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(54) Titre : PYRIDINONES ANTI-FIBROTIQUES
(54) Title: ANTI-FIBROTIC PYRIDINONES

(57) Abrégé/Abstract:
Disclosed are pyridinone compounds, method for preparing these compounds, and methods for treating fibrotic disorders.

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(54) Title: ANTI-FIBROTIC PYRIDINONES

(57) **Abstract**: Disclosed are pyridinone compounds, method for preparing these compounds, and methods for treating fibrotic disorders.

ANTI-FIBROTIC PYRIDINONES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of priority to U.S. Appl. No. 61/709,075, filed October 2, 2012, U.S. Appl. No. 61/777,499, filed March 12, 2013 and U.S. Appl. No. 61/872,157, filed August 30, 2013, all of which are herely incorporated by references in their entireties.

BACKGROUND

Field

[0002] Pyridinone compounds, method of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases, disorders, or conditions associated with fibrosis are provided.

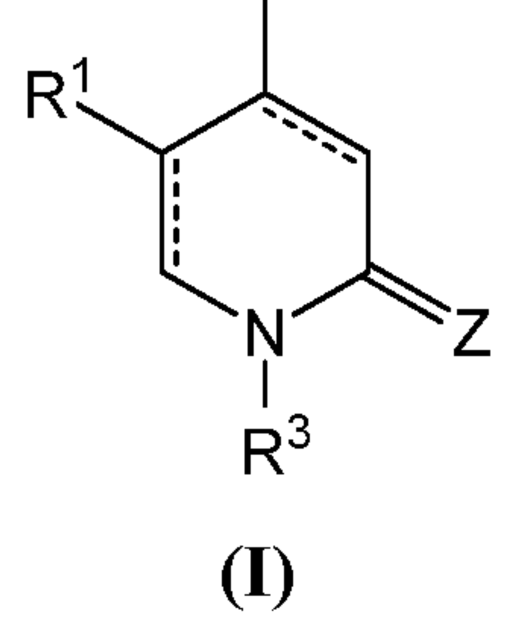
Description

[0003] Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. Examples of fibrosis include, but are not limited to pulmonary fibrosis, liver fibrosis, dermal fibrosis, and renal fibrosis. Pulmonary fibrosis, also called idiopathic pulmonary fibrosis (IPF), interstitial diffuse pulmonary fibrosis, inflammatory pulmonary fibrosis, or fibrosing alveolitis, is a lung disorder and a heterogeneous group of conditions characterized by abnormal formation of fibrous tissue between alveoli caused by alveolitis comprising cellular infiltration into the alveolar septae with resulting fibrosis. The effects of IPF are chronic, progressive, and often fatal.

[0004] There continues to be a need for safe and effective drugs to treat fibrotic conditions such as idiopathic pulmonary fibrosis.

SUMMARY

[0005] Some embodiments of the present application provide a compound having the structure of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of halogen, -CN, -C(O)R^8, -SO_2R^{16}, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

R^2 is selected from the group consisting of halogen, -CN, -OR^5, -SR^5, -NR^6R^7, and -C(O)R^8;

R^3 is selected from the group consisting of hydrogen, -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form a 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^9 is independently selected from the group consisting of hydroxy, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, -CN, $-SO_2R^{16}$, and $-NO_2$;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-O-(CH_2)_n-C_{1-8}$ alkoxy, $-C(O)R^8$, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond, provided that

when R^3 is H, then R^1 is selected from C_{6-10} aryl optionally substituted with one or more R^4, or 5-10 membered heteroaryl optionally substituted with one or more R^4;

when R^2 is -NH-(2-fluoro-4-bromo-phenyl) and R^1 is C(O)OH, then R^3 cannot be -CH_2-phenyl;

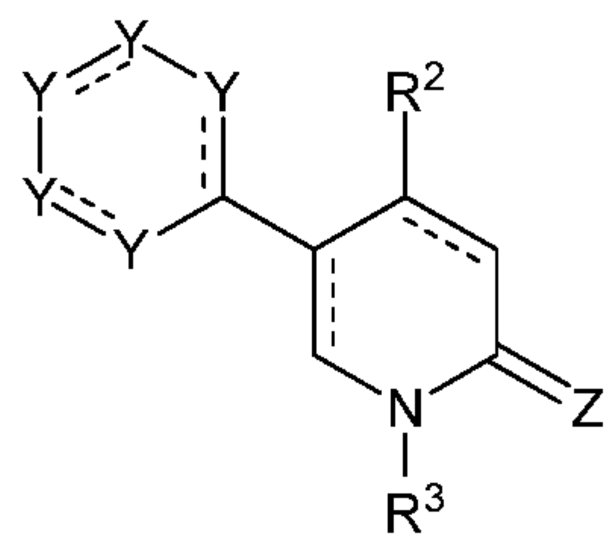
when R^2 is methoxy, R^1 is 4-methoxyphenyl, and Z is O, then R^3 is not -(CH_2)-2-fluro- 4-chloro-phenyl;

when R^3 is a phenyl; R^2 is OR^5 or NR^6R^7; then R^1 is not triazolyl;

when R^3 is 4-methyl phenyl, R^2 is morpholinyl, and Z is O; then R^1 is not methyl; and

when R^3 is 4-methyl phenyl, R^2 is -$N(CH_3)_2$, Z is O; then R^1 is not methyl.

[0006] Some embodiments of the present application provide a compound having the structure of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^2 is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl;

R^3 is selected from the group consisting of hydrogen, -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

Y is selected from N and CR^4;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two adjacent R^4 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl, optionally substituted C_{3-7} carbocyclyl, and optionally substituted 3-7 membered heterocyclyl;

each R^9 is independently selected from the group consisting of hydroxy, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, -CN, $-SO_2R^{16}$, and $–NO_2$;

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and $-(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

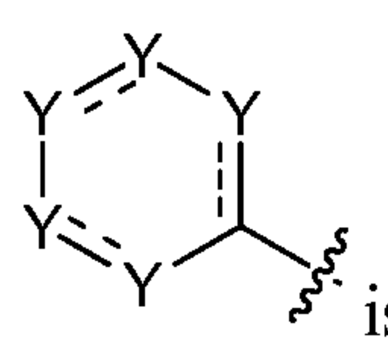
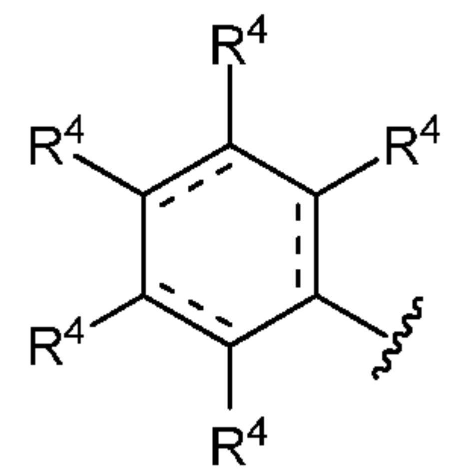
each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

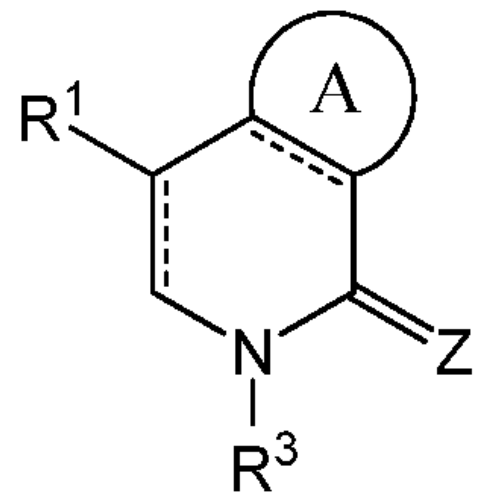
Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

[0007] In some embodiments, if R^3 is hydrogen, then  is , and the two adjacent R^4 together with the carbon atoms to which they are attached form a fused ring selected from optionally substituted 5 or 6 membered heteroaryl or optionally substituted 5 or 6 membered heterocyclyl.

[0008] Some embodiments of the present application provide a compound having the structure of formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of halogen, -CN, $-C(O)R^8$, $-SO_2R^{16}$, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

R^3 is selected from the group consisting of hydrogen, -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

ring A is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^9 is independently selected from the group consisting of hydroxy, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -$NR^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, -CN and –NO_2;

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -$NR^{12}R^{13}$, and -OR^5;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -$NR^{12}R^{13}$, and -OR^5;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond, provided that

when R^3 is H, then R^1 is selected from C_{6-10} aryl optionally substituted with one or more R^4, or 5-10 membered heteroaryl optionally substituted with one or more R^4;

when R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then ring A cannot be optionally substituted phenyl;

when ring A is selected from cyclopentenyl, optionally substituted pyrrolyl or optionally substituted dihydropyrrolidinyl, R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then R^1 is not halogen, 3-methoxy phenyl or 3,5-dimethoxy phenyl;

when ring A is pyridyl, R^1 is optionally substituted phenyl, and Z is O; then n in R^3 is zero and R^3 is not halogen substituted phenyl;

when ring A is optionally substituted pyrimidyl, R^3 is phenyl or benzyl, and Z is O; then R^1 is not methyl or benzyl;

