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

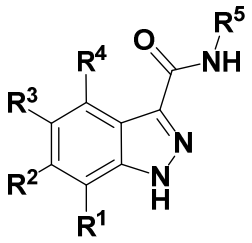
[010] The present disclosure provides methods and reagents, involving contacting a cell with an agent, such as an indazole compound, in a sufficient amount to antagonize a Wnt activity, e.g., to reverse or control an aberrant growth state or correct a genetic disorder due to mutations in Wnt signaling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

[011] This disclosure features the use of one or more indazole-3-carboxamide compounds or salts or analogs thereof, in the treatment of one or more diseases or conditions independently selected from the group consisting of a tendinopathy, dermatitis, psoriasis, morphea, ichthyosis, Raynaud's syndrome, and Darier's disease; and/or for promoting wound healing. The methods include administering to a subject (e.g., a subject in need thereof) a therapeutically effective amount of one or more indazole-3-carboxamide compounds or salts or analogs thereof as described anywhere herein.

[012] The present disclosure also provides methods and reagents, involving contacting a cell with an agent, such as an indazole 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.

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

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

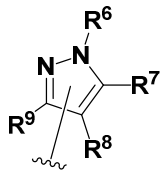
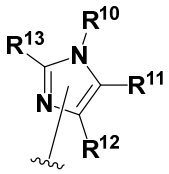
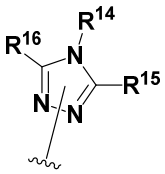
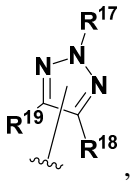
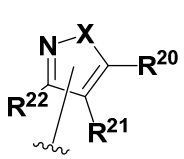
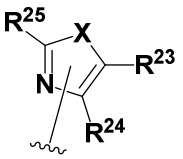


as well as prodrugs and pharmaceutically acceptable salts thereof.

[015] In some examples of Formula (**I**):

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

R^3 is selected from the group consisting of:






, and

;

wherein each of R^6-R^{25} is, independently, a substituent as defined anywhere herein or a single bond connecting R^3 to the indazole ring; wherein only one of R^6-R^9 (when present) is a bond, only one of R^{10}-R^{13} (when present) is a bond, only one of R^{14}-R^{16} (when present) is a bond, only one of R^{17}-R^{19} (when present) is a bond, only one of R^{20}-R^{22} is a bond, and only one of R^{23}-R^{25} (when present) is a bond; for purposes of clarification, any one of the nitrogen atoms attached to R^6, R^{10}, R^{14}, or R^{17} can serve as the point of attachment of R^3 to the indazole ring; likewise, any one of the carbon atoms attached to R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} can serve as the point of attachment of R^3 to the indazole ring; accordingly:

when the nitrogen atom to which R^6 is attached serves as the point of attachment of R^3 to the indazole ring, then R^6 is a single bond connecting R^3 to the indazole ring;

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

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

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

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

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

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

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

each R^{39} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

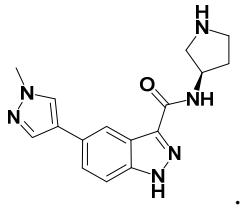
each R^{40} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{41} is independently selected from the group consisting of H and –(C_{1-9} alkyl);each R^{46} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each X is O or S;

each p is independently 0 or 1; and

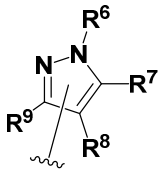
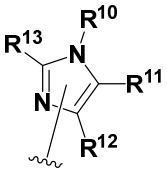
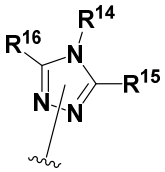
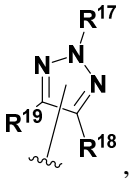
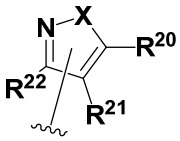
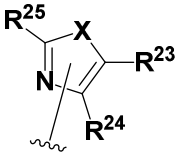
with the proviso that Formula I is not a structure selected from the group consisting of:


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[016] In some examples of Formula **(I)**:

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

R^3 is selected from the group consisting of:


,

,

,

,

, and

;

wherein each of R^6-R^{25} is, independently, a substituent as defined anywhere herein or a single bond connecting R^3 to the indazole ring; wherein only one of R^6-R^9 (when present) is a bond, only one of R^{10}-R^{13} (when present) is a bond, only one of R^{14}-R^{16} (when present) is a bond, only one of R^{17}-R^{19} (when present) is a bond, only one of R^{20}-R^{22} is a bond, and only one of R^{23}-R^{25} (when present) is a bond; for purposes of clarification, any one of the nitrogen atoms attached to R^6, R^{10}, R^{14}, or R^{17} can serve as the point of attachment of R^3 to the indazole ring; likewise, any one of the carbon atoms attached to R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} can serve as the point of attachment of R^3 to the indazole ring; accordingly:

when the nitrogen atom to which R^6 is attached serves as the point of attachment of R^3 to the indazole ring, then R^6 is a single bond connecting R^3 to the indazole ring;

each R^{33} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{34} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), and unsubstituted –(C_{1-4} haloalkyl);

each R^{35} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{36} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{37} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{38} is independently selected from the group consisting of H, unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), and unsubstituted –(C_{1-4} haloalkyl);

each R^{39} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

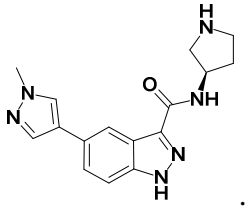
each R^{40} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{41} is independently selected from the group consisting of H and –(C_{1-9} alkyl);

each X is O or S;

each p is independently 0 or 1; and

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



.

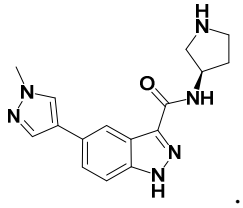
[017] In another example of Formula **(I)**:

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

each R^{46} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each p is independently 0 or 1; and

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



.

[018] In another example of Formula **(I)**:

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

R^3 is a 5-membered heteroaryl ring optionally substituted as defined anywhere herein, e.g., R^3 is a 5-membered heteroaryl ring optionally substituted with from 1-4 R^{42};

R^5 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), –heteroaryl substituted with 1-4 R^{26}, a monocyclic –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{27}, a spirocyclic –heterocyclyl optionally substituted with 1-10 R^{27}, –(C_{1-4} alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{28}, and –aryl optionally substituted with 1-5 R^{29}; wherein each –(C_{1-4} alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

each R^{26} is independently selected from the group consisting of halide, –OR^{34}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), –C(C=O)N(R^{41})$_2$, –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{35}, and –O(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}; wherein each –(C_{1-4} alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

each R^{27} is independently selected from the group consisting of halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), and –carbocyclyl optionally substituted with 1-12 R^{28};

each R^{28} is independently selected from the group consisting of halide, –OR^{38}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), and –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10

alternatively, two adjacent R^{42} groups are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{45} and –carbocyclyl optionally substituted with 1-12 R^{46};

each R^{43} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

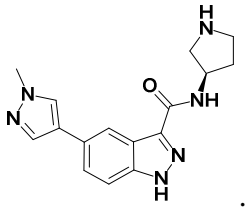
each R^{44} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{45} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{46} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

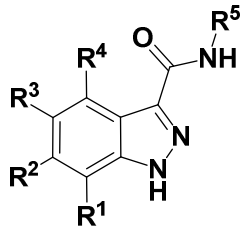
each p is independently 0 or 1; and

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



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[018a] In one aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof, of Formula **I**:

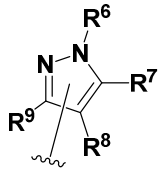


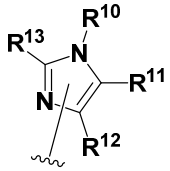
I

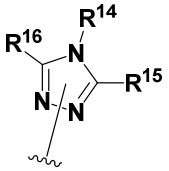
wherein:

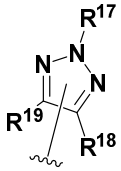
R^1, R^2, and R^4 are independently selected from the group consisting of H and halide;

