PYRIDYL IMIDAZOLES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[1] This application claims priority to European Application No. 23306385.8, filed August 17, 2023, the disclosure of which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[2] Disclosed herein are substituted pyridyl imidazole compounds, processes for their preparation, pharmaceutical compositions containing the compounds, as well as therapeutic uses thereof.

BACKGROUND

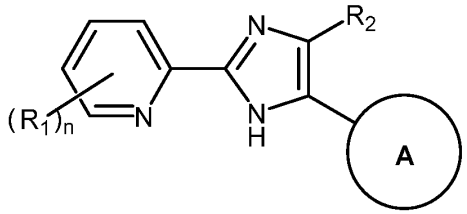
[3] MRGPRX2 is a G-protein coupled receptor (GPCR) expressed on mast cells involved in inflammation pathways, including the non-histaminergic activation of mast cells. *See* Meixong, J., et al., *Immunity*, 50, 1163-1171 (2019). MRGPRX2 is a member of the X subfamily of the Mas family of GPCRs. MRGPRX2 is activated by numerous secretagogues, including neuropeptides, eosinophil granule proteins, and antimicrobial peptides. In response to MRGPRX2 activation, mast cells may undergo degranulation and release tryptase, which preferentially triggers non-histaminergic itch, as well as chymase, carboxipeptidases, histamine, serotonin, chemokines, and cytokines. *See* Corbiere, A., et al., *Experimental Dermatology* 30, 193-200 (2020). This activation can lead to type 2 inflammation, pruritis, and pain. Preclinical data demonstrates that blocking the activation of MRGPRX2 has the potential to effectively treat a range of mast-cell-mediated diseases. *See, e.g.*, Meixong, J., et al.; Ogasawara, H. & Noguchi, M., *Cells*, 10, 2906 (2021); Quan, P.L., et al., *Intl. J. Molecular Sciences*, 22, 4421 (2021); Al Hamwi, G., et al., *Pharmacology & Therapeutics*, 2:38, 108529 (2022).

[4] Currently used treatments for inflammatory diseases typically have one or more of the following drawbacks: limited efficacy, need for injection, or significant side effects. MRGPRX2 antagonists of the present disclosure may provide safe, oral, and efficacious treatments for diseases, disorders and conditions involving inflammation, itch, and/or pain.

BRIEF SUMMARY

[5] The present disclosure describes substituted pyridyl imidazole compounds, processes for their preparation, pharmaceutical compositions containing the compounds, as well as therapeutic uses thereof.

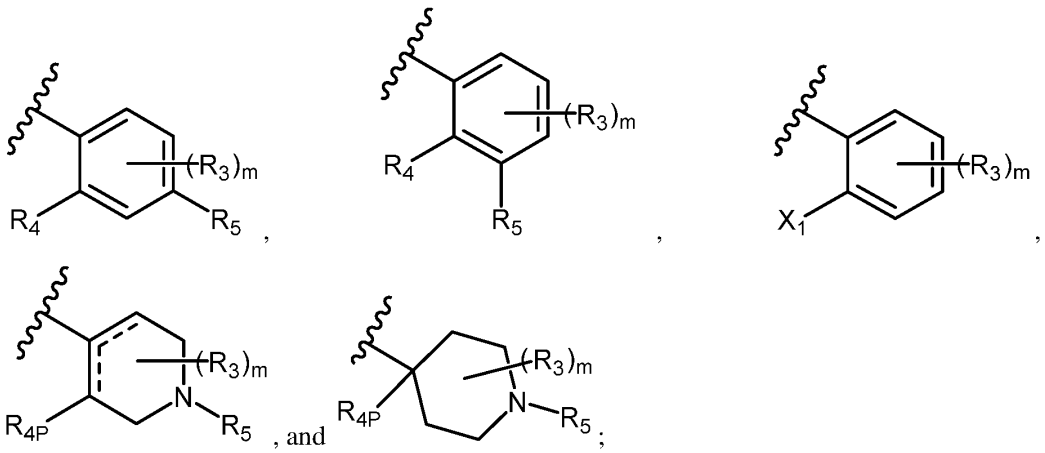
[6] One aspect of the present disclosure is a compound of formula I



I,

wherein:

A is selected from



each ----- is a single or a double bond, provided two adjacent ----- are not both double bonds;

each instance of R_1 is independently selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_2 is selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

each instance of R_3 is independently selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_4 is selected from halogen, cyano, $-OR_{11}$, $-NR_{11}R_{12}$, $-SR_{11}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_{4P} is selected from hydrogen, halogen, cyano, $-OR_{11}$, $-NR_{11}R_{12}$, $-SR_{11}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-C(=NR_9)NR_7R_8$, $-OC(=O)R_6$, $-OC(=O)OR_7$, $-OC(=O)NR_7R_8$, $-NR_9C(=O)R_6$, $-NR_9C(=O)OR_7$, $-NR_9C(=O)NR_7R_8$, $-NR_9C(=NR_9)NR_7R_8$, $-SR_7$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, $-S(=O)(=NR_9)R_6$, and $-S(=O)(=NR_9)NR_7R_8$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, aryl, C_1-C_3 arylalkyl, monocyclic heteroaryl, and C_1-C_3 heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pNR_{11}R_{12}$, $-(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(arylene)R_{13}, heterocyclyl, or -(heterocyclylene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, aryl, C_1-C_3 arylalkyl, heteroaryl, and C_1-C_3 heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, or $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, or $-NR_9S(=O)_2NR_{11}R_{12}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic

heteroarylalkyl, and -N=S(Me)$_2$=O, which groups are unsubstituted or substituted with one or more R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or more R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_4 alkyl), -C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)OH, -OC(=O)O(C_1-C_4 alkyl), -OC(=O)NH_2, -OC(=O)NH(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(=O)(C_1-C_4 alkyl), -NHC(=O)OH, -NHC(=O)O(C_1-C_4 alkyl), -NHC(=O)NH_2, -NHC(=O)NH(C_1-C_4 alkyl), -NHC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)OH, -N(C_1-C_4 alkyl)C(=O)O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)NH_2, -N(C_1-C_4 alkyl)C(=O)NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$OH, -$(CH_2)_q$O(C_1-C_4 alkyl), -$(CH_2)_q$$NH_2$, -$(CH_2)_q$NH($C_1$-$C_4$ alkyl), -$(CH_2)_q$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)OH, -$(CH_2)_q$C(=O)O(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)NH_2, -$(CH_2)_q$C(=O)NH(C_1-C_4 alkyl), -$(CH)_q$C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -S(=O)$_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a heterocyclyl ring;

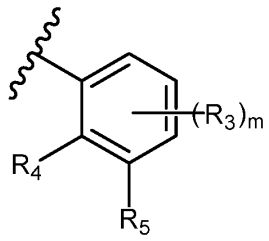
X_1 is halogen;

m is 0 or 1;

n is 1 or 2;

each p is independently 1, 2, or 3; and

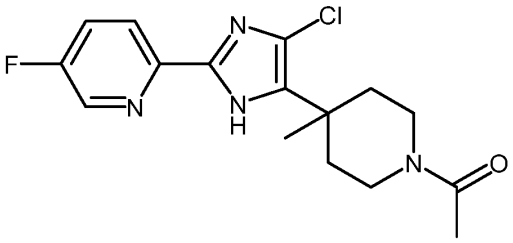
each q is independently 1, 2, or 3;



wherein when A is , R_4 and R_5 may be taken together with the carbons connecting them to form a 5- or 6-membered heterocyclyl ring;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,

provided the compound of formula I is not of formula



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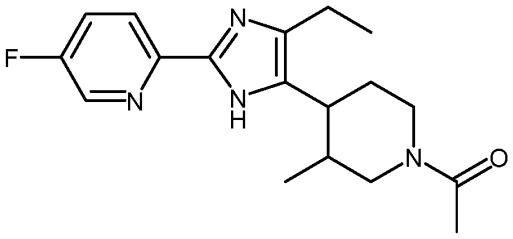

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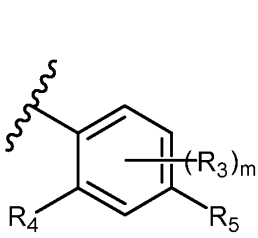
[7] One embodiment is a compound of formula I, wherein:

A is selected from



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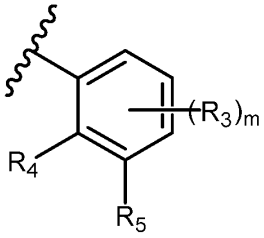

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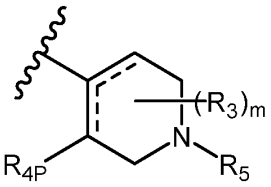

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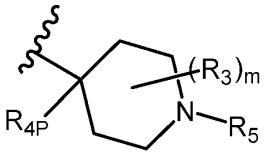

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R_1 is selected from halogen, -OR_{11}, -$NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_2 is selected from halogen, -OR_{11}, -$NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

each instance of R_3 is independently selected from halogen, -OR_{11}, -$NR_{11}R_{12}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_4 is selected from halogen, -OR_{11}, -$NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_{4P} is selected from halogen, -OR_{11}, -$NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$C(=NR_9)NR_7R_8$, -SR_7, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, -$S(=O)(=NR_9)R_6$, and -$S(=O)(=NR_9)NR_7R_8$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, phenyl, C_1-C_3 phenylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, cyano, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$N^+(O^-)R_{11}R_{12}$, -SR_{11}, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$OC(=O)OR_{11}$, -$OC(=O)NR_{11}R_{12}$, -$NR_9C(=O)R_{10}$, -$NR_9C(=O)OR_{11}$, -$NR_9C(=O)NR_{11}R_{12}$, -$NR_9C(=NR_9)NR_{11}R_{12}$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$, -$S(=O)_2NR_{11}R_{12}$, -$S(=O)(=NR_9)R_{10}$, -$S(=O)(=NR_9)NR_{11}R_{12}$, -$NR_9S(=O)_2R_{10}$, -$NR_9S(=O)_2NR_{11}R_{12}$, -$(CH_2)_pOR_{11}$, -$(CH_2)_pNR_{11}R_{12}$, -

$(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(phenylene)R_{13}, 4- to 6-membered heterocyclyl, or -(4- to 6-membered heterocyclene)R_{13}; and

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, phenyl, C_1-C_3 phenylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, or $-S(=O)(=NR_9)NR_{11}R_{12}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, and $-N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), $-C(=O)NH_2$, -C(=O)NH(C_1-C_4 alkyl), -C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)OH, -OC(=O)O(C_1-C_4 alkyl), $-OC(=O)NH_2$, -OC(=O)NH(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(=O)(C_1-C_4 alkyl), -NHC(=O)OH, -NHC(=O)O(C_1-C_4 alkyl), $-NHC(=O)NH_2$, -NHC(=O)NH(C_1-C_4 alkyl), -NHC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)OH, -N(C_1-C_4 alkyl)C(=O)O(C_1-C_4 alkyl), -N(C_1-C_4

alkyl)C(=O)NH_2, -N(C_1-C_4 alkyl)C(=O)NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$OH, -$(CH_2)_q$O(C_1-C_4 alkyl), -$(CH_2)_q$$NH_2$, -$(CH_2)_q$NH($C_1$-$C_4$ alkyl), -$(CH_2)_q$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)OH, -$(CH_2)_q$C(=O)O(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)NH_2, -$(CH_2)_q$C(=O)NH(C_1-C_4 alkyl), -$(CH)_q$C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -S(=O)$_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a 4- to 6-membered heterocyclyl ring;

m is 0 or 1;

n is 1;

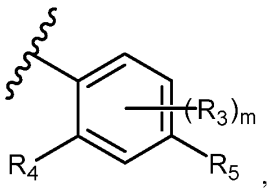
each p is 1; and

each q is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[8] One embodiment is a compound of formula I, wherein:

A is selected from



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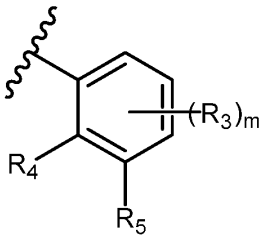

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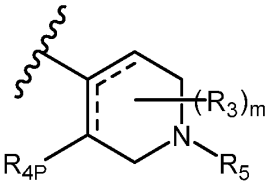

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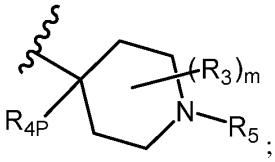

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R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -SR_7, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_p$(phenylene)R_{13}, or –(4- to 6-membered heterocyclene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, and $-N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6- membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), $-NH_2$, -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), $-C(=O)NH_2$, -OC(=O)(C_1-C_4 alkyl), -OC(=O)O(C_1-C_4 alkyl), $-(CH_2)_qOH$, and $-S(=O)_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a 4-membered heterocyclyl ring;

m is 0;

n is 1;

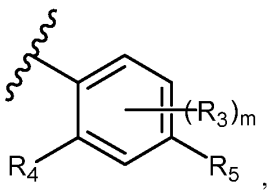
each p is 1; and

each q is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[9] One embodiment is a compound of formula I, wherein:

A is selected from



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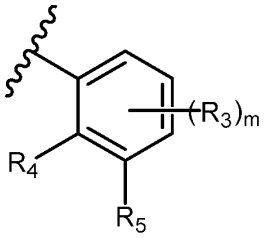

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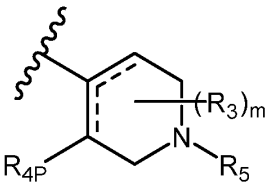
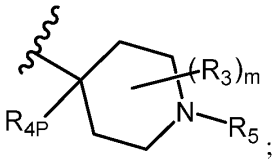


, and


;

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro, chloro, and methyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -SR_7, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -NHC(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$, -NR_9S(=O)$_2R_{10}$, -NR_9S(=O)$_2$N$R_{11}R_{12}$, -(CH$_2$)OR_{11}, -(CH$_2$)C(=O)OR_{11}, -(CH$_2$)(phenylene)R_{13}, or –(4- to 6-membered heterocyclene)R_{13};

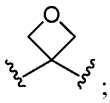
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4 to 6-membered heterocyclyl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are

unsubstituted or substituted with one, two, or three of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, or -$C(=O)NR_{11}R_{12}$,;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6- membered heterocyclyl, and -$N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3- to 6-membered cycloalkylalkyl, 4- to 6- membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

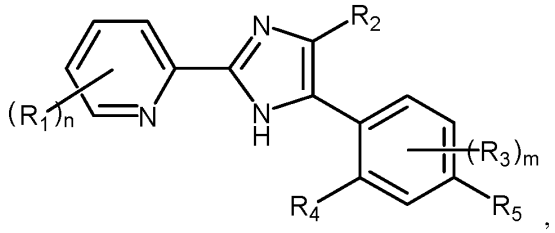
each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -OMe, -NH_2, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -$C(=O)NH_2$, -C(=O)OtBu, -OC(=O)Me, -OC(=O)OMe, -OC(=O)OEt, -(CH_2)OH, and -$S(=O)_2$(Me), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form:  ;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

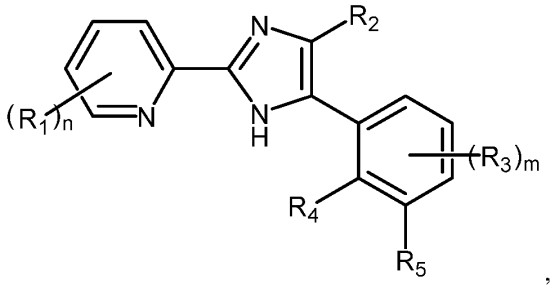
[10] One embodiment is a compound of formula I, wherein the compound is of formula I-A



I-A,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

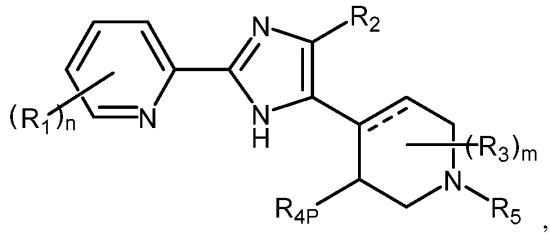
[11] One embodiment is a compound of formula I according to any one of claims 1-4, wherein the compound is of formula I-B



I-B,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

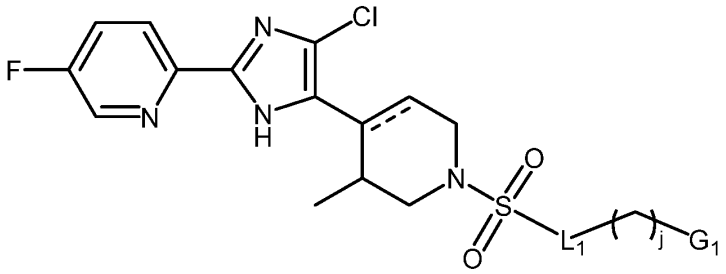
[12] One embodiment is a compound of formula I, wherein the compound is of formula I-D



I-D,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[13] One embodiment is a compound of formula I, wherein the compound is of formula I-G1



I-G1,

wherein:

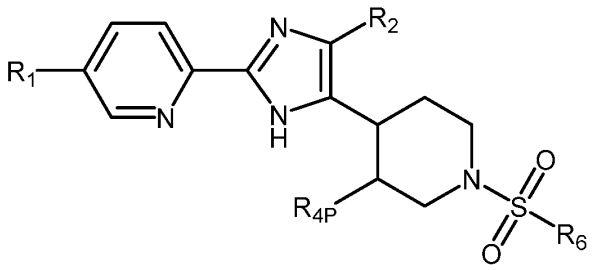
L_1 is selected from -CH_2- and -$N(R_{11})$-;

G_1 is selected from -OR_{11}, $NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$,, -$S(=O)_2R_{10}$, -$S(=O)_2NR_{11}R_{12}$, 4- to 6-membered heterocyclyl, and monocyclic heteroaryl; and

j is 0, 1, or 2;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

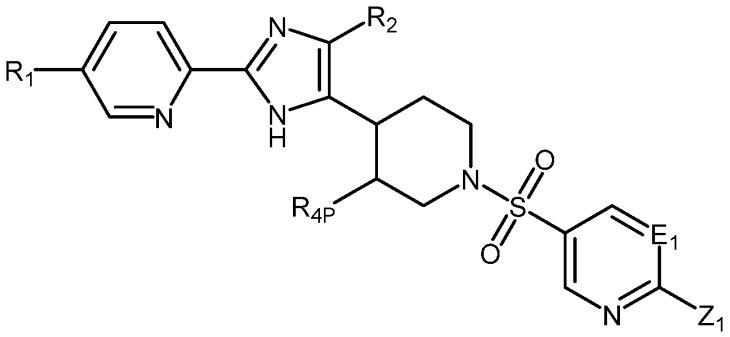
[14] One embodiment is a compound of formula I, wherein the compound is of formula I-H



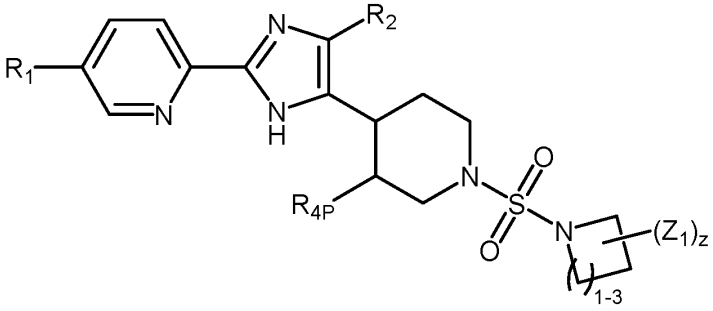
I-H,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

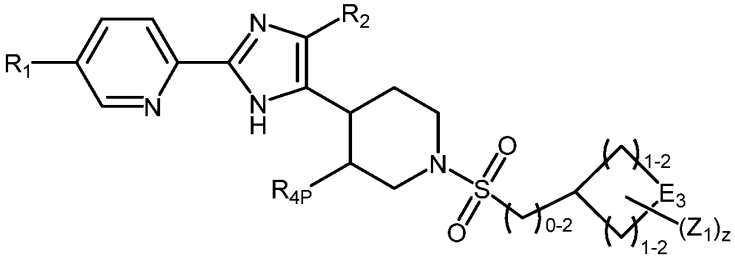
[15] One embodiment is a compound of formula I, wherein the compound is of any one of formulas -J1 to I-J5,



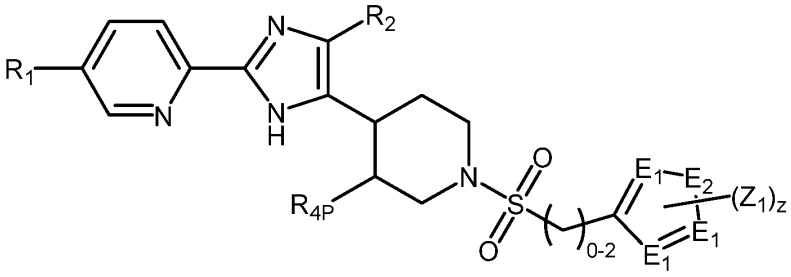
I-J1,



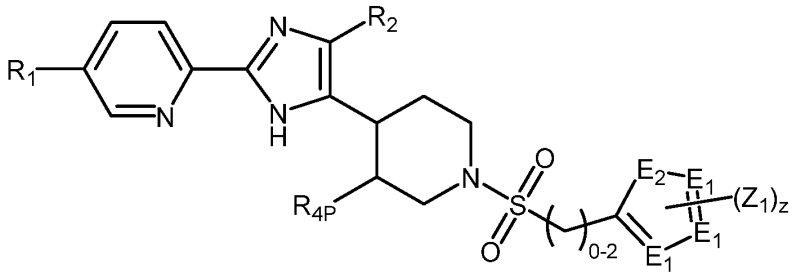
I-J2,



I-J3,



I-J4,



I-J5,

wherein:

z is 0, 1, or 2 where valency permits;

each instance of Z_1 is independently selected from halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pNR_{11}R_{12}$, $-(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(arylene)R_{13}, heterocyclyl, or -(heterocyclene)R_{13};

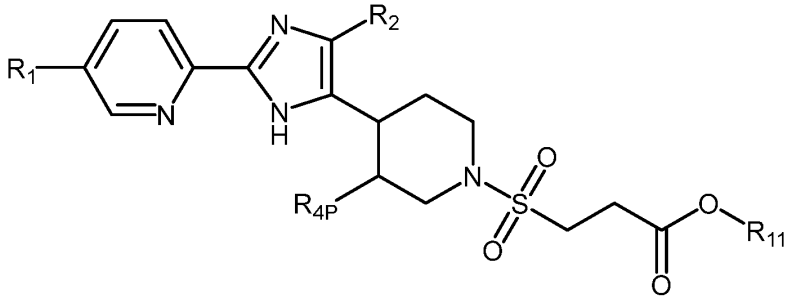
each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-; and

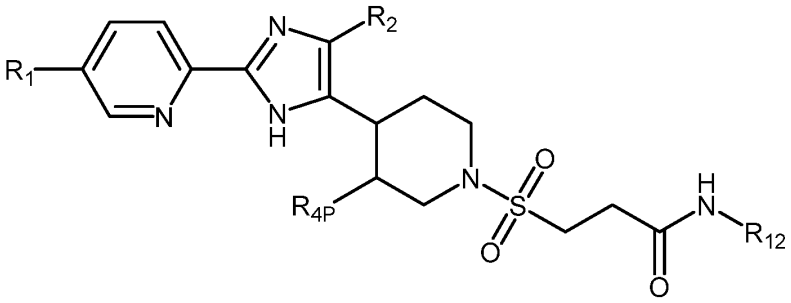
E_3 is selected from $-CH_2-$, -NH-, and -O-;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

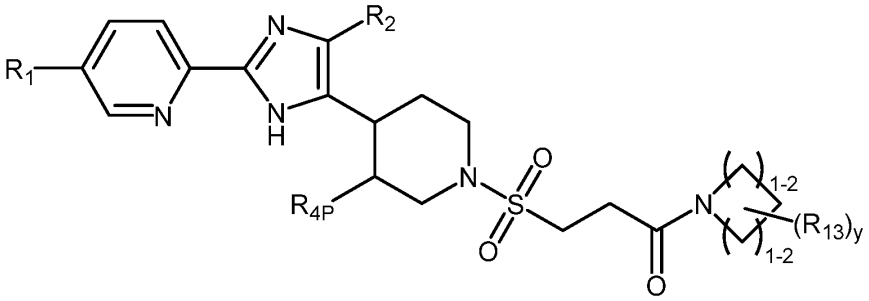
[16] One embodiment is a compound of formula I, wherein the compound is of any one of formulas I-K1 to I-K8



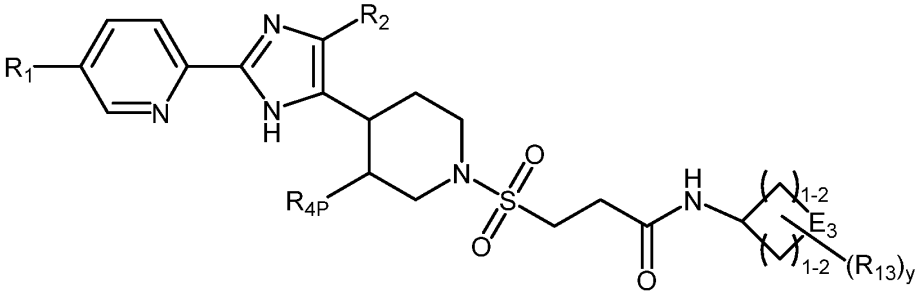
I-K1,



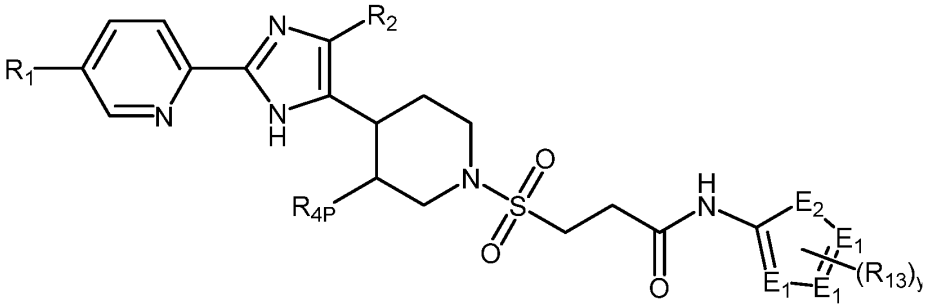
I-K2,



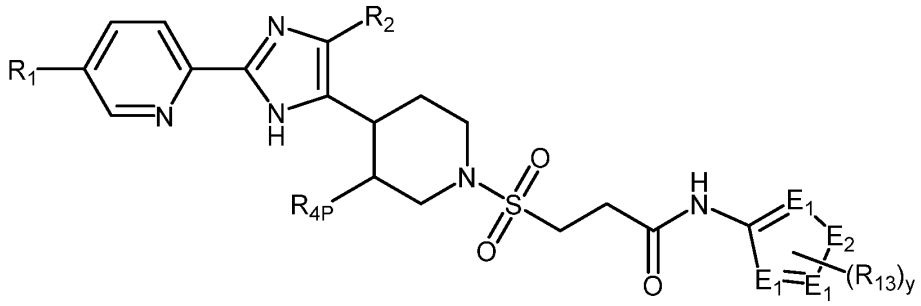
I-K3,



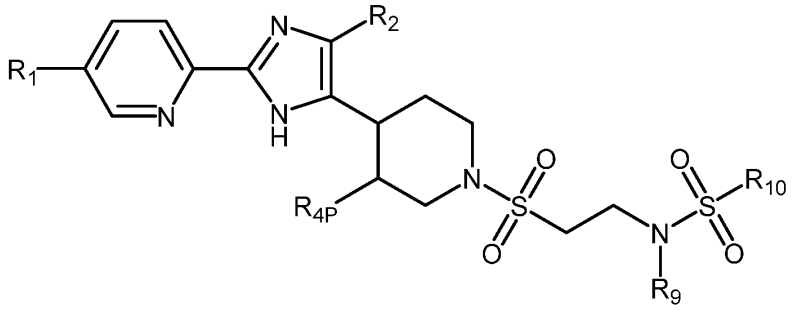
I-K4,



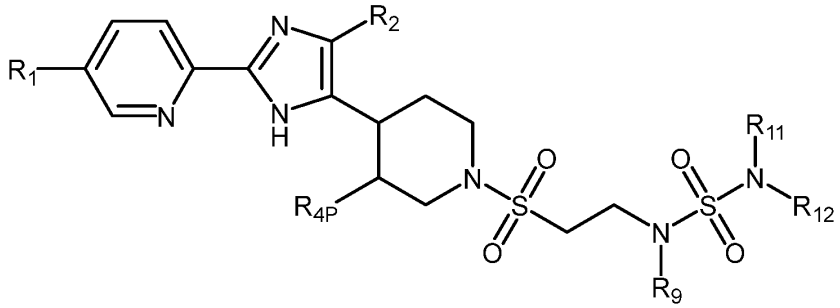
I-K5,



I-K6,



I-K7,



I-K8

wherein:

y is 0, 1, or 2 where valency permits;

each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-; and

E_3 is selected from -CH_2-, -NH-, and -O-;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[17] One embodiment is a compound of formula I, wherein

R_1 is selected from halogen and C_1-C_4 alkyl;

R_2 is selected from halogen and C_1-C_4 alkyl; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[18] One embodiment is a compound of formula I, wherein

R_1 is fluoro;

R_2 is chloro; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[19] One embodiment is a compound of formula I, wherein

R_4 is selected from halogen and C_1-C_4 alkyl;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[20] One embodiment is a compound of formula I according to any one of claims 1 to 7, wherein

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[21] One embodiment is a compound of formula I, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[22] One embodiment is a compound of formula I, wherein R_5 is $-S(=O)_2R_6$;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[23] One embodiment is a compound selected from the compounds listed in Table 1,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[24] Another aspect of the present disclosure is a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

[25] Another aspect of the present disclosure is a method of treating a disease, disorder, or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,

wherein the disease, disorder, or condition is selected from an inflammatory disorder, an allergic disorder, a skin disorder, a mast cell disorder, a pain disorder, and an itch disorder.

[26] Another aspect of the present disclosure is a method of treating a disease, disorder, or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,

wherein the disease, disorder, or condition is selected from atopic dermatitis, chronic urticaria, chronic spontaneous urticaria, inducible urticaria, prurigo, prurigo nodularis, pruritus, asthma, rosacea, contact dermatitis, allergic contact dermatitis, anaphylaxis, anaphylactoid drug reaction, allergy, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, allergic rhinitis, chronic rhinosinusitis, aggressive periodontitis, systemic mastocytosis, cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, interstitial cystitis, heriditary alpha tryptasemia, chronic itch, and chronic pain.

[27] In one embodiment, the disease, disorder, or condition is selected from atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma.

[28] Another aspect of the present disclosure is a compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use as a medicament.

[29] Another aspect of the present disclosure is a compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically

acceptable salt thereof, for use in the treatment of a disease, disorder, or condition selected from an inflammatory disorder, an allergic disorder, skin disorder, a mast cell disorder, a pain disorder, and an itch disorder.

[30] Another aspect of the present disclosure is a compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition selected from atopic dermatitis, chronic urticaria, chronic spontaneous urticaria, inducible urticaria, prurigo, prurigo nodularis, pruritus, asthma, rosacea, contact dermatitis, allergic contact dermatitis, anaphylaxis, anaphylactoid drug reaction, allergy, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, allergic rhinitis, chronic rhinosinusitis, aggressive periodontitis, systemic mastocytosis, cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, interstitial cystitis, heriditary alpha tryptasemia, chronic itch, and chronic pain.

[31] In one embodiment, the disease, disorder, or condition is selected from atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma.

[32] Another aspect of the present disclosure is a medicament, characterized in that it comprises the compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[33] Another aspect of the present disclosure is the use of a compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for preparing a medicament intended for the treatment of a disease, disorder, or condition selected from an inflammatory disorder, an allergic disorder, skin disorder, a mast cell disorder, a pain disorder, and an itch disorder.

DETAILED DESCRIPTION

[34] It is to be understood that the disclosed embodiments are merely examples of the disclosure, which may be embodied in various forms. Well-known functions or constructions are not described in detail to avoid obscuring the present disclosure in unnecessary detail. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a basis for the claims and as a representative basis for teaching one

skilled in the art to variously employ the present disclosure in virtually any appropriately detailed structure.

[35] As used herein "H," "-H," or "hydrogen" refer to a hydrogen atom or radical. In some embodiments, the hydrogen is an isotope of hydrogen. In some embodiments, the hydrogen is deuterium (D), for example a methyl, Me, or CH_3 group may be CD_3.

[36] As used herein, the term "alkyl" refers to a linear or branched saturated hydrocarbon group. A C_X-C_Y alkyl group refers to an alkyl group having between X and Y carbon atoms, for example a C_1-C_6 alkyl group refers to an alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms. Exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isopentyl, neopentyl, and the like.

[37] As used herein, the term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms have been substituted by a halogen atom. A C_X-C_Y haloalkyl group refers to a haloalkyl group having between X and Y carbon atoms, for example a C_1-C_6 haloalkyl group refers to a haloalkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms (in addition to one or more halogen atoms). Exemplary haloalkyl groups include chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, 1,2-difluoroethyl, 1,1,2,2-tetrafluoroethyl, and the like.

[38] As used herein, the term "halogen" refers to fluoro, chloro, bromo, or iodo.

[39] As used herein, the term "heteroalkyl" refers to a linear or branched, non-cyclic saturated group containing 1, 2, or 3 heteroatoms, such as nitrogen, oxygen, or sulfur, which in the case of a group containing 2 or more heteroatoms the heteroatoms may be the same or different. Heteroalkyl groups include alkoxy, alkoxyalkyl, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylthio, and alkylthioalkyl groups. A C_X-C_Y heteroalkyl group refers to a heteroalkyl group having between X and Y carbon atoms, for example a C_1-C_6 heteroalkyl group refers to a heteroalkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms (in addition to 1, 2, or 3 heteroatoms). Exemplary heteroalkyl groups include methoxy, ethoxy, propoxy, isopropoxy, methoxymethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxymethyl, 2-methoxyethyl, 2-methoxyethoxy, (2-hydroxyethoxy)ethyl, (2-methoxyethoxy)ethyl, 3-hydroxy-2-(hydroxymethyl)propyl, 3-methoxy-2-(methoxymethyl)propyl, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 1-aminoethyl, 2-aminoethyl, methanethiolato, ethanethiolato, or the like.

[40] As used herein, the term "aryl" refers to an aromatic monocyclic or bicyclic ring system containing between 5 and 10 carbon atoms. Exemplary aryl groups include phenyl and naphthyl.

[41] As used herein, the term "arylalkyl" refers to an alkyl group substituted with an aryl group. A C_X-C_Y arylalkyl group refers to an arylalkyl group having between X and Y carbon atoms in the alkyl chain, for example a C_1-C_3 arylalkyl group refers to an arylalkyl group having an alkyl group of 1, 2, or 3 carbon atoms substituted with an aryl group. Exemplary arylalkyl groups include benzyl and phenethyl.

[42] As used herein, the term "cycloalkyl" refers to a non-aromatic monocyclic ring system containing between 3 and 8 carbon atoms. A C_X-C_Y cycloalkyl group (or an X- to Y-membered cycloalkyl group) refers to a cycloalkyl group having between X and Y carbon atoms, for example a C_3-C_6 cycloalkyl group (or a 3- to 6-membered cycloalkyl group) to refers to a cycloalkyl group having 3, 4, 5, or 6 carbon atoms. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, and the like.

[43] As used herein, the term "cycloalkylalkyl" refers to an alkyl group substituted with a cycloalkyl group. A C_X-C_Y M- to N-membered cycloalkylalkyl group refers to a cycloalkylalkyl group having between X and Y carbon atoms in the alkyl chain and between M and N carbon atoms in the cycloalkyl ring, for example a C_1-C_3 3- to 6-membered cycloalkylalkyl group refers to a cycloalkylalkyl group having an alkyl group of 1, 2, or 3 carbon atoms substituted with a cycloalkyl group of 3, 4, 5, or 6 carbon atoms. Exemplary cycloalkyl groups include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl.

[44] As used herein, the term "heteroaryl" refers to a cyclic aromatic group containing between 1 and 10 carbon atoms and containing between 1 and 4 heteroatoms, such as nitrogen, oxygen, or sulfur, which in the case of a group containing 2 or more heteroatoms the heteroatoms may be the same or different, wherein the group contains between 5 and 10 carbon atoms or heteroatoms. Heteroaryl groups include those where a nitrogen atom of the heteroaryl ring is substituted with an oxide ($-O^-$), for example, pyridinyl N-oxide and the like, where the context so permits. Heteroaryl groups may be monocyclic or bicyclic. As used

herein, the term "monocyclic heteroaryl" means a cyclic aromatic group containing 1 to 5 carbon atoms and containing between 1 and 4 heteroatoms, such as nitrogen, oxygen, or sulfur, which in the case of a group containing 2 or more hetero atoms may be the same or different, wherein the monocyclic ring contains between 5 and 6 carbon atoms or heteroatoms. Exemplary heteroaryl groups include benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzofuranyl, benzotriazolyl, benzoxazolyl, furanyl, furazanyl, indolyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridinyl N-oxide, pyrimidinyl, pyrrolo[2,3-b]pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrrolyl, 1,2,4-thiadiazolyl, 1,2,4-triazinyl, 1,3,4-thiadiazolyl, thiazolyl, triazolyl, tetrazolyl, thiophenyl, and the like.

[45] As used herein, the term "heteroarylalkyl" refers to an alkyl group substituted with a heteroaryl group. A C_X-C_Y heteroarylalkyl group refers to a heteroarylalkyl group having between X and Y carbon atoms in the alkyl chain, for example a C_1-C_3 heteroarylalkyl group refers to a heteroarylalkyl group having an alkyl group of 1, 2, or 3 carbon atoms substituted with a heteroaryl group. A "monocyclic heteroarylalkyl" group refers to an alkyl group substituted with a monocyclic heteroaryl group. Exemplary heteroarylalkyl groups include pyridylmethyl, pyrrolylmethyl, furanylmethyl, and the like.

[46] As used herein, the term "heterocyclyl" refers to a non-aromatic (saturated or unsaturated) monocyclic group containing between 1 and 5 carbon atoms and between 1 and 4 heteroatoms, such as nitrogen, oxygen, or sulfur, which in the case of a group containing 2 or more heteroatoms the heteroatoms may be the same or different, wherein the monocyclic ring contains between 3 and 6 carbon atoms or heteroatoms. Heterocyclyl groups include those where one or more carbon atoms of the heterocyclyl ring is substituted with an oxo (=O), for example, lactones, lactams, oxopyrrolidinyl, oxopiperidinyl, oxoimidazolidinyl, oxo-4,5-dihydrotetrazolyl, and the like; or a nitrogen atom of the heterocyclyl ring is substituted with an oxide ($-O^-$), for example, pyrrolidinyl N-oxide, piperidinyl N-oxide, and the like, where the context so permits. An X- to Y-membered heterocyclyl group refers to a heterocyclyl group having between X and Y ring atoms (which may be carbon or heteroatoms). Exemplary heterocyclyl groups include azetidinyl, oxetanyl, thietanyl, diazetidinyl, dioxetanyl, dithietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl,

dithiolanyl, piperidinyl, tetrahydropyridinyl, tetrahydropyranyl, thianyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, lactones, lactams, oxopyrrolidinyl, oxopiperidinyl, oxoimidazolidinyl, oxo-4,5-dihydrotetrazolyl, pyrrolidinyl N-oxide, piperidinyl N-oxide, and the like.

[47] As used herein, the term "heterocyclylalkyl" refers to an alkyl group substituted with a heterocyclyl group. A C_X-C_Y heterocyclylalkyl group refers to a heterocyclylalkyl group having between X and Y carbon atoms in the alkyl chain, for example a C_1-C_3 heterocyclylalkyl group refers to a heterocyclylalkyl group having an alkyl group of 1, 2, or 3 carbon atoms substituted with a heterocyclyl group. Exemplary heterocyclylalkyl groups include piperidinylmethyl, pyrrolidinylmethyl, azetidinylmethyl, 2-(oxo-4,5-dihydrotetrazolyl)ethyl, and the like.

[48] As used herein, the term "acyl" refers to a group attached through a carbonyl (-C(=O)-) linker, wherein the linker is bonded to an alkyl, hydroxy, alkoxy, amino, alkylamino, or dialkylamino group. A C_X-C_Y acyl group refers to an acyl group wherein any alkyl, if present in the acyl group, has between X and Y carbon atoms, for example, a C_1-C_4 acyl group refers to an acyl group selected from -C(=O)(C_1-C_4-alkyl), -C(=O)OH, -C(=O)O(C_1-C_4-alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_4-alkyl), and -C(=O)N(C_1-C_4-alkyl)$_2$.

[49] As used herein, the term "sulfonyl" refers to a group attached through a sulfonyl (-S(=O)$_2$-) linker, wherein the linker is bonded to an alkyl, amino, alkylamino, or dialkylamino group. A C_X-C_Y sulfonyl group refers to a sulfonyl group wherein any alkyl, if present in the sulfonyl group, has between X and Y carbon atoms, for example, a C_1-C_4 sulfonyl group refers to a sulfonyl group selected from -S(=O)$_2$(C_1-C_4-alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$NH(C_1-C_4-alkyl), and -S(=O)$_2$N(C_1-C_4-alkyl)$_2$.

[50] As used herein, the term "substituted" refers to a hydrogen radical of the designated moiety being replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. Unless otherwise noted, a substituent can be in any position, provided that the respective compound is sufficiently stable and is suitable as a pharmaceutical active compound. The prerequisite that a specific group and a compound of the formula I are sufficiently stable and suitable as a pharmaceutical active

compound applies in general with respect to the definitions of all groups in the compounds of the formula I, and compounds of a subformula of formula I.

[51] As used herein, the terms "independently" or "independently selected" means that the same or different values may be selected for multiple instances of a given variable in a single compound.

[52] As used herein, the term "unsubstituted" indicates that the respective group does not carry any of the specified non-hydrogen substituents.

[53] As used herein, the term "pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid and base addition salts of a compound of formula I, or a compound of a subformula of formula I. These salts can be prepared *in situ* during the final isolation and purification of the compounds.

[54] As used herein, " " indicates the bond between two atoms may be either a single or a double bond. When is a single bond between two carbon atoms, the carbon atoms each are bonded to one more hydrogen atom (or substituent in place of a hydrogen atom) than if had been a double bond. Correspondingly, when is a double bond, the carbon atoms each are bonded to one fewer hydrogen atom (or substituent in place of a hydrogen atom) than if had been a single bond. If two bonds are adjacent, both bonds may be a single bond, either may be single and the other a double bond, but both bonds may not be a double bond.

[55] If the compounds of the formula I, or compounds of a subformula of formula I, comprise one or more acidic or basic groups, for example basic heterocyclic groups, the corresponding physiologically or toxicologically acceptable salts are also included in the disclosure, especially the pharmaceutically acceptable salts. The compounds of the formula I, or compounds of a subformula of formula I, may thus be deprotonated on an acidic group and be used for example as alkali metal salts or as ammonium salts. Compounds of formula I, or compounds of a subformula of formula I, comprising at least one basic group may also be prepared and used in the form of their acid addition salts, for example in the form of pharmaceutically acceptable salts with inorganic acids and organic acids. Salts can in general be prepared from acidic and basic compounds of the formula I, or compounds of a subformula of formula I, by reaction with an acid or base in a solvent or diluent according to customary

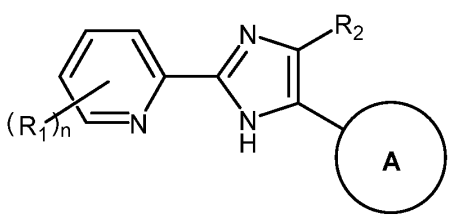
procedures. If the compounds of the formula I, or compounds of a subformula of formula I, simultaneously contain an acidic and a basic group in the molecule, the disclosure also includes internal salts (betaines, zwitterions) in addition to the salt forms mentioned. The present disclosure also comprises all salts of the compounds of the formula I, or compounds of a subformula of formula I, which, because of low physiological tolerability, are not directly suitable for use as a pharmaceutical, but are suitable as intermediates for chemical reactions or for the preparation of physiologically acceptable salts, for example by means of anion exchange or cation exchange.

[56] As used herein, the term "pharmaceutically acceptable excipient" refers to a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with the compound of the present disclosure to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the subject. The said excipients are selected, in accordance with the pharmaceutical form and method of administration desired, from the customary excipients, which are known to a person skilled in the art.

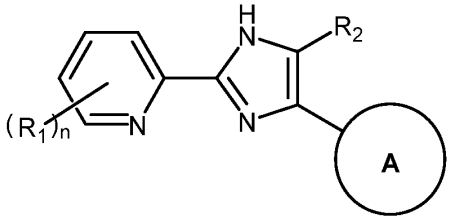
[57] As used herein, the term "therapeutically effective amount" refers to an amount of a compound/composition according to the present disclosure effective in producing the desired therapeutic effect.

[58] As used herein, the term "subject" refers to a human or animal subject. In some embodiments, the subject is human (i.e., a "patient"). In some embodiments, the subject is an animal.

[59] As used herein, the term "compounds of formula I", or "compounds of a subformula of formula I," and equivalent expressions, include racemic compounds of formula I, or compound of a subformula of formula I, and their enantiomers, diastereoisomers, tautomers, atropisomers, and mixtures thereof, where the context so permits. Tautomeric compounds of formula I are exemplified by formulas I (tautomer 1) an I (tautomer 2).



I (tautomer 1)



I (tautomer 2)

[60] Generally, in an imidazole with different substituents in the 3- and 4- position, substitution of the tautomeric proton, e.g., by alkylation, may generate a mixture of discrete regioisomers. For example, in the case of the alkylating agent is SEM-Cl, such a mixture will be referred to as "mixture of SEM-regioiosmers" herein.

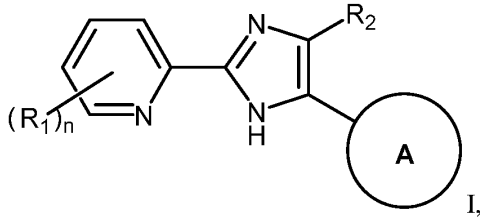
[61] As used herein, the term "subformula" refers to subsets of compound of formula I, such as compounds of formula I which are a compound of formula I-A, I-A1, I-A2, I-A3, I-A4, I-A5, I-A6, I-A7, I-B, I-B1, I-B2, I-B3, I-B4, I-B5, I-B6, I-B7, I-C, I-C1, I-C2, I-C3, I-D, I-D1, I-D2, I-D3, I-D4, I-D5, I-D6, I-D7, I-E, I-E1, I-E2, I-E3, I-E4, I-E5, I-E6, I-E7, I-F, I-F1, I-F2, I-F3, I-F4, I-F5, I-F6, I-F7, I-G1, I-G2, I-H, any one of I-J1 to I-J21, or any one of I-K1 to I-K8 where the context so permits.

[62] As used herein, the term "isomers" refers to compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space. The labels "isomer 1" and "isomer 2," or the like, can be assigned to isomers of known absolute configuration or can be used to describe stereoisomers of unknown absolute configuration. Likewise, the labels "R*" or "S*" may be assigned to stereocenters of some enantiomeric compounds of unknown absolute configuration. The use of the labels "isomer 1," "isomer 2," R*, and S* is not to be interpreted as indicating that the absolute configuration of both isomers is known. The term "isomeric mixture" refers to a mixture of isomers.

[63] As used herein, the term "stereoisomers" is a general term used for all isomers of the individual molecules that differ only in the orientation of their atoms in space. The term "diastereomers" refers to stereoisomers that are not mirror images of one another and the term "enantiomers" refers to stereoisomers that are non-superimposable mirror images of each other. An enantiomer can be characterized by the absolute configurations of its asymmetric

centers, chiral axes and planes, and is described by the R- and S-sequencing rules of Cahn, Ingold and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (−)-isomers respectively). A chiral compound can exist as either individual enantiomer, individual diastereomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture." A mixture containing any proportions of the diastereomers is called a "diastereomeric mixture". For a compound with two chiral centers in a cyclic system, "trans" refers to the substituents (other than hydrogen) of the chiral centers are on opposite sides of the ring; "cis" refers to the substituents of the chiral centers are on the same sides of the ring. "Racemic trans" refers to equal proportions of two trans enantiomers and "racemic cis" refers to equal proportions of two cis enantiomers. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can also be directly separated using chiral chromatographic techniques or indirectly using enzymatic methods. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present disclosure.

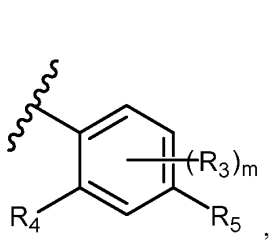
[64] One aspect of the present disclosure is a compound of formula I



I,

wherein:

A is selected from



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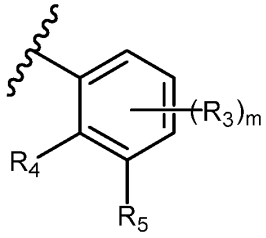

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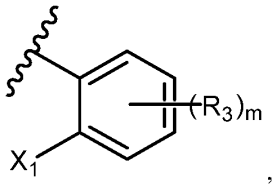

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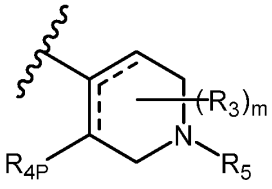

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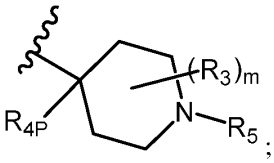


;

each ═══ is a single or a double bond, provided two adjacent ═══ are not both double bonds;

each instance of R_1 is independently selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_2 is selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

each instance of R_3 is independently selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_4 is selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_{4P} is selected from hydrogen, halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$C(=NR_9)NR_7R_8$, -$OC(=O)R_6$, -$OC(=O)OR_7$, -$OC(=O)NR_7R_8$, -$NR_9C(=O)R_6$, -$NR_9C(=O)OR_7$, -$NR_9C(=O)NR_7R_8$, -$NR_9C(=NR_9)NR_7R_8$, -SR_7, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, -$S(=O)(=NR_9)R_6$, and -$S(=O)(=NR_9)NR_7R_8$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, aryl, C_1-C_3 arylalkyl, monocyclic heteroaryl, and C_1-C_3 heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, cyano, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$N^+(O^-)R_{11}R_{12}$, -SR_{11}, -$C(=O)R_{10}$, -

$C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pNR_{11}R_{12}$, $-(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(arylene)R_{13}, heterocyclyl, or -(heterocyclylene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, aryl, C_1-C_3 arylalkyl, heteroaryl, and C_1-C_3 heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, or $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, or $-NR_9S(=O)_2NR_{11}R_{12}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, and $-N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or more R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or more R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), $-C(=O)NH_2$, -C(=O)NH(C_1-C_4 alkyl), -C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)OH, -OC(=O)O(C_1-C_4

alkyl), -OC(=O)NH_2, -OC(=O)NH(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(=O)(C_1-C_4 alkyl), -NHC(=O)OH, -NHC(=O)O(C_1-C_4 alkyl), -NHC(=O)NH_2, -NHC(=O)NH(C_1-C_4 alkyl), -NHC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)OH, -N(C_1-C_4 alkyl)C(=O)O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)NH_2, -N(C_1-C_4 alkyl)C(=O)NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$OH, -$(CH_2)_q$O(C_1-C_4 alkyl), -$(CH_2)_q$$NH_2$, -$(CH_2)_q$NH($C_1$-$C_4$ alkyl), -$(CH_2)_q$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)OH, -$(CH_2)_q$C(=O)O(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)NH_2, -$(CH_2)_q$C(=O)NH(C_1-C_4 alkyl), -$(CH)_q$C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -S(=O)$_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a heterocyclyl ring;

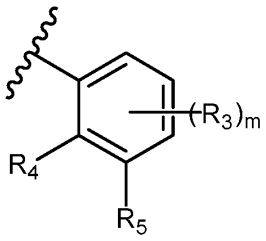
X_1 is halogen;

m is 0 or 1;

n is 1 or 2;

each p is independently 1, 2, or 3; and

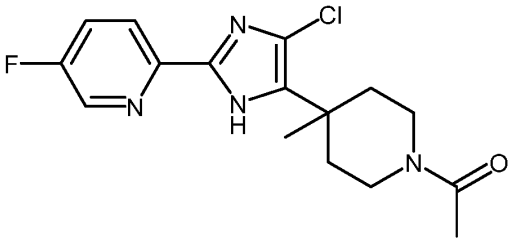
each q is independently 1, 2, or 3;



wherein when A is , R_4 and R_5 may be taken together with the carbons connecting them to form a 5- or 6-membered heterocyclyl ring;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,

provided the compound of formula I is not of formula



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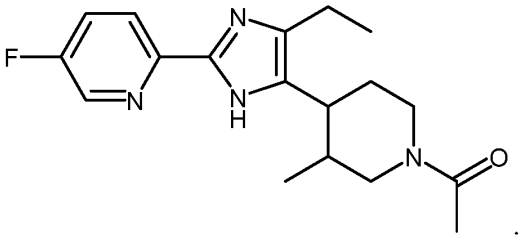

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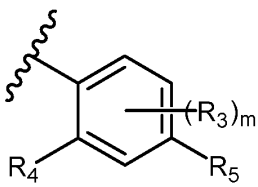
[65] One embodiment is a compound of formula I, wherein:

A is selected from



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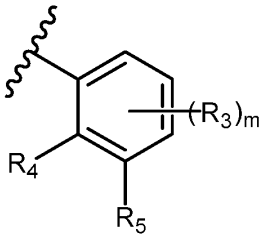

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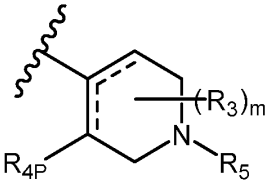
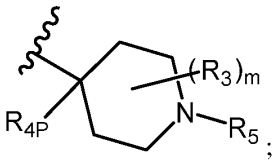


, and



;

R_1 is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_2 is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

each instance of R_3 is independently selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_4 is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_{4P} is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-C(=NR_9)NR_7R_8$, $-SR_7$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, $-S(=O)(=NR_9)R_6$, and $-S(=O)(=NR_9)NR_7R_8$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, phenyl, C_1-C_3 phenylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pNR_{11}R_{12}$, $-(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(phenylene)R_{13}, 4- to 6-membered heterocyclyl, or -(4- to 6-membered heterocyclene)R_{13}; and

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, phenyl, C_1-C_3 phenylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, or $-S(=O)(=NR_9)NR_{11}R_{12}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, and $-N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_4 alkyl), -C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)OH, -OC(=O)O(C_1-C_4 alkyl), -OC(=O)NH_2, -OC(=O)NH(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(=O)(C_1-C_4 alkyl), -NHC(=O)OH, -NHC(=O)O(C_1-C_4 alkyl), -NHC(=O)NH_2, -NHC(=O)NH(C_1-C_4 alkyl), -NHC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)OH, -N(C_1-C_4 alkyl)C(=O)O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)NH_2, -N(C_1-C_4 alkyl)C(=O)NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$OH, -$(CH_2)_q$O(C_1-C_4 alkyl), -$(CH_2)_q$$NH_2$, -$(CH_2)_q$NH($C_1$-$C_4$ alkyl), -$(CH_2)_q$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)OH, -$(CH_2)_q$C(=O)O(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)NH_2, -$(CH_2)_q$C(=O)NH(C_1-C_4 alkyl), -$(CH)_q$C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -$S(=O)_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a 4- to 6-membered heterocyclyl ring;

m is 0 or 1;

n is 1;

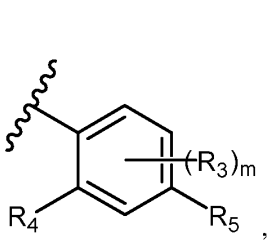
each p is 1; and

each q is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[66] One embodiment is a compound of formula I, wherein:

A is selected from



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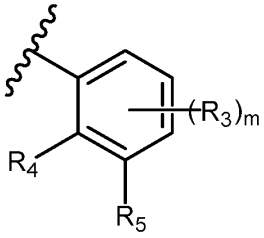

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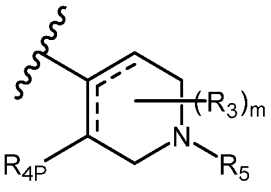

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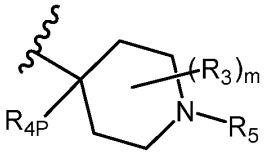


;

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -SR_7, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, -S(=O)$_2$N$R_{11}R_{12}$, -NR_9S(=O)$_2R_{10}$, -NR_9S(=O)$_2$N$R_{11}R_{12}$, -(CH_2)$_p$OR_{11}, -(CH_2)$_p$C(=O)OR_{11}, -(CH_2)$_p$(phenylene)R_{13}, or –(4- to 6-membered heterocyclene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -OC(=O)OR_{11}, -OC(=O)N$R_{11}R_{12}$, -NR_9C(=O)R_{10}, -NR_9C(=O)OR_{11}, -NR_9C(=O)N$R_{11}R_{12}$, -S(=O)$_2R_{10}$, -S(=O)$_2$N$R_{11}R_{12}$, -NR_9S(=O)$_2R_{10}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, and -N=S(Me)$_2$=O, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6- membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), -NH$_2$, -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), -C(=O)NH$_2$, -OC(=O)(C_1-C_4 alkyl), -OC(=O)O(C_1-C_4 alkyl), -(CH$_2$)$_q$OH, and -S(=O)$_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a 4-membered heterocyclyl ring;

m is 0;

n is 1;

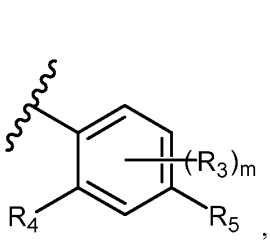
each p is 1; and

each q is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[67] One embodiment is a compound of formula I, wherein:

A is selected from



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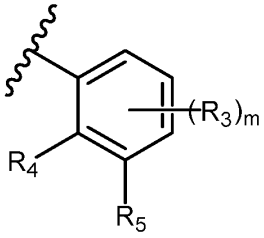

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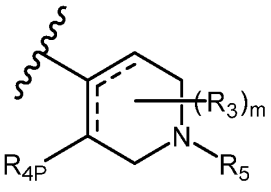

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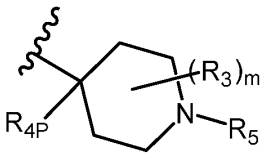


;

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro, chloro, and methyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -SR_7, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

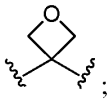
R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -NHC(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$, -NR_9S(=O)$_2R_{10}$, -NR_9S(=O)$_2$N$R_{11}R_{12}$, -(CH$_2$)OR_{11}, -(CH$_2$)C(=O)OR_{11}, -(CH$_2$)(phenylene)R_{13}, or –(4- to 6-membered heterocyclene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4 to 6-membered heterocyclyl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, or -C(=O)N$R_{11}R_{12}$,;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6- membered heterocyclyl, and -N=S(Me)$_2$=O, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3- to 6-membered cycloalkylalkyl, 4- to 6- membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

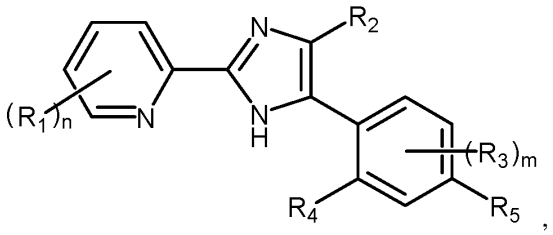
each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -OMe, -NH_2, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -C(=O)NH_2, -C(=O)OtBu, -OC(=O)Me, -OC(=O)OMe, -OC(=O)OEt, -(CH_2)OH, and -S(=O)$_2$(Me), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form:  ;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[68] One embodiment is a compound of formula I which is a compound of formula I-A



I-A

wherein R_1, R_2, R_3, R_4, R_5, n, and m are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[69] One embodiment is a compound of formula I which is a compound of formula I-A, wherein:

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[70] One embodiment is a compound of formula I which is a compound of formula I-A, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-

C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

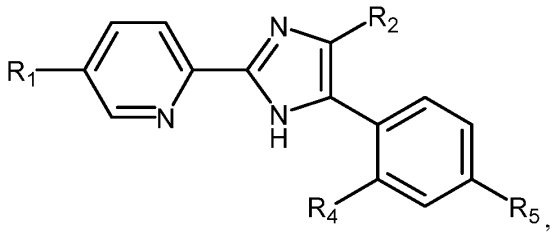
each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[71] One embodiment is a compound of formula I which is a compound of formula I-A1



I-A1

wherein R_1, R_2, R_4, and R_5 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[72] One embodiment is a compound of formula I which is a compound of formula I-A1, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[73] One embodiment is a compound of formula I which is a compound of formula I-A1, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NHC(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

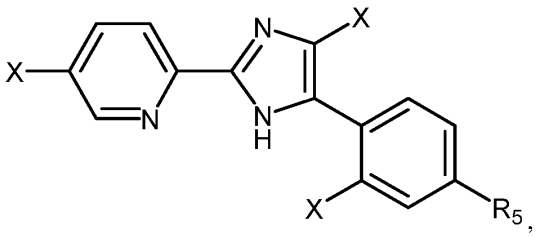
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[74] One embodiment is a compound of formula I which is a compound of formula I-A2



I-A2

wherein:

each instance of X is independently selected from halogen; and

R_5 is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[75] One embodiment is a compound of formula I which is a compound of formula I-A2, wherein:

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen,

C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[76] One embodiment is a compound of formula I which is a compound of formula I-A2, wherein

each instance of X is independently selected from fluoro and chloro;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

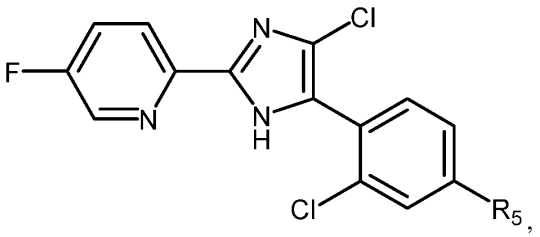
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[77] One embodiment is a compound of formula I which is a compound of formula I-A3



I-A3

wherein R_5 is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[78] One embodiment is a compound of formula I which is a compound of formula I-A3, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[79] One embodiment is a compound of formula I which is a compound of formula I-A3, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

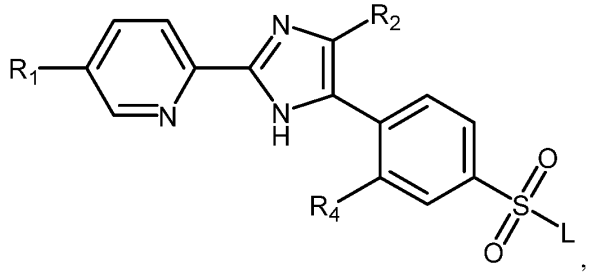
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[80] One embodiment is a compound of formula I which is a compound of formula I-A4



I-A4

wherein:

L is selected from -R_6 and -NR_7R_8; and

R_1, R_2, R_4, R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[81] One embodiment is a compound of formula I which is a compound of formula I-A4, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[82] One embodiment is a compound of formula I which is a compound of formula I-A4, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

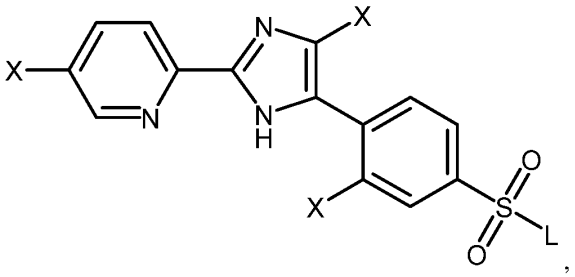
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[83] One embodiment is a compound of formula I which is a compound of formula I-A5



I-A5

wherein:

each instance of X is independently selected from halogen;

L is selected from -R_6 and -NR_7R_8; and

R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[84] One embodiment is a compound of formula I which is a compound of formula I-A5, wherein

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[85] One embodiment is a compound of formula I which is a compound of formula I-A5, wherein

each instance of X is independently selected from fluoro and chloro;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

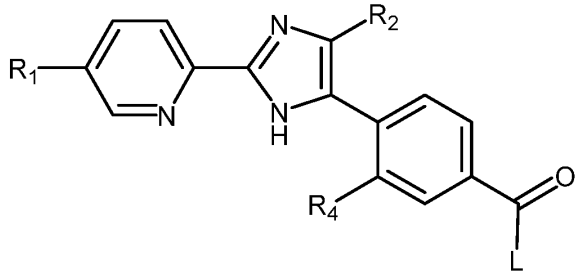
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[86] One embodiment is a compound of formula I which is a compound of formula I-A6



I-A6

wherein:

L is selected from -R_6, -OR_7, and -NR_7R_8; and

R_1, R_2, R_4, R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[87] One embodiment is a compound of formula I which is a compound of formula I-A6, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[88] One embodiment is a compound of formula I which is a compound of formula I-A6, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

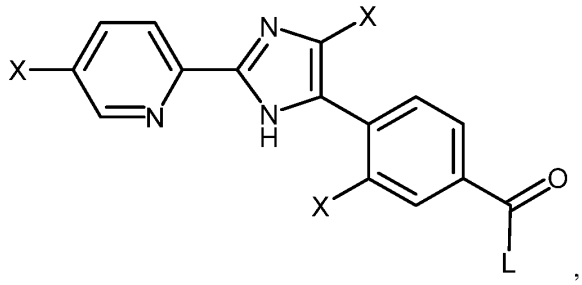
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[89] One embodiment is a compound of formula I which is a compound of formula I-A7



I-A7

wherein:

each instance of X is independently selected from halogen;

L is selected from -R_6, -OR_7, and -NR_7R_8; and

R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[90] One embodiment is a compound of formula I which is a compound of formula I-A7, wherein

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[91] One embodiment is a compound of formula I which is a compound of formula I-A7, wherein

each instance of X is independently selected from fluoro and chloro;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

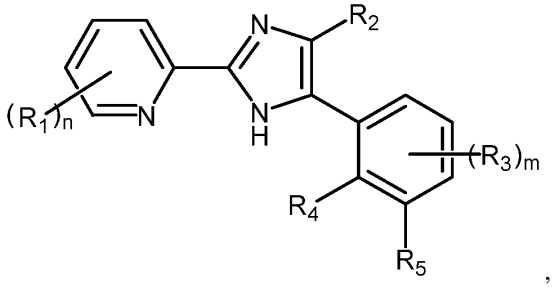
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[92] One embodiment is a compound of formula I which is a compound of formula I-B



I-B

wherein R_1, R_2, R_3, R_4, R_5, n, and m are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[93] One embodiment is a compound of formula I which is a compound of formula I-B, wherein:

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[94] One embodiment is a compound of formula I which is a compound of formula I-B, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

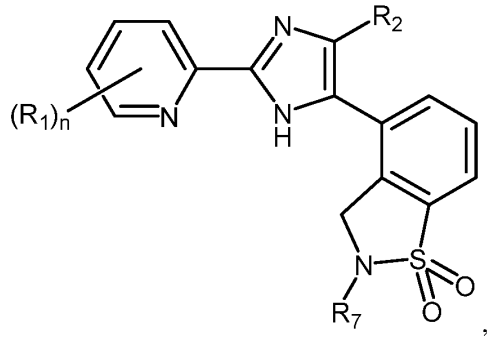
each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[95] One embodiment is a compound of formula I which is a compound of formula I-B, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are joined, such that hydrogen other radicals of the two moieties are replaced with a bond between the two moieties, provided that the joining results in a stable or chemically feasible compound. For example, a compound of formula



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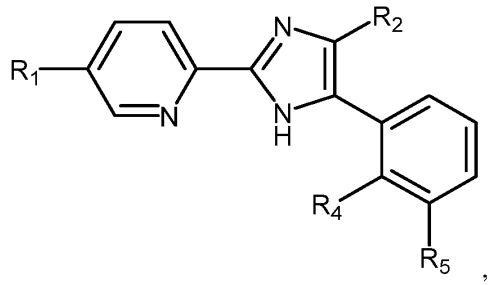
wherein R_1, R_2, R_7, and n are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[96] One embodiment is a compound of formula I which is a compound of formula I-B1



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I-B1

wherein R_1, R_2, R_4, and R_5 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[97] One embodiment is a compound of formula I which is a compound of formula I-B1, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[98] One embodiment is a compound of formula I which is a compound of formula I-B1, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NHC(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

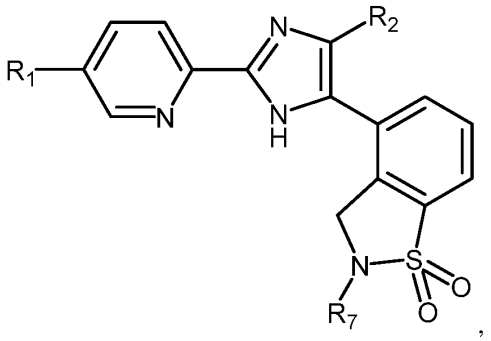
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[99] One embodiment is a compound of formula I which is a compound of formula I-B1, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R_4 and R_5 are joined, such that hydrogen other radicals of the two moieties are replaced with a bond between the two moieties, provided that the joining results in a stable or chemically feasible compound. For example, a compound of formula



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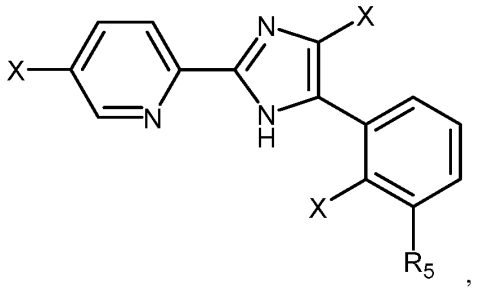
wherein R_1, R_2, and R_7 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[100] One embodiment is a compound of formula I which is a compound of formula I-B2



,

I-B2

wherein:

each instance of X is independently selected from halogen; and

R_5 is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[101] One embodiment is a compound of formula I which is a compound of formula I-B2, wherein:

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic

heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[102] One embodiment is a compound of formula I which is a compound of formula I-B2, wherein

each instance of X is independently selected from fluoro and chloro;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

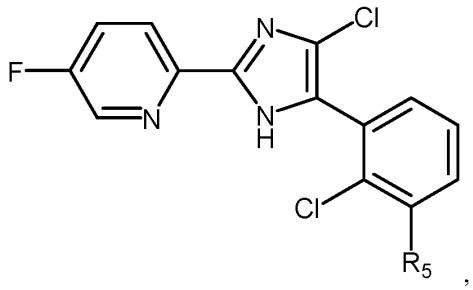
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[103] One embodiment is a compound of formula I which is a compound of formula I-B3



I-B3

wherein R_5 is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[104] One embodiment is a compound of formula I which is a compound of formula I-B3, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or

substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[105] One embodiment is a compound of formula I which is a compound of formula I-B3, wherein

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

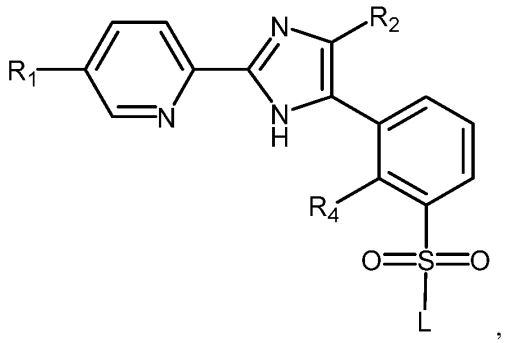
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[106] One embodiment is a compound of formula I which is a compound of formula I-B4



I-B4

wherein:

L is selected from -R_6 and -NR_7R_8; and

R_1, R_2, R_4, R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[107] One embodiment is a compound of formula I which is a compound of formula I-B4, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[108] One embodiment is a compound of formula I which is a compound of formula I-B4, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

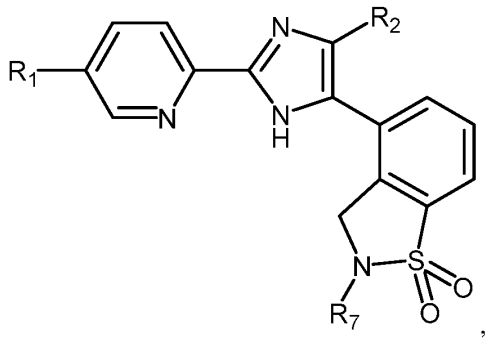
each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[109] One embodiment is a compound of formula I which is a compound of formula I-B4, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R_4 and L are joined, such that hydrogen

other radicals of the two moieties are replaced with a bond between the two moieties, provided that the joining results in a stable or chemically feasible compound. For example, a compound of formula



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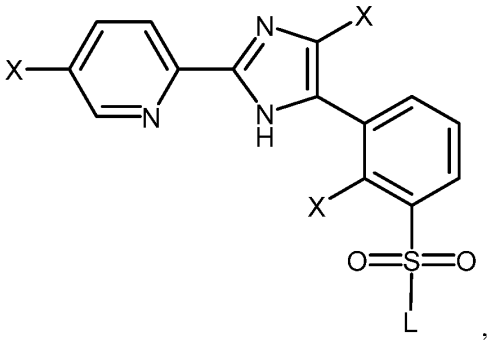
wherein R_1, R_2, and R_7 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[110] One embodiment is a compound of formula I which is a compound of formula I-B5



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I-B5

wherein:

each instance of X is independently selected from halogen;

L is selected from $-R_6$ and $-NR_7R_8$; and

R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[111] One embodiment is a compound of formula I which is a compound of formula I-B5, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[112] One embodiment is a compound of formula I which is a compound of formula I-B5, wherein

each instance of X is independently selected from fluoro and chloro;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

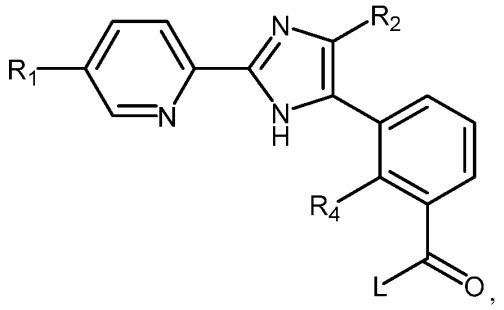
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[113] One embodiment is a compound of formula I which is a compound of formula I-B6



I-B6

wherein:

L is selected from $-R_6$, $-OR_7$, and $-NR_7R_8$; and

R_1, R_2, R_4, R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[114] One embodiment is a compound of formula I which is a compound of formula I-B6, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[115] One embodiment is a compound of formula I which is a compound of formula I-B6, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro and chloro;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

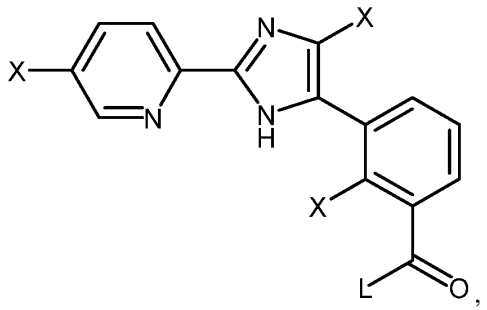
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[116] One embodiment is a compound of formula I which is a compound of formula I-B7



I-B7

wherein:

each instance of X is independently selected from halogen;

L is selected from $-R_6$, $-OR_7$, and $-NR_7R_8$; and

wherein R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[117] One embodiment is a compound of formula I which is a compound of formula I-B7, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen,

C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[118] One embodiment is a compound of formula I which is a compound of formula I-B7, wherein

each instance of X is independently selected from fluoro and chloro;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

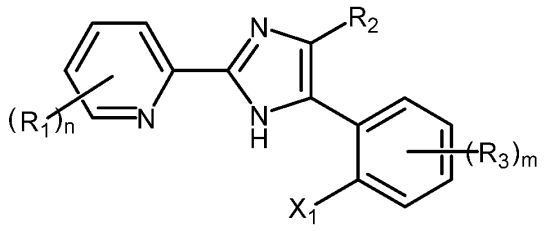
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[119] One embodiment is a compound of formula I which is a compound of formula I-C



,

I-C

wherein R_1, R_2, R_3, X_1, n, and m are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[120] One embodiment is a compound of formula I which is a compound of formula I-C, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_3 is selected from halogen and C_1-C_4 alkyl;

m is 0 or 1; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[121] One embodiment is a compound of formula I which is a compound of formula I-C, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_3 is selected from fluoro, chloro, and methyl;

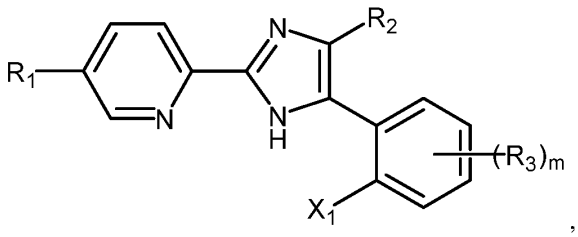
X_1 is selected from fluoro and chloro;

m is 1; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[122] One embodiment is a compound of formula I which is a compound of formula I-C1



,

I-C1

wherein R_1, R_2, R_3, X_1, and m are as defined for a compound of formula I; and

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[123] One embodiment is a compound of formula I which is a compound of formula I-C1, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_3 is selected from halogen and C_1-C_4 alkyl; and

m is 0 or 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[124] One embodiment is a compound of formula I which is a compound of formula I-C1, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

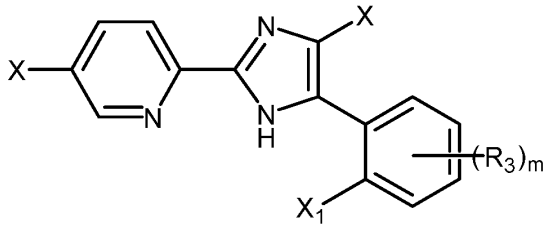
R_3 is selected from fluoro, chloro, and methyl;

X_1 is selected from fluoro and chloro; and

m is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[125] One embodiment is a compound of formula I which is a compound of formula I-C2



I-C2

wherein

each instance of X is independently selected from halogen; and

R_3, X_1, and m are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[126] One embodiment is a compound of formula I which is a compound of formula I-C2, wherein

R_3 is selected from halogen and C_1-C_4 alkyl; and

m is 0 or 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[127] One embodiment is a compound of formula I which is a compound of formula I-C2, wherein

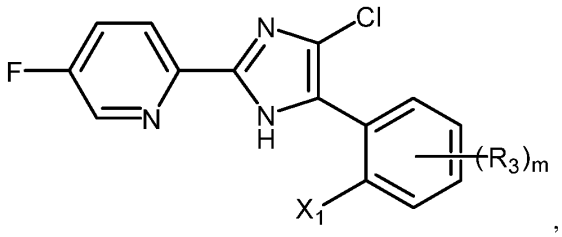
each instance of X is independently selected from fluoro, chloro, and bromo;

R_3 is selected from fluoro, chloro, and methyl; and

m is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[128] One embodiment is a compound of formula I which is a compound of formula I-C3



I-C3

wherein R_3, X_1, and m are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[129] One embodiment is a compound of formula I which is a compound of formula I-C3, wherein

R_3 is selected from halogen and C_1-C_4 alkyl; and

m is 0 or 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[130] One embodiment is a compound of formula I which is a compound of formula I-C3, wherein

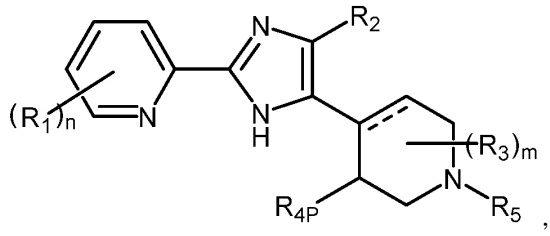
each instance of X is independently selected from fluoro, chloro, and bromo;

R_3 is selected from fluoro, chloro, and methyl; and

m is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[131] One embodiment is a compound of formula I which is a compound of formula I-D



I-D

wherein R_1, R_2, R_3, R_{4P}, R_5, n, m, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[132] One embodiment is a compound of formula I which is a compound of formula I-D, wherein:

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[133] One embodiment is a compound of formula I which is a compound of formula I-D, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

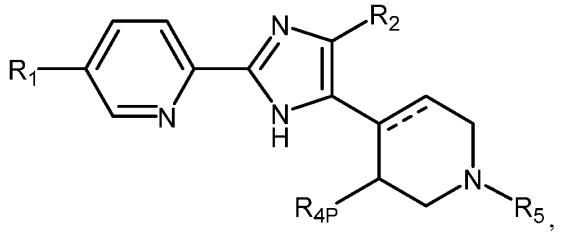
each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[134] One embodiment is a compound of formula I which is a compound of formula I-D1



I-D1

wherein R_1, R_2, R_{4P}, R_5, and ---- are as defined for a compound of formula I; or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[135] One embodiment is a compound of formula I which is a compound of formula I-D1, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[136] One embodiment is a compound of formula I which is a compound of formula I-D1, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

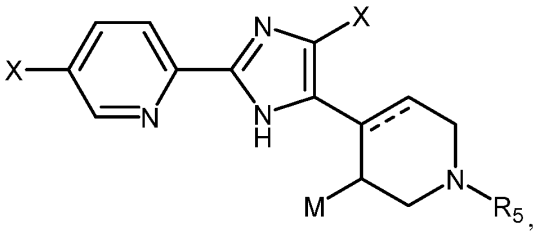
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[137] One embodiment is a compound of formula I which is a compound of formula I-D2



I-D2

wherein:

each instance of X is independently selected from halogen;

M is selected from hydrogen and C_1-C_4 alkyl; and

R_5 and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[138] One embodiment is a compound of formula I which is a compound of formula I-D2, wherein:

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[139] One embodiment is a compound of formula I which is a compound of formula I-D2, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

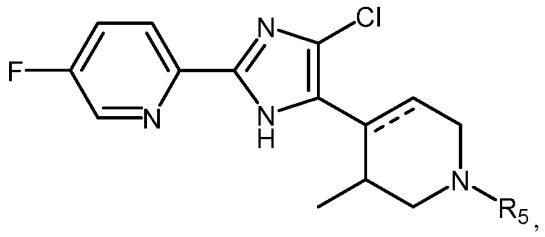
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[140] One embodiment is a compound of formula I which is a compound of formula I-D3



I-D3

wherein R_5 and ==== are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[141] One embodiment is a compound of formula I which is a compound of formula I-D3, wherein

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[142] One embodiment is a compound of formula I which is a compound of formula I-D3, wherein

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

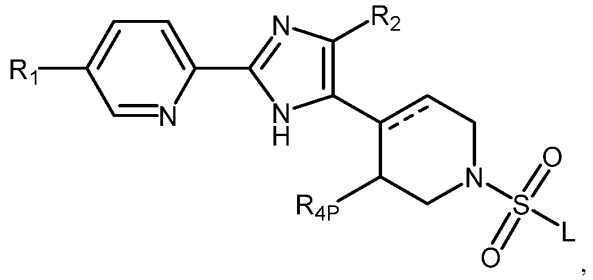
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[143] One embodiment is a compound of formula I which is a compound of formula I-D4



I-D4

wherein L is selected from $-R_6$ and $-NR_7R_8$; and

R_1, R_2, R_{4P}, R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[144] One embodiment is a compound of formula I which is a compound of formula I-D4, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[145] One embodiment is a compound of formula I which is a compound of formula I-D4, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

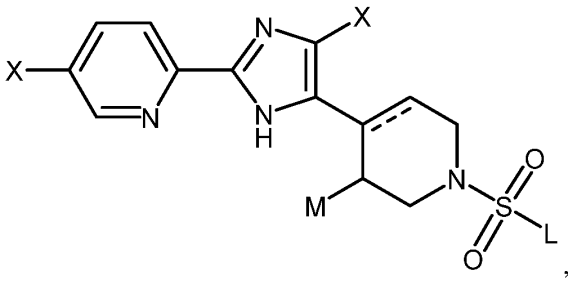
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[146] One embodiment is a compound of formula I which is a compound of formula I-D5



I-D5

wherein:

each instance of X is independently selected from halogen;

M is selected from hydrogen and C_1-C_4 alkyl; and

L is selected from -R_6 and -NR_7R_8; and

R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[147] One embodiment is a compound of formula I which is a compound of formula I-D5, wherein

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or

substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[148] One embodiment is a compound of formula I which is a compound of formula I-D5, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

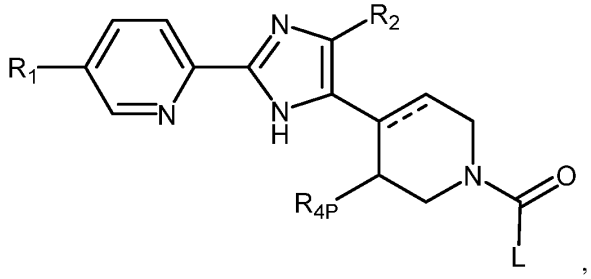
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[149] One embodiment is a compound of formula I which is a compound of formula I-D6



I-D6

wherein:

L is selected from -R_6, -OR_7, and -NR_7R_8; and

R_1, R_2, R_{4P}, R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[150] One embodiment is a compound of formula I which is a compound of formula I-D6, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[151] One embodiment is a compound of formula I which is a compound of formula I-D6, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

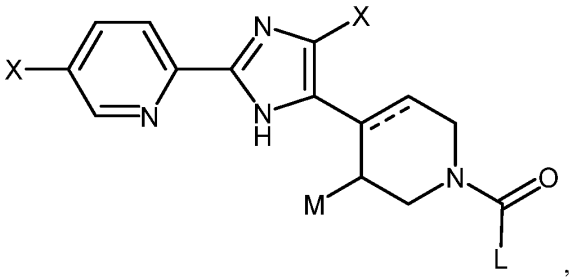
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[152] One embodiment is a compound of formula I which is a compound of formula I-D7



I-D7

wherein:

each instance of X is independently selected from halogen;

L is selected from -R_6, -OR_7, and -NR_7R_8; and

R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[153] One embodiment is a compound of formula I which is a compound of formula I-D7, wherein

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2NR_7R_8$, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[154] One embodiment is a compound of formula I which is a compound of formula I-D7, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

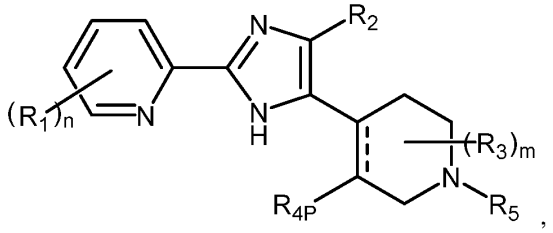
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[155] One embodiment is a compound of formula I which is a compound of formula I-E



I-E

wherein R_1, R_2, R_3, R_{4P}, R_5, n, m, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[156] One embodiment is a compound of formula I which is a compound of formula I-E, wherein:

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[157] One embodiment is a compound of formula I which is a compound of formula I-E, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

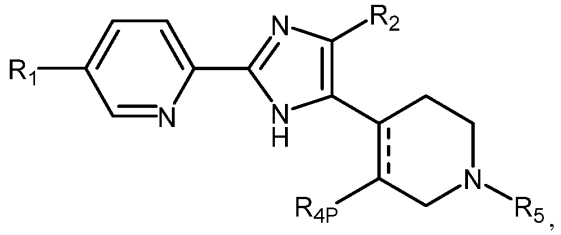
each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[158] One embodiment is a compound of formula I which is a compound of formula I-E1



I-E1

wherein R_1, R_2, R_{4P}, R_5, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[159] One embodiment is a compound of formula I which is a compound of formula I-E1, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[160] One embodiment is a compound of formula I which is a compound of formula I-E1, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

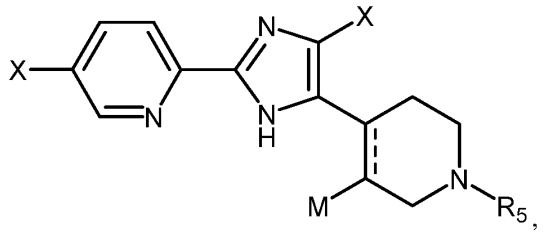
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[161] One embodiment is a compound of formula I which is a compound of formula I-E2



I-E2

wherein:

each instance of X is independently selected from halogen;

M is selected from hydrogen and C_1-C_4 alkyl; and

R_5 and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[162] One embodiment is a compound of formula I which is a compound of formula I-E2, wherein:

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[163] One embodiment is a compound of formula I which is a compound of formula I-E2, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

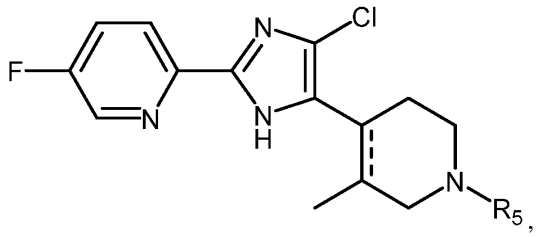
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[164] One embodiment is a compound of formula I which is a compound of formula I-E3



I-E3

wherein R_5 and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[165] One embodiment is a compound of formula I which is a compound of formula I-E3, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[166] One embodiment is a compound of formula I which is a compound of formula I-E3, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

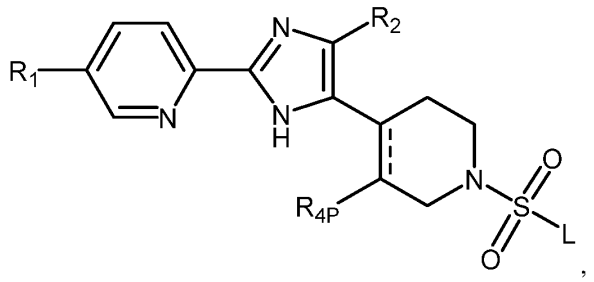
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[167] One embodiment is a compound of formula I which is a compound of formula I-E4



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I-E4

wherein L is selected from $-R_6$ and $-NR_7R_8$; and

R_1, R_2, R_{4P}, R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[168] One embodiment is a compound of formula I which is a compound of formula I-E4, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[169] One embodiment is a compound of formula I which is a compound of formula I-E4, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

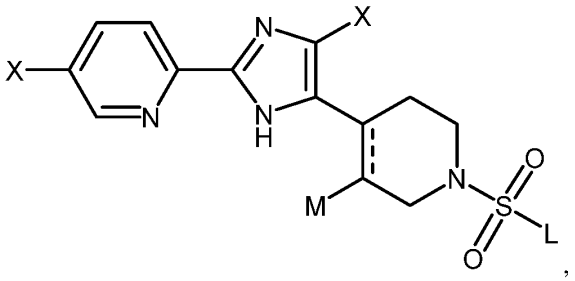
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[170] One embodiment is a compound of formula I which is a compound of formula I-E5



I-E5

wherein:

each instance of X is independently selected from halogen;

M is selected from hydrogen and C_1-C_4 alkyl;

L is selected from $-R_6$ and $-NR_7R_8$; and

R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[171] One embodiment is a compound of formula I which is a compound of formula I-E5, wherein

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[172] One embodiment is a compound of formula I which is a compound of formula I-E5, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-

C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

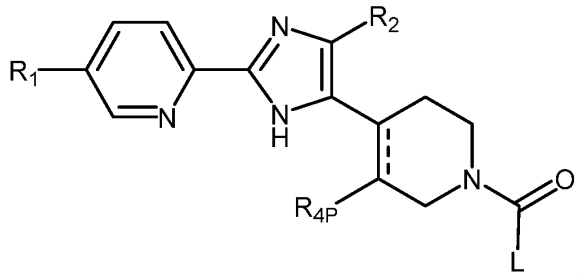
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[173] One embodiment is a compound of formula I which is a compound of formula I-E6



,

I-E6

wherein:

L is selected from $-R_6$, $-OR_7$, and $-NR_7R_8$; and

R_1, R_2, R_{4P}, R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[174] One embodiment is a compound of formula I which is a compound of formula I-E6, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[175] One embodiment is a compound of formula I which is a compound of formula I-E6, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, -

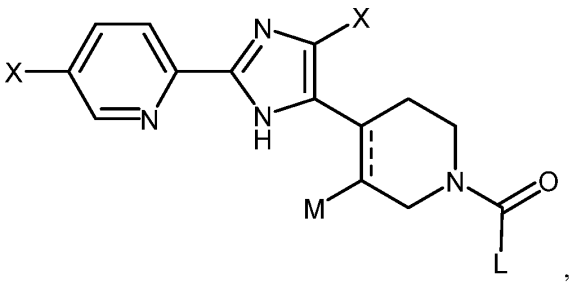
$NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[176] One embodiment is a compound of formula I which is a compound of formula I-E7



I-E7

wherein:

each instance of X is independently selected from halogen;

L is selected from $-R_6$, $-OR_7$, and $-NR_7R_8$; and

R_6, R_7, R_8, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[177] One embodiment is a compound of formula I which is a compound of formula I-E7, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen,

C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[178] One embodiment is a compound of formula I which is a compound of formula I-E7, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

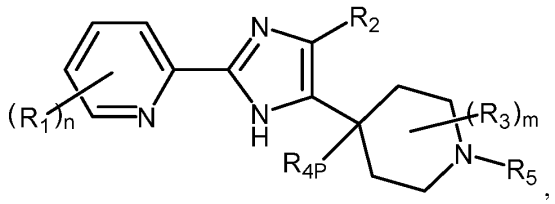
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[179] One embodiment is a compound of formula I which is a compound of formula I-F



I-F

wherein R_1, R_2, R_3, R_{4P}, R_5, n, and m are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[180] One embodiment is a compound of formula I which is a compound of formula I-F, wherein:

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or

substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[181] One embodiment is a compound of formula I which is a compound of formula I-F, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl;

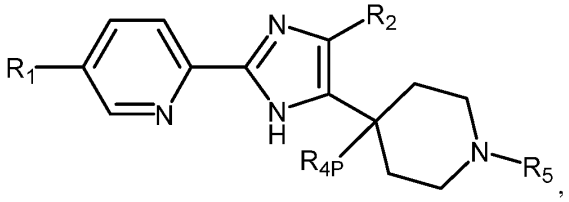
each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[182] One embodiment is a compound of formula I which is a compound of formula I-F1



I-F1

wherein R_1, R_2, R_{4P}, and R_5 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[183] One embodiment is a compound of formula I which is a compound of formula I-F1, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or

substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[184] One embodiment is a compound of formula I which is a compound of formula I-F1, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

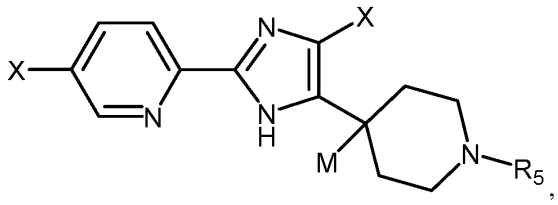
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[185] One embodiment is a compound of formula I which is a compound of formula I-F2



I-F2

wherein:

each instance of X is independently selected from halogen;

M is selected from hydrogen and C_1-C_4 alkyl; and

R_5 is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[186] One embodiment is a compound of formula I which is a compound of formula I-F2, wherein:

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[187] One embodiment is a compound of formula I which is a compound of formula I-F2, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

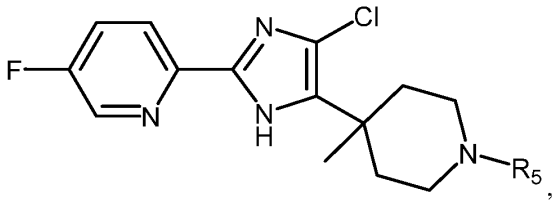
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[188] One embodiment is a compound of formula I which is a compound of formula I-F3



I-F3

wherein R_5 is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[189] One embodiment is a compound of formula I which is a compound of formula I-F3, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[190] One embodiment is a compound of formula I which is a compound of formula I-F3, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

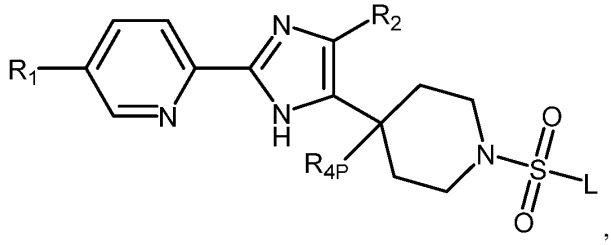
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[191] One embodiment is a compound of formula I which is a compound of formula I-F4



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I-F4

wherein L is selected from $-R_6$ and $-NR_7R_8$; and

R_1, R_2, R_{4P}, R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[192] One embodiment is a compound of formula I which is a compound of formula I-F4, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[193] One embodiment is a compound of formula I which is a compound of formula I-F4, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

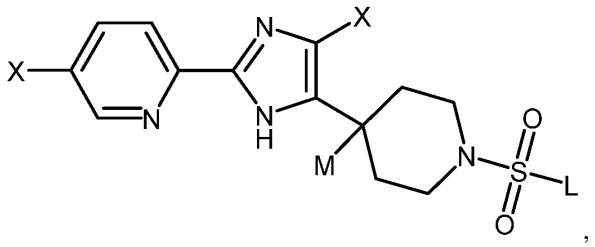
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[194] One embodiment is a compound of formula I which is a compound of formula I-F5



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I-F5

wherein:

each instance of X is independently selected from halogen;

M is selected from hydrogen and C_1-C_4 alkyl; and

L is selected from -R_6 and -NR_7R_8; and

R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[195] One embodiment is a compound of formula I which is a compound of formula I-F5, wherein

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[196] One embodiment is a compound of formula I which is a compound of formula I-F5, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-

C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

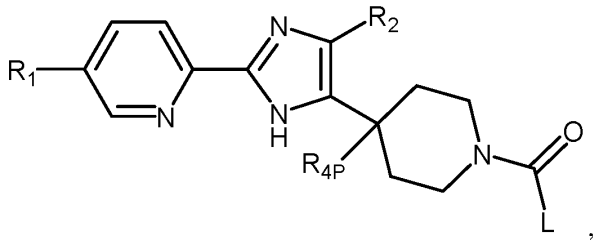
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[197] One embodiment is a compound of formula I which is a compound of formula I-F6



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I-F6

wherein:

L is selected from -R_6, -OR_7, and -NR_7R_8; and

R_1, R_2, R_{4P}, R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[198] One embodiment is a compound of formula I which is a compound of formula I-F6, wherein

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[199] One embodiment is a compound of formula I which is a compound of formula I-F6, wherein

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_{4P} is selected from hydrogen and methyl;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of $-OR_{11}$, -

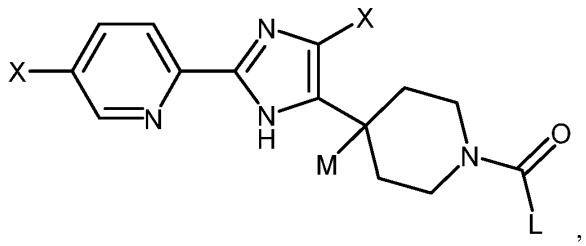
$NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-NR_9C(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[200] One embodiment is a compound of formula I which is a compound of formula I-F7



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I-F7

wherein:

each instance of X is independently selected from halogen;

L is selected from $-R_6$, $-OR_7$, and $-NR_7R_8$; and

R_6, R_7, and R_8 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[201] One embodiment is a compound of formula I which is a compound of formula I-F7, wherein

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen,

C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[202] One embodiment is a compound of formula I which is a compound of formula I-F7, wherein

each instance of X is independently selected from fluoro and chloro;

M is selected from hydrogen and methyl;

R_5 is selected from -$C(=O)R_6$, -$C(=O)OR_7$, -$C(=O)NR_7R_8$, -$S(=O)R_6$, -$S(=O)_2R_6$, -$S(=O)_2NR_7R_8$, and -$S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4- to 6-membered heterocyclyl, and monocyclic heteroaryl, which groups are unsubstituted or substituted with one or more of C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NHC(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

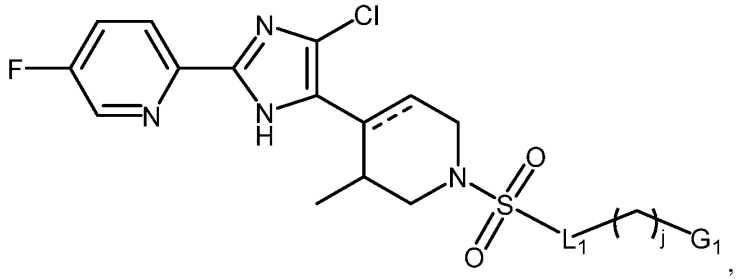
R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, and C_1-C_4 heteroalkyl, which groups are unsubstituted or substituted with one or more of -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[203] One embodiment is a compound of formula I which is a compound of formula I-G1



I-G1

wherein:

L_1 is selected from $-CH_2-$ and $-N(R_{11})-$;

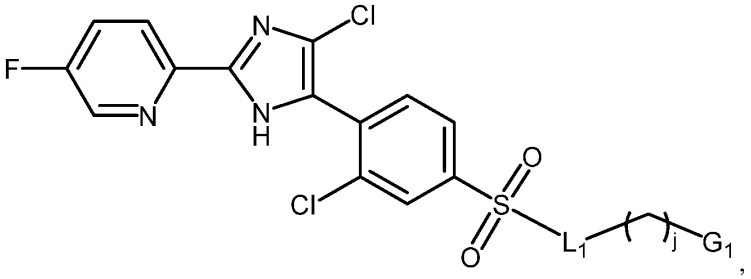
G_1 is selected from $-OR_{11}$, $NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$,, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, 4- to 6-membered heterocyclyl, and monocyclic heteroaryl;

j is 0, 1, or 2; and

R_{10}, R_{11}, R_{12}, and ---- are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[204] One embodiment is a compound of formula I which is a compound of formula I-G2



I-G2

wherein:

L_1 is selected from $-CH_2-$ and $-N(R_{11})-$;

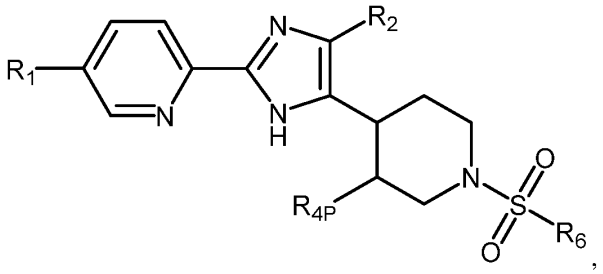
G_1 is selected from $-OR_{11}$, $NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$,, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, 4- to 6-membered heterocyclyl, and monocyclic heteroaryl;

j is 0, 1, or 2; and

R_{10}, R_{11}, and R_{12} are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[205] One embodiment is a compound of formula I which is a compound of formula I-H



I-H

wherein:

R_1, R_2, R_{4P}, and R_6 are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[206] One embodiment is a compound of formula I which is a compound of formula I-H, wherein:

R_1 is fluoro;

R_2 is chloro;

R_{4P} is methyl;

R_6 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $S(=O)R_{10}$, -

$S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)OR_{11}$, $-(CH_2)NR_{11}R_{12}$, $-(CH_2)C(=O)R_{10}$, $-(CH_2)C(=O)OR_{11}$, $-(CH_2)C(=O)NR_{11}R_{12}$, $-(CH_2)_p$(phenylene)R_{13}, 4- to 6-membered heterocyclyl, or –(4- to 6-membered heterocyclene)R_{13}; and

R_{10}, R_{11}, R_{12}, and R_{13} are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[207] One embodiment is a compound of formula I which is a compound of formula I-H, wherein:

R_1 is fluoro;

R_2 is chloro;

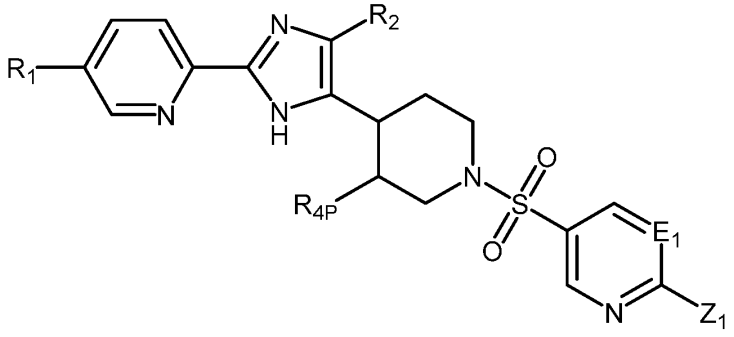
R_{4P} is methyl;

R_6 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)OR_{11}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-S(=O)_2R_{10}$, $-NR_9S(=O)_2R_{10}$, $-(CH_2)C(=O)OR_{11}$, $-(CH_2)$(phenylene)R_{13}, or -(4- to 6-membered heterocyclene)R_{13}; and

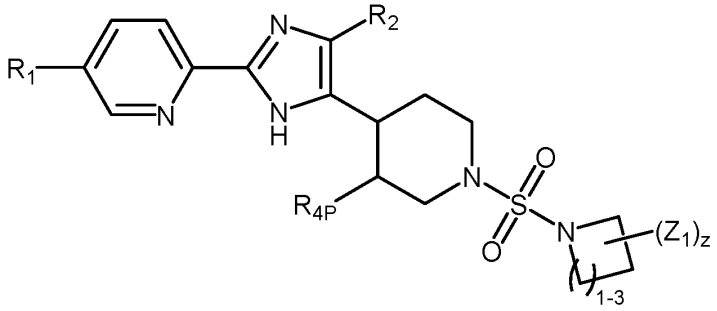
R_{10}, R_{11}, R_{12}, and R_{13} are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

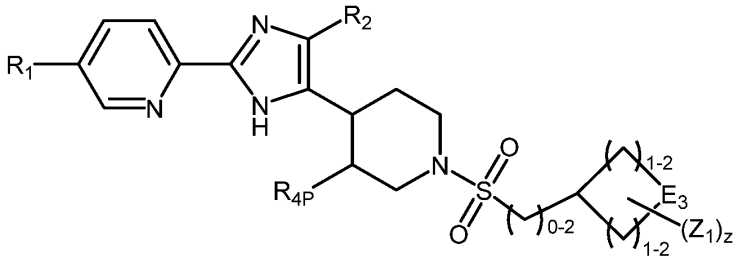
[208] In other embodiments, a compound of formula I is a compound of any one of formulas I-J1 to I-J5:



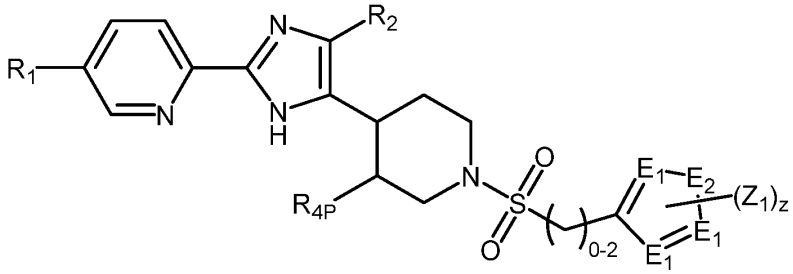
I-J1,



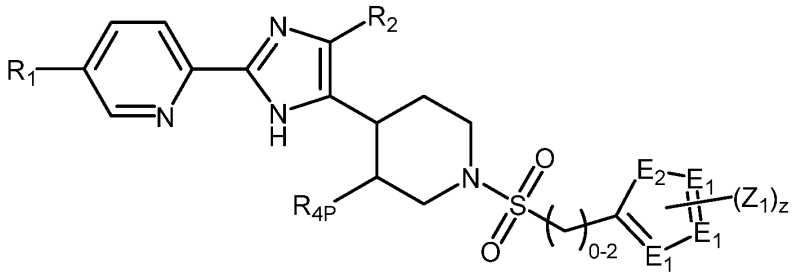
I-J2,



I-J3,



I-J4,



I-J5,

wherein:

z is 0, 1, or 2 where valency permits;

each instance of Z_1 is independently selected from halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pNR_{11}R_{12}$, $-(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(arylene)R_{13}, heterocyclyl, and -(heterocyclene)R_{13};

each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-;