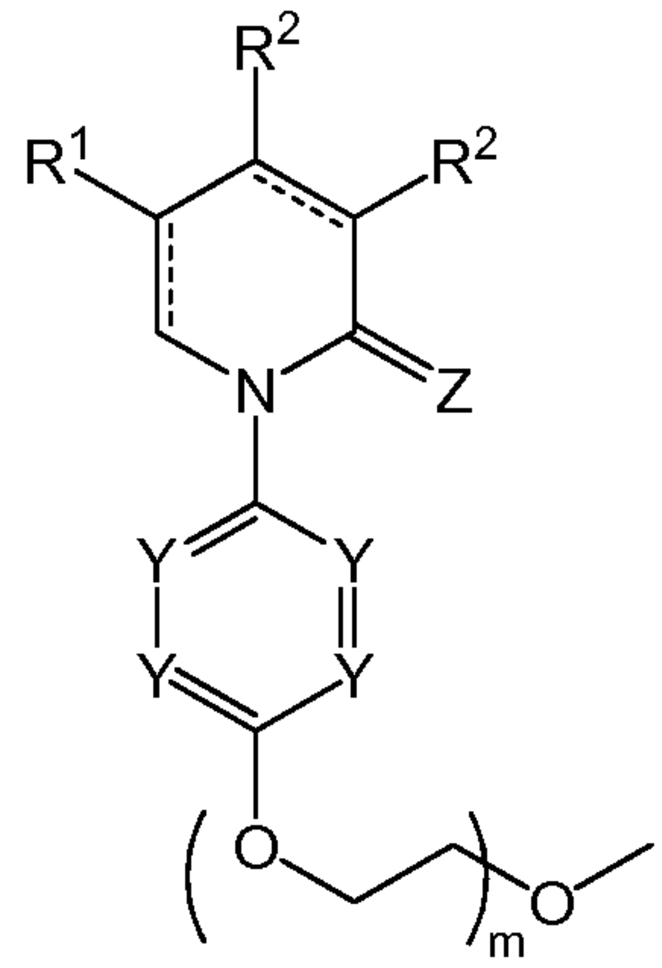
when ring A is optionally substituted furanyl, R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then R^1 is not fluoro;

when ring A is optionally substituted pyrrolyl, R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then R^1 is not methyl;

when ring A is tetrahydrofuranyl, R^3 is phenyl, and Z is O; then R^1 is not methyl or phenyl; and

when ring A is pyradizinyl, R^3 is 4-NO_2-phenyl, and Z is O; then R^1 is not methyl.

[0009] Some embodiments of the present application provide a compound, having the structure of formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -$C(O)R^8$,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10}, and $-(CH_2)_n-(C_{6-10}$ aryl) optionally substituted with one or more R^{11};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, $-C(O)R^8$, and $-C(O)OR^5$;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, $-C(O)R^8$, and $-C(O)OR^5$;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-NR^{12}R^{13}$, and $-OR^5$;

each Y is independently N or CR^9;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, and $-NR^{14}R^{15}$,

or independently two adjacent R^9 together with the ring atoms to which they are attached form a fused optionally substituted 3-10 membered heterocyclyl or a fused optionally substituted 5-10 membered heteroaryl;

each R^{10} is independently selected from the group consisting of oxo, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

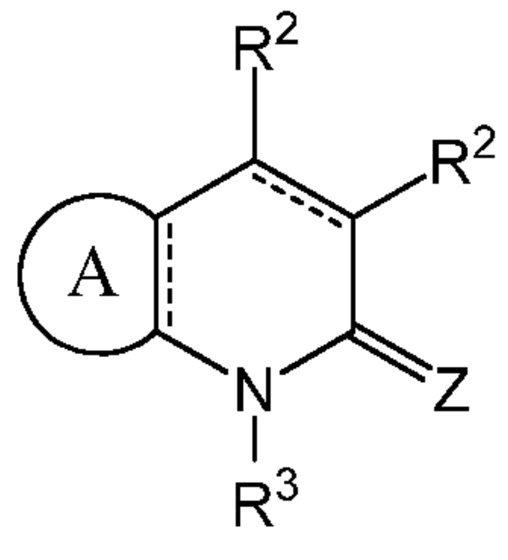
Z is selected from oxygen and sulfur;

n is an integer from 0 to 4;

m is an integer from 1 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

[0010] Some embodiments of the present application provide a compound having the structure of formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

A is a C_{5-7} carbocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -C(O)R^8, or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl,

C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

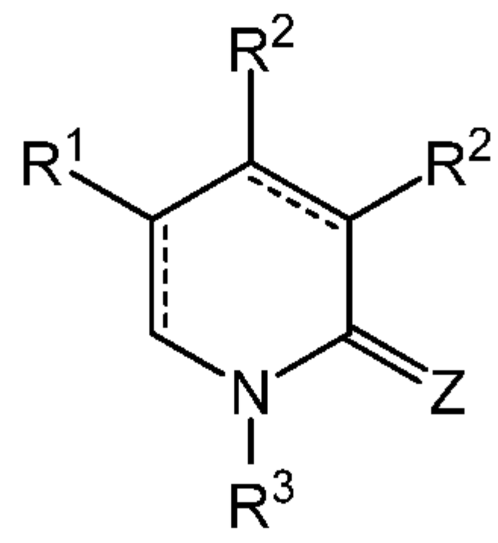
each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

[0011] Some embodiments of the present application provide a compound having the structure of formula (VIa):



(VIa)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is a C_{4-7} carbocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, $-OR^5$, $-NR^6R^7$, and $-C(O)R^8$,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of $-(CH_2)_n-(C_{6-10}$ aryl), $-(CH_2)_n-$(5-10 membered heteroaryl), $-(CH_2)_n-(C_{3-10}$ carbocyclyl), and $-(CH_2)_n-$(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, $-C(O)R^8$, $-SO_2R^{16}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and $-(CH_2)_n-$(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, $-C(O)R^8$, and $-C(O)OR^5$;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, $-C(O)R^8$, and $-C(O)OR^5$;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

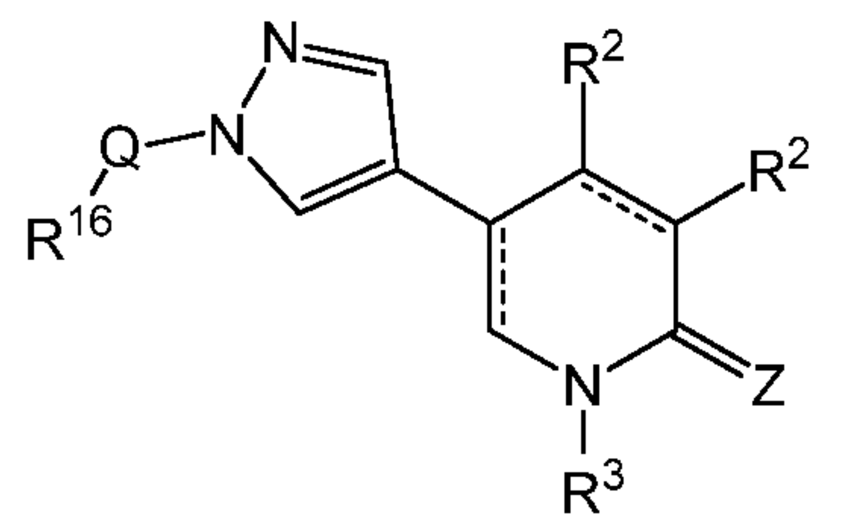
each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

[0012] Some embodiments of the present application provide a compound having the structure of formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof, wherein

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -C(O)R^8,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted

C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -N$R^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, and –NO_2;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

Q is selected from C(O) and $S(O)_t$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

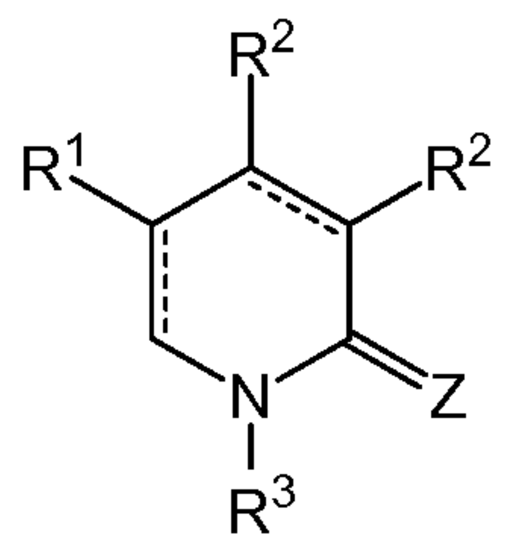
Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4;

t is 1 or 2; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

[0013] Some embodiments of the present application provide a compound having the structure of formula (VIb):



(VIb)

R^1 is selected from the group consisting of halogen, -CN, -C(O)R^8, -SO_2R^{16}, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -C(O)R^8,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of -$(CH_2)_{1-4}$-(C_{6-10} aryl), -$(CH_2)_{1-4}$-(5-10 membered heteroaryl), -$(CH_2)_{1-4}$-(C_{3-10} carbocyclyl), and -$(CH_2)_{1-4}$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -N$R^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, and –NO_2;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

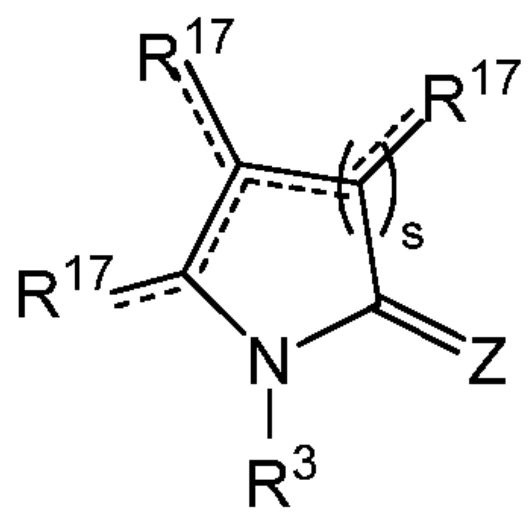
each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond; provided that

when R^1 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted 6 to 10 membered heterocyclyl, optionally substituted hexyl, optionally substituted alkyl, optionally substituted alkenyl; each of R^2 is hydrogen or one of R^2 is hydrogen and the other R^2 is methyl; and Z is O; then R^3 is not $-CH_2$-phenyl substituted with one or more halogen atoms; and provided that

R^1 is not 4-methoxy phenyl.