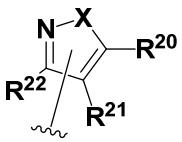
R^3 is selected from the group consisting of:

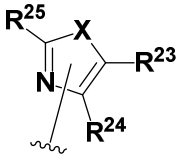


,


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, and


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wherein each of R^6-R^{25} is, independently, a substituent as defined below or a single bond connecting R^3 to the indazole ring; wherein only one of R^6-R^9 (when present) is a bond, only one of R^{10}-R^{13} (when present) is a bond, only one of R^{14}-R^{16} (when present) is a bond, only one of R^{17}-R^{19} (when present) is a bond, only one of R^{20}-R^{22} is a bond, and only one of R^{23}-R^{25} (when present) is a bond; for purposes of clarification, any one of the nitrogen atoms attached to R^6, R^{10}, R^{14}, or R^{17} can serve as the point of attachment of R^3 to the indazole ring; likewise, any one of the carbon atoms attached to R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} can serve as the point of attachment of R^3 to the indazole ring; accordingly:

when the nitrogen atom to which R^6 is attached serves as the point of attachment of R^3 to the indazole ring, then R^6 is a single bond connecting R^3 to the indazole ring;

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

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

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

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

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

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

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

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

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

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

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

when the carbon atom to which R^{18} is attached serves as the point of attachment of R^3 to the indazole ring, then R^{18} is a single bond connecting R^3 to the indazole ring;

when the carbon atom to which R^{19} is attached is instead attached to the indazole ring then R^{19} is a single bond connecting R^3 to the indazole ring;

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

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

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

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

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

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

R^5 is selected from the group consisting of unsubstituted –($C_{1\text{-}9}$ alkyl), unsubstituted –($C_{2\text{-}9}$ alkenyl), unsubstituted –($C_{2\text{-}9}$ alkynyl), unsubstituted –($C_{1\text{-}9}$ haloalkyl), –heteroaryl substituted with 1-4 R^{26}, a monocyclic –($C_{1\text{-}4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{27}, a spirocyclic –heterocyclyl optionally substituted with 1-10 R^{27}, –($C_{1\text{-}4}$ alkylene)$_p$carbocyclyl optionally substituted with 1-12 R^{28}, and –aryl optionally substituted with 1-5 R^{29}; wherein each –($C_{1\text{-}4}$ alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

R^6 is independently selected from the group consisting of H, unsubstituted –($C_{1\text{-}9}$ alkyl), unsubstituted –($C_{2\text{-}9}$ alkenyl), unsubstituted –($C_{2\text{-}9}$ alkynyl), unsubstituted –($C_{1\text{-}9}$ haloalkyl), –($C_{1\text{-}4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –($C_{1\text{-}4}$ alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^7, R^8, and R^9 are independently selected from the group consisting of H, halide, unsubstituted –($C_{1\text{-}9}$ alkyl), unsubstituted –($C_{2\text{-}9}$ alkenyl), unsubstituted –($C_{2\text{-}9}$ alkynyl),

unsubstituted –(C_{1-9} haloalkyl), –(C_{1-4} alkylene)$_p$OH, and –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{27}; wherein each –(C_{1-4} alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

alternatively, one of R^6 and R^7, R^7 and R^8, or R^8 and R^9 are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{10} 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), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, one of R^{10} and R^{11}, R^{11} and R^{12}, or R^{13} and R^{10} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{14} 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), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^{15} and R^{16} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, one of R^{14} and R^{15} or R^{16} and R^{14} are taken together to form a heterocyclyl optionally substituted with 1-10 R^{32};

R^{17} 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), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^{18} and R^{19} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, R^{18} and R^{19} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, one of R^{20} and R^{21} or R^{21} and R^{22} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, R^{23} and R^{24} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

each R^{26} is independently selected from the group consisting of halide, –OR^{34}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), –$C(C{=}O)N(R^{41})_2$, –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{35}, and –O(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}; wherein each –(C_{1-4} alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

each R^{27} is independently selected from the group consisting of halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), –carbocyclyl optionally substituted with 1-12 R^{28}, and –aryl optionally substituted with 1-5 R^{46};

each R^{28} is independently selected from the group consisting of halide, –OR^{38}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), and –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{37}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

each R^{29} is independently selected from the group consisting of halide, –OR^{38}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl),

unsubstituted –(C_{1-9} haloalkyl), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{39}, –NHheterocyclyl optionally substituted with 1-10 R^{40}, and –O(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{40}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

each R^{30} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{31} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{32} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{33} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{34} is independently selected from the group consisting of unsubstituted –(C_{2-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), and unsubstituted –(C_{1-4} haloalkyl);

each R^{35} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{36} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{37} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{38} is independently selected from the group consisting of H, unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), and unsubstituted –(C_{1-4} haloalkyl);

each R^{39} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{40} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

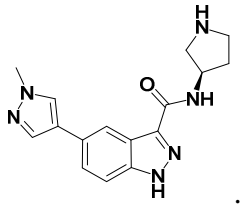
each R^{41} is independently selected from the group consisting of H and –(C_{1-9} alkyl);

each R^{46} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each X is O or S;

each p is independently 0 or 1; and

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



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[019] Some examples include administering stereoisomers and pharmaceutically acceptable salts of a compound of general Formula (**I**).

[020] Some examples include administering pro-drugs of a compound of general Formula (**I**).

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

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

the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation and correct a genetic disorder due to mutations in Wnt signaling components.

[023] Other examples 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.

[024] Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, sepsis, ankylosing spondylitis, psoriasis, scleroderma, mycotic and viral infections, osteochondrodysplasia, Alzheimer's disease, lung disease, bone/osteoporotic (wrist, spine, shoulder and hip) fractures, articular cartilage (chondral) defects, degenerative disc disease (or intervertebral disc degeneration), polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-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.

[024a] In one aspect, the present disclosure refers to use of any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder or disease in a patient, wherein the disorder or disease is selected from: tendinopathy, dermatitis, psoriasis, morphea, ichthyosis, Raynaud's syndrome, Darier's disease, cancer, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), degenerative disc disease, bone/osteoporotic fractures, a bone or cartilage disease, a neurological disorder, osteoarthritis, lung disease, and a fibrotic disorder, wherein the patient is human.

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

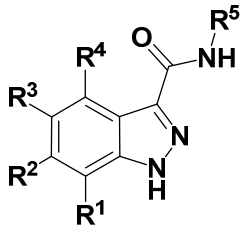
[026] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the disclosure, as claimed.

DETAILED DESCRIPTION

[027] 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

CLAIMS

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

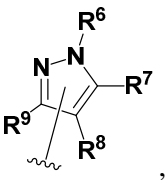
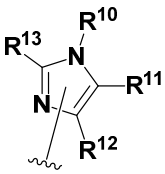
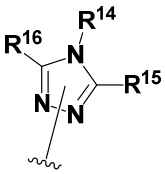
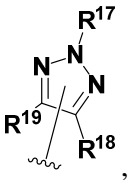
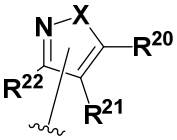
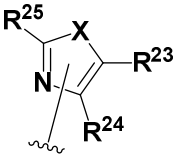


I

wherein:

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

R^3 is selected from the group consisting of:

, , , , , and ;

wherein each of R^6-R^{25} is, independently, a substituent as defined below or a single bond connecting R^3 to the indazole ring; wherein only one of R^6-R^9 (when present) is a bond, only one of R^{10}-R^{13} (when present) is a bond, only one of R^{14}-R^{16} (when present) is a bond, only one of R^{17}-R^{19} (when present) is a bond, only one of R^{20}-R^{22} is a bond, and only one of R^{23}-R^{25} (when present) is a bond; for purposes of clarification, any one of the nitrogen atoms attached to R^6, R^{10}, R^{14}, or R^{17} can serve as the point of attachment of R^3 to the indazole ring; likewise, any one of the carbon atoms attached to R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} can serve as the point of attachment of R^3 to the indazole ring; accordingly:

when the nitrogen atom to which R^6 is attached serves as the point of attachment of R^3 to the indazole ring, then R^6 is a single bond connecting R^3 to the indazole ring;