E_3 is selected from $-CH_2-$, -NH-, and -O-; and

R_1, R_2, R_{4P}, R_{10}, R_{11}, R_{12} and R_{13} are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[209] In other embodiments, a compound of formula I is a compound of any one of formulas I-J1 to I-J5, wherein:

R_1 is fluoro;

R_2 is chloro;

R_{4P} is methyl;

z is 0, 1, or 2 where valency permits;

each instance of Z_1 is independently selected from halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)OR_{11}$, $-NR_9C(=O)R_{10}$, -

$NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-S(=O)_2R_{10}$, $-NR_9S(=O)_2R_{10}$, $-(CH_2)C(=O)OR_{11}$, $-(CH_2)$(phenylene)R_{13}, and -(4- to 6-membered heterocyclene)R_{13};

each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-;

E_3 is selected from $-CH_2-$, -NH-, and -O-; and

R_{10}, R_{11}, R_{12} and R_{13} are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[210] In other embodiments, a compound of formula I is a compound of any one of formulas I-J1 to I-J5, wherein:

R_1 is fluoro;

R_2 is chloro;

R_{4P} is methyl;

z is 0, 1, or 2 where valency permits;

each instance of Z_1 is independently selected from chloro, C_1-C_4 alkyl, -OH, -O(C_1-C_4 alkyl), $-NH_2$, -NH(C_1-C_4 alkyl), -NH(C_1-C_4 heteroalkyl), -NH(C_3-C_6 cycloalkyl), -C(=O)Me, -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), -C(=O)OtBu, $-C(=O)NH_2$, -OC(=O)O(C_1-C_4 alkyl), -NHC(=O)Me, -NHC(=O)O(C_1-C_4 alkyl), $-NHC(=O)NH_2$, $-S(=O)_2Me$, $-NHS(=O)_2Me$, $-CH_2C(=O)OH$, $-(CH_2)C(=O)O(C_1$-C_4 alkyl), $-(CH_2)$(phenylene)R_{13}, or -(4- to 6-membered heterocyclene)R_{13}; wherein if z is 2, the second instance of Z_1 is C_1-C_4 alkyl;

each instance of E_1 is independently selected from -CH- and -N-;

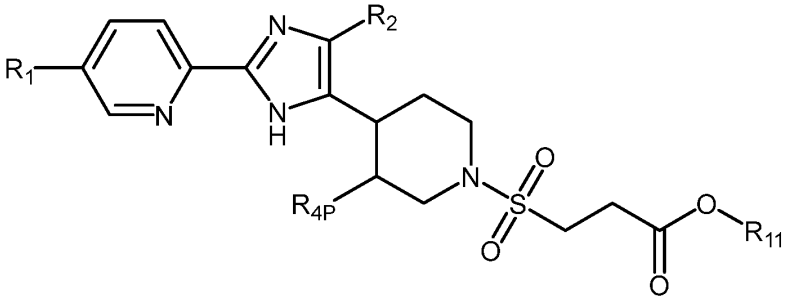
E_2 is selected from -NH-, -O-, and -S-;

E_3 is selected from $-CH_2-$, -NH-, and -O-; and

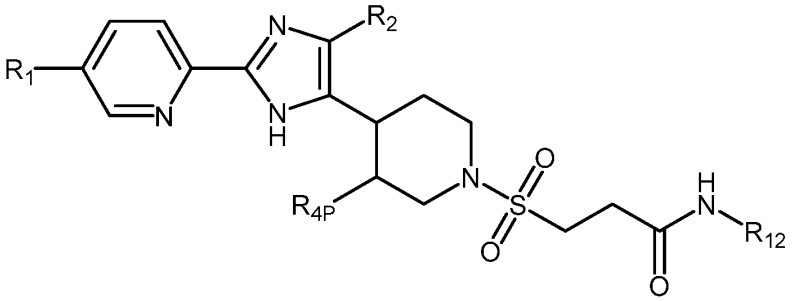
R_{13} is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

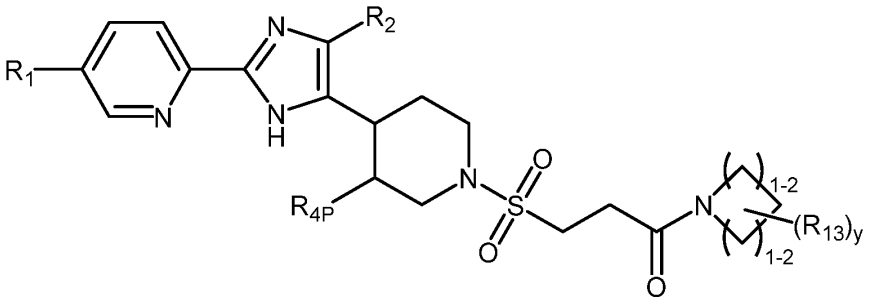
[211] In other embodiments, a compound of formula I is a compound of any one of formulas I-K1 to I-K8:



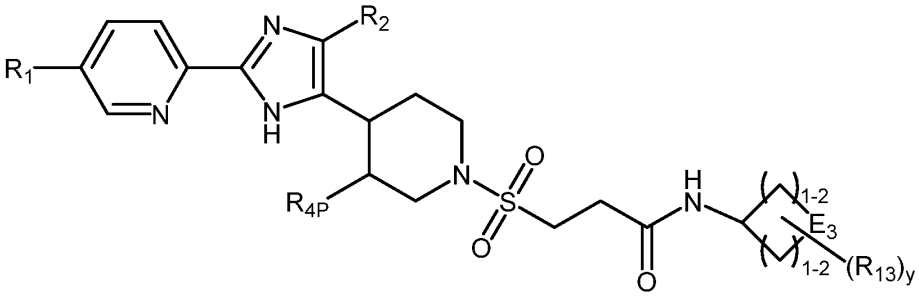
I-K1,



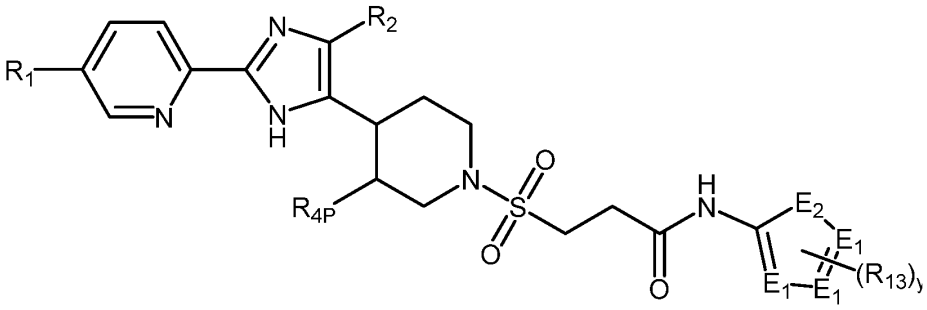
I-K2,



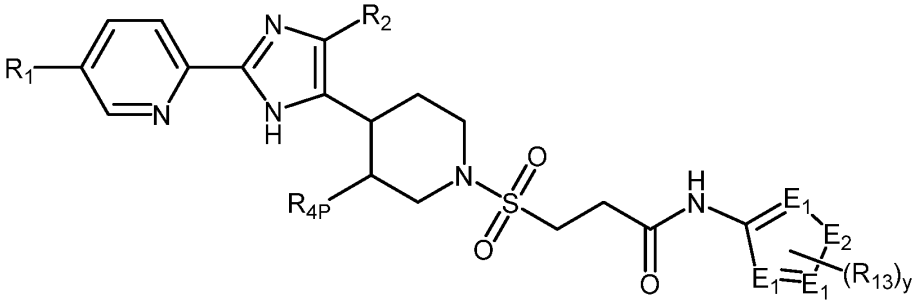
I-K3,



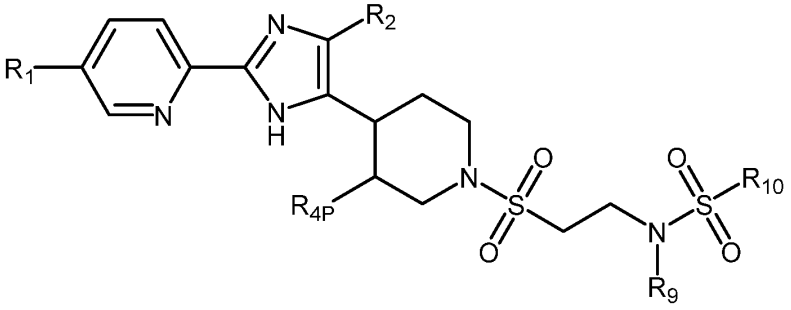
I-K4,



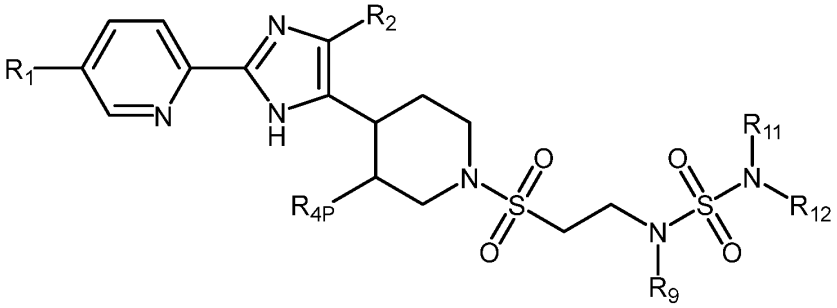
I-K5,



I-K6,



I-K7,



I-K8

wherein:

y is 0, 1, or 2 where valency permits;

each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-;

E_3 is selected from $-CH_2-$, -NH-, and -O-; and

R_1, R_2, R_{4P}, R_9, R_{10}, R_{11}, R_{12} and R_{13} are as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[212] In other embodiments, a compound of formula I is a compound of any one of formulas I-K1 to I-K8, wherein:

R_1 is fluoro;

R_2 is chloro;

R_{4P} is methyl;

y is 0, 1, or 2 where valency permits;

each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-;

E_3 is selected from $-CH_2-$, -NH-, and -O-; and

each instance of R_9 is H;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_3-C_6 cycloalkyl; which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

and R_{13} is as defined for a compound of formula I;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[213] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

R_1 is selected from halogen and C_1-C_4 alkyl; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[214] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

R_1 is fluoro; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[215] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

R_2 is selected from halogen and C_1-C_4 alkyl;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[216] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

R_2 is selected from chloro, bromo, methyl, and ethyl;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[217] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

R_2 is chloro;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[218] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

R_1 is selected from halogen and C_1-C_4 alkyl;

R_2 is selected from chloro, bromo, methyl, and ethyl; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[219] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[220] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, I-F6, I-H, any one of I-J1 to I-J5, or any one of I-K1 to I-K8, wherein:

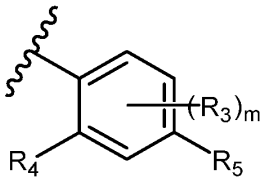
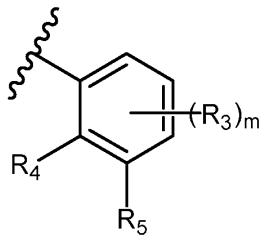
R_1 is fluoro;

R_2 is chloro; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[221] One embodiment is a compound of formula I, wherein:

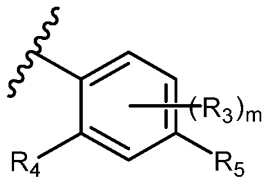
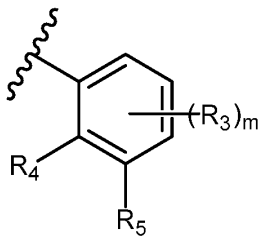
A is selected from  and  ;

R_4 is selected from halogen and C_1-C_4 alkyl; and

m is 0;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[222] One embodiment is a compound of formula I, wherein:

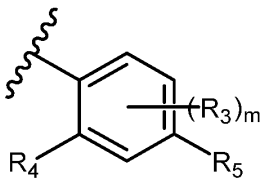
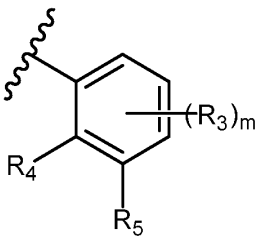
A is selected from  and  ;

R_4 is selected from fluoro, chloro, and methyl; and

m is 0;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[223] One embodiment is a compound of formula I, wherein:

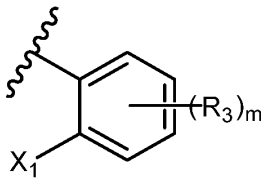
A is selected from  and  ;

R_4 is chloro; and

m is 0;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[224] One embodiment is a compound of formula I, wherein:

A is  ;

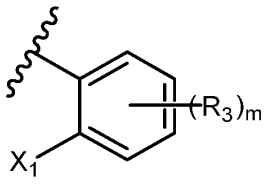
X_1 is selected from halogen;

R_3 is selected from halogen and C_1-C_4 alkyl; and

m is 0 or 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[225] One embodiment is a compound of formula I, wherein:

A is  ;

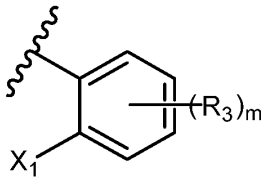
X_1 is selected from fluoro and chloro;

R_3 is selected from fluoro, chloro, and methyl; and

m is 0 or 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[226] One embodiment is a compound of formula I, wherein:

A is  ;

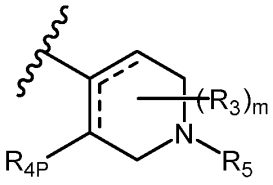
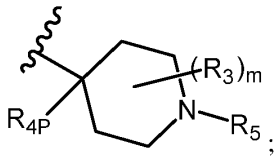
X_1 is selected from fluoro and chloro;

R_3 is selected from fluoro, chloro, and methyl; and

m is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[227] One embodiment is a compound of formula I, wherein:

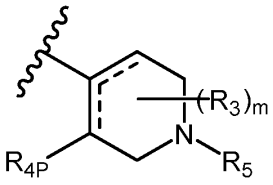
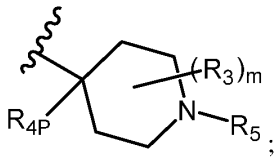
A is selected from  and  ;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl; and

m is 0;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[228] One embodiment is a compound of formula I, wherein:

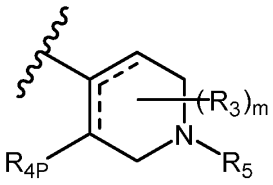
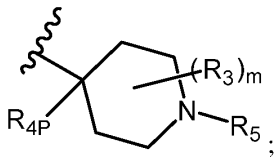
A is selected from  and  ;

R_{4P} is selected from hydrogen and methyl; and

m is 0;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[229] One embodiment is a compound of formula I, wherein:

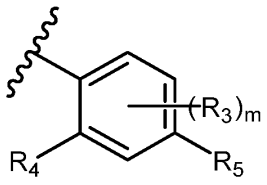
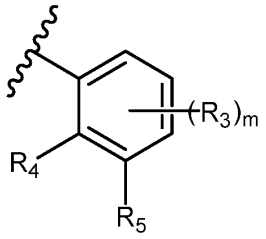
A is selected from  and  ;

R_{4P} is methyl; and

m is 0;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[230] One embodiment is a compound of formula I, wherein:

A is selected from  and  ;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

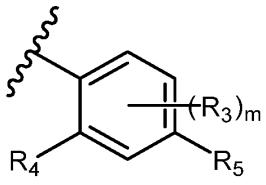
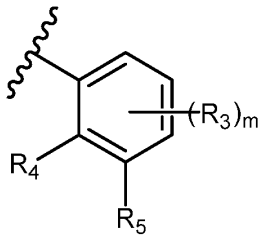
R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2$N$R_{11}R_{12}$;

each instance of R_{10} is independently selected from C_1-C_4 alkyl and C_1-C_4 heteroalkyl; and

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_3 acyl, and C_1-C_3 sulfonyl, provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[231] One embodiment is a compound of formula I, wherein:

A is selected from  and  ;

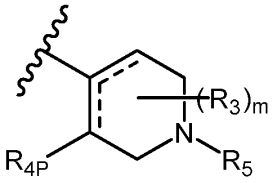
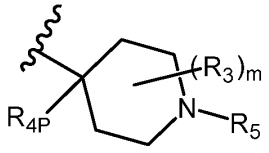
R_5 is selected from -C(=O)NR_7R_8, -S(=O)$_2R_6$, and -S(=O)$_2NR_7R_8$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$; and

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)$NR_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, or -S(=O)$_2NR_{11}R_{12}$;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[232] One embodiment is a compound of formula I, wherein:

A is selected from  and  ;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2NR_7R_8$, and -S(=O)(=NR_9)R_6;

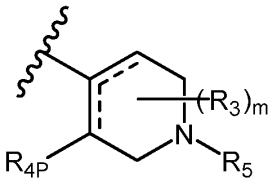
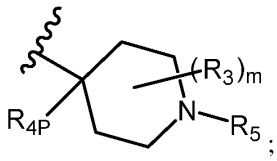
R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen,

C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$; and

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[233] One embodiment is a compound of formula I, wherein:

A is selected from  and  ;

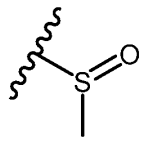
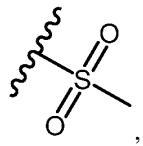
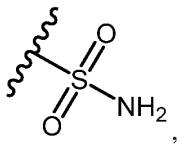
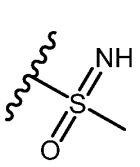
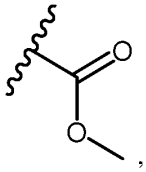
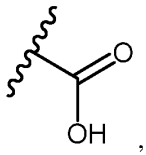
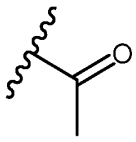
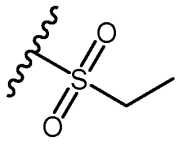
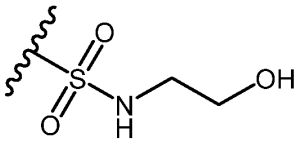
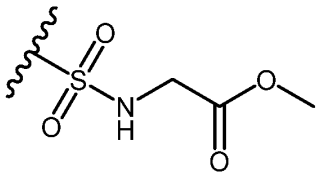
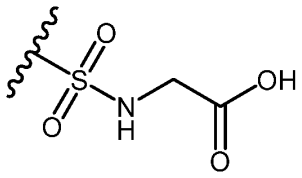
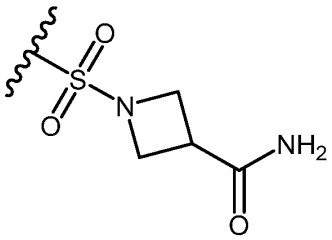
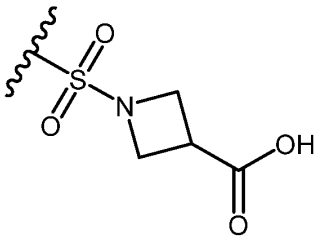
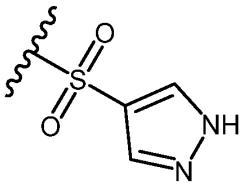
R_5 is selected from -$C(=O)NR_7R_8$, -$S(=O)_2R_6$, and -$S(=O)_2NR_7R_8$;

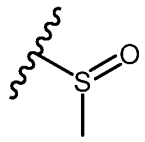
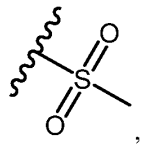
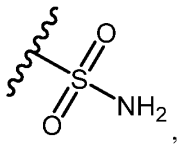
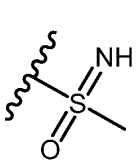
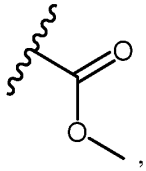
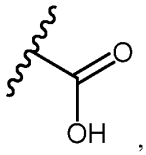
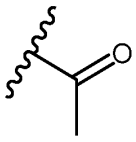
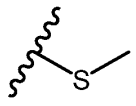
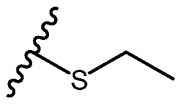
R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$; and

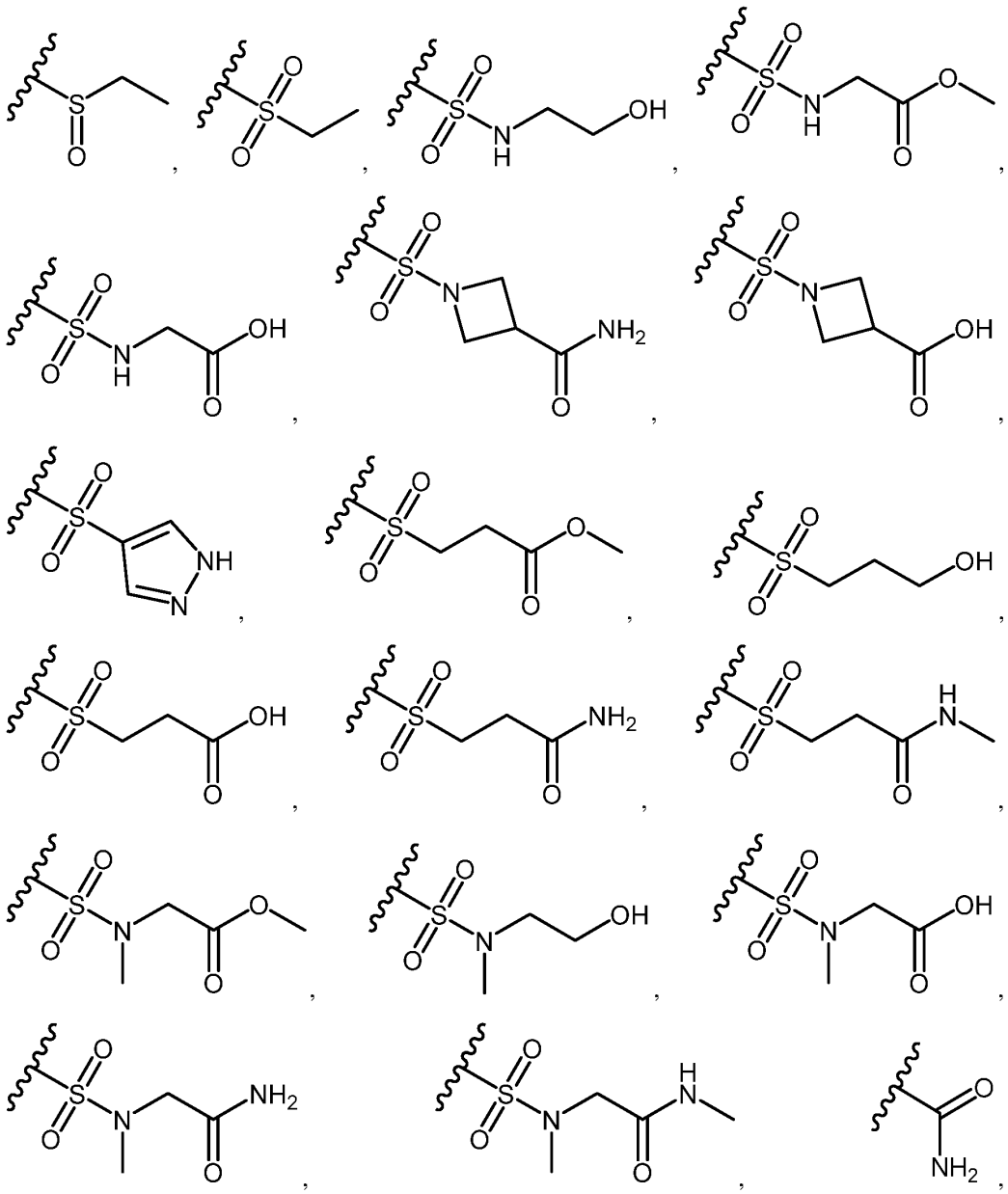
R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$NR_9C(=O)R_{10}$, -$S(=O)_2R_{10}$, or -$S(=O)_2NR_{11}R_{12}$;

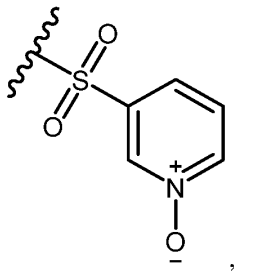
or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[234] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F,

I-F1, I-F4, or I-F6, wherein R_5 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

5 **[235]** One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, or I-F6, wherein R_5 is selected from  ,  ,  ,  ,  ,  ,  ,  , 

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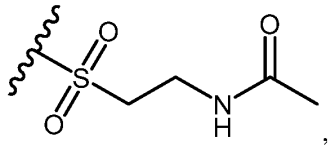
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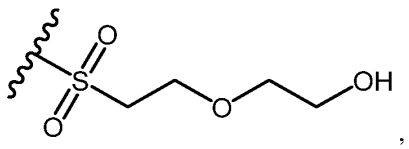
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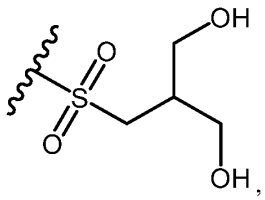
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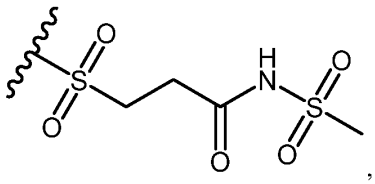
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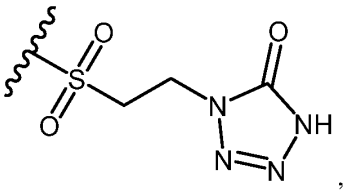
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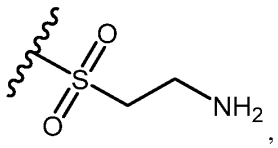
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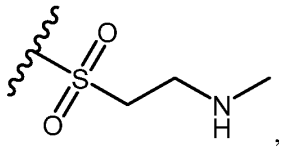
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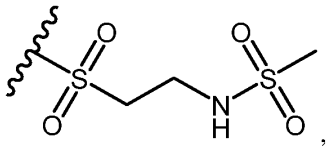
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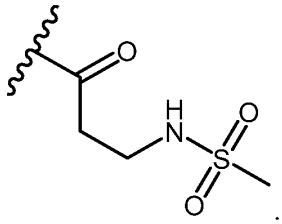
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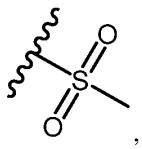
[236] One embodiment is a compound of formula I, or a compound of formula I-A, I-A1, I-A4, I-A6, I-B, I-B1, I-B4, I-B6, I-C, I-C1, I-D, I-D1, I-D4, I-D6, I-E, I-E1, I-E4, or I-E6, I-F, I-F1, I-F4, or I-F6, wherein R_5 is selected from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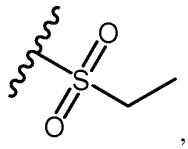
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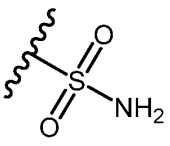
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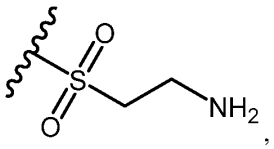
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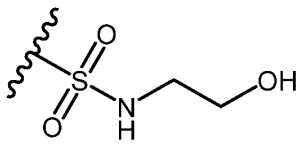
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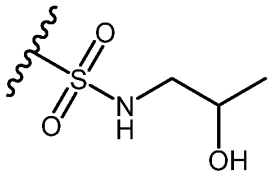
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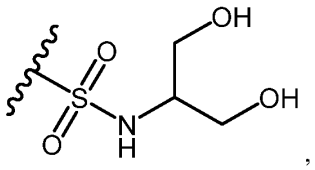
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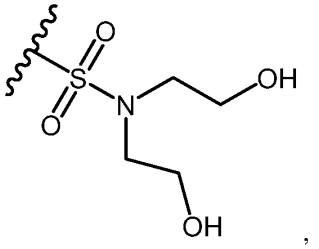
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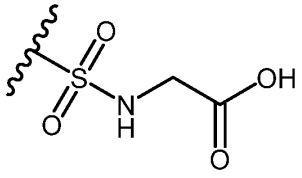
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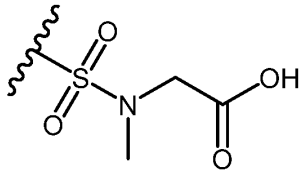
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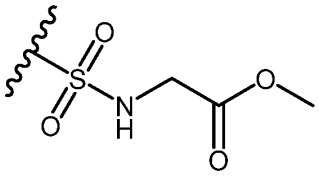
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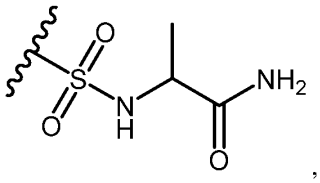
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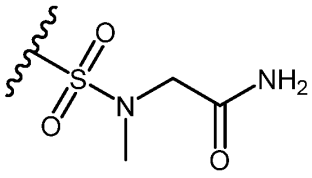
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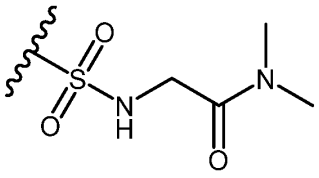
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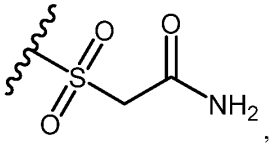
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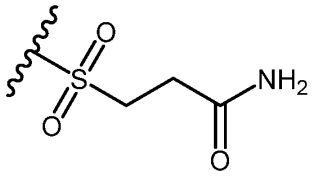
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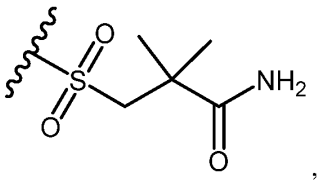
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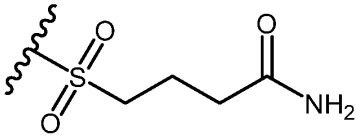
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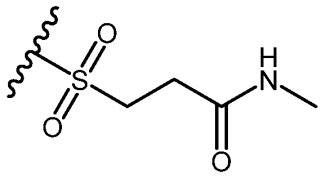
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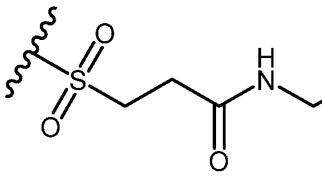
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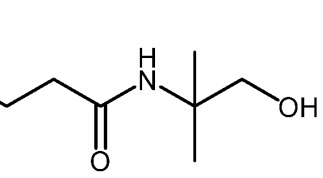
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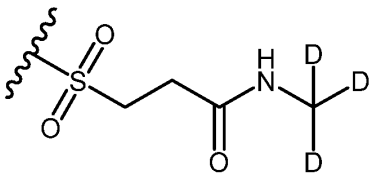
5 
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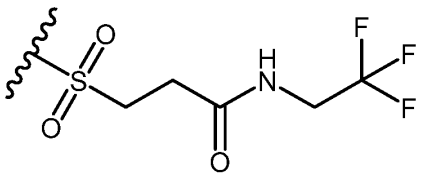
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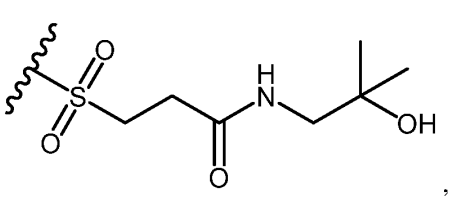
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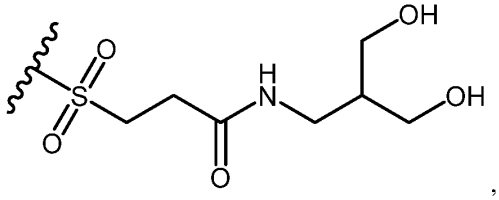
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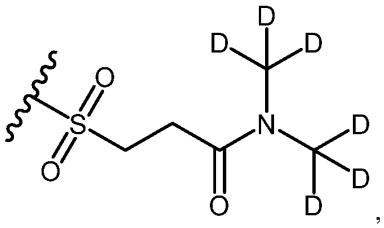
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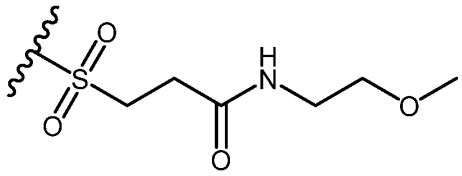
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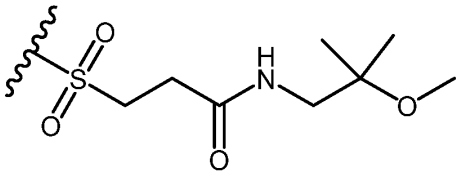
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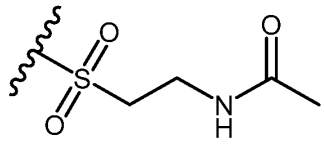
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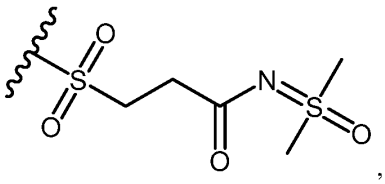
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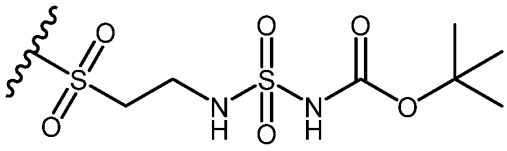
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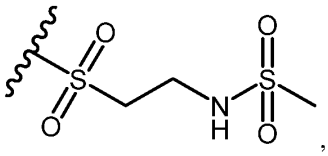
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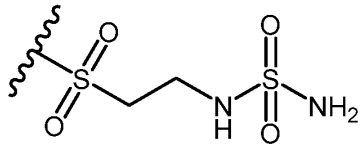
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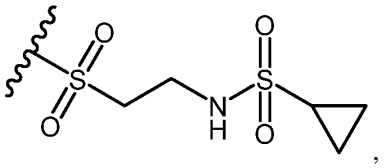
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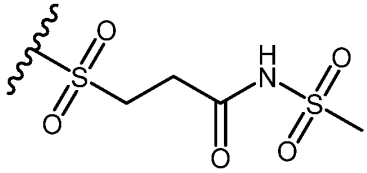
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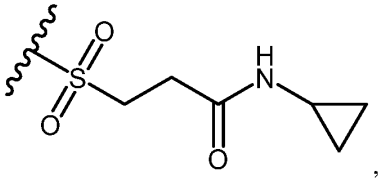
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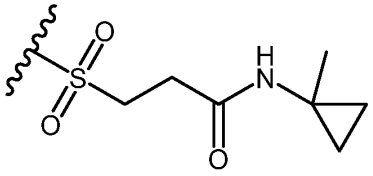
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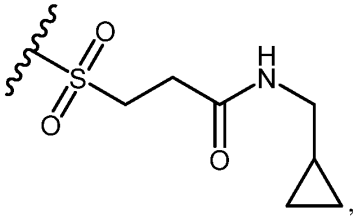
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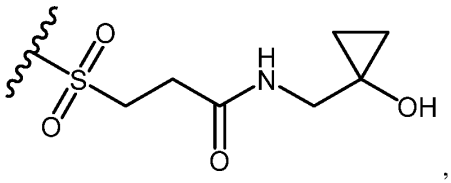
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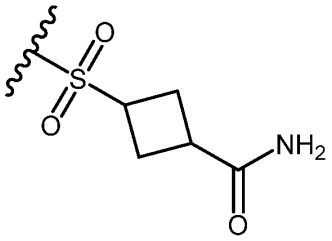
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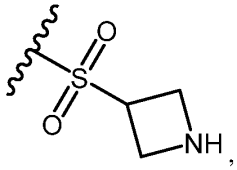
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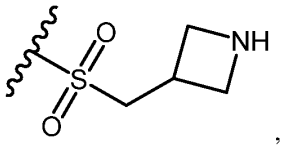
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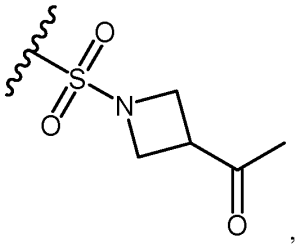
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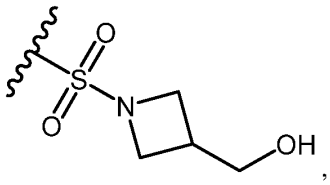
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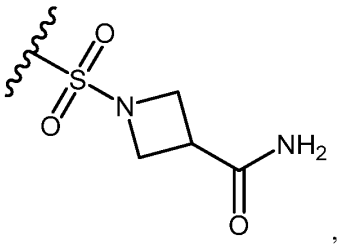
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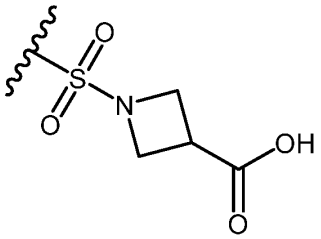
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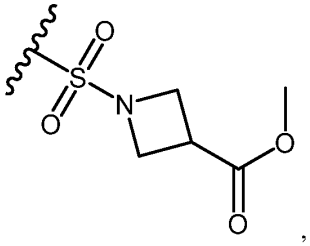
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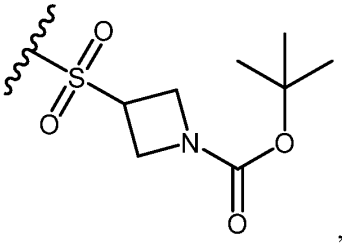
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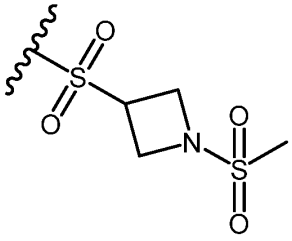
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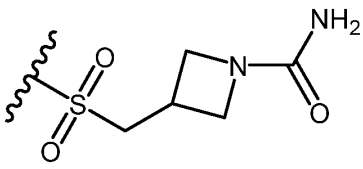
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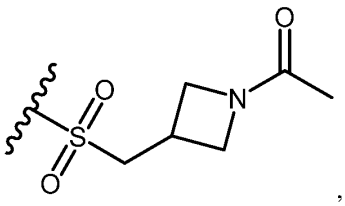
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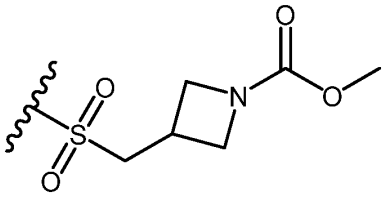
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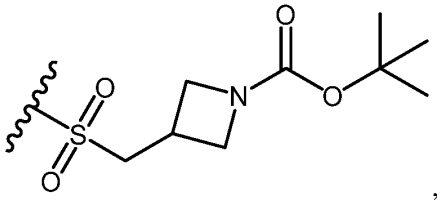
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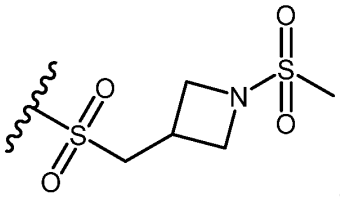
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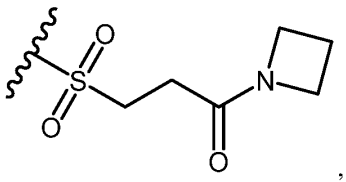
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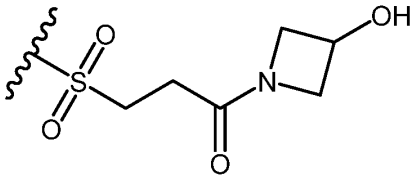
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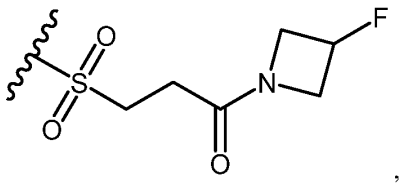
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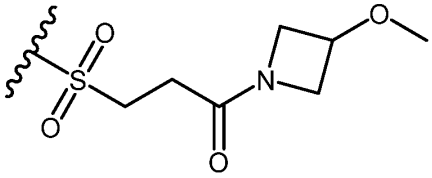
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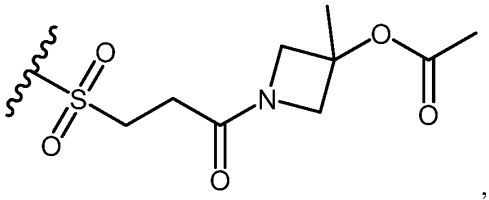
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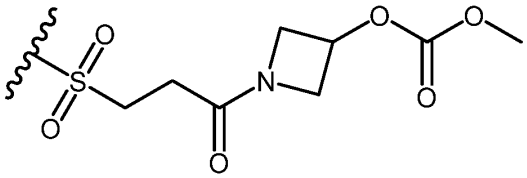
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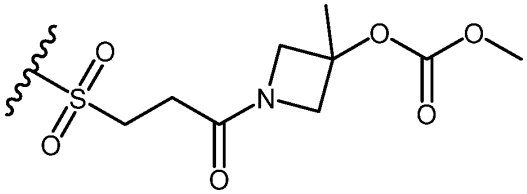
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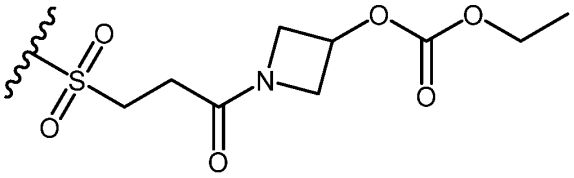
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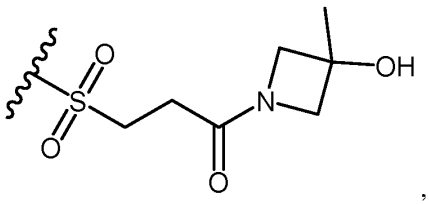
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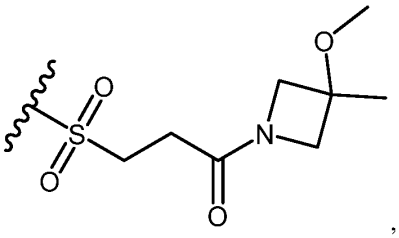
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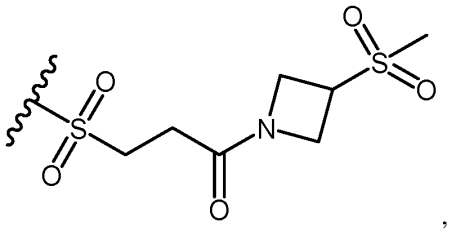
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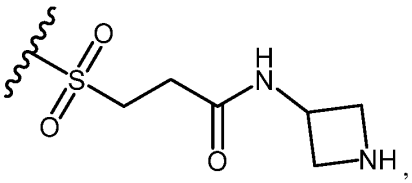
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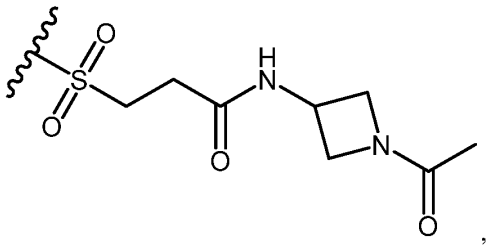
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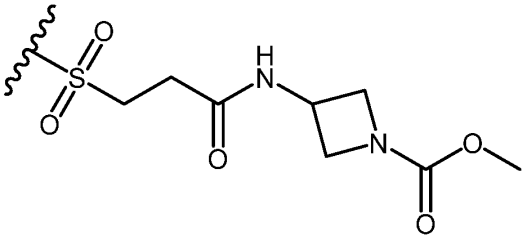
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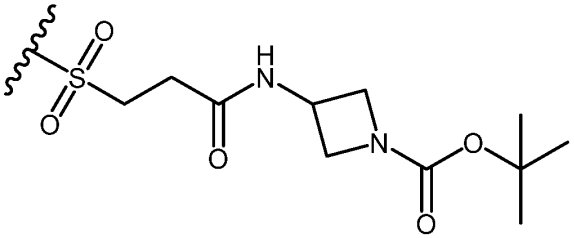
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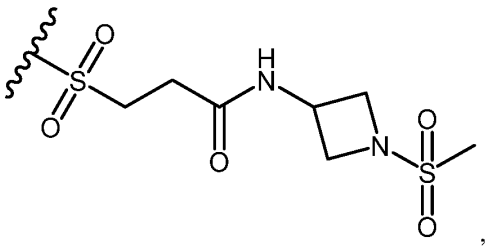
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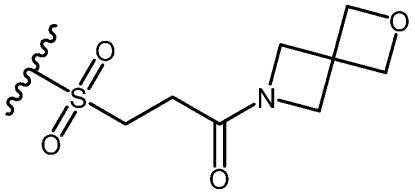
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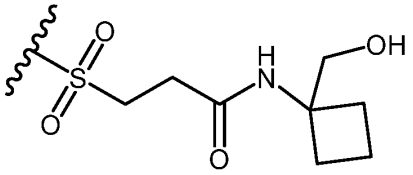
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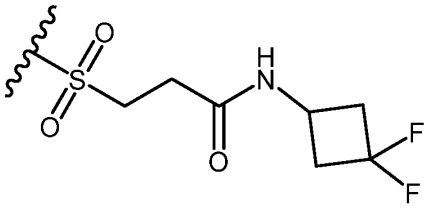
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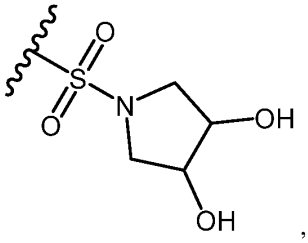
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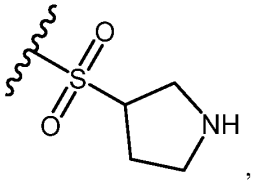
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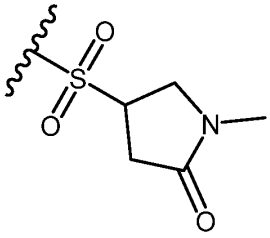
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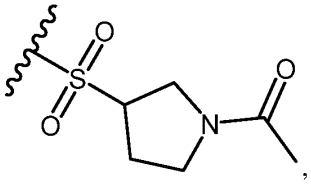
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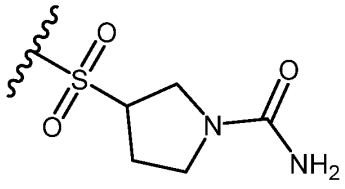
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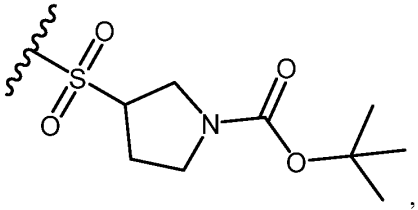
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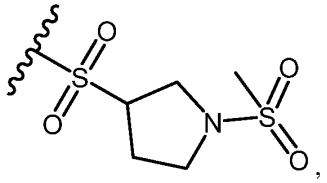
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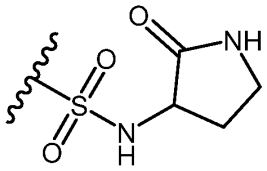
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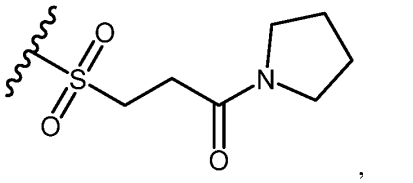
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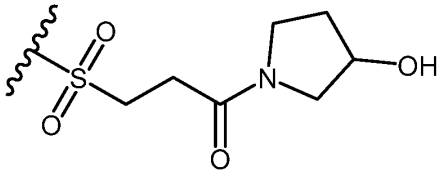
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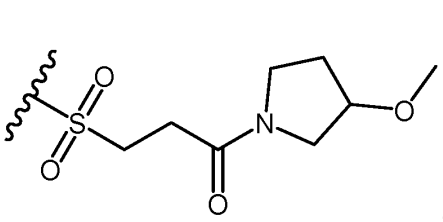
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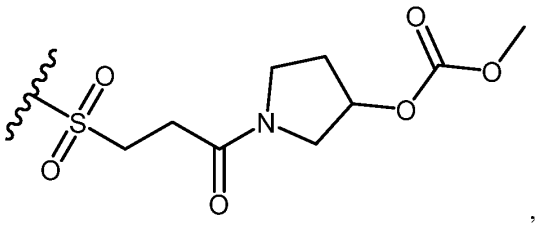
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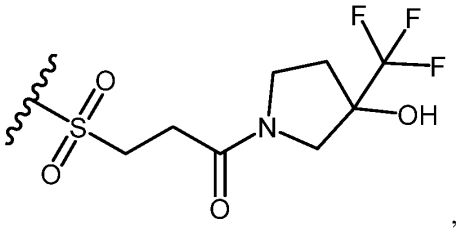
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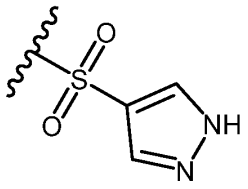
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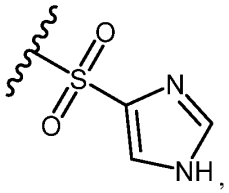
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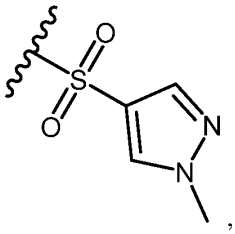
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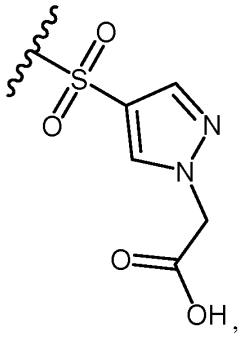
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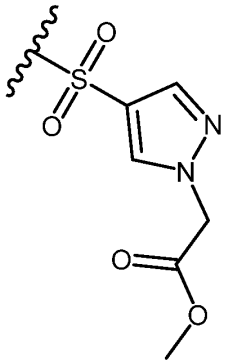
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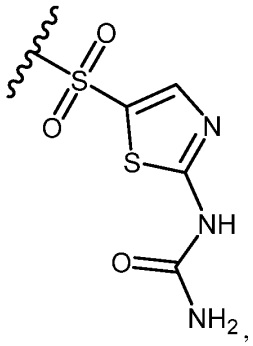
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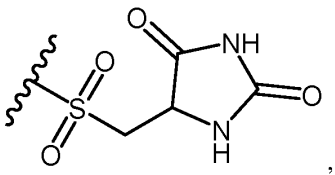
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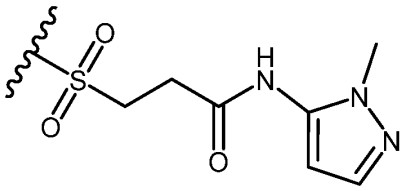
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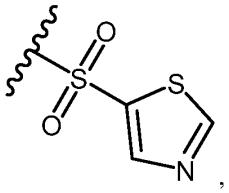
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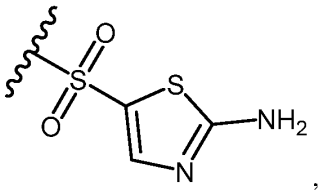
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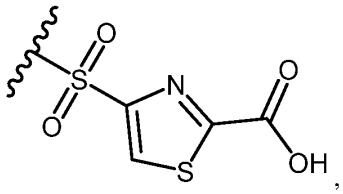
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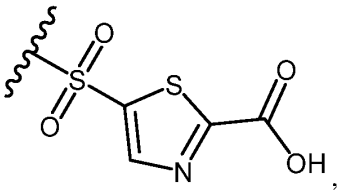
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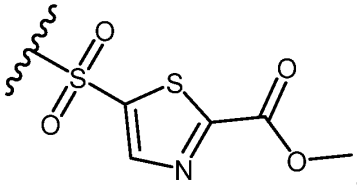
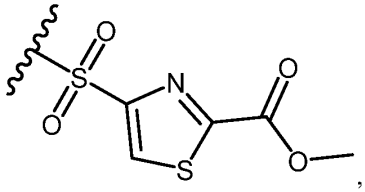
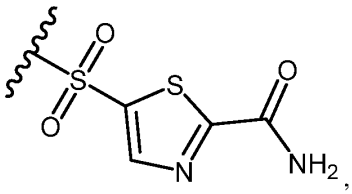
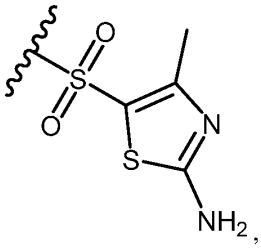
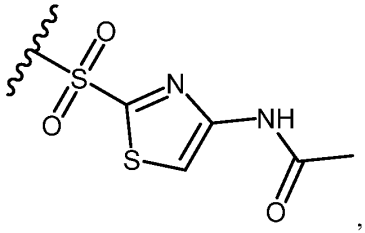
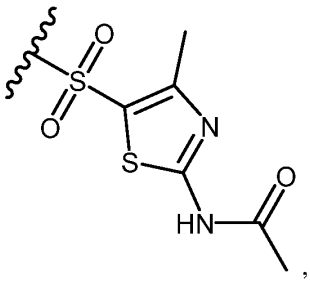
 ,

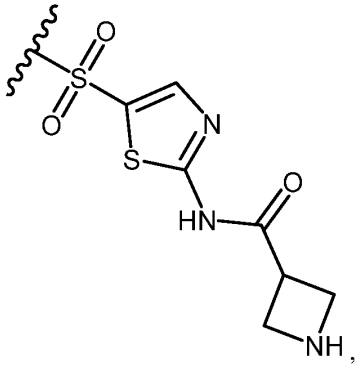
 ,

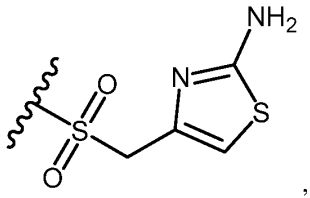
 ,

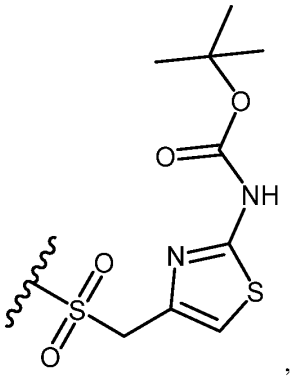
 ,

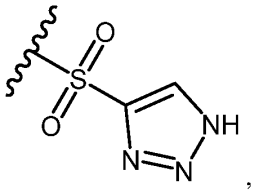
 ,

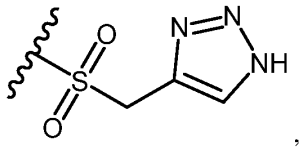
 ,

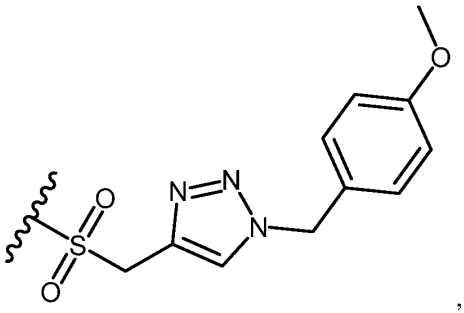
 ,

 ,

 ,

 ,

 ,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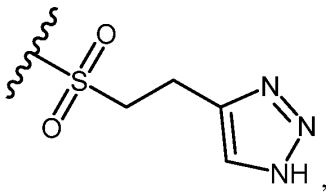
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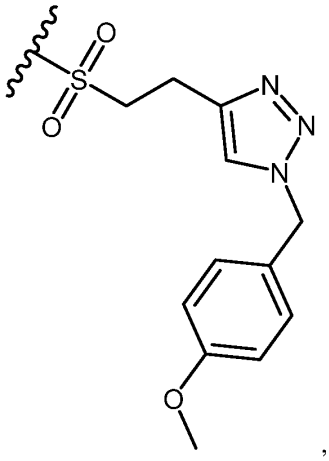
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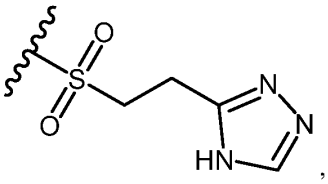
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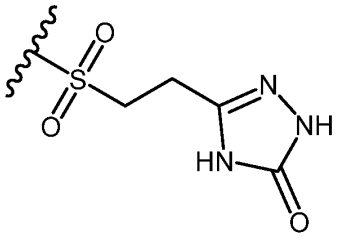
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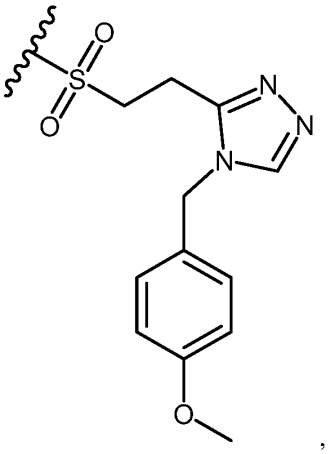
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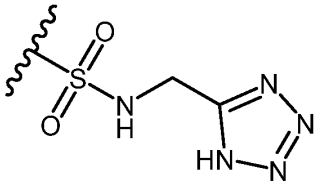
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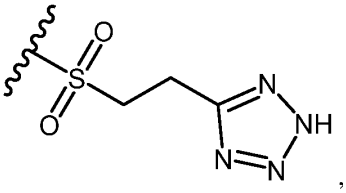
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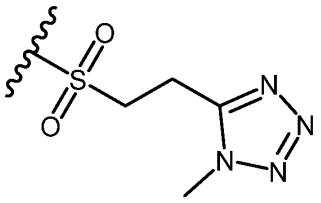
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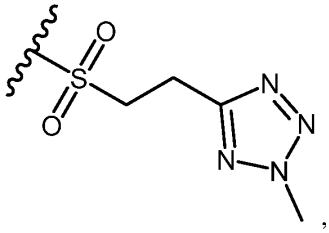
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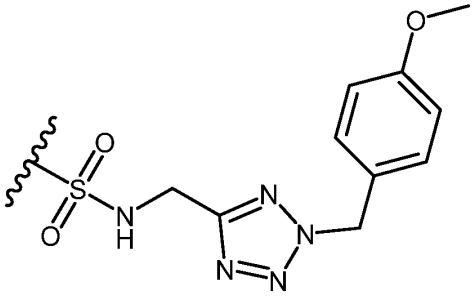
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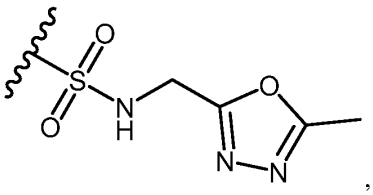
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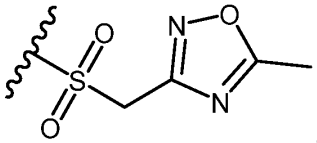
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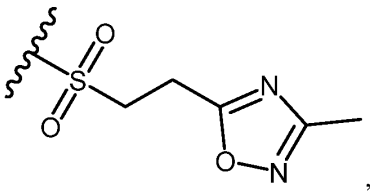
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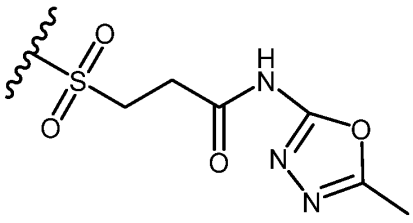
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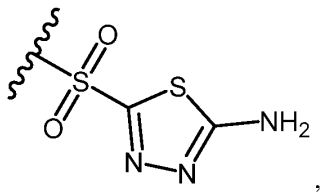
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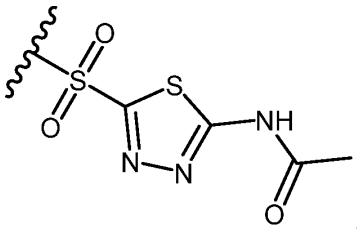
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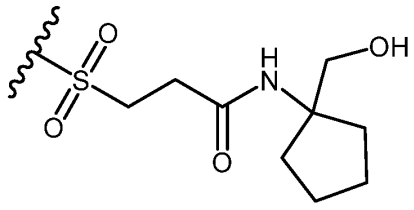
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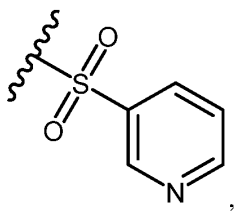
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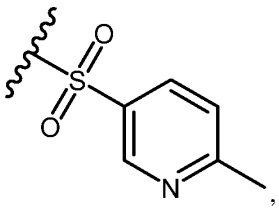
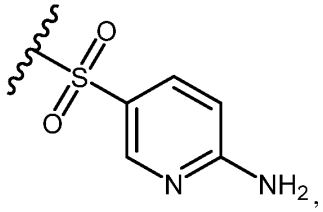
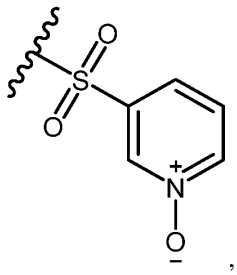
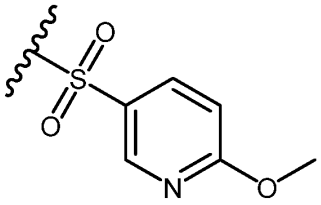
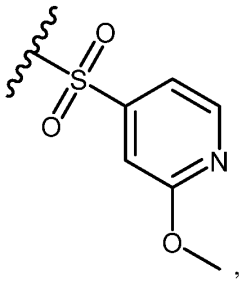
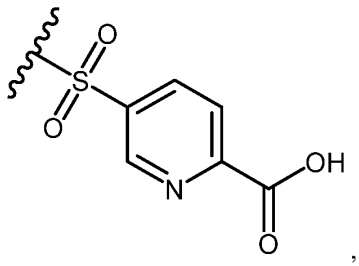
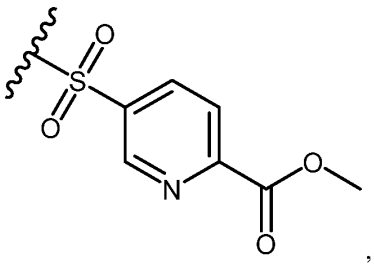
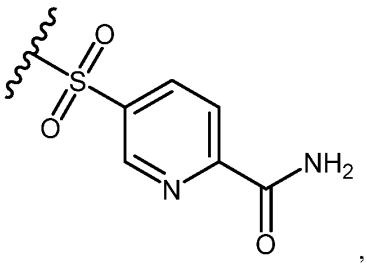
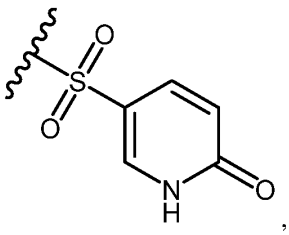
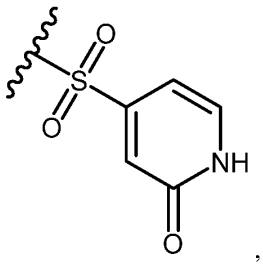
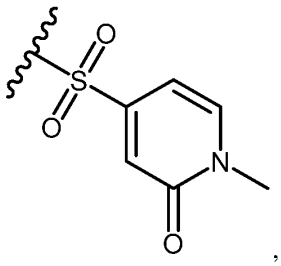
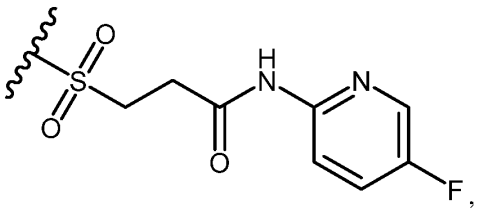
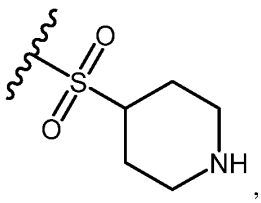
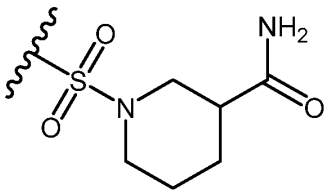
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,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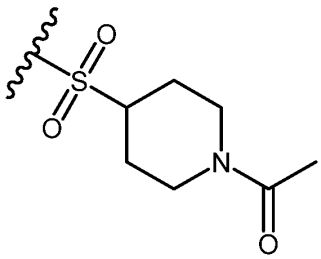
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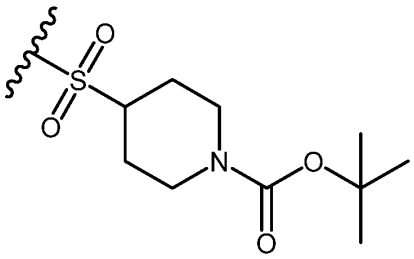
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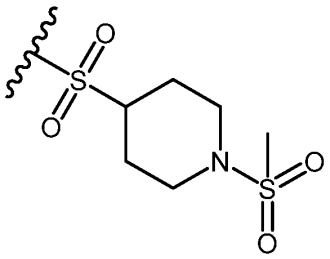
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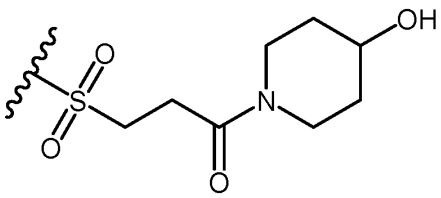
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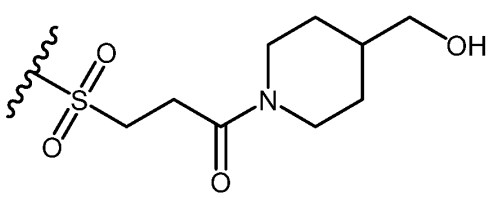
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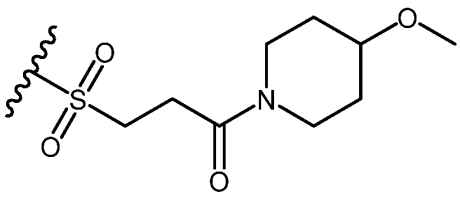
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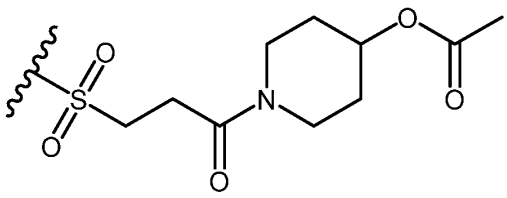
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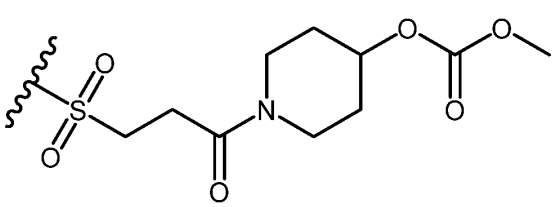
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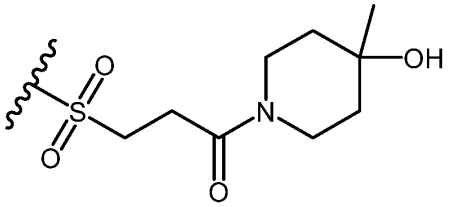
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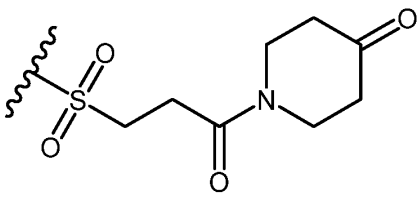
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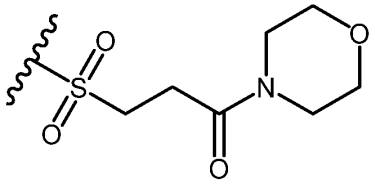
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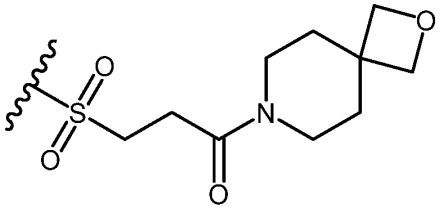
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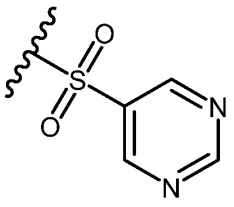
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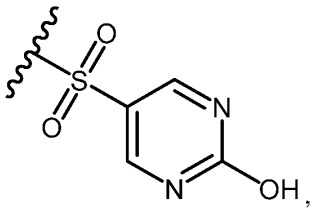
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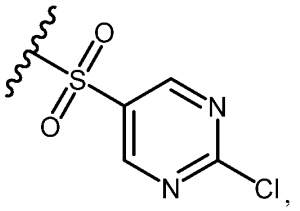
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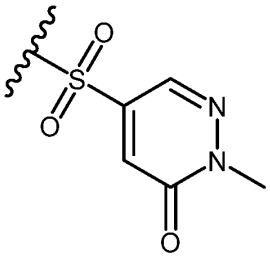
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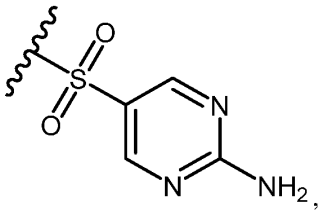
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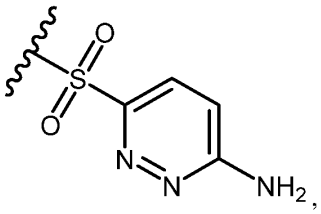
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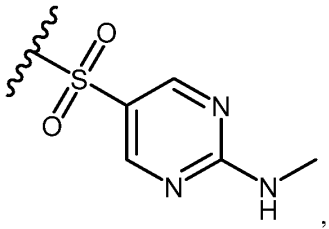
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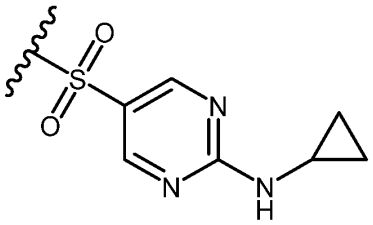
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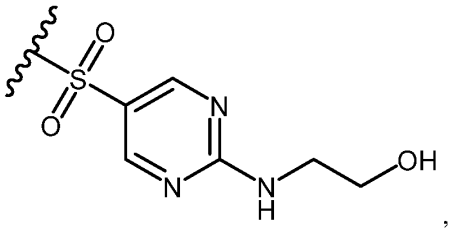
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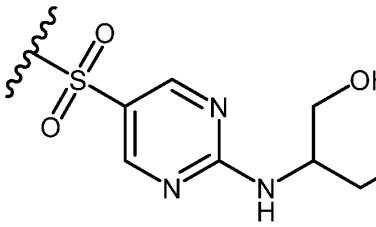
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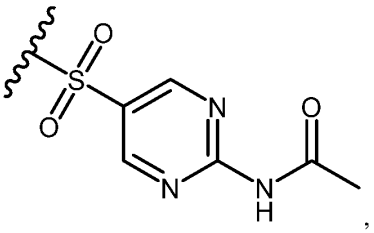
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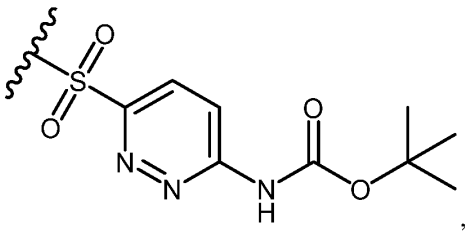
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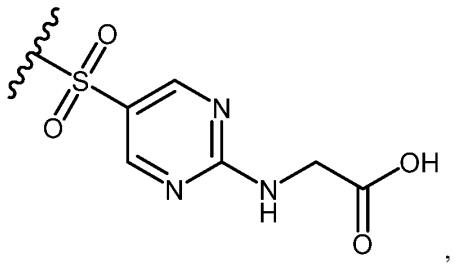
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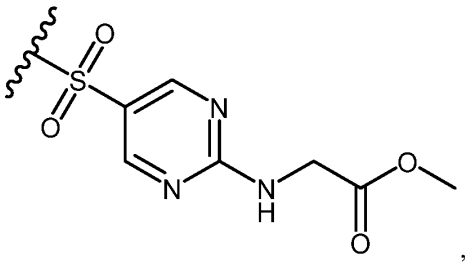
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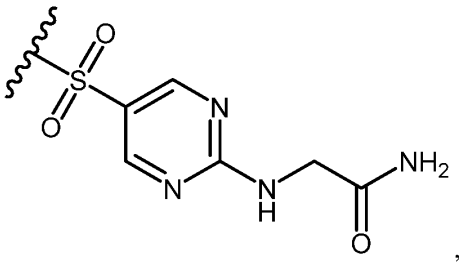
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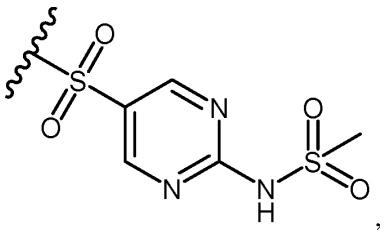
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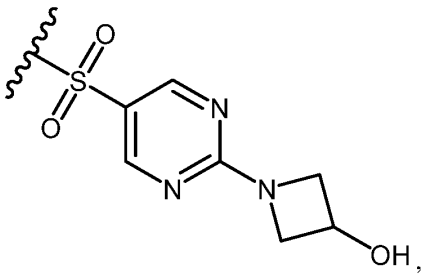
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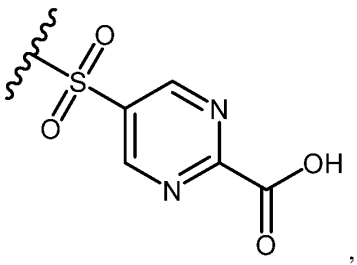
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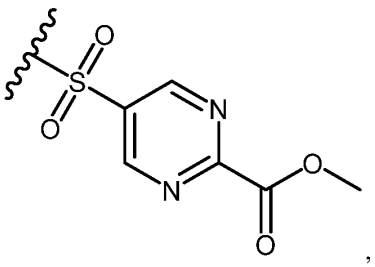
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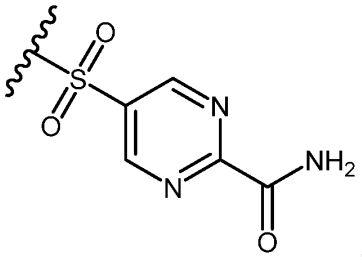
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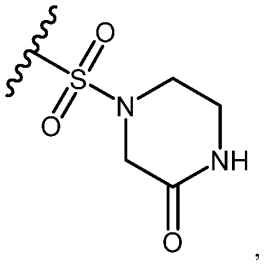
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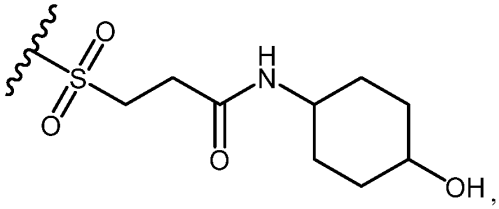
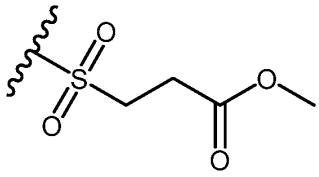
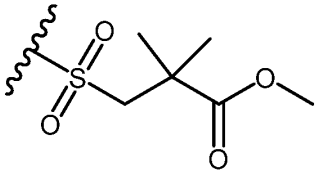
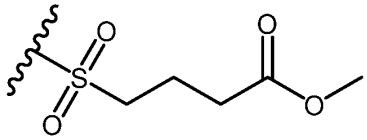
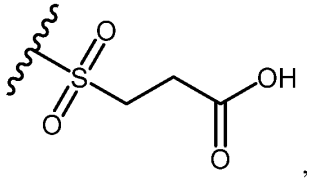
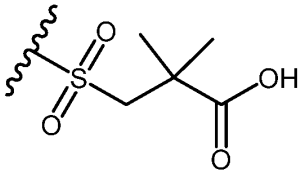
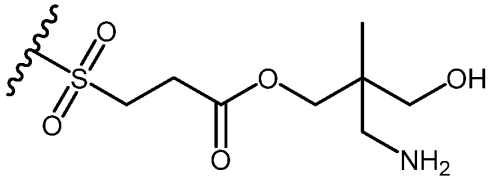
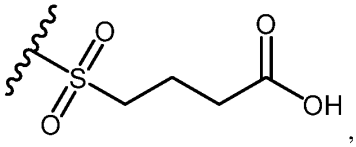
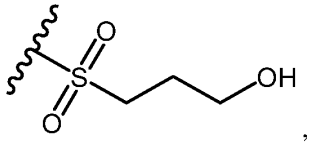
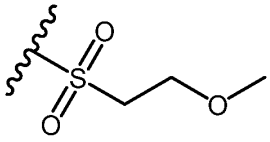
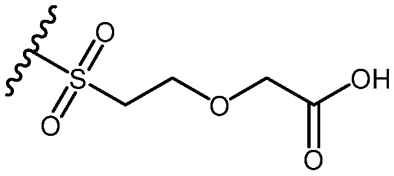
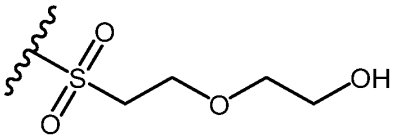
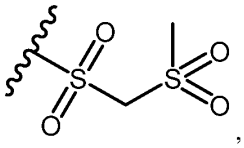
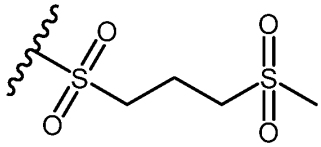
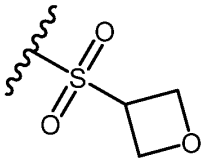
 ,  ,

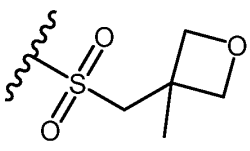
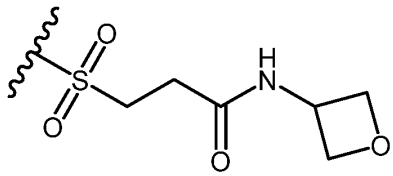
 ,  ,  ,

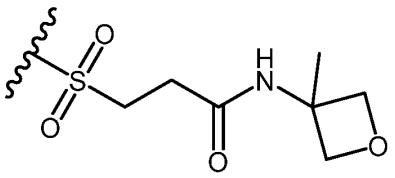
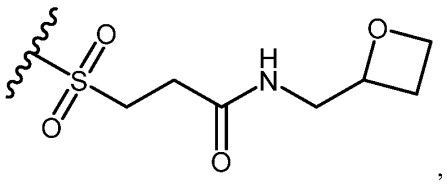
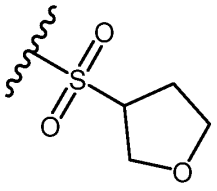
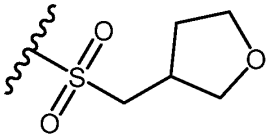
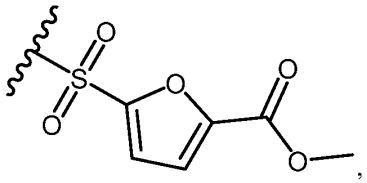
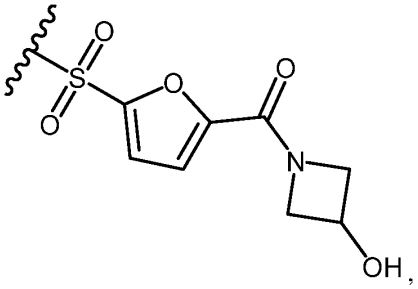
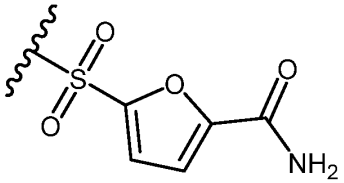
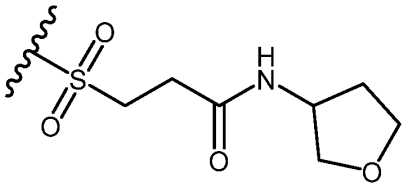
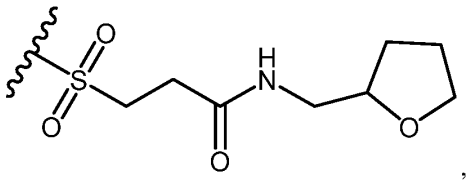
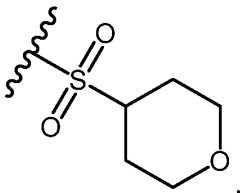
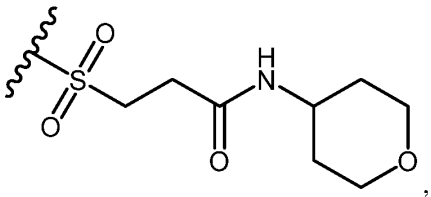
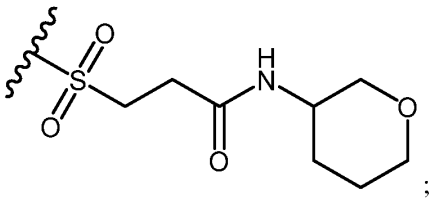
 ,  ,

 ,  ,  ,

 ,  ,

 ,  ,  ,

 ,  ,

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 , and
 ;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[237] All these subgroups taken alone or in combination are part of the description.

[238] One embodiment is a compound of formula I, selected from the compounds listed in Table 1, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[239] One embodiment is a compound of formula I, selected from:

Methyl 3-(((3S*,4S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propanoate;

3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propan-1-ol;

3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propanoic acid;

3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propanamide;

3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)-N-methylpropanamide;

Methyl N-(((3S*,4S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)-N-methylglycinate;

(3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-N,3-dimethylpiperidine-1-sulfonamide;

N-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)-N-methylglycine;

2-((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethylpiperidine-1-sulfonamido)acetamide;

2-((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethylpiperidine-1-sulfonamido)-N-methylacetamide;

Methyl (S*)-3-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propanoate;

(S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propan-1-ol;

(S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propanoic acid;

(S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propanamide;

(S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)-N-methylpropanamide;

Methyl (S*)-N-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)-N-methylglycinate;

(S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-N,3-dimethyl-3,6-dihydropyridine-1(2H)-sulfonamide;

(S*)-N-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)-N-methylglycine;

(S*)-2-(4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethyl-1,2,3,6-tetrahydropyridine-1-sulfonamido)acetamide;

(S*)-2-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethyl-1,2,3,6-tetrahydropyridine)-1-sulfonamido)-N-methylacetamide;

(S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxamide;

3-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)propan-1-ol; and

3-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)propanoic acid;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[240] One embodiment is a compound of formula I, or a compound of a subformula of formula I, that has sufficient solubility to avoid, for example, advanced formulations or advanced delivery systems, which include but are not limited to liposomal suspensions, inclusion complexes, solid dispersions in polymers, mechano-chemically activated systems,

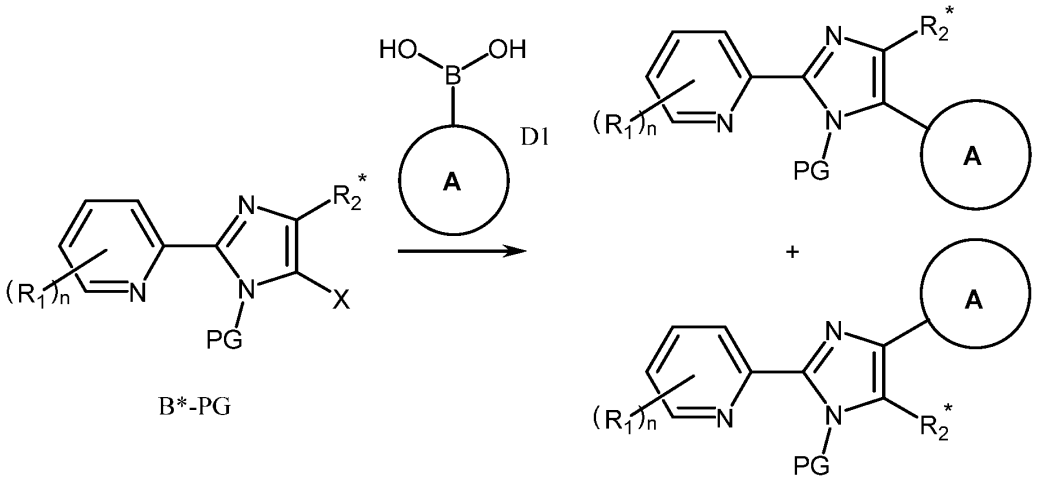
microparticles or nanoparticles, micro- or nano-emulsions, and vesicular systems. In some embodiments a compound of formula I, or a compound of a subformula of formula I, has a solubility of 20 μM or greater at pH 7.4. In some embodiments a compound of formula I, or a compound of a subformula of formula I, has a solubility of 100 μM or greater at pH 7.4. In some embodiments a compound of formula I, or a compound of a subformula of formula I, has a solubility of 500 μM or greater at pH 7.4. In some embodiments a compound of formula I, or a compound of a subformula of formula I, has a solubility of 1000 μM or greater at pH 7.4.

[241] The compounds of formula I, and subformulas thereof, may comprise one or more asymmetric atoms and/or chiral axes. They may thus exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures are provided herein.

[242] Some of the compounds of formula I, and subformulas thereof, may exist in the form of acids or of base-addition salts. Such addition salts form part of the disclosure. These salts are advantageously prepared with pharmaceutically acceptable bases or cations, but the salts of other bases or cations that are useful, for example, for purification or isolation of the compounds of formula I, and subformulas thereof, also form part of the disclosure.

[243] Some of the compounds of formula I, and subformulas thereof, may exist in the form of bases or of acid-addition salts. Such addition salts form part of the disclosure. These salts are advantageously prepared with pharmaceutically acceptable acids or anions, but the salts of other acids or anions that are useful, for example, for purification or isolation of the compounds of formula I, and subformulas thereof, also form part of the disclosure.

[244] Another aspect of the present disclosure is a process for preparing a compound of formula I, or a subformula thereof, comprising reacting an intermediate of formula B*-PG with an intermediate of formula D1 in the presence of a catalyst and a base to give an intermediate of formula C2:



C2

wherein R_1, A, and n are as defined for a compound of formula I, R_2^* is as defined for a compound of formula I or hydrogen, PG is a protecting group, and X is selected from halogen. C2 may be obtained as a mixture of positional isomers, where A is adjacent to the protected nitrogen atom in a first isomer and not adjacent to the protected nitrogen isomer in a second isomer. In some embodiments, the protecting group is 2-(trimethylsilyl)ethoxymethyl. In some embodiments, the catalyst is selected from bis(di-tert-butylphosphino)palladium dichloride ($Pd(dtbpf)Cl_2$) and bis(diphenylphosphino)palladium dichloride ($Pd(dppf)Cl_2$). In some embodiments, the base is selected from potassium carbonate, potassium acetate, and sodium carbonate. In some embodiments, the protecting group is 2-(trimethylsilyl)ethoxymethyl, the catalyst is selected from $Pd(dtbpf)Cl_2$ and $Pd(dppf)Cl_2$, and the base is selected from potassium carbonate, potassium acetate, and sodium carbonate. In some embodiments, an intermediate of formula C2 is subsequently deprotected to give a compound of formula I. In some embodiments, an intermediate of formula C2, wherein R_2^* is hydrogen is subsequently halogenated and deprotected to give a compound of formula I, wherein R_2 is selected from halogen.

[245] Yet another aspect of the present disclosure is a pharmaceutical composition that includes a compound described herein as an active ingredient. These pharmaceutical compositions comprise a therapeutically effective amount of a compound of formula I, or a

compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, and also at least one pharmaceutically acceptable excipient.

[246] The said excipients may be selected, in accordance with the pharmaceutical form and method of administration desired, from the customary excipients, which are known to a person skilled in the art.

[247] In these pharmaceutical compositions for oral, inhalative, topical, or transdermal administration, the active ingredient of formula I, or a compound of a subformula of formula I, or its pharmaceutically acceptable salt, may be administered in a unit administration form, in a mixture with conventional pharmaceutical excipients, to animals or to human beings for the treatment of a disease, disorder, or condition.

[248] Appropriate unit administration forms include oral forms such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, forms for inhalative administration, and forms for topical or transdermal administration. For topical and transdermal administration, it is possible to use the herein described compounds in creams, gels, ointments, or lotions.

[249] By the oral route, the dose of active principle per day may reach 2000 mg/day, taken all at once or in portions. By the inhalative route, the dose of active principle per day may reach 50 mg/day. By parenteral routes, the dose of active principle per day may reach 400 mg/day.

[250] There may be particular cases in which higher or lower dosages are appropriate; such dosages do not depart from the scope of the disclosure. According to usual practice, the dosage that is appropriate for each subject is determined by the doctor according to the mode of administration and the weight and response of the said subject.

[251] Compounds described herein have an antagonistic activity for MRGPRX2. The compounds according to the present disclosure can, therefore, be used for preparing medicaments, especially medicaments which are antagonists of MRGPRX2.

[252] Accordingly, yet another aspect of the present disclosure is a medicament, characterized in that it comprises a compound of formula I, or a compound of a subformula of

formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[253] The medicaments of the present disclosure can be employed therapeutically, especially in the treatment of a disease, disorder, or condition selected from the group consisting of inflammatory disorders, autoimmune disorders, allergic disorders, skin disorders, mast cell disorders, pain disorders, and itch disorders. In yet another aspect, also provided is the use of a compound of formula I, or a compound of a subformula of formula I, for preparing a medicament for the treatment of a disease, disorder, or condition selected from the group consisting of inflammatory disorders, autoimmune disorders, allergic disorders, skin disorders, mast cell disorders, pain disorders, and itch disorders.

[254] In one embodiment, the disease, disorder, or condition is selected from the group consisting of atopic dermatitis, chronic urticaria, chronic spontaneous urticaria, inducible urticaria, prurigo, prurigo nodularis, pruritus, asthma, rosacea, contact dermatitis, allergic contact dermatitis, anaphylaxis, anaphylactoid drug reaction, allergy, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, allergic rhinitis, chronic rhinosinusitis, aggressive periodontitis, systemic mastocytosis, cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, interstitial cystitis, hereditary alpha tryptasemia, chronic itch, and chronic pain.

[255] In one embodiment, the disease, disorder, or condition is selected from the group consisting of atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma. In one embodiment, the disease, disorder, or condition is atopic dermatitis. In one embodiment, the disease, disorder, or condition is chronic spontaneous urticaria. In one embodiment, the disease, disorder, or condition is prurigo nodularis. In one embodiment, the disease, disorder, or condition is asthma.

[256] Yet another aspect of the present disclosure is a method of treating a disease, disorder, or condition associated with MRGPRX2, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[257] One embodiment is a method for treating a disease, disorder, or condition associated with undesired mast cell activity or mast cell degranulation, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[258] One embodiment is a method for treating a disease, disorder, or condition for which modulation of MRGPRX2 is indicated, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof. Modes of modulating MRGPRX2 include antagonism, inhibition, blocking, agonism, partial agonism, inverse agonism, and combinations thereof.

[259] One embodiment is a method for treating a disease, disorder, or condition for which antagonism of MRGPRX2 is indicated, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[260] One embodiment is a method for treating a disease, disorder, or condition selected from the group consisting of inflammatory disorders, autoimmune disorders, allergic disorders, mast cell disorders, pain disorders, and itch disorders, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[261] One embodiment is a method for treating a disease, disorder, or condition selected from the group consisting of atopic dermatitis, chronic urticaria, chronic spontaneous urticaria, inducible urticaria, prurigo, prurigo nodularis, pruritus, asthma, rosacea, contact dermatitis, allergic contact dermatitis, anaphylaxis, anaphylactoid drug reaction, allergy, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, allergic rhinitis, chronic rhinosinusitis, aggressive periodontitis, systemic mastocytosis, cutaneous mastocytosis, mastocytic

enterocolitis, mast cell activation syndrome, interstitial cystitis, hereditary alpha tryptasemia, chronic itch, and chronic pain, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[262] One embodiment is a method for treating a disease, disorder, or condition selected from the group consisting of atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[263] One embodiment is a method for treating atopic dermatitis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[264] One embodiment is a method for treating chronic spontaneous urticaria, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[265] One embodiment is a method for treating prurigo nodularis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[266] One embodiment is a method for treating asthma, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[267] According to another aspect, also provided is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease disorder or condition associated with MRGPRX2.

[268] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition associated with undesired mast cell activity or mast cell degranulation.

[269] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition for which modulation of MRGPRX2 is indicated. Modes of modulating MRGPRX2 include antagonism, inhibition, blocking, agonism, partial agonism, inverse agonism, and combinations thereof.

[270] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition for which antagonism of MRGPRX2 is indicated.

[271] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition selected from the group consisting of inflammatory disorders, allergic disorders, skin disorders, mast cell disorders, pain disorders, and itch disorders.

[272] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition selected from the group consisting of atopic dermatitis, chronic urticaria, chronic spontaneous urticaria, inducible urticaria, prurigo, prurigo nodularis, pruritus, asthma, rosacea, contact dermatitis, allergic contact dermatitis, anaphylaxis, anaphylactoid drug reaction, allergy, rheumatoid arthritis, inflammatory bowel disease,

ulcerative colitis, allergic rhinitis, chronic rhinosinusitis, aggressive periodontitis, systemic mastocytosis, cutaneous mastocytosis, mastocytic enterocolitis, mast cell activation syndrome, interstitial cystitis, hereditary alpha tryptasemia, chronic itch, and chronic pain.

[273] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition selected from the group consisting of atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma.

[274] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of atopic dermatitis.

[275] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic spontaneous urticaria.

[276] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of prurigo nodularis.

[277] One embodiment is a compound of formula I, or a compound of a subformula of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma.

[278] One embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, wherein the compound of formula I is selected from the compounds listed in Table 1.

[279] One embodiment is a compound of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt

thereof, for use as a medicament, wherein the compound of formula I is selected from one of the above three lists.

[280] One embodiment is the use of a compound of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a disease, disorder, or condition selected from the group consisting of inflammatory disorders, allergic disorders, skin disorders, mast cell disorders, pain disorders, and itch disorders, for example, atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma, wherein the compound of formula I is selected from one of the above three lists.

[281] One embodiment is a compound of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition selected from the group consisting of inflammatory disorders, allergic disorders, skin disorders, mast cell disorders, pain disorders, and itch disorders, for example, atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma, wherein the compound of formula I is selected from one of the above three lists.

[282] One embodiment is a method of treating a disease, disorder, or condition selected from the group consisting of inflammatory disorders, allergic disorders, skin disorders, mast cell disorders, pain disorders, and itch disorders, for example, atopic dermatitis, chronic spontaneous urticaria, prurigo nodularis, and asthma, comprising administering to a subject in need thereof, in particular a human, a therapeutically effective amount of a compound of formula I, or an enantiomer, diastereomer, or tautomer, or atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the compound of formula I is selected from one of the above three lists.

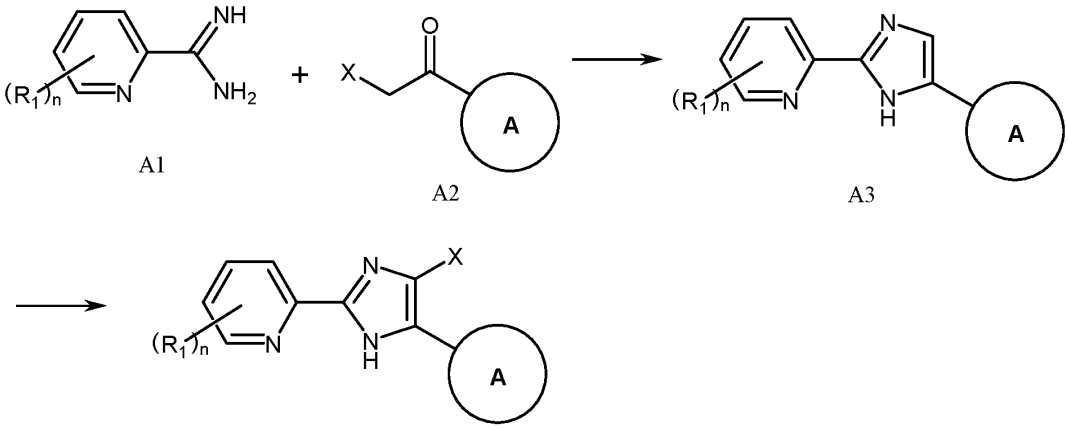
[283] **GENERAL SYNTHETIC METHODS**

[284] The compounds of formula I herein can be prepared by the methods outlined in the following reaction schemes and examples. In the schemes and examples, the addition of a protecting group (PG) to an imidazole ring nitrogen may lead to positional isomers, which are depicted herein as two structures. A given substituent on the adjacent carbon atoms of the imidazole ring may be either adjacent or not adjacent to the protected nitrogen atom. Because

protected imidazoles do not typically tautomerize, these intermediates may be prepared, isolated, characterized, and modified as a mixture of discrete positional isomers. After removal of the protecting group, the imidazole ring of the resulting intermediate or compound of formula I will no longer be restricted from tautomerization and may no longer exist as discrete positional isomers or a mixture thereof.

[285] In certain embodiments, the preparation of the compounds of formula I can be carried out according to Scheme 1.

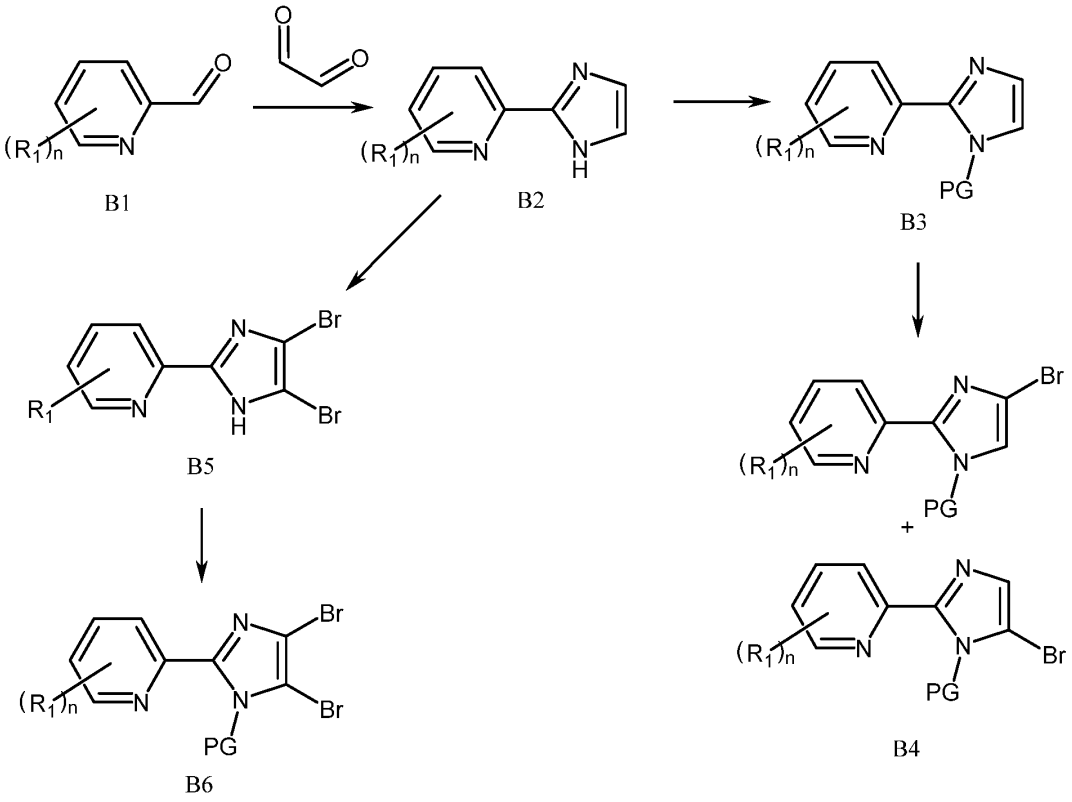
[286] **Scheme 1**



[287] In Scheme 1, each X is independently selected from halogen. Carbamimidoyl pyridine intermediates of formula A1 may be commercially available, such as 5-fluoropyridine-2-carboxamidine, or can be prepared according to Scheme 5 or by methods known to those skilled in the art. Haloacetyl intermediates of formula A2 may be commercially available or can be prepared by methods known to those skilled in the art. A carbamimidoyl pyridine intermediate of formula A1 can be cyclized to a pyridyl-imidazole intermediate of formula A3 by reacting with a haloacetyl intermediate of formula A2 in the presence of a base, such as potassium carbonate, in a solvent, such as ethanol. The pyridyl-imidazole intermediate of formula A3 can be converted to a compound of formula I, wherein R_2 is selected from halogen (e.g., -Cl), by reacting with a halogenation reagent, such as N-chlorosuccinimide, in a solvent such as DMF.

[288] In certain embodiments, the preparation of the compounds of formula I can be carried out according to Schemes 2-6. Schemes 2-6 depict methods of preparing different pyridyl-imidazole halide intermediates which can be coupled with boronic ester intermediates to give compounds of formula I or other intermediates which can be converted to compounds of formula I.

[289] **Scheme 2**



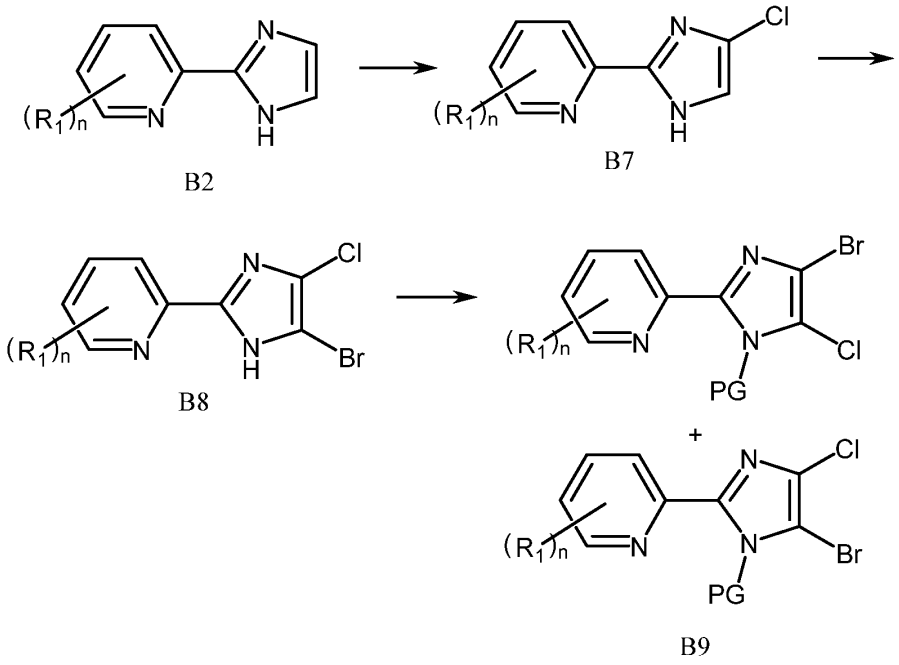
[290] Picolinaldehyde intermediates of formula B1 may be commercially available, such as 5-fluoropicolinaldehyde, or can be prepared by methods known to those skilled in the art. A picolinaldehyde intermediate of formula B1 can be converted to a pyridyl-imidazole intermediate of formula B2 by reacting with oxalaldehyde and ammonium hydroxide in a solvent, such as ethanol. The pyridyl-imidazole intermediate of formula B2 can be converted to a protected pyridyl-imidazole intermediate of formula B3 by addition of a protecting group

to the imidazole, such as by reacting with a base, such as sodium hydride, and a protecting group reagent, such as SEM-Cl, in an aprotic solvent, such as THF.

[291] A protected pyridyl-imidazole intermediate of formula B3 can be converted to a protected pyridyl-imidazole bromide intermediate of formula B4 (an isomeric mixture) by reacting with a bromination reagent, such as N-bromosuccinimide, in a solvent, such as chloroform.

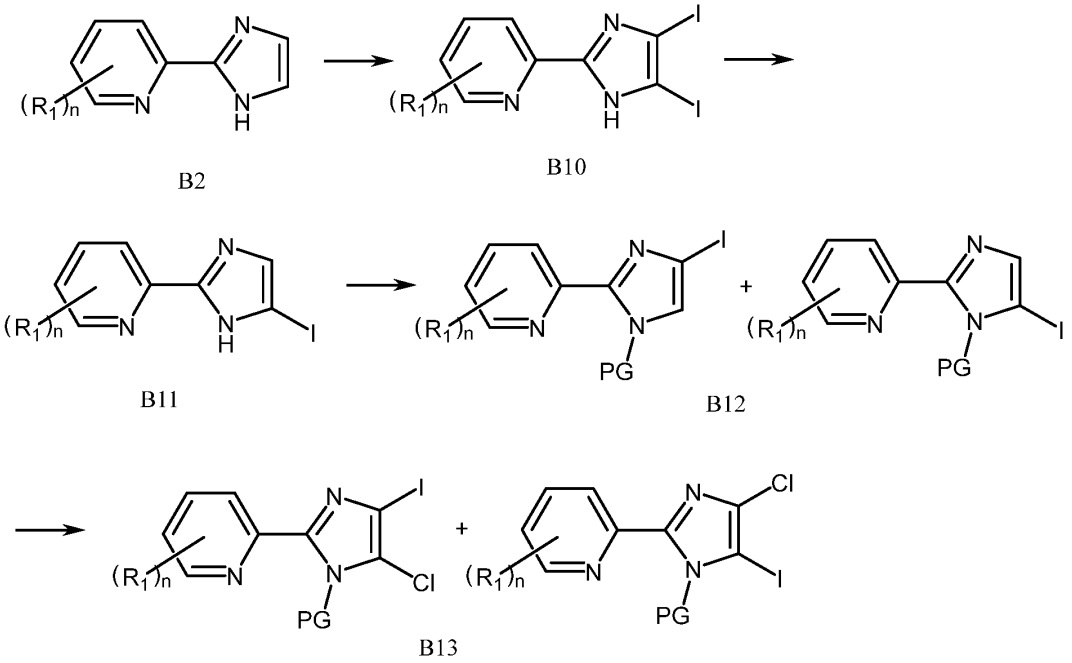
[292] A protected pyridyl imidazole intermediate of formula B2 can be converted to a pyridyl-imidazole dibromide intermediate of formula B5 by reacting with a bromination reagent, such as N-bromosuccinimide, in a solvent, such as chloroform. The pyridyl-imidzole dibromide intermediate of formula B5 can be converted to a protected pyridyl-imidazole dibromide intermediate of formula B6 by addition of a protecting group to the imidazole, such as by reacting with a base, such as sodium hydride, and a protecting group reagent, such as SEM-Cl, in an aprotic solvent, such as THF.

[293] **Scheme 3**



[294] Pyridyl-imidazole intermediates of formula B2 can be prepared according to Scheme 2. A pyridyl-imidazole intermediate of formula B2 can be converted to a pyridyl-imidazole chloride intermediate of formula B7 by reacting with a chlorination reagent, such as N-chlorosuccinimide, in a solvent, such as DMF. The pyridyl-imidazole chloride intermediate of formula B7 can be converted to a pyridyl-imidazole chloride bromide intermediate of formula B8 by reacting with a bromination reagent, such as N-bromosuccinimide, in a solvent, such as THF. The pyridyl-imidazole chloride bromide intermediate of formula B8 can be converted to a protected pyridyl-imidazole chloride bromide intermediate of formula B9 (an isomeric mixture) by addition of a protecting group to the imidazole, such as by reacting with a base, such as sodium hydride, and a protecting group reagent, such as SEM-Cl, in an aprotic solvent, such as THF.