[0014] Some embodiments of the present application provide a compound having the structure of formula (VIII):



(VIII)

R^3 is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-(CH_2)_n-(C_{6-10}$ aryl) optionally substituted with one or more R^9, $-(CH_2)_n$-(5-10 membered heteroaryl) optionally substituted with one or more R^9, $-(CH_2)_n-(C_{3-10}$ carbocyclyl) optionally substituted with one or more R^9, and $-(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^9;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$;

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and $-(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{17} is independently selected from the group consisting of hydrogen, oxo, halogen, -CN, $-C(O)R^8$, $-SO_2R^{16}$, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4,

or independently two adjacent R^{17} together with the carbon atoms to which they are attached form a fused phenyl or 5-6 membered heteroaryl, each optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -$NR^{12}R^{13}$, and -OR^5;

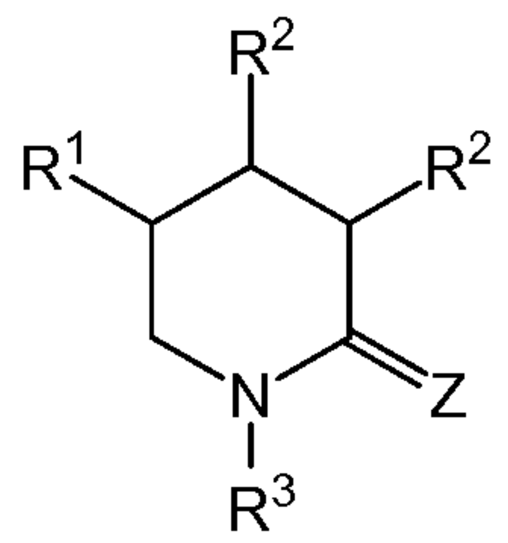
Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4;

s is 0, 1,or 3; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

[0015] Some embodiments of the present application provide a compound having the structure of formula (IX):



(IX)

R^1 is selected from the group consisting of hydrogen, halogen, -CN, -C(O)R^8, -SO_2R^{16}, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -C(O)R^8,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of C_{3-7} carbocyclyl and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$ -(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur; and

each n is independently an integer from 0 to 4.

[0016] Some embodiments disclosed herein relate to methods of treating a fibrotic condition, comprising administering a therapeutically effective amount of a compound of any one of Formulae (I), (II), (III), (IV), (V), (VIa), (VIb), (VII), (VIII) and (IX), a compound selected from Table 1, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof to a subject in need thereof. In some such embodiments, the method further comprises identifying the subject as having or at risk of having said fibrotic condition. In some such embodiments, the fibrotic condition is selected from the group consisting of pulmonary fibrosis, dermal fibrosis, pancreatic fibrosis, liver fibrosis, and renal fibrosis. In some embodiment, the fibrotic condition is idiopathic pulmonary fibrosis. In some embodiments, the subject receiving such method of treatment is a human.

[0017] Some embodiments disclosed herein relate to use of a therapeutically effective amount of a compound of any one of Formulae (I), (II), (III), (IV), (V), (VIa), (VIb), (VII), (VIII) and (IX), a compound selected from Table 1, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof in the preparation of a medicament for treating a fibrotic condition. In some such embodiments, the use further comprises identifying the subject as having or at risk of having said fibrotic condition. In some such embodiments, the fibrotic condition is selected from the group consisting of pulmonary fibrosis, dermal fibrosis, pancreatic fibrosis, liver fibrosis, and renal fibrosis. In some embodiments, the fibrotic condition is idiopathic pulmonary fibrosis. In some embodiments, the subject receiving such treatment is a human being.

[0018] Some embodiments disclosed herein relate to a therapeutically effective amount of a compound of any one of Formulae (I), (II), (III), (IV), (V), (VIa), (VIb), (VII), (VIII) and (IX), a compound selected from Table 1, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for use in treating a fibrotic condition. In some such embodiments, the use further comprises identifying the subject as having or at risk of having said fibrotic condition. In some such embodiments, the fibrotic condition is selected from the group consisting of pulmonary fibrosis, dermal fibrosis, pancreatic fibrosis, liver fibrosis, and renal fibrosis. In some embodiments, the fibrotic condition is idiopathic pulmonary fibrosis. In some embodiments, the subject receiving such treatment is a human being.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. The use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least." When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition, or device, the term "comprising" means that the compound, composition, or device includes at least the recited features or components, but may also include additional features or components.

[0020] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0021] As used herein, common organic abbreviations are defined as follows:

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
Bn	Benzyl
Bz	Benzoyl
BOC or Boc	tert-Butoxycarbonyl
Bu	n-Butyl
cat.	Catalytic
Cbz	Carbobenzyloxy
CDI	1,1'-carbonyldiimidazole
°C	Temperature in degrees Centigrade
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE	1,2-Dichloroethane
DCM	Methylene chloride
DIEA	Diisopropylethylamine
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	N,N'-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
ee%	Enantiomeric excess
Et	Ethyl
EtOAc or EA	Ethyl acetate
g	Gram(s)
h or hr	Hour(s)
HATU	2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
HOBT	N-Hydroxybenzotriazole
iPr	Isopropyl
LCMS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m or min	Minute(s)
mCPBA	meta-Chloroperoxybenzoic Acid
MeOH	Methanol
MeCN	Acetonitrile
mL	Milliliter(s)
MTBE	Methyl tertiary-butyl ether
NH_4OAc	Ammonium acetate
PE	Petroleum ether
PG	Protecting group
Pd/C	Palladium on activated carbon
Pd(dppf)Cl_2	1, 1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride
Ph	Phenyl
ppt	Precipitate

PMBC	4-Methoxybenzyl chloride
RCM	Ring closing metathesis
rt	Room temperature
sBuLi	sec-Butylithium
SFC	Supercritical fluid chromatography
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
TCDI	1,1'-Thiocarbonyl diimidazole
Tert, t	tertiary
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	Tetramethylethylenediamine
TMSNCO	trimethylsilyl isocyanate
μL	Microliter(s)

[0022] "Solvate" refers to the compound formed by the interaction of a solvent and a compound described herein or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0023] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of a compound and, which are not biologically or otherwise undesirable for use in a pharmaceutical. In many cases, the compounds disclosed herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

[0024] As used herein, "C_a to C_b" or "C_{a-b}" in which "a" and "b" are integers refer to the number of carbon atoms in the specified group. That is, the group can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" or "C_{1-4} alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-.

[0025] The term "halogen" or "halo," as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, *e.g.*, fluorine, chlorine, bromine, or iodine, with fluorine and chlorine being preferred.

[0026] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that is fully saturated (i.e., contains no double or triple bonds). The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 9 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be designated as "C_{1-4} alkyl" or similar designations. By way of example only, "C_{1-4} alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like.

[0027] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl as is defined above, such as "C_{1-9} alkoxy", including but not limited to methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy, and the like.

[0028] As used herein, "alkylthio" refers to the formula –SR wherein R is an alkyl as is defined above, such as "C_{1-9} alkylthio" and the like, including but not limited to methylmercapto,

ethylmercapto, n-propylmercapto, 1-methylethylmercapto (isopropylmercapto), n-butylmercapto, iso-butylmercapto, sec-butylmercapto, tert-butylmercapto, and the like.

[0029] As used herein, "alkenyl" refers to a straight or branched hydrocarbon chain containing one or more double bonds. The alkenyl group may have 2 to 20 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. The alkenyl group may also be a medium size alkenyl having 2 to 9 carbon atoms. The alkenyl group could also be a lower alkenyl having 2 to 4 carbon atoms. The alkenyl group may be designated as "C_{2-4} alkenyl" or similar designations. By way of example only, "C_{2-4} alkenyl" indicates that there are two to four carbon atoms in the alkenyl chain, i.e., the alkenyl chain is selected from the group consisting of ethenyl, propen-1-yl, propen-2-yl, propen-3-yl, buten-1-yl, buten-2-yl, buten-3-yl, buten-4-yl, 1-methyl-propen-1-yl, 2-methyl-propen-1-yl, 1-ethyl-ethen-1-yl, 2-methyl-propen-3-yl, buta-1,3-dienyl, buta-1,2,-dienyl, and buta-1,2-dien-4-yl. Typical alkenyl groups include, but are in no way limited to, ethenyl, propenyl, butenyl, pentenyl, and hexenyl, and the like.

[0030] As used herein, "alkynyl" refers to a straight or branched hydrocarbon chain containing one or more triple bonds. The alkynyl group may have 2 to 20 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. The alkynyl group may also be a medium size alkynyl having 2 to 9 carbon atoms. The alkynyl group could also be a lower alkynyl having 2 to 4 carbon atoms. The alkynyl group may be designated as "C_{2-4} alkynyl" or similar designations. By way of example only, "C_{2-4} alkynyl" indicates that there are two to four carbon atoms in the alkynyl chain, i.e., the alkynyl chain is selected from the group consisting of ethynyl, propyn-1-yl, propyn-2-yl, butyn-1-yl, butyn-3-yl, butyn-4-yl, and 2-butynyl. Typical alkynyl groups include, but are in no way limited to, ethynyl, propynyl, butynyl, pentynyl, and hexynyl, and the like.