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

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

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

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

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

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

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

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

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

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

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

when the carbon atom to which R^{18} is attached serves as the point of attachment of R^3 to the indazole ring, then R^{18} is a single bond connecting R^3 to the indazole ring;

when the carbon atom to which R^{19} is attached is instead attached to the indazole ring then R^{19} is a single bond connecting R^3 to the indazole ring;

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

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

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

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

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

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

R^5 is selected from the group consisting of unsubstituted –($C_{1\text{-}9}$ alkyl), unsubstituted –($C_{2\text{-}9}$ alkenyl), unsubstituted –($C_{2\text{-}9}$ alkynyl), unsubstituted –($C_{1\text{-}9}$ haloalkyl), –heteroaryl substituted with 1-4 R^{26}, a monocyclic –($C_{1\text{-}4}$ alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{27}, a spirocyclic –heterocyclyl optionally substituted with 1-10 R^{27}, –($C_{1\text{-}4}$ alkylene)$_p$carbocyclyl

optionally substituted with 1-12 R^{28}, and –aryl optionally substituted with 1-5 R^{29}; wherein each –(C_{1-4} alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

R^6 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), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^7, R^8, and R^9 are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), –(C_{1-4} alkylene)$_p$OH, and –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{27}; wherein each –(C_{1-4} alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

alternatively, one of R^6 and R^7, R^7 and R^8, or R^8 and R^9 are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{10} 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), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^{11}, R^{12}, and R^{13} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, one of R^{10} and R^{11}, R^{11} and R^{12}, or R^{13} and R^{10} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{14} 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), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^{15} and R^{16} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, one of R^{14} and R^{15} or R^{16} and R^{14} are taken together to form a heterocyclyl optionally substituted with 1-10 R^{32};

R^{17} 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), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{30}, and –carbocyclyl optionally substituted with 1-12 R^{31}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

R^{18} and R^{19} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, R^{18} and R^{19} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, one of R^{20} and R^{21} or R^{21} and R^{22} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

R^{23}, R^{24}, and R^{25} are independently selected from the group consisting of H, halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), and unsubstituted –(C_{1-9} haloalkyl);

alternatively, R^{23} and R^{24} are taken together to form a ring which is selected from the group consisting of –heterocyclyl optionally substituted with 1-10 R^{32} and –carbocyclyl optionally substituted with 1-12 R^{33};

each R^{26} is independently selected from the group consisting of halide, –OR^{34}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), –$C(C{=}O)N(R^{41})_2$, –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{35}, and –O(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{36}; wherein each –(C_{1-4} alkylene) is, independently, optionally substituted with a substituent as defined anywhere herein;

each R^{27} is independently selected from the group consisting of halide, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), –carbocyclyl optionally substituted with 1-12 R^{28}, and –aryl optionally substituted with 1-5 R^{46};

each R^{28} is independently selected from the group consisting of halide, –OR^{38}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), and –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{37}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

each R^{29} is independently selected from the group consisting of halide, –OR^{38}, unsubstituted –(C_{1-9} alkyl), unsubstituted –(C_{2-9} alkenyl), unsubstituted –(C_{2-9} alkynyl), unsubstituted –(C_{1-9} haloalkyl), –(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{39}, –NHheterocyclyl optionally substituted with 1-10 R^{40}, and –O(C_{1-4} alkylene)$_p$heterocyclyl optionally substituted with 1-10 R^{40}; wherein –(C_{1-4} alkylene) is, optionally substituted with a substituent as defined anywhere herein;

each R^{30} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{31} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{32} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{33} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{34} is independently selected from the group consisting of unsubstituted –(C_{2-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), and unsubstituted –(C_{1-4} haloalkyl);

each R^{35} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{36} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{37} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{38} is independently selected from the group consisting of H, unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), and unsubstituted –(C_{1-4} haloalkyl);

each R^{39} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each R^{40} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

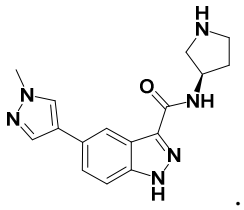
each R^{41} is independently selected from the group consisting of H and –(C_{1-9} alkyl);

each R^{46} is independently selected from the group consisting of unsubstituted –(C_{1-4} alkyl), unsubstituted –(C_{2-4} alkenyl), unsubstituted –(C_{2-4} alkynyl), unsubstituted –(C_{1-4} haloalkyl), halide, and –CN;

each X is O or S;

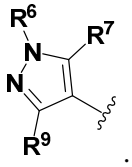
each p is independently 0 or 1; and

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



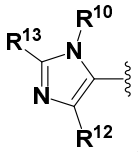
.

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

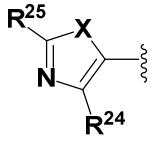
3. The compound according to any one of claims 1-2, wherein R^3 is 

.

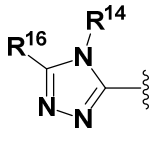
4. The compound according to any one of claims 1-3, wherein R^6 is selected from the group consisting of H, methyl, $–CF_3$, and cyclopropyl optionally substituted with 1-2 R^{31}, optionally wherein R^7 is selected from the group consisting of H, F, methyl, and $–CF_3$, and optionally wherein R^9 is selected from the group consisting of H and F.

5. The compound according to any one of claims 1-2, wherein R^3 is .

6. The compound according to any one of claims 1-2 and 5, wherein R^{10} is selected from the group consisting of H, methyl, $–CF_3$, and cyclopropyl optionally substituted with 1-2 R^{31}, optionally wherein R^{12} is selected from the group consisting of H and F, and optionally wherein R^{13} is selected from the group consisting of H, F, methyl, and $–CF_3$.

7. The compound according to any one of claims 1-2, wherein R^3 is .

8. The compound according to any one of claims 1-2 and 7, wherein R^{24} is selected from the group consisting of H and F, and optionally wherein R^{25} is selected from the group consisting of H, F, methyl, and $–CF_3$.

9. The compound according to any one of claims 1-2, wherein R^3 is .

10. The compound according to any one of claims 1-2 and 9, wherein R^{14} is selected from the group consisting of H, methyl, $–CF_3$, and cyclopropyl optionally substituted with 1-2 R^{31}, and optionally wherein R^{16} is selected from the group consisting of H, F, methyl, and $–CF_3$.

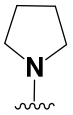
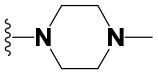
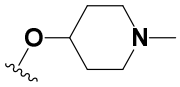
11. The compound according to any one of claims 1-10, wherein R^5 is selected from the group consisting of unsubstituted $–(C_{1-4}$ alkyl) and unsubstituted $–(C_{1-3}$ fluoroalkyl).

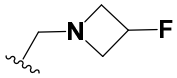
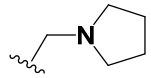
12. The compound according to any one of claims 1-10, wherein R^5 is selected from the group consisting of –pyridinyl substituted with 1 R^{26} and –thiazolyl substituted with 1 R^{26}.

13. The compound according to any one of claims 1-10, wherein R^5 is selected from the group consisting of a 6-membered monocyclic –heterocyclyl optionally substituted with 1-2 R^{27} and a spirocyclic –heterocyclyl optionally substituted with 1 R^{27}.

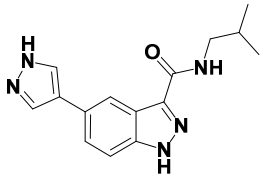
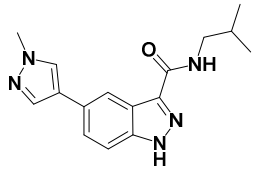
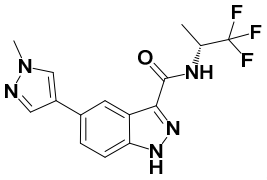
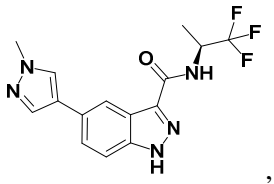
14. The compound according to any one of claims 1-10, wherein R^5 is selected from the group consisting of –carbocyclyl optionally substituted with 1-2 R^{28} and $–CH_2$carbocyclyl optionally substituted with 1-2 R^{28}.