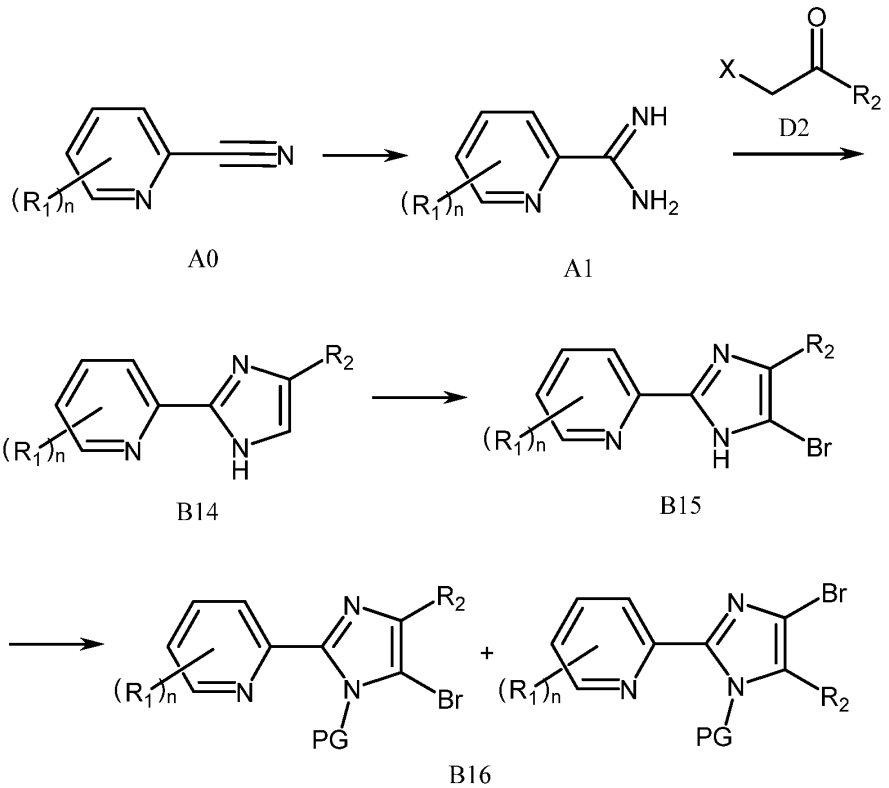
[295] **Scheme 4**



[296] Pyridyl-imidazole intermediates of formula B2 can be prepared according to Scheme 2. A pyridyl-imidazole intermediate of formula B2 can be converted to a pyridyl-imidazole diiodide intermediate of formula B10 by reacting with an iodination reagent, such as

N-iodosuccinimide, in a solvent, such as acetonitrile. The pyridyl-imidazole diiodide intermediate of formula B10 can be converted to a pyridyl-imidazole iodide intermediate of formula B11 by reacting with a reducing agent, such as sodium sulfite (Na_2SO_3), in the presence of water, in a solvent such as DMF, water, or a mixture thereof. The pyridyl-imidazole iodide intermediate of formula B11 can be converted to a protected pyridyl-imidazole iodide intermediate of formula B12 (an isomeric mixture) by addition of a protecting group to the imidazole, such as by reacting with a base, such as sodium hydride, and a protecting group reagent, such as SEM-Cl, in an aprotic solvent, such as THF. The protected pyridyl-imidazole iodide intermediate of formula B12 (an isomeric mixture) can be converted to a protected pyridyl-imidazole chloride iodide intermediate of formula B13 (an isomeric mixture) by reacting with a chlorination reagent, such as N-chlorosuccinimide.

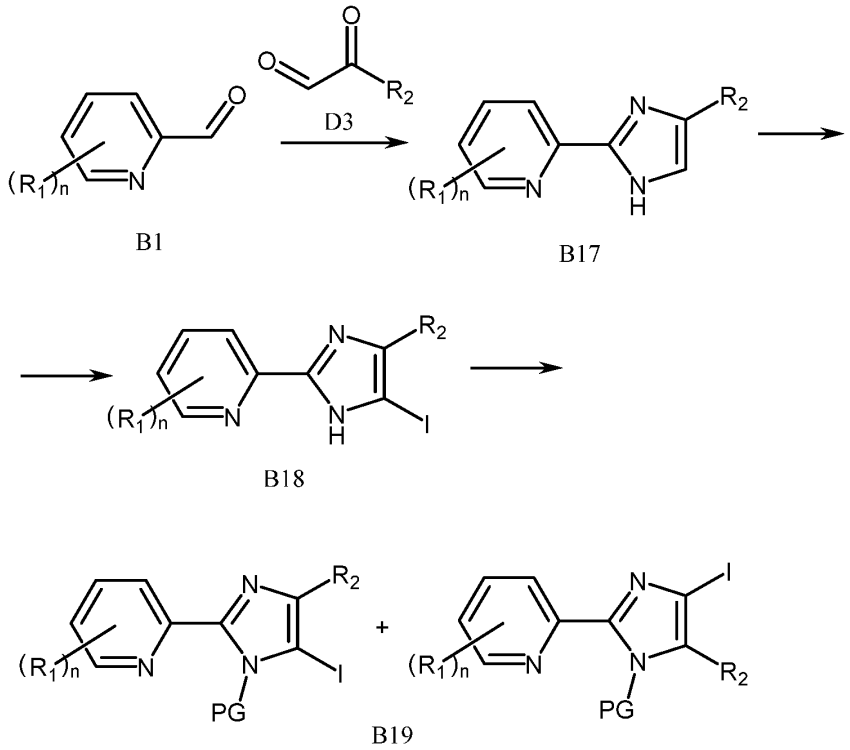
[297] Scheme 5



[298] Picolinonitrile intermediates of formula A0 may be commercially available, such as 5-methyl-picolinonitrile, or may be prepared by methods known to those skilled in the art. A picolinonitrile intermediate of formula A0 can be converted to a carbamimidoyl pyridine intermediate of formula A1 by reacting with a base, such as LiHMDS, in a solvent such as THF, and quenching with ammonium chloride.

[299] Haloacetyl intermediates of formula D2 may be commercially available, such as when R_2 is methyl or ethyl, or can be prepared by methods known to those skilled in the art. A carbamimidoyl pyridine intermediate of formula A1 can be converted to a pyridyl-imidazole intermediate of formula B14 by reacting with a haloacetyl intermediate of formula D2 in the presence of a base, such as potassium carbonate, in a solvent, such as ethanol. A pyridyl-imidazole intermediate of formula B14 can be converted to a pyridyl-imidazole bromide intermediate of formula B15 by reacting with a bromination reagent, such as N-bromosuccinimide, in a solvent, such as acetonitrile. A pyridyl-imidazole bromide intermediate of formula B15 can be converted to a protected pyridyl-imidazole bromide intermediate of formula B16 (an isomeric mixture) by addition of a protecting group to the imidazole, such as by reacting with a base, such as sodium hydride, and a protecting group reagent, such as SEM-Cl, in an aprotic solvent, such as THF.

[300] **Scheme 6**

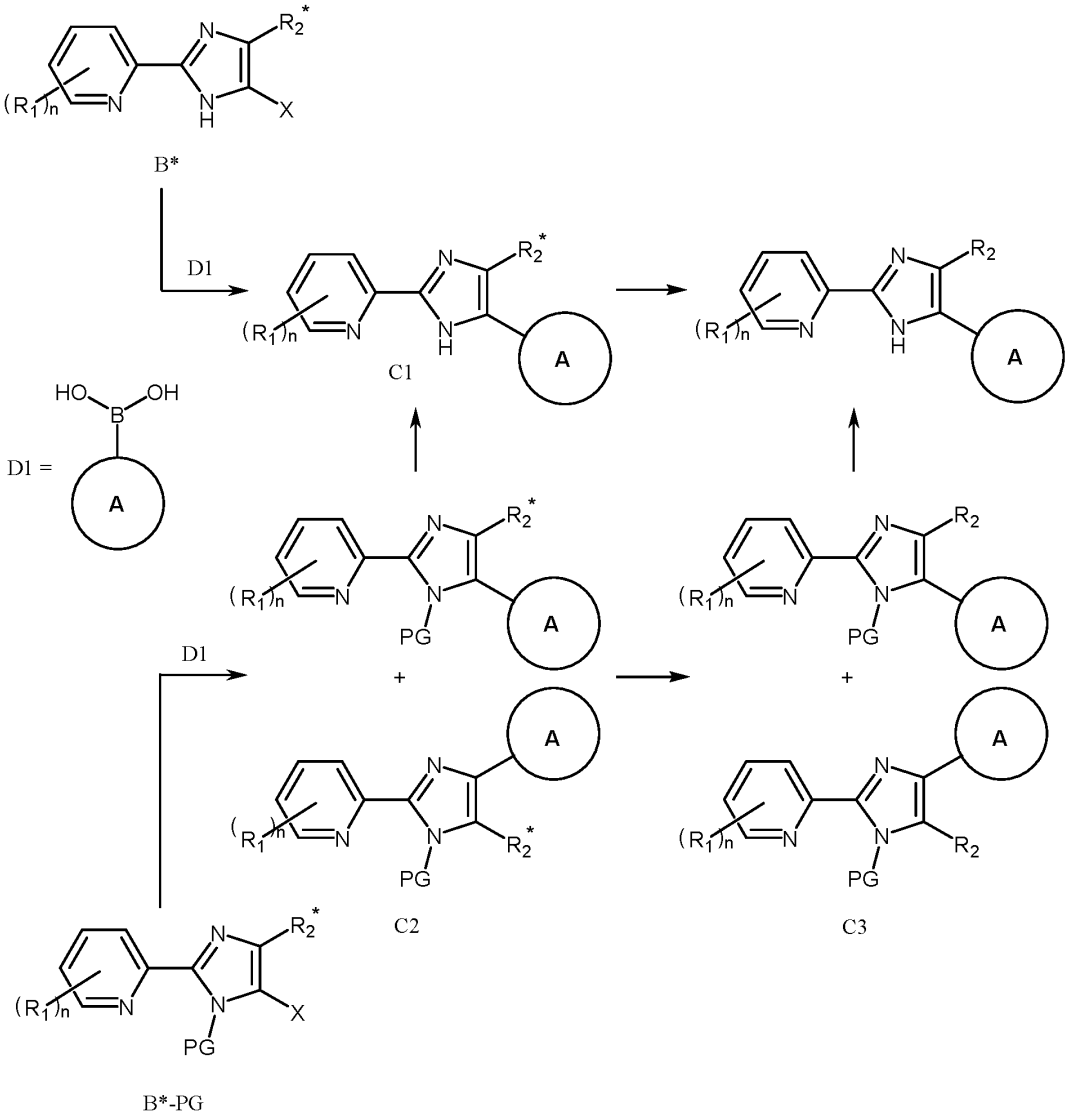


[301] Picolinaldehyde intermediates of formula B1 may be commercially available, such as 5-fluoropicolinaldehyde, or can be prepared by methods known to those skilled in the art. An oxoacetyl intermediate of formula D13 may be commercially available, such as wherein R_2 is methyl or ethyl, or can be prepared by methods known to those skilled in the art. A picolinaldehyde intermediate of formula B1 can be converted to a pyridyl-imidazole intermediate of formula B17 by reacting with an oxoacetyl intermediate of formula D13 in the presence of ammonium acetate in a solvent, such as methanol. A pyridyl-imidazole intermediate of formula B17 can be converted to a pyridyl-imidazole iodide intermediate of formula B18 by reacting with an iodination reagent, such as N-iodosuccinimide, in a solvent, such as acetonitrile. A pyridyl-imidazole iodide intermediate of formula B18 can be converted to a protected pyridyl-imidazole iodide intermediate of formula B19 (an isomeric mixture) by addition of a protecting group to the imidazole, such as by reacting with a base, such as

sodium hydride, and a protecting group reagent, such as SEM-Cl, in an aprotic solvent, such as THF.

[302] In certain embodiments, the preparation of the compounds of formula I can be carried out according to Scheme 7, which depicts the coupling of various pyridyl-imidazole halide intermediates (such as those prepared according to Schemes 2-6) with a boronic acid intermediate. In Scheme 7, R_2* is R_2 as defined for a compound of formula I, but may also be selected from hydrogen.

[303] **Scheme 7**



[304] Intermediates of formula B* are non-protected pyridyl-imidazoles including intermediates of formula B5, B7, B8, B10, B11, B15, and B18, which can be prepared according to Schemes 2-6. Intermediates of formula B*-PG are protected pyridyl-imidazoles

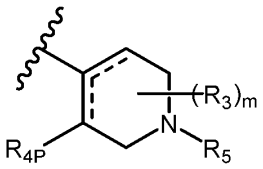
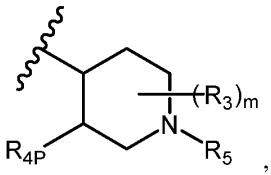
including intermediates of formula B4, B6, B9, B12, B13, B16, and B19, which can be prepared according to Schemes 2-6.

[305] An intermediate of formula B* can be converted to an intermediate of formula C1 (which may also be a compound of formula I) by coupling with a boronic acid intermediate of formula D1, which may be commercially available or can be prepared by methods known to those skilled in the art. The coupling can be accomplished in the presence of a catalyst, such as bis(di-tert-butylphosphino)palladium dichloride ($Pd(dtbpf)Cl_2$) bis(diphenylphosphino)palladium dichloride ($Pd(dppf)Cl_2$), and a base, such as potassium carbonate, potassium acetate, or sodium carbonate, in a solvent, such as NMP, DMF, dioxane, or DMSO, or a mixture with water thereof.

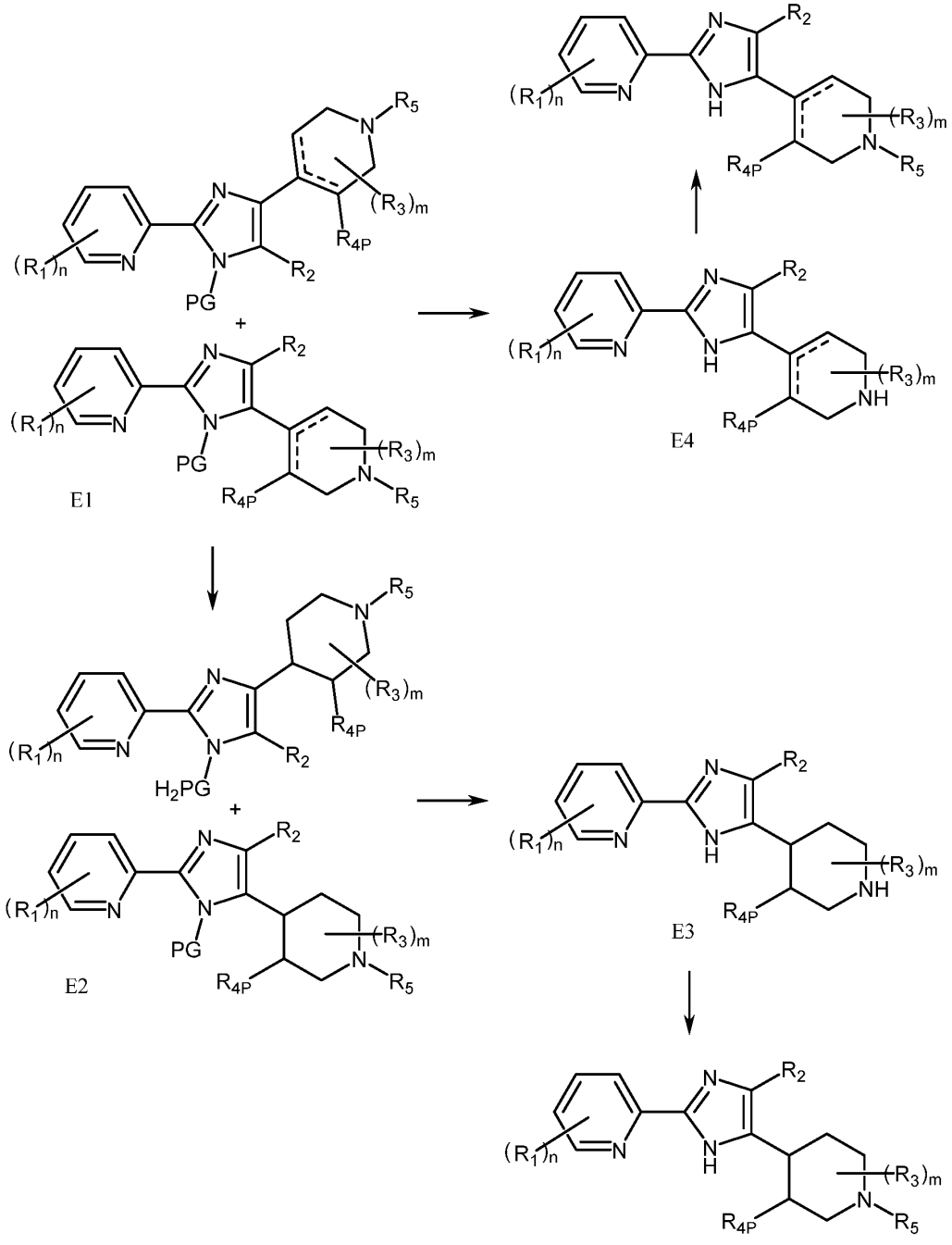
[306] An intermediate of formula B*-PG (an isomeric mixture) can be converted to an intermediate of formula C2 (an isomeric mixture) by coupling with a boronic acid intermediate of formula D1, which may be commercially available or can be prepared by methods known to those skilled in the art. The coupling can be accomplished in the presence of a catalyst, such as bis(di-tert-butylphosphino)palladium dichloride ($Pd(dtbpf)Cl_2$) bis(diphenylphosphino)palladium dichloride ($Pd(dppf)Cl_2$), and a base, such as potassium carbonate, potassium acetate, or sodium carbonate, in a solvent, such as NMP, DMF, dioxane, or DMSO, or a mixture with water thereof. An intermediate of formula C2 may be deprotected to convert to an intermediate of formula C1 (which may also be a compound of formula I) by reacting with an acid, such as TFA.

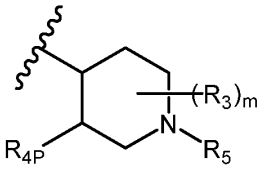
[307] In embodiments wherein R_2* is hydrogen, an intermediate of formula C1 may be converted to a compound of formula I, wherein R_2 is selected from halogen by reacting with a halogenation agent, such as N-chlorosuccinimide, N-bromosuccinimide, or N-iodosuccinimide, in a solvent, such as THF, acetonitrile, DMF, or chloroform.

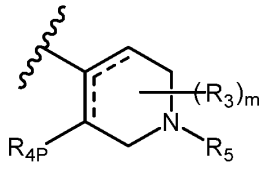
[308] In embodiments wherein R_2* is hydrogen, an intermediate of formula C2 (an isomeric mixture) may be converted to an intermediate of formula C3 (an isomeric mixture), wherein R_2 is selected from halogen by reacting with a halogenation agent, such as N-chlorosuccinimide, N-bromosuccinimide, or N-iodosuccinimide, in a solvent, such as THF, acetonitrile, DMF, or chloroform. An intermediate of formula C3 may be deprotected to convert to a compound of formula I by reacting with an acid, such as TFA.

[309] In certain embodiments, wherein A is  , and one ==== is a double bond, or  , the preparation of compounds of formula I can be carried out according to Scheme 8.

[310] **Scheme 8**



[311] An intermediates of formula E1 (an isomeric mixture) may be prepared according to Scheme 8 (as an intermediate of formula C2 (an isomeric mixture)). An intermediate of formula E1 (an isomeric mixture) can be converted to an intermediate of formula E2 (an isomeric mixture) by reacting with a hydrogen source, such as molecular hydrogen (H_2), in the presence of a catalyst, such as palladium on carbon (Pd/C), in a solvent, such as methanol or ethanol. An intermediate of formula E2, wherein R_5 is an acid cleavable group (e.g., BOC), can be converted to a piperidine intermediate of formula E3, or an acid addition salt thereof, by reacting with an acid, such as TFA or HCl. A piperidine intermediate of formula E3, or an acid additional salt thereof, can be converted to a compound of formula I, wherein A is  , by reacting with an electrophilic reagent, such as acetyl chloride, methanesulfonyl chloride, or (tert-butoxycarbonyl)((4-(dimethyliminio)pyridin-1(4H)-yl)sulfonyl)amide, in the presence of a base, such as DIEA, in a solvent, such as DCM.

[312] An intermediate of formula E1 (an isomeric mixture) can be converted to an intermediate of formula E4, , wherein R_5 is an acid cleavable group (e.g., BOC), or an acid addition salt thereof, by reacting with an acid, such as TFA or HCl. An intermediate of formula E4, or an acid addition salt thereof, can be converted to a to a compound of formula I, wherein A is  , and one ==== is a double bond, by reacting with an electrophilic reagent, such as acetyl chloride, methanesulfonyl chloride, (tert-butoxycarbonyl)((4-(dimethyliminio)pyridin-1(4H)-yl)sulfonyl)amide, in the presence of a base, such as DIEA, in a solvent, such as THF or DCM.

[313] In certain embodiments, a compound of formula I, for example a compound of formula I prepared according to methods depicted in Schemes 1 to 8, or any combination thereof, can also be an intermediate to one or more additional compounds of formula I. In certain embodiments, such additional compounds of formula I, can be prepared by modifying

R_5 by methods known to those skilled in the art. The synthetic examples herein provide exemplary modifications of R_5.

[314] In another aspect, also provided are compounds of formula A0, A1, A2, A3, B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11, B12, B13, B14, B15, B16, B17, B18, B19, B*, B*-PG, C1, C2, C3, D1, D2, D3, E1, E2, E3, or E4. These compounds are useful as synthetic intermediates for the compounds of formula I, or compounds of a subformula of formula I.

EXAMPLES

[315] The embodiments provided herein will be explained more specifically with reference to the following examples, however, the scope of the embodiments provided herein is not limited to these examples. The isomeric configuration for stereocenters of some enantiomeric compounds described in the Examples has been assigned as R* or S*, but the absolute configuration has not been determined.

[316] **ABBREVIATIONS**

[317] Unless otherwise stated, the following abbreviations have the stated meanings:

dba	dibenzylideneacetone
DCM	dichloromethane
DIEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dtbpf	1,1'-bis(di-*tert*-butyl-phosphino)ferrocene
eq.	equivalent
EA	ethyl acetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
EtOH	ethanol
FA	formic acid
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography

LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
NMP	*N*-methyl-2-pyrrolidone
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MOPS	3-(*N*-morpholino)propanesulfonic acid
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic spectroscopy
OAc	acetate
Pd/C	palladium on carbon
PE	petroleum ether
RT	room temperature
SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
t-Bu	*tert*-butyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Xantphos	(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)

[318] Generally, crude products were purified by column chromatography or flash chromatography. LCMS analysis or separation was performed using the following methods or methods described for specific examples.

[319] **LCMS METHODS**

[320] Method A

[321] A: H_2O (0.01% TFA), B: MeCN (0.01% TFA); Gradient: 5%-95%B in 1.5min; Flow Rate: 1.8ml/min; Column: SunFire C18, 3.5μm, 4.6x50mm; Column Temperature: 50°C

[322] Method B

[323] A: H_2O (10mM NH_4HCO_3), B: MeCN; Gradient: 5%-95%B in 1.3min, 95%B for 1.7min; Flow Rate: 1.8ml/min; Column: XBridge C18, 3.5μm, 4.6x50mm; Column Temperature: 50°C

[324] Method C

[325] A: H_2O (0.01% TFA), B: MeCN (0.01% TFA); Gradient: 5%-95%B in 1.3min, 95%B for 1.7min; Flow Rate: 2.0ml/min; Column: SunFire C18, 3.5μm, 4.6x50mm; Column Temperature: 50°C

[326] Method D

[327] A: H_2O (10mM NH_4HCO_3), B: MeCN; Gradient: 5%-95%B in 1.3min, 95%B for 1.7min; Flow Rate: 2.0ml/min; Column: XBridge C18, 3.5μm, 4.6x50mm; Column Temperature: 45°C

[328] Method E

[329] A: H_2O (10mmol NH_4HCO_3), B: MeCN; Gradient: 10-95%B in 1.5min; Flow Rate: 1.8mL/min; Column: XBridge C18, 3.5μm, 4.6x50mm; Column Temperature: 50°C

[330] Method F

[331] A: H_2O (0.05% TFA), B: MeCN (0.05% TFA); Gradient: 5%-95%B in 1.3min, 95%B for 2.9min, 95%-5%B in 0.1min; Flow Rate: 2ml/min; Column: XBridge C18, 3.5μm, 4.6x50mm; Column Temperature: 45°C

[332] Method G

[333] A: H_2O (10mM NH_4HCO_3), B: MeCN; Gradient: 5%-95%B in 1.4min, 95%B for 1.6min; Flow Rate: 1.8ml/min; Column: XBridge C18, 3.5μm, 4.6x50mm; Column Temperature: 45°C

[334] Method H

[335] A: H_2O (10mM NH_4HCO_3), B: MeCN; Gradient: 5%-95%B in 1.3.min, 95%B for 1.7min; Flow Rate: 1.8ml/min; Column: XBridge C18, 3.5μm, 4.6x50mm; Column Temperature: 45°C

[336] Method I

[337] A: H_2O (10mM NH_4HCO_3), B: MeCN; Gradient: 10-95%B in 1.5min; Flow Rate: 1.8ml/min; Column: XBridge C18, 3.5μm, 4.6x50mm; Column Temperature: 45°C

[338] Method J

[339] A: H_2O (0.01% TFA), B: MeCN(0.01% TFA); Gradient: 5%B-95%B in 1min, 95%B for 1min; Flow Rate: 1.6ml/min; Column: Agilent Poroshell 2.7μm, 3.0mmx30mm; Column Temperature: 50°C

[340] Method K

[341] A: H_2O (0.1% FA), B: MeCN (0.1% FA); Gradient: 10%B for 0.2min, increase to 90%B in 1.3min, 90%B for 1.5min; Flow Rate: 2ml/min; Column: Agilent Poroshell 120 C18, 4.0μm, 4.6x50mm; Column Temperature: 50°C

[342] Method L:

[343] A: H_2O (0.01% TFA), B: MeCN (0.01% TFA); Gradient: 5%-95%B in 1.3min; Flow Rate: 2.0ml/min; Column: SunFire C18, 3.5μm, 4.6x50mm; Column Temperature: 50°C

[344] Method M:

[345] A: H_2O (0.01% TFA), B: MeCN (0.01% TFA); Gradient: 10%-90%B in 1.5min, 95%B for 3min, 95%-10%B in 0.01 min; Flow Rate: 2.0ml/min; Column: SunFire C18, 3.5μm, 4.6x50mm; Column Temperature: 50°C

[346] Method N:

[347] A: H_2O (0.05% FA), B: MeCN (0.035% FA); Gradient: 2%B for 0.2min, 2-98%B in 3.6min, 98%B for 0.5min, 98%-2%B in 0.2min; Flow Rate: 1.0ml/min; Column: Waters ACQUITY UPLC BEH C18, 1.7μm, 2.1x50mm; Column Temperature: 55°C

[348] Method O:

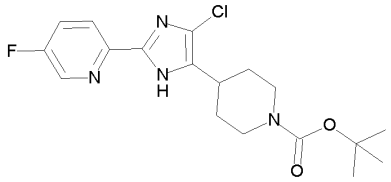
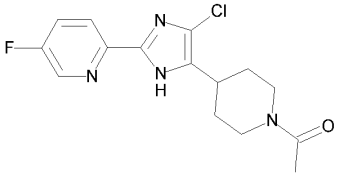
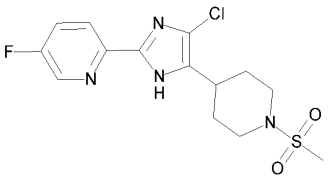
[349] A: H_2O (0.05% FA), B: MeCN (0.035% FA); Gradient: 2%B for 0.2min, 2-98%B in 8.3min, 98%B for 1min, 98%-2%B in 0.5min; Flow Rate: 0.6ml/min; Column: Waters ACQUITY UPLC BEH C18, 1.7μm, 2.1x50mm; Column Temperature: 55°C

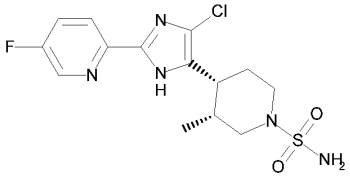
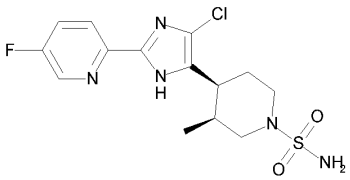
[350] Method P:

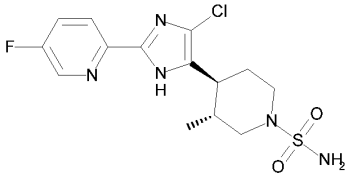
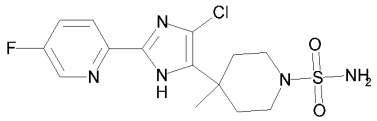
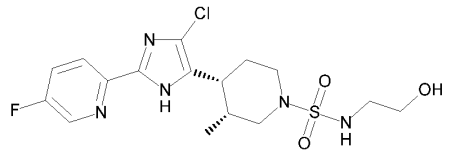
[351] A: H_2O (0.05% FA), B: MeCN (0.045% TFA); Gradient: 2%B for 1min, 2-98%B in 22.5min, 98%B for 4min, 98%-2%B in 2.5min; Flow Rate: 0.6ml/min; Column: Waters ACQUITY UPLC CSHC18, 1.7μm, 2.1x100mm; Column Temperature: 55°C

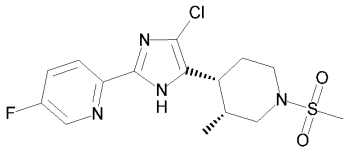
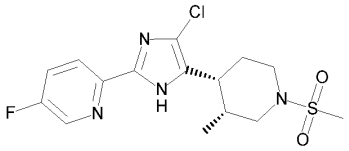
[352] **SYNTHETIC METHODS**

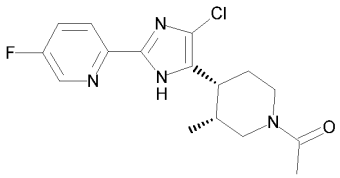
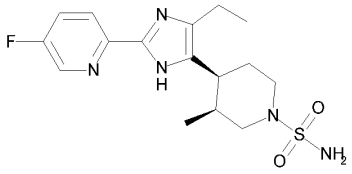
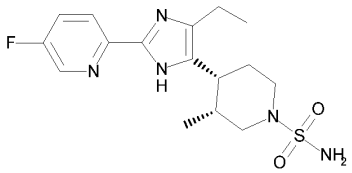
[353] **Table 1**: Structure and analytical data of examples.

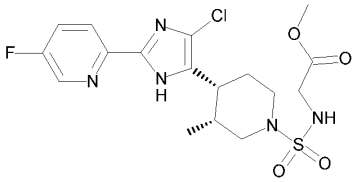
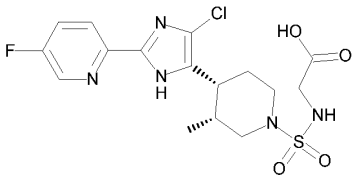
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
1	Tert-butyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate 	N 381.1 [M+H]+ 1.39 min	(400.23 MHz, DMSO-d6) δ ppm 12.99 (s, 1 H), 8.60 (d, J=2.8 Hz, 1 H), 7.98 (dd, J=8.8, 4.5 Hz, 1 H), 7.82 (td, J=8.8, 8.8, 2.9 Hz, 1 H), 4.06 (br d, J=11.5 Hz, 2 H), 2.88 (m, 1H), 2.78 (br s, 2 H), 1.84 (qd, J=12.6, 12.6, 12.6, 4.2 Hz, 2 H), 1.63 (br d, J=11.0 Hz, 2 H), 1.43 (s, 9 H).
2	1-[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-1-piperidyl]ethenone 	N 323.1 [M+H]+ 1.52 min	(400.23 MHz, DMSO-d6) δ ppm: 12.98 (br s, 1 H), 8.59 (d, J=2.8 Hz, 1 H), 7.98 (dd, J=8.9, 4.5 Hz, 1 H), 7.82 (td, J=8.8, 8.8, 2.9 Hz, 1 H), 4.49 (br d, J=13.2 Hz, 1 H), 3.90 (br d, J=13.7 Hz, 1 H), 3.11 (m, 1 H), 2.97 (tt, J=12.2, 12.2, 3.8, 3.8 Hz, 1 H), 2.57 (m, 1 H), 2.03 (s, 3 H), 1.94 (m, 1 H), 1.77 (m, 1 H), 1.66 (m, 2 H).
3	2-[4-Chloro-5-(1-methylsulfonyl-4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 359.0 [M+H]+ 1.64 min	(400.23 MHz, DMSO-d6) δ ppm 13.06 (br s, 1 H), 8.61 (d, J=2.8 Hz, 1 H), 8.00 (dd, J=8.9, 4.5 Hz, 1 H), 7.83 (td, J=8.8, 8.8, 2.9 Hz, 1 H), 3.67 (br d, J=12.0 Hz, 2 H), 2.91 (s, 3 H), 2.83 (m, 2 H), 2.00 (qd, J=12.6, 12.6, 12.6, 3.7 Hz, 2 H), 1.77 (br d, J=10.9 Hz, 2 H).

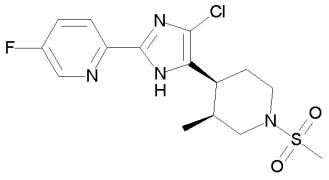
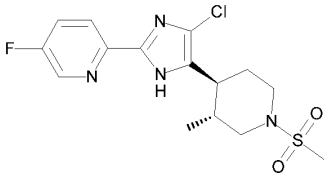
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
4	(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide 	O 374.0 [M+H]+ 3.68 min	(400 MHz, CDCl3) δ 10.14 (s, 1H), 8.35 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 8.8, 4.4 Hz, 1H), 7.50 (td, J = 8.4, 2.8 Hz, 1H), 4.59 (s, 2H), 3.88 (d, J = 11.8 Hz, 1H), 3.60 (d, J = 11.6 Hz, 1H), 3.14 (dt, J = 12.6, 4.0 Hz, 1H), 3.00 (dd, J = 11.6, 2.8 Hz, 1H), 2.83 (td, J = 11.6, 2.8 Hz, 1H), 2.36 (dd, J = 6.8, 3.6 Hz, 1H), 2.25 (ddd, J = 24.8, 12.6, 4.2 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H) ppm
5	(3S,4S)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide 	A 374.1 [M+H]+ 2.04 min	(400 MHz, CDCl3) δ 10.10 (s, 1H), 8.36 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 7.50 (td, J = 8.4, 2.8 Hz, 1H), 4.49 (s, 2H), 3.89 (d, J = 11.8 Hz, 1H), 3.57 (t, J = 24.0 Hz, 1H), 3.19 – 3.09 (m, 1H), 3.00 (dd, J = 11.8, 2.8 Hz, 1H), 2.83 (dd, J = 11.6, 9.0 Hz, 1H), 2.36 (s, 1H), 2.24 (qd, J = 12.8, 4.4 Hz, 1H), 1.89 (d, J = 10.0 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H) ppm

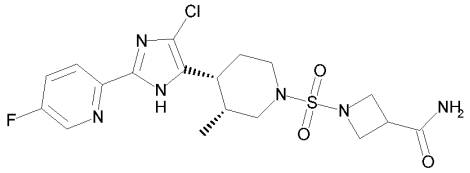
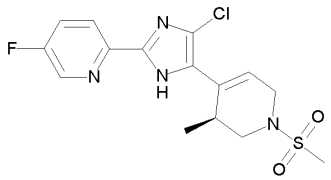
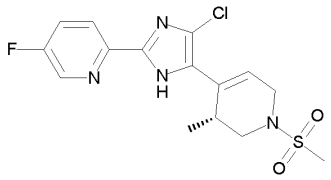
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
6	(3R*,4S*/3S*,4R*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide 	A 374.1 [M+H]+ 2.04 min	(400 MHz, DMSO-d6) δ 13.04 (s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.4, 2.8 Hz, 1H), 6.76 (s, 2H), 3.55 (t, J = 10.6 Hz, 2H), 2.56 (d, J = 12.0 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.24 (t, J = 11.2 Hz, 1H), 2.19 – 1.99 (m, 2H), 1.74 (d, J = 10.0 Hz, 1H), 0.70 (d, J = 6.4 Hz, 3H) ppm
7	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methylpiperidine-1-sulfonamide 	F 374.1 [M+H]+ 1.48 min	(400 MHz, DMSO-d6) δ ppm 12.61 (s, 1H), 8.61 (s, 1H), 8.02-7.99 (m, 1H), 7.86-7.81 (m, 1H), 6.62 (s, 1H), 3.23-3.21 (m, 2H), 2.63-2.59 (m, 4H), 1.65 (t, J = 10.8 Hz, 2H), 1.25 (s, 3H)
8	(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-3-methylpiperidine-1-sulfonamide 	B 418.1 [M+H]+ 1.55 min	(400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.00 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.8, 2.8 Hz, 1H), 7.20 (t, J = 5.6 Hz, 1H), 4.72 (t, J = 5.6 Hz, 1H), 3.63 (d, J = 10.8 Hz, 1H), 3.51– 3.38 (m, 3H), 3.05 (d, J = 12.8 Hz, 1H), 3.00 – 2.92 (m, 2H), 2.86 (d, J = 10.8 Hz, 1H), 2.67 (t, J = 10.8 Hz, 1H), 2.60 – 2.55 (m, 1H), 2.13 (s, 1H), 1.63 (d, J = 12.4 Hz, 1H), 0.86 (d, J = 6.8 Hz, 3H) ppm

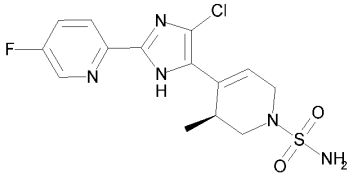
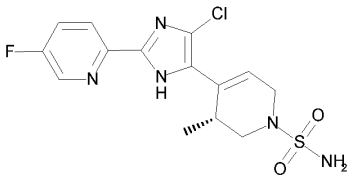
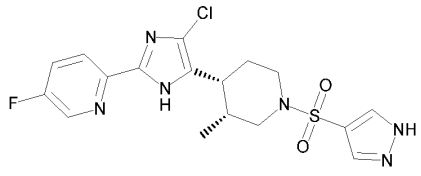
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
9	(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxamide 	C 338.3 [M+H]+ 1.43 min	(400 MHz, DMSO-d6) δ 12.88 (s, 1H), 8.60 (d, J = 2.6 Hz, 1H), 7.99 (dd, J = 8.8, 4.4 Hz, 1H), 7.82 (td, J = 8.8, 2.8 Hz, 1H), 5.90 (s, 2H), 4.12 (d, J = 13.0 Hz, 1H), 3.88 (d, J = 13.0 Hz, 1H), 3.09 (d, J = 13.0 Hz, 1H), 2.91 (d, J = 11.2 Hz, 1H), 2.69 (t, J = 12.2 Hz, 1H), 2.33 (d, J = 9.0 Hz, 1H), 1.99 (s, 1H), 1.48 (d, J = 11.0 Hz, 1H), 0.76 (d, J = 7.0 Hz, 3H) ppm
10	2-(4-Chloro-5-((3R,4R)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine 	C 373.2 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 12.94 (s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.8, 2.8 Hz, 1H), 3.67 (d, J = 11.4 Hz, 1H), 3.42 (d, J = 11.4 Hz, 1H), 3.07 (d, J = 13.2 Hz, 1H), 2.98 – 2.91 (m, 1H), 2.87 (s, 3H), 2.76 (t, J = 10.6 Hz, 1H), 2.57 – 2.54 (m, 1H), 2.15 (s, 1H), 1.66 (d, J = 11.0 Hz, 1H), 0.86 (d, J = 7.0 Hz, 3H) ppm

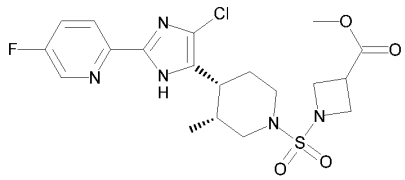
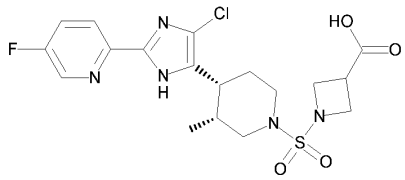
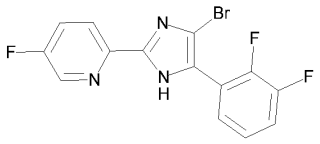
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
11	1-((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)ethan-1-one 	C 337.2 [M+H]+ 1.52 min	(400 MHz, DMSO-d6) δ 12.88 (s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 7.99 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.8, 2.8 Hz, 1H), 4.55 (d, J = 12.2 Hz, 0.5H), 4.34 (d, J = 12.8 Hz, 0.5H), 3.93 (d, J = 13.2 Hz, 0.5H), 3.73 (d, J = 13.6 Hz, 0.5H), 3.32 – 3.30 (m, 0.5H), 3.19 (d, J = 13.2 Hz, 1H), 3.09 (t, J = 11.8 Hz, 0.5H), 2.75 (d, J = 10.8 Hz, 0.5H), 2.56 (d, J = 13.4 Hz, 0.5H), 2.47 – 2.40 (m, 0.5H), 2.29 (dd, J = 13.0, 4.4 Hz, 0.5H), 2.08 (s, 1H), 2.02 (d, J = 27.0 Hz, 3H), 1.55 (t, J = 12.8 Hz, 1H), 0.74 (dd, J = 31.2, 7.0 Hz, 3H) ppm
12	(3S*,4S*)-4-(4-Ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide 	D 368 [M+H]+ 1.51 min	(400 MHz, CDCl3) δ 8.35 (d, J = 2.8 Hz 1H), 8.21 (s, 1H), 7.49-7.47 (m, 1H), 4.41 (s, 2H), 3.89-3.87 (m, 1H), 3.62-3.57 (m, 1H), 3.19-2.98 (m, 3H), 2.66 (q, J = 7.2 Hz, 2H), 2.22-2.20 (m, 2H), 1.97-1.92 (m, 1H), 1.28 (t, J = 7.6 Hz, 3H), 0.92 (d, J = 5.2 Hz, 3H) ppm
13	(3R*,4R*)-4-(4-Ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide 	D 368 [M+H]+ 1.51 min	(400 MHz, CDCl3) δ 8.35 (d, J = 2.8 Hz, 1H), 8.21 (s, 1H), 7.49-7.47 (m, 1H), 4.41 (s, 2H), 3.89-3.87 (m, 1H), 3.62-3.57 (m, 1H), 3.19-2.98 (m, 3H), 2.66 (q, J = 7.2 Hz, 2H), 2.22-2.20 (m, 2H), 1.97-1.92 (m, 1H), 1.28 (t, J = 7.6 Hz, 3H), 0.92 (d, J = 5.2 Hz, 3H) ppm

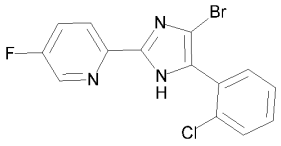
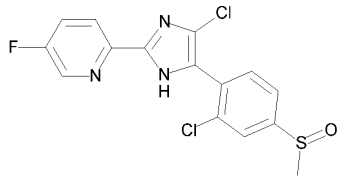
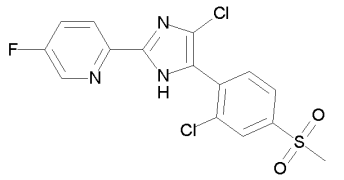
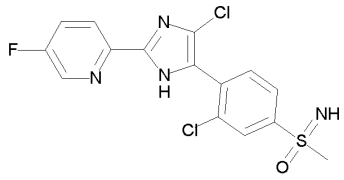
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
14	Methyl (((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycinate 	G 446.2 [M+H]+ 1.77 min	(400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.8, 2.8 Hz, 2H), 3.77 (s, 2H), 3.70 – 3.57 (m, 4H), 3.40 (d, J = 11.4 Hz, 1H), 3.04 (dt, J = 13.0, 3.6 Hz, 1H), 2.86 (dd, J = 11.6, 2.4 Hz, 1H), 2.66 (dd, J = 11.8, 9.6 Hz, 1H), 2.45 (dd, J = 12.8, 8.8 Hz, 1H), 2.13 (s, 1H), 1.63 (d, J = 10.8 Hz, 1H), 0.83 (d, J = 7.0 Hz, 3H) ppm
15	(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycine 	G 432.2 [M+H]+ 1.44 min	(400 MHz, DMSO-d6) δ 12.90 (s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.8, 2.8 Hz, 1H), 7.58 (s, 1H), 3.65 (d, J = 4.8 Hz, 3H), 3.41 (d, J = 11.4 Hz, 1H), 3.03 (d, J = 13.2 Hz, 1H), 2.87 (d, J = 9.4 Hz, 1H), 2.67 (t, J = 11.0 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.12 (s, 1H), 1.63 (d, J = 11.2 Hz, 1H), 0.84 (d, J = 7.0 Hz, 3H) ppm

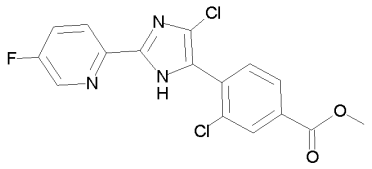
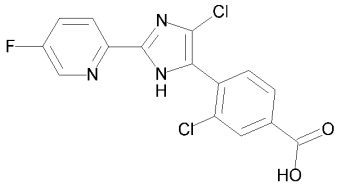
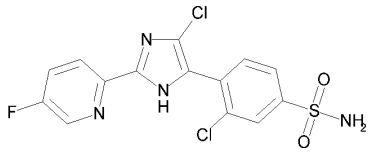
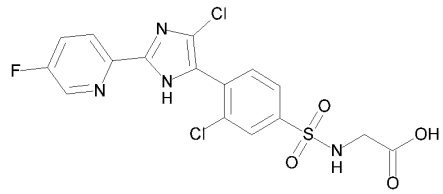
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
16	2-(4-Chloro-5-((3S,4S)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine 	A 373.1 [M+H]+ 2.02 min	(400 MHz, DMSO-d6) δ 13.00 (s, 1H), 8.67 (d, J = 2.8 Hz, 1H), 8.06 (dd, J = 8.8, 4.4 Hz, 1H), 7.89 (td, J = 8.8, 2.8 Hz, 1H), 3.73 (d, J = 11.4 Hz, 1H), 3.48 (d, J = 11.4 Hz, 1H), 3.13 (dt, J = 13.2, 3.6 Hz, 1H), 3.01 (dd, J = 11.4, 2.6 Hz, 1H), 2.93 (s, 3H), 2.80 (dt, J = 23.4, 11.8 Hz, 1H), 2.55 – 2.45 (m, 1H), 2.27 – 2.15 (m, 1H), 1.72 (d, J = 10.8 Hz, 1H), 0.92 (d, J = 7.0 Hz, 3H) ppm
17	2-(4-Chloro-5-((3R*,4S*/3S*,4R*)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine 	A 373.1 [M+H]+ 2.09 min	(400 MHz, DMSO-d6) δ 13.09 (s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.8, 2.8 Hz, 1H), 3.64 (dd, J = 20.2, 7.4 Hz, 2H), 2.92 (s, 3H), 2.79 (dd, J = 22.6, 12.6 Hz, 1H), 2.49 – 2.40 (m, 2H), 2.18 – 1.96 (m, 2H), 1.73 (d, J = 10.4 Hz, 1H), 0.70 (d, J = 6.6 Hz, 3H) ppm

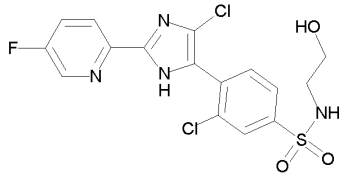
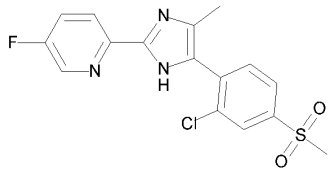
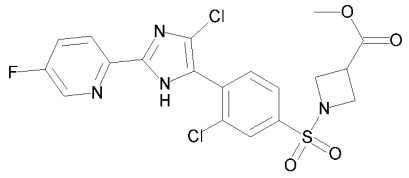
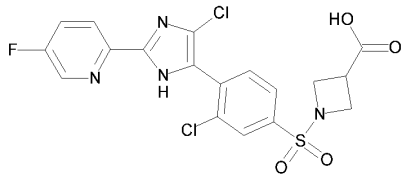
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
18	1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxamide 	H 457.0 [M+H]+ 1.58 min	(500 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.60 (d, J = 2.5 Hz, 1H), 8.00 (dd, J = 9.0, 4.0 Hz, 1H), 7.83 (td, J = 8.5, 2.5 Hz, 1H), 7.46 (s, 1H), 7.09 (s, 1H), 3.97 – 3.79 (m, 4H), 3.69 (d, J = 12.0 Hz, 1H), 3.46 (d, J = 12.5 Hz, 1H), 3.31 – 3.23 (m, 1H), 3.06 (dd, J = 27.0, 13.0 Hz, 2H), 2.85 (t, J = 11.5 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.10 (s, 1H), 1.61 (d, J = 12.0 Hz, 1H), 0.84 (d, J = 7.0 Hz, 3H) ppm
19	(S*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine 	I 371.0 [M+H]+ 1.74 min	(400 MHz, DMSO-d6) δ 13.09 (s, 1H), 8.63 (d, J = 2.6 Hz, 1H), 8.04 (dd, J = 8.8, 4.4 Hz, 1H), 7.85 (td, J = 8.8, 2.8 Hz, 1H), 6.18 (s, 1H), 3.96 – 3.71 (m, 2H), 3.28 – 3.14 (m, 3H), 2.95 (s, 3H), 0.97 (d, J = 5.6 Hz, 3H) ppm
20	(R*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine 	I 371.0 [M+H]+ 1.71 min	(400 MHz, DMSO-d6) δ 8.63 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.8, 4.4 Hz, 1H), 7.85 (td, J = 8.8, 2.8 Hz, 1H), 6.18 (s, 1H), 3.95 – 3.69 (m, 2H), 3.27 – 3.16 (m, 3H), 2.95 (s, 3H), 0.97 (d, J = 6.2 Hz, 3H) ppm

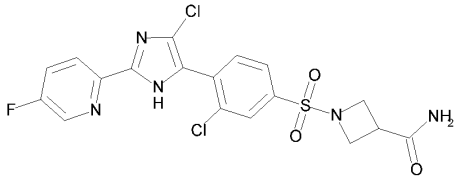
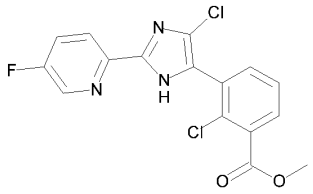
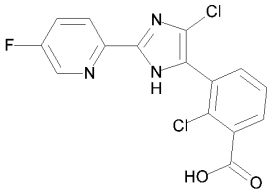
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
21	(S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide 	G 372.0 [M+H]+ 1.65 min	(400 MHz, DMSO-d6) δ 13.07 (s, 1H), 8.63 (d, J = 2.4 Hz, 1H), 8.04 (dd, J = 8.8, 4.4 Hz, 1H), 7.85 (td, J = 8.8, 2.8 Hz, 1H), 6.86 (s, 2H), 6.17 (s, 1H), 3.73 (d, J = 14.4 Hz, 1H), 3.60 (d, J = 17.4 Hz, 1H), 3.19 (s, 1H), 3.11 (dd, J = 11.6, 3.8 Hz, 1H), 3.02 (dd, J = 11.4, 4.0 Hz, 1H), 0.98 (d, J = 6.8 Hz, 3H) ppm
22	(R*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide 	G 372.0 [M+H]+ 1.65 min	(400 MHz, DMSO-d6) δ 13.07 (s, 1H), 8.63 (d, J = 2.4 Hz, 1H), 8.04 (dd, J = 8.8, 4.4 Hz, 1H), 7.85 (td, J = 8.8, 2.8 Hz, 1H), 6.86 (s, 2H), 6.17 (s, 1H), 3.74 (d, J = 14.8 Hz, 1H), 3.60 (d, J = 17.2 Hz, 1H), 3.19 (s, 1H), 3.14 – 3.06 (m, 1H), 3.02 (dd, J = 11.4, 4.0 Hz, 1H), 0.98 (d, J = 6.8 Hz, 3H) ppm
23	2-(5-((3R,4R)-1-((1H-Pyrazol-4-yl)sulfonyl)-3-methylpiperidin-4-yl)-4-chloro-1H-imidazol-2-yl)-5-fluoropyridine 	A 425.0 [M+H]+ 1.84 min	(400 MHz, DMSO-d6) δ 13.09 (s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.21 – 7.90 (m, 3H), 7.82 (t, J = 8.6 Hz, 1H), 3.66 (s, 1H), 3.45 (d, J = 10.2 Hz, 1H), 2.90 (d, J = 12.8 Hz, 1H), 2.42 – 2.01 (m, 4H), 1.63 (d, J = 11.6 Hz, 1H), 0.88 (d, J = 4.8 Hz, 3H) ppm

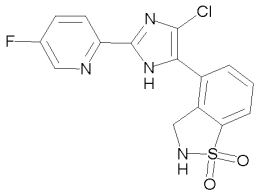
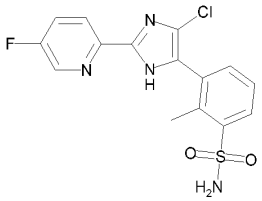
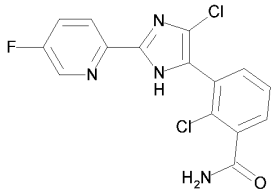
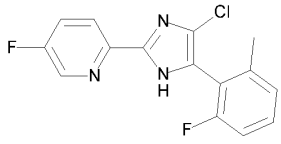
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
24	Methyl 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylate 	A 472.1 [M+H]+ 1.99 min	(500 MHz, DMSO-d6) δ 12.90 (s, 1H), 8.61 (d, J = 2.5 Hz, 1H), 8.00 (dd, J = 9.0, 4.0 Hz, 1H), 7.83 (td, J = 8.5, 2.5 Hz, 1H), 3.96 (dt, J = 17.0, 2.0 Hz, 4H), 3.74 – 3.62 (m, 4H), 3.60 – 3.51 (m, 1H), 3.45 (d, J = 12.5 Hz, 1H), 3.06 (dd, J = 27.0, 13.0 Hz, 2H), 2.85 (t, J = 11.5 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.10 (s, 1H), 1.60 (d, J = 12.0 Hz, 1H), 0.84 (d, J = 7.0 Hz, 3H) ppm
25	1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylic acid 	A 458.0 [M+H]+ 1.85 min	(400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.4 Hz, 1H), 7.83 (td, J = 8.8, 2.8 Hz, 1H), 4.13 – 3.77 (m, 4H), 3.68 (d, J = 11.4 Hz, 1H), 3.50 – 3.38 (m, 2H), 3.06 (dd, J = 22.2, 12.6 Hz, 2H), 2.84 (t, J = 10.8 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.10 (s, 1H), 1.60 (d, J = 11.2 Hz, 1H), 0.84 (d, J = 6.8 Hz, 3H) ppm
26	2-(4-Bromo-5-(2,3-difluorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine 	J 355.9 [M+H]+ 1.13 min	(500 MHz, DMSO-d6) δ 13.69 (s, 1H), 8.67 (d, J = 1.5 Hz, 1H), 8.12 (dd, J = 8.5, 4.5 Hz, 1H), 7.89 (td, J = 8.5, 2.5 Hz, 1H), 7.60 – 7.23 (m, 3H) ppm

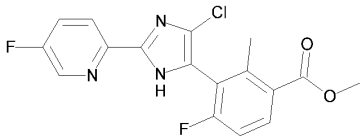
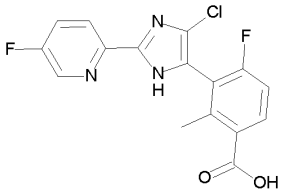
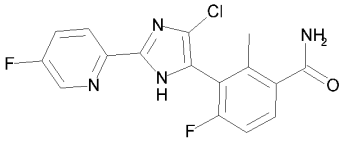
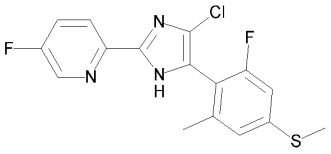
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
27	2-(4-Bromo-5-(2-chlorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine 	K 353.8 [M+H]+ 1.97 min	(500 MHz, DMSO-d6) δ 13.56 (s, 1H), 8.64 (d, J = 3.0 Hz, 1H), 8.10 (dd, J = 8.5, 4.5 Hz, 1H), 7.88 (td, J = 8.5, 2.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.55 – 7.39 (m, 3H) ppm
28	2-[4-Chloro-5-(2-chloro-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine 	B 372 [M+H]+ 1.62 min	(400 MHz, DMSO-d6) δ 13.61 (s, 1H), 8.66 (d, J = 2.8 Hz, 1H), 8.10 (m, 1H), 7.91 (s, 1H), 7.89 (m, 1H), 7.75 (s, 2H), 2.87 (s, 3H) ppm
29	2-[4-Chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine 	B 386.0 [M+H]+ 1.71 min	(400 MHz, DMSO-d6) δ 13.70 (s, 1H), 8.66 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H), 8.10 (m, 1H), 7.99 (m, 1H), 7.85 (m, 1H), 7.83 (m, 1H), 3.38 (s, 3H) ppm
30	2-[4-Chloro-5-(2-chloro-4-(methylsulfonimidoyl)phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine 	B 385.0 [M+H]+ 1.57 min	(400 MHz, DMSO-d6) δ 13.68 (s, 1H), 8.66 (d, J = 2.8 Hz, 1H), 8.10 (m, 1H), 8.09 (s, 1H), 7.95 (m, 1H), 7.78 (m, 1H), 7.76 (m, 1H), 3.19 (s, 3H) ppm

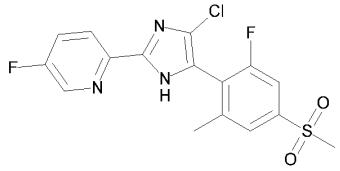
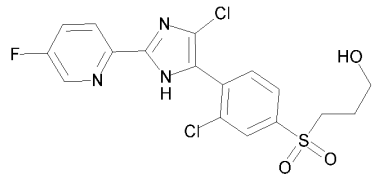
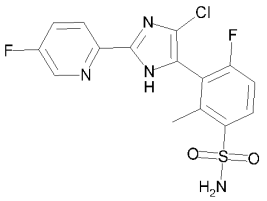
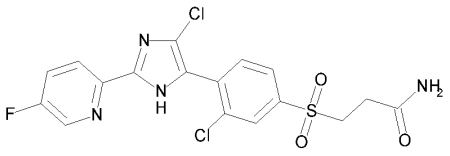
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
31	Methyl 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoate 	H 366 [M+H]+ 1.91 min	(400 MHz, DMSO-d6) δ 13.67 (s, 1H), 8.66 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 8.8, 4.4 Hz, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.99 (dd, J = 8.0, 1.6 Hz, 1H), 7.89 (td, J = 8.8, 2.8 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H) ppm
32	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoic acid 	L 352 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 8.65 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 8.01 (d, J = 1.2 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.90 – 7.84 (m, 1H), 7.58 (d, J = 8.0 Hz, 1H) ppm
33	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide 	E 387 [M+H]+ 1.64 min	(400 MHz, DMSO-d6) δ 13.68 (s, 1H), 8.67 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 8.8, 4.4 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.94 – 7.87 (m, 1H), 7.87 – 7.83 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.64 (s, 2H) ppm
34	2-[[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]acetic acid 	E 445 [M+H]+ 1.32 min	(400 MHz, DMSO-d6) δ 8.65 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.86 – 7.82 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 3.25 (s, 2H) ppm

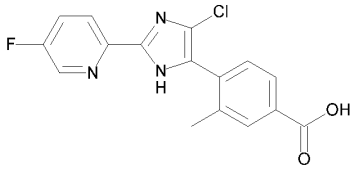
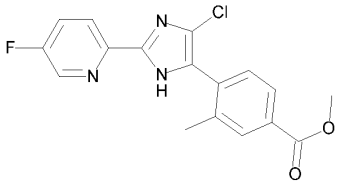
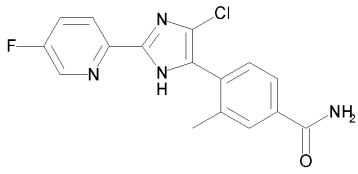
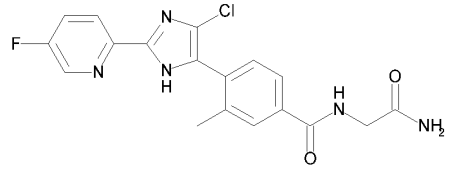
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
35	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-(2-hydroxyethyl)benzenesulfonamide 	H 43 [M+H]+ 1.64 min	(500 MHz, DMSO-d6) δ 13.64 (s, 1H), 8.66 (d, J = 2.5 Hz, 1H), 8.11 (dd, J = 8.5, 4.5 Hz, 1H), 7.97 (d, J = 1.5 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.84 (dd, J = 8.0, 1.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 4.77 (t, J = 6.0 Hz, 1H), 3.42 (q, J = 6.0 Hz, 2H), 2.89 (q, J = 6.0 Hz, 2H) ppm
36	2-[5-(2-Chloro-4-methylsulfonyl-phenyl)-4-methyl-1H-imidazol-2-yl]-5-fluoro-pyridine 	E 366 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 13.00 (s, 1H), 8.62 (t, J = 2.8 Hz, 1H), 8.14-8.07 (m, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.0, 2.0 Hz, 1H), 7.84 (td, J = 8.8, 2.8 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 3.33 (s, 3H), 2.25 (s, 3H) ppm
37	Methyl 1-((3-chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxylate 	G 484.9 [M+H]+ 1.85 min	(400 MHz, CD3OD) δ 8.53 (d, J = 3.2 Hz, 1H), 8.12-8.08 (m, 1H), 8.03 (s, 1H), 7.91-7.84 (m, 2H), 7.74-7.70 (m, 1H), 4.10-4.06 (m, 2H), 3.99-3.95 (m, 2H), 3.63 (s, 3H), 3.41-3.34 (m, 1H) ppm
38	1-((3-Chloro-4-(4-chloro-2-(5-fluoro-pyridin-2-yl)-1H-imidazol-5-yl)-phenyl) sulfonyl)azetidine-3-carboxylic acid 	H 471.0 [M+H]+ 1.49 min	(500 MHz, DMSO-d6) δ 8.66 (d, J = 2.5 Hz, 1H), 8.12-8.10 (m, 1H), 7.97 (s, 1H), 7.90-7.84 (m, 3H), 3.93-3.89 (m, 2H), 3.81-3.76 (m, 2H), 3.17-3.11 (m, 1H) ppm

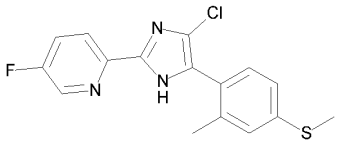
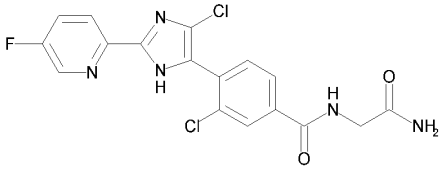
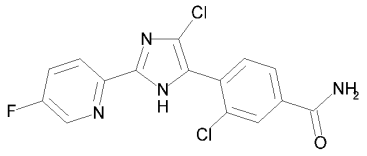
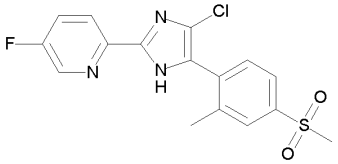
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
39	1-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxamide 	G 470.0 [M+H]+ 1.70 min	(400 MHz, CD3OD) δ 8.53 (d, J = 2.8 Hz, 1H), 8.12-8.09 (m, 1H), 8.02 (s, 1H), 7.88-7.82 (m, 2H), 7.73-7.72 (m, 1H), 4.04-4.00 (m, 2H), 3.94-3.90 (m, 2H), 3.35-3.28 (m, 1H) ppm
40	Methyl 2-chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoate 	G 366.0 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 13.60 (s, 1H), 8.65 (d, J = 2.4 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 7.87 (ddd, J = 17.2, 11.6, 4.4 Hz, 2H), 7.70 (dd, J = 7.6, 1.4 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 3.90 (s, 3H) ppm
41	2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoic acid 	H 352.0 [M+H]+ 1.32 min	(400 MHz, DMSO-d6) δ 13.54 (s, 1H), 8.64 (d, J = 2.6 Hz, 1H), 8.09 (dd, J = 8.8, 4.4 Hz, 1H), 7.87 (td, J = 8.6, 2.8 Hz, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.51 – 7.32 (m, 2H) ppm

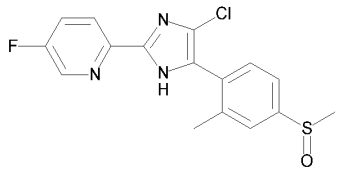
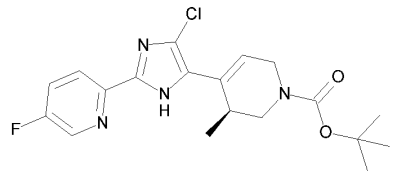
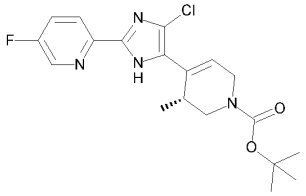
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
42	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-2,3-dihydro-1,2-benzothiazole 1,1-dioxide 	M 365 [M+H]+ 1.62 min	(500 MHz, DMSO-d6) δ 13.60 (s, 1H), 8.67 (d, J = 2.5 Hz, 1H), 8.12 (dd, J = 8.5, 4.5 Hz, 1H), 7.93-7.89 (m, 3H), 7.79 (d, J = 7.5 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 4.47 (d, J = 4.5 Hz, 2H) ppm
43	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-2-methylbenzenesulfonamide 	I 367 [M+H]+ 1.66 min	(500 MHz, CD3OD) δ 8.50 (d, J = 3.0 Hz, 1H), 8.12 (dd, J = 7.5, 1.0 Hz, 1H), 8.07 (dd, J = 8.5, 4.0 Hz, 1H), 7.71 (td, J = 8.5, 3.0 Hz, 1H), 7.59 (dd, J = 7.5, 1.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 2.61 (s, 3H) ppm
44	2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzamide 	A 351.0 [M+H]+ 1.75 min	(500 MHz, DMSO-d6) δ 13.59 (s, 1H), 8.64 (d, J = 3.0 Hz, 1H), 8.09 (dd, J = 9.0, 4.5 Hz, 1H), 7.98 (s, 1H), 7.88 (td, J = 8.5, 2.5 Hz, 1H), 7.64 (s, 1H), 7.58 – 7.42 (m, 3H) ppm
45	2-(4-Chloro-5-(2-fluoro-6-methylphenyl)-1H-imidazol-2-yl)-5-fluoropyridine 	I 306 [M+H]+ 1.96 min	(500 MHz, DMSO-d6) δ 13.46 (s, 1H), 8.63 (d, J = 3.0 Hz, 1H), 8.09 (dd, J = 9.0, 4.5 Hz, 1H), 7.88 (td, J = 9.0, 3.0 Hz, 1H), 7.45-7.40 (m, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 8.5 Hz, 1H), 2.22 (s, 3H) ppm

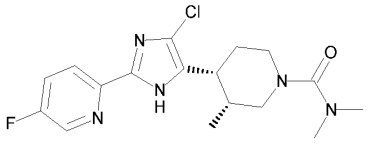
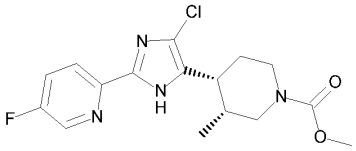
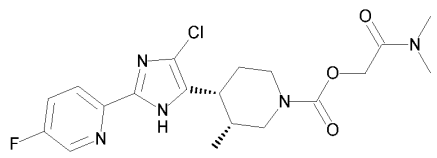
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
46	Methyl 3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoate 	N 364.0 [M+H]+ 2.21 min	(500 MHz, DMSO-d6) δ 13.53 (s, 1H), 8.64 (d, J = 3.0 Hz, 1H), 8.10 (dd, J = 8.5, 4.5 Hz, 1H), 7.97 (dd, J = 9.0, 6.0 Hz, 1H), 7.90-7.86 (m, 1H), 7.33 (t, J = 8.5 Hz, 1H), 3.86 (s, 3H), 2.36 (s, 3H) ppm
47	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoic acid 	N 347.9 [M-H]- 1.84 min	(400 MHz, DMSO-d6) δ 13.52 (s, 1H), 13.15 (s, 1H), 8.64 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 7.97 (dd, J = 8.8, 6.0 Hz, 1H). 7.91-7.86 (m, 1 H), 7.29 (t, J = 8.8 Hz, 1H), 2.38 (s, 3H) ppm
48	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzamide 	N 349.0 [M+H]+ 1.57 min	(400 MHz, DMSO-d6) δ 13.53 (s, 1H), 8.64 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 7.97 – 7.78 (m, 2H), 7.52-7.49 (m, 2H), 7.22 (t, J = 8.8 Hz, 1H), 2.23 (s, 3H) ppm
49	2-(4-Chloro-5-(2-fluoro-6-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine 	N 351.9 [M+H]+ 2.42 min	(500 MHz, CDCl3) δ 10.30 (s, 1H), 8.36 (d, J = 2.5 Hz, 1H), 8.18 (dd, J = 8.5, 4.5 Hz, 1H), 7.51 (tt, J = 16.5, 8.5 Hz, 1H), 6.97 (s, 1H), 6.87 (d, J = 10.0 Hz, 1H), 2.51 (s, 3H), 2.30 (s, 3H) ppm

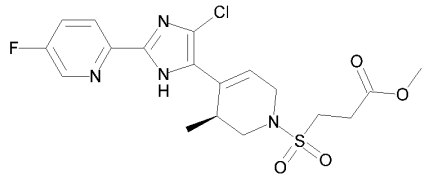
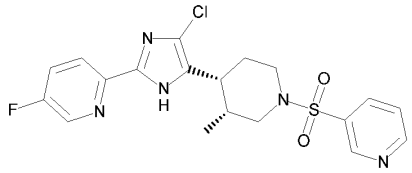
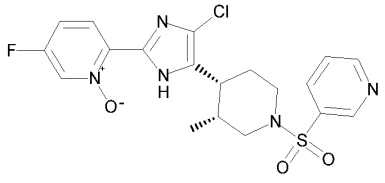
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
50	2-[4-Chloro-5-(2-fluoro-6-methyl-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 384.0 [M+H]+ 1.92 min	(400 MHz, DMSO-d6) δ 13.62 (br s, 1H), 8.65 (d, J = 2.9 Hz, 1H), 8.11 (dd, J = 8.9, 4.5 Hz, 1H), 7.93 – 7.86 (m, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.76 (dd, J = 8.5, 1.8 Hz, 1H), 3.35 (s, 3H), 2.35 (s, 3H).
51	3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropan-1-ol 	N 430.0 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 13.67 (br s, 1H), 8.66 (d, J = 2.9 Hz, 1H), 8.15 – 8.08 (m, 2H), 7.96 (dd, J = 8.1, 1.8 Hz, 1H), 7.93 – 7.82 (m, 2H), 4.69 (t, J = 5.3 Hz, 1H), 3.51 – 3.42 (m, 4H), 1.78 – 1.68 (m, 2H).
52	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzenesulfonamide 	N 384.9 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 13.56 (br s, 1H), 8.64 (d, J = 2.9 Hz, 1H), 8.14 – 8.02 (m, 2H), 7.93 – 7.84 (m, 1H), 7.58 (br s, 2H), 7.43 – 7.35 (m, 1H), 2.47 (s, 3H).
53	3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropanamide 	N 442.9 [M+H]+ 1.71 min	(400 MHz, DMSO-d6) δ 13.67 (br s, 1H), 8.67 (d, J = 2.9 Hz, 1H), 8.15 – 8.09 (m, 2H), 7.96 (dd, J = 8.1, 1.9 Hz, 1H), 7.93 – 7.86 (m, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.48 (br s, 1H), 6.99 (br s, 1H), 3.69 – 3.62 (m, 2H), 2.49 – 2.43 (m, 2H).

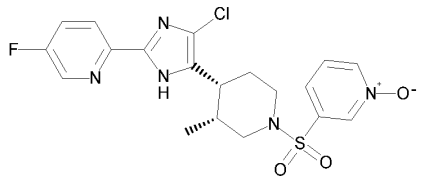
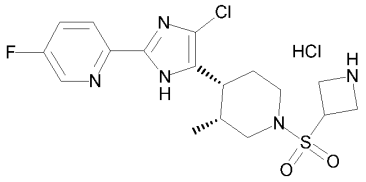
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
54	4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoic acid 	N 332.1 [M+H]+ 1.84 min	(400 MHz, DMSO-d6) δ 13.52 (s, 1H), 8.64 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.5 Hz, 1H), 7.98 – 7.80 (m, 3H), 7.51 (d, J = 8.0 Hz, 1H), 3.88 (s, 3H), 2.35 (s, 3H) ppm
55	Methyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoate 	N 346.1 [M+H]+ 2.21 min	(400 MHz, DMSO-d6) δ 13.49 (s, 1H), 13.05 (s, 1H), 8.64 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 7.97 – 7.75 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 2.34 (s, 3H) ppm
56	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide 	N 331.0 [M+H]+ 1.60 min	(400 MHz, DMSO-d6) δ 13.44 (br s, 1H), 8.63 (d, J = 2.9 Hz, 1H), 8.09 (dd, J = 8.8, 4.5 Hz, 1H), 8.00 (br s, 1H), 7.91 – 7.81 (m, 2H), 7.75 (dd, J = 7.9, 1.8 Hz, 1H), 7.44 – 7.36 (m, 2H), 2.32 (s, 3H).
57	N-(2-Amino-2-oxo-ethyl)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide 	N 388.0 [M+H]+ 1.51 min	(400 MHz, DMSO-d6) δ 13.47 (br s, 1H), 8.71 (t, J = 5.9 Hz, 1H), 8.63 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.9, 4.5 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.76 (dd, J = 8.0, 1.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.38 (br s, 1H), 7.04 (br s, 1H), 3.83 (d, J = 5.9 Hz, 2H), 2.33 (s, 3H).

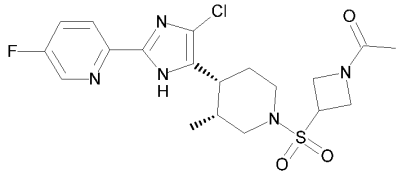
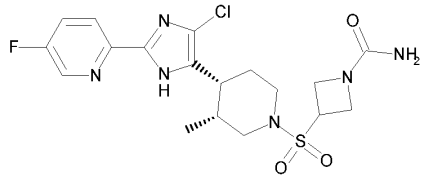
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
58	2-(4-Chloro-5-(2-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine 	N 334.0 [M+H]+ 2.38 min	(400 MHz, DMSO-d6) δ 13.35 (s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.08 (dd, J = 8.8, 4.4 Hz, 1H), 7.87 (td, J = 8.8, 2.8 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.16 (dd, J = 8.0, 1.6 Hz, 1H), 2.51 (s, 3H), 2.24 (s, 3H) ppm
59	N-(2-Amino-2-oxo-ethyl)-3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide 	N 407.9 [M+H]+ 1.57 min	(400 MHz, DMSO-d6) δ 13.63 (br s, 1H), 8.93 (t, J = 5.9 Hz, 1H), 8.65 (d, J = 2.9 Hz, 1H), 8.14 – 8.07 (m, 2H), 7.94 – 7.84 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.43 (br s, 1H), 7.06 (br s, 1H), 3.84 (d, J = 5.9 Hz, 2H).
60	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide 	N 350.9 [M+H]+ 1.67 min	(400 MHz, DMSO-d6) δ 13.58 (br s, 1H), 8.65 (d, J = 2.8 Hz, 1H), 8.17 (br s, 1H), 8.10 (dd, J = 8.9, 4.5 Hz, 1H), 8.06 (d, J = 1.7 Hz, 1H), 7.93 – 7.84 (m, 2H), 7.65 – 7.56 (m, 2H).
61	2-[4-Chloro-5-(2-methyl-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 365.9 [M+H]+ 1.84 min	(400 MHz, DMSO-d6) δ 13.55 (br s, 1H), 8.65 (d, J = 2.9 Hz, 1H), 8.14 – 8.08 (m, 1H), 7.94 – 7.80 (m, 3H), 7.63 (d, J = 8.0 Hz, 1H), 3.28 (s, 3H), 2.39 (s, 3H).

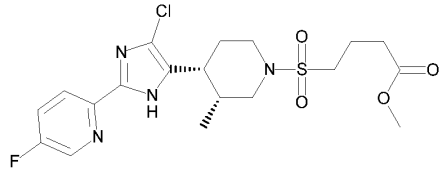
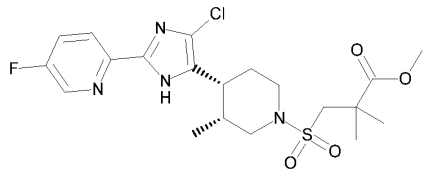
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
62	2-[4-Chloro-5-(2-methyl-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 349.9 [M+H]+ 1.67 min	n/a
63	Tert-butyl (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate 	N 393.3 [M+H]+ 2.48 min	(400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.63 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.8, 4.4 Hz, 1H), 7.85 (td, J = 8.8, 2.8 Hz, 1H), 6.13 (s, 1H), 4.33 – 4.12 (m, 1H), 3.97 – 3.60 (m, 2H), 3.23 (s, 1H), 3.09 (s, 1H), 1.43 (s, 9H), 0.91 (d, J = 6.8 Hz, 3H) ppm
64	Tert-butyl (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate 	N 393.3 [M+H]+ 2.48 min	(400 MHz, DMSO-d6) δ 13.04 (s, 1H), 8.63 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.8, 4.4 Hz, 1H), 7.85 (td, J = 8.8, 2.8 Hz, 1H), 6.14 (s, 1H), 4.35 – 4.10 (m, 1H), 3.96 – 3.59 (m, 2H), 3.23 (s, 1H), 3.09 (s, 1H), 1.43 (s, 9H), 0.92 (d, J = 6.4 Hz, 3H) ppm

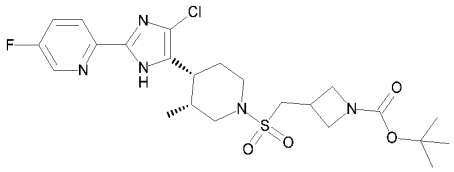
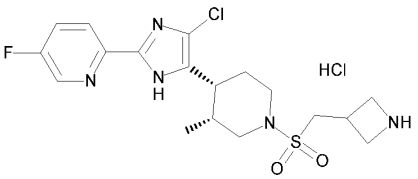
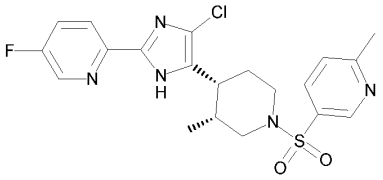
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
65	(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N,3-trimethyl-piperidine-1-carboxamide 	N 366.0 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 12.86 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.97 (m, 1H), 7.86 – 7.78 (m, 1H), 3.71 – 3.63 (m, 1H), 3.53 – 3.46 (m, 1H), 3.14 – 3.06 (m, 1H), 2.97 – 2.90 (m, 1H), 2.79 – 2.68 (m, 7H), 2.61 – 2.47 (m, 1H, overlapping solvent), 2.09 – 1.99 (m, 1H), 1.56 – 1.48 (m, 1H), 0.81 (d, J = 7.1 Hz, 3H).
66	Methyl (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate 	N 353.0 [M+H]+ 1.92 min	(400 MHz, DMSO-d6) δ 12.85 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 7.99 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 4.17 – 4.04 (m, 1H), 3.97 – 3.77 (m, 1H), 3.60 (s, 3H), 3.19 – 2.72 (m, 3H), 2.44 – 2.30 (m, 1H), 2.10 – 1.99 (m, 1H), 1.57 – 1.49 (m, 1H), 0.75 (d, J = 7.0 Hz, 3H).
67	[2-(Dimethylamino)-2-oxo-ethyl] (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate 	N 424.0 [M+H]+ 1.73 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 4.72 (br s, 2H), 4.25 – 4.06 (m, 1H), 3.97 – 3.87 (m, 1H, partially overlapping water), 3.22 – 2.77 (m, 9H), 2.49 – 2.31 (m, 1H), 2.12 – 2.01 (m, 1H), 1.59 – 1.51 (m, 1H), 0.86 – 0.73 (m, 3H).

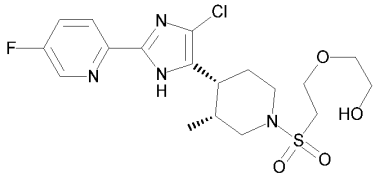
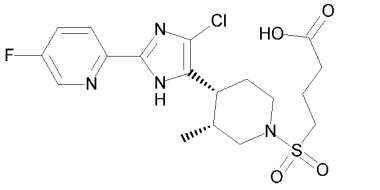
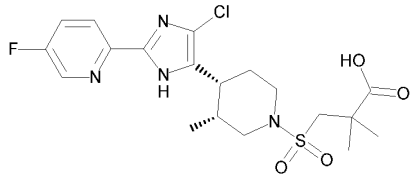
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
68	Methyl 3-[[(3S*)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate 	N 443.2 [M+H]+ 1.97 min	n/a
69	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 436.2 [M+H]+ 1.96 min	(400 MHz, DMSO-d6) δ 12.88 (br s, 1H), 8.95 – 8.89 (m, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.21 – 8.15 (m, 1H), 7.96 (br s, 1H), 7.86 – 7.78 (m, 1H), 7.72 (dd, J = 8.0, 4.8 Hz, 1H), 3.85 – 3.74 (m, 1H), 3.61 – 3.34 (m, 1H, overlapping water), 3.01 – 2.93 (m, 1H), 2.65 – 2.35 (m, 3H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.70 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).
70	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-1-oxido-pyridin-1-ium 	N 452.1 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 12.95 (br s, 1H), 8.96 – 8.88 (m, 2H), 8.74 (dd, J = 4.8, 2.4 Hz, 1H), 8.22 – 8.10 (m, 2H), 7.72 (dd, J = 8.0, 4.8 Hz, 1H), 7.58 – 7.51 (m, 1H), 3.86 – 3.75 (m, 1H), 3.66 – 3.36 (m, 1H, overlapping water), 3.17 – 3.07 (m, 1H), 2.64 – 2.27 (m, 3H, overlapping solvent), 2.26 – 2.17 (m, 1H), 1.81 – 1.70 (m, 1H), 0.86 (d, J = 7.1 Hz, 3H).

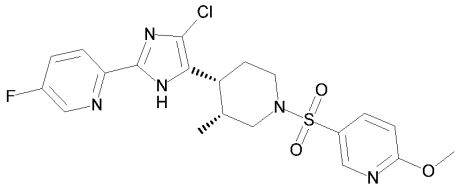
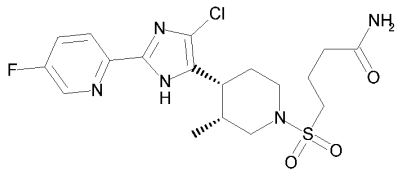
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
71	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-oxidopyridin-1-ium-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 452.0 [M+H]+ 1.68 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.53 – 8.48 (m, 1H), 8.26 – 8.14 (m, 1H), 8.04 – 7.94 (m, 1H), 7.86 – 7.79 (m, 1H), 7.70 – 7.60 (m, 2H), 3.86 – 3.73 (m, 1H), 3.70 – 3.30 (m, 1H, overlapping water), 3.07 – 2.97 (m, 1H), 2.81 – 2.71 (m, 1H), 2.60 – 2.37 (m, 2H, overlapping solvent), 2.19 – 2.08 (m, 1H), 1.70 – 1.60 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).
72	2-[5-[(3R,4R)-1-(Azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride) 	N 414.1 [M+H]+ 1.19 min	(400 MHz, DMSO-d6) δ 12.96 (br s, 1H), 9.66 (br s, 1H), 9.38 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.02 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.79 (m, 1H), 4.58 – 4.46 (m, 1H), 4.38 – 4.25 (m, 2H), 4.12 (s, 2H), 3.77 – 3.58 (m, 1H, overlapping water), 3.50 – 3.42 (m, 1H), 3.20 – 3.05 (m, 2H), 3.01 – 2.91 (m, 1H), 2.52 – 2.38 (m, 1H, partially overlapping solvent), 2.14 – 2.08 (m, 1H), 1.69 – 1.61 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

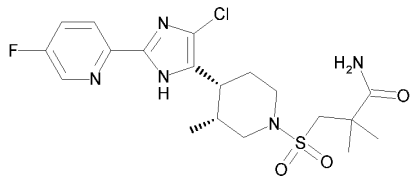
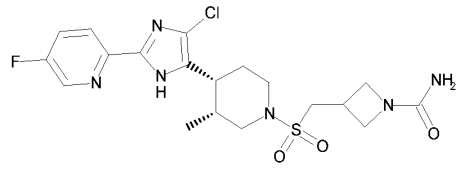
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
73	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidin-1-yl]ethenone 	N 456.1 [M+H]+ 1.68 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.49 – 4.40 (m, 1H), 4.36 – 4.25 (m, 2H), 4.20 – 4.11 (m, 1H), 4.00 – 3.92 (m, 1H), 3.80 – 3.72 (m, 1H, partially overlapping water), 3.55 – 3.46 (m, 1H, partially overlapping water), 3.14 – 3.05 (m, 2H), 2.95 – 2.85 (m, 1H), 2.52 – 2.39 (m, 1H, partially overlapping solvent), 2.16 – 2.06 (m, 1H), 1.79 (s, 3H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 6.9 Hz, 3H).
74	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxamide 	N 457.1 [M+H]+ 1.57 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 6.05 (br s, 2H), 4.32 – 4.23 (m, 1H), 4.11 – 4.04 (m, 2H), 3.99 – 3.91 (m, 2H), 3.78 – 3.58 (m, 1H, overlapping water), 3.52 – 3.44 (m, 1H), 3.13 – 3.03 (m, 2H), 2.92 – 2.82 (m, 1H), 2.52 – 2.38 (m, 1H, partially overlapping solvent), 2.16 – 2.06 (m, 1H), 1.67 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

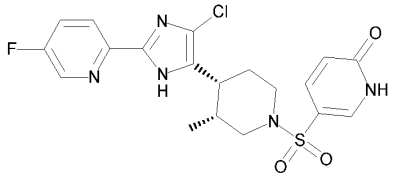
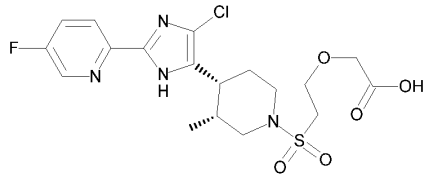
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
75	Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoate 	N 459.2 [M+H]+ 1.99 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.67 (m, 1H), 3.62 (s, 3H), 3.50 – 3.44 (m, 1H, overlapping water), 3.13 – 3.01 (m, 4H), 2.91 – 2.81 (m, 1H), 2.54 – 2.39 (m, 3H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.98 – 1.88 (m, 2H), 1.69 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
76	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoate 	N 473.2 [M+H]+ 2.15 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.68 – 3.61 (m, 4H), 3.50 – 3.31 (m, 3H, overlapping water), 3.13 – 3.05 (m, 1H), 3.05 – 2.98 (m, 1H), 2.88 – 2.78 (m, 1H), 2.54 – 2.40 (m, 1H, overlapping solvent), 2.19 – 2.09 (m, 1H), 1.70 – 1.62 (m, 1H), 1.30 (s, 6H), 0.84 (d, J = 7.0 Hz, 3H).

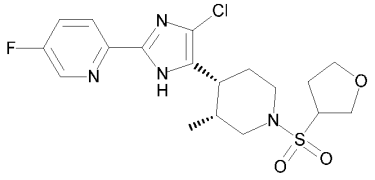
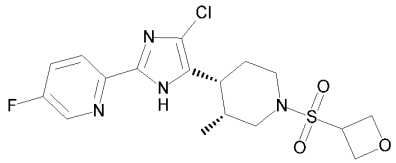
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
77	Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate 	N 528.3 [M+H]+ 2.32 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.01 – 3.92 (m, 2H), 3.73 – 3.66 (m, 2H), 3.57 – 3.39 (m, 4H, overlapping water), 3.13 – 2.91 (m, 3H), 2.91 – 2.80 (m, 1H), 2.54 – 2.38 (m, 1H, overlapping solvent.), 2.17 – 2.07 (m, 1H), 1.69 – 1.61 (m, 1H), 1.38 (s, 9H), 0.84 (d, J = 7.0 Hz, 3H).
78	2-[5-[(3R,4R)-1-(Azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride) 	N 428.2 [M+H]+ 1.20 min	n/a
79	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methyl-pyridine 	N 450.2 [M+H]+ 2.06 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.78 (d, J = 2.5 Hz, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.2, 2.5 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.85 – 7.78 (m, 1H), 7.56 (d, J = 8.2 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.60 – 3.40 (m, 1H, overlapping water), 2.99 – 2.91 (m, 1H), 2.65 – 2.31 (m, 6H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).

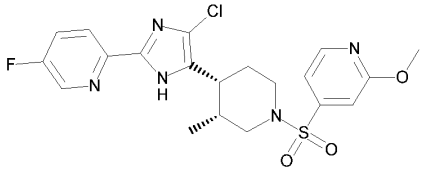
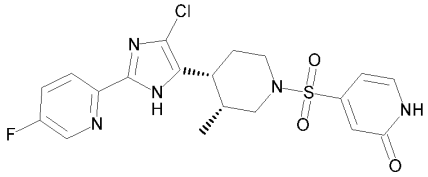
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
80	2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethanol 	N 447.1 [M+H]+ 1.65 min	n/a
81	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoic acid 	N 445.1 [M+H]+ 1.73 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 12.21 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.67 (m, 1H), 3.50 – 3.43 (m, 1H), 3.13 – 3.01 (m, 4H), 2.92 – 2.81 (m, 1H), 2.54 – 2.37 (m, 3H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.95 – 1.84 (m, 2H), 1.68 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
82	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoic acid 	N 459.1 [M+H]+ 1.88 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 12.43 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.70 – 3.62 (m, 1H), 3.50 – 3.24 (m, 3H, overlapping water), 3.13 – 3.05 (m, 1H), 3.04 – 2.98 (m, 1H), 2.87 – 2.77 (m, 1H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.69 – 1.61 (m, 1H), 1.28 (s, 6H), 0.84 (d, J = 7.0 Hz, 3H).

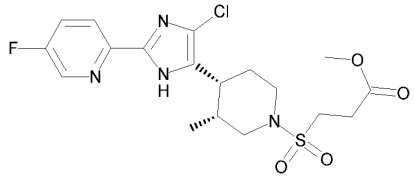
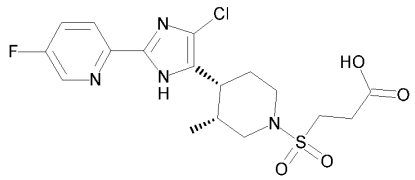
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
83	2-[4-Chloro-5-[(3R,4R)-1-[(6-methoxy-3-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 466.1 [M+H]+ 2.27 min	(400 MHz, DMSO-d6) δ 12.87 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.55 (d, J = 2.5 Hz, 1H), 8.02 (dd, J = 8.8, 2.6 Hz, 1H), 8.00 – 7.93 (m, 1H), 7.85 – 7.78 (m, 1H), 7.07 (d, J = 8.8 Hz, 1H), 3.97 (s, 3H), 3.79 – 3.71 (m, 1H), 3.55 – 3.39 (m, 1H, overlapping water), 3.00 – 2.92 (m, 1H), 2.60 – 2.30 (m, 3H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.68 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).
84	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanamide 	N 444.1 [M+H]+ 1.59 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.32 (br s, 1H), 6.80 (br s, 1H), 3.75 – 3.67 (m, 1H), 3.49 – 3.43 (m, 1H), 3.13 – 3.02 (m, 4H), 2.91 – 2.82 (m, 1H), 2.54 – 2.39 (m, 1H, overlapping solvent), 2.22 (t, J = 7.3 Hz, 2H), 2.17 – 2.08 (m, 1H), 1.94 – 1.83 (m, 2H), 1.69 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

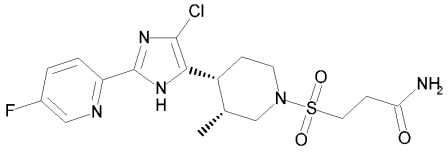
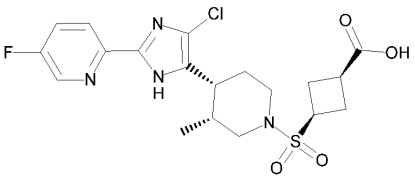
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
85	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanamide 	N 458.2 [M+H]+ 1.70 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.14 (br s, 1H), 6.93 (br s, 1H), 3.70 – 3.62 (m, 1H, partially overlapping water), 3.46 – 3.39 (m, 1H), 3.26 (s, 2H), 3.11 – 3.04 (m, 1H), 3.02 – 2.96 (m, 1H), 2.86 – 2.75 (m, 1H), 2.52 – 2.38 (m, 1H, partially overlapping solvent), 2.17 – 2.08 (m, 1H), 1.69 – 1.60 (m, 1H), 1.27 (s, 6H), 0.84 (d, J = 7.0 Hz, 3H).
86	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxamide 	N 471.2 [M+H]+ 1.59 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 5.84 (br s, 2H), 3.95 – 3.88 (m, 2H), 3.74 – 3.36 (m, 6H, overlappinng water), 3.13 – 3.02 (m, 2H), 2.98 – 2.81 (m, 2H), 2.54 – 2.39 (m, 1H, overlapping solvet), 2.17 – 2.07 (m, 1H), 1.65 (d, J = 13.1 Hz, 1H), 0.85 (d, J = 7.0 Hz, 3H).

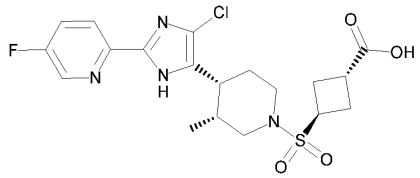
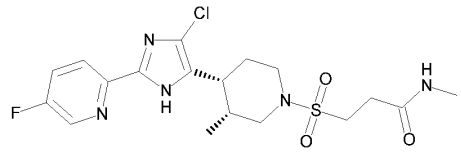
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
87	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one 	N 452.2 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 12.32 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.88 – 7.78 (m, 2H), 7.62 (dd, J = 9.7, 2.7 Hz, 1H), 6.48 (d, J = 9.6 Hz, 1H), 3.74 – 3.39 (m, 2H, overlapping water), 3.05 – 2.97 (m, 1H), 2.71 – 2.62 (m, 1H), 2.57 – 2.44 (m, 2H, overlapping solvent), 2.17 – 2.09 (m, 1H), 1.66 (d, J = 11.2 Hz, 1H), 0.86 (d, J = 7.0 Hz, 3H).
88	2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]acetic acid 	N 461.1 [M+H]+ 1.67 min	(400 MHz, DMSO-d6) δ 13.20 – 12.20 (m, 2H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.09 (s, 2H), 3.85 – 3.79 (m, 2H), 3.73 – 3.66 (m, 1H), 3.53 – 3.32 (m, 3H, overlapping water), 3.12 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.54 – 2.39 (m, 1H, overlapping solvent), 2.15 – 2.07 (m, 1H), 1.66 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

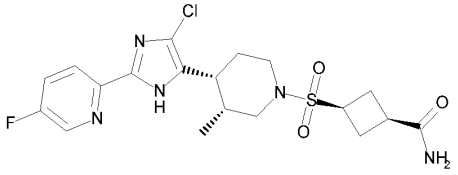
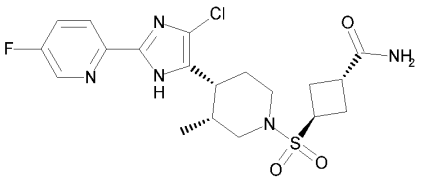
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
89	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydrofuran-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 429.1 [M+H]+ 1.85 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.06 – 3.93 (m, 2H), 3.91 – 3.45 (m, 5H, overlapping water), 3.15 – 3.06 (m, 2H), 2.98 – 2.86 (m, 1H), 2.54 – 2.39 (m, 1H, overlapping solvent), 2.30 – 2.19 (m, 1H), 2.16 – 2.04 (m, 2H), 1.66 – 1.59 (m, 1H), 0.87 – 0.82 (m, 3H). Compound is a mixture of diastereoisomers (1:1).
90	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(oxetan-3-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 415.1 [M+H]+ 1.78 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.87 – 4.70 (m, 5H), 3.76 – 3.64 (m, 1H, overlapping water), 3.49 – 3.43 (m, 1H), 3.11 – 2.99 (m, 2H), 2.88 – 2.78 (m, 1H), 2.52 – 2.37 (m, 1H, partially overlapping solvent), 2.14 – 2.05 (m, 1H), 1.66 – 1.58 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

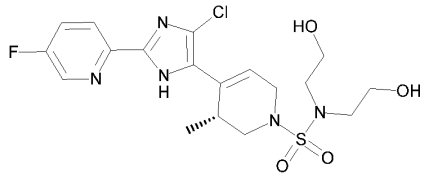
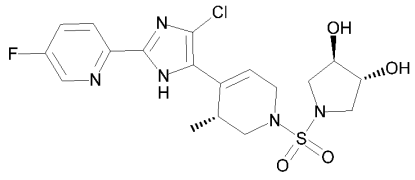
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
91	2-[4-Chloro-5-[(3R,4R)-1-[(2-methoxy-4-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 464.0 [M-H]- 2.30 min	(400 MHz, DMSO-d6) δ 12.88 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.03 – 7.90 (m, 1H), 7.85 – 7.78 (m, 1H), 7.27 (dd, J = 5.3, 1.5 Hz, 1H), 7.06 (br s, 1H), 3.95 (s, 3H), 3.81 – 3.73 (m, 1H), 3.60 – 3.36 (m, 1H, overlapping water), 3.03 – 2.95 (m, 1H), 2.69 – 2.59 (m, 1H), 2.57 – 2.41 (m, 2H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).
92	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one 	N 452.0 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 12.25 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.86 – 7.79 (m, 1H), 7.66 (d, J = 6.8 Hz, 1H), 6.60 (d, J = 1.8 Hz, 1H), 6.37 (dd, J = 6.8, 1.8 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.63 – 3.46 (m, 1H, overlapping water), 3.08 – 3.00 (m, 1H), 2.83 – 2.74 (m, 1H), 2.66 – 2.40 (m, 2H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.71 – 1.62 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

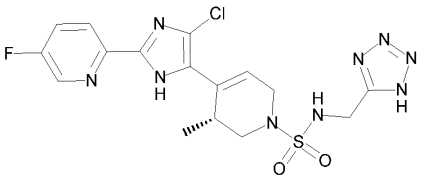
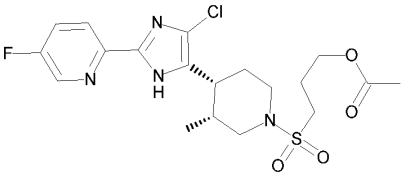
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
93	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate 	N 445.1 [M+H]+ 1.94 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.6 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.66 (m, 1H), 3.65 (s, 3H), 3.49 – 3.43 (m, 1H), 3.36 – 3.30 (m, 2H, partially overlapping water), 3.14 – 3.05 (m, 2H), 2.94 – 2.84 (m, 1H), 2.77 – 2.71 (m, 2H), 2.54 – 2.41 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.67 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
94	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid 	N 431.1 [M+H]+ 1.69 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 12.56 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.67 (m, 1H), 3.50 – 3.43 (m, 1H), 3.31 – 3.25 (m, 2H, partially overlapping water), 3.14 – 3.05 (m, 2H), 2.94 – 2.84 (m, 1H), 2.69 – 2.61 (m, 2H), 2.54 – 2.40 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.67 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

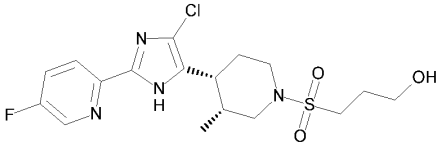
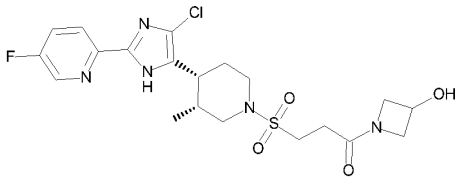
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
95	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide 	N 430.1 [M+H]+ 1.56 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.49 (br s, 1H), 7.00 (br s, 1H), 3.74 – 3.66 (m, 1H), 3.49 – 3.42 (m, 1H), 3.28 – 3.21 (m, 2H), 3.13 – 3.04 (m, 2H), 2.93 – 2.83 (m, 1H), 2.54 – 2.39 (m, 3H, overlapping solvent), 2.15 – 2.08 (m, 1H), 1.68 – 1.60 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H).
96	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 1) 	N 457.1 [M+H]+ 1.74 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.98 – 3.88 (m, 1H), 3.75 – 3.55 (m, 1H, overlapping water), 3.47 – 3.41 (m, 1H), 3.15 – 2.98 (m, 3H), 2.89 – 2.79 (m, 1H), 2.54 – 2.37 (m, 5H, overlapping solvent), 2.13 – 2.06 (m, 1H), 1.65 – 1.58 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H). COOH not observed due to fast exchange with water.

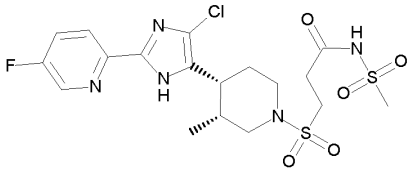
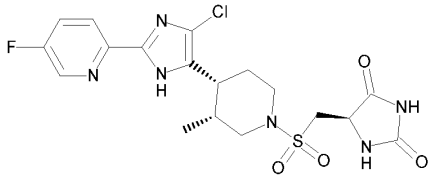
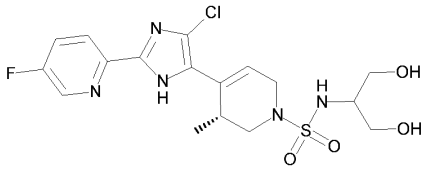
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
97	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 2) 	N 455.0 [M-H]- 1.78 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.04 – 3.91 (m, 1H), 3.76 – 3.68 (m, 1H), 3.50 – 3.43 (m, 1H, overlapping water), 3.19 – 3.02 (m, 3H), 2.92 – 2.82 (m, 1H), 2.58 – 2.37 (m, 5H, overlapping solvent), 2.13 – 2.04 (m, 1H), 1.64 – 1.56 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H). COOH not observed due to fast exchange with water.
98	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-propanamide 	N 444.1 [M+H]+ 1.63 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.03 – 7.93 (m, 2H), 7.86 – 7.79 (m, 1H), 3.73 – 3.65 (m, 1H), 3.48 – 3.42 (m, 1H), 3.28 – 3.22 (m, 2H), 3.13 – 3.02 (m, 2H), 2.91 – 2.82 (m, 1H), 2.60 (d, J = 4.6 Hz, 3H), 2.54 – 2.40 (m, 3H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

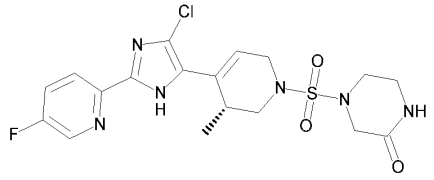
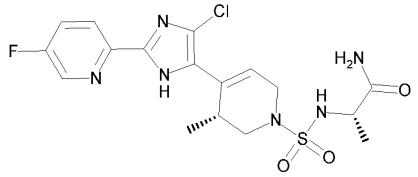
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
99	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 1) 	N 456.1 [M+H]+ 1.60 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.26 (br s, 1H), 6.85 (br s, 1H), 3.96 – 3.85 (m, 1H), 3.74 – 3.65 (m, 1H, overlapping water), 3.48 – 3.40 (m, 1H), 3.12 – 2.79 (m, 4H), 2.52 – 2.28 (m, 5H, overlapping solvent), 2.14 – 2.05 (m, 1H), 1.66 – 1.58 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
100	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 2) 	N 456.1 [M+H]+ 1.64 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.31 (br s, 1H), 6.88 (br s, 1H), 3.97 – 3.86 (m, 1H, overlapping water), 3.76 – 3.69 (m, 1H), 3.50 – 3.43 (m, 1H), 3.14 – 3.01 (m, 3H), 2.91 – 2.81 (m, 1H), 2.54 – 2.38 (m, 5H, overlapping solvent), 2.13 – 2.04 (m, 1H), 1.65 – 1.56 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H).

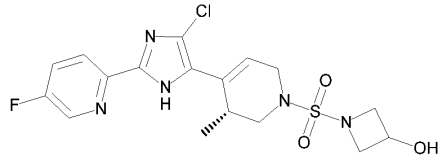
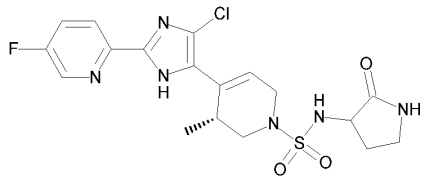
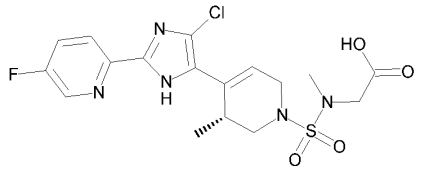
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
101	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N-bis(2-hydroxyethyl)-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide 	N 460.1 [M+H]+ 1.66 min	(400 MHz, DMSO-d6) δ 13.07 (br s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.18 – 6.14 (m, 1H), 3.90 – 3.81 (m, 1H), 3.78 – 3.69 (m, 1H, partially overlapping water), 3.59 – 3.53 (m, 4H, overlapping water), 3.35 – 3.13 (m, 7H), 0.98 (d, J = 6.7 Hz, 3H). 2 x OH not observed due to fast exchange with water.
102	(3R,4R)-1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]pyrrolidine-3,4-diol 	N 458.1 [M+H]+ 1.63 min	(400 MHz, DMSO-d6) δ 13.04 (br s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.17 – 6.13 (m, 1H), 3.98 – 3.95 (m, 2H), 3.94 – 3.87 (m, 1H), 3.81 – 3.72 (m, 1H), 3.52 – 3.45 (m, 2H, overlapping water), 3.36 – 3.29 (m, 1H), 3.27 – 3.12 (m, 4H), 0.98 (d, J = 6.8 Hz, 3H). 2 x OH not observed due to fast exchange with water.

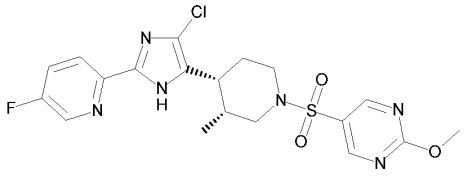
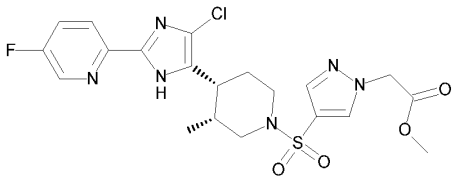
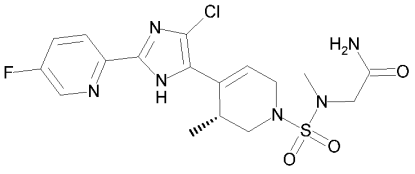
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
103	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(1H-tetrazol-5-ylmethyl)-3,6-dihydro-2H-pyridine-1-sulfonamide 	N 454.1 [M+H]+ 1.64 min	(400 MHz, DMSO-d6) δ 13.05 (br s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.15 (t, J = 6.0 Hz, 1H), 8.04 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.19 – 6.15 (m, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.89 – 3.80 (m, 1H), 3.75 – 3.66 (m, 1H), 3.30 – 3.08 (m, 3H, partially overlapping water), 0.96 (d, J = 6.5 Hz, 3H). Tetrazine NH not observed due to fast exchange with water.
104	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propyl acetate 	N 459.1 [M+H]+ 1.98 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.7 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.10 (t, J = 6.5 Hz, 2H), 3.75 – 3.68 (m, 1H), 3.51 – 3.44 (m, 1H), 3.16 – 3.02 (m, 4H), 2.92 – 2.82 (m, 1H), 2.56 – 2.41 (m, 1H, overlapping solvent), 2.17 – 2.09 (m, 1H), 2.06 – 1.95 (m, 5H), 1.68 – 1.60 (m, 1H), 0.86 (d, J = 6.8 Hz, 3H).

