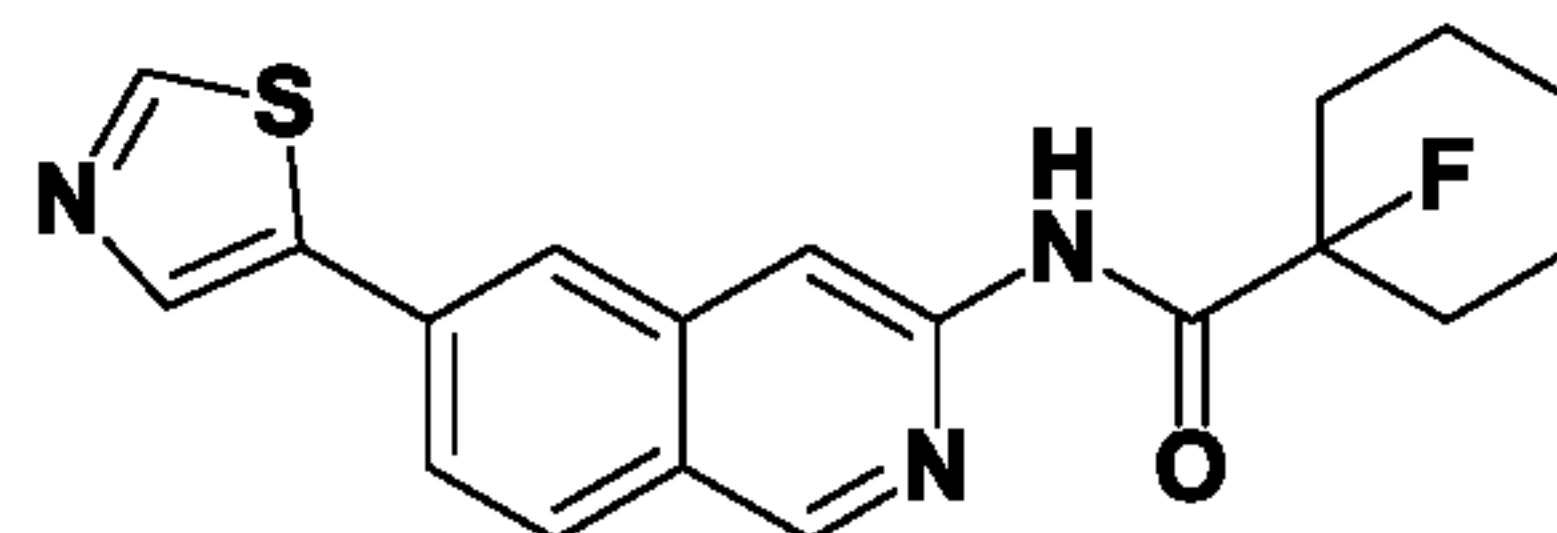
H, s), 8.56 (1 H, s), 8.57 (1 H, s), 9.14 (1 H, s), 9.20 (1 H, s), 10.82 (1 H, s); ESIMS found for $C_{17}H_{13}F_2N_3OS$ m/z 346.05 (M+1).



700

[0982] 2-Methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide **700**.

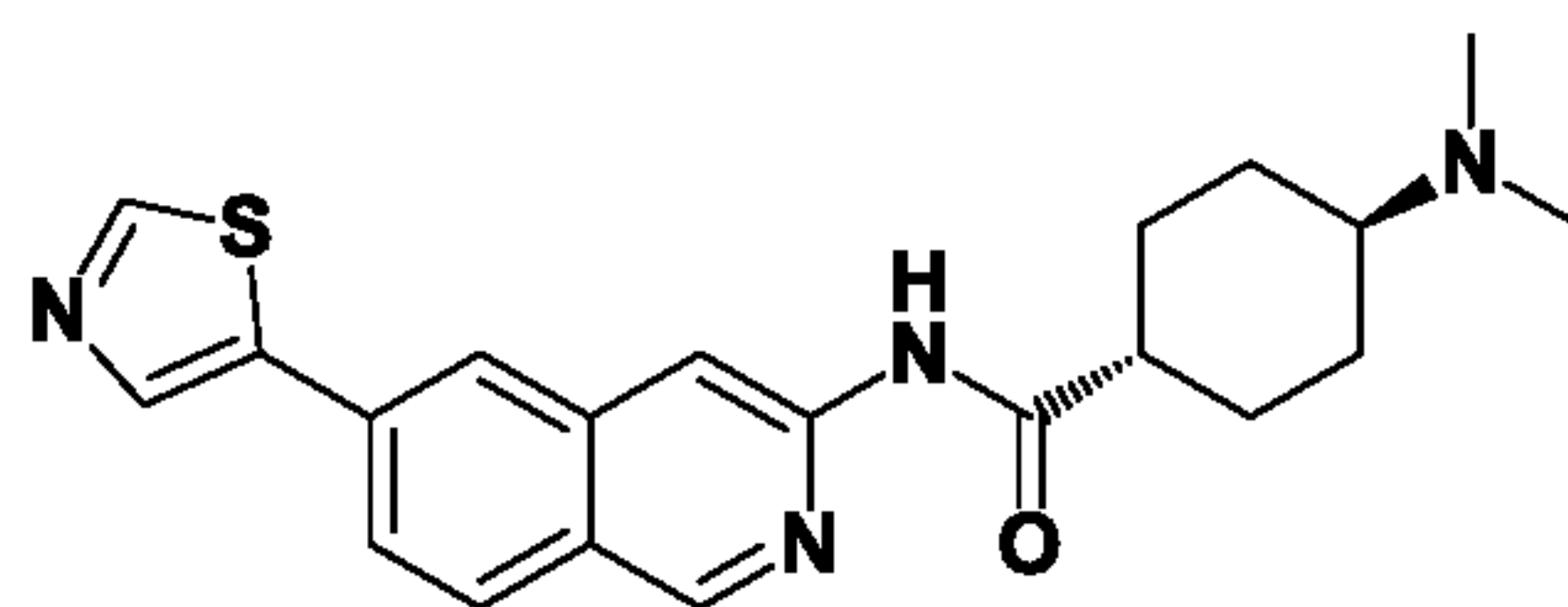
[0983] Beige solid (4.0 mg, 0.011 mmol, 12.8% yield). ^1H NMR (499 MHz, METHANOL- d_4) δ ppm 2.39 (3 H, s), 2.42 - 2.55 (4 H, m), 3.22 - 3.29 (1 H, m), 3.41 (2 H, s), 3.48 (2 H, s), 7.83 (1 H, dd, $J=8.51$, 1.65 Hz), 8.05 (1 H, d, $J=8.51$ Hz), 8.11 (1 H, d, $J=0.82$ Hz), 8.40 (1 H, s), 8.50 (1 H, s), 9.02 (1 H, s), 9.06 (1 H, s); ESIMS found for $C_{20}H_{20}N_4OS$ m/z 365.1 (M+1).



704

[0984] 1-Fluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **704**.

[0985] Light pink solid (14.0 mg, 0.039 mmol, 17.9% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.28 - 1.42 (1 H, m), 1.49 - 1.62 (2 H, m), 1.68 (3 H, br d, $J=9.61$ Hz), 1.85 - 2.02 (4 H, m), 7.93 (1 H, dd, $J=8.64$, 1.78 Hz), 8.15 (1 H, d, $J=8.78$ Hz), 8.28 (1 H, s), 8.49 (1 H, s), 8.58 (1 H, s), 9.18 (1 H, s), 9.20 (1 H, s), 9.87 (1 H, d, $J=4.12$ Hz); ESIMS found for $C_{19}H_{18}FN_3OS$ m/z 355.9 (M+1).

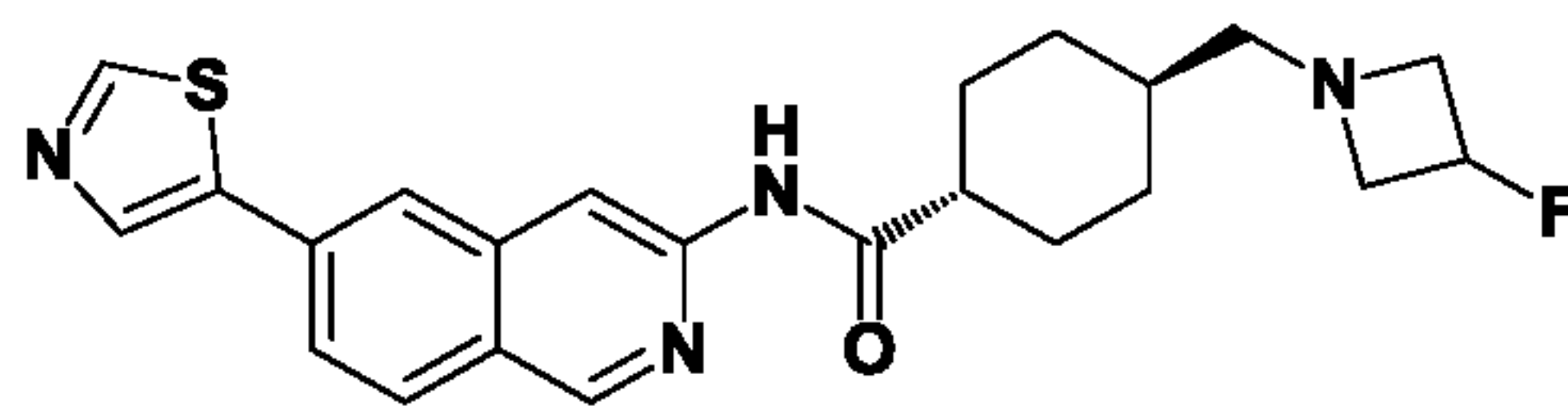


707

[0986] *trans*-4-(Dimethylamino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **707**.

[0987] White solid (48.0 mg, 0.126 mmol, 25.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.12 - 1.22 (2 H, m), 1.42 - 1.54 (2 H, m), 1.83 - 1.97 (4 H, m), 2.11 - 2.16 (1 H, m), 2.18 (6 H, s), 2.43 - 2.49 (1 H, m), 7.85 (1 H, dd, $J=8.64$, 1.51 Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.19 (1 H,

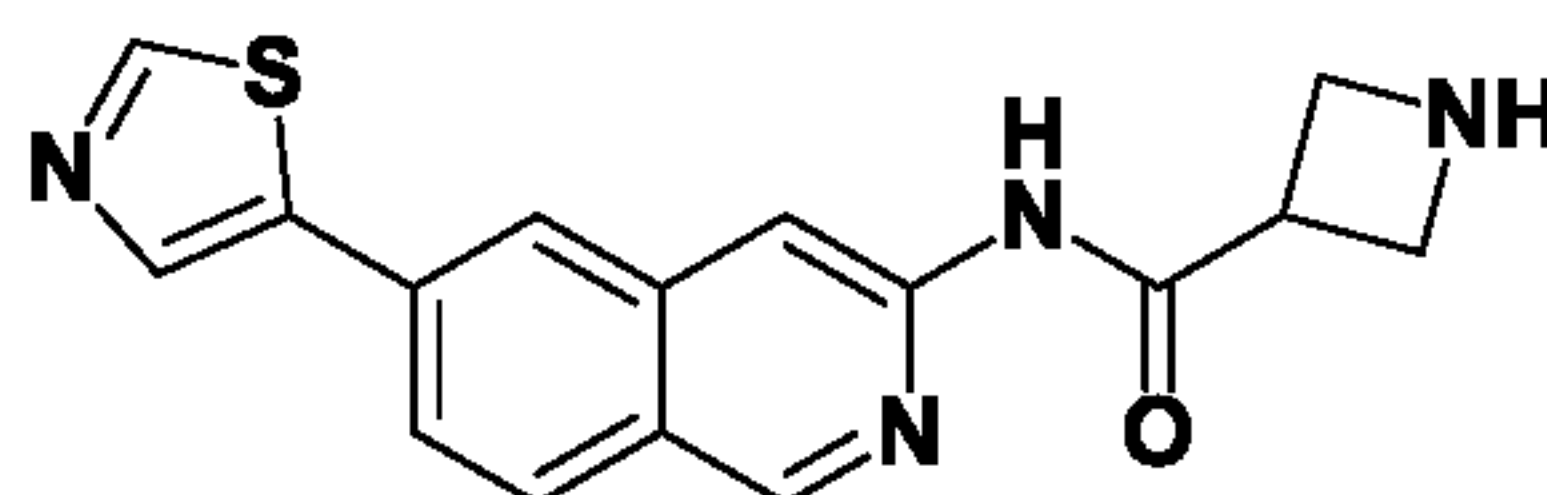
s), 8.52 (1 H, s), 8.55 (1 H, s), 9.12 (1 H, s), 9.19 (1 H, s), 10.49 (1 H, s); ESIMS found for $C_{21}H_{24}N_4OS$ m/z 381.2 (M+1).



711

[0988] *trans*-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **711**.

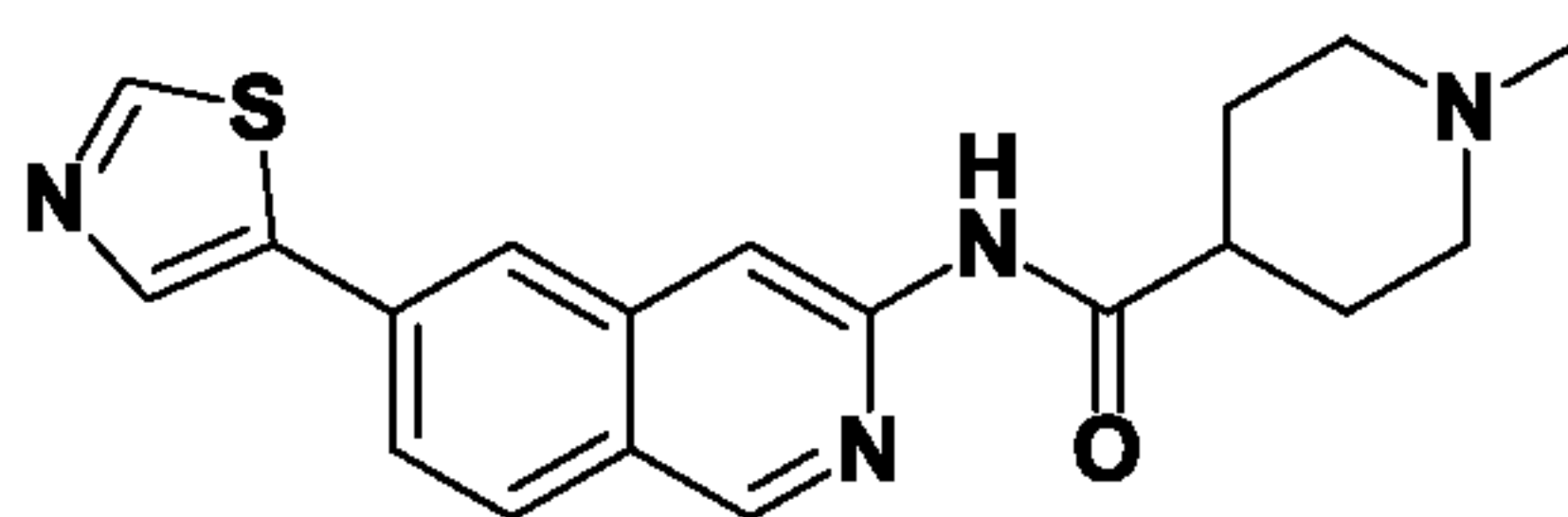
[0989] Beige solid (22.0 mg, 0.052 mmol, 21.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.84 - 0.97 (2 H, m), 1.21 - 1.33 (1 H, m), 1.44 (2 H, qd, $J=12.76$, 2.88 Hz), 1.80 (2 H, br dd, $J=12.76$, 2.33 Hz), 1.86 (2 H, br d, $J=10.70$ Hz), 2.29 (2 H, d, $J=6.86$ Hz), 2.45 - 2.49 (1 H, m), 2.97 - 3.08 (2 H, m), 3.48 - 3.60 (2 H, m), 5.12 (1 H, dq, $J=58.00$, 5.20 Hz), 7.86 (1 H, dd, $J=8.51$, 1.65 Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.19 (1 H, s), 8.52 (1 H, s), 8.56 (1 H, s), 9.12 (1 H, s), 9.19 (1 H, s), 10.49 (1 H, s); ESIMS found for $C_{23}H_{25}FN_4OS$ m/z 425.2 (M+1).



713

[0990] N-(6-(Thiazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide **713**.

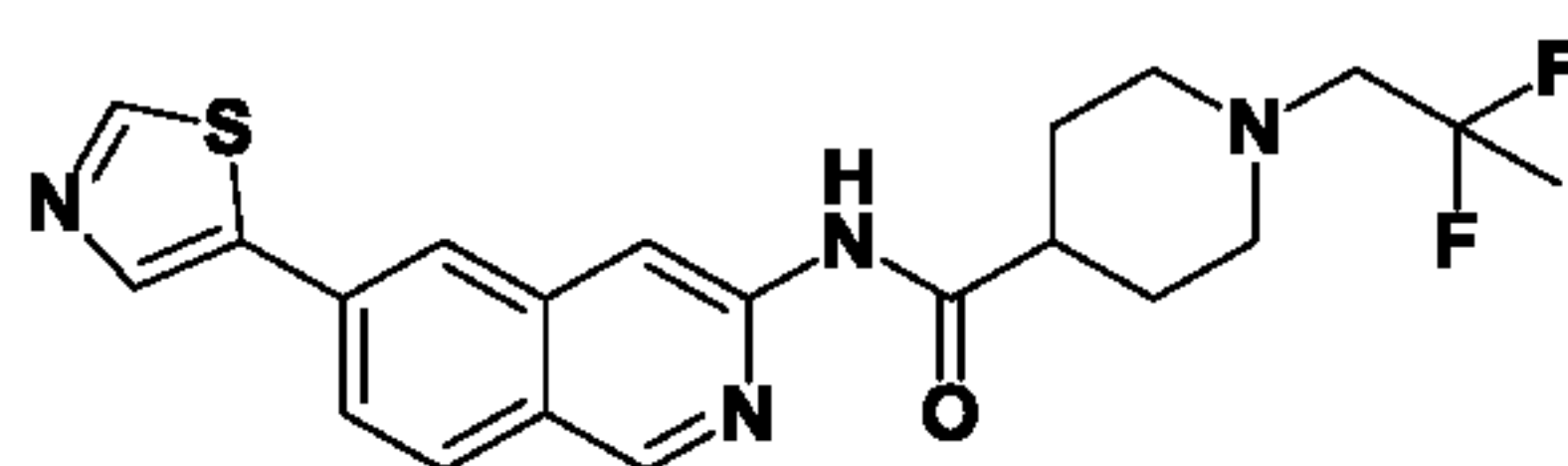
[0991] Orange solid (6.0 mg, 0.019 mmol, 8.4% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 3.70 (2 H, br t, $J=7.96$ Hz), 3.82 (1 H, dt, $J=15.09$, 7.55 Hz), 3.87 - 3.93 (2 H, m), 7.88 (1 H, dd, $J=8.51$, 1.92 Hz), 8.11 (1 H, d, $J=8.51$ Hz), 8.24 (1 H, s), 8.57 (1 H, br s), 8.57 (1 H, s), 9.13 (1 H, s), 9.20 (1 H, s), 10.65 (1 H, br s); ESIMS found for $C_{16}H_{14}N_4OS$ m/z 311.1 (M+1).



718

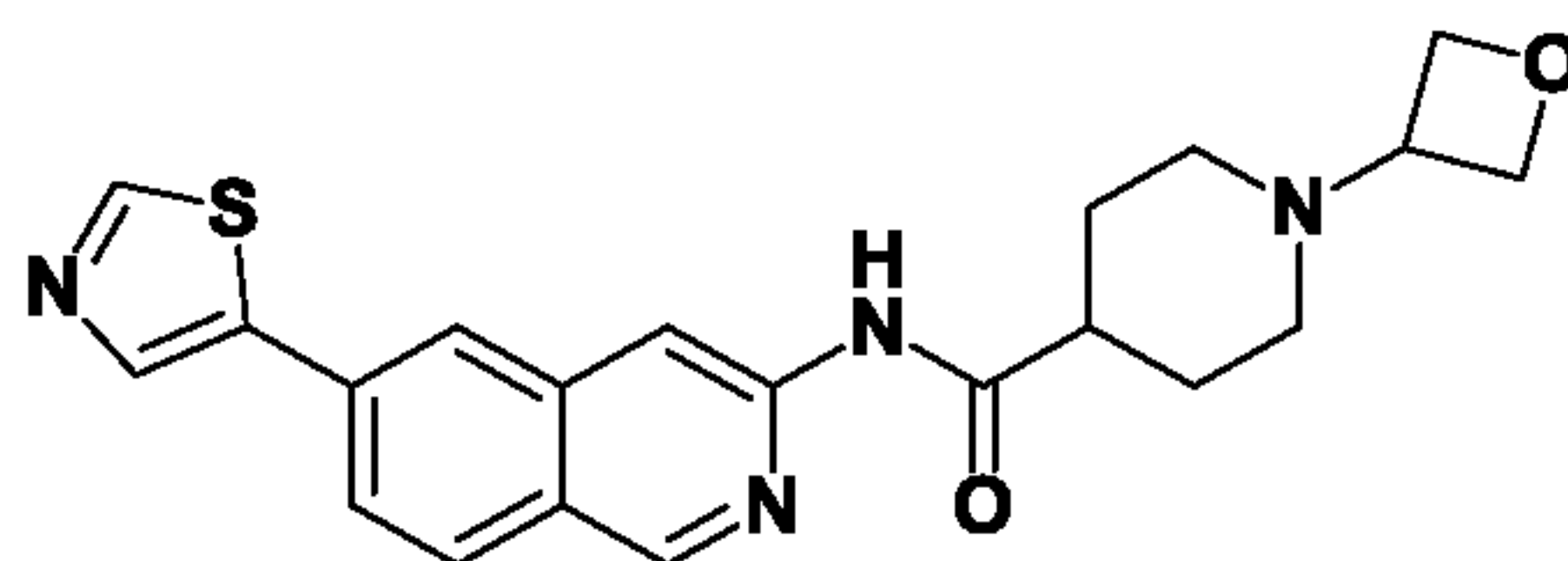
[0992] 1-Methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **718**.

[0993] Beige solid (16.0 mg, 0.045 mmol, 21.1% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.62 - 1.73 (2 H, m), 1.74 - 1.81 (2 H, m), 1.87 (2 H, td, $J=11.53$, 1.92 Hz), 2.16 (3 H, s), 2.51 - 2.56 (1 H, m), 2.81 (2 H, br d, $J=11.25$ Hz), 7.86 (1 H, dd, $J=8.64$, 1.51 Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.20 (1 H, s), 8.53 (1 H, s), 8.55 (1 H, s), 9.12 (1 H, s), 9.19 (1 H, s), 10.54 (1 H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 352.9 (M+1).

**731**

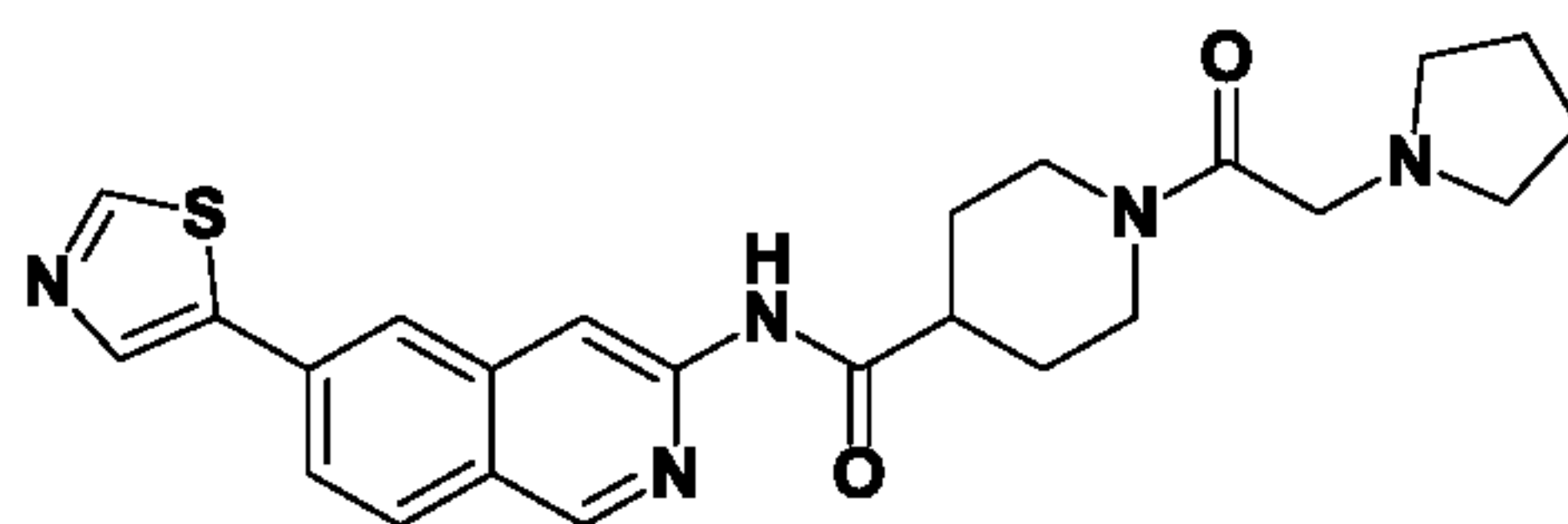
[0994] 1-(2,2-Difluoropropyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **731**.

[0995] White solid (54.3 mg, 0.131 mmol, 52.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.63 (3 H, t, *J*=19.07 Hz), 1.68 - 1.75 (2 H, m), 1.75 - 1.81 (2 H, m), 2.22 (2 H, td, *J*=11.66, 2.47 Hz), 2.51 - 2.60 (1 H, m), 2.71 (2 H, t, *J*=14.00 Hz), 2.95 (2 H, br d, *J*=11.53 Hz), 7.86 (1 H, dd, *J*=8.64, 1.78 Hz), 8.10 (1 H, d, *J*=8.78 Hz), 8.21 (1 H, d, *J*=0.82 Hz), 8.53 (1 H, s), 8.56 (1 H, s), 9.13 (1 H, s), 9.19 (1 H, s), 10.56 (1 H, s); ESIMS found for C₂₁H₂₂F₂N₄OS *m/z* 417.2 (M+1).

**737**

[0996] 1-(Oxetan-3-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **737**.

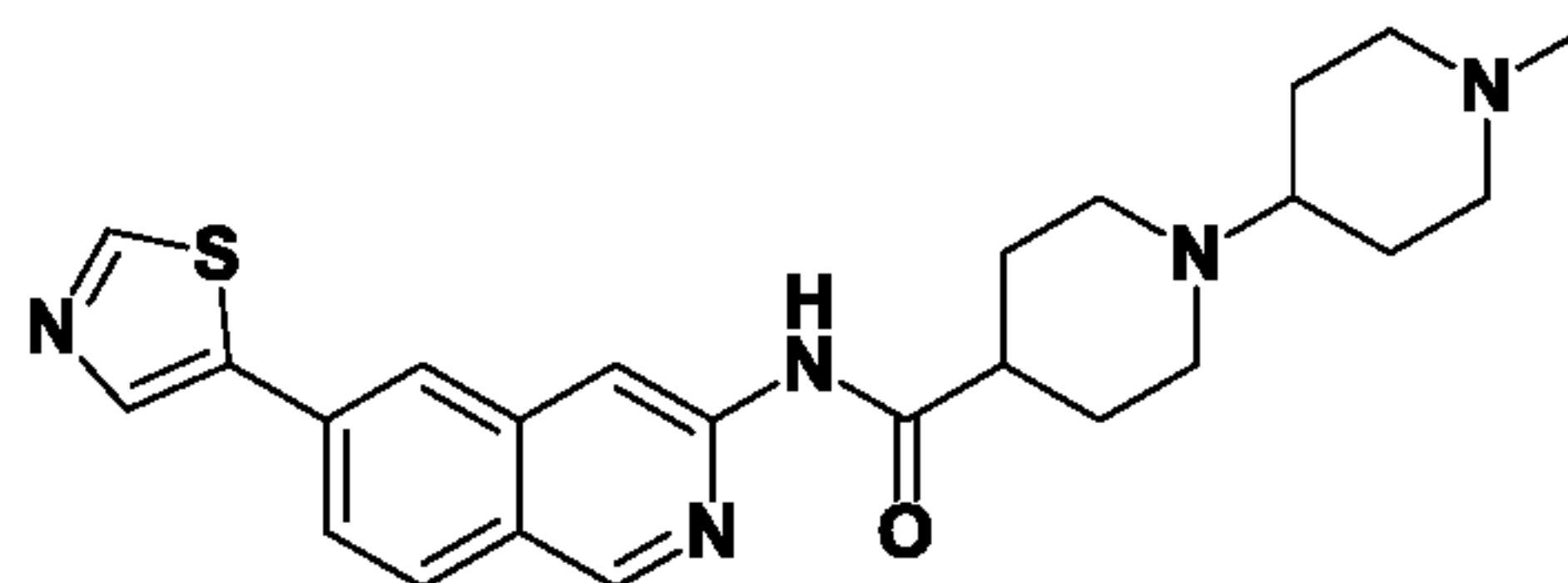
[0997] White solid (39.0 mg, 0.099 mmol, 42.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.64 - 1.73 (2 H, m), 1.75 - 1.85 (4 H, m), 2.53 - 2.61 (1 H, m), 2.71 - 2.78 (2 H, m), 3.35 - 3.41 (1 H, m), 4.43 (2 H, t, *J*=6.17 Hz), 4.53 (2 H, t, *J*=6.45 Hz), 7.86 (1 H, dd, *J*=8.51, 1.65 Hz), 8.10 (1 H, d, *J*=8.51 Hz), 8.21 (1 H, d, *J*=1.10 Hz), 8.55 (1 H, s), 8.56 (1 H, s), 9.12 (1 H, s), 9.19 (1 H, s), 10.56 (1 H, s) ESIMS found for C₂₁H₂₂N₄O₂S *m/z* 395.1 (M+1).

**741**

[0998] 1-(2-(Pyrrolidin-1-yl)acetyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **741**.

[0999] White solid (124.6 mg, 0.277 mmol, 69.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.42 - 1.55 (1 H, m), 1.57 - 1.68 (1 H, m), 1.72 (4 H, br s), 1.85 (2 H, br d, *J*=10.98 Hz), 2.55 (4 H, br s), 2.58 - 2.67 (1 H, m), 2.78 - 2.88 (1 H, m), 3.03 (1 H, br t, *J*=11.94 Hz), 3.25 - 3.30 (1 H, m), 3.44 (1 H, br d, *J*=13.17 Hz), 4.07 (1 H, br d, *J*=14.00 Hz), 4.40 (1 H, br

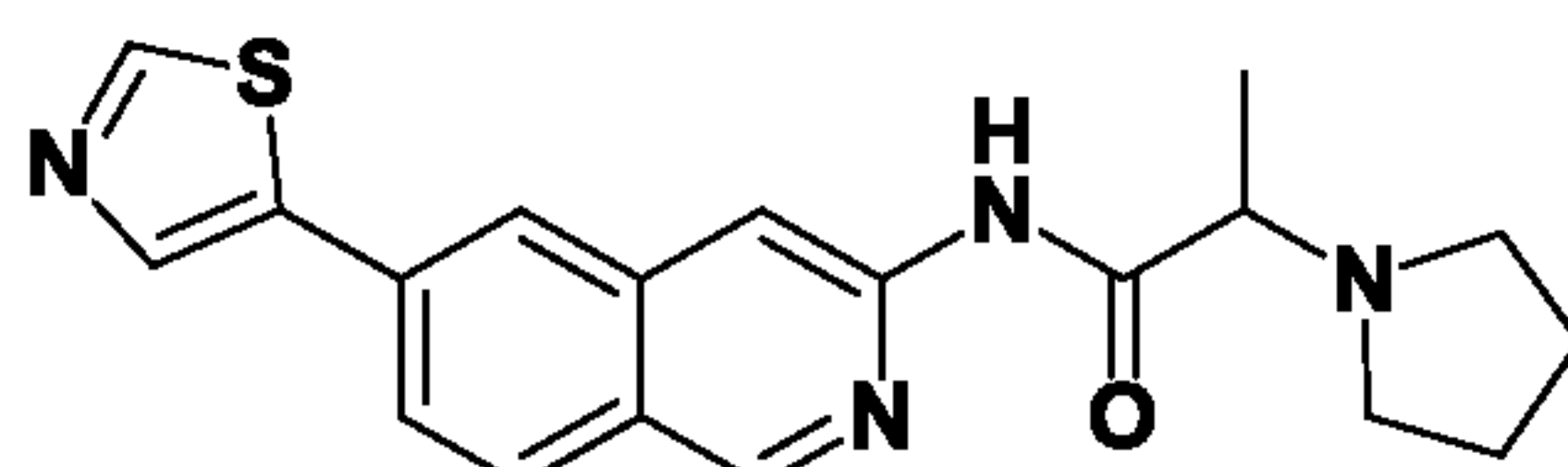
d, $J=12.62$ Hz), 7.87 (1 H, dd, $J=8.51, 1.65$ Hz), 8.11 (1 H, d, $J=8.78$ Hz), 8.21 (1 H, s), 8.53 (1 H, s), 8.56 (1 H, s), 9.13 (1 H, s), 9.19 (1 H, s), 10.64 (1 H, s); ESIMS found for $C_{24}H_{27}N_5O_2S$ m/z 449.9 (M+1).



743

[01000] 1'-Methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide **743**.

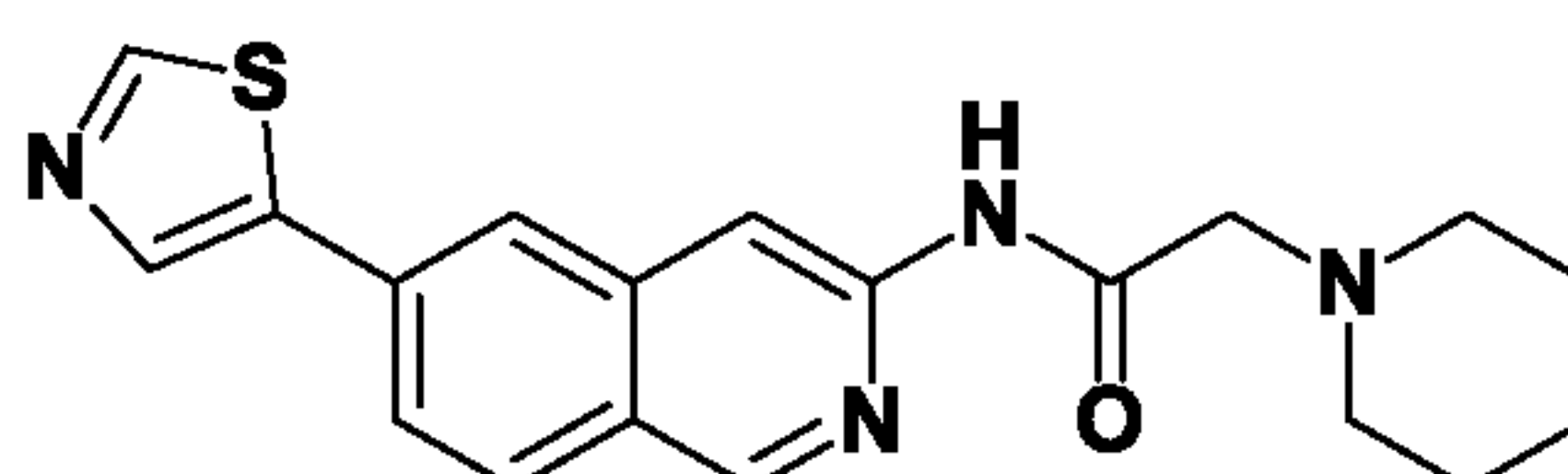
[01001] Beige solid (55.0 mg, 0.126 mmol, 36.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.43 (2 H, qd, $J=11.94, 3.70$ Hz), 1.58 - 1.71 (4 H, m), 1.75 - 1.87 (4 H, m), 2.09 - 2.20 (3 H, m), 2.12 (3 H, s), 2.51 - 2.57 (1 H, m), 2.77 (2 H, br d, $J=11.53$ Hz), 2.90 (2 H, br d, $J=11.25$ Hz), 7.86 (1 H, dd, $J=8.51, 1.65$ Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.20 (1 H, s), 8.54 (1 H, s), 8.55 (1 H, s), 9.12 (1 H, s), 9.19 (1 H, s), 10.52 (1 H, s); ESIMS found for $C_{24}H_{29}N_5OS$ m/z 436.2 (M+1).



758

[01002] 2-(Pyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)propanamide **758**.

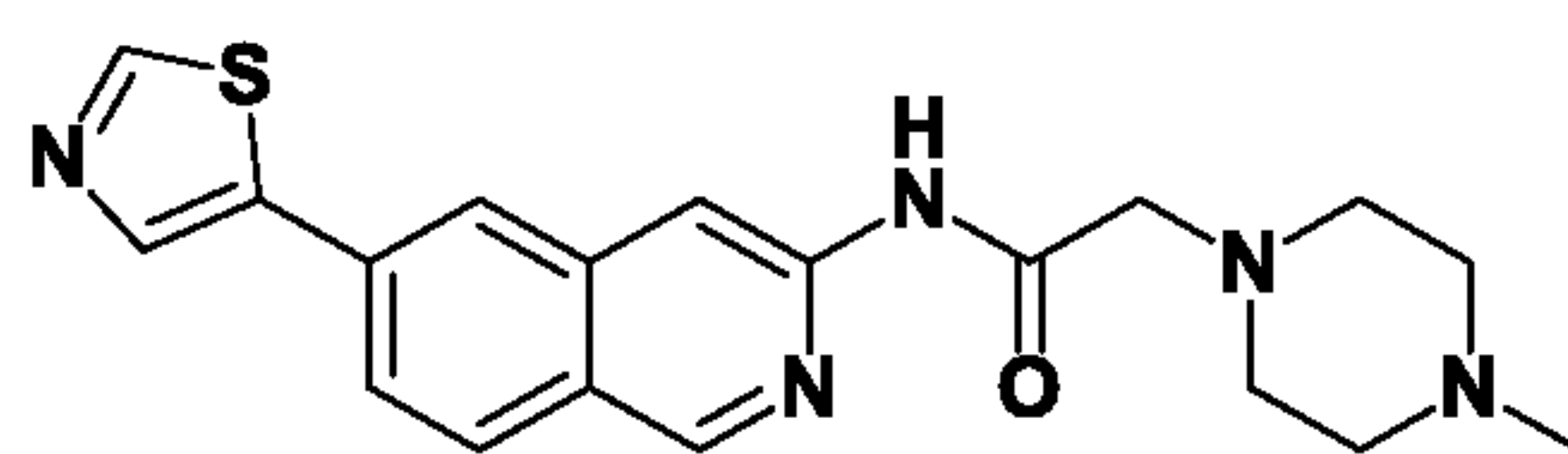
[01003] Beige solid (40.0 mg, 0.114 mmol, 26.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.30 (3 H, d, $J=6.86$ Hz), 1.74 (4 H, br s), 2.56 - 2.68 (4 H, m), 3.27 - 3.34 (1 H, m), 7.88 (1 H, dd, $J=8.64, 1.78$ Hz), 8.12 (1 H, d, $J=8.78$ Hz), 8.25 (1 H, d, $J=0.82$ Hz), 8.53 (1 H, s), 8.57 (1 H, s), 9.13 (1 H, s), 9.20 (1 H, s), 10.04 (1 H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 353.2 (M+1).



760

[01004] 2-(Piperidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide **760**.

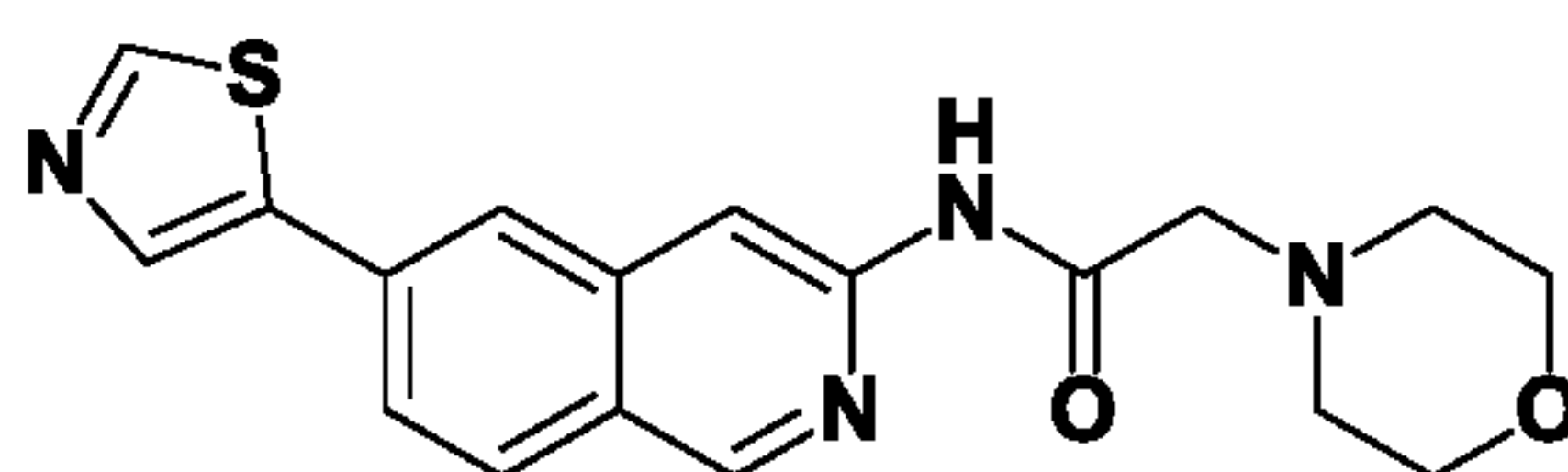
[01005] Yellow-white solid (8.0 mg, 0.023 mmol, 16.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.40 - 1.48 (2 H, m), 1.59 (4 H, dt, $J=11.05, 5.59$ Hz), 2.51 - 2.57 (4 H, m), 3.18 (2 H, s), 7.89 (1 H, dd, $J=8.51, 1.92$ Hz), 8.13 (1 H, d, $J=8.51$ Hz), 8.27 (1 H, d, $J=1.10$ Hz), 8.53 (1 H, s), 8.58 (1 H, d, $J=0.82$ Hz), 9.14 (1 H, s), 9.20 (1 H, s), 9.99 (1 H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 353.1 (M+1).



767

[01006] 2-(4-Methylpiperazin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide 767.

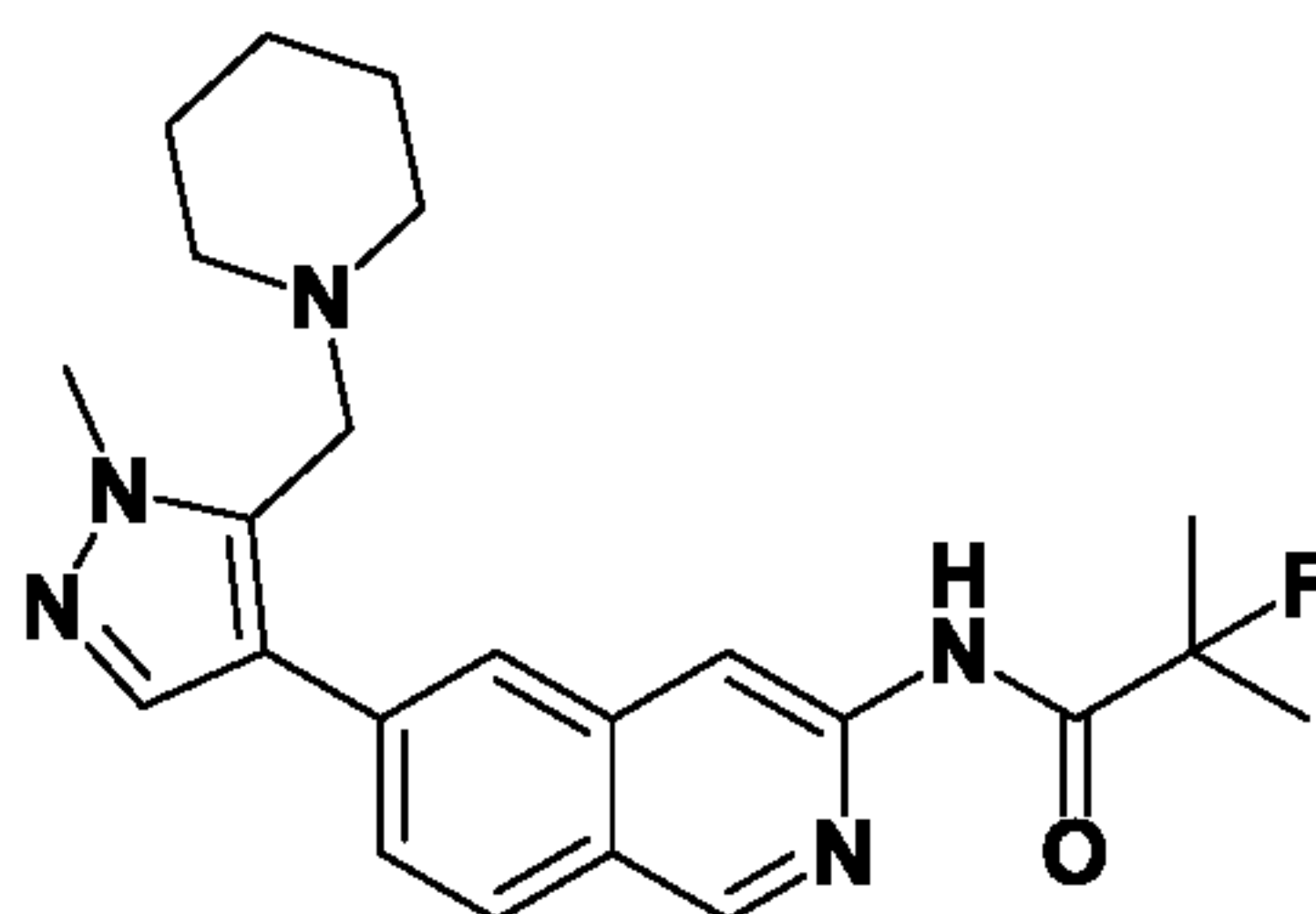
[01007] Beige solid (10.0 mg, 0.027 mmol, 8.2% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 2.19 (3 H, s), 2.40 (4 H, br s), 2.59 (4 H, br s), 3.23 (2 H, s), 7.89 (1 H, dd, $J=8.51, 1.65$ Hz), 8.13 (1 H, d, $J=8.78$ Hz), 8.28 (1 H, s), 8.53 (1 H, s), 8.58 (1 H, s), 9.14 (1 H, s), 9.20 (1 H, s), 10.02 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{21}\text{N}_5\text{OS}$ m/z 368.0 ($\text{M}+1$).



773

[01008] 2-Morpholino-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide 773.

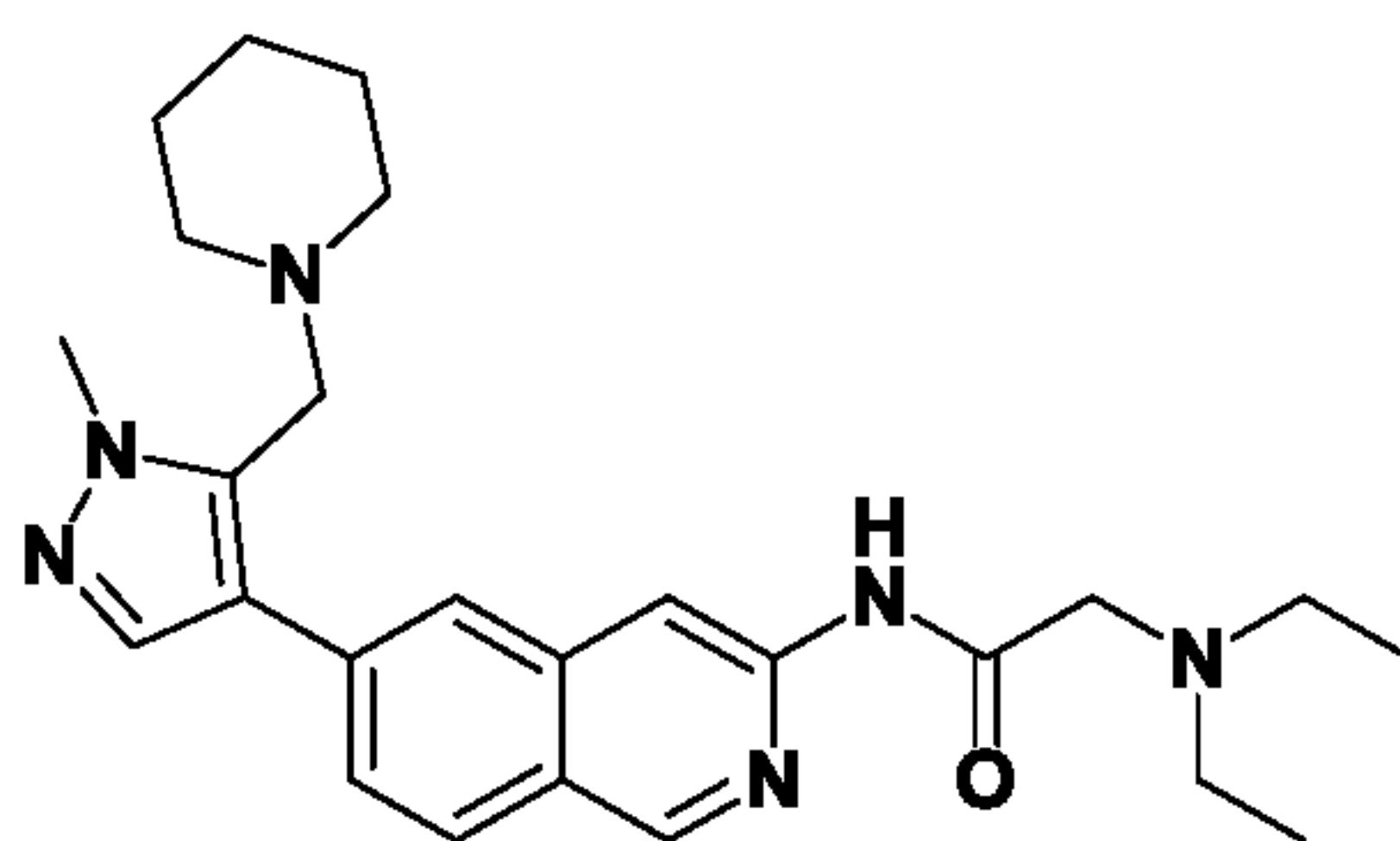
[01009] Pale green solid (43.0 mg, 0.121 mmol, 42.5% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 2.54 - 2.62 (4 H, m), 3.26 (2 H, s), 3.62 - 3.69 (4 H, m), 7.89 (1 H, dd, $J=8.64, 1.78$ Hz), 8.13 (1 H, d, $J=8.51$ Hz), 8.27 (1 H, s), 8.53 (1 H, s), 8.58 (1 H, s), 9.15 (1 H, s), 9.20 (1 H, s), 10.10 (1 H, s); ESIMS found for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ m/z 355.1 ($\text{M}+1$).



784

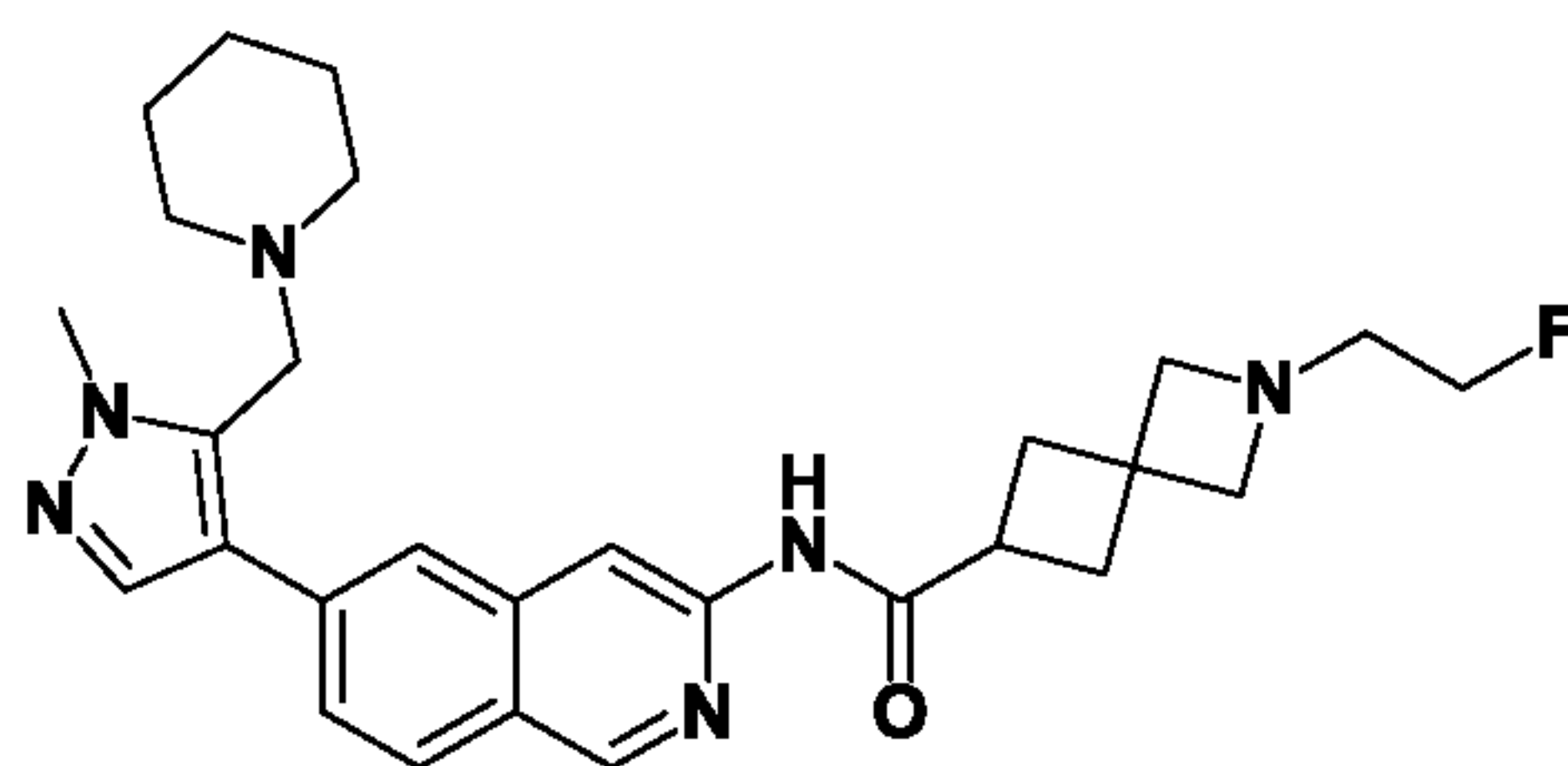
[01010] 2-Fluoro-2-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)propanamide 784.

[01011] Beige solid (40.0 mg, 0.098 mmol, 36.9% yield). ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ ppm 1.38 (2 H, br d, $J=3.29$ Hz), 1.49 (4 H, quin, $J=5.21$ Hz), 1.64 (6 H, d, $J=22.00$ Hz), 2.37 (4 H, br s), 3.65 (2 H, s), 3.92 (3 H, s), 7.76 (1 H, dd, $J=8.51, 1.65$ Hz), 7.82 (1 H, s), 8.08 (1 H, d, $J=8.51$ Hz), 8.13 (1 H, s), 8.42 (1 H, s), 9.13 (1 H, s), 9.85 (1 H, d, $J=3.84$ Hz); ESIMS found for $\text{C}_{23}\text{H}_{28}\text{FN}_5\text{O}$ m/z 410.2 ($\text{M}+1$).

**785**

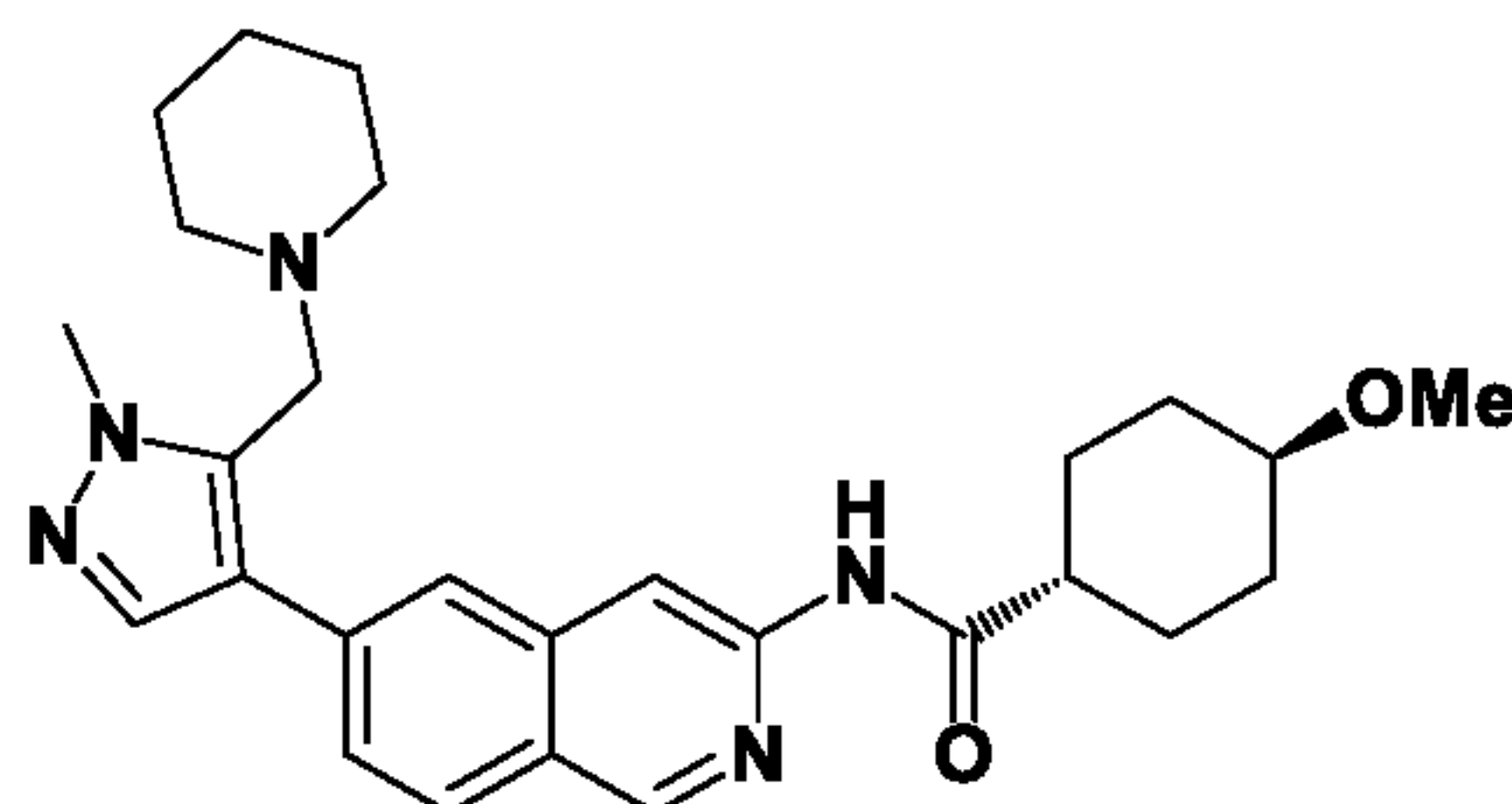
[01012] 2-(Diethylamino)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **785**.

[01013] Orange gum (200.0 mg, 0.460 mmol, 60.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.05 (6 H, t, $J=7.14$ Hz), 1.34 - 1.42 (2 H, m), 1.44 - 1.54 (4 H, m), 2.36 (4 H, br s), 2.64 (4 H, q, $J=6.95$ Hz), 3.24 (2 H, s), 3.64 (2 H, s), 3.91 (3 H, s), 7.72 (1 H, dd, $J=8.37$, 1.51 Hz), 7.81 (1 H, s), 8.04 (1 H, d, $J=8.51$ Hz), 8.12 (1 H, s), 8.45 (1 H, s), 9.08 (1 H, s), 9.93 (1 H, s); ESIMS found for $\text{C}_{25}\text{H}_{34}\text{N}_6\text{O}$ m/z 435.3 (M+1).

**791**

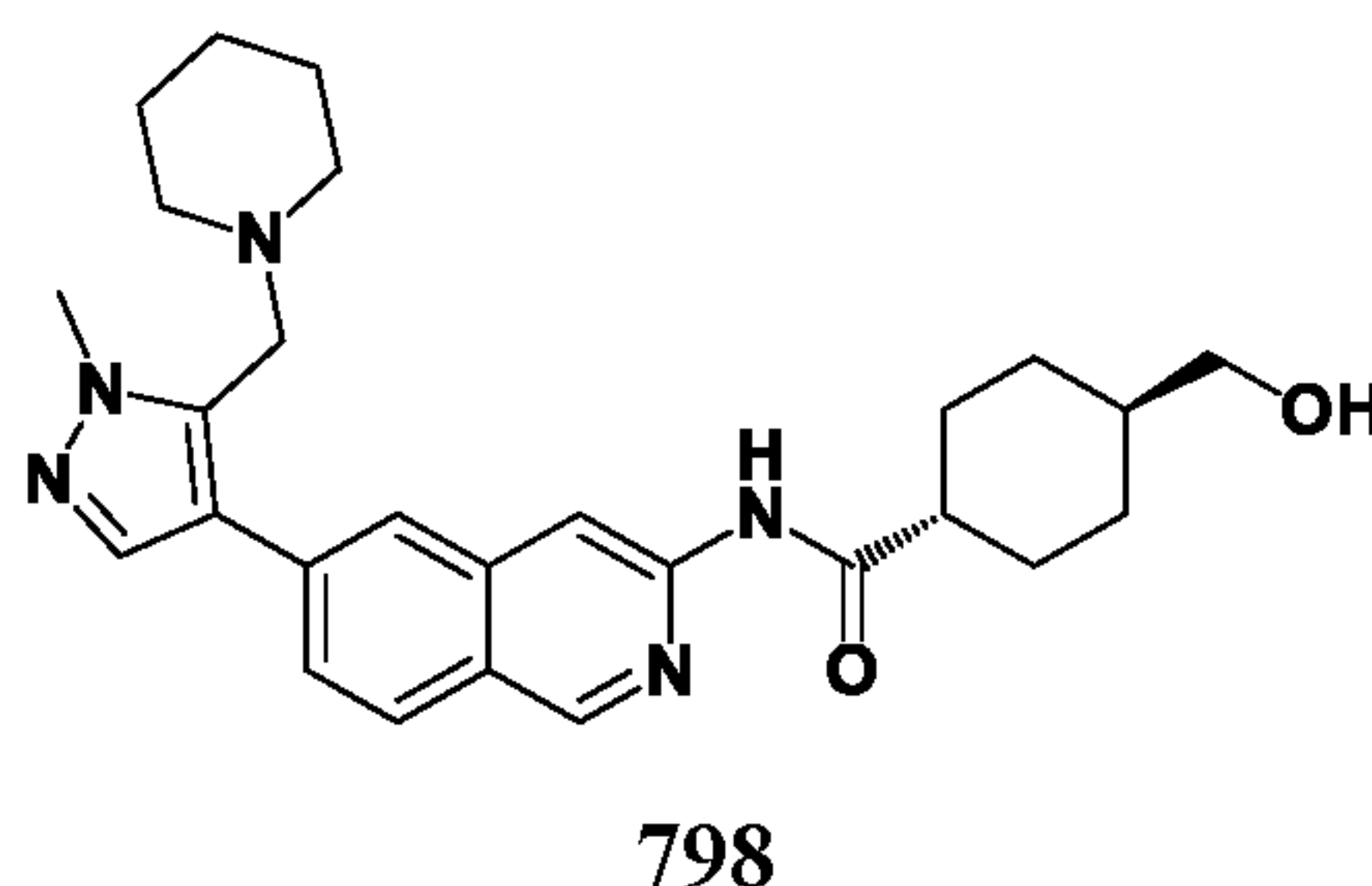
[01014] 2-(2-Fluoroethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide **791**.

[01015] White solid (20.0 mg, 0.041 mmol, 23.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.38 (2 H, br d, $J=3.57$ Hz), 1.45 - 1.54 (4 H, m), 2.24 - 2.33 (4 H, m), 2.36 (4 H, br s), 2.60 (2 H, dt, $J=28.60$, 4.95 Hz), 3.12 (2 H, s), 3.22 (2 H, s), 3.27 (1 H, t, $J=8.37$ Hz), 3.65 (2 H, s), 3.91 (3 H, s), 4.36 (2 H, dt, $J=47.80$, 4.95 Hz), 7.69 (1 H, dd, $J=8.51$, 1.37 Hz), 7.80 (1 H, s), 8.02 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, s), 8.46 (1 H, s), 9.06 (1 H, s), 10.39 (1 H, s); ESIMS found for $\text{C}_{28}\text{H}_{35}\text{FN}_6\text{O}$ m/z 491.3 (M+1).

**795**

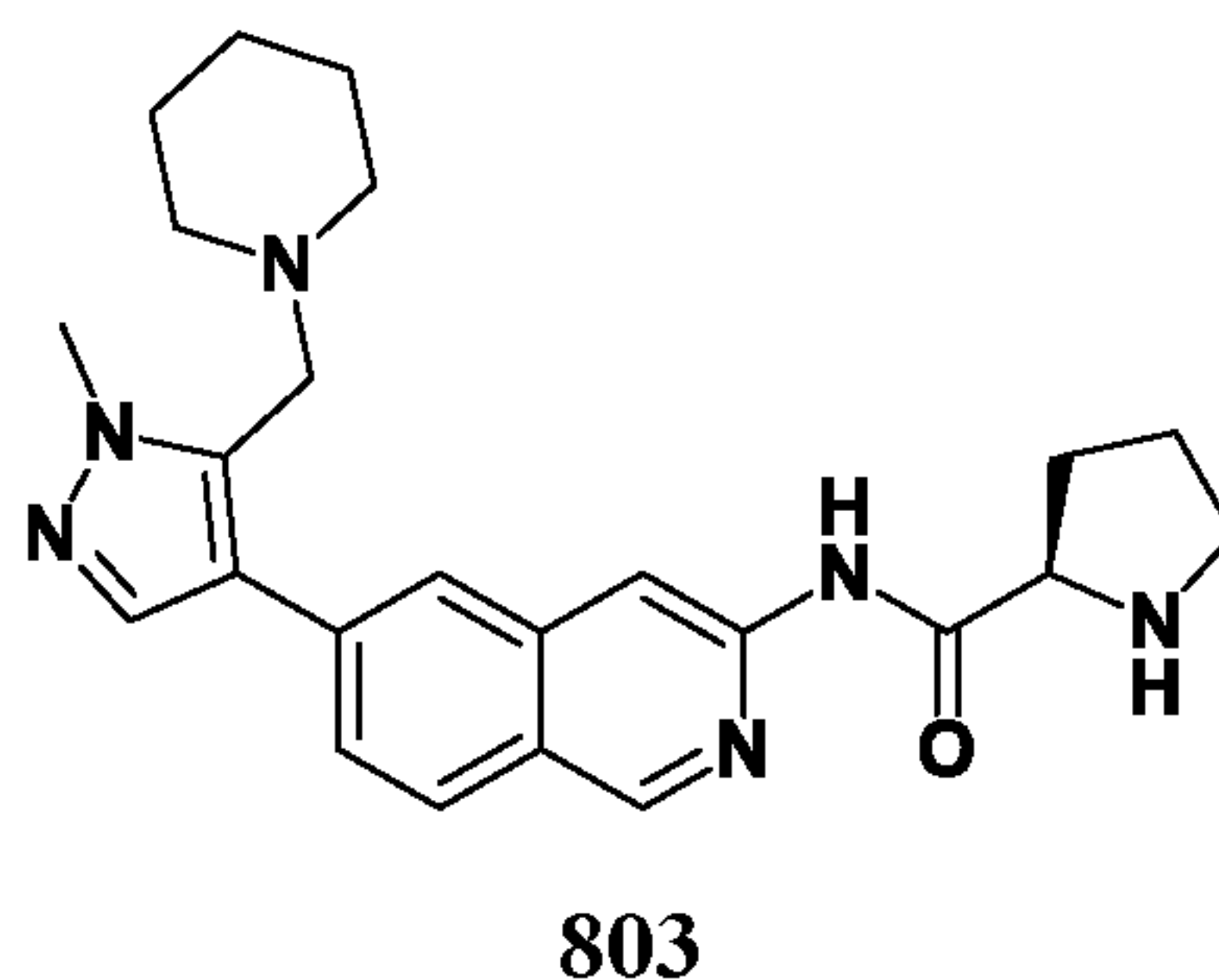
[01016] *trans*-4-Methoxy-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **795**.

[01017] White solid (33.7 mg, 0.073 mmol, 54.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.07 - 1.18 (2 H, m), 1.38 (2 H, br d, *J*=3.29 Hz), 1.43 - 1.52 (6 H, m), 1.89 (2 H, br d, *J*=11.53 Hz), 2.04 - 2.12 (2 H, m), 2.36 (4 H, br s), 2.51 - 2.57 (1 H, m), 3.12 (1 H, tt, *J*=10.67, 4.15 Hz), 3.25 (3 H, s), 3.64 (2 H, s), 3.91 (3 H, s), 7.69 (1 H, dd, *J*=8.37, 1.51 Hz), 7.80 (1 H, s), 8.02 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, br s), 8.45 (1 H, s), 9.07 (1 H, s), 10.46 (1 H, s); ESIMS found for C₂₇H₃₅N₅O₂ *m/z* 462.3 (M+1).



[01018] *trans*-4-(Hydroxymethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **798**.

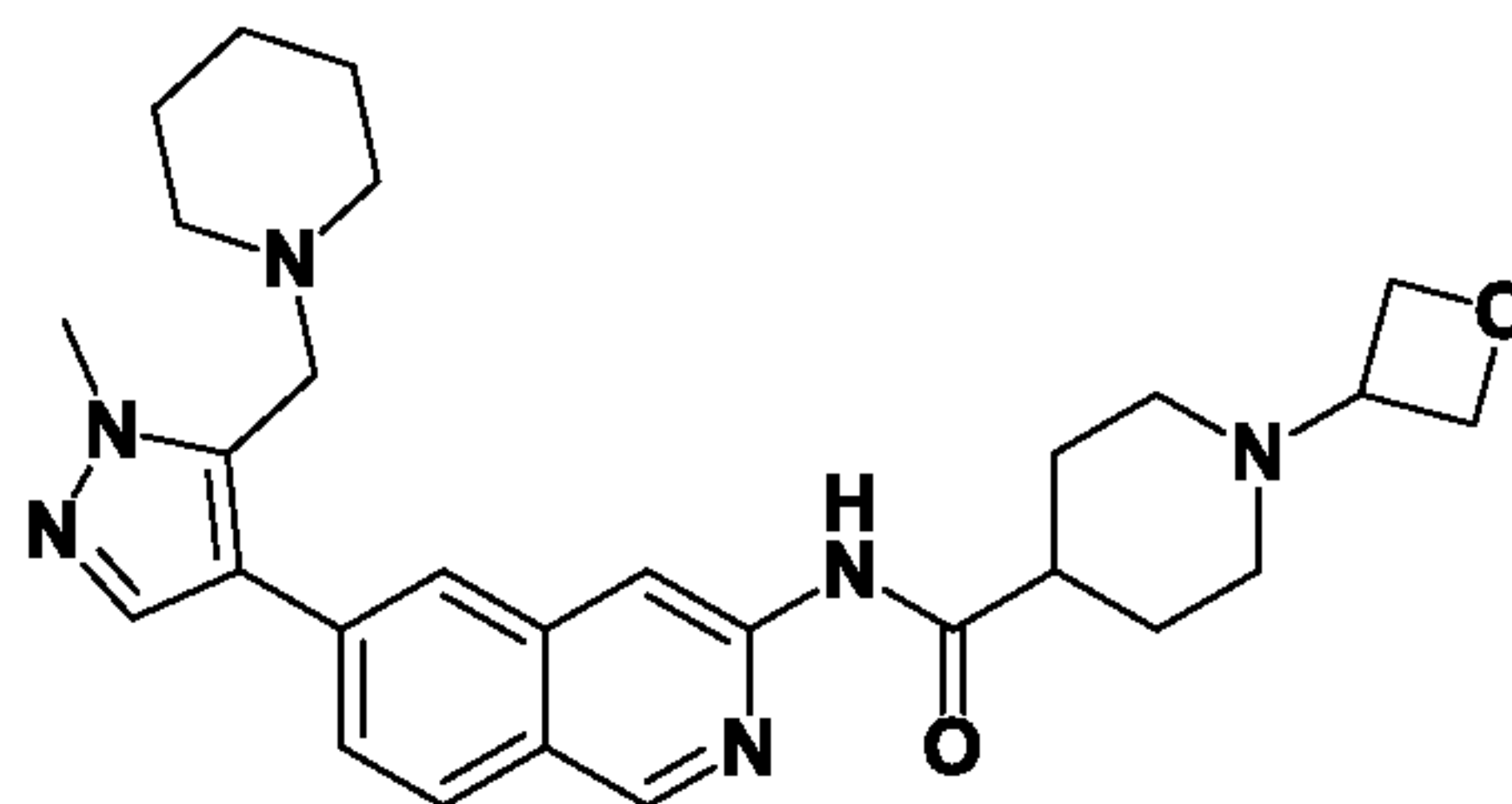
[01019] White solid (50.6 mg, 0.110 mmol, 103% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.90 - 1.01 (2 H, m), 1.32 - 1.42 (4 H, m), 1.42 - 1.53 (6 H, m), 1.80 (2 H, br dd, *J*=13.04, 2.61 Hz), 1.85 - 1.91 (2 H, m), 2.36 (4 H, br s), 3.24 (2 H, t, *J*=5.63 Hz), 3.64 (2 H, s), 3.91 (3 H, s), 4.39 (1 H, t, *J*=5.21 Hz), 7.68 (1 H, dd, *J*=8.37, 1.51 Hz), 7.80 (1 H, s), 8.00 - 8.06 (2 H, m), 8.46 (1 H, s), 9.07 (1 H, s), 10.42 (1 H, s); ESIMS found for C₂₇H₃₅N₅O₂ *m/z* 462.3 (M+1).



[01020] (R)-N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide **803**.

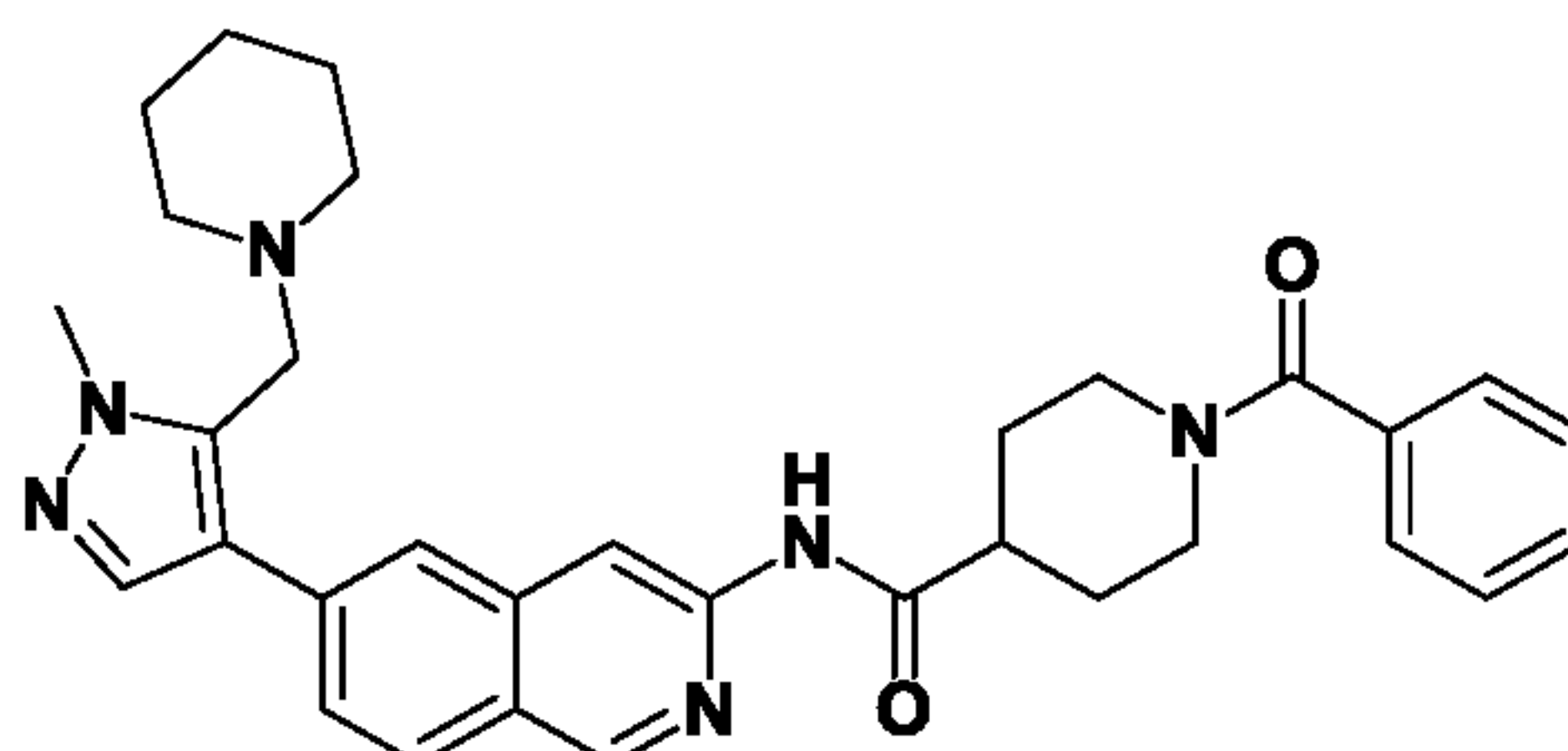
[01021] Off-white solid (40.0 mg, 0.096 mmol, 58.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.38 (2 H, br s), 1.46 - 1.52 (4 H, m), 1.67 (2 H, quin, *J*=6.79 Hz), 1.80 - 1.89 (1 H, m), 2.05 - 2.15 (1 H, m), 2.36 (4 H, br s), 2.87 (1 H, dt, *J*=10.15, 6.31 Hz), 2.97 (1 H, dt, *J*=10.15, 6.72 Hz), 3.64 (2 H, s), 3.80 (1 H, dd, *J*=9.06, 5.49 Hz), 3.91 (3 H, s), 7.71 (1 H, dd, *J*=8.51, 1.65

Hz), 7.81 (1 H, s), 8.04 (1 H, d, $J=8.51$ Hz), 8.10 (1 H, s), 8.46 (1 H, s), 9.07 (1 H, s), 10.36 (1 H, s); ESIMS found for $C_{24}H_{30}N_6O$ m/z 419.3 (M+1).

**826**

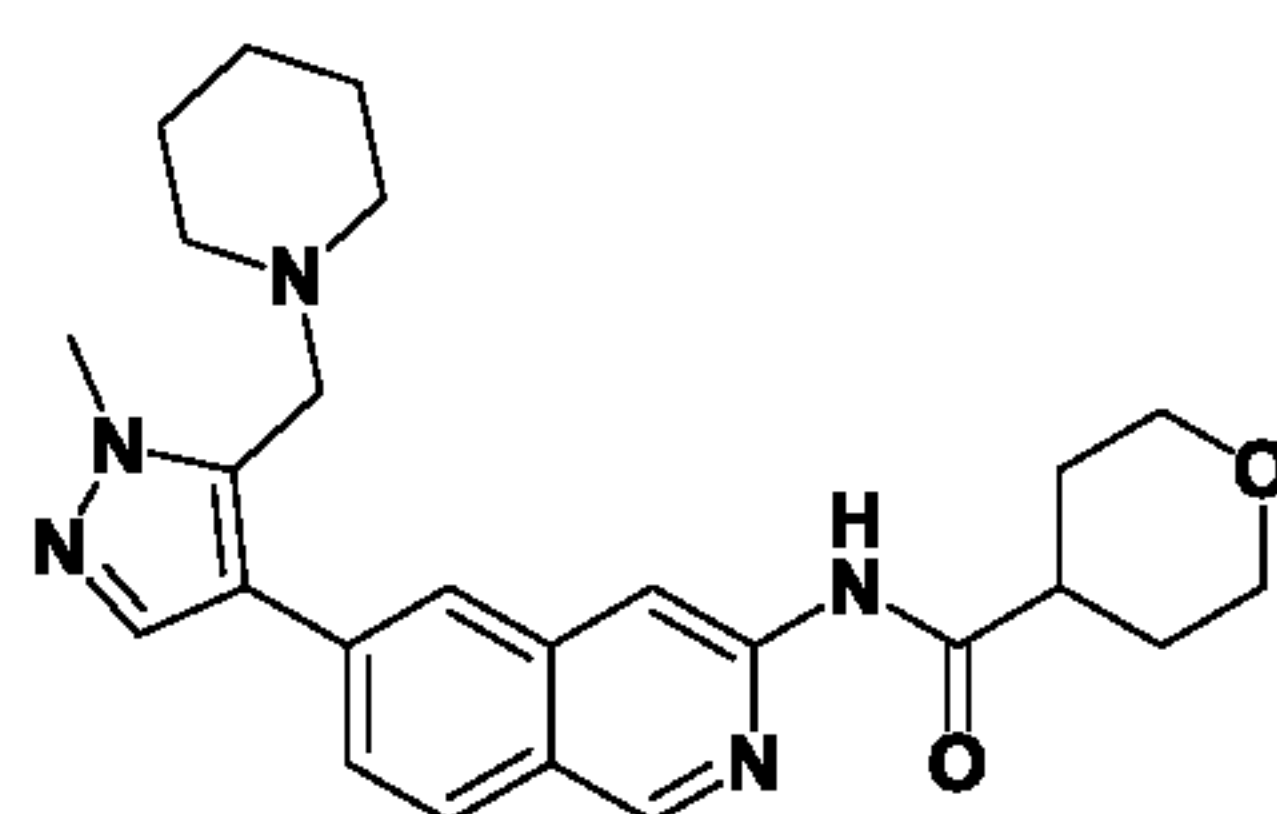
[01022] N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide **826**.