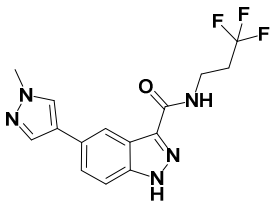
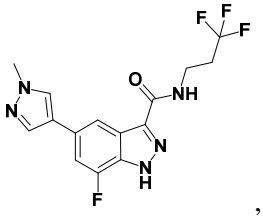
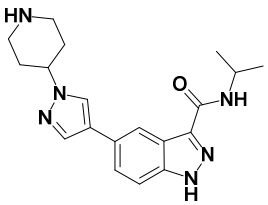
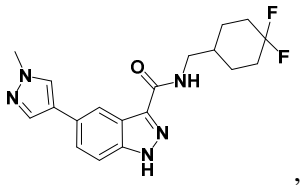
15. The compound according to any one of claims 1-10, wherein R^5 is –phenyl substituted with 1-2 R^{29}.

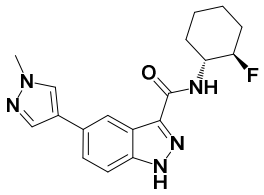
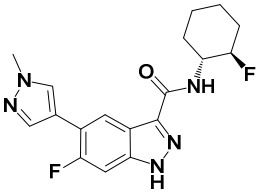
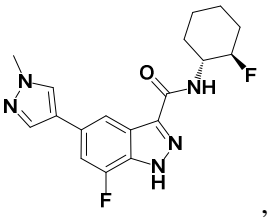
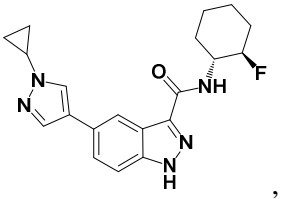
16. The compound according to any one of claims 1-10 and 12, wherein R^{26} is selected from the group consisting of F, $–OCHF_2$, $–OCF_3$, methyl, $–CF_3$, , , and .

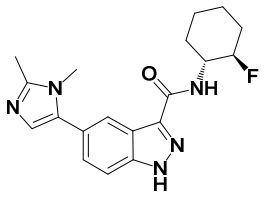
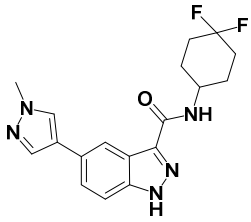
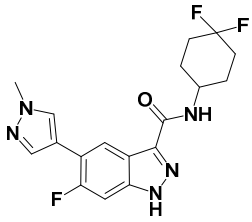
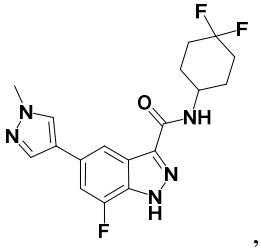
17. The compound according to any one of claims 1-10 and 14, wherein R^{28} is selected from the group consisting of F, –OMe, , and .

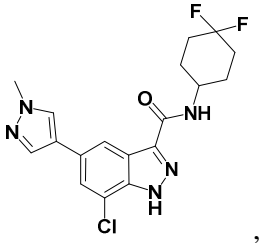
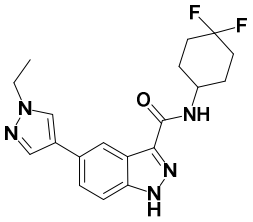
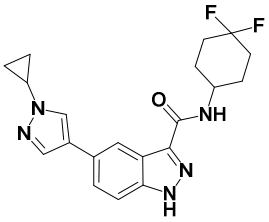
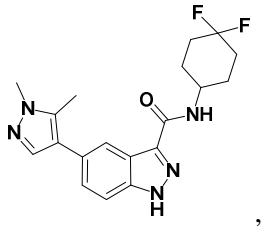
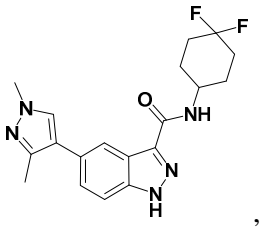
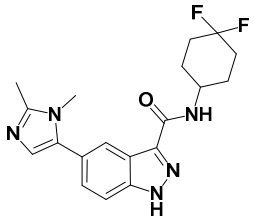
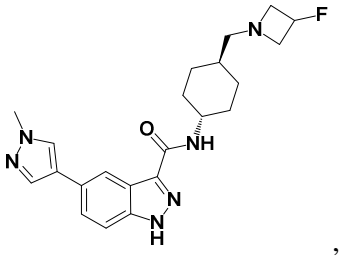
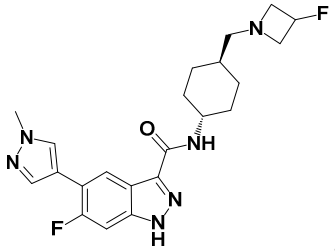
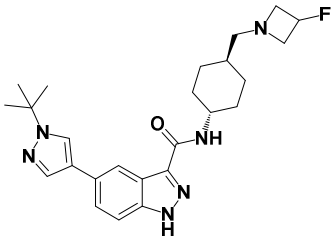
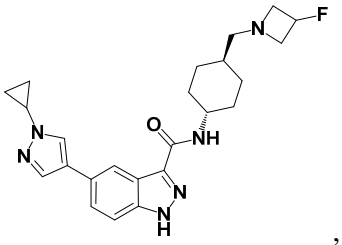
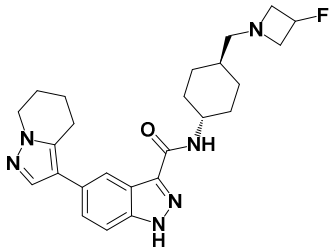
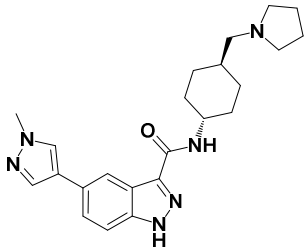
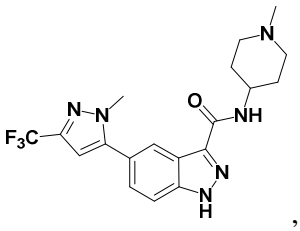
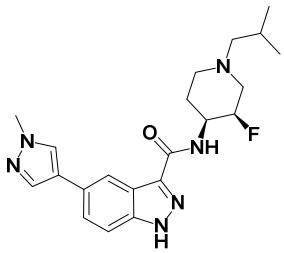
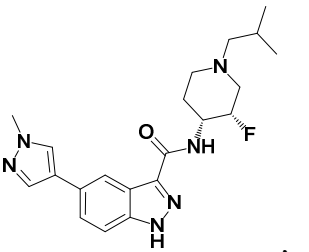
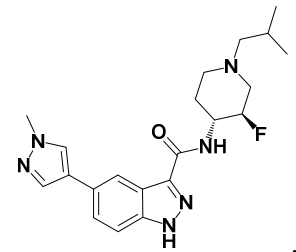
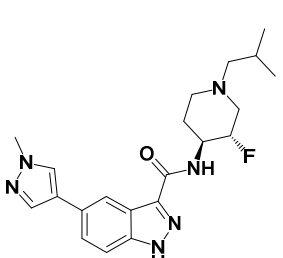
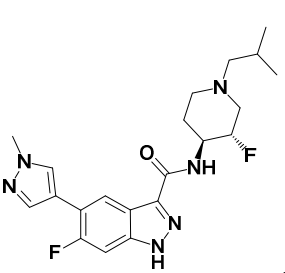
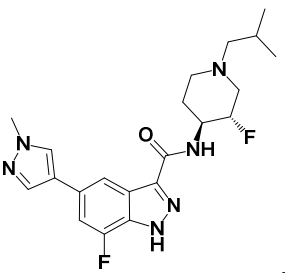
18. The compound of claim 1, wherein the compound of Formula **I** is selected from the group consisting of:

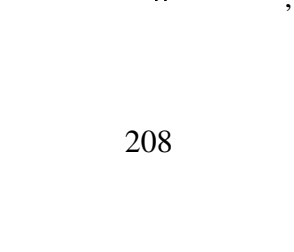
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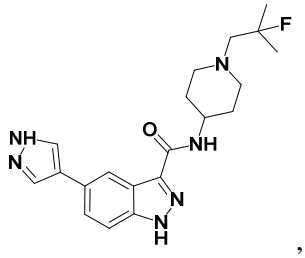
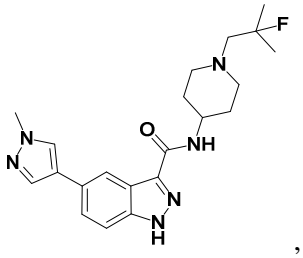
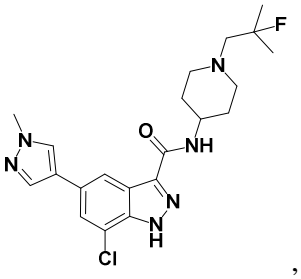
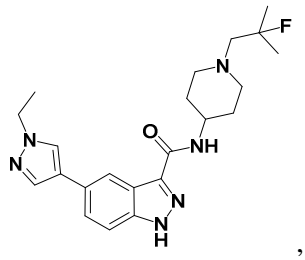
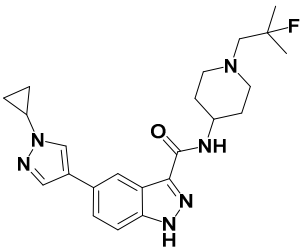
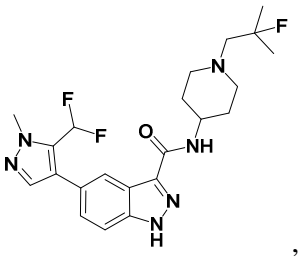
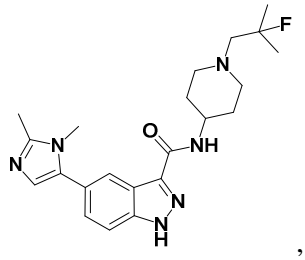
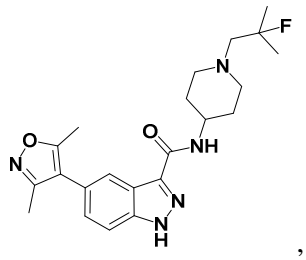
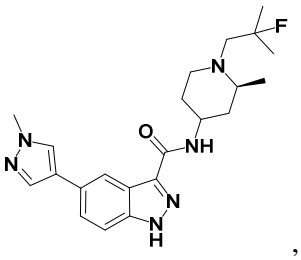
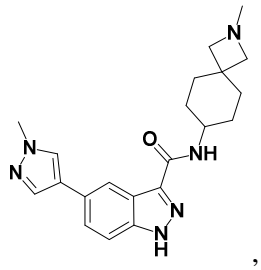
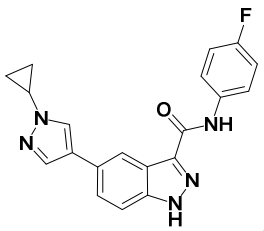
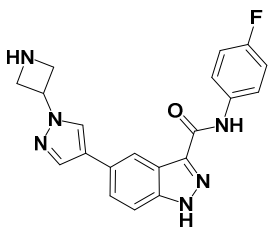
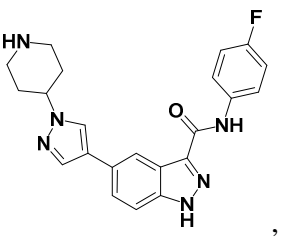
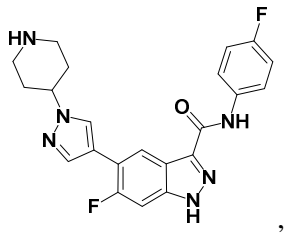
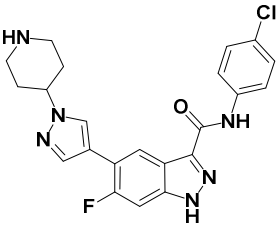
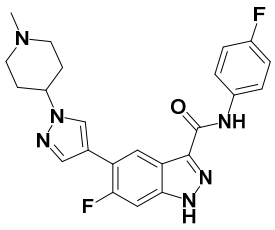
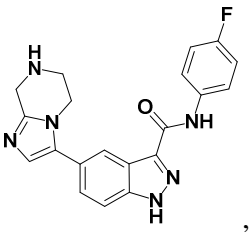
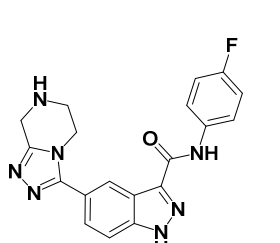
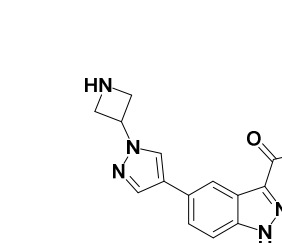
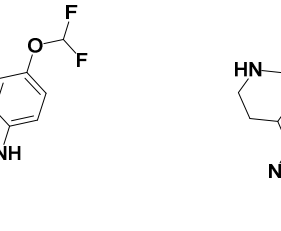
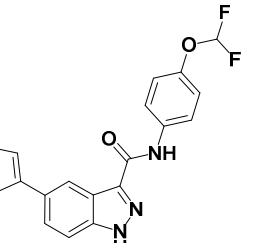
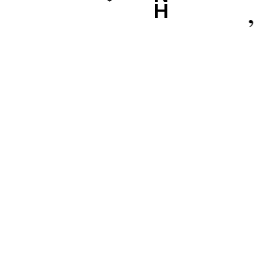
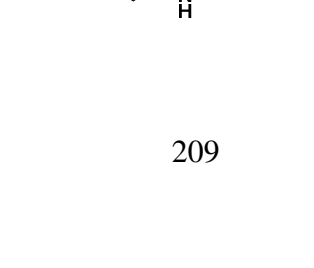
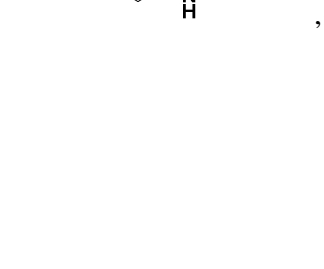
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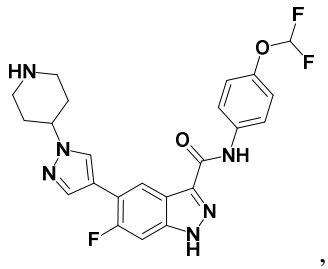
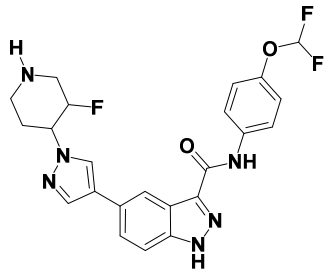
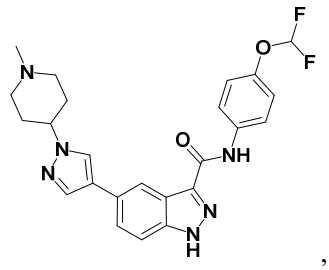
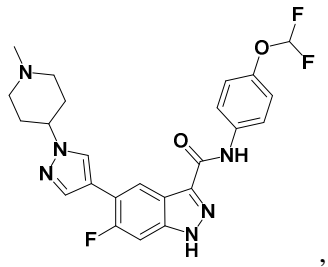
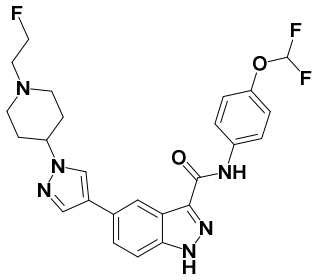
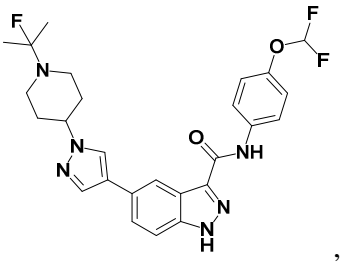
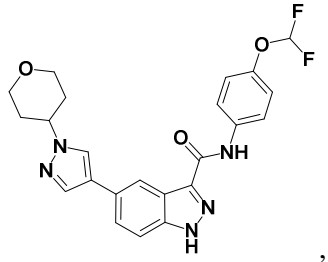
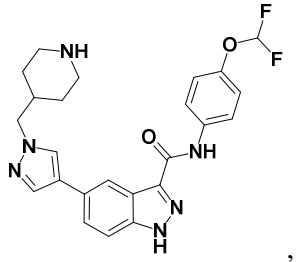
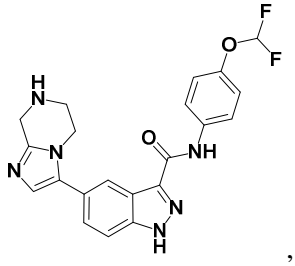
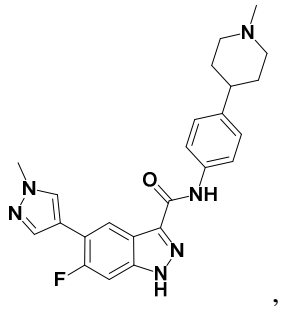
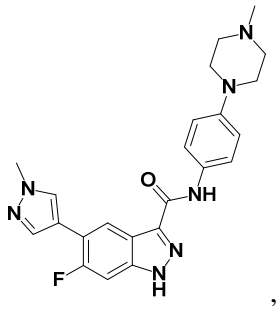
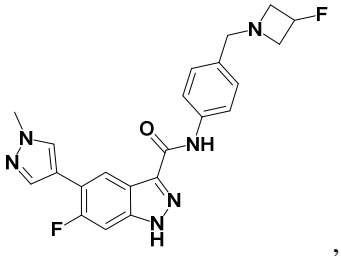
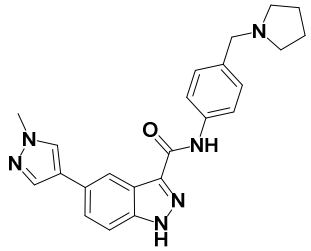
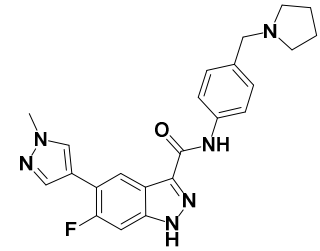
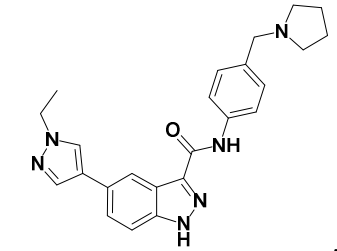
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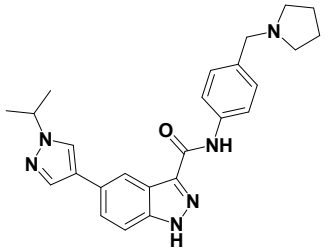
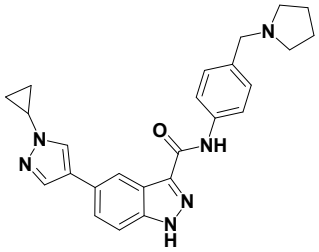
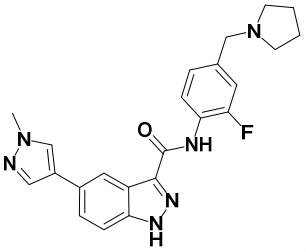