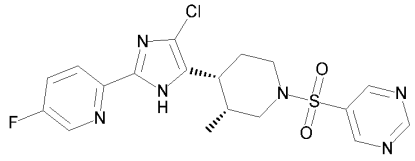
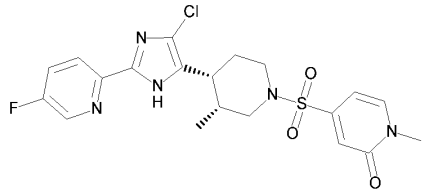
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
105	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-ol 	N 417.1 [M+H]+ 1.66 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.6 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.65 (t, J = 5.2 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.53 – 3.44 (m, 3H), 3.13 – 3.00 (m, 4H), 2.90 – 2.80 (m, 1H), 2.54 – 2.41 (m, 1H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.87 – 1.77 (m, 2H), 1.68 – 1.60 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).
106	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-1-one 	N 486.1 [M+H]+ 1.57 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.50 – 4.42 (m, 1H), 4.36 – 4.30 (m, 1H), 4.08 – 4.01 (m, 1H), 3.92 – 3.86 (m, 1H), 3.73 – 3.66 (m, 1H), 3.62 – 3.56 (m, 1H), 3.49 – 3.39 (m, 1H, overlapping water), 3.27 – 3.20 (m, 2H), 3.13 – 3.03 (m, 2H), 2.93 – 2.83 (m, 1H), 2.52 – 2.38 (m, 3H, partially overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.

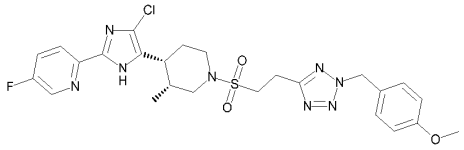
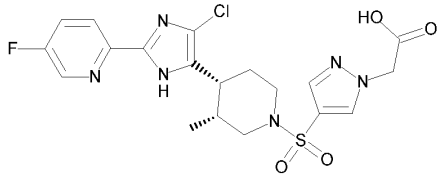
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
107	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methylsulfonyl-propanamide 	N 508.1 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 11.89 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.66 (m, 1H), 3.49 – 3.42 (m, 1H partially overlapping water), 3.35 – 3.28 (m, 2H), 3.25 (s, 3H), 3.14 – 3.05 (m, 2H), 2.95 – 2.85 (m, 1H), 2.78 – 2.71 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.69 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
108	(5R)-5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]imidazolidine-2,4-dione 	N 471.1 [M+H]+ 2.12 min	n/a
109	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[2-hydroxy-1-(hydroxymethyl)ethyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide 	N 446.1 [M+H]+ 1.56 min	(400 MHz, DMSO-d6) δ 13.08 (br s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.19 – 6.14 (m, 1H), 3.89 – 3.69 (m, 2H, partially overlapping water), 3.50 – 3.41 (m, 4H), 3.28 – 3.12 (m, 4H), 0.98 (d, J = 6.7 Hz, 3H). 2 x OH not observed due to fast exchange with water.

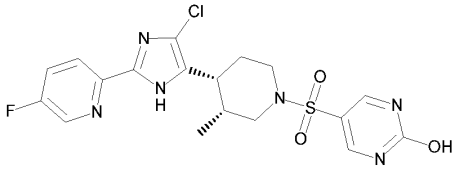
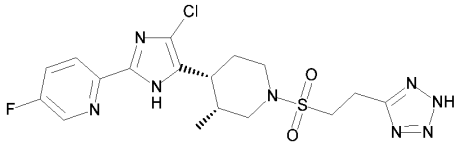
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
110	4-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperazin-2-one 	N 455.1 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 13.07 (br s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.11 – 8.07 (m, 1H), 8.04 (dd, J = 8.8, 4.6 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.19 – 6.14 (m, 1H), 3.98 – 3.90 (m, 1H), 3.89 – 3.79 (m, 1H, partially overlapping water), 3.73 (s, 2H, overlapping water), 3.45 – 3.39 (m, 2H), 3.36 – 3.32 (m, 2H), 3.29 – 3.24 (m, 2H), 3.23 – 3.13 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H).
111	(2S)-2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonylamino]propenamide 	N 443.1 [M+H]+ 1.62 min	(400 MHz, DMSO-d6) δ 13.04 (br s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 8.04 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.36 (br s, 1H), 7.08 (br s, 1H), 6.18 – 6.13 (m, 1H), 3.85 – 3.74 (m, 2H), 3.73 – 3.65 (m, 1H), 3.25 – 3.20 (m, 1H), 3.19 – 3.13 (m, 1H), 3.12 – 3.06 (m, 1H), 1.26 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H).

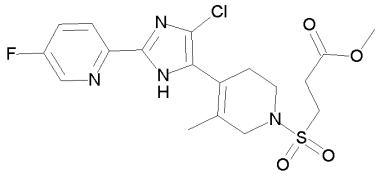
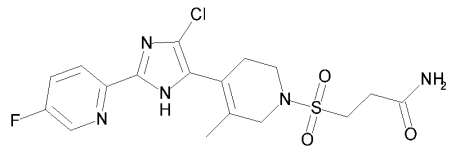
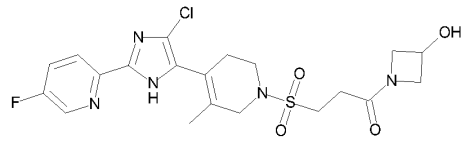
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
112	1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-ol 	N 428.0 [M+H]+ 1.79 min	(400.23 MHz, DMSO-d6) δ ppm 13.08 (br s, 1 H), 8.62 (d, J=2.81 Hz, 1 H), 8.04 (dd, J=8.80, 4.52 Hz, 1 H), 7.84 (td, J=8.74, 8.74, 2.93 Hz, 1 H), 6.16 (t, J=3.30, 3.30 Hz, 1 H), 4.41 (quin, J=6.24, 6.24, 6.24, 6.24 Hz, 1 H), 3.93 (m, 2 H), 3.87 (br d, J=3.18 Hz, 1 H), 3.78 (m, 1 H), 3.66 (dd, J=8.25, 5.93 Hz, 2 H), 3.25 (m, 3 H), 0.96 (d, J=6.72 Hz, 3 H)
113	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(2-oxopyrrolidin-3-yl)-3,6-dihydro-2H-pyridine-1-sulfonamide 	N 455.0 [M+H]+ 1.67 min	(400.23 MHz, DMSO-d6) δ ppm 13.05 (br s, 1 H), 8.62 (d, J=2.69 Hz, 1 H), 8.04 (dd, J=8.93, 4.52 Hz, 1 H), 7.85 (m, 2 H), 7.62 (t, J=9.60, 9.60 Hz, 1 H), 6.17 (q, J=3.59, 3.59, 3.59 Hz, 1 H), 3.91 (m, 2 H), 3.81 (br s, 1 H), 3.20 (m, 5 H), 2.35 (m, 1 H), 1.83 (m, 1 H), 0.98 (d, J=6.72 Hz, 3 H)
114	2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetic 	N 444.1 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 8.27 (d, J = 2.9 Hz, 1H), 7.87 (dd, J = 9.0, 4.8 Hz, 1H), 7.57 – 7.49 (m, 1H), 6.02 – 5.97 (m, 1H), 3.95 – 3.87 (m, 1H), 3.76 – 3.68 (m, 1H), 3.46 – 3.40 (m, 3H), 3.20 – 3.12 (m, 1H), 3.09 – 3.02 (m, 1H), 2.85 (s, 3H), 1.10 (d, J = 6.8 Hz, 3H). Imidazole NH and COOH not observed due to fast exchange with water.

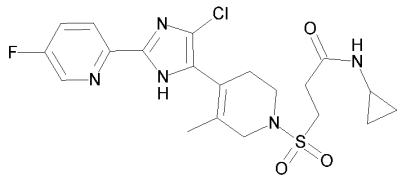
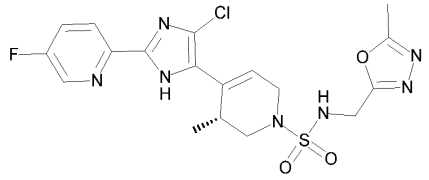
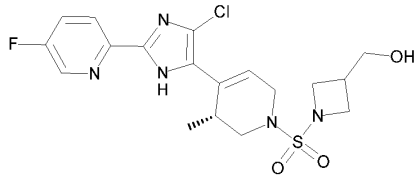
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
115	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methoxy-pyrimidine acid 	N 467.0 [M+H]+ 2.09 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.95 (s, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.01 – 7.94 (m, 1H), 7.86 – 7.78 (m, 1H), 4.05 (s, 3H), 3.80 – 3.73 (m, 1H), 3.58 – 3.39 (m, 1H, overlapping water), 3.03 – 2.95 (m, 1H), 2.71 – 2.64 (m, 1H), 2.60 – 2.42 (m, 2H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.68 – 1.61 (m, 1H), 0.88 (d, J = 7.0 Hz, 3H).
116	Methyl 2-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetate 	N 497.1 [M+H]+ 1.96 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.38 (s, 1H), 7.98 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 (s, 1H), 7.86 – 7.78 (m, 1H), 5.21 (s, 2H), 3.77 – 3.68 (m, 4H, overlapping water), 3.49 – 3.43 (m, 1H), 2.97 – 2.89 (m, 1H), 2.61 – 2.39 (m, 2H, overlapping solvent), 2.31 – 2.20 (m, 1H), 2.20 – 2.12 (m, 1H), 1.72 – 1.64 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H).
117	2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetamide 	N 443.1 [M+H]+ 1.69 min	(400 MHz, DMSO-d6) δ 13.02 (br s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.38 (br s, 1H), 7.13 (br s, 1H), 6.18 – 6.13 (m, 1H), 3.96 – 3.87 (m, 1H), 3.85 – 3.74 (m, 3H), 3.37 – 3.30 (m, 1H), 3.28 – 3.21 (m, 1H), 3.21 – 3.13 (m, 1H), 2.88 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H).

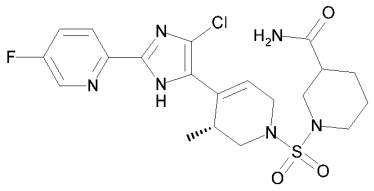
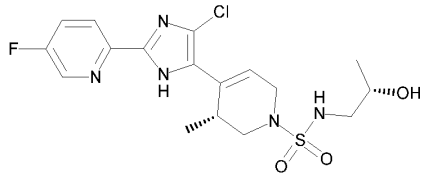
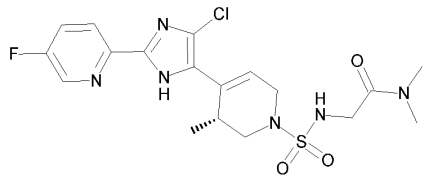
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
118	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine 	N 437.01 [M+H]+ 1.92 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 9.52 (s, 1H), 9.18 (s, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.92 (m, 1H), 7.86 – 7.79 (m, 1H), 3.88 – 3.53 (m, 2H, overlapping water), 3.05 – 2.97 (m, 1H), 2.80 – 2.72 (m, 1H), 2.64 – 2.45 (m, 2H, overlapping solvent), 2.17 – 2.09 (m, 1H), 1.70 – 1.62 (m, 1H), 0.87 (d, J = 7.1 Hz, 3H).
119	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyridin-2-one 	N 466.1 [M+H]+ 1.80 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.95 (m, 2H), 7.86 – 7.78 (m, 1H), 6.65 (d, J = 2.0 Hz, 1H), 6.43 (dd, J = 7.0, 2.1 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.55 – 3.47 (m, 4H), 3.07 – 2.98 (m, 1H), 2.80 – 2.73 (m, 1H), 2.65 – 2.42 (m, 2H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.69 – 1.62 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).

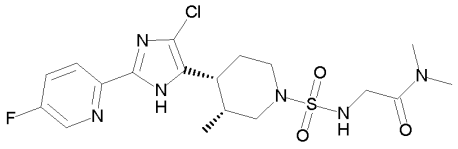
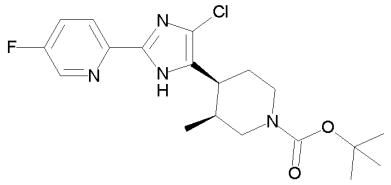
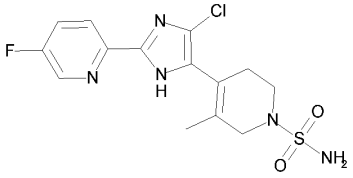
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
120	2-[4-Chloro-5-[(3R,4R)-1-[2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 575.2 [M+H]+ 2.30 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.37 – 7.31 (m, 2H), 6.97 – 6.91 (m, 2H), 5.81 (s, 2H), 3.74 – 3.60 (m, 4H, overlapping water), 3.54 – 3.41 (m, 3H), 3.29 – 3.22 (m, 2H), 3.07 – 2.97 (m, 2H), 2.84 – 2.73 (m, 1H), 2.52 – 2.36 (m, 1H, partially overlapping solvent), 2.13 – 2.02 (m, 1H), 1.62 – 1.53 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H).
121	2-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetic acid 	N 483.0 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 13.60 – 12.60 (m, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.35 (d, J = 0.7 Hz, 1H), 7.98 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 2H), 5.07 (s, 2H), 3.73 – 3.65 (m, 1H), 3.50 – 3.42 (m, 1H), 2.97 – 2.88 (m, 1H), 2.63 – 2.38 (m, 2H, overlapping solvent), 2.32 – 2.20 (m, 1H), 2.19 – 2.10 (m, 1H), 1.67 (d, J = 13.1 Hz, 1H), 0.89 (d, J = 7.0 Hz, 3H).

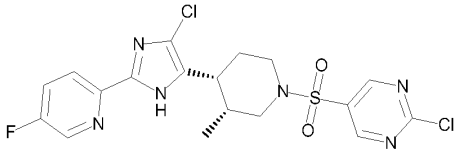
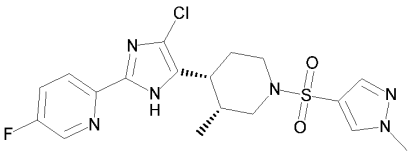
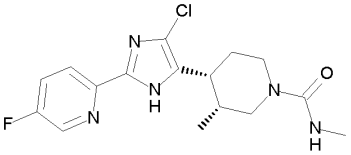
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
122	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-ol 	N 453.0 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.58 (s, 2H), 8.01 – 7.94 (m, 1H), 7.86 – 7.78 (m, 1H), 3.73 – 3.66 (m, 1H), 3.50 – 3.41 (m, 1H), 3.07 – 2.99 (m, 1H), 2.80 – 2.72 (m, 1H), 2.65 – 2.43 (m, 2H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.70 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.
123	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2H-tetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 455.0 [M+H]+ 1.65 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.77 – 3.69 (m, 1H), 3.59 – 3.51 (m, 2H), 3.51 – 3.44 (m, 1H), 3.37 – 3.29 (m, 2H), 3.14 – 3.04 (m, 2H), 2.95 – 2.85 (m, 1H), 2.54 – 2.39 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H). Tetrazole NH not observed due to fast exchange with water.

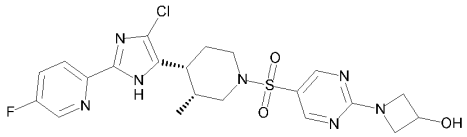
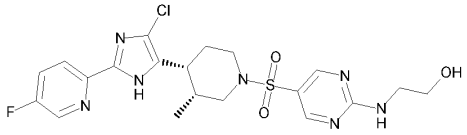
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
124	Methyl 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate 	N 443.0 [M+H]+ 1.95 min	(400 MHz, DMSO-d6) δ 13.14 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.03 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.80 (m, 1H), 3.82 – 3.78 (m, 2H), 3.64 (s, 3H), 3.44 – 3.36 (m, 4H, partially overlapping water), 2.75 (t, J = 7.2 Hz, 2H), 2.47 – 2.41 (m, 2H), 1.65 (s, 3H).
125	3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propenamide 	N 428.0 [M+H]+ 1.58 min	(400 MHz, DMSO-d6) δ 13.14 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.03 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.49 (br s, 1H), 7.00 (br s, 1H), 3.81 – 3.77 (m, 2H, overlapping water), 3.42 – 3.36 (m, 2H), 3.35 – 3.29 (m, 2H), 2.56 – 2.50 (m, 2H, partially overlapping solvent), 2.48 – 2.41 (m, 2H), 1.65 (s, 3H).
126	3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-1-one 	N 484.0 [M+H]+ 1.60 min	(400 MHz, DMSO-d6) δ 13.14 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.80 (m, 1H), 4.49 – 4.41 (m, 1H), 4.36 – 4.29 (m, 1H), 4.08 – 4.00 (m, 1H), 3.92 – 3.86 (m, 1H), 3.82 – 3.77 (m, 2H), 3.61 – 3.55 (m, 1H,overlapping water), 3.42 – 3.35 (m, 2H), 3.35 – 3.28 (m, 2H), 2.52 – 2.41 (m, 4H, partially overlapping solvent), 1.65 (s, 3H). OH not observed due to fast exchange with water.

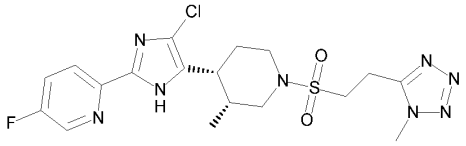
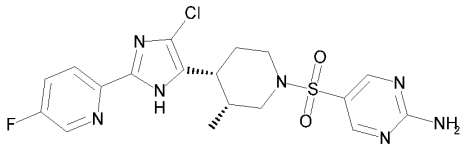
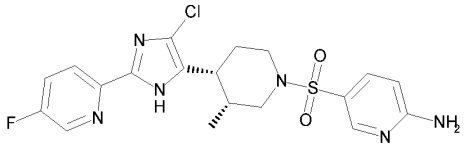
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
127	3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-N-cyclopropyl-propanamide 	N 468.0 [M+H]+ 1.79 min	(400 MHz, DMSO-d6) δ 13.14 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.09 (d, J = 4.1 Hz, 1H), 8.03 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.80 (m, 1H), 3.80 – 3.76 (m, 2H, overlapping water), 3.41 – 3.29 (m, 4H), 2.65 – 2.57 (m, 1H), 2.52 – 2.41 (m, 4H, partially overlapping sovent), 1.65 (s, 3H), 0.64 – 0.58 (m, 2H), 0.42 – 0.36 (m, 2H).
128	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]piperidine-1-sulfonamide 	N 467.9 [M+H]+ 1.75 min	(400 MHz, DMSO-d6) δ 13.05 (br s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 8.18 (t, J = 6.1 Hz, 1H), 8.04 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.19 – 6.15 (m, 1H), 4.37 (d, J = 6.1 Hz, 2H), 3.86 – 3.78 (m, 1H), 3.73 – 3.64 (m, 1H), 3.27 – 3.09 (m, 3H), 2.49 (s, 3H, overlapping solvent), 0.96 (d, J = 6.6 Hz, 3H).
129	[1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-yl]methanol 	N 442.0 [M+H]+ 1.80 min	(400 MHz, DMSO-d6) δ 13.07 (br s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 8.04 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.16 (t, J = 3.5 Hz, 1H), 3.93 – 3.74 (m, 4H), 3.66 – 3.61 (m, 2H), 3.51 (d, J = 6.2 Hz, 2H, overlapping water), 3.34 – 3.13 (m, 3H), 2.72 – 2.60 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H). OH not observed due to fast exchange with water.

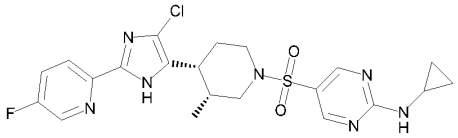
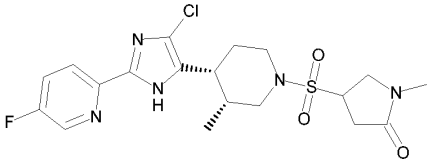
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
130	N-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperidine-3-carboxamide 	N 483.1 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 13.06 (br s, 1H), 8.62 (d, J = 2.8 Hz, 1H), 8.04 (dd, J = 8.9, 4.6 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.39 (br s, 1H), 6.90 (br s, 1H), 6.18 – 6.14 (m, 1H), 3.94 – 3.49 (m, 4H, overlapping water), 3.35 – 3.13 (m, 3H), 2.94 – 2.77 (m, 2H), 2.40 – 2.29 (m, 1H), 1.90 – 1.80 (m, 1H), 1.78 – 1.68 (m, 1H), 1.53 – 1.39 (m, 2H), 0.98 (dd, J = 6.8, 1.3 Hz, 3H).
131	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[(2S)-2-hydroxypropyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide 	N 430.0 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 13.04 (br s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 8.04 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.25 (t, J = 6.1 Hz, 1H), 6.20 – 6.15 (m, 1H), 3.86 – 3.77 (m, 1H), 3.71 – 3.63 (m, 2H), 3.28 – 3.08 (m, 3H), 2.93 – 2.76 (m, 2H), 1.06 (d, J = 6.2 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H). OH not observed due to fast exchange with water.
132	2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonylamino]-N,N-dimethyl-acetamide 	N 455.0 [M-H]- 1.80 min	(400 MHz, DMSO-d6) δ 13.04 (br s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 8.04 (dd, J = 8.8, 4.5 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.25 (br s, 1H), 6.18 – 6.13 (m, 1H), 3.89 – 3.80 (m, 3H), 3.77 – 3.68 (m, 1H), 3.29 – 3.21 (m, 1H), 3.19 – 3.11 (m, 2H), 2.93 (s, 3H), 2.84 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H).

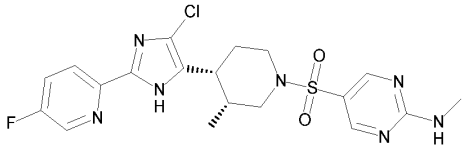
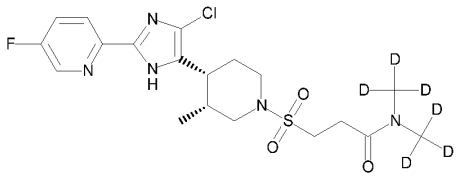
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
133	2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylamino]-N,N-dimethyl-acetamide 	N 459.1 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 12.86 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.11 (br s, 1H), 3.87 – 3.74 (m, 2H), 3.70 – 3.62 (m, 1H), 3.48 – 3.30 (m, 1H, overlapping water), 3.07 – 2.99 (m, 1H), 2.97 – 2.84 (m, 7H), 2.76 – 2.64 (m, 1H), 2.55 – 2.37 (m, 1H, overlapping solvent), 2.18 – 2.07 (m, 1H), 1.66 – 1.58 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H).
134	Tert-butyl (3S,4S)-4-[4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl]-3-methylpiperidine-1-carboxylate 	N 395.2 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 12.86 (s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 7.99 (dd, J = 8.8, 4.4 Hz, 1H), 7.82 (td, J = 8.8, 2.8 Hz, 1H), 4.11 (s, 1H), 3.87 (s, 1H), 3.20 – 2.61 (m, 3H), 2.38 (dd, J = 22.0, 12.4 Hz, 1H), 2.01 (s, 1H), 1.55 – 1.31 (m, 10H), 0.77 (d, J = 6.4 Hz, 3H) ppm
135	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide 	N 372.0 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 13.09 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.03 (dd, J = 8.9, 4.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 6.86 (br s, 2H), 3.56 (s, 2H), 3.19 – 3.11 (m, 2H), 2.50 – 2.43 (m, 2H, partially overlapping solvent), 1.65 (s, 3H).

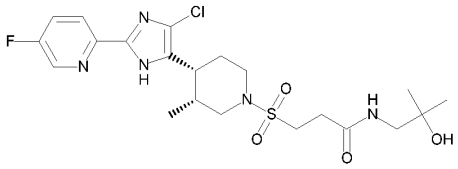
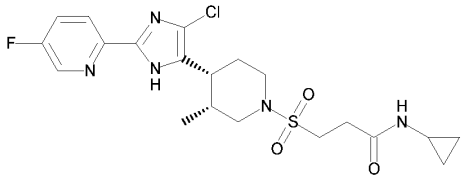
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
136	2-Chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine 	N 470.9 [M+H]+ 2.23 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 9.13 (s, 2H), 8.61 (d, J = 2.9 Hz, 1H), 7.98 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 3.92 – 3.69 (m, 1H, overlapping water), 3.59 – 3.51 (m, 1H), 3.05 – 2.96 (m, 1H), 2.85 – 2.77 (m, 1H), 2.69 – 2.47 (m, 2H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.69 – 1.61 (m, 1H), 0.88 (d, J = 7.0 Hz, 3H).
137	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylpyrazol-4-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 439 [M+H]+ 1.88 min	(400 MHz, DMSO-d6) δ 12.88 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.33 (s, 1H), 7.98 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.77 (m, 2H), 3.92 (s, 3H), 3.70 – 3.62 (m, 1H), 3.48 – 3.39 (m, 1H), 2.98 – 2.89 (m, 1H), 2.61 – 2.39 (m, 2H, overlapping solvent), 2.33 – 2.19 (m, 1H), 2.18 – 2.10 (m, 1H), 1.70 – 1.62 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H).
138	(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,3-dimethyl-piperidine-1-carboxamide 	N 352.0 [M+H]+ 1.54 min	(400 MHz, DMSO-d6) δ 12.84 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 7.99 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 6.35 (br s, 1H), 4.14 – 4.05 (m, 1H), 3.92 – 3.84 (m, 1H), 3.14 – 3.05 (m, 1H), 2.93 – 2.85 (m, 1H), 2.73 – 2.62 (m, 1H), 2.57 (s, 3H), 2.39 – 2.26 (m, 1H), 2.05 – 1.96 (m, 1H), 1.53 – 1.45 (m, 1H), 0.75 (d, J = 7.0 Hz, 3H).

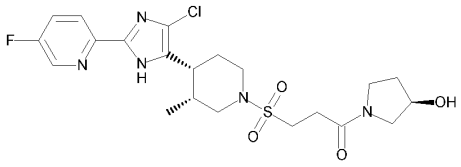
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
139	1-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]azetidin-3-ol 	N 508.0 [M+H]+ 1.81 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.58 (s, 2H), 7.98 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 4.66 – 4.58 (m, 1H), 4.41 – 4.33 (m, 2H), 3.93 – 3.87 (m, 2H), 3.74 – 3.66 (m, 1H), 3.52 – 3.44 (m, 1H), 3.02 – 2.94 (m, 1H), 2.60 – 2.33 (m, 3H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.68 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.
140	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]ethanol 	N 496.0 [M+H]+ 1.79 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.56 (d, J = 3.2 Hz, 1H), 8.51 (d, J = 3.2 Hz, 1H), 8.19 (t, J = 5.8 Hz, 1H), 8.03 – 7.92 (m, 1H), 7.86 – 7.78 (m, 1H), 3.75 – 3.66 (m, 1H), 3.54 (t, J = 6.2 Hz, 2H), 3.51 – 3.38 (m, 3H), 3.04 – 2.94 (m, 1H), 2.65 – 2.32 (m, 3H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.69 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.

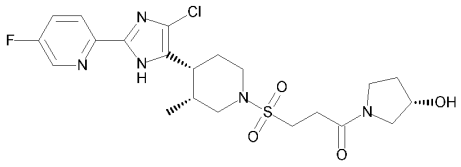
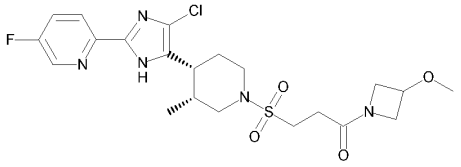
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
141	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 469.0 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 4.04 (s, 3H), 3.79 – 3.71 (m, 1H), 3.60 – 3.53 (m, 2H), 3.52 – 3.46 (m, 1H), 3.36 – 3.29 (m, 2H), 3.16 – 3.06 (m, 2H), 2.99 – 2.88 (m, 1H), 2.54 – 2.40 (m, 1H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.70 – 1.62 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).
142	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine 	N 452.1 [M+H]+ 1.78 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.50 (s, 2H), 8.03 – 7.90 (m, 1H), 7.87 – 7.79 (m, 1H), 7.72 (s, 2H), 3.74 – 3.63 (m, 1H), 3.52 – 3.40 (m, 1H), 3.04 – 2.95 (m, 1H), 2.66 – 2.34 (m, 3H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.72 – 1.60 (m, 1H), 0.86 (d, J = 6.9 Hz, 3H).
143	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridin-2-amine 	N 450.9 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 12.87 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.01 – 7.91 (m, 1H), 7.86 – 7.79 (m, 1H), 7.74 (dd, J = 9.0, 2.4 Hz, 1H), 7.36 (br s, 2H), 6.68 (d, J = 9.0 Hz, 1H), 3.73 – 3.63 (m, 1H), 3.50 – 3.39 (m, 1H), 2.99 – 2.91 (m, 1H), 2.63 – 2.26 (m, 3H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.70 – 1.61 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).

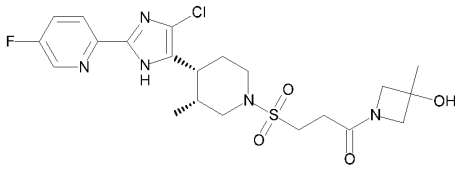
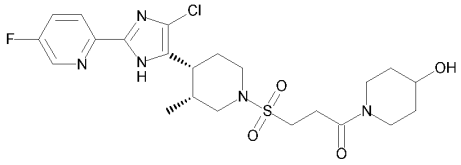
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
144	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-pyrimidin-2-amine 	N 492.0 [M+H]+ 2.08 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.65 – 8.58 (m, 2H), 8.51 (br s, 1H), 8.44 (d, J = 4.1 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.86 – 7.78 (m, 1H), 3.80 – 3.60 (m, 1H, overlapping water), 3.49 (s, 1H), 3.04 – 2.96 (m, 1H), 2.88 – 2.79 (m, 1H), 2.65 – 2.35 (m, 3H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.69 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H), 0.77 – 0.70 (m, 2H), 0.59 – 0.52 (m, 2H).
145	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyrrolidin-2-one 	N 456.0 [M+H]+ 1.68 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.6 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.21 – 4.10 (m, 1H), 3.82 – 3.74 (m, 1H), 3.74 – 3.66 (m, 1H), 3.60 – 3.49 (m, 2H), 3.18 – 3.07 (m, 2H), 3.00 – 2.90 (m, 1H), 2.80 – 2.70 (m, 4H), 2.54 – 2.39 (m, 2H, overlapping solvent), 2.15 – 2.05 (m, 1H), 1.67 – 1.58 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

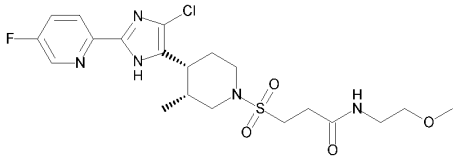
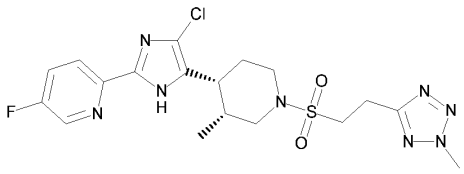
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
146	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-pyrimidin-2-amine 	N 466.0 [M+H]+ 1.96 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.58 (d, J = 3.1 Hz, 1H), 8.50 (d, J = 3.1 Hz, 1H), 8.22 – 8.16 (m, 1H), 8.02 – 7.92 (m, 1H), 7.86 – 7.78 (m, 1H), 3.73 – 3.66 (m, 1H), 3.51 – 3.43 (m, 1H), 3.03 – 2.95 (m, 1H), 2.88 (d, J = 4.8 Hz, 3H), 2.62 – 2.35 (m, 3H overlapping solvent), 2.17 – 2.09 (m, 1H), 1.69 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).
147	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N,N-bis(trideuteriomethyl)propenamide 	N 464.1 [M+H]+ 1.75 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.77 – 3.66 (m, 1H, overlapping water), 3.50 – 3.43 (m, 1H), 3.31 – 3.23 (m, 2H), 3.14 – 3.04 (m, 2H), 2.95 – 2.84 (m, 1H), 2.76 – 2.69 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.06 (m, 1H), 1.68 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

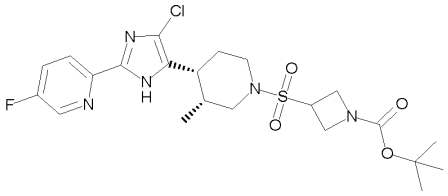
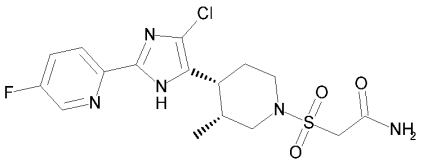
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
148	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-2-methyl-propyl)propenamide 	N 502.1 [M+H]+ 1.67 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.92 (t, J = 6.0 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.67 (m, 1H), 3.49 – 3.42 (m, 1H, partially overlapping water), 3.29 – 3.22 (m, 2H), 3.13 – 3.02 (m, 4H), 2.94 – 2.84 (m, 1H), 2.63 – 2.57 (m, 2H), 2.53 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.06 (m, 1H), 1.68 – 1.60 (m, 1H), 1.06 (s, 6H), 0.85 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.
149	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-propanamide 	N 470.0 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.09 (d, J = 4.1 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.65 (m, 1H, overlapping water), 3.48 – 3.41 (m, 1H), 3.28 – 3.21 (m, 2H), 3.13 – 3.02 (m, 2H), 2.92 – 2.82 (m, 1H), 2.67 – 2.58 (m, 1H), 2.54 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H), 0.65 – 0.58 (m, 2H), 0.43 – 0.36 (m, 2H).

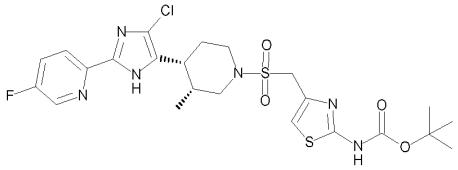
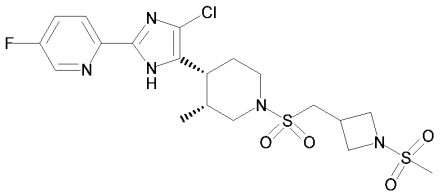
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
150	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-hydroxypyrrolidin-1-yl]propan-1-one 	N 500.0 [M+H]+ 1.60 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.36 – 4.22 (m, 1H, overlapping water), 3.75 – 3.66 (m, 1H), 3.60 – 3.24 (m, 7H), 3.14 – 3.04 (m, 2H), 2.95 – 2.84 (m, 1H), 2.72 – 2.60 (m, 2H), 2.52 – 2.38 (m, 1H, partially overlapping solvent), 2.16 – 2.07 (m, 1H), 2.01 – 1.70 (m, 2H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H). OH not observed due to fast exchange with water. Compound exists as a mixture of t-amide rotamers (ca. 1:1).

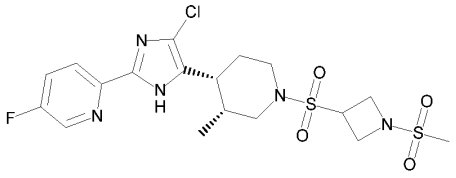
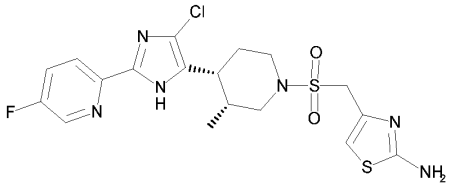
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
151	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-hydroxypyrrolidin-1-yl]propan-1-one 	N 500.0 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.36 – 4.22 (m, 1H), 3.75 – 3.66 (m, 1H, overlapping water), 3.60 – 3.23 (m, 7H, partially overlapping water), 3.14 – 3.04 (m, 2H), 2.95 – 2.84 (m, 1H), 2.73 – 2.59 (m, 2H), 2.53 – 2.39 (m, 1H, partially overlapping solvent), 2.16 – 2.07 (m, 1H), 2.00 – 1.70 (m, 2H), 1.67 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water. Compound exists as a mixture of t-amide rotamers (ca. 1:1).
152	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxyazetidin-1-yl)propan-1-one 	N 500.0 [M+H]+ 1.77 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.36 – 4.29 (m, 1H), 4.24 – 4.16 (m, 1H), 4.07 – 3.96 (m, 2H), 3.74 – 3.62 (m, 2H), 3.49 – 3.42 (m, 1H), 3.28 – 3.19 (m, 5H), 3.14 – 3.03 (m, 2H), 2.94 – 2.83 (m, 1H), 2.56 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

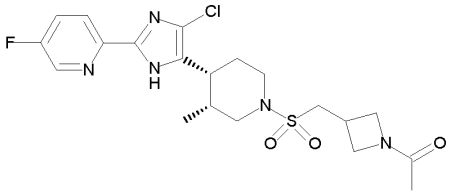
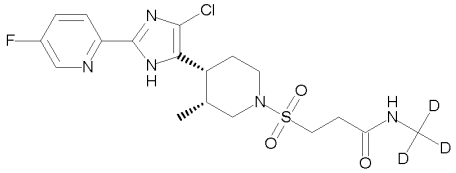
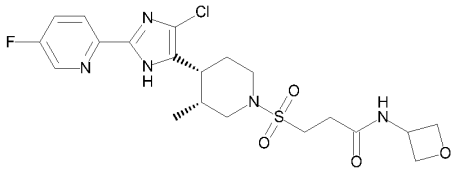
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
153	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxy-3-methyl-azetidin-1-yl)propan-1-one 	N 500.1 [M+H]+ 1.64 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.03 – 3.94 (m, 2H), 3.75 – 3.65 (m, 3H, overlapping water), 3.49 – 3.42 (m, 1H), 3.24 (t, J = 7.5 Hz, 2H), 3.14 – 3.03 (m, 2H), 2.94 – 2.83 (m, 1H), 2.56 – 2.40 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 1.37 (s, 3H), 0.85 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.
154	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-1-piperidyl)propan-1-one 	N 514.1 [M+H]+ 1.66 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.94 – 3.85 (m, 1H), 3.75 – 3.62 (m, 3H, overlapping water), 3.50 – 3.43 (m, 1H), 3.32 – 3.24 (m, 2H), 3.23 – 3.00 (m, 4H), 2.95 – 2.85 (m, 1H), 2.78 – 2.71 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.81 – 1.59 (m, 3H), 1.42 – 1.31 (m, 1H), 1.31 – 1.20 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.

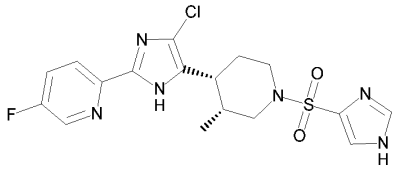
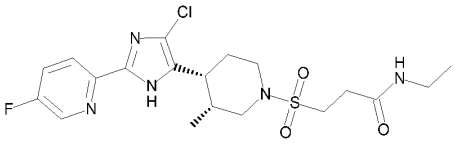
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
155	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxyethyl)propenamide 	N 488.0 [M+H]+ 1.70 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 3.0 Hz, 1H), 8.13 (t, J = 5.6 Hz, 1H), 8.03 – 7.97 (m, 1H), 7.86 – 7.79 (m, 1H), 3.73 – 3.65 (m, 1H), 3.48 – 3.41 (m, 1H), 3.38 – 3.32 (m, 2H), 3.29 – 3.20 (m, 7H), 3.13 – 3.03 (m, 2H), 2.93 – 2.83 (m, 1H), 2.58 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
156	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 469.0 [M+H]+ 1.85 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.34 (s, 3H), 3.79 – 3.70 (m, 1H, overlapping water), 3.55 – 3.45 (m, 3H), 3.31 – 3.23 (m, 2H), 3.14 – 3.05 (m, 2H), 2.96 – 2.85 (m, 1H), 2.55 – 2.40 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

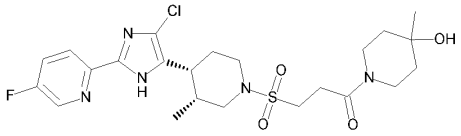
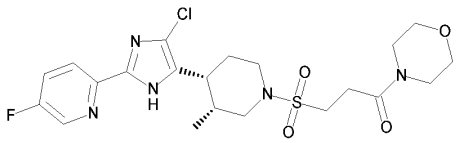
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
157	Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate 	N 514.1 [M+H]+ 2.30 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.34 – 4.24 (m, 1H), 4.23 – 4.12 (m, 2H), 4.03 – 3.93 (m, 2H), 3.78 – 3.70 (m, 1H), 3.52 – 3.45 (m, 1H), 3.12 – 3.03 (m, 2H), 2.93 – 2.82 (m, 1H), 2.54 – 2.37 (m, 1H, overlapping solvent), 2.15 – 2.05 (m, 1H), 1.66 – 1.58 (m, 1H), 1.40 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H).
158	2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetamide 	N 416.0 [M+H]+ 1.53 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.6 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.65 (br s, 1H), 7.37 (br s, 1H), 3.92 (s, 2H), 3.76 – 3.68 (m, 1H), 3.53 – 3.36 (m, 1H, overlapping water), 3.15 – 3.03 (m, 2H), 2.98 – 2.88 (m, 1H), 2.56 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.70 – 1.61 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

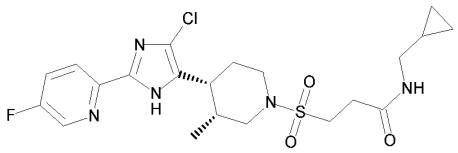
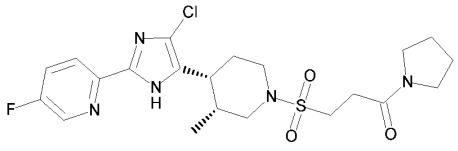
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
159	Tert-butyl N-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-yl]carbamate 	N 571.0 [M+H]+ 2.36 min	(400 MHz, DMSO-d6) δ 12.87 (br s, 1H), 11.56 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.17 (s, 1H), 4.39 (s, 2H), 3.67 – 3.59 (m, 1H, partially overlapping water), 3.41 – 3.34 (m, 1H, partially overlapping water), 3.12 – 3.04 (m, 1H), 3.03 – 2.96 (m, 1H), 2.94 – 2.83 (m, 1H), 2.48 – 2.35 (m, 1H), 2.12 – 2.01 (m, 1H), 1.63 – 1.56 (m, 1H), 1.49 (s, 9H), 0.80 (d, J = 7.0 Hz, 3H).
160	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonylazetidin-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 506.0 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 4.02 – 3.94 (m, 2H), 3.77 – 3.67 (m, 3H), 3.50 – 3.40 (m, 3H, overlapping water), 3.14 – 2.99 (m, 6H), 2.94 – 2.82 (m, 1H), 2.56 – 2.39 (m, 1H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.69 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

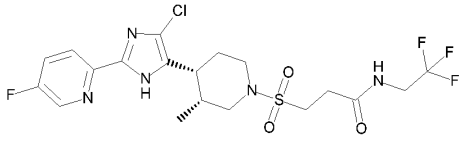
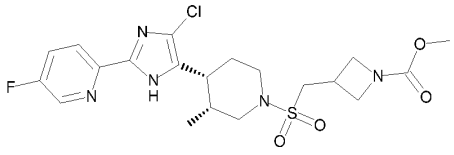
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
161	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylazetidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 492.0 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.45 – 4.35 (m, 1H), 4.25 – 4.16 (m, 2H), 4.15 – 4.07 (m, 2H), 3.81 – 3.73 (m, 1H), 3.56 – 3.47 (m, 1H, overlapping water), 3.13 – 3.04 (m, 5H), 2.94 – 2.84 (m, 1H), 2.56 – 2.38 (m, 1H, overlapping solvent), 2.15 – 2.06 (m, 1H), 1.67 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
162	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-amine 	N 470.8 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 12.88 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.30 – 7.50 (m, 4H), 6.75 (s, 1H), 4.33 (s, 2H), 3.72 – 3.65 (m, 1H, overlapping water), 3.46 – 3.39 (m, 1H), 3.11 – 3.01 (m, 2H), 2.94 – 2.83 (m, 1H), 2.52 – 2.36 (m, 1H, partially overlapping solvent), 2.14 – 2.04 (m, 1H), 1.67 – 1.57 (m, 1H), 0.82 (d, J = 7.0 Hz, 3H).

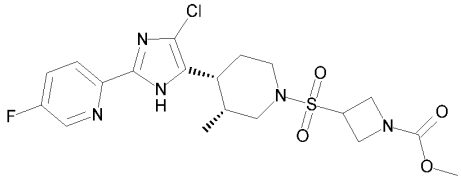
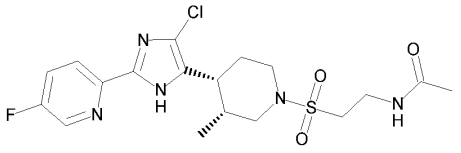
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
163	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidin-1-yl]ethenone 	N 470.0 [M+H]+ 1.69 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.28 – 4.21 (m, 1H), 4.00 – 3.91 (m, 2H), 3.75 – 3.40 (m, 5H, overlapping water), 3.14 – 2.94 (m, 3H), 2.92 – 2.82 (m, 1H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.73 (s, 3H), 1.69 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
164	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(trideuteriomethyl)propenamide 	N 447.0 [M+H]+ 1.62 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.94 (br s, 1H), 7.86 – 7.79 (m, 1H), 3.73 – 3.65 (m, 1H), 3.48 – 3.40 (m, 1H, overlapping water), 3.29 – 3.22 (m, 2H), 3.13 – 3.02 (m, 2H), 2.92 – 2.82 (m, 1H), 2.55 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
165	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-yl)propenamide 	N 486.0 [M+H]+ 1.62 min	n/a

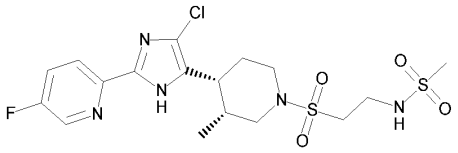
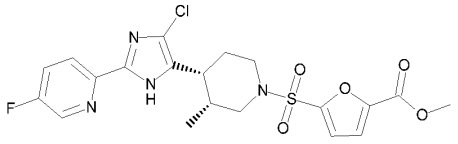
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
166	2-[4-Chloro-5-[(3R,4R)-1-(1H-imidazol-4-ylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 425.0 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 7.98 (dd, J = 8.8, 4.5 Hz, 1H), 7.92 (d, J = 1.2 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.78 (d, J = 1.2 Hz, 1H), 3.77 – 3.70 (m, 1H, partially overlapping water), 3.53 – 3.45 (m, 1H), 2.97 – 2.89 (m, 1H), 2.71 – 2.62 (m, 1H), 2.55 – 2.40 (m, 2H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.70 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). Terminal imidazole NH not observed due to fast exchange with water.
167	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-ethyl-propanamide 	N 458.0 [M+H]+ 1.74 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.06 – 7.97 (m, 2H), 7.86 – 7.79 (m, 1H), 3.74 – 3.65 (m, 1H), 3.49 – 3.42 (m, 1H, partially overlapping water), 3.29 – 3.21 (m, 2H), 3.14 – 3.02 (m, 4H), 2.93 – 2.82 (m, 1H), 2.56 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 1.03 (t, J = 7.3 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H).

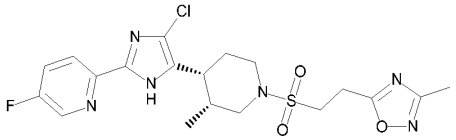
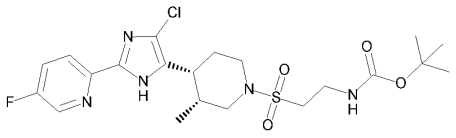
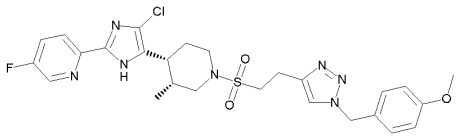
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
168	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-4-methyl-1-piperidyl)propan-1-one 	N 528.1 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.00 – 3.91 (m, 1H), 3.75 – 3.67 (m, 1H), 3.62 – 3.43 (m, 2H, overlapping water), 3.39 – 3.24 (m, 3H), 3.14 – 3.00 (m, 3H), 2.95 – 2.85 (m, 1H), 2.78 – 2.70 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 1.54 – 1.41 (m, 3H), 1.38 – 1.27 (m, 1H), 1.13 (s, 3H), 0.85 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water .
169	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-morpholino-propan-1-one 	N 500.0 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.5, 4.8 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.75 – 3.67 (m, 1H), 3.62 – 3.53 (m, 4H), 3.50 – 3.39 (m, 5H, overlapping water), 3.32 – 3.25 (m, 2H), 3.14 – 3.05 (m, 2H), 2.96 – 2.85 (m, 1H), 2.80 – 2.72 (m, 2H), 2.52 – 2.39 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

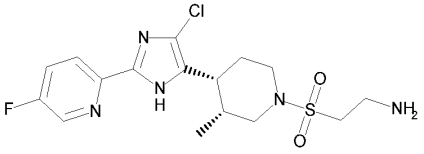
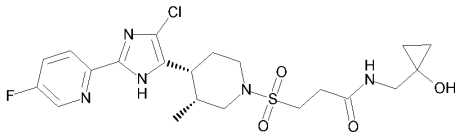
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
170	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(cyclopropylmethyl)propenamide 	N 484.1 [M+H]+ 1.91 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.13 (t, J = 5.7 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.65 (m, 1H), 3.52 – 3.36 (m, 1H, overlapping water), 3.29 – 3.22 (m, 2H), 3.12 – 3.03 (m, 2H), 2.99 – 2.93 (m, 2H), 2.93 – 2.83 (m, 1H), 2.57 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.68 – 1.59 (m, 1H), 0.95 – 0.81 (m, 4H), 0.45 – 0.38 (m, 2H), 0.19 – 0.12 (m, 2H).
171	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-pyrrolidin-1-yl-propan-1-one 	N 484.1 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.75 – 3.66 (m, 1H), 3.51 – 3.40 (m, 3H, partially overlapping water), 3.34 – 3.24 (m, 4H), 3.14 – 3.04 (m, 2H), 2.95 – 2.84 (m, 1H), 2.70 – 2.63 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.94 – 1.83 (m, 2H), 1.83 – 1.72 (m, 2H), 1.68 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

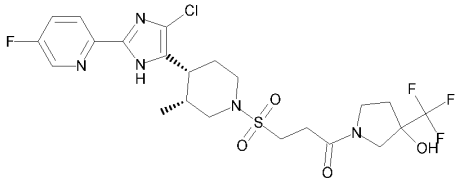
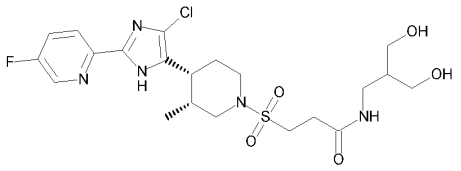
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
172	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2,2,2-trifluoroethyl)propenamide 	N 512.0 [M+H]+ 1.94 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.72 (t, J = 6.4 Hz, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.00 – 3.88 (m, 2H), 3.74 – 3.66 (m, 1H), 3.49 – 3.41 (m, 1H, partially overlapping water), 3.32 – 3.25 (m, 2H, partially overlapping water), 3.13 – 3.03 (m, 2H), 2.94 – 2.83 (m, 1H), 2.68 – 2.60 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
173	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate 	N 486.1 [M+H]+ 1.91 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.11 – 3.95 (m, 2H), 3.84 – 3.65 (m, 3H), 3.55 (s, 3H), 3.48 – 3.40 (m, 3H, overlapping water), 3.13 – 2.95 (m, 3H), 2.91 – 2.80 (m, 1H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

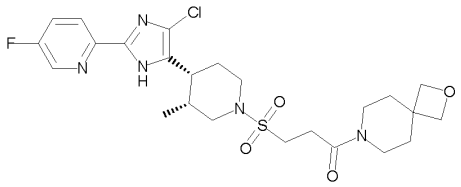
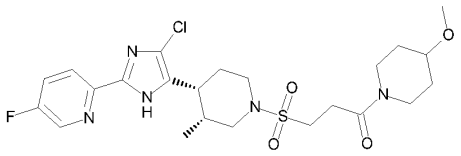
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
174	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate 	N 472.1 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.38 – 4.19 (m, 3H), 4.11 – 3.98 (m, 2H), 3.79 – 3.71 (m, 1H), 3.60 (s, 3H), 3.53 – 3.45 (m, 1H, overlapping water), 3.13 – 3.04 (m, 2H), 2.94 – 2.83 (m, 1H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.14 – 2.05 (m, 1H), 1.66 – 1.58 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H).
175	N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]acetamide 	N 444.0 [M+H]+ 1.62 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.06 (t, J = 5.7 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.75 – 3.55 (m, 1H, overlapping water), 3.49 – 3.36 (m, 3H), 3.19 – 3.13 (m, 2H), 3.13 – 3.02 (m, 2H), 2.92 – 2.81 (m, 1H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.82 (s, 3H), 1.69 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

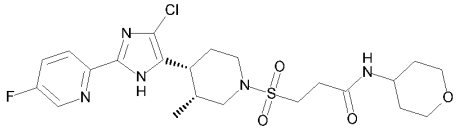
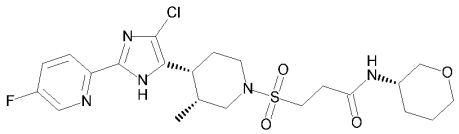
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
176	N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]methanesulfonamide 	N 480.0 [M+H]+ 1.71 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.23 (t, J = 5.8 Hz, 1H), 3.76 – 3.68 (m, 1H, partially overlapping water), 3.50 – 3.43 (m, 1H, partially overlapping water), 3.38 – 3.30 (m, 2H), 3.28 – 3.21 (m, 2H), 3.15 – 3.05 (m, 2H), 2.97 (s, 3H), 2.95 – 2.85 (m, 1H), 2.54 – 2.39 (m, 1H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.70 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
177	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylate 	N 480.9 [M-H]- 2.22 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 7.98 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.35 (d, J = 3.7 Hz, 1H), 3.88 (s, 3H), 3.83 – 3.75 (m, 1H), 3.65 – 3.50 (m, 1H, overlapping water), 3.11 – 3.02 (m, 1H), 2.95 – 2.86 (m, 1H), 2.80 – 2.67 (m, 1H), 2.60 – 2.42 (m, 1H, overlapping solvent), 2.20 – 2.11 (m, 1H), 1.73 – 1.64 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

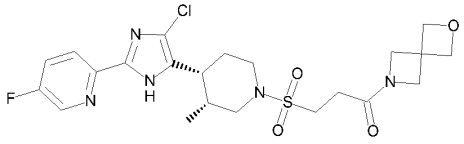
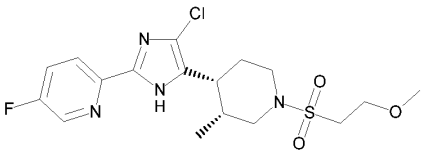
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
178	5-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-3-methyl-1,2,4-oxadiazole 	N 469.0 [M+H]+ 1.94 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.76 – 3.68 (m, 1H, partially overlapping water), 3.60 – 3.53 (m, 2H, partially overlapping water), 3.51 – 3.44 (m, 1H), 3.36 – 3.29 (m, 2H), 3.14 – 3.06 (m, 2H), 2.98 – 2.87 (m, 1H), 2.55 – 2.39 (m, 1H, overlapping solvent), 2.33 (s, 3H), 2.16 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
179	Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]carbamate 	N 502.1 [M+H]+ 2.21 min	n/a
180	2-[4-Chloro-5-[(3R,4R)-1-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 574.1 [M+H]+ 2.15 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.02 – 7.96 (m, 2H), 7.86 – 7.78 (m, 1H), 7.32 – 7.26 (m, 2H), 6.95 – 6.90 (m, 2H), 5.48 (s, 2H), 3.75 – 3.66 (m, 4H), 3.50 – 3.33 (m, 3H, overlapping water), 3.08 – 2.99 (m, 4H), 2.86 – 2.74 (m, 1H), 2.54 – 2.37 (m, 1H overlapping solvent), 2.14 – 2.05 (m, 1H), 1.64 – 1.55 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

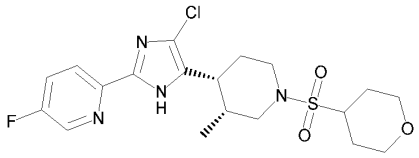
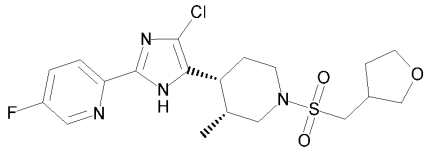
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
181	2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethanamine 	N 402.1 [M+H]+ 1.21 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.04 – 7.95 (m, 3H), 7.87 – 7.79 (m, 1H), 3.77 – 3.69 (m, 1H), 3.52 – 3.44 (m, 1H), 3.23 – 3.08 (m, 4H), 3.00 – 2.89 (m, 1H), 2.57 – 2.47 (m, 3H, overlapping solvent), 2.20 – 2.10 (m, 1H), 1.73 – 1.64 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).
182	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(1-hydroxycyclopropyl)methyl]propenamide 	N 500.1 [M+H]+ 1.66 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.08 (t, J = 5.7 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.66 (m, 1H, overlapping water), 3.49 – 3.42 (m, 1H), 3.30 – 3.19 (m, 4H), 3.14 – 3.02 (m, 2H), 2.94 – 2.84 (m, 1H), 2.61 – 2.54 (m, 2H), 2.53 – 2.38 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H), 0.57 – 0.44 (m, 4H). OH not observed due to fast exchange with water.

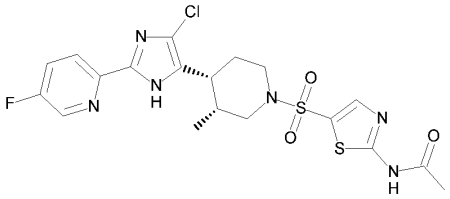
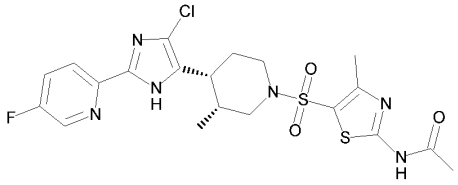
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
183	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]propan-1-one 	N 568.1 [M+H]+ 1.93 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 6.50 (br s, 1H), 3.85 – 3.37 (m, 6H, partially overlapping water), 3.34 – 3.24 (m, 2H), 3.14 – 3.05 (m, 2H), 2.96 – 2.85 (m, 1H), 2.80 – 2.64 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.27 – 1.94 (m, 3H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H).
184	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-ylmethyl)propenamide 	N 518.1 [M+H]+ 1.29 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 7.71 (br s, 2H), 4.94 (br s, 1H), 4.16 – 4.04 (m, 2H), 3.75 – 3.67 (m, 1H), 3.57 – 3.27 (m, 5H, overlapping water), 3.16 – 3.06 (m, 2H), 2.98 – 2.82 (m, 3H), 2.81 – 2.74 (m, 2H), 2.56 – 2.40 (m, 1H, overlapping solvent), 2.18 – 2.04 (m, 2H), 1.70 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

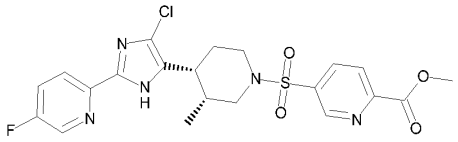
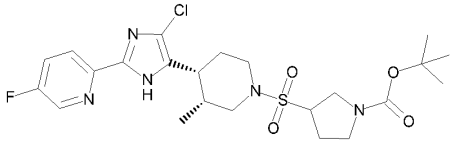
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
185	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-7-azaspiro[3.5]nonan-7-yl)propan-1-one 	N 540.2 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 4.36 – 4.29 (m, 4H), 3.74 – 3.66 (m, 1H, partially overlapping water), 3.49 – 3.43 (m, 1H, partially overlapping water), 3.43 – 3.32 (m, 4H), 3.31 – 3.23 (m, 2H), 3.13 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.78 – 2.71 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.83 – 1.77 (m, 2H), 1.74 – 1.68 (m, 2H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
186	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-methoxy-1-piperidyl)propan-1-one 	N 528.1 [M+H]+ 1.92 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.82 (td, J = 8.8, 2.9 Hz, 1H), 3.87 – 3.55 (m, 3H, overlapping water), 3.50 – 3.36 (m, 2H), 3.32 – 3.04 (m, 9H), 2.95 – 2.85 (m, 1H), 2.79 – 2.72 (m, 2H), 2.54 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.91 – 1.73 (m, 2H), 1.68 – 1.59 (m, 1H), 1.51 – 1.27 (m, 2H), 0.84 (d, J = 7.0 Hz, 3H).

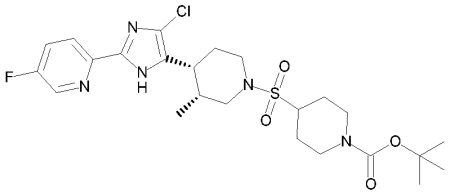
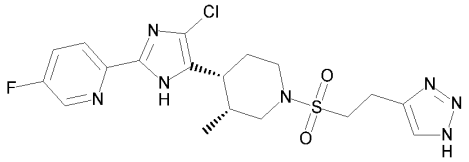
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
187	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-tetrahydropyran-4-yl-propanamide 	N 514.1 [M+H]+ 1.73 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.06 – 7.97 (m, 2H), 7.86 – 7.79 (m, 1H), 3.86 – 3.65 (m, 4H), 3.49 – 3.42 (m, 1H, partially overlapping water), 3.40 – 3.30 (m, 2H), 3.29 – 3.22 (m, 2H), 3.12 – 3.03 (m, 2H), 2.93 – 2.83 (m, 1H), 2.56 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.75 – 1.59 (m, 3H), 1.45 – 1.32 (m, 2H), 0.84 (d, J = 7.0 Hz, 3H).
188	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3S)-tetrahydropyran-3-yl]propenamide 	N 514.1 [M+H]+ 1.79 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.86 – 7.79 (m, 1H), 3.74 – 3.61 (m, 4H), 3.49 – 3.41 (m, 1H), 3.40 – 3.30 (m, 1H), 3.29 – 3.21 (m, 2H), 3.14 – 3.02 (m, 3H), 2.93 – 2.82 (m, 1H), 2.59 – 2.37 (m, 3H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.87 – 1.78 (m, 1H), 1.73 – 1.59 (m, 2H), 1.56 – 1.37 (m, 2H), 0.84 (d, J = 7.0 Hz, 3H).

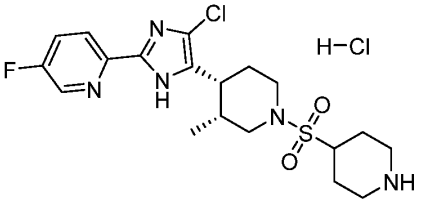
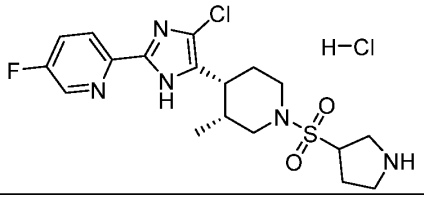
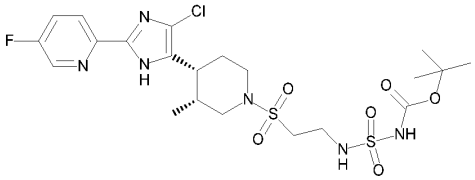
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
189	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propan-1-one 	N 512.1 [M+H]+ 1.67 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 4.70 – 4.63 (m, 4H), 4.33 (s, 2H), 4.03 (s, 2H), 3.73 – 3.65 (m, 1H, partially overlapping water), 3.51 – 3.41 (m, 1H, partially overlapping water), 3.25 – 3.18 (m, 2H), 3.13 – 3.02 (m, 2H), 2.93 – 2.82 (m, 1H), 2.53 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.06 (m, 1H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
190	2-[4-Chloro-5-[(3R,4R)-1-(2-methoxyethylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 417.1 [M+H]+ 1.88 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.73 – 3.64 (m, 3H), 3.48 – 3.38 (m, 1H, overlapping water), 3.35 – 3.28 (m, 5H), 3.12 – 2.99 (m, 2H), 2.89 – 2.79 (m, 1H), 2.55 – 2.39 (m, 1H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

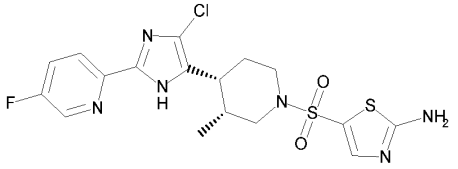
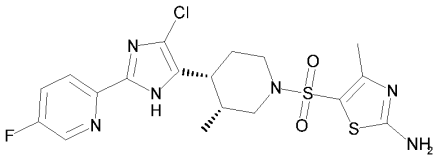
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
191	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydropyran-4-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 443.1 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 3.97 – 3.89 (m, 2H), 3.80 – 3.72 (m, 1H), 3.55 – 3.48 (m, 1H), 3.47 – 3.30 (m, 3H, overlapping water), 3.23 – 3.08 (m, 2H), 3.06 – 2.94 (m, 1H), 2.56 – 2.39 (m, 1H, overlapping solvent), 2.13 – 2.02 (m, 1H), 1.92 – 1.83 (m, 2H), 1.71 – 1.55 (m, 3H), 0.84 (d, J = 7.0 Hz, 3H).
192	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(tetrahydrofuran-3-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 443.1 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.90 – 3.82 (m, 1H), 3.79 – 3.61 (m, 3H), 3.52 – 3.38 (m, 2H, overlapping water), 3.24 – 3.00 (m, 4H), 2.92 – 2.80 (m, 1H), 2.64 – 2.38 (m, 2H, overlapping solvent), 2.17 – 2.05 (m, 2H), 1.74 – 1.60 (m, 2H), 0.85 (d, J = 7.0 Hz, 3H).

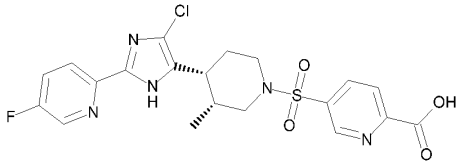
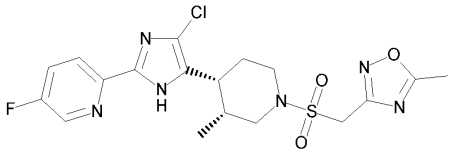
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
193	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]acetamide 	N 499.0 [M+H]+ 1.98 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 12.74 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.92 (m, 2H), 7.86 – 7.78 (m, 1H), 3.80 – 3.68 (m, 1H, overlapping water), 3.53 – 3.46 (m, 1H), 3.03 – 2.95 (m, 1H), 2.70 – 2.60 (m, 1H), 2.57 – 2.39 (m, 2H, overlapping solvent), 2.24 – 2.12 (m, 4H), 1.73 – 1.64 (m, 1H), 0.88 (d, J = 7.0 Hz, 3H).
194	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-yl]acetamide 	N 513.0 [M+H]+ 2.04 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 12.62 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.03 – 7.93 (m, 1H), 7.86 – 7.78 (m, 1H), 3.80 – 3.71 (m, 1H), 3.64 – 3.42 (m, 1H, overlapping water), 3.05 – 2.96 (m, 1H), 2.78 – 2.68 (m, 1H), 2.64 – 2.41 (m, 5H, overlapping solvent), 2.21 – 2.10 (m, 4H), 1.73 – 1.63 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).

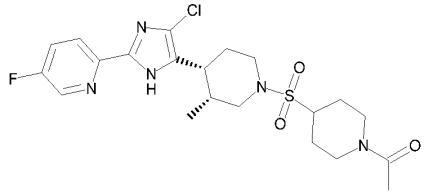
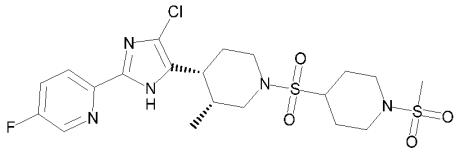
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
195	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylate 	N 494.1 [M+H]+ 2.05 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 9.04 (dd, J = 2.3, 0.8 Hz, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.36 (dd, J = 8.2, 2.3 Hz, 1H), 8.29 (dd, J = 8.2, 0.8 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.85 – 7.77 (m, 1H), 3.95 (s, 3H), 3.86 – 3.78 (m, 1H, partially overlapping water), 3.68 – 3.53 (m, 1H, overlapping water), 3.02 – 2.93 (m, 1H), 2.71 – 2.61 (m, 1H), 2.58 – 2.42 (m, 2H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.70 – 1.60 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).
196	Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxylate 	N 528.1 [M+H]+ 2.34 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.07 – 3.40 (m, 6H, overlapping water), 3.55 – 3.40 (m, 2H), 3.32 – 3.20 (m, 1H), 3.20 – 3.08 (m, 2H), 3.02 – 2.89 (m, 1H), 2.55 – 2.38 (m, 1H, overlapping solvent), 2.30 – 2.04 (m, 3H), 1.68 – 1.59 (m, 1H), 1.41 (d, J = 0.9 Hz, 9H), 0.84 (dd, J = 7.1, 1.2 Hz, 3H).

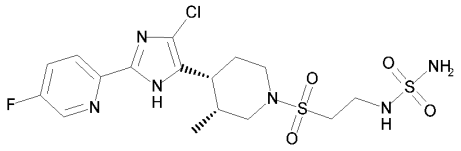
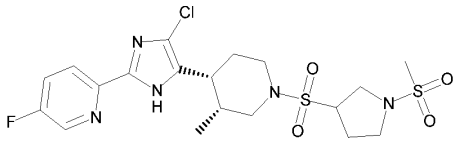
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
197	Tert-butyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]piperidine-1-carboxylate 	N 542.1 [M+H]+ 2.42 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.06 – 3.99 (m, 1H), 3.80 – 3.30 (m, 4H, overlapping water), 3.23 – 3.16 (m, 1H), 3.16 – 3.08 (m, 1H), 3.05 – 2.94 (m, 1H), 2.78 (s, 2H), 2.55 – 2.37 (m, 1H, overlapping solvent), 2.12 – 2.03 (m, 1H), 2.01 – 1.92 (m, 2H), 1.63 – 1.55 (m, 1H), 1.51 – 1.37 (m, 11H), 0.84 (d, J = 7.0 Hz, 3H).
198	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1H-triazol-4-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 454.0 [M+H]+ 1.69 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.77 (s, 1H), 3.78 – 3.70 (m, 1H), 3.53 – 3.45 (m, 1H), 3.44 – 3.36 (m, 2H), 3.13 – 3.04 (m, 4H), 2.95 – 2.84 (m, 1H), 2.55 – 2.40 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H). Triazole NH not observed due to fast exchange with water.

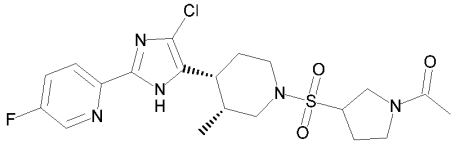
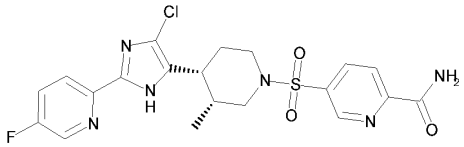
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
199	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(4-piperidylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride) 	N 442.0 [M+H]+ 1.25 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 11.54 (br s, 1H), 10.75 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 3.80 – 3.72 (m, 1H), 3.54 – 3.45 (m, 3H, overlapping water), 3.41 – 3.33 (m, 1H), 3.25 – 3.18 (m, 1H), 3.13 (d, J = 13.3 Hz, 1H), 3.07 – 2.85 (m, 3H), 2.55 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.05 (m, 3H), 1.92 – 1.78 (m, 2H), 1.67 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
200	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-pyrrolidin-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride) 	N 428.0 [M+H]+ 1.23 min	n/a
201	Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethylsulfamoyl]carbamate 	N 581.0 [M+H]+ 2.11 min	n/a

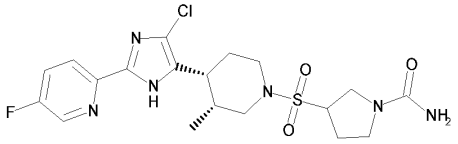
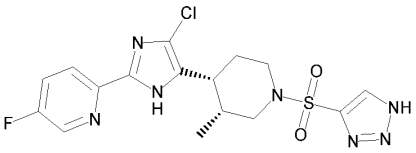
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
202	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-amine 	N 456.9 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 12.87 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.03 – 7.88 (m, 3H), 7.86 – 7.79 (m, 1H), 7.46 (s, 1H), 3.80 – 3.62 (m, 1H), 3.48 – 3.39 (m, 1H, overlapping water), 3.05 – 2.97 (m, 1H), 2.71 – 2.60 (m, 1H), 2.58 – 2.38 (m, 2H, overlapping solvent), 2.21 – 2.11 (m, 1H), 1.75 – 1.63 (m, 1H), 0.86 (d, J = 6.9 Hz, 3H).
203	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-amine 	N 471.0 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.03 – 7.94 (m, 1H), 7.87 – 7.70 (m, 3H), 3.80 – 3.55 (m, 1H, overlapping water), 3.50 – 3.43 (m, 1H), 3.07 – 2.98 (m, 1H), 2.77 – 2.67 (m, 1H), 2.65 – 2.38 (m, 2H, overlapping solvent), 2.32 (s, 3H), 2.20 – 2.10 (m, 1H), 1.73 – 1.63 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).

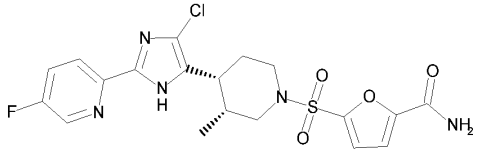
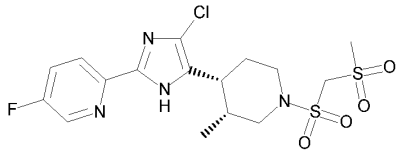
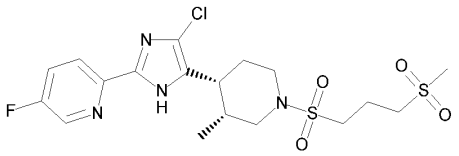
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
204	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylic acid 	N 480.0 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 9.02 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.34 (dd, J = 8.2, 2.2 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.03 – 7.92 (m, 1H), 7.86 – 7.77 (m, 1H), 3.86 – 3.77 (m, 1H), 3.67 – 3.46 (m, 1H, overlapping water), 3.02 – 2.94 (m, 1H), 2.72 – 2.61 (m, 1H), 2.58 – 2.40 (m, 2H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.70 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). COOH not observed due to fast exchange with water.
205	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]-5-methyl-1,2,4-oxadiazole 	N 455.0 [M+H]+ 1.90 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 4.68 (s, 2H), 3.76 – 3.69 (m, 1H), 3.51 – 3.42 (m, 1H, overlapping water), 3.14 – 3.05 (m, 2H), 2.97 – 2.86 (m, 1H), 2.64 (s, 3H), 2.57 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.61 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H).

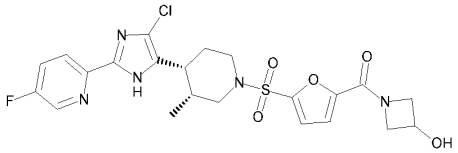
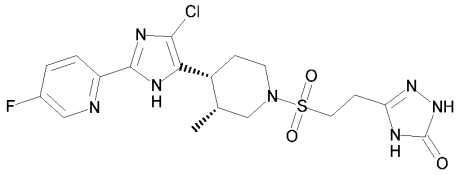
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
206	1-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-piperidyl]ethenone 	N 484.0 [M+H]+ 1.75 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.51 – 4.42 (m, 1H), 3.94 – 3.86 (m, 1H), 3.80 – 3.39 (m, 3H, overlapping water), 3.24 – 2.95 (m, 4H), 2.62 – 2.36 (m, 2H, overlapping solvent), 2.14 – 1.93 (m, 6H), 1.65 – 1.51 (m, 2H), 1.48 – 1.32 (m, 1H), 0.84 (d, J = 6.9 Hz, 3H).
207	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonyl-4-piperidyl)sulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 520.0 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.81 – 3.73 (m, 1H), 3.71 – 3.63 (m, 2H), 3.61 – 3.48 (m, 1H, overlapping water), 3.37 – 3.27 (m, 1H), 3.25 – 3.18 (m, 1H), 3.17 – 3.09 (m, 1H), 3.07 – 2.97 (m, 1H), 2.89 (s, 3H), 2.84 – 2.74 (m, 2H), 2.56 – 2.38 (m, 1H, overlapping solvent), 2.13 – 2.04 (m, 3H), 1.71 – 1.56 (m, 3H), 0.84 (d, J = 7.0 Hz, 3H).

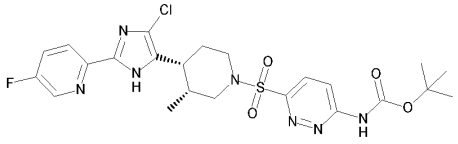
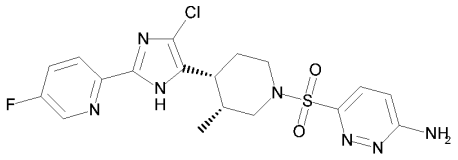
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
208	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(sulfamoylamino)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 481.0 [M+H]+ 1.61 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 6.80 – 6.60 (m, 3H), 3.75 – 3.61 (m, 1H, overlapping water), 3.50 – 3.43 (m, 1H), 3.27 (s, 4H), 3.14 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.55 – 2.39 (m, 1H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.70 – 1.62 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
209	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylpyrrolidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 506.0 [M+H]+ 1.86 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.14 – 4.03 (m, 1H, partially overlapping water), 3.80 – 3.73 (m, 1H, partially overlapping water), 3.73 – 3.63 (m, 1H), 3.54 – 3.47 (m, 1H), 3.46 – 3.35 (m, 2H), 3.34 – 3.25 (m, 1H), 3.22 – 3.09 (m, 2H), 3.04 – 2.91 (m, 4H), 2.54 – 2.39 (m, 1H, overlapping solvent), 2.37 – 2.26 (m, 1H), 2.24 – 2.06 (m, 2H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

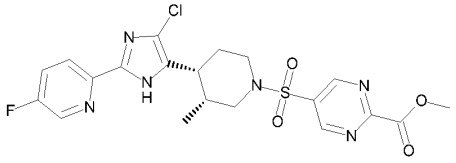
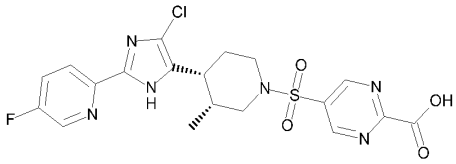
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
210	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidin-1-yl]ethenone 	N 470.1 [M+H]+ 1.71 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.13 – 3.23 (m, 7H, overlapping water), 3.21 – 3.08 (m, 2H), 3.04 – 2.90 (m, 1H), 2.56 – 2.39 (m, 1H, overlapping solvent), 2.39 – 2.04 (m, 3H), 2.00 – 1.93 (m, 3H), 1.68 – 1.59 (m, 1H), 0.88 – 0.81 (m, 3H). Compound exists as a mixture of t-amide rotamers.
211	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxamide 	N 479.0 [M+H]+ 1.87 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.93 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.38 – 8.24 (m, 3H), 8.04 – 7.77 (m, 3H), 3.86 – 3.54 (m, 2H, overlapping water), 3.03 – 2.94 (m, 1H), 2.74 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.08 (m, 1H), 1.72 – 1.59 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).

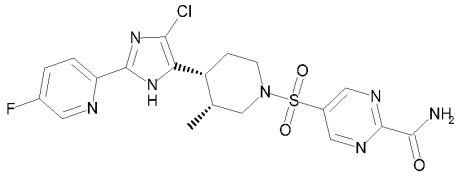
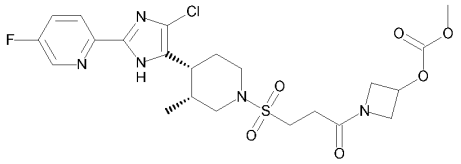
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
212	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxamide 	N 471.1 [M+H]+ 2.30 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 5.86 (br s, 2H), 4.05 – 3.70 (m, 2H, overlapping water), 3.65 – 3.56 (m, 1H), 3.54 – 3.39 (m, 3H), 3.28 – 3.19 (m, 1H), 3.18 – 3.08 (m, 2H), 3.01 – 2.89 (m, 1H), 2.56 – 2.39 (m, 1H, overlapping solvent), 2.30 – 2.20 (m, 1H), 2.18 – 2.05 (m, 2H), 1.67 – 1.59 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H).
213	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 426.1 [M+H]+ 1.76 min	(400 MHz, DMSO-d6) δ 16.08 (br s, 1H), 12.89 (br s, 1H), 8.78 (br s, 1H), 8.60 (d, J = 3.0 Hz, 1H), 8.03 – 7.93 (m, 1H), 7.86 – 7.78 (m, 1H), 3.86 – 3.68 (m, 1H, overlapping water), 3.58 – 3.51 (m, 1H), 3.03 – 2.95 (m, 1H), 2.74 – 2.65 (m, 1H), 2.60 – 2.44 (m, 2H, overlapping solvent), 2.20 – 2.10 (m, 1H), 1.72 – 1.62 (m, 1H), 0.88 (d, J = 7.0 Hz, 3H).

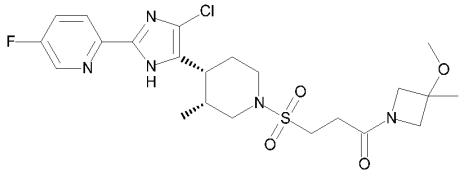
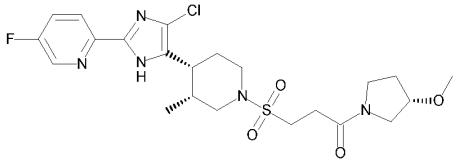
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
214	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxamide 	N 468.0 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 12.90 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.04 (s, 1H), 8.02 – 7.93 (m, 1H), 7.86 – 7.78 (m, 1H), 7.74 (s, 1H), 7.30 (d, J = 3.7 Hz, 1H), 7.27 (d, J = 3.7 Hz, 1H), 3.83 – 3.75 (m, 1H), 3.65 – 3.45 (m, 1H, overlapping water), 3.11 – 3.02 (m, 1H), 2.94 – 2.85 (m, 1H), 2.81 – 2.65 (m, 1H), 2.57 – 2.40 (m, 1H overlapping solvent), 2.20 – 2.10 (m, 1H), 1.74 – 1.64 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
215	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(methylsulfonylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 451.0 [M+H]+ 1.77 min	n/a
216	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-methylsulfonylpropylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 479.0 [M+H]+ 1.73 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.77 – 3.68 (m, 1H), 3.52 – 3.44 (m, 1H), 3.31 – 3.18 (m, 4H), 3.15 – 3.04 (m, 2H), 3.02 (s, 3H), 2.94 – 2.83 (m, 1H), 2.55 – 2.39 (m, 1H, overlapping solvent), 2.18 – 2.05 (m, 3H), 1.70 – 1.62 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).

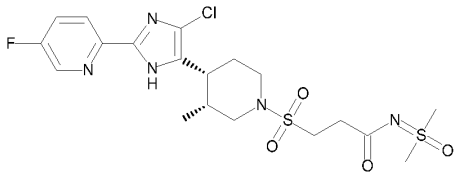
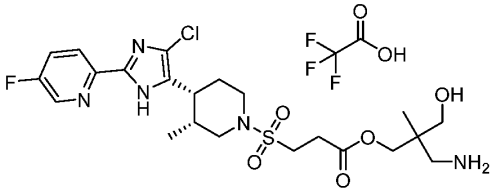
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
217	[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-furyl]-(3-hydroxyazetidin-1-yl)methanone 	N 524.0 [M+H]+ 1.81 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.03 – 7.94 (m, 1H), 7.86 – 7.77 (m, 1H), 7.29 (d, J = 3.7 Hz, 1H), 7.24 – 7.19 (m, 1H), 4.73 – 4.65 (m, 1H), 4.59 – 4.51 (m, 1H), 4.30 – 4.18 (m, 2H), 3.83 – 3.73 (m, 2H), 3.60 – 3.46 (m, 1H, partially overlapping water), 3.11 – 3.04 (m, 1H), 2.94 – 2.85 (m, 1H), 2.79 – 2.64 (m, 1H), 2.60 – 2.42 (m, 1H, overlapping solvent), 2.20 – 2.11 (m, 1H), 1.74 – 1.62 (m, 1H), 0.86 (d, J = 6.8 Hz, 3H). OH not observed due to fast exchange with water.
218	3-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-1,4-dihydro-1,2,4-triazol-5-one 	N 470.0 [M+H]+ 1.53 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 11.26 (br s, 1H), 11.23 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.76 – 3.68 (m, 1H, partially overlapping water), 3.51 – 3.44 (m, 1H, partially overlapping water), 3.41 – 3.33 (m, 2H), 3.14 – 3.04 (m, 2H), 2.96 – 2.78 (m, 3H), 2.56 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

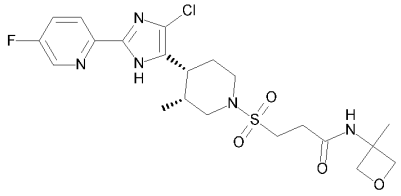
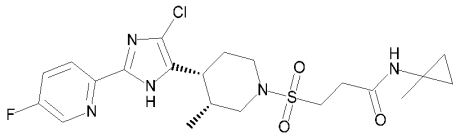
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
219	Tert-butyl N-[6-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-yl]carbamate 	N 552.1 [M+H]+ 2.40 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 11.07 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.33 (d, J = 9.4 Hz, 1H), 8.09 (d, J = 9.4 Hz, 1H), 8.04 – 7.92 (m, 1H), 7.86 – 7.78 (m, 1H), 3.91 – 3.81 (m, 1H), 3.66 – 3.56 (m, 1H), 3.08 – 2.99 (m, 1H), 2.97 – 2.86 (m, 1H), 2.81 – 2.67 (m, 1H), 2.60 – 2.42 (m, 1H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.72 – 1.61 (m, 1H), 1.51 (s, 9H), 0.86 (d, J = 7.0 Hz, 3H).
220	6-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-amine 	N 552.1 [M+H]+ 2.40 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.94 (m, 1H), 7.87 – 7.79 (m, 1H), 7.67 (d, J = 9.3 Hz, 1H), 7.34 (br s, 2H), 6.94 (d, J = 9.3 Hz, 1H), 3.85 – 3.72 (m, 1H, overlapping water), 3.60 – 3.52 (m, 1H, partially overlapping water), 3.06 – 2.97 (m, 1H), 2.90 – 2.82 (m, 1H), 2.76 – 2.61 (m, 1H), 2.57 – 2.39 (m, 1H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.71 – 1.61 (m, 1H), 0.86 (d, J = 6.9 Hz, 3H).

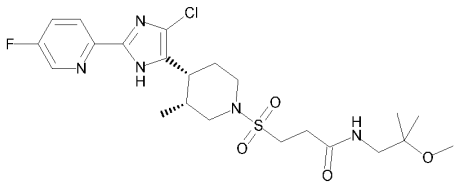
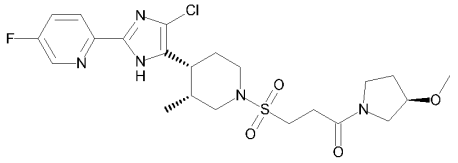
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
221	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylate 	N 495.1 [M+H]+ 1.96 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 9.33 (s, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.94 (m, 1H), 7.86 – 7.77 (m, 1H), 3.97 (s, 3H), 3.88 – 3.80 (m, 1H), 3.68 – 3.55 (m, 1H, overlapping water), 3.04 – 2.95 (m, 1H), 2.86 – 2.77 (m, 1H), 2.70 – 2.43 (m, 2H, overlapping solvent), 2.19 – 2.08 (m, 1H), 1.70 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).
222	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylic acid 	N 481.0 [M+H]+ 1.69 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 9.30 (s, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.86 – 7.78 (m, 1H), 3.88 – 3.79 (m, 1H), 3.64 – 3.54 (m, 1H, overlapping water), 3.05 – 2.96 (m, 1H), 2.86 – 2.78 (m, 1H), 2.69 – 2.40 (m, 2H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.70 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). COOH not observed due to fast exchange with water.

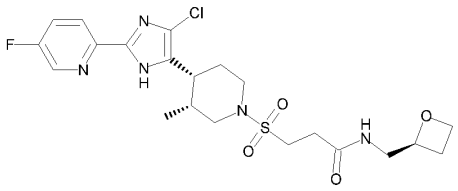
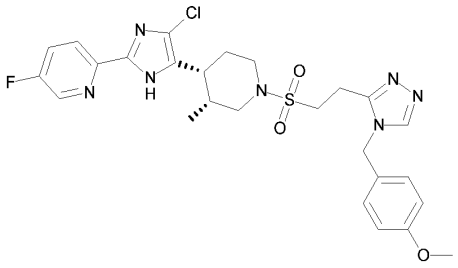
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
223	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxamide 	N 480.0 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 9.26 (s, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.36 (br s, 1H), 8.03 (br s, 1H), 8.01 – 7.92 (m, 1H), 7.86 – 7.78 (m, 1H), 3.88 – 3.79 (m, 1H), 3.70 – 3.50 (m, 1H, overlapping water), 3.05 – 2.96 (m, 1H), 2.85 – 2.76 (m, 1H), 2.70 – 2.38 (m, 2H, overlapping solvent), 2.19 – 2.08 (m, 1H), 1.71 – 1.62 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).
224	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] methyl carbonate 	N 544.1 [M+H]+ 1.85 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 5.17 – 5.09 (m, 1H), 4.55 – 4.47 (m, 1H), 4.24 – 4.15 (m, 2H), 3.86 – 3.79 (m, 1H), 3.76 – 3.66 (m, 4H), 3.60 – 3.41 (m, 3H, overlapping water), 3.28 – 3.20 (m, 2H), 3.13 – 3.04 (m, 2H), 2.94 – 2.83 (m, 1H), 2.58 – 2.38 (m, 1H, overlapping solvent), 2.16 – 2.08 (m, 1H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 6.9 Hz, 3H).

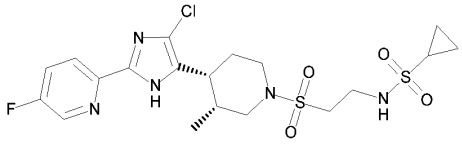
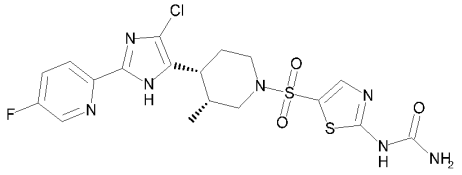
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
225	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxy-3-methyl-azetidin-1-yl)propan-1-one 	N 514.1 [M+H]+ 1.86 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.11 (d, J = 8.8 Hz, 1H), 3.95 (d, J = 8.8 Hz, 1H), 3.78 (d, J = 10.1 Hz, 1H), 3.73 – 3.62 (m, 2H), 3.50 – 3.40 (m, 1H, overlapping water), 3.28 – 3.21 (m, 2H), 3.17 (s, 3H), 3.14 – 3.04 (m, 2H), 2.94 – 2.83 (m, 1H), 2.58 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 1.41 (s, 3H), 0.85 (d, J = 7.0 Hz, 3H).
226	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-methoxypyrrolidin-1-yl]propan-1-one 	N 514.1 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 4.04 – 3.91 (m, 1H, partially overlapping water), 3.75 – 3.66 (m, 1H), 3.61 – 3.39 (m, 4H), 3.37 – 3.20 (m, 6H), 3.13 – 3.04 (m, 2H), 2.96 – 2.84 (m, 1H), 2.76 – 2.58 (m, 2H), 2.52 – 2.39 (m, 1H, partially overlapping solvent), 2.17 – 1.80 (m, 3H), 1.67 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H). Compound exists as a mixture of t-amide rotamers (ca. 1:1).

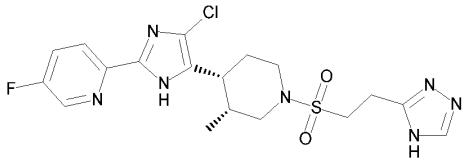
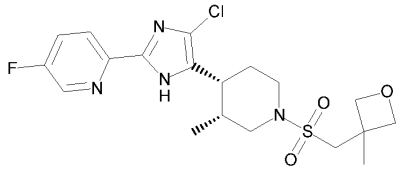
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
227	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[dimethyl(oxo)-6-sulfanylidene]propenamide 	N 506.1 [M+H]+ 1.67 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 3.74 – 3.67 (m, 1H, overlapping water), 3.50 – 3.42 (m, 1H), 3.35 (s, 6H), 3.31 – 3.23 (m, 2H), 3.14 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.64 – 2.57 (m, 2H), 2.52 – 2.38 (m, 1H, partially overlapping solvent), 2.17 – 2.06 (m, 1H), 1.68 – 1.58 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
228	[2-(Aminomethyl)-3-hydroxy-2-methyl-propyl] 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate (2,2,2-trifluoroacetic acid) 	N 530.1 [M-H]- 1.34 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.67 (br s, 3H), 5.09 (br s, 1H), 3.99 (d, J = 11.2 Hz, 1H), 3.94 (d, J = 11.2 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.50 – 3.43 (m, 1H, overlapping water), 3.43 – 3.30 (m, 4H), 3.15 – 3.06 (m, 2H), 2.96 – 2.74 (m, 5H), 2.55 – 2.38 (m, 1H, overlapping solent), 2.18 – 2.08 (m, 1H), 1.69 – 1.61 (m, 1H), 0.92 (s, 3H), 0.85 (d, J = 7.0 Hz, 3H).

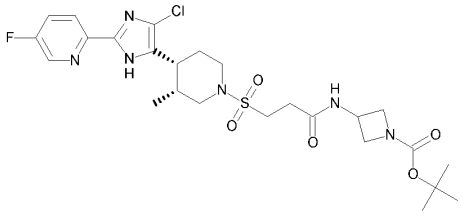
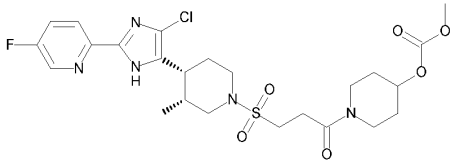
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
229	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3-methyloxetan-3-yl)propenamide 	N 500.1 [M+H]+ 1.71 min	n/a
230	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylcyclopropyl)propenamide 	N 484.1 [M+H]+ 1.88 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.23 (s, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.73 – 3.64 (m, 1H, partially overlapping water), 3.48 – 3.40 (m, 1H, partially overlapping water), 3.26 – 3.18 (m, 2H), 3.12 – 3.02 (m, 2H), 2.93 – 2.82 (m, 1H), 2.56 – 2.36 (m, 3H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.68 – 1.59 (m, 1H), 1.27 (s, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.63 – 0.48 (m, 4H).

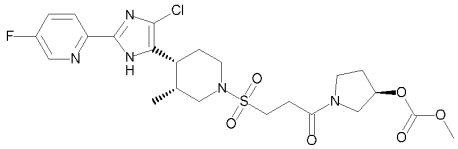
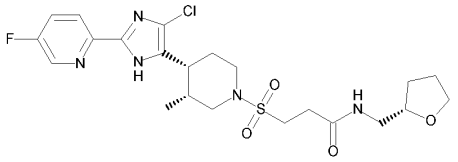
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
231	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxy-2-methyl-propyl)propenamide 	N 516.2 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.92 (t, J = 6.0 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.74 – 3.66 (m, 1H, overlapping water), 3.49 – 3.42 (m, 1H), 3.30 – 3.21 (m, 2H), 3.16 – 3.04 (m, 7H), 2.94 – 2.84 (m, 1H), 2.64 – 2.57 (m, 2H), 2.53 – 2.38 (m, 1H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 1.06 (s, 6H), 0.85 (d, J = 6.9 Hz, 3H).
232	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-methoxypyrrolidin-1-yl]propan-1-one 	N 514.1 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.01 (ddd, J = 8.8, 4.6, 0.6 Hz, 1H), 7.87 – 7.79 (m, 1H), 4.04 – 3.91 (m, 1H), 3.75 – 3.66 (m, 1H), 3.61 – 3.39 (m, 4H), 3.37 – 3.20 (m, 6H), 3.13 – 3.04 (m, 2H), 2.96 – 2.84 (m, 1H), 2.76 – 2.58 (m, 2H), 2.52 – 2.39 (m, 1H, partially overlapping solvent), 2.17 – 1.80 (m, 3H), 1.67 – 1.60 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H).

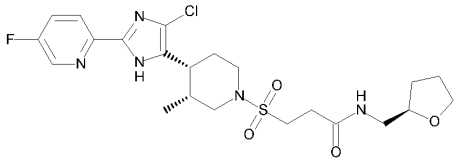
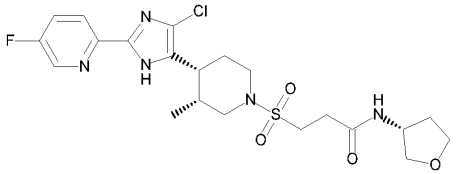
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
233	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-oxetan-2-yl]methyl]propenamide 	N 500.1 [M+H]+ 1.68 min	n/a
234	2-[4-Chloro-5-[(3R,4R)-1-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 572.1 [M-H]- 2.09 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.56 (s, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.30 – 7.24 (m, 2H), 6.94 – 6.87 (m, 2H), 5.27 (s, 2H), 3.75 – 3.52 (m, 4H, overlapping water), 3.48 – 3.36 (m, 3H), 3.06 – 2.94 (m, 4H), 2.82 – 2.71 (m, 1H), 2.54 – 2.36 (m, 1H, overlapping solvent), 2.11 – 2.02 (m, 1H), 1.60 – 1.51 (m, 1H), 0.83 (d, J = 6.9 Hz, 3H).

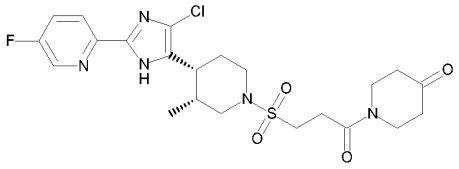
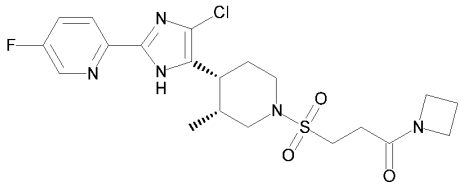
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
235	N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]cyclopropanesulfonamide 	N 506.1 [M+H]+ 1.86 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.29 (t, J = 5.9 Hz, 1H), 3.75 – 3.64 (m, 1H, overlapping water), 3.51 – 3.43 (m, 1H), 3.41 – 3.33 (m, 2H), 3.29 – 3.22 (m, 2H), 3.14 – 3.05 (m, 2H), 2.96 – 2.85 (m, 1H), 2.70 – 2.61 (m, 1H), 2.56 – 2.38 (m, 1H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.70 – 1.61 (m, 1H), 1.03 – 0.88 (m, 4H), 0.85 (d, J = 7.0 Hz, 3H).
236	[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]urea 	N 500.0 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 11.10 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.03 – 7.89 (m, 1H), 7.86 – 7.77 (m, 2H), 6.67 (br s, 2H), 3.75 – 3.65 (m, 1H), 3.56 – 3.25 (m, 1H, overlapping water), 3.05 – 2.94 (m, 1H), 2.71 – 2.35 (m, 3H, overlapping solvent), 2.22 – 2.10 (m, 1H), 1.75 – 1.62 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H).

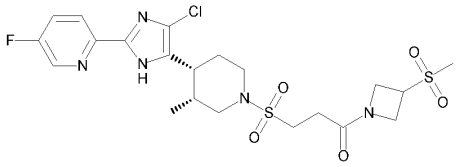
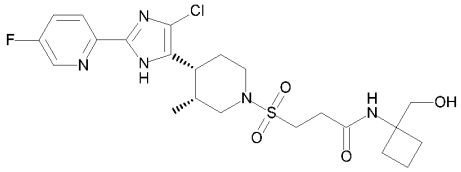
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
237	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(4H-1,2,4-triazol-3-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 454.0 [M+H]+ 1.58 min	(400 MHz, DMSO-d6) δ 12.93 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.32 (br s, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.77 – 3.69 (m, 1H), 3.52 – 3.42 (m, 3H), 3.16 – 3.02 (m, 4H), 2.93 – 2.83 (m, 1H), 2.55 – 2.39 (m, 1H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H). Triazole NH not observed due to fast exchange with water.
238	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(3-methyloxetan-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 443.1 [M+H]+ 1.89 min	n/a

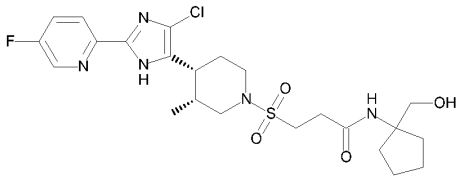
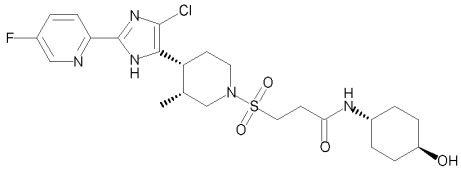
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
239	Tert-butyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino] azetidine-1-carboxylate 	N 585.1 [M+H]+ 2.09 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.66 (d, J = 6.9 Hz, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.45 – 4.34 (m, 1H), 4.11 – 4.02 (m, 2H), 3.82 – 3.64 (m, 3H, overlapping water), 3.49 – 3.41 (m, 1H), 3.31 – 3.22 (m, 2H), 3.13 – 3.01 (m, 2H), 2.93 – 2.82 (m, 1H), 2.59 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 1.38 (s, 9H), 0.84 (d, J = 6.9 Hz, 3H).
240	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] methyl carbonate 	N 572.1 [M+H]+ 2.00 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.78 (m, 1H), 4.84 – 4.74 (m, 1H), 3.98 – 3.59 (m, 6H, overlapping water), 3.50 – 3.43 (m, 1H), 3.40 – 3.21 (m, 4H), 3.14 – 3.04 (m, 2H), 2.95 – 2.85 (m, 1H), 2.81 – 2.72 (m, 2H), 2.55 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.05 (m, 1H), 1.99 – 1.79 (m, 2H), 1.68 – 1.56 (m, 2H), 1.56 – 1.43 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

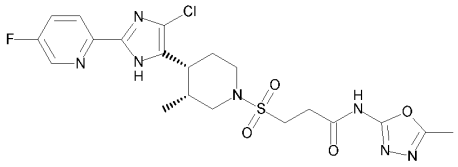
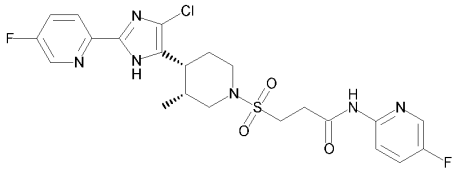
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
241	[(3R)-1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]pyrrolidin-3-yl] methyl carbonate 	N 558.1 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 5.24 – 5.12 (m, 1H), 3.80 – 3.41 (m, 9H, overlapping water), 3.37 – 3.23 (m, 2H), 3.13 – 3.04 (m, 2H), 2.94 – 2.83 (m, 1H), 2.77 – 2.57 (m, 2H), 2.53 – 2.38 (m, 1H, overlapping solvent), 2.25 – 1.97 (m, 3H), 1.68 – 1.59 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H). Compound exists as a mixture of t-amide rotamers (ca. 1:1).
242	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-tetrahydrofuran-2-yl]methyl]propenamide 	N 514.1 [M+H]+ 1.80 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.13 (t, J = 5.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.78 (m, 1H), 3.88 – 3.66 (m, 3H, partially overlapping water), 3.65 – 3.58 (m, 1H), 3.49 – 3.41 (m, 1H), 3.29 – 3.22 (m, 2H), 3.22 – 3.03 (m, 4H), 2.93 – 2.83 (m, 1H), 2.59 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.93 – 1.72 (m, 3H), 1.68 – 1.59 (m, 1H), 1.55 – 1.44 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

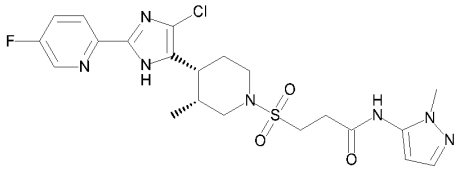
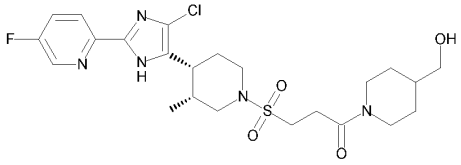
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
243	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2R)-tetrahydrofuran-2-yl]methyl]propenamide 	N 514.2 [M+H]+ 1.80 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.13 (t, J = 5.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.78 (m, 1H), 3.88 – 3.57 (m, 4H, overlapping water), 3.49 – 3.41 (m, 1H), 3.29 – 3.21 (m, 2H), 3.21 – 3.03 (m, 4H), 2.93 – 2.83 (m, 1H), 2.59 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.93 – 1.72 (m, 3H), 1.68 – 1.59 (m, 1H), 1.55 – 1.44 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
244	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3R)-tetrahydrofuran-3-yl]propenamide 	N 500.1 [M+H]+ 1.68 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.27 (d, J = 6.6 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 4.29 – 4.19 (m, 1H), 3.83 – 3.63 (m, 4H, overlapping water), 3.49 – 3.42 (m, 2H), 3.30 – 3.21 (m, 2H), 3.13 – 3.02 (m, 2H), 2.93 – 2.82 (m, 1H), 2.58 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.02 (m, 2H), 1.77 – 1.59 (m, 2H), 0.84 (d, J = 7.0 Hz, 3H).

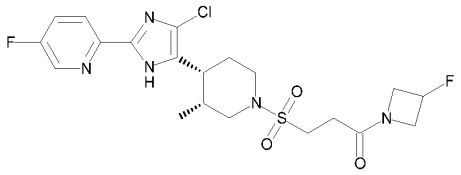
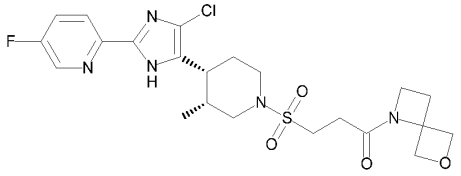
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
245	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]piperidin-4-one 	N 512.1 [M+H]+ 1.73 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.81 – 3.68 (m, 3H), 3.66 – 3.44 (m, 3H, overlapping water), 3.35 – 3.27 (m, 2H), 3.15 – 3.06 (m, 2H), 2.97 – 2.82 (m, 3H), 2.56 – 2.40 (m, 3H, overlapping solvent), 2.39 – 2.32 (m, 2H), 2.17 – 2.08 (m, 1H), 1.69 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
246	1-(Azetidin-1-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-one 	N 470.1 [M+H]+ 1.77 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 4.19 – 4.12 (m, 1H), 3.96 – 3.65 (m, 4H, overlapping water), 3.50 – 3.42 (m, 1H), 3.33 – 3.19 (m, 2H), 3.14 – 3.03 (m, 2H), 2.95 – 2.83 (m, 1H), 2.69 – 2.61 (m, 1H), 2.54 – 2.38 (m, 3H, overlapping solvent), 2.25 – 2.06 (m, 2H), 1.68 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).