[01023] Off-white solid (40.0 mg, 0.082 mmol, 27.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.34 - 1.42 (2 H, m), 1.44 - 1.53 (4 H, m), 1.63 - 1.73 (2 H, m), 1.74 - 1.86 (4 H, m), 2.36 (4 H, br s), 2.53 - 2.61 (1 H, m), 2.71 - 2.82 (2 H, m), 3.40 (1 H, br s), 3.65 (2 H, br s), 3.91 (3 H, s), 4.44 (2 H, br t, $J=5.90$ Hz), 4.50 - 4.57 (2 H, m), 7.69 (1 H, dd, $J=8.64$, 1.51 Hz), 7.79 (1 H, s), 7.99 - 8.06 (2 H, m), 8.47 (1 H, s), 9.07 (1 H, s), 10.48 (1 H, s); ESIMS found for $C_{28}H_{36}N_6O_2$ m/z 489.3 (M+1).

**831**

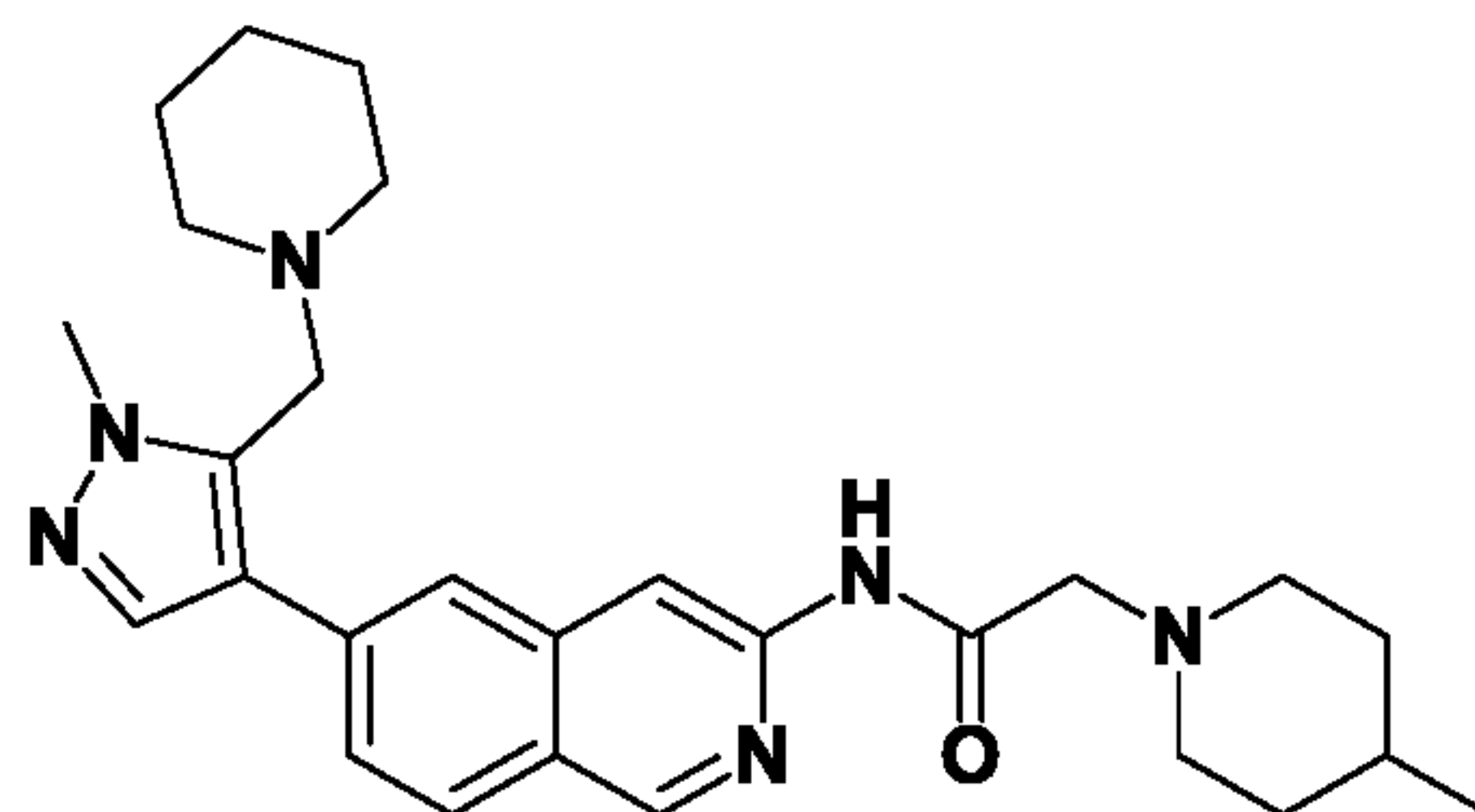
[01024] 1-Benzoyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **831**.

[01025] White solid (53.0 mg, 0.099 mmol, 58.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.38 (2 H, br d, $J=3.02$ Hz), 1.45 - 1.54 (4 H, m), 1.57 - 1.71 (2 H, m), 1.74 - 1.86 (1 H, m), 1.89 - 1.98 (1 H, m), 2.36 (4 H, br s), 2.45 - 2.49 (1 H, m), 2.86 (2 H, ddt, $J=11.25$, 7.55, 3.77, 3.77 Hz), 3.02 - 3.16 (1 H, m), 3.65 (2 H, s), 3.91 (3 H, s), 4.46 - 4.61 (1 H, m), 7.37 - 7.43 (2 H, m), 7.43 - 7.49 (3 H, m), 7.70 (1 H, dd, $J=8.51$, 1.37 Hz), 7.80 (1 H, s), 8.03 (1 H, d, $J=8.51$ Hz), 8.06 (1 H, s), 8.46 (1 H, s), 9.08 (1 H, s), 10.58 (1 H, s); ESIMS found for $C_{32}H_{36}N_6O_2$ m/z 537.3 (M+1).

**839**

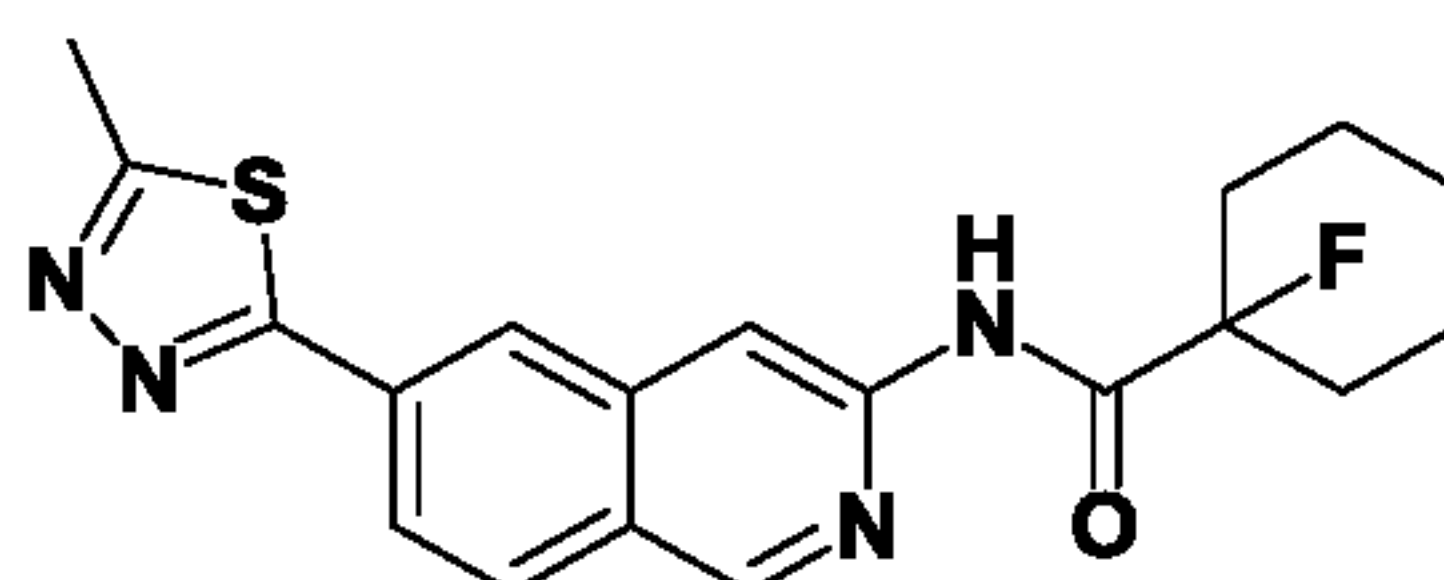
[01026] N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide **839**.

[01027] White amorphous solid (25.8 mg, 0.060 mmol, 69.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.35 - 1.41 (2 H, m), 1.46 - 1.52 (4 H, m), 1.66 - 1.77 (4 H, m), 2.36 (4 H, br d, *J*=1.65 Hz), 2.77 - 2.88 (1 H, m), 3.33 - 3.39 (2 H, m), 3.65 (2 H, s), 3.89 - 3.94 (2 H, m), 3.91 (3 H, s), 7.66 - 7.73 (1 H, m), 7.80 (1 H, s), 8.00 - 8.06 (2 H, m), 8.46 (1 H, s), 9.08 (1 H, s), 10.52 (1 H, s); ESIMS found for C₂₅H₃₁N₅O₂ *m/z* 434.2 (M+1).

**851**

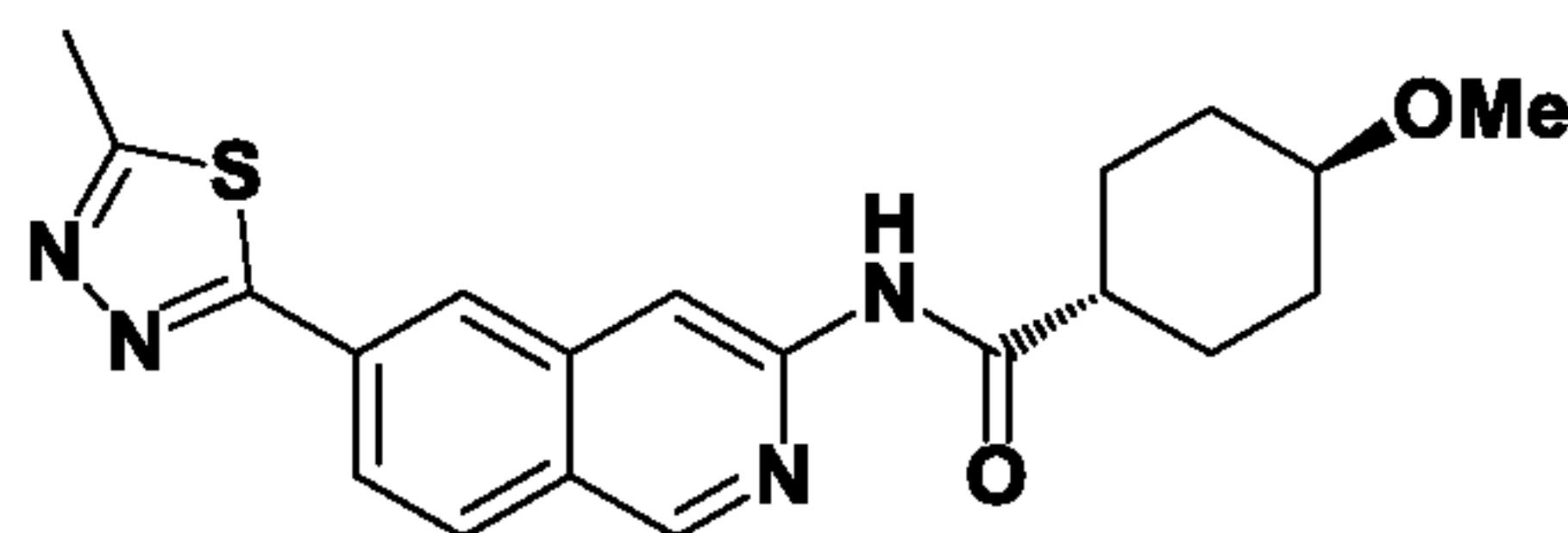
[01028] N-(6-(1-Methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide **851**.

[01029] Off-white solid (180.0 mg, 0.391 mmol, 54.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.93 (3 H, d, *J*=6.31 Hz), 1.20 - 1.30 (2 H, m), 1.33 - 1.42 (3 H, m), 1.44 - 1.53 (4 H, m), 1.63 (2 H, br d, *J*=11.53 Hz), 2.16 - 2.24 (2 H, m), 2.36 (4 H, br s), 2.87 (2 H, br d, *J*=11.53 Hz), 3.18 (2 H, s), 3.65 (2 H, s), 3.91 (3 H, s), 7.72 (1 H, dd, *J*=8.51, 1.37 Hz), 7.82 (1 H, s), 8.05 (1 H, d, *J*=8.78 Hz), 8.12 (1 H, s), 8.45 (1 H, s), 9.08 (1 H, s), 9.91 (1 H, s); ESIMS found for C₂₇H₃₆N₆O *m/z* 461.3 (M+1).

**883**

[01030] 1-Fluoro-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **883**.

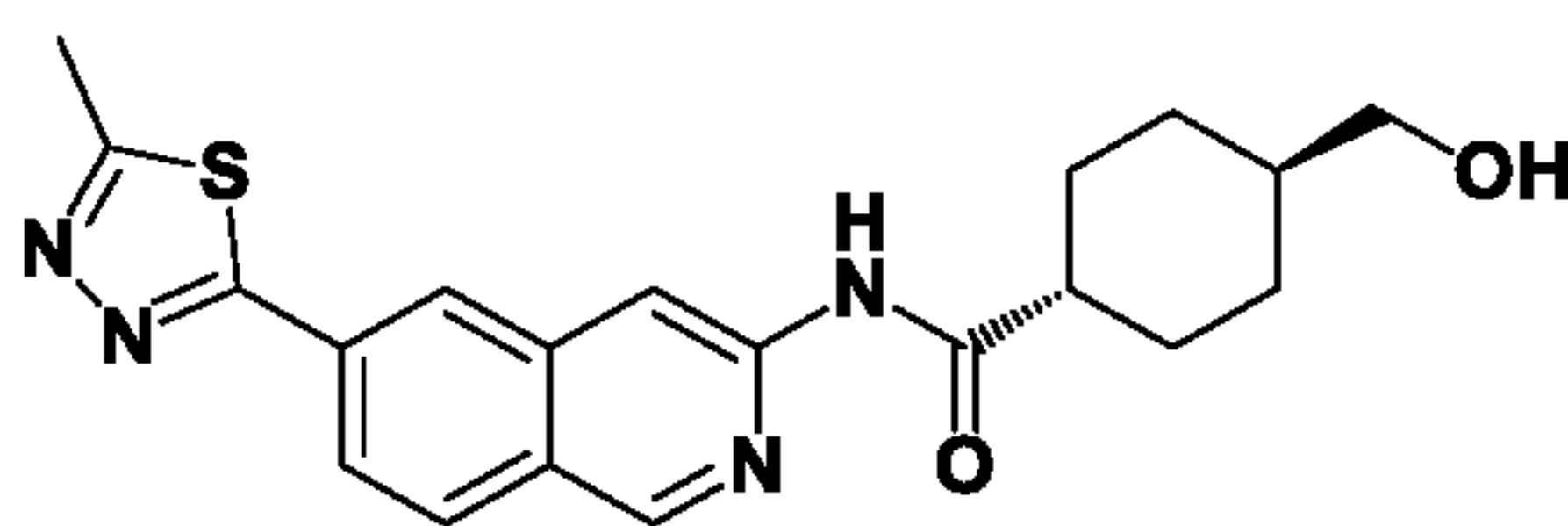
[01031] Off-white solid (36.5 mg, 0.099 mmol, 63.5% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.31 - 1.40 (1 H, m), 1.51 - 1.62 (2 H, m), 1.69 (3 H, br d, $J=9.33$ Hz), 1.87 - 2.02 (4 H, m), 2.83 (3 H, s), 8.15 (1 H, dd, $J=8.51$, 1.65 Hz), 8.24 (1 H, d, $J=8.51$ Hz), 8.53 (1 H, s), 8.58 (1 H, s), 9.27 (1 H, s), 9.97 (1 H, d, $J=3.84$ Hz); ESIMS found for $\text{C}_{19}\text{H}_{19}\text{FN}_4\text{OS}$ m/z 371.1 (M+1).



885

[01032] *trans*-4-Methoxy-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **885**.

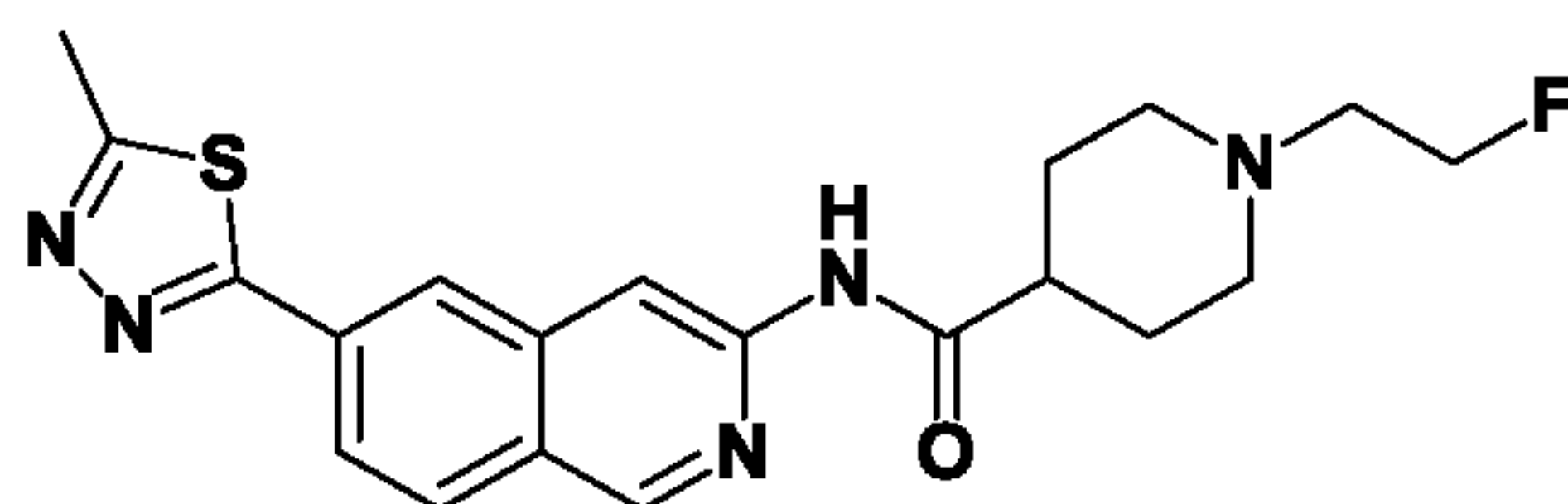
[01033] White solid (33.4 mg, 0.087 mmol, 21.2% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.08 - 1.19 (2 H, m), 1.44 - 1.56 (2 H, m), 1.88 - 1.94 (2 H, m), 2.05 - 2.13 (2 H, m), 2.52 - 2.58 (1 H, m), 2.83 (3 H, s), 3.09 - 3.17 (1 H, m), 3.25 (3 H, s), 8.09 (1 H, dd, $J=8.65$, 1.51 Hz), 8.19 (1 H, d, $J=8.51$ Hz), 8.44 (1 H, s), 8.60 (1 H, s), 9.21 (1 H, s), 10.60 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ m/z 383.15 (M+1).



888

[01034] *trans*-4-(Hydroxymethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **888**.

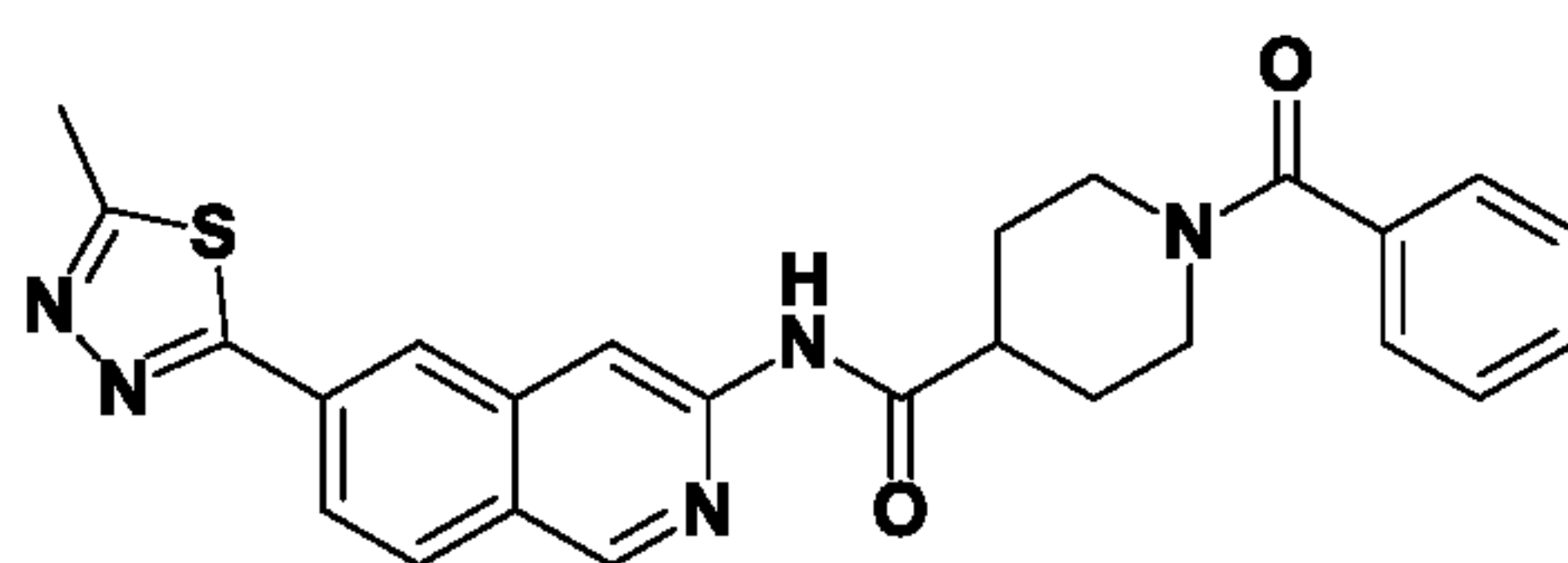
[01035] White solid (12.4 mg, 0.032 mmol, 39.0% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 0.90 - 1.02 (2 H, m), 1.30 - 1.40 (1 H, m), 1.46 (2 H, qd, $J=12.76$, 3.43 Hz), 1.81 (2 H, br dd, $J=13.04$, 2.61 Hz), 1.86 - 1.93 (2 H, m), 2.52 - 2.56 (1 H, m), 2.83 (3 H, s), 3.24 (2 H, t, $J=5.76$ Hz), 4.39 (1 H, t, $J=5.35$ Hz), 8.08 (1 H, dd, $J=8.51$, 1.65 Hz), 8.19 (1 H, d, $J=8.51$ Hz), 8.43 (1 H, s), 8.61 (1 H, s), 9.21 (1 H, s), 10.57 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ m/z 383.1 (M+1).



900

[01036] 1-(2-Fluoroethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide **900**.

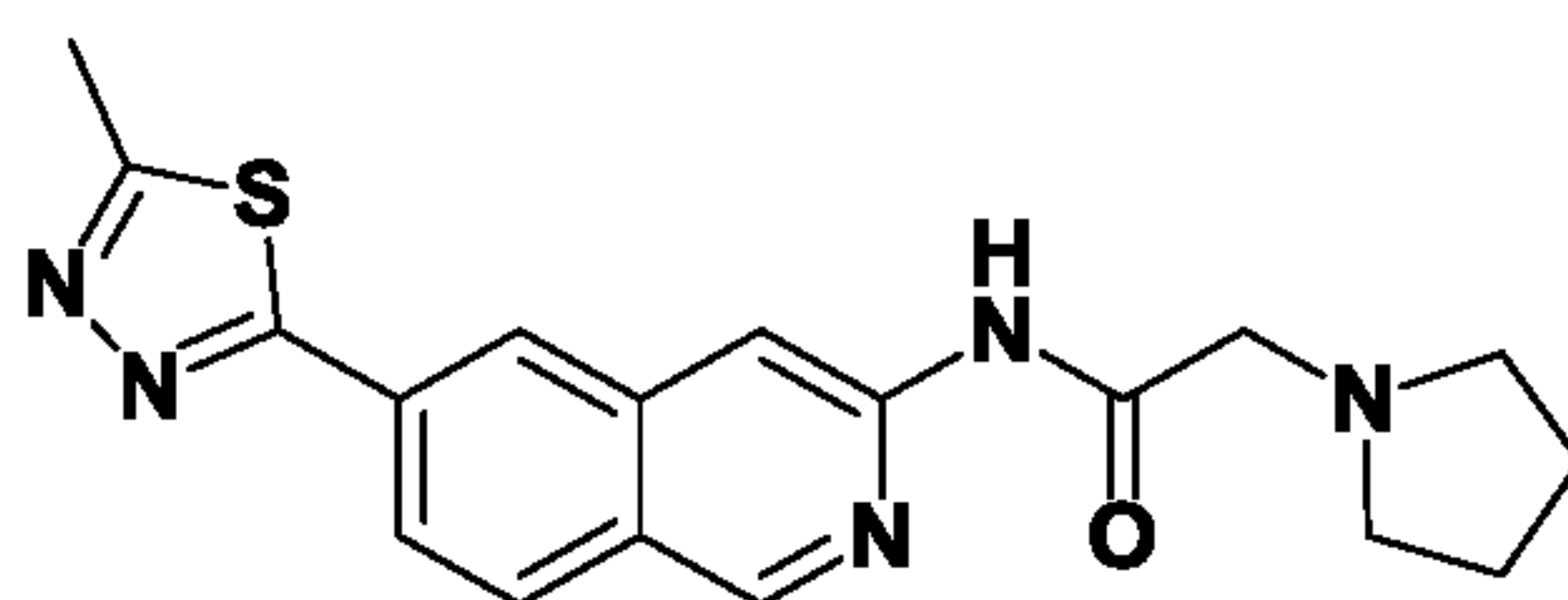
[01037] Beige solid (41.0 mg, 0.103 mmol, 19.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.69 (2 H, qd, *J*=12.12, 3.70 Hz), 1.76 - 1.85 (2 H, m), 2.02 - 2.09 (2 H, m), 2.52 - 2.57 (1 H, m), 2.62 (2 H, dt, *J*=28.35, 4.95 Hz), 2.83 (3 H, s), 2.95 (2 H, br d, *J*=11.53 Hz), 4.54 (2 H, dt, *J*=47.80, 4.95 Hz), 8.09 (1 H, dd, *J*=8.51, 1.65 Hz), 8.19 (1 H, d, *J*=8.51 Hz), 8.44 (1 H, s), 8.63 (1 H, s), 9.21 (1 H, s), 10.62 (1 H, s); ESIMS found for C₂₀H₂₂FN₅OS *m/z* 400.15 (M+1).



921

[01038] 1-Benzoyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide **921**.

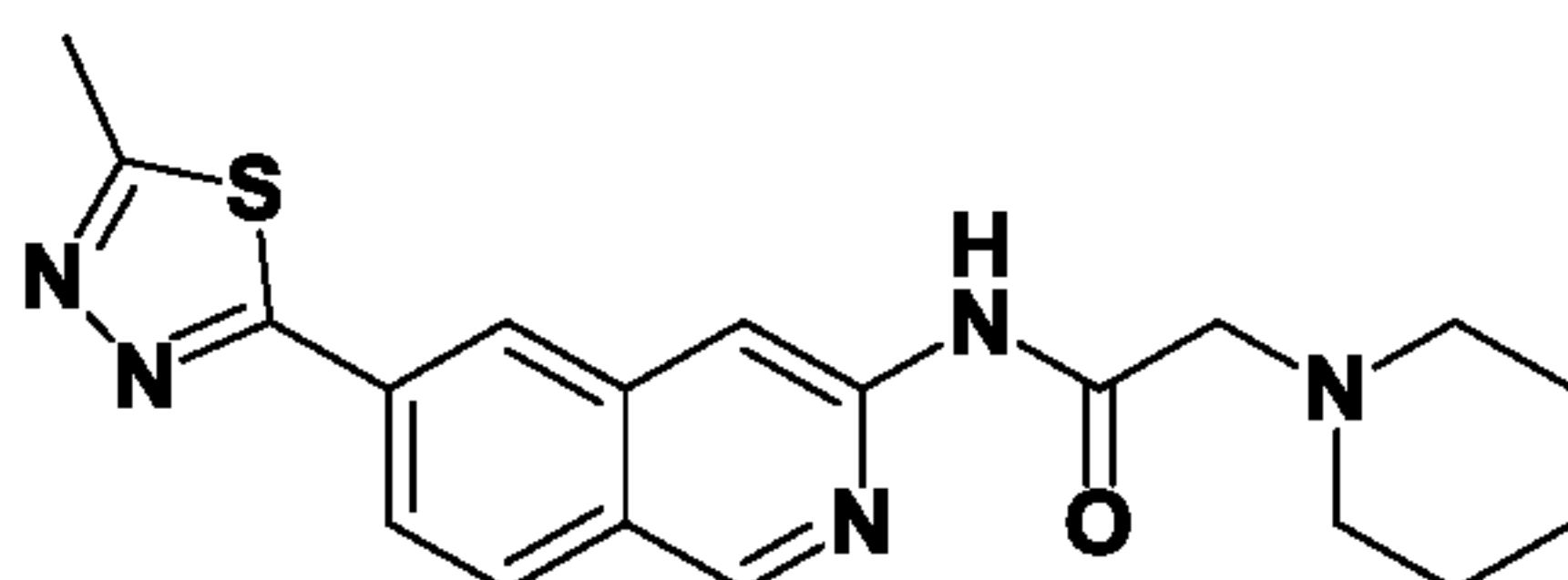
[01039] Off-white solid (78.5 mg, 0.172 mmol, 42.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.64 (2 H, br s), 1.77 - 1.89 (1 H, m), 1.90 - 2.04 (1 H, m), 2.78 - 2.92 (2 H, m), 2.83 (3 H, s), 3.10 (1 H, tdd, *J*=5.01, 5.01, 2.88, 1.37 Hz), 3.58 - 3.76 (1 H, m), 4.42 - 4.61 (1 H, m), 7.37 - 7.43 (2 H, m), 7.43 - 7.49 (3 H, m), 8.10 (1 H, dd, *J*=8.51, 1.65 Hz), 8.19 (1 H, d, *J*=8.51 Hz), 8.46 (1 H, d, *J*=0.82 Hz), 8.62 (1 H, s), 9.22 (1 H, s), 10.72 (1 H, s); ESIMS found for C₂₅H₂₃N₅O₂S *m/z* 458.2 (M+1).



932

[01040] N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **932**.

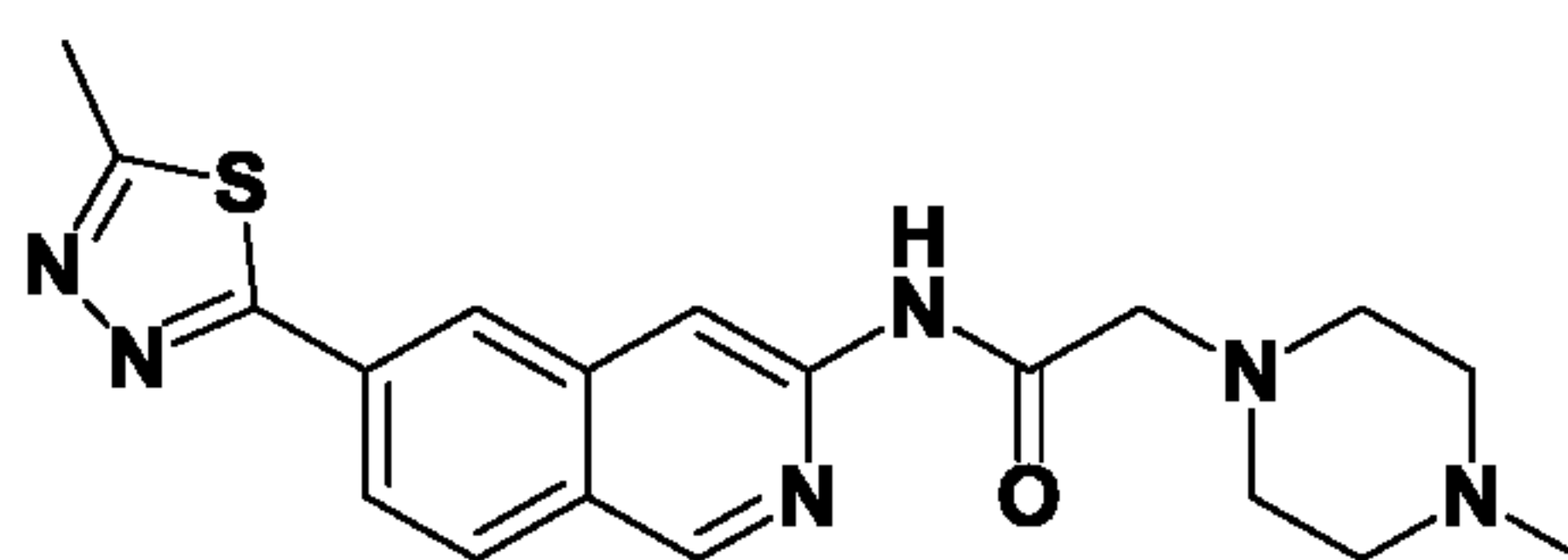
[01041] Beige solid (46.0 mg, 0.130 mmol, 21.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.78 (7 H, dt, *J*=6.86, 3.16 Hz), 2.62 - 2.70 (4 H, m), 2.83 (3 H, s), 3.38 (2 H, s), 8.12 (1 H, dd, *J*=8.51, 1.65 Hz), 8.21 (1 H, d, *J*=8.51 Hz), 8.50 (1 H, s), 8.61 (1 H, s), 9.22 (1 H, s), 10.08 (1 H, s); ESIMS found for C₁₈H₁₉N₅OS *m/z* 354.1 (M+1).



939

[01042] N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide **939**.

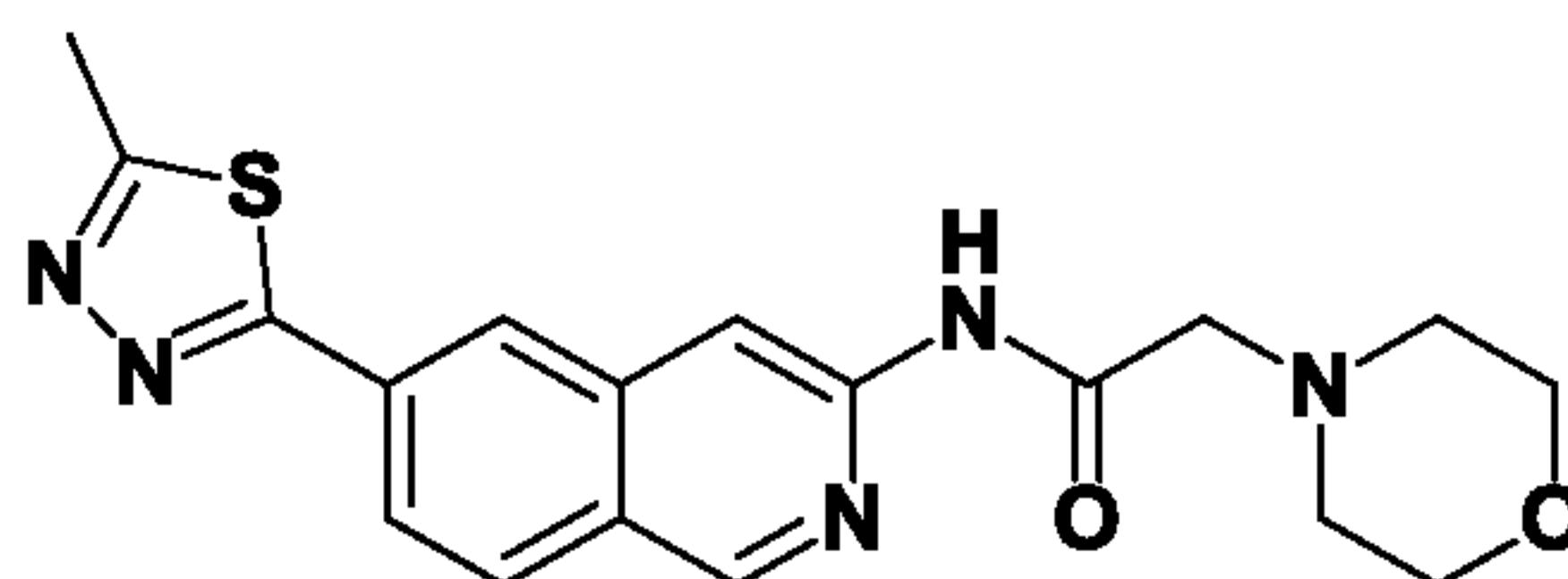
[01043] Beige solid (77.0 mg, 0.210 mmol, 21.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.39 - 1.47 (2 H, m), 1.59 (4 H, quin, *J*=5.56 Hz), 2.52 - 2.57 (4 H, m), 2.83 (3 H, s), 3.19 (2 H, s), 8.12 (1 H, dd, *J*=8.51, 1.65 Hz), 8.21 (1 H, d, *J*=8.51 Hz), 8.51 (1 H, s), 8.61 (1 H, s), 9.22 (1 H, s), 10.06 (1 H, s); ESIMS found for C₁₉H₂₁N₅OS *m/z* 368.2 (M+1).



946

[01044] N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **946**.

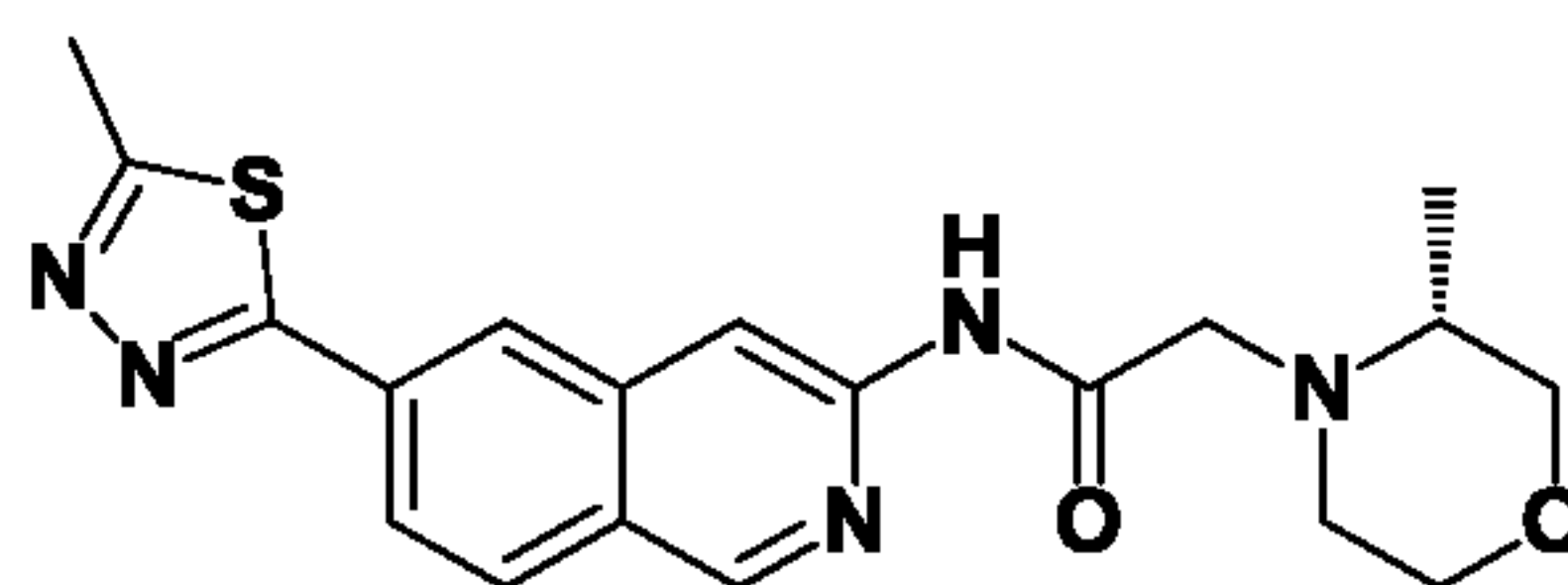
[01045] Beige solid (11.0 mg, 0.029 mmol, 8.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.19 (3 H, s), 2.40 (4 H, br s), 2.59 (4 H, br s), 2.83 (3 H, s), 3.24 (2 H, s), 8.12 (1 H, dd, *J*=8.78, 1.65 Hz), 8.21 (1 H, d, *J*=8.51 Hz), 8.51 (1 H, s), 8.61 (1 H, s), 9.23 (1 H, s), 10.09 (1 H, s); ESIMS found for C₁₉H₂₂N₆OS *m/z* 383.2 (M+1).



952

[01046] N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide **952**.

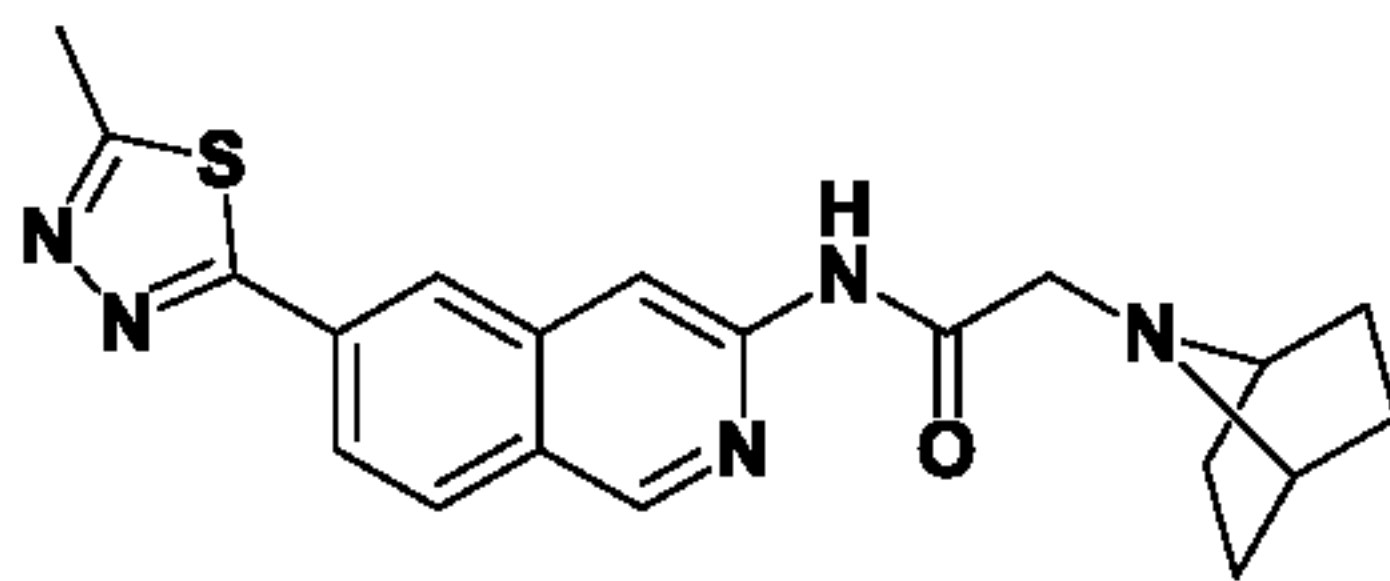
[01047] Pale yellow solid (11.0 mg, 0.030 mmol, 9.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.55 - 2.61 (4 H, m), 2.83 (3 H, s), 3.27 (2 H, s), 3.62 - 3.70 (4 H, m), 8.12 (1 H, dd, *J*=8.51, 1.65 Hz), 8.21 (1 H, d, *J*=8.78 Hz), 8.51 (1 H, s), 8.62 (1 H, s), 9.23 (1 H, s), 10.17 (1 H, s); ESIMS found for C₁₈H₁₉N₅O₂S *m/z* 370.1 (M+1).



953

[01048] (R)-N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide **953**.

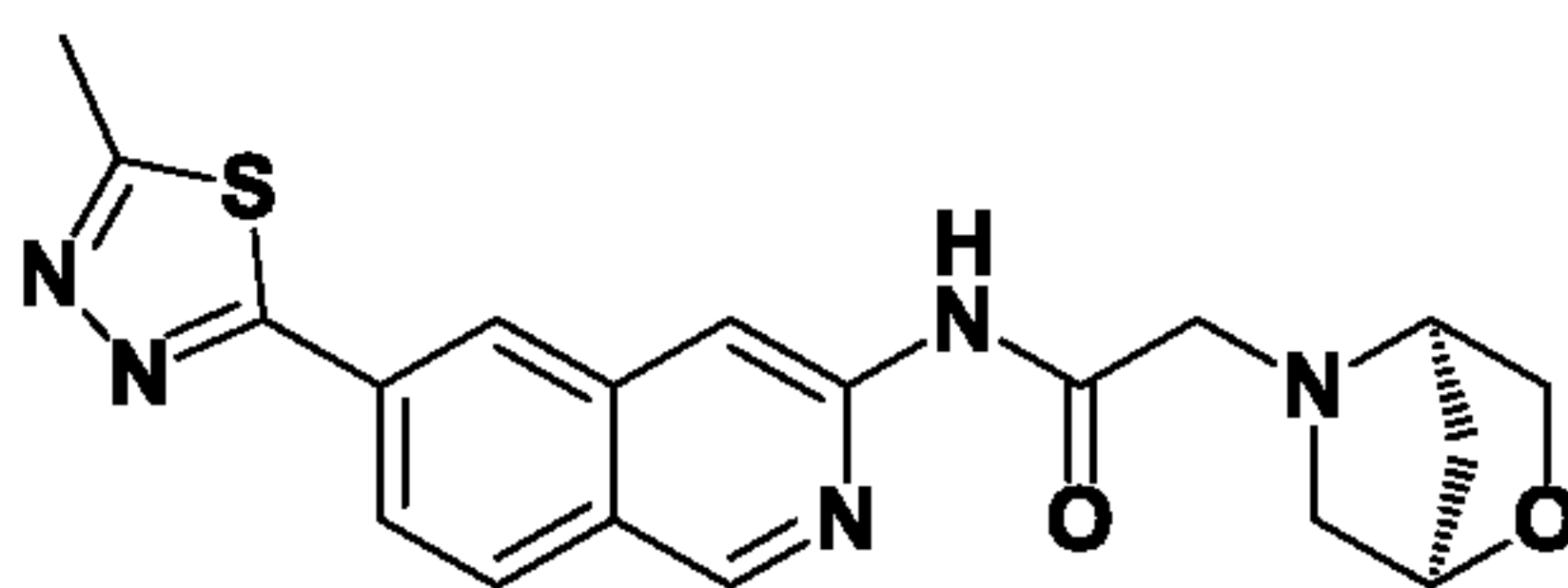
[01049] Beige solid (66.0 mg, 0.172 mmol, 23.1% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 0.96 (3 H, d, $J=6.31$ Hz), 2.54 - 2.60 (1 H, m), 2.63 (1 H, ddd, $J=9.06, 6.17, 2.88$ Hz), 2.80 - 2.82 (1 H, m), 2.83 (3 H, s), 3.19 (1 H, dd, $J=11.11, 8.92$ Hz), 3.21 (1 H, d, $J=16.47$ Hz), 3.49 (1 H, d, $J=16.47$ Hz), 3.54 - 3.62 (1 H, m), 3.68 (1 H, dd, $J=11.25, 3.02$ Hz), 3.71 - 3.79 (1 H, m), 8.08 - 8.18 (1 H, m), 8.22 (1 H, d, $J=8.51$ Hz), 8.51 (1 H, s), 8.62 (1 H, s), 9.23 (1 H, s), 10.13 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}_2\text{S}$ m/z 384.2 ($\text{M}+1$).



959

[01050] 2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide **959**.

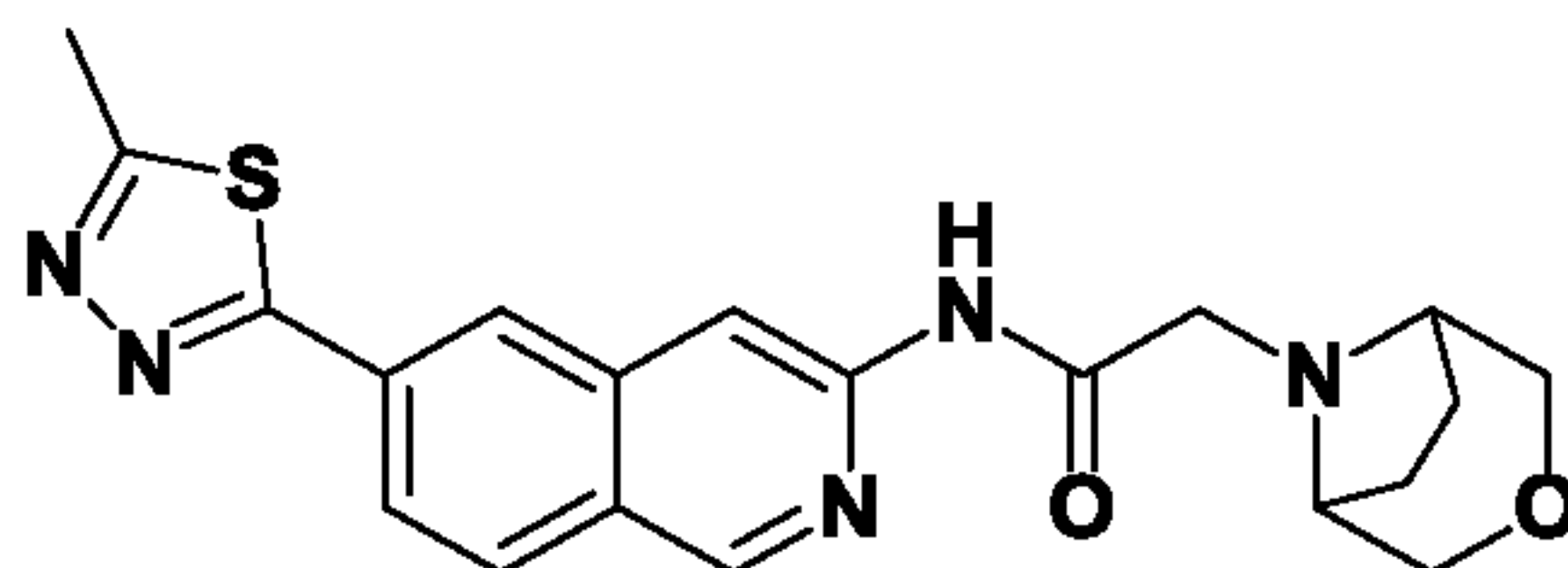
[01051] Beige solid (27.0 mg, 0.071 mmol, 18.7% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.34 (4 H, d, $J=7.14$ Hz), 1.71 - 1.79 (4 H, m), 2.83 (3 H, s), 3.21 (2 H, s), 3.35 - 3.40 (2 H, m), 8.12 (1 H, dd, $J=8.51, 1.65$ Hz), 8.22 (1 H, d, $J=8.51$ Hz), 8.52 (1 H, s), 8.63 (1 H, s), 9.22 (1 H, s), 10.21 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{OS}$ m/z 380.1 ($\text{M}+1$).



960

[01052] 2-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide **960**.

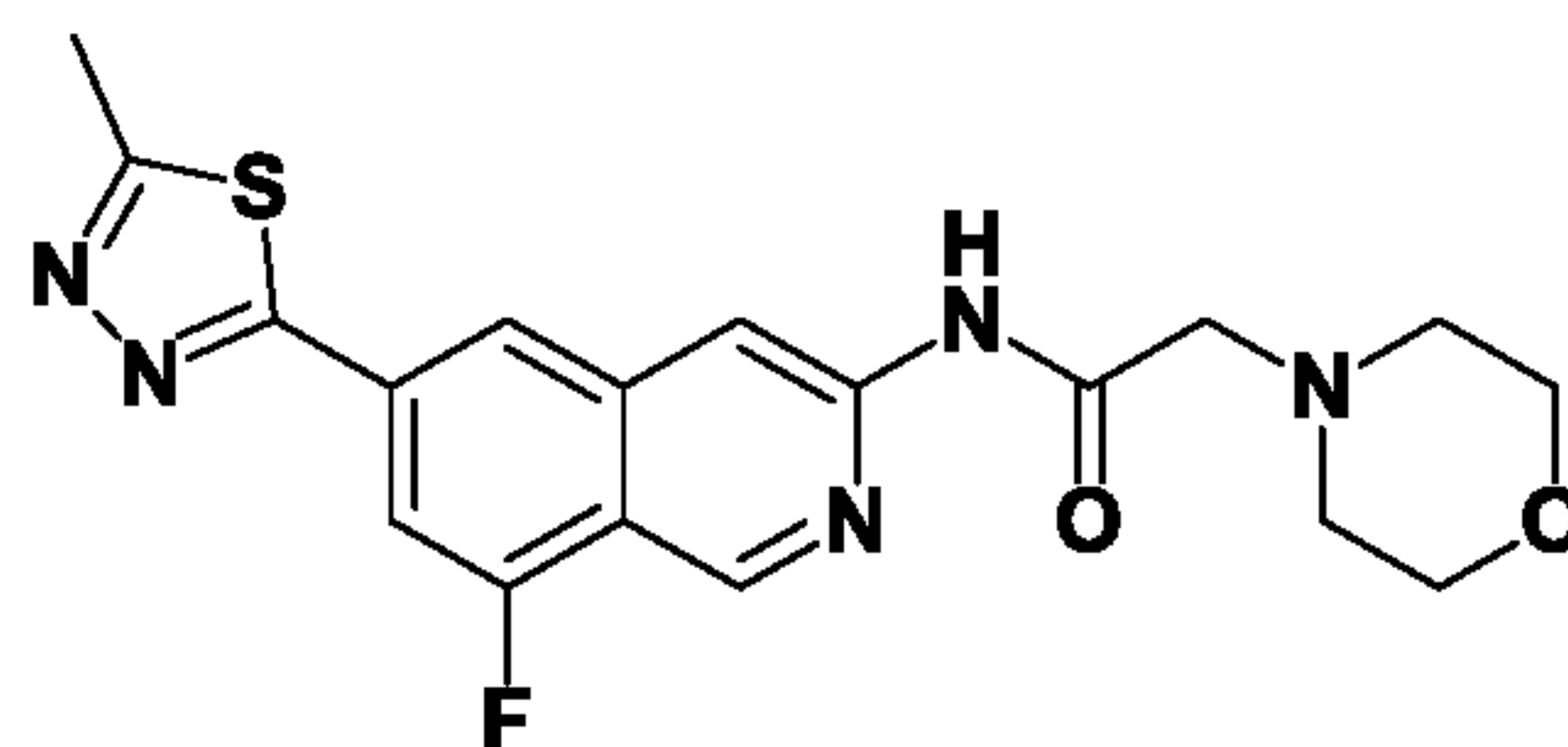
[01053] Off-white solid (110.0 mg, 0.288 mmol, 47.5% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.67 (1 H, dd, $J=9.74, 0.96$ Hz), 1.87 (1 H, dd, $J=9.74, 1.78$ Hz), 2.63 (1 H, d, $J=9.88$ Hz), 2.83 (3 H, s), 2.96 (1 H, dd, $J=9.88, 1.65$ Hz), 3.48 (2 H, d, $J=4.94$ Hz), 3.59 (1 H, dd, $J=7.68, 1.65$ Hz), 3.64 (1 H, s), 3.88 (1 H, d, $J=7.41$ Hz), 4.41 (1 H, s), 8.12 (1 H, dd, $J=8.51, 1.65$ Hz), 8.22 (1 H, d, $J=8.78$ Hz), 8.51 (1 H, s), 8.62 (1 H, s), 9.23 (1 H, s), 10.07 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}_2\text{S}$ m/z 382.1 ($\text{M}+1$).



962

[01054] 2-(3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide **962**.

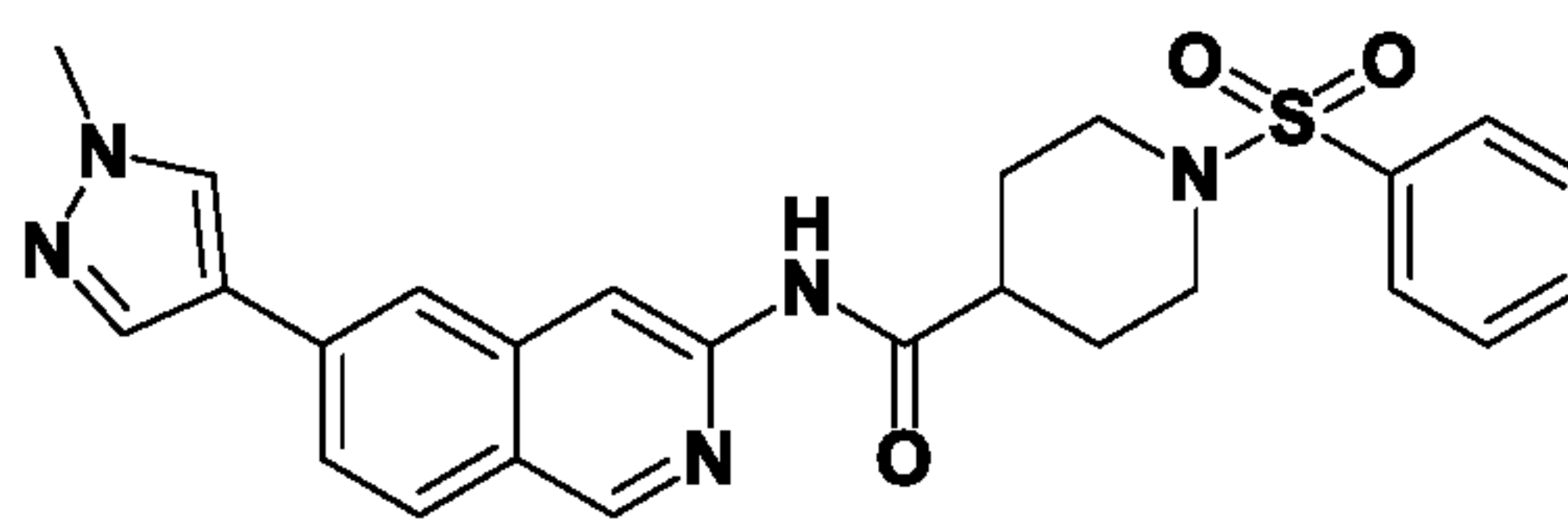
[01055] Off-white solid (175.0 mg, 0.065 mmol, 17.4% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.76 - 1.82 (2 H, m), 1.87 - 1.94 (2 H, m), 2.83 (3 H, s), 3.16 (2 H, s), 3.18 (2 H, br d, *J*=1.10 Hz), 3.52 (2 H, dd, *J*=10.57, 1.51 Hz), 3.68 (2 H, d, *J*=10.43 Hz), 8.13 (1 H, dd, *J*=8.51, 1.65 Hz), 8.22 (1 H, d, *J*=8.78 Hz), 8.52 (1 H, s), 8.63 (1 H, s), 9.25 (1 H, s), 10.28 (1 H, s); ESIMS found for C₂₀H₂₁N₅O₂S *m/z* 396.15 (M+1).



963

[01056] N-(8-Fluoro-6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide **963**.

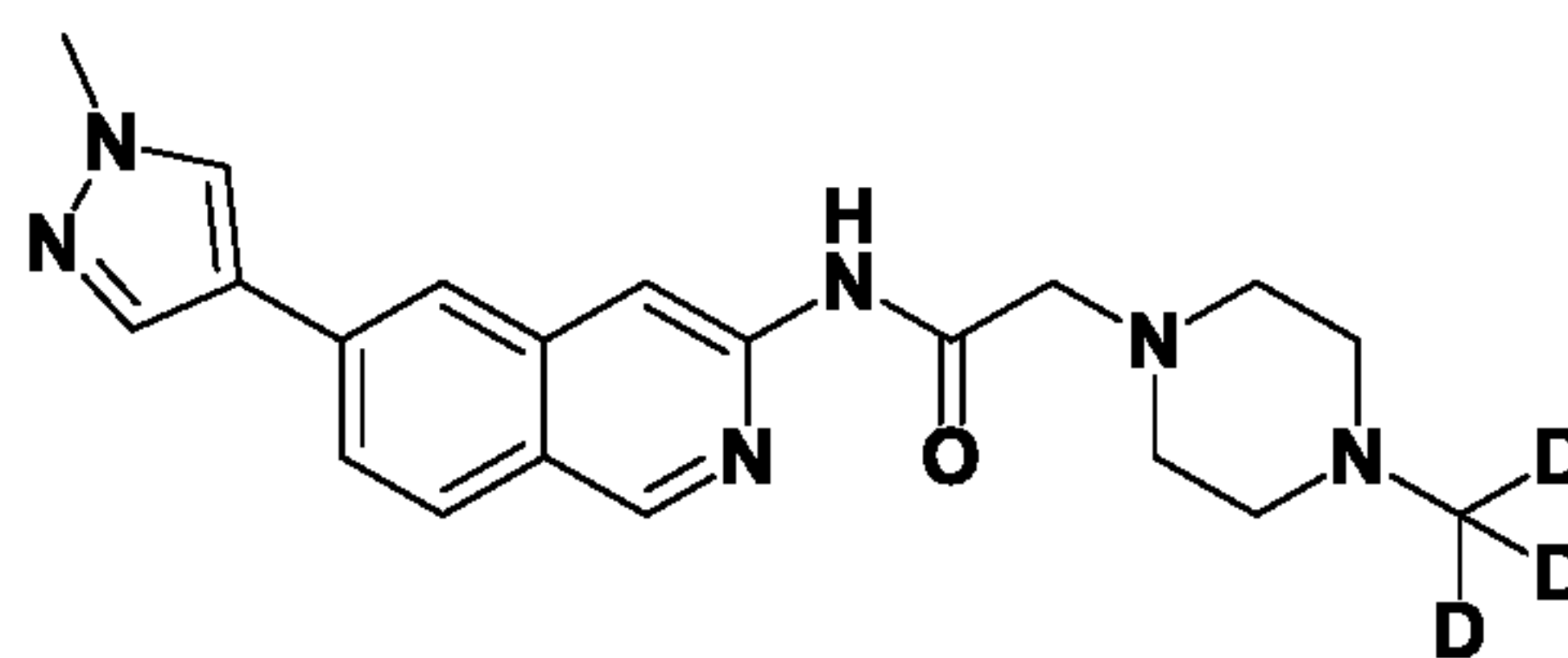
[01057] Beige solid (25.0 mg, 0.065 mmol, 17.4% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.55 - 2.63 (4 H, m), 2.83 (3 H, s), 3.28 (2 H, s), 3.61 - 3.69 (4 H, m), 7.89 (1 H, dd, *J*=11.11, 1.24 Hz), 8.40 (1 H, s), 8.68 (1 H, s), 9.34 (1 H, s), 10.32 (1 H, s); ESIMS found for C₁₈H₁₈FN₅O₂S *m/z* 388.1 (M+1).



964

[01058] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(phenylsulfonyl)piperidine-4-carboxamide **964**.

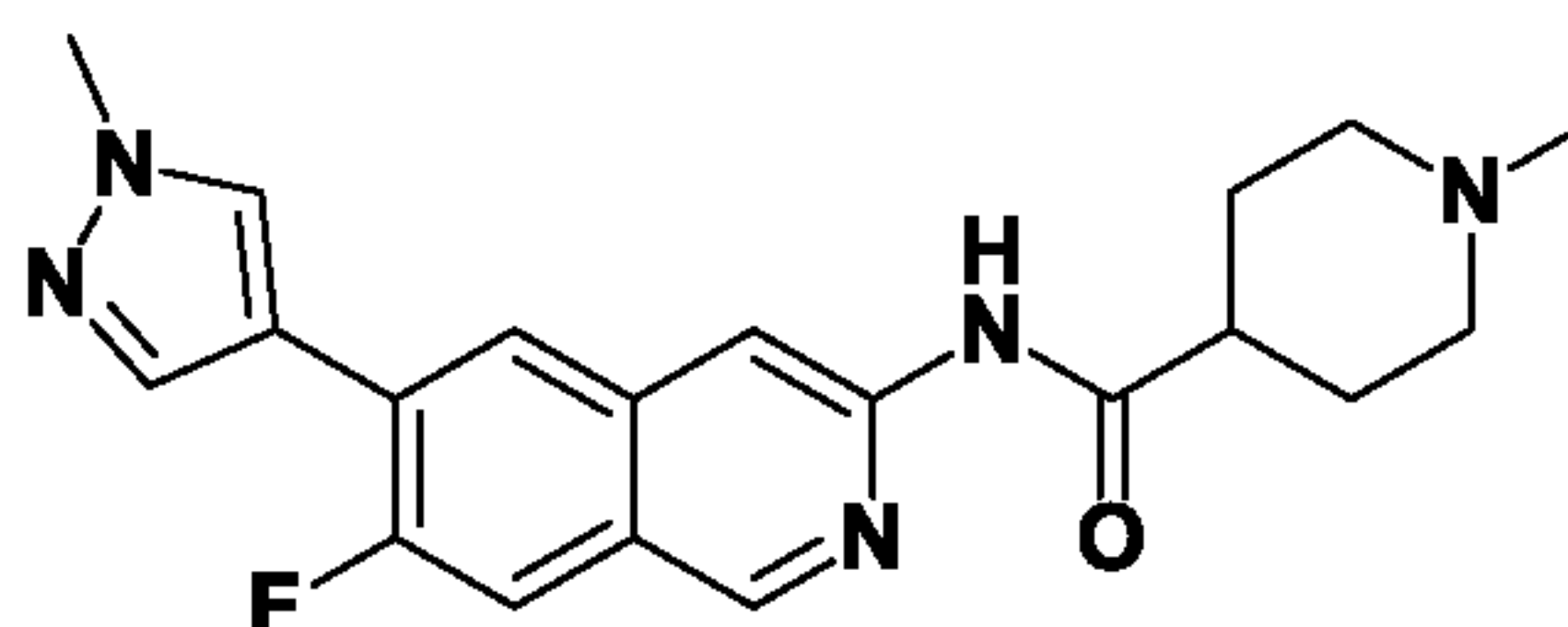
[01059] White solid (81.0 mg, 0.170 mmol, 63.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.75 (2 H, m), 1.90 (2 H, br dd, *J*=13.58, 2.88 Hz), 2.27 - 2.36 (2 H, m), 2.51 - 2.56 (1 H, m), 3.69 (2 H, br d, *J*=12.08 Hz), 3.90 (3 H, s), 7.65 - 7.70 (2 H, m), 7.72 - 7.80 (4 H, m), 7.99 (1 H, d, *J*=8.51 Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.39 (1 H, s), 9.01 (1 H, s), 10.45 (1 H, s); ESIMS found for C₂₅H₂₅N₅O₃S *m/z* 475.9 (M+1).



965

[01060] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(methyl-*d*3) piperazin-1-yl)acetamide **965**.

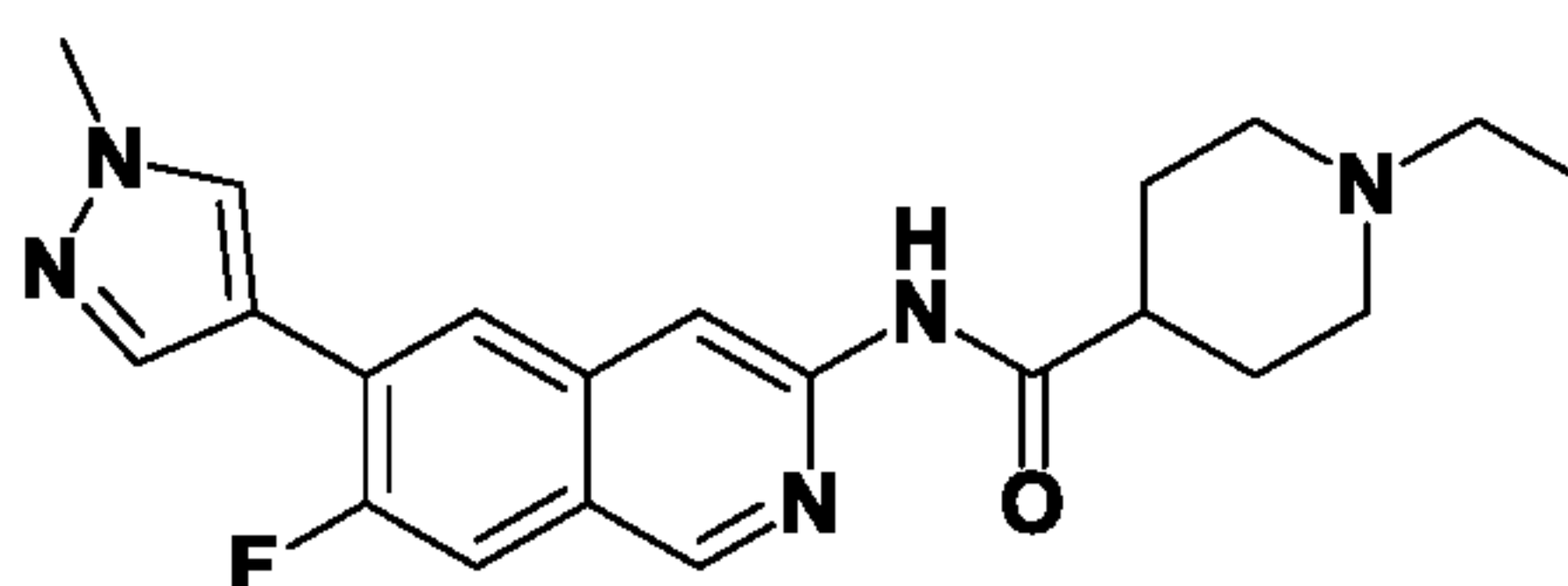
[01061] Beige solid (70.0 mg, 0.191 mmol, 28.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.40 (4 H, br s), 2.58 (4 H, br s), 3.22 (2 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.92 (1 H, s); ESIMS found for C₂₀H₂₁[²H₃]N₆O *m/z* 368.2 (M+1).



966

[01062] N-(7-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide **966**.

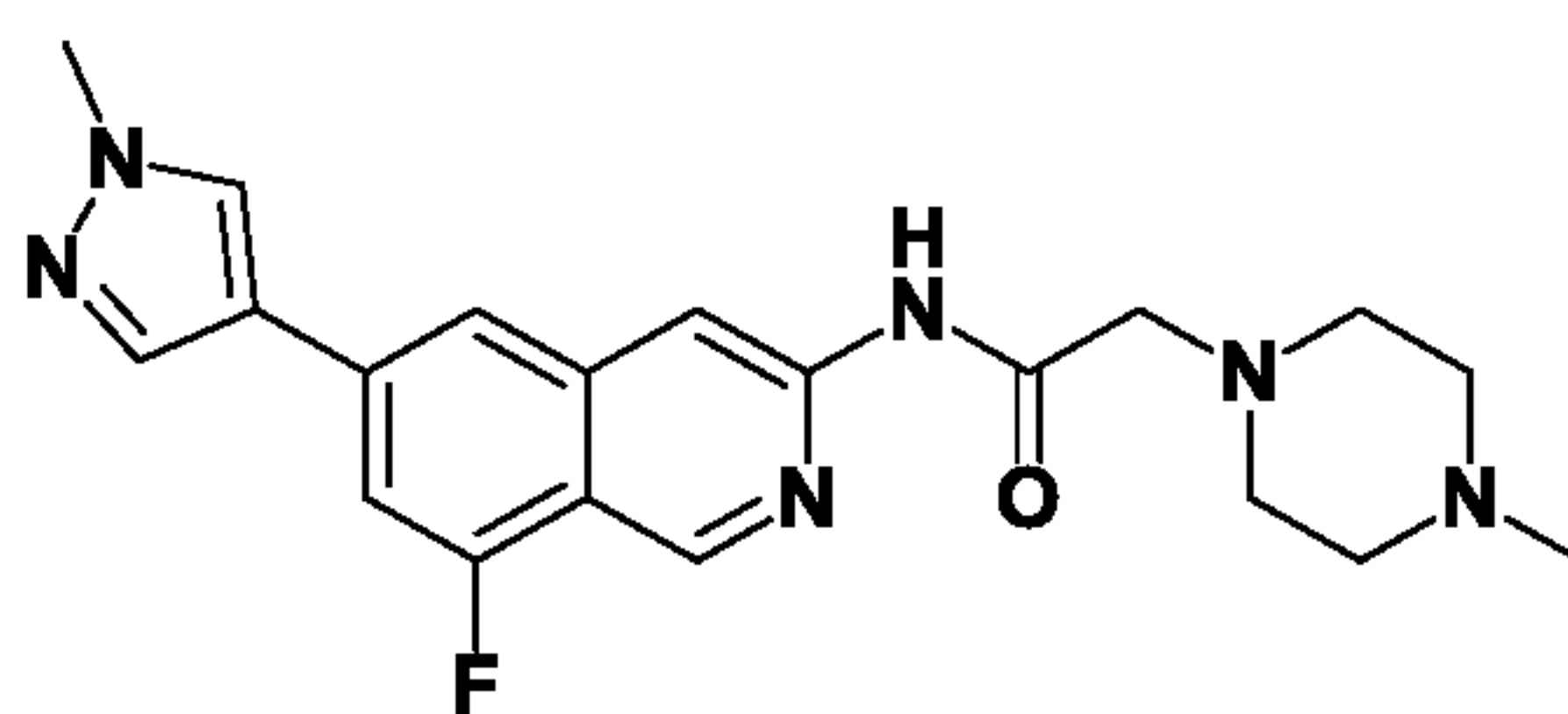
[01063] White solid (65.0 mg, 0.177 mmol, 80.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.72 (2 H, m), 1.73 - 1.80 (2 H, m), 1.86 (2 H, td, *J*=11.66, 2.20 Hz), 2.16 (3 H, s), 2.45 - 2.55 (1 H, m), 2.76 - 2.85 (2 H, m), 3.93 (3 H, s), 7.89 (1 H, d, *J*=11.80 Hz), 8.10 (1 H, s), 8.26 (1 H, d, *J*=7.41 Hz), 8.30 (1 H, d, *J*=2.74 Hz), 8.49 (1 H, s), 9.03 (1 H, s), 10.49 (1 H, s); ESIMS found for C₂₀H₂₂FN₅O *m/z* 368.2 (M+1).



967

[01064] 1-Ethyl-N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide **967**.

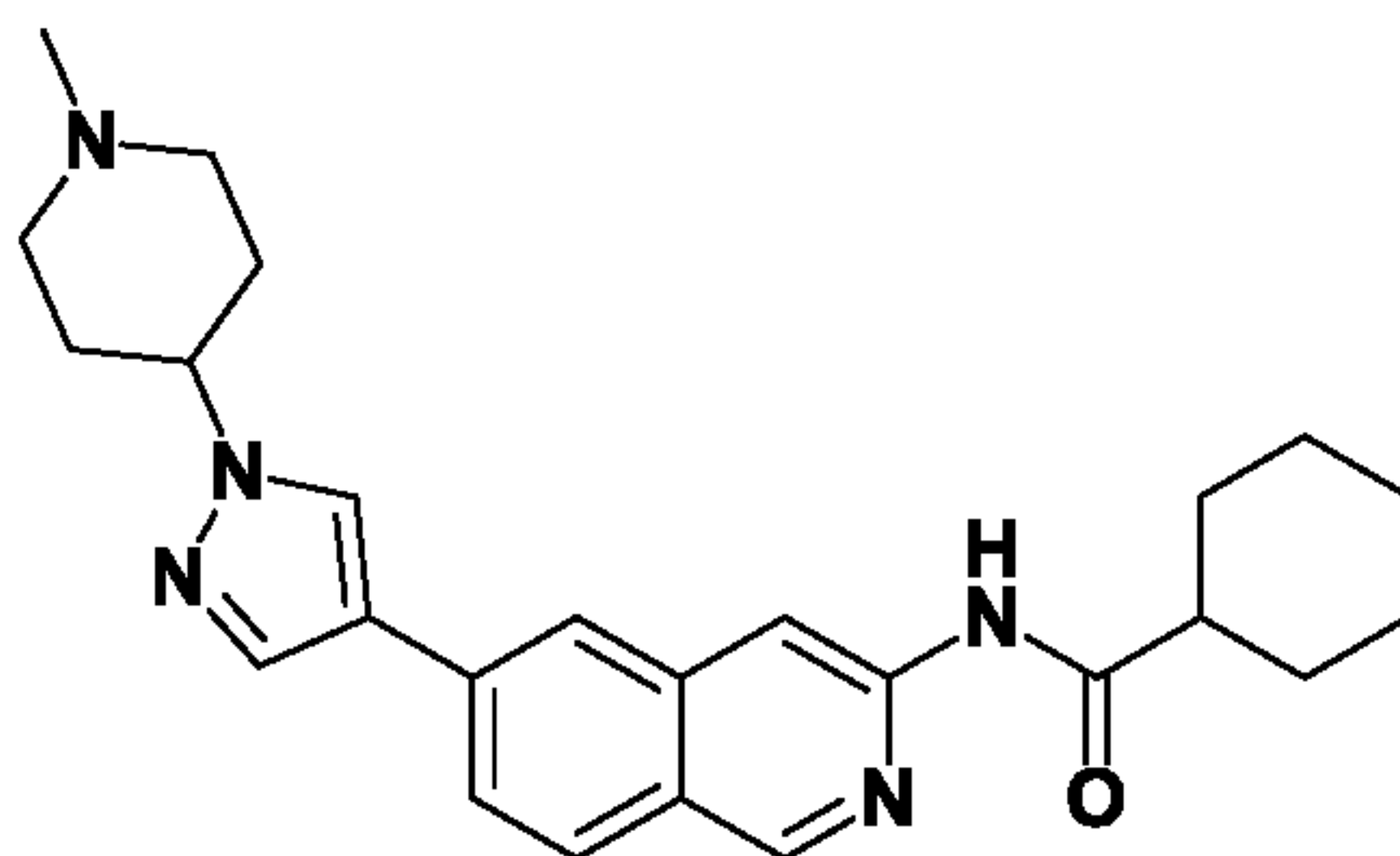
[01065] White solid (20.0 mg, 0.052 mmol, 26.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.00 (3 H, t, *J*=7.14 Hz), 1.67 (2 H, td, *J*=12.21, 3.57 Hz), 1.75 - 1.81 (2 H, m), 1.86 (2 H, td, *J*=11.73, 2.06 Hz), 2.31 (2 H, q, *J*=7.14 Hz), 2.51 - 2.58 (1 H, m), 2.87 - 2.95 (2 H, m), 3.93 (3 H, s), 7.89 (1 H, d, *J*=11.53 Hz), 8.10 (1 H, d, *J*=0.82 Hz), 8.26 (1 H, d, *J*=7.41 Hz), 8.30 (1 H, d, *J*=2.47 Hz), 8.50 (1 H, s), 9.03 (1 H, s), 10.49 (1 H, s); ESIMS found for C₂₁H₂₄FN₅O *m/z* 382.2 (M+1).



968

[01066] N-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **968**.