[0031] As used herein, "heteroalkyl" refers to a straight or branched hydrocarbon chain containing one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the chain backbone. The heteroalkyl group may have 1 to 20 carbon atom, although the present definition also covers the occurrence of the term "heteroalkyl" where no numerical range is designated. The heteroalkyl group may also be a medium size heteroalkyl having 1 to 9 carbon atoms. The heteroalkyl group could also be a lower heteroalkyl having 1 to 4 carbon atoms. The heteroalkyl group may be designated as "C_{1-4} heteroalkyl" or similar designations. The heteroalkyl group may contain one or more heteroatoms. By way of example only, "C_{1-4} heteroalkyl" indicates that there are one to four carbon atoms in the heteroalkyl chain and additionally one or more heteroatoms in the backbone of the chain.

[0032] As used herein, "alkylene" means a branched, or straight chain fully saturated di-radical chemical group containing only carbon and hydrogen that is attached to the rest of the molecule via two points of attachment (i.e., an alkanediyl). The alkylene group may have 1 to 20 carbon atoms, although the present definition also covers the occurrence of the term alkylene where no numerical range is designated. The alkylene group may also be a medium size alkylene having 1 to 9 carbon atoms. The alkylene group could also be a lower alkylene having 1 to 4 carbon atoms. The alkylene group may be designated as "C_{1-4} alkylene" or similar designations. By way of example only, "C_{1-4} alkylene" indicates that there are one to four carbon atoms in the alkylene chain, i.e., the alkylene chain is selected from the group consisting of methylene, ethylene, ethan-1,1-diyl, propylene, propan-1,1-diyl, propan-2,2-diyl, 1-methyl-ethylene, butylene, butan-1,1-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 1-methyl-propylene, 2-methyl-propylene, 1,1-dimethyl-ethylene, 1,2-dimethyl-ethylene, and 1-ethyl-ethylene.

[0033] As used herein, "alkenylene" means a straight or branched chain di-radical chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond that is attached to the rest of the molecule via two points of attachment. The alkenylene group may have 2 to 20 carbon atoms, although the present definition also covers the occurrence of the term alkenylene where no numerical range is designated. The alkenylene group may also be a medium size alkenylene having 2 to 9 carbon atoms. The alkenylene group could also be a lower alkenylene having 2 to 4 carbon atoms. The alkenylene group may be designated as "C_{2-4} alkenylene" or similar designations. By way of example only, "C_{2-4} alkenylene" indicates that there are two to four carbon atoms in the alkenylene chain, i.e., the alkenylene chain is selected from the group consisting of ethenylene, ethen-1,1-diyl, propenylene, propen-1,1-diyl, prop-2-en-1,1-diyl, 1-methyl-ethenylene, but-1-enylene, but-2-enylene, but-1,3-dienylene, buten-1,1-diyl, but-1,3-dien-1,1-diyl, but-2-en-1,1-diyl, but-3-en-1,1-diyl, 1-methyl-prop-2-en-1,1-diyl, 2-methyl-prop-2-en-1,1-diyl, 1-ethyl-ethenylene, 1,2-dimethyl-ethenylene, 1-methyl-propenylene, 2-methyl-propenylene, 3-methyl-propenylene, 2-methyl-propen-1,1-diyl, and 2,2-dimethyl-ethen-1,1-diyl.

[0034] The term "aromatic" refers to a ring or ring system having a conjugated pi electron system and includes both carbocyclic aromatic (e.g., phenyl) and heterocyclic aromatic groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of atoms) groups provided that the entire ring system is aromatic.

[0035] As used herein, "aryl" refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent carbon atoms) containing only carbon in the ring backbone. When the aryl is a ring system, every ring in the system is aromatic. The aryl group may have 6 to 18 carbon atoms, although the present definition also covers the occurrence of the term "aryl" where no numerical range is designated. In some embodiments, the aryl group has 6 to 10 carbon atoms. The aryl group may be designated as "C_{6-10} aryl," "C_6 or C_{10} aryl," or similar designations. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, azulenyl, and anthracenyl.

[0036] As used herein, "aryloxy" and "arylthio" refers to RO- and RS-, in which R is an aryl as is defined above, such as "C_{6-10} aryloxy" or "C_{6-10} arylthio" and the like, including but not limited to phenyloxy.

[0037] An "aralkyl" or "arylalkyl" is an aryl group connected, as a substituent, via an alkylene group, such as "C_{7-14} aralkyl" and the like, including but not limited to benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C_{1-4} alkylene group).

[0038] As used herein, "heteroaryl" refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent atoms) that contain(s) one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the ring backbone. When the heteroaryl is a ring system, every ring in the system is aromatic. The heteroaryl group may have 5-18 ring members (i.e., the number of atoms making up the ring backbone, including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term "heteroaryl" where no numerical range is designated. In some embodiments, the heteroaryl group has 5 to 10 ring members or 5 to 7 ring members. The heteroaryl group may be designated as "5-7 membered heteroaryl," "5-10 membered heteroaryl," or similar designations. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, phthalazinyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolinyl, isoquinlinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, and benzothienyl.

[0039] A "heteroaralkyl" or "heteroarylalkyl" is heteroaryl group connected, as a substituent, via an alkylene group. Examples include but are not limited to 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazollylalkyl, and imidazolylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C_{1-4} alkylene group).

[0040] As used herein, "carbocyclyl" means a non-aromatic cyclic ring or ring system containing only carbon atoms in the ring system backbone. When the carbocyclyl is a ring system, two or more rings may be joined together in a fused, bridged or spiro-connected fashion. Carbocyclyls may have any degree of saturation provided that at least one ring in a ring system is not aromatic. Thus, carbocyclyls include cycloalkyls, cycloalkenyls, and cycloalkynyls. The carbocyclyl group may have 3 to 20 carbon atoms, although the present definition also covers the occurrence of the term "carbocyclyl" where no numerical range is designated. The carbocyclyl group may also be a medium size carbocyclyl having 3 to 10 carbon atoms. The carbocyclyl group could also be a carbocyclyl having 3 to 6 carbon atoms. The carbocyclyl group may be designated as "C_{3-6} carbocyclyl" or similar designations. Examples of carbocyclyl rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,3-dihydro-indene, bicycle[2.2.2]octanyl, adamantyl, and spiro[4.4]nonanyl.

[0041] A "(carbocyclyl)alkyl" is a carbocyclyl group connected, as a substituent, via an alkylene group, such as "C_{4-10} (carbocyclyl)alkyl" and the like, including but not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylethyl, cyclopropylisopropyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl, and the like. In some cases, the alkylene group is a lower alkylene group.

[0042] As used herein, "cycloalkyl" means a fully saturated carbocyclyl ring or ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0043] As used herein, "cycloalkenyl" means a carbocyclyl ring or ring system having at least one double bond, wherein no ring in the ring system is aromatic. An example is cyclohexenyl.

[0044] As used herein, "heterocyclyl" means a non-aromatic cyclic ring or ring system containing at least one heteroatom in the ring backbone. Heterocyclyls may be joined together in a fused, bridged or spiro-connected fashion. Heterocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. The heteroatom(s) may be present in either a non-aromatic or aromatic ring in the ring system. The heterocyclyl group may have 3 to 20 ring members (i.e., the number of atoms making up the ring backbone, including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term "heterocyclyl" where no numerical range is designated. The heterocyclyl group may also be a medium size heterocyclyl having 3 to 10 ring members. The heterocyclyl group could also be a heterocyclyl having 3 to 6 ring members. The heterocyclyl group may be designated as "3-6 membered heterocyclyl" or similar designations. In preferred six membered monocyclic heterocyclyls, the heteroatom(s) are selected from one up to three of O, N or S, and in preferred five membered monocyclic heterocyclyls, the heteroatom(s) are selected from one or two heteroatoms selected from O, N, or S. Examples of heterocyclyl rings include, but are not limited to, azepinyl, acridinyl, carbazolyl, cinnolinyl, dioxolanyl, imidazolinyl, imidazolidinyl, morpholinyl, oxiranyl, oxepanyl, thiepanyl, piperidinyl, piperazinyl, dioxopiperazinyl, pyrrolidinyl, pyrrolidonyl, pyrrolidionyl, 4-piperidonyl, pyrazolinyl, pyrazolidinyl, 1,3-dioxinyl, 1,3-dioxanyl, 1,4-dioxinyl, 1,4-dioxanyl, 1,3-oxathianyl, 1,4-oxathiinyl, 1,4-oxathianyl, 2*H*-1,2-oxazinyl, trioxanyl, hexahydro-1,3,5-triazinyl, 1,3-dioxolyl, 1,3-dioxolanyl, 1,3-dithiolyl, 1,3-dithiolanyl, isoxazolinyl, isoxazolidinyl, oxazolinyl, oxazolidinyl, oxazolidinonyl, thiazolinyl, thiazolidinyl, 1,3-oxathiolanyl, indolinyl, isoindolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydro-1,4-thiazinyl, thiamorpholinyl, dihydrobenzofuranyl, benzimidazolidinyl, and tetrahydroquinoline.

[0045] A "(heterocyclyl)alkyl" is a heterocyclyl group connected, as a substituent, via an alkylene group. Examples include, but are not limited to, imidazolinylmethyl and indolinylethyl.

[0046] As used herein, "acyl" refers to –C(=O)R, wherein R is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. Non-limiting examples include formyl, acetyl, propanoyl, benzoyl, and acryl.

[0047] An "O-carboxy" group refers to a "-OC(=O)R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0048] A "C-carboxy" group refers to a "-C(=O)OR" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. A non-limiting example includes carboxyl (i.e., -C(=O)OH).

[0049] A "cyano" group refers to a "-CN" group.

[0050] A "cyanato" group refers to an "-OCN" group.