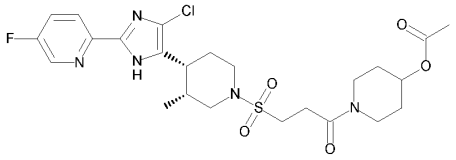
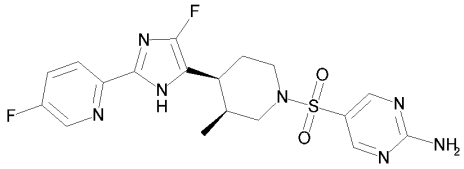
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
247	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methylsulfonylazetidin-1-yl)propan-1-one 	N 548.1 [M+H]+ 1.65 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.87 – 7.78 (m, 1H), 4.53 – 4.45 (m, 1H), 4.42 – 4.26 (m, 2H), 4.20 – 4.11 (m, 1H), 4.05 (dd, J = 10.4, 5.2 Hz, 1H, partially overlapping water), 3.75 – 3.66 (m, 1H), 3.50 – 3.42 (m, 1H), 3.31 – 3.19 (m, 2H), 3.14 – 3.02 (m, 5H), 2.95 – 2.84 (m, 1H), 2.57 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.06 (m, 1H), 1.68 – 1.59 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
248	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclobutyl]propenamide 	N 514.2 [M+H]+ 1.77 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (q, J = 4.7 Hz, 2H), 7.86 – 7.79 (m, 1H), 3.74 – 3.66 (m, 1H, partially overlapping water), 3.52 (s, 2H), 3.49 – 3.42 (m, 1H), 3.27 – 3.19 (m, 2H), 3.13 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.56 – 2.38 (m, 3H, overlapping solvent), 2.16 – 1.98 (m, 5H), 1.86 – 1.59 (m, 3H), 0.85 (d, J = 6.9 Hz, 3H). OH not observed due to fast exchange with water.

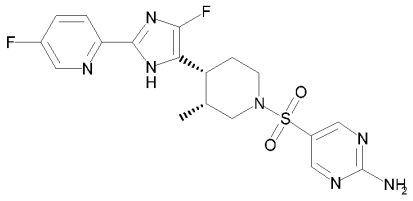
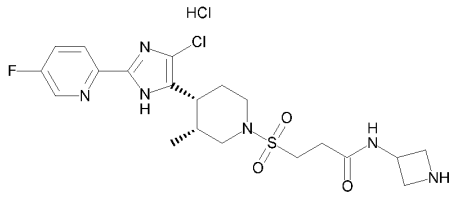
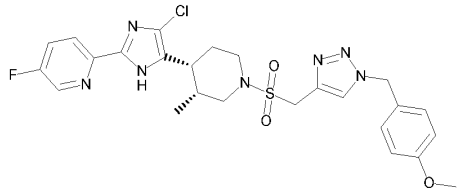
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
249	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclopentyl]propenamide 	N 528.2 [M+H]+ 1.89 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.87 – 7.78 (m, 1H), 7.64 (s, 1H), 3.76 – 3.66 (m, 1H, overlapping water), 3.50 – 3.42 (m, 3H), 3.26 – 3.18 (m, 2H), 3.13 – 3.03 (m, 2H), 2.94 – 2.83 (m, 1H), 2.57 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.06 (m, 1H), 1.87 – 1.73 (m, 2H), 1.71 – 1.44 (m, 7H), 0.85 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.
250	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(4-hydroxycyclohexyl)propenamide 	N 528.2 [M+H]+ 1.66 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.91 – 7.79 (m, 2H), 3.73 – 3.65 (m, 1H), 3.53 – 3.32 (m, 3H), 3.28 – 3.20 (m, 2H), 3.12 – 3.02 (m, 2H), 2.92 – 2.82 (m, 1H), 2.54 – 2.37 (m, 3H, overlapping solvent), 2.16 – 2.06 (m, 1H), 1.85 – 1.71 (m, 4H), 1.68 – 1.59 (m, 1H), 1.26 – 1.09 (m, 4H), 0.84 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.

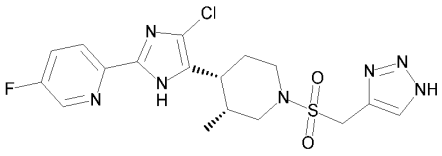
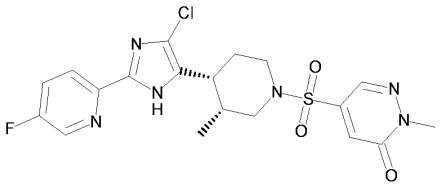
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
251	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-methyl-1,3,4-oxadiazol-2-yl)propenamide 	N 512.1 [M+H]+ 1.65 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 11.68 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 3.75 – 3.67 (m, 1H), 3.50 – 3.32 (m, 3H, overlapping water), 3.14 – 3.05 (m, 2H), 2.96 – 2.81 (m, 3H), 2.56 – 2.38 (m, 4H, overlapping solvent), 2.18 – 2.07 (m, 1H), 1.70 – 1.61 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
252	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-fluoro-2-pyridyl)propenamide 	N 525.1 [M+H]+ 2.03 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 10.76 (s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.33 (d, J = 3.1 Hz, 1H), 8.12 (dd, J = 9.3, 4.2 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.71 (m, 2H), 3.80 – 3.59 (m, 1H, overlapping water), 3.52 – 3.45 (m, 1H), 3.41 – 3.33 (m, 2H), 3.13 – 3.05 (m, 2H), 2.96 – 2.83 (m, 3H), 2.55 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.61 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H).

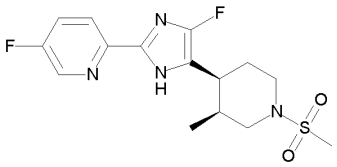
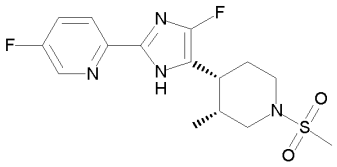
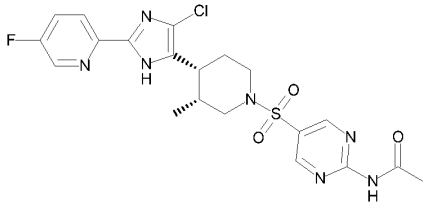
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
253	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methylpyrazol-3-yl)propenamide 	N 510.1 [M+H]+ 1.73 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 10.11 (s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.32 (d, J = 2.0 Hz, 1H), 6.19 (d, J = 2.0 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.67 (s, 3H), 3.52 – 3.44 (m, 1H), 3.41 – 3.32 (m, 2H), 3.15 – 3.05 (m, 2H), 2.96 – 2.79 (m, 3H), 2.55 – 2.38 (m, 1H, overlapping solvent), 2.19 – 2.08 (m, 1H), 1.70 – 1.62 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).
254	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one 	N 528.2 [M+H]+ 1.73 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.42 – 4.34 (m, 1H), 3.90 – 3.66 (m, 2H, overlapping water), 3.50 – 3.42 (m, 1H), 3.32 – 3.22 (m, 4H), 3.14 – 3.04 (m, 2H), 3.04 – 2.94 (m, 1H), 2.94 – 2.84 (m, 1H), 2.78 – 2.70 (m, 2H), 2.61 – 2.38 (m, 2H, overlapping solvent), 2.17 – 2.06 (m, 1H), 1.75 – 1.52 (m, 4H), 1.16 – 0.89 (m, 2H), 0.84 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.

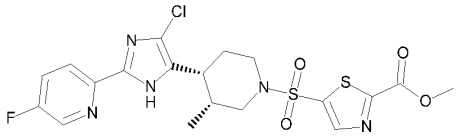
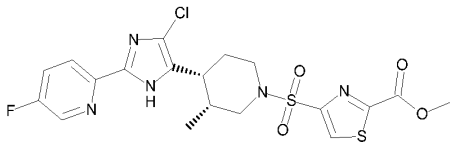
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
255	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-fluoroazetidin-1-yl)propan-1-one 	N 488.1 [M+H]+ 1.79 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 5.51 – 5.30 (m, 1H), 4.56 – 4.43 (m, 1H), 4.34 – 4.13 (m, 2H), 3.97 – 3.66 (m, 2H, overlapping water), 3.49 – 3.42 (m, 1H), 3.31 – 3.18 (m, 2H), 3.14 – 3.04 (m, 2H), 2.94 – 2.83 (m, 1H), 2.60 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H).
256	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(6-oxa-1-azaspiro[3.3]heptan-1-yl)propan-1-one 	N 512.1 [M+H]+ 1.75 min	(400 MHz, DMSO-d6) δ 12.90 (s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.78 (m, 1H), 5.21 – 4.93 (m, 2H), 4.85 – 4.48 (m, 2H), 4.00 – 3.59 (m, 3H, partially overlapping water), 3.51 – 3.23 (m, 3H), 3.14 – 3.04 (m, 2H), 2.95 – 2.84 (m, 1H), 2.56 – 2.38 (m, 5H, overlapping solvent), 2.18 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H). Compound exists as a mixture of t-amide rotamers (ca. 3:1).

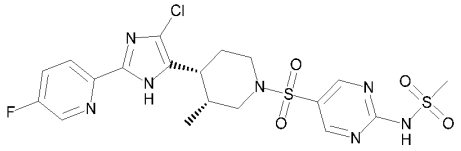
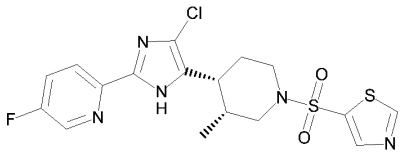
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
257	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] acetate 	N 556.1 [M+H]+ 1.97 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.87 – 7.79 (m, 1H), 4.93 – 4.83 (m, 1H), 3.90 – 3.56 (m, 3H, overlapping water), 3.50 – 3.43 (m, 1H), 3.38 – 3.18 (m, 4H), 3.14 – 3.05 (m, 2H), 2.95 – 2.85 (m, 1H), 2.82 – 2.72 (m, 2H), 2.55 – 2.38 (m, 1H, overlapping solvent), 2.17 – 2.07 (m, 1H), 2.02 (s, 3H), 1.93 – 1.75 (m, 2H), 1.68 – 1.38 (m, 3H), 0.85 (d, J = 7.0 Hz, 3H).
258	5-[[(3S,4S)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine 	N 436.2 [M+H]+ 1.74 min	(400 MHz, DMSO-d6) δ 12.66 (br s, 1H), 8.58 (d, J = 2.9 Hz, 1H), 8.51 (s, 2H), 7.90 (dd, J = 8.9, 4.6 Hz, 1H), 7.84 – 7.77 (m, 1H), 7.71 (br s, 2H), 3.64 – 3.56 (m, 1H), 3.42 – 3.34 (m, 1H), 2.98 – 2.90 (m, 1H), 2.62 – 2.55 (m, 1H), 2.53 – 2.43 (m, 1H, overlapping solvent), 2.29 – 2.07 (m, 2H), 1.84 – 1.75 (m, 1H), 0.84 (d, J = 6.9 Hz, 3H).

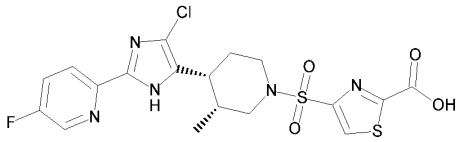
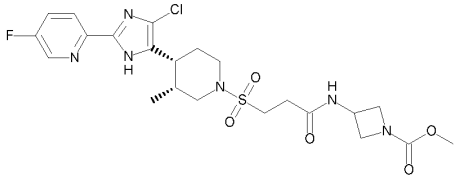
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
259	5-[[(3R,4R)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine 	N 436.1 [M+H]+ 1.74 min	(400 MHz, DMSO-d6) δ 12.66 (br s, 1H), 8.58 (d, J = 2.9 Hz, 1H), 8.51 (s, 2H), 7.90 (dd, J = 8.8, 4.5 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.71 (br s, 2H), 3.64 – 3.56 (m, 1H), 3.42 – 3.34 (m, 1H), 2.98 – 2.90 (m, 1H), 2.62 – 2.55 (m, 1H), 2.53 – 2.43 (m, 1H, overlapping solent), 2.30 – 2.07 (m, 2H), 1.84 – 1.75 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
260	N-(Azetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanamide (hydrochloride) 	N 483.1 [M-H]- 1.23 min	n/a
261	2-[4-Chloro-5-[(3R,4R)-1-[[1-[(4-methoxyphenyl)methyl]triazol-4-yl]methylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 560.1 [M+H]+ 2.13 min	n/a

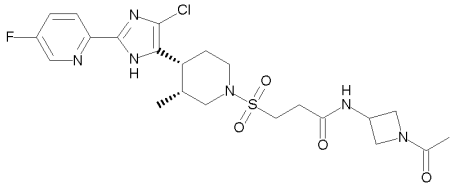
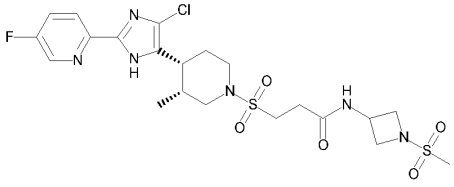
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
262	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine 	N 440.0 [M+H]+ 1.64 min	(400 MHz, DMSO-d6) δ 12.88 (br s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.93 (br s, 1H), 7.86 – 7.78 (m, 1H), 4.58 (s, 2H), 3.70 – 3.52 (m, 1H, overlapping water), 3.41 – 3.35 (m, 1H), 3.08 – 3.00 (m, 1H), 2.98 – 2.91 (m, 1H), 2.82 – 2.72 (m, 1H), 2.51 – 2.34 (m, 1H, partially overlapping solvent), 2.11 – 2.02 (m, 1H), 1.64 – 1.56 (m, 1H), 0.80 (d, J = 7.0 Hz, 3H). Triazole NH not observed due to fast exchange with water.
263	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-3-methoxy-pyridazine 	N 467.0 [M+H]+ 1.95 min	(400 MHz, DMSO-d6) δ 12.92 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.99 (dd, J = 8.7, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.23 (d, J = 2.2 Hz, 1H), 3.84 – 3.77 (m, 1H), 3.72 (s, 3H), 3.60 – 3.42 (m, 1H, overlapping water), 3.10 – 3.02 (m, 1H), 2.97 – 2.89 (m, 1H), 2.80 – 2.68 (m, 1H), 2.62 – 2.40 (m, 1H, overlapping solvent), 2.19 – 2.09 (m, 1H), 1.70 – 1.61 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H).

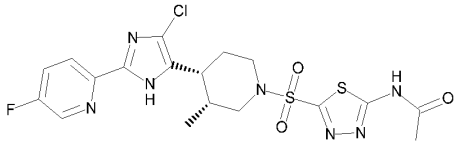
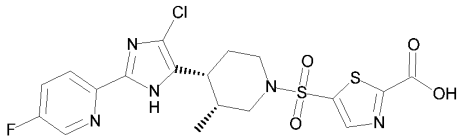
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
264	5-Fluoro-2-[4-fluoro-5-[(3S,4S)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine 	N 357.1 [M+H]+ 1.70 min	(400 MHz, DMSO-d6) δ 12.68 (br s, 1H), 8.59 (d, J = 2.8 Hz, 1H), 7.91 (dd, J = 8.9, 4.5 Hz, 1H), 7.85 – 7.77 (m, 1H), 3.65 – 3.58 (m, 1H), 3.42 – 3.35 (m, 1H), 3.06 – 2.98 (m, 1H), 2.97 – 2.90 (m, 1H), 2.87 (s, 3H), 2.84 – 2.75 (m, 1H), 2.30 – 2.21 (m, 1H), 2.19 – 2.05 (m, 1H), 1.85 – 1.77 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H).
265	5-Fluoro-2-[4-fluoro-5-[(3R,4R)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine 	N 357.1 [M+H]+ 1.70 min	(400 MHz, DMSO-d6) δ 12.68 (br s, 1H), 8.59 (d, J = 2.8 Hz, 1H), 7.91 (dd, J = 8.8, 4.5 Hz, 1H), 7.85 – 7.77 (m, 1H), 3.65 – 3.58 (m, 1H, overlapping water), 3.42 – 3.35 (m, 1H), 3.06 – 2.98 (m, 1H), 2.97 – 2.90 (m, 1H), 2.87 (s, 3H), 2.85 – 2.75 (m, 1H), 2.31 – 2.21 (m, 1H), 2.19 – 2.05 (m, 1H), 1.85 – 1.77 (m, 1H), 0.83 (d, J = 6.9 Hz, 3H).
266	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]acetamide 	N 494.1 [M+H]+ 1.80 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 11.14 (s, 1H), 8.94 (s, 2H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.86 – 7.78 (m, 1H), 3.82 – 3.73 (m, 1H), 3.60 – 3.43 (m, 1H, overlapping water), 3.04 – 2.96 (m, 1H), 2.76 – 2.64 (m, 1H), 2.62 – 2.38 (m, 2H, overlapping solvent), 2.25 (s, 3H), 2.18 – 2.09 (m, 1H), 1.70 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).

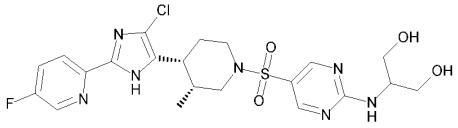
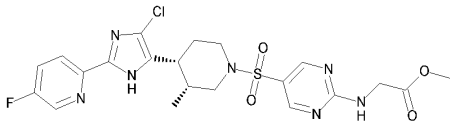
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
267	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate 	N 500.1 [M+H]+ 2.21 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.56 (s, 1H), 8.03 – 7.93 (m, 1H), 7.86 – 7.77 (m, 1H), 3.97 (s, 3H), 3.82 – 3.75 (m, 1H), 3.59 – 3.51 (m, 1H), 3.06 – 2.98 (m, 1H), 2.80 – 2.72 (m, 1H), 2.65 – 2.46 (m, 2H, overlapping solvent), 2.21 – 2.12 (m, 1H), 1.75 – 1.64 (m, 1H), 0.88 (d, J = 7.0 Hz, 3H).
268	Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate 	N 500.1 [M+H]+ 2.11 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.77 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 7.98 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.78 (m, 1H), 3.96 (s, 3H), 3.86 – 3.78 (m, 1H), 3.63 – 3.44 (m, 1H, overlapping water), 3.04 – 2.96 (m, 1H), 2.86 – 2.78 (m, 1H), 2.70 – 2.43 (m, 2H, overlapping solvent), 2.19 – 2.09 (m, 1H), 1.71 – 1.63 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).

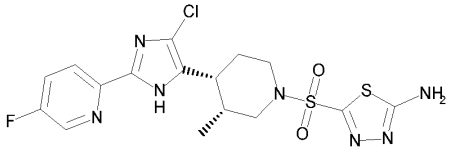
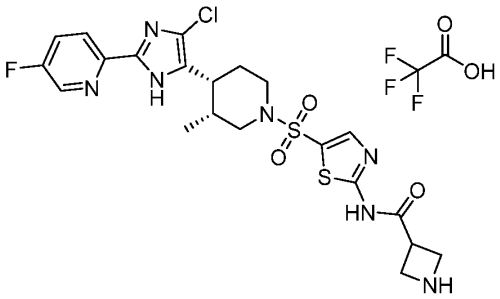
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
269	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]methanesulfonamide 	N 530.1 [M+H]+ 1.88 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.96 – 8.91 (m, 2H), 8.60 (d, J = 2.8 Hz, 1H), 8.03 – 7.94 (m, 1H), 7.86 – 7.78 (m, 1H), 3.82 – 3.72 (m, 1H), 3.60 – 3.20 (m, 4H, overlapping water), 3.06 – 2.96 (m, 1H), 2.76 – 2.65 (m, 1H), 2.60 – 2.43 (m, 2H, overlapping solvent), 2.19 – 2.09 (m, 1H), 1.72 – 1.59 (m, 1H), 0.88 (d, J = 6.9 Hz, 3H). Sulfonamide NH not observed due to fast exchange with water.
270	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid 	N 442.1 [M+H]+ 2.01 min	(400 MHz, DMSO-d6) δ 12.89 (s, 1H), 9.50 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.41 (s, 1H), 8.03 – 7.91 (m, 1H), 7.87 – 7.78 (m, 1H), 3.82 – 3.48 (m, 2H, overlapping water), 3.06 – 2.97 (m, 1H), 2.72 – 2.61 (m, 1H), 2.60 – 2.38 (m, 2H, overlapping solvent), 2.21 – 2.13 (m, 1H), 1.74 – 1.65 (m, 1H), 0.88 (d, J = 7.0 Hz, 3H).

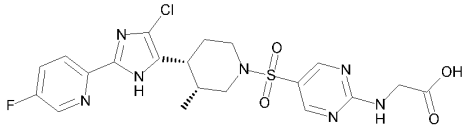
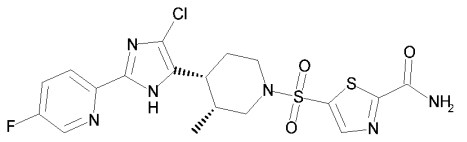
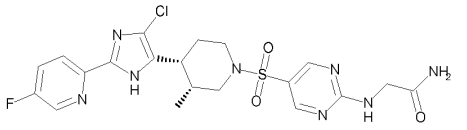
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
271	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid 	N 486.0 [M+H]+ 1.72 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.72 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.85 – 7.78 (m, 1H), 3.86 – 3.77 (m, 1H), 3.70 – 3.42 (m, 1H, overlapping water), 3.05 – 2.97 (m, 1H), 2.88 – 2.80 (m, 1H), 2.72 – 2.59 (m, 1H), 2.58 – 2.41 (m, 1H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.71 – 1.63 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H). COOH not observed due to fast exchange with water.
272	Methyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino] azetidine-1-carboxylate 	N 543.2 [M+H]+ 1.83 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.69 (d, J = 6.9 Hz, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.50 – 4.39 (m, 1H), 4.19 – 4.09 (m, 2H), 3.78 – 3.65 (m, 3H, overlapping water), 3.56 (s, 3H), 3.49 – 3.41 (m, 1H), 3.30 – 3.23 (m, 2H), 3.13 – 3.02 (m, 2H), 2.92 – 2.82 (m, 1H), 2.59 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

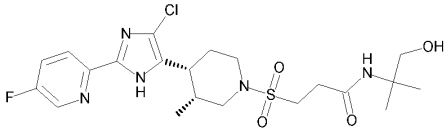
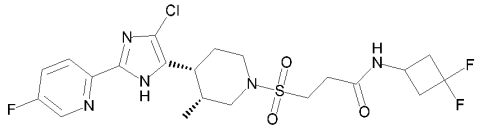
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
273	N-(1-Acetylazetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide 	N 527.2 [M+H]+ 1.58 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.69 (d, J = 6.6 Hz, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.47 – 4.31 (m, 2H), 4.10 – 4.02 (m, 1H), 3.92 – 3.86 (m, 1H), 3.74 – 3.63 (m, 2H), 3.49 – 3.40 (m, 1H, partially overlapping water), 3.31 – 3.23 (m, 2H), 3.13 – 3.02 (m, 2H), 2.93 – 2.82 (m, 1H), 2.59 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.75 (s, 3H), 1.69 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).
274	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylsulfonylazetidin-3-yl)propenamide 	N 563.1 [M+H]+ 1.70 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.74 (d, J = 7.0 Hz, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.52 – 4.41 (m, 1H), 4.10 – 4.03 (m, 2H), 3.77 – 3.65 (m, 3H), 3.49 – 3.41 (m, 1H, partially overlapping water), 3.30 – 3.23 (m, 2H), 3.13 – 2.99 (m, 5H), 2.93 – 2.82 (m, 1H), 2.60 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

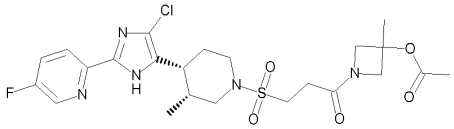
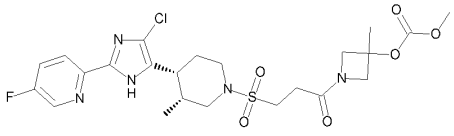
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
275	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-yl]acetamide 	N 500.0 [M+H]+ 1.99 min	(400 MHz, DMSO-d6) δ 13.18 (br s, 1H), 12.93 (s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.03 – 7.95 (m, 1H), 7.86 – 7.79 (m, 1H), 3.91 – 3.83 (m, 1H), 3.66 – 3.58 (m, 1H), 3.11 – 3.03 (m, 1H), 2.98 (d, J = 11.8 Hz, 1H), 2.87 – 2.75 (m, 1H), 2.63 – 2.42 (m, 1H, overlapping solvent), 2.26 (s, 3H), 2.22 – 2.14 (m, 1H), 1.76 – 1.65 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).
276	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid 	N 486.0 [M+H]+ 1.82 min	(400 MHz, DMSO-d6) δ 8.22 – 8.13 (m, 1H), 8.11 (s, 1H), 7.78 – 7.66 (m, 1H), 7.40 – 7.28 (m, 1H), 3.72 – 3.62 (m, 1H), 3.33 – 3.23 (m, 1H, overlapping water), 3.16 – 2.94 (m, 2H), 2.89 – 2.80 (m, 1H), 2.14 – 2.02 (m, 1H), 1.94 – 1.74 (m, 2H), 0.66 (d, J = 6.7 Hz, 3H). Imidazole NH and COOH not observed due to fast exchange with water.

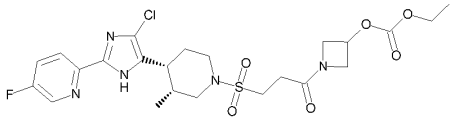
Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
277	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]propane-1,3-diol 	N 526.1 [M+H]+ 1.69 min	(400 MHz, DMSO-d6) δ 12.88 (br s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.55 (d, J = 3.2 Hz, 1H), 8.52 (d, J = 3.2 Hz, 1H), 7.98 (dd, J = 9.1, 4.5 Hz, 1H), 7.86 – 7.79 (m, 2H), 4.09 – 3.99 (m, 1H, partially overlapping water), 3.74 – 3.67 (m, 1H, partially overlapping water), 3.58 – 3.44 (m, 5H), 3.05 – 2.95 (m, 1H), 2.65 – 2.36 (m, 3H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.70 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). 2 x OH not observed due to fast exchange with water.
278	Methyl 2-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetate 	N 524.1 [M+H]+ 2.01 min	(400 MHz, DMSO-d6) δ 12.88 (br s, 1H), 8.63 – 8.57 (m, 4H), 8.03 – 7.94 (m, 1H), 7.86 – 7.78 (m, 1H), 4.13 (d, J = 6.2 Hz, 2H), 3.77 – 3.63 (m, 4H), 3.55 – 3.43 (m, 1H, overlapping water), 3.04 – 2.96 (m, 1H), 2.65 – 2.35 (m, 3H, overlapping solvent), 2.18 – 2.08 (m, 1H), 1.69 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).

Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
279	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-amine 	N 458.0 [M+H]+ 1.81 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.07 – 7.96 (m, 3H), 7.86 – 7.79 (m, 1H), 3.86 – 3.77 (m, 1H), 3.62 – 3.54 (m, 1H), 3.13 – 3.05 (m, 1H), 3.00 – 2.92 (m, 1H), 2.86 – 2.74 (m, 1H), 2.61 – 2.48 (m, 1H, overlapping solvent), 2.22 – 2.14 (m, 1H), 1.73 – 1.65 (m, 1H), 0.87 (d, J = 7.1 Hz, 3H).
280	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]azetidine-3-carboxamide (2,2,2-trifluoroacetate) 	N 270.7 [M+2H] 2+ 1.43 min	(400 MHz, DMSO-d6) δ 12.95 (br s, 1H), 12.90 (br s, 1H), 8.74 (br s, 2H), 8.61 (d, J = 2.9 Hz, 1H), 8.04 (s, 1H), 8.03 – 7.94 (m, 1H), 7.86 – 7.78 (m, 1H), 4.20 – 4.06 (m, 4H), 3.98 – 3.86 (m, 1H), 3.79 – 3.71 (m, 1H), 3.59 – 3.37 (m, 1H, overlapping water), 3.01 – 2.93 (m, 1H), 2.68 – 2.36 (m, 3H, overlapping solvent), 2.22 – 2.12 (m, 1H), 1.75 – 1.65 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H).

Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
281	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetic acid 	N 510.1 [M+H]+ 1.79 min	(400 MHz, DMSO-d6) δ 12.89 (br s, 1H), 8.62 – 8.57 (m, 3H), 8.48 (t, J = 6.3 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.86 – 7.78 (m, 1H), 4.02 (d, J = 6.2 Hz, 2H), 3.76 – 3.67 (m, 1H), 3.62 – 3.41 (m, 1H, overlapping water), 3.04 – 2.96 (m, 1H), 2.65 – 2.35 (m, 3H, overlapping solvent), 2.19 – 2.09 (m, 1H), 1.69 – 1.60 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H). COOH not observed due to fast exchange with water.
282	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxamide 	N 485.0 [M+H]+ 1.94 min	n/a
283	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetamide 	N 509.1 [M+H]+ 1.68 min	(400 MHz, DMSO-d6) δ 12.86 (s, 1H), 8.60 (d, J = 2.9 Hz, 1H), 8.57 (s, 2H), 8.27 (t, J = 6.2 Hz, 1H), 7.97 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.39 (br s, 1H), 7.03 (br s, 1H), 3.91 (d, J = 6.2 Hz, 2H), 3.82 – 3.67 (m, 1H, overlapping water), 3.53 – 3.45 (m, 1H), 3.03 – 2.95 (m, 1H), 2.64 – 2.36 (m, 3H, overlapping solvent), 2.18 – 2.09 (m, 1H), 1.70 – 1.61 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H).

Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
284	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-1,1-dimethyl-ethyl)propenamide 	N 502.1 [M+H]+ 1.75 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.51 (br s, 1H), 3.75 – 3.60 (m, 1H, overlapping water), 3.49 – 3.42 (m, 1H), 3.40 (s, 2H), 3.25 – 3.18 (m, 2H), 3.13 – 3.04 (m, 2H), 2.94 – 2.83 (m, 1H), 2.56 – 2.38 (m, 3H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.68 – 1.59 (m, 1H), 1.18 (s, 6H), 0.85 (d, J = 7.0 Hz, 3H). OH not observed due to fast exchange with water.
285	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3,3-difluorocyclobutyl)propenamide 	N 520.1 [M+H]+ 1.96 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.52 (d, J = 6.6 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.11 – 3.98 (m, 1H), 3.75 – 3.55 (m, 1H, overlapping water), 3.49 – 3.41 (m, 1H), 3.30 – 3.23 (m, 2H), 3.13 – 3.02 (m, 2H), 2.98 – 2.82 (m, 3H), 2.62 – 2.38 (m, 5H, overlapping solvent), 2.16 – 2.07 (m, 1H), 1.69 – 1.60 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H).

Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
286	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] acetate 	N 542.1 [M+H]+ 1.93 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.9 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.31 (d, J = 9.5 Hz, 1H), 4.20 (d, J = 9.5 Hz, 1H), 3.94 (d, J = 10.5 Hz, 1H), 3.88 (d, J = 10.5 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.49 – 3.42 (m, 1H), 3.28 – 3.20 (m, 2H), 3.14 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.54 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 2.03 (s, 3H), 1.69 – 1.57 (m, 4H), 0.85 (d, J = 7.0 Hz, 3H).
287	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] methyl carbonate 	N 558.1 [M+H]+ 1.96 min	(400 MHz, DMSO-d6) δ 12.91 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.9, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 4.35 (d, J = 9.6 Hz, 1H), 4.22 (d, J = 9.6 Hz, 1H), 3.97 (d, J = 10.6 Hz, 1H), 3.89 (d, J = 10.6 Hz, 1H, partially overlapping water), 3.75 – 3.65 (m, 4H, partially overlapping water), 3.49 – 3.42 (m, 1H), 3.30 – 3.18 (m, 2H), 3.14 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.56 – 2.38 (m, 3H, overlapping water), 2.17 – 2.07 (m, 1H), 1.68 – 1.60 (m, 4H), 0.85 (d, J = 7.0 Hz, 3H).

Ex. No.	Name & Structure	LCMS Method m/z [Ion] tR	^{1}H NMR
288	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] ethyl carbonate 	N 558.1 [M+H]+ 1.98 min	(400 MHz, DMSO-d6) δ 12.90 (br s, 1H), 8.61 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.8, 4.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 5.17 – 5.09 (m, 1H), 4.54 – 4.47 (m, 1H), 4.23 – 4.11 (m, 4H), 3.86 – 3.79 (m, 1H, partially overlapping water), 3.76 – 3.64 (m, 1H, overlapping water), 3.49 – 3.42 (m, 1H), 3.29 – 3.19 (m, 2H), 3.14 – 3.04 (m, 2H), 2.94 – 2.84 (m, 1H), 2.58 – 2.38 (m, 3H, overlapping solvent), 2.17 – 2.07 (m, 1H), 1.68 – 1.60 (m, 1H), 1.26 – 1.19 (m, 3H), 0.84 (d, J = 7.0 Hz, 3H).

[354] Example 1: Tert-butyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate

[355] Step 1: Preparation of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate

[356] A mixture of 5-fluoropyridine-2-carboxamidine (100.0 mg, 0.7188 mmol), tert-butyl 4-(2-bromoacetyl)piperidine-1-carboxylate (330.1 mg, 1.078 mmol) and K2CO3 (397.3 mg, 2.875 mmol) was stirred in ethanol (3 mL) at 80°C for 2 hours. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and separated by vacuum filtration. The filtrate was concentrated and purified by flash chromatography (n-heptane / ethyl acetate 100:0 to 50:50) to give tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate (151 mg, purity: 95%, yield: 58%). MS m/z 347.2 [M+H]+.

[357] Step 2: Preparation of tert-butyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate

[358] A mixture of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate (129.0 mg, 0.3724 mmol) and N-chlorosuccinimide (54.70 mg, 0.4096 mmol) was stirred in dimethylformamide (3 mL) at 70°C for 3 hours. After cooling to room temperature, the solution was purified by flash chromatography (n-heptane / ethyl acetate 100:0 to 50:50) to give 170 mg crude product. Flash chromatography was repeated (n-heptane / ethyl acetate 100:0 to 90:10 to 75:25) to afford the title compound (11 mg, purity: 95%, yield: 7.4%).

[359] Example 2: 1-[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-1-piperidyl]ethanone

[360] Step 1: Preparation of 2-[4-chloro-5-(4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)

[361] Tert-butyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate (10.0 mg, 0.0263 mmol) was dissolved in 1,4-dioxane (2 mL). 4M HCl in 1,4-dioxane (1 mL) was added and the reaction was stirred for 21 hours. The crude product was concentrated in vacuo and used in the next step without further purification.

[362] Step 2: Preparation of 1-[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-1-piperidyl]ethanone

[363] 2-[4-Chloro-5-(4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine hydrochloride (10.0 mg, 0.0315 mmol) was added to dichloromethane (2 mL). Diisopropylethylamine (0.00824 mL, 0.0473 mmol) was added, and the mixture was cooled to 0°C. Acetyl chloride (2.97 mg, 0.0378 mmol) was dissolved in dichloromethane (1 mL) and added via syringe to the mixture within 1 min. The mixture was allowed to reach room temperature and stirred for 16 hours. The mixture was concentrated in vacuo and purified by prep-HPLC to afford the title compound (11.5 mg, purity: 95%, yield: quantitative).

[364] Example 3: 2-[4-Chloro-5-(1-methylsulfonyl-4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[365] A mixture of 2-[4-chloro-5-(4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine hydrochloride (14.0 mg, 0.0441 mmol), dichloromethane (2 ml), N-ethyl-N-isopropyl-propan-2-amine (19.2 µl, 0.110 mmol) and methane sulfonyl chloride (6.13 mg, 0.0530 mmol) dissolved in dichloromethane (1 ml) was stirred for 16 h. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC to afford the title compound (3.5 mg, purity: 95%, yield: 22%).

[366] Example 4, Example 5, and Example 6: (3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (Example 4), (3S,4S)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (Example 5), and (3R*,4S*/3S*,4R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (Example 6)

[367] Step 1: Preparation of 5-fluoro-2-(1H-imidazol-2-yl)pyridine

[368] To a mixture of 5-fluoropicolinaldehyde (100.0 g, 799.35 mmol) and oxalaldehyde (463.91 g, 7.99 mol) in EtOH (2000 mL) was added NH3*H2O (560.28 g, 15.99 mol) dropwise at 0°C under N2 atmosphere. The reaction mixture was stirred at room temperature for 16 hours. Then the solvent was removed under reduced pressure. The residue was poured into water (2000 mL) and extracted with DCM (1000 mL x 3). The combined

organic layers were washed with brine (3000 mL x 2), dried with anhydrous Na2SO4, filtered and concentrated to give 5-fluoro-2-(1H-imidazol-2-yl)pyridine (102 g, purity: 98%, yield: 78%) which was used directly in the next step. MS m/z 164.1 [M+H]+.

[369] Step 2: Preparation of 5-fluoro-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyridine

[370] To a solution of 5-fluoro-2-(1H-imidazol-2-yl)pyridine (102 g, 0.63 mol) in THF (2000 mL) was added NaH (60% in oil, 37.55 g, 0.94 mol) in several portions at 0°C under N2 atmosphere. The reaction was stirred at 0°C for 1 hour. Then, SEM-Cl (125.4 g, 0.75 mol) was added dropwise maintaining the temperature at 0°C. The reaction mixture was stirred at room temperature for another 6 hours. Then the mixture was quenched with water (2000 mL) and extracted with ethyl acetate (2000 mL x 3). The combined organic layers were washed with brine (2000 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 30:70) to give 5-fluoro-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyridine (156 g, purity: 85%, yield: 84%). MS m/z 294.0 [M+H]+.

[371] Step 3: Preparation of a mixture of 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine

[372] 5-Fluoro-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyridine (156 g, 0.53 mol) was dissolved in chloroform (1000 mL) under N2 atmosphere. Then, NBS (94.77 g, 0.53 mol) was added in several portions at 0°C. The reaction was stirred at room temperature for 16 hours. Then the solvent was removed. The mixture was poured into water (2000 mL) and extracted with ethyl acetate (1000 mL x 3). The organic layers were washed with brine (1000 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography (ethyl acetate / petroleum ether 10:90) to give the desired crude product as a mixture of 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (150 g, purity: 85%, yield: 76%). MS m/z 372.0 [M+H]+.

[373] Step 4: Preparation of a mixture of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate

and tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate

[374] To a solution of a mixture of 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (65 g, 0.18 mol) in THF (500 mL) and water (50 mL) were added (1-tert-butoxycarbonyl-3-methyl-3,6-dihydro-2H-pyridin-4-yl)boronic acid (55 g, 0.23 mol), potassium carbonate (72.5 g, 0.53 mol) and Pd(dtbpf)Cl2 (17.4 g, 0.027 mol) under nitrogen atmosphere. The reaction was stirred at 80°C for 16 hours. Then the mixture was quenched with water (500 mL) and extracted with ethyl acetate (1000 mL x 3). The combined organic layers were washed with brine (1000 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (petroleum ether 30:70) to afford the subtitle mixture of compounds (54 g, purity: 85%, yield: 63%). MS m/z 489.2 [M+H]+.

[375] Step 5: Preparation of a mixture of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate

[376] To a solution of a mixture of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate and tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (9 g, 0.02 mol) in methanol (150 mL) was added Pd/C (10%, 0.9 g). The reaction was stirred under hydrogen at room temperature for 72 hours. This reaction was performed in 6 batches in parallel. The mixtures were filtered and washed with methanol (100 mL x 3). The combined filtrates were concentrated and purified by flash chromatography (ethyl acetate / petroleum ether 40:60) to give a mixture of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate (35 g, purity: 90%, yield: 65%). MS m/z 491.4 [M+H]+.

[377] Step 6: Preparation of a mixture of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate

[378] To a solution of a mixture of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate (54 g, 0.11 mol) in chloroform (500 mL) was added NCS (17.59 g, 0.13 mol) in several portions at 0°C. The reaction was stirred at 40°C for 16 hours. Then the solvent was removed. The mixture was poured into water (500 mL) and extracted with ethyl acetate (800 mL x 3). The combined organic layers were washed with brine (1000 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography (ethyl acetate / petroleum ether 25:75) to give the desired product as a mixture of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate (55 g, purity: 85%, yield: 90%). MS m/z 525.3 [M+H]+.

[379] Step 7: Preparation of 2-(4-chloro-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (hydrochloride)

[380] To a solution of a mixture of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate (44 g, 84 mmol) in THF (40 mL) was added 4 M HCl in 1,4-dioxane (80 mL). The reaction was stirred at room temperature for 16 hours. Then the mixture was concentrated and 4 M HCl in dioxane (80 mL) was added again. The reaction was stirred at room temperature for another 8 hours. LCMS showed the reaction was completed. Then the mixture was concentrated to give 2-(4-chloro-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine hydrochloride (44 g, crude), which was used in the next step without further purification. MS m/z 295.2 [M+H]+.

[381] Step 8: Preparation of tert-butyl ((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)carbamate

[382] To a solution of 2-(4-chloro-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine hydrochloride (44 g, crude, 84 mmol) in THF (150 mL) were added DIEA (54 g, 0.42 mol) and (tert-butoxycarbonyl)((4-(dimethyliminio)pyridin-1(4H)-yl)sulfonyl)amide (27.8 g, 92.4 mmol). The reaction was stirred at room temperature for 36 hours. Then the mixture was quenched with water (200 mL) and extracted with ethyl acetate (400 mL x 3). The organic layers were combined, washed with brine (200 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by silica gel column chromatography (ethyl acetate / petroleum ether 40:60) to give tert-butyl ((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)carbamate (25 g, purity: 95%, yield (2 steps): 70%). MS m/z 474.4 [M+H]+.

[383] Step 9: Preparation of 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide

[384] To a mixture of tert-butyl ((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)carbamate (33 g, 69.8 mmol) in THF (30 mL) was added 4 M HCl in dioxane (60 mL). The reaction was stirred at room temperature for 16 hours. Then the mixture was concentrated, and water (100 mL) was added. The mixture was basified with saturated K2CO3 solution to pH 9 and extracted with ethyl acetate (300 mL x 3). The organic layers were combined, washed with brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (24 g, purity: 95%, yield: 92%). The product is subjected to chiral-HPLC without further purification. MS m/z 374.2 [M+H]+.

[385] Step 10: Preparation of (3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide and (3S,4S)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide and (3R*,4S*/3S*,4R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide

[386] The mixture of isomers of 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (24.3 g, purity: 95%) was separated by SFC to afford the title compounds.

[387] Preparative chiral HPLC conditions: Instrument: SFC-200 (Waters); Column: AS 25x250mm, 10μm (Daicel); Column temperature: 35°C; Mobile phase: CO2/MeOH [0.2% NH3 (7M in MeOH)] 75:25; Flow rate: 120 ml/min; Back pressure: 100 bar; Detection wavelength: 214 nm; Cycle time: 8.6 min; Sample solution: 24 g dissolved in 700 ml methanol; Injection volume: 6.0 ml.

[388] Analytical chiral HPLC conditions: Column: AS-3 4.6*100mm 3μm, Column temperature: 40°C; Mobile phase: CO2/MeOH [0.2% NH3 (7M in MeOH)] 85:15; Flow rate: 3 ml/min; Back pressure: 2000 psi; Detection wavelength: 254 nm; Run time: 6 min; Injection volume: 5.00 μl.

[389] (3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (9.055 g, yield 38%). Chiral HPLC t=2.53min.

[390] (3S,4S)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (9.5 g, yield 40%). Chiral HPLC t=4.47min.

[391] (3R*,4S*/3S*,4R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (1.1 g, yield 4.6%). Chiral HPLC t=2.04/2.11min.

[392] Example 7: 4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methylpiperidine-1-sulfonamide

[393] Step 1: Preparation of tert-butyl 4-(2-chloroacetyl)-4-methyl-piperidine-1-carboxylate

[394] To a solution of 1-(tert-butyl) 4-ethyl 4-methylpiperidine-1,4-dicarboxylate (1.0 g, 3.69 mmol) and chloro(iodo)methane (2.59 g, 14.76 mmol) in THF (40 mL), LDA (2 M in THF, 9.23 mL) was added at -78°C. After addition, the reaction was stirred for 10 minutes, and then a solution of acetic acid (2 mL) in THF (20 mL) was added while keeping the reaction mixture temperature below -65°C. The mixture was stirred for an additional 10 minutes, quenched with water (80 mL) and extracted with ethyl acetate (60 mL x 2). The organic layers were combined, washed with brine (60 mL x 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate / petroleum ether = 0:100 to 10:90) to give tert-butyl 4-(2-chloroacetyl)-4-methyl-piperidine-1-carboxylate (864 mg, 85.0% yield). MS m/z 220.1 [M-55]+.

[395] Step 2: Preparation of tert-butyl 4-(2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-methylpiperidine-1-carboxylate

[396] A mixture of 5-fluoropyridine-2-carboxamidine (764 mg, 2.77 mmol), KHCO3 (1.09 g, 10.98 mmol) and tert-butyl 4-(2-chloroacetyl)-4-methyl-piperidine-1-carboxylate (1.51 g, 5.49 mmol) in DMF (20 mL) was stirred at 50°C for 16 h. The reaction mixture was quenched with water (40 mL) and extracted with ethyl acetate (40 mL x 3). The organic layers were combined, washed with brine (40 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product tert-butyl 4-(2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4- methylpiperidine-1-carboxylate (544 mg, 54.5% yield). MS m/z 361.6 [M+H]+.

[397] Step 3: Preparation of tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl) -1H-imidazol-5-yl)-4-methylpiperidine-1-carboxylate

[398] To a solution of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methyl-piperidine-1-carboxylate (544 mg, 1.5 mmol) in MeCN (5 mL) was added NCS (202 mg, 1.8 mmol). The reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer were combined, washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate / petroleum ether 70:30 to 100:0) to give tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-methylpiperidine-1-carboxylate (338 mg, 57% yield). MS m/z 395.3 [M+H]+.

[399] Step 4: Preparation of 2-(4-chloro-5-(4-methylpiperidin-4-yl)-1H-imidazol -2-yl)-5-fluoropyridine

[400] To a solution of tert-butyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methyl-piperidine-1-carboxylate (96 mg, 0.243 mmol) in DCM (2 mL) was added TFA (1 mL) at 0°C. The reaction was stirred at room temperature for 2 h. The resulting mixture was concentrated to give the crude product 2-(4-chloro-5-(4-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (54 mg, 75% yield). MS m/z 295.3 [M+H]+.

[401] Step 5: Preparation of tert-butyl ((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4–methylpiperidin-1-yl)sulfonyl)carbamate

[402] A solution of [1-(ethoxycarbonylsulfamoyl)-4-pyridylidene]-dimethyl-ammonium (54 mg, 0.18 mmol), 2-[4-chloro-5-(4-methyl-4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine (66 mg, 0.22 mmol) and TEA (36 mg, 0.36 mmol) in DCM (4 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (ethyl acetate / petroleum ether 50:50 to 70:30) to give tert-butyl ((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-methylpiperidin-1-yl)sulfonyl)carbamate (44 mg, 51.7% yield). MS m/z 474.1 [M+H]+.

[403] Step 6: Preparation of 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methylpiperidine-1-sulfonamide

[404] To a solution of tert-butyl N-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methyl-1- piperidyl]sulfonyl]carbamate (44 mg, 0.093 mmol) in DCM (0.9 mL) was added TFA (0.3 mL) at 0°C. The reaction was stirred at room temperature for 1 h. The resulting mixture was concentrated and purified by prep-HPLC to afford title compound (4.2 mg, 12.1% yield).

[405] Example 8: (3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-3-methylpiperidine-1-sulfonamide

[406] Step 1: Resolution of 2-(4-chloro-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine: Preparation of 2-(4-chloro-5-((3S*,4R*/3R*,4S*)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine, 2-(4-chloro-5-((3S,4S)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[407] The mixture of isomers of 2-(4-chloro-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (1.6 g) was separated by SFC to afford the title compounds.

[408] Preparative chiral HPLC conditions: Instrument: Instrument: SFC-150 (Waters); Column: AS 20x250mm, 10μm (Daicel); Column temperature: 35°C; Mobile phase: CO2/EtOH (0.5% NH3 (7M in MeOH) 80:20; Flow rate: 100 ml/min; Back pressure: 100 bar;

Detection wavelength: 214 nm; Cycle time: 4.3 min; Sample solution: 1600 mg dissolved in 100 ml methanol; Injection volume: 2.0 ml.

[409] Analytical chiral HPLC conditions: Column: AS-H 4.6*100mm 5µm; Column temperature: 40°C; Mobile phase: CO2/EtOH (0.5% NH3 (7M in MeOH) 90:10; Flow rate: 3 ml/min; Back pressure: 2000 psi; Detection wavelength: 214 nm; Run time: 7 min; Injection volume: 5.00 µl.

[410] 2-(4-Chloro-5-((3S*,4R*/3R*,4S*)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (500 mg, impure). MS (method A) 295.1 (M+H)+, t=1.48min. 1H NMR (500 MHz, DMSO-d6) δ (selected signals) 8.61 – 8.54 (m, 1H), 8.03 (m, 1H), 7.85 – 7.76 (m, 1H), 3.31 – 3.22 (m, 2H), 3.20 – 2.73 (m, 2H), 2.48 – 2.26 (m, 1H), 2.19 – 1.90 (m, 2H), 1.73 – 1.45 (m, 1H), 0.99 – 0.54 (m, 3H) ppm. Chiral HPLC t=1.32min.

[411] 2-(4-Chloro-5-((3S,4S)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (400 mg, purity: 99%, yield 25%). MS (method A) m/z 295.1 (M+H)+, t=1.41min. 1H NMR (500 MHz, DMSO-d6) δ 8.60 (d, J = 2.5 Hz, 1H), 7.99 (dd, J = 8.5, 4.5 Hz, 1H), 7.82 (td, J = 9.0, 3.0 Hz, 1H), 3.03 (d, J = 13.0 Hz, 2H), 2.77 (d, J = 2.0 Hz, 2H), 2.57 – 2.51 (m, 1H), 2.39 – 2.23 (m, 1H), 1.94 – 1.84 (m, 1H), 1.40 (d, J = 11.0 Hz, 1H), 0.86 (d, J = 7.0 Hz, 3H) ppm. Chiral HPLC t=2.74min.

[412] 2-(4-Chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (420 mg, purity: 100%, yield 26%). MS (method A) m/z 295.2 (M+H)+, t=1.41min. 1H NMR (500 MHz, DMSO-d6) δ 8.60 (d, J = 2.5 Hz, 1H), 7.99 (dd, J = 8.5, 4.5 Hz, 1H), 7.82 (td, J = 9.0, 3.0 Hz, 1H), 3.03 (d, J = 13.0 Hz, 2H), 2.77 (d, J = 2.0 Hz, 2H), 2.56 – 2.51 (m, 1H), 2.38 – 2.23 (m, 1H), 1.90 (s, 1H), 1.39 (d, J = 11.0 Hz, 1H), 0.86 (d, J = 7.0 Hz, 3H) ppm. Chiral HPLC t=3.64min.

[413] Step 2: Preparation of 3-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)oxazolidin-2-one

[414] To a solution of sulfurisocyanatidic chloride (48 mg, 0.34 mmol) in dichloromethane (2 mL) was added 2-bromoethan-1-ol (43 mg, 0.34 mmol) under N2. The solution was cooled to 0°C and stirred for 1 hour. Then 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (100 mg, 0.34 mmol) and triethylamine (103 mg, 1.02 mmol) were added. The mixture was stirred at room temperature

for 4 h. The reaction was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (ethyl acetate / petroleum ether 40:60) to afford the title compound (110 mg, yield: 73%). MS m/z 444.1 [M+H]+.

[415] Step 3: Preparation of (3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-3-methylpiperidine-1-sulfonamide

[416] To a solution of 3-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)oxazolidin-2-one (110 mg, 0.25 mmol) in ethanol (2 mL) was added a solution of sodium hydroxide (12 mg, 0.3 mmol) in water (2 mL). The reaction was stirred at room temperature for 2 h. Then the mixture was concentrated under reduced pressure and then water (20 mL) was added. The resulting mixture was extracted with ethyl acetate (25 mL x 3), washed with brine (20 mL x 2), dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC to afford the title compound (68.5 mg, 0.16 mmol, yield: 66%).

[417] Example 9: (3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxamide

[418] To a solution of 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (80 mg, 0.27 mmol) in dichloromethane (2 mL) was added DIEA (70 mg, 0.54 mmol) at 0°C and stirred for 10 min. Then trimethylsilylisocyanate (31 mg, 0.41 mmol) was added slowly. The reaction was stirred at room temperature for 16 h. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (57.3 mg, 0.17 mmol, yield: 62%).

[419] Example 10: 2-(4-Chloro-5-((3R,4R)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[420] To a solution of 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (80 mg, 0.27 mmol) in dichloromethane (2 mL) was added DIEA (176

mg, 1.36 mmol) at 0°C and stirred for 10 min. Then methanesulfonyl chloride (47 mg, 0.41 mmol) was added slowly. The reaction was stirred at room temperature for 2 h. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (45.3 mg, 0.12 mmol, yield: 45%).

[421] Example 11: 1-((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)ethan-1-one

[422] To a solution of 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (80 mg, 0.27 mmol) in dichloromethane (2 mL) was added DIEA (105 mg, 0.82 mmol) at 0°C and stirred for 10 min. And then acetyl chloride (25 mg, 0.33 mmol) was added slowly. The reaction was stirred at room temperature for 2 h. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (50.6 mg, 0.15 mmol, yield: 56%).

[423] Example 12 and Example 13: (3S*,4S*)-4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (Example 12) and (3R*,4R*)-4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (Example 13)

[424] Step 1: Preparation of 5-fluoropicolinimidamide

[425] To a solution of 4-fluoro-benzonitrile (20 g, 164 mmol) in dry THF (300 mL) was added LiHMDS (1M in THF, 328 mL, 328 mmol) slowly at -78°C. The reaction was stirred at room temperature for 2 h. The reaction was quenched with saturated ammonium chloride (300 mL) and extracted with dichloromethane (300 mL x 3). The organic layers were combined, washed with brine (200 mL x 3), dried over anhydrous sodium sulfate and concentrated to give 5-fluoropicolinimidamide (8 g, 35% yield). MS m/z 140 [M+H]+.

[426] Step 2: Preparation of 2-(4-ethyl-1H-imidazol-2-yl)-5-fluoropyridine

[427] To a solution of 5-fluoropicolinimidamide (5 g, 36 mmol) in EtOH (30 ml) was added 1-bromobutan-2-one (5.6 g, 36 mmol) and K2CO3 (4.9 g, 36 mmol). The reaction mixture was stirred at 80°C for 16 h. The resulting mixture was diluted with water (200 mL) and extracted with EA (200 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated to give 2-(4-ethyl-1H-imidazol-2-yl)-5-fluoropyridine (3 g, crude), which was used for the next step without further purification. MS m/z 192 [M+H]+.

[428] Step 3: Preparation of 2-(5-bromo-4-ethyl-1H-imidazol-2-yl)-5-fluoro-pyridine

[429] To a solution of 2-(4-ethyl-1H-imidazol-2-yl)-5-fluoro-pyridine (3 g, 15 mmol) in MeCN (100 mL) was added N-bromosuccinimide (3.2 g, 18 mmol). The reaction was stirred at room temperature for 16 h. The resulting mixture was diluted with EA (200 mL), washed with brine (200 mL x 3), dried over anhydrous sodium sulfate and concentrated. The crude was purified by column chromatography on silica gel (ethyl acetate/petroleum ether 20:80) to give 2-(5-bromo-4-ethyl-1H-imidazol-2-yl)-5-fluoro-pyridine (3.2 g, 75.5% yield). MS m/z 270 [M+H]+.

[430] Step 4: Preparation of a mixture of 2-[[5-bromo-4-ethyl-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-bromo-5-ethyl-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane

[431] To a solution of 2-(5-bromo-4-ethyl-1H-imidazol-2-yl)-5-fluoro-pyridine (1 g, 3.7 mmol) in THF (dry, 30 mL) was added NaH (133 mg, 5.5 mmol) and 2-(chloromethoxy)ethyl-trimethyl-silane (926 mg, 5.5 mmol) at 0°C. The reaction was stirred at room temperature for 4 h. The mixture was diluted with EA (100 mL), washed with brine (100 mL x 3), dried over anhydrous sodium sulfate and concentrated. The crude was purified by column chromatography (petroleum ether/ethyl acetate = 1/5) to afford the subtitle compounds (700 mg, 47.2% yield). MS m/z 400 [M+H]+.

[432] Step 5: Preparation of a mixture of tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate and tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate

[433] To a solution of a mixture of 2-[[5-bromo-4-ethyl-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-bromo-5-ethyl-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (700 mg, 1.7 mmol) in dioxane (30 mL) and water (3 mL) were added (1-(tert-butoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridin-4-yl)boronic acid (750 mg, 2.5 mmol), potassium carbonate (470 mg, 3.4 mmol) and Pd(tbdpf)Cl2 (115 mg, 0.17 mmol) under nitrogen atmosphere. The reaction was stirred at 70°C for 4 hours. Then the mixture was quenched with water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 20:80) to afford the subtitle compounds (741 mg, 1.43 mmol, yield: 85%). MS m/z 517 [M+H]+.

[434] Step 6: Preparation of a mixture of tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate

[435] To a solution of a mixture of tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate and tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (741 mg, 1.43 mmol) in methanol (10 mL) was added Pd/C (10%, 100 mg). The reaction was stirred under hydrogen at room temperature for 16 hours. The mixture was filtered and the solid washed with methanol (10 mL x 3). The combined filtrates were concentrated and the residue purified by flash chromatography (ethyl acetate / petroleum ether 30:70) to give a mixture of tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate (703 mg, 1.35 mmol, 95% yield). MS m/z 519 [M+H]+.

[436] Step 7: Preparation of 2-(4-ethyl-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[437] To a solution of a mixture of tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl 4-[5-ethyl-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate (800 mg, 1.54 mmol) in 1,4-dioxane (20 mL) was added 4 M HCl in dioxane (20 mL). The reaction was stirred at room temperature for 16 hours. LCMS showed the reaction was completed. Then the mixture was concentrated to give the product 2-(4-ethyl-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (400 mg, 1.38 mmol, crude), which was used in the next step without further purification. MS m/z 289 [M+H]+.

[438] Step 8: Preparation of tert-butyl ((4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)carbamate

[439] To a solution of 2-(4-ethyl-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (270 mg, 0.93 mmol) in DCM (10 mL) were added DIEA (232 mg, 1.86 mmol) and (tert-butoxycarbonyl)((4-(dimethyliminio)pyridin-1(4H)-yl)sulfonyl)amide (308 mg, 0.99 mmol). The reaction was stirred at room temperature for 4 hours. Then the mixture was quenched with water (50 mL) and extracted with ethyl acetate (100 mL x 3). The organic layers were combined, washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by silica gel column chromatography (ethyl acetate / petroleum ether 50:50) to give tert-butyl ((4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)carbamate (340 mg, 0.72 mmol, 78% yield). MS m/z 468 [M+H]+.

[440] Step 9: Preparation of 4-[4-ethyl-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-sulfonamide

[441] To a solution of tert-butyl N-[[4-[4-ethyl-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]carbamate (370 mg, 1 mmol) in 1,4-dioxane (5 mL) was added 4 M HCl in dioxane (5 mL). The reaction was stirred at room temperature for 2 hours. Then the mixture was concentrated, and water (40 mL) was added. The mixture was basified with saturated K2CO3 solution to pH = 9 and extracted with ethyl acetate (40 mL x 3). The organic layers were combined, washed with brine (60 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give 4-[4-ethyl-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-sulfonamide (250 mg, 0.68 mmol, 68% yield).

[442] Step 10: Preparation of (3R*,4R*)-4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide and (3S*,4S*)-4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide

[443] The isomers of 4-[4-ethyl-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-sulfonamide were separated by chiral SFC to afford the title compounds.

[444] Preparative chiral separation conditions: Instrument: SFC-150 (Waters); Column: AS 25x250mm, 10μm (Daicel); Column temperature: 35°C; Mobile phase: CO2/MeOH [0.2% NH3 (7M in MeOH) 70:30; Flow rate: 100ml/min; Back pressure: 100bar; Detection wavelength: 214nm; Cycle time: 4.5min; Sample solution: 270mg dissolved in 25ml methanol; Injection volume: 1ml.

[445] Analytical chiral separation conditions: Column: AS3 4.6x100mm, 3μm; Column temperature: 40°C; Mobile phase: CO2/MeOH [0.2% NH3 (7M in MeOH) 80:20; Flow rate: 3ml/min; Back pressure: 2000psi; Detection wavelength: 214nm; Run time: 5min; Injection volume: 5μl.

[446] (3R*,4R*)-4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (70 mg, 28% yield). Chiral HPLC 1.54min.

[447] (3S*,4S*)-4-(4-ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide (90 mg, 36% yield). Chiral HPLC 1.23min.

[448] Example 14: Methyl (((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycinate

[449] To a solution of 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (150 mg, 0.51 mmol) in dichloromethane (3 mL) was added triethylamine (155 mg, 1.53 mmol) under N2. And then methyl (chlorosulfonyl)glycinate (954 mg, 5.10 mmol) was added. The mixture was stirred at room temperature for 16 h. The reaction was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 40:60) to afford the title compound (120 mg, 0.27 mmol, yield: 53%).

[450] Example 15: (((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycine

[451] To a solution of methyl (((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycinate (90 mg, 0.20 mmol) in THF (2 mL) was added a solution of lithium hydroxide (15 mg, 0.6 mmol) in water (2 mL). The reaction was stirred at room temperature for 2 h. The mixture was extracted with ethyl acetate (15 mL x 3), washed with brine (10 mL x 2), dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-HPLC to afford the title compound (74 mg, 0.17 mmol, yield: 85%).

[452] Example 16: 2-(4-Chloro-5-((3S,4S)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[453] To a solution of 2-(4-chloro-5-((3S,4S)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (100 mg, 0.34 mmol) in dichloromethane (2 mL) was added DIEA (132 mg, 1.02 mmol) at 0°C and stirred for 10 min. And then methanesulfonyl chloride (58 mg, 0.51 mmol) was added slowly. The reaction was stirred at room temperature for 2 h. The mixture was quenched with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (19.6 mg, 0.05 mmol, yield: 15%).

[454] Example 17: 2-(4-Chloro-5-((3R*,4S*/3S*,4R*)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[455] To a solution of 2-(4-chloro-5-((3R*,4S*/3S*,4R*)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (200 mg, 0.68 mmol) in THF (4 mL) was added DIEA (263 mg, 2.04 mmol) at 0°C and stirred for 10 min. And then methanesulfonyl chloride (116 mg, 1.02 mmol) was added slowly. The reaction was stirred at room temperature for 2 h. The mixture was quenched with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate,

filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (16.3 mg, 0.04 mmol, yield: 6%).

[456] Example 18: 1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxamide

[457] Step 1: Preparation of methyl-1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylate

[458] To a solution of 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (190 mg, 0.65 mmol) in THF (2 mL) was added DIEA (167 mg, 1.3 mmol) at 0°C and stirred for 10 min. And then methyl-1-(chlorosulfonyl)azetidine-3-carboxylate (96 mg, 0.78 mmol) was added slowly. The reaction was stirred at room temperature for 16 h. The mixture was quenched with water (30 mL) and extracted with EA (30 mL x 3). The combined organic layer was washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 30:70) to afford the subtitle compound (180 mg, 0.38 mmol, yield: 59%). MS m/z 472.1 [M+H]+.

[459] Step 2: Preparation of 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylic acid

[460] To a solution of methyl 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylate (180 mg, 0.38 mmol) in MeOH (2 mL) was added a solution of sodium hydroxide (76 mg, 1.91 mmol) in water (2 mL). The reaction was stirred at room temperature for 16 h. Then the mixture was diluted with water (20 mL), acidified with 1 M HCl solution to pH 4, and extracted with ethyl acetate (20 mL x 3). The organic phases were combined, washed with brine (20 mL x 2), dried over sodium sulfate, filtered, and concentrated in vacuum to afford the subtitle compound (130 mg, 0.28 mmol, yield: 74%). MS m/z 458.0 [M+H]+.

[461] Step 3: Preparation of 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxamide

[462] To a solution of 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylic acid (100 mg, 0.22 mmol) in DCM

(2 mL) were added DIEA (225 mg, 1.75 mmol), NH4Cl (59 mg, 1.09 mmol), EDCI (83 mg, 0.44 mmol) and HOBt (59 mg, 0.44 mmol). The reaction was stirred at room temperature for 16 hours. Then the crude product was purified by prep-HPLC to afford the title compound (83.6 mg, 0.18 mmol, yield: 84%).

[463] Example 19: (S*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[464] Step 1: Preparation of 5-fluoro-2-(1H-imidazol-2-yl)pyridine

[465] To a mixture of 5-fluoropicolinaldehyde (100.0 g, 799.35 mmol) and oxalaldehyde (463.91 g, 7.99 mol) in EtOH (2000 mL) was added NH3*H2O (560.28 g, 15.99 mol) dropwise at 0°C under N2 atmosphere. The reaction mixture was stirred at room temperature for 16 hours. Then the solvent was removed under reduced pressure. The residue was poured into water (2000 mL) and extracted with DCM (1000 mL x 3). The combined organic layers were washed with brine (3000 mL x 2), dried with Na2SO4, filtered and concentrated to give the crude product 5-fluoro-2-(1H-imidazol-2-yl)pyridine (100 g) which was used directly in the next step. MS m/z 164.1 (M+H)+.

[466] Step 2: Preparation of 2-(4,5-diiodo-1H-imidazol-2-yl)-5-fluoropyridine

[467] 5-Fluoro-2-(1H-imidazol-2-yl)pyridine (100 g, 612.91 mmol) was dissolved acetonitrile (1000 ml) under N2 atmosphere. Then, NIS (303.4 g, 1.35 mol) was added in several portions at 0°C. The reaction mixture was stirred at room temperature for 6 hours. Then the solvent was removed. The residue was poured into water (2000 mL) and extracted with ethyl acetate (1000 mL x 3). The organic layers were washed with brine (1000 mL x 3), dried with Na2SO4, filtered and concentrated to afford the crude subtitle compound (219 g) which was used directly in the next step. MS m/z 415.8 (M+H)+.

[468] Step 3: Preparation of 5-fluoro-2-(4-iodo-1H-imidazol-2-yl)pyridine

[469] To a solution of 2-(4,5-diiodo-1H-imidazol-2-yl)-5-fluoropyridine (219 g, 527.78 mmol) in DMF (2000 mL) and water (1000 mL) was added Na2SO3 (399 g, 3.166 mol) in several portions. The reaction was stirred at 120°C for 16 hours. Then the reaction mixture was poured into water (5000 mL) and extracted with ethyl acetate (3000 mL x 3). The combined organic layers were washed with brine (5000 mL x 3), dried with Na2SO4, filtered

and concentrated to give the crude product 5-fluoro-2-(4-iodo-1H-imidazol-2-yl)pyridine (130 g) which was used directly in the next step. MS m/z 289.9 (M+H)+.

[470] Step 4: Preparation of a mixture of 5-fluoro-2-(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyridine and 5-fluoro-2-(5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyridine

[471] To a solution of 5-fluoro-2-(4-iodo-1H-imidazol-2-yl)pyridine (130 g, 0.45 mol) in THF (2000 mL) was added NaH (26.99 g, 0.675 mol, 60%) in several portions at 0°C under N2 atmosphere. The resulting mixture was stirred at 0°C for 1 hour. Then, SEM-Cl (90 g, 0.54 mol) was added dropwise maintaining the temperature at 0°C. The reaction was stirred at room temperature for another 6 hours. The reaction mixture was quenched by adding water (2000 mL) slowly and extracted with ethyl acetate (2000 mL x 3). The combined organic layers were washed with brine (5000 mL x 2), dried with Na2SO4, filtered and concentrated. The residue was purified by flash column chromatography (Biotage Flash, ethyl acetate/petroleum ether 25:75) to afford the subtitle compounds (170 g, 0.405 mol, yield: 50.7% in 4 steps). MS m/z 420.0 (M+H)+.

[472] Step 5: Preparation of a mixture of 2-(5-chloro-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-chloro-5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine

[473] To a solution of a mixture of 5-fluoro-2-(4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyridine and 5-fluoro-2-(5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyridine (10 g, 23.9 mmol) in THF (100 mL) was added NCS (3.81 g, 28.6 mmol) in several portions. The reaction mixture was stirred at 40°C for 16 h. The mixture was poured into water (150 mL) and extracted with EA (150 mL x 3). The organic layers were washed with brine (150 mL x 2), dried with Na2SO4 and concentrated. The crude was purified by flash chromatography (ethyl acetate / petroleum ether 20:80) to give the desired mixture of 2-(5-chloro-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-chloro-5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (5.6 g, 12.4 mmol, yield: 52%). MS m/z 454.0 [M+H]+.

[474] Step 6: Preparation of a mixture of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate and tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate

[475] To a solution of a mixture of 2-(5-chloro-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-chloro-5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (1 g, 2.2 mmol) in THF (10 mL) were added (1-(tert-butoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridin-4-yl)boronic acid (798 mg, 3.3 mmol) and potassium carbonate (914 mg, 6.6 mmol) in water (2 mL). And then Pd(dtbpf)Cl2 (285 mg, 0.44 mmol) was added under N2 atmosphere. The reaction was stirred at 80°C for 16 h. The reaction mixture was quenched with adding water (80 mL) and extracted with EA (80 mL x 3). The combined organic layers were washed with brine (80 mL x 2), dried and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 30:70) to give a mixture of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate and tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (500 mg, 0.96 mmol, yield: 43 %). MS m/z 523.2 [M+H]+.

[476] Step 7: Preparation of 2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[477] A mixture of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate and tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (500 mg, 0.96 mmol) and TFA (4 mL) was stirred at room temperature for 2 hours. Then the mixture was concentrated, diluted with water (20 mL), basified with saturated K2CO3 solution to pH 9 and extracted with ethyl acetate (40 mL x 3). The organic layers were combined, washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give 2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (200 mg, 0.68 mmol,

yield: 72%). The crude product is subjected to chiral HPLC without further purification. MS m/z 293.1 [M+H]+.

[478] Step 8: Preparation of (S*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine and (R*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[479] The enantiomeric mixture 2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (270 mg) was separated by chiral HPLC to give (S*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (130 mg) and (R*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (125 mg).

[480] Preparative chiral HPLC conditions: Instrument: SFC-150 (Waters); Column: AD 25x250mm, 10µm (Daicel); Column temperature: 35°C; Mobile phase: CO2/ MeOH (0.2% NH3(7M in MeOH) 75:25; Flow rate: 100 ml/min; Back pressure: 100 bar; Detection wavelength: 214 nm; Cycle time: 3.0 min; Sample solution: 300 mg dissolved in 35 ml methanol; Injection volume: 1.0 ml.

[481] Analytical chiral HPLC conditions: Column: AD-H 4.6x100µm, 5µm; Column temperature: 40°C; Mobile phase: CO2/ MeOH (0.2% NH3(7M in MeOH) 75:25; Flow rate: 3ml/min; Back pressure: 2000psi; Detection wavelength: 214 nm; Run time: 4.0 min; Injection volume: 7.00 µl. (S*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine. Chiral HPLC 0.87 min. (R*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine. Chiral HPLC 1.12min.

[482] Step 9: Preparation of (S*)-2-(4-chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[483] To a solution of (S*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (65 mg, 0.22 mmol) in DCM (2 mL) was added DIEA (86 mg, 0.67 mmol) at 0°C. Then methanesulfonyl chloride (30 mg, 0.27 mmol) was added dropwise. The reaction was stirred at room temperature for 3 hours. Then the mixture was quenched with water (10 mL) and extracted with DCM (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and

concentrated. The crude product was purified by prep-HPLC to afford the title compound (36.5 mg, 0.10 mmol, yield: 44%).

[484] Example 20: (R*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine

[485] To a solution of (R*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (60 mg, 0.21 mmol) in DCM (2 mL) was added DIEA (80 mg, 0.62 mmol) at 0°C. Then methanesulfonyl chloride (28 mg, 0.25 mmol) was added slowly. The reaction was stirred at room temperature for 3 hours. Then the mixture was quenched with water (10 mL) and extracted with DCM (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (28.1 mg, 0.08 mmol, yield: 37%).

[486] Example 21: (S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide

[487] Step 1: Preparation of tert-butyl (S*)-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)carbamate

[488] To a solution of (S*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (65 mg, 0.22 mmol) in DCM (2 mL) were added DIEA (86 mg, 0.67 mmol) and (tert-butoxycarbonyl)((4-(dimethyliminio)pyridin-1(4H)-yl)sulfonyl)amide (67 mg, 0.22 mmol). The reaction was stirred at room temperature for 2 hours. Then the mixture was quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate / petroleum ether 50:50) to give tert-butyl (S*)-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)carbamate (72 mg, 0.15 mmol, yield: 68%). MS m/z 472.0 [M+H]+.

[489] Step 2: Preparation of (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide

[490] A mixture of tert-butyl (S*)-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)carbamate (72 mg, 0.15 mmol) and 4 M HCl in dioxane (4 mL) was stirred at room temperature for 16 hours. Then the mixture was concentrated, diluted with water (10 mL), basified with saturated K2CO3 solution to pH 9, and extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (27.6 mg, 0.07 mmol, yield: 49%).

[491] Example 22: (R*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide

[492] Step 1: Preparation of tert-butyl (R*)-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)carbamate

[493] To a solution of (R*)-2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (80 mg, 0.27 mmol) in DCM (2 mL) were added DIEA (106 mg, 0.82 mmol) and (tert-butoxycarbonyl)((4-(dimethyliminio)pyridin-1(4H)-yl)sulfonyl)amide (82 mg, 0.27 mmol). The reaction was stirred at room temperature for 2 hours. Then the mixture was quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate / petroleum ether 50:50) to give tert-butyl (R*)-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)carbamate (88 mg,0.19 mmol, yield 68%). MS m/z 472.1 [M+H]+.

[494] Step 2: Preparation of (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide

[495] A mixture of tert-butyl (R*)-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)carbamate (88 mg, 0.19 mmol) and 4 M HCl in 1,4-dioxane (4 mL) was stirred at room temperature for 16 hours. Then the mixture was concentrated, diluted with water (10 mL), basified with saturated K2CO3 solution to pH 9, and extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed

with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (44.4 mg, 0.12 mmol, yield: 64%).

[496] Example 23: 2-(5-((3R,4R)-1-((1H-Pyrazol-4-yl)sulfonyl)-3-methylpiperidin-4-yl)-4-chloro-1H-imidazol-2-yl)-5-fluoropyridine

[497] To a solution of 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (60 mg, 0.20 mmol) in THF (2 mL) was added DIEA (53 mg, 0.41 mmol) at 0°C and stirred for 10 min. And then 1H-pyrazole-4-sulfonyl chloride (41 mg, 0.24 mmol) was added slowly. The reaction was stirred at room temperature for 16 h. The mixture was quenched with water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (22.1 mg, 0.05 mmol, yield: 25%).

[498] Example 24: Methyl 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylate

[499] To a solution of 2-(4-chloro-5-((3R,4R)-3-methylpiperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (190 mg, 0.65 mmol) in THF (2 mL) was added DIEA (167 mg, 1.3 mmol) at 0°C and stirred for 10 min. And then methyl 1-(chlorosulfonyl)azetidine-3-carboxylate (96 mg, 0.78 mmol) was added slowly. The reaction was stirred at room temperature for 16 h. The mixture was quenched with water (30 mL) and extracted with EA (30 mL x 3). The combined organic layer was washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 30:70) to afford the title compound (180 mg, 0.38 mmol, yield: 59%).

[500] Example 25: 1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylic acid

[501] To a solution of methyl 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylate (180 mg, 0.38 mmol) in MeOH (2 mL) was added a solution of sodium hydroxide (76 mg, 1.91 mmol) in water (2 mL). The reaction was stirred at room temperature for 16 h. Then the mixture was diluted with water (20 mL), acidified with 1 M HCl solution to pH 4 and extracted with ethyl acetate (20 mL x 3). The organic phases were combined, washed with brine (20 mL x 2), dried over sodium sulfate, filtered and concentrated in vacuum to afford the title compound (130 mg, 0.28 mmol, yield: 74%).

[502] Example 26: 2-(4-Bromo-5-(2,3-difluorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[503] Step 1: Preparation of 2-(4,5-dibromo-1H-imidazol-2-yl)-5-fluoro-pyridine

[504] To a solution of 5-fluoro-2-(1H-imidazol-2-yl)pyridine (350 mg, 2.15 mmol) in chloroform (7 mL) was added NBS (764 mg, 4.29 mmol) under N2 atmosphere. The reaction was stirred at room temperature for 2 h. The mixture was quenched with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layers were combined, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography (ethyl acetate / petroleum ether 30:70) to give 2-(4,5-dibromo-1H-imidazol-2-yl)-5-fluoro-pyridine (650 mg, 2.03 mmol, 94% yield). MS m/z 321.6 [M+H]+.

[505] Step 2: Preparation of 2-(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine

[506] To a solution of 2-(4,5-dibromo-1H-imidazol-2-yl)-5-fluoropyridine (300 mg, 0.93 mmol) in THF (10 mL) at 0°C under N2 atmosphere was added NaH (45 mg, 1.12 mmol, 60%) slowly. The reaction mixture was stirred at 0°C for 30 min. Then, SEM-Cl (202 mg, 1.21 mmol) was added dropwise maintaining the temperature at 0°C and the reaction mixture was stirred at room temperature for another 2 h. The reaction mixture was quenched with adding water (30 mL) slowly and extracted with EA (50 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 15:85) to give 2-

(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (355 mg, 0.79 mmol, yield: 84%). MS m/z 450.0 [M+H]+.

[507] Step 3: Preparation of a mixture of 2-(4-bromo-5-(2,3-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-bromo-4-(2,3-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine

[508] To a solution of 2-(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (300 mg, 0.67 mmol) in 1,4-dioxane (6 mL) and water (1.2 mL) were added (2,3-difluorophenyl)boronic acid (105 mg, 0.67 mmol), sodium carbonate (211 mg, 2 mmol), and Pd(dppf)Cl2 (49 mg, 0.07 mmol) under nitrogen atmosphere. The reaction was stirred at 80°C for 18 hours. Then the mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 40:60) to give a mixture of 2-(4-bromo-5-(2,3-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-bromo-4-(2,3-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (180 mg, 0.37 mmol, yield: 56%)

[509] Step 4: Preparation of 2-(4-bromo-5-(2,3-difluorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[510] A mixture of 2-(4-bromo-5-(2,3-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-bromo-4-(2,3-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (180 mg, 0.37 mmol) and TFA (5 mL) was stirred at room temperature for 2 hours. Then the mixture was concentrated, and the crude product was purified by prep-HPLC to afford the title compound (80 mg, 0.23 mmol, yield: 61 %).

[511] Example 27: 2-(4-Bromo-5-(2-chlorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[512] To a solution of 2-(4,5-dibromo-1H-imidazol-2-yl)-5-fluoropyridine (600 mg, 1.87 mmol) in 1,4-dioxane (6 mL) and water (1.2 mL) were added (2-chlorophenyl)boronic acid (292 mg, 1.87 mmol), potassium carbonate (774 mg, 5.6 mmol), CataCXium A (161 mg, 0.45

mmol) and Pd(OAc)2 (42 mg, 0.19 mmol) under nitrogen atmosphere. The reaction was stirred at 80°C for 18 hours. Then the mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC to afford the title compound (45.9 mg, 0.13 mmol, yield: 7%).

[513] Example 28: 2-[4-Chloro-5-(2-chloro-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[514] Step 1: Preparation of 2-(4-chloro-1H-imidazol-2-yl)-5-fluoropyridine

[515] 5-Fluoro-2-(1H-imidazol-2-yl)pyridine (3 g, 18.4 mmol) was dissolved in N,N-dimethylformamide (40 mL). Then N-chlorosuccinimide (2.4 g, 18.4 mmol) and acetic acid (1.1 g, 18.4 mmol) were added. The reaction was stirred at 60°C for 16 hours. Then water (80 mL) was added. The mixture was extracted with dichloromethane (100 mL x 3). The combined organic layer was washed with brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 25:75) to afford 2-(4-chloro-1H-imidazol-2-yl)-5-fluoropyridine (1.9 g, 9.6 mmol, yield: 52%). MS m/z 198 [M+H]+.

[516] Step 2: Preparation of 2-(5-bromo-4-chloro-1H-imidazol-2-yl)-5-fluoropyridine

[517] 2-(4-Chloro-1H-imidazol-2-yl)-5-fluoropyridine (1.9 g, 9.6 mmol) was dissolved in tetrahydrofuran (20 mL). The solution was cooled to 0°C. Then N-bromosuccinimide (2.1 g, 11.57 mmol) was added. The reaction was stirred at room temperature for 3 hours. Then water (80 mL) was added. The resulting mixture was extracted with dichloromethane (80 mL x 3). The combined organic layer was washed with brine (80 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 25:75) to afford 2-(5-bromo-4-chloro-1H-imidazol-2-yl)-5-fluoropyridine (2 g, 7.3 mmol, yield: 76%). MS m/z 278 [M+H]+.

[518] Step 3: Preparation of a mixture of 2-(5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine

[519] 2-(5-Bromo-4-chloro-1H-imidazol-2-yl)-5-fluoropyridine (1.8 g, 6.55 mmol) was dissolved in tetrahydrofuran (20 mL). The solution was cooled to 0°C. Then sodium hydride (236 mg, 9.82 mmol) was added. The mixture was stirred at 0°C for 30 min. Then 2-(trimethylsilyl)ethoxymethyl chloride (1.64 g, 9.82 mmol) was added. The reaction was stirred at room temperature for another 2 hours. Then water (50 mL) was added. The mixture was extracted with ethyl acetate (80 mL x 3). The combined organic layer was washed with brine (80 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 25:75) to afford a mixture of 2-(5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (2.5 g, 6.2 mmol, yield: 94%). MS m/z 349.9 [M+H]+.

[520] Step 4: Preparation of a mixture of 2-(4-chloro-5-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-chloro-4-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine

[521] To a solution of a mixture of 2-(5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (500 mg, 1.23 mmol) in 1,4-dioxane (6 mL) and water (1.2 mL) were added (2,3-difluorophenyl)boronic acid (443 mg, 1.48 mmol), sodium carbonate (263 mg, 2.46 mmol), and Pd(dtbpf)Cl2 (160 mg, 0.246 mmol) under nitrogen atmosphere. The reaction was stirred at 50°C for 2 hours. Then the mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 40:60) to give a mixture of 2-(4-chloro-5-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-chloro-4-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (130 mg, 0.248 mmol, yield: 20.1%). MS m/z 499.7 [M+H]+.

[522] Step 5: Preparation of 2-[4-chloro-5-(2-chloro-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[523] The mixture of 2-(4-chloro-5-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-chloro-4-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (100 mg, 0.2 mmol) was dissolved in trifluoroacetic acid (1 mL). The mixture was stirred at room temperature for 4 h. Then, the solvent was removed, and water (10 mL) was added. The mixture was basified with saturated K_2CO_3 solution to pH 9 and extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product which was purified by column chromatography (ethyl acetate / petroleum ether 50:50) to afford the title compound (60 mg, 0.162 mmol, yield: 81.1%).

[524] Example 29: 2-[4-Chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[525] Step 1: Preparation of a mixture of 2-[[4-chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane

[526] A mixture of 2-(4-chloro-5-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-chloro-4-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (70 mg, 0.14 mmol) was dissolved in acetone (1 mL) and water (0.3 mL). Then potassium monopersulfate triple salt (Oxone) (172 mg, 0.28 mmol) was added in one portion. The reaction was stirred at room temperature for 2 hours. Then the mixture was poured into water (5 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate / petroleum ether 50:50) to give a mixture of 2-[[4-chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-(2-chloro-4-

methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (70 mg, 0.129 mmol, yield: 92.1%). MS m/z 515.7 [M+H]+.

[527] Step 2: Preparation of 2-[4-chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[528] A mixture of 2-[[4-chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (100 mg, 0.194 mmol) was dissolved in trifluoroacetic acid (1 mL). The mixture was stirred at room temperature for 4 h. Then, the solvent was removed, and water (10 mL) was added. The mixture was basified with saturated K2CO3 solution to pH 9 and extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (ethyl acetate / petroleum ether 50:50) to afford the title compound (28.5 mg, 0.162 mmol, yield: 54.8%).

[529] Example 30: 2-[4-Chloro-5-(2-chloro-4-(methylsulfonimidoyl)phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[530] Step 1: Preparation of a mixture of 2-[[4-chloro-5-[2-chloro-4-(methylsulfonimidoyl)phenyl]-2-(5-fluoro- 2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-[2-chloro-4-(methylsulfonimidoyl)phenyl]-2-(5-fluoro- 2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane

[531] To a solution of a mixture of 2-(4-chloro-5-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(5-chloro-4-(2-chloro-4-(methylsulfinyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (120 mg, 0.24 mmol) and (NH4)2CO3 (46.1 mg, 0.48 mmol) in MeOH (2 mL), [acetoxy(phenyl)-lambda3-iodanyl] acetate (178 mg, 0.551 mmol) was added in one portion under N2 atmosphere. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed. The resulting mixture was poured into water (10 mL) and extracted with EA (20 mL x 3). The organic layers were combined, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was

purified by column chromatography (ethyl acetate / petroleum ether 50:50). This provided a mixture of 2-[[4-chloro-5-[2-chloro-4-(methylsulfonimidoyl)phenyl]-2-(5-fluoro- 2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-[2-chloro-4-(methylsulfonimidoyl)phenyl]-2-(5-fluoro- 2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (100 mg, 0.194 mmol, yield: 80.9%). MS m/z 514.7 [M+H]+.

[532] Step 2: Preparation of 2-[4-chloro-5-(2-chloro-4-(methylsulfonimidoyl)phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[533] A mixture of 2-[[4-chloro-5-[2-chloro-4-(methylsulfonimidoyl)phenyl]-2-(5-fluoro- 2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-[2-chloro-4-(methylsulfonimidoyl)phenyl]-2-(5-fluoro- 2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (100 mg, 0.194 mmol) was dissolved in trifluoroacetic acid (1 mL). The mixture was stirred at room temperature for 4 h. Then, the solvent was removed, and water (10 mL) was added. The mixture was basified with saturated K2CO3 solution to pH 9 and extracted with ethyl acetate (20 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product which was purified by column chromatography (ethyl acetate / petroleum ether 50:50) to afford the title compound (20.3 mg, 0.053 mmol, yield: 27.2%).

[534] Example 31: Methyl 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoate

[535] Step 1: Preparation of a mixture of methyl 3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate and methyl 3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate

[536] To a mixture of 2-(5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-5-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (250 mg, 0.615 mmol) and (2-chloro-4-methoxycarbonyl-phenyl)boronic acid (158 mg, 0.738 mmol) in THF (5 mL) and water (0.5 mL) were added Pd(dtbpf)Cl2 (80.1 mg, 0.123 mmol) and K2CO3 (170 mg, 1.23 mmol). The reaction was stirred at 70°C for 16 h under nitrogen. LCMS indicated the reaction was completed. The reaction mixture was cooled to room temperature, diluted with water (10

mL), acidified with 1 M HCl solution until pH 5 and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over anhydrous sodium sulfate and concentrated to give the residue, which was purified by silica gel column chromatography (ethyl acetate / petroleum ether 20:80) to give a mixture of methyl 3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate and methyl 3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate (133 mg, 0.255 mmol, yield: 41.4%). MS m/z 497 [M+H]+.

[537] Step 2: Preparation of methyl 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoate

[538] A solution of a mixture of methyl 3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate and methyl 3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate (133 mg, 0.268 mmol) in 4 M HCl in 1,4-dioxane (4 mL) was stirred at room temperature for 16 h. Then the reaction mixture was concentrated. The residue was diluted with water (5 mL), basified with sat. ammonium bicarbonate solution until pH 7 and extracted with ethyl acetate (15 ml x 3). The combined organic layers were washed with brine (15 mL x 3), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate) to afford the title compound (84.5 mg, 0.219 mmol, yield: 81.8%).

[539] Example 32: 3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoic acid

[540] To a solution of methyl 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoate (40 mg, 0.109 mmol) in MeOH (1 mL) was added a solution of lithium hydroxide monohydrate (91.7 mg, 2.18 mmol) in water (1 mL). The reaction mixture was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (10 mL), acidified with 1 M HCl solution until pH 5 and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over anhydrous sodium sulfate and concentrated to give the residue,

which was purified by prep-HPLC to afford the title compound (23.2 mg, 0.064 mmol, yield: 59.1%).

[541] Example 33: 3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide

[542] Step 1: Preparation of 4-bromo-3-chloro-N,N-bis[(2,4-dimethoxyphenyl)methyl]benzenesulfonamide

[543] To a solution of 4-bromo-3-chloro-benzenesulfonyl chloride (5.0 g, 17.2 mmol) in dichloromethane (50 mL) was added 1-(2,4-dimethoxyphenyl)-N-[(2,4-dimethoxyphenyl)methyl]methanamine (6.57 g, 20.7 mmol) and triethylamine (6.98 g, 69.0 mmol) slowly. The reaction was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was concentrated to give the crude product, which was purified by silica gel column chromatography (ethyl acetate / petroleum ether 50:50) to afford 4-bromo-3-chloro-N,N-bis[(2,4-dimethoxyphenyl)methyl]benzenesulfonamide (9.8 g, 17.2 mmol, yield: 99.5%). MS (method B) 2.51min.

[544] Step 2: Preparation of 4-bromo-3-chloro-N,N-bis[(2,4-dimethoxyphenyl)methyl]benzenesulfonamide

[545] A mixture of 4-bromo-3-chloro-N,N-bis[(2,4-dimethoxyphenyl)methyl]benzenesulfonamide (9.8 g, 17.2 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.23 g, 20.6 mmol), Pd(dppf)Cl2*DCM (628 mg, 0.858 mmol) and potassium acetate (5.05 g, 51.5 mmol) in dry 1,4-dioxane (100 mL) was stirred at 80°C for 6 h under nitrogen atmosphere. LCMS indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography (Biotage, ethyl acetate / petroleum ether 40:60) to afford 4-bromo-3-chloro-N,N-bis[(2,4-dimethoxyphenyl)methyl]benzenesulfonamide (11 g, 16.9 mmol, yield: 98.5%). MS (method E) 1.99min.

[546] Step 3: Preparation of [4-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-chloro-phenyl]boronic acid

[547] To a solution of 3-chloro-N,N-bis[(2,4-dimethoxyphenyl)methyl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (11 g, 16.9 mmol) in acetone (100 mL) and water (30 mL) was added ammonium acetate (3.6 g, 47.3 mmol) and sodium periodate (11.9 g, 55.8 mmol) in potions. The reaction was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography (Biotage, ethyl acetate / petroleum ether 50:50) to give [4-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-chloro-phenyl]boronic acid (2.5 g, 4.43 mmol, yield: 26.2%). MS (method E) 1.98min.

[548] Step 4: Preparation of a mixture of 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide and 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide

[549] A mixture of 2-[[5-bromo-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-bromo-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1.1 g, 2.95 mmol), [4-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-chloro-phenyl]boronic acid (1.58 g, 2.95 mmol), Pd(dtbpf)Cl2 (385 mg, 0.591 mmol) and potassium carbonate (817 mg, 5.91 mmol) were added to 1,4-dioxane (15 ml) and water (3 ml). The reaction mixture was stirred at 70°C for 16 h under nitrogen. LCMS indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (Biotage, ethyl acetate / petroleum ether 15:85) to give a mixture of 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide and 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide (1.37 g, 1.95 mmol, yield: 65.2%). MS m/z 633 [M+H]+.

[550] Step 5: Preparation of 3-chloro-4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide

[551] A mixture of 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide and 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide (870 mg, 1.24 mol) in TFA (10 mL) was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure. The residue was basified with sat. sodium bicarbonate solution until pH 8, extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate / petroleum ether 70:30) to give 3-chloro-4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide (230 mg, 0.652 mmol, yield: 50.1%). MS m/z 353 [M+H]+.

[552] Step 6: Preparation of 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide

[553] To a solution of 3-chloro-4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide (230 mg, 0.652 mmol) in DMF (2 mL) was added NCS (113 mg, 0.848 mmol). The reaction mixture was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was purified by prep-HPLC to afford title compound (140 mg, 0.343 mmol, yield: 52.6%).

[554] Example 34: 2-[[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]acetic acid

[555] Step 1: Preparation of a mixture of tert-butyl 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate and tert-butyl 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate

[556]

[557] To a solution of a mixture of 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide and 3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzenesulfonamide (500 mg, 0.790 mmol) in dry

THF (5 ml) was added NaH (47.4 mg, 1.18 mmol) at 0°C. The reaction mixuture was stirred at 0°C for 10 min. Then tert-butyl 2-bromoacetate (185 mg, 0.948 mmol) was added into the reaction mixture. The reaction was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was quenched with sat. ammonium chloride solution, diluted with water (100 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate and concentrated to give the crude product, which was purified by silica gel chromatography (ethyl acetate / petroleum ether 20:80) to afford a mixture of tert-butyl 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate and tert-butyl 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate (224 mg, 0.285 mmol, yield: 36.1%). MS m/z 747 [M+H]+.

[558] Step 2: Preparation of a mixture of tert-butyl 2-[[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trime-thylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate and tert-butyl 2-[[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate

[559] To a solution of a mixture of tert-butyl 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate and tert-butyl 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate (220 mg, 0.294 mmol) in dry DMF (3 mL) was added NCS (59.0 mg, 0.442 mmol). The reaction mixture was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried with anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (Biotage Flash, ethyl acetate / petroleum ether 10:90) to give a mixture of tert-butyl 2-[[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-

dimethoxyphenyl)methyl]amino]acetate and tert-butyl 2-[[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate (190 mg, 0.231 mmol, yield: 78.4%). MS m/z 747 [M+H]+.

[560] Step 3: Preparation of 2-[[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]acetic acid

[561] A solution of a mixture of tert-butyl 2-[[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trime-thylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate and tert-butyl 2-[[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]acetate (100 mg, 0.128 mol) in TFA (5 ml) was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford title compound (5.2 mg, 0.014 mmol, yield: 8.95%). MS (method E) m/z 445 [M+H]+, t=1.32min. 1H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 8.8, 4.4 Hz, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.86 – 7.82 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 3.25 (s, 2H) ppm.

[562] Example 35: 3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-(2-hydroxyethyl)benzenesulfonamide

[563] Step 1: Preparation of 2-[(2,4-dimethoxyphenyl)methylamino]ethanol

[564] To a solution of 2,4-dimethoxybenzaldehyde (6.0 g, 0.0361 mol) and 2-aminoethanol (2.21 g, 0.0361 mmol) in methanol (44 mL), anhydrous sodium sulfate (2.31 g, 0.0162 mol) was added. The mixture was stirred at room temperature for 16 hours. Then sodium borohydride (0.683 g, 0.0181 mol) was added over 15 minutes, and the mixture was stirred at room temperature for 30 minutes. After that, acetic acid (1.08 g, 0.0181 mol) was added. The mixture was stirred for 10 minutes and concentrated to approximately 1/2 of the volume under reduced pressure. The concentrated mixture was diluted with sat. sodium carbonate solution and extracted with dicholoromethane (150 mL x 3). The combined organic layers were washed with brine (150 mL x 2), dried with anhydrous sodium sulfate and

concentrated. The residue was triturated with petroleum ether (40 mL) and ethyl acetate (1.6 mL). The precipitate was filtered, washed with petroleum ether (50 mL) and dried in vacuo to give 2-[(2,4-dimethoxyphenyl)methylamino]ethanol (5.6 g, yield: 73%). MS m/z 212 [M+H]+.

[565] Step 2: Preparation of 4-bromo-3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-N-(2-hydroxyethyl)benzenesulfonamide

[566] To a solution of 2-[(2,4-dimethoxyphenyl)methylamino]ethanol (1.1 g, 5.21 mmol) and DIEA (2.02 g, 15.6 mmol) in DCM (20 mL) was added 4-bromo-3-chloro-benzenesulfonyl chloride (1.51 g, 5.21 mmol). The reaction mixture was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate / petroleum ether 15:85) to give 4-bromo-3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-N-(2-hydroxyethyl)benzenesulfonamide (2.05 g, yield: 85%). MS (method B) 1.30min.

[567] Step 3: Preparation of 2-[(4-bromo-3-chloro-phenyl)sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate

[568] To a solution of 4-bromo-3-chloro-N-[(2,4-dimethoxyphenyl)methyl]-N-(2-hydroxyethyl)benzenesulfonamide (1.9 g, 4.09 mmol), N,N-diethylethanamine (1.65 g, 16.36 mmol) in DCM (20 mL) was added acetyl chloride (0.642 g, 8.18 mmol) dropwise at 0°C. The mixture was stirred at room temperature for 16 h. The reaction was quenched with water (100 mL), extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate / petroleum ether 10:90) to afford 2-[(4-bromo-3-chloro-phenyl)sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate (1.65 g, yield: 80%). MS m/z 508 [M+H]+.

[569] Step 4: Preparation of 2-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate

[570] A mixture of 2-[(4-bromo-3-chloro-phenyl)sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate (1.55 g, 3.06 mmol), bis(pinacolato)diboron (932 mg, 3.67 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (224 mg, 0.306 mmol) and potassium acetate (900 mg, 9.18 mmol) in dry 1,4-dioxane (15 mL) was

stirred at 80°C for 16 hours under nitrogen atmosphere. LCMS indicated the reaction was completed. The reaction was diluted with water (100 mL), extracted with ethyl actate (100 mL x 3). The organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 2-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate (1.6 g, yield: 94%). MS (method G) 1.76min.

[571] Step 5: Preparation of [4-[2-acetoxyethyl-[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-chloro-phenyl]boronic acid

[572] To a solution of 2-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate (1.6 g, 2.89 mmol) in acetone (20 mL) and water (10 mL) were added ammonium acetate (623 mg, 8.09 mmol) and sodium periodate (2.06 g, 9.54 mmol). The reaction was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (ethyl acetate / petroleum ether 50:50) to give [4-[2-acetoxyethyl-[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-chloro-phenyl]boronic acid (660 mg, yield: 48%). MS (method I) 1.77min.

[573] Step 6: Preparation of a mixture of 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate and 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate

[574] A mixture of [4-[2-acetoxyethyl-[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-2-chloro-phenyl]boronic acid (500 mg, 1.06 mmol), a mixture of 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine and 2-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (395 mg, 1.06 mmol), 1,1'-bis (di-t-butylphosphino)ferrocene palladium dichloride (68.4 mg, 0.106 mmol) and potassium carbonate (293 mg, 2.12 mmol) in THF (5 mL) and water (1 mL) was stirred at 65°C for 16

hours under nitrogen atmosphere. LCMS indicated the reaction was completed. The reaction was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate / petroleum ether 10:90) to give a mixture of 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate and 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate (354 mg, yield: 46%). MS m/z 719 [M+H]+.

[575] Step 7: Preparation of 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]ethyl acetate

[576] A solution of a mixture of 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate and 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonyl-[(2,4-dimethoxyphenyl)methyl]amino]ethyl acetate (354 mg, 0.492 mmol) in TFA (5 mL) was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was concentrated, diluted with water (10 mL), basified with sat. sodium bicarbonate solution until pH 8 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate / petroleum ether 10:90) to give 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]ethyl acetate (117 mg, yield: 54%). MS m/z 349 [M+H]+.

[577] Step 8: Preparation of 2-[[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]ethyl acetate

[578] To a solution of 2-[[3-chloro-4-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]ethyl acetate (117 mg, 0.267 mmol) in DMF (3 mL) was added NCS (53.4 mg, 0.400 mmol) slowly. The reaction mixture was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed

with brine (30 mL x 2), dried with anhydrous sodium sulfate, and concentrated to give 2-[[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]ethyl acetate (108 mg, crude). MS m/z 473 [M+H]+.

[579] Step 9: Preparation of 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-(2-hydroxyethyl)benzenesulfonamide

[580] To a solution of 2-[[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]ethyl acetate (108 mg, 0.228 mmol) in MeOH (2 mL) was added a solution of lithium hydroxide monohydrate (95.7 mg, 2.28 mmol) in water (1 mL). The reaction was stirred at room temperature for 16 h. The mixture was diluted with water (10 mL), acidified with 1 M HCl solution to pH 7 and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL x 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to afford the title compound (45.3 mg, yield: 46%).

[581] Example 36: 2-[5-(2-Chloro-4-methylsulfonyl-phenyl)-4-methyl-1H-imidazol-2-yl]-5-fluoro-pyridine

[582] Step 1: Preparation of 5-fluoro-2-(4-methyl-1H-imidazol-2-yl)pyridine

[583] To a solution of 5-fluoropyridine-2-carbaldehyde (3.5 g, 28.0 mmol) in MeOH (250 mL) were added ammonium acetate (21.6 g, 280.0 mmol), 2-oxopropanal (25.2 g of 40% aq. solution, 140 mmol). The reaction was stirred at 70°C for 2 h. LCMS indicated the reaction was completed. The reaction mixture was concentrated and purified by silica gel column chromatography (ethyl acetate / petroleum ether 70:30) to give 5-fluoro-2-(4-methyl-1H-imidazol-2-yl)pyridine (4.25 g, 23.98 mmol, yield: 86%). MS m/z 178 [M+H]+.

[584] Step 2: Preparation of 5-fluoro-2-(5-iodo-4-methyl-1H-imidazol-2-yl)pyridine

[585] To a solution of 5-fluoro-2-(4-methyl-1H-imidazol-2-yl)pyridine (4.25 g, 24.0 mmol) in MeCN (40 mL) was added NIS (5.94 g, 26.4 mmol) slowly at room temperature. The reaction mixture was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (100 mL), extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate and concentrated to give the crude product, which was purified

by silica gel column chromatography (ethyl acetate / petroleum ether 20:80) to afford 5-fluoro-2-(5-iodo-4-methyl-1H-imidazol-2-yl)pyridine (4.7 g, 15.5 mmol, yield: 65%). MS m/z 304 [M+H]+.

[586] Step 3: Preparation of a mixture of 2-[[2-(5-fluoro-2-pyridyl)-5-iodo-4-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[2-(5-fluoro-2-pyridyl)-4-iodo-5-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane

[587] To a solution of 5-fluoro-2-(5-iodo-4-methyl-1H-imidazol-2-yl)pyridine (4.75 g, 15.7 mmol) in THF (50 mL) was added 60% NaH in mineral oil (940 mg, 23.5 mmol) slowly at 0°C. The mixture was stirred at 0°C for 10 min. Then SEM-Cl (3.9 g, 23.5 mmol) was added. The reaction was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (100 mL), extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous sodium sulfate and concentrated to give the crude product, which was purified by silica gel column chromatography (ethyl acetate / petroleum ether 30:70) to afford a mixture of 2-[[2-(5-fluoro-2-pyridyl)-5-iodo-4-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[2-(5-fluoro-2-pyridyl)-4-iodo-5-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (5.6 g, 12.9 mmol, yield: 82%). MS m/z 434 [M+H]+.

[588] Step 4: Preparation of a mixture of 2-[[5-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)-4-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)-5-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane

[589] A mixture of 2-[[2-(5-fluoro-2-pyridyl)-5-iodo-4-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[2-(5-fluoro-2-pyridyl)-4-iodo-5-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (110 mg, 0.346 mmol), Pd(dtbpf)Cl2 (22.6 mg, 0.0346 mmol) and potassium carbonate (95.7 mg, 0.692 mmol) in 1,4-dioxane (1.5 mL) and water (0.3 mL) was stirred at 70°C for 16 h under nitrogen atmosphere. LCMS indicated the reaction was completed. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous sodium sulfate and concentrated to give the crude product, which was purified by silica gel column chromatography (ethyl acetate / petroleum ether 30:70) to afford a mixture

of 2-[[5-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)-4-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)-5-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (130 mg, 0.262 mmol, yield: 76%). MS m/z 496 [M+H]+.

[590] Step 5: Preparation of 2-[5-(2-chloro-4-methylsulfonyl-phenyl)-4-methyl-1H-imidazol-2-yl]-5-fluoro-pyridine

[591] A solution of a mixture of 2-[[5-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)-4-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-(2-chloro-4-methylsulfonyl-phenyl)-2-(5-fluoro-2-pyridyl)-5-methyl-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (130 mg, 0.262 mmol) in TFA (3 mL) was stirred at room temperature for 16 h. LCMS indicated the reaction was completed. The reaction mixture was concentrated to give the crude product, which was purified by prep-HPLC to afford title compound (54.4 mg, 0.148 mmol, yield: 56%). MS (method E) m/z 366 [M+H]+, t=1.61min. 1H NMR (400 MHz, DMSO-d6) δ 13.00 (s, 1H), 8.62 (t, J = 2.8 Hz, 1H), 8.14-8.07 (m, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.0, 2.0 Hz, 1H), 7.84 (td, J = 8.8, 2.8 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 3.33 (s, 3H), 2.25 (s, 3H) ppm.

[592] Example 37: Methyl 1-((3-chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxylate

[593] Step 1: Preparation of methyl 1-((4-bromo-3-chlorophenyl)sulfonyl) azetidine-3-carboxylate

[594] To a solution of 4-bromo-3-chloro-benzenesulfonyl chloride (8.0 g, 27.6 mmol) and methyl azetidine-3-carboxylate (3.5 g, 30.3 mmol) in the DCM (100 mL) was added TEA (5.58 g, 55.2 mmol) in several portions. The reaction was stirred at room temperature for 2 h. The reaction mixture was poured into water (100 mL), extracted with ethyl acetate (100 mL x 3). The organic layers were combined, washed with brine (100 mL x 2), dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography (EA/PE 70:30 to 100:0) to give methyl 1-((4-bromo-3-chlorophenyl)sulfonyl)azetidine-3-carboxylate (9.7 g, 95.4% yield). MS m/z 369.9 [M+H]+.

[595] Step 2: Preparation of methyl 1-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2–dioxaborolan-2-yl)phenyl)sulfonyl)azetidine-3-carboxylate

[596] To a solution of methyl 1-(4-bromo-3-chloro-phenyl)sulfonylazetidine-3-carboxylate (11.2 g, 30.4 mmol) and 4,4,5,5-tetramethyl-2-(3,3,4,4-tetramethylborolan-1-yl)-1,3,2-dioxaborolane (8.35 g, 33.4 mmol) in 1,4-dioxane (120 mL) was added potassium acetate (5.96 g, 60.8 mmol) in several portions. Then 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.22 g, 3.04 mmol) was added. The reaction was stirred at 90°C for 16h under nitrogen. The reaction mixture was poured into water (100 mL) and extracted with EA (100 mL x 2). The organic layers were combined, washed with brine (100 mL x 2), dried with anhydrous Na2SO4 and concentrated. The residue was purified by flash chromatography (EA/PE 10:90) to give methyl 1-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2–dioxaborolan-2-yl)phenyl)sulfonyl)azetidine-3-carboxylate (6.8 g, 53.8% yield). MS m/z 334.0 [M-82+H]+.

[597] Step 3: Preparation of a mixture of 1-[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonylazetidine-3-carboxylic acid and 1-[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonylazetidine-3-carboxylic acid

[598] To a solution of a mixture of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-2-(5-fluoro-2-pyridyl)-4-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1.23 g, 2.7 mmol) and methyl 1-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)sulfonyl)azetidine-3-carboxylate (1.25 g, 3.0 mmol) in 1,4-dioxane/H2O (20 mL, 10:1) was added potassium carbonate (829 mg, 6.0 mmol). Then 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (195 mg, 0.3 mmol) was added under N2. The reaction was stirred at 80°C for 16 h. Then the mixture was poured into water (100 mL) and extracted with EA (100 mL x 2). The organic layers were combined, washed with brine (100 mL x 2), dried with anhydrous Na2SO4 and concentrated. The residue was purified by flash chromatography (MeOH/DCM 0:100 to 10:90) to give a mixture of 1-[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonylazetidine-3-carboxylic acid and 1-

[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonylazetidine-3-carboxylic acid (172 mg, 9.54% yield). MS m/z 601.0 [M+H]+.