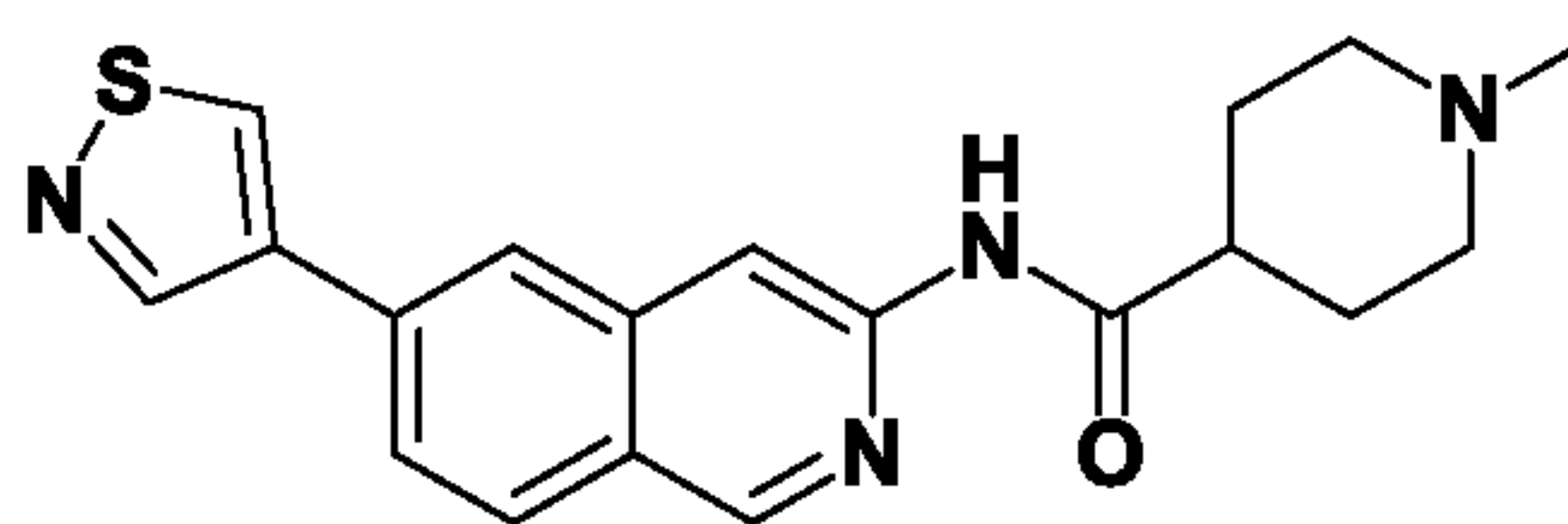
[01067] Beige solid (25.0 mg, 0.065 mmol, 23.1% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.33 (3 H, br s), 2.52 - 2.77 (8 H, m), 3.27 (2 H, s), 3.90 (3 H, s), 7.62 (1 H, dd, *J*=12.08, 1.37 Hz), 7.99 (1 H, s), 8.14 (1 H, d, *J*=0.82 Hz), 8.41 (1 H, s), 8.48 (1 H, s), 9.17 (1 H, s), 10.12 (1 H, br s); ESIMS found for C₂₀H₂₃FN₆O *m/z* 383.2 (M+1).



969

[01068] N-(6-(1-(1-Methylpiperidin-4-yl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexanecarboxamide **969**.

[01069] Beige solid (79.0 mg, 0.189 mmol, 63.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.13 - 1.34 (3 H, m), 1.39 - 1.51 (2 H, m), 1.66 (1 H, br d, *J*=11.25 Hz), 1.72 - 1.79 (2 H, m), 1.82 (2 H, br d, *J*=12.90 Hz), 1.94 - 2.11 (6 H, m), 2.22 (3 H, s), 2.52 - 2.60 (1 H, m), 2.87 (2 H, br d, *J*=11.25 Hz), 4.10 - 4.20 (1 H, m), 7.77 (1 H, dd, *J*=8.51, 1.37 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.05 (1 H, s), 8.10 (1 H, s), 8.43 (1 H, s), 8.47 (1 H, s), 9.01 (1 H, s), 10.37 (1 H, s) ESIMS found for C₂₅H₃₁N₅O *m/z* 418.25 (M+1).

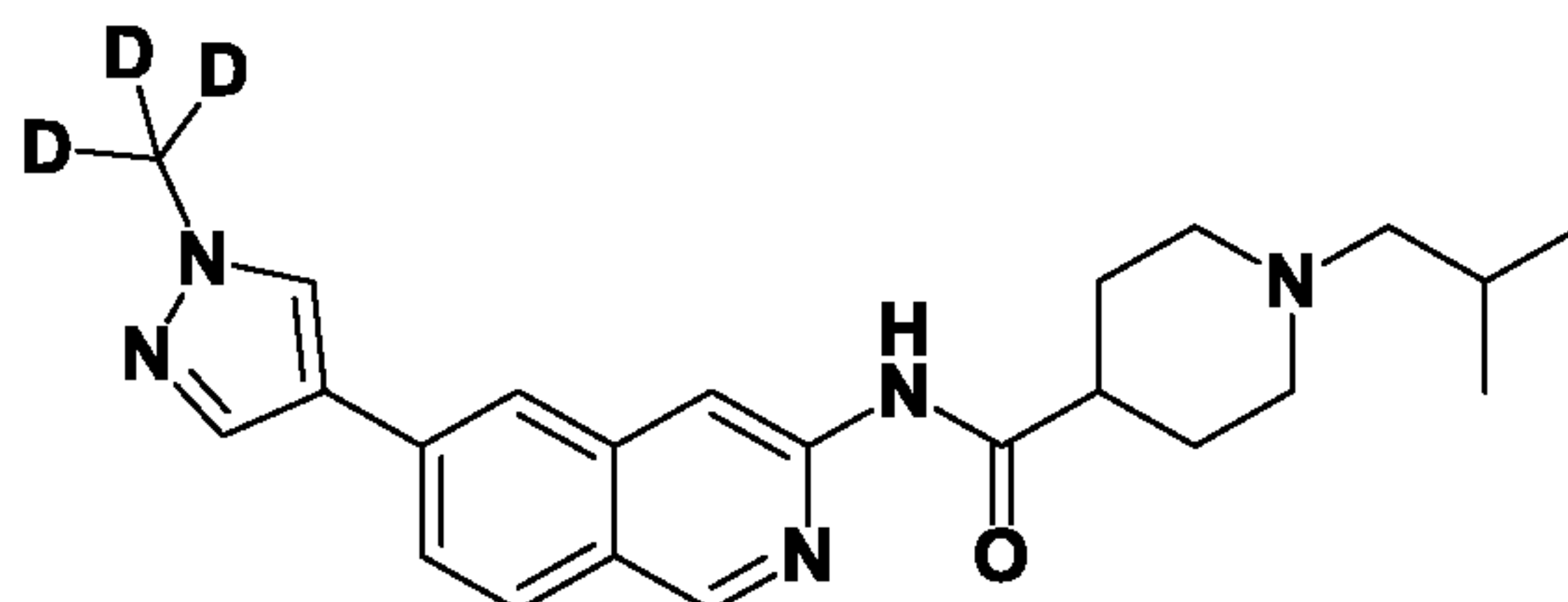


970

[01070] N-(6-(Isothiazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide **970**.

[01071] Beige solid (28.0 mg, 0.079 mmol, 17.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.63 - 1.74 (2 H, m), 1.75 - 1.84 (2 H, m), 1.88 (2 H, td, *J*=11.46, 2.06 Hz), 2.17 (3 H,

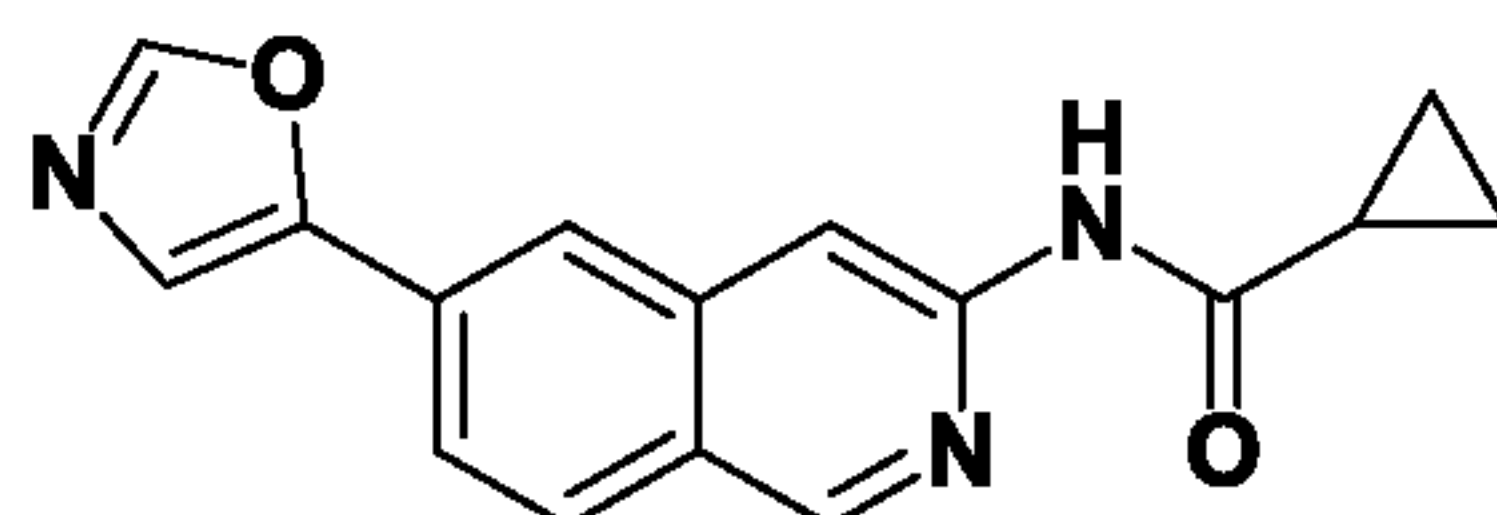
s), 2.51 - 2.57 (1 H, m), 2.81 (2 H, br d, $J=11.53$ Hz), 7.95 (1 H, dd, $J=8.51, 1.65$ Hz), 8.11 (1 H, d, $J=8.51$ Hz), 8.35 (1 H, s), 8.54 (1 H, s), 9.12 (1 H, s), 9.25 (1 H, s), 9.59 (1 H, s), 10.49 (1 H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 352.9 (M+1).



972

[01072] 1-Isobutyl-N-(6-(1-(methyl- d_3)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **972**.

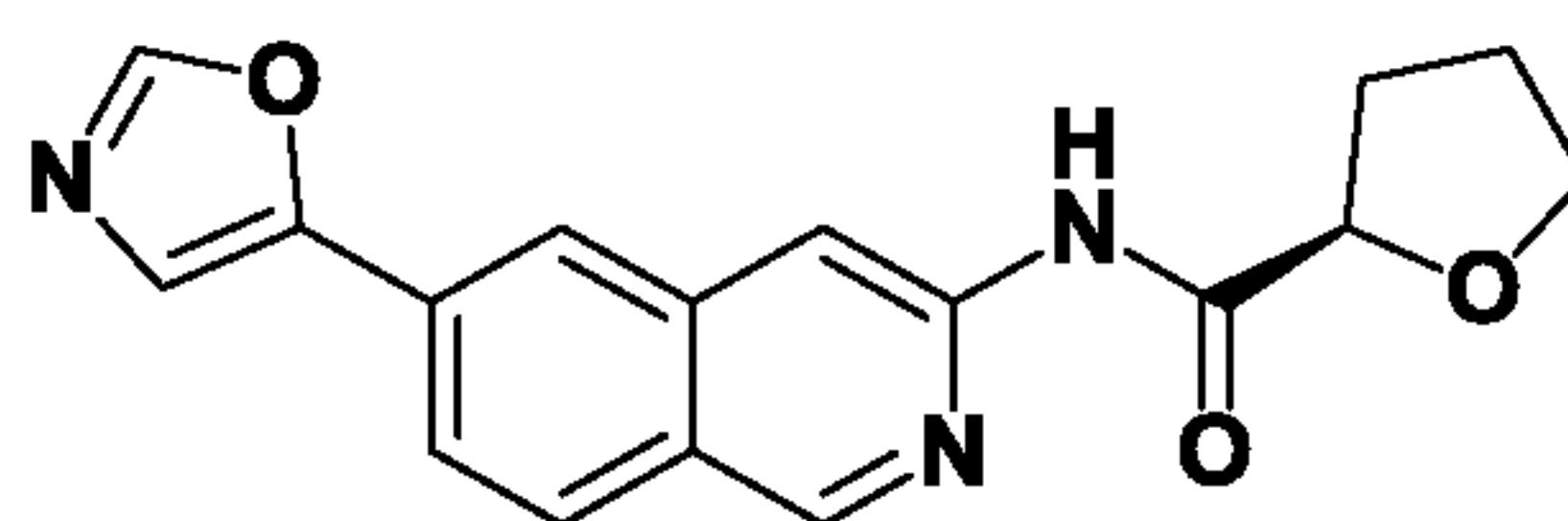
[01073] White solid (165.0 mg, 0.418 mmol, 49.8% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 0.86 (6 H, d, $J=6.59$ Hz), 1.62 - 1.72 (2 H, m), 1.73 - 1.81 (3 H, m), 1.82 - 1.91 (2 H, m), 2.02 (2 H, d, $J=7.41$ Hz), 2.51 - 2.59 (1 H, m), 2.81 - 2.90 (2 H, m), 7.74 (1 H, dd, $J=8.51, 1.65$ Hz), 8.00 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, s), 8.08 (1 H, d, $J=0.82$ Hz), 8.35 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.45 (1 H, s); ESIMS found for $C_{23}H_{26}[^2H_3]N_5O$ m/z 395.2 (M+1).



973

[01074] N-(6-(Oxazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide **974**.

[01075] Beige solid (34.0 mg, 0.122 mmol, 25.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.78 - 0.91 (4 H, m), 2.04 - 2.12 (1 H, m), 7.86 (1 H, dd, $J=8.51, 1.65$ Hz), 7.95 (1 H, s), 8.13 (1 H, d, $J=8.78$ Hz), 8.17 (1 H, s), 8.50 (1 H, s), 8.57 (1 H, s), 9.14 (1 H, s), 10.93 (1 H, s); ESIMS found for $C_{16}H_{13}N_3O_2$ m/z 280.1 (M+1).

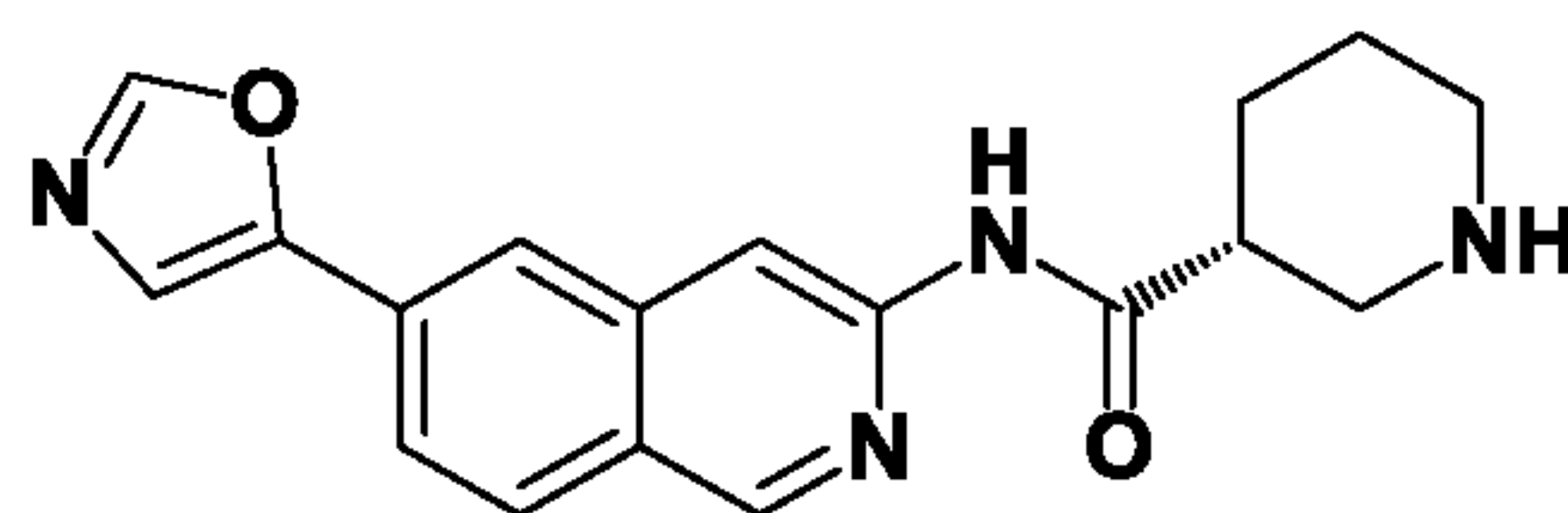


974

[01076] (R)-N-(6-(Oxazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide **974**.

[01077] Light yellow solid (120.0 mg, 0.388 mmol, 41.0% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.83 - 1.97 (2 H, m), 1.98 - 2.08 (1 H, m), 2.20 - 2.31 (1 H, m), 3.82 - 3.91 (1 H, m), 3.97 - 4.06 (1 H, m), 4.54 (1 H, dd, $J=8.37, 5.63$ Hz), 7.90 (1 H, dd, $J=8.64, 1.51$ Hz), 7.96 (1

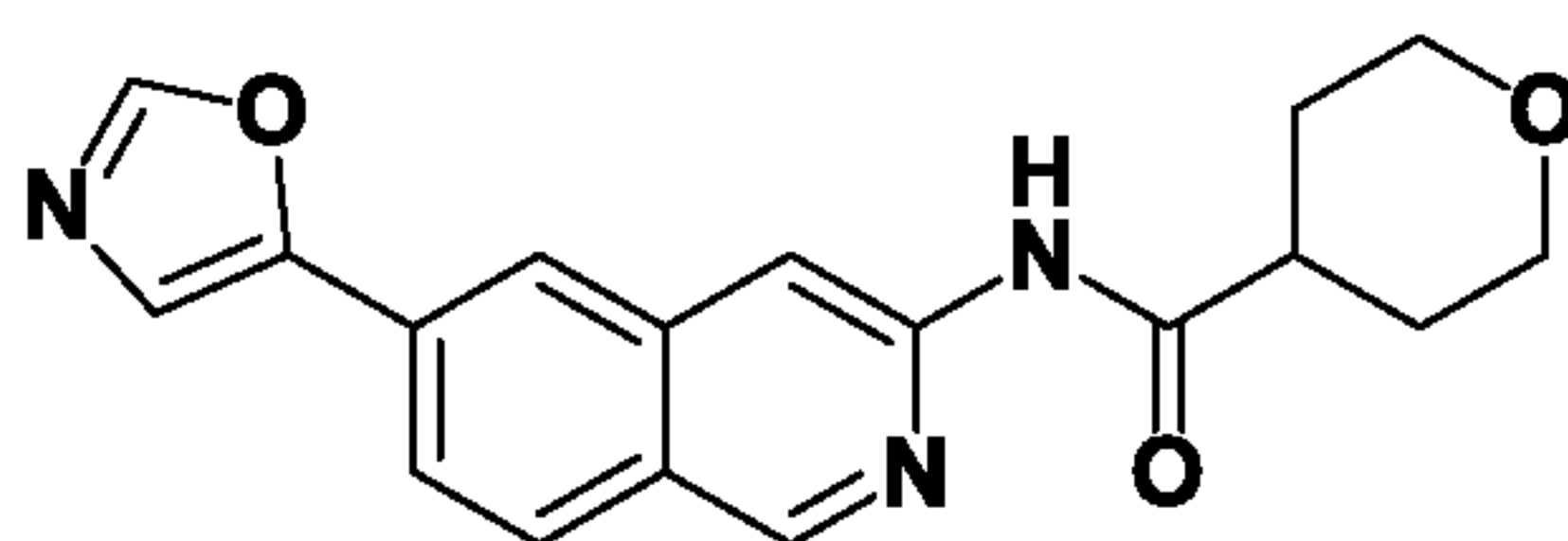
H, s), 8.16 (1 H, d, $J=8.51$ Hz), 8.25 (1 H, s), 8.52 (1 H, s), 8.58 (1 H, s), 9.15 (1 H, s), 9.88 (1 H, s); ESIMS found for $C_{17}H_{15}N_3O_3$ m/z 310.1 (M+1).



975

[01078] (R)-N-(6-(Oxazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide 975.

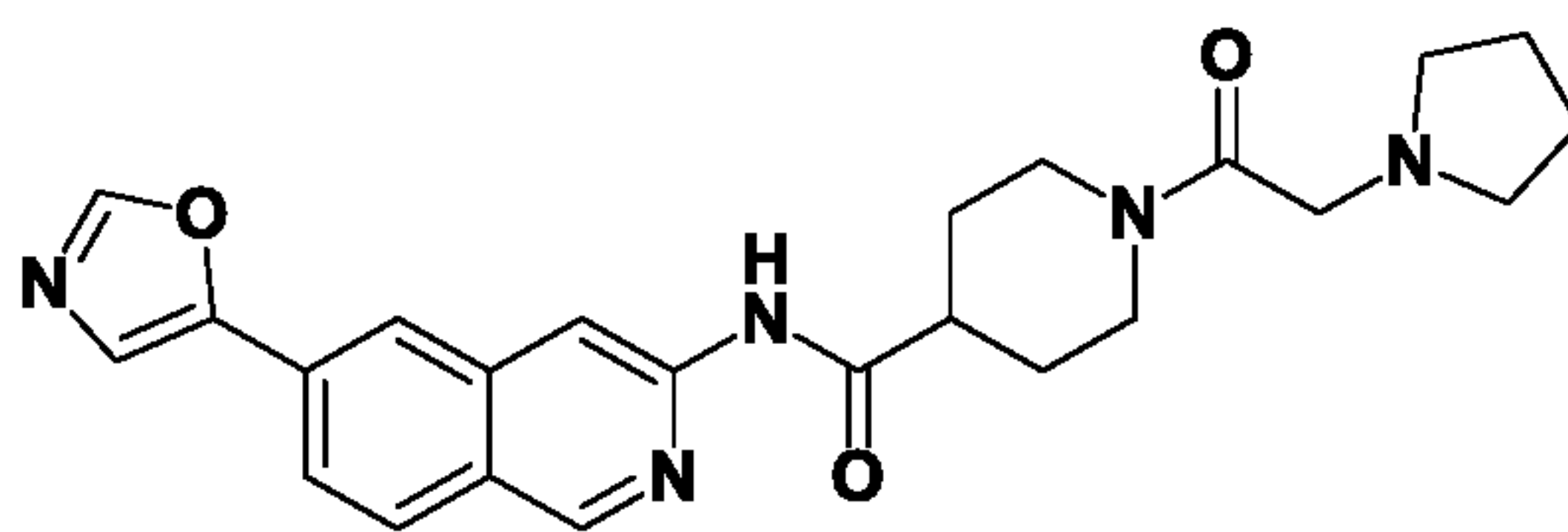
[01079] Beige solid (19.0 mg, 0.059 mmol, 24.9% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.36 - 1.47 (1 H, m), 1.56 - 1.64 (1 H, m), 1.64 - 1.72 (1 H, m), 1.87 (1 H, dt, $J=8.58$, 4.08 Hz), 2.52 - 2.59 (1 H, m), 2.59 - 2.67 (1 H, m), 2.75 (1 H, br dd, $J=11.94$, 8.92 Hz), 2.78 - 2.85 (1 H, m), 2.99 (1 H, br dd, $J=12.08$, 3.02 Hz), 7.86 (1 H, dd, $J=8.51$, 1.65 Hz), 7.95 (1 H, s), 8.13 (1 H, d, $J=8.51$ Hz), 8.19 (1 H, s), 8.52 (1 H, s), 8.58 (1 H, s), 9.12 (1 H, s), 10.85 (1 H, s); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.0 (M+1).



976

[01080] N-(6-(Oxazol-5-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide 976.

[01081] Beige solid (17.5 mg, 0.054 mmol, 24.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.63 - 1.78 (4 H, m), 2.78 - 2.87 (1 H, m), 3.33 - 3.40 (2 H, m), 3.88 - 3.96 (2 H, m), 7.87 (1 H, dd, $J=8.64$, 1.51 Hz), 7.95 (1 H, s), 8.13 (1 H, d, $J=8.78$ Hz), 8.20 (1 H, s), 8.54 (1 H, s), 8.58 (1 H, s), 9.13 (1 H, s), 10.60 (1 H, s); ESIMS found for $C_{18}H_{17}N_3O_3$ m/z 323.9 (M+1).

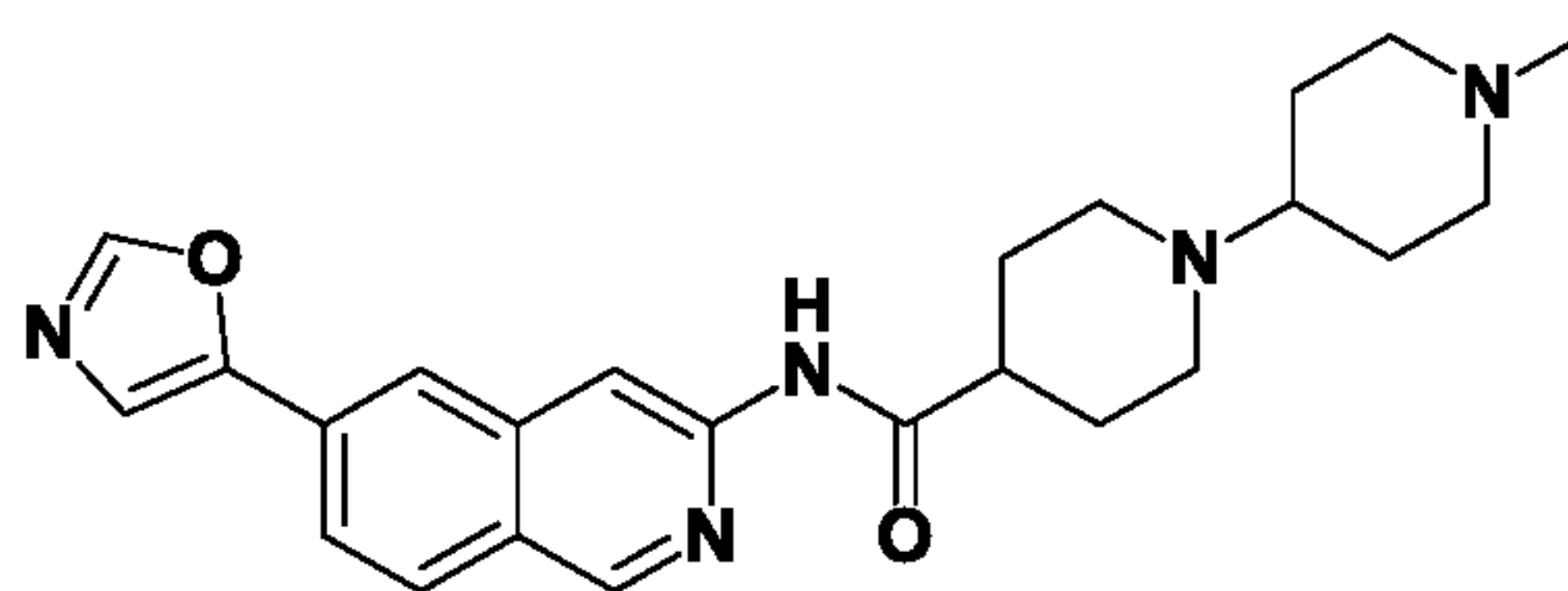


977

[01082] N-(6-(Oxazol-5-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide 977.

[01083] White solid (33.4 mg, 0.077 mmol, 43.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.41 - 1.53 (1 H, m), 1.55 - 1.66 (1 H, m), 1.69 (4 H, br s), 1.84 (2 H, br d, $J=10.98$ Hz), 2.48 (4 H, br s), 2.56 - 2.66 (1 H, m), 2.82 (1 H, ddt, $J=11.25$, 7.55, 3.91, 3.91 Hz), 3.01 (1 H, br t, $J=12.21$ Hz), 3.14 - 3.21 (1 H, m), 3.33 - 3.37 (1 H, m), 4.11 (1 H, br d, $J=13.45$ Hz), 4.40 (1 H, br d, $J=13.17$ Hz), 7.87 (1 H, dd, $J=8.51$, 1.10 Hz), 7.95 (1 H, s), 8.13 (1 H, d, $J=8.51$ Hz), 8.20 (1 H,

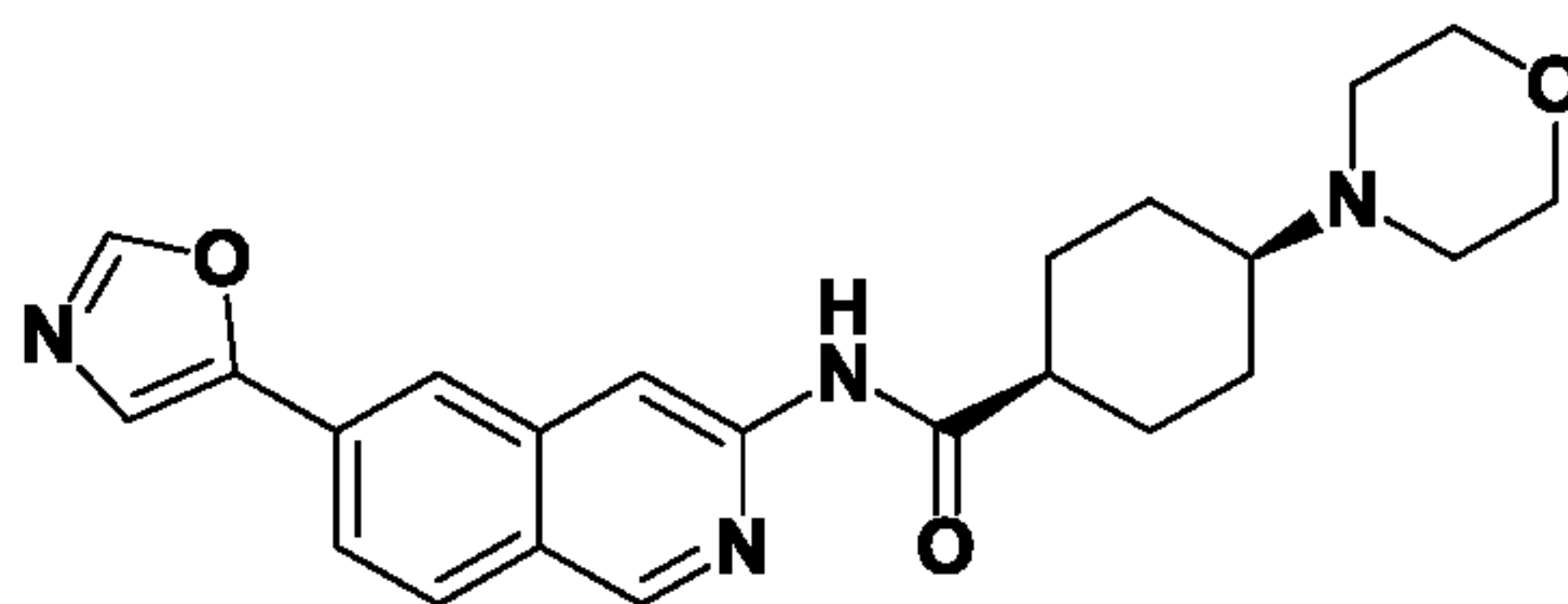
s), 8.53 (1 H, s), 8.57 (1 H, s), 9.14 (1 H, s), 10.64 (1 H, s); ESIMS found for $C_{24}H_{27}N_5O_3$ m/z 434.0 (M+1).



978

[01084] 1'-Methyl-N-(6-(oxazol-5-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide **978**.

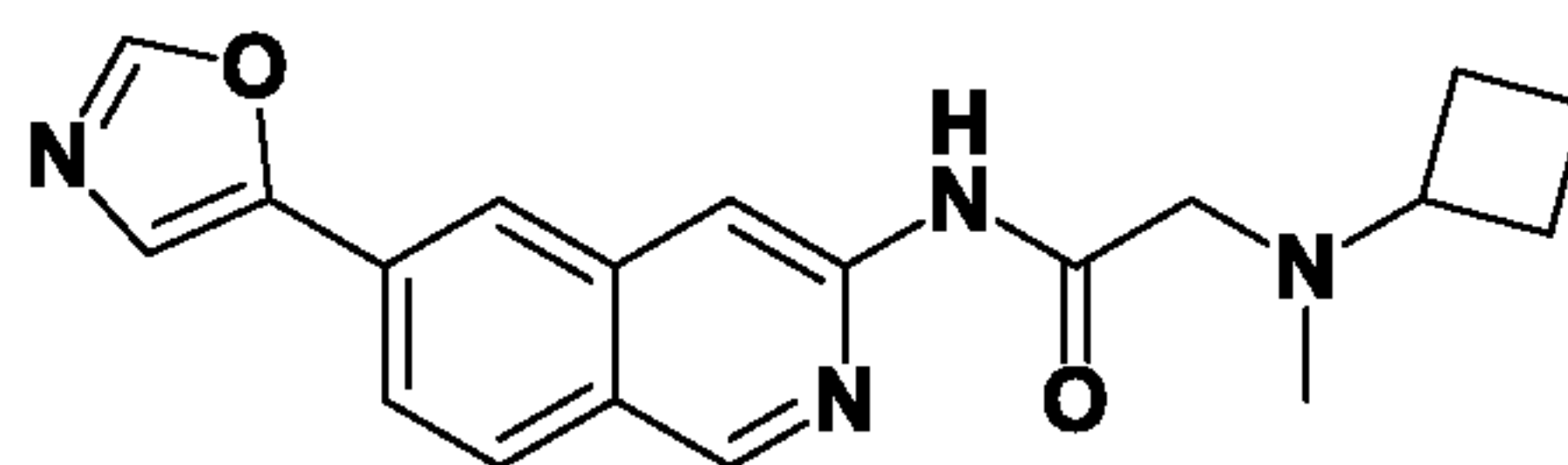
[01085] Beige solid (90.0 mg, 0.215 mmol, 61.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.43 (2 H, qd, $J=11.85, 3.43$ Hz), 1.58 - 1.71 (4 H, m), 1.75 - 1.86 (4 H, m), 2.07 - 2.20 (3 H, m), 2.12 (3 H, s), 2.51 - 2.57 (1 H, m), 2.77 (2 H, br d, $J=11.53$ Hz), 2.90 (2 H, br d, $J=11.25$ Hz), 7.86 (1 H, dd, $J=8.51, 1.65$ Hz), 7.94 (1 H, s), 8.12 (1 H, d, $J=8.78$ Hz), 8.19 (1 H, s), 8.54 (1 H, s), 8.57 (1 H, s), 9.12 (1 H, s), 10.53 (1 H, s); ESIMS found for $C_{24}H_{29}N_5O_2$ m/z 420.2 (M+1).



979

[01086] *cis*-4-Morpholino-N-(6-(oxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **979**.

[01087] Off-white solid (125.0 mg, 0.308 mmol, 51.7% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.15 - 1.27 (2 H, m), 1.42 - 1.55 (2 H, m), 1.91 (4 H, br t, $J=12.62$ Hz), 2.17 - 2.26 (1 H, m), 2.45 - 2.49 (4 H, m), 2.51 - 2.53 (1 H, m), 3.52 - 3.59 (4 H, m), 7.86 (1 H, dd, $J=8.51, 1.37$ Hz), 7.95 (1 H, s), 8.12 (1 H, d, $J=8.51$ Hz), 8.18 (1 H, s), 8.52 (1 H, s), 8.57 (1 H, s), 9.12 (1 H, s), 10.53 (1 H, s); ESIMS found for $C_{23}H_{26}N_4O_3$ m/z 407.2 (M+1).

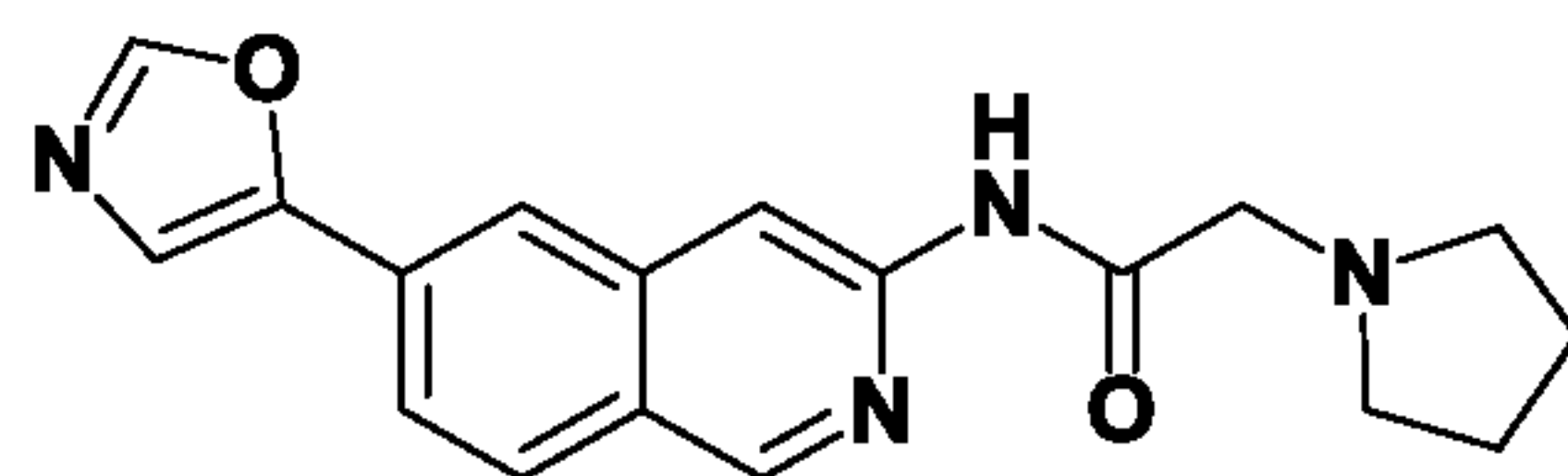


980

[01088] 2-(Cyclobutyl(methyl)amino)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide **980**.

[01089] Beige solid (31.5 mg, 0.094 mmol, 49.2% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.54 - 1.69 (2 H, m), 1.80 - 1.92 (2 H, m), 1.98 - 2.06 (2 H, m), 2.23 (3 H, s), 3.03 - 3.11

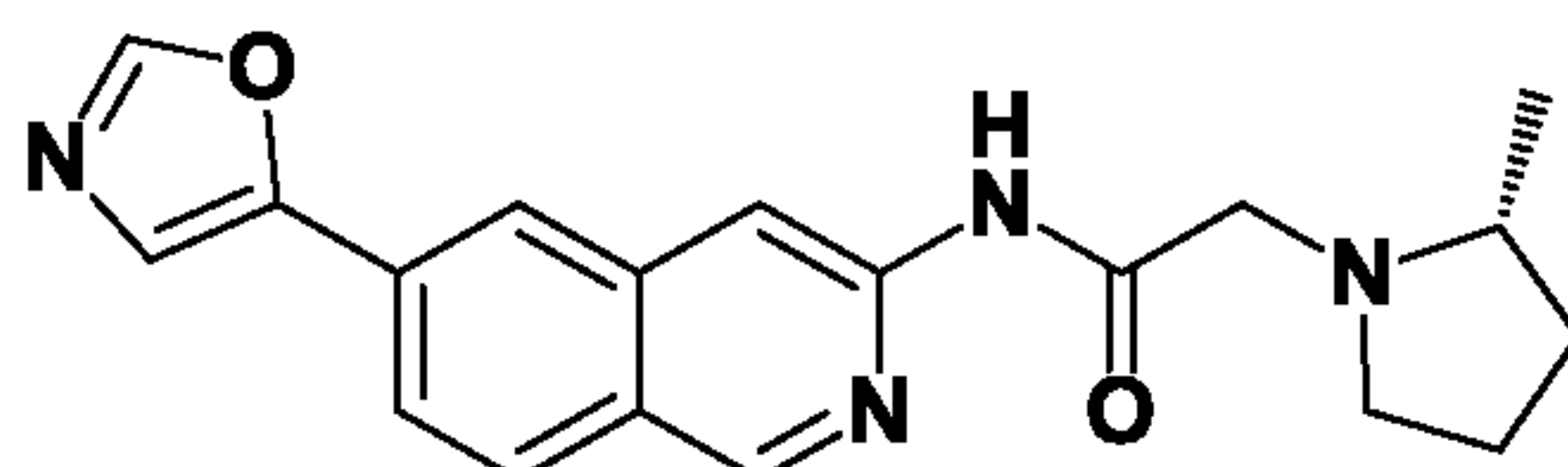
(1 H, m), 3.13 (2 H, s), 7.89 (1 H, dd, $J=8.51, 1.65$ Hz), 7.97 (1 H, s), 8.16 (1 H, d, $J=8.51$ Hz), 8.27 (1 H, s), 8.53 (1 H, s), 8.58 (1 H, s), 9.15 (1 H, s), 10.01 (1 H, s); ESIMS found for $C_{19}H_{20}N_4O_2$ m/z 337.1 (M+1).



981

[01090] N-(6-(Oxazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **981**.

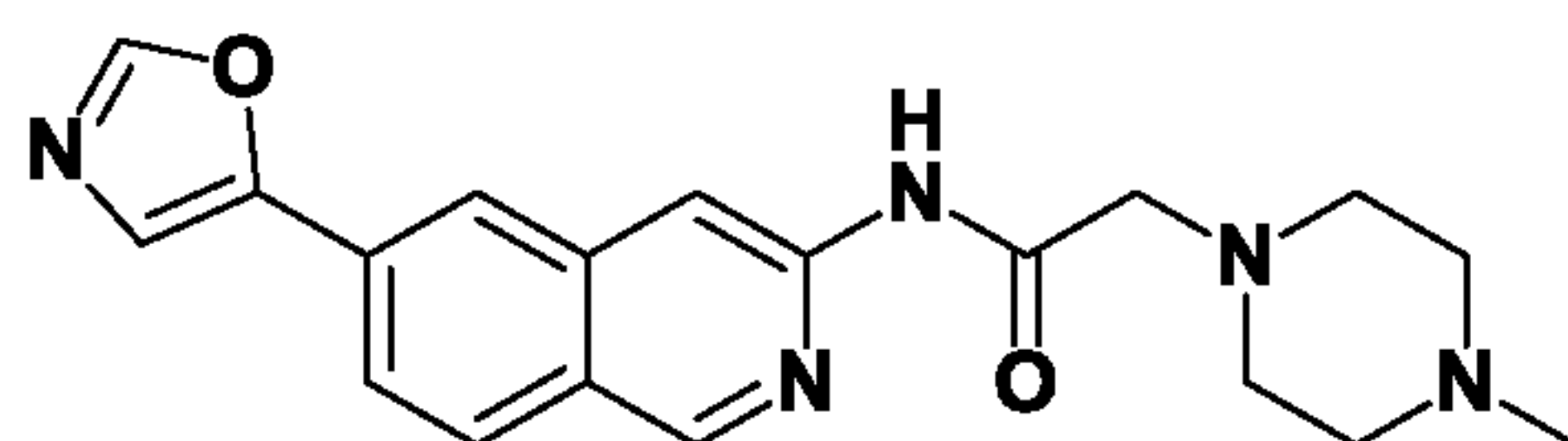
[01091] Off-white solid (45.0 mg, 0.140 mmol, 42.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.78 (4 H, dt, $J=6.79, 3.33$ Hz), 2.62 - 2.70 (4 H, m), 3.37 (2 H, s), 7.89 (1 H, dd, $J=8.78, 1.65$ Hz), 7.96 (1 H, s), 8.15 (1 H, d, $J=8.51$ Hz), 8.26 (1 H, s), 8.53 (1 H, s), 8.58 (1 H, s), 9.14 (1 H, s), 10.01 (1 H, s); ESIMS found for $C_{18}H_{18}N_4O_2$ m/z 323.1 (M+1).



982

[01092] (R)-2-(2-Methylpyrrolidin-1-yl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide **982**.

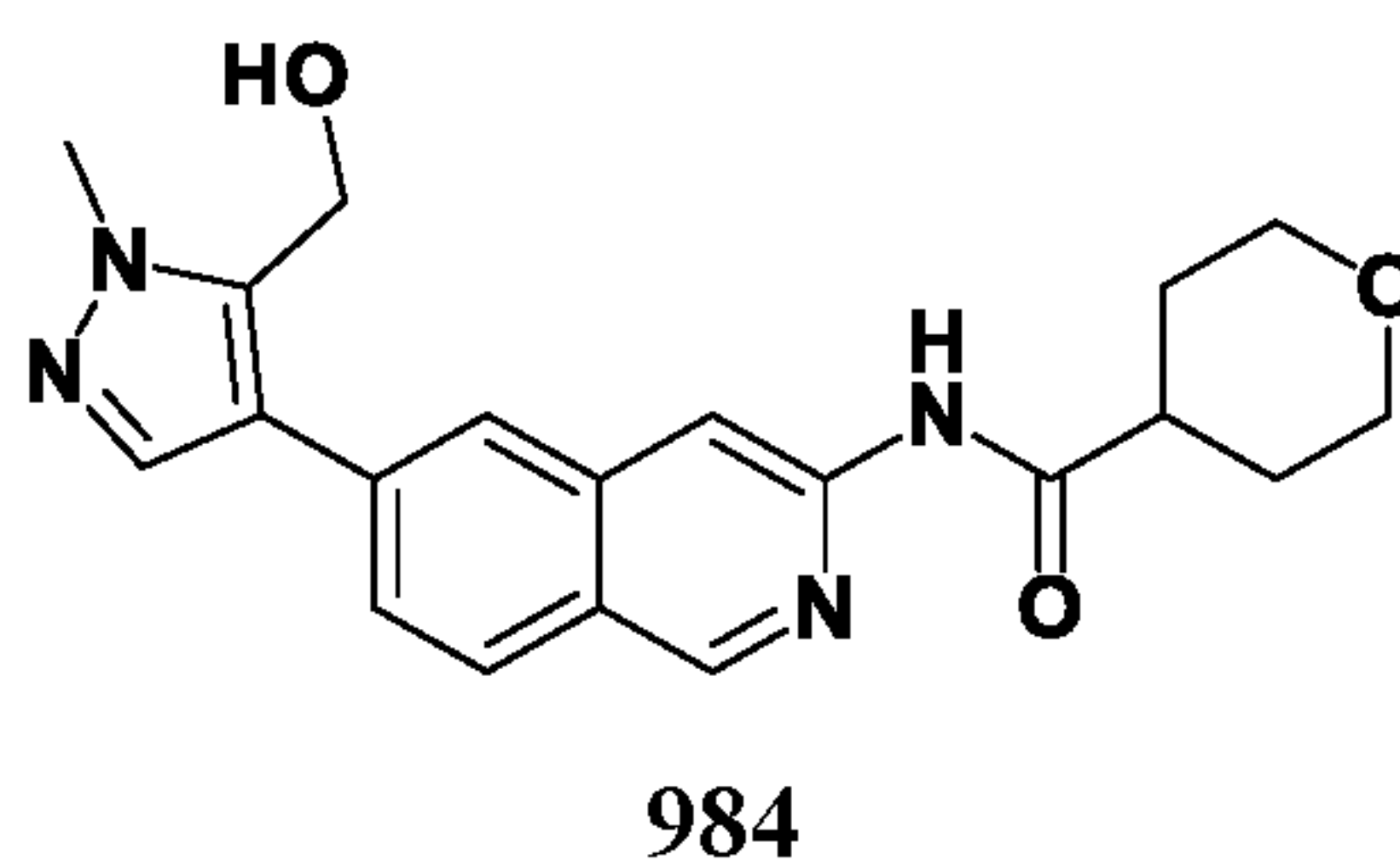
[01093] Beige solid (8.0 mg, 0.024 mmol, 23.8% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.09 (3 H, d, $J=6.04$ Hz), 1.41 (1 H, dddd, $J=12.32, 10.39, 8.30, 6.31$ Hz), 1.67 - 1.84 (2 H, m), 1.91 - 2.02 (1 H, m), 2.40 (1 H, q, $J=8.78$ Hz), 2.57 - 2.66 (1 H, m), 3.13 (1 H, d, $J=16.19$ Hz), 3.13 - 3.20 (1 H, m), 3.55 (1 H, d, $J=16.19$ Hz), 7.89 (1 H, dd, $J=8.51, 1.65$ Hz), 7.97 (1 H, s), 8.16 (1 H, d, $J=8.51$ Hz), 8.27 (1 H, s), 8.53 (1 H, s), 8.58 (1 H, s), 9.14 (1 H, s), 9.98 (1 H, s); ESIMS found for $C_{19}H_{20}N_4O_2$ m/z 337.2 (M+1).



983

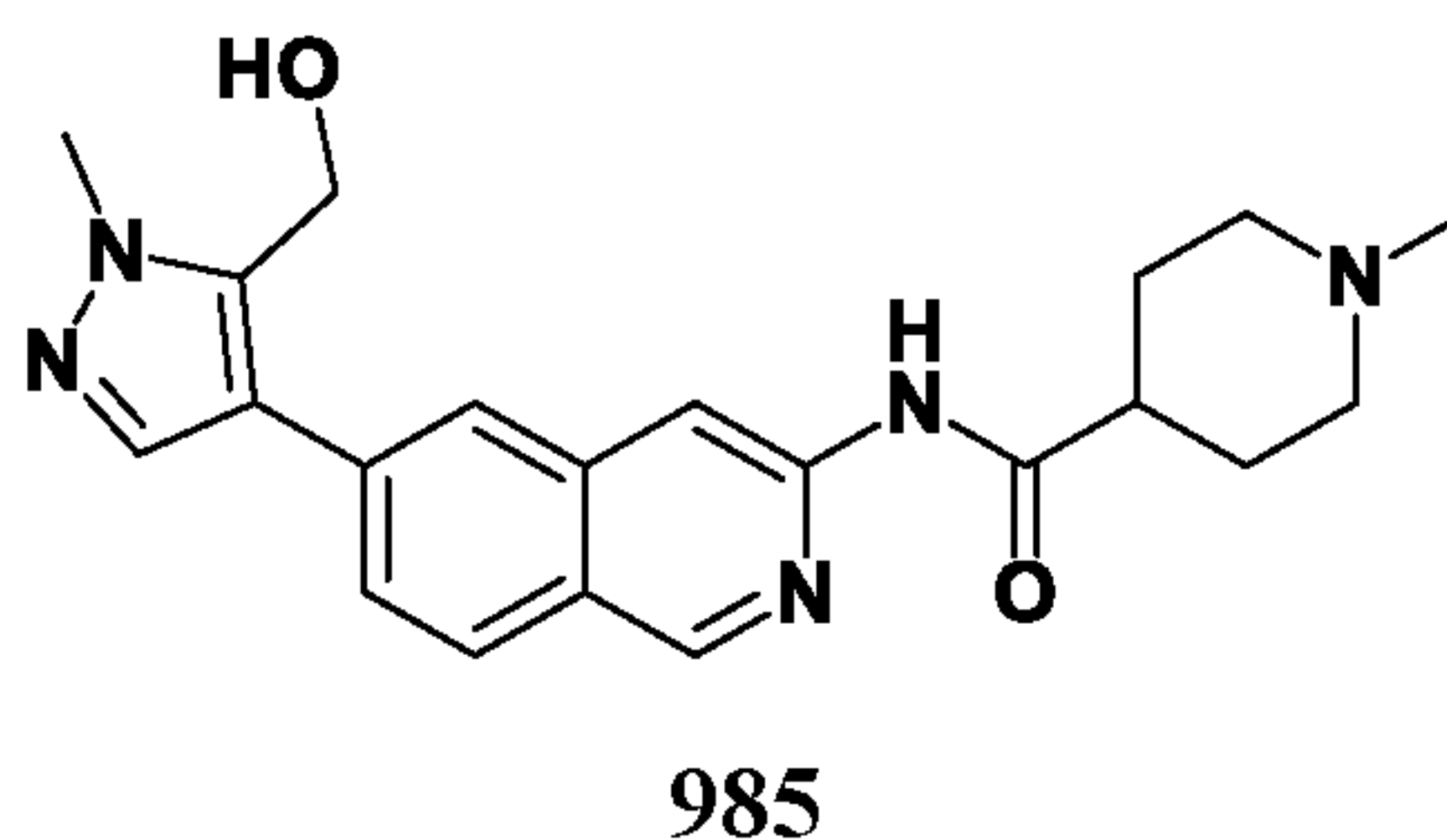
[01094] 2-(4-Methylpiperazin-1-yl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide **983**.

[01095] Pale yellow solid (43.0 mg, 0.122 mmol, 37.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.19 (3 H, s), 2.40 (4 H, br s), 2.58 (4 H, br s), 3.23 (2 H, s), 7.89 (1 H, dd, $J=8.51, 1.65$ Hz), 7.96 (1 H, s), 8.15 (1 H, d, $J=8.78$ Hz), 8.26 (1 H, s), 8.53 (1 H, s), 8.58 (1 H, s), 9.15 (1 H, s), 10.01 (1 H, s); ESIMS found for $C_{19}H_{21}N_5O_2$ m/z 352.2 (M+1).



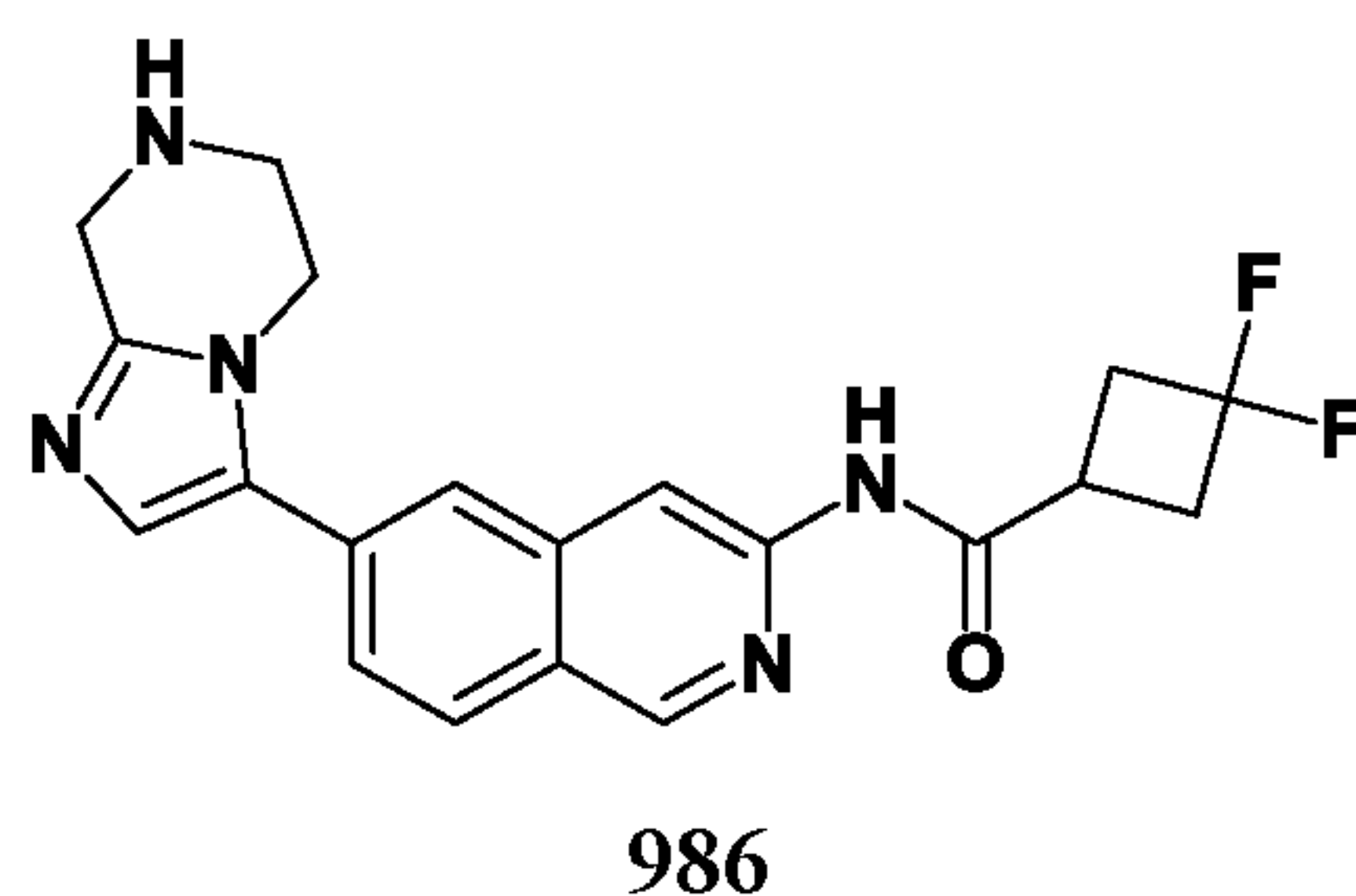
[01096] N-(6-(5-(Hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide **984**.

[01097] Beige solid (30.0 mg, 0.082 mmol, 25.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.63 - 1.79 (4 H, m), 2.77 - 2.87 (1 H, m), 3.33 - 3.40 (2 H, m), 3.91 (2 H, br d, *J*=2.47 Hz), 3.93 (3 H, s), 4.64 (2 H, d, *J*=5.21 Hz), 5.56 (1 H, t, *J*=5.35 Hz), 7.68 (1 H, dd, *J*=8.51, 1.37 Hz), 7.81 (1 H, s), 7.94 (1 H, s), 8.05 (1 H, d, *J*=8.51 Hz), 8.48 (1 H, s), 9.09 (1 H, s), 10.54 (1 H, s); ESIMS found for C₂₀H₂₂N₄O₃ *m/z* 367.0 (M+1).



[01098] N-(6-(5-(Hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide **985**.

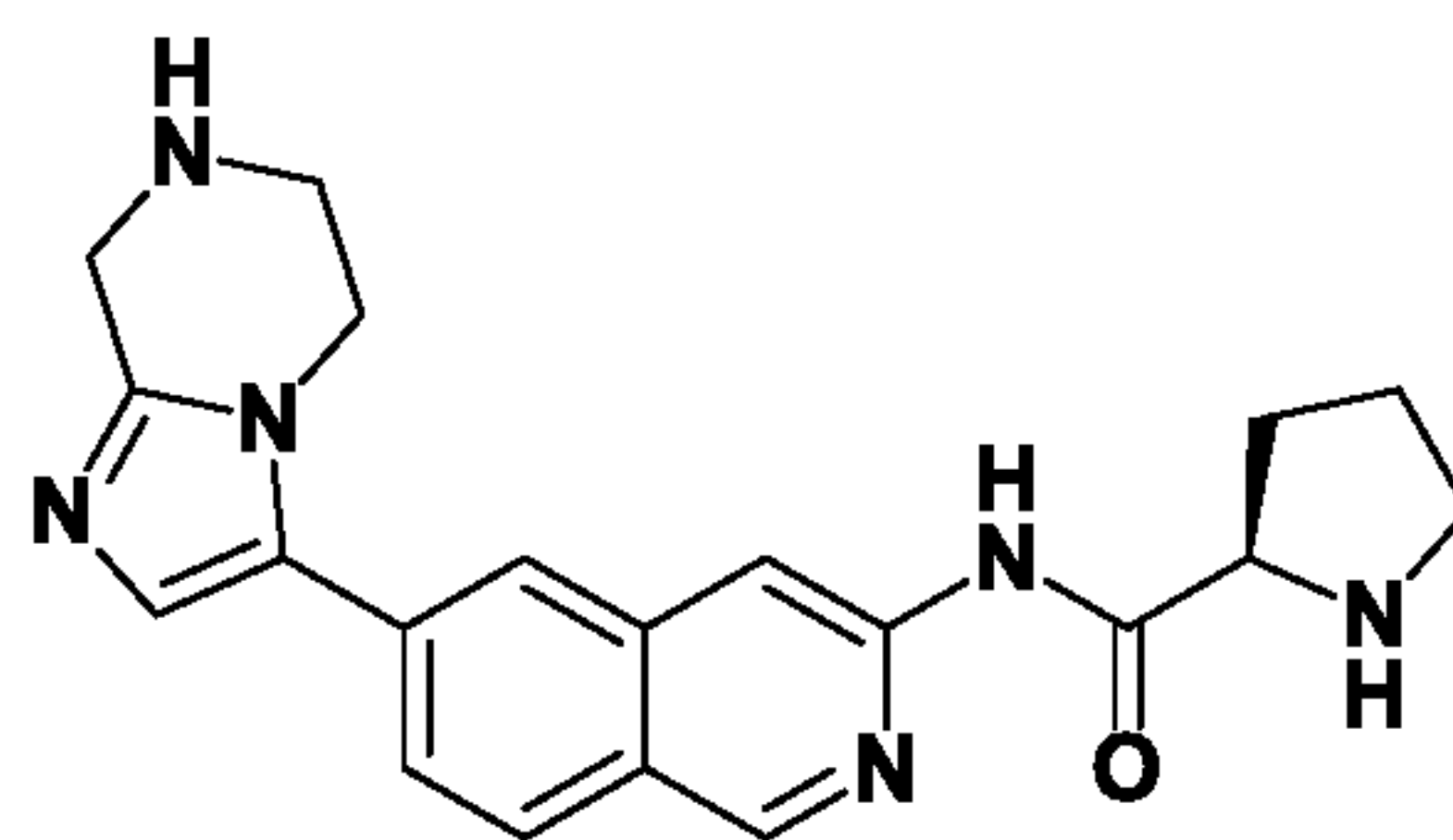
[01099] Beige solid (26.0 mg, 0.069 mmol, 12.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.62 - 1.73 (2 H, m), 1.74 - 1.81 (2 H, m), 1.86 (2 H, td, *J*=11.60, 2.06 Hz), 2.16 (3 H, s), 2.46 - 2.55 (1 H, m), 2.77 - 2.85 (2 H, m), 3.93 (3 H, s), 4.63 (2 H, d, *J*=5.21 Hz), 5.56 (1 H, t, *J*=5.35 Hz), 7.67 (1 H, dd, *J*=8.51, 1.65 Hz), 7.81 (1 H, s), 7.94 (1 H, s), 8.05 (1 H, d, *J*=8.51 Hz), 8.48 (1 H, s), 9.08 (1 H, s), 10.50 (1 H, s); ESIMS found for C₂₁H₂₅N₅O₂ *m/z* 380.0 (M+1).



[01100] 3,3-Difluoro-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide **986**.

[01101] White solid (33.0 mg, 0.086 mmol, 28.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.75 - 2.90 (5 H, m), 3.07 (2 H, br t, *J*=5.21 Hz), 3.95 (2 H, s), 4.11 (2 H, t, *J*=5.35 Hz),

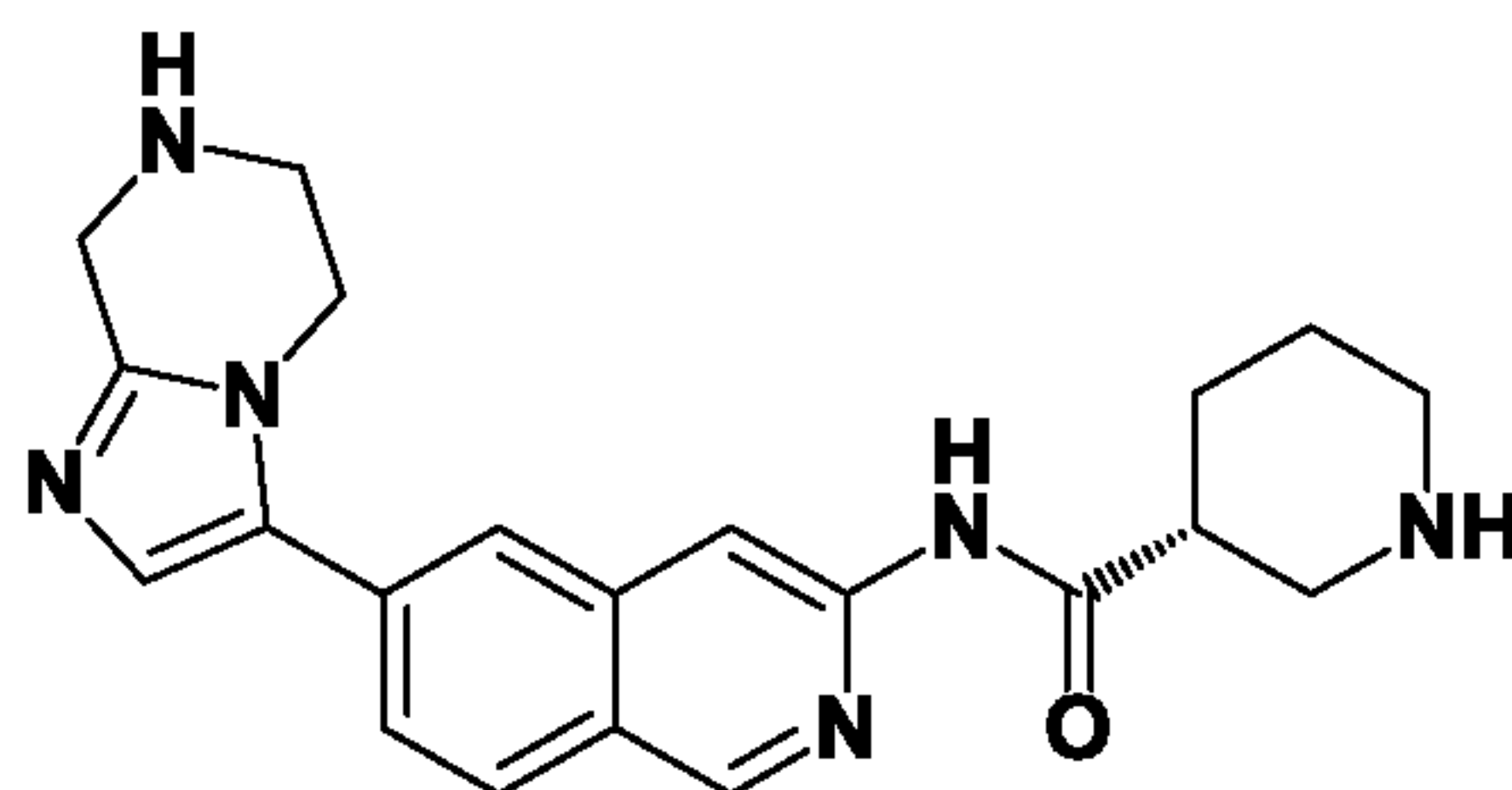
7.30 (1 H, s), 7.68 (1 H, dd, $J=8.51, 1.65$ Hz), 7.97 (1 H, s), 8.07 (1 H, d, $J=8.51$ Hz), 8.55 (1 H, s), 9.11 (1 H, s), 10.78 (1 H, s); ESIMS found for $C_{20}H_{19}F_2N_5O$ m/z 384.15 ($M+1$).



987

[01102] (R)-N-(6-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide **987**.

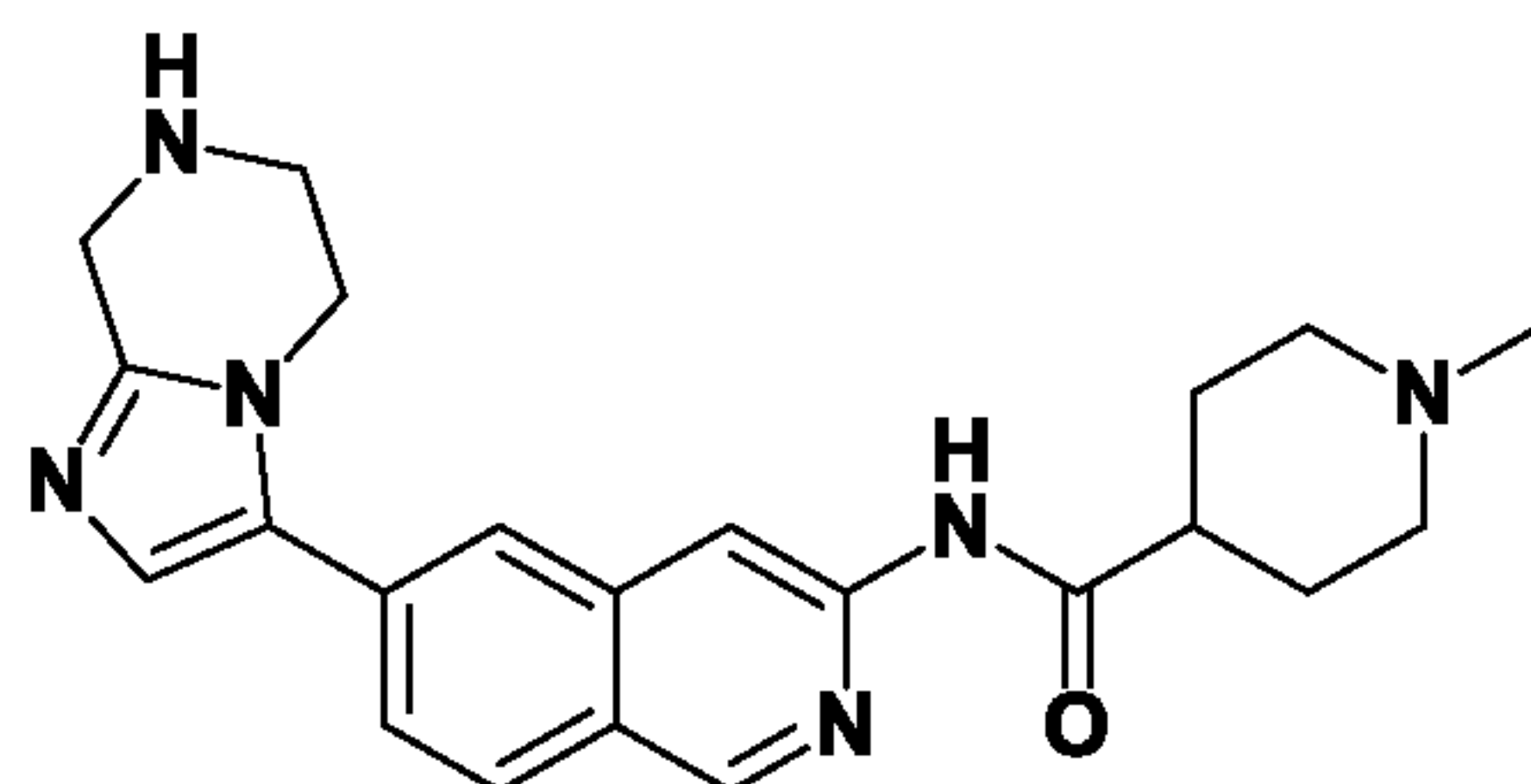
[01103] Beige solid (20.0 mg, 0.055 mmol, 34.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.67 (2 H, quin, $J=6.72$ Hz), 1.78 - 1.90 (1 H, m), 2.05 - 2.16 (1 H, m), 2.87 (1 H, dt, $J=10.15, 6.45$ Hz), 2.97 (1 H, dt, $J=10.15, 6.72$ Hz), 3.07 (2 H, t, $J=5.49$ Hz), 3.81 (1 H, dd, $J=9.06, 5.49$ Hz), 3.95 (2 H, s), 4.12 (2 H, t, $J=5.35$ Hz), 7.30 (1 H, s), 7.67 (1 H, dd, $J=8.51, 1.65$ Hz), 7.98 (1 H, s), 8.07 (1 H, d, $J=8.78$ Hz), 8.52 (1 H, s), 9.09 (1 H, s), 10.38 (1 H, s); ESIMS found for $C_{20}H_{22}N_6O$ m/z 363.2 ($M+1$).



988

[01104] (R)-N-(6-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-3-carboxamide **988**.

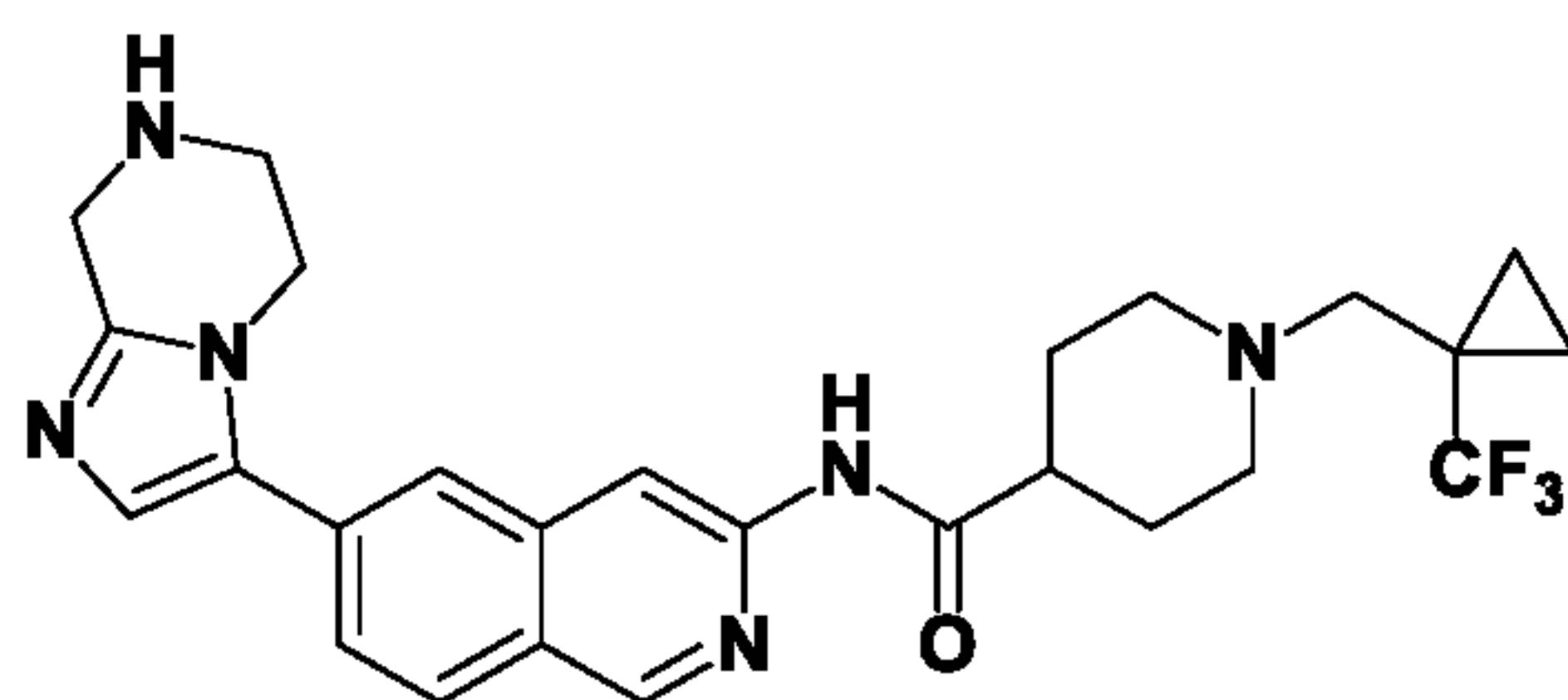
[01105] Dark brown gum (36.0 mg, 0.096 mmol, 55.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.31 - 1.56 (2 H, m), 1.57 - 1.74 (2 H, m), 2.32 - 2.46 (1 H, m), 2.52 - 2.66 (2 H, m), 2.70 - 2.88 (2 H, m), 3.07 (2 H, t, $J=5.35$ Hz), 3.95 (2 H, s), 4.11 (2 H, t, $J=5.21$ Hz), 7.29 (1 H, s), 7.65 (1 H, dd, $J=8.51, 1.65$ Hz), 7.93 (1 H, s), 8.05 (1 H, d, $J=8.51$ Hz), 8.51 (1 H, s), 9.08 (1 H, s), 10.79 (1 H, s); ESIMS found for $C_{21}H_{24}N_6O$ m/z 377.0 ($M+1$).



989

[01106] 1-Methyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide **989**.

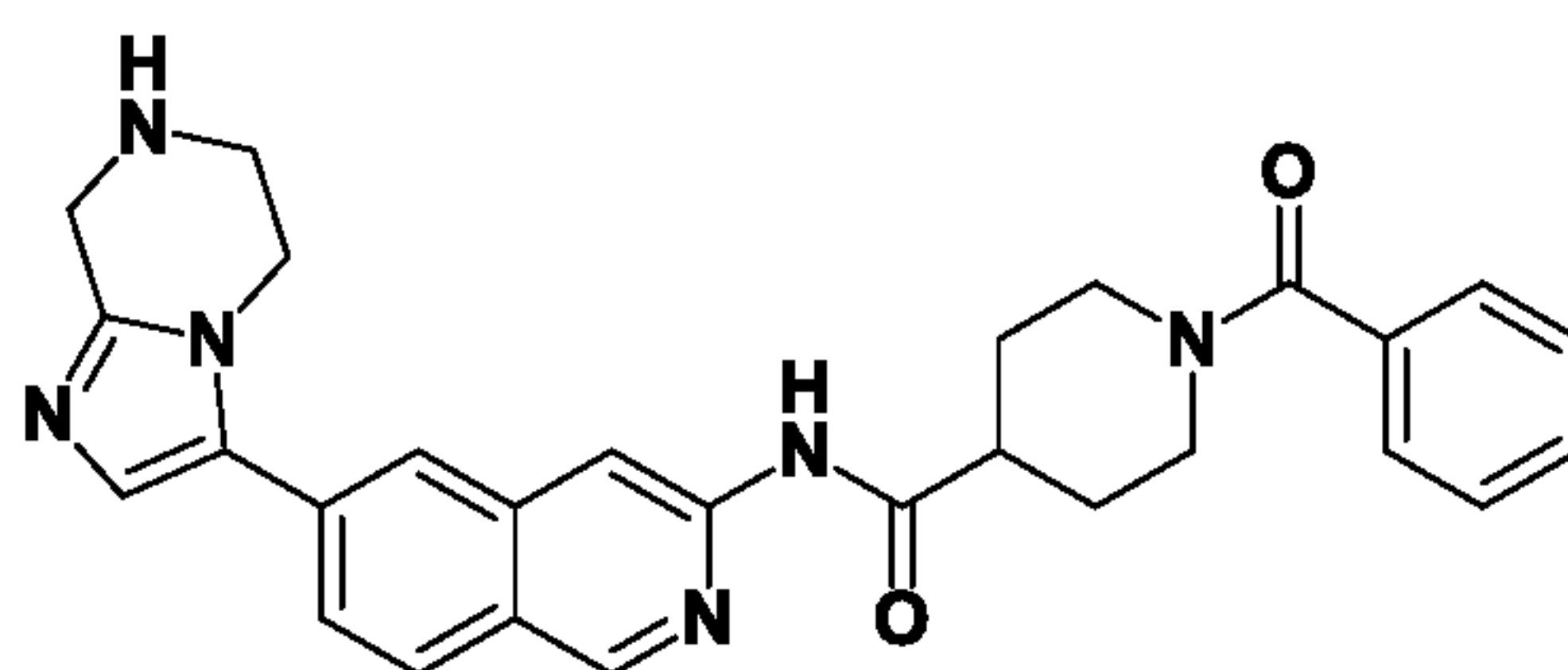
[01107] White solid (3.0 mg, 0.008 mmol, 6.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.61 - 1.72 (2 H, m), 1.73 - 1.80 (2 H, m), 1.87 (2 H, td, $J=11.60$, 2.06 Hz), 2.16 (3 H, s), 2.51 - 2.56 (1 H, m), 2.76 - 2.86 (3 H, m), 3.07 (2 H, br t, $J=5.21$ Hz), 3.95 (2 H, s), 4.10 (2 H, t, $J=5.49$ Hz), 7.28 (1 H, s), 7.65 (1 H, dd, $J=8.51$, 1.65 Hz), 7.93 (1 H, s), 8.05 (1 H, d, $J=8.51$ Hz), 8.52 (1 H, s), 9.09 (1 H, s), 10.51 (1 H, s); ESIMS found for $\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}$ m/z 391.2 ($M+1$).



990

[01108] N-(6-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide **990**.

[01109] Tan solid (31.0 mg, 0.062 mmol, 49.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.73 (2 H, br s), 0.93 - 0.98 (2 H, m), 1.62 - 1.71 (2 H, m), 1.77 (2 H, br d, $J=10.70$ Hz), 1.91 - 1.99 (2 H, m), 2.53 - 2.59 (1 H, m), 2.96 (2 H, br d, $J=11.25$ Hz), 3.08 (2 H, br t, $J=5.21$ Hz), 3.95 (2 H, s), 4.11 (2 H, br t, $J=5.21$ Hz), 7.29 (1 H, s), 7.65 (1 H, dd, $J=8.51$, 1.65 Hz), 7.94 (1 H, s), 8.05 (1 H, d, $J=8.51$ Hz), 8.52 (1 H, s), 9.09 (1 H, s), 10.51 (1 H, s); ESIMS found for $\text{C}_{26}\text{H}_{29}\text{F}_3\text{N}_6\text{O}$ m/z 499.2 ($M+1$).