[0051] An "isocyanato" group refers to a "-NCO" group.

[0052] A "thiocyanato" group refers to a "-SCN" group.

[0053] An "isothiocyanato" group refers to an " -NCS" group.

[0054] A "sulfinyl" group refers to an "-S(=O)R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0055] A "sulfonyl" group refers to an "$-SO_2R$" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0056] An "S-sulfonamido" group refers to a "$-SO_2NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0057] An "N-sulfonamido" group refers to a "$-N(R_A)SO_2R_B$" group in which R_A and R_b are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0058] An "O-carbamyl" group refers to a "$-OC(=O)NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0059] An "N-carbamyl" group refers to an "$-N(R_A)OC(=O)R_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0060] An "O-thiocarbamyl" group refers to a "$-OC(=S)NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0061] An "N-thiocarbamyl" group refers to an "$-N(R_A)OC(=S)R_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0062] A "C-amido" group refers to a "$-C(=O)NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0063] An "N-amido" group refers to a "$-N(R_A)C(=O)R_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0064] An "amino" group refers to a "$-NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. A non-limiting example includes free amino (i.e., $-NH_2$).

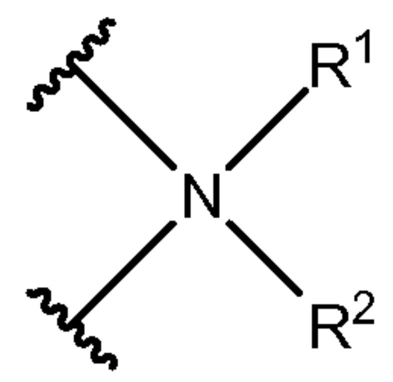
[0065] An "aminoalkyl" group refers to an amino group connected via an alkylene group.

[0066] An "alkoxyalkyl" group refers to an alkoxy group connected via an alkylene group, such as a "C_{2-8} alkoxyalkyl" and the like.

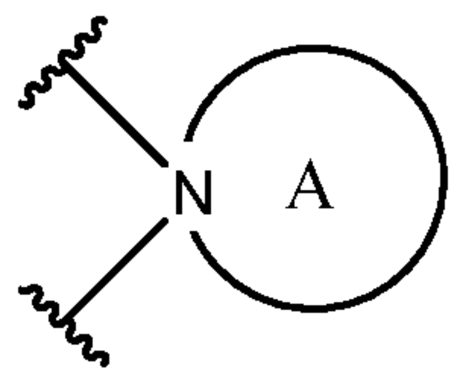
[0067] As used herein, a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when a group is deemed to be "substituted," it is meant that the group is substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_7 carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7-carbocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heterocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heterocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C_1-C_6)alkyl (e.g., $-CF_3$), halo(C_1-C_6)alkoxy (e.g., $-OCF_3$), C_1-C_6 alkylthio, arylthio, amino, amino(C_1-C_6)alkyl, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, acyl, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, and oxo (=O). Wherever a group is described as "optionally substituted" that group can be substituted with the above substituents.

[0068] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment includes di-radicals such as $–CH_2–$, $–CH_2CH_2–$, $–CH_2CH(CH_3)CH_2–$, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as "alkylene" or "alkenylene."

[0069] When two R groups are said to form a ring (e.g., a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring) "together with the atom to which they are attached," it is meant that the collective unit of the atom and the two R groups are the recited ring. The ring is not otherwise limited by the definition of each R group when taken individually. For example, when the following substructure is present:

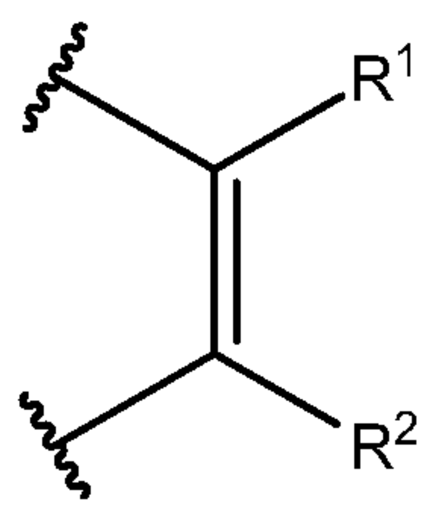


and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a heterocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:

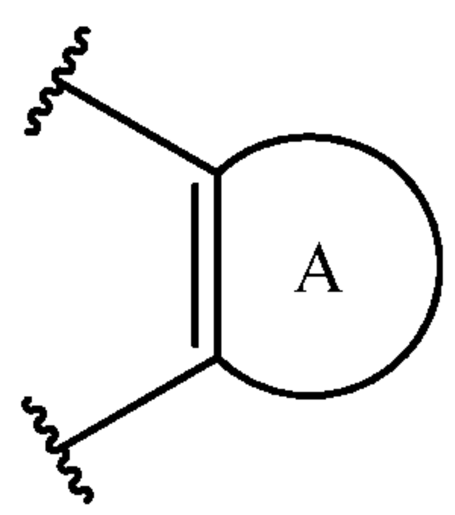


where ring A is a heteroaryl ring containing the depicted nitrogen.

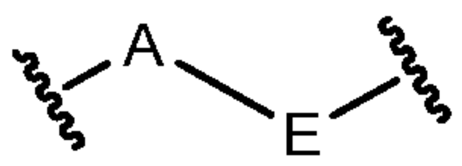
[0070] Similarly, when two "adjacent" R groups are said to form a ring "together with the atom to which they are attached," it is meant that the collective unit of the atoms, intervening bonds, and the two R groups are the recited ring. For example, when the following substructure is present:



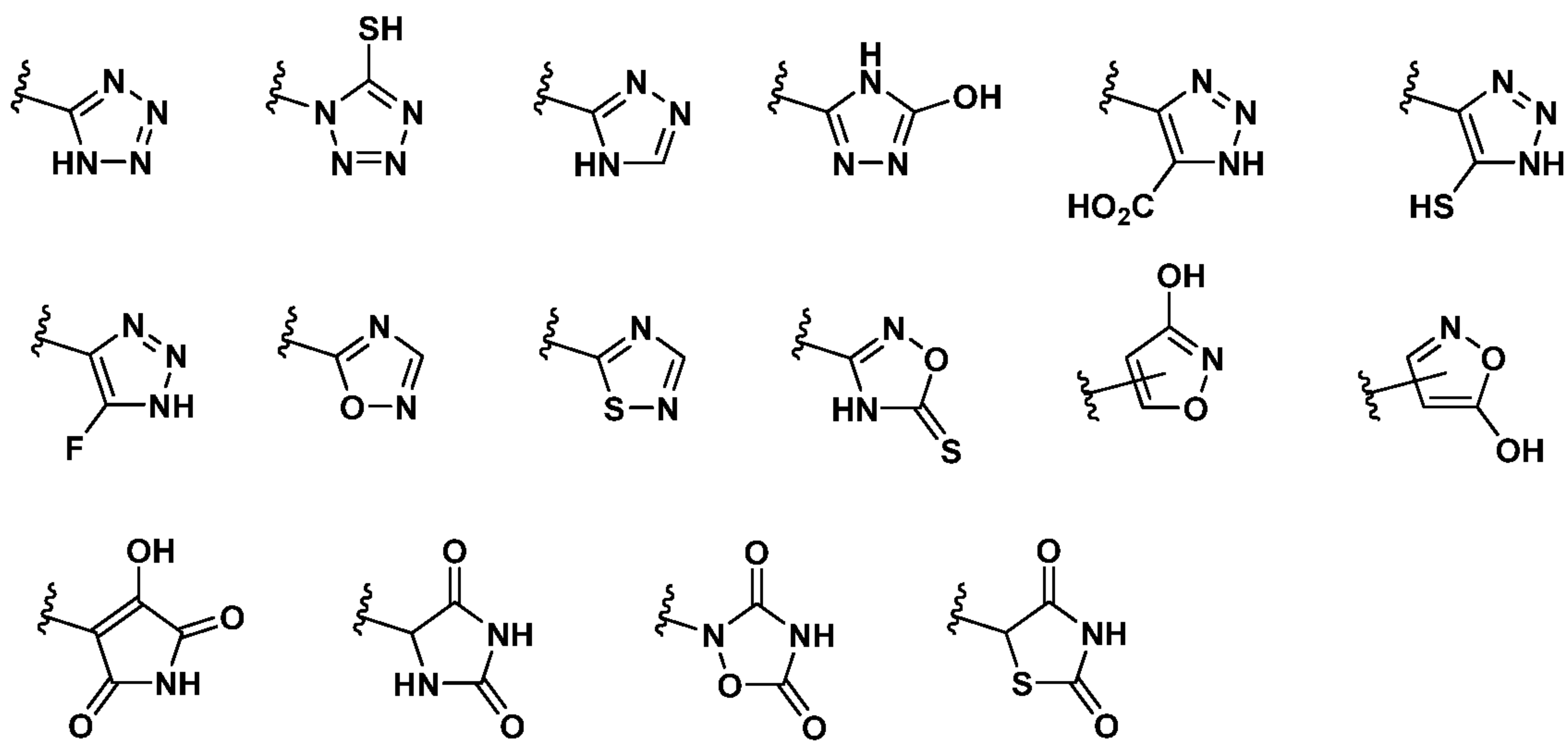
and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the atoms to which they are attached form an aryl or carbocylyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:



where A is an aryl ring or a carbocylyl containing the depicted double bond.

[0071] Wherever a substituent is depicted as a di-radical (*i.e.*, has two points of attachment to the rest of the molecule), it is to be understood that the substituent can be attached in any directional configuration unless otherwise indicated. Thus, for example, a substituent depicted as –AE– or  includes the substituent being oriented such that the **A** is attached at the leftmost attachment point of the molecule as well as the case in which **A** is attached at the rightmost attachment point of the molecule.