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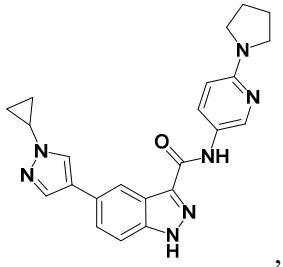
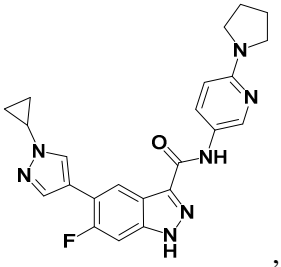
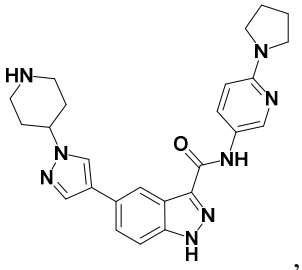
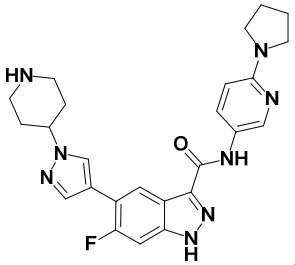
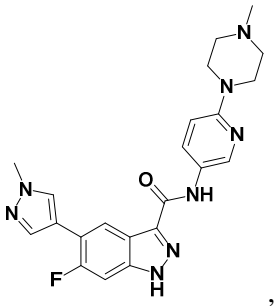
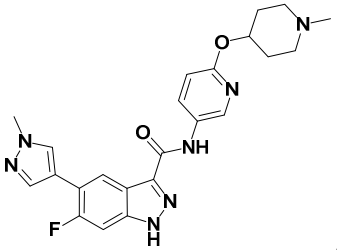
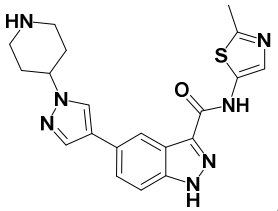
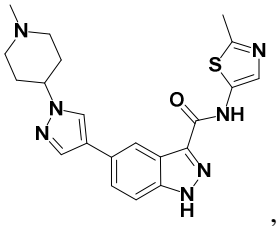
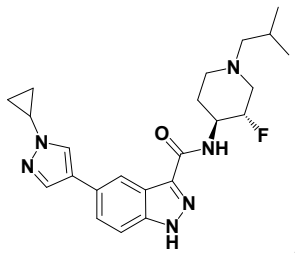
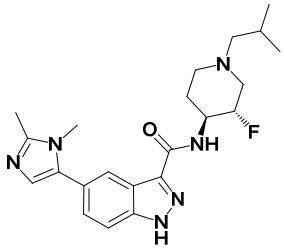
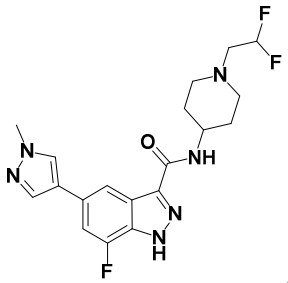
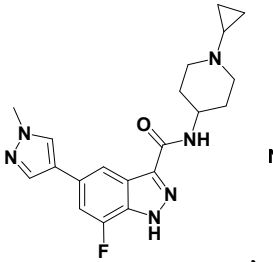
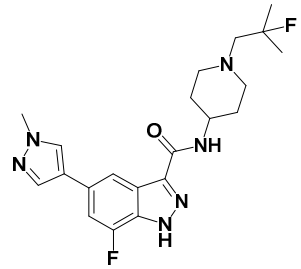
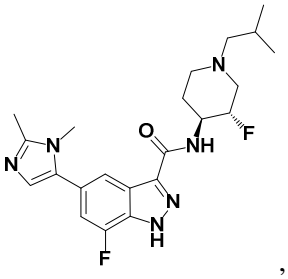
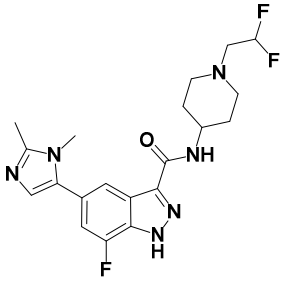
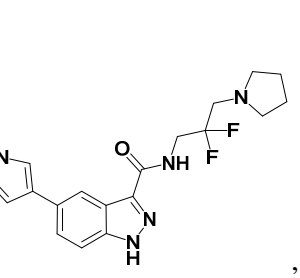