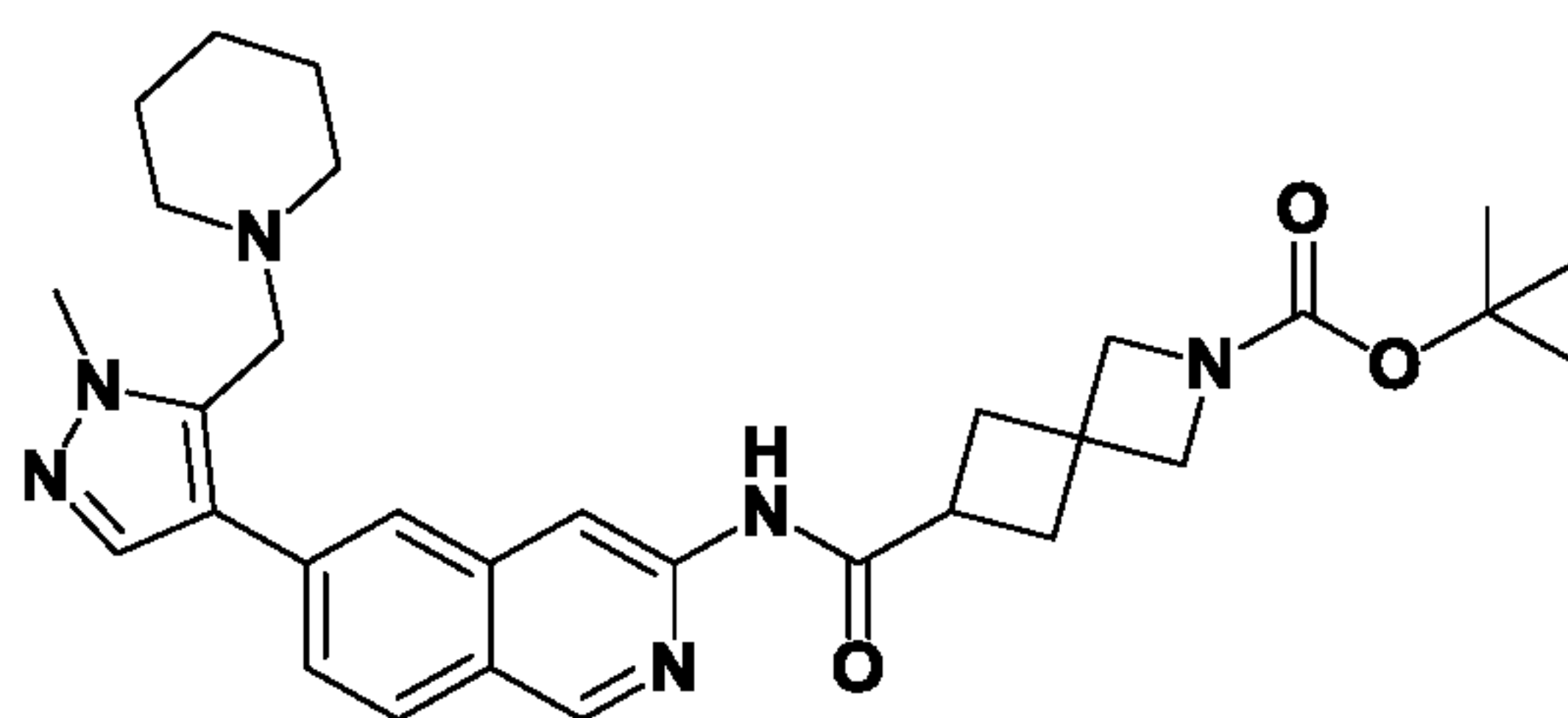


991

[01110] 1-Benzoyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide **991**.

[01111] White solid (27.7 mg, 0.058 mmol, 70.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.63 (2 H, br s), 1.75 - 1.98 (2 H, m), 2.69 - 2.96 (1 H, m), 2.86 (2 H, ddt, $J=11.22$, 7.51, 3.81, 3.81 Hz), 3.02 - 3.17 (1 H, m), 3.07 (2 H, br t, $J=5.08$ Hz), 3.95 (2 H, s), 4.11 (2 H, t, $J=5.21$ Hz), 7.29 (1 H, s), 7.36 - 7.43 (2 H, m), 7.43 - 7.50 (3 H, m), 7.66 (1 H, dd, $J=8.51$, 1.65 Hz), 7.94

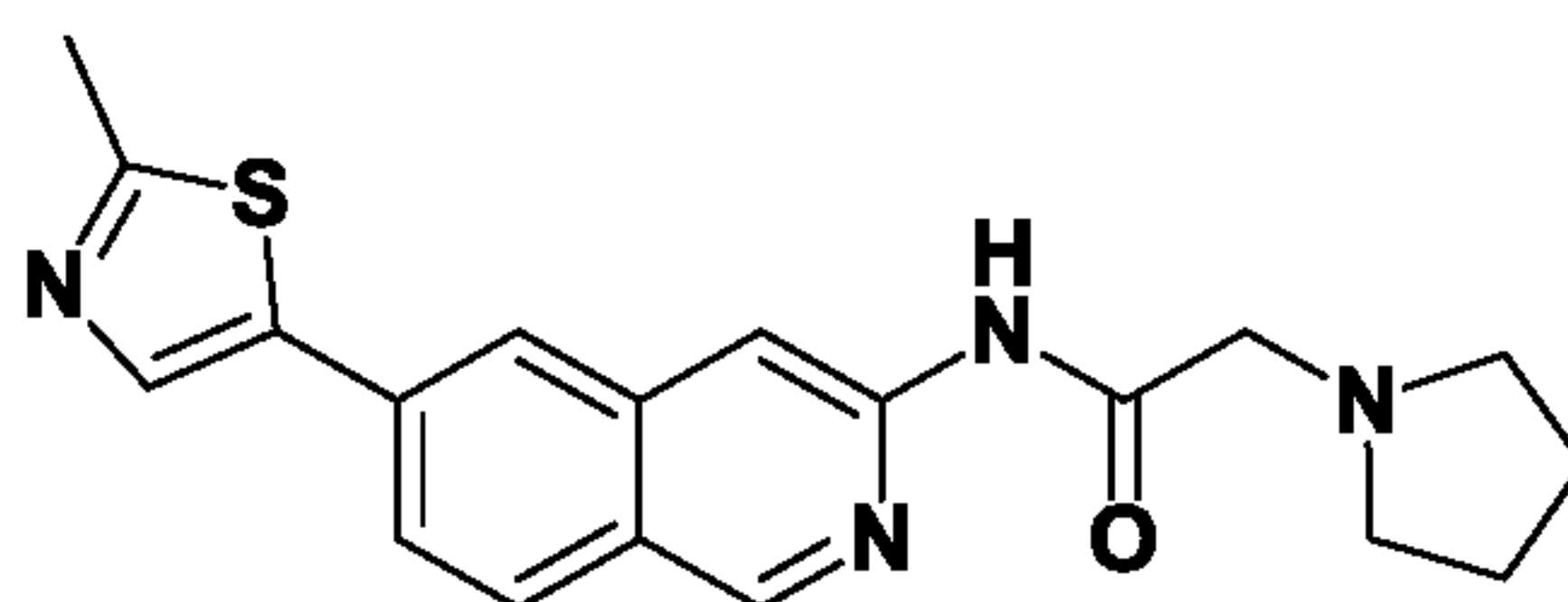
(1 H, s), 8.06 (1 H, d, $J=8.78$ Hz), 8.52 (1 H, s), 9.10 (1 H, s), 10.61 (1 H, s); ESIMS found for $C_{28}H_{28}N_6O_2$ m/z 481.2 (M+1).



992

[01112] *tert*-Butyl 6-((6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate **992**.

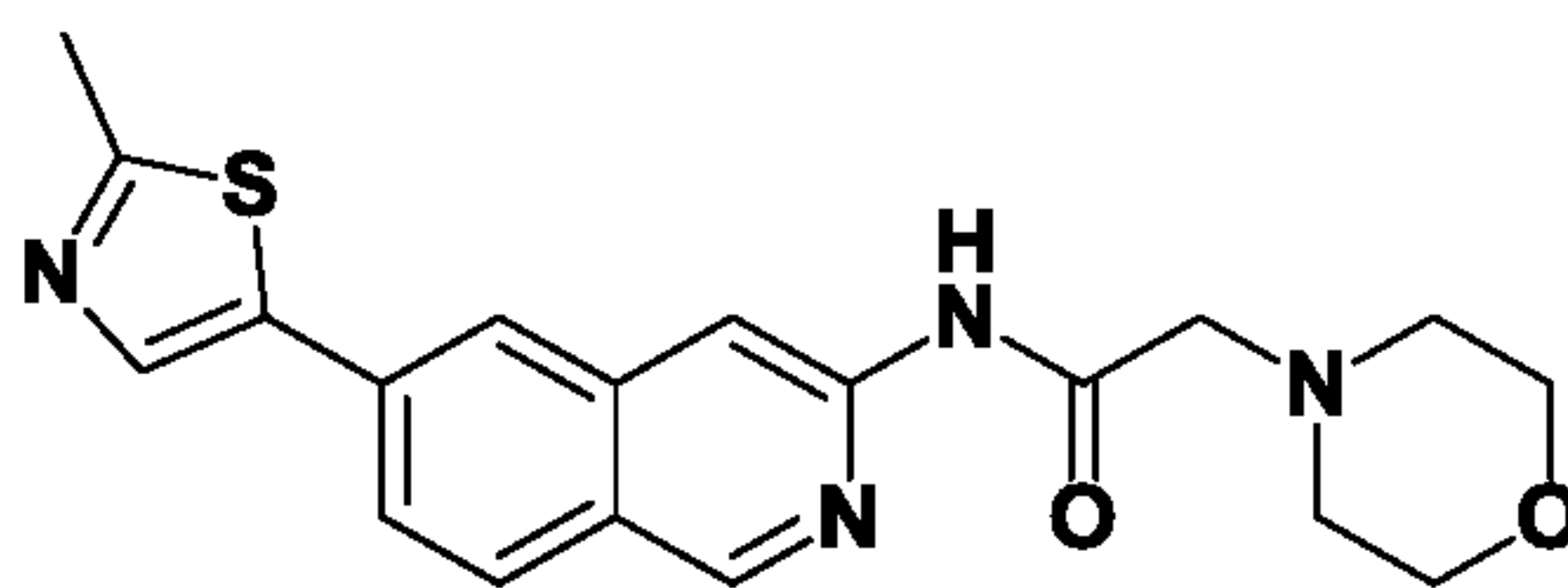
[01113] White solid (200.0 mg, 0.367 mmol, 78.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.37 (11 H, s), 1.45 - 1.54 (4 H, m), 2.37 (4 H, s), 2.38 (4 H, s), 3.21 - 3.30 (1 H, m), 3.65 (2 H, s), 3.81 (2 H, br s), 3.88 (2 H, br s), 3.91 (3 H, s), 7.69 (1 H, dd, $J=8.51$, 1.65 Hz), 7.80 (1 H, s), 8.02 (1 H, d, $J=8.78$ Hz), 8.05 (1 H, s), 8.47 (1 H, s), 9.06 (1 H, s), 10.44 (1 H, s); ESIMS found for $C_{31}H_{40}N_6O_3$ m/z 545.3 (M+1).



993

[01114] N-(6-(2-Methylthiazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **993**.

[01115] Beige solid (25.0 mg, 0.071 mmol, 21.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.78 (4 H, dt, $J=6.79$, 3.33 Hz), 2.62 - 2.69 (4 H, m), 2.72 (3 H, s), 3.36 (2 H, s), 7.82 (1 H, dd, $J=8.51$, 1.92 Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.15 (1 H, d, $J=0.82$ Hz), 8.30 (1 H, s), 8.50 (1 H, s), 9.11 (1 H, s), 9.99 (1 H, s); ESIMS found for $C_{19}H_{20}N_4OS$ m/z 353.1 (M+1).

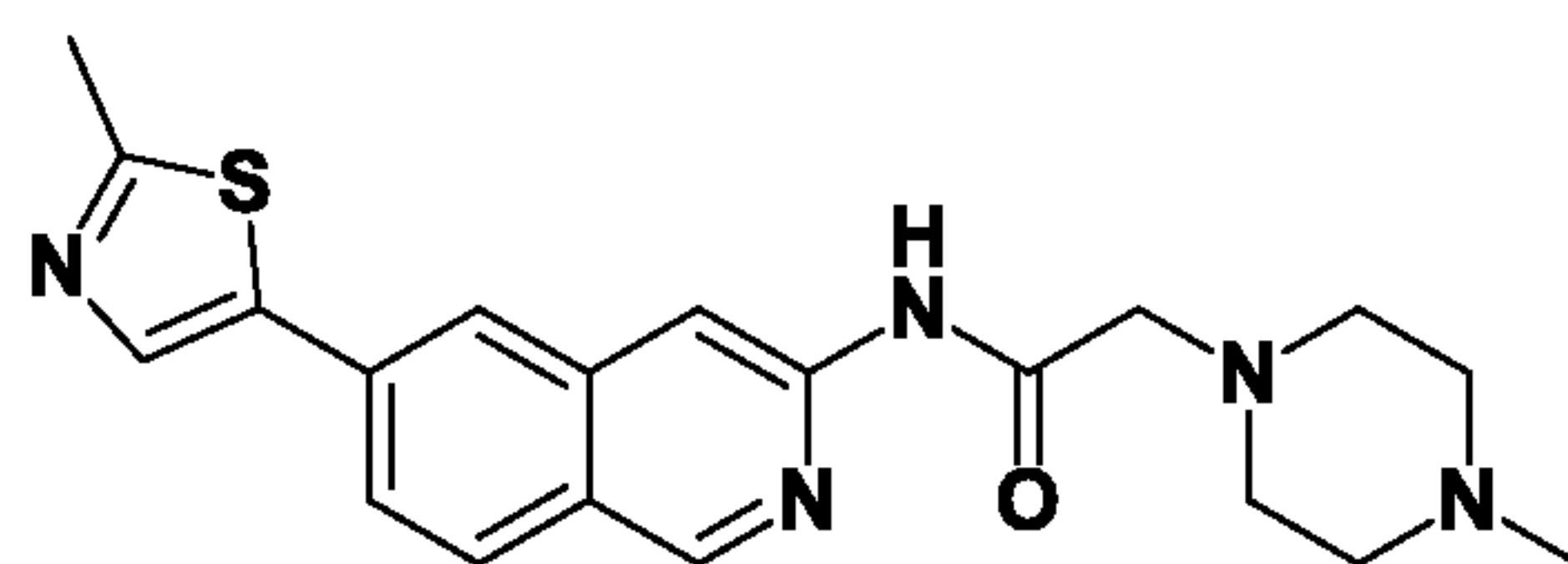


994

[01116] N-(6-(2-Methylthiazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide **994**.

[01117] Beige solid (44.0 mg, 0.119 mmol, 41.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.55 - 2.61 (4 H, m), 2.72 (3 H, s), 3.25 (2 H, s), 3.60 - 3.68 (4 H, m), 7.82 (1 H, dd,

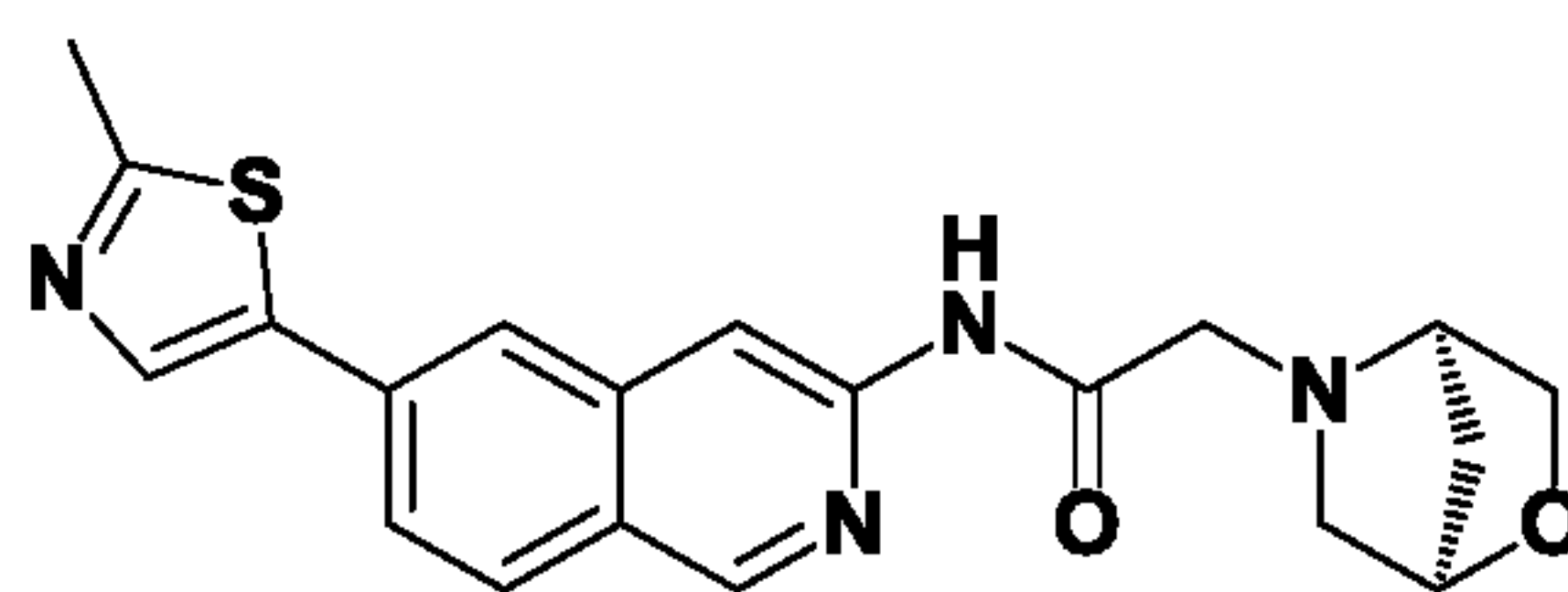
$J=8.64, 1.78$ Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.15 (1 H, d, $J=0.82$ Hz), 8.30 (1 H, s), 8.50 (1 H, s), 9.12 (1 H, s), 10.08 (1 H, s); ESIMS found for $C_{19}H_{20}N_4O_2S$ m/z 369.1 (M+1).



995

[01118] 2-(4-Methylpiperazin-1-yl)-N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl)acetamide **995**.

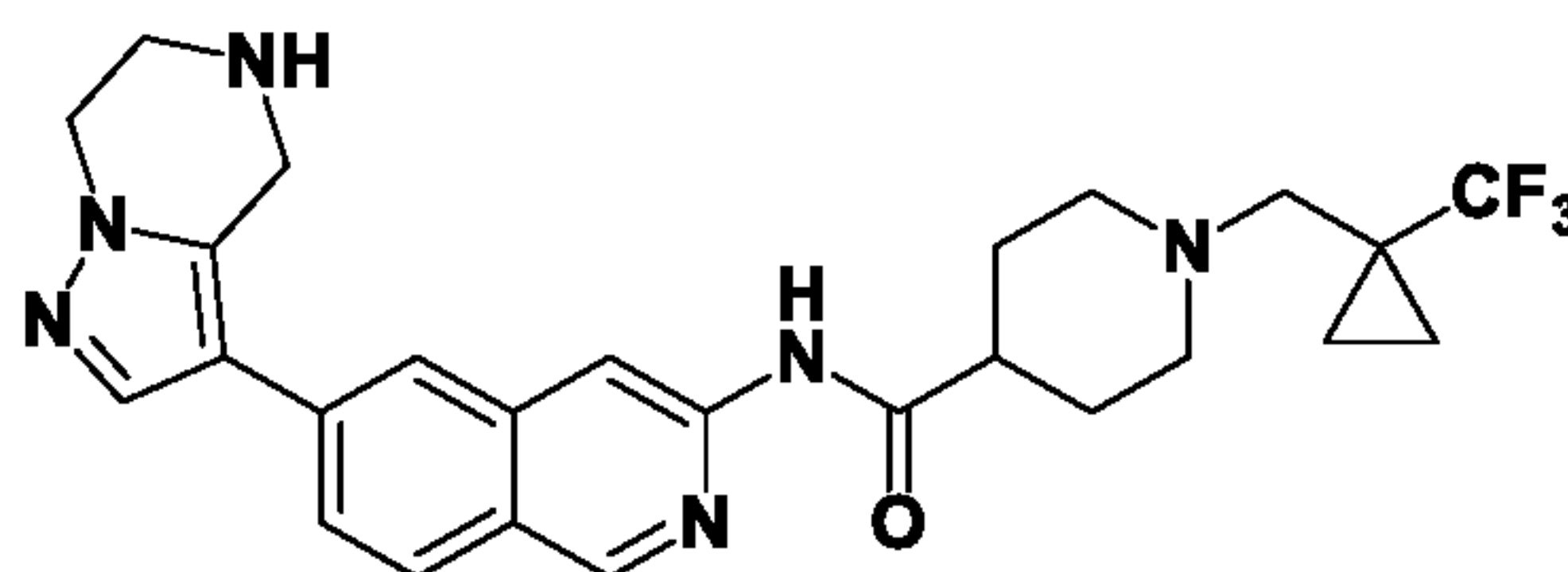
[01119] Brown solid (31.0 mg, 0.081 mmol, 31.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.19 (3 H, s), 2.40 (4 H, br s), 2.58 (4 H, br s), 2.72 (3 H, s), 3.23 (2 H, s), 7.82 (1 H, dd, $J=8.51, 1.65$ Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.15 (1 H, s), 8.30 (1 H, s), 8.50 (1 H, s), 9.12 (1 H, s), 10.00 (1 H, s); ESIMS found for $C_{20}H_{23}N_5OS$ m/z 382.2 (M+1).



996

[01120] 2-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl)acetamide **996**.

[01121] Beige solid (50.0 mg, 0.131 mmol, 43.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.64 - 1.71 (1 H, m), 1.87 (1 H, dd, $J=9.47, 1.78$ Hz), 2.63 (1 H, d, $J=9.88$ Hz), 2.72 (3 H, s), 2.95 (1 H, dd, $J=9.88, 1.65$ Hz), 3.46 (2 H, d, $J=4.39$ Hz), 3.59 (1 H, dd, $J=7.68, 1.92$ Hz), 3.63 (1 H, s), 3.88 (1 H, d, $J=7.68$ Hz), 4.41 (1 H, s), 7.82 (1 H, dd, $J=8.64, 1.78$ Hz), 8.10 (1 H, d, $J=8.51$ Hz), 8.15 (1 H, d, $J=0.82$ Hz), 8.30 (1 H, s), 8.50 (1 H, s), 9.12 (1 H, s), 9.98 (1 H, s); ESIMS found for $C_{20}H_{20}N_4O_2S$ m/z 381.1 (M+1).

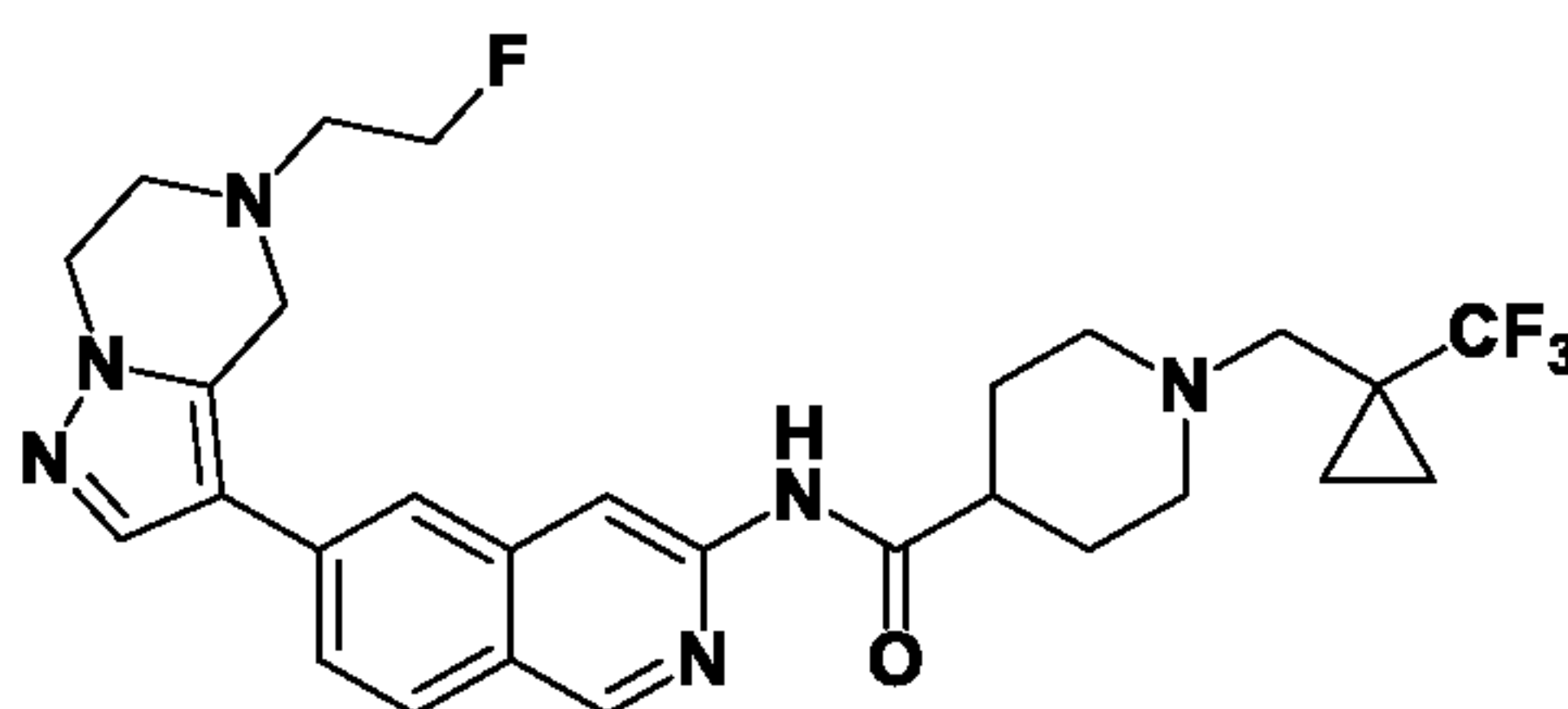


997

[01122] N-(6-(4,5,6,7-Tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide **997**.

[01123] Tan solid (33.6 mg, 0.067 mmol, 47.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.73 (2 H, br s), 0.94 - 0.99 (2 H, m), 1.62 - 1.72 (2 H, m), 1.74 - 1.81 (2 H, m), 1.91 -

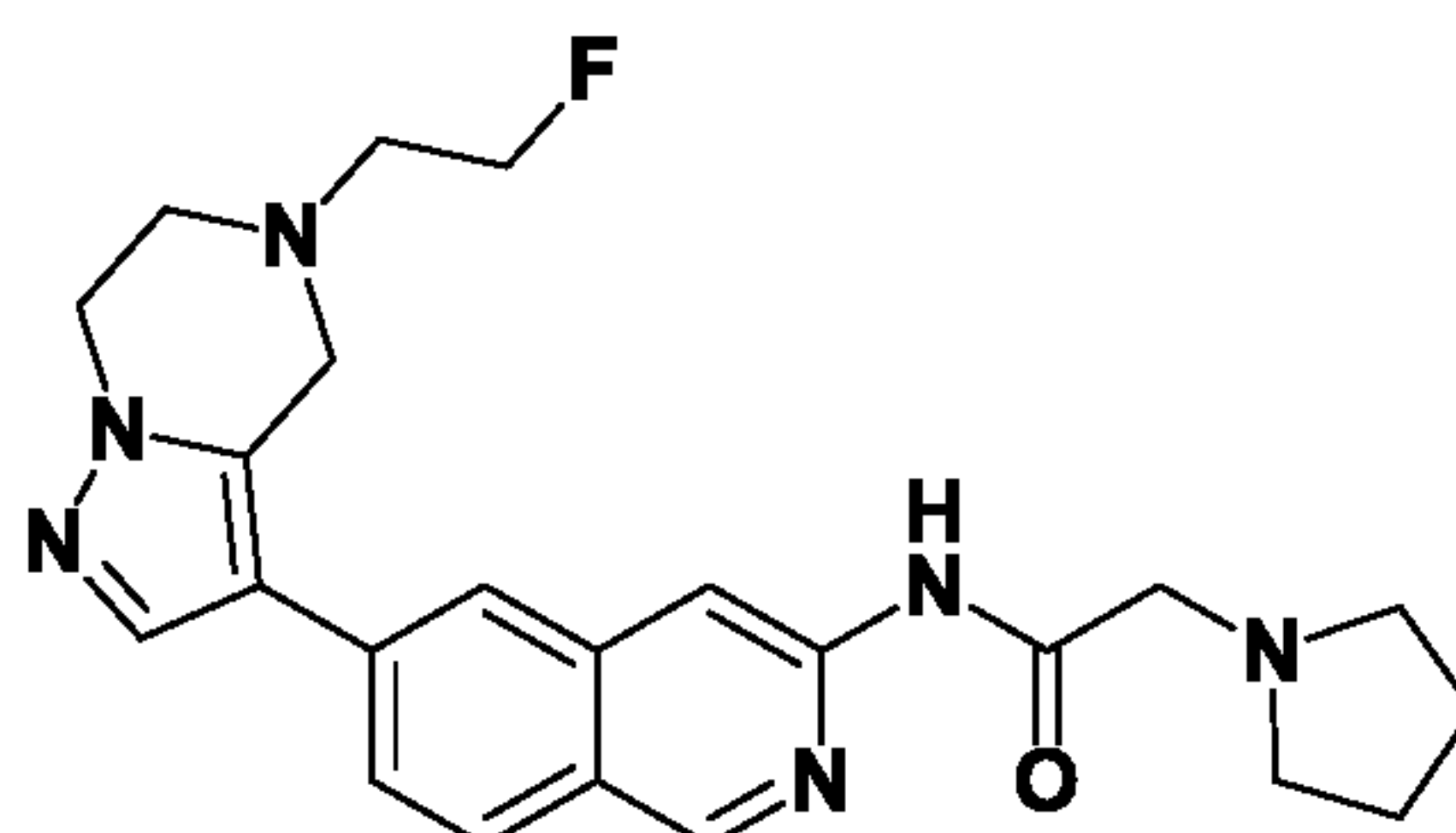
1.99 (2 H, m), 2.53 - 2.58 (1 H, m), 2.93 - 2.99 (2 H, m), 3.16 (2 H, br t, $J=5.21$ Hz), 4.06 (2 H, br t, $J=5.35$ Hz), 4.22 (2 H, s), 7.63 (1 H, dd, $J=8.51$, 1.65 Hz), 7.76 (1 H, s), 7.98 (1 H, s), 8.01 (1 H, d, $J=8.51$ Hz), 8.47 (1 H, s), 9.04 (1 H, s), 10.46 (1 H, s); ESIMS found for $C_{26}H_{29}F_3N_6O$ m/z 499.25 (M+1).



998

[01124] N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide **998**.

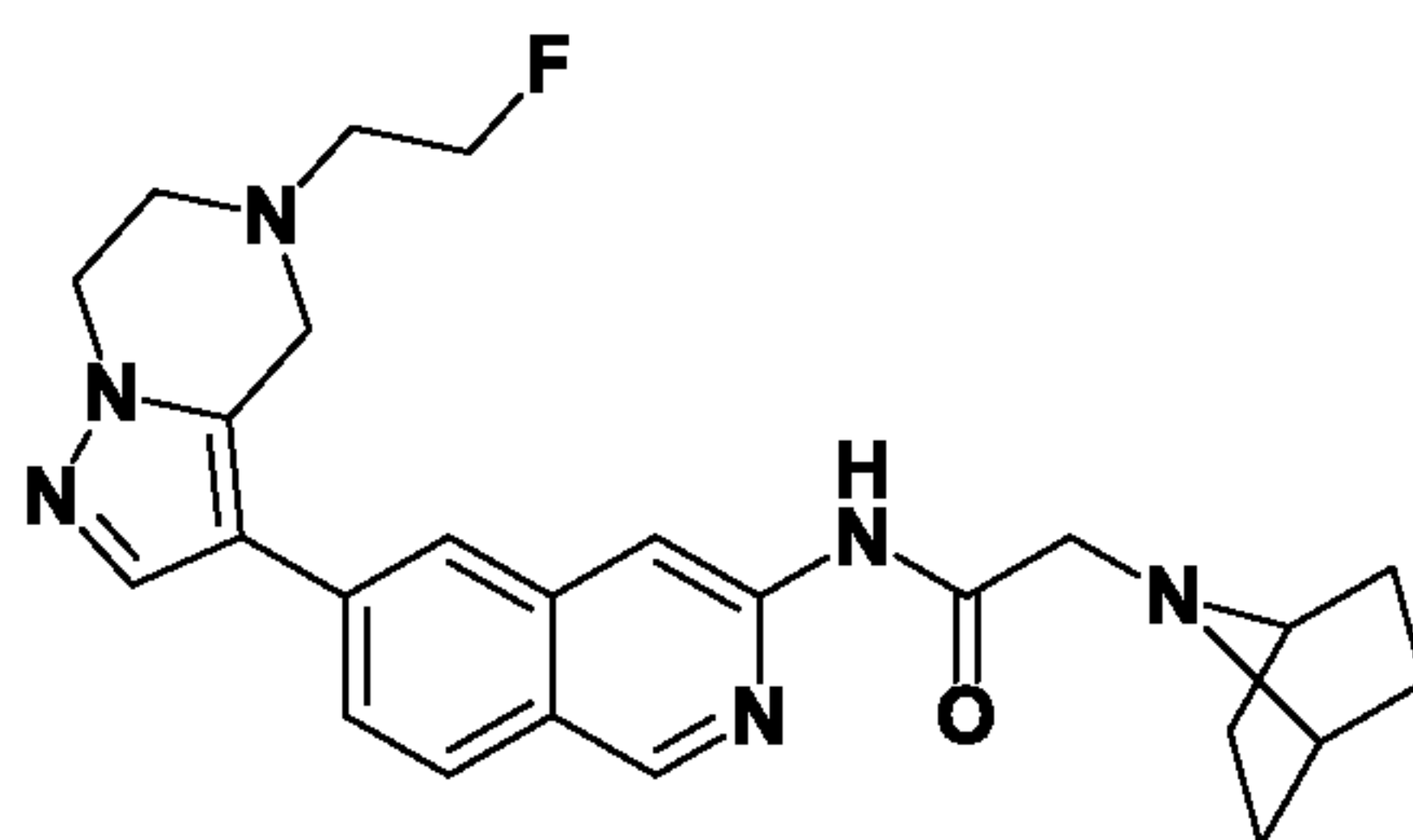
[01125] Off-white solid (15.0 mg, 0.028 mmol, 41.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.73 (2 H, br s), 0.94 - 0.99 (2 H, m), 1.62 - 1.72 (2 H, m), 1.74 - 1.82 (2 H, m), 1.91 - 1.99 (2 H, m), 2.52 - 2.59 (1 H, m), 2.93 - 3.03 (4 H, m), 3.07 (2 H, t, $J=5.35$ Hz), 4.08 (2 H, s), 4.18 (2 H, t, $J=5.49$ Hz), 4.66 (2 H, dt, $J=47.85$, 4.70 Hz), 7.64 (1 H, dd, $J=8.51$, 1.37 Hz), 7.76 (1 H, s), 8.00 (1 H, s), 8.02 (1 H, d, $J=8.51$ Hz), 8.48 (1 H, s), 9.05 (1 H, s), 10.48 (1 H, s); ESIMS found for $C_{28}H_{32}F_4N_6O$ m/z 545.3 (M+1).



999

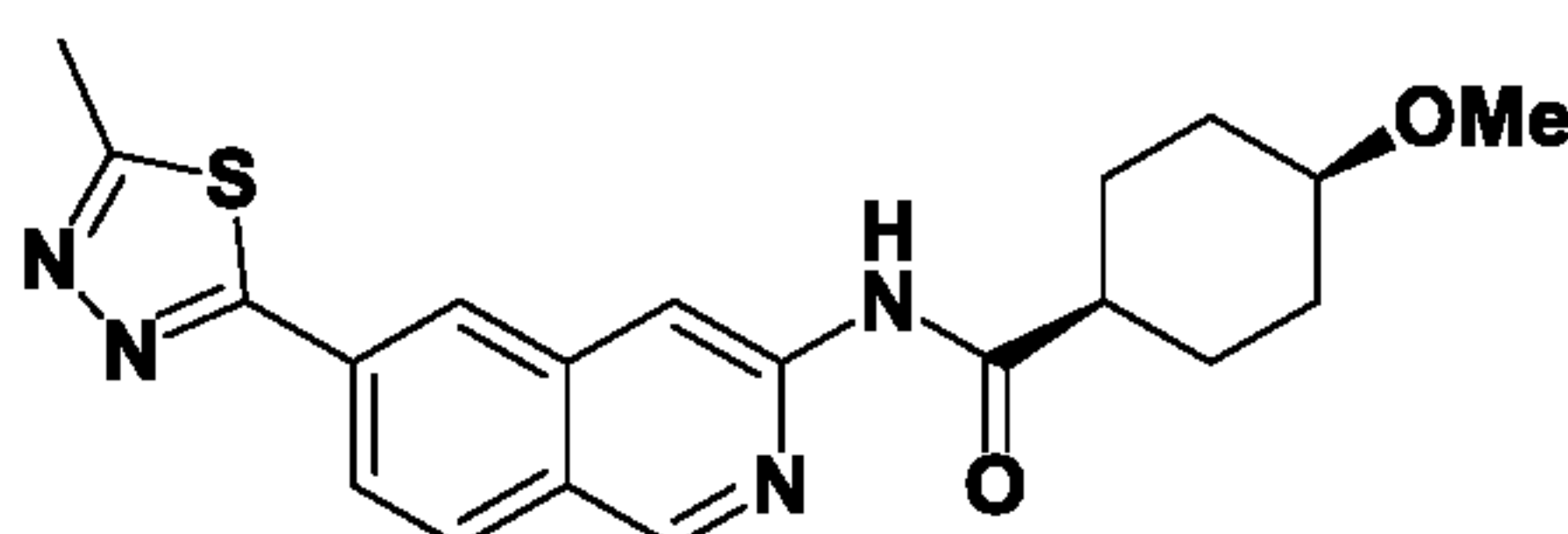
[01126] N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide **999**.

[01127] Yellow oil (5.6 mg, 0.013 mmol, 38.4% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.78 (4 H, dt, $J=6.72$, 3.22 Hz), 2.66 (4 H, br s), 2.98 (3 H, dt, $J=28.55$, 4.95 Hz), 3.07 (2 H, t, $J=5.49$ Hz), 3.36 (2 H, s), 4.09 (2 H, s), 4.18 (2 H, t, $J=5.49$ Hz), 4.66 (3 H, dt, $J=47.75$, 4.95 Hz), 7.65 (1 H, dd, $J=8.51$, 1.65 Hz), 7.82 (1 H, s), 8.01 (1 H, s), 8.05 (1 H, d, $J=8.51$ Hz), 8.47 (1 H, s), 9.06 (1 H, s), 9.96 (1 H, s); ESIMS found for $C_{23}H_{27}FN_6O$ m/z 423.2 (M+1).

**1000**

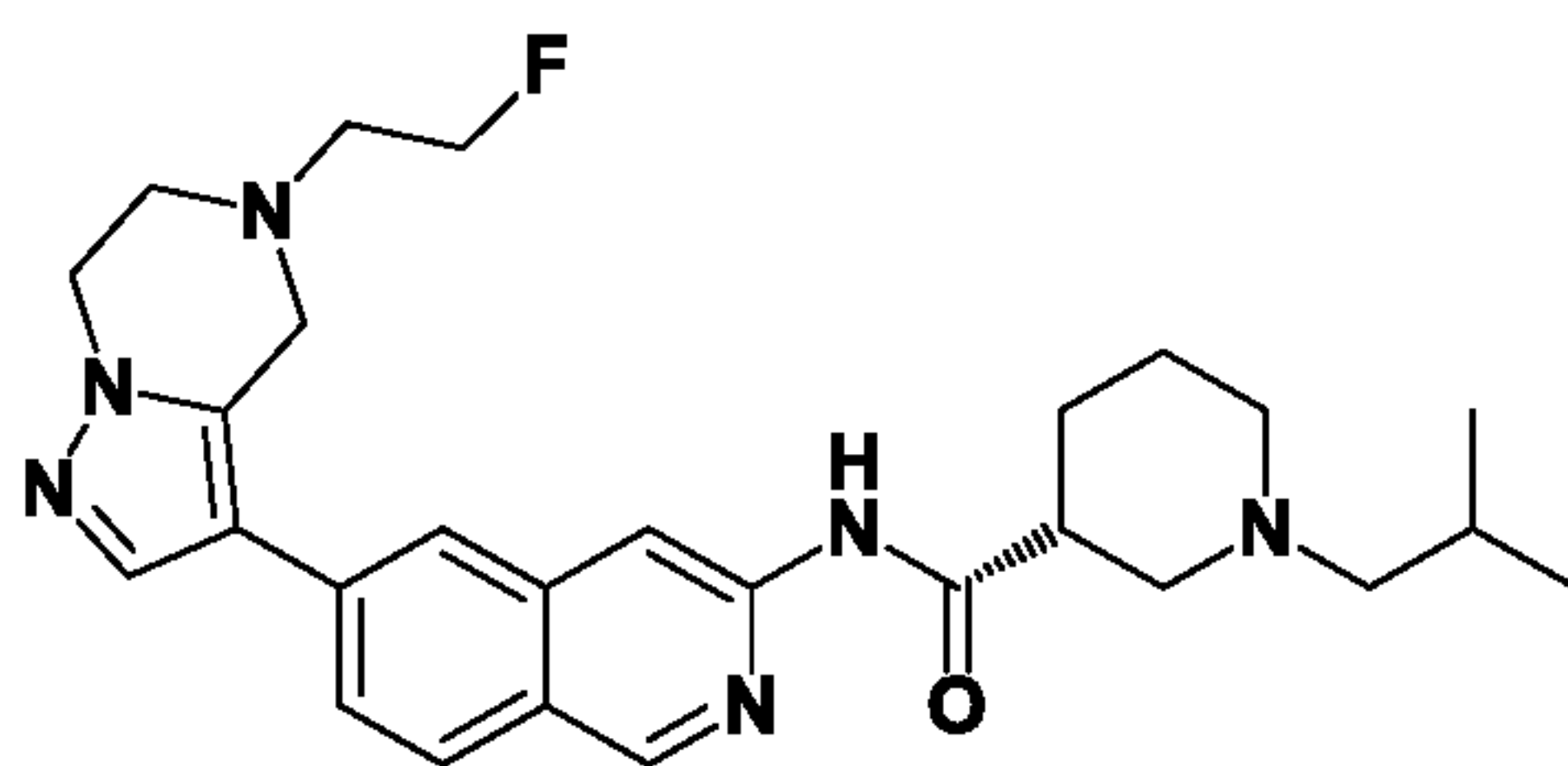
[01128] 2-(7-Azabicyclo[2.2.1]heptan-7-yl)-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)acetamide **1000**.

[01129] Yellow solid (26.5 mg, 0.059 mmol, 52.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.35 (4 H, br d, *J*=6.86 Hz), 1.69 - 1.79 (4 H, m), 2.99 (2 H, dt, *J*=28.90, 4.95 Hz), 3.08 (2 H, br t, *J*=5.49 Hz), 3.19 (2 H, s), 3.36 (2 H, br s), 4.09 (2 H, s), 4.18 (2 H, br t, *J*=5.49 Hz), 4.66 (2 H, dt, *J*=47.85, 4.95 Hz), 7.65 (1 H, dd, *J*=8.51, 1.65 Hz), 7.82 (1 H, s), 8.00 (1 H, s), 8.05 (1 H, d, *J*=8.78 Hz), 8.48 (1 H, s), 9.06 (1 H, s), 10.08 (1 H, s); ESIMS found for C₂₅H₂₉FN₆O *m/z* 449.25 (M+1).

**1001**

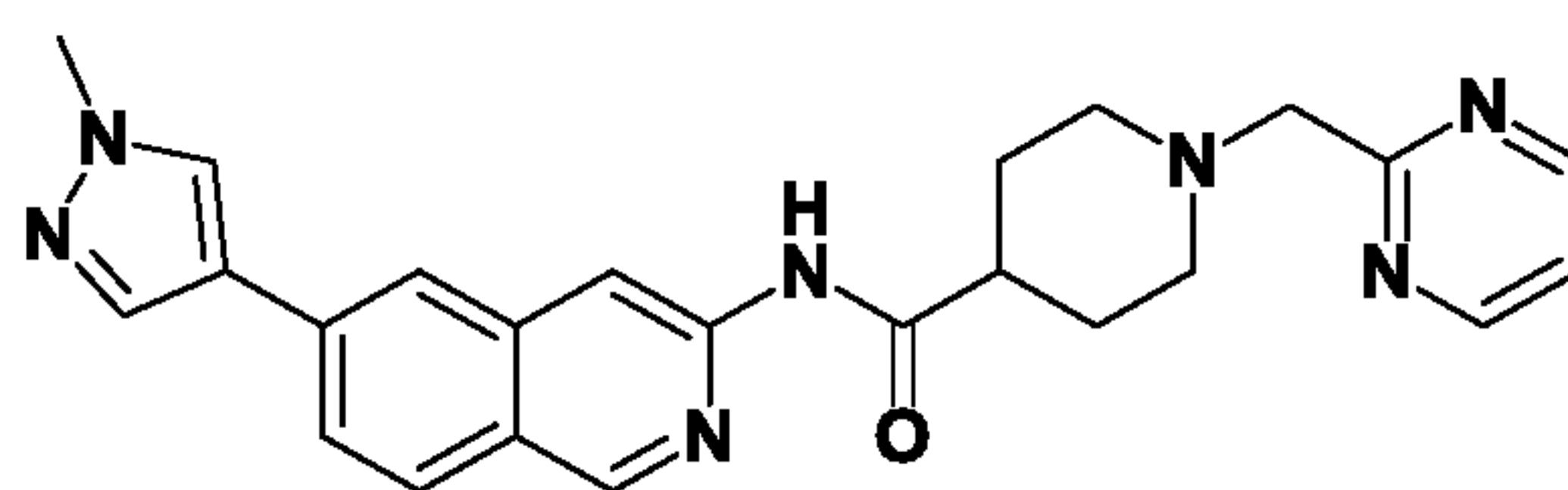
[01130] *cis*-4-Methoxy-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **1001**.

[01131] White solid (33.4 mg, 0.087 mmol, 21.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.08 - 1.18 (2 H, m), 1.45 - 1.55 (2 H, m), 1.88 - 1.94 (2 H, m), 2.05 - 2.11 (2 H, m), 2.52 - 2.58 (1 H, m), 2.83 (3 H, s), 3.09 - 3.16 (1 H, m), 3.25 (3 H, s), 8.09 (1 H, dd, *J*=8.65, 1.51 Hz), 8.19 (1 H, d, *J*=8.51 Hz), 8.44 (1 H, s), 8.60 (1 H, s), 9.21 (1 H, s), 10.60 (1 H, s); ESIMS found for C₂₀H₂₂N₄O₂S *m/z* 383.15 (M+1).

**1002**

[01132] (R)-N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-isobutylpiperidine-3-carboxamide **1002**.

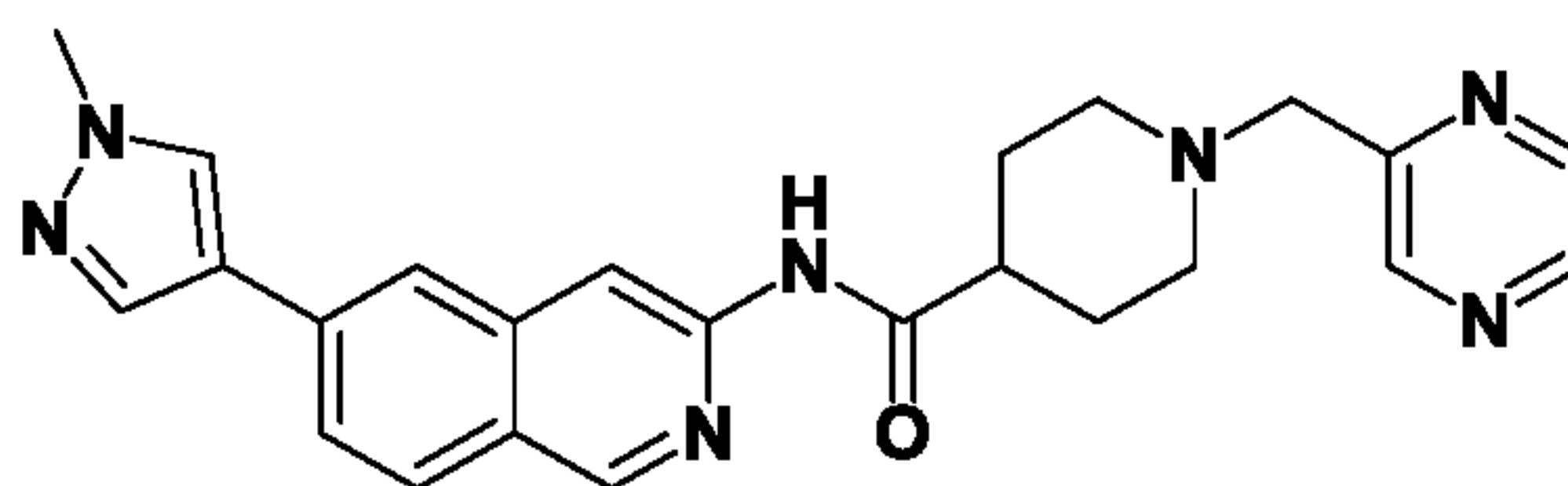
[01133] Light yellow gum (31.1 mg, 0.065 mmol, 40.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.89 (6 H, dd, $J=11.11$, 6.45 Hz), 1.50 - 1.58 (2 H, m), 1.69 (1 H, br dd, $J=8.37$, 3.98 Hz), 1.78 - 1.86 (2 H, m), 2.11 (1 H, d, $J=7.14$ Hz), 2.09 - 2.17 (1 H, m), 2.28 - 2.37 (1 H, m), 2.60 - 2.66 (1 H, m), 2.75 - 2.84 (2 H, m), 2.98 (3 H, dt, $J=28.60$, 4.95 Hz), 3.07 (2 H, br t, $J=5.49$ Hz), 4.07 (2 H, s), 4.18 (2 H, t, $J=5.35$ Hz), 4.66 (2 H, dt, $J=47.80$, 4.95 Hz), 7.64 (1 H, dd, $J=8.51$, 1.65 Hz), 7.75 (1 H, s), 8.00 (1 H, s), 8.02 (1 H, d, $J=8.78$ Hz), 8.46 (1 H, s), 9.05 (1 H, s), 10.69 (1 H, s); ESIMS found for $\text{C}_{27}\text{H}_{35}\text{FN}_6\text{O}$ m/z 479.3 (M+1).



1003

[01134] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyrimidin-2-ylmethyl)piperidine-4-carboxamide **1003**.

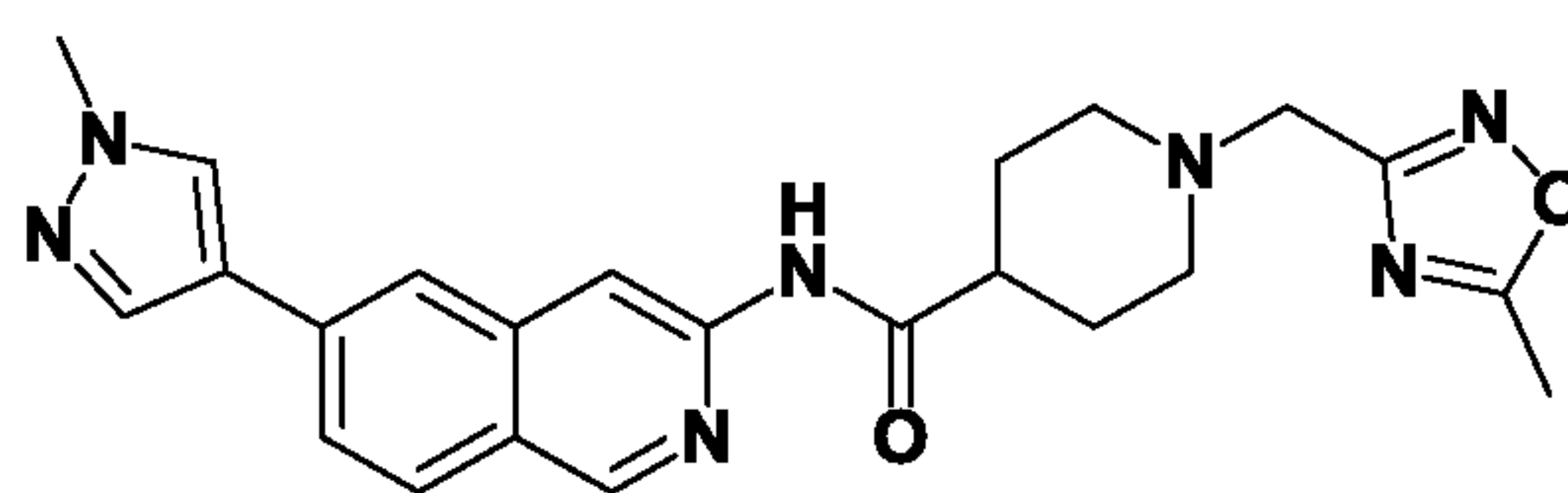
[01135] Beige solid (75.0 mg, 0.175 mmol, 29.4% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.63 - 1.74 (2 H, m), 1.74 - 1.82 (2 H, m), 2.18 (2 H, br t, $J=10.70$ Hz), 2.52 - 2.59 (1 H, m), 2.98 (2 H, br d, $J=10.98$ Hz), 3.74 (2 H, s), 3.90 (3 H, s), 7.41 (1 H, t, $J=4.80$ Hz), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.03 (1 H, s), 8.07 (1 H, d, $J=0.82$ Hz), 8.34 (1 H, s), 8.44 (1 H, s), 8.79 (2 H, d, $J=4.94$ Hz), 9.02 (1 H, s), 10.44 (1 H, s); ESIMS found for $\text{C}_{24}\text{H}_{25}\text{N}_7\text{O}$ m/z 428.2 (M+1).



1004

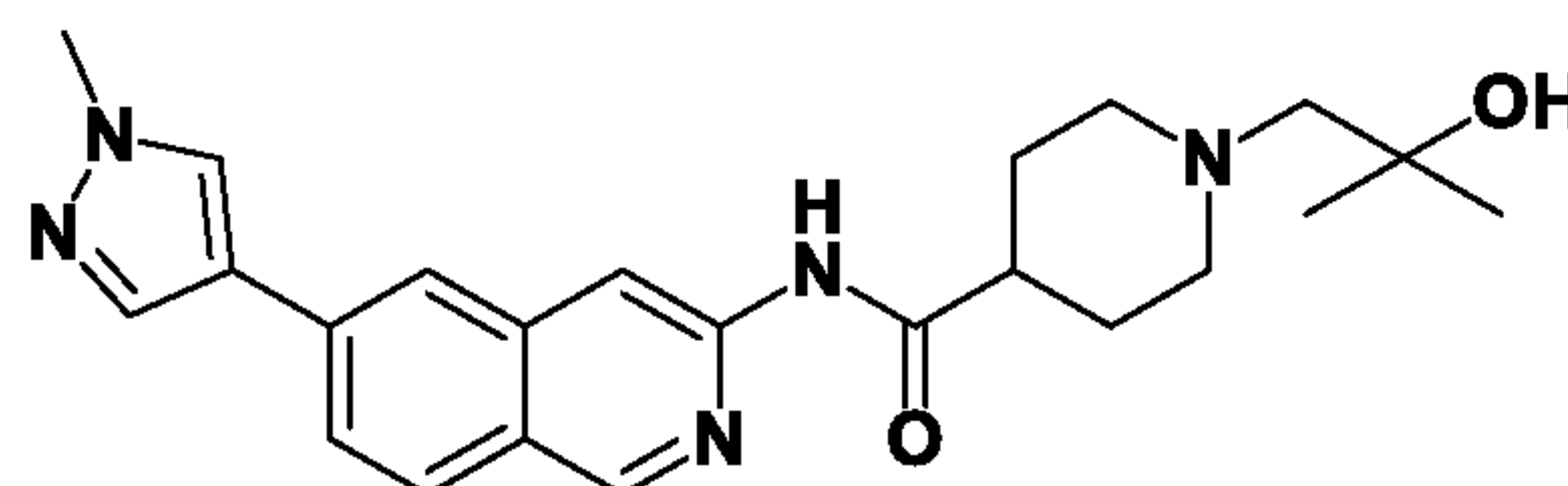
[01136] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyrazin-2-ylmethyl)piperidine-4-carboxamide **1004**.

[01137] Orange solid (20.0 mg, 0.047 mmol, 7.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.66 - 1.76 (2 H, m), 1.76 - 1.83 (2 H, m), 2.09 (2 H, td, $J=11.60$, 2.33 Hz), 2.52 - 2.61 (1 H, m), 2.90 (2 H, br d, $J=11.53$ Hz), 3.67 (2 H, s), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.35 (1 H, s), 8.44 (1 H, s), 8.54 (1 H, d, $J=2.74$ Hz), 8.58 (1 H, dd, $J=2.61$, 1.51 Hz), 8.70 (1 H, d, $J=1.37$ Hz), 9.02 (1 H, s), 10.46 (1 H, s); ESIMS found for $\text{C}_{24}\text{H}_{25}\text{N}_7\text{O}$ m/z 428.2 (M+1).

**1005**

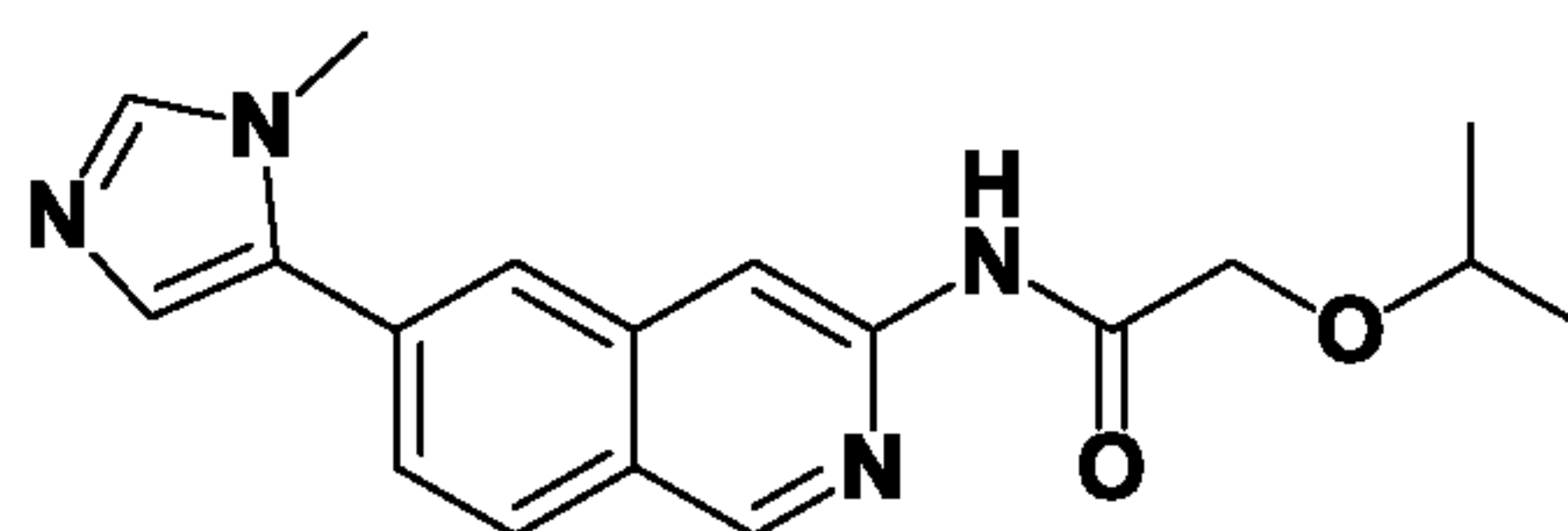
[01138] 1-((5-Methyl-1,2,4-oxadiazol-3-yl)methyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1005**.

[01139] White solid (45.0 mg, 0.104 mmol, 17.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.63 - 1.74 (2 H, m), 1.78 - 1.84 (2 H, m), 2.18 (2 H, td, *J*=11.53, 2.20 Hz), 2.35 (3 H, s), 2.52 - 2.57 (1 H, m), 2.89 - 2.96 (2 H, m), 3.87 (2 H, s), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.45 (1 H, s); ESIMS found for C₂₃H₂₅N₇O₂ *m/z* 432.2 (M+1).

**1006**

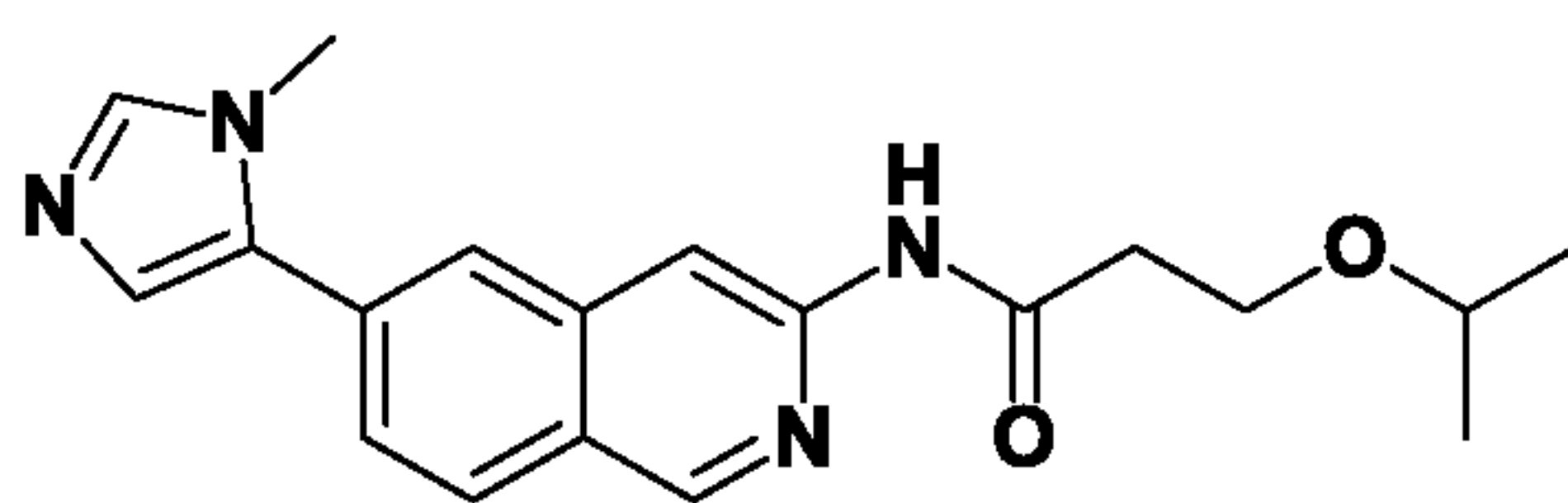
[01140] 1-(2-Hydroxy-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1006**.

[01141] White solid (45.0 mg, 0.110 mmol, 18.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.09 (6 H, s), 1.72 (4 H, br d, *J*=2.74 Hz), 2.13 (2 H, br s), 2.20 (2 H, br s), 2.46 - 2.55 (1 H, m), 2.99 (2 H, br d, *J*=9.88 Hz), 3.90 (3 H, s), 4.04 (1 H, br s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.08 (1 H, d, *J*=0.82 Hz), 8.35 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.44 (1 H, s); ESIMS found for C₂₃H₂₉N₅O₂ *m/z* 408.2 (M+1).

**1008**

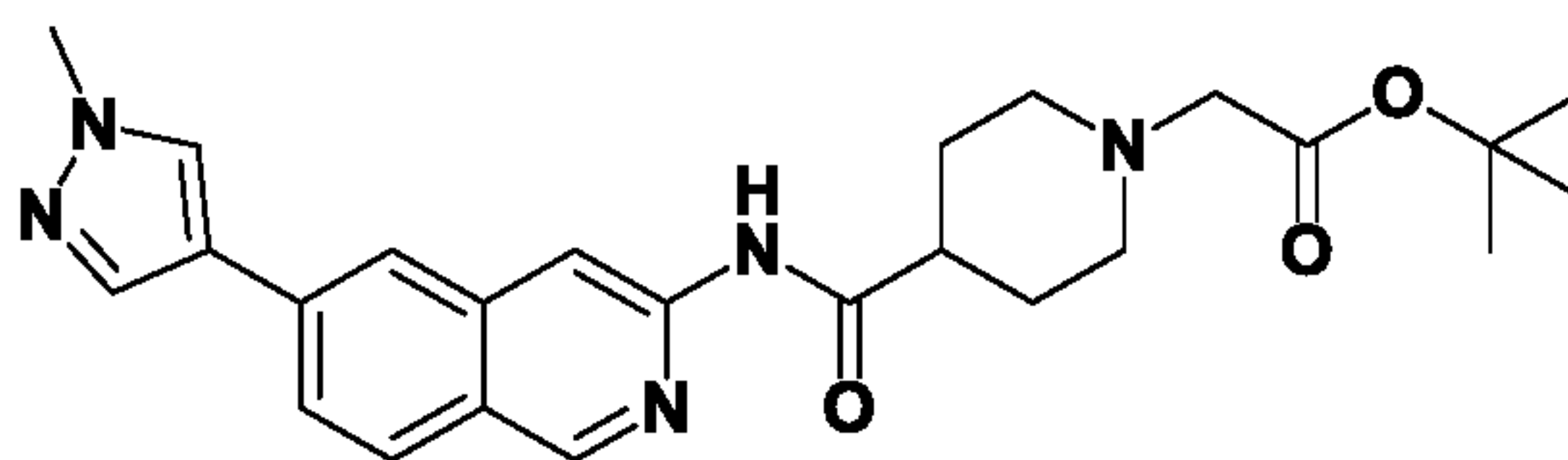
[01142] 2-Isopropoxy-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide **1008**.

[01143] White solid (35.0 mg, 0.108 mmol, 18.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.20 (6 H, d, *J*=6.04 Hz), 3.75 (1 H, spt, *J*=6.13 Hz), 3.91 (3 H, s), 4.15 (2 H, s), 7.69 (1 H, s), 7.73 (1 H, dd, *J*=8.37, 1.78 Hz), 8.17 (1 H, br s), 8.18 (1 H, d, *J*=8.78 Hz), 8.51 (1 H, s), 8.57 (1 H, s), 9.20 (1 H, s), 9.80 (1 H, s); ESIMS found for C₁₈H₂₀N₄O₂ *m/z* 325.2 (M+1).

**1009**

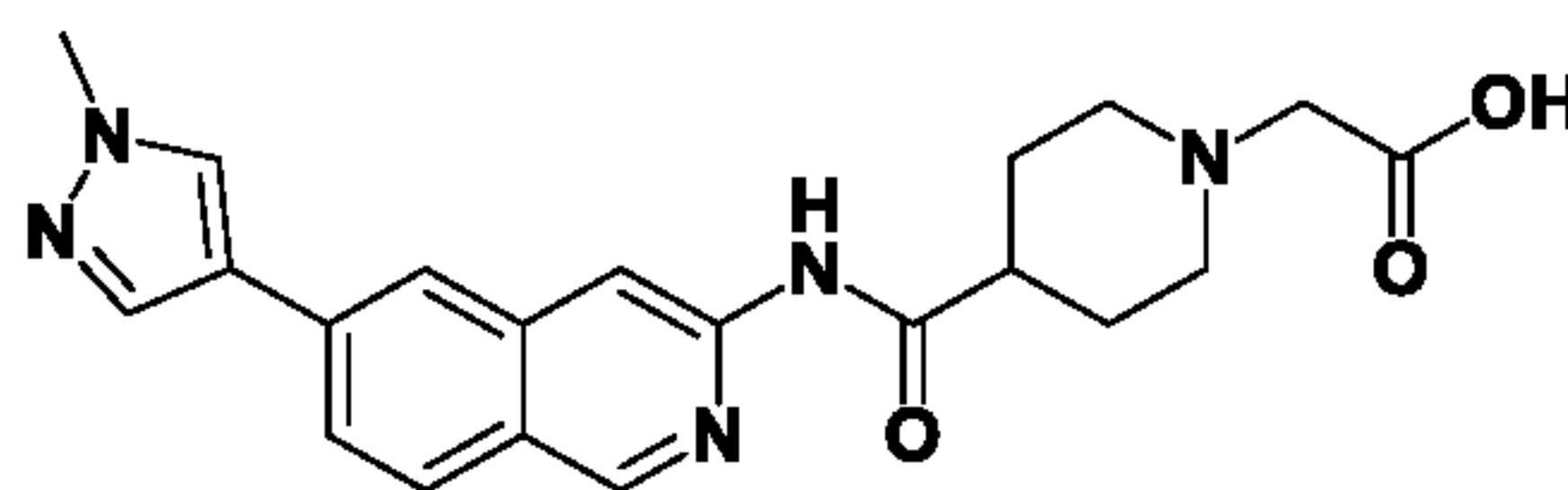
[01144] 3-Isopropoxy-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)propanamide **1009**.

[01145] White solid (105.0 mg, 0.310 mmol, 43.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.08 (6 H, d, *J*=6.04 Hz), 2.66 (2 H, t, *J*=6.31 Hz), 3.58 (1 H, spt, *J*=6.08 Hz), 3.69 (2 H, t, *J*=6.17 Hz), 3.84 (3 H, s), 7.34 (1 H, s), 7.67 (1 H, dd, *J*=8.51, 1.65 Hz), 7.87 (1 H, s), 8.03 (1 H, d, *J*=0.82 Hz), 8.09 (1 H, d, *J*=8.51 Hz), 8.55 (1 H, s), 9.13 (1 H, s), 10.55 (1 H, s); ESIMS found for C₁₉H₂₂N₄O₂ *m/z* 339.2 (M+1).

**1010**

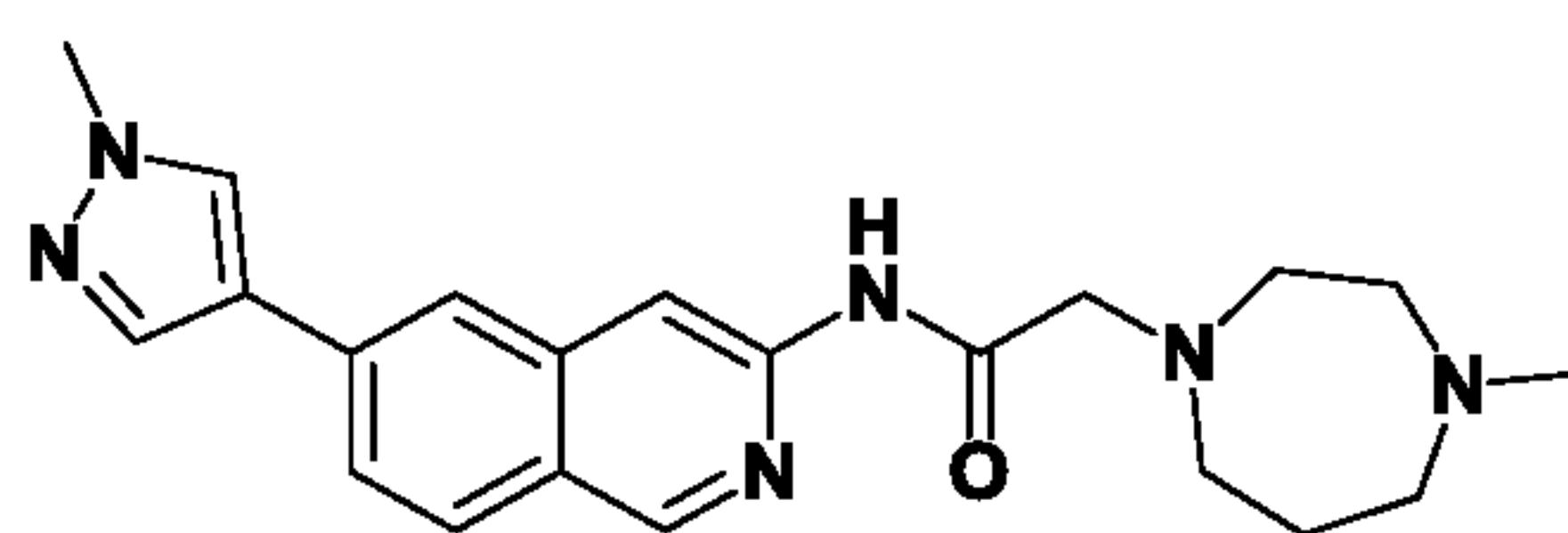
[01146] *tert*-Butyl 2-(4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl) carbamoyl) piperidin-1-yl)acetate **1010**.

[01147] White solid (75.0 mg, 0.167 mmol, 18.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.42 (9 H, s), 1.62 - 1.73 (2 H, m), 1.74 - 1.81 (2 H, m), 2.22 (2 H, td, *J*=11.53, 2.20 Hz), 2.51 - 2.57 (1 H, m), 2.83 - 2.91 (2 H, m), 3.10 (2 H, s), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.03 (1 H, s), 8.07 (1 H, s), 8.34 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.46 (1 H, s); ESIMS found for C₂₅H₃₁N₅O₃ *m/z* 450.2 (M+1).

**1011**

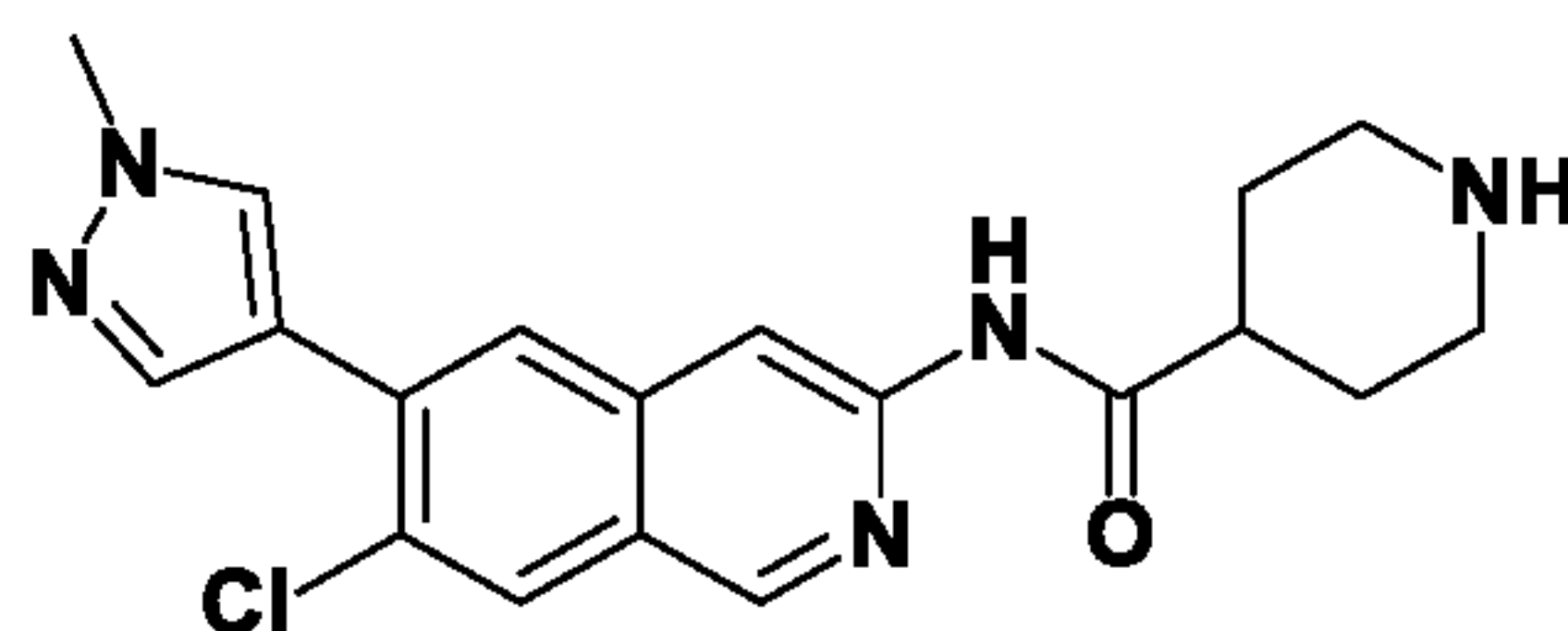
[01148] 2-(4-((6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetic acid **1011**.

[01149] White solid. ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.76 - 1.90 (4 H, m), 2.41 - 2.48 (2 H, m), 2.57 - 2.66 (1 H, m), 3.10 - 3.19 (4 H, m), 3.90 (3 H, s), 7.75 (1 H, dd, *J*=8.51, 1.65 Hz), 8.00 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.36 (1 H, br s), 8.44 (1 H, s), 9.03 (1 H, s), 10.53 (1 H, s); ESIMS found for C₂₁H₂₃N₅O₃ *m/z* 394.2 (M+1).

**1012**

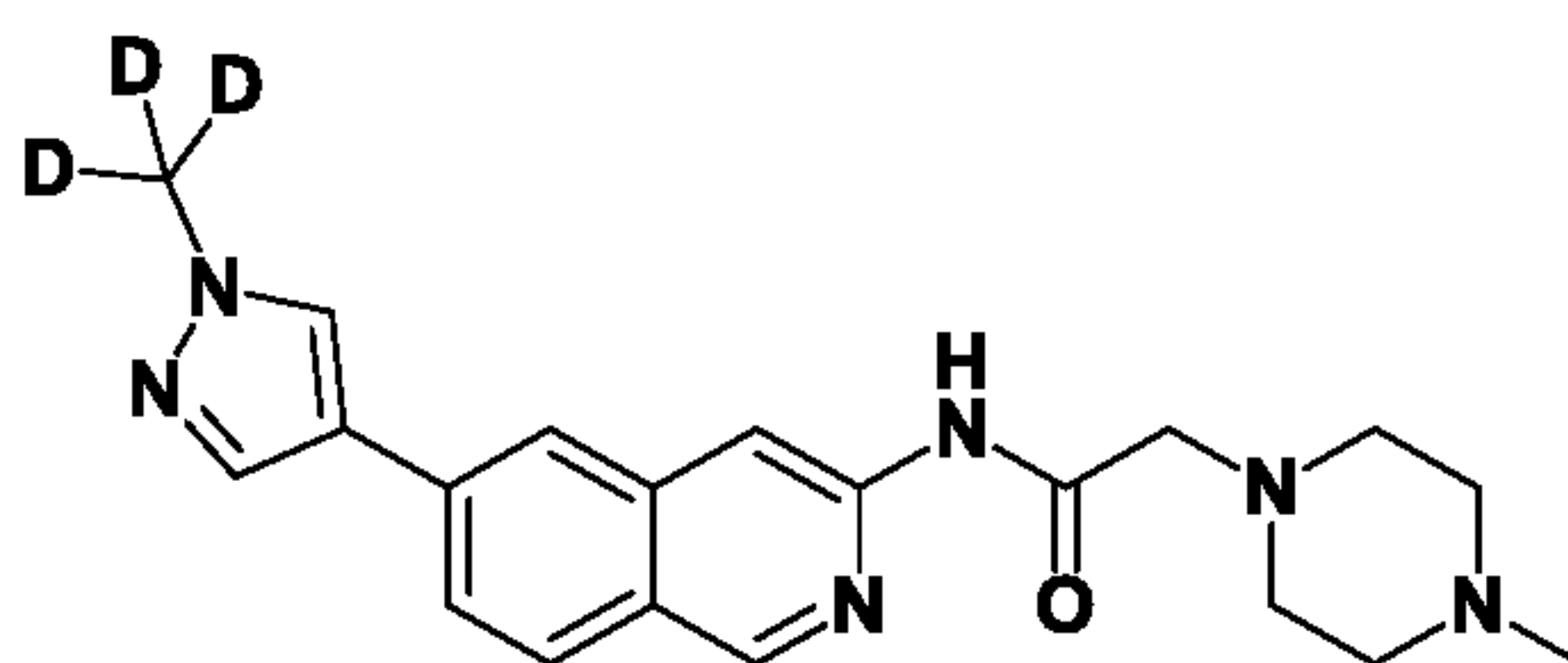
[01150] 2-(4-Methyl-1,4-diazepan-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide **1012**.

[01151] Off-white solid (40.0 mg, 0.106 mmol, 48.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.78 (2 H, quin, *J*=5.97 Hz), 2.28 (3 H, s), 2.56 - 2.64 (4 H, m), 2.79 - 2.87 (4 H, m), 3.36 (2 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.08 - 8.13 (2 H, m), 8.36 (1 H, s), 8.44 (1 H, s), 9.04 (1 H, s), 9.96 (1 H, s); ESIMS found for C₂₁H₂₆N₆O *m/z* 379.2 (M+1).