[0072] As used herein, "isosteres" of a chemical group are other chemical groups that exhibit the same or similar properties. For example, tetrazole is an isostere of carboxylic acid because it mimics the properties of carboxylic acid even though they both have very different molecular formulae. Tetrazole is one of many possible isosteric replacements for carboxylic acid. Other carboxylic acid isosteres contemplated include $-SO_3H$, $-SO_2HNR$, $-PO_2(R)_2$, $-PO_3(R)_2$, $-CONHNHSO_2R$, $-COHNSO_2R$, and –CONRCN, where R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. In addition, carboxylic acid isosteres can include 5-7 membered carbocycles or heterocycles containing any combination of CH_2, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions. The following structures are non-limiting examples of carbocyclic and heterocyclic isosteres contemplated. The atoms of said ring structure may be optionally substituted at one or more positions with R as defined above.



[0073] It is also contemplated that when chemical substituents are added to a carboxylic isostere, the compound retains the properties of a carboxylic isostere. It is contemplated that when a carboxylic isostere is optionally substituted with one or more moieties selected from R as defined above, then the substitution and substitution position is selected such that it does not eliminate the carboxylic acid isosteric properties of the compound. Similarly, it is also contemplated that the placement of one or more R substituents upon a carbocyclic or heterocyclic carboxylic acid isostere is not a substitution at one or more atom(s) that maintain(s) or is/are integral to the carboxylic acid isosteric properties of the compound, if such substituent(s) would destroy the carboxylic acid isosteric properties of the compound.

[0074] Other carboxylic acid isosteres not specifically exemplified in this specification are also contemplated.

[0075] "Subject" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0076] The term "mammal" is used in its usual biological sense. Thus, it specifically includes, but is not limited to, primates, including simians (chimpanzees, apes, monkeys) and humans, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rodents, rats, mice guinea pigs, or the like.

[0077] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press.

[0078] A therapeutic effect relieves, to some extent, one or more of the symptoms of a disease or condition, and includes curing a disease or condition. "Curing" means that the symptoms of a disease or condition are eliminated; however, certain long-term or permanent effects may exist even after a cure is obtained (such as extensive tissue damage).

[0079] "Treat," "treatment," or "treating," as used herein refers to administering a compound or pharmaceutical composition to a subject for prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a subject who does not yet exhibit symptoms of a disease or condition, but who is susceptible to, or otherwise at risk of, a particular disease or condition, whereby the treatment reduces the likelihood that the patient will develop the disease or condition. The term "therapeutic treatment" refers to administering treatment to a subject already suffering from a disease or condition.

[0080] Where the compounds disclosed herein have at least one chiral center, they may exist as individual enantiomers and diastereomers or as mixtures of such isomers, including racemates. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art. Unless otherwise indicated, all such isomers and mixtures thereof are included in the scope of the compounds disclosed herein. Furthermore, compounds disclosed herein may exist in one or more crystalline or amorphous forms. Unless otherwise indicated, all such forms are included in the scope of the compounds disclosed herein including any polymorphic forms. In addition, some of the compounds disclosed herein may form solvates with water (i.e., hydrates) or common organic solvents. Unless otherwise indicated, such solvates are included in the scope of the compounds disclosed herein.

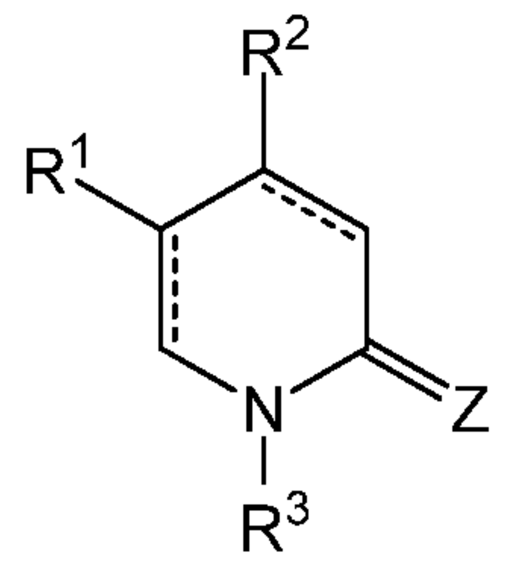
[0081] The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures, even when kinetically; the artisan recognizes that such structures may only represent a very small portion of a sample of such compound(s). Such compounds are considered within the scope of the structures depicted, though such resonance forms or tautomers are not represented herein.

[0082] Isotopes may be present in the compounds described. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

<u>Compounds</u>

<u>Formula I</u>

[0083] Some embodiments disclosed herein relate to a compound of formula (I) as described above or a pharmaceutically acceptable salt thereof.



(I)

[0084] Some embodiments disclosed herein with respect to the compounds of formula (I), R^2 is selected from the group consisting of halogen, $-OR^5$, $-NR^6R^7$, and $-C(O)R^8$;R^3 is selected from the group consisting of $-(CH_2)_n-(C_{6-10}$ aryl), $-(CH_2)_n-$(5-10 membered heteroaryl), $-(CH_2)_n-(C_{3-10}$ carbocyclyl), and $-(CH_2)_n-$(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$; and each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy.

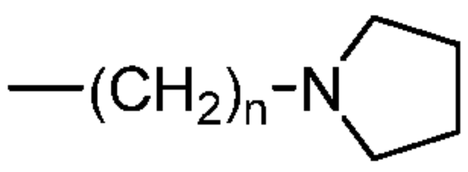
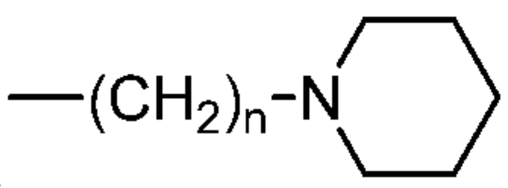
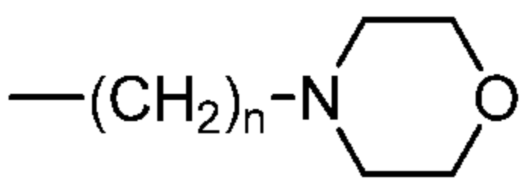
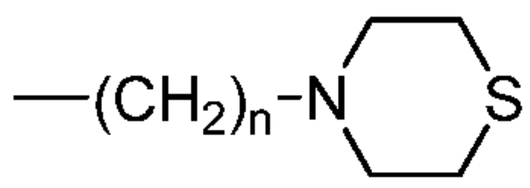
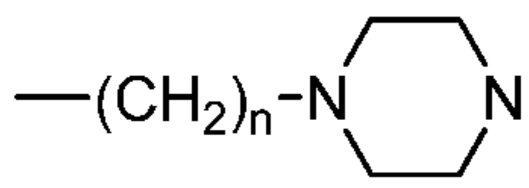
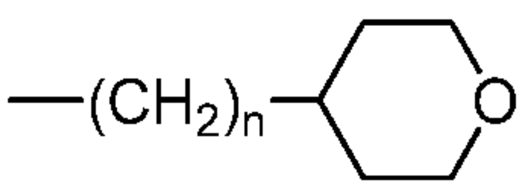
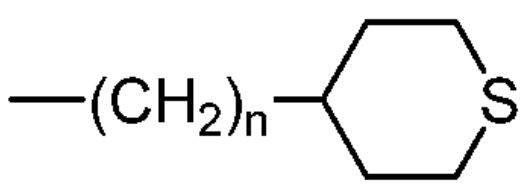
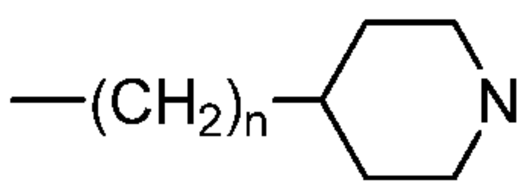
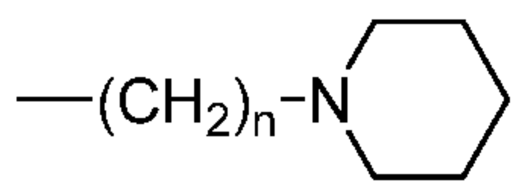
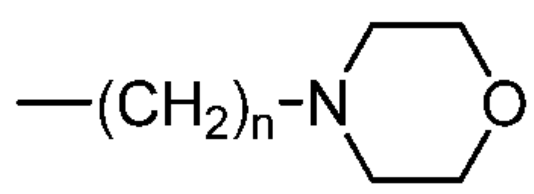
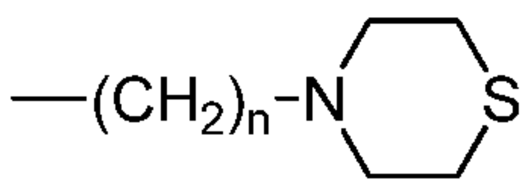
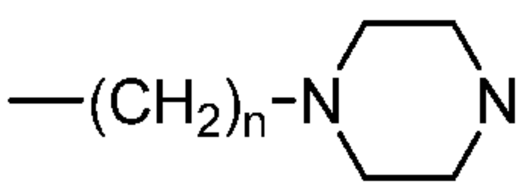
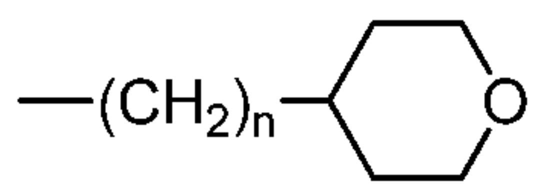
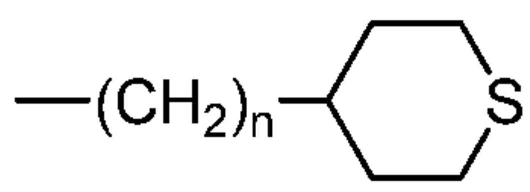
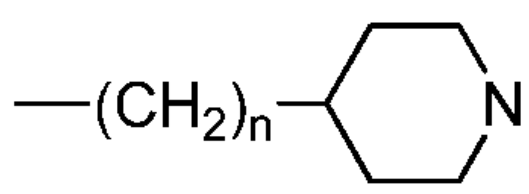
[0085] In some embodiments, R^1 is a C_{6-10} aryl optionally substituted with one or more R^4. In some further embodiments, R^1 is a phenyl optionally substituted with one or more R^4.