[599] Step 4: Preparation of methyl 1-((3-chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxylate

[600] A solution of a mixture of 1-[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonylazetidine-3-carboxylic acid and 1-[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonylazetidine-3-carboxylic acid (59 mg, 0.09 mmol) in HCl/MeOH (4 M, 4 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated and purified by prep-HPLC to afford the title compound (5.9 mg, 12.4% yield).

[601] Example 38: 1-((3-Chloro-4-(4-chloro-2-(5-fluoro-pyridin-2-yl)-1H-imidazol-5-yl)-phenyl) sulfonyl)azetidine-3-carboxylic acid

[602] A solution of 1-[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl) imidazol-4-yl]phenyl]sulfonylazetidine-3-carboxylic acid (82 mg, 0.14 mmol) in HCl/1,4-dioxane (4 M, 4 mL) was stirred at room temperature for 6 h. Then the mixture was concentrated and purified by prep-HPLC to afford title compound (6.6 mg, 10.2% yield).

[603] Example 39: 1-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxamide

[604] To a solution of 1-[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylazetidine-3-carboxylic acid (97 mg, 0.21 mmol), EDCI (59 mg, 0.31 mmol) and HOBt (42 mg, 0.31 mmol) in DMF (4 mL) were added DIEA (54 mg, 0.42 mmol) and ammonium chloride (22.5 mg, 0.42 mmol). The reaction was stirred at room temperature for 6 h. Then the mixture was poured into water (20 mL) and extracted with EA (20 mL x 2). The organic layers were combined, washed with brine (20 mL x 2), dried with anhydrous Na2SO4 and concentrated. The residue was purified by prep-HPLC to afford the title compound (2.9 mg, 3.33% yield).

[605] Example 40: Methyl 2-chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoate

[606] Step 1: Preparation of a mixture of methyl 2-chloro-3-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate and methyl 2-chloro-3-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate

[607] To a solution of a mixture of 2-[[5-chloro-2-(5-fluoro-2-pyridyl)-4-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1.3 g, 2.9 mmol) in 1,4-dioxane (13 mL) were added methyl 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.7 g, 5.7 mmol) and potassium carbonate (1.2 g, 8.6 mmol) in water (2.6 mL). And then Pd(dtbpf)Cl2 (185 mg, 0.29 mmol) was added under N2 atmosphere. The reaction was stirred at 80°C for 16 h. The reaction mixture was quenched with water (80 mL) and extracted with EA (80 mL x 3). The combined organic layers were washed with brine (80 mL x 2), dried and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 20:80) to give a mixture of methyl 2-chloro-3-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate and methyl 2-chloro-3-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate (465 mg, 0.94 mmol, yield: 33%). MS m/z 496.0 [M+H]+.

[608] Step 2: Preparation of methyl 2-chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoate

[609] A mixture of methyl 2-chloro-3-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate and methyl 2-chloro-3-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]benzoate (465 mg, 0.94 mmol) and 4 M HCl in 1,4-dioxane (10 mL) was stirred at room temperature for 16 hours. Then the mixture was diluted with water (20 mL), basified with saturated K2CO3 solution until pH 9 and extracted with ethyl acetate (40 mL x 3). The organic layers were combined, washed with brine (40 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether 30:70) to afford the title compound (190 mg, 0.52 mmol, yield: 55%).

[610] Example 41: 2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoic acid

[611] To a solution of methyl 2-chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoate (180 mg, 0.49 mmol) in MeOH (2 mL) was added a solution of sodium hydroxide (98 mg, 2.46 mmol) in water (2 mL). The mixture was stirred at room temperature for 16 h. Then the mixture was diluted with water (20 mL), acidified with 1 M HCl solution to pH 4 and extracted with ethyl acetate (20 mL x 3). The organic phases were combined, washed with brine (20 mL x 2), dried over sodium sulfate, filtered and concentrated in vacuum to afford title compound (105 mg, 0.30 mmol, yield: 61%).

[612] Example 42: 4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-2,3-dihydro-1,2-benzothiazole 1,1-dioxide

[613] Step 1: Preparation of 1-benzylsulfanyl-3-bromo-2-methyl-benzene

[614] A mixture of 1,3-dibromo-2-methyl-benzene (25 g, 100 mmol), phenylmethanethiol (9.94 g, 80 mmol), DIEA (20.7 g, 160 mmol), Pd2(dba)3 (2.29 g, 2.5 mmol) and Xantphos (2.49 g, 5 mmol) in 1,4-dioxane (600 mL) was stirred at 100°C for 6 h. The resulting mixture was cooled to room temperature and water (300 mL) was added. The aqueous layer was extracted with DCM (300 mL x 3). The organic layers were combined, dried over Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (PE) to give 1-benzylsulfanyl-3-bromo-2-methyl-benzene (17.2 g, 58% yield). MS (method M) 2.23min.

[615] Step 2: Preparation of 3-bromo-2-methyl-benzenesulfonyl chloride

[616] A mixture of 1-benzylsulfanyl-3-bromo-2-methyl-benzene (12.2 g, 41.6 mmol), H2O (3.0 g, 166 mmol) and acetic acid (12.5 g, 208 mmol) in DCM (400 mL) was stirred at 0°C for 5 min. Then sulfuryl chloride (22.5 g, 166 mmol) was added dropwise. After addition, the mixture was stirred at 0°C for 5 min, then warmed to room temperature and stirred for 20 min. Then the mixture was cooled to 0°C and water (50 mL) was added. The mixture was stirred at room temperature for another 1 h. The resulting mixture was washed with water (200 mL) and brine (200 mL). The organic layer was dried over Na2SO4 and concentrated to give

3-bromo-2-methyl-benzenesulfonyl chloride (16.2 g, crude). The crude product was used for the next step without further purification. MS m/z 320 [M+H]+.

[617] Step 3: Preparation of 3-bromo-N-tert-butyl-2-methyl-benzenesulfonamide

[618] A mixture of 3-bromo-2-methyl-benzenesulfonyl chloride (8.1 g, crude) and DMAP (2.44 g, 20 mmol) in DCM (200 mL) was stirred at room temperature. Then 2-methylpropan-2-amine (8.78 g, 120 mmol) and DIEA (15.5 g, 120 mmol) was added. The mixture was stirred at room temperature for 16 h. Then DCM (300 mL) was added. The organic layer was washed with brine (200 mL x 2), dried over Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (DCM / PE 50:50) to give 3-bromo-N-tert-butyl-2-methyl-benzenesulfonamide (4.8 g, yield: 78%). MS m/z 250 [M-55]+.

[619] Step 4: Preparation of 3-bromo-2-(bromomethyl)-N-tert-butyl-benzenesulfonamide

[620] A mixture of 3-bromo-N-tert-butyl-2-methyl-benzenesulfonamide (4.8 g, 15.6 mmol) in DCM (150 mL) was stirred at room temperature. NBS (16.7 g, 94 mmol) was added. The mixture was stirred at room temperature for 72 h. The resulting mixture was filtered. The solution was concentrated and purified by silica gel column chromatography (DCM / PE 50:50) to give 3-bromo-2-(bromomethyl)-N-tert-butyl-benzenesulfonamide (5.2 g, yield: 86%). MS m/z 330 [M-55]+.

[621] Step 5: Preparation of 4-bromo-2-tert-butyl-3H-1,2-benzothiazole 1,1-dioxide

[622] A mixture of 3-bromo-2-(bromomethyl)-N-tert-butyl-benzenesulfonamide (5.2 g, 13.5 mmol), K2CO3 (3.73 g, 27 mmol) and tetra-n-butylammonium iodide (1.0 g, 1.35 mmol) in CH3CN (100 mL) was stirred at 50°C for 16 h. The resulting mixture was cooled to room temperature and filtered. The solution was concentrated and purified by silica gel column chromatography (DCM / PE 50:50) to give 4-bromo-2-tert-butyl-3H-1,2-benzothiazole 1,1-dioxide (3.7 g, yield: 90%). MS m/z 248 [M-55]+.

[623] Step 6: Preparation of 2-tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-1,2-benzothiazole 1,1-dioxide

[624] A mixture of 4-bromo-2-tert-butyl-3H-1,2-benzothiazole 1,1-dioxide (3.7 g, 12.2 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.71 g, 14.6 mmol), KOAc (2.98 g, 30 mmol) and Pd(dppf)Cl2 (890 mg, 1.22 mmol) in 1,4-dioxane (80 mL) was stirred at 80°C for 6 h under N2. The resulting mixture

was cooled to room temperature and filtered. The solution was concentrated and the residue was purified by silica gel column chromatography (DCM / PE 60:40) to afford the subtitle compound (3.6 g, yield: 84%). MS m/z 296 [M-55]+.

[625] Step 7: Preparation of (2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)boronic acid

[626] A mixture of 2-tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-1,2-benzothiazole 1,1-dioxide (430 mg, 1.2 mmol) and ammonium acetate (264 mg, 3.4 mmol) in acetone/H2O (10 mL / 2 mL) was stirred at room temperature. Then NaIO4 (916 mg, 4.3 mmol) was added. The mixture was stirred at room temperature for 16 h. The resulting mixture was poured into water (20 mL). The aqueous layer was extracted with EA (20 mL x 3). The organic layers were combined, dried over Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (MeOH / DCM 5:95) to give (2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)boronic acid (240 mg, 72% yield). MS m/z 214 [M-55]+.

[627] Step 8: Preparation of a mixture of 2-[[5-(2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)-4-chloro-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-(2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)-5-chloro-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane

[628] A mixture of (2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)boronic acid (240 mg, 0.89 mmol), a mixture of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-2-(5-fluoro-2-pyridyl)-4-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (243 mg, 0.53 mmol), Pd(dtbpf)Cl2 (117 mg, 0.178 mmol) and K2CO3 (246 mg, 1.78 mmol) in 1,4-dioxane/H2O (8 mL/2 mL) was stirred at 80°C for 16 h under N2. The resulting mixture was cooled to room temperature, filtered and concentrated. The residue was purified by silica gel column chromatography (MeOH / DCM 4:96) to give a mixture of 2-[[5-(2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)-4-chloro-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-(2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)-5-chloro-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (110 mg, 22.4% yield). MS m/z 551 [M+H]+.

[629] Step 9: Preparation of 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-2,3-dihydro-1,2-benzothiazole 1,1-dioxide

[630] A mixture of 2-[[5-(2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)-4-chloro-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[4-(2-tert-butyl-1,1-dioxo-3H-1,2-benzothiazol-4-yl)-5-chloro-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (110 mg, 0.2 mmol) in TFA (5 mL) was stirred at 40°C for 16 h. The resulting mixture was cooled to room temperature and concentrated. The residue was purified by reversed-phase column chromatography to afford the title compound (27 mg, 37% yield).

[631] Example 43: 3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-2-methylbenzenesulfonamide

[632] Step 1: Preparation of 3-bromo-N,N-bis(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide

[633] To a solution of 3-bromo-2-methylbenzenesulfonyl chloride (8.0 g, 29.8 mmol) and pyridine (4.77 g, 59.6 mmol) in DCM (100 mL) was added 1-(2,4-dimethoxyphenyl)-N-[(2,4-dimethoxyphenyl)methyl]methanamine (9.45 g, 29.8 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was poured into water (300 mL) and extracted with ethyl acetate (400 mL x 3). The combined organic layers were washed with brine (500 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography (ethyl acetate / petroleum ether 10:90) to give 3-bromo-N,N-bis(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide (8.1 g, 14.7 mmol, 49% yield). MS m/z 574 [M+Na]+.

[634] Step 2: Preparation of N,N-bis(2,4-dimethoxybenzyl)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide

[635] To a solution of 3-bromo-N,N-bis(2,4-dimethoxybenzyl)-2-methylbenzenesulfonamide (8.1 g, 14.8 mmol) in 1,4-dioxane (100 mL) were added bis(pinacolato)diboron (5.64 g, 22.2 mmol), potassium carbonate (2.9 g, 29.6 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.07 g, 1.48 mmol) under nitrogen atmosphere. The reaction was stirred at 80°C for 16 hours. Then the mixture was quenched with water (200 mL) and extracted with ethyl acetate (400 mL x 3). The combined organic layers were washed with brine (400 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum

ether 20:80) to give N,N-bis(2,4-dimethoxybenzyl)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (8 g, 13 mmol, yield: 87%). MS m/z 620 [M+Na]+.

[636] Step 3: Preparation of (3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)-2-methylphenyl)boronic acid

[637] To a solution of N,N-bis(2,4-dimethoxybenzyl)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (8 g, 13.3 mmol) in acetone (50 mL) and water (50 mL) were added ammonium acetate (2.9 g, 37.2 mmol) and sodium periodate (9.4 g, 43.9 mmol). The reaction was stirred at room temperature for 16 h. Then the mixture was quenched with water (200 mL) and extracted with ethyl acetate (400 mL x 3). The combined organic layers were washed with brine (400 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 40:60) to give (3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)-2-methylphenyl)boronic acid (4.5 g, 8.7 mmol, 65.4% yield). MS m/z 538 [M+Na]+.

[638] Step 4: Preparation of mixture of 3-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-benzenesulfonamide and 3-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-benzenesulfonamide

[639] To a solution of (3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)-2-methylphenyl)boronic acid (200 mg, 0.38 mmol) in 1,4-dioxane (10 mL) and water (2 mL) were added a mixture of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-2-(5-fluoro-2-pyridyl)-4-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (171 mg, 0.38 mmol), potassium carbonate (104 g, 0.76 mmol) and Pd(dtbpf)Cl2 (24.8 mg, 0.038 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 80°C for 8 hours. Then the mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 20:80) to give a mixture of 3-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-benzenesulfonamide and 3-[5-chloro-2-(5-fluoro-

2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-benzenesulfonamide (50 mg, 0.06 mmol, 16.5% yield). MS m/z 797 [M+H]+.

[640] Step 5: Preparation of 3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-2-methylbenzenesulfonamide

[641] A solution of a mixture of 3-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-benzenesulfonamide and 3-[5-chloro-2-(5-fluoro-2-pyridyl)-1-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-N,N-bis[(2,4-dimethoxyphenyl)methyl]-2-methyl-benzenesulfonamide (50 mg, 0.06 mmol) in acetic acid (3 mL) was stirred at RT for 16 h. LCMS indicated the reaction was completed. The mixture was poured into water (20 mL) and extracted with ethyl acetate (20 mL x 3). The organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to afford the title compound (15 mg, 0.04 mmol, 68% yield).

[642] Example 44: 2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzamide

[643] To a solution of 2-chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoic acid (60 mg, 0.17 mmol) in DMF (2 mL) were added DIEA (176 mg, 1.36 mmol), NH4Cl (46 mg, 0.85 mmol), EDCI (65 mg, 0.34 mmol) and HOBt (46 mg, 0.34 mmol). The reaction was stirred at room temperature for 16 hours. Then the crude product was purified by prep-HPLC to afford the title compound (23.8 mg, 0.07 mmol, yield: 40%).

[644] Example 45: 2-(4-Chloro-5-(2-fluoro-6-methylphenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[645] Step 1: Preparation of a mixture of 2-[[4-chloro-5-(2-fluoro-6-methyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-(2-fluoro-6-methyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane

[646] A mixture of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-2-(5-fluoro-2-pyridyl)-4-iodo-imidazol-1-

yl]methoxy]ethyl-trimethyl-silane (200 mg, 0.441 mmol), (2-fluoro-6-methylphenyl)boronic acid (81.43 mg, 0.529 mmol), Pd(dtbpf)Cl2 (32.9 mg, 0.044 mmol) and K2CO3 (121.8 mg, 0.881 mmol) in THF (2 mL) and water (0.4 mL) was stirred at 80°C for 16 hours under nitrogen atmosphere. LCMS indicated the reaction was completed. Then the mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 0:100 to 10:90) to give a mixture of 2-[[4-chloro-5-(2-fluoro-6-methyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-(2-fluoro-6-methyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (101 mg, 0.232 mmol, yield: 52%). MS m/z 436 [M+H]+.

[647] Step 2: Preparation of 2-(4-chloro-5-(2-fluoro-6-methylphenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[648] A solution of a mixture of 2-[[4-chloro-5-(2-fluoro-6-methyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane and 2-[[5-chloro-4-(2-fluoro-6-methyl-phenyl)-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (101 mg, 0.232 mmol) in TFA (2 mL) was stirred at room temperature for 2 h. LCMS indicated the reaction was completed. Then the mixture was concentrated under reduced pressure and purified by prep-HPLC to afford the title compound (31.5 mg, 0.103 mmol, yield: 44%).

[649] Example 46: Methyl 3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoate

[650] Step 1: Preparation of 3-bromo-4-fluoro-2-methylbenzoic acid

[651] To a stirred solution of 2,2,6,6-tetramethylpiperidine (42.6 g, 0.301 mol) in dry THF (400 mL) was added n-BuLi (2.5 M, 121 mL, 0.301 mol) dropwise at -5 °C under nitrogen atmosphere. The mixture was stirred at this temperature for 15 min. The reaction mixture was cooled to -50 °C. A solution of 3-bromo-4-fluoro-benzoic acid (30.0 g, 0.137 mmol) in dry THF (300 mL) was added dropwise into the reaction system. The resulting mixture was stirred at -50 °C for 2.5 h. The reaction mixture was cooled to -70 °C. Methyl iodide (42.8 g, 0.301 mol) was added dropwise into the reaction system. The reaction mixture

was allowed to warm to room temperature for 16 h. The reaction mixture was quenched with water (100 mL) under cooling with an ice/water bath, concentrated under reduced pressure, acidified with HCl (4M, 200 mL), until pH = 1 was reached, diluted with water (500 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the subtitle compound (33 g crude) as white solid which was used directly in the next step.

[652] Step 2: Preparation of methyl 3-bromo-4-fluoro-2-methylbenzoate

[653] To a suspension, cooled with an ice/water batch, of 3-bromo-4-fluoro-2-methyl-benzoic acid (33 g, 0.142 mol) and potassium carbonate (58.7 g, 0.425 mol) in DMF (300 mL) was added methyl iodide (40.2 g, 0.283 mmol) dropwise under nitrogen atmosphere. The mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (1000 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with water (500 mL x 2), brine (500 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the subtitle compound (7.176 g, 29.0 mmol, yield: 20.5%) as white solid which was used in the next step directly.

[654] Step 3: Preparation of methyl 4-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

[655] Under nitrogen, a mixture of methyl 3-bromo-4-fluoro-2-methyl-benzoate (3.05 g, 12.3 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.76 g, 14.8 mmol), Pd(dppf)Cl2 (903 mg, 1.23 mmol) and potassium acetate (3.63 g, 37.0 mmol) in dry 1,4-dioxane (50 mL) was prepared. The resulting mixture was stirred at 100 °C for 40 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with flash chromatography (Biotage, 40 g silica gel column, eluting with 0%-10% ethyl acetate in petroleum ether) to give the subtitle compound (2.8 g, 9.52 mmol, yield: 77.1%) as colorless oil. MS m/z 295 [M+H]+.

[656] Step 4: Preparation of (6-fluoro-3-(methoxycarbonyl)-2-methylphenyl)boronic acid

[657] To a mixture of methyl 4-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2.0 g, 6.80 mmol), acetone (20 mL) and water (6 mL) was added ammonium acetate (1.47 g, 19.0 mmol), sodium periodate (4.8 g, 22.4 mmol) successively under cooling with an ice\water bath. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (100 mL), extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage, 25 g silica gel column, eluting with 0%-75% ethyl acetate in petroleum ether) to give the subtitle compound (1.4 g, 6.60 mmol, yield: 97.1%) as white solid. MS m/z 212 [M+H]+.

[658] Step 5: Preparation of methyl 4-fluoro-3-(2-(5-fluoropyridin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-2-methylbenzoate (mixture of SEM-regioisomers)

[659] A mixture of (6-fluoro-3-methoxycarbonyl-2-methyl-phenyl)boronic acid (1.1 g, 5.19 mmol), 2-[[5-bromo-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1.93 g, 5.19 mmol, mixture of SEM-regioisomers), Pd(dtbpf)Cl2 (335 mg, 0.519 mmol) and potassium carbonate (2.15 g, 15.6 mmol) in dioxane (20 mL) and water (4 mL) was prepared under nitrogen atmosphere. The resulting mixture was stirred at 80 °C under nitrogen atmosphere for 16 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 25 g silica gel column, eluting with 0%-30% ethyl acetate in petroleum ether) to give the subtitle compound (1.4 g, 3.05 mmol, yield: 58.7%) as colorless oil. MS m/z 460 [M+H]+.

[660] Step 6: Preparation of methyl 3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoate

[661] To a mixture of methyl 4-fluoro-3-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-2-methyl-benzoate (1.3 g, 2.83 mmol) and TsOH.H2O (53.8 mg, 0.283 mmol) in MeCN (13 mL) was added NCS (453 mg, 3.39 mmol) in portions. The resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was

cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography (Biotage 25 g silica gel column, eluting with 0%-60% ethyl acetate in petroleum ether) to give the title compound (740 mg, 2.03 mmol, yield: 71.9%) as white solid.

[662] Example 47: 3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoic acid

[663] To a stirred solution of methyl 3-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-fluoro-2-methyl-benzoate (230 mg, 0.632 mmol) in MeOH (3 mL) was added a solution of sodium hydroxide (253 mg, 6.32 mmol) in water (2 mL) dropwise. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The remaining aqueous phase was acidified with 1 M HCl until pH = 5 was reached. The precipitate formed was filtered off and washed with water. The filter cake was dried in vacuum to afford the title compound (295 mg, 0.844 mmol, yield: 95.9%) as white solid. 1H NMR.

[664] Example 48: 3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzamide

[665] To a stirred mixture of 3-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-fluoro-2-methyl-benzoic acid (126 mg, 0.360 mmol) in DMF (2 mL) was added HOBt (97.4 mg, 0.721 mmol), EDCI (138 mg, 0.721 mmol), then ammonium chloride (96.4 mg, 1.80 mmol) and DIPEA (373 mg, 2.88 mmol) were added. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with water (80 mL x 2), brine (80 mL), dried over anhydrous sodium sulfate, and concentrated under pressure. The residue was purified by preparative HPLC to give the title compound (76.1 mg, 0.128 mmol, yield: 60.6%) as white solid. 1H NMR.

[666] Example 49: 2-(4-Chloro-5-(2-fluoro-6-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[667] Step 1: Preparation of 2-bromo-1-fluoro-3-methyl-5-methylsulfanyl-benzene

[668] 4-bromo-3-fluoro-5-methyl-aniline (5 g, 24.5 mmol) was dissolved in 1,2-dimethyldisulfane (35 mL, 394 mmol) and heated to 75°C under nitrogen. Isoamyl nitrite (8.52 mL, 63.7 mmol) was added dropwise to the reaction via an addition funnel through a reflux condenser (about 1 drop/sec). After the addition was complete, the reaction was heated to 95°C for 1 hour and allowed to cool to ambient temperature. The reaction was concentrated and purified by chromatography over silica gel (100% hexanes) to the subtitle compound (3.5 g, yield: 61%) as an orange solid. MS m/z 234.1 [M+H]+.

[669] Step 2: Preparation of 2-(2-fluoro-6-methyl-4-methylsulfanyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[670] To a solution of 2-bromo-1-fluoro-3-methyl-5-methylsulfanyl-benzene (3.5 g, 14.9 mmol) in 1,4-dioxane (35 mL) were added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (4.16 g, 16.4 mmol) and KOAc (2.92 g, 29.8 mmol). And then Pd(dppf)Cl2 (1.09 g, 1.49 mmol) was added under N2 atmosphere. The reaction was stirred at 90°C for 16 hrs. The reaction mixture was quenched by adding water (100 mL) and extracted with EA (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether = 30%) to afford the subtitle compound (1.22 g, yield: 29%) as a white solid. MS m/z 283.2 [M+H]+.

[671] Step 3: Preparation of 2-(4-chloro-5-(2-fluoro-6-methyl-4-(methylthio)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (mixture of SEM-regioisomers)

[672] To a solution of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (400 mg, 0.88 mmol, mixture of SEM-regioisomers) in 1,4-dioxane (4 mL) were added 2-(2-fluoro-6-methyl-4-methylsulfanyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (373 mg, 1.32 mmol) and K3PO4 (561 mg, 2.64 mmol) in water (0.8 mL). Pd(PPh3)2Cl2 (62 mg, 0.09 mmol) was added under N2 atmosphere. The reaction was stirred at 110°C for 16 hrs. The reaction mixture was quenched with water (30

mL) and extracted with EA (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether = 40%) to give the subtitle compound (180 mg, yield: 42%) as a yellow oil. MS m/z 482.1 [M+H]+.

[673] Step 4: Preparation of 2-(4-chloro-5-(2-fluoro-6-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[674] A solution of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (180 mg, 0.4 mmol) in 1,4-dioxane (1 mL) was added 4M HCl in 1,4-dioxane (2 mL) and stirred at room temperature for 4 hours. Then the mixture was concentrated and diluted with water (10 mL). The mixture was basified with saturated K2CO3 solution to pH = 9 and extracted with ethyl acetate (15 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound (56.1 mg, yield 40%) as a white solid.

[675] Example 50: 2-[4-Chloro-5-(2-fluoro-6-methyl-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[676] MCPBA (50 mg) was added to a mixture of 2-[4-chloro-5-(2-fluoro-6-methyl-4-methylsulfanyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine (55 mg) and DCM (3 mL). After 2 hours, the mixture was concentrated and purified by preparative HPLC to afford the title compound.

[677] Example 51: 3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropan-1-ol

[678] Step 1: Preparation of 3-((4-bromo-3-chlorophenyl)sulfonyl)propan-1-ol

[679] A mixture of 4-bromo-3-chloro-benzenesulfonyl chloride (8.3 g, 28.6 mmol), Na2SO3 (7.22 g, 57.2 mmol), NaHCO3 (4.81 g, 57.2 mmol) and water (60 mL) was stirred at 100 °C for 1.5 h. Then the mixture was cooled to 50 °C. TBAB (9.23 g, 28.6 mmol) and 3-bromopropan-1-ol (11.9 g, 85.9 mmol) were added. The mixture was stirred at 50 °C for 3 h. The resulting mixture was cooled to room temperature and extracted with chloroform (30 mL

x 3). The organic layers were combined, dried over Na2SO4 and concentrated. The residue was purified by silica gel column (70% EtOAc in PE) to give the subtitle compound (7.0 g, 78% yield) as white solid. MS m/z 335 [M+Na]+.

[680] Step 2: Preparation of (3-((4-bromo-3-chlorophenyl)sulfonyl)propoxy)(tert-butyl)dimethylsilane

[681] A mixture of 3-(4-bromo-3-chloro-phenyl)sulfonylpropan-1-ol (5.0 g, 15.9 mmol) and imidazole (3.26 g, 47.8 mmol) in DCM (50 mL) was stirred at room temperature. TBS-Cl (3.6 g, 23.9 mmol) was added. The mixture was stirred at room temperature for 4 h. The resulting mixture was poured into 100 mL DCM. The organic layer was washed with water (50 mL), dried over Na2SO4 and concentrated. The residue was purified by silica gel column (100% PE) to give the subtitle compound (5.5 g, 80% yield) as white solid. MS m/z 445 [M+Na]+.

[682] Step 3: Preparation of tert-butyl(3-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)propoxy)dimethylsilane

[683] To a solution of 3-(4-bromo-3-chloro-phenyl)sulfonylpropoxy-tert-butyl-dimethyl-silane (5 g, 11.7 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.86 g, 15.2 mmol) in 1,4-dioxane (75 mL) under N2 atmosphere, was added KOAc (2.29 g, 23.4 mmol) followed by Pd(dppf)Cl2 (855 mg, 0.1 eq). The reaction mixture was stirred at 60 °C for 6 hrs. The mixture was poured into water (200 mL) and extracted with EA (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried and concentrated. The residue was purified by flash column on silica gel (PE/EA= 3:1) to afford the desired product (4.1 g, 73.9% yield) as a white solid. MS m/z 475 [M+H]+.

[684] Step 4: Preparation of 2-(5-(4-((3-((tert-butyldimethylsilyl)oxy)propyl)sulfonyl)-2-chlorophenyl)-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (mixture of SEM-regioisomers)

[685] To a solution of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl- trimethyl-silane (3 g, 6.61 mmol, mixture of SEM-regioisomers) and tert-butyl-[3-[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)phenyl] sulfonylpropoxy]-dimethyl-silane (4.40 g, 9.26 mmol) in 1,4-dioxane (50 mL), K3PO4 (4.21 g, 19.8 mmol) was

added followed by Pd(PPh3)2Cl2 (464 mg. The reaction mixture was stirred at 110 °C for 16 hrs. The mixture was poured into water (200 mL) and extracted with EA (100 mL x 3). The combined organic layers were washed with brine (500 mL), dried and concentrated. The residue was purified by flash column on silica gel (PE/EA=3:1) to afford the subtitle compound (2.1 g, 47.1% yield) as a light-yellow oil. MS m/z 674.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.70 (d, J = 2.8 Hz, 1H), 8.19-8.16 (m, 2H), 8.03-8.00 (m, 1H), 7.94-7.91 (m, 2 H), 5.87-5.76 (ABq, 2 H), 3.65-3.62 (t, J=6.0 Hz, 2H), 3.51-3.47 (m, 2H), 3.24-3.20 (t, J=5.6 Hz, 1H), 4.46-4.44 (d, J=6.4 Hz, 2H), 1.78-1.74 (m, 2H), 0.83 (s, 9 H), 0.60-0.56 (t, J=8.4 Hz, 2 H), 0.01 (s, 6 H), -0.22 (s, 9 H) ppm.

[686] Step 5: Preparation of 3-[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropan-1-ol

[687] Tert-butyl-[3-[3-chloro-4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]phenyl]sulfonylpropoxy]-dimethyl-silane (200 mg) was added TFA (2 mL). After 48 hours, the mixture was concentrated. The crude was dissolved in MeOH (10 mL) and heated to 50°C for 1 hour. After 14 hours at RT, the precipitate formed was collected by filtration. The solid was washed with EA and dried in vacuo to afford the title compound.

[688] Example 52: 3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzenesulfonamide

[689] Step 1: Preparation of 2-bromo-1-fluoro-3-methyl-4-nitrobenzene

[690] 2-Bromo-1-fluoro-3-methyl-benzene (21 g, 0.111 mmol) was dissolved in HOAc (105 mL) and HNO3 (105 mL). The reaction mixture was stirred at 80 °C for 5 hrs. The mixture was poured into ice-water (1500 mL) and extracted with EA (1000 mL x 3). The organic layers were washed with brine and concentrated to give the crude product. The residue was purified by flash column chromatography on silica gel (PE:EA=1:20) to the subtitle compound (17.5 g, 67.3%) as a yellow solid. MS m/z 235.8 [M+H]+.

[691] Step 2: Preparation of 3-bromo-4-fluoro-2-methylaniline

[692] 2-Bromo-1-fluoro-3-methyl-4-nitro-benzene (17.5 g, 74.8 mmol) was dissolved in MeOH (170 mL) and HOAc (80 mL). Iron powder (41.8 g, 748 mmol) was added with several

portions. The reaction mixture was stirred at RT for 16 hrs. The reaction was monitored by LCMS. The solid was filtered out and washed with MeOH (1000 mL). The filtrate was concentrated. The residue was purified by flash column on silica gel (PE/EA=3/1) to afford the subtitle compound (13 g, 63.7 mmol) as a light-yellow solid. MS m/z 205.0 [M+H]+.

[693] Step 3: Preparation of 3-bromo-4-fluoro-2-methylbenzenesulfonyl chloride

[694] 3-bromo-4-fluoro-2-methyl-aniline (13 g, 0.0637 mol) was dissolved in HCl (9 N, 150 mL). $NaNO_2$ (5.71 g, 82.8 mmol) in water (25 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h (solution 1). $NaHSO_3$ (13.1 g, 0.127 mol) was dissolved in water (43 mL) and aliquoted into two portions. To one portion, $CuSO_4.5H_2O$ (1.02 g, 6.37 mmol) dissolved in HCl (112 mL, 12 N) was added (solution 2). Solution 1 and solution 2 were added dropwise simultaneously to the other portion of the $NaHSO_3$ solution. The reaction mixture was stirred at RT for 16 hrs. The reaction mixture was poured into water and extracted with DCM. The organic layer was dried and concentrated to afford the subtitle compound (11 g, crude) as a brown oil which was used directly in the next step.

[695] Step 4: Preparation of 3-bromo-N,N-bis(2,4-dimethoxybenzyl)-4-fluoro-2-methylbenzenesulfonamide

[696] 1-(2,4-dimethoxyphenyl)-N-[(2,4-dimethoxyphenyl)methyl]methanamine (8.5 g, 26.8 mmol) and DIEA (14.8 g, 0.115 mol) were dissolved in DCM (150 mL). 3-bromo-4-fluoro-2-methyl- benzenesulfonyl chloride (11 g, 0.0383 mol) was added with several portions. The reaction mixture was stirred at RT for 16 hrs. The mixture was poured into water (200 mL). The aqueous layer was extracted with DCM (100 mL x 3), dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=1:10) to afford the subtitle compound (13 g, yield 59.8%) as a light-yellow solid. MS m/z 590.0 [M+Na]+.

[697] Step 5: Preparation of N,N-bis(2,4-dimethoxybenzyl)-4-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide

[698] To a solution of 3-bromo-N,N-bis[(2,4-dimethoxyphenyl)methyl]-4-fluoro-2-methyl- benzenesulfonamide (12 g, 21.1 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)-1,3,2-dioxaborolane (6.97 g, 27.4 mmol) in 1,4-dioxane (150 mL) under N_2 atmosphere, KOAc (6.22 g, 63.3 mmol) was added followed by $Pd(dppf)Cl_2$ (1.54 g, 2.11 mmol). The reaction mixture was stirred at 80 °C for 16 hrs. The

mixture was poured into water (300 mL) and extracted with EA (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA=1:5) to afford the subtitle compound (10.5 g, 80.8% yield) as a white solid. MS m/z 616.3 [M+H]+.

[699] Step 6: Preparation of (3-(N,N-bis(2,4-dimethoxybenzyl)sulfamoyl)-6-fluoro-2-methylphenyl)boronic acid

[700] To a mixture of N,N-bis[(2,4-dimethoxyphenyl)methyl]-4-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (7 g, 11.4 mmol), NH4OAc (2.45 g, 31.8 mmol), acetone (100 mL) and H2O (30 mL), sodium periodate (8.03 g, 37.5 mmol) was added with several portions. The mixture was stirred at RT for 16 hrs. The mixture was poured into water (200 mL) and filtered. The filter cake was washed with EA and the filtrate was extracted with EA (200 mL x 3). The organic layers were washed with brine (500 mL), dried and concentrated. The residue was purified by flash chromatography on silica gel to afford the subtitle compound (6.1 g, 9.72 mmol, 85.5% yield) as a white solid. MS m/z 556.0 [M+Na]+.

[701] Step 7: Preparation of N,N-bis(2,4-dimethoxybenzyl)-4-fluoro-3-(2-(5-fluoropyridin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-2-methylbenzenesulfonamide (mixture of SEM-regioisomers)

[702] To a mixture of 2-[[5-bromo-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1.5 g, 4.03 mmol, mixture of SEM-regioisomers), [3-[bis[(2,4-dimethoxyphenyl)methyl]sulfamoyl]-6-fluoro-2-methyl-phenyl] boronic acid (2.58 g, 4.83 mmol) and K2CO3 (1.67 g, 12.1 mmol),1,4-dioxane (15 mL) and H2O (3 mL) under N2 atmosphere, Pd(dtbpf)Cl2 (263 mg, 0.403 mmol) was added. The reaction was stirred at 80 °C for 16 hrs. The mixture was poured into water (100 mL) and extracted with EA (50 mL x 3). The combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel to afford the subtitle compound (1.1 g, 35% yield) as a light yellow solid. MS m/z 781.0 [M+H]+.

[703] Step 8: Preparation of 4-fluoro-3-(2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-2-methylbenzenesulfonamide

[704] A solution of N,N-bis[(2,4-dimethoxyphenyl)methyl]-4-fluoro-3-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoymethyl)imidazol-4-yl]-2-methyl-benzenesulfonamide (600 mg, 0.768 mmol) in 4 M HCl in 1,4-dioxane (9.6 mL) was stirred at room temperature for 16 hrs. The reaction mixture was concentrated under reduced pressure. The residue was dissolved with water (50 mL), basified with sat. sodium bicarbonate solution, until pH = 8, and extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 25 g silica gel column, eluting with 0%-40% ethyl acetate in petroleum ether) to afford the subtitle compound (130 mg, 0.371 mmol, yield: 48.3%) as white solid. MS m/z 351 [M+H]+. 1H NMR (500 MHz, DMSO) δ 13.11 (s, 1H), 8.65 (d, J = 2.5 Hz, 0.80H), 8.62 (d, J = 2.5 Hz, 0.20H), 8.15 (dd, J = 8.5, 4.5 Hz, 0.20H), 8.10 (dd, J = 8.5, 4.5 Hz, 0.80H), 8.01 – 7.96 (m, 0.20H), 7.94 (dd, J = 9.0, 6.0 Hz, 0.80H), 7.862-7.821 (m, 1H), 7.55 (s, 0.40H), 7.49 (s, 1.60H), 7.41 (s, 0.80H), 7.35 (d, J = 9.0 Hz, 0.20H), 7.29 (t, J = 8.5 Hz, 0.80H), 7.17 (s, 0.20H), 2.58 (s, 2.40H), 2.52 (s, 0.60H) ppm.

[705] Step 9: Preparation of 3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzenesulfonamide

[706] To a solution of 4-fluoro-3-[2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-2-methyl-benzenesulfonamide (130 mg, 0.371 mmol) in THF (3 mL) was added NCS (59.5 mg, 0.445 mmol) in portions. The resulting mixture was stirred at 40 °C for 16 hrs. The reaction mixture was cooled to room temperature and purified by preparative HPLC to afford the title compound (23.0 mg, 0.0597 mmol, yield: 16.1%) as white solid.

[707] Example 53: 3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropanamide

[708] Step 1: Preparation of 3-[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropanoic acid

[709] A mixture of 3-[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropan-1-ol (105 mg), MeCN (15 mL) and H2O (1.5 mL) was added TEMPO (11.4 mg) and diacetoxyiodo-benzene (160 mg). After stirring overnight, more diacetoxyiodo-benzene (160 mg) was added and stirring continued for 1 day. The mixture was

concentrated and purified by preparative HPLC to afford the subtitle compound. MS m/z 444 [M+H]+.

[710] Step 2: Preparation of 3-[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropanamide

[711] A mixture of 3-[3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropanoic acid (15 mg), ammonium chloride (7.2 mg), DMF (0.5 mL) and DIPEA (35 mg) was added EDC (12.9 mg) and HOBt (4.6 mg). After stirring for 14 hours, the mixture was diluted with MeOH (1 mL), filtrated, and purified by preparative HPLC to afford the title compound.

[712] Example 54: Methyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoate

[713] Step 1: Preparation of methyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-3-methylbenzoate (mixture of SEM-regioisomers)

[714] To a solution of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1 g, 2.2 mmol, mixture of SEM-regioisomers) in 1,4-dioxane (10 mL) and water (2 mL) under N2 atmosphere was added (4-methoxycarbonyl-2-methyl-phenyl)boronic acid (641 mg, 3.31 mmol) and K2CO3 (920 mg, 6.6 mmol) followed by Pd(dtbpf)Cl2 (144 mg, 0.22 mmol). The mixture was stirred at 80°C for 16 hrs. The reaction mixture was quenched with water (20 mL), concentrated and extracted with DCM (30 mL x 3). The organic layers were combined, washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate / petroleum ether = 19:1) to afford the subtitle compound (570 mg, yield: 54%) as a white solid. MS m/z 476.0 [M+H]+.

[715] Step 2: Preparation of methyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoate

[716] A mixture of methyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-3-methyl-benzoate (0.85 g, 1.8 mmol) and 4 M HCl in 1,4-dioxane (5 mL) was kept at RT for 16 h. The reaction mixture was concentrated.

The crude product was purified by silica gel column chromatography (ethyl acetate / petroleum ether = 9:1) to afford the title compound (502 mg, yield: 81%) as a white solid.

[717] Example 55: 4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoic acid

[718] To a solution of methyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzoate (0.4 g, 1.2 mmol) in MeOH (4 mL) was added NaOH (0.28 g, 6.9 mmol) in H2O (20 mL). The reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated and acidified with 1 M HCl solution until pH=4, and then extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated to afford the title compound (354 mg) as a white solid.

[719] Example 56: 4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide

[720] A mixture of 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzoic acid (30 mg), DMF (0.5 mL) and DIPEA (48 mg) was added HATU (52 mg). After 20 min, ammonium chloride (9.7 mg) was added. After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[721] Example 57: N-(2-Amino-2-oxo-ethyl)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide

[722] A mixture of 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzoic acid (30 mg), DMF (0.5 mL) and DIPEA (48 mg) was added HATU (52 mg). After 20 min, 2-aminoacetamide (hydrochloride, 20 mg) was added. After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[723] Example 58: 2-(4-Chloro-5-(2-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine

[724] Step 1: Preparation of 1-bromo-2-methyl-4-methylsulfanyl-benzene

[725] To a solution of 1-bromo-4-fluoro-2-methyl-benzene (10 g, 53 mmol) in DMF (80 mL) was added methylsulfanylsodium (4.08 g, 58.2 mmol). The reaction was stirred at 100°C for 16 h. The reaction mixture was quenched with water (200 mL) and extracted with DCM (200 mL x 3). The organic layers were combined, washed with brine (200 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography with petroleum ether to afford the subtitle compound (7 g, yield 61%) as a colorless oil.

[726] Step 2: Preparation of (2-methyl-4-methylsulfanyl-phenyl)boronic acid

[727] 1-bromo-2-methyl-4-methylsulfanyl-benzene (5 g, 23 mmol) was dissolved in tetrahydrofuran (30 mL). Then 2.5 M n-butyllithium (13.8 mL, 34.5 mmol) was added slowly at -78°C under N2 atmosphere. After stirring for 1h, trimethyl borate (7.2 g, 69.1 mmol) was added dropwise at -78°C. The mixture stirred at -78°C for another 2 h and at RT for 16 h. The mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL x3). The organic layers were washed with brine (50 ml x 2), dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by flash chromatography (ethyl acetate / petroleum ether = 50%) to afford the subtitle compound (800 mg, 19% yield) as a white solid. MS m/z 183.1 [M+H]+.

[728] Step 3: Preparation of 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-(2-methyl-4-methylsulfanyl-phenyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (mixture of SEM-regioisomers)

[729] To a solution of (2-methyl-4-methylsulfanyl-phenyl)boronic acid (800 mg, 4.4 mmol) in 1,4-dioxane (20 mL) and water (4 mL) were added 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-iodo-imidazol-1-yl]methoxy]ethyl-trimethyl-silane (2.0 g, 4.4 mmol, mixture of SEM-regioisomers), potassium carbonate (1.84 g, 13.2 mmol) and Pd(dtbpf)Cl2 (286 mg, 0.44 mmol) under nitrogen atmosphere. The reaction was stirred at 100°C for 16 hours. Then the mixture was quenched with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium

sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether = 15%) to afford the title compound (0.5 g, yield: 18%) as a brown oil. MS m/z 464.0 [M+H]+.

[730] Step 4: Preparation of 2-[4-chloro-5-(2-methyl-4-methylsulfanyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[731] 2-[[4-chloro-2-(5-fluoro-2-pyridyl)-5-(2-methyl-4-methylsulfanyl-phenyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (0.5 g) was added 4M HCl in 1,4-dioxane (5 mL). The reaction was stirred at RT for 4 h. The reaction was concentrated and basified with 1 M NaOH solution until pH=10, and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether = 30%) to afford the title compound (233.9 mg, yield: 90%) as a white solid.

[732] Example 59: N-(2-Amino-2-oxo-ethyl)-3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide

[733] A mixture of 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoic acid (17.5 mg), DMF (0.5 mL) and DIPEA (26 mg) was added HATU (24 mg). After 5 min, 2-aminoacetamide (hydrochloride, 7.4 mg) was added. After 1 hour, the mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[734] Example 60: 3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide

[735] A mixture of 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoic acid (17.5 mg), DMF (0.5 mL) and DIPEA (26 mg) was added HATU (24 mg). After 5 min, ammonium chloride (5.3 mg) was added. After 1 hour, the mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[736] Example 61 and Example 62: 2-[4-Chloro-5-(2-methyl-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine and 2-[4-chloro-5-(2-methyl-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[737] MCPBA (78 mg) was added to a mixture of 2-[4-chloro-5-(2-methyl-4-methylsulfanyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg) and DCM (2 mL). After 30 min, more MCPBA (25 mg) was added. After standing overnight, the mixture was concentrated, and the residue dissolved in DMF (0.5 mL) and MeOH (0.5 mL). The mixture was separated by preparative HPLC to afford the title compounds.

[738] Example 63 and Example 64: Tert-butyl (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate and tert-butyl (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[739] Step 1: Preparation of tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (mixture of SEM-regioisomers)

[740] To a solution of 2-(5-chloro-4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-5-fluoropyridine (18 g, 39.7 mmol, mixture of SEM-regioisomers) in 1,4-dioxane (180 mL) were added (1-(tert-butoxycarbonyl)-3-methyl-1,2,3,6-tetrahydropyridin-4-yl)boronic acid (14.4 g, 59.6 mmol) and potassium carbonate (16.5 g, 119 mmol) in water (36 mL). And then Pd(dtbpf)Cl2 (5.2 g, 8.0 mmol) was added under N2 atmosphere. The reaction was stirred at 80°C for 16 hrs. The reaction mixture was quenched by adding water (100 mL) and extracted with EA (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether = 30%) to afford the subtitle compound (10.8 g, yield: 52%) as a yellow oil. MS m/z 523.3 [M+H]+.

[741] Step 2: Preparation of 2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (hydrochloride)

[742] A solution of tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-

carboxylate (10.8 g, 20.7 mmol, mixture of SEM-regioisomers) in 1,4-dioxane (20 mL) was added 4M HCl in 1,4-dioxane (40 mL) and stirred at room temperature for 16 hours. The mixture was concentrated to afford the subtitle compound (11 g) as an off-white solid. The crude product is used for the next step without further purification. MS m/z 293.1 [M+H]+.

[743] Step 3: Preparation of tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[744] To a solution of 2-(4-chloro-5-(3-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine (11 g, crude hydrochloride) in DCM (100 mL) were added TEA (10.4 g, 103.4 mmol) and tert-butoxycarbonyl tert-butyl carbonate (4.7 g, 21.7 mmol). The reaction mixture was stirred at room temperature for 16 hours. The mixture was poured into water (200 mL) and extracted with DCM (150 mL x 3). The organic layers were washed with brine (150 mL x 2), dried with Na2SO4 and concentrated. The crude was purified by flash chromatography (ethyl acetate / petroleum ether = 30%) to afford the subtitle compound (6.4 g, yield: 79% two steps) as a white solid. MS m/z 393.1 [M+H]+.

[745] Step 4: Preparation of tert-butyl (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate and tert-butyl (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[746] Tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (10 g) was separated by chiral-HPLC to afford tert-butyl (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (4.989 g) and tert-butyl (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (4.878 g).

[747] Preparative chiral HPLC conditions: instrument: SFC-150 (Waters); column: AD 25x250mm, 10μm (Daicel); column temperature: 35°C; mobile phase: CO_2/ MeOH (0.2% NH_3(7M in MeOH) 80:20; flow rate: 100 ml/min; back pressure: 100 bar; detection wavelength: 214 nm; cycle time: 4.1 min; sample solution: 10 g dissolved in 200 ml methanol; injection volume: 2.5 ml.

[748] Analytical chiral HPLC conditions: column: AD-3 4.6*100mm, 3μm; column temperature: 40°C; mobile phase: CO_2/ MeOH (0.2% NH_3(7M in MeOH) 85:15; flow rate:

3ml/min; back pressure: 2000psi; detection wavelength: 214 nm; run time: 4.0 min; injection volume: 5.00 µl.

[749] Tert-butyl (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate. Chiral HPLC 1.005 min.

[750] Tert-butyl (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate. Chiral HPLC 1.384 min.

[751] Example 65: (3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N,3-trimethyl-piperidine-1-carboxamide

[752] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (60 mg) and DCM (4 mL) was added DIPEA (1.2 mL) followed by N,N-dimethylcarbamoyl chloride (60 mg). After 1 hour at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[753] Example 66: Methyl (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate

[754] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (60 mg) and DCM (3 mL) was added DIPEA (1 mL) followed by methyl carbonochloridate (90 mg). After 1 hour at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[755] Example 67: [2-(Dimethylamino)-2-oxo-ethyl] (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate

[756] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (70 mg) and THF (4 mL) was added DIPEA (1.5 mL) followed by [2-(dimethylamino)-2-oxo-ethyl] imidazole-1-carboxylate (200 mg). After 8 hours at 90°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[757] Example 68: Methyl 3-[[(3S*)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate

[758] A mixture of 2-[4-chloro-5-[(3S*)-3-methyl-1,2,3,6-tetrahydropyridin-4-yl]-1H-imidazol-2-yl]-5-fluoro-pyridine (250 mg), DCM (5 mL) and DIPEA (0.41 mL) was added methyl 3-(chlorosulfonyl)propanoate (186 mg). The mixture was stirred overnight, diluted with EA (20 mL) and washed with 1N HCl (5 mL x2) and brine (5 mL). The organic layer was dried (Na2SO4) and concentrated. The residue was purified by preparative HPLC to afford the title compound.

[759] Example 69: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[760] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (200 mg), DIPEA (3.5 mL) and DCM (12 mL) was added pyridine-3-sulfonyl chloride (150 mg). After 20 min at 40°C, the reaction mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[761] Example 70 and Example 71: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-1-oxido-pyridin-1-ium and 2-[4-chloro-5-[(3R,4R)-3-methyl-1-(1-oxidopyridin-1-ium-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[762] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (200 mg) and DCM (5 mL) was added MCPBA (75% purity, 50 mg). After 2 hours, the reaction mixture was concentrated, and the residue purified by preparative HPLC to afford the title compounds.

[763] Example 72: 2-[5-[(3R,4R)-1-(Azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)

[764] Step 1: Preparation of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate

[765] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (302 mg), DIPEA (5 mL) and DCM (15 mL) was added tert-butyl 3-chlorosulfonylazetidine-1-carboxylate (300 mg). After 20 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compound.

[766] Step 2: Preparation of 2-[5-[(3R,4R)-1-(azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)

[767] A mixture of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate (294 mg) and DCM (3 mL) was added HCl (6N in iPrOH, 5 mL). After 0.5 h, the mixture was concentrated to afford the title compound.

[768] Example 73: 1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidin-1-yl]ethanone

[769] A mixture of 2-[5-[(3R,4R)-1-(Azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 80 mg), DIPEA (1.5 mL), DCM (5 mL) and 1,4-dioxane (5 mL) was added acetyl chloride (30 mg). After 15 min, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[770] Example 74: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxamide

[771] A mixture of 2-[5-[(3R,4R)-1-(azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 50 mg), triethylamine (70 mg) and DCM (2 mL) was added isocyanato(trimethyl)silane (18 mg). After 15 min, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[772] Example 75: Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoate

[773] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (1.8 mL) and DCM (6 mL) was added methyl 4-

chlorosulfonylbutanoate (120 mg). After 20 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[774] Example 76: Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoate

[775] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (2 mL) and DCM (6 mL) was added methyl 3-chlorosulfonyl-2,2-dimethyl-propanoate (160 mg). After 20 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[776] Example 77: Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate

[777] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (2 mL) and DCM (7 mL) was added tert-butyl 3-(chlorosulfonylmethyl)azetidine-1-carboxylate (180 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[778] Example 78: 2-[5-[(3R,4R)-1-(Azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)

[779] A mixture of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate (102 mg) and DCM (3 mL) was added HCl (6N in iPrOH, 5 mL). After 0.5 h, the mixture was concentrated to afford the title compound.

[780] Example 79: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methyl-pyridine

[781] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (90 mg), DIPEA (1.5 mL), DCM (6 mL) was added 6-methylpyridine-3-sulfonyl chloride (115 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[782] Example 80: 2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethanol

[783] Step 1: Preparation of 2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethanol

[784] To a stirred solution of 2-(2-hydroxyethoxy)ethanol (46.3 g, 437.0 mmol) in pyridine (34.5 g, 437.0 mmol) was added tert-butyl-chloro-diphenyl-silane (20.0 g, 72.8 mmol) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 120 g silica gel column, eluting with 0%-40% ethyl acetate in petroleum ether) to afford the subtitle compound (24.0 g, 69.66 mmol, yield: 95.7%) as colorless oil.

[785] Step 2: Preparation of S-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl] ethanethioate

[786] To a stirred solution of triphenylphosphine (16.7 g, 63.9 mmol) in dry THF (130 mL) was added DIAD (12.9 g, 63.9 mmol) dropwise at 0°C under nitrogen atmosphere. After 20 min, a solution of 2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethanol (10.0 g, 29.0 mmol) in dry THF (10 mL) was added into the reaction system. After 10 min, neat ethanethioic S-acid (4.86 g, 63.9 mmol) was added into the reaction system. The reaction mixture was stirred at 0°C for 1 h, and at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure. To the residue was added petroleum ether (200 mL), and the mixture stirred for 10 min. The filter cake obtained after filtration was washed with petroleum ether (100 mL). The filtrate was concentrated. The residue was purified by flash chromatography (Biotage 80 g silica gel column, eluting with 0%-40% dichloromethane in petroleum ether) to afford the subtitle compound (10.6 g, 26.3 mmol, yield: 90.7%) as colorless oil.

[787] Step 3: Preparation of 2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethane sulfonyl chloride

[788] To a stirred solution of S-[2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethyl] ethanethioate (10.6 g, 26.3 mmol) in acetonitrile (100 mL) was added 2 M HCl (4.74 mL) and

NCS (14.1 g, 105.0 mmol) slowly at 0°C. The reaction mixture was stirred at 0°C for 15 min. The reaction mixture was diluted with water (400 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 80 g silica gel column, eluting with 0%-40% dichloromethane in petroleum ether) to afford the subtitle compound (4.1 g, 9.6 mmol, yield: 36.5%) as colorless oil. MS m/z 449 [M+Na]+.

[789] Step 4: Preparation of tert-butyl-[2-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethoxy]-diphenyl-silane

[790] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (85 mg), DIPEA (1.5 mL) and DCM (6 mL) was added 2-[2-[tert-butyl(diphenyl)silyl]oxyethoxy]ethanesulfonyl chloride (290 mg). After 20 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compound. MS m/z 685.4 [M+H]+.

[791] Step 5: Preparation of 2-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethanol

[792] A mixture of tert-butyl-[2-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethoxy]-diphenyl-silane (170 mg) and THF (10 mL) was added TBAF (1M in THF, 1 mL). After 30 min, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[793] Example 81: 4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoic acid

[794] A mixture of methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoate (115 mg), water (1.5 mL) and THF (6 mL) was added LiOH (22 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[795] Example 82: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoic acid

[796] A mixture of methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoate (132 mg), water (1.5 mL) and THF (6 mL) was added LiOH (45 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[797] Example 83: 2-[4-Chloro-5-[(3R,4R)-1-[(6-methoxy-3-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[798] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (80 mg), DIPEA (1.5 mL) and DCM (6 mL) was added 6-methoxypyridine-3-sulfonyl chloride (100 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[799] Example 84: 4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanamide

[800] A mixture of 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoic acid (92 mg), DIPEA (0.15 mL) and DMF (5 mL) was added EDC (55 mg) and HOBt (50 mg). After 15 min, ammonium chloride (30 mg) was added. After 2d, the mixture was filtered, the filtrate concentrated, and the residue purified by preparative HPLC to afford the title compound.

[801] Example 85: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanamide

[802] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoic acid (112 mg), DIPEA (0.15 mL) and DMF (5 mL) was added EDC (65 mg) and HOBt (60 mg). After 15 min, ammonium chloride (35 mg) was added. After 2d, the mixture was filtered, the filtrate concentrated, and the residue purified by preparative HPLC to afford the title compound.

[803] Example 86: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxamide

[804] A mixture of 2-[5-[(3S,4S)-1-(azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 75 mg), triethylamine (0.3 mL) and DCM (3 mL) was added isocyanato(trimethyl)silane (50 mg). After 3h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[805] Example 87: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one

[806] A mixture of 2-[4-chloro-5-[(3R,4R)-1-[(6-methoxy-3-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), MeCN (3 mL) and NaI (50 mg) was added TMSCl (40 µL). After 2h at 60°C, the mixture was filtered, the filtrate concentrated, and the residue purified by preparative HPLC to afford the title compound.

[807] Example 88: 2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]acetic acid

[808] A mixture of 2-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethanol (70 mg) and acetone (3 mL) was added Jones reagent (0.1 mL). After 1 h, the mixture was diluted with EA and washed with water. The organic phase was dried (Na2SO4), concentrated, and the residue purified by preparative HPLC to afford the title compound.

[809] Example 89: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydrofuran-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[810] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (0.8 mL) and DCM (3 mL) was added tetrahydrofuran-3-sulfonyl chloride (55 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[811] Example 90: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(oxetan-3-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[812] Step 1: Preparation of S-(oxetan-3-yl) ethanethioate

[813] A mixture of 3-iodooxetane (12.0 g, 65.2 mmol) and potassium thioacetate (14.9 g, 130.5 mmol) in DMF (60 mL) in a sealed tube was stirred at 50°C for 16 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL), extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed brine (100 mL x 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 80 g silica gel column, eluting with 0%-10% ethyl acetate in petroleum ether) to afford the subtitle compound (7.1 g, 53.7 mmol, yield: 82.4%) as light yellow oil. MS m/z 133 [M+H]+.

[814] Step 2: Preparation of oxetane-3-sulfonyl chloride

[815] To a stirred aqueous solution of NaClO (7.5%, 160 g, 0.161 mol) was added 1 M HCl (161 mL, 0.161 mol) dropwise at 0°C. This solution was added into another solution of S-(oxetan-3-yl) ethanethioate (7.1 g, 53.7 mmol) in DCM (70 mL) at 0°C slowly. The reaction mixture was stirred at 0°C for 0.5 h. The reaction mixture was extracted with DCM (100 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Biotage 80 g silica gel column, eluting with 0%-45% dichloromethane in petroleum ether) to afford the subtitle compound (2.5 g, 1.60 mmol, yield: 29.7%) as colorless oil. 1H NMR (400 MHz, CDCl3) δ 5.48 – 4.53 (m, 5H) ppm.

[816] Step 3: Preparation of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-(oxetan-3-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[817] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (1 mL) and DCM (3 mL) was added oxetane-3-sulfonyl chloride (55 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[818] Example 91: 2-[4-Chloro-5-[(3R,4R)-1-[(2-methoxy-4-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[819] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (2 mL) and DCM (6 mL) was added 2-methoxypyridine-4-

sulfonyl chloride (95 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[820] Example 92: 4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one

[821] A mixture of 2-[4-chloro-5-[(3R,4R)-1-[(2-methoxy-4-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), MeCN (5 mL) and NaI (100 mg) was added TMSCl (80 µL). After 2 h at 60°C, the mixture was filtered, the filtrate concentrated, and the residue purified by preparative HPLC to afford the title compound.

[822] Example 93: Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate

[823] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 200 mg), DIPEA (0.43 mL) and DCM (4 mL) was added methyl 3-chlorosulfonylpropanoate (175 mg). After 45 min, the mixture was diluted with NH4Cl solution (2M, 3 mL). The pH was adjusted to 1 with 1M HCl. The mixture was extracted with EA (10 mL). The organic layer was washed with brine (2 mL), dried (Na2SO4) and concentrated. The residue purified by chromatography (15 g silica gel, n-heptane/EA 100:0 to 0:100) to afford the title compound.

[824] Example 94: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid

[825] A mixture of methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate (400 mg) and THF (5 mL) was added LiOH 2M (1 mL). After 3 h, the mixture was adjusted to pH = 1 by addition of HCl (1M) and extracted with EA (30 mL). The organic phase was washed with HCl (0.1M, 5 mL) and brine (5 mL), dried (Na2SO4) and concentrated. The residue was stirred with MeCN. The mixture was filtered to afford the title compound as solid.

[826] Example 95: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanamide

[827] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (200 mg), DMF (2 mL) and DIPEA (0.33 mL) was added EDC (116 mg), HOBt (69 mg) and ammonium chloride (50 mg). After stirring overnight, the mixture was added an additional amount of EDC (23 mg) and stirring was continued for 1 h. The mixture was filtered and purified by preparative HPLC. The product (146 mg) was dissolved in EA (1.5 mL). After 5 min, a precipitate formed. The suspension was stirred overnight. The solid was filtered off and dried in vacuo to afford the title compound.

[828] Example 96: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 1)

[829] Step 1: Preparation of methyl (1r,3r)-3-(acetylthio)cyclobutane-1-carboxylate

[830] To a solution of methyl (1s,3s)-3-hydroxycyclobutane-1-carboxylate (8 g, 61.5 mmol) in dry THF (50 mL) was added ethanethioic S-acid (7 g, 92 mmol) and PPh3 (35 g, 135 mmol). The reaction was stirred at 0°C under nitrogen atmosphere for 10 min. Then DIAD (27 g, 135 mmol) was added slowly. The reaction mixture was stirred at 0°C for 16 h. The reaction was quenched with saturated ammonium chloride solution (300 mL) and extracted with dichloromethane (300 mL x 3). The crude product was purified by flash chromatography (ethyl acetate / petroleum ether = 10%) to afford the subtitle compound (6 g, 32 mmol, yield: 52%) as a colorless oil. MS m/z 189 [M+H]+.

[831] Step 2: Preparation of methyl (1r,3r)-3-(chlorosulfonyl)cyclobutane-1-carboxylate

[832] To a solution of methyl (1r,3r)-3-(chlorosulfonyl)cyclobutane-1-carboxylate (6 g, 32 mmol) in MeCN (30 mL) was added NCS (4.3 g, 32 mmol) and aqueous HCl (16 mL, 1M) at 0°C. The reaction mixture was stirred at 0°C for 1 h. The resulting mixture was diluted with water (200 mL) and extracted with EA (200 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (ethyl acetate / petroleum ether = 10%) to afford the subtitle compound (3.9 g, 18.3 mmol, yield:57%) as a colorless oil. MS m/z 213 [M+H]+.

[833] Step 3: Preparation of methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylate (isomer 1) and methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylate (isomer 2)

[834] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (120 mg), DIPEA (2 mL) and DCM (6 mL) was added methyl 3-chlorosulfonylcyclobutanecarboxylate (190 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compounds. Isomer 1: MS (method N) m/z 471.1 [M+H]+, t=2.01min. Isomer 2: MS (method N) m/z 471.1 [M+H]+, t=2.07min.

[835] Step 4: Preparation of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 1)

[836] A mixture of methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylate (isomer 1, 137 mg), THF (4 mL) and water (1.5 mL) was added LiOH (25 mg). After 3 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[837] Example 97: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 2)

[838] A mixture of methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylate (isomer 2, 118 mg), THF (4 mL) and water (1 mL) was added LiOH (22 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[839] Example 98: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-propanamide

[840] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (500 mg), DMF (3 mL) and DIPEA (1.25 mL) was added EDC (278 mg), HOBt (157 mg) and methanamine (hydrochloride, 200 mg). After stirring overnight, the mixture was diluted with MeOH (6.5 mL), filtered and purified by

preparative HPLC. The solid obtained was suspended with MTBE (5 mL) for 48 h. The suspension was filtered, and the solid dried (stream of air) to afford the title compound.

[841] Example 99: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 1)

[842] A mixture of 3-[[(3S,4S)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 1, 100 mg), DMF (4 mL) and DIPEA (0.2 mL) was stirred for 15 min, and added EDC (90 mg), HOBt (75 mg) and ammonium chloride (50 mg). After stirring overnight, the mixture was filtered and purified by preparative HPLC to afford the title compound.

[843] Example 100: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 2)

[844] A mixture of 3-[[(3S,4S)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 2, 105 mg), DMF (4 mL) and DIPEA (0.3 mL) was stirred for 15 min, and added EDC (90 mg), HOBt (75 mg) and ammonium chloride (50 mg). After stirring overnight, the mixture was filtered and purified by preparative HPLC to afford the title compound.

[845] Example 101: (3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N-bis(2-hydroxyethyl)-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide

[846] Step 1: Preparation of (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride

[847] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (360 mg), DCM (5 mL) and DIPEA (0.3 mL) under argon was cooled to -78°C. Sulfuryl chloride (440 mg) as solution in DCM (5 mL) was added dropwise. The cooling bath was removed. The mixture was stirred at RT for 1 h, diluted with EA and washed with HCl (1N) and brine. The organic phase was dried (Na2SO4) and concentrated. The residue was purified by preparative HPLC to afford the subtitle compound.

[848] Step 2: Preparation of (3R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N-bis(2-hydroxyethyl)-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide

[849] A mixture of 2-(2-hydroxyethylamino)ethanol (45 mg), DIPEA (0.3 mL) and DCM (4 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (35 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[850] Example 102: (3R,4R)-1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]pyrrolidine-3,4-diol

[851] A mixture of (3R,4R)-pyrrolidine-3,4-diol (50 mg), DIPEA (0.2 mL) and DCM (4 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (35 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[852] Example 102: (3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(1H-tetrazol-5-ylmethyl)-3,6-dihydro-2H-pyridine-1-sulfonamide

[853] A mixture of 1H-tetrazol-5-ylmethanamine (50 mg), DIPEA (0.5 mL) and DMF (4 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (35 mg). After 6 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[854] Example 104: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propyl acetate

[855] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 100 mg), DIPEA (0.22 mL) and DCM (2 mL) was added 3-chlorosulfonylpropyl acetate (76 mg). After 45 min, the mixture was diluted with NH4Cl solution (2M, 3 mL). The pH was adjusted to 1 with 1M HCl. The mixture was extracted with EA (10 mL). The organic layer was washed with HCl (0.1M, 2mL) and brine (2 mL), dried (Na2SO4) and concentrated. The residue purified by chromatography (15 g silica gel, n-heptane/EA 100:0 to 0:100) to afford the title compound.

[856] Example 105: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-ol

[857] A mixture of methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propyl acetate (61 mg) and THF (1 mL) was added LiOH (2M, 1 mL). After 2 h, the mixture was diluted with ammonium chloride solution (2M, 2 mL) and HCl (1M, 2 mL) and extracted with EA (10 mL). The organic phase was washed with HCl (0.1M, 2 mL) and brine (2 mL), dried (Na2SO4) and concentrated to afford the title compound.

[858] Example 106: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-1-one

[859] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (500 mg), azetidin-3-ol (170 mg), DMF (5 mL) and DIPEA (0.83 mL) was added HATU (552 mg). After stirring overnight, the mixture was diluted with MeOH (1 mL), filtered and purified by preparative HPLC. The oily material obtained (337 mg) was suspended with MTBE (5 mL) for 48 h. The solid was isolated by filtration to afford the title compound.

[860] Example 107: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methylsulfonyl-propanamide

[861] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (50 mg), DMF (1 mL), DIPEA (0.15 mL) was added EDC (30 mg) and HOBt (20 mg). After 15 min, the mixture was added methanesulfonamide (30 mg). After 2 h, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[862] Example 108: (5R)-5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]imidazolidine-2,4-dione

[863] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (0.8 mL) and DCM (3 mL) was added [(4R)-2,5-dioxoimidazolidin-4-yl]methanesulfonyl chloride (70 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[864] Example 109: (3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[2-hydroxy-1-(hydroxymethyl)ethyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide

[865] A mixture of (3R,4R)-pyrrolidine-3,4-diol (40 mg), DIPEA (0.5 mL) and DCM (4 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (40 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[866] Example 110: 4-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperazin-2-one

[867] A mixture of piperazin-2-one (30 mg), DIPEA (0.6 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (30 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[868] Example 111: (2S)-2-Amino-N-[[(3R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanamide

[869] A mixture of (2S)-2-aminopropanamide (20 mg), DIPEA (0.6 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (30 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[870] Example 112: 1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-ol

[871] A mixture of azetidin-3-ol (20 mg), DIPEA (0.6 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-

dihydropyridine-1(2H)-sulfonyl chloride (30 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[872] Example 113: (3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(2-oxopyrrolidin-3-yl)-3,6-dihydro-2H-pyridine-1-sulfonamide

[873] A mixture of 3-aminopyrrolidin-2-one (27 mg), DIPEA (0.6 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (30 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[874] Example 114: 2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetic acid

[875] Step 1: Preparation of methyl 2-[[(3R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetate

[876] dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetic acid

[877] A mixture of methyl 2-(methylamino)acetate (110 mg), DIPEA (1.5 mL), DMF (2 mL) and DCM (10 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (130 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compound. MS m/z 458.1 [M+H]+.

[878] Step 2: Preparation of 2-[[(3R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetic acid

[879] A mixture of methyl 2-[[(3R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetate (36 mg), water (0.5 mL) and THF (2 mL) was added LiOH (7 mg). After 1 h, the mixture was concentrated to afford the title compound.

[880] Example 115: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methoxy-pyrimidine

[881] Step 1: Preparation of 2-methoxy-5-[(4-methoxyphenyl)methylsulfanyl]pyrimidine

[882] A mixture of 5-bromo-2-methoxy-pyrimidine (5.0 g, 26.5 mmol), (4-methoxyphenyl)methanethiol (6.1 g, 26.5 mmol), Pd2(dba)3 (1.45 g, 1.59 mmol), Xantphos (1.83 g, 3.17 mmol), DIPEA (10.3 g, 79.4 mmol) and toluene (50 mL) was exchanged with nitrogen three times. The reaction mixture was stirred at 100°C for 16 h under nitrogen atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 40 g silica gel column, eluting with 0%-20% ethyl acetate in petroleum ether) to afford the subtitle compound (6.0 g, 22.9 mmol, yield: 86.5%) as yellow solid. MS m/z 263 [M+H]+.

[883] Step 2: Preparation of 2-methoxypyrimidine-5-sulfonyl chloride

[884] To a solution of 2-methoxy-5-[(4-methoxyphenyl)methylsulfanyl]pyrimidine (5.9 g, 22.5 mmol) in acetic acid (60 mL) and water (20 mL) was added NCS (12.0 g, 90.0 mmol) slowly at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (80 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 40 g silica gel column, eluting with 0%-50% dichloromethane in petroleum ether) to give the crude product, which was triturated with petroleum ether (30 mL). The precipitate formed was isolated by filtration and dried in vacuo to afford the subtitle compound (1.2 g, 5.75 mmol, yield: 25.6%) as white solid. MS m/z 209 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 9.09 (s, 2H), 4.18 (s, 3H) ppm.

[885] Step 3: Preparation of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methoxy-pyrimidine

[886] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (71 mg), DIPEA (0.8 mL) and DCM (3 mL) was added 2-methoxypyrimidine-5-sulfonyl chloride (105 mg). After 60 min, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[887] Example 116: Methyl 2-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetate

[888] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (1.0 mL) and DCM (3 mL) was added methyl 2-(4-chlorosulfonylpyrazol-1-yl)acetate (110 mg). After 60 min, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[889] Example 117: 2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetamide

[890] A mixture of 2-[[(3R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetic acid (40 mg), DMF (2.5 mL) and DIPEA (0.1 mL) was stirred for 15 min, and added EDC (25 mg), HOBt (22 mg) and ammonium chloride (15 mg). After stirring overnight, the mixture was filtered and purified by preparative HPLC to afford the title compound.

[891] Example 118: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine

[892] Step 1: Preparation of 5-((4-methoxybenzyl)thio)pyrimidine

[893] To a solution of 5-bromopyrimidine (9 g, 57 mmol) in toluene (50 mL) was added PMB-SH (8.7 g, 57 mmol), DIPEA (22 g, 171 mmol), Pd2(dba)3 (3.1 g, 3.4 mmol) and Xantphos (3.3 g, 5.7 mmol) under nitrogen atmosphere. The reaction was stirred at 80°C under nitrogen atmosphere for 16 h. The reaction was quenched with saturated ammonium chloride (300 mL) and extracted with dichloromethane (500 mL x 3). The crude product was purified by flash chromatography (ethyl acetate / petroleum ether = 10%) to afford the subtitle compound (12 g, 51 mmol, yield: 89%) as a yellow oil. MS m/z 233 [M+H]+.

[894] Step 2: Preparation of pyrimidine-5-sulfonyl chloride

[895] To a solution of aqueous HCl solution (1 N, 206 mL), NaClO (206 g) was added in portions. The mixture was stirred at -5°C for 30 mins. Then, the mixture was dropwise to a solution of 1,3-dichloro-5,5-dimethyl-imidazolidine-2,4-dione (8 g, 34 mmol) in DCM (100 mL). The reaction mixture was stirred at RT for 30 mins. The desired product was found in LCMS. The mixture was filtered and concentrated. The crude product was purified by flash chromatography (ethyl acetate / petroleum ether = 20%) to afford the subtitle compound (244

mg, yield: 4%) as a colorless oil. MS m/z 179 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.16 (s, 1H), 8.90 (s, 2H) ppm.

[896] Step 3: Preparation of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine

[897] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (0.8 mL), DMF (0.5 mL) and DCM (2 mL) was added pyrimidine-5-sulfonyl chloride (100 mg). After 60 min, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[898] Example 119: 4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyridin-2-one

[899] Step 1: Preparation of 4-[(4-methoxyphenyl)methylsulfanyl]-1 -methyl-pyridin-2-one

[900] To a solution of 4-bromo-1-methyl-pyridin-2-one (4.0 g, 21.3 mmol) and (4-methoxyphenyl)methanethiol (3.61 g, 23.4 mmol) in toluene (50 mL) was added DIPEA (5.5 g, 42.5 mL). Then (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one palladium (734 mg, 1.28 mmol) and (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (739 mg, 1.28 mmol) were added under N2 atmosphere. The reaction was stirred at 80°C for 16 h. Then the mixture was poured into water (50 mL) and extracted with EA (50 mL x 2). The organic layers were combined, washed with brine (50 mL x 2), dried with anhydrous Na2SO4 and concentrated. The residue was purified by flash chromatography (EA/PE= 35%) to afford the subtitle compound (5.4 g, yield: 97.1%) as colorless oil. MS m/z 262.1 [M+H]+.

[901] Step 2: Preparation of 1-methyl-2-oxo-pyridine-4-sulfonyl chloride

[902] To a solution of 4-[(4-methoxyphenyl)methylsulfanyl]-1-methyl-pyridin-2-one (5.4 g, 20.7 mmol) in AcOH/H2O (100 mL, v/v=1/1) was added 1-chloropyrrolidine-2,5-dione (11.0 g, 827 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 hrs. The mixture was poured into water (100 mL) and extracted with DCM (100 mL x 3). The organic layers were washed with brine (100 mL x 2), dried with Na2SO4 and concentrated. The crude product was purified by flash chromatography (EA: PE= 80%) to afford the subtitle compound (1.44 g, yield: 33.6 %) as a white solid. MS m/z 208.1 [M+H]+. 1H NMR (500

MHz, CDCl3) δ 7.57 (d, J = 7.2 Hz, 1 H), 7.20 (d, J = 2.2 Hz, 1 H), 6.64 (dd, J = 7.2, 2.2 Hz, 1 H), 3.63 (s, 3 H).

[903] Step 3: Preparation of 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyridin-2-one

[904] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (43 mg), DIPEA (0.7 mL), DMF (0.5 mL) and DCM (2 mL) was added 1-methyl-2-oxo-pyridine-4-sulfonyl chloride (95 mg). After 60 min, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[905] Example 120: 2-[4-Chloro-5-[(3R,4R)-1-[2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[906] Step 1: Preparation of ethyl 2-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H- tetrazol-5-yl)acetate

[907] To a solution of ethyl 2-(2H-tetrazol-5-yl)acetate (10 g, 64.0 mmol) in DMF (30 mL) under argon atmosphere at 25°C was added potassium carbonate (10.6 g, 76.9 mmol) and 1-(chloromethyl)-4-methoxy-benzene (12.0 g, 76.9 mmol). The reaction mixture was stirred overnight. LCMS showed the reaction was completed. The mixture was extracted with EtOAc (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL) and water (50 mL), dried over Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (15-48% EtOAc in hexanes) to afford the subtitle compound (7.0 g, 0.0196 mol, yield: 30.6%) as a white solid. MS m/z 277.1 [M+H]+.

[908] Step 2: Preparation of 2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethanol

[909] To a solution of ethyl 2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]acetate (6.8 g, 24.6 mmol) in THF (70 mL) under argon atmosphere at 0°C was added LiAlH4 (1.49 g, 39.4 mmol). The reaction mixture was stirred overnight at RT. LCMS showed the reaction was completed. The mixture was quenched with water (1.49 mL), NaOH (20%, 1.49 mL), water (4.5 mL) and was filtrated to afford the crude product. The crude product was dissolved in DCM, loaded to a silica column (SanTai, 80 g), purified by flash chromatography (Biotage) and rinsed with EA/PE (0% to 5%) to afford the subtitle compound (3.8 g, 0.0142 mol, yield: 57.6%) as a colorless oil. MS m/z 235.1 [M+H]+.

[910] Step 3: Preparation of 2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethyl 4-methylbenzenesulfonate

[911] To a solution of 2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethanol (3.6 g, 15.6 mmol), N,N-diethylethanamine (3.11 g, 30.7 mmol) in THF (40 mL) under argon atmosphere was added 4-methylbenzenesulfonyl chloride (4.39 g, 23.1 mmol) slowly at 0°C. The reaction mixture was stirred overnight. LCMS showed the reaction was completed. The mixture was concentrated and was diluted with EtOAc (100 mL) and H2O (100 mL). The organic phase was separated. The aqueous layer was extracted with EA (100 ml ×2). The organic phases were combined, washed with water (100 ml ×2), dried over Na2SO4 and concentrated. The crude product was dissolved in DCM, loaded to a silica column (SanTai, 120 g), purified by flash chromatography (Biotage) and rinsed with EA/PE (0% to 50%, 80 mL/ min) to afford the subtitle compound (4.7 g, 0.012 mol, yield 77.8%) as a colorless oil. MS m/z 389.1 [M+H]+.

[912] Step 4: Preparation of S-[2-[2-[(4-methoxyphenyl)methyl]tetrazol -5-yl]ethyl] ethanethioate

[913] To a solution of 2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethyl 4-methylbenzenesulfonate (4.3 g, 11.1 mmol) in DMF (30 mL) were added ethanethioic S-acid (1.69 g, 22.1 mmol) and potassium carbonate (6.12 g, 44.3 mmol). The reaction mixture was stirred at 60°C for 16 hours. LCMS showed the reaction was completed. The mixture was diluted with EtOAc (100 mL) and H2O (100 mL). The organic phase was separated. The aqueous layer was extracted with EA (100 mL ×2). The organic phases were combined, washed with water (100 mL × 2), dried over Na2SO4 and concentrated. The crude product was dissolved in DCM, loaded to a silica column (SanTai, 120 g), purified by flash chromatography (Biotage) and rinsed with EA/PE (0% to 50%) to afford the subtitle compound (3.0 g, 9.67 mmol, yield 87.3%) as a yellow oil. MS m/z 293.1 [M+H]+.

[914] Step 5: Preparation of 2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethanesulfonyl chloride

[915] To a solution of 1-chloropyrrolidine-2,5-dione (333 mg) in ACN (5 mL) was added hydrogen chloride (3 mL) slowly, the mixture was stirred at 0°C for 15 mins. S-[2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethyl] ethanethioate (292 mg) was added. The reaction was stirred at 0°C for 30 mins. LCMS showed the reaction was completed. The mixture was

concentrated and purified by reverse flash chromatography (Biotage, gradient: 20%-50% ACN in water (0.01%TFA), flow rate: 30 mL/min; column: Boston C18, 40 g) (reaction was repeated with 3 batches) to afford the subtitle compound (581.4 mg, yield: 42.8%) as a white solid.MS m/z 339.0 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 7.37 – 7.29 (m, 2H), 6.92 – 6.87 (m, 2H), 5.66 (s, 2H), 4.16 – 4.11 (m, 2H), 3.80 (s, 3H), 3.62 – 3.57 (m, 2H).

[916] Step 6: Preparation of 2-[4-chloro-5-[(3R,4R)-1-[2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[917] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (70 mg), DIPEA (1.5 mL), DMF (1.0 mL) and DCM (4 mL) was added 2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethanesulfonyl chloride (190 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[918] Example 121: 2-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetic acid

[919] A mixture of methyl 2-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetate (56 mg), water (1 mL) and THF (4 mL) was added LiOH (10 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[920] Example 122: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-ol

[921] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methoxy-pyrimidine (60 mg), water (1 mL) and THF (4 mL) was added LiOH (11 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[922]

[923] Example 123: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2H-tetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[924] A mixture of 2-[4-chloro-5-[(3R,4R)-1-[2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (65 mg) and TFA (3 mL) was stirred at 50°C for 2h. The mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[925] Example 124: Methyl 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate

[926] Step 1: Preparation of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-carboxylate

[927] To a solution of 2-[[5-bromo-2-(5-fluoro-2-pyridyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (5 g, 13.4 mmol) in 1,4-dioxane (50 mL) were added tert-butyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (4.34 g, 13.4 mmol) and potassium carbonate (5.57 g, 40.3 mmol) in water (10 mL). And then Pd(dtbpf)Cl2 (876 mg, 1.34 mmol) was added under N2 atmosphere. The reaction was stirred at 80°C for 48 hrs. The reaction mixture was quenched by adding water (100 mL) and extracted with EA (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried and concentrated. The crude product was purified by flash column chromatography (ethyl acetate / petroleum ether = 30%) to afford the subtitle compound (3.02 g, yield: 46%) as a yellow oil. MS m/z 489.2 [M+H]+.

[928] Step 2: Preparation of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-carboxylate

[929] To a solution of tert-butyl 4-[2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (2 g, 4.09 mmol) in THF (20 mL) was added NCS (653 mg, 4.91 mmol) in several portions at RT (water bath). The reaction mixture was stirred at 40°C for 16 hrs. The solvent was removed, and the residue taken up into water (50 mL) followed by extraction with EA (50 mL x 3). The organic layers were washed with brine, dried with Na2SO4 and concentrated. The crude was purified by flash chromatography (ethyl acetate / petroleum ether = 25%) to afford the subtitle compound (540 mg, yield: 25%) as a yellow oil. MS m/z 523.0 [M+H]+.

[930] Step 3: Preparation of 2-[4-chloro-5-(5-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl]-5-fluoro-pyridine

[931] A solution of tert-butyl 4-[5-chloro-2-(5-fluoro-2-pyridyl)-3-(2-trimethylsilylethoxymethyl)imidazol-4-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (540 mg, 1.03 mmol) in 1,4-dioxane (2 mL) was added 4M HCl in 1,4-dioxane (4 mL) and stirred at room temperature for 4 hours. Then the mixture was concentrated and diluted with water (10 mL). The mixture was basified with saturated K2CO3 solution to pH = 9 and was extracted with ethyl acetate (15 mL x 3). The organic layers were combined, washed with brine (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated to afford the subtitle compound (174.5 mg, yield 57.6%) as a white solid. MS m/z 293.2 [M+H]+. 1H NMR (500 MHz, CDCl3) δ 8.35 (d, J = 2.5 Hz, 1H), 8.15 (dd, J = 8.5, 4.5 Hz, 1H), 7.49 (td, J = 8.5, 2.5 Hz, 1H), 3.43 (s, 2H), 3.10 (t, J = 5.5 Hz, 2H), 2.35 (s, 2H), 1.68 (s, 3H) ppm.

[932] Step 4: Preparation of methyl 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate

[933] A mixture of 2-[4-chloro-5-(5-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl]-5-fluoro-pyridine (150 mg), DIPEA (0.3 mL) and DCM (5 mL) was added methyl 3-chlorosulfonylpropanoate (105 mg). After stirring overnight, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[934] Example 125: 3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanamide

[935] Step 1: Preparation of 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoic acid

[936] A mixture of methyl 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate (100 mg) and THF (1 mL) was added LiOH (2M, 0.17 mL). After stirring overnight, the mixture was diluted with ammonium chloride solution (2M, 2 mL), acidified with 1M HCl and extracted with EA (5 mL). The organic phase was washed with HCl (0.1M, 2 mL) and brine (2 mL x2), dried (Na2SO4) and concentrated to afford the subtitle compound.

[937] Step 2: Preparation of 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanamide

[938] A mixture of 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was stirred for 15 min, and added EDC (20 mg), HOBt (9.5 mg) and ammonium chloride (7.5 mg). After stirring overnight, the mixture was filtered and purified by preparative HPLC to afford the title compound.

[939] Example 126: 3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-1-one

[940] A mixture of 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was stirred for 15 min, and added EDC (20 mg), HOBt (9.5 mg) and azetidin-3-ol (10 mg). After stirring overnight, the mixture was filtered and purified by preparative HPLC to afford the title compound.

[941] Example 127: 3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-N-cyclopropyl-propanamide

[942] A mixture of 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was stirred for 15 min, and added EDC (20 mg), HOBt (9.5 mg) and cyclopropanamine (8 mg). After stirring overnight, the mixture was filtered and purified by preparative HPLC to afford the title compound.

[943] Example 128: (3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-3,6-dihydro-2H-pyridine-1-sulfonamide

[944] A mixture of (5-methyl-1,3,4-oxadiazol-2-yl)methanamine (40 mg), DIPEA (0.6 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (25 mg). After 1 h at

50°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compound.

[945] Example 129: [1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-yl]methanol

[946] A mixture of azetidin-3-ylmethanol (30 mg), DIPEA (0.8 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (40 mg). After 1 h at 50°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[947] Example 130: N-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperidine-3-carboxamide

[948] A mixture of piperidine-3-carboxamide (45 mg), DIPEA (0.8 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (40 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[949] Example 131: (3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[(2S)-2-hydroxypropyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide

[950] A mixture of (2S)-1-aminopropan-2-ol (25 mg), DIPEA (0.8 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (40 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[951] Example 132 and Example 133: 2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonylamino]-N,N-dimethyl-acetamide and 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylamino]-N,N-dimethyl-acetamide

[952] A mixture of 2-amino-N,N-dimethyl-acetamide (35 mg), DIPEA (0.8 mL), DMF (1 mL) and DCM (3 mL) was added (R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-

3-methyl-3,6-dihydropyridine-1(2H)-sulfonyl chloride (40 mg, containing (3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonyl chloride as impurity). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compounds.

[953] Example 134: Tert-butyl (3S,4S)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate

[954] Step 1: Preparation of tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxylate

[955] A mixture of tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxylate (147 g, 0.28 mol, mixture of SEM-regioisomers) and 1 M HCl in dioxane (365 mL) was stirred at room temperature for 4 hours. Then solution was concentrated by rotary evaporator and slurried with MTBE/PE=10/1 three times to afford the subtitle compound (85 g, crude) as a yellow solid. MS m/z 395.0 [M+H]+.

[956] Step 2: Preparation of tert-butyl (3S,4S)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate

[957] The isomeric mixture tert-butyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxylate (85 g, crude) was separated by preparative chiral HPLC to afford tert-butyl (3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxylate (35.448 g) and the title compound (36.128 g).

[958] Preparative chiral HPLC conditions: instrument: SFC-150 (Waters); column: OD 25x250mm, 10μm (Daicel); column temperature: 35°C; mobile phase: CO_2/ MeOH (0.2% NH_3(7M in MeOH) 85:15; flow rate: 100 ml/min; back pressure: 100 bar; detection wavelength: 214 nm; cycle time: 3.5 min; sample solution: 85 g dissolved in 1000 ml methanol; injection volume: 1 ml.

[959] Analytical chiral HPLC conditions: column: IG 4.6*100mm, 5μm; column temperature: 40°C; mobile phase: CO_2/ MeOH (0.2% NH_3(7M in MeOH) 90:10; flow rate: 3ml/min; back pressure: 2000psi; detection wavelength: 214 nm; run time: 4.0 min; injection volume: 5.00 μl.

[960] Tert-butyl (3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxylate. Chiral HPLC 2.060 min. 1H NMR (400 MHz, DMSO-d6) δ 12.86 (s, 1H), 8.60 (d, J = 2.8 Hz, 1H), 7.99 (dd, J = 8.8, 4.4 Hz, 1H), 7.82 (td, J = 8.8, 2.8 Hz, 1H), 4.10 (s, 1H), 3.87 (s, 1H), 3.21 – 2.60 (m, 3H), 2.38 (dd, J = 22.0, 12.4 Hz, 1H), 2.00 (s, 1H), 1.55 – 1.30 (m, 10H), 0.76 (d, J = 6.4 Hz, 3H) ppm.

[961] Tert-butyl (3S,4S)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate. Chiral HPLC 2.343 min.

[962] Example 135: 4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide

[963] Step 1: Preparation of tert-butyl N-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]carbamate

[964] A mixture of 2-[4-chloro-5-(5-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl]-5-fluoro-pyridine (25 mg), DIPEA (30 µL) and DCM (1 mL) was added (tert-butoxycarbonyl)(4-dimethylimino)pyridine-1(4H)-yl)sulfamoyl)amide (39 mg). After stirring overnight, the mixture was diluted with ammonium chloride solution (2M, 2 mL), acidified with 1M HCl and extracted with EA (5 mL). The organic phase was washed with HCl (0.1M, 1 mL) and brine (1 mL x2), dried (Na2SO4) and concentrated to afford the crude subtitle compound.

[965] Step 2: Preparation of 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide

[966] A mixture of tert-butyl N-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]carbamate (40 mg, crude) and DCM (1 mL) was added HCl (6M in iPrOH, 1 mL). After 3d, the mixture was concentrated and purified by preparative HPLC to afford the title compound.

[967] Example 136: 2-Chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine

[968] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (230 mg), DIPEA (2 mL) and DCM (5 mL) was added 2-chloropyrimidine-5-

sulfonyl chloride (220 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[969] Example 137: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylpyrazol-4-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[970] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (63 mg), DIPEA (1 mL) and DCM (3 mL) was added 1-methylpyrazole-4-sulfonyl chloride (100 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[971] Example 138: (3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,3-dimethyl-piperidine-1-carboxamide

[972] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (60 mg), DIPEA (1 mL) and DCM (3 mL) was added N-methylcarbamoyl chloride (50 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[973] Example 139: 1-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]azetidin-3-ol

[974] A mixture of azetidin-3-ol (17 mg), DIPEA (0.5 mL) and DMF (2 mL) was added 2-chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine (33 mg). After 1 h at 60°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[975] Example 140: 2-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]ethanol

[976] A mixture of 2-aminoethanol (15 mg), DIPEA (0.5 mL) and DMF (2 mL) was added 2-chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine (33 mg). After 1 h at 60°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[977] Example 141: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[978] Step 1: Preparation of ethyl 2-(1-methyltetrazol-5-yl)acetate

[979] To a stirred suspension of ethyl 2-(1H-tetrazol-5-yl)acetate (10.5 g, 67.2 mmol) in MeCN (100 mL) was added potassium carbonate (9.29 g, 67.2 mmol) in portions. Then methyl iodide (11.5 g, 81.7 mmol) was added into the reaction system dropwise. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was filtered, and the solid washed with ethyl acetate (100 mL). The filtrate was concentrated. The residue was purified by flash chromatography (Biotage 120 g silica gel column, eluting with 0%-50% ethyl acetate in petroleum ether) to the subtitle compound (6.1 g, 35.8 mmol, yield: 53.3%) as white solid. MS m/z 171 [M+H]+.

[980] Step 2: Preparation of 2-(1-methyltetrazol-5-yl)ethanol

[981] To a stirred solution of ethyl 2-(1-methyltetrazol-5-yl)acetate (6.1 g, 35.8 mmol) in MeOH (60 mL) was added sodium borohydride (2.71 g, 71.7 mmol) in portions at 0°C. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with water (20 mL) and concentrated. The residue was purified by flash chromatography (Biotage 40 g silica gel column, eluting with 0%-20% MeOH in DCM) to afford the subtitle compound (4.5 g, 35.1 mmol, yield: 98%) as colorless oil. MS m/z 129 [M+H]+.

[982] Step 3: Preparation of O-[2-(1-methyltetrazol-5-yl)ethyl] ethanethioate

[983] To a solution of triphenylphosphine (20.3 g, 77.3 mol) in dry THF (200 mL) was added DIAD (15.6 g, 77.3 mmol) dropwise at 0°C under nitrogen atmosphere. After 20 min, a solution of 2-(1-methyltetrazol-5-yl)ethanol (4.5 g, 35.1 mmol) in dry THF (20 mL) was added into the reaction system. After 10 min, neat ethanethioic S-acid (5.88 g, 77.3 mmol) was added into the reaction system. The resulting mixture was stirred at 0°C for 1 h and at room temperature for 4 h. The reaction mixture was concentrated. The residue was purified by flash chromatography (Biotage 120 g silica gel column, eluting with 0%-30% ethyl acetate in petroleum ether) to afford the subtitle compound (12.5 g, crude) as light-yellow solid. MS m/z 187 [M+H]+.

[984] Step 4: Preparation of 2-(1-methyltetrazol-5-yl)ethanesulfonyl chloride

[985] To a solution of O-[2-(1-methyltetrazol-5-yl)ethyl] ethanethioate (12.5 g, crude) in MeCN (65 mL) were added HCl (2 M, 105 mL, 0.209 mmol) slowly and NCS (11.7 g, 87.3 mmol) in portions at 0°C. The resulting mixture was stirred at 0°C for 2 h. The reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic layers were dried with anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography (Biotage 80 g silica gel column, eluting with 0%-30% ethyl acetate in petroleum ether) to afford the subtitle compound (3.8 g, 18.04 mmol, yield: 51.4%) as white solid. MS m/z 211 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 4.46 – 4.24 (m, 2H), 4.10 (s, 3H), 3.74 – 3.39 (m, 2H) ppm.

[986] Step 5: Preparation of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-[2-(1-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[987] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (65 mg), DIPEA (1 mL) and DCM (3 mL) was added 2-(1-methyltetrazol-5-yl)ethanesulfonyl chloride (165 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[988] Example 142: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine

[989] Step 1: Preparation of 2-aminopyrimidine-5-sulfonyl chloride

[990] A mixture of pyrimidin-2-amine (20 g, 210 mmol) and SOCl2/ClSO2OH (280 mL, v/v=9/5) was stirred at 150°C for 96 hrs. The mixture was poured into water (200 mL) and extracted with DCM (200 mL x 3). The organic layers were washed with brine (200 mL x 2), dried with Na2SO4 and concentrated. The crude product was purified by flash chromatography (EA: PE= 40%) to give to afford the subtitle compound (4.2 g, yield: 10.3%) as a white solid. MS m/z 193.9 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 8.83 (s, 2H), 5.95 (s, 2H) ppm.

[991] Step 2: Preparation of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine

[992] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (500 mg), DIPEA (5 mL) and DCM (20 mL) was added 2-aminopyrimidine-5-

sulfonyl chloride (550 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC. The solid obtained (610 mg) was dissolved in EA. The solution was washed with sat. NaHCO3, dried (Na2SO4), filtered and concentrated. The residue was suspended with EA/n-heptane. The solid was isolated by filtration and dried in vacuo to afford the title compound.

[993] Example 143: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridin-2-amine

[994] Step 1: Preparation of 2-aminopyrimidine-5-sulfonyl chloride

[995] A mixture of pyrimidin-2-amine (5.0 g, 52.6 mmol) and sulfurochloridic acid (50 mL) was stirred at 150°C for 4 hrs. The mixture was poured into water (50 mL) and extracted with DCM (50 mL x 3). The organic layers were washed with brine (50 mL x 2), dried with Na2SO4 and concentrated. The crude product was purified by flash chromatography (EA: PE= 70%) to give to afford the subtitle compound (1.96 g, yield: 19.3%) as a white solid. MS m/z 192.9 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 8.70 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 9.2, 2.8 Hz, 1H), 6.56 (dd, J = 9.2, 0.4 Hz, 1H), 5.30 (s, 2H).

[996] Step 2: Preparation of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridin-2-amine

[997] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (65 mg), DIPEA (1 mL) and DCM (3 mL) was added 6-aminopyridine-3-sulfonyl chloride (192 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[998] Example 144: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-pyrimidin-2-amine

[999] A mixture of cyclopropanamine (14 mg), DIPEA (0.5 mL) and DMF (2 mL) was added 2-chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine (33 mg). After 1 h at 60°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1000] Example 145: 4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyrrolidin-2-one

[1001] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (65 mg), DIPEA (1 mL) and DCM (3 mL) was added 1-methyl-5-oxo-pyrrolidine-3-sulfonyl chloride (100 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1002] Example 146: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-pyrimidin-2-amine

[1003] A mixture of methanamine (10 mg), DIPEA (1 mL) and DMF (1.5 mL) was added 2-chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine (33 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1004] Example 147: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N,N-bis(trideuteriomethyl)propanamide

[1005] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added 1,1,1-trideuterio-N-(trideuteriomethyl)methanamine (7.1 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1006] Example 148: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-2-methyl-propyl)propanamide

[1007] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added 1-amino-2-methyl-propan-2-ol (12 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1008] Example 149: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-propanamide

[1009] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added cyclopropanamine (8 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1010] Example 150: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-hydroxypyrrolidin-1-yl]propan-1-one

[1011] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added (3R)-pyrrolidin-3-ol (12 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1012] Example 151: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-hydroxypyrrolidin-1-yl]propan-1-one

[1013] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added (3S)-pyrrolidin-3-ol (12 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1014] Example 152: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxyazetidin-1-yl)propan-1-one

[1015] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added 3-

methoxyazetidine (12 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1016] Example 153: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxy-3-methyl-azetidin-1-yl)propan-1-one

[1017] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added 3-methylazetidin-3-ol (12 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1018] Example 154: 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-1-piperidyl)propan-1-one

[1019] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added piperidin-4-ol (14 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1020] Example 155: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxyethyl)propanamide

[1021] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL), DIPEA (50 µL) was added EDC (20 mg) and HOBt (9.4 mg). After 10 min, the mixture was added 2-methoxyethanamine (10 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1022] Example 156: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1023] Step 1: Preparation of ethyl 2-(2-methyltetrazol-5-yl)acetate

[1024] To a stirred suspension of ethyl 2-(1H-tetrazol-5-yl)acetate (10.5 g, 67.2 mmol) in MeCN (100 mL) was added potassium carbonate (9.29 g, 67.2 mmol) slowly. Then methyl iodide (11.5 g, 81.7 mmol) was added into the reaction system dropwise. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was filtered and the cake washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 120 g silica gel column, eluting with 0%-50% ethyl acetate in petroleum ether) to afford the subtitle compound (4.2 g, 24.7 mmol, yield: 36.7%) as colorless oil. MS m/z 171 [M+H]+.

[1025] Step 2: Preparation of 2-(1-methyltetrazol-5-yl)ethanol

[1026] To a stirred solution of ethyl 2-(1-methyltetrazol-5-yl)acetate (4.2 g, 24.7 mmol) in MeOH (40 mL) was added sodium borohydride (1.87 g, 49.4 mmol) in portions at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with water (30 mL) and concentrated. The residue was purified by flash chromatography (Biotage 40 g silica gel column, eluting with 0%-20% MeOH in DCM) to afford the subtitle compound (3.1 g, 24.2 mmol, yield: 98%) as colorless oil. MS m/z 129 [M+H]+.

[1027] Step 3: Preparation of O-[2-(2-methyltetrazol-5-yl)ethyl] ethanethioate

[1028] To a stirred solution of triphenylphosphine (14.0 g, 53.2 mol) in dry THF (140 mL) was added DIAD (10.8 g, 53.2 mmol) dropwise at 0 °C under nitrogen atmosphere. After 20 min, a solution of 2-(2-methyltetrazol-5-yl)ethanol (3.1 g, 24.2 mmol) in dry THF (30 mL) was added into the reaction system. After 10 min, neat ethanethioic S-acid (4.05 g, 53.2 mmol) was added into the reaction system. The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 80 g silica gel column, eluting with 0%-30% ethyl acetate in petroleum ether) to afford the subtitle compound (11.5 g, crude) as light yellow oil. MS m/z 187 [M+H]+.

[1029] Step 4: Preparation of (2-(2-methyltetrazol-5-yl)ethanesulfonyl chloride

[1030] To a stirred solution of O-[2-(2-methyltetrazol-5-yl)ethyl] ethanethioate (11.5 g, crude) in MeCN (100 mL) was added 2 M HCl (72.6 mL, 145.2 mmol) dropwise followed by NCS (8.08 g, 60.5 mmol) in portions at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (50 mL

x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography (Biotage 80 g silica gel column, eluting with 0%-25% ethyl acetate in petroleum ether) to give the crude product, into which was added water (100 mL). The mixture was stirred at 100 °C for 1 h, cooled to room temperature and extracted with ethyl acetate (50 mL x 3). The aqueous phase was concentrated under reduced pressure. The residue was dissolved in POCl3 (37.1 g, 242.0 mmol). The resulting mixture was stirred at 70 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 40 g silica gel column, eluting with 0%-30% ethyl acetate in petroleum ether) to afford the subtitle compound (2.0 g, 9.49 mmol, two steps' yield: 39.2%) as light yellow oil. MS m/z 211 [M+H]+. 1H NMR (500 MHz, CDCl3) δ 4.35 (s, 3H), 4.18-4.15 (m, 2H), 3.72-3.57 (m, 2H) ppm.

[1031] Step 5: Preparation of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-[2-(2-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1032] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (1 mL) and DCM (3 mL) was added 2-(2-methyltetrazol-5-yl)ethanesulfonyl chloride (120 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1033] Example 157: Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate

[1034] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (2 mL) and DCM (6 mL) was added tert-butyl 3-chlorosulfonylazetidine-1-carboxylate (120 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1035] Example 158: 2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetamide

[1036] Step 1: Preparation of methyl 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetate

[1037] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (2 mL) and DCM (6 mL) was added methyl 2-chlorosulfonylacetate (210 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compound.

[1038] Step 2: Preparation of 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetic acid

[1039] A mixture of methyl 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetate (42 mg), water (1.0 mL) and THF (4 mL) was added LiOH (8 mg). After 1 h, the mixture was concentrated to afford the crude subtitle compound.

[1040] Step 3: Preparation of 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetamide

[1041] A mixture of 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetic acid (40 mg, crude), DMF (2 mL), DIPEA (0.3 mL) was added EDC (25 mg) and HOBt (22 mg). After 15 min, the mixture was added ammonium chloride (18 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1042] Example 159: Tert-butyl N-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-yl]carbamate

[1043] Step 1: Preparation of tert-butyl N-[4-(chloromethyl)thiazol-2-yl]carbamate

[1044] A mixture of 4-(chloromethyl)thiazol-2-amine (hydrochloride, 10 g, 54 mmol), TEA (16.4 g, 162 mmol) and DMAP (cat.) in THF (150 mL) was stirred at room temperature for 5 min. Then Boc2O (14.2 g, 64.8 mmol) was added in portions. After addition, the mixture was stirred at room temperature for 16 h. The mixture was concentrated. The residue was poured into 150 mL water. The water layer was extracted with EtOAc (150 mL x 3). Organic layers were combined, dried over Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (30% EtOAc in PE) to afford the subtitle compound (5.4 g, 40% yield) as yellow solid. MS m/z 249 [M+H]+.

[1045] Step 2: Preparation of S-[[2-(tert-butoxycarbonylamino)thiazol-4-yl]methyl] ethanethioate

[1046] A mixture of tert-butyl N-[4-(chloromethyl)thiazol-2-yl]carbamate (2.5 g, 10 mmol) in acetone (50 mL) was stirred at room temperature. Potassium ethanethioate (2.3 g, 20 mmol) was added. The mixture was stirred at 40°C for 4 h. The mixture was cooled to room temperature and concentrated. The residue was poured into water (50 mL). The water layer was extracted with EtOAc (50 mL x 3). The organic layers were combined, dried over Na2SO4 and concentrated to afford the subtitle compound (3.0 g, crude) as yellow solid. MS m/z 289 [M+H]+.

[1047] Step 3: Preparation of [2-(tert-butoxycarbonylamino)thiazol-4-yl]methanesulfonic acid

[1048] A mixture of S-[[2-(tert-butoxycarbonylamino)thiazol-4-yl]methyl] ethanethioate (100 mg, 0.35 mmol) in HCOOH/ H2O (10/10 mL) was stirred at room temperature. H2O2 (4 g, 35 mmol) was added dropwise. After addition, the mixture was stirred at room temperature for 3 h. Then water (50 mL) was added. The mixture was freeze-dried directly to afford the subtitle compound (1.8 g, 88%) as white solid which was used without further purification. MS m/z 239 [M-tBu+H]+.

[1049] Step 4: Preparation of tert-butyl N-[4-(chlorosulfonylmethyl)thiazol-2-yl]carbamate

[1050] A mixture of [2-(tert-butoxycarbonylamino)thiazol-4-yl]methanesulfonic acid (600 mg, 2 mmol mmol) in DCM (10 mL) was stirred at room temperature. DMF (cat.) was added. The mixture was stirred at 0°C. Oxalyl dichloride (310 mg, 2.4 mmol) was added dropwise. After addition, the mixture was warmed to room temperature and stirred at room temperature for 5 h. The mixture was washed with water (10 mL). The organic layer was dried over Na2SO4 and concentrated to afford the subtitle compound (420 mg, 52% yield) as off-white solid. MS m/z 355 [M+Na]+. 1H NMR (400 MHz, DMSO) δ 7.02 (s, 1H), 3.82 (s, 2H), 1.49 (s, 9H).

[1051] Step 5: Preparation of tert-butyl N-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-yl]carbamate

[1052] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (80 mg), DIPEA (1.5 mL) and DCM (6 mL) was added tert-butyl N-[4-(chlorosulfonylmethyl)thiazol-2-yl]carbamate (170 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1053] Example 160: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonylazetidin-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1054] Step 1: Preparation of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate

[1055] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (130 mg), DIPEA (3 mL) and DCM (10 mL) was added tert-butyl 3-(chlorosulfonylmethyl)azetidine-1-carboxylate (230 mg). After 30 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compound.

[1056] Step 2: Preparation of 2-[5-[(3R,4R)-1-(azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine

[1057] A mixture of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate (135 mg) and DCM (5 mL) was added HCl (6M in iPrOH, 10 mL). After 30 min at RT, the mixture was concentrated to afford the crude subtitle compound.

[1058] Step 3: Preparation of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonylazetidin-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1059] A mixture of 2-[5-[(3R,4R)-1-(azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (30 mg), DIPEA (0.4 mL) and DCM (2 mL) was added methanesulfonyl chloride (15 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1060] Example 161: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylazetidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1061] Step 1: Preparation of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate

[1062] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (2 mL) and DCM (6 mL) was added tert-butyl 3-chlorosulfonylazetidine-1-carboxylate (120 mg). After 20 min at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the subtitle compound.

[1063] Step 2: Preparation of 2-[5-[(3R,4R)-1-(azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine

[1064] A mixture of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate (90 mg) and DCM (4 mL) was added HCl (6M in iPrOH, 8 mL). After 3 h at RT, the mixture was concentrated to afford the crude subtitle compound.

[1065] Step 3: Preparation of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylazetidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1066] A mixture of 2-[5-[(3R,4R)-1-(azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (30 mg), DIPEA (0.4 mL) and DCM (2 mL) was added methanesulfonyl chloride (15 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1067] Example 162: 4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-amine

[1068] A mixture of tert-butyl N-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-yl]carbamate (50 mg) and DCM (3 mL) was added HCl (6M in iPrOH, 6 mL). After stirring overnight, the mixture was concentrated, and the residue purified by preparative HPLC to afford the crude title compound.