**1013**

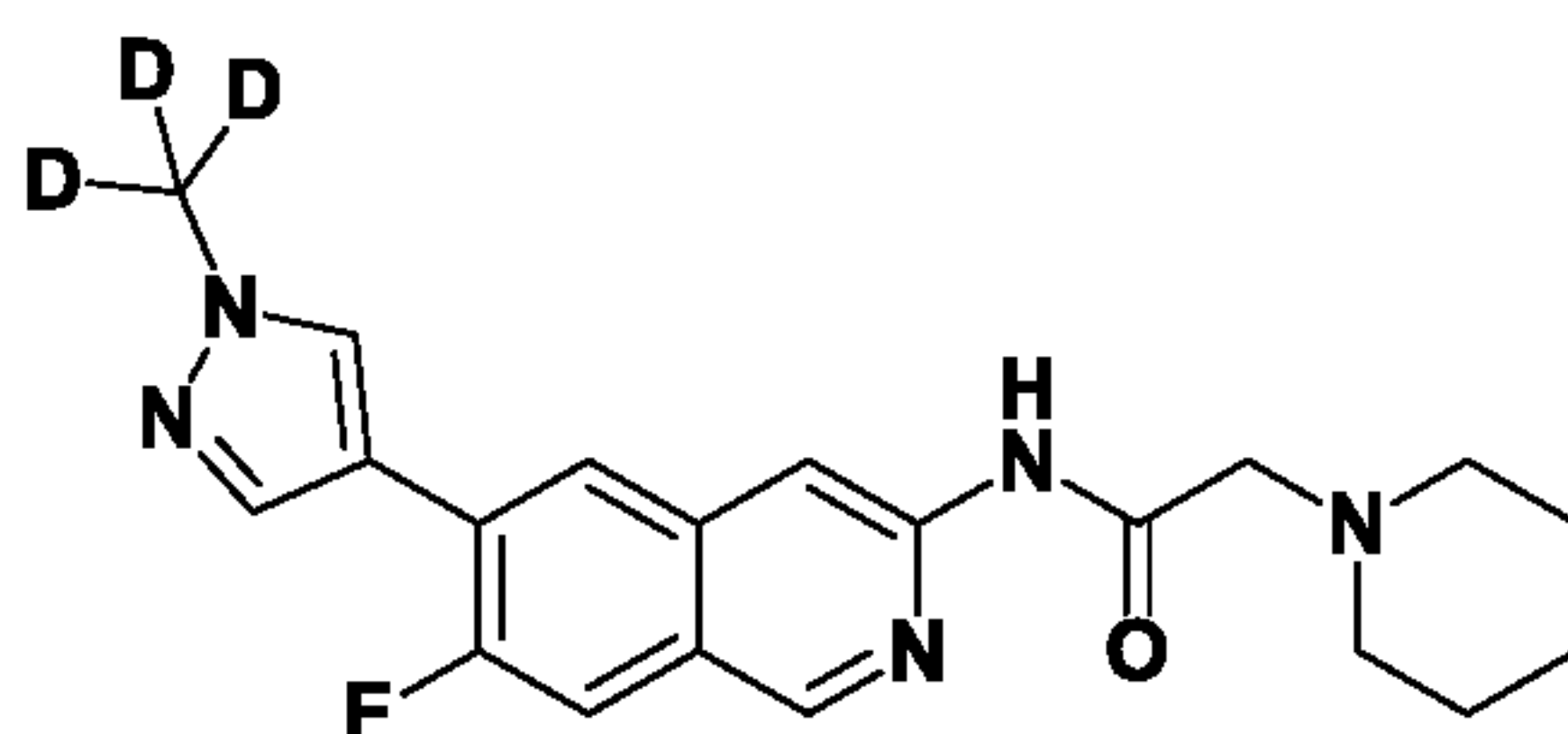
[01152] N-(7-Chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1013**.

[01153] Off-white solid (200.0 mg, 0.541 mmol, 99.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.75 - 1.85 (2 H, m), 1.93 - 1.99 (2 H, m), 2.79 - 2.90 (3 H, m), 3.28 - 3.34 (2 H, m), 3.93 (3 H, s), 7.98 (1 H, s), 8.11 (1 H, s), 8.26 (1 H, s), 8.31 (1 H, s), 8.47 (1 H, s), 9.09 (1 H, s), 10.71 (1 H, s); ESIMS found for C₁₉H₂₀ClN₅O *m/z* 370.1 (M+1).

**1014**

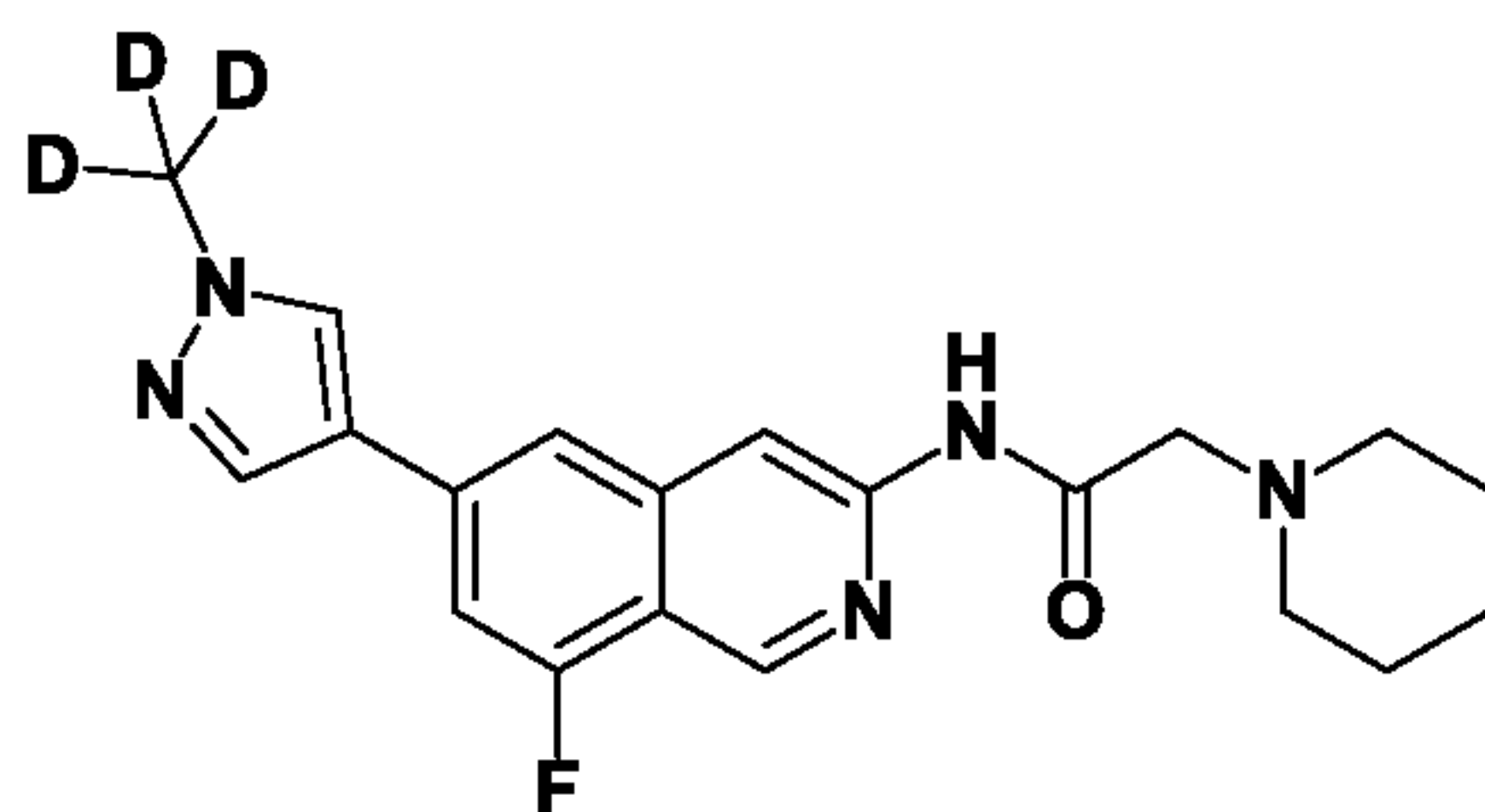
[01154] N-(6-(1-(Methyl-*d*₃)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **1014**.

[01155] Light brown solid (92.0 mg, 0.250 mmol, 50.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.24 (3 H, s), 2.46 (4 H, br s), 2.60 (4 H, br s), 3.23 (2 H, s), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (2 H, s), 8.36 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.94 (1 H, s); ESIMS found for C₂₀H₂₁[²H₃]N₆O *m/z* 368.2 (M+1).

**1015**

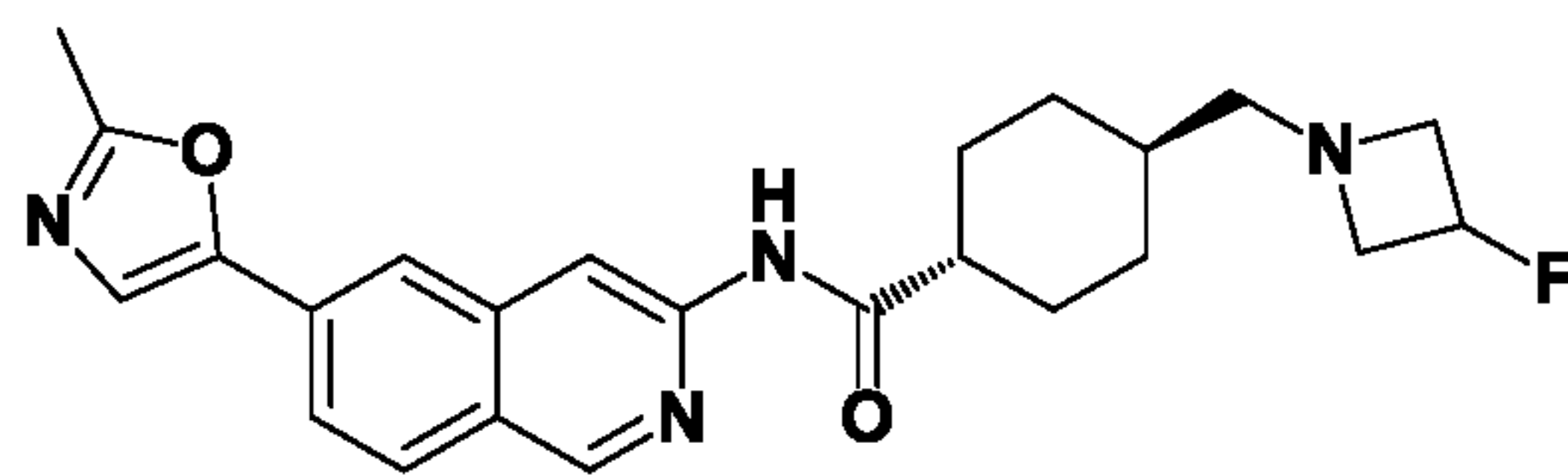
[01156] N-(7-Fluoro-6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide **1015**.

[01157] Brown solid (20.0 mg, 0.054 mmol, 33.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.43 (2 H, br d, *J*=5.21 Hz), 1.58 (4 H, quin, *J*=5.56 Hz), 2.52 (4 H, br s), 3.17 (2 H, s), 7.92 (1 H, d, *J*=11.53 Hz), 8.13 (1 H, s), 8.31 (1 H, d, *J*=2.47 Hz), 8.33 (1 H, d, *J*=7.68 Hz), 8.49 (1 H, s), 9.05 (1 H, s), 9.93 (1 H, s); ESIMS found for C₂₀H₁₉[²H₃]FN₅O *m/z* 371.2 (M+1).

**1016**

[01158] N-(8-Fluoro-6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide **1016**.

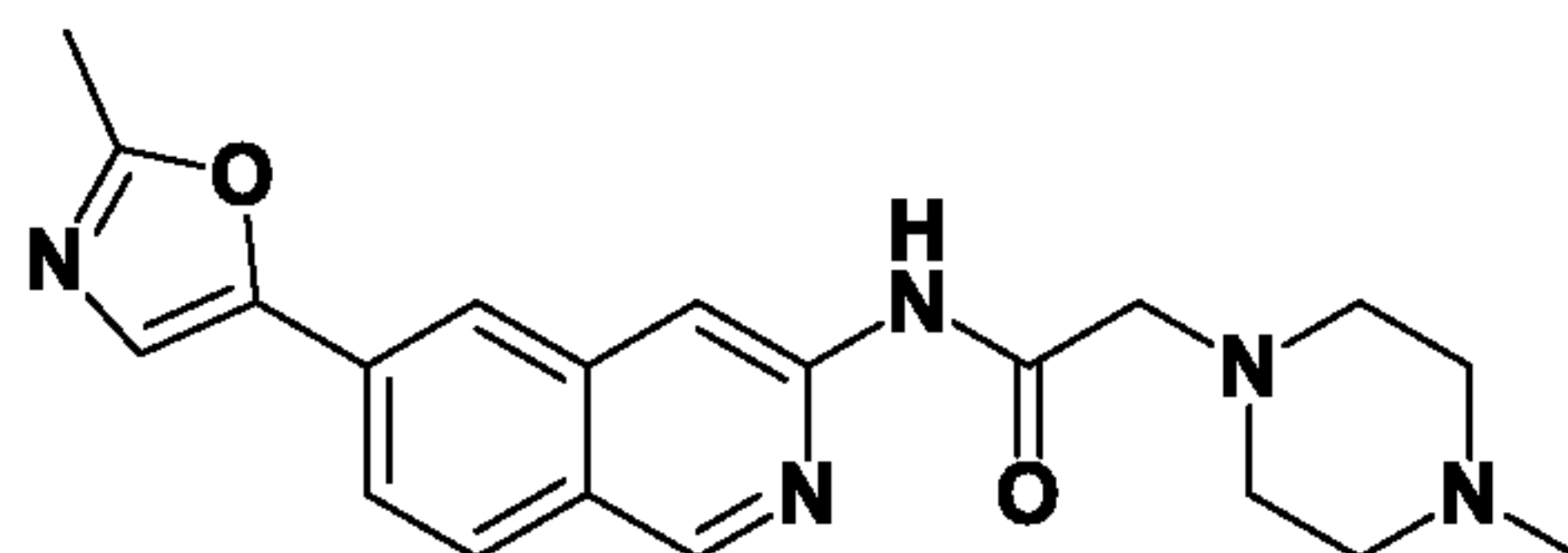
[01159] Pale yellow solid (46.0 mg, 0.124 mmol, 40.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.43 (2 H, br d, *J*=4.94 Hz), 1.58 (4 H, quin, *J*=5.56 Hz), 2.51 - 2.57 (4 H, m), 3.19 (2 H, s), 7.62 (1 H, dd, *J*=12.08, 1.10 Hz), 7.99 (1 H, s), 8.13 (1 H, s), 8.40 (1 H, d, *J*=0.82 Hz), 8.48 (1 H, s), 9.16 (1 H, s), 10.04 (1 H, s); ESIMS found for C₂₀H₁₉[²H₃]FN₅O *m/z* 371.2 (M+1).

**1018**

[01160] *trans*-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **1018**.

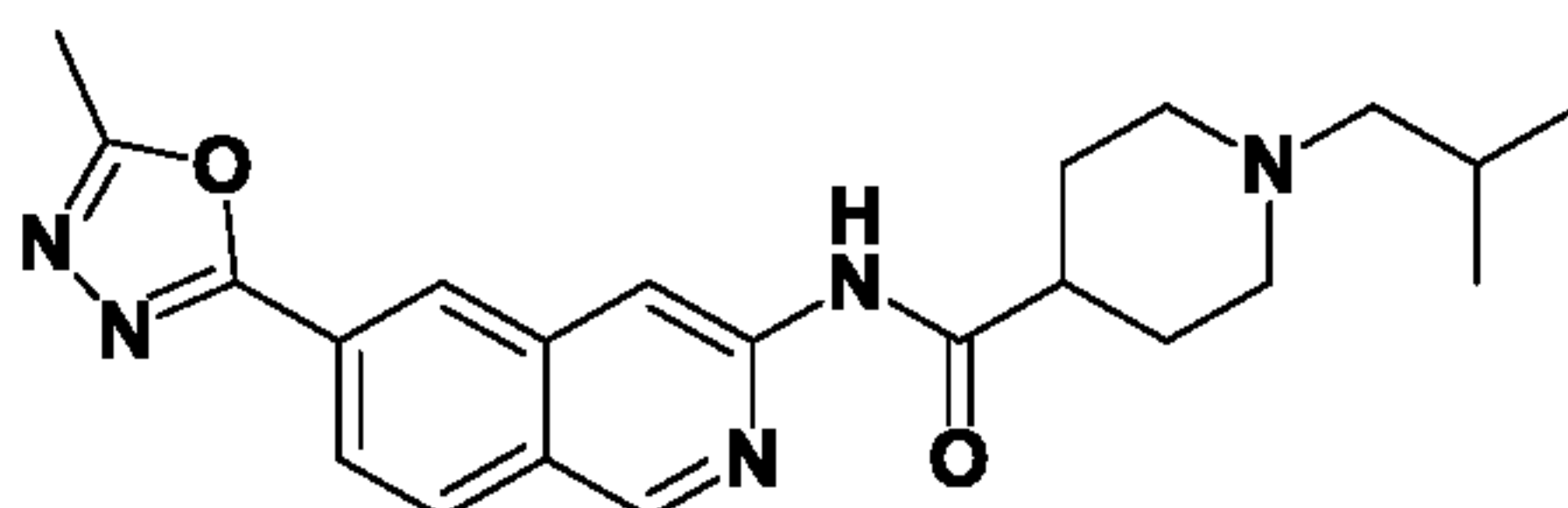
[01161] Off-white solid (52.0 mg, 0.123 mmol, 51.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.91 (2 H, qd, *J*=12.72, 3.02 Hz), 1.22 - 1.32 (1 H, m), 1.44 (2 H, qd, *J*=12.72, 3.29 Hz), 1.79 (2 H, br dd, *J*=13.17, 2.47 Hz), 1.82 - 1.89 (2 H, m), 2.29 (2 H, d, *J*=6.59 Hz), 2.44

- 2.49 (1 H, m), 2.53 (3 H, s), 2.96 - 3.08 (2 H, m), 3.49 - 3.59 (2 H, m), 5.12 (1 H, dq, $J=58.00$, 5.20 Hz), 7.78 (1 H, s), 7.79 - 7.83 (1 H, m), 8.06 - 8.12 (2 H, m), 8.50 (1 H, s), 9.10 (1 H, s), 10.48 (1 H, s); ESIMS found for $C_{24}H_{27}FN_4O_2$ m/z 423.2 (M+1).

**1019**

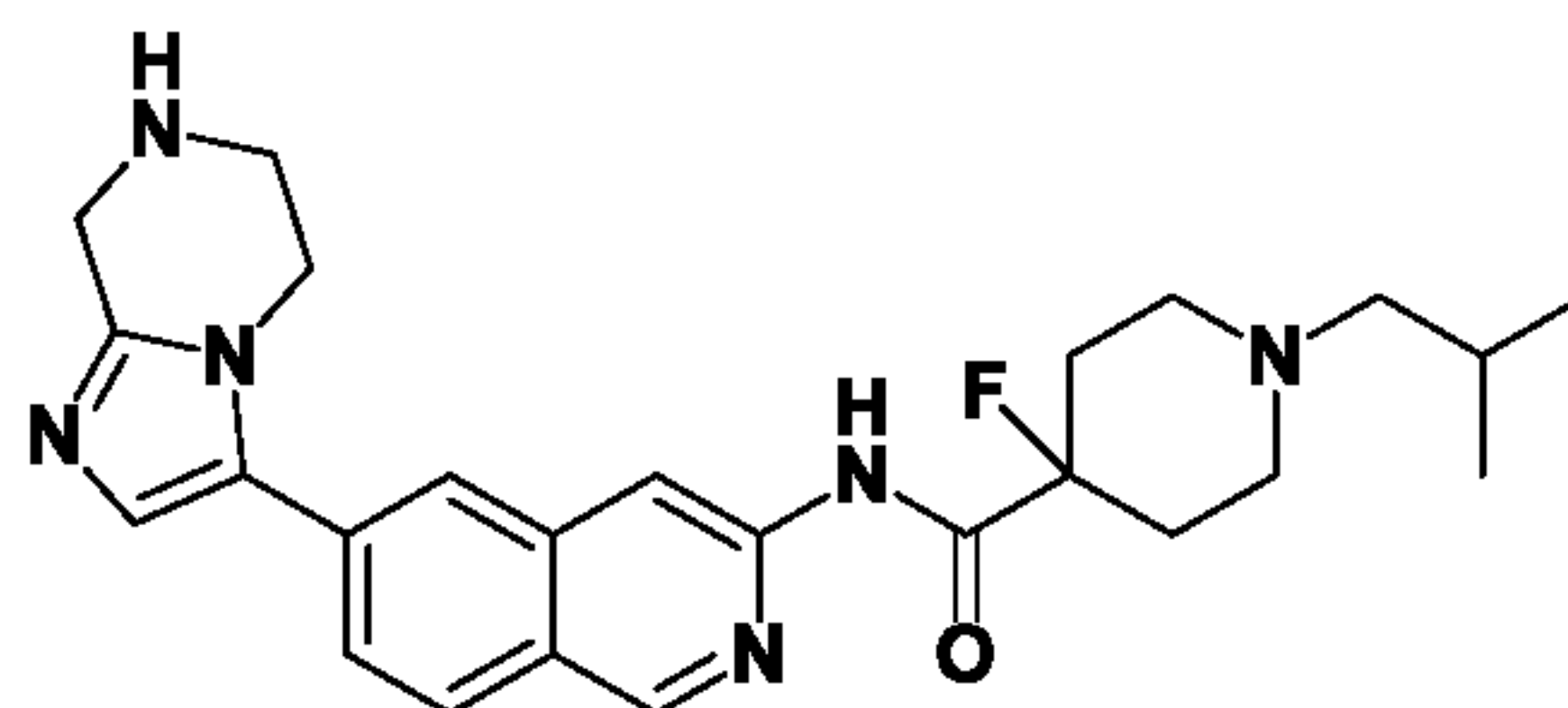
[01162] N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **1019**.

[01163] Off-white solid (60.0 mg, 0.164 mmol, 49.8% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.19 (3 H, s), 2.40 (4 H, br s), 2.53 (3 H, s), 2.58 (4 H, br s), 3.23 (2 H, s), 7.80 (1 H, s), 7.83 (1 H, dd, $J=8.51$, 1.65 Hz), 8.12 (1 H, d, $J=8.51$ Hz), 8.16 (1 H, s), 8.50 (1 H, s), 9.12 (1 H, s), 10.00 (1 H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

**1020**

[01164] 1-Isobutyl-N-(6-(5-methyl-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1020**.

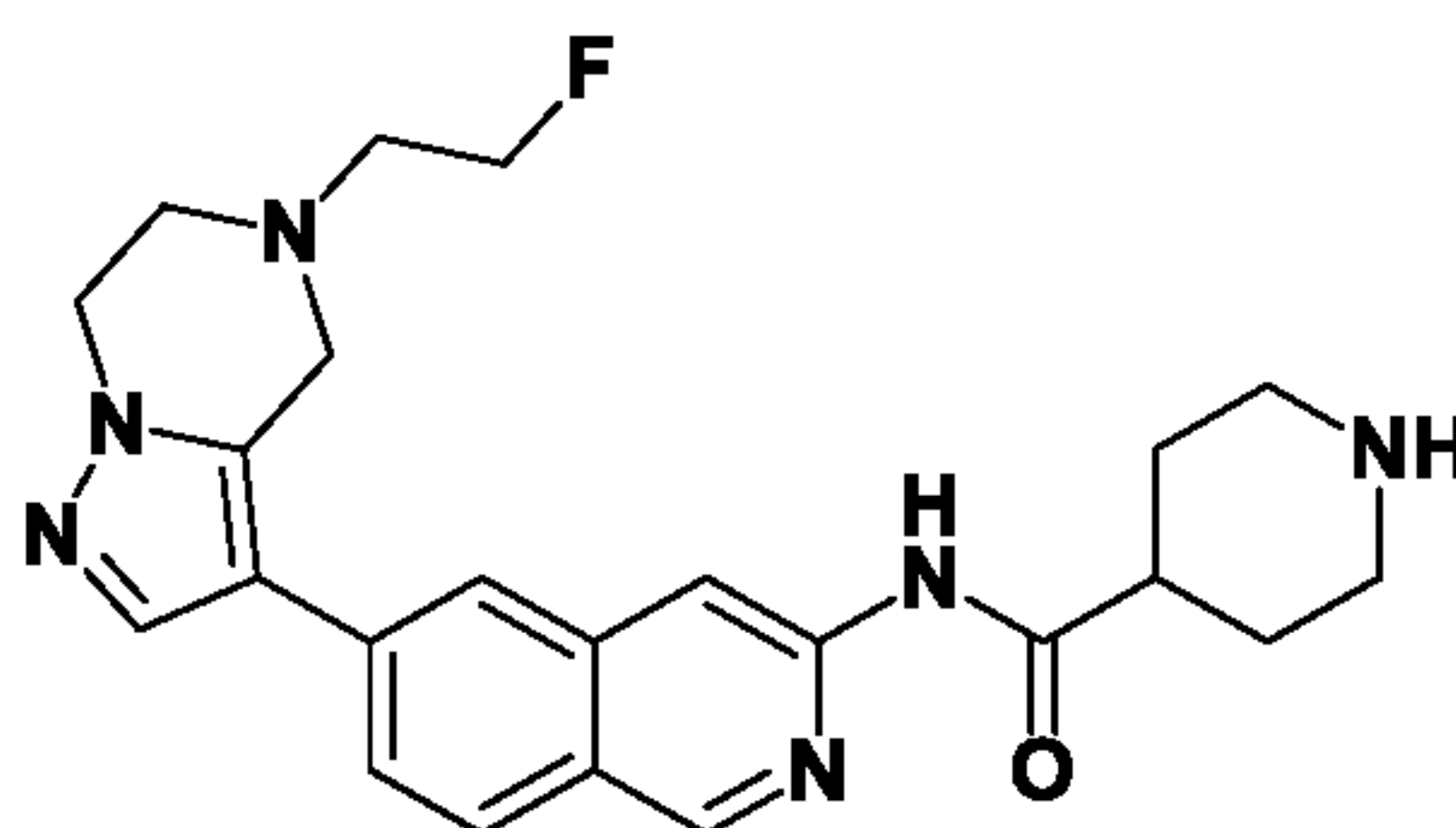
[01165] Off-white solid (40.0 mg, 0.102 mmol, 34.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.86 (6 H, d, $J=6.59$ Hz), 1.62 - 1.73 (2 H, m), 1.73 - 1.82 (3 H, m), 1.83 - 1.92 (2 H, m), 2.02 (2 H, d, $J=7.41$ Hz), 2.52 - 2.59 (1 H, m), 2.64 (3 H, s), 2.87 (2 H, br d, $J=11.25$ Hz), 8.04 (1 H, dd, $J=8.51$, 1.37 Hz), 8.23 (1 H, d, $J=8.78$ Hz), 8.47 (1 H, s), 8.62 (1 H, s), 9.24 (1 H, s), 10.64 (1 H, s); ESIMS found for $C_{22}H_{27}N_5O_2$ m/z 394.2 (M+1).

**1021**

[01166] 4-Fluoro-1-isobutyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1021**.

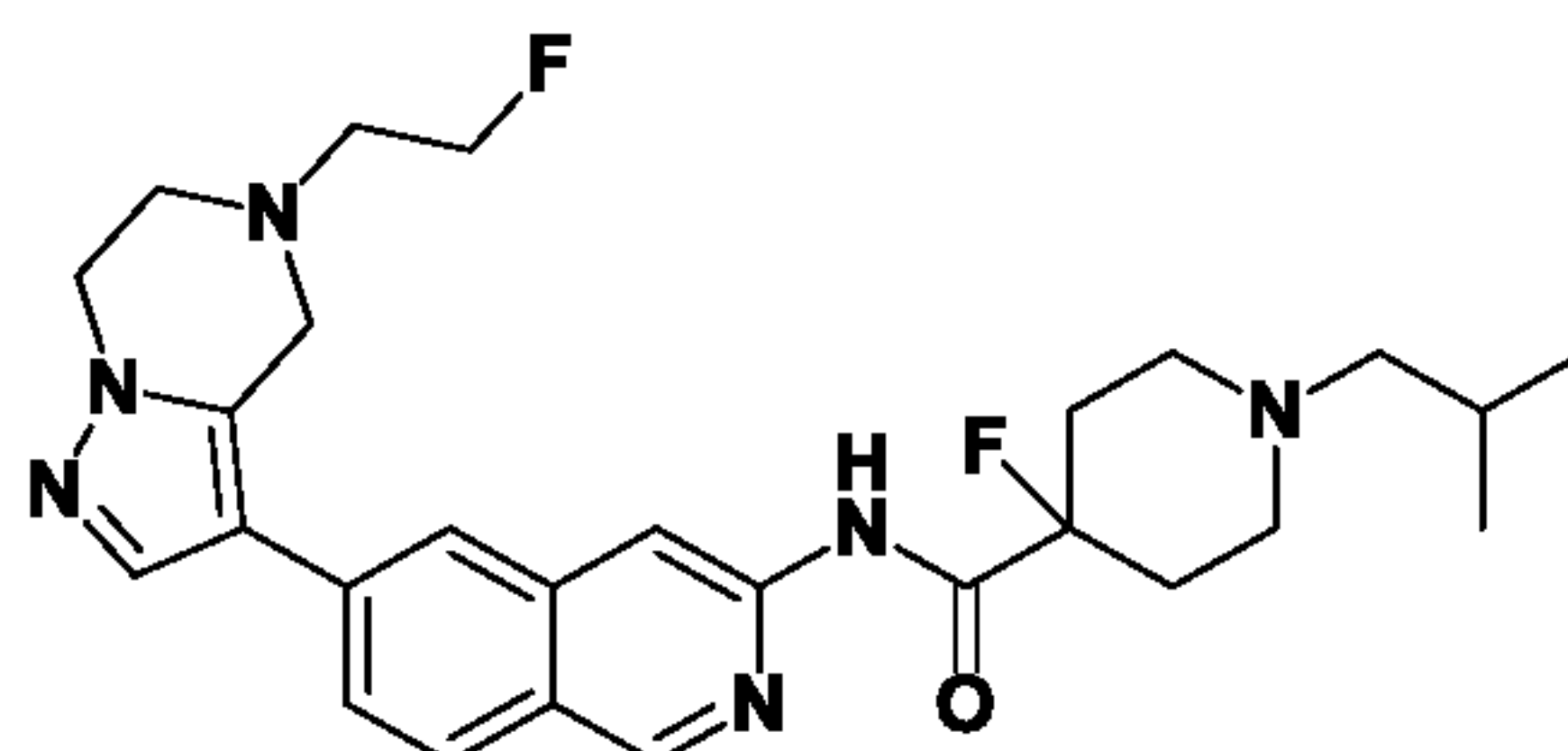
[01167] White solid (66.0 mg, 0.147 mmol, 47.5% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.88 (6 H, d, $J=6.59$ Hz), 1.75 - 1.86 (1 H, m), 1.91 - 2.01 (2 H, m), 2.05 - 2.22 (4 H, m),

2.09 (2 H, d, $J=7.41$ Hz), 2.78 (2 H, br d, $J=7.68$ Hz), 3.07 (2 H, br t, $J=5.21$ Hz), 3.95 (2 H, s), 4.12 (2 H, t, $J=5.21$ Hz), 7.31 (1 H, s), 7.72 (1 H, dd, $J=8.64, 1.51$ Hz), 8.02 (1 H, s), 8.11 (1 H, d, $J=8.51$ Hz), 8.49 (1 H, s), 9.15 (1 H, s), 9.91 (1 H, d, $J=4.12$ Hz); ESIMS found for $C_{25}H_{31}FN_6O$ m/z 451.25 (M+1).

**1022**

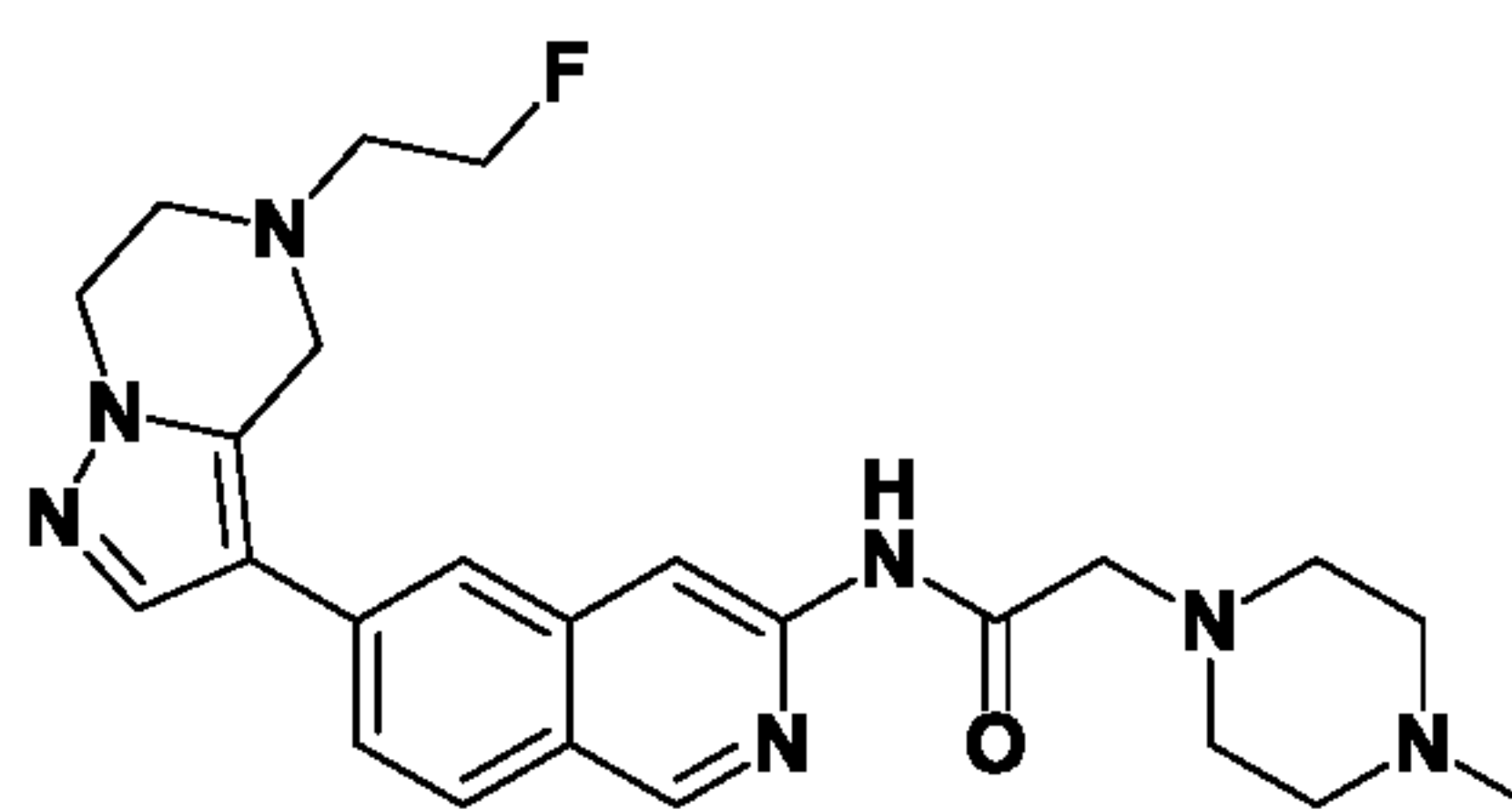
[01168] N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1022**.

[01169] White solid (14.0 mg, 0.033 mmol, 46.7% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.54 (2 H, qd, $J=12.12, 3.70$ Hz), 1.70 (2 H, br d, $J=10.98$ Hz), 2.47 (2 H, br s), 2.64 (1 H, tt, $J=11.46, 3.50$ Hz), 2.93 - 3.04 (4 H, m), 3.07 (2 H, br t, $J=5.49$ Hz), 4.08 (2 H, s), 4.18 (2 H, t, $J=5.35$ Hz), 4.66 (2 H, dt, $J=47.80, 4.70$ Hz), 7.63 (1 H, dd, $J=8.51, 1.65$ Hz), 7.75 (1 H, s), 8.00 (1 H, s), 8.02 (1 H, d, $J=8.78$ Hz), 8.48 (1 H, s), 9.05 (1 H, s), 10.42 (1 H, s); ESIMS found for $C_{23}H_{27}FN_6O$ m/z 423.2 (M+1).

**1023**

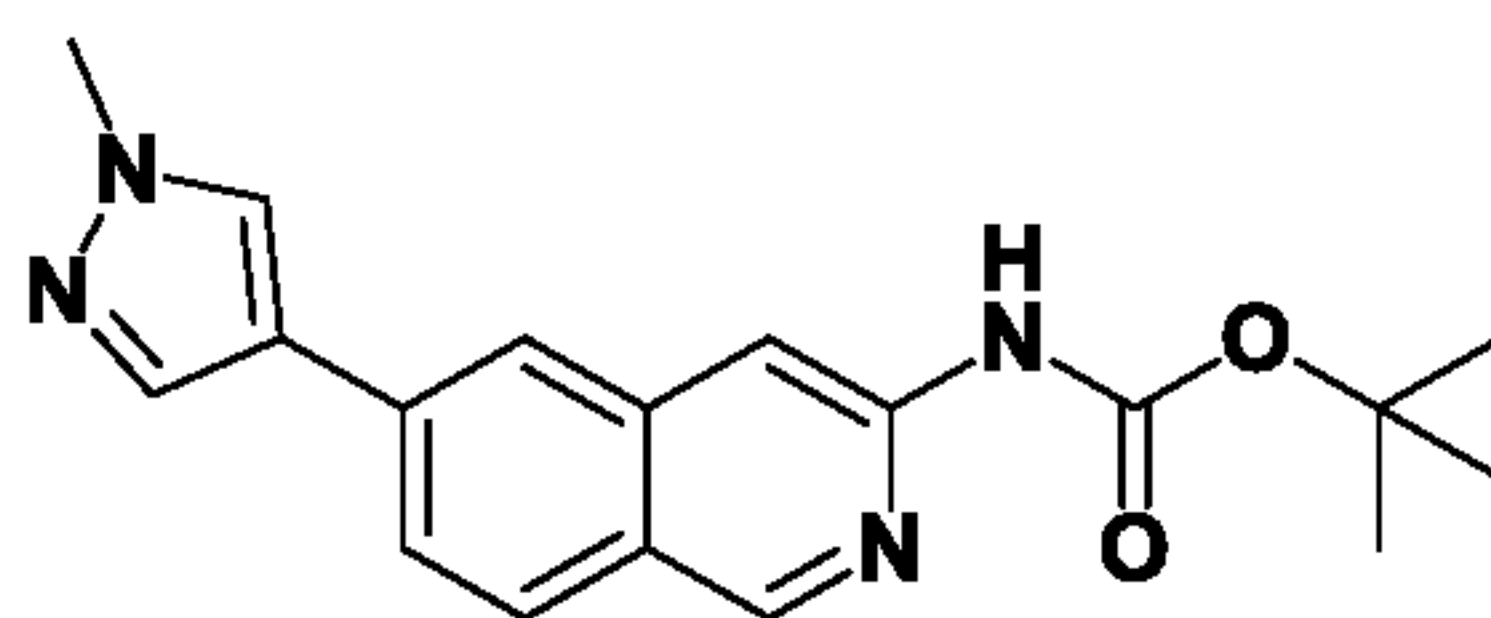
[01170] 4-Fluoro-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide **1023**.

[01171] White amorphous solid (48.8 mg, 0.098 mmol, 88.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.88 (6 H, d, $J=6.59$ Hz), 1.79 (1 H, dt, $J=13.52, 6.83$ Hz), 1.95 (2 H, br t, $J=11.66$ Hz), 2.06 - 2.22 (4 H, m), 2.09 (2 H, d, $J=7.68$ Hz), 2.78 (2 H, br d, $J=7.96$ Hz), 2.99 (2 H, dt, $J=28.60, 4.95$ Hz), 3.08 (2 H, t, $J=5.49$ Hz), 4.09 (2 H, s), 4.18 (2 H, t, $J=5.49$ Hz), 4.66 (2 H, dt, $J=47.85, 4.95$ Hz), 7.70 (1 H, dd, $J=8.51, 1.65$ Hz), 7.84 (1 H, s), 8.01 (1 H, s), 8.08 (1 H, d, $J=8.78$ Hz), 8.45 (1 H, s), 9.11 (1 H, s), 9.86 (1 H, d, $J=4.39$ Hz); ESIMS found for $C_{27}H_{34}F_2N_6O$ m/z 497.3 (M+1).

**1024**

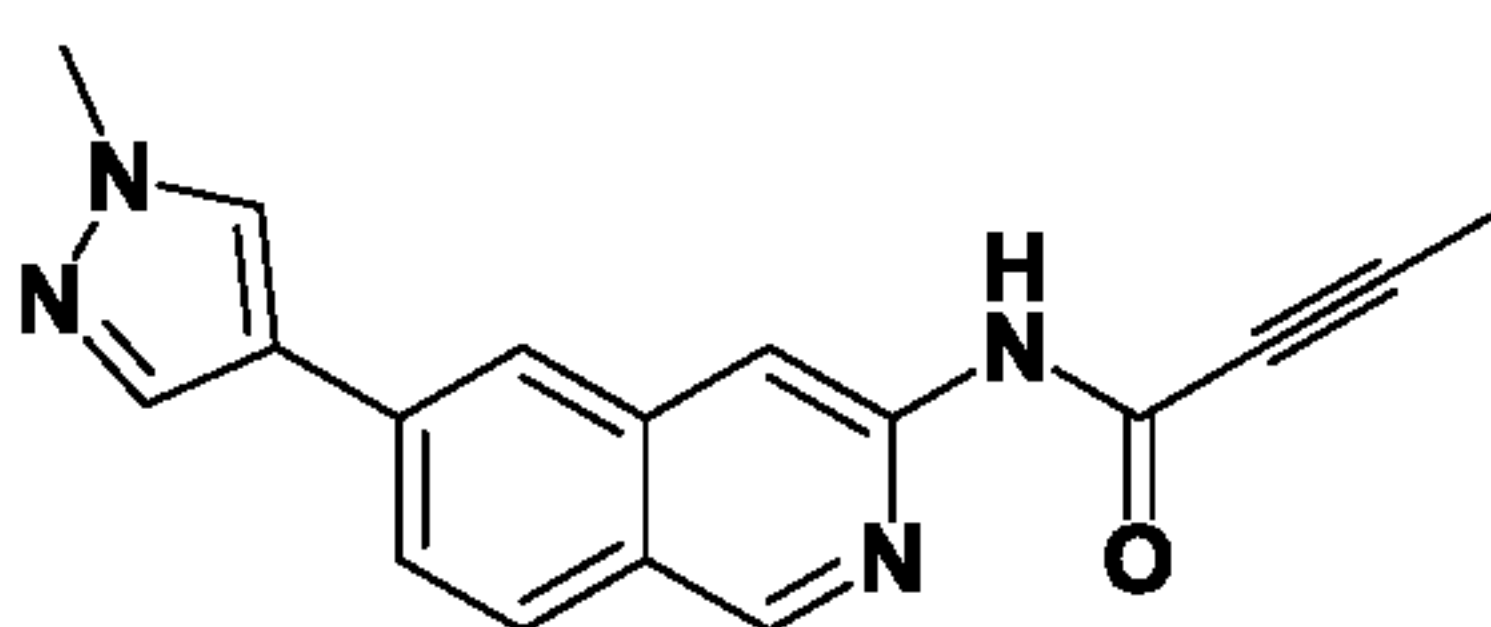
[01172] N-(6-(5-(2-Fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **1024**.

[01173] Orange solid (3.0 mg, 0.007 mmol, 4.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.19 (3 H, s), 2.40 (4 H, br s), 2.58 (4 H, br s), 2.99 (2 H, dt, *J*=28.60, 4.95 Hz), 3.07 (2 H, t, *J*=5.49 Hz), 3.22 (2 H, s), 4.09 (2 H, s), 4.18 (2 H, t, *J*=5.35 Hz), 4.66 (2 H, dt, *J*=47.80, 4.95 Hz), 7.66 (1 H, dd, *J*=8.51, 1.65 Hz), 7.82 (1 H, s), 8.01 (1 H, s), 8.05 (1 H, d, *J*=8.51 Hz), 8.47 (1 H, s), 9.07 (1 H, s), 9.94 (1 H, s); ESIMS found for C₂₄H₃₀FN₇O *m/z* 452.2 (M+1).

**1025**

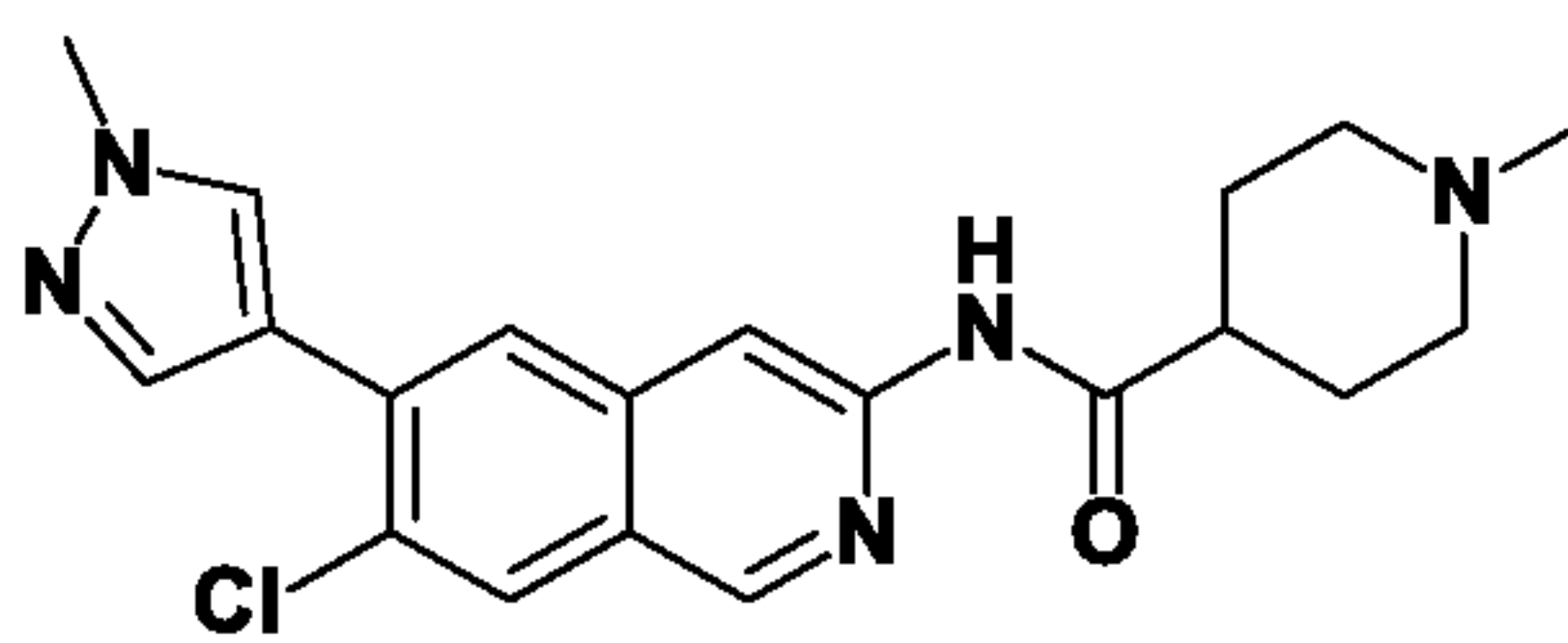
[01174] *tert*-Butyl (6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamate **1025**.

[01175] White solid (96.0 mg, 0.296 mmol, 28.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.51 (9 H, s), 3.90 (3 H, s), 7.71 (1 H, dd, *J*=8.51, 1.65 Hz), 7.97 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.07 (1 H, s), 8.10 (1 H, s), 8.33 (1 H, s), 8.97 (1 H, s), 9.78 (1 H, s); ESIMS found for C₁₈H₂₀N₄O₂ *m/z* 325.2 (M+1).

**1026**

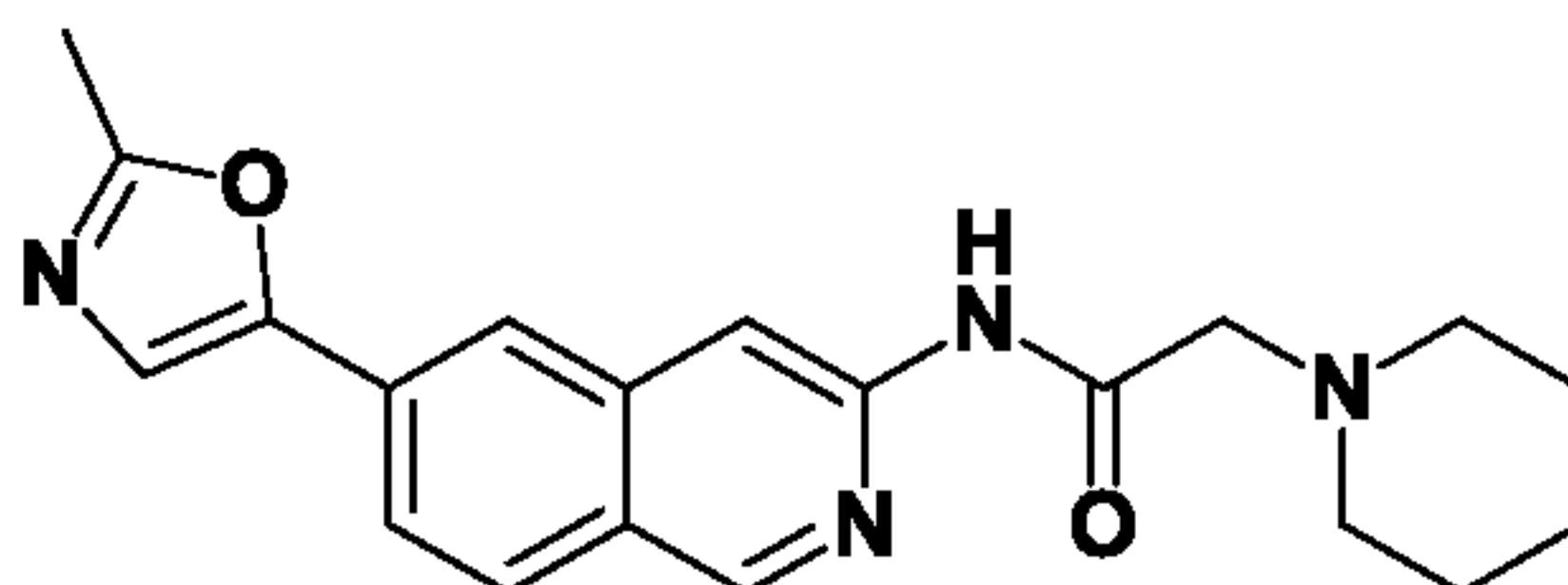
[01176] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)but-2-ynamide **1026**.

[01177] Yellow solid (3.7 mg, 0.013 mmol, 2.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.05 (3 H, s), 3.90 (3 H, s), 7.78 (1 H, dd, *J*=8.78, 1.65 Hz), 8.01 (1 H, d, *J*=8.78 Hz), 8.08 (1 H, s), 8.09 (1 H, s), 8.34 (2 H, s), 9.03 (1 H, s), 11.06 (1 H, br s); ESIMS found for C₁₇H₁₄N₄O *m/z* 290.9 (M+1).

**1027**

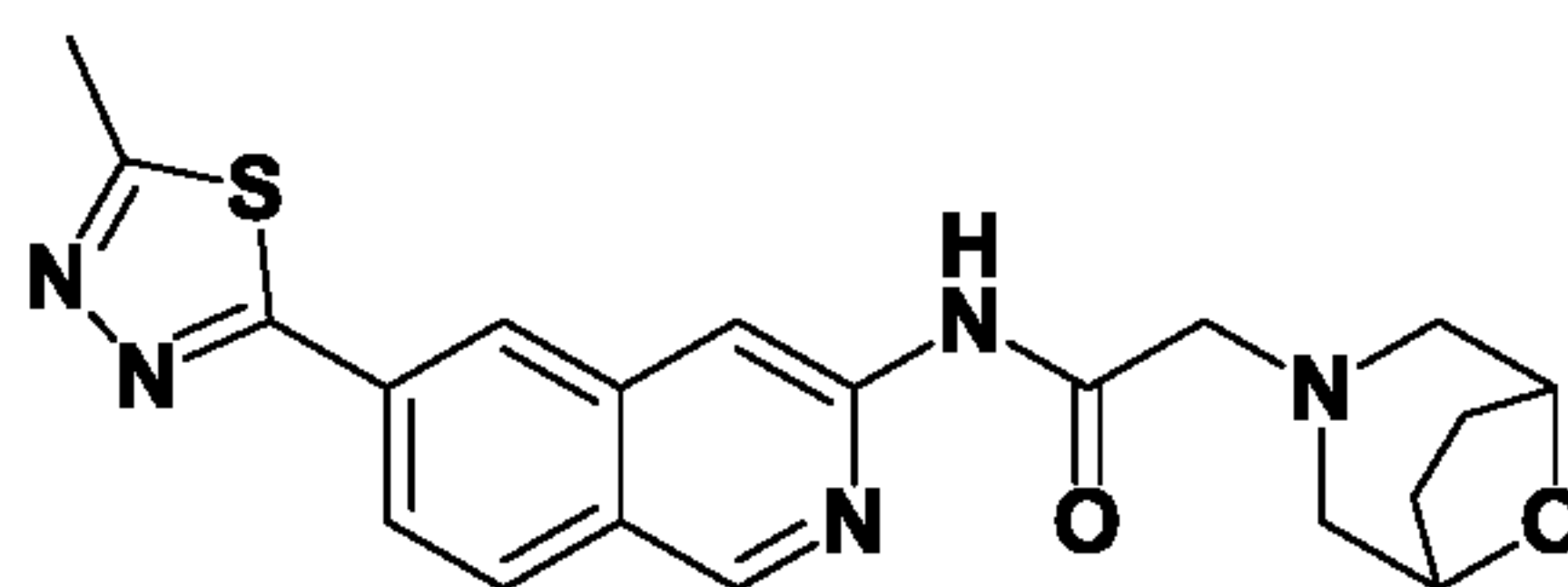
[01178] N-(7-Chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide **1027**.

[01179] White solid (2.0 mg, 0.005 mmol, 1.3% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.61 - 1.72 (2 H, m), 1.73 - 1.80 (2 H, m), 1.83 - 1.90 (2 H, m), 2.16 (3 H, s), 2.45 - 2.49 (1 H, m), 2.81 (2 H, br d, *J*=11.25 Hz), 3.93 (3 H, s), 7.97 (1 H, s), 8.09 (1 H, s), 8.25 (1 H, s), 8.30 (1 H, s), 8.48 (1 H, s), 9.08 (1 H, s), 10.56 (1 H, s); ESIMS found for C₂₀H₂₂ClN₅O *m/z* 384.2 (M+1).

**1028**

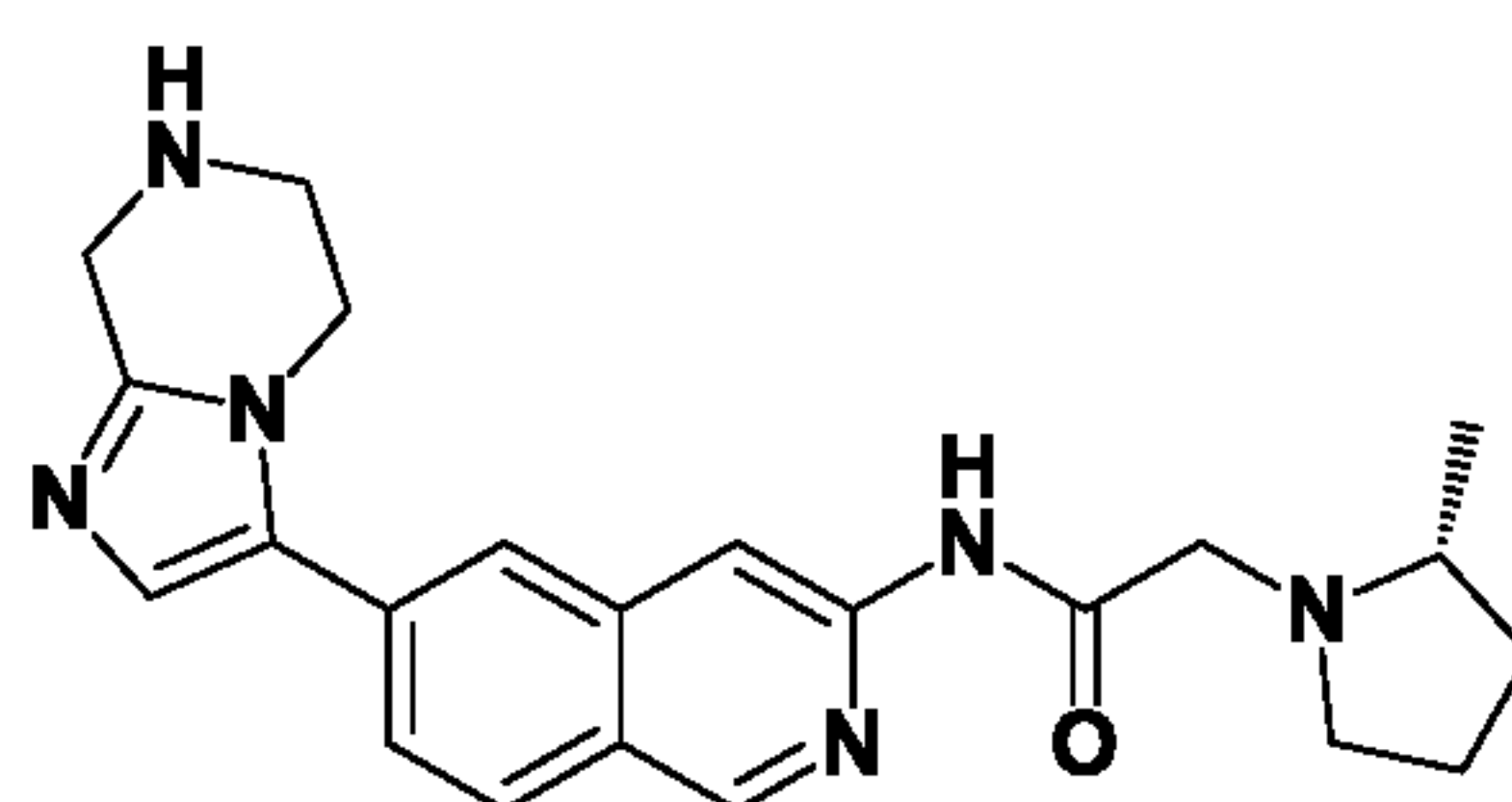
[01180] N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide **1028**.

[01181] Off-white solid (57.0 mg, 0.163 mmol, 32.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.43 (2 H, br d, *J*=5.21 Hz), 1.58 (4 H, quin, *J*=5.56 Hz), 2.52 (4 H, br s), 2.53 (3 H, s), 3.18 (2 H, s), 7.80 (1 H, s), 7.83 (1 H, dd, *J*=8.51, 1.65 Hz), 8.12 (1 H, d, *J*=8.78 Hz), 8.16 (1 H, s), 8.50 (1 H, s), 9.12 (1 H, s), 9.98 (1 H, s); ESIMS found for C₂₀H₂₂N₄O₂ *m/z* 351.15 (M+1).

**1029**

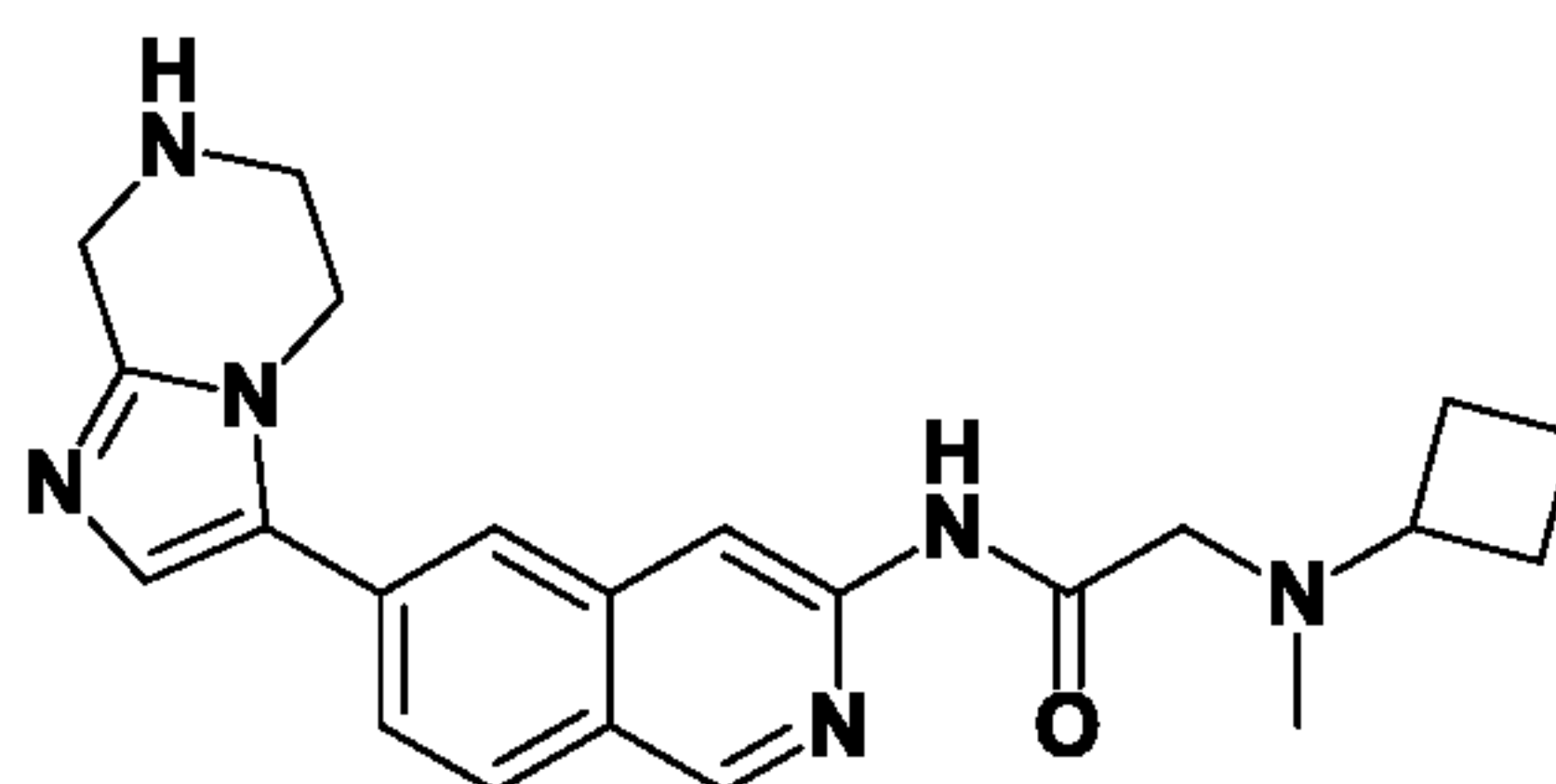
[01182] 2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide **1029**.

[01183] Beige solid (200.0 mg, 0.506 mmol, 56.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.80 - 1.88 (2 H, m), 2.00 - 2.06 (2 H, m), 2.48 (2 H, br s), 2.67 (2 H, br d, *J*=10.98 Hz), 2.83 (3 H, s), 3.20 (2 H, s), 4.27 (2 H, br d, *J*=1.92 Hz), 8.12 (1 H, dd, *J*=8.51, 1.65 Hz), 8.20 (1 H, d, *J*=8.78 Hz), 8.51 (1 H, s), 8.61 (1 H, s), 9.24 (1 H, s), 10.09 (1 H, s); ESIMS found for C₂₀H₂₁N₅O₂S *m/z* 396.15 (M+1).

**1030**

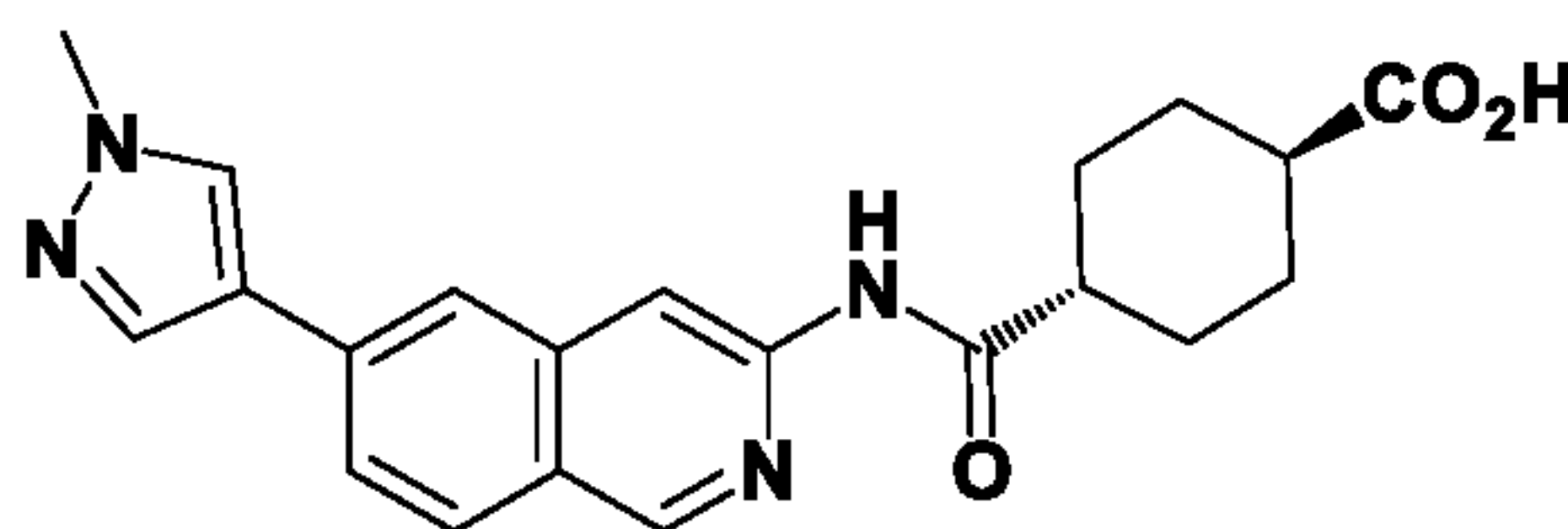
[01184] (R)-2-(2-Methylpyrrolidin-1-yl)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)acetamide **1030**.

[01185] White solid (25.2 mg, 0.065 mmol, 36.0% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.09 (3 H, d, $J=6.04$ Hz), 1.42 (1 H, dddd, $J=12.18, 10.26, 8.30, 6.59$ Hz), 1.67 - 1.85 (2 H, m), 1.90 - 2.02 (1 H, m), 2.41 (1 H, q, $J=8.51$ Hz), 2.57 - 2.67 (1 H, m), 3.08 (2 H, br t, $J=5.21$ Hz), 3.13 - 3.20 (2 H, m), 3.54 (1 H, d, $J=16.19$ Hz), 3.95 (2 H, s), 4.12 (2 H, t, $J=5.21$ Hz), 7.30 (1 H, s), 7.68 (1 H, dd, $J=8.51, 1.65$ Hz), 7.99 (1 H, s), 8.08 (1 H, d, $J=8.51$ Hz), 8.51 (1 H, s), 9.10 (1 H, s), 9.93 (1 H, s); ESIMS found for $\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}$ m/z 391.2 ($\text{M}+1$).

**1031**

[01186] 2-(Cyclobutyl(methyl)amino)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)acetamide **1031**.

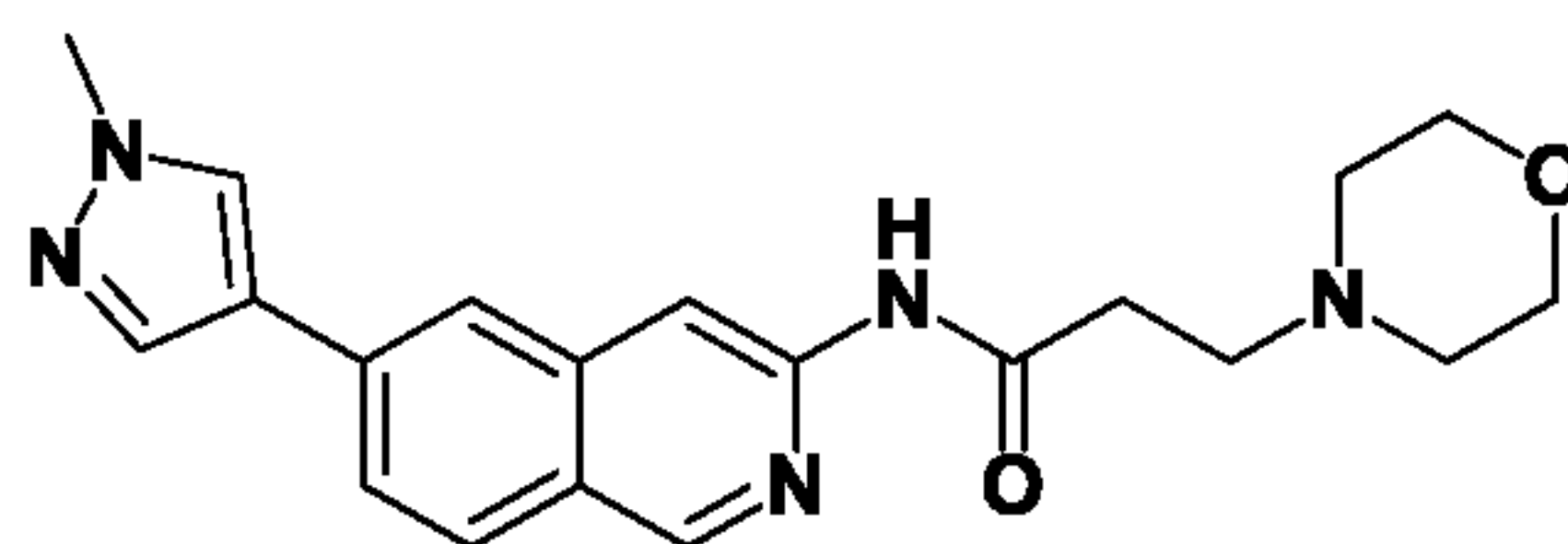
[01187] Light olive-colored gum (43.2 mg, 0.111 mmol, 46.4% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.54 - 1.71 (2 H, m), 1.80 - 1.93 (2 H, m), 1.96 - 2.07 (2 H, m), 2.23 (3 H, s), 3.12 (1 H, br d, $J=14.27$ Hz), 3.06 - 3.09 (2 H, m), 3.12 (2 H, s), 3.95 (2 H, s), 4.12 (2 H, t, $J=5.21$ Hz), 7.30 (1 H, s), 7.68 (1 H, dd, $J=8.51, 1.65$ Hz), 7.99 (1 H, s), 8.08 (1 H, d, $J=8.51$ Hz), 8.51 (1 H, s), 9.11 (1 H, s), 9.96 (1 H, s); ESIMS found for $\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}$ m/z 391.2 ($\text{M}+1$).

**1032**

[01188] *trans*-4-((6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)cyclohexane-1-carboxylic acid **1032**.

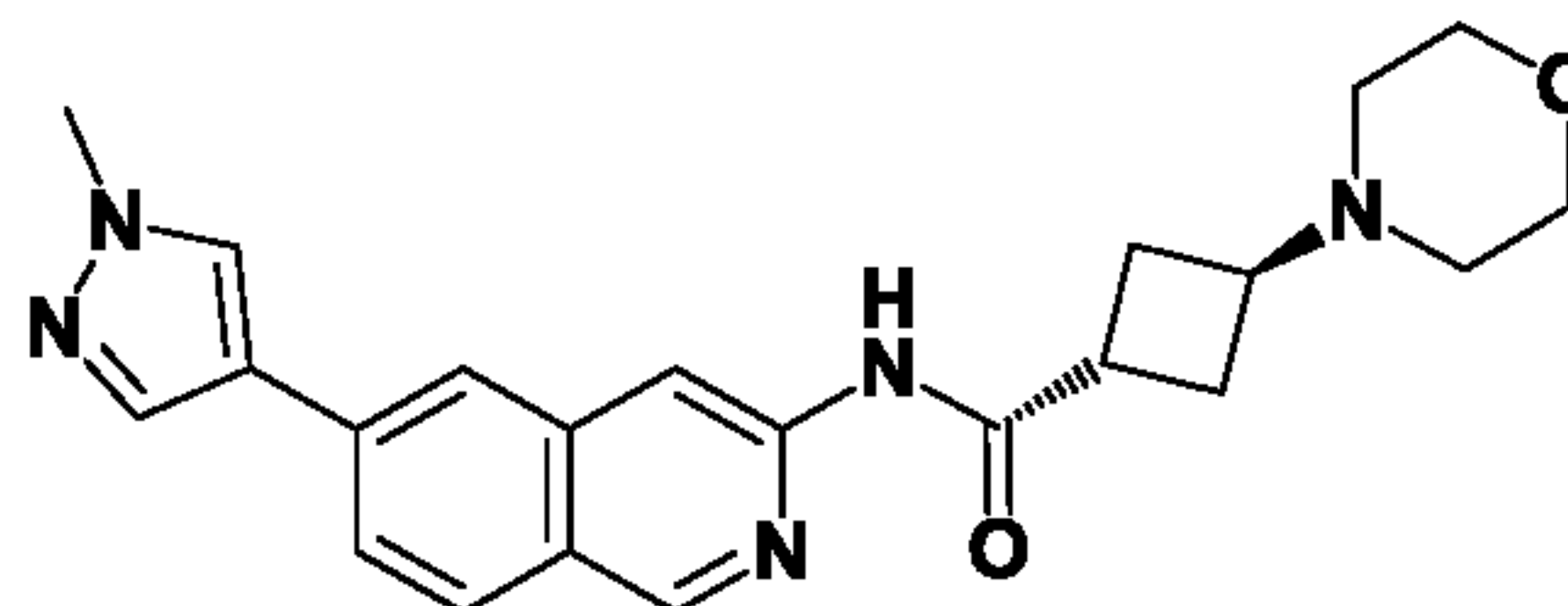
[01189] Beige solid (135.0 mg, 0.357 mmol, 70.0% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.29 - 1.40 (2 H, m), 1.49 (2 H, qd, $J=12.76, 3.16$ Hz), 1.85 - 1.94 (2 H, m), 1.97

(2 H, br dd, $J=13.45$, 2.74 Hz), 2.22 (1 H, tt, $J=12.18$, 3.60 Hz), 2.51 - 2.58 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 8.00 (1 H, d, $J=8.51$ Hz), 8.03 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.42 (1 H, s), 9.02 (1 H, s), 10.43 (1 H, s), 12.07 (1 H, br s); ESIMS found for $C_{21}H_{22}N_4O_3$ m/z 379.1 (M+1).

**1034**

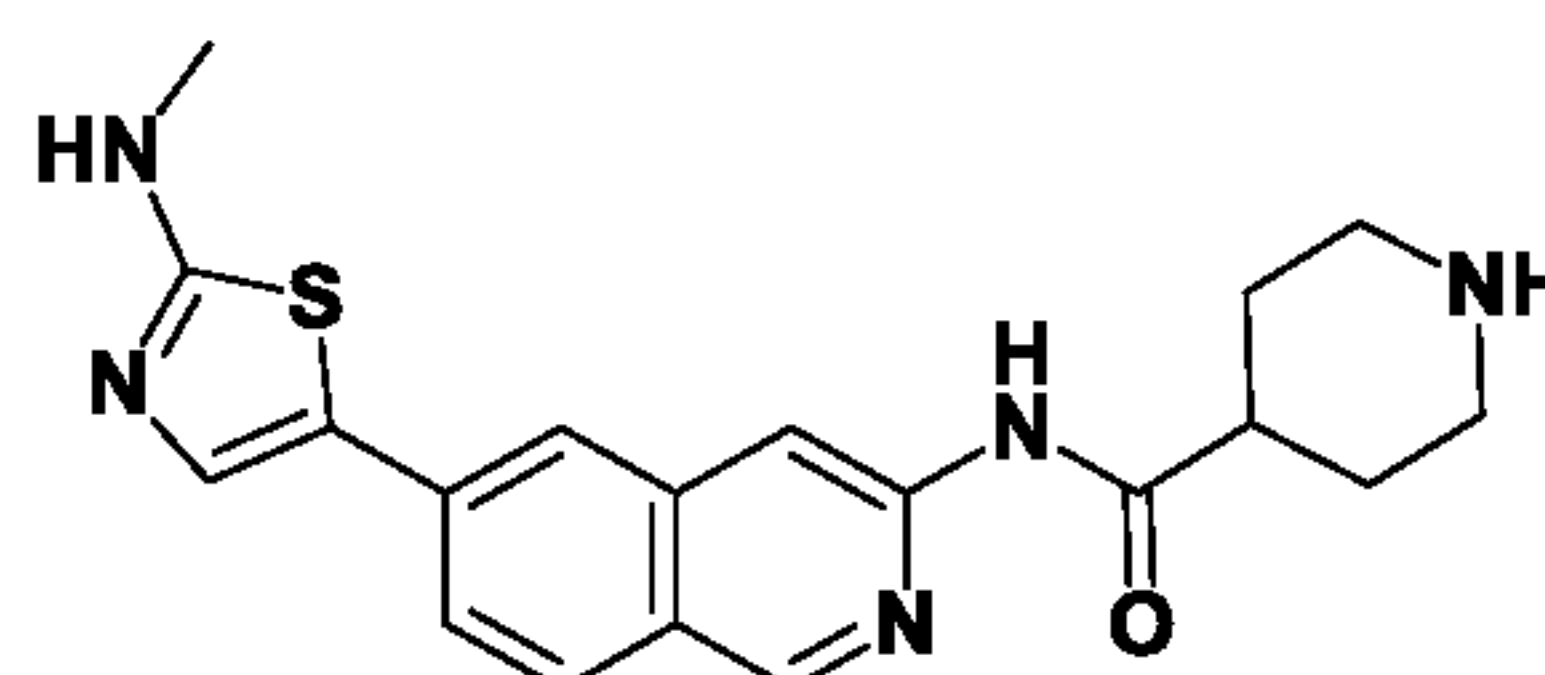
[01190] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-morpholinopropanamide **1034**.

[01191] White solid (12.0 mg, 0.033 mmol, 12.0% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.44 (4 H, br s), 2.57 - 2.63 (2 H, m), 2.63 - 2.70 (2 H, m), 3.59 (4 H, t, $J=4.67$ Hz), 3.90 (3 H, s), 7.75 (1 H, dd, $J=8.51$, 1.65 Hz), 8.00 (1 H, d, $J=8.51$ Hz), 8.06 (1 H, s), 8.09 (1 H, s), 8.36 (1 H, s), 8.44 (1 H, s), 9.03 (1 H, s), 10.74 (1 H, s); ESIMS found for $C_{20}H_{23}N_5O_2$ m/z 366.2 (M+1).

**1035**

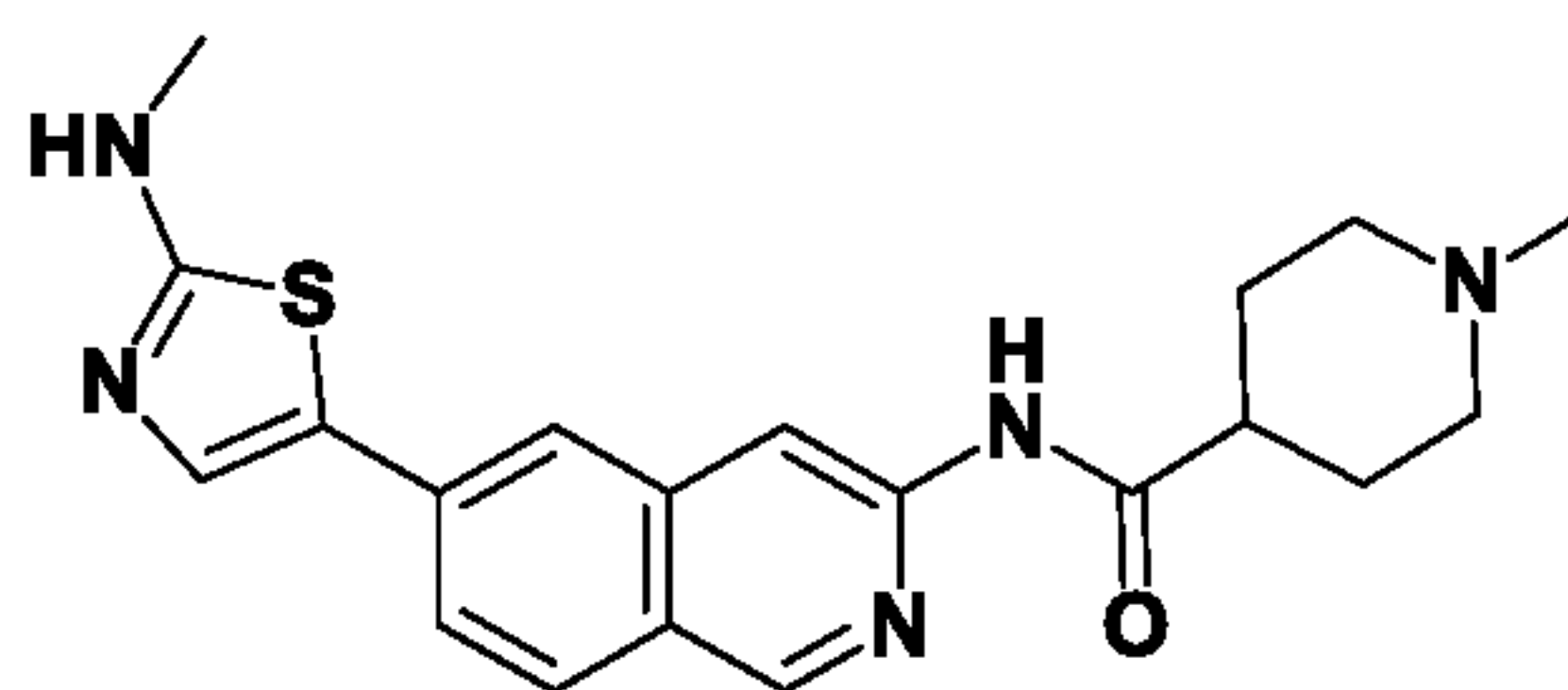
[01192] *trans*-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-morpholinocyclobutane-1-carboxamide **1035**.

[01193] White solid (18.0 mg, 0.075 mmol, 23.92% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.07 - 2.16 (2 H, m), 2.22 - 2.32 (6 H, m), 2.85 - 2.95 (1 H, m), 3.22 - 3.30 (1 H, m), 3.59 (4 H, t, $J=4.39$ Hz), 3.91 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 8.00 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.47 (1 H, s), 9.01 (1 H, s), 10.41 (1 H, s); ESIMS found for $C_{22}H_{25}N_5O_2$ m/z 392. (M+1).