[0086] In some embodiments, R^1 is a 5-10 membered heteroaryl optionally substituted with one or more R^4. In some such embodiments, R^1 is a pyrazolyl or 1-methyl pyrazolyl optionally substituted with one or more R^4. In some such embodiments, R^1 is a pyridazinyl optionally substituted with one or more R^4. In some such embodiments, R^1 is a pyrimidinyl optionally substituted with one or more R^4.

[0087] In any of the embodiments of Formula (I) described herein, each R^4 is independently selected from halogen, or optionally substituted C_{1-6} alkyl. In some embodiments, R^4 is halogen. In some embodiments, R^4 is substituted C_{1-6} alkyl. In some other embodiments, R^4 is unsubstituted C_{1-6} alkyl. In some embodiments, R^4 is fluoro. In some other embodiments, R^4 is methyl.

[0088] In some embodiments, R^2 is halogen. In some further embodiments, R^2 is selected from bromo or chloro.

[0089] In some embodiments, R^2 is –CN.

[0090] In some embodiments, R^2 is $-OR^5$. In some embodiments, R^5 is selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, C_{7-14} aralkyl optionally substituted with one or more R^{11}, C_{6-10} aryl optionally substituted with one or more R^{11}, and $-(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10}. In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is optionally substituted C_{1-6} alkyl. In some such embodiments, R^5 is methyl. In some such embodiments, R^5 is halogen substituted ethyl. In some embodiments, R^5 is C_{6-10} aryl optionally substituted with one or more R^{11}. In some such embodiments, R^5 is phenyl optionally substituted with one or more R^{11}. In some such embodiments, R^5 is unsubstituted phenyl. In some embodiments, R^5 is C_{7-14} aralkyl optionally substituted with one or more R^{11}. In some such embodiments, R^5 is benzyl optionally substituted with one or more R^{11}. In some such embodiments, R^5 is unsubstituted benzy. In some such embodiments, R^5 is optionally substituted C_{2-8} alkoxyalkyl. In some such embodiments, R^5 is selected from $-(CH_2)_2OCH_3$, $-(CH_2)_2OC_3H_7$ or $-(CH_2)_2O(CH_2)OCH_3$. In some such embodiments, R^5 is $-(CH_2)_n$-(5 or 6 membered heterocyclyl) optionally substituted with one or more R^{10}. In some such embodiments, R^5 is , optionally substituted with one or more R^{10}. In some such embodiments, R^5 is selected from , , , , , , or , each optionally substituted with one or more R^{10}. In some embodiments, R^5 can be optionally substituted . In some embodiments, R^5 can be optionally substituted . In some embodiments, R^5 can be optionally substituted . In some embodiments, R^5 can be optionally substituted . In some embodiments, R^5 can be optionally substituted . In some embodiments, R^5 can be optionally substituted . In some embodiments, R^5 can be optionally substituted . In some embodiments of this paragraph, n is 0. In some embodiments of this paragraph, n is 1. In some embodiments of this paragraph, R^5 is substituted with one or more substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl, -$O(CH_2)_2OCH_3$, halogen or -$C(O)NH_2$.

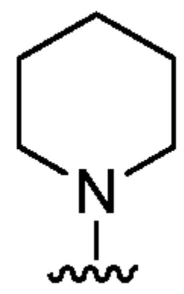
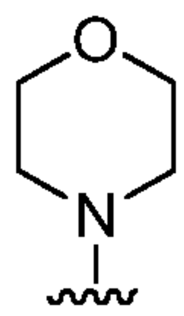
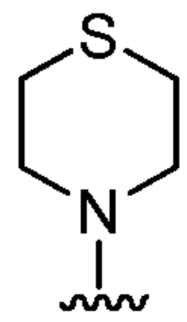
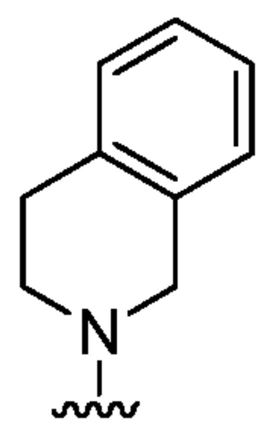
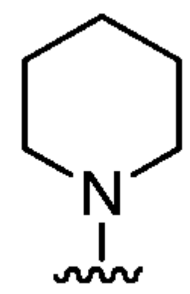
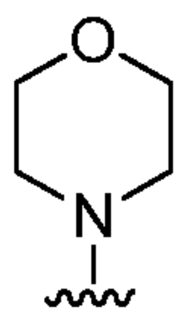
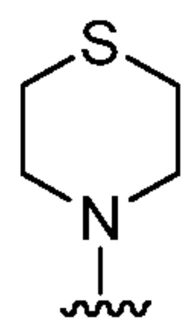
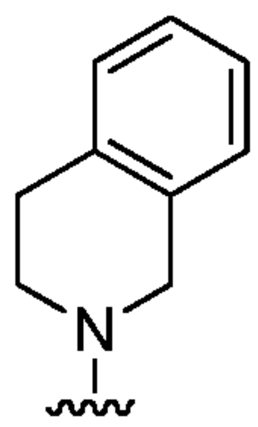
[0091] In some embodiments, R^2 is -NR^6R^7. In some embodiments, each R^6 and R^7 is independently selected from hydrogen, C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -$C(O)R^8$, or -$C(O)OR^5$. In some embodiments, R^6 is hydrogen. In some other embodiments, R^6 is C_{1-6} alkyl. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is C_{1-6} alkyl. In some embodiments, R^7 is C_{6-10} aryl optionally substituted with one or more R^{11}. In some embodiments, R^7 is phenyl optionally substituted with one or more R^{11}. In some other embodiments, R^7 is unsubstituted phenyl.

[0092] In some embodiments, R^7 is C_{7-14} aralkyl optionally substituted with one or more R^{11}. In some embodiments, R^7 is benzyl or –$(CH_2)_2Ph$, each optionally substituted with one or more R^{11}. In some such embodiments, R^7 is substituted with one or more substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl, -$O(CH_2)_2OCH_3$, halogen or -CN. In some embodiments, R^7 is unsubstituted benzyl. In some other embodiments, R^7 is unsubstituted –$(CH_2)_2Ph$.

[0093] In some embodiments, R^7 is (6 membered heteroaryl)alkyl optionally substituted with one or more R^{11}. In some embodiments, R^7 is –CH_2-pyridyl, -CH_2-pyrimidinyl or –CH_2-pyrazinyl, each optionally substituted with one or more R^{11}. In some embodiments, R^7 is unsubstituted –CH_2-pyridyl. In some embodiments, R^7 is unsubstituted –CH_2-pyrazinyl. In some embodiments, R^7 is unsubstituted -CH_2-pyrimidinyl.

[0094] In some embodiments, R^7 is -$C(O)R^8$. In some embodiments, R^8 is selected from C_{1-6} alkyl, C_{6-10} aryl, or -$NR^{12}R^{13}$. In some embodiments, R^8 is selected from methyl, ethyl, propyl, isopropyl, butyl, pentyl or phenyl. In some embodiments, R^8 is methyl. In some other embodiments, R^8 is phenyl. In some embodiments, R^8 is -$NR^{12}R^{13}$. In some embodiments, each R^{12} and R^{13} is independently selected from hydrogen, C_{1-6} alkyl, or benzyl.

[0095] In some embodiments, R^7 is -$C(O)OR^5$. In some embodiments, R^5 is selected from hydrogen, C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, or C_{7-14} aralkyl optionally substituted with one or more R^{11}. In some embodiments, R^5 is selected from methyl, ethyl, isopropyl, or butyl. In some embodiments, R^5 is selected from phenyl or benzyl, each optionally substituted with one or more R^{11}.

[0096] In some embodiments, R^6 and R^7 together with the nitrogen to which they are attached form a 6-10 membered heterocyclyl optionally substituted with one or more R^{10}. In some embodiments, the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached is selected from  ,  ,  , or  , each optionally substituted with one or more R^{10}. In some such embodiments, the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached can be optionally substituted  . In some such embodiments, the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached can be optionally substituted  . In some such embodiments, the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached can be optionally substituted  . In some such embodiments, the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached can be optionally substituted  . In some embodiments, R^{10} is C_{1-6} alkyl. In some embodiments, two geminal R^{10} together are oxo. In some other embodiments, the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached is unsubstituted.

[0097] In some embodiments, R^2 is -SR^5. In some such embodiments, R^5 is C_{6-10} aryl optionally substituted with one or more R^{11}. In some further such embodiments, R^5 is optionally substituted phenyl.

[0098] In some embodiments, R^2 is -$C(O)R^8$. In some embodiments, R^8 is selected from -$NR^{12}R^{13}$. In some embodiments, each R^{12} and R^{13} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, or C_{7-14} aralkyl optionally substituted with one or more R^{11}. In some embodiments, each R^{12} and R^{13} is independently selected from hydrogen, C_{1-6} alkyl, phenyl optionally substituted with one or more R^{11} or benzyl optionally substituted with one or more R^{11}. In some embodiments, the phenyl or benzyl is unsubstituted.