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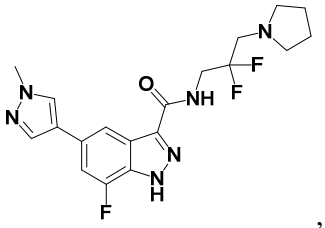
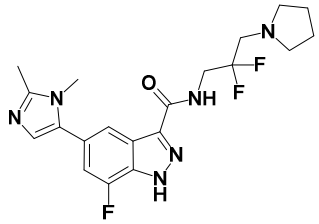
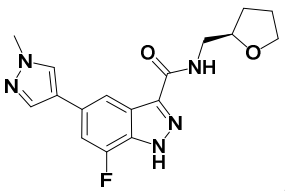
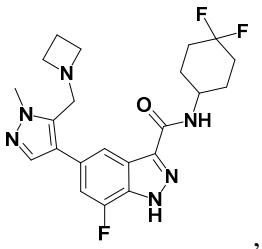
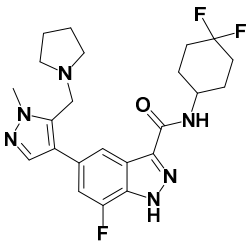
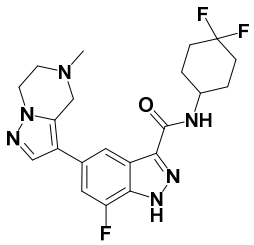
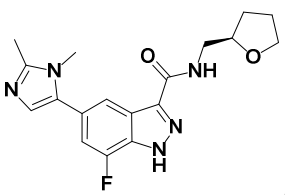
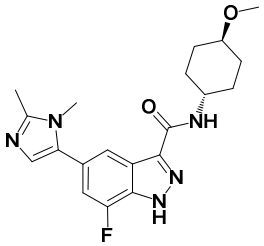
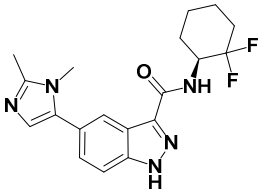
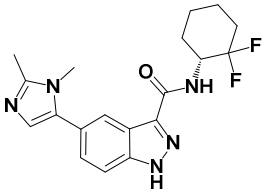
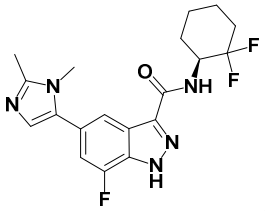
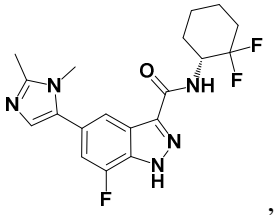
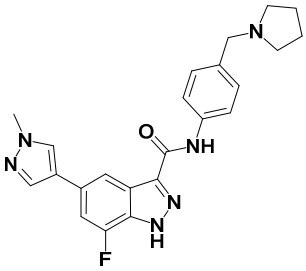
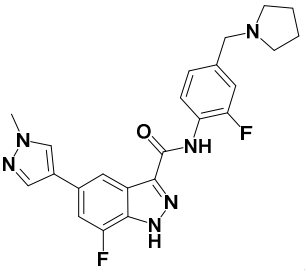
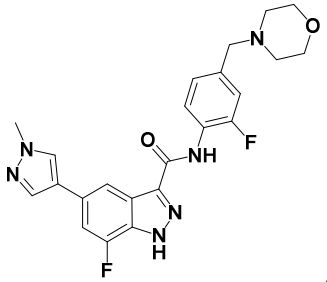
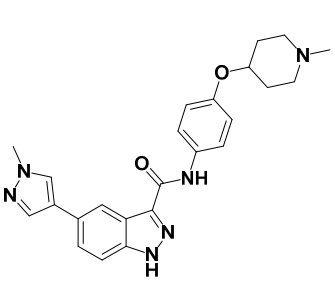
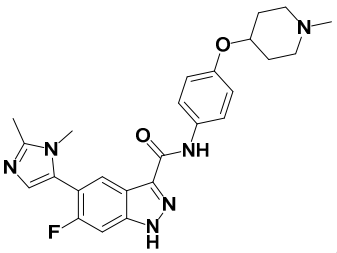
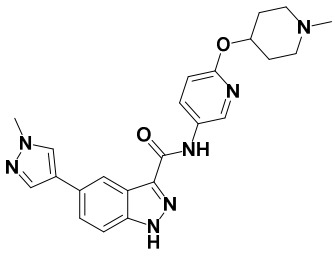
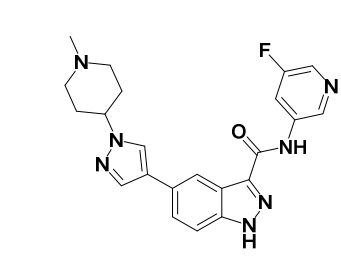
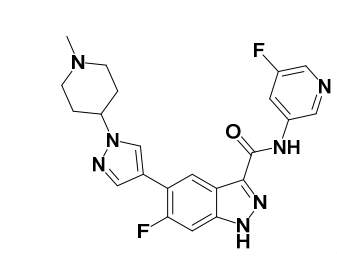

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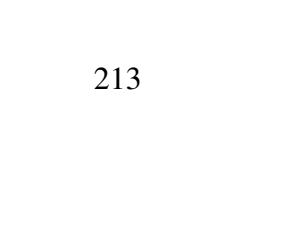