[1069] Example 163: 1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidin-1-yl]ethanone

[1070] A mixture of 2-[5-[(3R,4R)-1-(azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (30 mg), DIPEA (0.4 mL) and DCM (2 mL) was added acetyl chloride (10 mg). After 1 h at RT, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1071] Example 164: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(trideuteriomethyl)propanamide

[1072] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 min, trideuteriomethanamine (hydrochloride, 10 mg) was added. After 16 hours, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1073] Example 165: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-yl)propanamide

[1074] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 min, oxetan-3-amine (10 mg) was added. After 16 hours, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1075] Example 166: 2-[4-Chloro-5-[(3R,4R)-1-(1H-imidazol-4-ylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1076] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (28 mg), DIPEA (0.4 mL) and DCM (2 mL) was added 1H-imidazole-4-sulfonyl chloride (15 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1077] Example 167: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-ethyl-propanamide

[1078] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 min, ethanamine (hydrochloride,11 mg) was added. After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1079] Example 168: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-4-methyl-1-piperidyl)propan-1-one

[1080] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 min, 4-methylpiperidin-4-ol (16 mg) was added. After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1081] Example 169: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-morpholino-propan-1-one

[1082] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), morpholine (12 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1083] Example 170: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(cyclopropylmethyl)propanamide

[1084] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), cyclopropylmethanamine (10 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1085] Example 171: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-pyrrolidin-1-yl-propan-1-one

[1086] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), pyrrolidine (10 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1087] Example 172: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2,2,2-trifluoroethyl)propanamide

[1088] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 2,2,2-trifluoroethanamine (14 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1089] Example 173: Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate

[1090] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (45 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added methyl carbonochloridate (12 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1091] Example 174: Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate

[1092] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (33 mg), DIPEA (0.4 mL) and DCM (2 mL) was added methyl carbonochloridate (12 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1093] Example 175: N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]acetamide

[1094] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (35 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added acetyl chloride (10 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1095] Example 176: N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]methanesulfonamide

[1096] A mixture of 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethanamine (27 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added methanesulfonyl chloride (15 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1097] Example 177: Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylate

[1098] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (35 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added methyl 5-chlorosulfonylfuran-2-carboxylate (25 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1099] Example 178: 5-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-3-methyl-1,2,4-oxadiazole

[1100] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (122 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (110 mg). After 1 hour, N'-hydroxyacetamidine (21.5 mg) was added. After 1 h, the mixture was heated to 100°C for 1h. The mixture was diluted with MeOH (1.5 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1101] Example 179: Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]carbamate

[1102] Step 1: Preparation of tetrabutylammonium 2-(tert-butoxycarbonylamino) ethanesulfonate

[1103] To a solution of 2-aminoethanesulfonic acid (30 g, 0.24 mol) and tetrabutylammonium hydroxide (62.2 g, 0.24 mol) in acetone/ H2O (400 mL, 1:1), was added tert-butoxycarbonyl tert-butyl carbonate (52.3 g, 0.24 mol). The reaction mixture was stirred at room temperature for 4 hrs. The mixture was poured into water (400 mL) and extracted with DCM (400 mL x 3). The organic layers were washed with brine (400 mL x 2), dried with Na2SO4 and concentrated. The crude product purified by flash chromatography (EA: PE= 20%) to afford the subtitle compound (86 g, yield: 76.9%) as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 6.12 (s, 1H), 3.57-3.55 (m, 2H), 3.32-3.27 (m, 8 H), 2.94-2.91 (m, 2H), 1.70-1.62 (m, 8H), 1.50-1.47 (m, 17H), 1.03-0.99 (m, 12H) ppm.

[1104] Step 2: Preparation of tert-butyl N-(2-chlorosulfonylethyl)carbamate

[1105] To a solution of tetrabutylammonium 2-(tert-butoxycarbonylamino) ethanesulfonate (4.7 g) in DCM (42 mL) was added DMF (77 μL) followed by a solution of triphosgene in DCM (0.5M, 8 mL at 0°C). The mixture was warmed to RT and stirred for 0.5h. The solution was concentrated and used in the next step directly.

[1106] Step 3: Preparation of tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]carbamate

[1107] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (500 mg), DIPEA (6 mL) and DCM (20 mL) was added tert-butyl N-(2-chlorosulfonylethyl)carbamate (1000 mg, crude). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1108] Example 180: 2-[4-Chloro-5-[(3R,4R)-1-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1109] Step 1: Preparation of 4-(2-bromoethyl)-1-[(4-methoxyphenyl)methyl]triazole

[1110] A mixture of 1-(azidomethyl)-4-methoxy-benzene (1.6 g, 10 mmol) and 4-bromobut-1-yne (1.95 g, 15 mmol) in EtOH/H2O (50 mL/50 mL) was stirred at room

temperature. CuSO4.5H2O (50 mg, 0.2 mmol) and sodium (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (117 mg, 0.6 mmol) was added. The mixture was stirred at room temperature for 40 h. The result mixture was extracted with EtOAc (100 mL x 3). The organic layers were combined, dried over Na2SO4 and concentrated. The residue was purified by chromatography on a silica gel column (30% EtOAc in PE) to afford the subtitle compound (2.7 g, 93% yield) as white solid. MS m/z 296 [M+H]+.

[1111] Step 2: Preparation of S-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethyl] ethanethioate

[1112] A mixture of 4-(2-bromoethyl)-1-[(4-methoxyphenyl)methyl]triazole (2.7 g, 9 mmol) in acetone (40 mL) was stirred at room temperature. Ethanethioyloxypotassium (2.08 g, 18 mmol) was added. The mixture was stirred at 50°C for 4 h. Then the mixture was cooled to room temperature and poured into water (100 mL). The water layer was extracted with EtOAc (100 mL x 3). The organic layers were combined, dried over Na2SO4 and concentrated. The residue was purified by chromatography (silica gel, 60% EtOAc in PE) to afford the subtitle compound (2.5 g, 94% yield) as light yellow solid. MS m/z 292 [M+H]+.

[1113] Step 3: Preparation of 2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl] ethanesulfonic acid

[1114] A mixture of S-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethyl] ethanethioate (2.0 g, 6.9 mmol) in HCOOH (10 mL) was stirred at room temperature. H2O2 (30% aqueous solution, 4 g, 35 mmol) was added dropwise. After the addition was complete, the mixture was stirred at room temperature for 6 h. Then water (50 mL) was added. The mixture was freeze-dried directly to afford the title compound (1.83 g, 88%) as white solid without further purification. MS m/z 298 [M+H]+.

[1115] Step 4: Preparation of 2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethanesulfonyl chloride

[1116] A mixture of [2-(tert-butoxycarbonylamino)thiazol-4-yl]methanesulfonic acid (1.8 g, 6 mmol) in DCM (30 mL) was stirred at room temperature. DMF (cat.) was added. The mixture was stirred at 0°C. Oxalyl dichloride (1.15 g, 9 mmol) was added dropwise. After the addition was complete, the mixture was warmed to room temperature and stirred at room temperature for 6 h. Then the mixture was washed with water (20 mL). The organic layer was

dried over Na2SO4 and concentrated to afford the subtitle compound (1.82 g, 76% yield) as yellow solid without further purification. MS m/z 316 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 7.34 (s, 1H), 7.23 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.45 (s, 2H), 4.11-4.07 (m, 2H), 3.81 (s, 3H), 3.48 – 3.35 (m, 2H).

[1117] Step 5: Preparation of 2-[4-chloro-5-[(3R,4R)-1-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1118] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (60 mg), DIPEA (1 mL) and DMF (5 mL) was added 2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethanesulfonyl chloride (130 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1119] Example 181: 2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethanamine (hydrochloride)

[1120] A mixture of tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]carbamate (245 mg) and DCM (10 mL) was added HCl (6N in iPrOH, 20 mL). After 1 h at 40°C, the mixture was concentrated to afford the title compound.

[1121] Example 182: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(1-hydroxycyclopropyl)methyl]propanamide

[1122] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 1-(aminomethyl)cyclopropanol (12 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 1 hour, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1123] Example 183: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]propan-1-one

[1124] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 3-(trifluoromethyl)pyrrolidin-3-ol (hydrochloride, 27 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After standing overnight, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1125] Example 184: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-ylmethyl)propanamide

[1126] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), oxetan-3-ylmethanamine (12 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After standing overnight, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1127] Example 185: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-7-azaspiro[3.5]nonan-7-yl)propan-1-one

[1128] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 2-oxa-7-azaspiro[3.5]nonane (18 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After standing overnight, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1129] Example 186: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-methoxy-1-piperidyl)propan-1-one

[1130] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 4-methoxypiperidine (16 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After standing overnight, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1131] Example 187: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-tetrahydropyran-4-yl-propanamide

[1132] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), tetrahydropyran-4-amine (14 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After standing overnight, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1133] Example 188: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3S)-tetrahydropyran-3-yl]propanamide

[1134] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), (S)-tetrahydro-2H-pyran-3-amine (hydrochloride, 20 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After standing overnight, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1135] Example 189: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propan-1-one

[1136] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 2-oxa-6-azaspiro[3.3]heptane (14 mg), (DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After standing overnight, the reaction was complete. The mixture was diluted with MeOH (1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1137] Example 190: 2-[4-Chloro-5-[(3R,4R)-1-(2-methoxyethylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1138] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (35 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added 2-methoxyethanesulfonyl chloride (25 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1139] Example 191: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydropyran-4-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1140] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (35 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added tetrahydropyran-4-sulfonyl chloride (25 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1141] Example 192: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(tetrahydrofuran-3-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1142] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (35 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added tetrahydrofuran-3-ylmethanesulfonyl chloride (27 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1143] Example 193: N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]acetamide

[1144] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (60 mg), DIPEA (1 mL) and DCM (5 mL) was added 2-acetamidothiazole-5-sulfonyl chloride (100 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1145] Example 194: N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-yl]acetamide

[1146] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (60 mg), DIPEA (1 mL) and DCM (5 mL) was added 2-acetamido-4-methyl-thiazole-5-sulfonyl chloride (100 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1147] Example 195: Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylate

[1148] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (1 mL) and DCM (5 mL) was added methyl 5-chlorosulfonylpyridine-2-carboxylate (100 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1149] Example 196: Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxylate

[1150] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (120 mg), DIPEA (1.2 mL) and DCM (6 mL) was added tert-butyl 3-chlorosulfonylpyrrolidine-1-carboxylate (150 mg). After 3 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1151] Example 197: Tert-butyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]piperidine-1-carboxylate

[1152] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (120 mg), DIPEA (1.2 mL) and DCM (6 mL) was added tert-butyl 4-chlorosulfonylpiperidine-1-carboxylate (150 mg). After 3 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1153] Example 198: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1H-triazol-4-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1154] A mixture of 2-[4-chloro-5-[(3R,4R)-1-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg) and TFA (5 mL) was stirred at 80°C for 8h. The mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1155] Example 199: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(4-piperidylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)

[1156] A mixture of tert-butyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]piperidine-1-carboxylate (70 mg) and DCM (2 mL) was added HCl (6M in iPrOH, 8 mL). After 1 h at 40°C, the mixture was concentrated to afford the title compound.

[1157] Example 200: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-pyrrolidin-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)

[1158] A mixture of tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxylate (135 mg) and DCM (12 mL) was added HCl (6M in iPrOH, 12 mL). After 1 h at 40°C, the mixture was concentrated to afford the title compound.

[1159] Example 201: Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethylsulfamoyl]carbamate

[1160] A mixture of 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethanamine (hydrochloride, 30 mg) and DCM (2 mL) was added DIPEA (0.3 mL). After 10 min, tert-butoxycarbonyl-[(4-dimethyliminio-1-pyridyl)sulfonyl]azanide (32 mg) was added. After stirring overnight, the mixture was diluted with EA, washed with sat. NH4Cl solution and brine. The organic layer was dried (Na2SO4) and concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1161] Example 202: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-amine

[1162] A mixture of N-[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]acetamide (49 mg) and EtOH (2 mL) was added HCl (6N, 2 mL). After 1 h at 80°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1163] Example 203: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-amine

[1164] A mixture of N-[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-yl]acetamide (45 mg) and EtOH (2 mL) was added HCl (6N, 2 mL). After 1 h at 80°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1165] Example 204: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylic acid

[1166] A mixture of methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylate (120 mg), water (1.5 mL) and THF (6 mL) was added LiOH (20 mg). After 1 h, the mixture was concentrated to afford the title compound.

[1167] Example 205: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]-5-methyl-1,2,4-oxadiazole

[1168] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (0.6 mL) and DCM (3 mL) was added (5-methyl-1,2,4-oxadiazol-3-yl)methanesulfonyl chloride (110 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1169] Example 206: 1-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-piperidyl]ethanone

[1170] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-(4-piperidylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (30 mg), DIPEA (0.5 mL) and DCM (2 mL) was added acetyl chloride (10 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1171] Example 207: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonyl-4-piperidyl)sulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1172] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-(4-piperidylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (30 mg), DIPEA (0.5 mL) and DCM (2 mL)

was added methanesulfonyl chloride (15 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1173] Example 208: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(sulfamoylamino)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1174] A mixture of tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethylsulfamoyl]carbamate (50 mg), DCM (1.5 mL) and MeOH (1.5 mL) was added HCl (6N in iPrOH, 5 mL). After 1 h at 40°C, the mixture was concentrated to afford the title compound.

[1175] Example 209: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylpyrrolidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1176] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-pyrrolidin-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 45 mg), DIPEA (0.5 mL) and DCM (3 mL) was added methanesulfonyl chloride (15 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1177] Example 210: 1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidin-1-yl]ethanone

[1178] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-pyrrolidin-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 45 mg), DIPEA (0.5 mL) and DCM (3 mL) was added acetyl chloride (15 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1179] Example 211: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxamide

[1180] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylic acid (100 mg, crude), DMF (4 mL), DIPEA (0.3 mL) was added EDC (55 mg) and HOBt (50 mg). After 15 min, the mixture was added

ammonium chloride (70 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1181] Example 212: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxamide

[1182] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-pyrrolidin-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride, 50 mg), triethylamine (0.35 mL) and DCM (5 mL) was added isocyanato(trimethyl)silane (20 mg). After 2h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1183] Example 213: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1184] Step 1: Preparation of disulfide 4-(1H-triazol-4-yldisulfanyl)-1H-triazole

[1185] Sodium 1H-1,2,3-triazole-4-thiolate (14 g, 0.11 mmol) was added in small portions to ice-cooled methanol (100 mL) followed by NH4Cl (9.12 g, 0.17 mmol) in H2O (40 mL). The reaction mixture was air bubbled for 16 hours at room temperature. It was then concentrated under reduced pressure. The mixture was poured into DCM (300 mL) and the solid was removed, the filtrate was concentrated to dryness to afford the subtitle compound (3.2 g, yield 14%) as a white solid. MS m/z 201.1 [M+H]+.

[1186] Step 2: Preparation of 1H-1,2,3-triazole-4-sulfonyl chloride

[1187] A solution of 4-(1H-triazol-4-yldisulfanyl)-1H-triazole (3.2 g, 16 mmol) in CHCl3 (30 mL) were added potassium nitrate (4.04 g, 40 mmol) and trimethylsilyl chloride (4.34 g, 40 mmol) and stirred vigorously at 50°C for 48 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to afford the subtitle compound (1.21 g, 45%) as a white solid. MS m/z 168.1 [M+H]+. 1H NMR (500 MHz, DMSO-d6) δ 14.62 (s, 1H), 7.77 (s, 1H) ppm.

[1188] Step 3: Preparation of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1189] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (40 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added 1H-triazole-4-sulfonyl chloride (15 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1190] Example 214: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxamide

[1191] Step 1: Preparation of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylic acid

[1192] A mixture of methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylate (240 mg), water (3 mL) and THF (12 mL) was added LiOH (50 mg). After 1 h, the mixture was concentrated to afford the title compound.

[1193] Step 2: Preparation of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxamide

[1194] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylic acid (60 mg, crude), DMF (2.5 mL), DIPEA (0.3 mL) was added EDC (50 mg) and HOBt (50 mg). After 15 min, the mixture was added ammonium chloride (40 mg). After stirring overnight, the mixture was filtered, and the filtrate purified by preparative HPLC to afford the title compound.

[1195] Example 215: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(methylsulfonylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1196] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (40 mg), DIPEA (0.5 mL) and DCM (2 mL) was added methylsulfonylmethanesulfonyl chloride (40 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1197] Example 216: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-methylsulfonylpropylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1198] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (40 mg), DIPEA (0.5 mL) and DCM (2 mL) was added 3-methylsulfonylpropane-1-sulfonyl chloride (40 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1199] Example 217: [5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-furyl]-(3-hydroxyazetidin-1-yl)methanone

[1200] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylic acid (50 mg), azetidin-3-ol (25 mg), (DMF (1 mL) and DIPEA (0.1 mL) was added HATU (80 mg). After 16h at 40°C, the mixture was diluted with MeOH (0.5 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1201] Example 218: 3-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-1,4-dihydro-1,2,4-triazol-5-one

[1202] Step 1: Preparation of ethyl 3-[(4-methoxyphenyl)methylsulfanyl]propanoate

[1203] To a solution of (4-methoxyphenyl)methanethiol (7.5 g, 48.7 mmol) in DMF (70 mL) were added cesium carbonate (31.7 g, 97.4 mmol) and tetrabutylammonium iodide (21.6 g, 58.4 mmol). The mixture was stirred at RT for 1 hour. Then, under ice-cooling, ethyl 3-bromopropanoate (9.68 g, 53.5 mmol) was added and the mixture was stirred overnight while returning to room temperature gradually. LCMS showed the reaction was completed. After addition of saturated aqueous ammonium chloride (300 mL) to the reaction mixture, it was extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine (500 mL x 3) and then water (500 mL), and dried over anhydrous sodium sulfate. After filtration, the mixture was concentrated to dryness. The residue was purified by medium pressure silica gel column chromatography (n-hexane: ethyl acetate = 95:5) to afford the subtitle compound (8 g, yield: 75 %) as a colorless liquid.

[1204] Step 2: Preparation of 3-((4-methoxybenzyl)thio)propanoic acid

[1205] To a solution of ethyl 3-[(4-methoxyphenyl)methylsulfanyl]propanoate (8 g, 31.5 mmol) in THF (100 mL) and H2O (50 mL) was added NaOH (12.6 g, 315.6 mmol), and the

mixture was stirred at RT for 16hours. The mixture was quenched with HCl (2M) to pH=7 and diluted with EtOAc (100 mL). The organic phase was separated. The aqueous layer was extracted with EA (100 ml ×2). The organic phases were combined, washed with water (100 ml ×2), dried over Na2SO4 and concentrated to the subtitle compound (6 g, yield: 84%) as a white solid. MS m/z 249 [M+Na]+.

[1206] Step 3: Preparation of 3-((4-methoxybenzyl)thio)propanoyl chloride

[1207] To a solution of 3-((4-methoxybenzyl)thio)propanoic acid (5 g, 22.1 mmol) in THF (50 mL) and DMF (0.5 mL) was added (COCl)2 (3.4 g, 26.5 mmol) slowly at 0°C, the mixture was stirred at RT for 2 hours. The mixture was concentrated to afford the subtitle compound (5.2 g, yield: 100%) as a colorless oil.

[1208] Step 4: Preparation of 2-(3-((4-methoxybenzyl)thio)propanoyl)hydrazine-1-carboxamide

[1209] To a solution of hydrazinecarboxamide (2.72 g, 36.3 mmol), DIPEA (11.0 g, 85.2 mmol) in THF (50 mL) and H2O (20 mL) was added 3-((4-methoxybenzyl)thio)propanoyl chloride (5.2 g, 21.3 mmol) slowly at 0°C, and the mixture was stirred at RT for 16 hours. The mixture was concentrated and diluted with EtOAc (100 mL) and H2O (100 mL). The organic phase was separated. The aqueous layer was extracted with EA (100 ml ×2). The organic phases were combined, washed with water (100 ml ×2), dried over Na2SO4 and concentrated to afford the subtitle compound (6 g, yield: 100%) as a colorless oil. MS m/z 284 [M+H]+.

[1210] Step 5: Preparation of 2-(3-((4-methoxybenzyl)thio)propanoyl)hydrazine-1-carboxamide

[1211] To a solution of 2-(3-((4-methoxybenzyl)thio)propanoyl)hydrazine-1-carboxamide (6.0 g, 21.2 mmol) in THF (50 mL) was added NaOH (2M, 150 mL), the mixture was stirred at 100°C for 16 hours. The mixture was concentrated and diluted with EtOAc (100 mL) and H2O (100 mL). The organic phase was separated. The aqueous layer was extracted with EA (100 mL ×2). The organic phases were combined, washed with water (100 mL ×2), dried over Na2SO4 and concentrated to afford the subtitle compound (1 g, yield: 18%) as a colorless oil. MS m/z 266 [M+H]+.

[1212] Step 6: Preparation of 2-(5-oxo-1,4-dihydro-1,2,4-triazol-3-yl)ethanesulfonyl chloride

[1213] To a solution of NCS (1.12 g, 13.4 mmol), HCl (1M, 0.671 mL, 0.671 mmol) in MeCN (9 mL) was added 3-[2-[(4-methoxyphenyl)methylsulfanyl]ethyl]-1,4-dihydro-1,2,4-triazol-5-one (890.0 mg, 3.35 mmol) in portions under ice/water bath cooling. The resulting mixture was stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure (water bath temperature below 30°C). The residue was purified by flash chromatography (Biotage 25 g silica gel column, eluting with 0%-100% ethyl acetate in petroleum ether) to afford the subtitle compound (515.1 mg, 2.43 mmol, yield: 72.6%) as white solid. MS m/z 212 [M+H]+. 1H NMR (500 MHz, DMSO) δ 14.57 (s, 1H), 12.52 (s, 1H), 2.79 (m, 2H), 2.74 – 2.60 (m, 2H) ppm.

[1214] Step 7: Preparation of 3-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-1,4-dihydro-1,2,4-triazol-5-one

[1215] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (40 mg), DIPEA (0.5 mL) and DCM (2.5 mL) was added 2-(5-oxo-1,4-dihydro-1,2,4-triazol-3-yl)ethanesulfonyl chloride (35 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1216] Example 219: Tert-butyl N-[6-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-yl]carbamate

[1217] Step 1: Preparation of tert-butyl N-(6-carbamimidoylsulfanylpyridazin-3-yl)carbamate

[1218] A mixture of tert-butyl N-(6-chloropyridazin-3-yl)carbamate (4.6 g, 20 mmol) in 1,4-dioxane (100 mL) was stirred at room temperature. Thiourea (1.52 g, 20 mmol) was added. The mixture was stirred at 75°C for 48 h. The mixture was cooled to room temperature and concentrated to afford the subtitle compound (4.3 g, crude) as brown solid. The residue was used for the next step directly without further purification.

[1219] Step 2: Preparation of tert-butyl N-(3-thioxo-4H-pyridazin-6-yl)carbamate

[1220] A mixture of tert-butyl N-(6-carbamimidoylsulfanylpyridazin-3-yl)carbamate (4.3 g, crude) in water (20 mL) was stirred at room temperature for 5 min. NaOH (5 g, 125 mmol) in water (80 mL) was added. The mixture was stirred at room temperature for 30 min. Then the mixture was extracted with EtOAc (100 mL x 6). The organic layers were combined, dried

over Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (40% EtOAc in PE) to afford the subtitle compound (1.3 g, 57% yield) as yellow solid. MS m/z 228 [M+H]+.

[1221] Step 3: Preparation of tert-butyl N-(6-chlorosulfonylpyridazin-3-yl)carbamate

[1222] NaClO (13.1 g, 132 mmol) was stirred at 0°C. HCl (0.1 M, 132 mL, 132 mmol) was added dropwise. After addition, the mixture was stirred at 0°C for 15 min. A solution of tert-butyl N-(3-thioxo-4H-pyridazin-6-yl)carbamate (1.0 g, 4.4 mmol) in CH3CN (5 mL) was prepared. The NaClO-HCl mixture was added dropwise at 0°C. After addition, the mixture was stirred at 0°C for 4 h. Then the mixture was filtered and the solid was washed with water and dried by lyophilization to afford the subtitle compound (1.1 g, 85% yield) as white solid. MS m/z 238 [M+H]+. 1H NMR (500 MHz, CDCl3) δ 8.53 (d, J = 9.5 Hz, 1H), 8.19 (s, 1H), 8.13 (d, J = 9.5 Hz, 1H), 1.57 (s, 9H).

[1223] Step 4: Preparation of tert-butyl N-[6-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-yl]carbamate

[1224] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (70 mg), DIPEA (1 mL) and DCM (4 mL) was added tert-butyl N-(6-chlorosulfonylpyridazin-3-yl)carbamate (70 mg). After 2 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1225] Example 220: 6-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-amine

[1226] A mixture of tert-butyl N-[6-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-yl]carbamate (70 mg), DCM (4 mL) and MeOH (4 mL) was added HCl (6N in iPrOH, 15 mL). After 4 h at 40°C, the mixture was concentrated and purified by preparative HPLC to afford the title compound.

[1227] Example 221: Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylate

[1228] Step 1: Preparation of methyl 5-[(4-methoxyphenyl)methylsulfanyl]pyrimidine-2-carboxylate

[1229] To a solution of methyl 5-bromopyrimidine-2-carboxylate (5 g, 23.0 mmol) and (4-methoxyphenyl) methanethiol (4.26 g, 27.6 mmol) in toluene (80 mL) was added DIPEA (7.9 mL, 46.1 mmol). Xantphos (1.33 g, 2.3 mmol) was added followed by Pd2(dba)3 (2.11 g, 2.3 mmol) under N2. The mixture was heated to 80°C for 12 h. The mixture was poured into water (100 mL) and extracted with DCM (200 mL x 3). The organic layers were washed with brine (100 mL x 2), dried with Na2SO4 and concentrated. The crude product was purified by flash chromatography (EA: PE= 20%) to afford the subtitle compound (4.7 g, yield: 70.3 %) as a yellow oil. MS m/z 291.1 [M+H]+.

[1230] Step 2: Preparation of methyl 5-chlorosulfonylpyrimidine-2-carboxylate

[1231] To a solution of NCS (3.68 g, 27.6 mmol), 2 M HCl (0.7 mL, 1.4 mmol) in MeCN (40 mL) was added methyl 5-[(4-methoxyphenyl)methylsulfanyl]pyrimidine-2-carboxylate (2.0 g, 6.89 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure (water bath temperature below 30 °C). The mixture was poured into water (40 mL) and extracted with DCM (40 mL x 3). The organic layers were washed with brine (40 mL x 2), dried with Na2SO4 and concentrated. The crude product was purified by flash chromatography (EA: PE= 60%) to the subtitle compound (220 mg, yield: 13.5%) as white solid. MS m/z 237.1 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 9.47 (s, 2 H), 4.13 (s, 3 H) ppm.

[1232] Step 3: Preparation of methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylate

[1233] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (1.5 mL) and DCM (6 mL) was added methyl 5-chlorosulfonylpyrimidine-2-carboxylate (100 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1234] Example 222: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylic acid

[1235] A mixture of methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylate (112 mg), water (2 mL) and

THF (8 mL) was added LiOH (20 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1236] Example 223: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxamide

[1237] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylic acid (50 mg), DMF (2 mL) and DIPEA (0.3 mL) was added HATU (80 mg). After 15 min, ammonium chloride (100 mg) was added. After 16h, the mixture was filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1238] Example 224: [1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] methyl carbonate

[1239] Step 1: Preparation of tert-butyl 3-((methoxycarbonyl)oxy)azetidine-1-carboxylate

[1240] To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (10.0 g, 57.7 mmol) in DCM (150 mL) was added pyridine (9.13 g, 115 mol) at -50°C. After 15 min, methyl carbonochloridate (8.18 g, 86.6 mmol) was added to the reaction mixture and stirring continued for another 30 minutes. The mixture was warmed to room temperature and stirred for 4 hrs. LCMS indicated the reaction was completed. The reaction was diluted with DCM (60 mL) and washed with saturated citric acid solution (50 mL), dried over Na2SO4 and concentrated. The residue was purified by flash chromatography (Biotage, 80 g silica gel column, 50 mL/min, eluting with 0-20% ethyl acetate in petroleum ether for 40 min) to afford the subtitle compound (9.8 g, 42.4 mmol, yield: 73.4%) as a colorless oil.

[1241] Step 2: Preparation of azetidin-3-yl methyl carbonate (hydrochloride)

[1242] To a solution of tert-butyl 3-methoxycarbonyloxyazetidine-1-carboxylate (9.8 g, 42.4 mmol) in DCM (100 mL) was added hydrogen chloride (4N in 1,4-dioxane, 63.6 mL, 254 mmol) at 0°C. The mixture was warmed to room temperature for 16 hrs. LCMS indicated the reaction was completed. Volatiles were removed to afford the subtitle compound (7.80 g, 46.5 mmol, yield: 90%) as a white solid. MS m/z 132 [M+H]+. 1H NMR (500 MHz, DMSO) δ

9.65 (s, 2H), 5.30 – 5.08 (m, 1 H), 4.23 (dd, J = 12.6, 7.0 Hz, 2 H), 4.00 (dd, J = 12.6, 5.3 Hz, 2 H), 3.75 (d, J = 7.5 Hz, 3 H) ppm.

[1243] Step 3: Preparation of [1-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] methyl carbonate

[1244] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), azetidin-3-yl methyl carbonate (18 mg of hydrochloride were treated with K2CO3 (19 mg) in DMF (0.2 mL)), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1245] Example 225: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxy-3-methyl-azetidin-1-yl)propan-1-one

[1246] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 3-methoxy-3-methyl-azetidine (19 mg of hydrochloride were treated with K2CO3 (19 mg) in DMF (0.2 mL)), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1247] Example 226: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-methoxypyrrolidin-1-yl]propan-1-one

[1248] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), (3S)-3-methoxypyrrolidine (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1249] Example 227: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[dimethyl(oxo)-λ^6-sulfanylidene]propanamide

[1250] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), imino-dimethyl-oxo-λ^6-sulfane (13 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1251] Example 228: [2-(Aminomethyl)-3-hydroxy-2-methyl-propyl] 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate (2,2,2-trifluoroacetic acid salt)

[1252] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), (3-methyloxetan-3-yl)methanamine (13 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1253] Example 229: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3-methyloxetan-3-yl)propanamide

[1254] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 3-methyloxetan-3-amine (hydrochloride, 13 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1255] Example 230: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylcyclopropyl)propanamide

[1256] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 3-methyloxetan-3-amine (hydrochloride, 13 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1257] Example 231: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxy-2-methyl-propyl)propanamide

[1258] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 2-methoxy-2-methyl-propan-1-amine (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1259] Example 232: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-methoxypyrrolidin-1-yl]propan-1-one

[1260] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), (3R)-3-methoxypyrrolidine (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1261] Example 233: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-oxetan-2-yl]methyl]propanamide

[1262] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), [(2S)-oxetan-2-yl]methanamine (12 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH/water (9:1, 1 mL), filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1263] Example 234: 2-[4-Chloro-5-[(3R,4R)-1-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1264] Step 1: Preparation of ethyl 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]acetate

[1265] To a stirred suspension of ethyl 2-(4H-1,2,4-triazol-3-yl)acetate (5.0 g, 32.2 mmol) and potassium carbonate (5.34 g, 38.7 mmol) in DMF (30 mL) was added 1-(chloromethyl)-4-methoxy-benzene (6.06 g, 38.7 mmol) dropwise. After the addition, the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography (Biotage 80 g silica gel, eluting with 0%-60% ethyl acetate in petroleum ether) to afford the subtitle compound (6.7 g, 24.3 mmol, yield: 75.5%) as brown oil. MS m/z 276 [M+H]+.

[1266] Step 2: Preparation of ethyl 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethanol

[1267] To a solution of ethyl 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]acetate (6.7 g, 24.3 mmol) in THF (70 mL) was added 2.5 M lithium aluminum hydride in THF (19.5 mL, 48.7 mmol) dropwise under cooling with an ice/water bath. The mixture was stirred at room temperature for 4 h. The mixture was quenched with water (200 mL), concentrated under reduced pressure to remove THF. The remaining aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic layers were concentrated. The residue was purified by flash chromatography (Biotage 80 g silica gel, eluting with 0%-70% ethyl acetate in petroleum ether) to afford the subtitle compound (3.3 g, 14.1 mmol, yield: 58.1%) as yellow solid. MS m/z 234 [M+H]+.

[1268] Step 3: Preparation of 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethyl 4-methylbenzenesulfonate

[1269] To a solution of 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethanol (3.3 g, 14.1 mmol) and triethylamine (4.29 g, 42.4 mmol) in THF (30 mL) was added TosCl (4.05 g, 21.2 mmol) in portions at 0°C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage 40 g silica gel, eluting with 0%-100% ethyl acetate in petroleum ether) to afford the subtitle compound (1.224 g, 3.16 mmol, yield: 22.3%) as light-yellow solid. MS m/z 388 [M+H]+.

[1270] Step 4: Preparation of S-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethyl] ethanethioate

[1271] A mixture of 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethyl 4-methylbenzenesulfonate (1.24 g, 3.20 mmol), ethanethioic S-acid (448 mg, 6.40 mmol) and potassium carbonate (1.77 g, 12.8 mmol) in DMF (6 mL) was stirred at 60°C for 16 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (40 mL x 3), dried over anhydrous sodium sulfate, and concentrated to afford the subtitle compound (860 mg, 2.95 mmol, yield: 92.2%) as brown oil. MS m/z 294 [M+H]+.

[1272] Step 5: Preparation of S-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethyl] ethanethioate

[1273] To a solution of S-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethyl] ethanethioate (860.0 mg, 2.95 mmol) in formic acid (10 mL) was added 30% hydrogen peroxide (1.34 g, 11.8 mmol) dropwise at 0°C. The reaction was stirred at room temperature for 4 h. The reaction mixture was diluted with water (20 mL) and then lyophilized to afford the subtitle compound (850 mg, 2.86 mmol, yield: 96.9%) as light yellow solid. MS m/z 298 [M+H]+.

[1274] Step 6: Preparation of 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethanesulfonyl chloride

[1275] To a suspension of 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethanesulfonic acid (277.0 mg, 0.932 mmol) in DCM (5 mL) was added DMF (6.81 mg, 0.093 mmol) and oxalyl chloride (177 mg, 1.44 mmol) dropwise under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated to afford the subtitle compound (303 mg, crude) as light yellow solid. MS m/z 316 [M+H]+. 1H NMR (500 MHz, CDCl3) δ 7.49 – 7.27 (m, 5H), 5.13 (s, 2H), 4.07 – 4.04 (m, 1H), 3.97 (d, J = 3.5 Hz, 1H), 3.76 – 3.64 (m, 2H), 3.41 – 3.24 (m, 1H), 3.15-3.08 (m, 1H), 2.21-2.10 (m, 1H), 1.97 (d, 1H), 1.26 (s, 1H), 1.02 (t, J = 6.5 Hz, 3H) ppm.

[1276] Step 7: Preparation of 2-[4-chloro-5-[(3R,4R)-1-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1277] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (80 mg), DIPEA (1 mL) and DCM (3 mL) was added 2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethanesulfonyl chloride (115 mg). After 3 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1278] Example 235: N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]cyclopropanesulfonamide

[1279] A mixture of 2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethanamine (hydrochloride, 80 mg), DIPEA (0.3 mL) and DCM (2 mL) was added cyclopropanesulfonyl chloride (15 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1280] Example 236: [5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]urea

[1281] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-amine (35 mg), triethylamine (0.5 mL) and DMF (3 mL) was added isocyanato(trimethyl)silane (150 mg). After 16h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1282] Example 237: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(4H-1,2,4-triazol-3-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1283] A mixture of 2-[4-chloro-5-[(3R,4R)-1-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (55 mg) and TFA (10 mL) was stirred at 80°C for 8h. The mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1284] Example 238: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(3-methyloxetan-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1285] Step 1: Preparation of S-((3-methyloxetan-3-yl)methyl) ethanethioate

[1286] To a solution of (3-methyloxetan-3-yl)methanol (10.0 g, 98 mmol) in dry THF (100 mL) was added ethanethioic S-acid (14.9 g,196 mmol) and PPh3 (51.0 g, 196 mmol). The reaction was stirred at 0°C under nitrogen atmosphere for 10 min. Then, DIAD (39.6 g, 196 mmol) was added slowly. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated ammonium chloride (300 mL) and extracted with dichloromethane (300 mL x 3). The organic layer was concentrated. The crude product was purified by flash chromatography (dichloromethane / petroleum ether = 20%) to afford the subtitle compound (8 g, 50 mmol, yield:51%) as a colorless oil. MS m/z 161 [M+H]+.

[1287] Step 2: Preparation of (3-methyloxetan-3-yl)methanesulfonyl chloride

[1288] To a solution of S-((3-methyloxetan-3-yl)methyl) ethanethioate (8.0 g, 50 mmol) in MeCN (30 ml) was added NCS (3.3 g, 25 mmol) and aqueous HCl (1 M, 5 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min. The resulting mixture was diluted with water (200 mL) and extracted with EA (200 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (dichloromethane / petroleum ether = 10%) to afford the subtitle compound (1.0 g, 5.4 mmol, yield:10.8%) as colorless oil. MS m/z 185 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 4.36 (d, J=9.2 Hz, 1H), 4.24 (d, J=9.6 Hz, 1H), 8.23 (s, 3 H), 3.53-3.45 (m, 2H), 1.33 (s, 3H) ppm.

[1289] Step 3: Preparation of 2-[4-chloro-5-[(3R,4R)-3-methyl-1-[(3-methyloxetan-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1290] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (50 mg), DIPEA (0.6 mL) and DCM (3 mL) was added (3-methyloxetan-3-yl)methanesulfonyl chloride (300 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1291] Example 239: Tert-butyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino]azetidine-1-carboxylate

[1292] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (300 mg), tert-butyl 3-aminoazetidine-1-carboxylate (240 mg), DMF (3 mL) and DIPEA (0.5 mL) was added HATU (331 mg). After

16 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 4.5 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1293] Example 240: [1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] methyl carbonate

[1294] Step 1: Preparation of tert-butyl 4-methoxycarbonyloxypiperidine-1-carboxylate

[1295] To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (10.0 g, 49.7 mmol) in DCM (100 mL) was added pyridine (9.83 g, 124 mmol). The reaction was stirred at -50°C under nitrogen atmosphere for 10 min. Then methyl carbonochloridate (8.45 g, 89.4 mmol) was added dropwise. The reaction mixture was stirred at RT for 16 h. The reaction was quenched with saturated ammonium chloride (100 mL) and extracted with dichloromethane (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried and concentrated. The residue was purified by flash chromatography (ethyl acetate / petroleum ether = 10%) to afford the subtitle compound (9.1 g, yield: 70.6%) as a colorless oil. MS m/z 260.2 [M+H]+.

[1296] Step 2: Preparation of methyl 4-piperidyl carbonate (hydrochloride)

[1297] Tert-butyl 4-methoxycarbonyloxypiperidine-1-carboxylate (9.1 g, 35.1 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 100 mL). The reaction mixture was stirred at room temperature for 2 hrs. Then, the mixture was concentrated to give the subtitle compound (7.34 g) as a white solid. MS m/z 196.1 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 9.70 (s, 1H), 4.94 (s, 1H), 3.80 (s, 3 H), 3.27 (s, 4H), 2.27-2.76 (m, 2H), 2.12-2.09 (m, 2H) ppm.

[1298] Step 3: Preparation of [1-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] methyl carbonate

[1299] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), methyl 4-piperidyl carbonate (22 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (40 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1300] Example 241: [(3R)-1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]pyrrolidin-3-yl] methyl carbonate

[1301] Step 1: Preparation of tert-butyl (3R)-3-methoxycarbonyloxypyrrolidine-1-carboxylate

[1302] To a solution of tert-butyl (3R)-3-hydroxypyrrolidine-1-carboxylate (8.0 g, 42.7 mmol) in DCM (50 mL) was added pyridine (6.76 g, 85.5 mmol) at -50°C. After 15 minutes, methyl carbonochloridate (8.18 g, 86.6 mmol) was added to the reaction mixture and stirring was continued for 30 minutes. The mixture was warmed to room temperature for 4 hrs. LCMS indicated the reaction was completed. The reaction was extracted with dichloromethane (50 mL x 3). The combined organic layer was washed with water (100 mL x 3) and brine (200 mL), dried over anhydrate sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (Biotage, 120 g silica gel column, 80 mL/min, eluting with 0-50% ethyl acetate in petroleum ether for 1 h) to afford the subtitle compound (6.0 g, 24.5 mmol, yield: 57 %) as a white solid. MS m/z 268 [M+Na]+.

[1303] Step 2: Preparation of methyl [(3R)-pyrrolidin-3-yl] carbonate (hydrochloride)

[1304] To a solution of tert-butyl (3R)-3-methoxycarbonyloxypyrrolidine-1-carboxylate (6.0 g, 24.5 mmol) in DCM (40 mL) was added hydrogen chloride (4 N in 1,4-dioxane, 36.7 mL, 147 mmol) at 0°C. The mixture was warmed to room temperature with stirring for 16 hrs. LCMS indicated the reaction was completed. Volatiles were removed under reduced pressure to afford the subtitle compound (4.20 g, 23.1 mmol, yield: 94.5%) as a white solid. MS m/z 146 [M+H]+. 1H NMR (500 MHz, DMSO) δ 9.50 (s, 2H), 5.23 (t, J = 4.8 Hz, 1H), 3.73 (s, 3H), 3.46 – 3.24 (m, 4H), 3.17 (dt, J = 18.7, 9.3 Hz, 1H), 2.21 – 2.03 (m, 2H) ppm.

[1305] Step 3: Preparation of [(3R)-1-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]pyrrolidin-3-yl] methyl carbonate

[1306] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), methyl [(3R)-pyrrolidin-3-yl] carbonate (20 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1307] Example 242: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-tetrahydrofuran-2-yl]methyl]propanamide

[1308] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), [(2S)-tetrahydrofuran-2-yl]methanamine (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1309] Example 243: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2R)-tetrahydrofuran-2-yl]methyl]propanamide

[1310] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), [(2R)-tetrahydrofuran-2-yl]methanamine (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1311] Example 244: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3R)-tetrahydrofuran-3-yl]propanamide

[1312] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), (3R)-tetrahydrofuran-3-amine (4-methylbenzenesulfonic acid salt, 36 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1313] Example 245: 1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]piperidin-4-one

[1314] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), piperidin-4-one (hydrate, hydrochloride; 36 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the

reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1315] Example 246: 1-(Azetidin-1-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-one

[1316] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), azetidine (8 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1317] Example 247: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methylsulfonylazetidin-1-yl)propan-1-one

[1318] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 3-methylsulfonylazetidine (hydrochloride, 24 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1319] Example 248: 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclobutyl]propanamide

[1320] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), (1-aminocyclopentyl)methanol (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1321] Example 249: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclopentyl]propanamide

[1322] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), (1-aminocyclopentyl)methanol (16 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1323] Example 250: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(4-hydroxycyclohexyl)propanamide

[1324] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 4-aminocyclohexanol (16 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1325] Example 251: 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-methyl-1,3,4-oxadiazol-2-yl)propanamide

[1326] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 5-methyl-1,3,4-oxadiazol-2-amine (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1327] Example 252: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-fluoro-2-pyridyl)propanamide

[1328] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 5-fluoropyridin-2-amine (16 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1329] Example 253: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methylpyrazol-3-yl)propanamide

[1330] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 2-methylpyrazol-3-amine (14 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1331] Example 254: 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one

[1332] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 4-piperidylmethanol (16 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1333] Example 255: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-fluoroazetidin-1-yl)propan-1-one

[1334] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 3-fluoroazetidine (10 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1335] Example 256: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(6-oxa-1-azaspiro[3.3]heptan-1-yl)propan-1-one

[1336] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 6-oxa-1-azaspiro[3.3]heptane (2,2,2-trifluoroacetic acid salt, 10 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total

volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1337] Example 257: [1-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] acetate

[1338] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), 4-piperidyl acetate (hydrochloride, 25 mg), DMF (0.5 mL) and DIPEA (0.05 mL) was added HATU (33 mg). After 2 h, the reaction was complete. The mixture was diluted with MeOH to a total volume of 1 mL, filtrated and the filtrate purified by preparative HPLC to afford the title compound.

[1339] Example 258: 5-[[(3S*,4S*)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine

[1340] Step 1: Preparation of 4-fluoro-1-(methoxymethyl)imidazole

[1341] To a stirred solution of 4-fluoro-1H-imidazole (7.0 g, 81.3 mmol) in dry THF (140 mL) was added 60% sodium hydride (4.88 g, 122.0 mmol) in portions at 0°C under nitrogen atmosphere. After 10 min, MOMBr (11.2 g, 81.5 mmol) was added dropwise into the reaction system at 0°C. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water (10 mL) under ice/water bath cooling and concentrated under reduced pressure. The residue was purified by flash chromatography (Biotage, 80 g silica gel, eluting with 0%-10% DCM in MeOH) to afford the subtitle compound (7.8 g, 59.9 mmol, yield: 73.7%) as light-yellow oil. MS m/z 131 [M+H]+.

[1342] Step 2: Preparation of 4-fluoro-5-iodo-1-(methoxymethyl)imidazole

[1343] To a solution of 4-fluoro-1-(methoxymethyl)imidazole (7.8 g, 59.9 mmol) in acetonitrile (80 mL) was added NIS (15.5 g, 68.9 mmol) in portions. The reaction mixture was stirred at room temperature for 72 h. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (80 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography (Biotage, 80 g silica gel, eluting with 0%-30% ethyl acetate in petroleum ether) to afford the subtitle compound (3.4 g, 13.3 mmol, yield: 22.2%) as brown solid. MS m/z 257 [M+H]+.

[1344] Step 3: Preparation of tert-butyl 4-[5-fluoro-3-(methoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate

[1345] A mixture of 4-fluoro-5-iodo-1-(methoxymethyl)imidazole (3.4 g, 13.3 mmol), (1-tert-butoxycarbonyl-3-methyl-3,6-dihydro-2H-pyridin-4-yl)boronic acid (3.52 g, 14.6 mmol), Pd(dtbpf)Cl2 (429.0 mg, 0.664 mmol) and potassium carbonate (5.51 g, 39.8 mmol) in 1,4-dioxane (30 mL) and water (6 mL) was exchanged with nitrogen three times, and the mixture was stirred at 80°C under nitrogen atmosphere for 16 h. The reaction mixture was cooled to room temperature and diluted with water (100 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Biotage 40 g silica gel column, eluting with 0%-60% ethyl acetate in petroleum ether) to afford the subtitle compound (4.11 g, 12.6 mmol, yield: 95.1%) as brown oil. MS m/z 326 [M+H]+.

[1346] Step 4: Preparation of tert-butyl 4-[5-fluoro-3-(methoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate

[1347] To a solution of tert-butyl 4-[5-fluoro-3-(methoxymethyl)imidazol-4-yl]-3-methyl-3,6-dihydro-2H-pyridine-1-carboxylate (4.11 g, 12.6 mmol) in EtOH (50 mL) was added 10% Pd/C (wet, 600 mg). The mixture was exchanged with hydrogen three times. The resulting mixture was stirred at room temperature under hydrogen atmosphere for 16 h. The reaction mixture was filtered through celite and washed with EtOH (50 mL). The filtrate was concentrated under reduced pressure to afford the subtitle compound (3.7 g, 11.3 mmol, yield: 89.5%) as white solid. MS m/z 328 [M+H]+.

[1348] Step 5: Preparation of tert-butyl 4-[5-fluoro-2-(5-fluoro-2-pyridyl)-3-(methoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate

[1349] To a solution of 1,1,2,2-tetramethylpiperidine (1.55 g, 11.0 mmol) in dry THF (10 mL) was added n-Bu2Mg (1 M in heptane, 5.55 mL, 5.55 mmol) dropwise at room temperature under nitrogen atmosphere. The reaction was stirred at 70°C under nitrogen atmosphere. A solution of tert-butyl 4-[5-fluoro-3-(methoxymethyl)imidazol-4-yl]-3-methyl-piperidine-1-carboxylate (1.8 g, 5.55 mmol) in dry THF (20 mL) was added into the reaction system. After 2 at RT, ZnCl2 (2 M in THF, 5.55 mL, 11.0 mmol) was added into the reaction

system. The resulting mixture was stirred at room temperature for another 2 h. To the reaction system were added 2-bromo-5-fluoro-pyridine (1.94 g, 11.0 mmol) and Pd(PPh3)4 (318.0 mg, 0.275 mmol). The mixture was exchanged with nitrogen three times. The resulting mixture was stirred at 70°C for 16 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Biotage 25 g silica gel column, eluting with 0%-25% ethyl acetate in petroleum ether) to afford the subtitle compound (530.0 mg, 1.25 mmol, yield: 22.8%) as light-yellow solid. MS m/z 423 [M+H]+.

[1350] Step 6: Preparation of 5-fluoro-2-(4-fluoro-5-(3-methylpiperidin-4-yl)-1H-imidazol-2-yl)pyridine (hydrochloride)

[1351] A mixture of tert-butyl 4-[5-fluoro-2-(5-fluoro-2-pyridyl)-3-(methoxymethyl)imidazol-4-yl]-3- methyl-piperidine-1-carboxylate (655 mg, 1.42 mmol) and HCl (4 M in 1,4-dioxane, 1.78 mL, 7.10 mmol) was stirred at 80°C for 16 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and dried under vacuum to afford the subtitle compound (520 mg, crude) as light-yellow solid. MS m/z 279 [M+H]+.

[1352] Step 7: Preparation of tert-butyl 4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate

[1353] To a solution of 5-fluoro-2-[4-fluoro-5-(3-methyl-4-piperidyl)-1H-imidazol-2-yl]pyridine (520 mg, crude) and triethylamine (784 mg, 7.75 mmol) in dry DCM (15 mL) was added di-tert-butyl carbonate (0.372 mg, 1.71 mmol) at room temperature. The reaction was stirred at room temperature. The reaction mixture was diluted with water (50 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (Biotage 25 g silica gel column, eluting with 0%-30% ethyl acetate in petroleum ether) to afford the subtitle compound (517.0 mg, 1.37 mmol, two steps' yield: 88.1%) as light-yellow solid. MS m/z 379 [M+H]+.

[1354] Step 8: Preparation of tert-butyl (3S*,4S*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate and tert-butyl (3R*,4R*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate

[1355] Tert-butyl 4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate (517.0 mg, 1.37 mmol) was separated by chiral SFC to give tert-butyl (3S*,4S*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate (210.4 mg, 0.556 mmol, yield: 40.7%) as white solid and tert-butyl (3R*,4R*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate (204.3 mg, 0.538 mmol, yield: 39.4%) as white solid.

[1356] Preparative chiral HPLC conditions: Instrument: SFC-150 (Waters); Column: IG 25*250mm, 10μm (Daicel); Column temperature: RT; Mobile phase: CO_2/MeOH [0.2% NH_3 (7M in MeOH)] 90:10; Flow rate: 85 ml/min; Back pressure: 100 bar; Detection wavelength: 214 nm; Cycle time: 8.75 min; Sample solution: 500 mg dissolved in 25 ml methanol; Injection volume: 1.0 ml.

[1357] Analytical chiral HPLC conditions: Column: IG 4.6*100mm 5μm, Column temperature: 40°C; Mobile phase: CO_2/MeOH [0.2% NH_3 (7M in MeOH)] 90:10; Flow rate: 3 ml/min; Back pressure: 2000 psi; Detection wavelength: 214 nm; Run time: 6 min; Injection volume: 7.5 μl.

[1358] Tert-butyl (3S*,4S*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate. MS m/z 379 [M+H]+. Chiral HPLC tR = 2.19 min. 1H NMR (400 MHz, CDCl3) δ 9.75 (s, 1H), 8.33 (d, J = 2.8 Hz, 1H), 7.98 (dd, J = 8.8, 4.4 Hz, 1H), 7.4-7.44 (m, 1H), 4.29 (s, 1H), 3.96 (s, 1H), 3.20 – 3.00 (m, 2H), 2.88 (s, 1H), 2.12 (s, 1H), 2.05 – 1.97 (m, 1H), 1.84 – 1.76 (m, 1H), 1.47 (s, 9H), 0.90 (d, J = 7.2 Hz, 3H) ppm.

[1359] Tert-butyl (3R*,4R*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate. MS m/z 379 [M+H]+. Chiral HPLC tR = 2.62 min. 1H NMR (400 MHz, CDCl3) δ 9.75 (s, 1H), 8.33 (d, J = 2.8 Hz, 1H), 7.98 (dd, J = 8.8, 4.4 Hz, 1H), 7.4-7.44 (m, 1H), 4.29 (s, 1H), 3.96 (s, 1H), 3.20 – 3.00 (m, 2H), 2.88 (s, 1H), 2.12 (s, 1H), 2.05 – 1.97 (m, 1H), 1.84 – 1.76 (m, 1H), 1.47 (s, 9H), 0.90 (d, J = 7.2 Hz, 3H) ppm.

[1360] Step 9: Preparation of 5-fluoro-2-[4-fluoro-5-[(3S*,4S*)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]pyridine (hydrochloride)

[1361] A mixture of tert-butyl (3S*,4S*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate (200 mg) and DCM (1 mL) was added HCl (6M in 1,4-dioxane, 2 mL). After 1h, the mixture was concentrated to afford the subtitle compound.

[1362] Step 10: Preparation of 5-[[(3S*,4S*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine

[1363] A mixture of 5-fluoro-2-[4-fluoro-5-[(3S*,4S*)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]pyridine (hydrochloride, 50 mg), DIPEA (0.07 mL) and DCM (0.5 mL) was added 2-aminopyrimidine-5-sulfonyl chloride (23 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1364] Example 259: 5-[[(3R*,4R*)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine

[1365] Step 1: Preparation of 5-fluoro-2-[4-fluoro-5-[(3S*,4S*)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]pyridine (hydrochloride)

[1366] A mixture of tert-butyl (3R*,4R*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate (200 mg) and DCM (1 mL) was added HCl (6M in 1,4-dioxane, 2 mL). After 1h, the mixture was concentrated to afford the subtitle compound.

[1367] Step 2: Preparation of 5-[[(3R*,4R*)-4-[4-fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine

[1368] A mixture of 5-fluoro-2-[4-fluoro-5-[(3R*,4R*)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]pyridine (hydrochloride, 50 mg), DIPEA (0.07 mL) and DCM (0.5 mL) was added 2-aminopyrimidine-5-sulfonyl chloride (23 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1369] Example 260: N-(Azetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide (hydrochloride)

[1370] A mixture of tert-butyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino]azetidine-1-carboxylate (360 mg) and EtOH (2 mL) was added HCl (6N in iPrOH, 3 mL). After 0.5 h, the mixture was concentrated to afford the title compound.

[1371] Example 261: 2-[4-Chloro-5-[(3R,4R)-1-[[1-[(4-methoxyphenyl)methyl]triazol-4-yl]methylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1372] Step 1: Preparation of 1-[(4-methoxyphenyl)methyl] triazol-4-yl]methanesulfonic acid

[1373] To a mixture of sodium prop-2-ynylsulfonyloxysodium (5.0 g, 35.2 mmol), sodium rac-(2R)-3-hydroxy-5-oxo-2-[rac-(1S)-1,2-dihydroxyethyl]-2H-furan-4-olate (1.39 g, 7.04 mmol) and CuSO4.5H2O (0.878 g, 3.52 mmol) in t-BuOH/ H2O (50/ 50 mL) at room temperature was added 1-(azidomethyl)-4-methoxy-benzene (6.03 g, 36.9 mmol). The mixture was warmed to room temperature and stirred for 16 hrs. The mixture was washed with water (20 mL). The organic layer was dried over Na2SO4 and concentrated to afford the subtitle compound (3.20 g, yield: 32.1%) as yellow solid. MS m/z 284 [M+H]+.

[1374] Step 2: Preparation of [1-[(4-methoxyphenyl)methyl]triazol-4-yl]methanesulfonyl chloride

[1375] A mixture of [1-[(4-methoxyphenyl)methyl]triazol-4-yl]methanesulfonic acid (3.0 g, 10.6 mmol) in chloroform (80 mL) was stirred at room temperature. DMF (cat.) was added. The mixture was stirred at 0°C. Oxalyl dichloride (1.34 mL, 15.9 mmol) was added dropwise. The mixture was warmed to room temperature and stirred at room temperature for 16 hrs. The mixture was washed with water (20 mL). The organic layer was dried over Na2SO4 and concentrated. The crude residue obtained was purified by silica gel column chromatography using PE/EA (50%) as eluent to afford the subtitle compound (0.5 g, 15.6% yield) as yellow solid. MS m/z 324 [M+Na]+. 1H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.05 – 6.75 (m, 2H), 5.50 (s, 2H), 3.77 (d, J = 23.4 Hz, 5H) ppm.

[1376] Step 3: Preparation of 2-[4-chloro-5-[(3R,4R)-1-[[1-[(4-methoxyphenyl)methyl]triazol-4-yl]methylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1377] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (200 mg), DIPEA (2.5 mL) and DCM (10 mL) was added [1-[(4-methoxyphenyl)methyl]triazol-4-yl]methanesulfonyl chloride (300 mg). After 3 h at 40°C, the

mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1378] Example 262: 2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine

[1379] A mixture of 2-[4-chloro-5-[(3R,4R)-1-[[1-[(4-methoxyphenyl)methyl]triazol-4-yl]methylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (25 mg) and TFA (8 mL) was stirred at 80°C for 5h. The mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1380] Example 263: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-3-methoxy-pyridazine

[1381] Step 1: Preparation of 5-iodo-2-methylpyridazin-3(2H)-one

[1382] A mixture of 5-iodopyridazin-3-ol (3.3 g, 15 mmol), MeOH (950 mg, 30 mmol) and PPh3 (7.8 g, 30 mmol) in THF (100 mL) was stirred at 0 °C for 15 min. DTBAD (5.13 g, 45 mmol) in THF (30 mL) was added dropwise. After the addition was complete, the mixture was warmed to room temperature and stirred at room temperature for 16 h. The resulting mixture was poured into water (200 mL). The water layer was extracted with EtOAc (100 mL x 3). The organic layers were combined, dried over Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (40% EtOAc in PE) to afford the subtitle compound (6.2 g, crude) as yellow solid. MS m/z 237 [M+H]+.

[1383] Step 2: Preparation of 5-((4-methoxybenzyl)thio)-2-methylpyridazin-3(2H)-one

[1384] A mixture of 5-iodo-2-methylpyridazin-3(2H)-one (6.0 g, crude, 15 mmol), (4-methoxyphenyl)methanethiol (2.31 g, 15 mmol), (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one palladium (234 mg, 0.26 mmol), Xantphos (148 mg, 0.3 mmol) and DIEA (5.8 g, 45 mmol) in toluene (100 mL) was stirred under N2 at 80 °C for 16 h. The resulting mixture was cooled to room temperature and concentrated. The residue was purified by silica gel column chromatography (3% MeOH in DCM) to afford the subtitle compound (2.9 g, yield: 73%) as yellow solid. MS m/z 263 [M+H]+. 1H NMR (500 MHz, CDCl3) δ 7.51 (d, J = 2.5 Hz, 1H),

7.30 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.60 (d, J = 2.5 Hz, 1H), 4.09 (s, 2H), 3.80 (s, 3H), 3.71 (s, 3H).

[1385] Step 3: Preparation of 1-methyl-6-oxo-1,6-dihydropyridazine-4-sulfonyl chloride

[1386] To a stirred solution of 5-((4-methoxybenzyl)thio)-2-methylpyridazin-3(2H)-one (260 mg) in acetonitrile (5 mL) was added 2 M HCl (0.2 mL) and NCS (536 mg) slowly at 0°C. The reaction mixture was stirred at 0°C for 15 min. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the subtitle compound (70 mg, crude), which was used in the next step directly.

[1387] Step 4: Preparation of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-3-methoxy-pyridazine

[1388] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (70 mg), DIPEA (1 mL) and DCM (5 mL) was added 6-methoxypyridazine-4-sulfonyl chloride (70 mg, crude). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1389] Example 264: 5-Fluoro-2-[4-fluoro-5-[(3S*,4S*)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine

[1390] A mixture of 5-fluoro-2-[4-fluoro-5-[(3S*,4S*)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]pyridine (hydrochloride, 30 mg), DIPEA (70 μL) and DCM (0.5 mL) was added methanesulfonyl chloride (12 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1391] Example 265: 5-Fluoro-2-[4-fluoro-5-[(3R*,4R*)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine

[1392] A mixture of 5-fluoro-2-[4-fluoro-5-[(3R*,4R*)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]pyridine (hydrochloride, 30 mg), DIPEA (70 μL) and DCM (0.5 mL) was added methanesulfonyl chloride (12 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1393] Example 266: N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]acetamide

[1394] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine (50 mg), pyridine (0.75 mL) and DCM (5 mL) was added acetyl chloride (75 mg). The mixture was stirred at 40° C until a clear solution was obtained. After one additional hour at RT, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1395] Example 267: Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate

[1396] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (250 mg), DIPEA (3.5 mL) and DCM (18 mL) was added methyl 5-chlorosulfonylthiazole-2-carboxylate (265 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1397]

[1398] Example 268: Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate

[1399] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (150 mg), DIPEA (2 mL) and DCM (10 mL) was added methyl 4-chlorosulfonylthiazole-2-carboxylate (165 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1400] Example 269: N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]methanesulfonamide

[1401] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine (20 mg), pyridine (0.3 mL) and DCM (2 mL) was added methanesulfonyl chloride (10 mg). The mixture was stirred at 40° C until a clear solution was obtained. After one additional hour at RT, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1402] Example 270: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole

[1403] A mixture of methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate (160 mg), water (2 mL) and THF (8 mL) was added LiOH (25 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1404] Example 271: 4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid

[1405] A mixture of methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate (160 mg), water (2 mL) and THF (8 mL) was added LiOH (25 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1406] Example 272: Methyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino]azetidine-1-carboxylate

[1407] A mixture of N-(azetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide (hydrochloride, 30 mg), DIPEA (41 μL) and DCM (0.5 mL) was added methyl carbonochloridate (6 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1408] Example 273: N-(1-Acetylazetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanamide

[1409] A mixture of N-(azetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide (hydrochloride, 30 mg), DIPEA (41 μL) and DCM (0.5 mL) was added acetyl chloride (5 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1410] Example 274: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylsulfonylazetidin-3-yl)propanamide

[1411] A mixture of N-(azetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide (hydrochloride, 30 mg), DIPEA (41 μL) and DCM (0.5 mL) was added methanesulfonyl chloride (7 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1412] Example 275: N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-yl]acetamide

[1413] Step 1: Preparation of 5-acetamido-1,3,4-thiadiazole-2-sulfonyl chloride

[1414] A mixture of 2 M HCl in water (20 mL) and acetonitrile (50 mL) was stirred at -10 °C for 30 min. Then N-(5-sulfanyl-1,3,4-thiadiazol-2-yl)acetamide (5 g, 28.5 mmol) and NCS (12.1 g, 91.3 mmol) were added slowly. The reaction was stirred at 10 °C for 2 h. The suspension was filtered through a pad of Celite and silica gel and the filter cake was washed with acetonitrile (20 mL × 2). The combined filtrates were concentrated and poured into water (50 mL), the resulting precipitate was collected by filtration and dried in vacuum to afford the subtitle compound (1.92 g, yield: 28%) as a white solid. MS m/z 242.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 12.49 (s, 1H), 11.08 (s, 2H), 2.17 (d, J = 1.6 Hz, 3H) ppm.

[1415] Step 2: Preparation of N-[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-yl]acetamide

[1416] A mixture of 2-[4-chloro-5-[(3R,4R)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (100 mg), DIPEA (1.4 mL) and DCM (7 mL) was added 5-acetamido-1,3,4-thiadiazole-2-sulfonyl chloride (500 mg). After 1 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1417] Example 276: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid

[1418] A mixture of methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate (100 mg), water (1.5 mL) and THF

(6 mL) was added LiOH (25 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1419] Example 277: 2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]propane-1,3-diol

[1420] A mixture of 2-chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine (90 mg), DIPEA (0.5 mL) and DCM (3 mL) was added 2-aminopropane-1,3-diol (40 mg). After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1421] Example 278: Methyl 2-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetate

[1422] A mixture of methyl 2-aminoacetate (hydrochloride, 110 mg), DCM (3 mL) and DMF (2 mL) was added DIPEA (1.2 mL). After 30 min at 40°C, 2-chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine (250 mg) was added. After 1 h at 40°C, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1423] Example 279: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-amine

[1424] A mixture of N-[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-yl]acetamide (5 mg), EtOH (0.5 mL) and HCl (6N, 0.5 mL) was heated at 80°C for 1h. The mixture was concentrated. The residue was purified by preparative HPLC to afford the title compound.

[1425] Example 280: N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]azetidine-3-carboxamide

[1426] Step 1: Preparation of tert-butyl 3-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]carbamoyl]azetidine-1-carboxylate (2,2,2-trifluoroacetate)

[1427] A mixture of 1-tert-butoxycarbonylazetidine-3-carboxylic acid and DCM (3 mL) was added 1-chloro-N,N,2-trimethyl-1-propenylamine (35 mg). After 30 min at RT, the mixture was added to a solution of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-amine (55 mg) in DCM (2 mL) and pyridine (1.2 mL). After 2 h, the reaction was quenched with water (0.2 mL). The mixture was concentrated. The residue was purified by preparative HPLC to afford the subtitle compound. MS m/z 640.2 [M+H]+.

[1428] Step 2: Preparation of N-[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]azetidine-3-carboxamide

[1429] A mixture of tert-butyl 3-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]carbamoyl]azetidine-1-carboxylate (32 mg) and DCM (2 mL) was added HCl (6N in iPrOH, 5 mL). After 1 h at 40°C, the mixture was concentrated and purified by preparative HPLC to afford the title compound.

[1430] Example 281: 2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetic acid

[1431] A mixture of methyl 2-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetate (155 mg), water (2 mL) and THF (8 mL) was added LiOH (40 mg). After 2 h, the mixture was concentrated, and the residue purified by preparative HPLC to afford the title compound.

[1432] Example 282: 5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxamide

[1433] A mixture of 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid (80 mg), DMF (3 mL) and DIPEA (0.5 mL) was added HATU (300 mg). After 15 min, ammonium chloride (300 mg) was added. After 14 hours, the mixture was filtrated, and the filtrate purified by preparative HPLC to afford the title compound.

[1434] Example 283: 2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetamide

[1435] A mixture of 2-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetic acid (100 mg), DMF (6 mL) and DIPEA (0.7 mL) was added EDC (130 mg) and HOBT (100 mG). After 15 min, ammonium chloride (300 mg) was added. After 14 hours, the mixture was filtrated, and the filtrate purified by preparative HPLC to afford the title compound.

[1436] Example 284: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-1,1-dimethyl-ethyl)propanamide

[1437] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (47 µL) was added HATU (33 mg). After 15 min, 2-amino-2-methyl-propan-1-ol (12 mg) was added. After 2 hours, the mixture was filtrated, and the filtrate purified by preparative HPLC to afford the title compound.

[1438] Example 285: 3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3,3-difluorocyclobutyl)propanamide

[1439] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (47 µL) was added HATU (33 mg). After 15 min, 3,3-difluorocyclobutaneamine (hydrochloride, 21 mg; mixed with DMF (0.2 mL) and NaHCO3) was added. After 2 hours, the mixture was filtrated, and the filtrate purified by preparative HPLC to afford the title compound.

[1440] Example 286: [1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] acetate

[1441] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (47 µL) was added HATU (33 mg). After 15 min, (3-methylazetidin-3-yl) acetate (hydrochloride, 23 mg;

mixed with DMF (0.2 mL) and NaHCO3) was added. After 2 hours, the mixture was filtrated, and the filtrate purified by preparative HPLC to afford the title compound.

[1442] Example 287: [1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] methyl carbonate

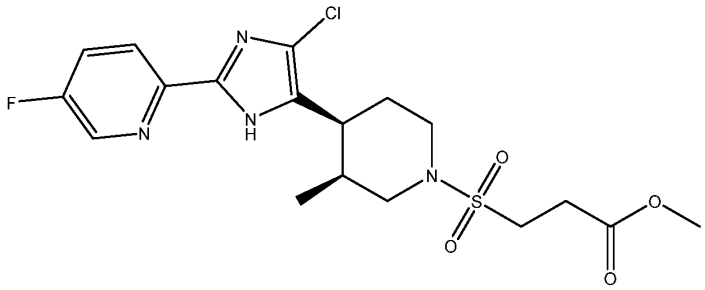
[1443] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (47 μL) was added HATU (33 mg). After 15 min, methyl (3-methylazetidin-3-yl) carbonate (hydrochloride, 25 mg; mixed with DMF (0.2 mL) and NaHCO3) was added. After 2 hours, the mixture was filtrated, and the filtrate purified by preparative HPLC to afford the title compound.

[1444] Example 288: [1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] ethyl carbonate

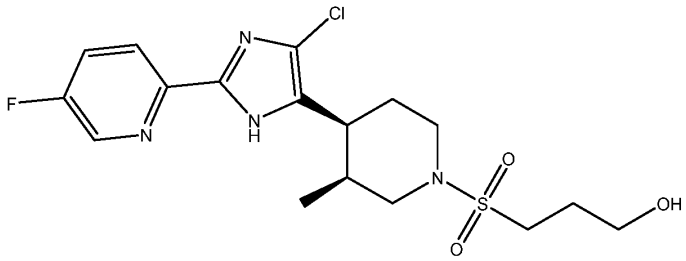
[1445] A mixture of 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid (30 mg), DMF (0.5 mL) and DIPEA (47 μL) was added HATU (33 mg). After 15 min, azetidin-3-yl ethyl carbonate (hydrochloride, 25 mg; mixed with DMF (0.2 mL) and NaHCO3) was added. After 2 hours, the mixture was filtrated, and the filtrate purified by preparative HPLC to afford the title compound.

[1446] One embodiment is a compound of formula I selected from Examples V1 to V23 below, which can be prepared according to the procedures described above and methods known to those skilled in the art.

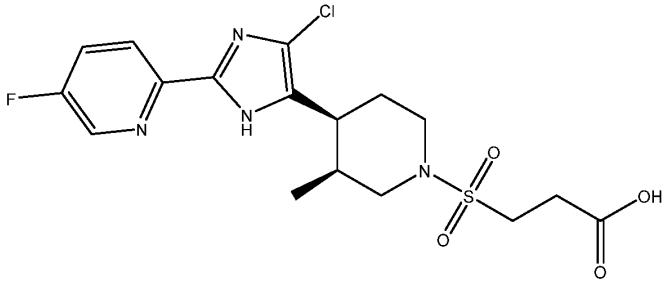
[1447] Example V1: Methyl 3-(((3S*,4S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propanoate



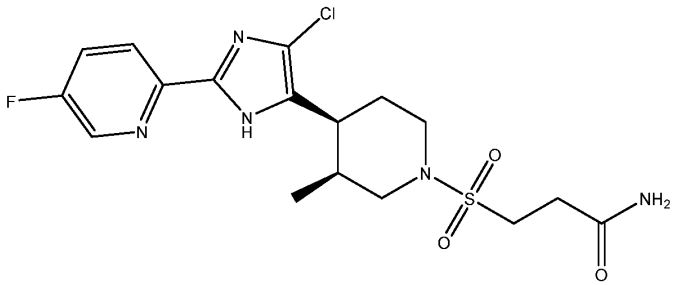
[1448] Example V2: 3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propan-1-ol



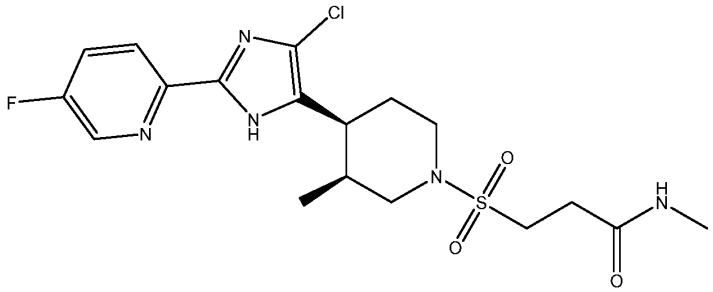
[1449] Example V3: 3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propanoic acid



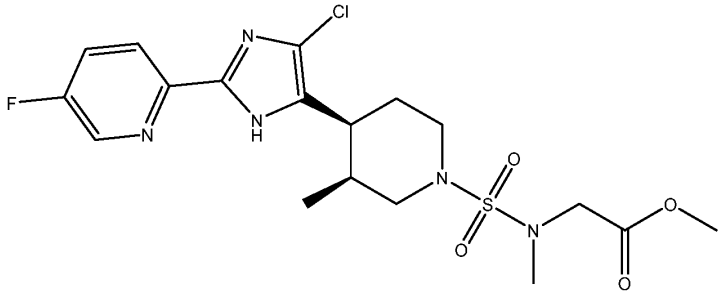
[1450] Example V4: 3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)propanamide



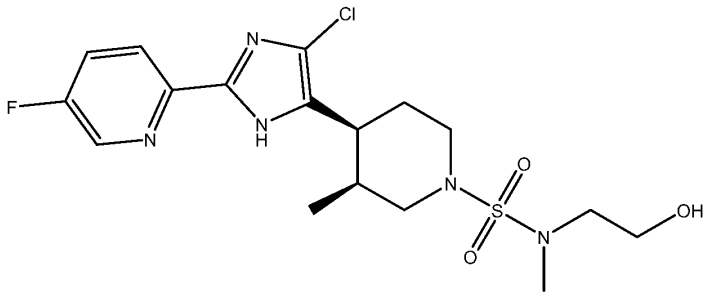
[1451] Example V5: 3-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)-N-methylpropanamide



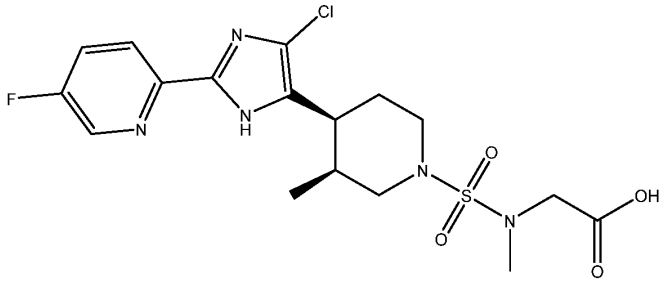
[1452] Example V6: Methyl N-(((3S*,4S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)-N-methylglycinate



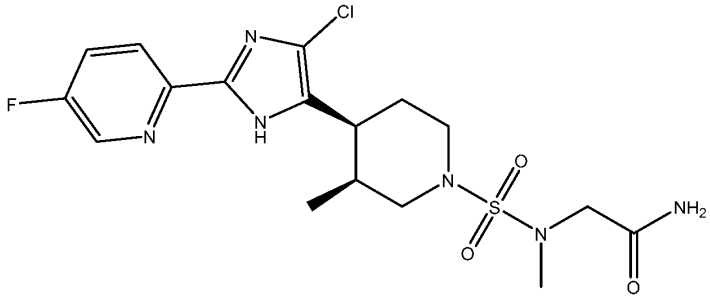
[1453] Example V7: (3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-N,3-dimethylpiperidine-1-sulfonamide



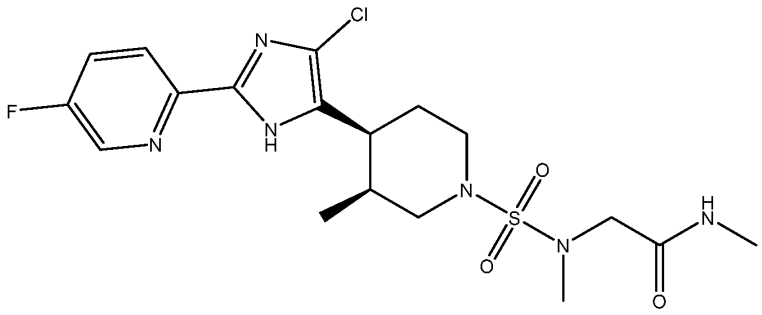
[1454] Example V8: N-(((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)-N-methylglycine



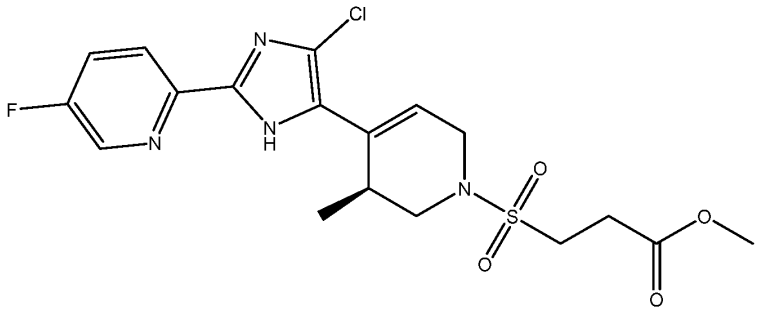
[1455] Example V9: 2-((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethylpiperidine-1-sulfonamido)acetamide



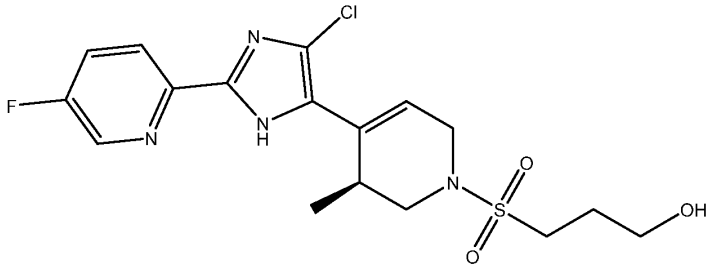
[1456] Example V10: 2-((3S*,4S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethylpiperidine-1-sulfonamido)-N-methylacetamide



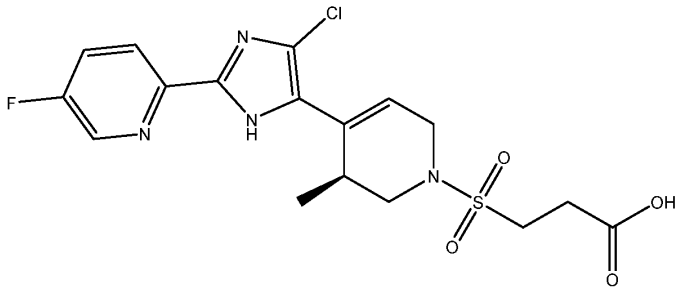
[1457] Example V11: Methyl (S*)-3-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propanoate



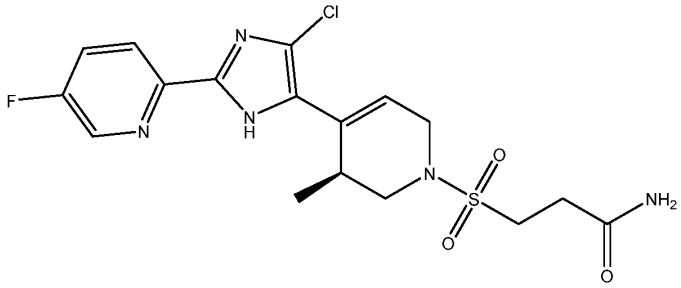
[1458] Example V12: (S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propan-1-ol



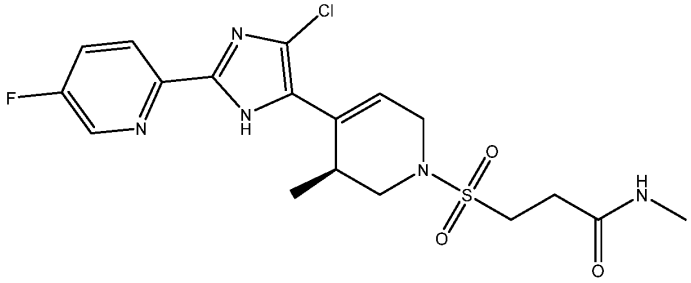
[1459] Example V13: (S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propanoic acid



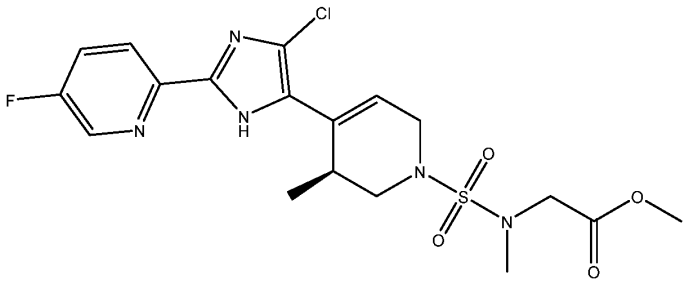
[1460] Example V14: (S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)propanamide



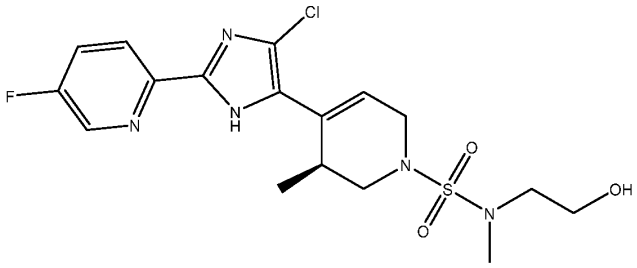
[1461] Example V15: (S*)-3-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)-N-methylpropanamide



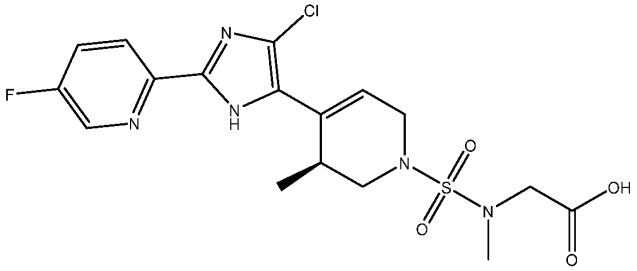
[1462] Example V16: Methyl (S*)-N-((4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)-N-methylglycinate



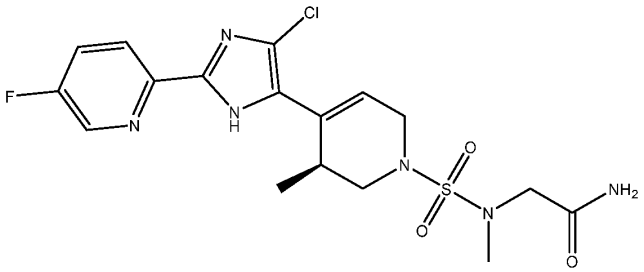
[1463] Example V17: (S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-N,3-dimethyl-3,6-dihydropyridine-1(2H)-sulfonamide



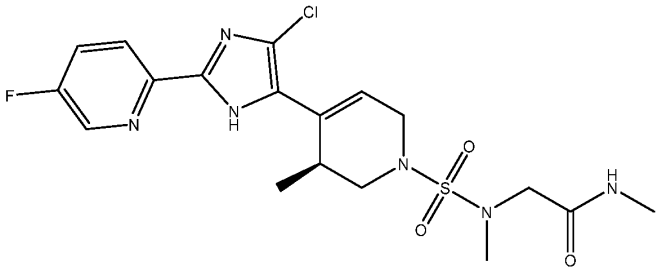
[1464] Example V18: (S*)-N-((4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridin-1(2H)-yl)sulfonyl)-N-methylglycine



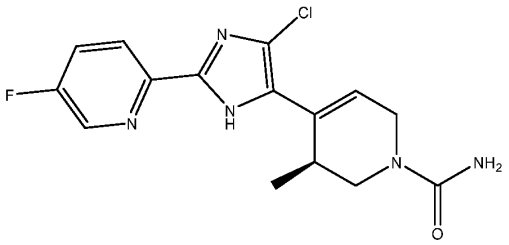
[1465] Example V19: (S*)-2-(4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethyl-1,2,3,6-tetrahydropyridine-1-sulfonamido)acetamide



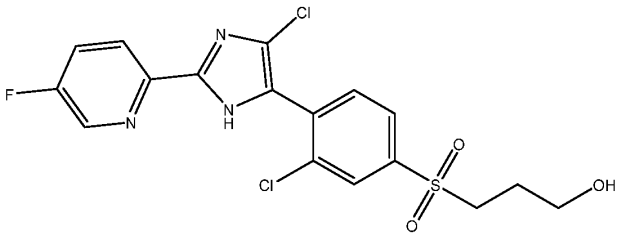
[1466] Example V20: (S*)-2-(4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N,3-dimethyl-1,2,3,6-tetrahydropyridine-1-sulfonamido)-N-methylacetamide



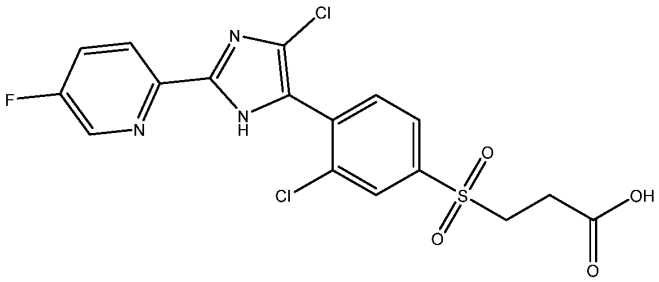
[1467] Example V21: (S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxamide



[1468] Example V22: 3-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)propan-1-ol



[1469] Example V23: 3-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)propanoic acid



[1470] PHARMACOLOGY AND PHYISCOCHEMICAL PROPERTIES

[1471] The *in vitro* potency of compounds described herein in antagonizing MRGPRX2, and solubility and logD of compounds described herein may be determined by the procedures detailed below.

[1472] Human MRGPRX2 calcium mobilization assay

[1473] The assay employs MRGPRX2 expressing cells pre-labelled with a calcium-sensitive dye. In particular, HEK293T cell line (Multiscreen^{TM} HEK293T, catalog no. C1257a, Multispan, Inc.) stably expressing the human MRGPRX2 receptor (MAS-related G-protein coupled receptor X2; NM_054030 with FLAG tag sequence at N-terminus) and the Calcium 6-QF assay kit (Molecular Devices) were used. Stimulation of the receptor results in an intracellular rise of calcium (Ca^{2+}) levels. In the assay, the Ca^{2+}-influx into cells results in fluorescence changes of a calcium sensitive dye which is included in the Calcium 6-QF assay

kit (Molecular Devices). When the dye complexes calcium, a large increase of the fluorescence quantum yield occurs and can be measured with the Fluorometric Imaging Plate Reader (FLIPR Tetra, Molecular Devices). The fluorescent dye enters the cell. Hence, influx of calcium to the cytoplasm can be detected and serve as a proxy for receptor activation.

[1474] In brief, frozen assay-ready HEK293T cells stably expressing hMRGPRX2 were plated at 12,500 cells/well (25 µl/well) in 384-well poly-D-Lysin coated plates (Corning # 356697) and incubated overnight at 37°C and 5% CO_2. On the second day, culture media was removed and cells were washed two times with a Biotek EL406 plate washer (residual volume 15 µl) (HBSS, 20 mM Hepes, 0,01% Pluronic F68). Subsequently, 10 µl Calcium 6-QF dye solution was added using a Multidrop Combi and cells were incubated for 90 min at 37°C, 5% CO_2 without lid. This was followed by incubation for 30 min at RT without lid. Next, 12.5 µl compound solution was added (4x concentrated) within the FLIPR Tetra device while recording fluorescence changes live (Ex 470-495; Em 515-575). Fluorescence changes during the first 15 min indicate agonistic compound activities. After 15 min, 12.5 µl pruritogenic neuropeptide Substance P (Sigma S6883) solution was added (4x concentrated; final concentration EC90 of hMRGPRX2 agonist) in the FLIPR Tetra. Fluorescence was recorded for an additional 240 sec. The maximum signal for each well (time-frame: 30 sec before, 240 sec after Substance P addition) was extracted.

[1475] To determine the activity of antagonist compounds, the maximum signal was used and the percent (%) inhibition at each concentration of a test compound was calculated relative to the responses in control wells contained within each assay plate. 0% inhibition was the activity determined from control wells lacking compound and 100% inhibition was derived from the measured activity in control wells containing a reference antagonist (1-(10H-phenazin-5-yl)ethanone) at 100 µM. The concentrations and percent inhibition values for a test compound were plotted and dose-response parameters including relative IC50 values were determined using a four parameter logistic dose-response equation.

[1476] Determination of thermodynamic solubility using DMSO stock solution (high throughput method)

[1477] In a first run, the actual compound concentration in a DMSO stock solution (nominal concentration 10 mM) is determined after dilution (1:40 with DMSO) using UPLC-UV/ELSD (Evaporative Light Scattering Detector) and quantifying against a standard solution of indometacin. This data point is used for the two-point calibration curve to quantify the solubility sample in a second run. Therefore, the DMSO stock solution on a U-shaped 96-well multi-titer plate is first evaporated to obtain a dry film (~100 µg). The dissolution medium to be tested (160 µL, e.g., phosphate buffer pH 7.4) is added to the dry film together with a stirring bead and the sample is shaken for 16 h at 25 °C on a thermomixer with 600 rpm after sealing the plate. This is followed by a centrifugation (5 min, 4000 rcf) and filtration (filter 0.45 µm) step to obtain a supernatant that is quantified using UPLC-UV (A: H2O (25 mM ammonium acetate), B: MeCN; Gradient: 2%-98% B in 2.3 min, 98% B for 0.6 min; Flow Rate: 0.9 ml/min; Column: Waters Acquity CSH C18 1.7 µm 2.1 x 75 mm; Column Temperature: 50°C) against the calibration curve determined above.

[1478] Determination of thermodynamic solubility using solid material

[1479] For the calibration samples (in duplicate) and for each buffer medium (selected from pH1.1, pH4.5, pH6.5, pH7.4, pH9.0, FaSSIF, and FeSSIF buffer solution) approx. 1 mg of the test item is accurately (with 3 decimal digits) weighed into a 1 ml HPLC glass vial. An adjusted volume of DMSO is added to the two calibration samples to obtain a starting concentration of 1 mg/ml for the calibration curves. From each calibration sample a DMSO dilution series is created in a U-shaped 96-well multititer plate with the concentration steps 500 µg/ml, 250 µg/ml, 100 µg/ml, 50 µg/ml, 20 µg/ml, 10 µg/ml, 5 µg/ml, 2 µg/ml, and 1 µg/ml. The two dilution series are measured using UPLC-UV (A: H2O (0.05% TFA), B: MeCN (0.045% TFA); Gradient: 2%-98% B in 11.5 min, 98% B for 1 min; Flow Rate: 0.7 ml/min; Column: Waters Acquity CSH C18 1.7 µm 2.1 x 75 mm; Column Temperature: 50°C) and a mean calibration curve (polynomial 2 order) is calculated using these data points.

[1480] An adjusted volume of the selected buffers is added to each buffer sample to reach a maximum concentration of 1 mg/ml. The cap sealed samples are then shaken for 16 h at 25

°C on a thermomixer with 600 rpm. This is followed by a centrifugation (10 min, 2500 rcf) and filtration (filter 0.45 µm) step to obtain a supernatant that is quantified using UPLC-UV against the calibration curve determined above.

[1481] Determination of logD7.4 by RP-UHPLC

[1482] The octanol/water distribution coefficient at pH 7.4 (logD7.4) is determined by a standardized reversed phase UHPLC-UV method (A: H_2O, B: MeCN, C: MOPS 100 mmol pH 7.4; Gradient: 95%/0%/5% – 0%/95%/5% in 6.0 min, 0%/95%/5% for 1 min; Flow Rate: 0.7 ml/min; Column: Waters BEH C18 1.7 µm 2.1x50 mm; Column Temperature: 30°C), which allows the fast relative differentiation of test items which are similar to standard compounds. Comparison of the retention times of the test items with those of standard compounds of known distribution coefficient between octanol and water at pH 7.4 (logD7.4) allows the calculation of the logD7.4 value for the test items. The retention times of the reference compounds in the calibration mixture (four basic and four acidic/neutral compounds – *see* Table 1 & 2) are plotted against their known logD7.4 values. The slope and the intercept of this calibration function are used to calculate the logD7.4 value of the test item from its retention time. The test sample solutions are prepared by diluting 5 µL of a 10 mM stock solution in DMSO with 195 µL of DMSO.

[1483] **Table 2:** HPLC logD7.4 standards for basic compounds

Standard	logD7.4	t_R/min
Metoprolol	-0.30	2.3
Desipramine	1.40	3.1
Ticlopidine	4.46	4.3
Amiodarone	6.44	5.0

[1484] **Table 3:** HPLC logD7.4 standards for acidic/neutral compounds

Standard	logD7.4	t_R/min
Caffeine	-0.20	1.9
Antipyrine	0.43	2.1
Ketoconazole	3.19	3.6

Triphenylene	5.50	4.6

[1485] Biological and Physical Property Data

[1486] Table 3 below lists the IC50 values obtained as described for the hMRGPRX2 calcium mobilization assay, logD values at pH 7.4 obtained by RP-HPLC as described herein, thermodynamic solubility values obtained using a DMSO stock solution method, except where otherwise indicated, as described herein, and the molecular weights for exemplified compounds.