**1040**

[01194] N-(6-(2-(Methylamino)thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1040**.

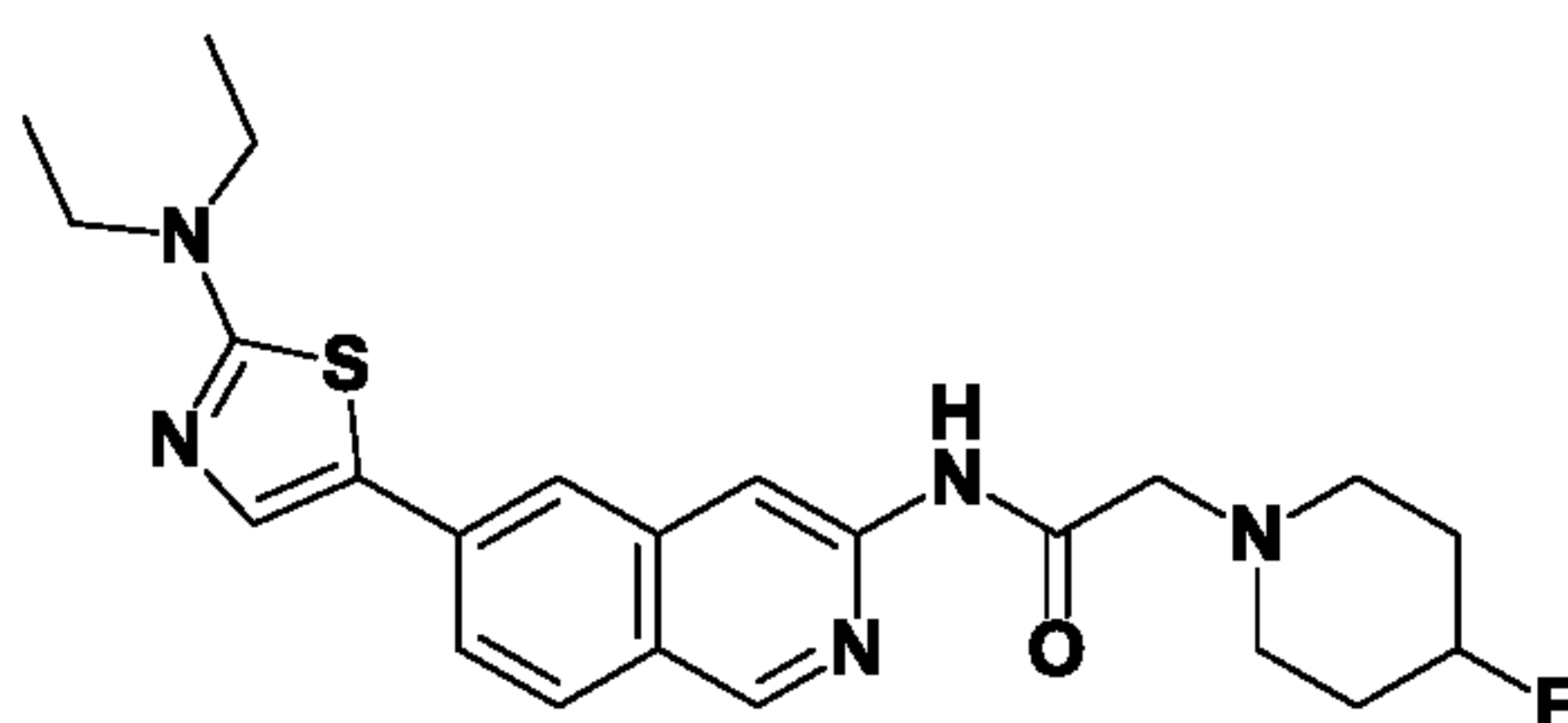
[01195] Beige solid (80.0 mg, 0.218 mmol, 91.1% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.46 - 1.60 (2 H, m), 1.66 - 1.74 (2 H, m), 2.43 - 2.49 (2 H, m), 2.59 - 2.68 (1 H, m), 2.89 (3 H, d, $J=4.94$ Hz), 2.93 - 3.01 (2 H, m), 7.69 (1 H, s), 7.70 - 7.74 (1 H, m), 7.78 (1 H, s), 7.90 - 7.98 (2 H, m), 8.40 (1 H, s), 8.99 (1 H, s), 10.40 (1 H, s); ESIMS found for $\text{C}_{19}\text{H}_{21}\text{N}_5\text{OS}$ m/z 368.15 (M+1).



1041

[01196] 1-Methyl-N-(6-(2-(methylamino)thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1041**.

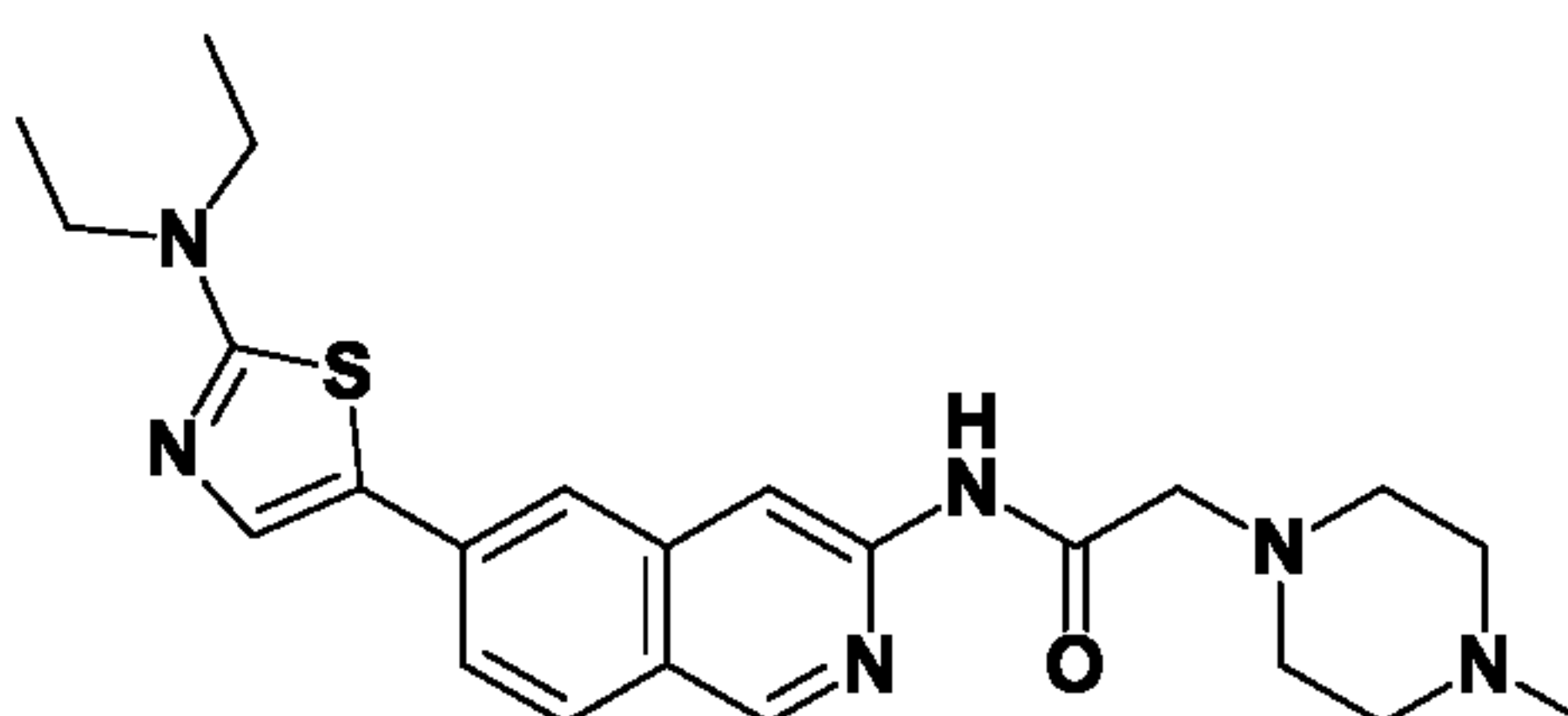
[01197] Yellow solid (32.0 mg, 0.084 mmol, 77.1% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.60 - 1.72 (2 H, m), 1.73 - 1.80 (2 H, m), 1.86 (2 H, td, $J=11.60, 2.06$ Hz), 2.16 (3 H, s), 2.44 - 2.49 (1 H, m), 2.77 - 2.85 (2 H, m), 2.89 (3 H, d, $J=4.94$ Hz), 7.69 (1 H, s), 7.72 (1 H, dd, $J=8.64, 1.78$ Hz), 7.77 (1 H, s), 7.89 - 7.97 (2 H, m), 8.40 (1 H, s), 8.99 (1 H, s), 10.45 (1 H, s); ESIMS found for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{OS}$ m/z 382.2 (M+1).



1047

[01198] N-(6-(2-(Diethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-fluoropiperidin-1-yl)acetamide **1047**.

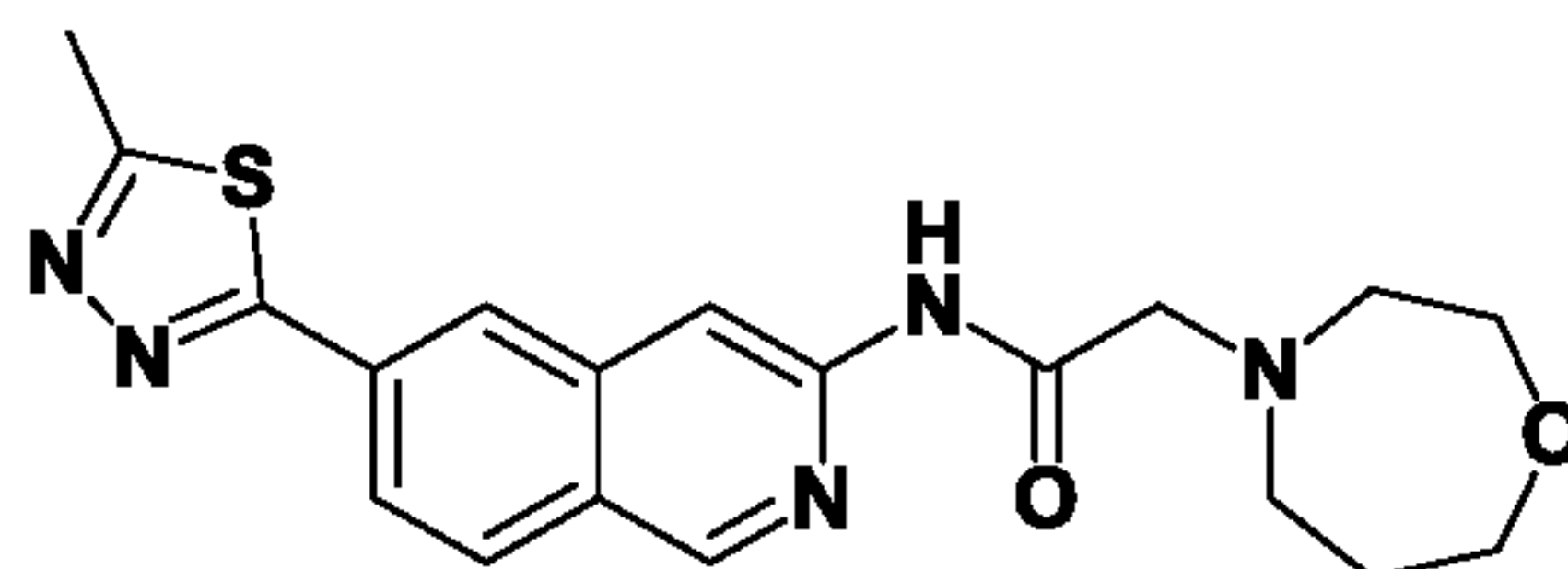
[01199] Yellow solid (22.0 mg, 0.050 mmol, 26.7% yield). ^1H NMR (499 MHz, $\text{DMSO-}d_6$) δ ppm 1.21 (6 H, t, $J=7.14$ Hz), 1.73 - 1.85 (2 H, m), 1.86 - 1.99 (2 H, m), 2.52 - 2.58 (2 H, m), 2.66 - 2.75 (2 H, m), 3.24 (2 H, s), 3.52 (4 H, q, $J=7.14$ Hz), 4.66 - 4.83 (1 H, m), 7.74 (1 H, dd, $J=8.51, 1.65$ Hz), 7.79 (1 H, s), 7.86 (1 H, s), 7.98 (1 H, d, $J=8.51$ Hz), 8.40 (1 H, s), 9.01 (1 H, s), 9.97 (1 H, s); ESIMS found for $\text{C}_{23}\text{H}_{28}\text{FN}_5\text{OS}$ m/z 442.2 (M+1).



1048

[01200] N-(6-(2-(Diethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide **1048**.

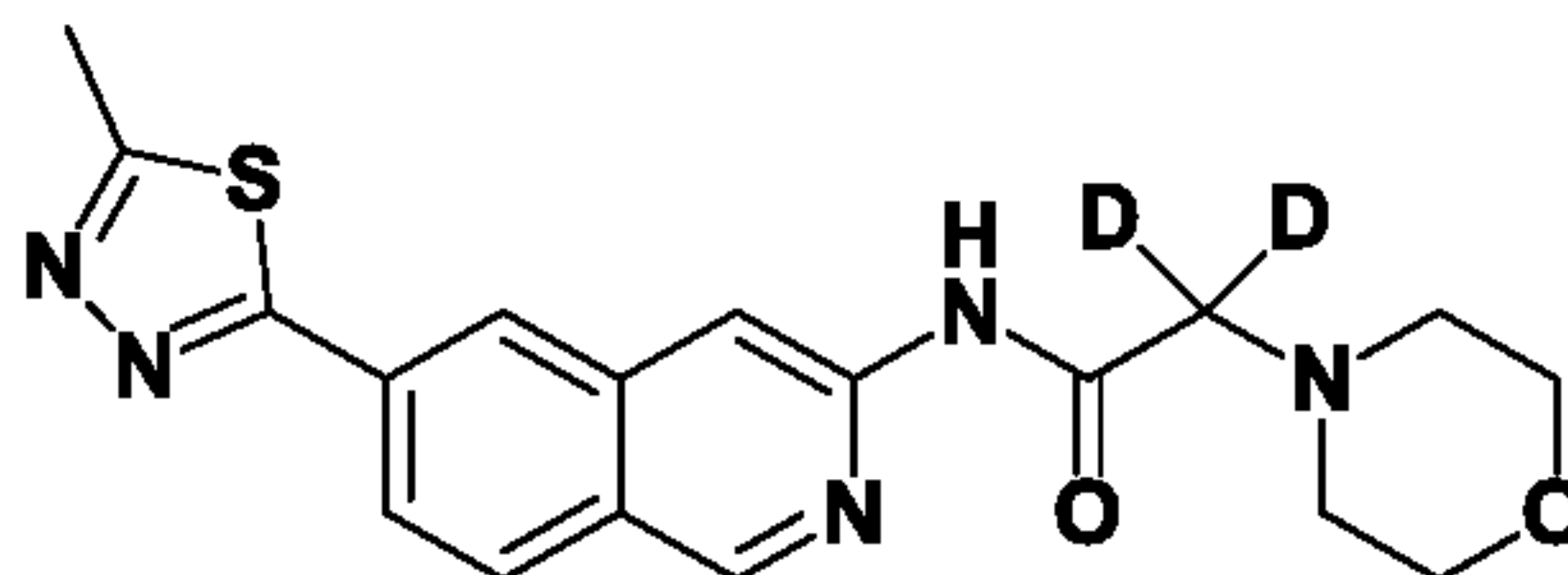
[01201] Beige solid (25.0 mg, 0.057 mmol, 30.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.21 (6 H, t, *J*=7.00 Hz), 2.19 (3 H, s), 2.40 (4 H, br s), 2.58 (4 H, br s), 3.21 (2 H, s), 3.52 (4 H, q, *J*=7.14 Hz), 7.74 (1 H, dd, *J*=8.64, 1.78 Hz), 7.79 (1 H, s), 7.86 (1 H, s), 7.98 (1 H, d, *J*=8.51 Hz), 8.39 (1 H, s), 9.01 (1 H, s), 9.92 (1 H, s); ESIMS found for C₂₃H₃₀N₆OS *m/z* 439.2 (M+1).



1049

[01202] N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(1,4-oxazepan-4-yl)acetamide **1049**.

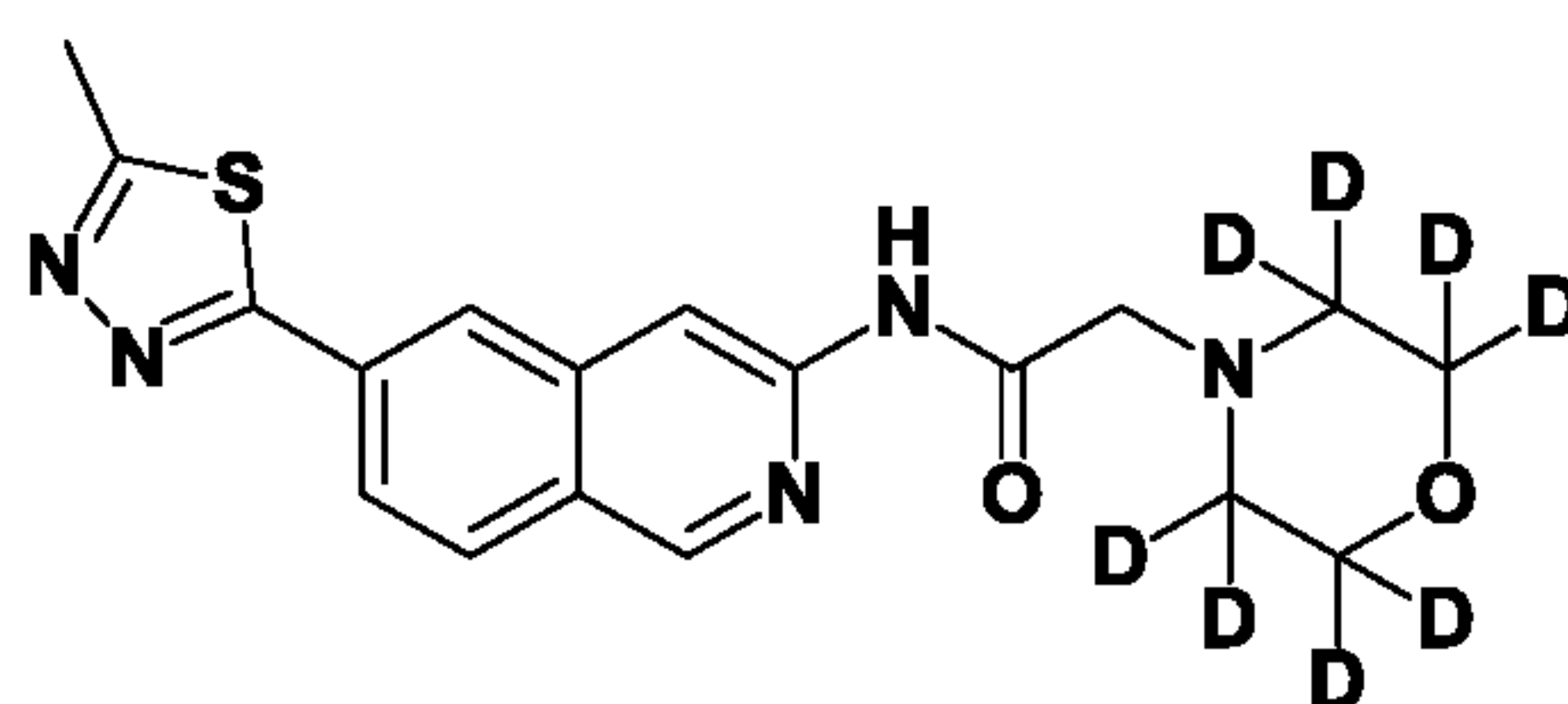
[01203] Beige solid (74.0 mg, 0.193 mmol, 35.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.87 (2 H, quin, *J*=5.83 Hz), 2.83 (3 H, s), 2.83 - 2.86 (4 H, m), 3.43 (2 H, s), 3.66 - 3.70 (2 H, m), 3.74 (2 H, t, *J*=6.04 Hz), 8.12 (1 H, dd, *J*=8.51, 1.65 Hz), 8.21 (1 H, d, *J*=8.51 Hz), 8.51 (1 H, d, *J*=0.82 Hz), 8.62 (1 H, s), 9.23 (1 H, s), 10.15 (1 H, s); ESIMS found for C₁₉H₂₁N₅O₂S *m/z* 384.15 (M+1).



1051

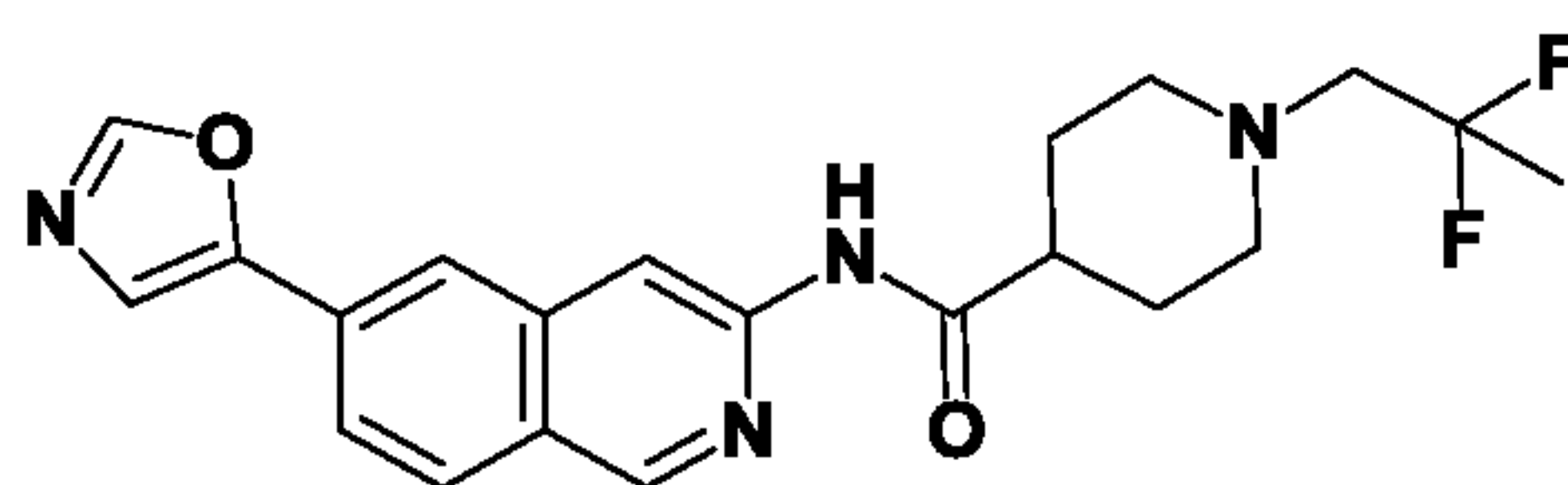
[01204] N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide-2,2-*d*₂ **1051**.

[01205] White solid (20.0 mg, 0.054 mmol, 32.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.55 - 2.61 (4 H, m), 2.83 (3 H, s), 3.62 - 3.69 (4 H, m), 8.12 (1 H, dd, *J*=8.64, 1.78 Hz), 8.21 (1 H, d, *J*=8.51 Hz), 8.51 (1 H, s), 8.62 (1 H, s), 9.23 (1 H, s), 10.18 (1 H, d, *J*=3.02 Hz); ESIMS found for C₁₈H₁₇[²H₂]N₅O₂S *m/z* 372.1 (M+1).

**1052**

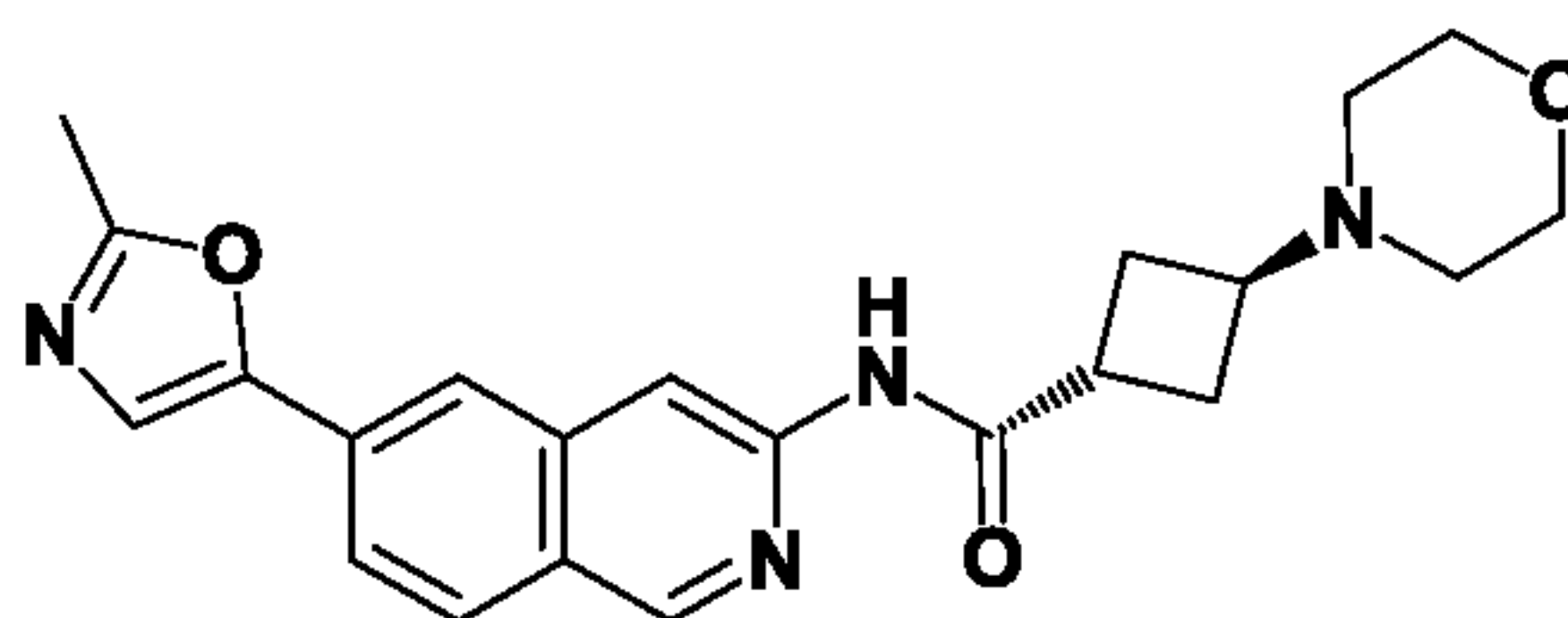
[01206] N-(6-(5-Methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(morpholino-*d*₈)acetamide **1052**.

[01207] Off-white solid (22.0 mg, 0.058 mmol, 7.2% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.83 (3 H, s), 3.26 (2 H, s), 8.12 (1 H, dd, *J*=8.51, 1.65 Hz), 8.21 (1 H, d, *J*=8.51 Hz), 8.51 (1 H, s), 8.62 (1 H, s), 9.23 (1 H, s), 10.17 (1 H, s); ESIMS found for C₁₈H₁₁[²H₈]N₅O₂S *m/z* 378.2 (M+1).

**1057**

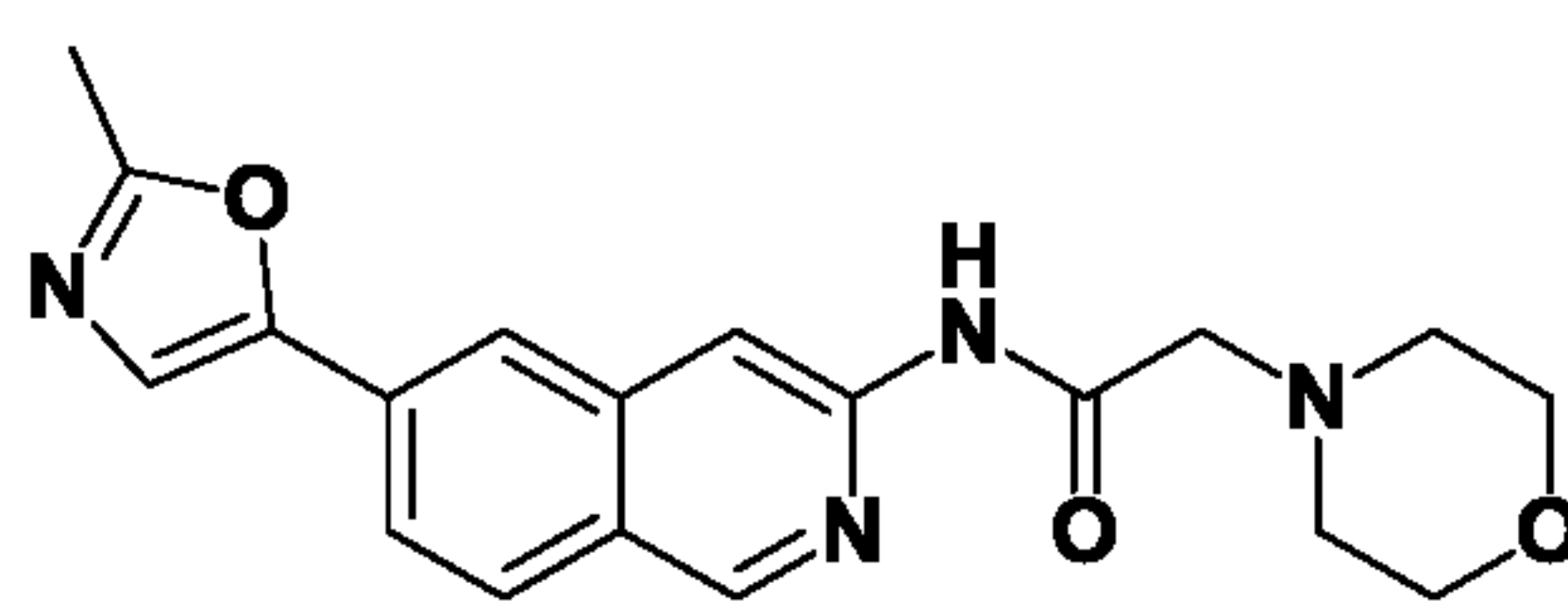
[01208] 1-(2,2-Difluoropropyl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1057**.

[01209] White solid (22.5 mg, 0.056 mmol, 22.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.63 (3 H, t, *J*=19.07 Hz), 1.67 - 1.74 (2 H, m), 1.75 - 1.81 (2 H, m), 2.22 (2 H, td, *J*=11.60, 2.06 Hz), 2.52 - 2.60 (1 H, m), 2.71 (2 H, t, *J*=14.13 Hz), 2.95 (2 H, br d, *J*=11.53 Hz), 7.87 (1 H, dd, *J*=8.51, 1.65 Hz), 7.95 (1 H, s), 8.13 (1 H, d, *J*=8.51 Hz), 8.20 (1 H, s), 8.54 (1 H, s), 8.58 (1 H, s), 9.13 (1 H, s), 10.58 (1 H, s); ESIMS found for C₂₁H₂₂F₂N₄O₂ *m/z* 401.2 (M+1).

**1061**

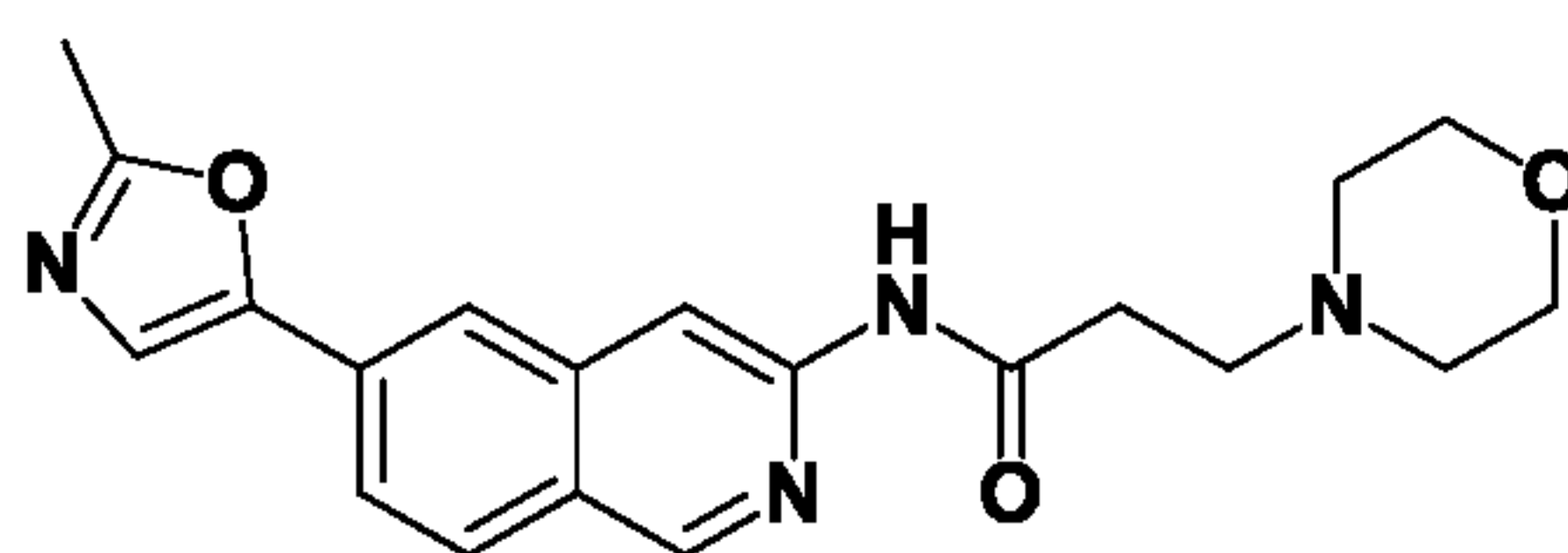
[01210] *trans*-N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-3-morpholinocyclobutane-1-carboxamide **1061**.

[01211] Grey solid (15.0 mg, 0.038 mmol, 19.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.07 - 2.16 (2 H, m), 2.22 - 2.32 (6 H, m), 2.54 (3 H, s), 2.90 (1 H, quin, *J*=7.14 Hz), 3.23 - 3.30 (1 H, m), 3.59 (4 H, t, *J*=4.39 Hz), 7.79 (1 H, s), 7.80 - 7.83 (1 H, m), 8.07 - 8.13 (2 H, m), 8.54 (1 H, s), 9.10 (1 H, s), 10.50 (1 H, s); ESIMS found for C₂₂H₂₄N₄O₃ *m/z* 393.2 (M+1).

**1067**

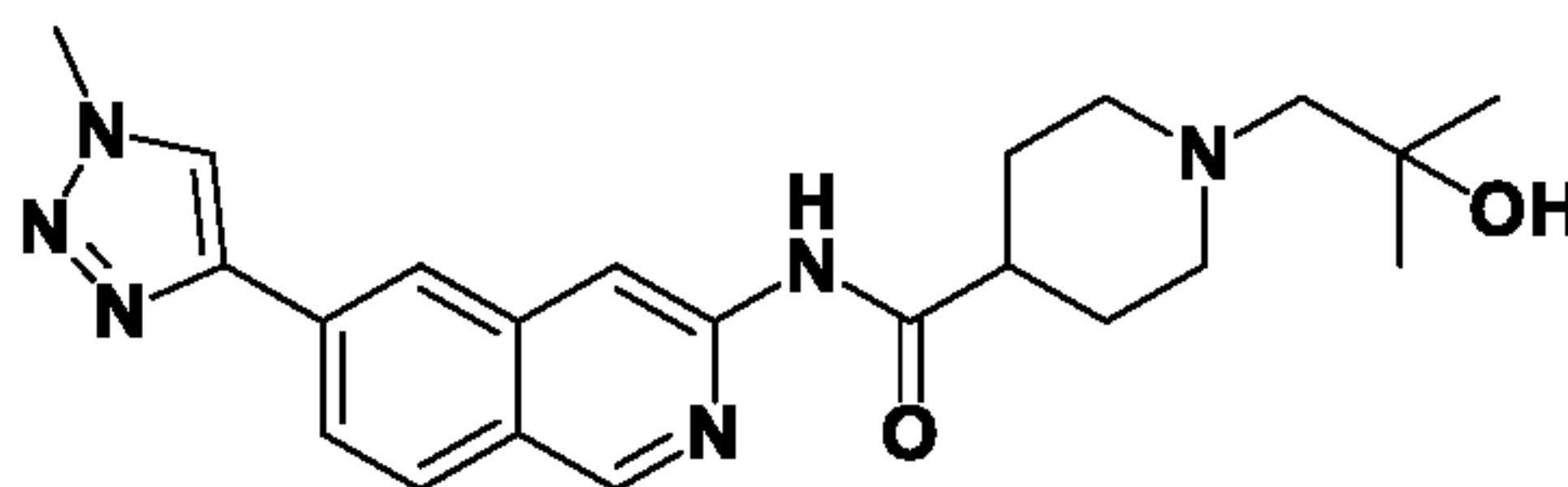
[01212] N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide **1067**.

[01213] Off-white solid (41.0 mg, 0.116 mmol, 40.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.53 (3 H, s), 2.55 - 2.60 (4 H, m), 3.25 (2 H, s), 3.62 - 3.69 (4 H, m), 7.80 (1 H, s), 7.83 (1 H, dd, *J*=8.51, 1.65 Hz), 8.12 (1 H, d, *J*=8.78 Hz), 8.16 (1 H, s), 8.51 (1 H, s), 9.12 (1 H, s), 10.08 (1 H, s); ESIMS found for C₁₉H₂₀N₄O₃ *m/z* 353.15 (M+1).

**1068**

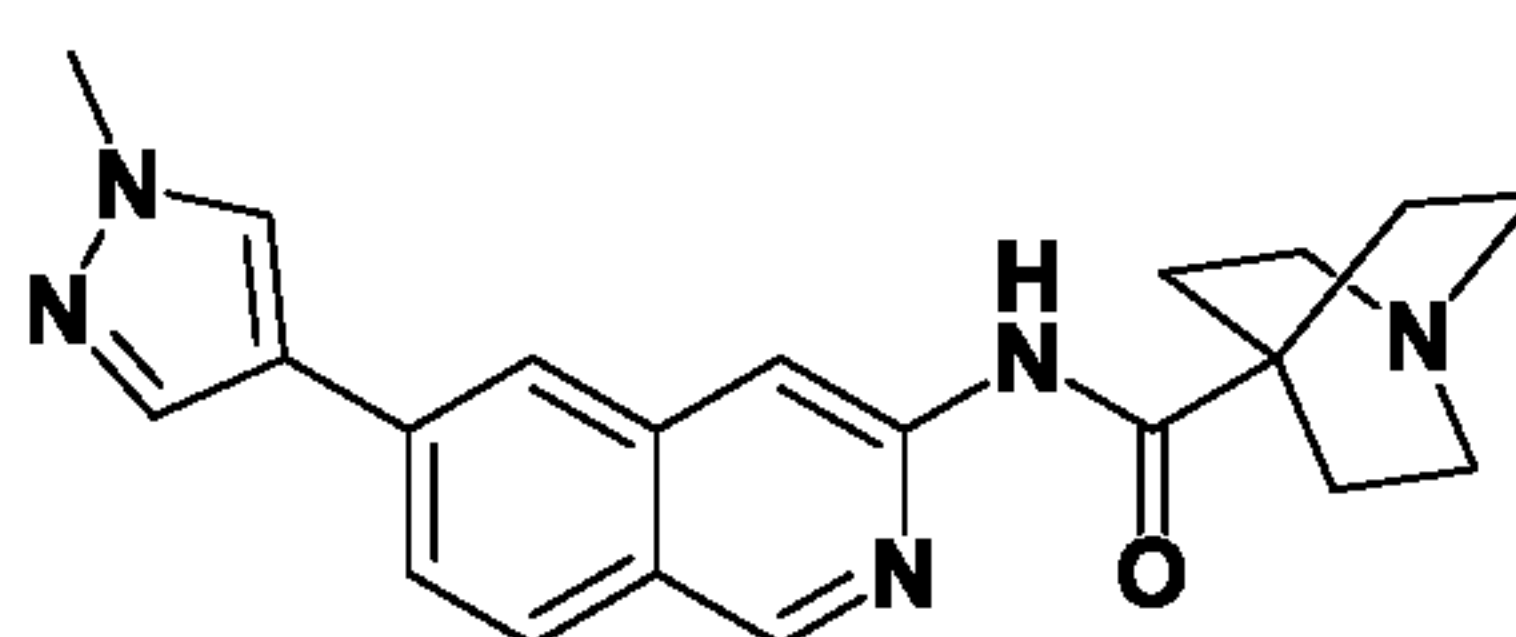
[01214] N-(6-(2-Methyloxazol-5-yl)isoquinolin-3-yl)-3-morpholinopropanamide **1068**.

[01215] Beige solid (21.0 mg, 0.057 mmol, 20.9% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 2.44 (4 H, br s), 2.53 (3 H, s), 2.57 - 2.64 (2 H, m), 2.64 - 2.71 (2 H, m), 3.59 (4 H, t, *J*=4.53 Hz), 7.79 (1 H, s), 7.81 (1 H, dd, *J*=8.51, 1.65 Hz), 8.10 (1 H, d, *J*=8.51 Hz), 8.12 (1 H, s), 8.50 (1 H, s), 9.11 (1 H, s), 10.82 (1 H, s); ESIMS found for C₂₀H₂₂N₄O₃ *m/z* 367.15 (M+1).

**1070**

[01216] 1-(2-Hydroxy-2-methylpropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1070**.

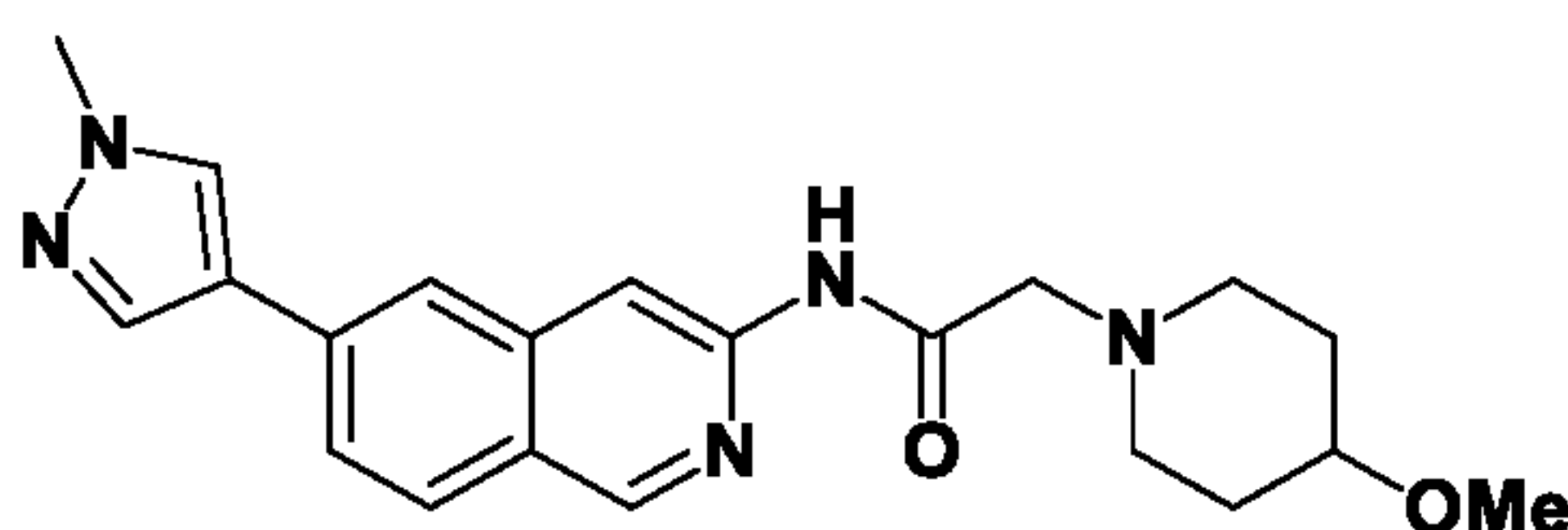
[01217] White solid (26.0 mg, 0.064 mmol, 22.5% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.86 (6 H, d, *J*=6.59 Hz), 1.62 - 1.73 (2 H, m), 1.74 - 1.81 (2 H, m), 1.83 - 1.92 (2 H, m), 2.02 (2 H, d, *J*=7.41 Hz), 2.52 - 2.59 (1 H, m), 2.87 (2 H, br d, *J*=11.53 Hz), 4.09 (1 H, s), 4.14 (3 H, s), 8.01 (1 H, dd, *J*=8.51, 1.37 Hz), 8.11 (1 H, d, *J*=8.51 Hz), 8.28 (1 H, s), 8.51 (1 H, s), 8.73 (1 H, s), 9.11 (1 H, s), 10.52 (1 H, s); ESIMS found for C₂₂H₂₈N₆O₂ *m/z* 409.2 (M+1).

**260**

1071

[01218] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)quinuclidine-4-carboxamide 1071.

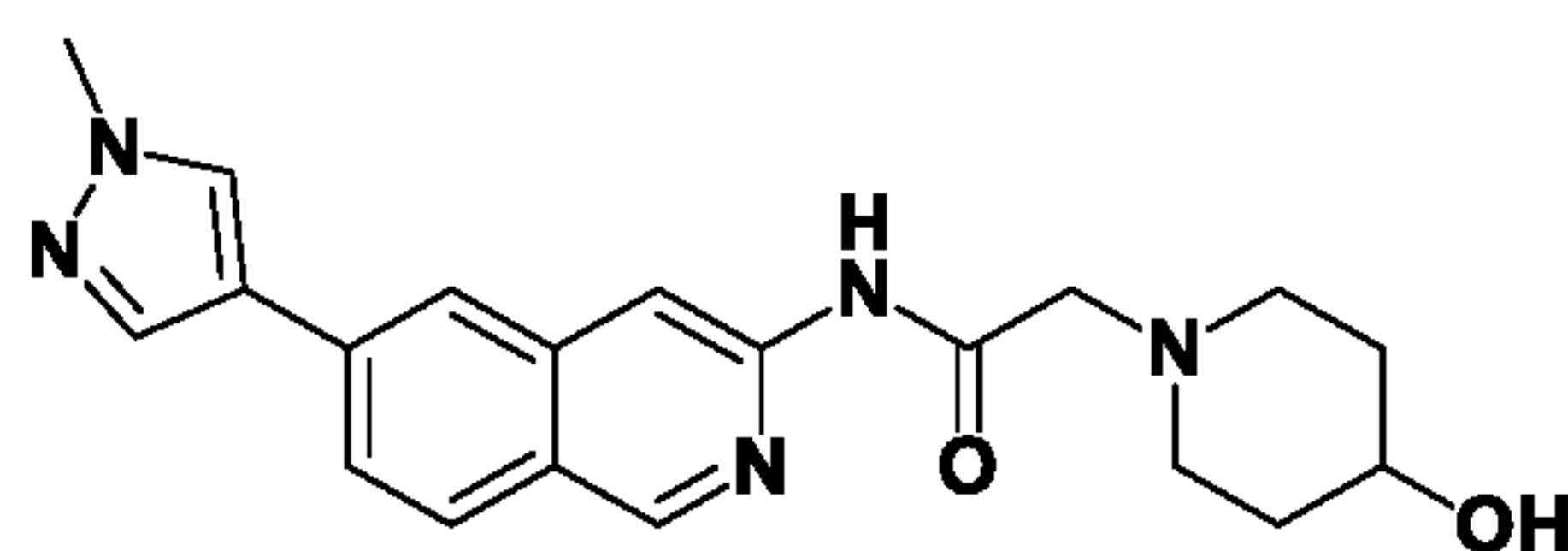
[01219] Beige solid (27.0 mg, 0.075 mmol, 53.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.72 - 1.81 (6 H, m), 2.74 - 2.83 (6 H, m), 3.90 (3 H, s), 7.75 (1 H, dd, *J*=8.51, 1.65 Hz), 8.01 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.07 (1 H, d, *J*=0.82 Hz), 8.35 (1 H, s), 8.41 (1 H, s), 9.04 (1 H, s), 9.59 (1 H, s); ESIMS found for C₂₁H₂₃N₅O *m/z* 362.2 (M+1).



1077

[01220] 2-(4-Methoxypiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 1077.

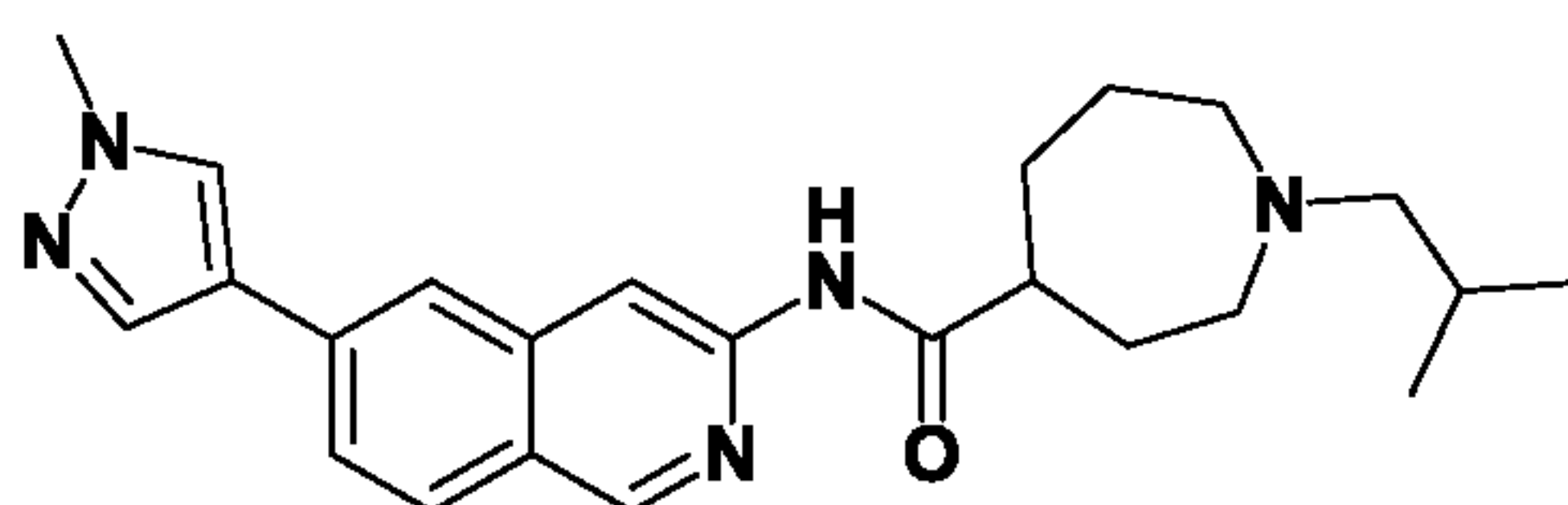
[01221] Off-white solid (79.0 mg, 0.208 mmol, 41.6% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.48 - 1.57 (2 H, m), 1.83 - 1.93 (2 H, m), 2.32 - 2.41 (2 H, m), 2.73 - 2.82 (2 H, m), 3.18 - 3.27 (1 H, m), 3.20 (2 H, s), 3.24 (3 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.78 Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.94 (1 H, s); ESIMS found for C₂₁H₂₅N₅O₂ *m/z* 380.2 (M+1).



1078

[01222] 2-(4-Hydroxypiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide 1078.

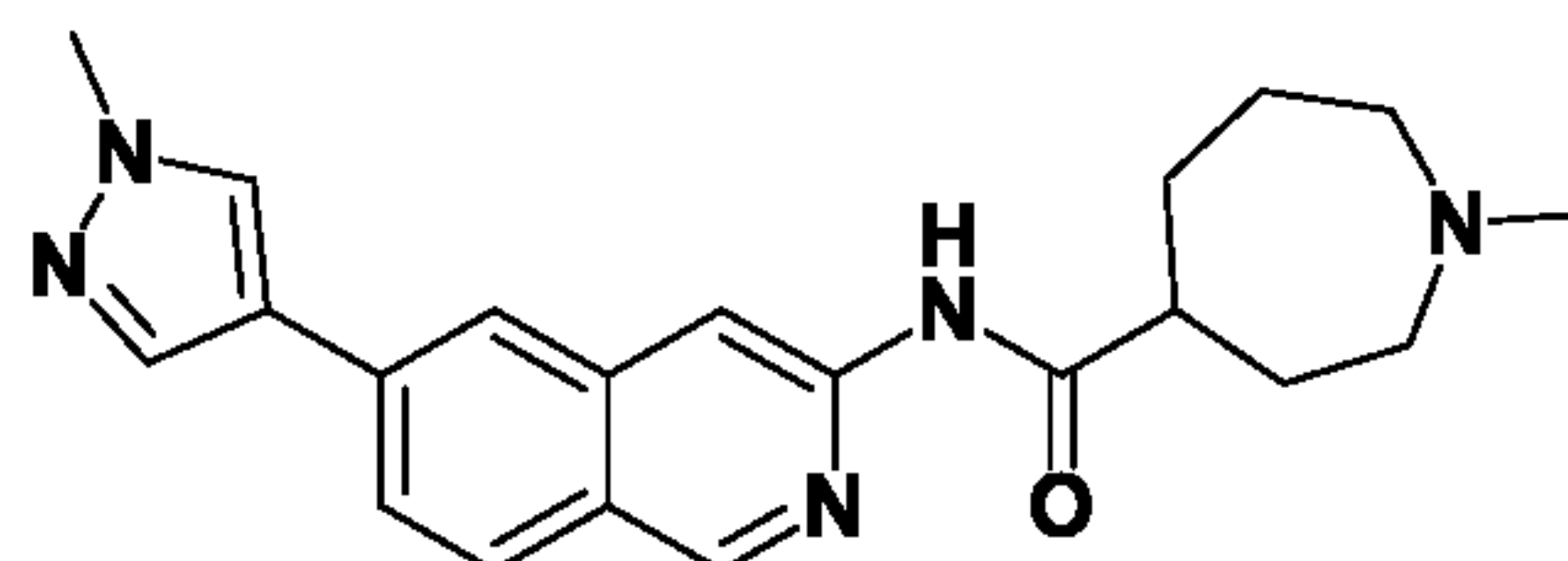
[01223] Off-white solid (84.0 mg, 0.230 mmol, 46.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.49 (2 H, dtd, *J*=12.66, 9.52, 9.52, 3.70 Hz), 1.73 - 1.82 (2 H, m), 2.28 - 2.35 (2 H, m), 2.76 - 2.83 (2 H, m), 3.19 (2 H, s), 3.47 - 3.56 (1 H, m), 3.90 (3 H, s), 4.60 (1 H, d, *J*=4.12 Hz), 7.77 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.04 (1 H, s), 9.93 (1 H, s); ESIMS found for C₂₀H₂₃N₅O₂ *m/z* 366.2 (M+1).



1079

[01224] 1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azepane-4-carboxamide **1079**.

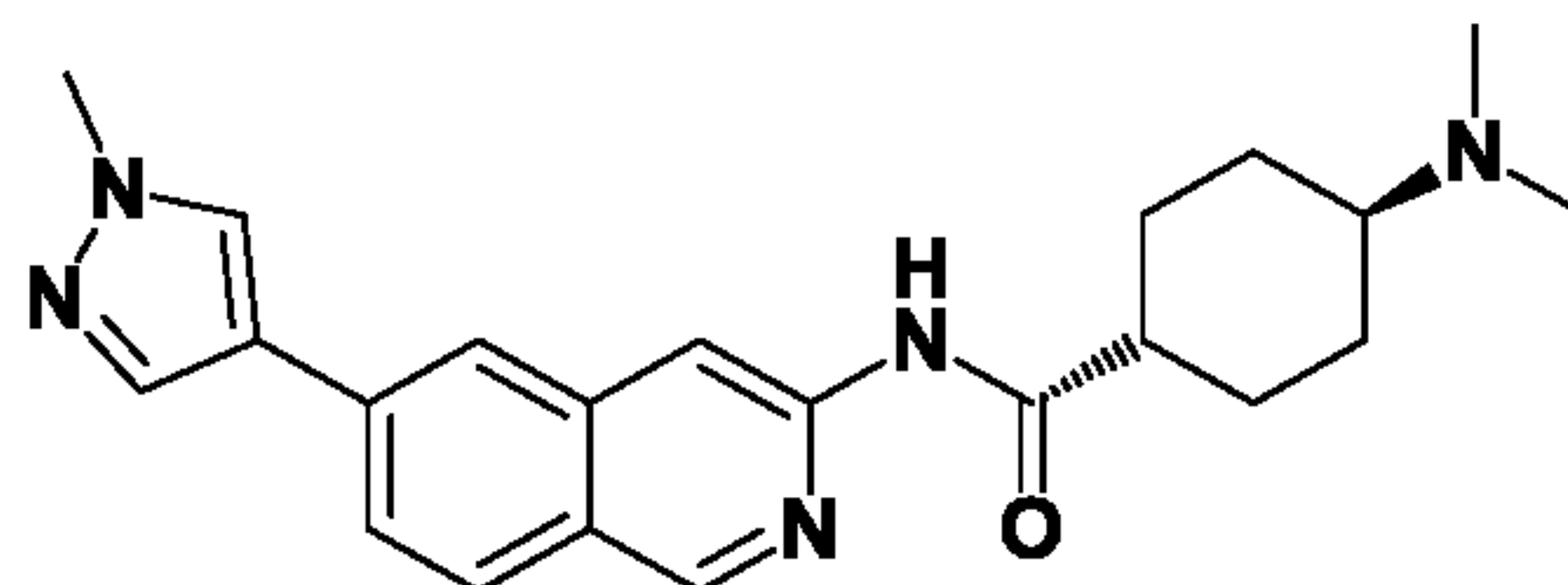
[01225] Beige solid (12.0 mg, 0.030 mmol, 14.8% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 0.86 (3 H, d, *J*=2.20 Hz), 0.88 (3 H, d, *J*=2.20 Hz), 1.53 - 1.62 (1 H, m), 1.64 - 1.82 (4 H, m), 1.82 - 1.93 (2 H, m), 2.13 - 2.25 (2 H, m), 2.54 - 2.62 (3 H, m), 2.66 - 2.74 (1 H, m), 2.80 - 2.89 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.37 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.02 (1 H, s), 8.07 (1 H, s), 8.35 (1 H, s), 8.42 (1 H, s), 9.02 (1 H, s), 10.42 (1 H, s); ESIMS found for C₂₄H₃₁N₅O *m/z* 406.25 (M+1).



1080

[01226] 1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azepane-4-carboxamide **1080**.

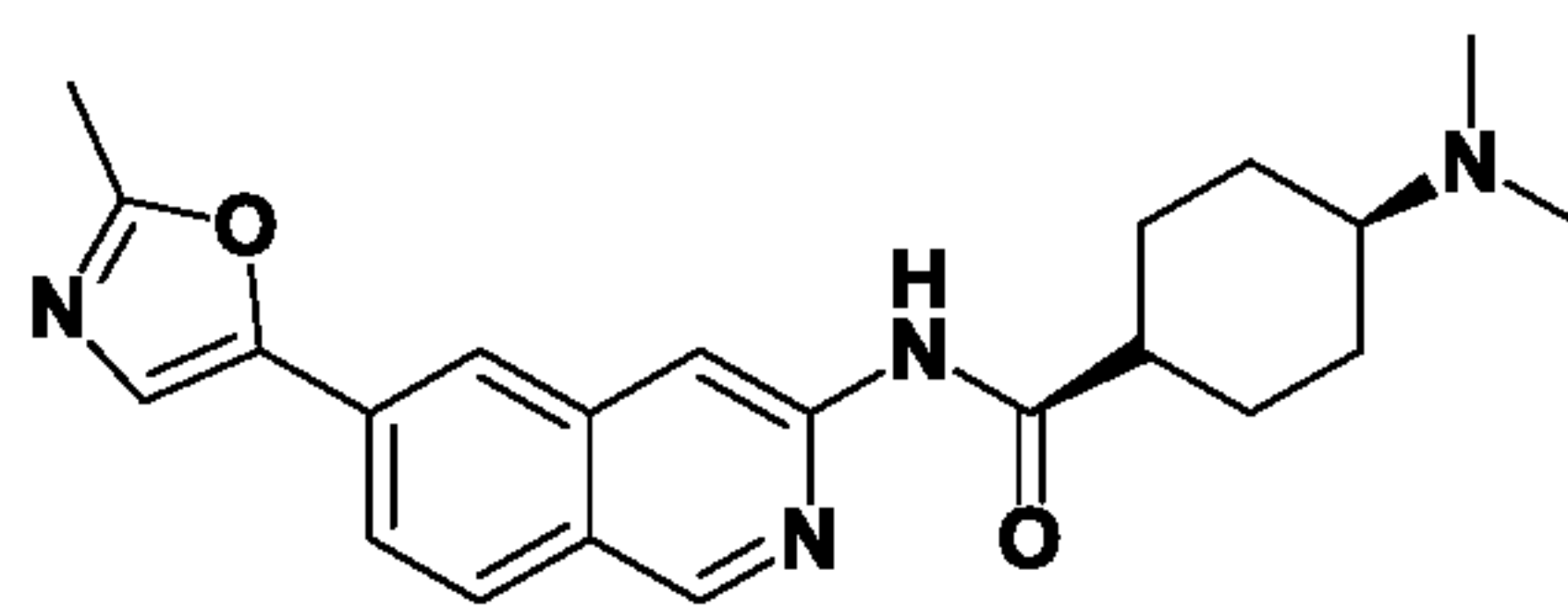
[01227] White solid (11.0 mg, 0.030 mmol, 15.1% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.56 - 1.66 (1 H, m), 1.71 - 1.82 (2 H, m), 1.82 - 1.93 (3 H, m), 2.27 (3 H, s), 2.45 - 2.58 (3 H, m), 2.62 - 2.72 (1 H, m), 2.81 - 2.90 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.37, 1.51 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.03 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.42 (1 H, s), 9.02 (1 H, s), 10.43 (1 H, s); ESIMS found for C₂₁H₂₅N₅O *m/z* 364.2 (M+1).



1081

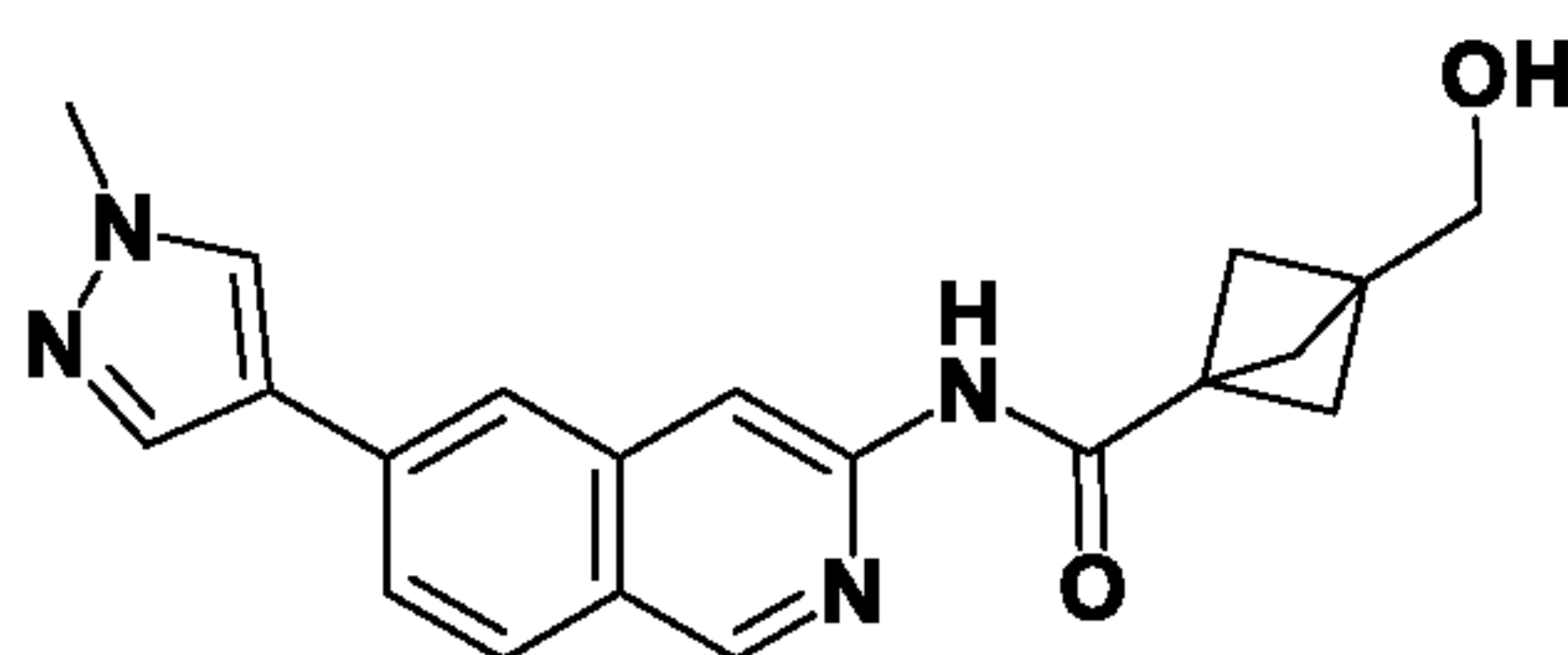
[01228] *trans*-4-(Dimethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **1081**.

[01229] Beige solid (5.0 mg, 0.013 mmol, 7.7% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.13 - 1.22 (2 H, m), 1.43 - 1.54 (2 H, m), 1.84 - 1.96 (4 H, m), 2.11 - 2.20 (1 H, m), 2.18 (6 H, s), 2.42 - 2.49 (1 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, *J*=8.51, 1.65 Hz), 7.99 (1 H, d, *J*=8.51 Hz), 8.02 (1 H, s), 8.07 (1 H, d, *J*=0.82 Hz), 8.35 (1 H, s), 8.42 (1 H, s), 9.02 (1 H, s), 10.41 (1 H, s); ESIMS found for C₂₂H₂₇N₅O *m/z* 378.2 (M+1).

**1082**

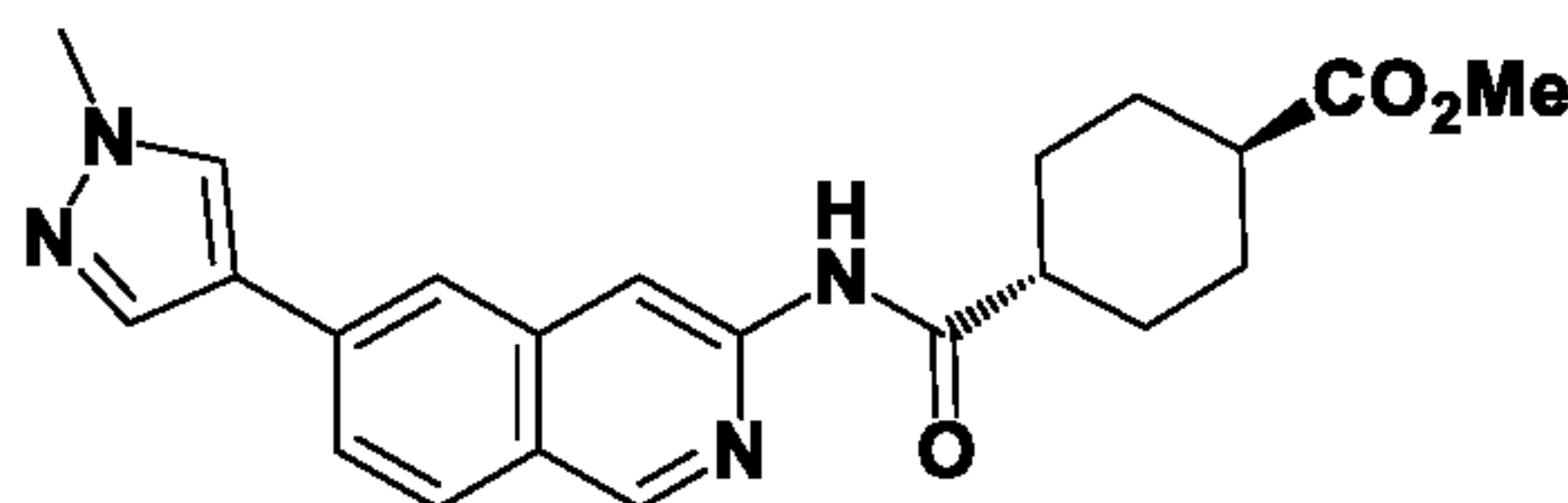
[01230] *trans*-4-(Dimethylamino)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide **1082**.

[01231] Brown solid (3.0 mg, 0.008 mmol, 4.6% yield). ¹H NMR (499 MHz, METHANOL-*d*₄) δ ppm 1.35 - 1.46 (2 H, m), 1.60 - 1.72 (2 H, m), 2.04 - 2.12 (4 H, m), 2.37 (6 H, s), 2.39 - 2.44 (1 H, m), 2.44 - 2.53 (1 H, m), 2.58 (3 H, s), 7.61 (1 H, s), 7.80 (1 H, dd, *J*=8.51, 1.65 Hz), 8.03 (1 H, d, *J*=8.51 Hz), 8.10 (1 H, s), 8.48 (1 H, s), 9.01 (1 H, s); ESIMS found for C₂₂H₂₆N₄O₂ *m/z* 379.2 (M+1).

**1083**

[01232] 3-(Hydroxymethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)bicyclo[1.1.1]pentane-1-carboxamide **1083**.

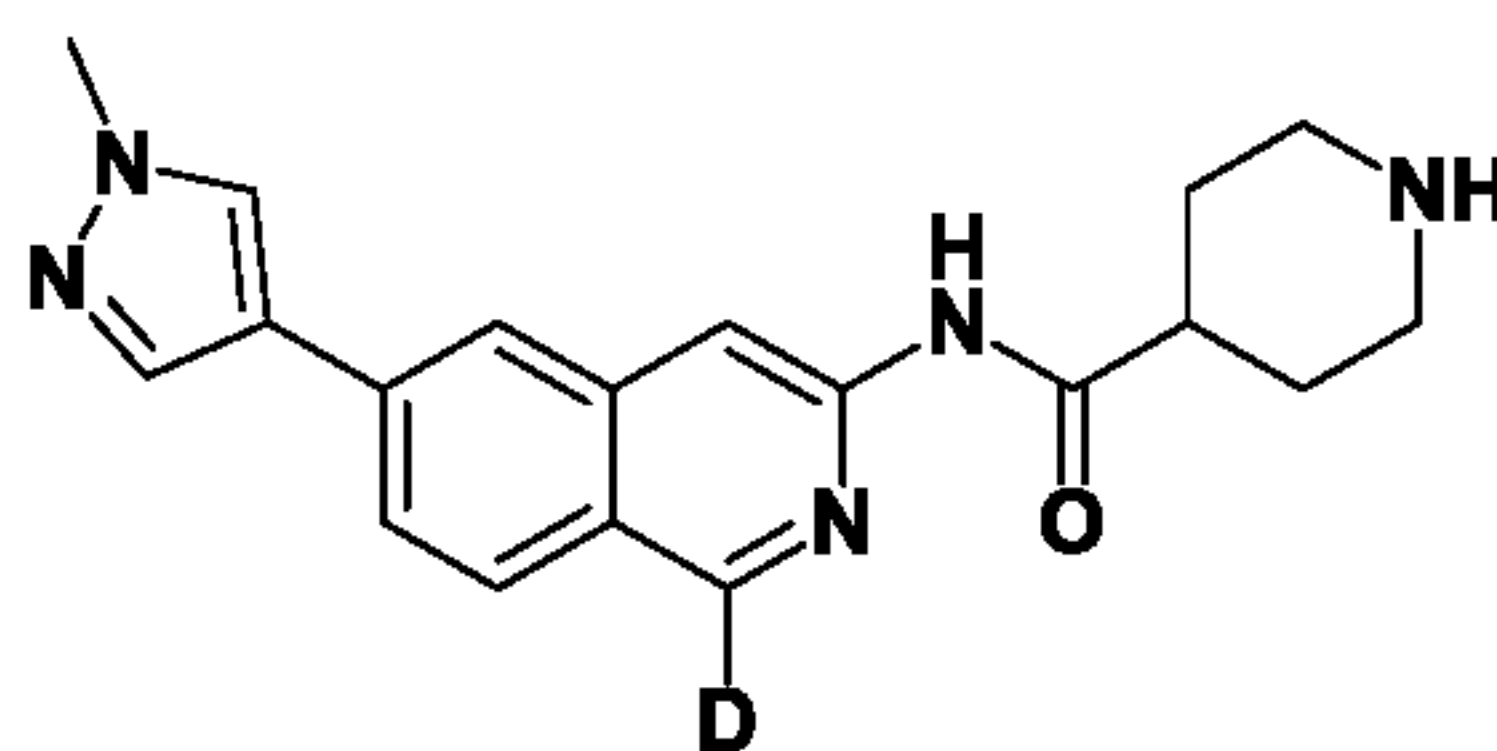
[01233] White solid (310.4 mg, 0.891 mmol, 96.0% yield). ¹H NMR (499 MHz, DMSO-*d*₆) δ ppm 1.97 (6 H, s), 3.41 (2 H, d, *J*=5.76 Hz), 3.90 (3 H, s), 4.56 (1 H, t, *J*=5.49 Hz), 7.76 (1 H, dd, *J*=8.51, 1.65 Hz), 8.02 (1 H, d, *J*=8.51 Hz), 8.04 (1 H, s), 8.09 (1 H, d, *J*=0.82 Hz), 8.37 (1 H, s), 8.40 (1 H, s), 9.05 (1 H, s), 10.13 (1 H, s); ESIMS found for C₂₀H₂₀N₄O₂ *m/z* 349.2 (M+1).

**1084**

[01234] Methyl *trans*-4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)cyclohexane-1-carboxylate **1084**.

[01235] Light yellow solid (350.0 mg, 0.892 mmol, 40.0% yield). ¹H NMR (499 MHz, METHANOL-*d*₄) δ ppm 1.47 - 1.58 (2 H, m), 1.64 (2 H, qd, *J*=12.76, 2.88 Hz), 2.04 (2 H, br dd, *J*=13.31, 2.88 Hz), 2.09 (2 H, br dd, *J*=13.31, 3.16 Hz), 2.39 (1 H, tt, *J*=12.08, 3.57 Hz), 2.51 (1 H, tt, *J*=11.87, 3.36 Hz), 3.68 (3 H, s), 3.96 (3 H, s), 7.73 (1 H, dd, *J*=8.51, 1.65 Hz), 7.93 - 7.99 (2 H,

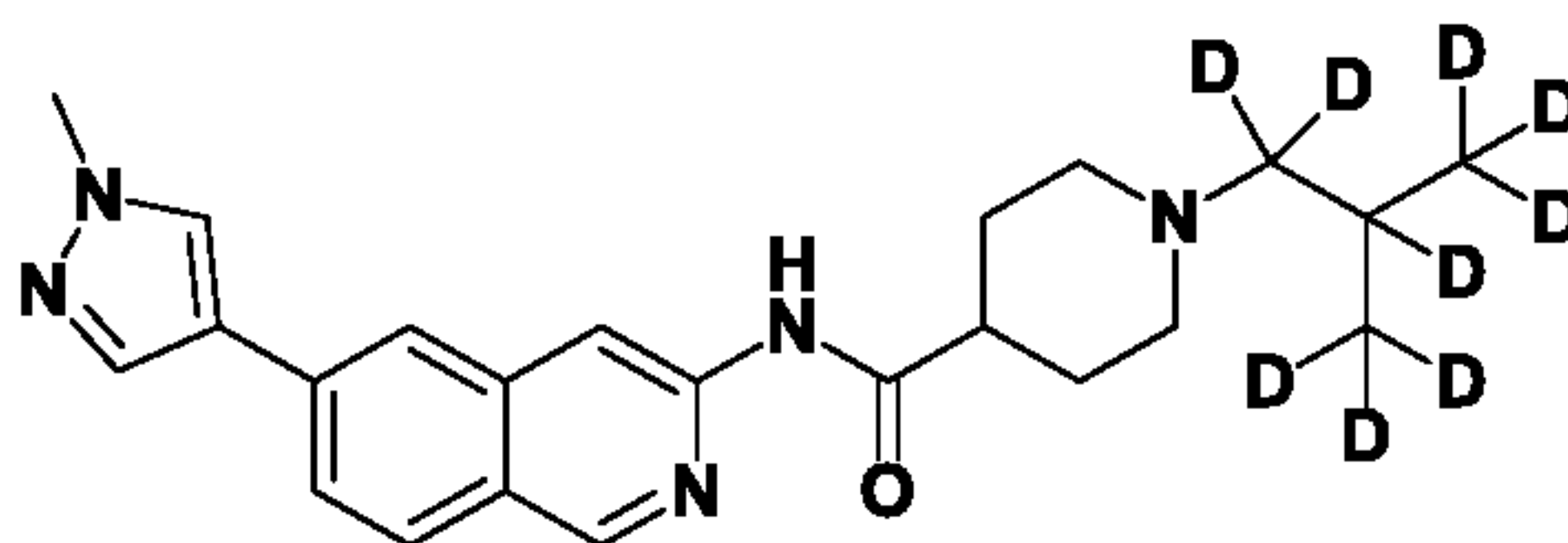
m), 8.00 (1 H, s), 8.16 (1 H, s), 8.40 (1 H, s), 8.94 (1 H, s); ESIMS found for $C_{22}H_{24}N_4O_3$ m/z 393.2 (M+1).



1085

[01236] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-*d*)piperidine-4-carboxamide **1085**.

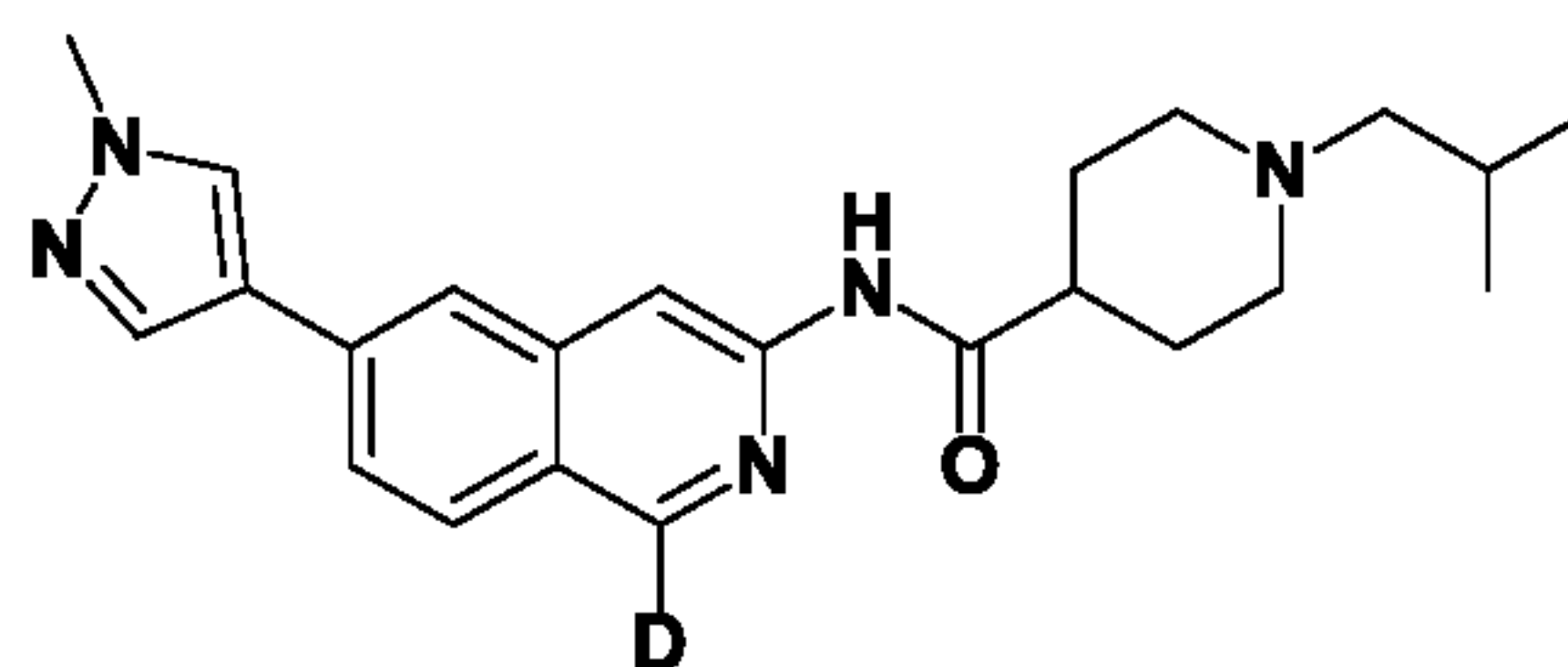
[01237] Off-white solid (105.0 mg, 0.312 mmol, 81.1% yield). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.53 (2 H, qd, $J=12.12$, 3.98 Hz), 1.70 (2 H, br dd, $J=12.21$, 1.78 Hz), 2.44 - 2.49 (2 H, m), 2.64 (1 H, tt, $J=11.60$, 3.64 Hz), 2.94 - 3.01 (2 H, m), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 8.00 (1 H, d, $J=8.51$ Hz), 8.03 (1 H, d, $J=1.37$ Hz), 8.08 (1 H, d, $J=0.82$ Hz), 8.35 (1 H, s), 8.44 (1 H, s), 10.40 (1 H, s); ESIMS found for $C_{19}H_{20}[^2H]N_5O$ m/z 337.2 (M+1).