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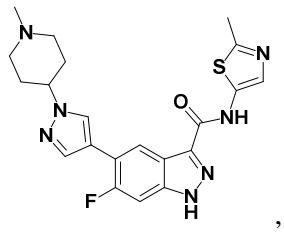
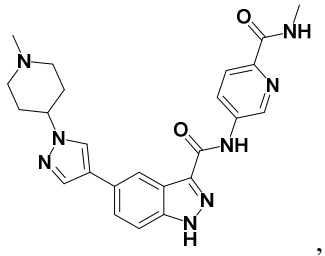
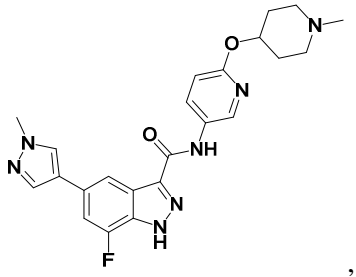
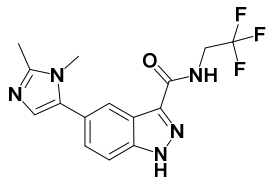
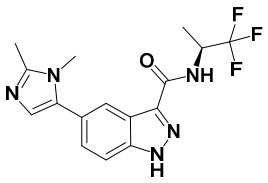
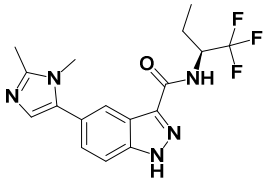
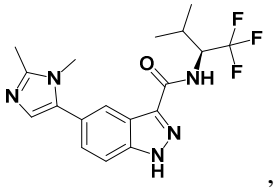
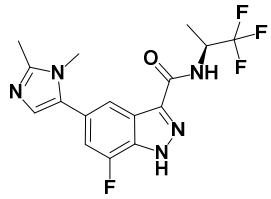
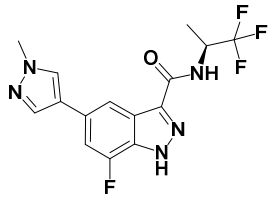
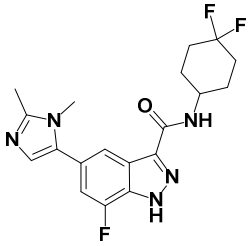
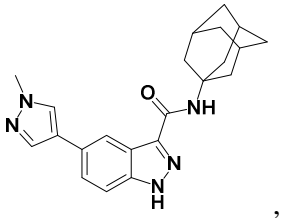
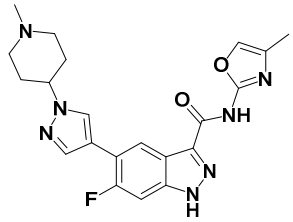
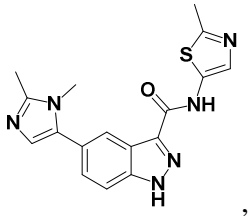
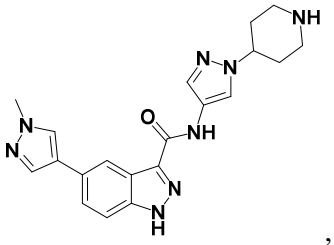
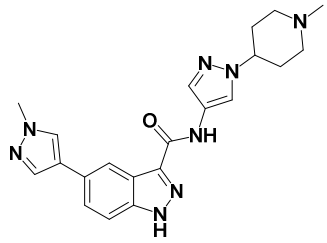
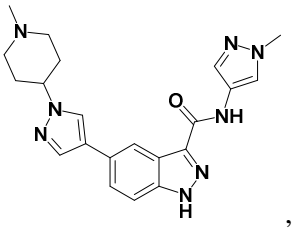
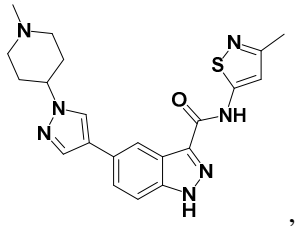
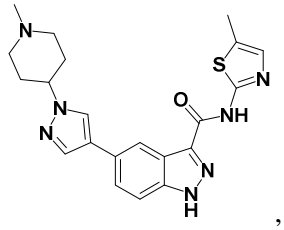
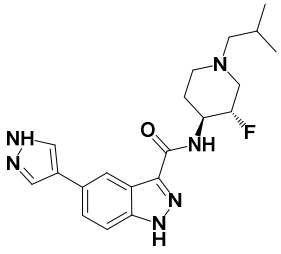
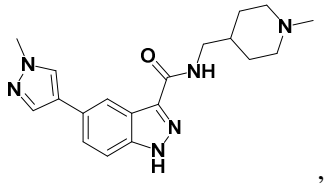
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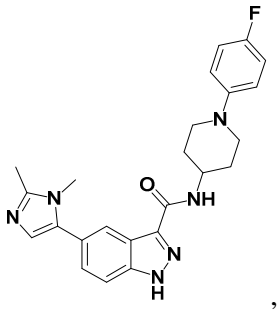
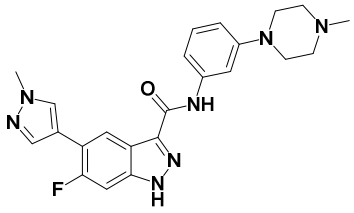
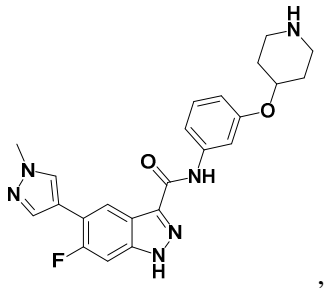
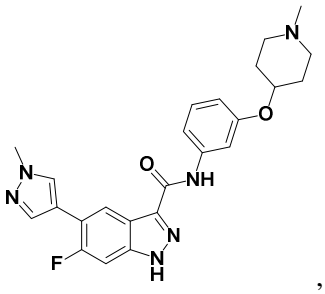
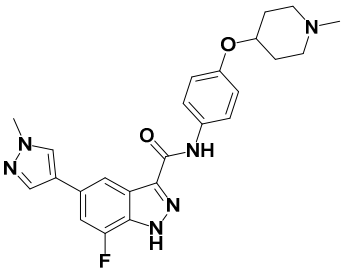
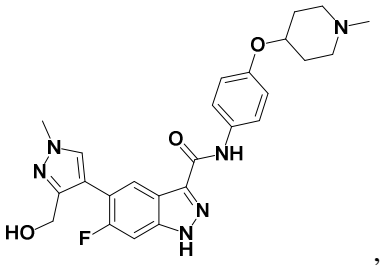
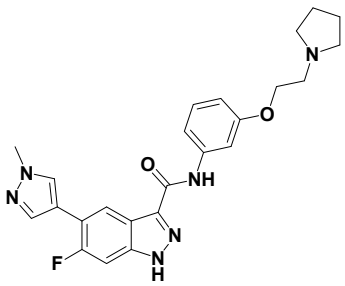
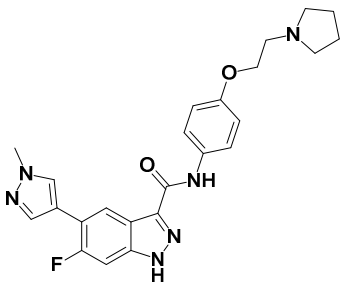
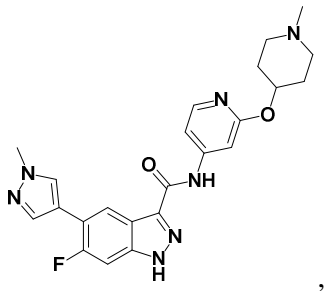
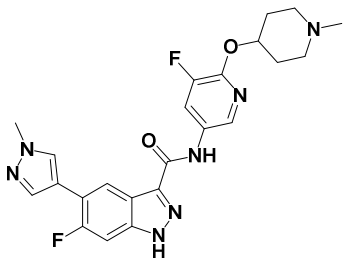
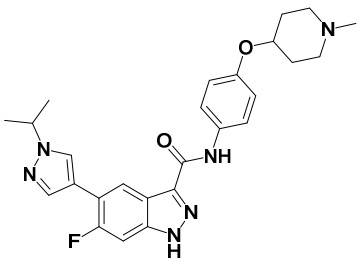
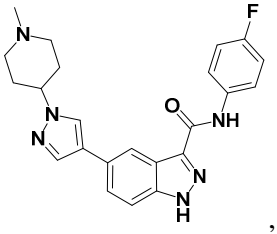
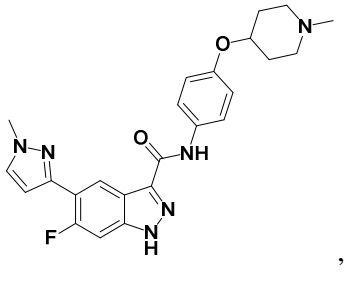
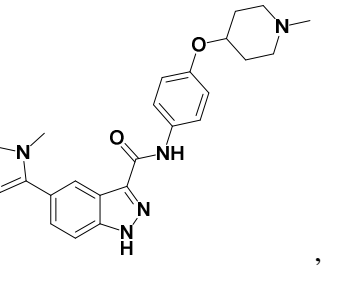
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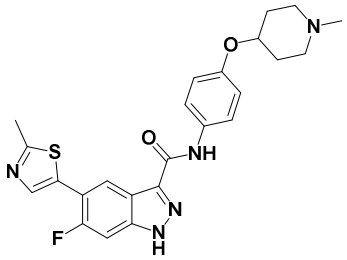

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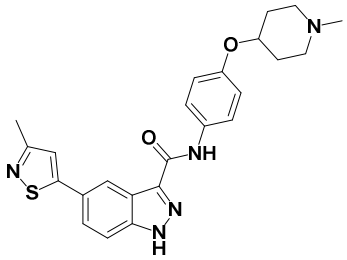
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, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1-18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

20. Use of the compound according to any of claims 1-18, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder or disease in a patient, wherein the disorder or disease is selected from: tendinopathy, dermatitis, psoriasis, morphea, ichthyosis, Raynaud's syndrome, Darier's disease, cancer, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), degenerative disc disease, bone/osteoporotic fractures, a bone or cartilage disease, a neurological disorder, osteoarthritis, lung disease, and a fibrotic disorder, wherein the patient is human.