[1487] Table 4

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
1	Tert-butyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate	2233	3.7	<3	381
2	1-[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-1-piperidyl]ethanone	3951	1.5	144	323
3	2-[4-Chloro-5-(1-methylsulfonyl-4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine	48	2.0	20	359
4	(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide	5.1	1.8	89	374
5	(3S,4S)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide	1434	1.8	77	374
6	(3R*,4S*/3S*,4R*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide	1373	1.8	47	374
7	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methylpiperidine-1-sulfonamide	17009	1.8	53	374
8	(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-3-methylpiperidine-1-sulfonamide	5.9	1.8	35	418
9	(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxamide	17.5	1.3	149	338
10	2-(4-Chloro-5-((3R,4R)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine	3.5	2.2	76[a]	373
11	1-((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)ethan-1-one	1196	1.7	623	337
12	(3S*,4S*)-4-(4-Ethyl-2-(5-fluoropyridin-2-yl)-	720	0.8	319	367

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide				
13	(3R*,4R*)-4-(4-Ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide	5894	0.8	295	367
14	Methyl (((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycinate	5	2.4	212	446
15	(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycine	19	0.9	>1158	432
16	2-(4-Chloro-5-((3S,4S)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine	39	2.2	141	373
17	2-(4-Chloro-5-((3R*,4S*/3S*,4R*)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine	51	2.3	6	373
18	1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxamide	15	1.9	127	457
19	(S*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine	2	2.3	56	371
20	(R*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine	106	2.3	51	371
21	(S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide	4.1	1.9	60	372
22	(R*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide	164	1.9	62	372
23	2-(5-((3R,4R)-1-((1H-Pyrazol-4-yl)sulfonyl)-3-methylpiperidin-4-yl)-4-chloro-1H-imidazol-2-yl)-5-fluoropyridine	2	2.2	<2	425
24	Methyl 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylate	20	3.0	11	472
25	1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-	70	1.1	>1092	458

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	yl)sulfonyl)azetidine-3-carboxylic acid				
26	2-(4-Bromo-5-(2,3-difluorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine	4	3.4	<3	354
27	2-(4-Bromo-5-(2-chlorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine	2	3.3	<3	353
28	2-[4-Chloro-5-(2-chloro-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine	18	2.0	115	370
29	2-[4-Chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine	3.6	2.6	<3	386
30	2-[4-Chloro-5-(2-chloro-4-(methylsulfonimidoyl)phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine	45	1.8	43	385
31	Methyl 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoate	15	3.6	<3	366
32	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoic acid	938	0.9	436	352
33	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide	8.1	2.2	<3	387
34	2-[[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]acetic acid	496	1.2	>1123	445
35	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-(2-hydroxyethyl)benzenesulfonamide	18	2.2	2	431
36	2-[5-(2-Chloro-4-methylsulfonyl-phenyl)-4-methyl-1H-imidazol-2-yl]-5-fluoro-pyridine	39	2.1	17	366
37	Methyl 1-((3-chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxylate	55	3.2	2	485
38	1-((3-Chloro-4-(4-chloro-2-(5-fluoro-pyridin-2-yl)-1H-imidazol-5-yl)-phenyl) sulfonyl)azetidine-3-carboxylic acid	1580	1.4	1061	471
39	1-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxamide	11	2.3	2	470
40	Methyl 2-chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoate	35	3.2	<3	366
41	2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoic acid	22688	0.6	>1420	352
42	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-2,3-dihydro-1,2-benzothiazole 1,1-dioxide	8019	2.0	17	365

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
43	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-2-methylbenzenesulfonamide	204	2.0	<3	367
44	2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzamide	1065	1.5	13	351
45	2-(4-Chloro-5-(2-fluoro-6-methylphenyl)-1H-imidazol-2-yl)-5-fluoropyridine	5	3.3	<3	306
46	Methyl 3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoate	50	3.4	<3	364
47	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoic acid	19025	0.7	>1430	350
48	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzamide	998	1.7	9	349
49	2-(4-Chloro-5-(2-fluoro-6-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine	7	3.9	<3	352
50	2-[4-Chloro-5-(2-fluoro-6-methyl-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine	3	2.6	106	384
51	3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropan-1-ol	21	2.3	<2	430
52	3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzenesulfonamide	261	2.2	40	385
53	3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropanamide	11	2.0	<2	443
54	4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoic acid	17216	0.8	>1507	332
55	Methyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoate	17	3.4	<3	346
56	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide	16	1.7	4	331
57	N-(2-Amino-2-oxo-ethyl)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide	50	1.5	13	388
58	2-(4-Chloro-5-(2-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine	8	n/a	n/a	334
59	N-(2-Amino-2-oxo-ethyl)-3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide	23	1.6	<2	408
60	3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide	4	1.9	<3	351
61	2-[4-Chloro-5-(2-methyl-4-methylsulfonyl-	5	2.5	13	366

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine				
62	2-[4-Chloro-5-(2-methyl-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine	31	1.9	134	350
63	Tert-butyl (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate	4107	4.0	<3	393
64	Tert-butyl (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate	2661	4.0	<3	393
65	(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N,3-trimethyl-piperidine-1-carboxamide	27852	n/a	n/a	366
66	Methyl (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate	3928	2.5	671	353
67	[2-(Dimethylamino)-2-oxo-ethyl] (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate	564	2.0	>1180	424
68	Methyl 3-[[(3S*)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate	5	2.8	8	443
69	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	<2	2.0	45	436
70	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-1-oxido-pyridin-1-ium	28	2.3	165	452
71	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-oxidopyridin-1-ium-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	31	2.0	101	452
72	2-[5-[(3R,4R)-1-(Azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)	73	0.5	59	414
73	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidin-1-yl]ethanone	62	1.9	18	456
74	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxamide	48	1.6	11	457
75	Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-	17	2.8	52	459

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	piperidyl]sulfonyl]butanoate				
76	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoate	2612	3.2	<2	473
77	Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate	8	3.6	<2	528
78	2-[5-[(3R,4R)-1-(Azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)	41	0.3	>1077	428
79	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methyl-pyridine	29	2.3	<2	450
80	2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethanol	66	1.9	182	447
81	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoic acid	361	1.0	>1124	445
82	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoic acid	72	1.1	>1090	459
83	2-[4-Chloro-5-[(3R,4R)-1-[(6-methoxy-3-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	12	3.5	<2	466
84	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanamide	48	1.7	19	444
85	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanamide	956	1.9	11	458
86	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxamide	14	1.7	21	471
87	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one	103	2.0	7	452
88	2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]acetic acid	204	1.0	585	461

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
89	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydrofuran-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	46	2.4	98	429
90	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(oxetan-3-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	31	2.2	78	415
91	2-[4-Chloro-5-[(3R,4R)-1-[(2-methoxy-4-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	17	3.6	<2	466
92	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one	5	2.1	<2	452
93	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate	2	2.7	35	445
94	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid	23	1.0	>1160	431
95	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanamide	8	1.7	81[a]	430
96	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 1)	1498	1.1	>1094	457
97	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 2)	50	1.1	>1094	457
98	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-propanamide	7	1.8	209[a]	444
99	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 1)	246	1.8	95	456
100	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 2)	39	1.9	14	456
101	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-	1840	1.9	35	460

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	imidazol-5-yl]-N,N-bis(2-hydroxyethyl)-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide				
102	(3R,4R)-1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]pyrrolidine-3,4-diol	71	1.8	114	458
103	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(1H-tetrazol-5-ylmethyl)-3,6-dihydro-2H-pyridine-1-sulfonamide	48	1.2	>1102	454
104	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propyl acetate	23	2.8	28	459
105	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-ol	9	1.9	73	417
106	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-1-one	8	1.7	385[a]	486
107	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methylsulfonyl-propanamide	21	1.2	>984	508
108	(5R)-5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]imidazolidine-2,4-dione	137	2.3	46	471
109	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[2-hydroxy-1-(hydroxymethyl)ethyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide	319	1.6	188	446
110	4-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperazin-2-one	18	2.1	<2	455
111	(2S)-2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonylamino]propanamide	390	1.8	390	443
112	1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-ol	5	2.2	<2	428
113	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(2-oxopyrrolidin-3-	14	1.9	509	455

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	yl)-3,6-dihydro-2H-pyridine-1-sulfonamide				
114	2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetic	192	1.2	1120	444
115	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methoxy-pyrimidine acid	4	3.0	22	467
116	Methyl 2-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetate	39	2.7	<2	497
117	2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetamide	102	2.0	102	443
118	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine	5	2.6	18	437
119	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyridin-2-one	8	2.2	100	466
120	2-[4-Chloro-5-[(3R,4R)-1-[2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	4	3.6	<2	575
121	2-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetic acid	72	1.2	>1035	483
122	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-ol	10	1.3	21	453
123	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2H-tetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	9	1.1	>1099	455
124	Methyl 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate	8	2.7	<2	443
125	3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanamide	6	1.7	27	428
126	3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-	8	1.7	124	484

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	1-one				
127	3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-N-cyclopropyl-propanamide	11	2.2	6	468
128	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]piperidine-1-sulfonamide	n/a	2.1	>1069	468
129	[1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-yl]methanol	41	2.2	30	442
130	N-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperidine-3-carboxamide	1056	2.3	70	483
131	(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[(2S)-2-hydroxypropyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide	9	2.1	45	430
132	2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonylamino]-N,N-dimethyl-acetamide	7	2.2	111	457
133	2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylamino]-N,N-dimethyl-acetamide	9	2.1	>1090	459
134	Tert-butyl (3S,4S)-4-[4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl]-3-methylpiperidine-1-carboxylate	1036	3.9	<2	395
135	4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide	15	1.8	25	372
136	2-Chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine	19	3.5	4	471
137	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylpyrazol-4-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	11	2.5	<2	439
138	(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,3-dimethyl-piperidine-1-carboxamide	12524	1.5	>1421	352
139	1-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]azetidin-3-ol	8	2.2	<2	508

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
140	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]ethanol	5	2.2	5	496
141	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	7	2.2	274	469
142	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine	5	2.2	2	452
143	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridin-2-amine	5	1.6	25	451
144	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-pyrimidin-2-amine	3	3.0	<2	492
145	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyrrolidin-2-one	38	1.9	726	456
146	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-pyrimidin-2-amine	4	2.7	2	466
147	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N,N-bis(trideuteriomethyl)propanamide	6	2.1	565	464
148	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-2-methyl-propyl)propanamide	10	1.8	850	502
149	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-propanamide	7	2.1	11	470
150	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-hydroxypyrrolidin-1-yl]propan-1-one	6	1.7	>1000	500
151	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-hydroxypyrrolidin-1-yl]propan-1-one	7	1.7	>1000	500

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
152	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxyazetidin-1-yl)propan-1-one	8	2.1	739	500
153	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxy-3-methyl-azetidin-1-yl)propan-1-one	9	1.8	324[a]	500
154	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-1-piperidyl)propan-1-one	6	1.8	>973	514
155	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxyethyl)propanamide	7	1.9	882	488
156	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	5	2.4	<2	469
157	Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate	5	3.6	<2	514
158	2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetamide	69	1.6	16	416
159	Tert-butyl N-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-yl]carbamate	82	3.7	<2	571
160	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonylazetidin-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	7	2.4	<2	506
161	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylazetidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	8	2.5	<2	492
162	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-amine	175	1.3	187	471
163	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidin-1-yl]ethanone	58	1.9	34	470
164	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-	7	1.8	310	447

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(trideuteriomethyl)propanamide				
165	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-yl)propanamide	11	1.8	761	486
166	2-[4-Chloro-5-[(3R,4R)-1-(1H-imidazol-4-ylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	26	1.8	9	425
167	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-ethyl-propanamide	5	2.1	55	458
168	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-4-methyl-1-piperidyl)propan-1-one	6	2.1	6	528
169	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-morpholino-propan-1-one	5	2.1	544	500
170	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(cyclopropylmethyl)propanamide	3	2.5	273	484
171	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-pyrrolidin-1-yl-propan-1-one	3	2.4	422	484
172	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2,2,2-trifluoroethyl)propanamide	4	2.7	398	512
173	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate	12	2.5	315	486
174	Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate	13	2.5	49	472
175	N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]acetamide	4	1.7	132	444
176	N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-	4	2.1	47	480

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]methanesulfonamide				
177	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylate	2	3.4	<2	483
178	5-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-3-methyl-1,2,4-oxadiazole	5	2.7	101	469
179	Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]carbamate	2	3.3	<2	502
180	2-[4-Chloro-5-[(3R,4R)-1-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	3	3.2	<2	574
181	2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethanamine	15	0.4	1162	402
182	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(1-hydroxycyclopropyl)methyl]propanamide	7	1.8	749	500
183	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]propan-1-one	6	2.6	287	568
184	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-ylmethyl)propanamide	5	1.5	766	518
185	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-7-azaspiro[3.5]nonan-7-yl)propan-1-one	8	2.2	177	540
186	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-methoxy-1-piperidyl)propan-1-one	6	2.5	352	528
187	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-	10	2.0	644	514

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	piperidyl]sulfonyl]-N-tetrahydropyran-4-yl-propanamide				
188	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3S)-tetrahydropyran-3-yl]propanamide	8	2.2	703	514
189	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propan-1-one	8	1.9	492	512
190	2-[4-Chloro-5-[(3R,4R)-1-(2-methoxyethylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	20	2.5	560	417
191	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydropyran-4-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	1109	2.5	456	443
192	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(tetrahydrofuran-3-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	26	2.5	218	443
193	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]acetamide	4	2.7	<2	499
194	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-yl]acetamide	8	2.9	<2	513
195	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylate	11	2.9	<2	494
196	Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxylate	27	3.7	<2	528
197	Tert-butyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]piperidine-1-carboxylate	979	3.9	<2	542
198	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1H-triazol-4-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	6	2.0	281	454
199	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(4-piperidylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)	3788	0.4	>1045	442

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
200	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-pyrrolidin-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine (hydrochloride)	707	0.5	>1077	428
201	Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethylsulfamoyl]carbamate	25	2.1	587	581
202	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-amine	2	1.6	4	457
203	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-amine	38	1.8	<2	471
204	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylic acid	18	1.3	>1042	480
205	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]-5-methyl-1,2,4-oxadiazole	13	n/a	n/a	455
206	1-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-piperidyl]ethanone	6536	2.1	4	484
207	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonyl-4-piperidyl)sulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	780	2.5	<2	520
208	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(sulfamoylamino)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	5	1.8	33[a]	481
209	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylpyrrolidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	290	2.5	4	506
210	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidin-1-yl]ethanone	1305	2.0	113	470
211	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxamide	7	2.4	<2	479
212	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxamide	414	1.7	146	471
213	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-	29	1.3	125	426

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	4-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine				
214	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxamide	4	2.3	<2	468
215	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(methylsulfonylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	26	2.3	69	451
216	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-methylsulfonylpropylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	9	2.1	46	479
217	[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-furyl]-(3-hydroxyazetidin-1-yl)methanone	8	2.3	36	524
218	3-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-1,4-dihydro-1,2,4-triazol-5-one	27	1.5	19	470
219	Tert-butyl N-[6-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-yl]carbamate	38	3.9	<2	552
220	6-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-amine	6	1.2	66	452
221	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylate	13	2.7	<2	495
222	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylic acid	2	1.2	>1040	481
223	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxamide	7	2.0	51[a]	480
224	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] methyl carbonate	3	2.4	420	544
225	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxy-3-methyl-	6	2.3	>973	514

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	azetidin-1-yl)propan-1-one				
226	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-methoxypyrrolidin-1-yl]propan-1-one	8	2.2	>973	514
227	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[dimethyl(oxo)-¿6-sulfanylidene]propanamide	11	1.9	224	506
228	[2-(Aminomethyl)-3-hydroxy-2-methyl-propyl] 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate (2,2,2-trifluoroacetic acid)	5	0.6	209	532
229	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3-methyloxetan-3-yl)propanamide	8	1.6	364	500
230	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylcyclopropyl)propanamide	7	2.4	5	484
231	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxy-2-methyl-propyl)propanamide	10	2.4	>969	516
232	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-methoxypyrrolidin-1-yl]propan-1-one	7	2.2	>973	514
233	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-oxetan-2-yl]methyl]propanamide	10	1.5	503	500
234	2-[4-Chloro-5-[(3R,4R)-1-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	4	2.4	<2	574
235	N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]cyclopropanesulfonamide	5	2.5	6	506

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
236	[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]urea	4	2.3	<2	500
237	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(4H-1,2,4-triazol-3-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	11	1.7	297	454
238	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(3-methyloxetan-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	24	n/a	n/a	443
239	Tert-butyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino]azetidine-1-carboxylate	3	3.0	41	585
240	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] methyl carbonate	9	2.8	116	572
241	[(3R)-1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]pyrrolidin-3-yl] methyl carbonate	7	2.5	390	558
242	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-tetrahydrofuran-2-yl]methyl]propanamide	6	2.2	788	514
243	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2R)-tetrahydrofuran-2-yl]methyl]propanamide	8	2.2	960	514
244	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3R)-tetrahydrofuran-3-yl]propanamide	9	1.9	>1000	500
245	1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]piperidin-4-one	8	2.1	374	512
246	1-(Azetidin-1-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-one	9	2.1	>1063	470
247	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-	7	1.9	26[a]	548

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	piperidyl]sulfonyl]-1-(3-methylsulfonylazetidin-1-yl)propan-1-one				
248	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclobutyl]propanamide	9	2.1	813	514
249	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclopentyl]propanamide	8	2.4	<2	528
250	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(4-hydroxycyclohexyl)propanamide	11	1.8	37	528
251	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-methyl-1,3,4-oxadiazol-2-yl)propanamide	6	1.8	66	512
252	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-fluoro-2-pyridyl)propanamide	4	2.9	<2	525
253	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methylpyrazol-3-yl)propanamide	5	2.1	336	510
254	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one	7	2.0	541	528
255	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-fluoroazetidin-1-yl)propan-1-one	5	2.2	785	488
256	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(6-oxa-1-azaspiro[3.3]heptan-1-yl)propan-1-one	10	2.1	310	512
257	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] acetate	8	2.7	264	556

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
258	5-[[(3S,4S)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine	6	2.2	<2	435
259	5-[[(3R,4R)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine	69	2.2	<2	435
260	N-(Azetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanamide (hydrochloride)	10	0.3	>959	485
261	2-[4-Chloro-5-[(3R,4R)-1-[[1-[(4-methoxyphenyl)methyl]triazol-4-yl]methylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	7	1.7	<2	560
262	2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine	17	1.9	4	440
263	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-3-methoxy-pyridazine	7	2.7	14	467
264	5-Fluoro-2-[4-fluoro-5-[(3S,4S)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine	9	2.1	104	356
265	5-Fluoro-2-[4-fluoro-5-[(3R,4R)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine	260	2.1	108	356
266	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]acetamide	7	2.3	70	494
267	Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate	6	3.4	<2	500
268	Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate	3	3.2	<2	500
269	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]methanesulfonamide	20	1.4	559	530
270	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid	3	2.9	<2	442

Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
271	4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid	29	1.4	>1029	486
272	Methyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino]azetidine-1-carboxylate	13	2.1	346	543
273	N-(1-Acetylazetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanamide	15	1.6	>949	527
274	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylsulfonylazetidin-3-yl)propanamide	9	2.0	336	563
275	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-yl]acetamide	8	2.7	<2	500
276	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid	9	1.5	>1029	486
277	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]propane-1,3-diol	5	1.9	270	526
278	Methyl 2-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetate	5	2.9	<2	524
279	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-amine	9	2.4	<2	458
280	N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]azetidine-3-carboxamide (2,2,2-trifluoroacetate)	6	0.8	109	540
281	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetic acid	24	1.3	>981	510
282	5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-	7	2.7	3	485

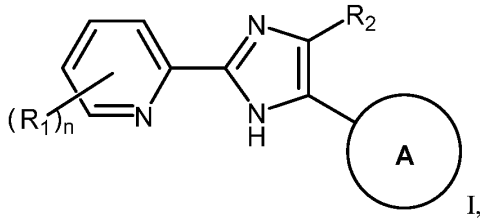
Ex. No.	Name	FLIPR IC50 nM	LogD pH7.4	Sol. pH7.4 µM	MW g/mol
	piperidyl]sulfonyl]thiazole-2-carboxamide				
283	2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetamide	7	2.0	8	509
284	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-1,1-dimethyl-ethyl)propanamide	18	2.1	727	502
285	3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3,3-difluorocyclobutyl)propanamide	7	2.7	304	520
286	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] acetate	8	2.6	642	542
287	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] methyl carbonate	8	2.7	260[a]	558
288	[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] ethyl carbonate	7	2.8	184	558

[a] Thermodynamic solubility determined from solid as described herein

[1488] From the foregoing, those skilled in the art will appreciate that certain modifications can also be made to the present disclosure without departing from the scope of the same. The above description should not be construed as limiting, but merely as exemplifications of particular embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

CLAIMS

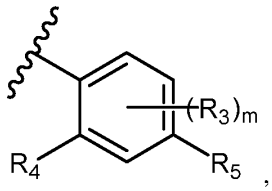
1. A compound of formula I



I,

wherein:

A is selected from



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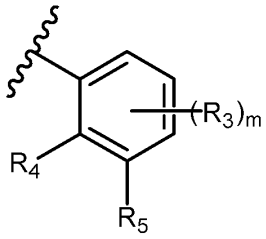

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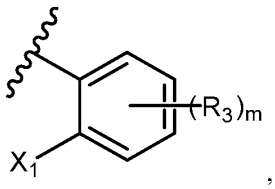

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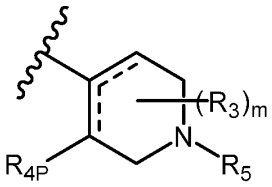

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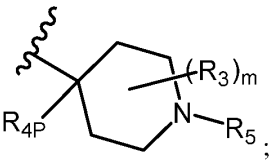


;

each ----- is a single or a double bond, provided two adjacent ----- are not both double bonds;

each instance of R_1 is independently selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_2 is selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

each instance of R_3 is independently selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_4 is selected from halogen, cyano, -OR_{11}, -$NR_{11}R_{12}$, -SR_{11}, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_{4P} is selected from hydrogen, halogen, cyano, $-OR_{11}$, $-NR_{11}R_{12}$, $-SR_{11}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-C(=NR_9)NR_7R_8$, $-OC(=O)R_6$, $-OC(=O)OR_7$, $-OC(=O)NR_7R_8$, $-NR_9C(=O)R_6$, $-NR_9C(=O)OR_7$, $-NR_9C(=O)NR_7R_8$, $-NR_9C(=NR_9)NR_7R_8$, $-SR_7$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, $-S(=O)(=NR_9)R_6$, and $-S(=O)(=NR_9)NR_7R_8$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, aryl, C_1-C_3 arylalkyl, monocyclic heteroaryl, and C_1-C_3 heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pNR_{11}R_{12}$, $-(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(arylene)R_{13}, heterocyclyl, or -(heterocyclylene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, aryl, C_1-C_3 arylalkyl, heteroaryl, and C_1-C_3 heteroarylalkyl, which groups are unsubstituted or substituted with one or more of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-C(=NR_9)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, or $-S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, or $-NR_9S(=O)_2NR_{11}R_{12}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, and $-N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or more R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or more R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_4 alkyl), -C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -OC(=O)(C_1-C_4 alkyl), -OC(=O)OH, -OC(=O)O(C_1-C_4 alkyl), -OC(=O)NH_2, -OC(=O)NH(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(=O)(C_1-C_4 alkyl), -NHC(=O)OH, -NHC(=O)O(C_1-C_4 alkyl), -NHC(=O)NH_2, -NHC(=O)NH(C_1-C_4 alkyl), -NHC(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)OH, -N(C_1-C_4 alkyl)C(=O)O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)NH_2, -N(C_1-C_4 alkyl)C(=O)NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$OH, -$(CH_2)_q$O(C_1-C_4 alkyl), -$(CH_2)_q$$NH_2$, -$(CH_2)_q$NH($C_1$-$C_4$ alkyl), -$(CH_2)_q$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)OH, -$(CH_2)_q$C(=O)O(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)NH_2, -$(CH_2)_q$C(=O)NH(C_1-C_4 alkyl), -$(CH)_q$C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -$S(=O)_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a heterocyclyl ring;

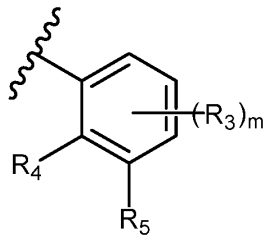
X_1 is halogen;

m is 0 or 1;

n is 1 or 2;

each p is independently 1, 2, or 3; and

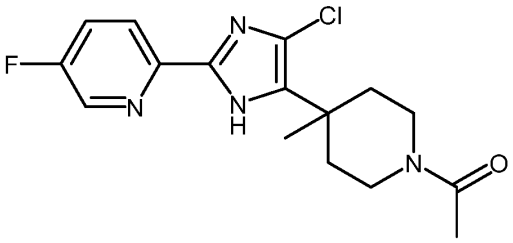
each q is independently 1, 2, or 3;



wherein when A is , R_4 and R_5 may be taken together with the carbons connecting them to form a 5- or 6-membered heterocyclyl ring;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,

provided the compound of formula I is not of formula



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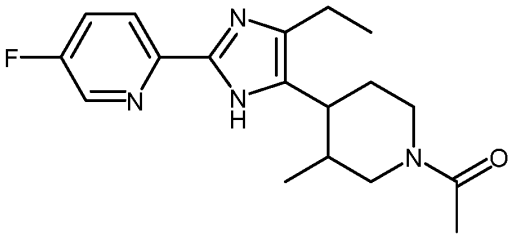

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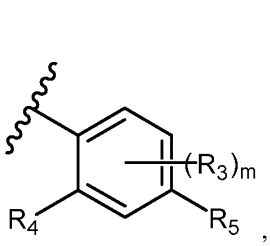
2. The compound of formula I according to claim 1, wherein:

A is selected from



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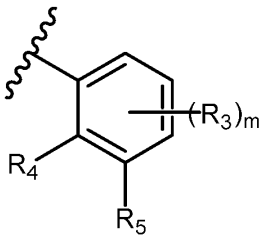

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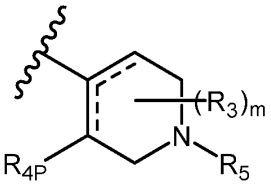

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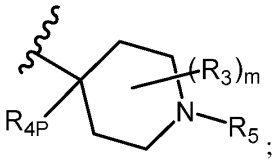

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R_1 is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_2 is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

each instance of R_3 is independently selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and C_1-C_6 haloalkyl;

R_4 is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_{4P} is selected from halogen, $-OR_{11}$, $-NR_{11}R_{12}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, and C_1-C_3 haloalkyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-C(=NR_9)NR_7R_8$, $-SR_7$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, $-S(=O)(=NR_9)R_6$, and $-S(=O)(=NR_9)NR_7R_8$;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, phenyl, C_1-C_3 phenylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, $-S(=O)(=NR_9)R_{10}$, -

$S(=O)(=NR_9)NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, $-(CH_2)_pOR_{11}$, $-(CH_2)_pNR_{11}R_{12}$, $-(CH_2)_pC(=O)R_{10}$, $-(CH_2)_pC(=O)OR_{11}$, $-(CH_2)_pC(=O)NR_{11}R_{12}$, $-(CH_2)_p$(phenylene)R_{13}, 4- to 6-membered heterocyclyl, or -(4- to 6-membered heterocyclene)R_{13}; and

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, phenyl, C_1-C_3 phenylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, cyano, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-N^+(O^-)R_{11}R_{12}$, $-SR_{11}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-OC(=O)R_{10}$, $-OC(=O)OR_{11}$, $-OC(=O)NR_{11}R_{12}$, $-NR_9C(=O)R_{10}$, $-NR_9C(=O)OR_{11}$, $-NR_9C(=O)NR_{11}R_{12}$, $-NR_9C(=NR_9)NR_{11}R_{12}$, $-S(=O)R_{10}$, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, or $-S(=O)(=NR_9)NR_{11}R_{12}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, and $-N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_3 monocyclic heteroarylalkyl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_3 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, $-O(C_1$-C_4 alkyl), $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-C(=O)(C_1$-C_4 alkyl), -C(=O)OH, $-C(=O)O(C_1$-C_4 alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_1$-C_4 alkyl), $-C(=O)N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-OC(=O)(C_1$-C_4 alkyl), -OC(=O)OH, $-OC(=O)O(C_1$-C_4 alkyl), $-OC(=O)NH_2$, $-OC(=O)NH(C_1$-C_4 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NHC(=O)(C_1$-C_4 alkyl), -NHC(=O)OH, $-NHC(=O)O(C_1$-C_4 alkyl), $-NHC(=O)NH_2$, $-NHC(=O)NH(C_1$-C_4 alkyl), $-NHC(=O)N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-N(C_1$-C_4 alkyl)$C(=O)(C_1$-

C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)OH, -N(C_1-C_4 alkyl)C(=O)O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)NH_2, -N(C_1-C_4 alkyl)C(=O)NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$OH, -$(CH_2)_q$O(C_1-C_4 alkyl), -$(CH_2)_q$$NH_2$, -$(CH_2)_q$NH($C_1$-$C_4$ alkyl), -$(CH_2)_q$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)OH, -$(CH_2)_q$C(=O)O(C_1-C_4 alkyl), -$(CH_2)_q$C(=O)NH_2, -$(CH_2)_q$C(=O)NH(C_1-C_4 alkyl), -$(CH)_q$C(=O)N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -S(=O)$_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a 4- to 6-membered heterocyclyl ring;

m is 0 or 1;

n is 1;

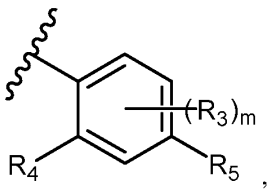
each p is 1; and

each q is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

3. The compound of formula I according to claim 1 or 2, wherein:

A is selected from



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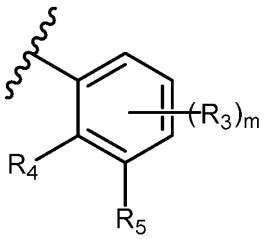

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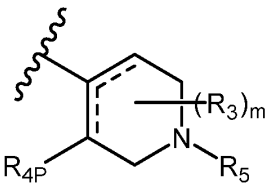

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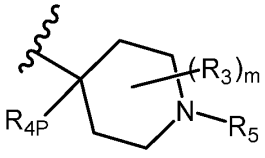


;

R_1 is selected from halogen;

R_2 is selected from halogen and C_1-C_4 alkyl;

R_4 is selected from halogen and C_1-C_4 alkyl;

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

R_5 is selected from -C(=O)R_6, -C(=O)OR_7, -C(=O)NR_7R_8, -SR_7, -S(=O)R_6, -S(=O)$_2R_6$, -S(=O)$_2$NR_7R_8, and -S(=O)(=NR_9)R_6;

R_6 is selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -NR_9C(=O)R_{10}, -S(=O)$_2R_{10}$, -S(=O)$_2$N$R_{11}R_{12}$, -NR_9S(=O)$_2R_{10}$, -NR_9S(=O)$_2$N$R_{11}R_{12}$, -(CH_2)$_p$OR_{11}, -(CH_2)$_p$C(=O)OR_{11}, -(CH_2)$_p$(phenylene)R_{13}, or –(4- to 6-membered heterocyclene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, -OR_{11}, -N$R_{11}R_{12}$, -C(=O)R_{10}, -C(=O)OR_{11}, -C(=O)N$R_{11}R_{12}$, -OC(=O)R_{10}, -OC(=O)OR_{11}, -OC(=O)N$R_{11}R_{12}$, -NR_9C(=O)R_{10}, -NR_9C(=O)OR_{11}, -NR_9C(=O)N$R_{11}R_{12}$, -S(=O)$_2R_{10}$, -S(=O)$_2$N$R_{11}R_{12}$, -NR_9S(=O)$_2R_{10}$;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, and -N=S(Me)$_2$=O, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3-to 6-membered cycloalkylalkyl, 4- to 6- membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -O(C_1-C_4 alkyl), -NH_2, -C(=O)(C_1-C_4 alkyl), -C(=O)OH, -C(=O)O(C_1-C_4 alkyl), -C(=O)NH_2, -OC(=O)(C_1-C_4 alkyl), -OC(=O)O(C_1-C_4 alkyl), -(CH_2)$_q$OH, and -S(=O)$_2$(C_1-C_4 alkyl), and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form a 4-membered heterocyclyl ring;

m is 0;

n is 1;

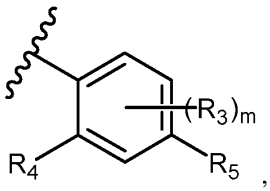
each p is 1; and

each q is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

4. The compound of formula I according to any one of claims 1-3, wherein:

A is selected from



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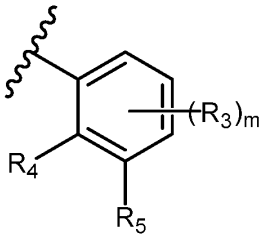

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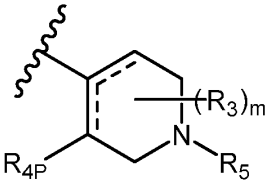
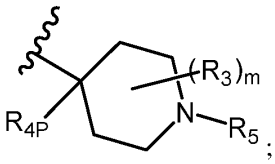


, and


;

R_1 is fluoro;

R_2 is selected from chloro, bromo, methyl, and ethyl;

R_4 is selected from fluoro, chloro, and methyl;

R_{4P} is selected from hydrogen and methyl;

R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-SR_7$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

R_6 is selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6-membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, and C_1-C_3 monocyclic heteroarylalkyl which groups are unsubstituted or substituted with one, two, or three of halogen, C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$, $-NHC(=O)R_{10}$, $-S(=O)_2R_{10}$, or $-S(=O)_2NR_{11}R_{12}$, $-NR_9S(=O)_2R_{10}$, $-NR_9S(=O)_2NR_{11}R_{12}$, -

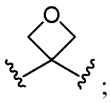
$(CH_2)OR_{11}$, $-(CH_2)C(=O)OR_{11}$, $-(CH_2)$(phenylene)R_{13}, or –(4- to 6-membered heterocyclene)R_{13};

R_7 and R_8 are independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, 4 to 6-membered heterocyclyl, and C_1-C_3 monocyclic heteroarylalkyl, which groups are unsubstituted or substituted with one, two, or three of C_1-C_4 alkyl, $-OR_{11}$, $-NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, or $-C(=O)NR_{11}R_{12}$,;

each instance of R_9 is independently selected from hydrogen and C_1-C_4 alkyl;

each instance of R_{10} is independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, 4- to 6- membered heterocyclyl, and $-N=S(Me)_2=O$, which groups are unsubstituted or substituted with one or two R_{13};

each instance of R_{11} and R_{12} is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_3-C_6 cycloalkyl, C_1-C_3 3- to 6-membered cycloalkylalkyl, 4- to 6- membered heterocyclyl, C_1-C_3 4- to 6-membered heterocyclylalkyl, monocyclic heteroaryl, C_1-C_4 acyl, and C_1-C_4 sulfonyl provided R_{11} is not C_1-C_4 sulfonyl when R_{11} is bonded to an oxygen or sulfur atom, which groups are unsubstituted or substituted with one or two R_{13};

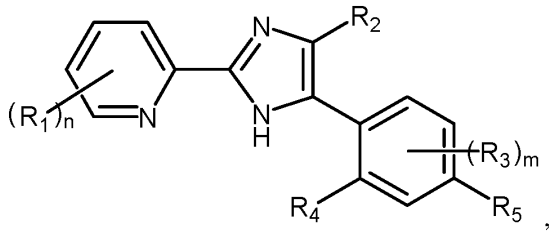
each instance of R_{13} is independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, -OH, -OMe, $-NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, $-C(=O)NH_2$, -C(=O)OtBu, -OC(=O)Me, -OC(=O)OMe, -OC(=O)OEt, $-(CH_2)OH$, and $-S(=O)_2(Me)$, and wherein two R_{13} groups substituting the same carbon of a heterocyclyl ring may be taken together with the carbon to which they are attached to form:  ;

m is 0; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

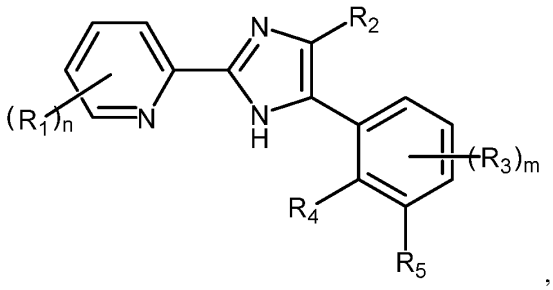
5. The compound of formula I according to any one of claims 1-4, wherein the compound is of formula I-A



I-A,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

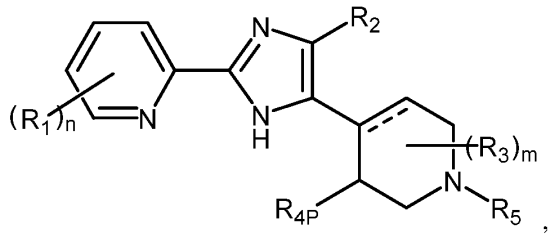
6. The compound of formula I according to any one of claims 1-4, wherein the compound is of formula I-B



I-B,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

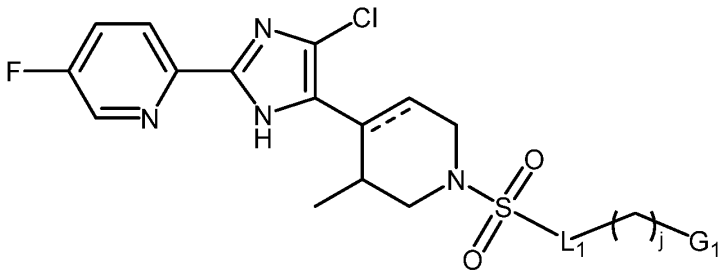
7. The compound of formula I according to any one of claims 1-4, wherein the compound is of formula I-D



I-D,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

8. The compound of formula I according to any one of claims 1-4, wherein the compound is of formula I-G1



I-G1,

wherein:

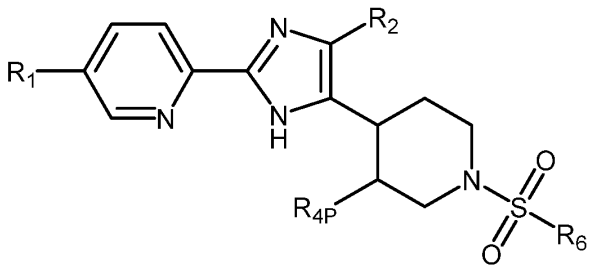
L_1 is selected from $-CH_2-$ and $-N(R_{11})-$;

G_1 is selected from $-OR_{11}$, $NR_{11}R_{12}$, $-C(=O)R_{10}$, $-C(=O)OR_{11}$, $-C(=O)NR_{11}R_{12}$,, $-S(=O)_2R_{10}$, $-S(=O)_2NR_{11}R_{12}$, 4- to 6-membered heterocyclyl, and monocyclic heteroaryl; and

j is 0, 1, or 2;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

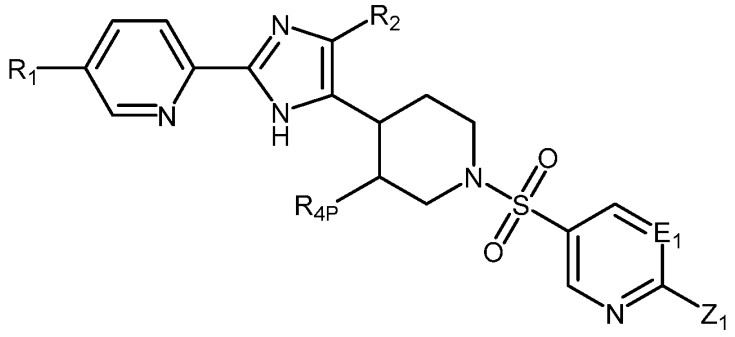
9. The compound of formula I according to any one of claims 1-4, wherein the compound is of formula I-H



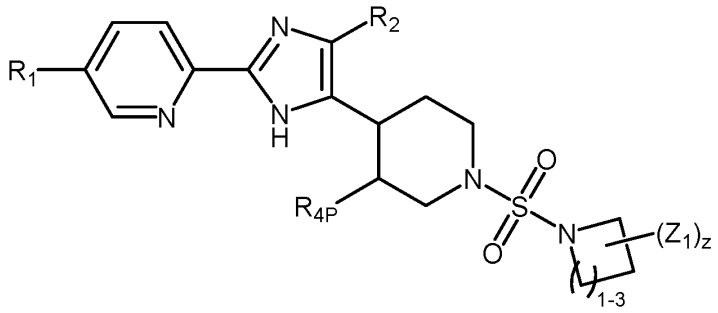
I-H,

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

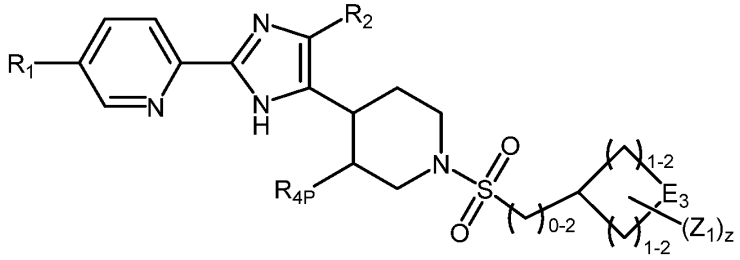
10. The compound of formula I according to any one of claims 1-4, wherein the compound is of any one of formulas I-J1 to I-J5,



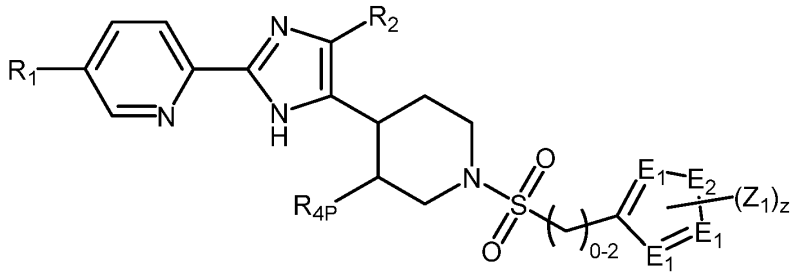
I-J1,



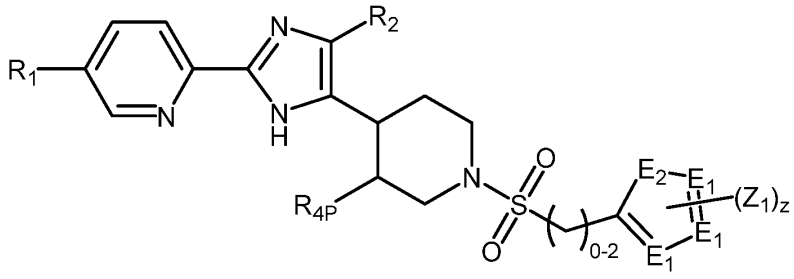
I-J2,



I-J3,



I-J4,



I-J5,

wherein:

z is 0, 1, or 2 where valency permits;

each instance of Z_1 is independently selected from halogen, cyano, C_1-C_4 alkyl, -OR_{11}, -$NR_{11}R_{12}$, -$N^+(O^-)R_{11}R_{12}$, -SR_{11}, -$C(=O)R_{10}$, -$C(=O)OR_{11}$, -$C(=O)NR_{11}R_{12}$, -$C(=NR_9)NR_{11}R_{12}$, -$OC(=O)R_{10}$, -$OC(=O)OR_{11}$, -$OC(=O)NR_{11}R_{12}$, -$NR_9C(=O)R_{10}$, -$NR_9C(=O)OR_{11}$, -$NR_9C(=O)NR_{11}R_{12}$, -$NR_9C(=NR_9)NR_{11}R_{12}$, -$S(=O)R_{10}$, -$S(=O)_2R_{10}$, -$S(=O)_2NR_{11}R_{12}$, -$S(=O)(=NR_9)R_{10}$, -$S(=O)(=NR_9)NR_{11}R_{12}$, -$NR_9S(=O)_2R_{10}$, -$NR_9S(=O)_2NR_{11}R_{12}$, -$(CH_2)_pOR_{11}$, -$(CH_2)_pNR_{11}R_{12}$, -$(CH_2)_pC(=O)R_{10}$, -$(CH_2)_pC(=O)OR_{11}$, -$(CH_2)_pC(=O)NR_{11}R_{12}$, -$(CH_2)_p$(arylene)$R_{13}$, heterocyclyl, or -(heterocyclene)R_{13};

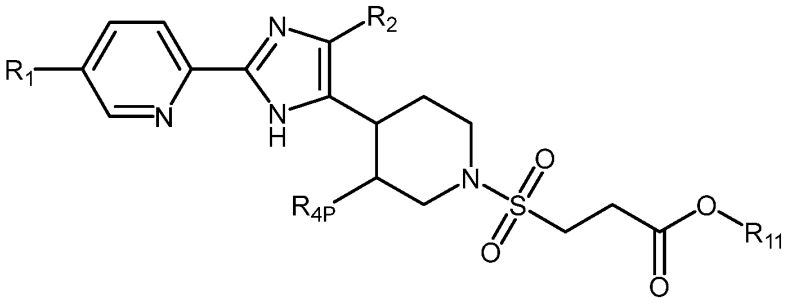
each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-; and

E_3 is selected from -CH_2-, -NH-, and -O-;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

11. The compound of formula I according to any one of claims 1-4, wherein the compound is of any one of formulas I-K1 to I-K8



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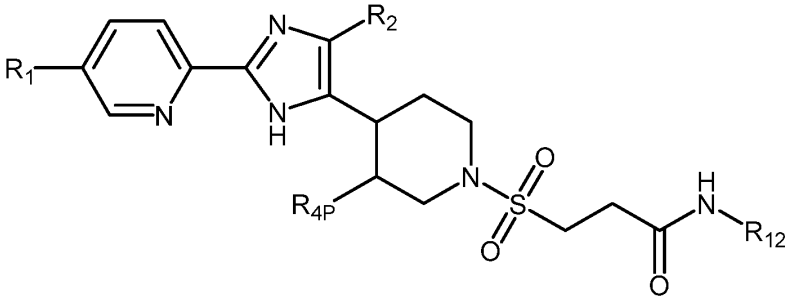

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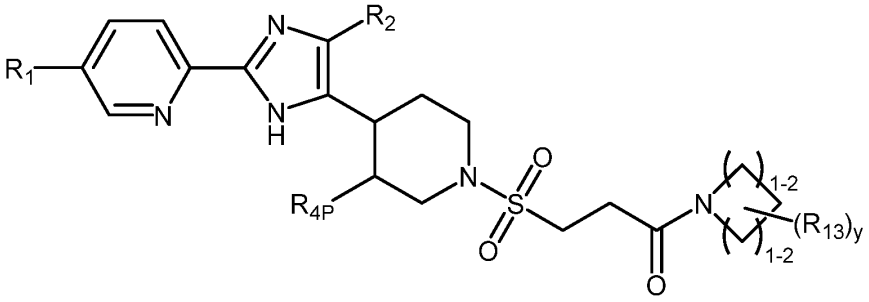

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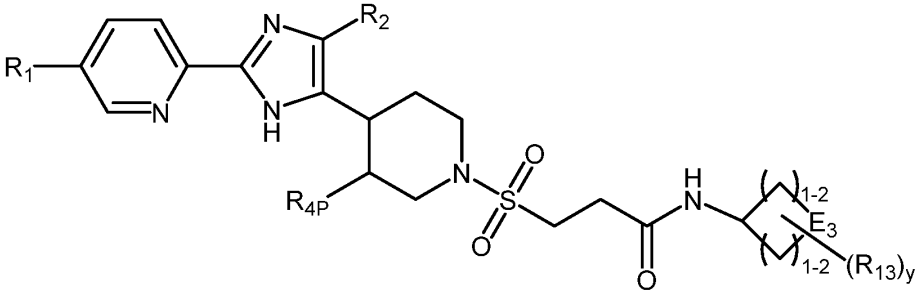

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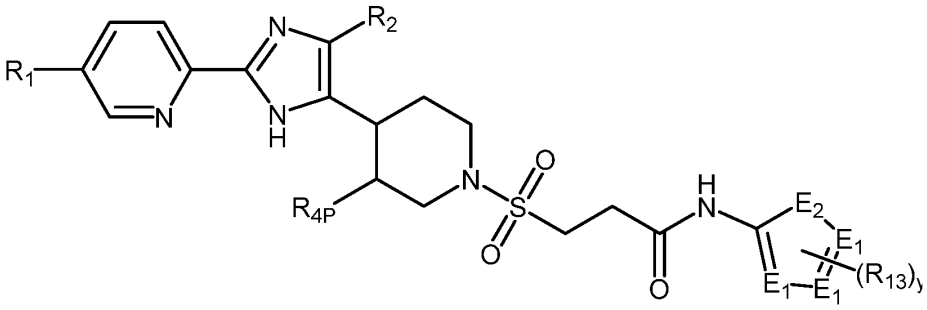

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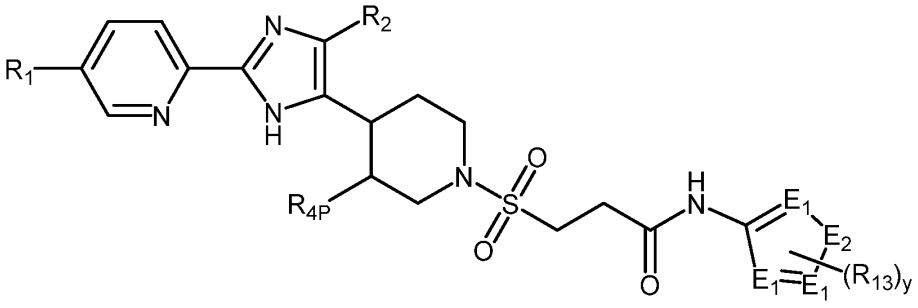

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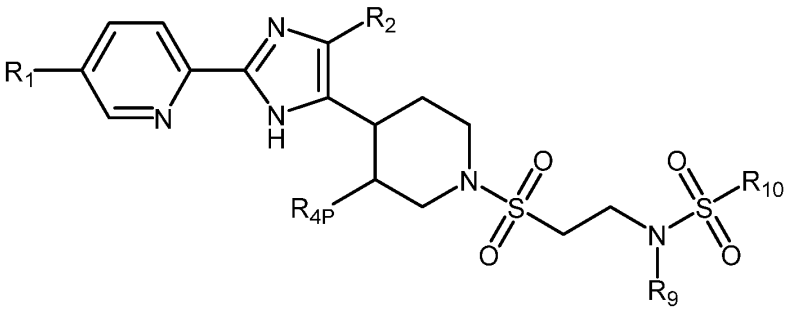

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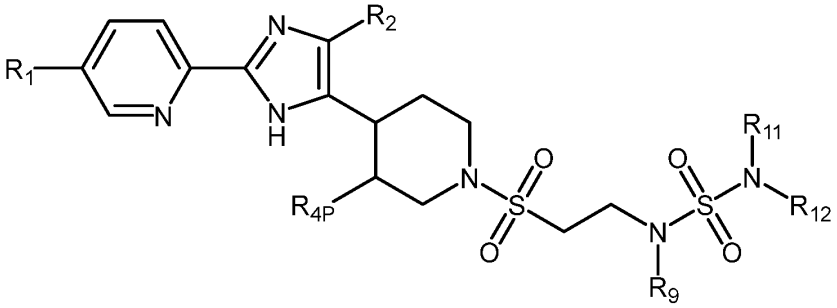


I-K8

wherein:

y is 0, 1, or 2 where valency permits;

each instance of E_1 is independently selected from -CH- and -N-;

E_2 is selected from -NH-, -O-, and -S-; and

E_3 is selected from $-CH_2-$, -NH-, and -O-;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

12. The compound of formula I according to any one of claims 1 to 11, wherein

R_1 is selected from halogen and C_1-C_4 alkyl;

R_2 is selected from halogen and C_1-C_4 alkyl; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

13. The compound of formula I according to any one of claims 1 to 12, wherein

R_1 is fluoro;

R_2 is chloro; and

n is 1;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

14. The compound of formula I according to any one of claims 1 to 6, wherein

R_4 is selected from halogen and C_1-C_4 alkyl;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

15. The compound of formula I according to any one of claims 1 to 4, 7, and 9-13, wherein

R_{4P} is selected from hydrogen and C_1-C_4 alkyl;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

16. The compound of formula I according to any one of claims 1 to 15, wherein

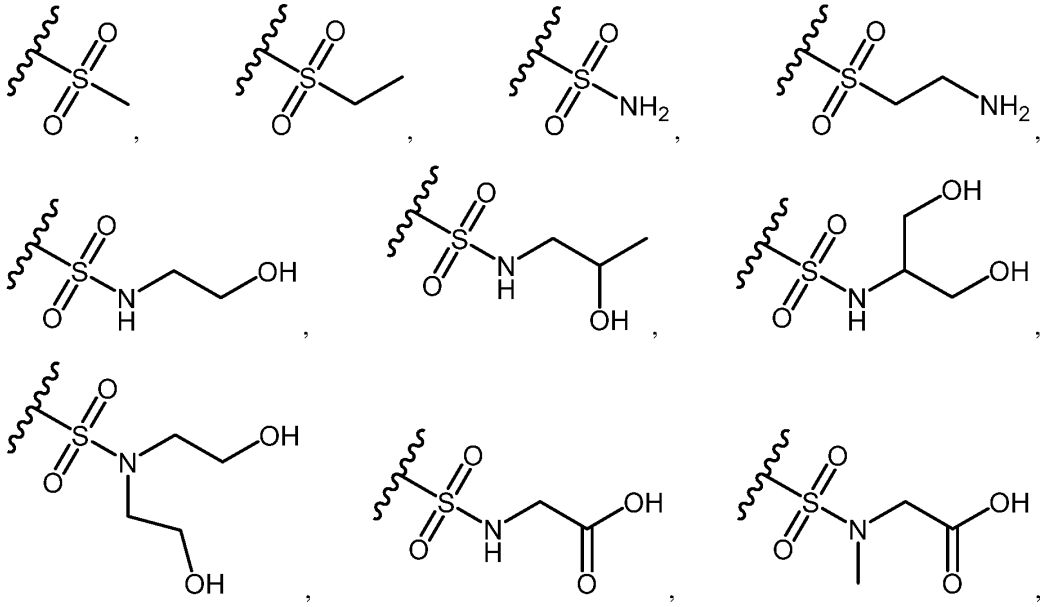
R_5 is selected from $-C(=O)R_6$, $-C(=O)OR_7$, $-C(=O)NR_7R_8$, $-S(=O)R_6$, $-S(=O)_2R_6$, $-S(=O)_2NR_7R_8$, and $-S(=O)(=NR_9)R_6$;

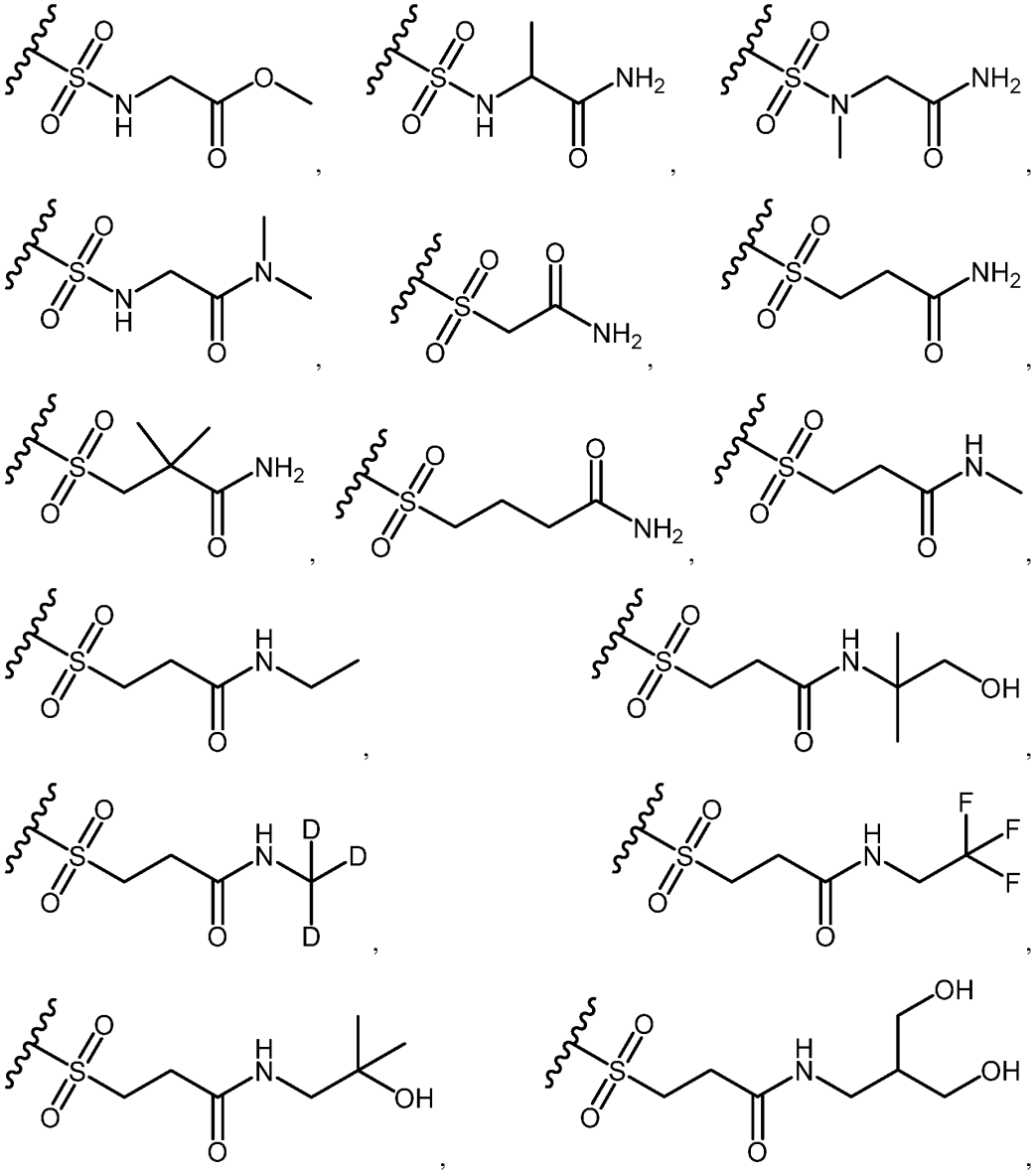
or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

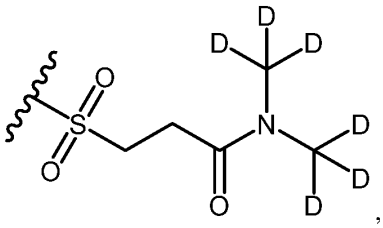
17. The compound of formula I according to claim 16, wherein R_5 is $-S(=O)_2R_6$;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

18. The compound of formula I according to claim 16, wherein R_5 is selected from



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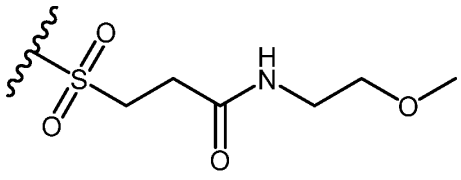
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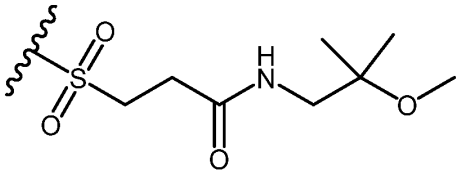
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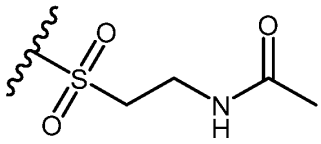
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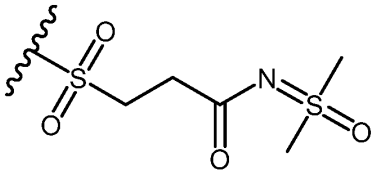
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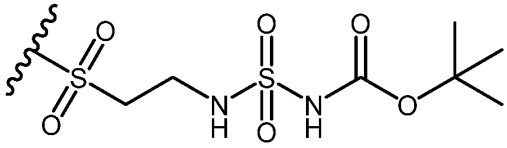
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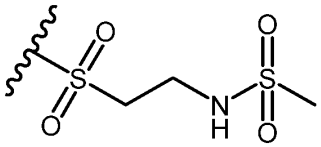
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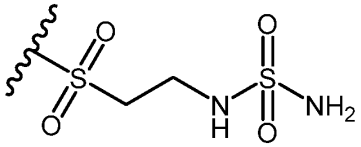
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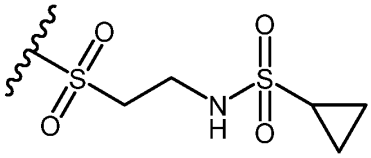
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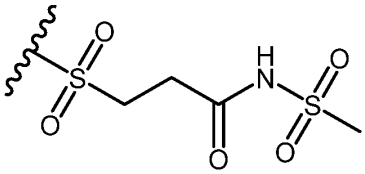
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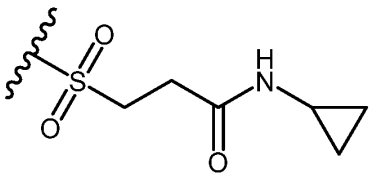
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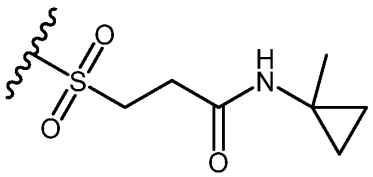
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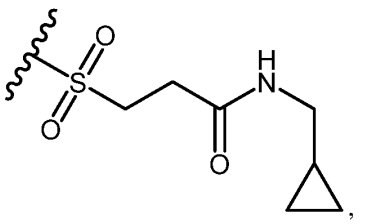
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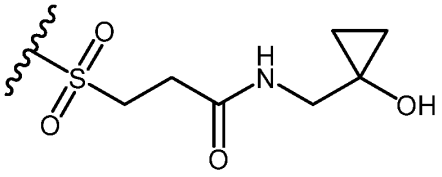
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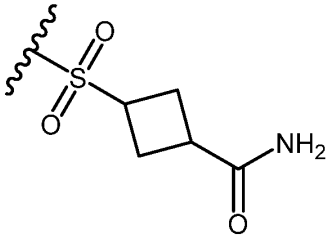
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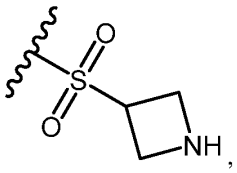
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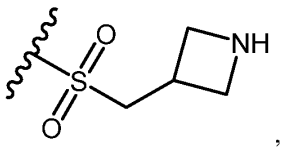
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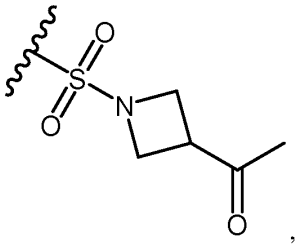
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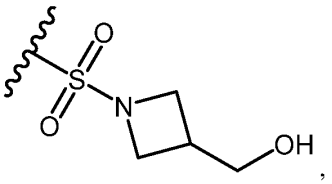
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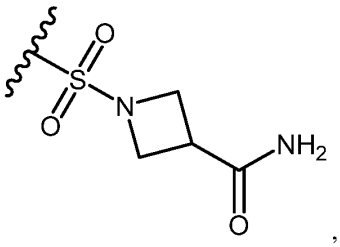
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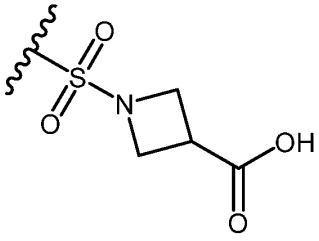
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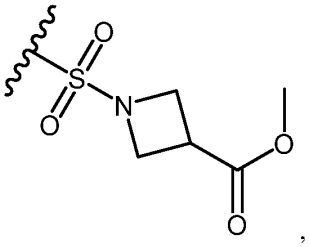
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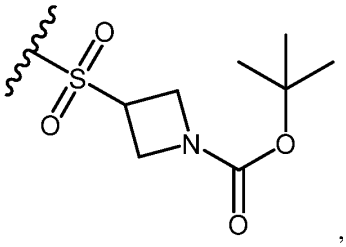
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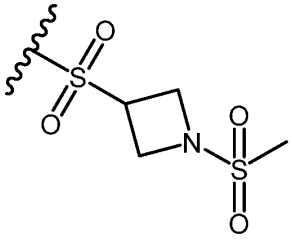
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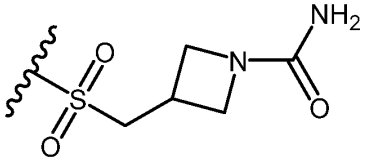
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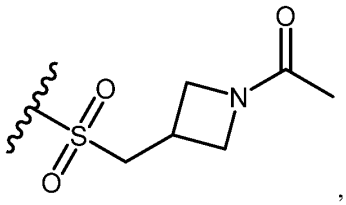
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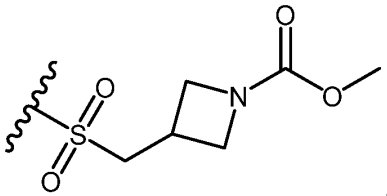
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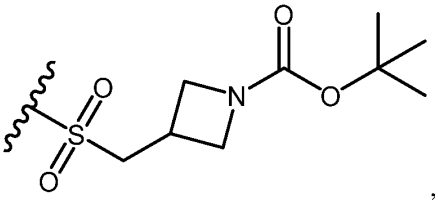
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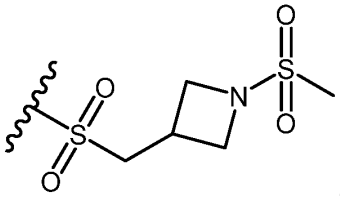
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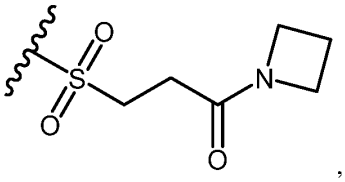
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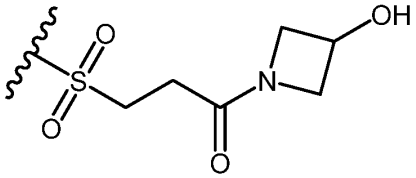
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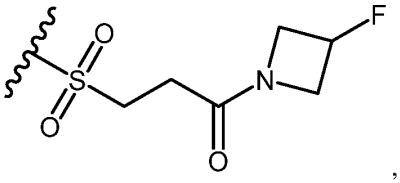
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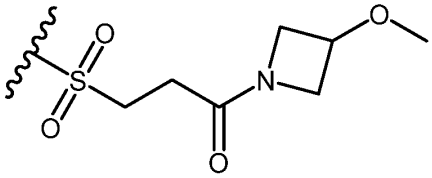
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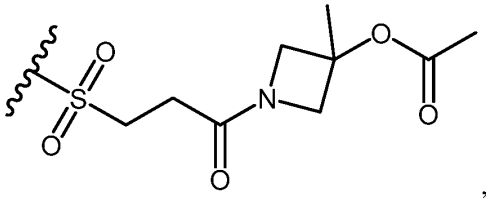
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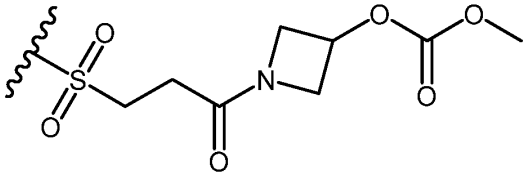
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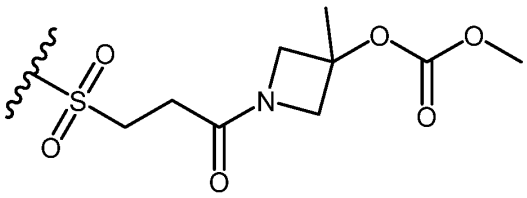
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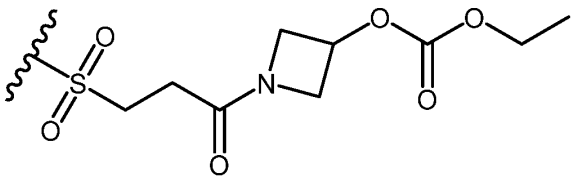
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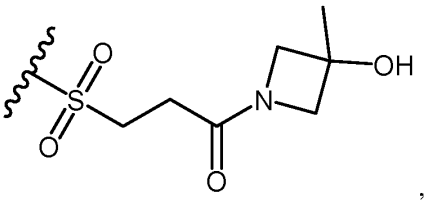
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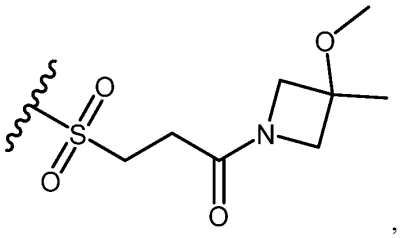
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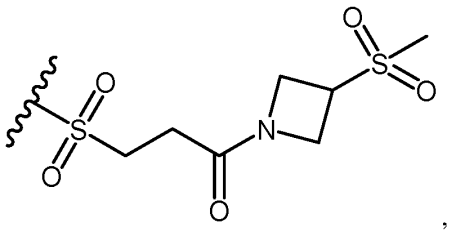
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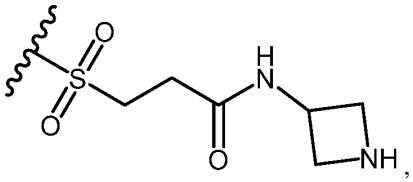
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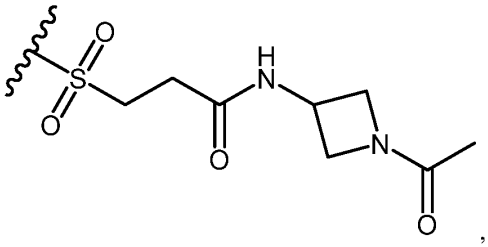
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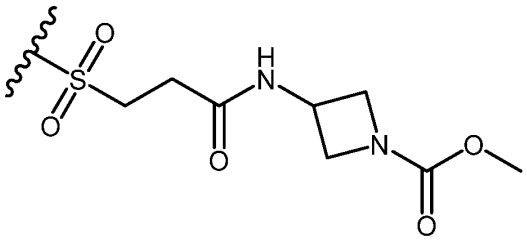
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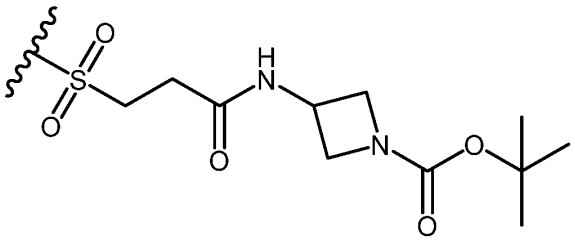
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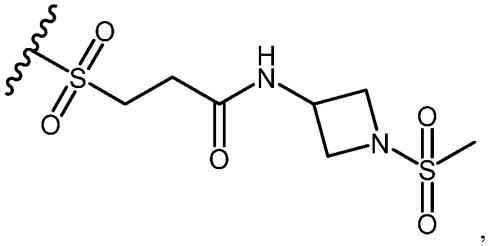
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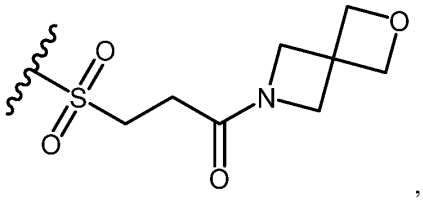
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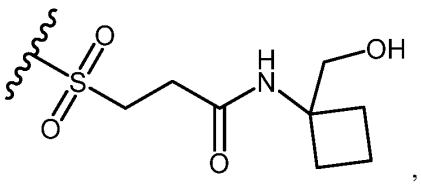
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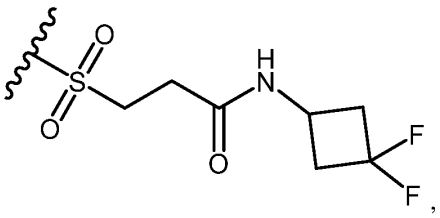
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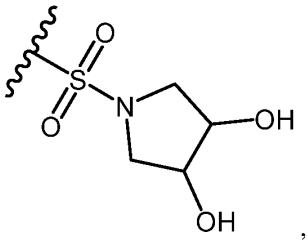
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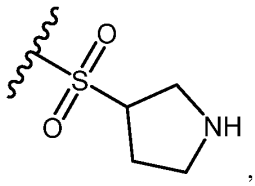
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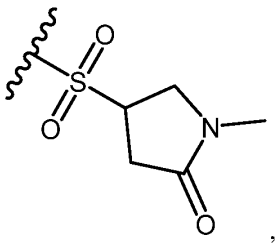
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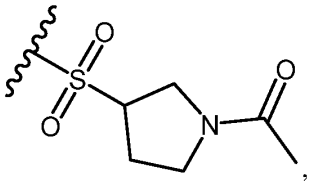
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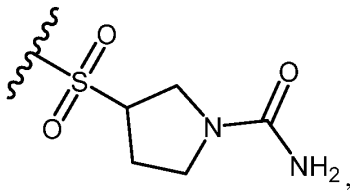
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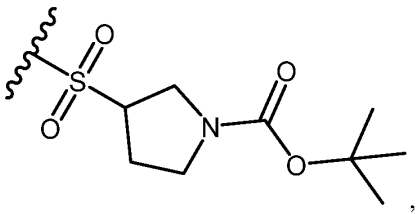
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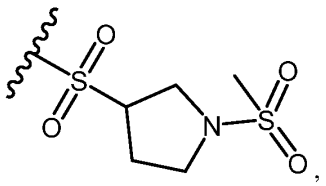
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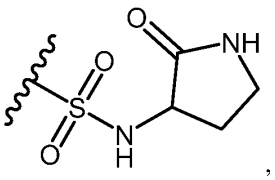
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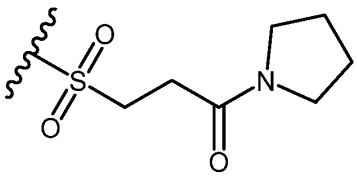
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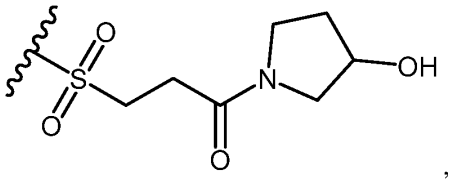
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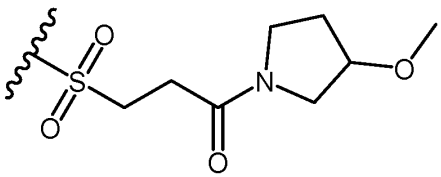
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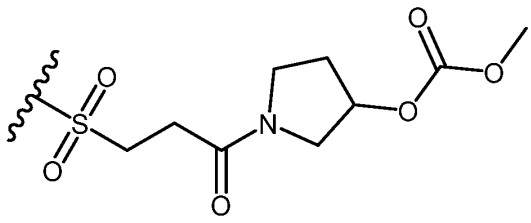
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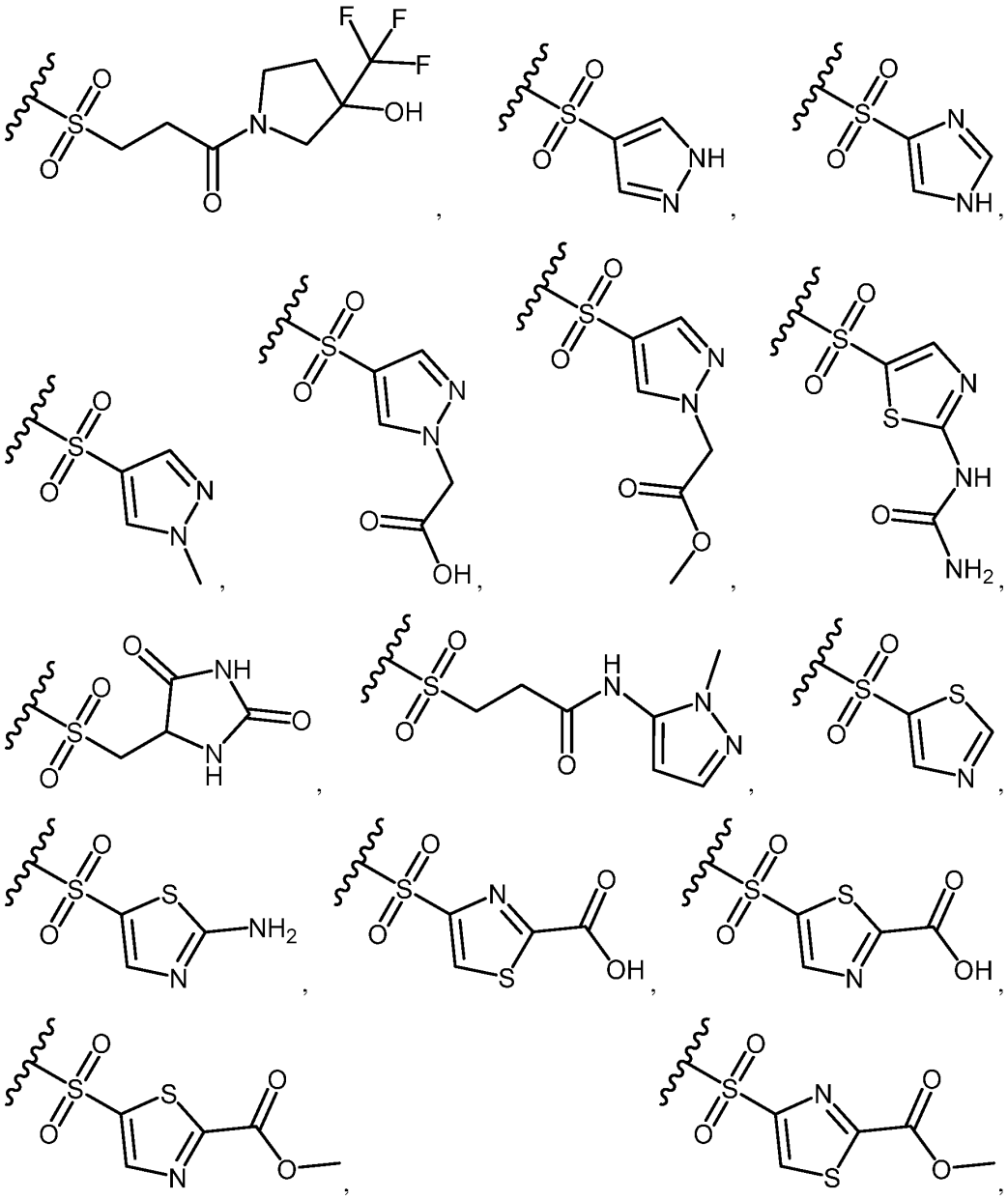
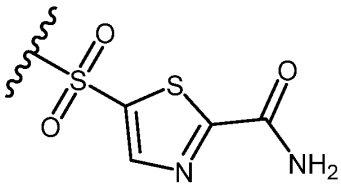
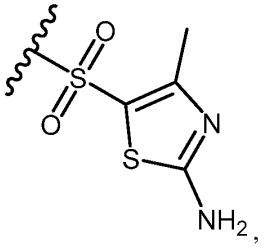
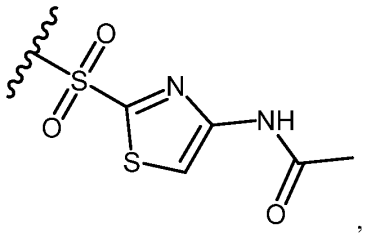
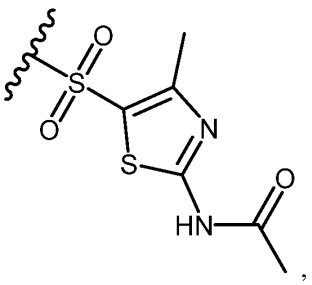
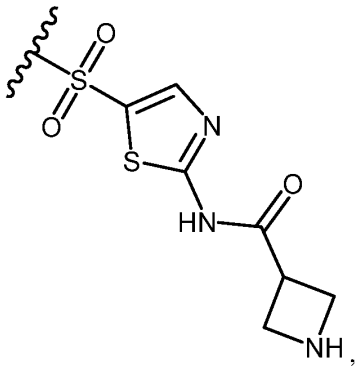
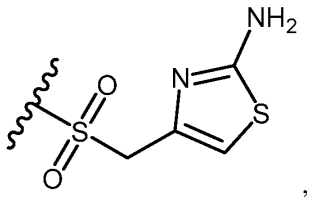
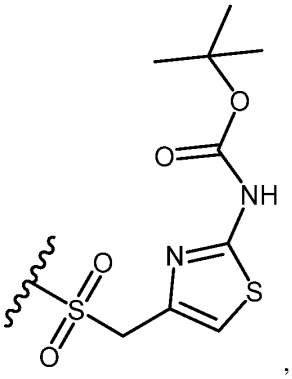
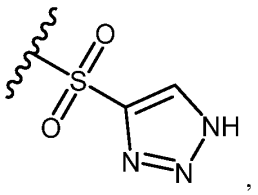
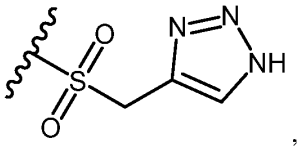
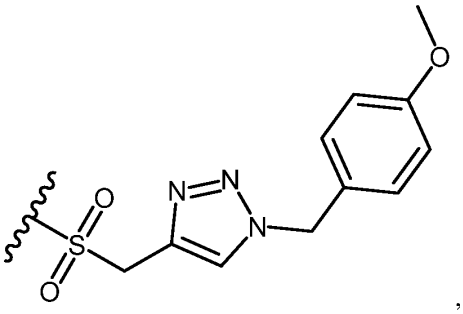
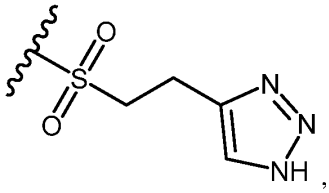
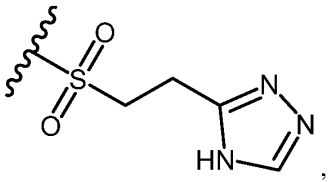


 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,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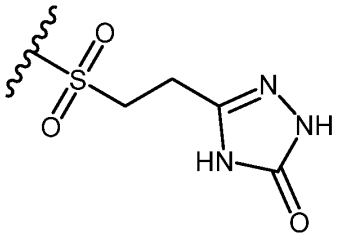
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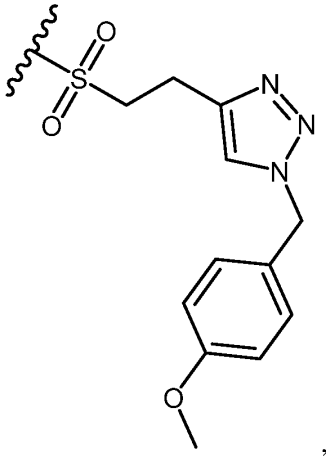
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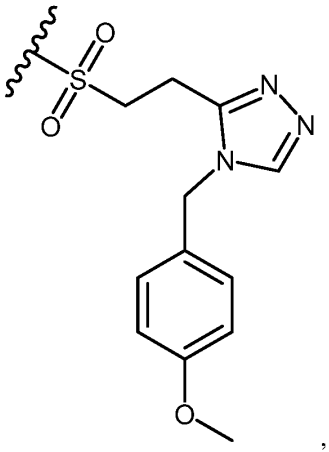
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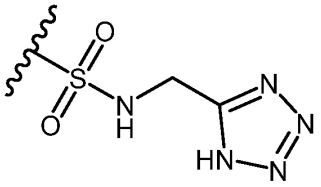
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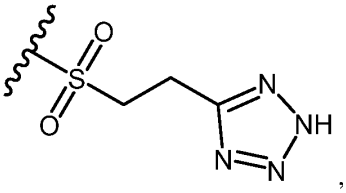
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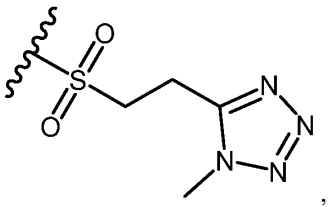
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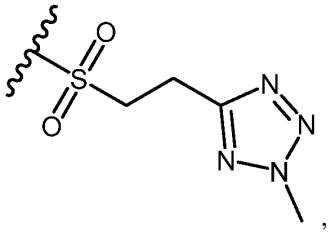
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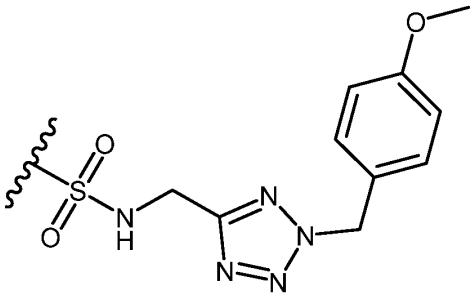
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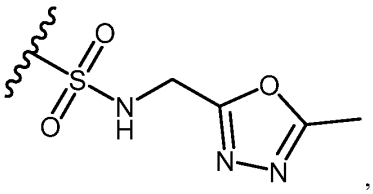
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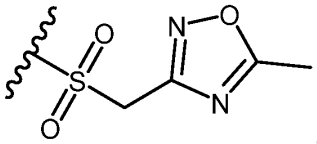
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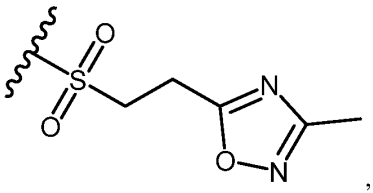
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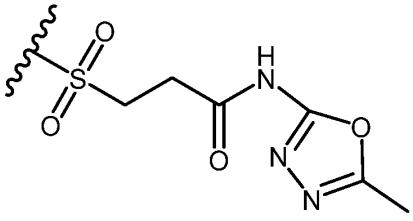
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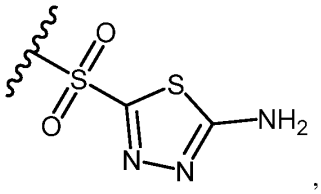
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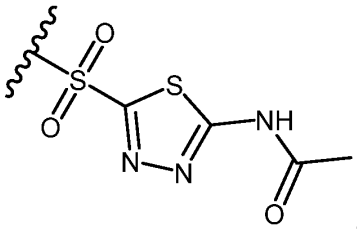
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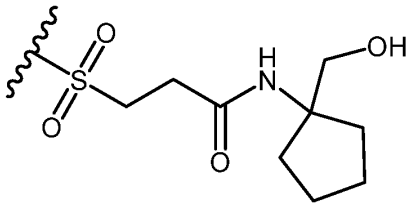
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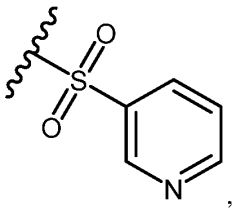
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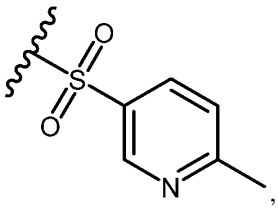
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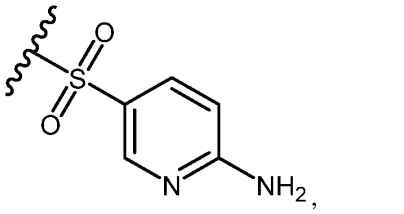
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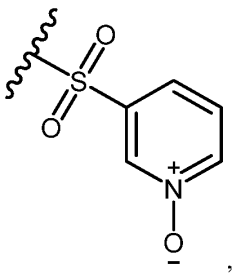
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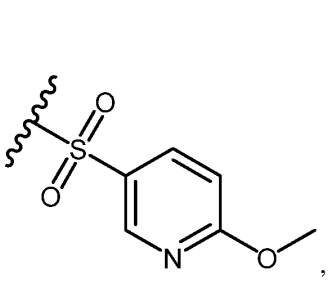
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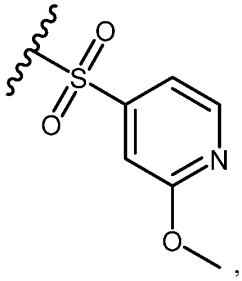
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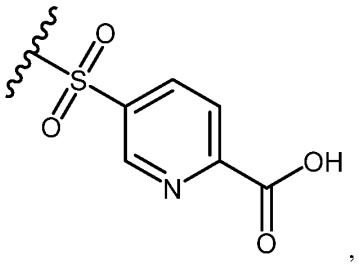
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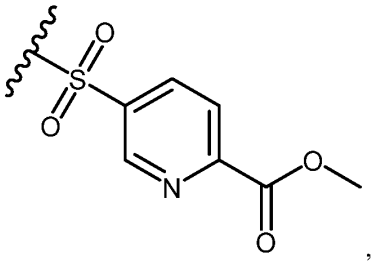
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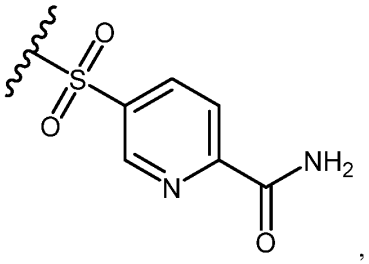
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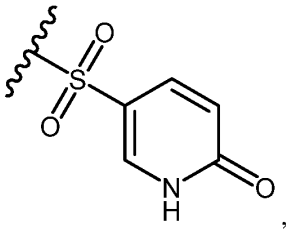
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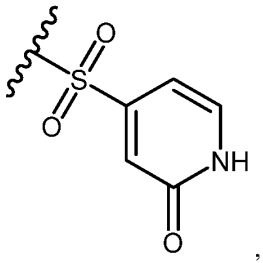
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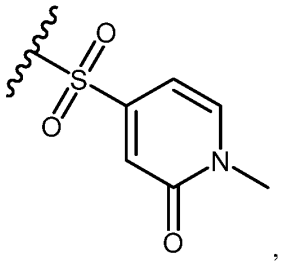
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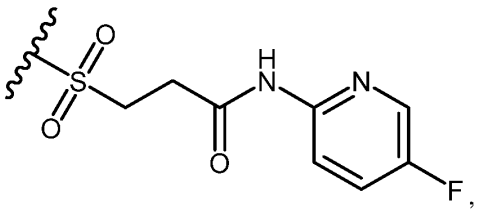
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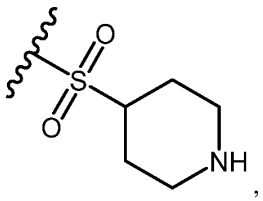
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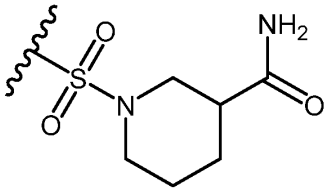
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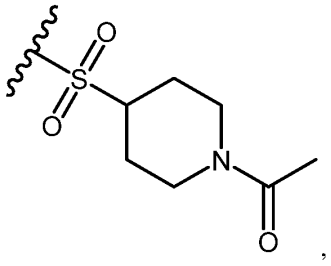
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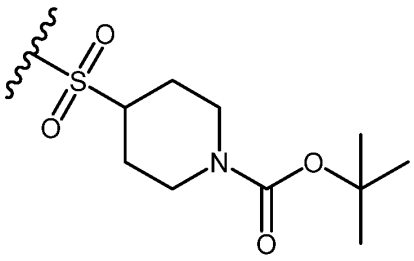
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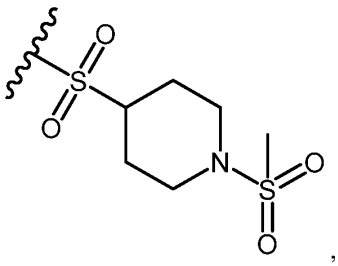
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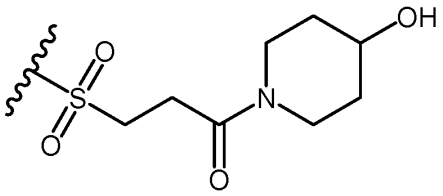
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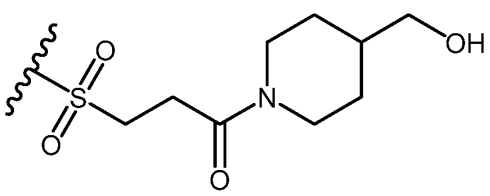
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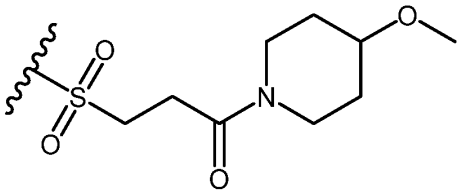
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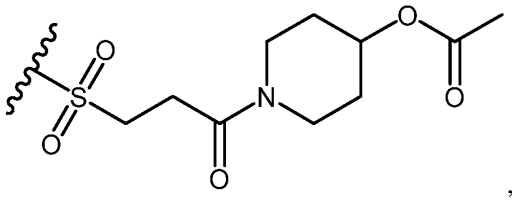
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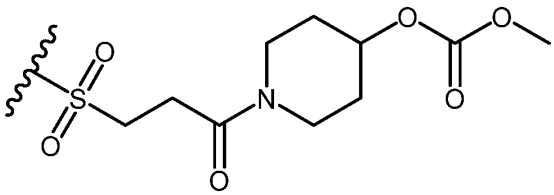
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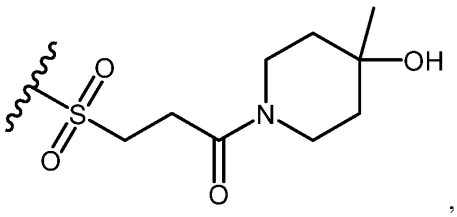
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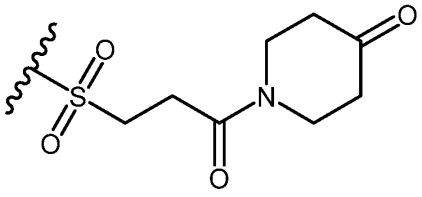
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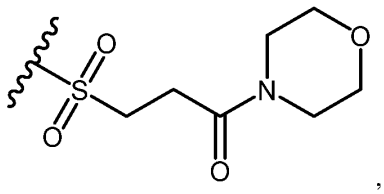
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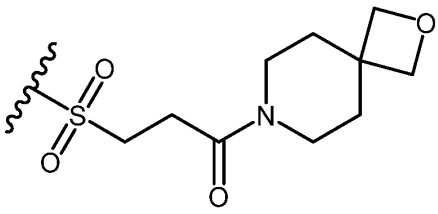
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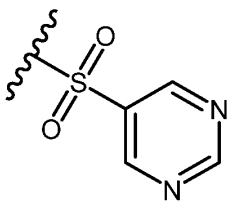
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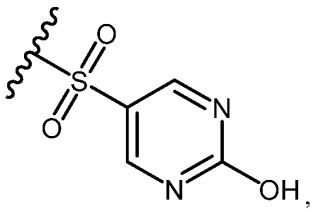
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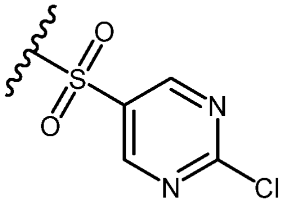
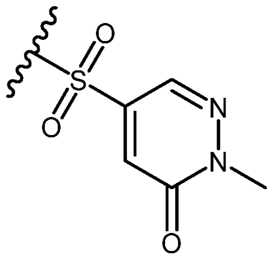
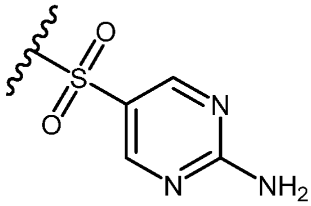
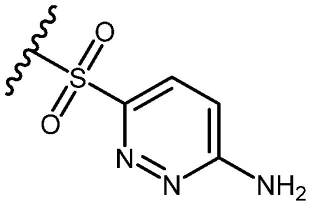
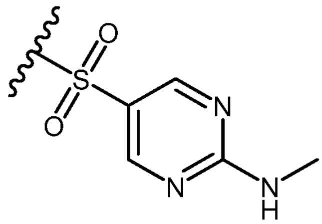
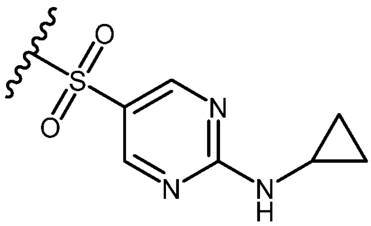
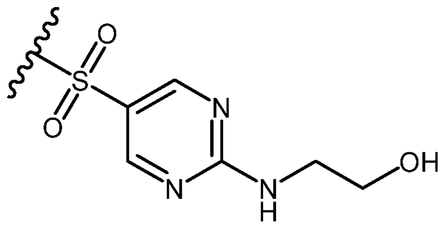
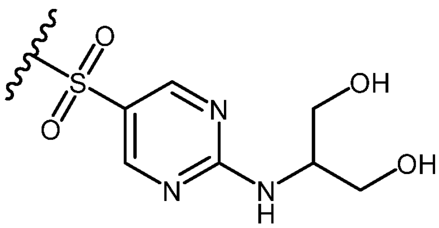
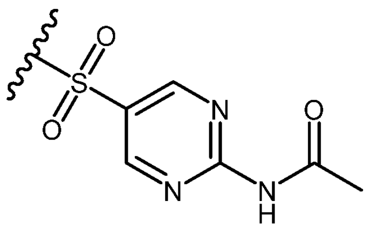
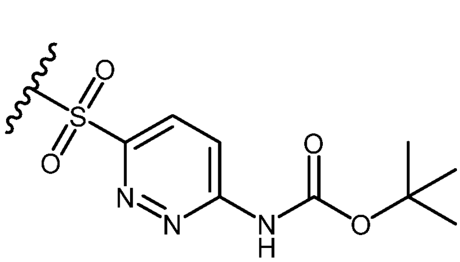
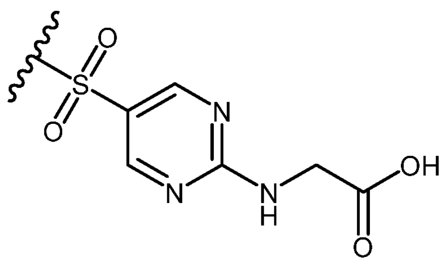
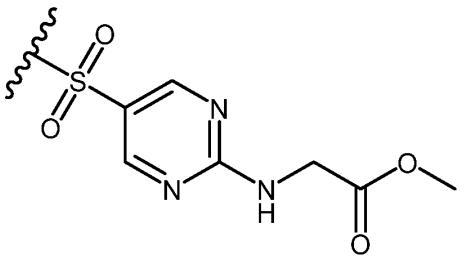
 ,
 ,
 ,

 ,
 ,

 ,
 ,

 ,
 ,

 ,
 ,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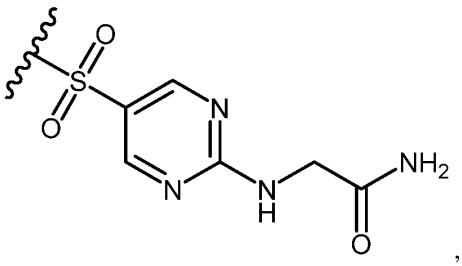
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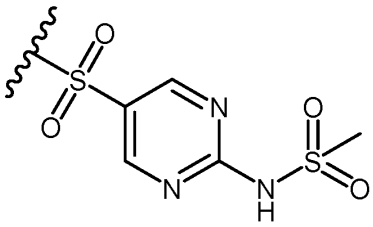
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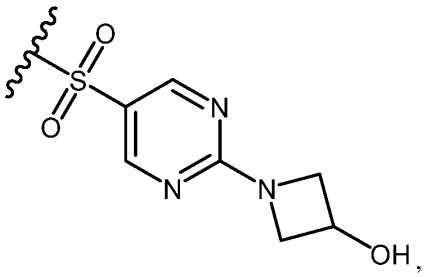
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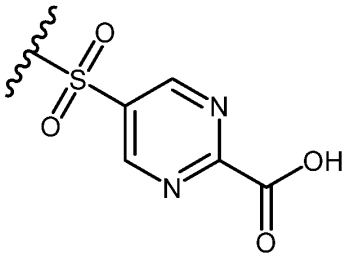
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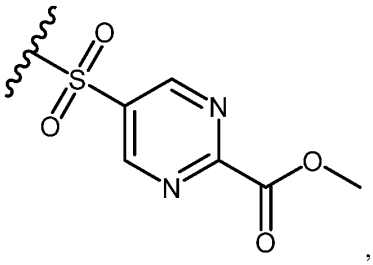
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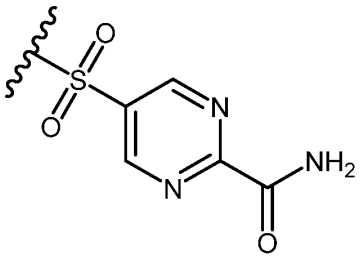
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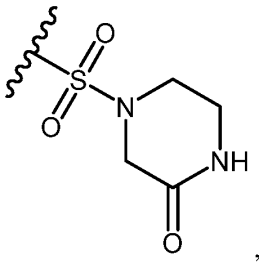
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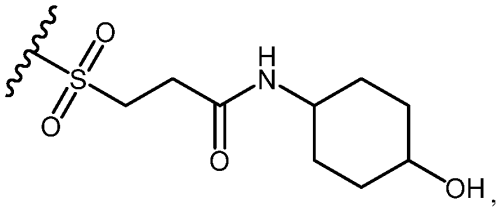
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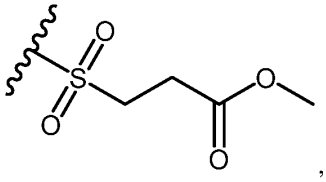
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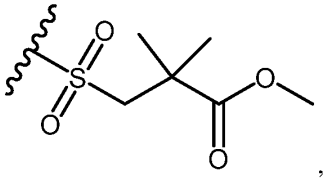
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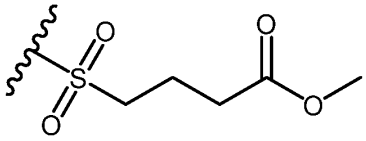
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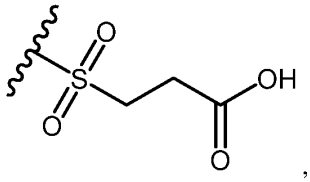
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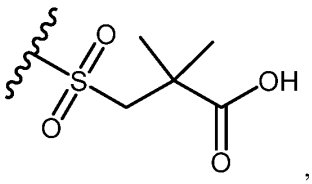
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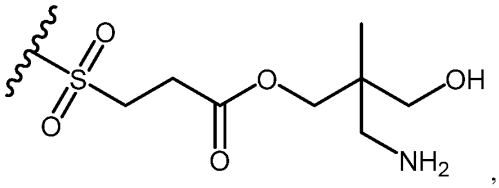
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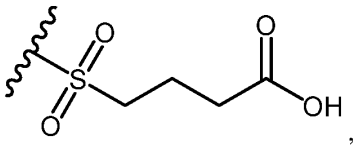
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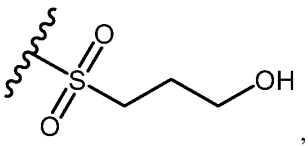
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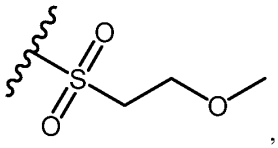
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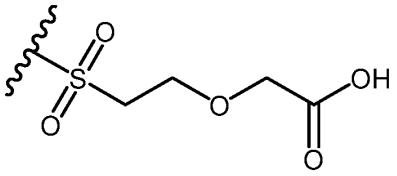
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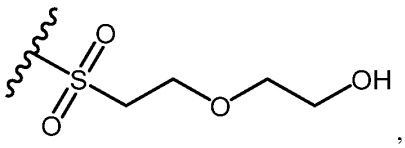
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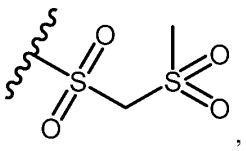
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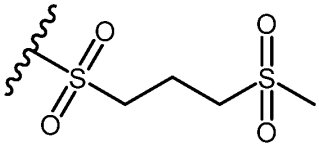
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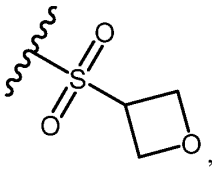
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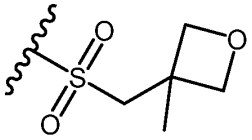
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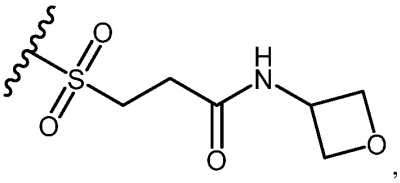
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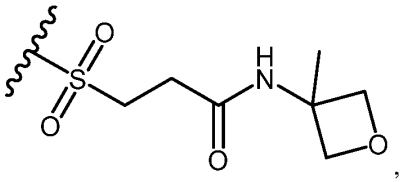
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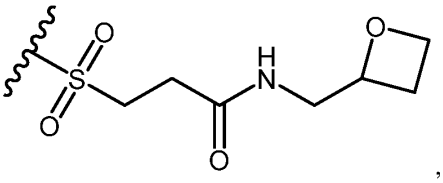
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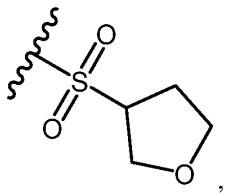
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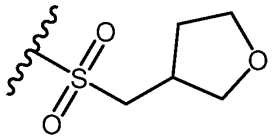
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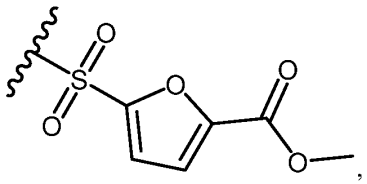
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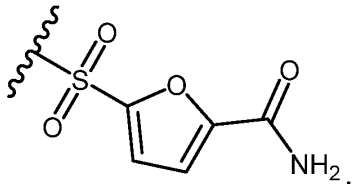
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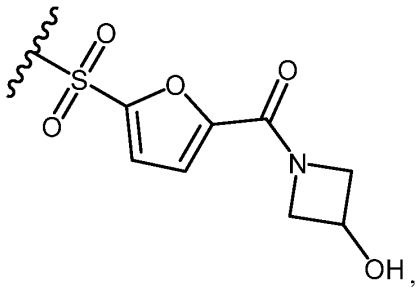
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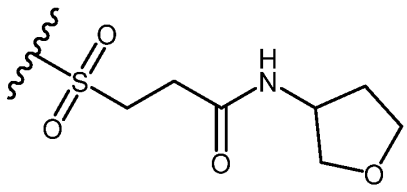
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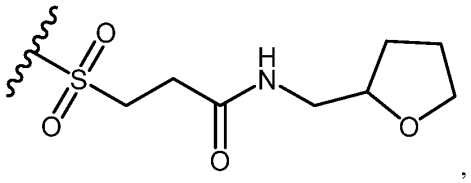
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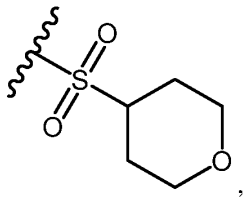
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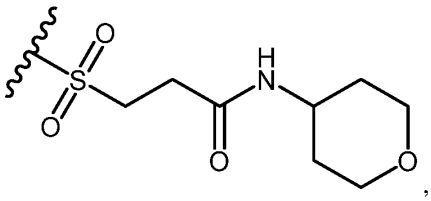
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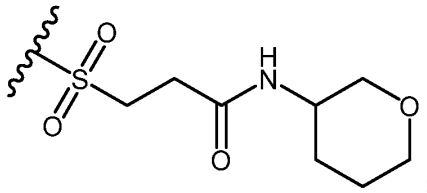
;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

19. A compound selected from:

Tert-butyl 4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]piperidine-1-carboxylate;

1-[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-1-piperidyl]ethenone;

2-[4-Chloro-5-(1-methylsulfonyl-4-piperidyl)-1H-imidazol-2-yl]-5-fluoro-pyridine;

(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide;

(3S,4S)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide;

(3R*,4S*/3S*,4R*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide;

4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-4-methylpiperidine-1-sulfonamide;

(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-N-(2-hydroxyethyl)-3-methylpiperidine-1-sulfonamide;

(3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-carboxamide;

2-(4-Chloro-5-((3R,4R)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine;

1-((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)ethan-1-one;

(3S*,4S*)-4-(4-Ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide;

(3R*,4R*)-4-(4-Ethyl-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidine-1-sulfonamide;

Methyl (((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycinate;

(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)glycine;

2-(4-Chloro-5-((3S,4S)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine;

2-(4-Chloro-5-((3R*,4S*/3S*,4R*)-3-methyl-1-(methylsulfonyl)piperidin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine;

1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxamide;

(S*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine;

(R*)-2-(4-Chloro-5-(3-methyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-2-yl)-5-fluoropyridine;

(S*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide;

(R*)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-sulfonamide;

2-(5-((3R,4R)-1-((1H-Pyrazol-4-yl)sulfonyl)-3-methylpiperidin-4-yl)-4-chloro-1H-imidazol-2-yl)-5-fluoropyridine;

Methyl 1-(((3R,4R)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylate;

1-(((3R,4R)-4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylpiperidin-1-yl)sulfonyl)azetidine-3-carboxylic acid;

2-(4-Bromo-5-(2,3-difluorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine;

2-(4-Bromo-5-(2-chlorophenyl)-1H-imidazol-2-yl)-5-fluoropyridine;

2-[4-Chloro-5-(2-chloro-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-(2-chloro-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-(2-chloro-4-(methylsulfonimidoyl)phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine;

Methyl 3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoate;

3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzoic acid;

3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzenesulfonamide;

2-[[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylamino]acetic acid;

3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-(2-hydroxyethyl)benzenesulfonamide;

2-[5-(2-Chloro-4-methylsulfonyl-phenyl)-4-methyl-1H-imidazol-2-yl]-5-fluoro-pyridine;

Methyl 1-((3-chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxylate;

1-((3-Chloro-4-(4-chloro-2-(5-fluoro-pyridin-2-yl)-1H-imidazol-5-yl)-phenyl) sulfonyl)azetidine-3-carboxylic acid;

1-((3-Chloro-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)phenyl)sulfonyl)azetidine-3-carboxamide;

Methyl 2-chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoate;

2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzoic acid;

4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-2,3-dihydro-1,2-benzothiazole 1,1-dioxide;

3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-2-methylbenzenesulfonamide;

2-Chloro-3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)benzamide;

2-(4-Chloro-5-(2-fluoro-6-methylphenyl)-1H-imidazol-2-yl)-5-fluoropyridine;

Methyl 3-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoate;

3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzoic acid;

3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzamide;

2-(4-Chloro-5-(2-fluoro-6-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine;

2-[4-Chloro-5-(2-fluoro-6-methyl-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine;

3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropan-1-ol;

3-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-4-fluoro-2-methylbenzenesulfonamide;

3-[3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]phenyl]sulfonylpropanamide;

4-(4-Chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoic acid;

Methyl 4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methylbenzoate;

4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide;

N-(2-Amino-2-oxo-ethyl)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-benzamide;

2-(4-Chloro-5-(2-methyl-4-(methylthio)phenyl)-1H-imidazol-2-yl)-5-fluoropyridine;

N-(2-Amino-2-oxo-ethyl)-3-chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide;

3-Chloro-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]benzamide;

2-[4-Chloro-5-(2-methyl-4-methylsulfonyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-(2-methyl-4-methylsulfinyl-phenyl)-1H-imidazol-2-yl]-5-fluoro-pyridine;

Tert-butyl (S*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate;

Tert-butyl (R*)-4-(4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate;

(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N,3-trimethyl-piperidine-1-carboxamide;

Methyl (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate;

[2-(Dimethylamino)-2-oxo-ethyl] (3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-piperidine-1-carboxylate;

Methyl 3-[[(3S*)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-pyridylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-1-oxido-pyridin-1-ium;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-oxidopyridin-1-ium-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[5-[(3R,4R)-1-(Azetidin-3-ylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine;

1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidin-1-yl]ethanone;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxamide;

Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoate;

Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoate;

Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate;

2-[5-[(3R,4R)-1-(Azetidin-3-ylmethylsulfonyl)-3-methyl-4-piperidyl]-4-chloro-1H-imidazol-2-yl]-5-fluoro-pyridine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methyl-pyridine;

2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]ethanol;

4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanoic acid;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanoic acid;

2-[4-Chloro-5-[(3R,4R)-1-[(6-methoxy-3-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]butanamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2,2-dimethyl-propanamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxamide;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one;

2-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethoxy]acetic acid;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydrofuran-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(oxetan-3-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-1-[(2-methoxy-4-pyridyl)sulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1H-pyridin-2-one;

Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoic acid;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 1);

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxylic acid (isomer 2);

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-propanamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 1);

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]cyclobutanecarboxamide (isomer 2);

(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,N-bis(2-hydroxyethyl)-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide;

(3R,4R)-1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]pyrrolidine-3,4-diol;

(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(1H-tetrazol-5-ylmethyl)-3,6-dihydro-2H-pyridine-1-sulfonamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propyl acetate;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-ol;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methylsulfonyl-propanamide;

(5R)-5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]imidazolidine-2,4-dione;

(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[2-hydroxy-1-(hydroxymethyl)ethyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide;

4-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperazin-2-one;

(2S)-2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonylamino]propenamide;

1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-ol;

(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-(2-oxopyrrolidin-3-yl)-3,6-dihydro-2H-pyridine-1-sulfonamide;

2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetic;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-methoxy-pyrimidine acid;

Methyl 2-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetate;

2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl-methyl-amino]acetamide;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine;

4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyridin-2-one;

2-[4-Chloro-5-[(3R,4R)-1-[2-[2-[(4-methoxyphenyl)methyl]tetrazol-5-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrazol-1-yl]acetic acid;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-ol;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2H-tetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

Methyl 3-[[4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propanoate;

3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]propenamide;

3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-1-(3-hydroxyazetidin-1-yl)propan-1-one;

3-[[4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]-N-cyclopropyl-propanamide;

(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-N-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]piperidine-1-sulfonamide;

[1-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]azetidin-3-yl]methanol;

N-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonyl]piperidine-3-carboxamide;

(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N-[(2S)-2-hydroxypropyl]-3-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide;

2-[[(3R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-3,6-dihydro-2H-pyridin-1-yl]sulfonylamino]-N,N-dimethyl-acetamide;

2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylamino]-N,N-dimethyl-acetamide;

Tert-butyl (3S,4S)-4-[4-chloro-2-(5-fluoropyridin-2-yl)-1H-imidazol-5-yl]-3-methylpiperidine-1-carboxylate;

4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-5-methyl-3,6-dihydro-2H-pyridine-1-sulfonamide;

2-Chloro-5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylpyrazol-4-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-N,3-dimethyl-piperidine-1-carboxamide;

1-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]azetidin-3-ol;

2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]ethanol;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridin-2-amine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-pyrimidin-2-amine;

4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-methyl-pyrrolidin-2-one;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-methyl-pyrimidin-2-amine;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N,N-bis(trideuteriomethyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-2-methyl-propyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-cyclopropyl-propanamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-hydroxypyrrolidin-1-yl]propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-hydroxypyrrolidin-1-yl]propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxyazetidin-1-yl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-hydroxy-3-methyl-azetidin-1-yl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-1-piperidyl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxyethyl)propenamide;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(2-methyltetrazol-5-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate;

2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]acetamide;

Tert-butyl N-[4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-yl]carbamate;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonylazetidin-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylazetidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]thiazol-2-amine;

1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidin-1-yl]ethenone;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(trideuteriomethyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-yl)propenamide;

2-[4-Chloro-5-[(3R,4R)-1-(1H-imidazol-4-ylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-ethyl-propanamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-hydroxy-4-methyl-1-piperidyl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-morpholino-propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(cyclopropylmethyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-pyrrolidin-1-yl-propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2,2,2-trifluoroethyl)propenamide;

Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]azetidine-1-carboxylate;

Methyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]azetidine-1-carboxylate;

N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]acetamide;

N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]methanesulfonamide;

Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxylate;

5-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-3-methyl-1,2,4-oxadiazole;

Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]carbamate;

2-[4-Chloro-5-[(3R,4R)-1-[2-[1-[(4-methoxyphenyl)methyl]triazol-4-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethanamine;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(1-hydroxycyclopropyl)methyl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(oxetan-3-ylmethyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-7-azaspiro[3.5]nonan-7-yl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(4-methoxy-1-piperidyl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-tetrahydropyran-4-yl-propanamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3S)-tetrahydropyran-3-yl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(2-oxa-6-azaspiro[3.3]heptan-6-yl)propan-1-one;

2-[4-Chloro-5-[(3R,4R)-1-(2-methoxyethylsulfonyl)-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-tetrahydropyran-4-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(tetrahydrofuran-3-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]acetamide;

N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-yl]acetamide;

Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylate;

Tert-butyl 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxylate;

Tert-butyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]piperidine-1-carboxylate;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(1H-triazol-4-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(4-piperidylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-pyrrolidin-3-ylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

Tert-butyl N-[2-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethylsulfamoyl]carbamate;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-amine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-4-methyl-thiazol-2-amine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxylic acid;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonylmethyl]-5-methyl-1,2,4-oxadiazole;

1-[4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-piperidyl]ethenone;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(1-methylsulfonyl-4-piperidyl)sulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(sulfamoylamino)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1-methylsulfonylpyrrolidin-3-yl)sulfonyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidin-1-yl]ethenone;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridine-2-carboxamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrrolidine-1-carboxamide;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]furan-2-carboxamide;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(methylsulfonylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(3-methylsulfonylpropylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-2-furyl]-(3-hydroxyazetidin-1-yl)methanone;

3-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]-1,4-dihydro-1,2,4-triazol-5-one;

Tert-butyl N-[6-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-yl]carbamate;

6-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyridazin-3-amine;

Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylate;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxylic acid;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidine-2-carboxamide;

[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] methyl carbonate;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methoxy-3-methyl-azetidin-1-yl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3S)-3-methoxypyrrolidin-1-yl]propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[dimethyl(oxo)-¿6-sulfanylidene]propenamide;

[2-(Aminomethyl)-3-hydroxy-2-methyl-propyl] 3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoate;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3-methyloxetan-3-yl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylcyclopropyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methoxy-2-methyl-propyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[(3R)-3-methoxypyrrolidin-1-yl]propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-oxetan-2-yl]methyl]propenamide;

2-[4-Chloro-5-[(3R,4R)-1-[2-[4-[(4-methoxyphenyl)methyl]-1,2,4-triazol-3-yl]ethylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

N-[2-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]ethyl]cyclopropanesulfonamide;

[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]urea;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[2-(4H-1,2,4-triazol-3-yl)ethylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-[(3-methyloxetan-3-yl)methylsulfonyl]-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

Tert-butyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino]azetidine-1-carboxylate;

[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] methyl carbonate;

[(3R)-1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]pyrrolidin-3-yl] methyl carbonate;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2S)-tetrahydrofuran-2-yl]methyl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[[(2R)-tetrahydrofuran-2-yl]methyl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[(3R)-tetrahydrofuran-3-yl]propenamide;

1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]piperidin-4-one;

1-(Azetidin-1-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-methylsulfonylazetidin-1-yl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclobutyl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-[1-(hydroxymethyl)cyclopentyl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(4-hydroxycyclohexyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-methyl-1,3,4-oxadiazol-2-yl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(5-fluoro-2-pyridyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-methylpyrazol-3-yl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-[4-(hydroxymethyl)-1-piperidyl]propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(3-fluoroazetidin-1-yl)propan-1-one;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1-(6-oxa-1-azaspiro[3.3]heptan-1-yl)propan-1-one;

[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-4-piperidyl] acetate;

5-[[(3S,4S)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine;

5-[[(3R,4R)-4-[4-Fluoro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-amine;

N-(Azetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanamide;

2-[4-Chloro-5-[(3R,4R)-1-[[1-[(4-methoxyphenyl)methyl]triazol-4-yl]methylsulfonyl]-3-methyl-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

2-[4-Chloro-5-[(3R,4R)-3-methyl-1-(1H-triazol-4-ylmethylsulfonyl)-4-piperidyl]-1H-imidazol-2-yl]-5-fluoro-pyridine;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-3-methoxy-pyridazine;

5-Fluoro-2-[4-fluoro-5-[(3S,4S)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine;

5-Fluoro-2-[4-fluoro-5-[(3R,4R)-3-methyl-1-methylsulfonyl-4-piperidyl]-1H-imidazol-2-yl]pyridine;

N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]acetamide;

Methyl 5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate;

Methyl 4-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylate;

N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]methanesulfonamide;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid;

4-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid;

Methyl 3-[3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoylamino]azetidine-1-carboxylate;

N-(1-Acetylazetidin-3-yl)-3-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(1-methylsulfonylazetidin-3-yl)propenamide;

N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-yl]acetamide;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxylic acid;

2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]propane-1,3-diol;

Methyl 2-[[5-[[(3R,4R)-4-[4-chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetate;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-1,3,4-thiadiazol-2-amine;

N-[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazol-2-yl]azetidine-3-carboxamide;

2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetic acid;

5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]thiazole-2-carboxamide;

2-[[5-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]pyrimidin-2-yl]amino]acetamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(2-hydroxy-1,1-dimethyl-ethyl)propenamide;

3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]-N-(3,3-difluorocyclobutyl)propenamide;

[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] acetate;

[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]-3-methyl-azetidin-3-yl] methyl carbonate; and

[1-[3-[[(3R,4R)-4-[4-Chloro-2-(5-fluoro-2-pyridyl)-1H-imidazol-5-yl]-3-methyl-1-piperidyl]sulfonyl]propanoyl]azetidin-3-yl] ethyl carbonate;

or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I according to any one of claims 1 to 19, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

21. A compound of formula I according to any one of claims 1 to 19, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use as a medicament.

22. A compound of formula I according to any one of claims 1 to 19, or an enantiomer, diastereomer, or tautomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease, disorder, or condition selected from an inflammatory disorder, an allergic disorder, skin disorder, a mast cell disorder, a pain disorder, and an itch disorder.