1086

[01238] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(methyl- d_3)propyl)-1,1,2,3,3,3- d_6)piperidine-4-carboxamide **1086**.

[01239] Beige solid (160.0 mg, 0.399 mmol, 67.0% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.61 - 1.73 (2 H, m), 1.74 - 1.80 (2 H, m), 1.86 (2 H, td, $J=11.66$, 2.20 Hz), 2.51 - 2.58 (1 H, m), 2.86 (2 H, br d, $J=11.25$ Hz), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.44 (1 H, s), 9.02 (1 H, s), 10.45 (1 H, s); ESIMS found for $C_{23}H_{20}[^2H_9]N_5O$ m/z 401.3 (M+1).

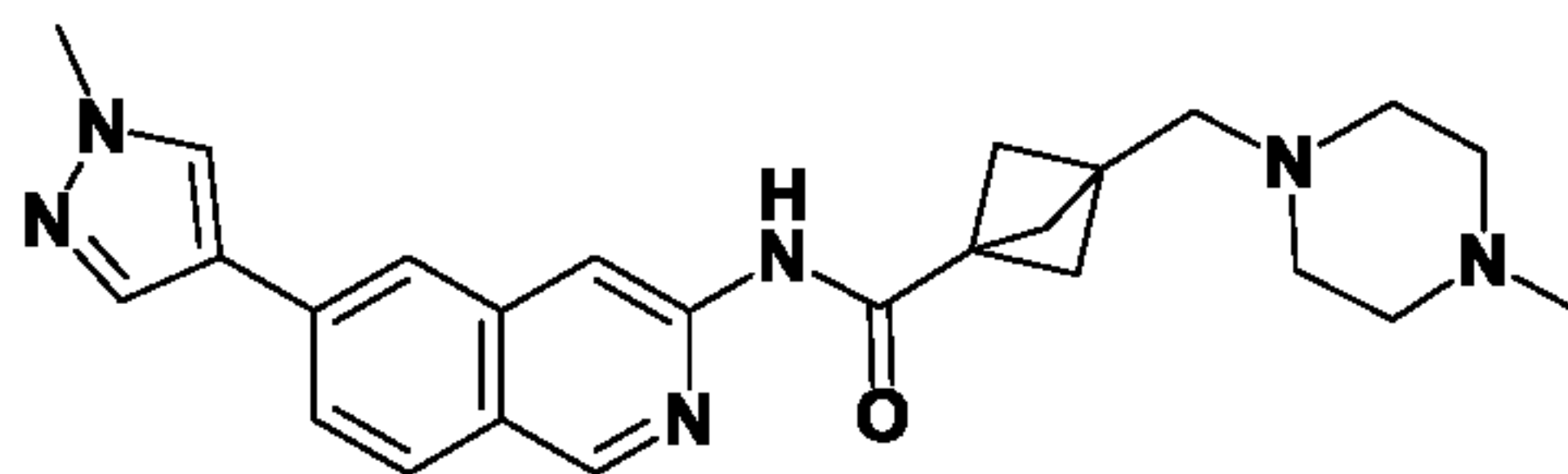


1087

[01240] 1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-*d*)piperidine-4-carboxamide **1087**.

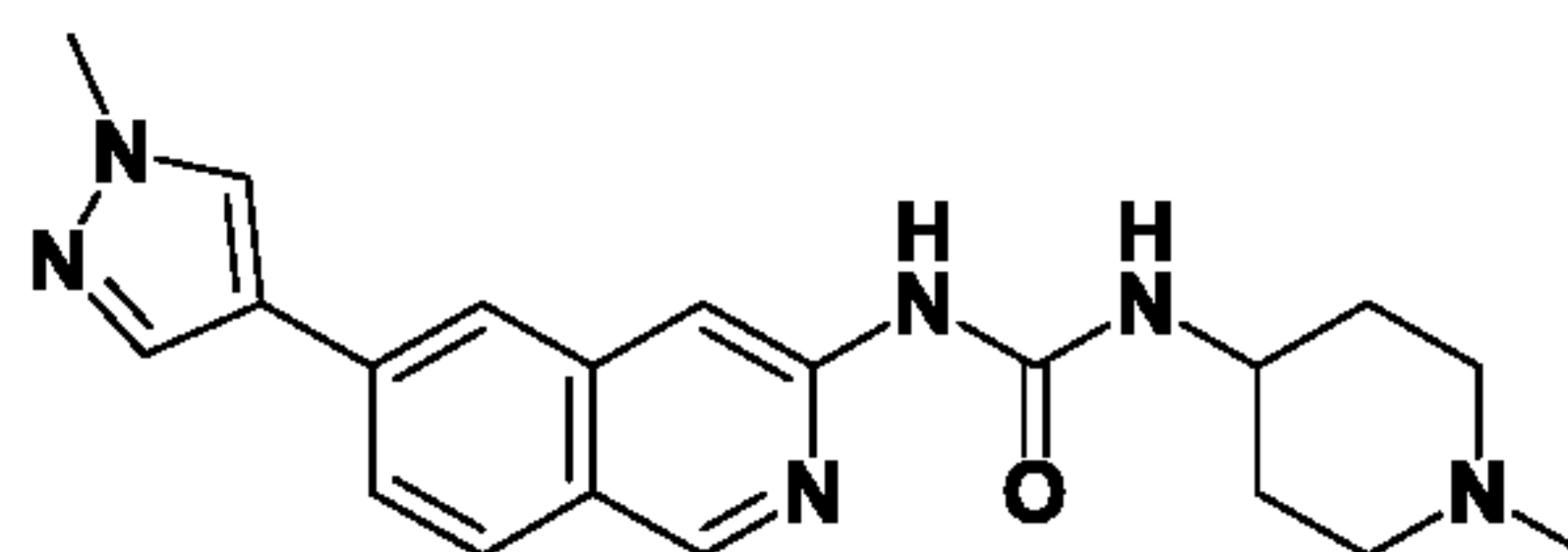
[01241] White solid (75.0 mg, 0.191 mmol, 64.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.86 (6 H, d, $J=6.59$ Hz), 1.63 - 1.73 (2 H, m), 1.74 - 1.80 (3 H, m), 1.83 - 1.90 (2 H, m),

2.02 (2 H, d, $J=7.41$ Hz), 2.51 - 2.57 (1 H, m), 2.86 (2 H, br d, $J=11.25$ Hz), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51, 1.65$ Hz), 8.00 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, d, $J=1.37$ Hz), 8.08 (1 H, s), 8.35 (1 H, s), 8.44 (1 H, s), 10.45 (1 H, s); ESIMS found for $C_{23}H_{28}[^2H]N_5O$ m/z 393.25 (M+1).

**1088**

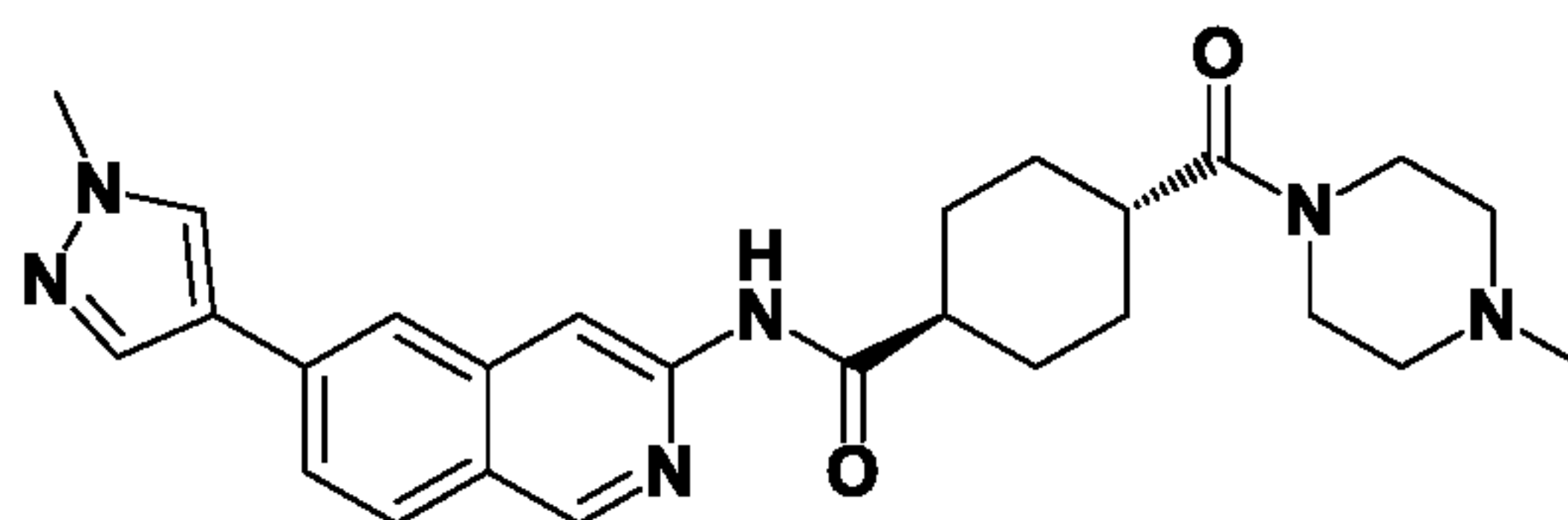
[01242] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-((4-methylpiperazin-1-yl)methyl)bicyclo[1.1.1]pentane-1-carboxamide **1088**.

[01243] Light brown amorphous solid (13.9 mg, 0.032 mmol, 30.2% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 2.04 (6 H, s), 2.14 (3 H, s), 2.31 (4 H, br d, $J=1.92$ Hz), 2.36 - 2.46 (4 H, m), 2.38 (2 H, s), 3.90 (3 H, s), 7.76 (1 H, dd, $J=8.51, 1.65$ Hz), 8.01 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, s), 8.09 (1 H, s), 8.36 (1 H, s), 8.39 (1 H, s), 9.04 (1 H, s), 10.13 (1 H, s); ESIMS found for $C_{25}H_{30}N_6O$ m/z 431.25 (M+1).

**1090**

[01244] 1-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-(1-methylpiperidin-4-yl)urea **1090**.

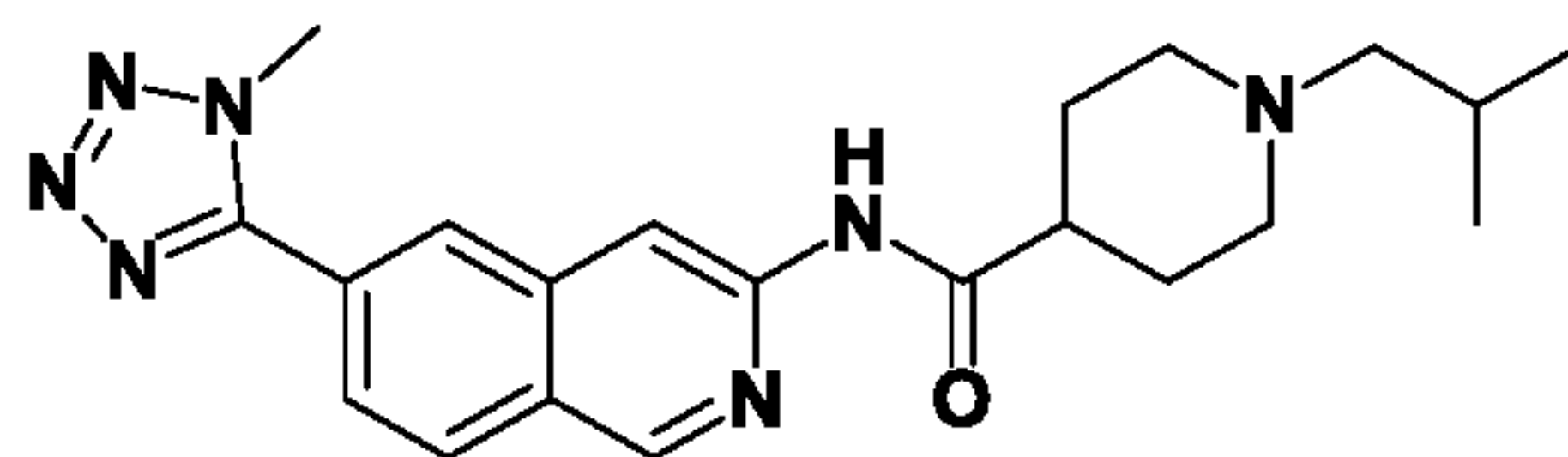
[01245] Beige solid (35.0 mg, 0.096 mmol, 87.3% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.35 - 1.49 (2 H, m), 1.77 - 1.88 (2 H, m), 1.98 - 2.09 (2 H, m), 2.17 (3 H, s), 2.63 (2 H, ddd, $J=5.35, 3.43, 1.65$ Hz), 3.54 (1 H, br dd, $J=4.12, 1.65$ Hz), 3.90 (3 H, s), 7.15 - 7.24 (1 H, m), 7.65 (1 H, dd, $J=8.51, 1.65$ Hz), 7.93 (3 H, d, $J=8.51$ Hz), 8.07 (1 H, s), 8.34 (1 H, s), 8.88 - 8.96 (2 H, m); ESIMS found for $C_{20}H_{24}N_6O$ m/z 365.2 (M+1).

**1091**

[01246] *trans*-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(4-methylpiperazine-1-carbonyl)cyclohexane-1-carboxamide **1091**.

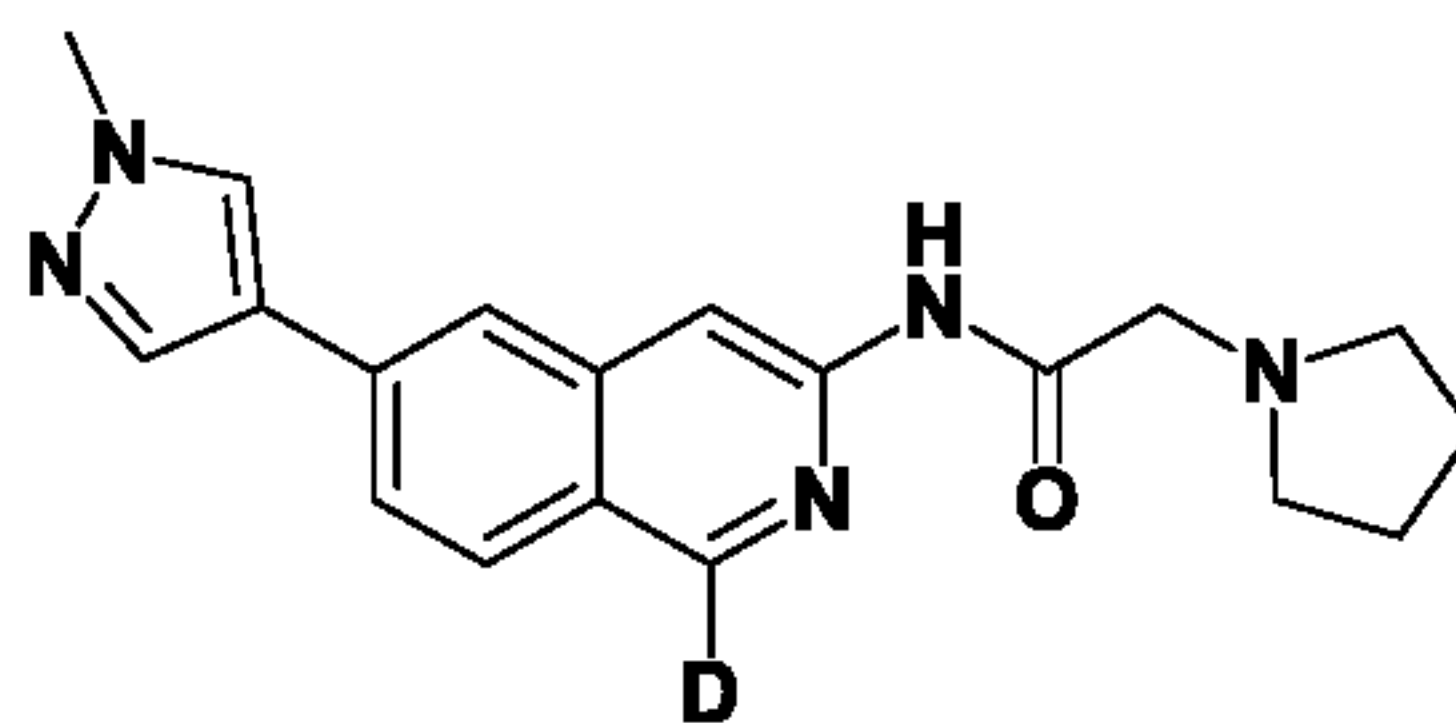
[01247] Beige solid (80.0 mg, 0.174 mmol, 50.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.35 - 1.47 (2 H, m), 1.57 (2 H, qd, $J=12.76, 2.88$ Hz), 1.69 - 1.75 (2 H, m), 1.84 - 1.93

(2 H, m), 2.18 (3 H, s), 2.23 (2 H, br s), 2.30 (2 H, br s), 2.51 - 2.60 (1 H, m), 2.64 (1 H, tt, $J=11.73$, 3.22 Hz), 3.44 (2 H, br s), 3.50 (2 H, br s), 3.90 (3 H, s), 7.74 (1 H, dd, $J=8.51$, 1.65 Hz), 7.99 (1 H, d, $J=8.51$ Hz), 8.04 (1 H, s), 8.08 (1 H, s), 8.35 (1 H, s), 8.43 (1 H, s), 9.02 (1 H, s), 10.43 (1 H, s); ESIMS found for $C_{26}H_{32}N_6O_2$ m/z 461.3 (M+1).

**1092**

[01248] 1-Isobutyl-N-(6-(1-methyl-1H-tetrazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide **1092**. N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1- d)-2-(pyrrolidin-1-yl)acetamide

[01249] Off-white solid (18.0 mg, 0.046 mmol, 7.1% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 0.86 (6 H, d, $J=6.59$ Hz), 1.61 - 1.72 (2 H, m), 1.74 - 1.82 (3 H, m), 1.82 - 1.94 (2 H, m), 2.02 (2 H, d, $J=7.41$ Hz), 2.52 - 2.61 (1 H, m), 2.87 (2 H, br d, $J=11.53$ Hz), 4.29 (3 H, s), 7.92 (1 H, dd, $J=8.51$, 1.65 Hz), 8.26 (1 H, d, $J=8.51$ Hz), 8.44 (1 H, s), 8.67 (1 H, s), 9.27 (1 H, s), 10.67 (1 H, s); ESIMS found for $C_{21}H_{27}N_7O$ m/z 394.2 (M+1).

**1093**

[01250] N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1- d)-2-(pyrrolidin-1-yl)acetamide **1093**.

[01251] Beige solid (45.0 mg, 0.134 mmol, 44.6% yield). ^1H NMR (499 MHz, DMSO- d_6) δ ppm 1.78 (4 H, dt, $J=6.59$, 3.29 Hz), 2.63 - 2.69 (4 H, m), 3.35 (2 H, s), 3.90 (3 H, s), 7.77 (1 H, dd, $J=8.64$, 1.51 Hz), 8.02 (1 H, d, $J=8.51$ Hz), 8.10 (2 H, s), 8.37 (1 H, s), 8.43 (1 H, s), 9.92 (1 H, s); ESIMS found for $C_{19}H_{20}[^2H]N_5O$ m/z 337.2 (M+1).

Example 13.

[01252] The screening assay for Wnt activity is described as follows. Reporter cell lines can be generated by stably transducing cancer cell lines (e.g., colon cancer) or primary cells (e.g., IEC-6 intestinal cells) with a lentiviral construct that includes a Wnt-responsive promoter driving expression of the firefly luciferase gene.

[01253] SW480 colon carcinoma cells were transduced with a lentiviral vector expressing luciferase with a human Sp5 promoter consisting of a sequence of eight TCF/LEF binding sites. SW480 cells stably expressing the Sp5-Luc reporter gene and a hygromycin resistance gene were selected by treatment with 150 µg/mL of hygromycin for 7 days. These stably transduced SW480 cells were expanded in cell culture and used for all further screening activities. Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 10-point dose-response curves starting from 10 µM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, CA) into 384-well white solid bottom assay plates (Greiner Bio-One) with appropriate DMSO backfill for a final DMSO concentration of 0.1%. For Sp5-Luc reporter gene assays, the cells were plated at 4,000 cells/well in 384-well plates with a DMEM medium containing 1% fetal bovine serum, and 1% Penicillin-Streptomycin and incubated for 36 to 48 hours at 37°C and 5% CO₂. Following incubation, 15 µl of BriteLite Plus luminescence reagent (Perkin Elmer) was added to each well of the 384-well assay plates. The plates were placed on an orbital shaker for 2 min and then luminescence was quantified using the Envision (Perkin Elmer) plate reader. Readings were normalized to DMSO only treated cells, and normalized activities were utilized for EC₅₀ calculations using the dose-response log (inhibitor) vs. response –variable slope (four parameters) nonlinear regression feature available in GraphPad Prism 5.0 (or Dotmatics). For EC₅₀ of >10 µM, the percent inhibition at 10 µM is provided.

[01254] Table 2 shows the measured activity for representative compounds of Formula I as described herein.

Table 2.

Compound	EC ₅₀ (µM)	Compound	EC ₅₀ (µM)	Compound	EC ₅₀ (µM)	Compound	EC ₅₀ (µM)
1	0.650	302	3.646	523	0.683	993	7.974
3	1.700	303	9.831	527	>10 (23.5%)	994	7.901
4	0.983	304	2.317	528	1.154	995	>10 (43.8%)
6	1.111	305	1.942	531	1.062	996	4.389
10	0.277	306	3.698	535	>10 (44.9%)	997	3.886
14	0.354	307	>10 (25.9%)	537	4.800	998	2.249
16	>10	308	1.809	547	2.226	999	3.100
69	3.700	309	>10 (43.5%)	554	0.272	1000	4.324
71	3.900	310	1.462	561	1.456	1001	0.593
72	0.920	311	0.578	579	0.899	1002	1.916
73	0.485	312	>10 (23.8%)	643	0.129	1003	1.315
75	0.520	313	0.577	699	0.541	1004	0.618
76	0.705	314	0.859	700	0.771	1005	1.396
77	0.610	315	1.588	704	>10 (10.2%)	1006	0.704
78	1.000	316	2.845	707	0.472	1007	1.130
81	0.735	317	1.266	711	0.703	1008	3.350
82	4.950	318	0.442	713	9.246	1009	1.108
83	2.900	320	1.142	718	0.589	1010	2.021
84	1.900	324	0.145	731	3.046	1011	>10 (25.0%)
85	1.200	325	0.552	737	1.291	1012	2.718
86	4.000	326	0.438	741	0.444	1013	>10 (42.9%)
87	1.000	327	0.258	743	9.487	1014	2.364

89	0.765	328	0.804	758	1.253	1015	3.734
90	1.100	329	1.173	760	3.970	1016	4.057
91	>10	330	0.449	767	3.225	1017	0.621
92	1.600	331	2.988	773	6.549	1018	0.608
96	>10	332	0.662	784	5.885	1019	3.799
110	1.100	333	0.384	785	2.837	1020	1.142
111	0.743	334	0.787	791	0.212	1021	>10 (16.5%)
112	3.200	335	0.993	795	0.471	1022	1.370
113	>10	336	0.395	798	0.594	1023	>10 (38.2%)
114	0.835	338	7.369	803	3.551	1024	3.510
115	2.400	340	0.932	822	0.517	1025	>10
116	7.100	341	4.097	826	0.603	1026	0.513
118	3.600	342	7.215	831	0.706	1027	0.875
119	1.060	343	3.587	839	0.776	1028	3.870
120	2.205	344	5.468	851	>10 (6.4%)	1029	3.336
121	3.500	345	2.123	883	>10 (43.2%)	1030	>10 (44.8%)
188	>10	346	4.358	885	4.475	1031	3.969
248	>10	347	9.442	888	1.038	1032	>10 (27.4%)
262	1.700	348	>10 (36.9%)	900	1.013	1034	2.040
263	1.300	349	0.712	921	0.779	1035	1.374
264	>10	350	1.005	932	0.946	1037	3.643
265	1.243	351	2.521	939	2.072	1040	1.211
266	2.441	352	2.958	946	1.881	1041	0.776
267	1.379	353	5.711	952	1.469	1047	>10 (32.6%)
268	2.072	354	2.320	953	>10 (48.7%)	1048	9.381
269	3.624	355	3.512	959	4.235	1049	2.544
270	>10	358	0.413	960	1.658	1051	0.480
271	1.715	359	0.669	962	>10 (45.0%)	1052	2.285
272	3.753	360	0.690	963	1.199	1057	>10 (5.0%)
273	1.511	362	0.951	964	1.449	1061	1.614
274	3.720	363	2.359	965	3.175	1064	4.119
275	1.917	364	>10 (24.1%)	966	1.592	1067	>10 (48.7%)
276	5.183	365	0.381	967	4.423	1068	3.718
277	5.264	366	0.334	968	>10 (38.0%)	1070	0.738
278	0.413	367	0.524	969	3.926	1071	>10 (43.2%)
279	5.650	368	0.689	970	1.356	1073	>10 (5.9%)
280	2.325	369	0.743	971	0.720	1074	>10 (19.7%)
281	>10 (47.0%)	370	0.608	972	0.420	1075	2.542
282	>10 (49.3%)	371	0.643	973	0.609	1076	0.640
283	2.486	372	3.398	974	3.742	1077	5.189
284	1.874	376	2.206	975	0.423	1078	4.033
285	3.405	433	0.191	976	2.965	1079	1.429
286	3.143	441	1.214	977	0.875	1080	1.218
287	7.330	443	0.397	978	2.223	1081	2.734
288	1.197	448	0.289	979	4.093	1082	9.902
289	2.647	452	0.787	980	>10 (40.5%)	1083	8.209
290	5.231	468	0.363	981	1.085	1084	3.407
291	4.641	470	1.184	982	2.709	1085	2.195
292	3.385	472	0.382	983	5.533	1086	0.485
293	3.222	475	0.701	984	2.987	1087	0.514
294	5.186	477	0.327	985	1.160	1088	7.403
295	2.571	481	1.536	986	1.380	1090	0.722
296	3.479	483	1.872	987	>10 (10.7%)	1091	2.949
297	4.811	487	0.446	988	>10 (11.1%)	1092	0.247
298	3.229	500	3.232	989	4.320	1093	1.781
299	1.529	513	6.428	990	2.865		
300	1.117	517	>10 (35.8%)	991	1.705		
301	0.467	521	1.805	992	3.209		

Example 14.

[01255] Representative compounds were screened using the assay procedure for DYRK1A kinase activity as described below.

[01256] Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 11-point dose-response curves from 10 μ M to 0.00016 μ M) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, CA) into 1536-well black-walled round bottom plates (Corning).

[01257] The DYRK1A kinase assay was run using the Ser/Thr 18 peptide Z-lyte assay kit according to manufacturer's instructions (Life Technologies- a Division of Thermo-Fisher). This is a non-radioactive assay using fluorescence resonance energy transfer (FRET) between coumarin and fluorescein to detect kinase activity which is represented as a ratio of coumarin emission/fluorescein emission.

[01258] Briefly, recombinant DYRK1A kinase, ATP and Ser/Thr peptide 18 were prepared in 1X Kinase buffer to final concentrations of 0.19 μ g/mL, 30 μ M, and 4 μ M respectively. The mixture was allowed to incubate with the representative compounds for one hour at room temperature. All reactions were performed in duplicate. Unphosphorylated ("0% Control") and phosphorylated ("100% control") forms of Ser/Thr 18 served as control reactions. Additionally, an 11-point dose-response curve of Staurosporine (1 μ M top) was run to serve as a positive compound control.

[01259] After incubation, Development Reagent A was diluted in Development Buffer then added to the reaction and allowed to further incubate for one hour at room temperature. The plate was read at Ex 400 Em 455 to detect the coumarin signal and Ex 400 Em 520 to measure the signal (EnVision Multilabel Plate Reader, PerkinElmer).

[01260] The Emission ratio (Em) was calculated as a ratio of the coumarin (C) emission signal (at 445 nm)/Fluorescein (F) emission signal (at 520 nm). The percent phosphorylation was then calculated using the following formula: $[1 - ((\text{Em ratio} \times F100\%) - C100\%) / ((C0\% - C100\%) + (\text{Em ratio} \times (F100\% - F0\%)))]$. Dose-response curves were generated and inhibitory concentration (IC₅₀) values were calculated using non-linear regression curve fit in the Dotmatics' Studies Software (Bishops Stortford, UK).

[01261] Table 3 shows the measured activity for representative compounds of Formula I as described herein.

Table 3.

Compound	EC ₅₀ (μ M)	Compound	EC ₅₀ (μ M)	Compound	EC ₅₀ (μ M)	Compound	EC ₅₀ (μ M)
1	0.0040	302	0.0077	523	0.0029	993	0.0147
3	0.0037	303	0.0080	527	0.0098	994	0.0129
4	0.0018	304	0.0027	528	0.0008	995	0.0133
6	0.0013	305	0.0082	531	0.0009	996	0.0134
10	0.0013	306	0.0072	535	0.0045	997	0.1864
14	0.0015	307	6.2229	537	0.0089	998	0.0062
16	0.0039	308	0.0024	547	0.0034	999	0.0209
69	0.0062	309	0.0343	554	0.0014	1000	0.0111

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71	0.0136	310	0.0062	561	0.0015	1001	0.0073
72	0.0025	311	0.0019	579	0.0250	1002	0.0285
73	0.0017	312	0.0127	643	0.0018	1003	0.0021
75	0.0026	313	0.0025	699	0.0021	1004	0.0020
76	0.0023	314	0.0221	700	0.0022	1005	0.0015
77	0.0016	315	0.0123	704	0.0082	1006	0.0030
78	0.0047	316	0.0042	707	0.0009	1007	0.0024
81	0.0015	317	0.0370	711	0.0010	1008	0.0075
82	0.0009	318	0.0588	713	0.0031	1009	0.0062
83	0.0012	320	0.0099	718	0.0013	1010	0.0026
84	0.0013	324	0.0021	731	0.0014	1011	0.0026
85	0.0014	325	0.0021	737	0.0010	1012	0.0130
86	0.0025	326	0.0029	741	0.0009	1013	0.0171
87	0.0033	327	0.0017	743	0.0013	1014	0.0094
89	0.0027	328	0.0019	758	0.0243	1015	0.0058
90	0.0030	329	0.0027	760	0.0038	1016	0.0291
91	0.0105	330	0.0016	767	0.0043	1017	0.0031
92	0.0065	331	0.0018	773	0.0038	1018	0.0025
96	0.0071	332	0.0035	784	0.0108	1019	0.0289
110	0.0047	333	0.0012	785	0.0101	1020	0.0104
111	0.0039	334	0.0016	791	0.0022	1021	0.0422
112	0.0206	335	0.0038	795	0.0024	1022	0.0042
113	0.0241	336	0.0029	798	0.0031	1023	0.0087
114	0.0019	338	0.0062	803	0.0126	1024	0.0170
115	0.0034	340	0.0019	822	0.0041	1025	0.0780
116	0.0043	341	0.0056	826	0.0039	1026	0.0050
118	0.0096	342	0.0065	831	0.0032	1027	0.0500
119	0.0029	343	0.0099	839	0.0038	1028	0.0225
120	0.0048	344	0.0105	851	5.0052	1029	0.0257
121	0.0034	345	0.0040	883	0.0089	1030	0.1938
188	0.0286	346	0.0099	885	0.0346	1031	0.0704
248	0.0374	347	0.0104	888	0.0014	1032	0.0012
262	0.0015	348	0.0775	900	0.0029	1034	0.0019
263	0.0013	349	0.0065	921	0.0021	1035	0.0026
264	0.3476	350	0.0062	932	0.0169	1037	0.0102
265	0.0037	351	0.0136	939	0.0139	1040	0.0048
266	0.0174	352	0.0215	946	0.0230	1041	0.0033
267	0.0294	353	0.0086	952	0.0072	1047	0.4629
268	0.0058	354	0.0044	953	0.0168	1048	0.5407
269	0.0050	355	0.0064	959	0.0154	1049	0.0069
270	0.9524	358	0.0006	960	0.0171	1051	0.0146
271	0.0021	359	0.0030	962	0.0236	1052	0.0180
272	0.0140	360	0.0019	963	0.0267	1057	0.0027
273	0.0107	362	0.1319	964	0.0052	1061	0.0043
274	0.0059	363	0.0503	965	0.0106	1064	0.0067
275	0.0047	364	0.8403	966	0.0020	1067	0.0188
276	0.0051	365	0.0027	967	0.0019	1068	0.0053
277	0.0023	366	0.0106	968	0.0314	1070	0.0076
278	0.0032	367	0.0111	969	0.0500	1071	0.0165
279	0.0078	368	0.0079	970	0.0023	1073	1.5241
280	0.0108	369	0.0028	971	0.0342	1074	0.0069
281	0.0081	370	0.0031	972	0.0030	1075	0.0137
282	0.0115	371	0.0024	973	0.0029	1076	0.0084
283	0.0070	372	0.0106	974	0.0135	1077	0.0045
284	0.0071	376	0.0055	975	0.0120	1078	0.0060
285	0.0442	433	0.0019	976	0.0061	1079	0.0057
286	0.0649	441	0.0091	977	0.0032	1080	0.0032
287	5.1353	443	0.0022	978	0.0039	1081	0.0022
288	0.0273	448	0.0012	979	0.0100	1082	0.0102
289	0.0137	452	0.0004	980	0.0191	1083	0.0042
290	0.0058	468	0.0049	981	0.0137	1084	0.0017
291	0.0082	470	0.0027	982	0.0192	1085	0.0024
292	0.0078	472	0.0032	983	0.0223	1086	0.0025
293	0.0050	475	0.0032	984	0.0055	1087	0.0035
294	0.0124	477	0.0011	985	0.0041	1088	0.0093
295	0.0028	481	0.0043	986	0.0110	1090	0.0069

296	0.0143	483	0.0113	987	0.0428	1091	0.0014
297	0.0237	487	0.0077	988	0.0249	1092	0.0627
298	0.0135	500	0.0106	989	0.0162	1093	0.0117
299	0.0067	513	0.0104	990	0.0213		
300	0.0082	517	0.0096	991	0.0033		
301	0.0020	521	0.0016	992	0.0253		

Example 15.

[01262] Representative compounds were screened using the assay procedure for GSK3 β kinase activity as described below.

[01263] Each compound is dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 11-point dose-response curves from 10 μ M to 0.0003 μ M) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, CA) into 1536-well black-walled round bottom plates (Corning).

[01264] The GSK3 β kinase assay is run using the Ser/Thr 09 peptide Z-lyte assay kit according to manufacturer's instructions (Life Technologies- a Division of Thermo-Fisher). This is a non-radioactive assay using fluorescence resonance energy transfer (FRET) between coumarin and fluorescein to detect kinase activity which is represented as ratio of coumarin emission/fluorescein emission.

[01265] Briefly, recombinant GSK3 β kinase, ATP and Ser/Thr peptide 09 are prepared in 1X Kinase buffer to final concentrations of 0.04 μ g/mL, 46 μ M, and 4 μ M respectively. The mixture is allowed to incubate with the representative compounds for one hour at room temperature. All reactions were performed in duplicate. Unphosphorylated ("0% Control") and phosphorylated ("100% control") forms of Ser/Thr 18 serve as control reactions.

[01266] After incubation, diluted Development Buffer is added to the reaction and allowed to further incubate for one hour at room temperature. The plate is read at Ex 400 Em 455 to detect the coumarin signal and Ex 400 Em 520 to measure the signal (EnVision Multilabel Plate Reader, PerkinElmer).

[01267] The Emission ratio (Em) is calculated as a ratio of the coumarin (C) emission signal (at 445 nm)/Fluorescein (F) emission signal (at 520 nm). The percent phosphorylation is then calculated using the following formula: $[1 - ((\text{Em ratio} \times \text{F100\%}) - \text{C100\%}) / ((\text{C0\%} - \text{C100\%}) + (\text{Em ratio} \times (\text{F100\%} - \text{F0\%})))]$.

[01268] Dose-response curves are generated and inhibitory concentration (IC₅₀) values are calculated using non-linear regression curve fit in the Dotmatics' Studies Software (Bishops Stortford, UK).

[01269] Table 4 shows the activity of representative compounds of Formula I as provided herein.

Table 4.

Compound	EC ₅₀ (μM)	Compound	EC ₅₀ (μM)	Compound	EC ₅₀ (μM)	Compound	EC ₅₀ (μM)
1	0.008	302	0.038	523	0.042	993	0.087
3	0.038	303	0.089	527	0.415	994	0.110
4	0.080	304	0.029	528	0.096	995	0.177
6	0.065	305	0.051	531	0.050	996	0.141
10	0.051	306	0.066	535	0.087	997	0.033
14	0.059	307	5.256	537	0.095	998	0.102
16	0.024	308	0.107	547	0.104	999	0.086
69	0.013	309	0.120	554	0.038	1000	0.270
71	0.062	310	0.105	561	0.012	1001	0.009
72	0.064	311	0.020	579	0.048	1002	0.425
73	0.049	312	0.031	643	0.049	1003	0.043
75	0.064	313	0.039	699	0.024	1004	0.037
76	0.031	314	0.012	700	0.049	1005	0.032
77	0.024	315	0.044	704	1.831	1006	0.050
78	0.063	316	0.509	707	0.046	1007	0.083
81	0.030	317	0.030	711	0.067	1008	0.091
82	0.022	318	0.012	713	0.098	1009	0.015
83	0.034	320	0.010	718	0.079	1010	0.053
84	0.020	324	0.030	731	0.042	1011	0.030
85	0.029	325	0.003	737	0.062	1012	0.155
86	0.048	326	0.019	741	0.107	1013	1.429
87	0.032	327	0.066	743	0.063	1014	0.096
89	0.064	328	0.016	758	0.050	1015	0.101
90	0.042	329	0.029	760	0.133	1016	0.087
91	0.838	330	0.015	767	0.157	1017	0.076
92	0.361	331	0.055	773	0.219	1018	0.054
96	0.350	332	0.039	784	0.133	1019	0.158
110	0.034	333	0.060	785	0.044	1020	0.013
111	0.040	334	0.047	791	0.005	1021	1.585
112	0.292	335	0.071	795	0.033	1022	0.124
113	0.586	336	0.083	798	0.031	1023	0.838
114	0.032	338	0.067	803	0.164	1024	0.150
115	0.030	340	0.257	822	0.009	1025	0.100
116	0.024	341	0.089	826	0.007	1026	0.508
118	0.079	342	0.137	831	0.010	1027	3.073
119	0.007	343	0.071	839	0.017	1028	0.104
120	0.138	344	0.175	851	5.005	1029	0.018
121	0.053	345	0.026	883	0.076	1030	0.390
188	0.265	346	0.084	885	0.046	1031	0.380
248	0.266	347	0.165	888	0.008	1032	0.072
262	0.024	348	0.221	900	0.011	1034	0.027
263	0.018	349	0.066	921	0.005	1035	0.010
264	>10	350	0.033	932	0.014	1037	1.923
265	0.007	351	0.130	939	0.013	1040	0.098
266	0.038	352	0.110	946	0.038	1041	0.058
267	0.039	353	0.029	952	0.008	1047	4.745
268	0.017	354	0.037	953	0.023	1048	5.812
269	1.022	355	0.228	959	0.045	1049	0.012
270	5.310	358	0.080	960	0.015	1051	0.009
271	0.003	359	0.082	962	0.057	1052	0.011
272	0.105	360	0.047	963	0.006	1057	0.097
273	0.048	362	1.102	964	0.102	1061	0.008
274	0.025	363	0.035	965	0.079	1064	0.126
275	0.115	364	3.122	966	0.032	1067	0.067
276	0.006	365	0.052	967	0.046	1068	0.036
277	0.104	366	0.116	968	0.061	1070	0.016
278	0.007	367	0.056	969	7.613	1071	2.733
279	0.014	368	0.051	970	0.478	1073	>10
280	0.185	369	0.101	971	0.034	1074	0.278
281	0.071	370	0.089	972	0.064	1075	0.015
282	0.134	371	0.023	973	0.020	1076	0.011
283	0.062	372	0.079	974	0.096	1077	0.032
284	0.037	376	0.710	975	1.094	1078	0.070

285	0.149	433	0.001	976	0.146	1079	0.048
286	0.186	441	0.005	977	0.246	1080	0.056
287	9.838	443	0.013	978	0.220	1081	0.082
288	0.020	448	0.011	979	0.791	1082	0.210
289	0.062	452	0.007	980	0.389	1083	0.914
290	0.075	468	0.007	981	0.141	1084	0.040
291	0.043	470	0.004	982	0.265	1085	0.083
292	0.173	472	0.008	983	0.303	1086	0.028
293	0.059	475	0.023	984	0.236	1087	0.037
294	0.041	477	0.006	985	0.283	1088	0.937
295	0.020	481	0.004	986	0.021	1090	0.288
296	0.080	483	0.045	987	2.316	1091	0.069
297	0.155	487	0.007	988	1.093	1092	0.132
298	0.125	500	0.023	989	0.298	1093	0.047
299	0.044	513	0.043	990	0.100		
300	0.031	517	0.470	991	0.029		
301	0.010	521	0.234	992	0.014		

Example 16.

[01270] Representative compounds were screened using the assay procedure for tau phosphorylation activity described below.

[01271] SH-SY5Y cells (human neuroblastoma) were cultured in DMEM/F-12 medium supplemented with 15% FBS, Non-essential Amino Acid and Penicillin/Streptomycin. Two days before treatment, cells were seeded onto 96 well plates at 5×10^4 cells/well.

[01272] The above synthesized compounds were screened using the cell assay procedure to assess decrease Tau phosphorylation at Ser396 (pSer396) described below.

[01273] DMSO-resuspended compounds were dispensed to 8 wells as a serial titration from 10 μ M to 4.6 nM final in medium and cells were exposed overnight (16-18 h) in a humidified incubator at 36.6c before harvest. Wells were visually checked for cell death or change in morphology and supernatants were tested for cytotoxicity by measurement of lactate dehydrogenase release (LDH, CytoToxOne kit, Promega) if necessary. As controls, commercially available DYRK1A inhibitors, Harmine and Indy which were shown to have good DYRK1A inhibition in the kinase assay with no CDK1 activity (EC_{50} 18 and 53 nM respectively, 6 μ M for CDK1) but weak EC_{50} in the Tau assay $>10 \mu$ M.

[01274] Cells were lysed with RIPA buffer complemented with phosphatase and protease inhibitors then lysates were spun down at 12,000g for 10 min to remove any cellular debris. Lysates are then either directly tested for pSer396 by ELISA (Life Technology, Kit KHB7031) or loaded on NuPage Bis-Tris gels for western blot analysis. Colorimetric detection of ELISA signal is performed by Cytation3 plate reader (Biotek) and the chemiluminescence signal for HRP-linked antibodies used in western blotting is detected using a Carestream Image Station. The same pSer396 antibody is used for detection of pTau in both assays.

[01275] Blot densitometry for pSer396 and β -actin were analyzed using ImageJ (NIH) and pSer396 Tau ELISA signal was used to plot, draw the curve fitting, and determine each compounds EC₅₀ in Prism (GraphPad).

[01276] Table 5 shows the activity of representative compounds as provided herein.

Table 5.

Compound	pSer396 Tau EC ₅₀ (μ M)	Compound	pSer396 Tau EC ₅₀ (μ M)	Compound	pSer396 Tau EC ₅₀ (μ M)	Compound	pSer396 Tau EC ₅₀ (μ M)
1	0.149	301	0.108	513	0.864	988	>10
3	0.288	302	0.628	517	1.300	989	>10
4	0.671	303	0.783	521	1.100	990	1.800
6	0.475	304	0.210	523	2.200	991	10.000
10	0.227	305	0.247	527	2.400	992	0.350
14	0.408	306	0.592	528	0.323	993	0.702
16	>10	307	2.080	531	0.146	994	1.900
69	0.383	308	0.361	535	6.200	995	2.400
71	1.510	309	1.220	537	0.451	996	3.100
72	0.757	310	0.628	547	0.379	997	1.300
73	0.199	311	0.163	554	0.095	998	0.638
75	0.227	312	0.762	561	0.395	999	0.659
76	0.219	313	0.330	579	0.062	1000	1.500
77	0.184	314	0.128	643	0.049	1001	3.300
78	0.265	315	0.346	699	0.423	1002	1.900
81	0.452	316	8.780	700	0.513	1003	0.732
82	0.315	317	0.200	704	10.000	1004	0.667
83	0.432	318	0.072	707	0.449	1005	0.898
84	0.454	320	0.280	711	0.443	1006	0.296
85	0.392	324	0.180	713	5.000	1007	0.435
86	0.682	325	0.440	718	0.294	1008	0.643
87	0.414	326	0.574	731	0.450	1009	0.068
89	0.364	327	0.411	737	0.865	1010	0.622
90	0.302	328	0.231	741	0.528	1011	>10
91	4.700	329	0.524	743	0.432	1012	0.555
92	3.900	330	0.246	758	0.384	1013	4.200
96	2.000	331	0.311	760	1.200	1014	0.767
110	0.636	332	0.249	767	1.000	1015	0.523
111	0.597	333	1.100	773	2.200	1016	0.631
112	1.750	334	0.820	784	2.200	1017	0.320
113	3.800	335	0.289	785	0.485	1018	0.280
114	0.286	336	0.820	791	0.055	1019	1.500
115	0.311	338	1.700	795	0.401	1020	0.049
116	0.870	340	2.300	798	0.320	1021	5.700
118	1.200	341	1.600	803	3.700	1022	9.600
119	0.418	342	3.600	822	0.247	1023	1.800
121	1.030	343	2.400	826	0.568	1024	1.200
188	4.220	344	3.500	831	0.189	1025	>10
248	0.905	345	0.774	839	0.254	1027	2.200
262	0.174	346	1.800	851	0.350	1028	0.536
263	0.119	347	4.400	883	1.100	1029	0.239
264	>10	348	2.000	885	0.878	1030	1.200
265	0.656	349	0.351	888	0.195	1031	0.969
266	1.200	350	0.417	900	0.180	1034	0.430
267	0.555	351	0.846	921	0.109	1035	0.129
268	0.478	352	1.300	932	0.357	1037	>10
269	4.300	353	0.724	939	0.274	1040	1.600
270	>10	354	1.200	946	0.571	1041	1.300
271	0.124	355	1.700	952	0.269	1047	>10
272	1.660	358	0.353	953	0.398	1048	4.700
273	0.492	359	0.521	959	0.443	1049	0.319

274	0.535	360	0.659	960	0.233	1051	0.147
275	0.232	363	0.406	962	0.447	1052	0.254
276	0.150	364	>10	963	0.252	1057	0.342
277	1.080	365	1.200	964	0.576	1061	0.058
278	0.076	366	1.100	965	1.000	1064	0.109
279	0.498	367	0.258	966	0.236	1067	0.729
280	0.677	368	0.660	967	0.373	1068	0.689
281	0.518	369	0.970	968	2.700	1070	0.091
282	0.973	370	0.256	970	0.862	1071	6.900
283	0.411	371	0.581	971	0.191	1074	1.300
284	0.359	372	1.100	972	0.355	1075	0.709
285	1.580	376	7.900	973	0.102	1076	0.041
286	1.150	433	0.032	974	2.000	1077	0.425
288	0.159	441	0.073	975	4.600	1078	0.458
289	0.185	443	0.289	976	0.536	1079	0.190
290	0.490	448	0.106	977	0.426	1080	0.251
291	0.716	452	0.912	978	0.274	1081	0.470
292	1.350	468	0.039	979	0.569	1082	1.100
293	0.668	470	0.095	980	2.100	1086	0.168
294	0.905	472	0.200	981	1.100	1087	0.160
295	0.430	475	1.800	982	1.100	1088	8.600
296	0.978	477	0.188	983	1.500	1090	0.969
297	1.420	481	0.662	984	2.100	1091	0.869
298	1.390	483	0.611	985	3.200	1092	0.131
299	0.573	487	0.161	986	0.387	1093	0.422
300	0.222	500	0.388	987	>10		

Example 17.

[01277] Representative compounds were screened using the cell-based assay procedure for secreted β -amyloid 40 (A β 40) peptide in an APP overexpressing cell line described below.

[01278] SH-SY5Y cells (human neuroblastoma) were cultured in 1:1 DMEM/F-12 medium supplemented with 15% FBS, 1% non-essential amino acids, and 1% penicillin/streptomycin. HEK293T cells (human kidney) were cultured in DMEM medium supplemented with 10% FBS and 1% penicillin/streptomycin.

[01279] SH-SY5Y cells were infected with lentivirus to overexpress amyloid (A4) beta precursor protein (APP), hereafter referred to as the SH-SY5Y-APP cells. Specifically, in a 10 cm dish, HEK293T cells were seeded at $2.5 \times 10^5 \frac{\text{cells}}{\text{mL}}$ and transfected with APP (Myc-DDK-tagged)-Human amyloid beta (A4) precursor protein (APP), transcript variant 3 pLenti-ORF expression construct (custom modification of RC215147 to include bicistronic IRES-puromycin, OriGene). Culture medium was changed 18 h post-transfection before a first batch of viral supernatant was then harvested at 42 h post-transfection. Culture medium was replenished once more before a second batch of viral supernatant was harvested 66 h post-transfection. The two batches of viral supernatant were combined and spun at 1800g, then filtered through a 0.45 μ m PVDF filter.

[01280] SH-SY5Y cells were seeded onto 6-well plates at $5.0 \times 10^5 \frac{\text{cells}}{\text{well}}$ and incubated overnight at 37°C. Cells were then infected with viral supernatant at concentrations ranging from

10%→100% viral supernatant (diluted in Opti-MEM as appropriate), with $10 \frac{\mu g}{mL}$ Polybrene added for permeability (H9268, Sigma). 24 hours post-transfection, the entire volume from each well was replaced with regular SH-SY5Y medium. 4 days post-transfection, APP-overexpressing SH-SY5Y cells were selected for by adding puromycin (A11138-03, Gibco) to each well at a final concentration of $2 \frac{\mu g}{mL}$. Puromycin-resistant cell were then expanded, harvested and banked. APP-overexpression was controlled by immunoblotting for total APP and Myc-DDK.

[01281] The cell assay procedure start 18 h prior to treatment, as SH-SY5Y-APP cells were seeded onto 96-well plates at $2.0 \times 10^4 \frac{cells}{well}$. The entire 200 μL volume of medium was removed from all wells, and replenished to reset any A β 40 peptide that may have been secreted prior to treatment. DMSO-resuspended compounds were dispensed to eight wells as a serial dilution from 10 μM to 4.6 nM final concentration in medium. At this time, designated wells were seeded with SH-SY5Y cells that were seeded and treated with puromycin at $10 \frac{\mu g}{mL}$. Cells were exposed overnight (16-18 hours) in a 37°C incubator before supernatant was harvested. Wells were visually checked for cell death before 150 μL of supernatant was harvested from each well into V-bottom 96-well plates (3894, Corning). The original plates with seeded cells were tested for cytotoxicity by measure of adenosine triphosphate (ATP) release by adding CellTiter-Glo® diluted 1:4 in distilled water (G7573, Promega) and transferring lysed cells to a completely black 96-well plate to be read with the Cytation3. Plates containing supernatant were spun down at 1200g for 10 minutes to remove any cellular debris. Supernatant was then diluted 1:2 with a diluent from V-PLEX A β 40 Peptide (6E10) Kit and directly tested for secreted A β 40 peptide (K150SKE, Meso Scale Discovery). The signal was used to plot, draw the curve fitting, and determine each compounds EC₅₀ in Prism (GraphPad).

[01282] Table 6 shows the activity of representative compounds as provided herein.

Table 6.

Compound	A β 40 IC ₅₀ (μM)	Compound	A β 40 IC ₅₀ (μM)	Compound	A β 40 IC ₅₀ (μM)	Compound	A β 40 IC ₅₀ (μM)
1	3.96	81	2.3	111	0.272	269	>10
72	2.1	82	5.1	115	0.956	271	4.6
76	1.2	83	>10	248	>10		
77	1.1	84	4.4	262	2.2		
78	0.889	85	1.3	263	5.3		

Example 18.

[01283] Representative compounds were screened using the assay procedure to assess the effect on cell viability as described below.

[01284] SW480 colon carcinoma cells were transduced with a lentiviral vector expressing luciferase with a human Sp5 promoter consisting of a sequence of eight TCF/LEF binding sites. SW480 cells stably expressing the Sp5-Luc reporter gene and a hygromycin resistance gene were selected by treatment with 150 µg/mL of hygromycin for 7 days. These stably transduced SW480 cells were expanded in cell culture and used for all further screening activities. Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 8-point dose-response curves from 10 µM to 0.0045 µM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, CA) into 384-well white solid bottom assay plates (Greiner Bio-One) with appropriate DMSO backfill for a final DMSO concentration of 0.1%.

[01285] For the Cell Viability Assays, the cells were plated at 2,000 cells/well in 384-well plates with a DMEM medium containing 1% fetal bovine serum, and 1% Penicillin-Streptomycin and incubated for four days hours at 37°C and 5% CO₂. Eight replicates of DMSO-treated cells served as controls and cells treated with compound were performed in duplicate.

[01286] After incubation, 10 µL of CellTiter-Glo (Promega) was added to each well allowed to incubate for approximately 12 minutes. This reagent “results in cell lysis and generation of a luminescent signal proportional to the amount of ATP present. The amount of ATP is directly proportional to the number of cells present in culture, in agreement with previous reports. The CellTiter-Glo® Assay generates a "glow-type" luminescent signal, produced by the luciferase reaction (Promega.com)”.

[01287] After incubation, the plates were read at Ex 560 nm Em 590 nm (Cytation 3, BioTek). Dose-response curves were generated and EC₅₀ concentration values were calculated using non-linear regression curve fit in the GraphPad Prism (San Diego, CA) or Dotmatics' Studies Software (Bishops Stortford, UK). For EC₅₀ of >10 µM, the percent inhibition at 10 µM is provided.

[01288] Table 7 shows the activity of representative compounds of Formula I as provided herein.

Table 7.

Compound	EC ₅₀ (µM)	Compound	EC ₅₀ (µM)	Compound	EC ₅₀ (µM)	Compound	EC ₅₀ (µM)
1	0.130	302	>10 (34.9%)	521	3.629	991	3.957
3	2.802	303	7.804	523	0.447	992	5.599
4	1.937	304	1.338	527	>10 (43.6%)	993	6.585
6	1.256	305	1.651	528	1.415	994	>10 (36.8%)
10	0.324	306	3.199	531	0.989	995	>10 (47.6%)
14	0.898	307	>10	535	>10 (42.0%)	996	>10 (32.2%)
16	7.845	308	>10 (32.0%)	537	8.303	997	5.060
69	3.931	309	>10 (9.6%)	547	0.931	998	4.753
71	8.098	310	5.347	554	0.366	999	7.514
72	0.911	311	0.751	561	0.924	1000	7.295
73	0.769	312	>10	579	0.954	1001	0.677
75	1.322	313	0.711	643	0.115	1002	>10 (37.6%)

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76	1.556	314	1.196	699	0.834	1003	0.804
77	0.767	315	1.251	700	0.623	1004	0.678
78	1.844	316	2.340	704	>10 (18.1%)	1005	1.126
81	0.949	317	6.336	707	0.947	1006	0.584
82	2.710	318	0.940	711	0.706	1007	0.922
83	6.336	320	1.784	713	6.976	1008	>10 (37.2%)
84	1.954	324	0.266	718	0.483	1009	2.351
85	1.637	325	0.526	731	1.103	1010	3.965
86	>10	326	0.400	737	4.342	1011	>10 (25.0%)
87	3.156	327	1.585	741	0.462	1012	3.195
89	0.738	328	0.929	743	1.544	1013	5.498
90	1.174	329	4.119	758	1.336	1014	5.417
91	9.592	330	6.784	760	3.284	1015	6.419
92	0.983	331	3.115	767	9.054	1016	6.136
96	>10	332	1.003	773	>10 (48.4%)	1017	0.659
110	1.049	333	0.641	784	>10 (39.7%)	1018	0.498
111	0.526	334	7.370	785	2.860	1019	9.381
112	6.425	335	1.120	791	0.137	1020	1.032
113	>10	336	0.510	795	0.806	1021	>10 (11.6%)
114	3.892	338	9.332	798	0.613	1022	3.337
115	3.505	340	2.232	803	4.533	1023	>10 (39.9%)
116	6.495	341	>10 (33.9%)	822	0.708	1024	6.773
118	5.936	342	>10 (40.0%)	826	0.897	1026	0.554
119	0.525	343	7.886	831	0.911	1027	0.488
120	2.486	344	7.678	839	1.177	1028	3.523
121	4.307	345	3.076	851	>10 (30.4%)	1029	>10 (34.6%)
188	>10	346	9.663	883	>10 (35.5%)	1030	>10 (19.3%)
248	>10	347	>10 (48.5%)	885	7.720	1031	3.892
262	1.391	348	>10 (22.4%)	888	2.471	1032	>10 (34.7%)
263	1.287	349	0.704	900	3.883	1034	3.242
264	8.750	350	1.081	921	1.624	1035	2.463
265	4.348	351	6.882	932	5.449	1037	>10 (32.7%)
266	6.316	352	8.599	939	>10 (31.6%)	1040	2.684
267	2.025	353	8.225	946	>10 (42.6%)	1041	2.763
268	2.774	354	4.992	952	7.090	1047	>10 (41.7%)
269	2.3303	355	8.634	953	>10 (40.3%)	1048	4.057
270	>10	358	2.372	959	>10 (45.0%)	1049	>10 (31.3%)
271	2.962	359	0.261	960	6.673	1051	>10 (22.5%)
272	5.869	360	0.570	962	>10 (30.9%)	1052	>10 (40.7%)
273	1.184	362	5.476	963	>10 (49.2%)	1057	4.505
274	4.051	363	3.057	964	3.828	1061	1.595
275	1.275	364	5.601	965	8.630	1064	4.851
276	>10 (29.6%)	365	0.522	966	0.259	1067	>10 (43.1%)
277	1.401	366	0.910	967	0.459	1068	>10 (46.0%)
278	1.232	367	8.240	968	>10 (14.5%)	1070	8.388
279	>10 (52.4%)	368	0.651	969	2.885	1071	>10 (26.2%)
280	9.566	369	0.864	970	1.255	1073	>10 (8.5%)
281	>10	370	1.246	971	1.197	1074	>10 (25.0%)
282	6.613	371	1.063	972	0.757	1075	5.281
283	3.121	372	8.816	973	0.391	1076	1.576
284	2.670	376	4.195	974	3.161	1077	5.246
285	7.023	433	0.615	975	0.334	1078	4.407
286	3.292	441	5.268	976	3.878	1079	2.605
287	>10 (47.8%)	443	1.676	977	0.615	1080	1.380
288	2.660	448	0.626	978	1.577	1081	4.648
289	7.755	452	1.453	979	2.223	1082	7.100
290	3.783	468	2.507	980	5.743	1083	0.901
291	>10 (24.4%)	470	4.187	981	0.546	1084	3.666
292	2.821	472	5.093	982	1.212	1085	1.240
293	2.857	475	1.063	983	4.619	1086	0.592
294	4.154	477	0.719	984	3.128	1087	0.746
296	3.465	481	1.368	985	1.722	1088	9.194
297	5.718	483	7.343	986	3.305	1090	0.994
298	2.381	487	2.684	987	>10 (10.6%)	1091	1.246
299	2.237	500	>10 (25.1%)	988	>10 (18.0%)	1092	2.984
300	1.298	513	9.064	989	>10 (36.4%)		

301	0.550	517	>10 (27.5%)	990	3.547

Example 19.

[01289] Representative compounds were screened using primary human fibroblasts (derived from IPF patients) treated with TGF- β 1 to determine their ability to inhibit the fibrotic process.

[01290] *Human Fibroblast Cell Culture:* Primary human fibroblasts derived from IPF patients (LL29 cells) [¹Xiaoqiu Liu, et.al., “Fibrotic Lung Fibroblasts Show Blunted Inhibition by cAMP Due to Deficient cAMP Response Element-Binding Protein Phosphorylation”, *Journal of Pharmacology and Experimental Therapeutics* (2005), 315(2), 678-687; ²Watts, K. L., et.al., “RhoA signaling modulates cyclin D1 expression in human lung fibroblasts; implications for idiopathic pulmonary fibrosis”, *Respiratory Research* (2006), 7(1), 88] were obtained from American Type Culture Collection (ATCC) and expanded in F12 medium supplemented with 15% Fetal Bovine Serum and 1% Penicillin/Streptomycin.

[01291] *Compound Screening:* Each compound was dissolved in DMSO as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:2, 11-point dose-response curves from 10 μ M to 0.94 nM) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, CA) into 384-well clear bottom assay plates (Greiner Bio-One) with appropriate DMSO backfill for a final DMSO concentration of 0.1%. LL29 cells were plated at 1,500 cells/well in 70 μ L/well F12 medium supplemented with 1% Fetal Bovine Serum. TGF- β 1 (Peprotech; 20 ng/mL) was added to the plates to induce fibrosis (ref. 1 and 2 above). Wells treated with TGF- β 1 and containing DMSO were used as positive control, and cells with only DMSO were negative control. Cells were incubated at 37°C and 5% CO₂ for 4 days. Following incubation for 4 days, SYTOX green nucleic acid stain (Life Technologies [Thermo Fisher Scientific]) was added to the wells at a final concentration of 1 μ M and incubated at room temperature for 30 min. Cells were then fixed using 4% formaldehyde (Electron Microscopy Sciences), washed 3 times with PBS followed by blocking and permeabilization using 3% Bovine Serum Albumin (BSA; Sigma) and 0.3% Triton X-100 (Sigma) in PBS. Cells were then stained with antibody specific to α -smooth muscle actin (α SMA; Abcam) (ref. 1 and 2 above) in 3% Bovine Serum Albumin (BSA; Sigma) and 0.3% Triton X-100 (Sigma) in PBS, and incubated overnight at 4°C. Cells were then washed 3 times with PBS, followed by incubation with Alexa Fluor-647 conjugated secondary antibody (Life Technologies [Thermo Fisher Scientific]) and DAPI in 3% Bovine Serum Albumin (BSA; Sigma) and 0.3% Triton X-100 (Sigma) in PBS at room temperature for 1 hour. Cells were then washed 3 times with PBS and plates were sealed for imaging. α SMA staining was imaged by excitation at

630 nm and emission at 665 nm and quantified using the Compartmental Analysis program on the CellInsight CX5 (Thermo Scientific). Dead or apoptotic cells were excluded from analysis based on positive SYTOX green staining. % of total cells positive for α SMA were counted in each well and normalized to the average of 11 wells treated with TGF- β 1 on the same plate using Dotmatics' Studies Software. The normalized averages (fold change over untreated) of 3 replicate wells for each compound concentration were used to create dose-responses curves and EC₅₀ values were calculated using non-linear regression curve fit in the Dotmatics' Studies Software. For EC₅₀ of >10 μ M, the percent inhibition at 10 μ M is provided.

[01292] Table 8 shows the activity of representative compounds of Formula I as provided herein.

Table 8.

Compound	EC ₅₀ (μ M)	Compound	EC ₅₀ (μ M)	Compound	EC ₅₀ (μ M)	Compound	EC ₅₀ (μ M)
1	0.135	290	1.056	367	0.211	965	1.369
3	0.103	291	>10 (49.6%)	368	0.272	966	0.014
4	0.068	292	2.216	369	0.295	967	0.079
6	>10 (45.6%)	293	7.768	370	0.379	968	>10 (24.1%)
10	>10 (39.6%)	294	>10 (41.3%)	371	0.394	969	0.935
14	0.035	295	4.465	372	0.504	970	1.239
16	1.266	296	1.964	376	>10 (21.0%)	971	0.866
69	0.394	297	0.447	433	0.052	972	0.754
71	>10 (33.4%)	298	1.340	441	0.057	973	0.134
72	0.096	299	1.208	443	0.371	974	>10 (49.6%)
73	0.169	300	0.511	448	0.059	975	0.138
75	0.148	301	4.807	452	0.220	976	1.174
76	0.087	302	0.901	470	0.387	977	0.136
77	0.146	303	0.817	472	0.243	978	0.722
78	0.108	304	0.150	475	0.140	979	1.032
81	0.104	305	5.510	477	0.077	980	>10 (40.3%)
82	0.156	306	0.282	481	1.021	981	0.605
83	0.067	307	7.150	483	0.315	982	0.767
84	0.148	308	>10 (27.6%)	487	0.367	983	0.679
85	0.097	309	0.014	500	0.675	984	1.239
86	>10 (14.6%)	310	0.294	513	1.353	985	>10 (38.0%)
87	0.081	311	0.076	517	>10 (29.9%)	986	0.158
89	0.137	312	>10 (36.5%)	521	1.991	987	>10 (42.0%)
90	0.096	313	0.105	523	>10 (32.6%)	988	>10 (46.5%)
91	>10 (17.3%)	314	0.045	527	>10 (37.3%)	989	4.418
92	>10 (16.7%)	315	1.822	528	0.103	990	0.782
96	0.677	316	1.082	531	0.153	991	2.678
110	0.286	317	0.174	535	>10 (17.7%)	992	2.972
111	0.280	318	0.073	537	0.599	993	1.487
112	0.546	320	0.069	547	0.160	994	0.567
113	2.113	324	0.068	554	0.190	995	1.254
114	0.735	325	1.304	561	0.600	996	1.204
115	0.605	326	>10 (47.2%)	579	0.167	997	0.567
116	0.830	327	0.058	643	0.138	998	0.260
118	0.821	328	>10 (34.5%)	699	0.234	999	0.779
119	1.410	329	0.212	700	0.275	1000	2.957
120	2.133	330	0.020	704	4.383	1001	0.065
121	1.083	331	0.096	707	4.242	1002	>10 (27.5%)
188	>10 (12.4%)	332	0.291	711	0.540	1003	0.049
248	7.922	333	0.061	713	>10 (37.6%)	1004	5.041
262	0.043	334	0.063	718	0.168	1005	0.072
263	0.134	335	0.111	737	0.080	1006	0.061
264	>10 (11.7%)	336	>10 (38.4%)	741	0.175	1007	0.942
265	2.563	338	0.643	743	0.447	1008	0.318

266	0.697	340	0.413	758	0.265	1009	>10 (22.4%)
267	0.590	341	2.372	760	0.765	1010	0.103
268	0.073	342	0.948	767	>10 (33.2%)	1011	>10 (15.9%)
269	0.396	343	0.446	773	>10 (30.3%)	1012	>10 (10.2%)
270	>10 (11.4%)	344	>10 (24.3%)	784	>10 (37.4%)	1013	2.436
271	0.064	345	>10 (38.0%)	785	1.174	1014	0.695
272	2.543	346	0.965	791	0.067	1015	>10 (9.7%)
273	0.515	347	5.220	795	0.227	1016	2.132
274	0.195	348	1.457	803	>10 (27.8%)	1017	0.097
275	0.431	349	0.145	822	0.212	1018	0.088
276	0.336	350	0.100	826	0.149	1019	6.529
277	0.245	351	>10 (38.8%)	831	0.244	1020	>10 (30.6%)
278	0.211	352	1.322	851	0.692	1021	4.494
279	1.202	353	>10 (31.7%)	883	>10 (14.0%)	1022	0.222
280	0.909	354	0.346	885	2.620	1023	4.671
281	0.486	355	6.191	900	0.449	1024	0.549
282	1.937	358	0.145	921	0.075	1025	>10 (31.4%)
283	0.782	359	0.127	932	0.594	1026	2.255
284	2.338	360	0.094	939	1.137	1029	>10 (31.8%)
285	1.473	362	0.782	946	0.970	1030	2.806
286	>10 (16.4%)	363	0.387	952	0.741	1031	>10 (39.2%)
287	2.347	364	>10 (15.0%)	960	0.957	1071	0.712
288	0.532	365	4.799	963	1.187	1073	>10
289	>10 (14.3%)	366	0.173	964	>10 (19.7%)	1074	>10

Example 20.

[01293] Representative compounds were screened using the following assay procedure to determine their ability to inhibit IL-6 and therefore demonstrate their anti-inflammatory properties.

[01294] *Human Peripheral Blood Mononuclear Cells:* Fresh Normal PB MNC (Catalog # PB001, AllCells, Alameda, CA) were shipped overnight at 4°C and resuspended in Roswell Park Memorial Institute (RPMI) 1640 Medium, with GlutaMAX Supplement (Catalog #61870127, ThermoFisher Scientific, Waltham, MA) supplemented with 1% Penicillin-Streptomycin (Catalog# 15140163, ThermoFisher Scientific, Waltham, MA) and 1% fetal bovine serum (FBS) (Catalog # 16140089, ThermoFisher Scientific, Waltham, MA) assay media.

[01295] *Compound Screening:* Fresh normal human peripheral blood mononuclear cells (huPBMCs) were resuspended in 1% FBS-RPMI assay media with 1% Penicillin-Streptomycin 1% to a cell concentration of 1×10^6 cells/mL. Each compound was dissolved in DMSO (Catalog # D8418-100ml, Sigma-Aldrich, St. Louis, MO) as a 10 mM stock and used to prepare compound source plates. Serial dilution (1:3, 10-point dose-response curves starting from 10 μ M) and compound transfer was performed using the ECHO 550 (Labcyte, Sunnyvale, CA) into 384-well white Proxiplate-Plus assay plates (Catalog #6008289, PerkinElmer, Shelton, CT) with appropriate DMSO backfill for a final DMSO concentration of 0.25%. huPBMCs were plated at 5000 cells/well in the 384-well Proxiplate-Plus assay plates and incubated at 37°C-5% CO₂ for 2 hours. 50 ng/mL of Lipopolysaccharides from Escherichia coli 0111:B4 (Catalog #L5293-2ML, Sigma-Aldrich, St. Louis, MO) was added after 2 hours and cells were incubated for another 22

hours at 37°C-5% CO₂ . After 22 hour incubation, a mixture of anti-IL6 XL665 and anti-IL-6 Cryptate diluted in reconstitution buffer (Catalog #62IL6PEC, Cisbio Inc., Bedford, MA) was added to each well. Following incubation for 3 hours at room temperature, Homogeneous Time-Resolved Fluorescence (HTRF) was measured using the Envision (Perkin Elmer, Shelton, CT) at 665 nm and 620 nm. The ratio of fluorescence at 665 nm to 620 nm was used as a readout for IL-6 quantification. All samples were processed in duplicate. Readings were normalized to DMSO treated cells and normalized activities were utilized for EC₅₀ calculations. EC₅₀ was determined using software generated by Dotmatics Limited (Windhill Bishops Stortford Herts, UK) using the Levenberg-Marquardt 4 parameter fitting procedure with finite different gradients. For EC₅₀ of >10 μM, the percent inhibition at 10 μM is provided.

[01296] Table 9 shows the activity of representative compounds of Formula I as provided herein.

Table 9.

Compound	EC ₅₀ (μM)	Compound	EC ₅₀ (μM)	Compound	EC ₅₀ (μM)	Compound	EC ₅₀ (μM)
1	0.338	300	2.739	487	3.299	988	>10 (8.8%)
3	0.792	301	0.393	500	>10 (4.0%)	989	>10 (12.5%)
4	1.131	302	7.698	513	>10 (14.5%)	990	>10 (0%)
6	1.286	303	5.235	517	9.068	991	3.236
10	0.399	304	1.144	521	3.248	992	>10 (2.6%)
14	0.643	305	1.144	523	0.201	993	8.836
16	2.166	306	2.517	527	9.975	994	>10 (31.8%)
69	2.157	307	>10 (4.3%)	528	1.785	995	8.930
71	6.733	308	9.229	531	0.698	996	>10 (10.6%)
72	1.127	309	>10 (4.5%)	535	>10 (3.1%)	997	>10 (28.6%)
73	0.963	310	1.167	537	1.243	998	7.082
75	0.806	311	0.396	547	1.119	999	>10 (30.3%)
76	1.127	312	>10 (3.9%)	554	0.439	1000	8.724
77	0.958	313	1.009	561	0.634	1001	>10 (49.7%)
78	2.941	314	1.273	579	1.017	1002	>10 (5.9%)
81	0.395	315	0.819	643	0.129	1003	1.146
82	1.186	316	0.395	699	0.410	1004	1.177
83	2.152	317	1.897	700	0.380	1005	2.890
84	2.463	318	1.031	704	>10 (4.8%)	1006	1.128
85	1.148	320	1.264	707	0.446	1007	1.262
86	1.772	324	0.321	711	1.080	1008	7.591
87	2.939	325	0.357	713	3.633	1009	1.840
89	1.136	326	0.380	718	0.406	1010	1.170
90	1.083	327	0.947	731	1.179	1011	>10 (15.3%)
91	>10 (40.0%)	328	0.398	737	1.179	1012	3.122
92	>10 (33.0%)	329	1.158	741	0.380	1013	6.824
96	>10 (5.8%)	330	1.157	743	1.127	1014	3.201
110	0.484	331	0.882	758	2.871	1015	3.119
112	2.989	332	1.066	760	1.245	1016	>10 (5.4%)
113	1.917	333	0.790	767	3.817	1017	0.655
114	1.140	334	0.263	773	3.481	1018	0.441
115	1.913	335	0.401	784	>10 (3.7%)	1019	8.973
116	1.334	336	0.569	785	9.147	1020	1.181
118	3.606	338	4.458	791	0.350	1021	>10 (5.1%)
119	1.198	340	0.562	795	1.218	1022	3.288
120	2.291	341	>10 (46.1%)	798	1.268	1023	>10 (20.7%)
121	3.653	342	4.167	803	3.317	1024	>10 (33.1%)
188	9.975	343	>10 (47.4%)	822	3.260	1025	>10 (13.6%)
248	9.730	344	9.133	826	3.294	1026	9.523
262	1.092	345	4.167	831	0.812	1027	>10 (0%)

263	0.451	346	9.438	839	3.276	1028	1.934
264	>10 (4.0%)	347	>10 (4.5%)	851	>10 (2.9%)	1029	>10 (7.3%)
265	2.997	348	>10 (19.0%)	883	>10 (9.1%)	1030	>10 (7.7%)
266	1.933	349	0.307	885	>10 (7.0%)	1031	>10 (2.0%)
267	9.407	350	0.578	888	3.944	1032	3.323
268	8.174	351	3.009	900	9.862	1034	3.325
269	3.389	352	5.026	921	>10 (9.9%)	1035	1.027
270	9.975	353	>10 (39.9%)	932	>10 (7.5%)	1037	7.521
271	3.084	354	7.000	939	>10 (3.6%)	1040	1.177
272	3.095	355	9.133	946	>10 (18.2%)	1041	0.941
273	0.842	358	0.613	952	>10 (10.1%)	1047	>10 (4.5%)
274	3.223	359	1.026	959	>10 (6.1%)	1048	>10 (4.3%)
275	1.142	360	1.167	960	>10 (8.2%)	1049	>10 (10.4%)
276	2.920	362	9.153	962	>10 (9.6%)	1057	3.202
277	>10 (4.0%)	363	1.223	963	>10 (8.2%)	1061	0.947
278	3.988	364	>10 (5.8%)	964	>10 (6.8%)	1064	3.505
279	>10 (14.2%)	365	0.526	965	3.263	1067	8.940
280	>10 (11.6%)	366	1.120	967	1.130	1068	3.404
281	>10 (0%)	367	1.153	968	9.238	1070	6.470
282	>10 (2.4%)	368	1.186	969	9.123	1071	>10 (8.8%)
283	5.452	369	1.128	970	1.132	1073	>10 (3.3%)
284	1.182	370	3.708	971	1.220	1074	>10 (5.6%)
285	2.273	371	1.209	972	1.134	1075	3.266
286	1.227	372	3.656	973	0.395	1076	>10 (3.0%)
287	9.578	376	>10 (11.8%)	974	>10 (45.9%)	1077	3.167
288	1.236	433	0.411	975	0.425	1078	3.242
289	3.195	441	3.351	977	0.404	1079	1.214
290	4.782	443	3.289	978	3.364	1080	1.073
291	9.827	448	2.185	979	4.303	1081	1.097
292	1.116	452	2.973	980	3.680	1082	2.929
293	1.170	468	5.776	981	1.104	1083	8.734
294	6.228	470	3.550	982	2.787	1084	0.752
295	>10 (5.9%)	472	5.409	983	>10 (9.1%)	1085	0.453
296	1.575	475	2.562	984	8.760	1086	0.394
297	1.170	477	2.994	985	3.891	1087	0.470
298	5.533	481	1.143	986	>10 (13.4%)	1088	5.978
299	4.528	483	9.616	987	>10 (6.5%)	1090	0.484

Example 21.

[01297] Representative compounds were screened using the cell-based assay procedure for secreted cytokines in a Lipopolysaccharide-stimulated mouse glial cell line described below.

[01298] BV-2 cells (mouse microglial cells) were cultured in 1:1 DMEM medium supplemented with 10% FBS, and 1% penicillin/streptomycin.

[01299] *Compound Screening:* BV-2 cells are plated at 35,000 cells/well in a volume of 100ul for at least 4 hours before compounds are added. DMSO-resuspended compounds were first dispensed in a 96 well plate and serial diluted from 10 μ M to 4.6 nM final concentration in medium. Compounds were added to cells overnight. Two hundred fifty ng per milliliter of lipopolysaccharide (Escherichia coli O55:B5, SIGMA) was added for 5 h. Supernatant is removed and saved for further cytokine detection. The original plates with seeded cells were tested for cytotoxicity by measure of adenosine triphosphate (ATP) release by adding CellTiter-Glo[®] diluted 1:4 in distilled water (G7573, Promega) and transferring lysed cells to a completely black 96-well

plate to be read with the Cytation3. Supernatant was then diluted 1:2 with a diluent from V-PLEX cytokine Kit and directly tested for the secreted cytokines TNF α , IL-6 and KC-GRO using electrochemiluminescence (Meso Scale Discovery). The standard curve for each cytokine was used to convert the electrochemiluminescent signal into pg of protein per mL. The signal was used to plot, draw the curve fitting, and determine each compounds EC₅₀ in Prism (GraphPad).

[01300] Table 10 shows the activity of representative compounds of Formula I as provided herein.

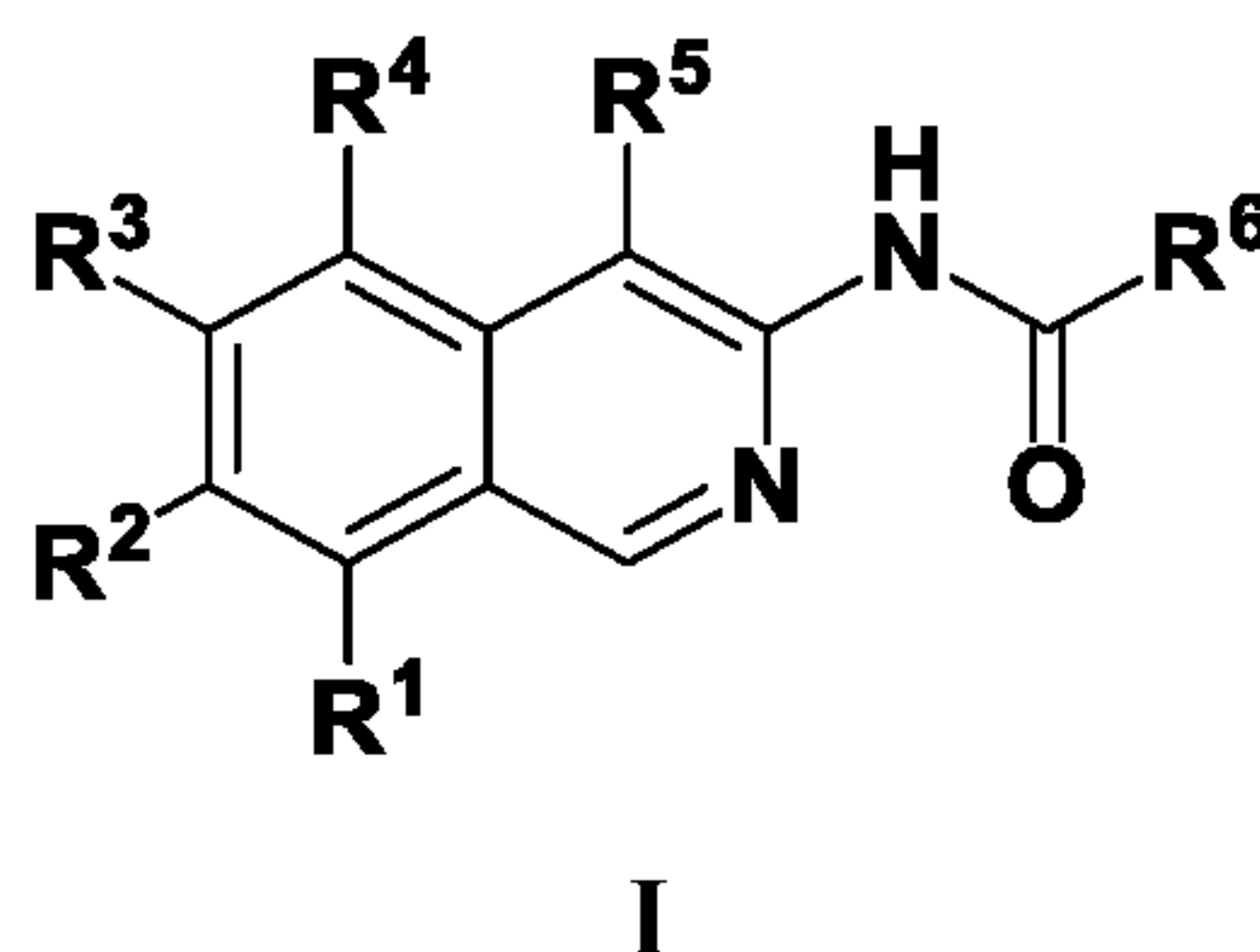
Table 10.

Compound	TNFα EC₅₀ (μM)	IL-6 EC₅₀ (μM)	KC/Gro EC₅₀ (μM)	Compound	TNFα EC₅₀ (μM)	IL-6 EC₅₀ (μM)	KC/Gro EC₅₀ (μM)
73	0.023	0.080	ND	500	1.2	0.034	0.007
81	>10	0.030	ND	966	0.060	0.022	0.071
83	ND	0.006	ND	1006	0.024	0.011	0.027
262	3.2	1.5	ND	1017	0.029	0.024	0.022
278	>10	0.217	ND	1020	0.597	0.087	0.708
324	0.033	0.020	ND	1064	0.030	0.006	0.014
338	0.724	0.144	ND	1070	ND	0.014	ND
468	2.1	0.023	ND	1076	1.8	0.008	0.291

ND = Not Determined

WHAT IS CLAIMED IS:

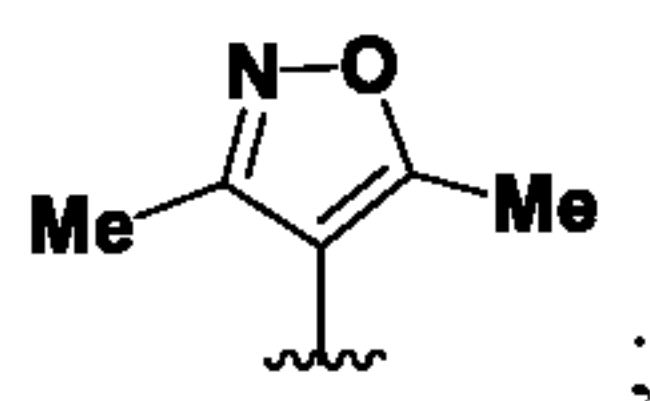
1. A compound, or a pharmaceutically acceptable salt thereof, of Formula I:



wherein:

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, 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} ;



with the proviso that R^3 is not

R^6 is selected from the group consisting of $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{36} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{37} , $-(C_{1-4} \text{ alkylene})N(R^{46})(R^{47})$, $-N(R^{48})(R^{49})$, $-CF(C_{1-9} \text{ alkyl})_2$, $-(C_{1-4} \text{ alkylene})_pO(C_{3-9} \text{ alkyl})$, and $-(C_{2-9} \text{ alkynyl})$ optionally substituted with one or more halides; wherein each alkyl of $-CF(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more halides; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

with the proviso that R^6 is not unsubstituted $-(CH_2)$ tetrahydropyranyl;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{43} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{44} , $-C(=O)(R^{50})$, $-(C_{1-4} \text{ alkylene})C(=O)OR^{51}$, $-(C_{1-4} \text{ alkylene})$ aryl optionally substituted with one or more halides, $-(C_{1-4} \text{ alkylene})_p$ heteroaryl optionally substituted with one or more halides, and $-SO_2(R^{52})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two R^{36} attached to the same carbon atom can together represent $=O$ to form a carbonyl group;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-N(R^{53})_2$, $-C(=O)(R^{50})$, $-C(=O)OR^{51}$, $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl

optionally substituted with 1-10 R⁴³, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R³⁸ independently 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 $-(C_{1-5} \text{ haloalkyl})$, $-\text{CN}$, and $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R³⁹ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴⁰ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴¹ 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 R⁴² 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 $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴³ 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 R⁴⁴; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

each R⁴⁴ 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 H, unsubstituted $-(C_{1-9}$ alkyl), unsubstituted $-(C_{2-9}$ alkenyl), unsubstituted $-(C_{2-9}$ alkynyl), unsubstituted $-(C_{1-9}$ haloalkyl), $-N(R^{53})_2$, $-(C_{1-4}$ alkylene)_pOR⁴², $-(C_{1-4}$ alkylene)_pheterocyclyl optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4}$ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two adjacent R^{45} 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^{46} is attached to the nitrogen and is selected from the group consisting of 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)_pheterocyclyl optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4}$ alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted $-(C_{1-9}$ alkyl), unsubstituted $-(C_{2-9}$ alkenyl), unsubstituted $-(C_{2-9}$ alkynyl), unsubstituted $-(C_{1-9}$ haloalkyl), $-(C_{1-4}$ alkylene)_pheterocyclyl optionally substituted with 1-10 R^{38} , and $-\text{carbocyclyl}$ optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4}$ alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

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

R^{49} is attached to the nitrogen and is selected from the group consisting of $-(C_{1-4}$ alkylene)_pheterocyclyl optionally substituted with 1-10 R^{38} , and $-(C_{1-4}$ alkylene)_pcarbocyclyl optionally substituted with 1-12 R^{39} ; wherein each $-(C_{1-4}$ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{50} is selected from the group consisting of H, unsubstituted $-(C_{3-5}$ alkyl), unsubstituted $-(C_{2-5}$ alkenyl), unsubstituted $-(C_{2-5}$ alkynyl), unsubstituted $-(C_{1-5}$ haloalkyl), $-(C_{1-4}$ alkylene)_paryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5}$ alkyl), $-(C_{1-4}$ alkylene)_pheteroaryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5}$ alkyl), and $-(C_{1-4}$ alkylene)_pheterocyclyl optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5}$ alkyl); wherein each $-(C_{1-4}$ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{51} is selected from the group consisting of H, unsubstituted $-(C_{1-5}$ alkyl), unsubstituted $-(C_{2-5}$ alkenyl), unsubstituted $-(C_{2-5}$ alkynyl), unsubstituted $-(C_{1-5}$ haloalkyl), $-(C_{1-4}$ alkylene)_paryl

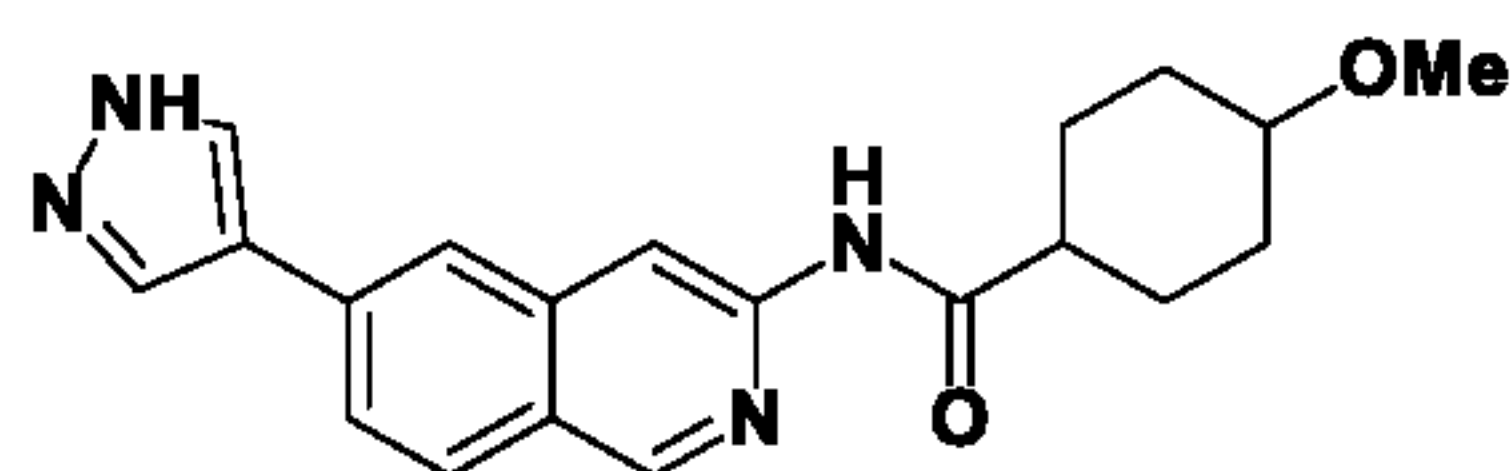
optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heteroaryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R^{52} is selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p$ aryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, $-(C_{1-4} \text{ alkylene})_p$ heteroaryl optionally substituted with one or more halides or unsubstituted $-(C_{1-5} \text{ alkyl})$, and $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with one or more halides or one or more unsubstituted $-(C_{1-5} \text{ alkyl})$; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

each R^{53} is independently selected from the group consisting of H, unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, and unsubstituted $-(C_{2-5} \text{ alkynyl})$;

each p is independently 0 or 1; and

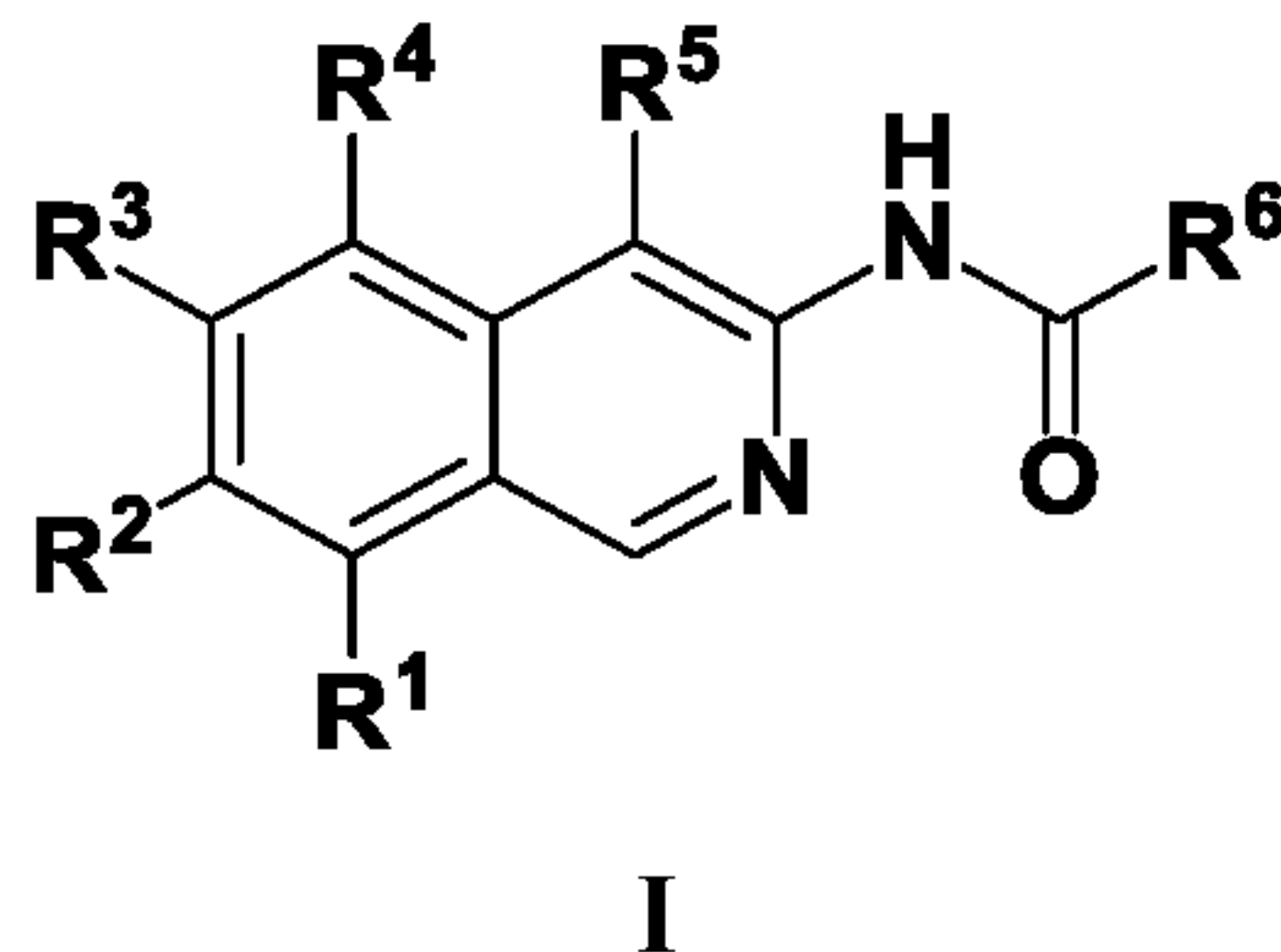
with the proviso that Formula I is not a structure selected from the group consisting of:



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

10. The compound according to any one of claims 1-2 and 8, wherein R^3 is a triazolyl substituted with one $-(C_{1-3} \text{ alkyl})$.

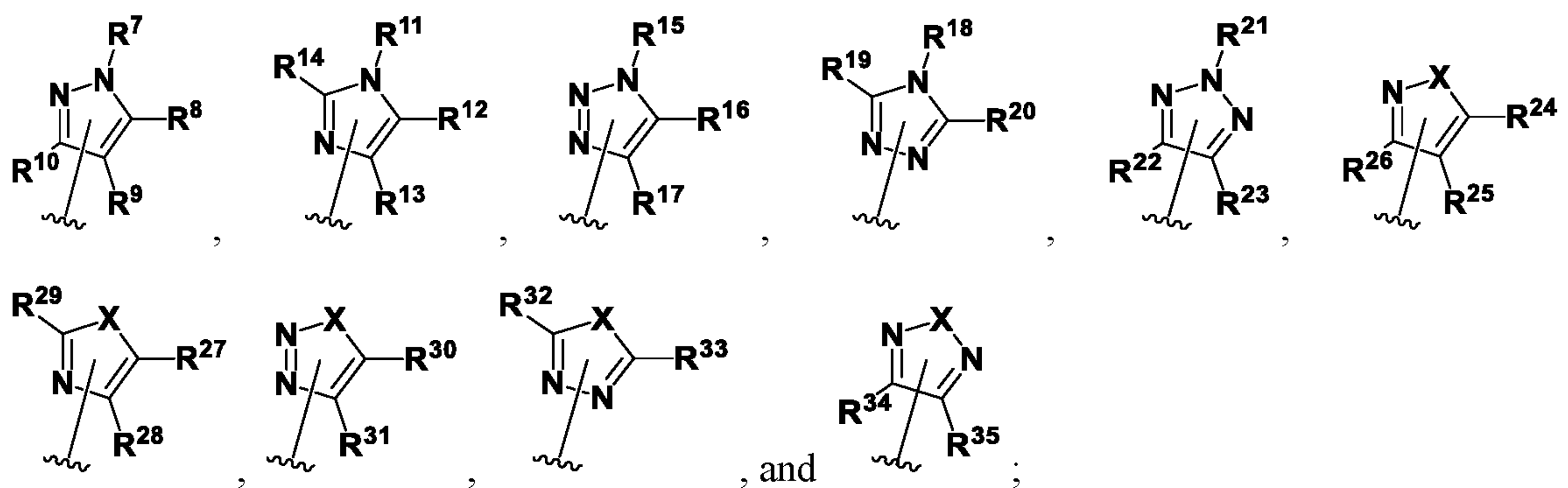
11. A compound, or a pharmaceutically acceptable salt thereof, of Formula I:



wherein:

R^1 , R^2 , R^4 , and R^5 are independently selected from the group consisting of H, halide, 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; so 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 nitrogen atom to which R^{18} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{18} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{19} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{19} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{20} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{20} is a single bond connecting R^3 to the isoquinoline ring;

when the nitrogen atom to which R^{21} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{21} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{22} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{22} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{23} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{23} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{24} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{24} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{25} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{25} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{26} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{26} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{27} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{27} is a single bond connecting R^3 to the isoquinoline ring;

when the carbon atom to which R^{28} is attached serves as the point of attachment of R^3 to the isoquinoline ring, then R^{28} 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 $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{36} , $-(C_{1-4} \text{ alkylene})_p$ carbocyclyl optionally substituted with 1-12 R^{37} , $-(C_{1-4} \text{ alkylene})N(R^{46})(R^{47})$, $-N(R^{48})(R^{49})$, $-CF(C_{1-9} \text{ alkyl})_2$, $-(C_{1-4} \text{ alkylene})_pO(C_{3-9} \text{ alkyl})$, and $-(C_{2-9} \text{ alkynyl})$ optionally substituted with one or more halides; wherein each alkyl of $-CF(C_{1-9} \text{ alkyl})_2$ is, independently, optionally substituted with one or more halides; wherein each $-(C_{1-4} \text{ alkylene})$ is, independently, optionally substituted with one or more substituents as defined anywhere herein;

with the proviso that R^6 is not unsubstituted $-(CH_2)$ tetrahydropyranyl;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, one of R^{11} and R^{12} , R^{12} and R^{13} , or R^{14} and R^{11} 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^{15} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

R^{16} and R^{17} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, one of R^{15} and R^{16} or R^{16} and R^{17} 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^{18} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

R^{19} and R^{20} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, one of R^{18} and R^{19} or R^{18} and R^{20} are taken together to form a heterocyclyl optionally substituted with 1-10 R^{40} ;

R^{21} 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 $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})OR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and –carbocyclyl optionally substituted with 1-12 R^{39} ; wherein $-(C_{1-4} \text{ alkylene})$ is, optionally substituted with one or more substituents as defined anywhere herein;

R^{22} and R^{23} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, R^{22} and R^{23} 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^{24} , R^{25} , and R^{26} 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 $-(C_{1-9} \text{ haloalkyl})$, $-N(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_pOR^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

with the proviso that when R^{25} is a single bond connecting R^3 to the isoquinoline ring, R^{24} and R^{26} are not methyls;

alternatively, one of R^{24} and R^{25} or R^{25} and R^{26} 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^{27} , R^{28} , and R^{29} 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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_p\text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, R^{27} and R^{28} 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^{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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_p\text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

alternatively, R^{30} and R^{31} 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^{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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_p\text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

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 $-(C_{1-9} \text{ haloalkyl})$, $-\text{N}(R^{53})_2$, $-(C_{1-4} \text{ alkylene})_p\text{OR}^{42}$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$

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, 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), –(C₁₋₄ alkylene)_pOR⁴², –(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with 1-10 R⁴³, –(C₁₋₄ alkylene)_pcarbocyclyl optionally substituted with 1-12 R⁴⁴, –C(=O)(R⁵⁰), –(C₁₋₄ alkylene)C(=O)OR⁵¹, –(C₁₋₄ alkylene)aryl optionally substituted with one or more halides, –(C₁₋₄ alkylene)_pheteroaryl optionally substituted with one or more halides, and –SO₂(R⁵²); wherein each –(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

alternatively, two R³⁶ attached to the same carbon atom can together represent =O to form a carbonyl group;

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), –(C₁₋₄ alkylene)_pOR⁴², –N(R⁵³)₂, –C(=O)(R⁵⁰), –C(=O)OR⁵¹, –(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 R³⁸ independently is 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 one or more substituents as defined anywhere herein;

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 one or more substituents as defined anywhere herein;

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 $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$ 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^{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 –CN;

each R^{42} is independently selected from the group consisting of unsubstituted $-(C_{1-5} \text{ alkyl})$, unsubstituted $-(C_{2-5} \text{ alkenyl})$, unsubstituted $-(C_{2-5} \text{ alkynyl})$, unsubstituted $-(C_{1-5} \text{ haloalkyl})$, 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^{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 $-(C_{1-5} \text{ haloalkyl})$, –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 one or more substituents as defined anywhere herein;

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 –CN;

R^{46} is attached to the nitrogen and is selected from the group consisting of H, unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

R^{47} is attached to the nitrogen and is selected from the group consisting of unsubstituted $-(C_{1-9} \text{ alkyl})$, unsubstituted $-(C_{2-9} \text{ alkenyl})$, unsubstituted $-(C_{2-9} \text{ alkynyl})$, unsubstituted $-(C_{1-9} \text{ haloalkyl})$, $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ 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 one or more substituents as defined anywhere herein;

R^{48} is attached to the nitrogen and 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 $-(C_{1-5} \text{ haloalkyl})$;

R^{49} is attached to the nitrogen and is selected from the group consisting of $-(C_{1-4} \text{ alkylene})_p\text{heterocyclyl}$ optionally substituted with 1-10 R^{38} , and $-(C_{1-4} \text{ alkylene})_p\text{carbocyclyl}$

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

R⁵⁰ is selected from the group consisting of H, unsubstituted -(C₃₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -(C₁₋₄ alkylene)_paryl optionally substituted with one or more halides or unsubstituted -(C₁₋₅ alkyl), -(C₁₋₄ alkylene)_pheteroaryl optionally substituted with one or more halides or unsubstituted -(C₁₋₅ alkyl), and -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with one or more halides or one or more unsubstituted -(C₁₋₅ alkyl); wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

R⁵¹ is 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)_paryl optionally substituted with one or more halides or unsubstituted -(C₁₋₅ alkyl), -(C₁₋₄ alkylene)_pheteroaryl optionally substituted with one or more halides or unsubstituted -(C₁₋₅ alkyl), and -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with one or more halides or one or more unsubstituted -(C₁₋₅ alkyl); wherein each -(C₁₋₄ alkylene) is, independently, optionally substituted with one or more substituents as defined anywhere herein;

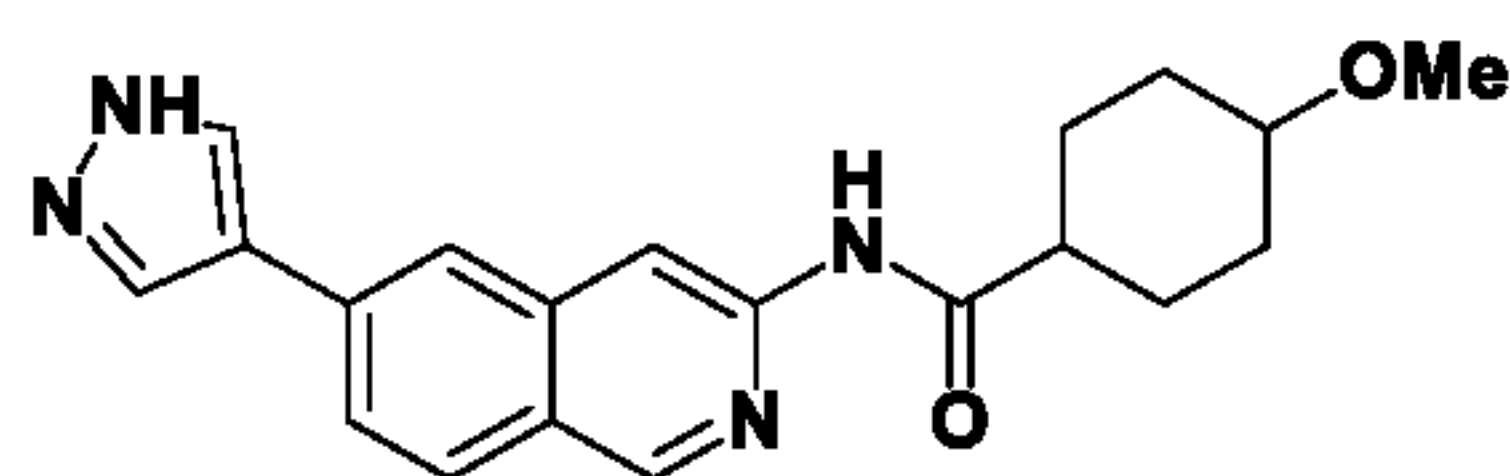
R⁵² is selected from the group consisting of unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), unsubstituted -(C₂₋₅ alkynyl), unsubstituted -(C₁₋₅ haloalkyl), -(C₁₋₄ alkylene)_paryl optionally substituted with one or more halides or unsubstituted -(C₁₋₅ alkyl), -(C₁₋₄ alkylene)_pheteroaryl optionally substituted with one or more halides or unsubstituted -(C₁₋₅ alkyl), and -(C₁₋₄ alkylene)_pheterocyclyl optionally substituted with one or more halides or one or more unsubstituted -(C₁₋₅ alkyl); wherein -(C₁₋₄ alkylene) is, optionally substituted with one or more substituents as defined anywhere herein;

each R⁵³ is independently selected from the group consisting of H, unsubstituted -(C₁₋₅ alkyl), unsubstituted -(C₂₋₅ alkenyl), and unsubstituted -(C₂₋₅ alkynyl);

each X is O or S; and

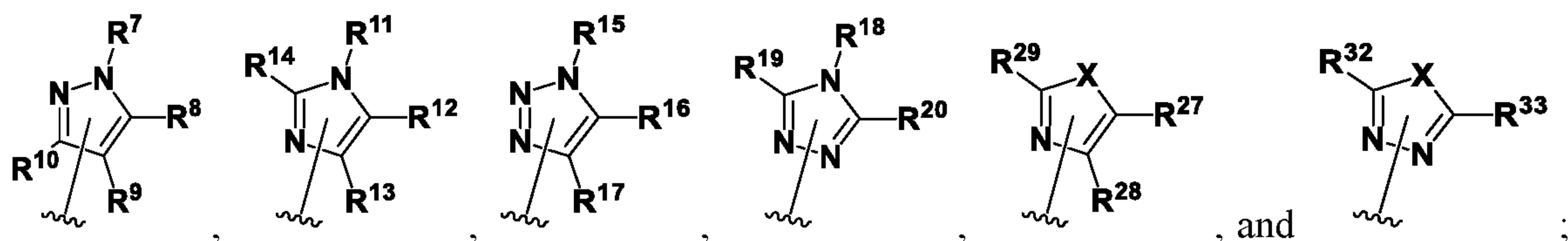
each p is independently 0 or 1; and

with the proviso that Formula I is not a structure selected from the group consisting of:



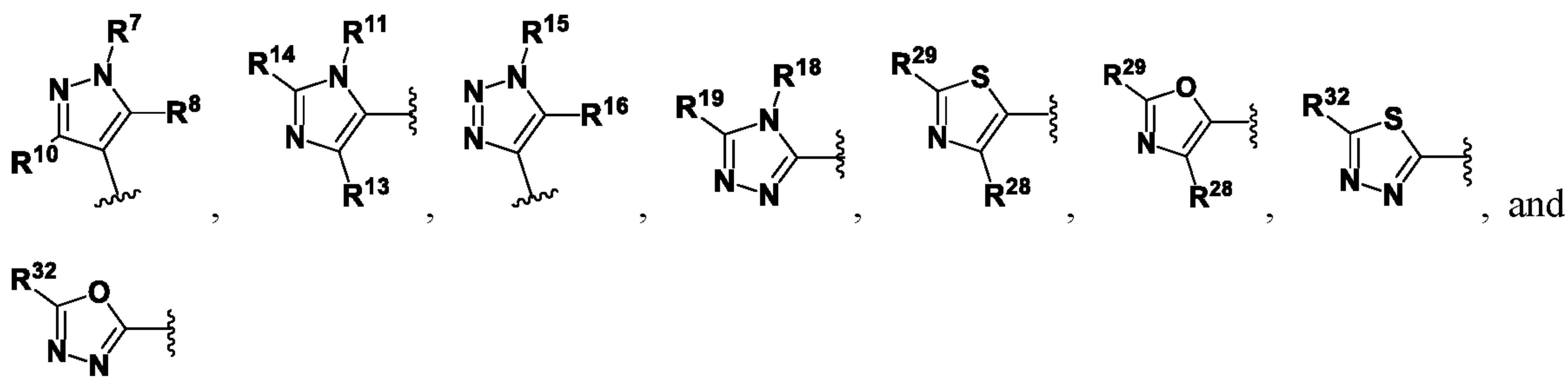
12. The compound of claim 11, wherein R¹, R², R⁴, and R⁵ are H.

13. The compound according to any one of claims 11-12, wherein R³ is selected from the group consisting of:

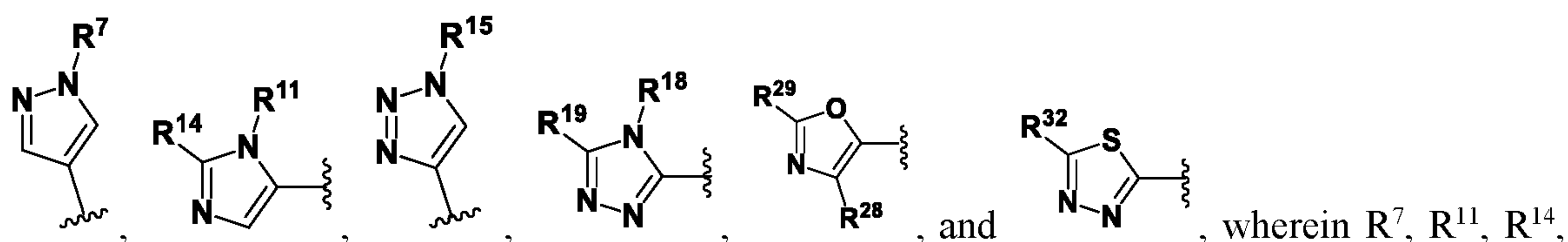


and X is O or S.

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:



wherein R^7 , R^{11} , R^{14} , R^{15} , R^{18} , R^{19} , R^{28} , R^{29} , and R^{32} 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 R^6 is a $-(C_{1-4} \text{ alkylene})_p$ heterocyclyl optionally substituted with 1-10 R^{36} .

17. The compound according to any one of claims 1-16, wherein R^6 is a $-$ heterocyclyl optionally substituted with 1-2 R^{36} .

18. The compound according to any one of claims 1-16, wherein R^6 is a $-CH_2$ heterocyclyl optionally substituted with 1-2 R^{36} .

19. The compound according to any one of claims 1-17, wherein R^6 is either a piperidinyl or a pyrrolidinyl both optionally substituted with 1-2 R^{36} .

20. The compound according to any one of claims 1-17 and 19, wherein R^6 is a piperidinyl substituted with one $-(C_{1-5} \text{ alkyl})$.

21. The compound according to any one of claims 1-17 and 19, wherein R^6 is a piperidinyl substituted with one $-(C_{1-3} \text{ haloalkyl})$.

22. The compound according to any one of claims 1-16, wherein R⁶ is either a –CH₂piperidinyl or a –CH₂pyrrolidinyl optionally substituted with 1-2 R³⁶.

23. The compound according to any one of claims 1-16, and 22, wherein R⁶ is a –CH₂piperidinyl substituted with one –(C₁₋₅ alkyl).

24. The compound according to any one of claims 1-16, and 22, wherein R⁶ is a –CH₂piperidinyl substituted with one –(C₁₋₃ haloalkyl).

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

N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclopropanecarboxamide [1];

N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexanecarboxamide [2];

4,4-Difluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [3];

trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [6];

cis-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [7];

trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(4-methylpiperazin-1-yl)cyclohexane-1-carboxamide [8];

cis-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(4-methylpiperazin-1-yl)cyclohexane-1-carboxamide [9];

trans-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [10];

cis-4-((3-Fluoroazetidin-1-yl)methyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [11];

trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(morpholinomethyl)cyclohexane-1-carboxamide [12];

cis-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(morpholinomethyl)cyclohexane-1-carboxamide [13];

trans-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [14];

cis-N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [15];

N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [16];

1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [17];

1-Ethyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [18];

1-Isopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [19];

1-Cyclopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [20];

1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [21];

N-(6-(1-Methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylazetidine-3-carboxamide [22];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)azetidine-3-carboxamide [23];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)azetidine-3-carboxamide [24];

1-(2-fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [25];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)azetidine-3-carboxamide [26];

1-(2,2-difluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [27];

1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [28];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)azetidine-3-carboxamide [29];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)azetidine-3-carboxamide [30];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)azetidine-3-carboxamide [31];

1-(2-methoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [32];

1-(2-isopropoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [33];

3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [34];

3-fluoro-1-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [35];

1-ethyl-3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [36];

3-fluoro-1-isopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [37];

1-cyclopropyl-3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [38];

3-fluoro-1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [39];

3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylazetidine-3-carboxamide [40];

3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)azetidine-3-carboxamide [41];

3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl) azetidine-3-carboxamide [42];

3-fluoro-1-(2-fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [43];

1-(2,2-difluoroethyl)-3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [44];

3-fluoro-1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [45];

3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)azetidine-3-carboxamide [46];

3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)azetidine-3-carboxamide [47];

3-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)azetidine-3-carboxamide [48];

3-fluoro-1-(2-methoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [49];

3-fluoro-1-(2-isopropoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [50];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [51];

1-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [52];

1-ethyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [53];

1-isopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [54];

1-cyclopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [55];

1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [56];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylpyrrolidine-3-carboxamide [57];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)pyrrolidine-3-carboxamide [58];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)pyrrolidine-3-carboxamide [59];
 1-(2-fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [60];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carboxamide [61];
 1-(2,2-difluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [62];
 1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [63];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)pyrrolidine-3-carboxamide [64];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)pyrrolidine-3-carboxamide [65];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)pyrrolidine-3-carboxamide [66];
 1-(2-methoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [67];
 1-(2-isopropoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [68];
 (S)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [69];
 (R)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [70];
 (S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [71];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [72];
 1-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [73];
 1-ethyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [74];
 1-isopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [75];
 1-cyclopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [76];
 1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [77];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [78];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)piperidine-4-carboxamide [79];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [80];

- 1-(2-fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [81];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [82];
- 1-(2,2-difluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [83];
- 1-(2,2-difluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [84];
- 1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [85];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [86];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide [87];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)piperidine-4-carboxamide [88];
- 1-(2-methoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [89];
- 1-(2-isopropoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [90];
- 4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [91];
- 4-fluoro-1-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [92];
- 1-ethyl-4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [93];
- 4-fluoro-1-isopropyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [94];
- 1-cyclopropyl-4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [95];
- 4-fluoro-1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [96];
- 4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [97];
- 4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)piperidine-4-carboxamide [98];

4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl) piperidine-4-carboxamide [99]; and 4-fluoro-1-(2-fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [100]; or a pharmaceutically acceptable salt thereof.

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

- 4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [101];
- 1-(2,2-difluoropropyl)-4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [102];
- 1-(2,2-difluoroethyl)-4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [103];
- 4-fluoro-1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [104];
- 4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [105];
- 4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide [106];
- 4-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)piperidine-4-carboxamide [107];
- 4-fluoro-1-(2-methoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [108];
- 4-fluoro-1-(2-isopropoxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [109];
- (S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [110];
- (R)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [111];
- (S)-1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [112];
- (R)-1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [113];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [115];
- 2-(4-fluoropiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [116];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide [117];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [118];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide [119];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexanecarboxamide [120];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4,4-difluorocyclohexane-1-carboxamide [121];

trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-methoxycyclohexane-1-carboxamide [122];

cis-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-methoxycyclohexane-1-carboxamide [123];

trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [124];

cis-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [125];

trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-(4-methylpiperazin-1-yl)cyclohexane-1-carboxamide [126];

cis-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-(4-methylpiperazin-1-yl)cyclohexane-1-carboxamide [127];

trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-((3-fluoroazetidin-1-yl)methyl)cyclohexane-1-carboxamide [128];

cis-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-((3-fluoroazetidin-1-yl)methyl)cyclohexane-1-carboxamide [129];

trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-(morpholinomethyl)cyclohexane-1-carboxamide [130];

cis-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-(morpholinomethyl)cyclohexane-1-carboxamide [131];

trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [132];

cis-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [133];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide [134];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-methylazetidine-3-carboxamide [135];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-ethylazetidine-3-carboxamide [136];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isopropylazetidine-3-carboxamide [137];

1-cyclopropyl-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide [138];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isobutylazetidine-3-carboxamide [139];

- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-neopentylazetidine-3-carboxamide [140];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)azetidine-3-carboxamide [141];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl) azetidine-3-carboxamide [142];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)azetidine-3-carboxamide [143];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)azetidine-3-carboxamide [144];
- 1-(2,2-difluoroethyl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide [145];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoro-2-methylpropyl)azetidine-3-carboxamide [146];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)azetidine-3-carboxamide [147];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)azetidine-3-carboxamide [148];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)azetidine-3-carboxamide [149];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-methoxyethyl)azetidine-3-carboxamide [150];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-isopropoxyethyl)azetidine-3-carboxamide [151];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoroazetidine-3-carboxamide [152];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-methylazetidine-3-carboxamide [153];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-ethyl-3-fluoroazetidine-3-carboxamide [154];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-isopropylazetidine-3-carboxamide [155];
- 1-cyclopropyl-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoroazetidine-3-carboxamide [156];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-isobutylazetidine-3-carboxamide [157];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-neopentylazetidine-3-carboxamide [158];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-((1-methylcyclopropyl)methyl) azetidine-3-carboxamide [159];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-((1-(trifluoromethyl)cyclopropyl) methyl)azetidine-3-carboxamide [160];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-(2-fluoroethyl)azetidine-3-carboxamide [161];

1-(2,2-difluoroethyl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoroazetidine-3-carboxamide [162];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-(2-fluoro-2-methylpropyl)azetidine-3-carboxamide [163];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-(oxetan-3-yl)azetidine-3-carboxamide [164];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-((3-methyloxetan-3-yl)methyl) azetidine-3-carboxamide [165];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-(oxetan-2-ylmethyl)azetidine-3-carboxamide [166];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-(2-methoxyethyl)azetidine-3-carboxamide [167];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3-fluoro-1-(2-isopropoxyethyl)azetidine-3-carboxamide [168];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [169];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-methylpyrrolidine-3-carboxamide [170];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-ethylpyrrolidine-3-carboxamide [171];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isopropylpyrrolidine-3-carboxamide [172];

1-cyclopropyl-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [173];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isobutylpyrrolidine-3-carboxamide [174];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-neopentylpyrrolidine-3-carboxamide [175];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)pyrrolidine-3-carboxamide [176];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)pyrrolidine-3-carboxamide [177];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)pyrrolidine-3-carboxamide [178];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carboxamide [179];

1-(2,2-difluoroethyl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [180];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoro-2-methylpropyl)pyrrolidine-3-carboxamide [181];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)pyrrolidine-3-carboxamide [182];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)pyrrolidine-3-carboxamide [183];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)pyrrolidine-3-carboxamide [184];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-methoxyethyl)pyrrolidine-3-carboxamide [185];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-isopropoxyethyl)pyrrolidine-3-carboxamide [186];

(R)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [187];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [188];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [189];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide [190];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-ethylpiperidine-4-carboxamide [191];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isopropylpiperidine-4-carboxamide [192];

1-cyclopropyl-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [193];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide [194];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [195];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((1-methylcyclopropyl)methyl)piperidine-4-carboxamide [196];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [197];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)piperidine-4-carboxamide [198];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [199]; and

1-(2,2-difluoropropyl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [200]; or a pharmaceutically acceptable salt thereof.

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

1-(2,2-difluoroethyl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [201];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoro-2-methylpropyl)piperidine-4-carboxamide [202];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [203];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide [204];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxetan-2-ylmethyl)piperidine-4-carboxamide [205];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-methoxyethyl)piperidine-4-carboxamide [206];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-isopropoxyethyl)piperidine-4-carboxamide [207];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoropiperidine-4-carboxamide [208];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-methylpiperidine-4-carboxamide [209];

- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-ethyl-4-fluoropiperidine-4-carboxamide [210];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-isopropylpiperidine-4-carboxamide [211];
- 1-cyclopropyl-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoropiperidine-4-carboxamide [212];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide [213];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-neopentylpiperidine-4-carboxamide [214];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-((1-methylcyclopropyl)methyl) piperidine-4-carboxamide [215];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-((1-(trifluoromethyl)cyclopropyl) methyl)piperidine-4-carboxamide [216];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-(2-fluoroethyl)piperidine-4-carboxamide [217];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [218];
- 1-(2,2-difluoropropyl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoropiperidine-4-carboxamide [219];
- 1-(2,2-difluoroethyl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoropiperidine-4-carboxamide [220];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-(2-fluoro-2-methylpropyl)piperidine-4-carboxamide [221];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxamide [222];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-((3-methyloxetan-3-yl)methyl) piperidine-4-carboxamide [223];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-(oxetan-2-ylmethyl)piperidine-4-carboxamide [224];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-(2-methoxyethyl)piperidine-4-carboxamide [225];
- N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-fluoro-1-(2-isopropoxyethyl)piperidine-4-carboxamide [226];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [227];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [228];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-fluoropiperidin-1-yl)acetamide [229];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide [230];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide [231];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)cyclohexanecarboxamide [232];

4,4-difluoro-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [233];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide [234];

1-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide [235];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [236];

1-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [237];

1-(2-fluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)pyrrolidine-3-carboxamide [238];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)pyrrolidine-3-carboxamide [239];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [240];

1-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [241];

1-ethyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [242];

1-isopropyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [243];

1-cyclopropyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [244];

1-isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [245];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [246];

1-(2-fluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [247];

N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [248];
 1-(2,2-difluoropropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [249];
 1-(2,2-difluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [250];
 1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [251];
 4-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [252];
 4-fluoro-1-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [253];
 4-fluoro-1-(2-fluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [254];
 4-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [255];
 1-(2,2-difluoropropyl)-4-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [256];
 1-(2,2-difluoroethyl)-4-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [257];
 4-fluoro-1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [258];
 N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [259];
 2-(4-fluoropiperidin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)acetamide [260];
 N-(6-(1-methyl-1H-1,2,3-triazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide [261];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [262];
 4,4-difluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [263];
 1-methyl-N-(6-(1-methyl-1H-pyrazol-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide [264];
 N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)cyclopropanecarboxamide [265];

N-(6-(7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)cyclopropanecarboxamide [266];
 3,3-difluoro-N-(6-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [267];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-3,3-difluorocyclobutane-1-carboxamide [268];
 2,2,3,3-tetramethyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [269];
 N-(6-(1-methyl-1H-pyrazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [270];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [271];
 2-(4-isobutylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [272];
 2-(3,3-dimethylazetidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [273];
 (R)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [274];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [275];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [276];
 2,2,3,3-tetramethyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [277];
 N-(6-(4-methyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [278];
 N-(6-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [279];
 4-fluoro-1-isobutyl-N-(6-(4-methyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide [280];
 4-fluoro-1-isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [281];
 1-ethyl-4-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [282];
 4,4-difluoro-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [283];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [284];
 N-(6-(1-ethyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [285];

N-(6-(1-cyclopropyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [286];
 2-(pyrrolidin-1-yl)-N-(6-(5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [287];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [288];
 (R)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide
 [289];
 (S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide
 [290];
 2-(3-azabicyclo[3.1.0]hexan-3-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide
 [291];
 2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide
 [292];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide [293];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)acetamide
 [294];
 2-(4-(difluoromethyl)piperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide
 [295];
 N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide [296];
 N-(6-(1-cyclopropyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-
 carboxamide [297];
 N-(6-(5-(azetidin-1-ylmethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4,4-
 difluorocyclohexane-1-carboxamide [298];
 4,4-difluoro-N-(6-(1-methyl-5-(pyrrolidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-
 yl)cyclohexane-1-carboxamide [299]; and
 4,4-difluoro-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-
 yl)cyclohexane-1-carboxamide [300]; or a pharmaceutically acceptable salt thereof.

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

7-(2-fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-
 carboxamide [301];
 2-(cyclobutyl(methyl)amino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [302];
 2-(diethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [303];
 N-(6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-
 carboxamide [304];
 N-(6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [305];

N-(6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [306];

N-(6-(3-methylisoxazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [307];

N-(6-(oxazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [308];

4-fluoro-1-isobutyl-N-(6-(5-methyl-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [309];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [310];

(S)-1-(2-fluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [311];

2-fluoro-2-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)propanamide [312];

(R)-1-(2-fluoropropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [313];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)propanamide [314];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl-2,2,5,5-*d*4)acetamide [315];

4-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperazine-1-carboxamide [316];

(S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [317];

(R)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [318];

2-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [319];

(R)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [320];

2-fluoro-2-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)propanamide [321];

1-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [322];

3,3-difluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [323];

2-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [324];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide [325];

2-(2-fluoroethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [326];

trans-4-(dimethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [327];

1-benzoyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [328];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide [330];

1'-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide [331];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide [332];

trans-4-(hydroxymethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [333];

methyl 2-(4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate [334];

1-benzyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [335];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide [336];

1-fluoro-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [337];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinoacetamide [338];

trans-4-formyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [339];

(S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-2-carboxamide [340];

(S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [341];

(R)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [342];

(S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide [343];

2-((2R,6S)-2,6-dimethylmorpholino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [344];

2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [345];

2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [346];

2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [347];

(S)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinopropanamide [348];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide [349];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide [350];

2-(4-ethylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [351];

2-(4-isopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [352];

- 2-(4-cyclopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [353];
- 2-(4-(2-fluoroethyl)piperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [354];
- (S)-2-(2,4-dimethylpiperazin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [355];
- 7-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide [356];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [357];
- 1-(2-hydroxyethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [358];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide [359];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl)piperidine-4-carboxamide [360];
- 2-(3,3-dimethylazetidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [361];
- (R)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-oxotetrahydro-1H-pyrrolo[1,2-c]imidazole-2(3H)-carboxamide [362];
- (R)-1-methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [363];
- N-(4-chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclopropanecarboxamide [364];
- trans*-4-amino-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [365];
- N-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [366];
- N-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide [367];
- N-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)piperidine-4-carboxamide [368];
- N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [369];
- N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide [370];
- N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)piperidine-4-carboxamide [371];
- N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [372];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-fluoro-2-methylpropanamide [373];
 2-(diethylamino)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [374];
 2-(cyclobutyl(methyl)amino)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide
 [375];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-fluorocyclopropane-1-carboxamide
 [376];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-methyl-2-azaspiro[3.3]heptane-6-
 carboxamide [377];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2-fluoroethyl)-2-azaspiro[3.3]heptane-
 6-carboxamide [378];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-
 azaspiro[3.3]heptane-6-carboxamide [379];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-7-methyl-7-azaspiro[3.5]nonane-2-
 carboxamide [380];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-fluorocyclohexane-1-carboxamide
 [381];
trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-(dimethylamino)cyclohexane-1-
 carboxamide [382];
trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-formylcyclohexane-1-
 carboxamide [383];
trans-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-(hydroxymethyl)cyclohexane-1-
 carboxamide [384];
 (R)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [385];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [386];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-hydroxyethyl)piperidine-4-
 carboxamide [387];
 methyl 2-(4-((6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-
 yl)acetate [388];
 (R)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoropropyl)piperidine-4-
 carboxamide [389];
 (S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-fluoropropyl)piperidine-4-
 carboxamide [390];
 N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-
 carboxamide [391];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide [392];

1-benzoyl-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [393];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1'-methyl-[1,4'-bipiperidine]-4-carboxamide [394];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide [395];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl)piperidine-4-carboxamide [396];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide [397];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [398];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isobutylpiperidine-3-carboxamide [399]; and

(R)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-isobutylpiperidine-3-carboxamide [400]; or a pharmaceutically acceptable salt thereof.

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

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-methylpiperazine-1-carboxamide [401];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(3,3-dimethylazetidin-1-yl)acetamide [402];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [403];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(3-fluoropyrrolidin-1-yl)acetamide [404];

(R)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(3-fluoropyrrolidin-1-yl)acetamide [405];

(R)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [406];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [407];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [408];

2-(3-azabicyclo[3.1.0]hexan-3-yl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [409];

2-(4-(difluoromethyl)piperidin-1-yl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [410];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)acetamide [411];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide [412];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)propanamide [413];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [414];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-ethylpiperazin-1-yl)acetamide [415];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-(2-fluoroethyl)piperazin-1-yl)acetamide [416];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2,4-dimethylpiperazin-1-yl)acetamide [417];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-isopropylpiperazin-1-yl)acetamide [418];

2-(4-cyclopropylpiperazin-1-yl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [419];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide [420];

(R)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [421];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [422];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide [423];

(S)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-morpholinopropanamide [424];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide [425];

N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide [426];

2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [427];

2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [428];

2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [429];

2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(1,2-dimethyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [430];

2-(diethylamino)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [431];

2-(cyclobutyl(methyl)amino)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [432];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclopropanecarboxamide [433];

1-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [434];

3,3-difluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [435];

2-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [436];

2-(2-fluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [437];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide [438];

7-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide [439];

1-fluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [440];

4,4-difluoro-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [441];

trans-4-methoxy-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [442];

trans-4-(dimethylamino)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [443];

trans-4-formyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [444];

trans-4-(hydroxymethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [445];

trans-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [446];

trans-4-((3-fluoroazetidin-1-yl)methyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [447];

trans-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [448];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [449];

(R)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [450];

(R)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [451];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [452];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [453];

1-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [454];

4-fluoro-1-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [455];

1-(2-fluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [456];

4-fluoro-1-(2-fluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [457];

1-(2,2-difluoroethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [458];

1-(2-hydroxyethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [459];

1-(2-methoxyethyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [460];

methyl 2-(4-((6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate [461];

1-isopropyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [462];

1-cyclopropyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [463];

(R)-1-(2-fluoropropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [464];

(S)-1-(2-fluoropropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [465];

1-(2,2-difluoropropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [466];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [467];

1-isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [468];

1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [469];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [470];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [471];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide [472];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [473];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide [474];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide [475];

1-benzoyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [476];

1'-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide [477];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide [478];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl)piperidine-4-carboxamide [479];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide [480];

(R)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [481];

1-isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [482];

(R)-1-isobutyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [483];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [484];

4-methyl-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperazine-1-carboxamide [485];
 2-(3,3-dimethylazetidin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide
 [486];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [487];
 (S)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide
 [488];
 (R)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide
 [489];
 (R)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide
 [490];
 (S)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide
 [491];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [492];
 2-(3-azabicyclo[3.1.0]hexan-3-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [493];
 2-(4-fluoropiperidin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide
 [494];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide
 [495];
 2-(4-(difluoromethyl)piperidin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [496];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)acetamide [497];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide
 [498];
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)propanamide [499]; and
 N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide
 [500]; or a pharmaceutically acceptable salt thereof.

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

2-(4-ethylpiperazin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [501];
 2-(4-(2-fluoroethyl)piperazin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [502];

(S)-2-(2,4-dimethylpiperazin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [503];

2-(4-isopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [504];

2-(4-cyclopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [505];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-morpholinoacetamide [506];

(R)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [507];

(S)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [508];

(S)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide [509];

(S)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-morpholinopropanamide [510];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide [511];

N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide [512];

2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [513];

2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [514];

2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [515];

2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)acetamide [516];

2-fluoro-2-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)propanamide [517];

2-(diethylamino)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [518];

2-(cyclobutyl(methyl)amino)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [519];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide [520];

1-fluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [521];

3,3-difluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [522];

2-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [523];

2-(2-fluoroethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [524];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide [525];

7-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide [526];

1-fluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [527];

trans-4-methoxy-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [528];

trans-4-(dimethylamino)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [529];

trans-4-formyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [530];

trans-4-(hydroxymethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [531];

trans-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [532];

trans-4-((3-fluoroazetidin-1-yl)methyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [533];

trans-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [534];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide [535];

(R)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [536];

(R)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [537];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [538];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [539];

1-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [540];

4-fluoro-1-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [541];

1-ethyl-4-fluoro-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [542];

- 1-(2-fluoroethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [543];
- 4-fluoro-1-(2-fluoroethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [544];
- 1-(2,2-difluoroethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [545];
- 1-(2-hydroxyethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [546];
- 1-(2-methoxyethyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [547];
- methyl 2-(4-((6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate [548];
- 1-isopropyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [549];
- 1-cyclopropyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [550];
- (R)-1-(2-fluoropropyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [551];
- (S)-1-(2-fluoropropyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [552];
- 1-(2,2-difluoropropyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [553];
- 1-isobutyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [554];
- 4-fluoro-1-isobutyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [555];
- 1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [556];
- N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [557];
- N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [558];
- N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide [559];
- N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [560];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide [561];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide [562];

1-benzoyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [563];

1'-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide [564];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide [565];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl)piperidine-4-carboxamide [566];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide [567];

(S)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [568];

1-isobutyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [569];

(R)-1-isobutyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [570];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [571];

4-methyl-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)piperazine-1-carboxamide [572];

2-(3,3-dimethylazetidin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [573];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [574];

(S)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [575];

(R)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [576];

(R)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [577];

(S)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [578];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [579];

2-(3-azabicyclo[3.1.0]hexan-3-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [580];

2-(4-fluoropiperidin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [581];

N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide [582];
 2-(4-(difluoromethyl)piperidin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [583];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)acetamide [584];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide [585];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)propanamide [586];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [587];
 2-(4-ethylpiperazin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [588];
 2-(4-(2-fluoroethyl)piperazin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [589];
 (S)-2-(2,4-dimethylpiperazin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [590];
 2-(4-isopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [591];
 2-(4-cyclopropylpiperazin-1-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [592];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide [593];
 (R)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [594];
 (S)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [595];
 (S)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide [596];
 (S)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-morpholinopropanamide [597];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide [598];
 N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide [599];
 and
 2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [600]; or a pharmaceutically acceptable salt thereof.

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

2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl) acetamide [601];
 2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl) acetamide [602];

2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [603];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-fluoro-2-methylpropanamide [604];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(diethylamino)acetamide [605];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(cyclobutyl(methyl)amino)acetamide [606];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)cyclopropanecarboxamide [607];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-fluorocyclopropane-1-carboxamide [608];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-3,3-difluorocyclobutane-1-carboxamide [609];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-methyl-2-azaspiro[3.3]heptane-6-carboxamide [610];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-fluoroethyl)-2-azaspiro[3.3]heptane-6-carboxamide [611];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide [612];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-7-methyl-7-azaspiro[3.5]nonane-2-carboxamide [613];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-fluorocyclohexane-1-carboxamide [614];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4,4-difluorocyclohexane-1-carboxamide [615];

trans-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(dimethylamino)cyclohexane-1-carboxamide [617];

trans-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-formylcyclohexane-1-carboxamide [618];

trans-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(hydroxymethyl)cyclohexane-1-carboxamide [619];

trans-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [620];

trans-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-((3-fluoroazetidin-1-yl)methyl)cyclohexane-1-carboxamide [621];

trans-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [622];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [623];

(R)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [624];

(R)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [625];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [626];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [627];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide [628];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-fluoro-1-methylpiperidine-4-carboxamide [629];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-ethyl-4-fluoropiperidine-4-carboxamide [630];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoroethyl)piperidine-4-carboxamide [631];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-fluoro-1-(2-fluoroethyl)piperidine-4-carboxamide [632];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2,2-difluoroethyl)piperidine-4-carboxamide [633];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-hydroxyethyl)piperidine-4-carboxamide [634];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-methoxyethyl)piperidine-4-carboxamide [635];
 methyl 2-(4-((6-(1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate [636];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isopropylpiperidine-4-carboxamide [637];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-cyclopropylpiperidine-4-carboxamide [638];
 (R)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoropropyl)piperidine-4-carboxamide [639];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoropropyl)piperidine-4-carboxamide [640];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2,2-difluoropropyl)piperidine-4-carboxamide [641];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [642];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide [643];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide [644];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-fluoro-2-methylpropyl)piperidine-4-carboxamide [645];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [646];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [647];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide [648];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [649];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide [650];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide [651];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-benzoylpiperidine-4-carboxamide [652];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1'-methyl-[1,4'-bipiperidine]-4-carboxamide [653];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide [654];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl)piperidine-4-carboxamide [655];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide [656];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [657];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-3-carboxamide [658];
 (R)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-1-isobutylpiperidine-3-carboxamide [659];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-4-methylpiperazine-1-carboxamide [661];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3,3-dimethylazetidin-1-yl)acetamide [662];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [663];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-fluoropyrrolidin-1-yl)acetamide [664];
 (R)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-fluoropyrrolidin-1-yl)acetamide [665];
 (R)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [666];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [667];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [668];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-azabicyclo[3.1.0]hexan-3-yl)acetamide [669];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [670];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-fluoropiperidin-1-yl)acetamide [671];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide [672];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(difluoromethyl)piperidin-1-yl)acetamide [673];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)acetamide [674];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide [675];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)propanamide [676];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [677];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-ethylpiperazin-1-yl)acetamide [678];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(2-fluoroethyl)piperazin-1-yl)acetamide [679];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2,4-dimethylpiperazin-1-yl)acetamide [680];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-isopropylpiperazin-1-yl)acetamide [681];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-cyclopropylpiperazin-1-yl)acetamide [682];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinoacetamide [683];
 (R)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [684];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide [685];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide [686];
 (S)-N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinopropanamide [687];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide [688];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide [689];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(7-azabicyclo[2.2.1]heptan-7-yl)acetamide [690];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)acetamide [691];

N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)acetamide [692];
 N-(6-(1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)acetamide [693];
 2-fluoro-2-methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)propanamide [694];
 2-(diethylamino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [695];
 2-(cyclobutyl(methyl)amino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [696];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide [697];
 1-fluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [698];
 3,3-difluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [699]; and
 2-methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [700]; or a pharmaceutically acceptable salt thereof.

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

2-(2-fluoroethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [701];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide [702];
 7-methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide [703];
 1-fluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [704];
 4,4-difluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [705];
trans-4-methoxy-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [706];
trans-4-(dimethylamino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [707];
trans-4-formyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [708];
trans-4-(hydroxymethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [709];
trans-4-morpholino-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [710];
trans-4-((3-fluoroazetidin-1-yl)methyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [711];
trans-4-((4-methylpiperazin-1-yl)methyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [712];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)azetidine-3-carboxamide [713];
 (R)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [714];
 (R)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [715];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [716];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [717];

1-methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [718];
 4-fluoro-1-methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [719];
 1-ethyl-4-fluoro-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [720];
 1-(2-fluoroethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [721];
 4-fluoro-1-(2-fluoroethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [722];
 1-(2,2-difluoroethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [723];
 1-(2-hydroxyethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [724];
 1-(2-methoxyethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [725];
 methyl 2-(4-((6-(thiazol-5-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate [726];
 1-isopropyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [727];
 1-cyclopropyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [728];
 (R)-1-(2-fluoropropyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [729];
 (S)-1-(2-fluoropropyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [730];
 1-(2,2-difluoropropyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [731];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [732];
 1-isobutyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [733];
 4-fluoro-1-isobutyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [734];
 1-(2-fluoro-2-methylpropyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [735];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [736];
 1-(oxetan-3-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [737];
 1-((3-methyloxetan-3-yl)methyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [738];
 1-neopentyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [739];
 1-(methylsulfonyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [740];
 1-(2-(pyrrolidin-1-yl)acetyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [741];
 1-benzoyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [742];
 1'-methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide [743];
 1-(tetrahydro-2H-pyran-4-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [744];
 1-(oxazol-2-ylmethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [745];
 1-(pyridin-2-ylmethyl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [746];
 (S)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [747];
 1-isobutyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [748];

(R)-1-isobutyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [749];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [750];
 4-methyl-N-(6-(thiazol-5-yl)isoquinolin-3-yl)piperazine-1-carboxamide [751];
 2-(3,3-dimethylazetidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [752];
 2-(pyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [753];
 (S)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [754];
 (R)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [755];
 (R)-2-(2-methylpyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [756];
 (S)-2-(2-methylpyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [757];
 2-(pyrrolidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)propanamide [758];
 2-(3-azabicyclo[3.1.0]hexan-3-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [759];
 2-(piperidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [760];
 2-(4-fluoropiperidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [761];
 2-(4-methylpiperidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [762];
 2-(4-(difluoromethyl)piperidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [763];
 N-(6-(thiazol-5-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)acetamide [764];
 2-(6-azaspiro[2.5]octan-6-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [765];
 2-(piperidin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)propanamide [766];
 2-(4-methylpiperazin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [767];
 2-(4-ethylpiperazin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [768];
 2-(4-(2-fluoroethyl)piperazin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [769];
 (S)-2-(2,4-dimethylpiperazin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [770];
 2-(4-isopropylpiperazin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [771];
 2-(4-cyclopropylpiperazin-1-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [772];
 2-morpholino-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [773];
 (R)-2-(3-methylmorpholino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [774];
 (S)-2-(3-methylmorpholino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [775];
 (S)-2-(2-methylmorpholino)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [776];
 (S)-2-morpholino-N-(6-(thiazol-5-yl)isoquinolin-3-yl)propanamide [777];
 2-(morpholin-2-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [778];
 2-(4-methylmorpholin-2-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [779];
 2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [780];
 2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide
 [781];

2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [782];

2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(thiazol-5-yl)isoquinolin-3-yl)acetamide [783];

2-fluoro-2-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)propanamide [784];

2-(diethylamino)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [785];

2-(cyclobutyl(methyl)amino)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [786];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclopropanecarboxamide [787];

1-fluoro-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [788];

3,3-difluoro-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [789];

2-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [790];

2-(2-fluoroethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [791];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide [792];

7-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide [793];

1-fluoro-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [794];

trans-4-methoxy-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [795];

trans-4-(dimethylamino)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [796];

trans-4-formyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [797];

trans-4-(hydroxymethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [798];

trans-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [799]; and
trans-4-((3-fluoroazetidin-1-yl)methyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)cyclohexane-1-carboxamide [800]; or a pharmaceutically acceptable salt thereof.

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

trans-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [801];
 N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)azetidine-3-carboxamide [802];
 (R)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [803];
 (R)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [804];
 N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [805];
 N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [806];
 1-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [807];
 4-fluoro-1-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [808];
 1-ethyl-4-fluoro-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [809];
 1-(2-fluoroethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [810];
 4-fluoro-1-(2-fluoroethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [811];
 1-(2,2-difluoroethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [812];
 1-(2-hydroxyethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [813];

1-(2-methoxyethyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [814];

methyl 2-(4-((6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) carbamoyl)piperidin-1-yl)acetate [815];

1-isopropyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [816];

1-cyclopropyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [817];

(R)-1-(2-fluoropropyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [818];

(S)-1-(2-fluoropropyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [819];

1-(2,2-difluoropropyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [820];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [821];

1-isobutyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [822];

4-fluoro-1-isobutyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [823];

1-(2-fluoro-2-methylpropyl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) piperidine-4-carboxamide [824];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl) cyclopropyl)methyl)piperidine-4-carboxamide [825];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [826];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl) methyl)piperidine-4-carboxamide [827];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [828];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide [829];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl) piperidine-4-carboxamide [830];

1-benzoyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [831];

1'-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide [832];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl) piperidine-4-carboxamide [833];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl) piperidine-4-carboxamide [834];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl) piperidine-4-carboxamide [835];

(R)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [836];

1-isobutyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [837];

(R)-1-isobutyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-3-carboxamide [838];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [839];

4-methyl-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperazine-1-carboxamide [840];

2-(3,3-dimethylazetidin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) acetamide [841];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [842];

(S)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [843];

(R)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [844];

(R)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [845];

(S)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [846];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [847];

2-(3-azabicyclo[3.1.0]hexan-3-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [848];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [849];

2-(4-fluoropiperidin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) acetamide [850];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl) acetamide [851];

2-(4-(difluoromethyl)piperidin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [852];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl) piperidin-1-yl)acetamide [853];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl) acetamide [854];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl) propanamide [855];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl) acetamide [856];

2-(4-ethylpiperazin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) acetamide [857];

2-(4-(2-fluoroethyl)piperazin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [858];

(S)-2-(2,4-dimethylpiperazin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [859];

2-(4-isopropylpiperazin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl) acetamide [860];

2-(4-cyclopropylpiperazin-1-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [861];

N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinoacetamide [862];

(R)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino) acetamide [863];

(S)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(3-methylmorpholino) acetamide [864];

- (S)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide [865];
- (S)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-morpholinopropanamide [866];
- N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide [867];
- N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl) acetamide [868];
- 2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [869];
- 2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [870];
- 2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [871];
- 2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(1-methyl-5-(piperidin-1-ylmethyl)-1H-pyrazol-4-yl) isoquinolin-3-yl)acetamide [872];
- 2-fluoro-2-methyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)propanamide [873];
- 2-(diethylamino)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [874];
- 2-(cyclobutyl(methyl)amino)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [875];
- N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclopropanecarboxamide [876];
- 1-fluoro-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclopropane-1-carboxamide [877];
- 3,3-difluoro-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [878];
- 2-methyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [879];
- 2-(2-fluoroethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide [880];
- N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(2,2,2-trifluoroacetyl)-2-azaspiro[3.3]heptane-6-carboxamide [881];
- 7-methyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-7-azaspiro[3.5]nonane-2-carboxamide [882];

1-fluoro-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [883];

4,4-difluoro-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [884];

trans-4-methoxy-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [885];

trans-4-(dimethylamino)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [886];

trans-4-formyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [887];

trans-4-(hydroxymethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [888];

trans-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [889];

trans-4-((3-fluoroazetidin-1-yl)methyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [890];

trans-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-4-((4-methylpiperazin-1-yl)methyl)cyclohexane-1-carboxamide [891];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)azetidine-3-carboxamide [892];

(R)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [893];

(R)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [894];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [895];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [896];

1-methyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [897];

4-fluoro-1-methyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [898];

1-ethyl-4-fluoro-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [899]; and

1-(2-fluoroethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [900]; or a pharmaceutically acceptable salt thereof.

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

4-fluoro-1-(2-fluoroethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [901];

- 1-(2,2-difluoroethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [902];
- 1-(2-hydroxyethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [903];
- 1-(2-methoxyethyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [904];
- methyl 2-(4-((6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate [905];
- 1-isopropyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [906];
- 1-cyclopropyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [907];
- (R)-1-(2-fluoropropyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [908];
- (S)-1-(2-fluoropropyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [909];
- 1-(2,2-difluoropropyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [910];
- N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-(3,3,3-trifluoropropyl)piperidine-4-carboxamide [911];
- 1-isobutyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [912];
- 4-fluoro-1-isobutyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [913];
- 1-(2-fluoro-2-methylpropyl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [914];
- N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [915];
- N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-(oxetan-3-yl)piperidine-4-carboxamide [916];
- N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-((3-methyloxetan-3-yl)methyl)piperidine-4-carboxamide [917];
- N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-neopentylpiperidine-4-carboxamide [918];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-(methylsulfonyl)piperidine-4-carboxamide [919];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide [920];

1-benzoyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [921];

1'-methyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide [922];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide [923];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-(oxazol-2-ylmethyl)piperidine-4-carboxamide [924];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide [925];

(S)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-3-carboxamide [926];

1-isobutyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-3-carboxamide [927];

(R)-1-isobutyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-3-carboxamide [928];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [929];

4-methyl-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperazine-1-carboxamide [930];

2-(3,3-dimethylazetidin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [931];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [932];

(S)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [933];

(R)-2-(3-fluoropyrrolidin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [934];

(R)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [935];

(S)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(2-methylpyrrolidin-1-yl)acetamide [936];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [937];

2-(3-azabicyclo[3.1.0]hexan-3-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [938];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [939];

2-(4-fluoropiperidin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [940];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(4-methylpiperidin-1-yl)acetamide
 [941];
 2-(4-(difluoromethyl)piperidin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)
 acetamide [942];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(4-(trifluoromethyl)piperidin-1-yl)
 acetamide [943];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(6-azaspiro[2.5]octan-6-yl)acetamide
 [944];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)propanamide [945];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide
 [946];
 2-(4-ethylpiperazin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [947];
 2-(4-(2-fluoroethyl)piperazin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)
 acetamide [948];
 (S)-2-(2,4-dimethylpiperazin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)
 acetamide [949];
 2-(4-isopropylpiperazin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide
 [950];
 2-(4-cyclopropylpiperazin-1-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide
 [951];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide [952];
 (R)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide
 [953];
 (S)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(3-methylmorpholino)acetamide
 [954];
 (S)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(2-methylmorpholino)acetamide
 [955];
 (S)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinopropanamide [956];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(morpholin-2-yl)acetamide [957];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(4-methylmorpholin-2-yl)acetamide
 [958];
 2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)
 acetamide [959];

2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [960];

2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [961];

2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [962];

N-(8-fluoro-6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide [963];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(phenylsulfonyl)piperidine-4-carboxamide [964];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-(methyl-*d*3)piperazin-1-yl)acetamide [965];

N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide [966];

1-ethyl-N-(7-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [967];

N-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [968];

N-(6-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexanecarboxamide [969];

N-(6-(isothiazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide [970];

(S)-N-(6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [971];

1-isobutyl-N-(6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [972];

N-(6-(oxazol-5-yl)isoquinolin-3-yl)cyclopropanecarboxamide [973];

(R)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)tetrahydrofuran-2-carboxamide [974];

(R)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)piperidine-3-carboxamide [975];

N-(6-(oxazol-5-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [976];

N-(6-(oxazol-5-yl)isoquinolin-3-yl)-1-(2-(pyrrolidin-1-yl)acetyl)piperidine-4-carboxamide [977];

1'-methyl-N-(6-(oxazol-5-yl)isoquinolin-3-yl)-[1,4'-bipiperidine]-4-carboxamide [978];

cis-4-morpholino-N-(6-(oxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [979];

2-(cyclobutyl(methyl)amino)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide [980];

N-(6-(oxazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [981];

(R)-2-(2-methylpyrrolidin-1-yl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide [982];

2-(4-methylpiperazin-1-yl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)acetamide [983];
 N-(6-(5-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide [984];
 N-(6-(5-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide [985];
 3,3-difluoro-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)cyclobutane-1-carboxamide [986];
 (R)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)pyrrolidine-2-carboxamide [987];
 (R)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-3-carboxamide [988];
 1-methyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide [989];
 N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [990];
 1-benzoyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide [991];
 N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [993];
 N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide [994];
 2-(4-methylpiperazin-1-yl)-N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl)acetamide [995];
 2-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(6-(2-methylthiazol-5-yl)isoquinolin-3-yl)acetamide [996];
 N-(6-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [997];
 N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine-4-carboxamide [998];
 N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide [999]; and
 2-(7-azabicyclo[2.2.1]heptan-7-yl)-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)acetamide [1000]; or a pharmaceutically acceptable salt thereof.

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

cis-4-methoxy-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [1001];

(R)-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-isobutylpiperidine-3-carboxamide [1002];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyrimidin-2-ylmethyl)piperidine-4-carboxamide [1003];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(pyrazin-2-ylmethyl)piperidine-4-carboxamide [1004];

1-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1005];

1-(2-hydroxy-2-methylpropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1006];

trans-4-((4-methylpiperazin-1-yl)methyl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [1007];

2-isopropoxy-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)acetamide [1008];

3-isopropoxy-N-(6-(1-methyl-1H-imidazol-5-yl)isoquinolin-3-yl)propanamide [1009];

tert-butyl 2-(4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetate [1010];

2-(4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)piperidin-1-yl)acetic acid [1011];

2-(4-methyl-1,4-diazepan-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [1012];

N-(7-chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1013];

N-(6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [1014];

N-(7-fluoro-6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [1015];

N-(8-fluoro-6-(1-(methyl-*d*3)-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [1016];

trans-4-(dimethylamino)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [1017];

trans-4-((3-fluoroazetidin-1-yl)methyl)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [1018];

N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [1019];

1-isobutyl-N-(6-(5-methyl-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1020];

- 4-fluoro-1-isobutyl-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1021];
- N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1022];
- 4-fluoro-N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-1-isobutylpiperidine-4-carboxamide [1023];
- N-(6-(5-(2-fluoroethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide [1024];
- tert*-butyl (6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamate [1025];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)but-2-ynamide [1026];
- N-(7-chloro-6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide [1027];
- N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [1028];
- 2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)acetamide [1029];
- (R)-2-(2-methylpyrrolidin-1-yl)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)acetamide [1030];
- 2-(cyclobutyl(methyl)amino)-N-(6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)isoquinolin-3-yl)acetamide [1031];
- trans*-4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)cyclohexane-1-carboxylic acid [1032];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide-2,2-*d*₂ [1033];
- N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-morpholinopropanamide [1034];
- trans*-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-morpholinocyclobutane-1-carboxamide [1035];
- 1-(1-isobutylpiperidin-4-yl)-3-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)urea [1036];
- 1-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(1-methylpiperidin-4-yl)urea [1037];
- 1-isobutyl-N-(6-(4-methyl-4H-1,2,4-triazol-3-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1038];
- 1-isobutyl-N-(6-(1-methyl-1H-tetrazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1039];
- N-(6-(2-(methylamino)thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1040];
- 1-methyl-N-(6-(2-(methylamino)thiazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1041];

N-(6-(2-(dimethylamino)thiazol-5-yl)isoquinolin-3-yl)quinuclidine-4-carboxamide [1042];
 N-(6-(2-(dimethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [1043];
 N-(6-(2-(dimethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-fluoropiperidin-1-yl)acetamide
 [1044];
 N-(6-(2-(dimethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide
 [1045];
 N-(6-(2-(diethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide [1046];
 N-(6-(2-(diethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-fluoropiperidin-1-yl)acetamide [1047];
 N-(6-(2-(diethylamino)thiazol-5-yl)isoquinolin-3-yl)-2-(4-methylpiperazin-1-yl)acetamide
 [1048];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(1,4-oxazepan-4-yl)acetamide [1049];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(piperidin-1-yl)acetamide-2,2-*d*2
 [1050];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide-2,2-*d*2 [1051];
 N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(morpholino-*d*8)acetamide [1052];
 N-(7-fluoro-6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-morpholinoacetamide [1053];
 N-(6-(5-(dimethylamino)-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide
 [1054];
 N-(6-(5-(dimethylamino)-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-1-methylpiperidine-4-
 carboxamide [1055];
 N-(6-(5-(dimethylamino)-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)quinuclidine-4-carboxamide
 [1056];
 1-(2,2-difluoropropyl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1057];
 1-((3-methyloxetan-3-yl)methyl)-N-(6-(oxazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide
 [1058];
 4-methyl-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)piperazine-1-carboxamide [1059];
trans-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-3-(4-methylpiperazin-1-yl)cyclobutane-1-
 carboxamide [1060];
trans-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-3-morpholinocyclobutane-1-carboxamide
 [1061];
trans-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-3-(morpholinomethyl)bicyclo[1.1.1]pentane-
 1-carboxamide [1062];
trans-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-3-((4-methylpiperazin-1-
 yl)methyl)bicyclo[1.1.1]pentane-1-carboxamide [1063];

trans-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-4-morpholinocyclohexane-1-carboxamide [1064];

trans-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-4-(4-methylpiperazin-1-yl)cyclohexane-1-carboxamide [1065];

(S)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)propanamide [1066];

N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-2-morpholinoacetamide [1067];

N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-3-morpholinopropanamide [1068];

N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)-3-(4-methylpiperazin-1-yl)propanamide [1069];

1-(2-hydroxy-2-methylpropyl)-N-(6-(5-methyl-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1070];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)quinuclidine-4-carboxamide [1071];

1-(2-hydroxy-2-methylpropyl)-N-(6-(1-methyl-1H-1,2,3-triazol-4-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1072];

N-(6-(2H-1,2,3-triazol-2-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide [1073];

N-(6-(1H-1,2,3-triazol-1-yl)isoquinolin-3-yl)-4-fluoro-1-isobutylpiperidine-4-carboxamide [1074];

N-(6-(5-(Dimethylamino)-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1075];

N-(6-(5-(Dimethylamino)-1,3,4-oxadiazol-2-yl)isoquinolin-3-yl)-1-methylpiperidine-4-carboxamide [1076];

2-(4-Methoxypiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [1077];

2-(4-Hydroxypiperidin-1-yl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)acetamide [1078];

1-Isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azepane-4-carboxamide [1079];

1-Methyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)azepane-4-carboxamide [1080];

cis-4-(Dimethylamino)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [1081];

cis-4-(dimethylamino)-N-(6-(2-methyloxazol-5-yl)isoquinolin-3-yl)cyclohexane-1-carboxamide [1082];

3-(hydroxymethyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)bicyclo[1.1.1]pentane-1-carboxamide [1083];

methyl *trans*-4-((6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)carbamoyl)cyclohexane-1-carboxylate [1084];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-*d*)piperidine-4-carboxamide [1085];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-1-(2-(methyl-*d*₃)propyl-1,1,2,3,3,3-*d*₆)piperidine-4-carboxamide [1086];

1-isobutyl-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-*d*)piperidine-4-carboxamide [1087];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-((4-methylpiperazin-1-yl)methyl)bicyclo[1.1.1] pentane-1-carboxamide [1088];

N-(6-(5-methyl-1,3,4-thiadiazol-2-yl)isoquinolin-3-yl)-2-(pyrrolidin-1-yl)acetamide-2,2-*d*₂ [1089];

1-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-3-(1-methylpiperidin-4-yl)urea [1090];

trans-N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl)-4-(4-methylpiperazine-1-carbonyl)cyclohexane-1-carboxamide [1091]; and

1-isobutyl-N-(6-(1-methyl-1H-tetrazol-5-yl)isoquinolin-3-yl)piperidine-4-carboxamide [1092];

N-(6-(1-methyl-1H-pyrazol-4-yl)isoquinolin-3-yl-1-*d*)-2-(pyrrolidin-1-yl)acetamide [1093]; or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-35, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

37. A method of treating a disorder or disease in a patient, wherein the disorder or disease is selected from the group consisting of: chronic inflammation, diabetes, cancer, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), degenerative disc disease, bone/osteoporotic fractures, a bone or cartilage disease, a neurological disorder, osteoarthritis, lung disease, a fibrotic disorder, the method comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1-35, or a pharmaceutically acceptable salt, or a pharmaceutical composition according to claim 36 thereof.

38. A method of claim 37, wherein the disorder or disease is cancer.

39. A method of claim 37, wherein the disorder or disease is pulmonary fibrosis.

40. A method of claim 37, wherein the disorder or disease is idiopathic pulmonary fibrosis (IPF).

41. The method of claim 37, wherein the disorder or disease is lung disease.

42. A method of claim 37, wherein the disorder or disease is degenerative disc disease.

43. A method of claim 37, wherein the disorder or disease is a bone/osteoporotic fracture.

44. A method of claim 37, wherein the disorder or disease is a bone or cartilage disease.

45. A method of claim 37, wherein the disorder or disease is osteoarthritis.

46. A method of claim 37, wherein the disorder or disease is a neurological disorder.

47. The method according to any one of claims 37-38, wherein the cancer is selected from the group consisting of: osteoma, hemangioma, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, and gliomatosis, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, oligodendrocytoma, schwannoma, retinoblastoma, and congenital tumors, neurofibroma, meningioma, glioma, and sarcoma.

48. The method according to any one of claims 37 and 46, wherein the disorder or disease is a neurological disorder, wherein the neurological condition/disorder/disease is selected from the group consisting of: frontotemporal dementias, dementia with lewy bodies, prion diseases, multiple system atrophy, inclusion body myositis, degenerative myopathies, diabetic neuropathy, other metabolic neuropathies, endocrine neuropathies, orthostatic hypotension, and Charcot-Marie-Tooth disease.

49. The method according to any one of claims 37 and 46, wherein the disorder or disease is selected from the group consisting of: Alzheimer's disease, amyotrophic lateral sclerosis (ALS), down syndrome, frontotemporal dementia (FTD) including FTD with Parkinsonism-17 (FTDP-17), behavioural variant frontotemporal dementia (bvFTD), FTD in patients with motor neuron disease (MND) (typically amyotrophic lateral sclerosis, also called FTD-ALS), corticobasal degeneration (CBD) (also called corticobasal ganglionic degeneration), progressive supranuclear palsy, primary progressive aphasia (PPA), Prion Diseases, globular glial tauopathy (GGT), myotonic dystrophy type 1 (DM1) (also called Steinert disease), myotonic dystrophy type 2 (DM2) (also called proximal myotonic myopathy), Guam complex, argyrophilic grain disease, dementia pugilistica, post-encephalitic parkinsonism, lewy body dementia, Parkinson's disease, Pick's disease, and additional diseases with pronounced neurodegeneration such as autism, dementia, epilepsy, Huntington's disease, multiple sclerosis; diseases and disorders associated with acquired brain injury such as chronic traumatic encephalopathy, traumatic brain injury, tumor, and stroke.

50. A method according to any one of claims 37, 46 and 49, wherein the disorder or disease is Alzheimer's disease.

51. The method according to any one of claims 37, 46 and 48-50, wherein the disorder or disease is a neurological disorder associated with tau protein, amyloid, alpha-synuclein, Tar DNA-binding Protein of 43KDa (TDP-43), Prion protein PrP or fused in sarcoma (FUS) pathology.

52. The method of claim 37, 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.

53. The method according to any one of claims 37-52, wherein the patient is a human.

54. The method according to any one of claims 37-53, wherein the compound inhibits one or more proteins in the Wnt pathway.

55. The method according to any one of claims 37-54, wherein the compound inhibits signaling induced by one or more Wnt proteins.

56. The method according to any one of claims 37-55, wherein the compound inhibits DYRK1A.

57. The method according to any one of claims 37-55, wherein the compound inhibits GSK3 β .

58. The method according to any one of claims 37-55, wherein the compound inhibits DYRK1A and GSK3 β .

59. The method according to any one of claims 37-58, wherein the compound inhibits a kinase activity.

60. A method of preventing or reducing angiogenesis in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1-35, or a pharmaceutically acceptable salt, or a pharmaceutical composition according to claim 36 thereof.