[0099] In some embodiments, R^2 is -$C(O)OR^5$. In some embodiments, R^5 is hydrogen or C_{1-6} alkyl.

[0100] In any of the embodiments of formula (I) described herein, each R^{11} is independently selected from –CN, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, O-$(CH_2)_n$-C_{2-8} alkoxy, or -C(O) $NR^{12}R^{13}$. In some such embodiments, R^{11} is selected from –CN, –Cl, –F, $-CH_3$, $-OCH_3$, $-OC_2H_5$, $-CF_3$ or $-OCF_3$. In some embodiments, R^{11} is –F. In some embodiments, R^{11} is $-OCF_3$. In yet some other embodiments, R^{11} is $-OC_2H_5$. In yet some other embodiments, R^{11} is methyl. In some embodiments, R^{11} is -O-$(CH_2)_2$-OCH_3. In some other embodiments, R^{11} is -C(O)NH_2.

[0101] Some embodiments disclosed herein with respect to the compounds of formula (I), R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9. In some embodiments, n is 0.

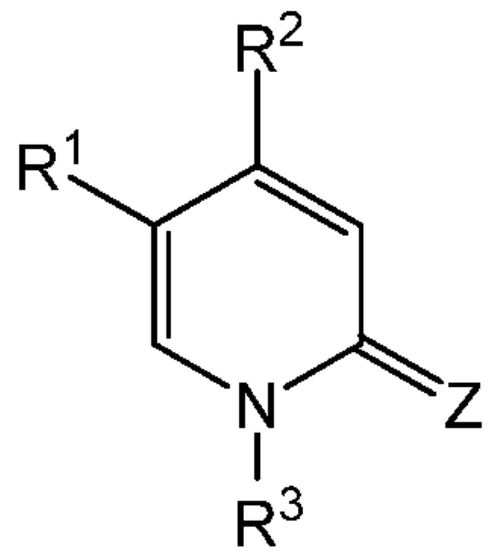
[0102] In some embodiments, R^3 is -$(CH_2)_n$-(C_{6-10} aryl) optionally substituted with one or more R^9. In some embodiments, R^3 is -$(CH_2)_n$-phenyl, optionally substituted with one or more R^9. In some embodiments, n is 0. In some other embodiments, R^3 is unsubstituted -$(CH_2)_n$-phenyl. In some other embodiments, R^3 is unsubstituted phenyl.

[0103] In any of the embodiments of formula (I) described herein, R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, or $-OR^5$. In some further embodiments, R^9 is selected from fluoro, chloro. In some further embodiments, R^9 is selected from methyl, ethyl, or trifluoromethyl. In some embodiments, R^9 is $-OR^5$. In some embodiment, R^5 is selected from hydrogen, C_{1-6} alkyl or halo substituted C_{1-6} alkyl. In some further embodiments, R^5 is selected from trifluoromethyl or ethyl. In some further embodiments, R^5 is optionally substituted C_{2-8} alkoxyalkyl. In some embodiment, R^9 is $NR^{14}R^{15}$. In some such embodiments, R^9 is -NH-C(O)R^8. In some further such embodiments, R^9 is selected from -NH-C(O)-C_{1-6} alkyl, or -NH-C(O)-NH_2. In some embodiments, R^9 is hydroxy.

[0104] Some embodiments described herein with respect to compounds of formula (I), R^3 is unsubstituted. In some other embodiments, R^3 is hydrogen.

[0105] In some embodiments, Z is oxygen.

[0106] In some embodiments, the bonds represented by a solid and dashed line are double bonds. In some such embodiments, compounds of formula (I) are also represented by



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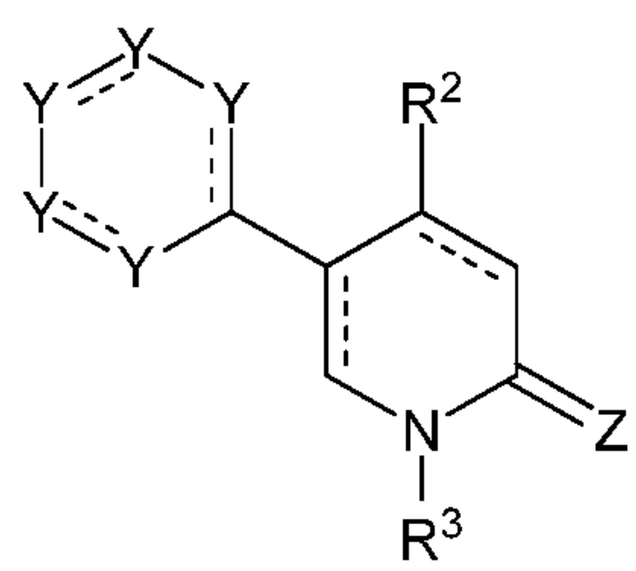
[0107] In some embodiments, the compound of formula (I) is selected from the group consisting of **Compounds 85-162**, **401-414**, **523-545, 550, 551** and **664** in Table 1. In some further embodiments, the compound of formula (I) is selected from the group consisting of **Compounds 85-162**, **401-414**, **523-538**, **540**, **541**, **543**, **545-**,**664** and **696-707** of Table 1.

[0108] Some alternative embodiments provide compounds of formula (I) with the same variable definitions as provided above with the exception that R^2 is selected from 5-10 membered heteroaryl or 3-10 membered heterocyclyl, each optionally substituted with one or more R^4. One non-limiting example of these alternative embodiments is where the compound of formula (I) is **Compound 708** of Table 1.

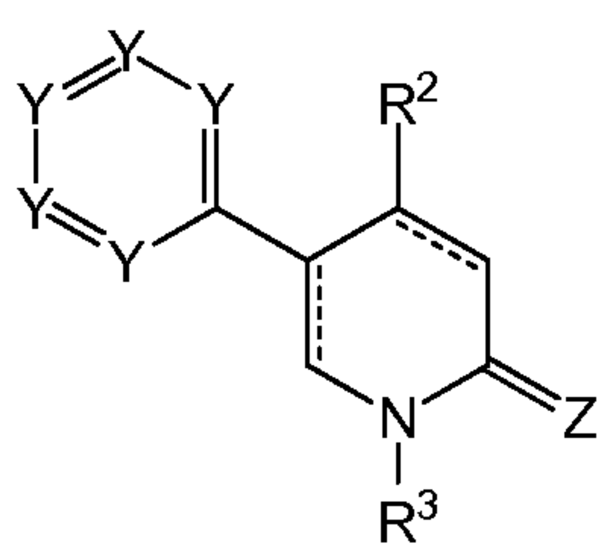
Formula II

[0109] Some embodiments disclosed herein relate to a compound of formula (II) as described above or a pharmaceutically acceptable salt thereof.



(II)

[0110] Some embodiments disclosed herein with respect to the compounds of formula (II), formula (II) is also represented by formula (IIa):



(IIa)

R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9; and

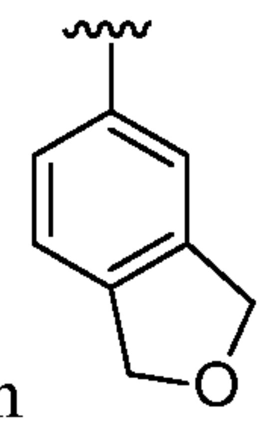
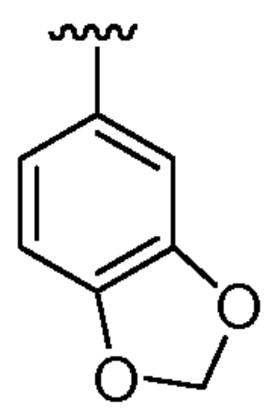
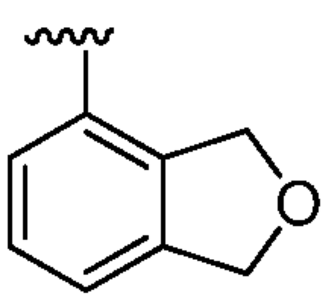
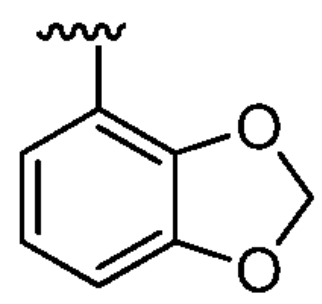
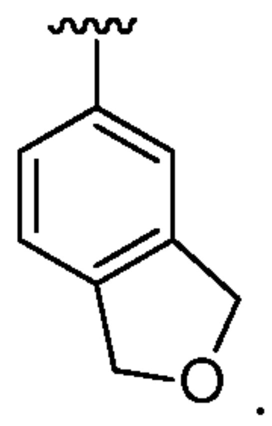
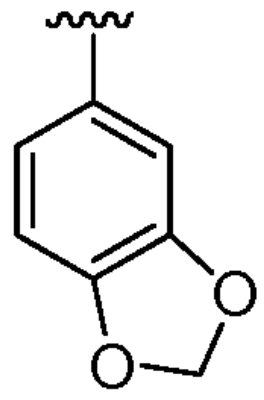
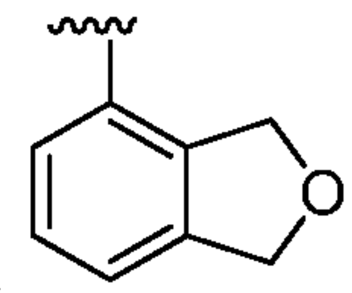
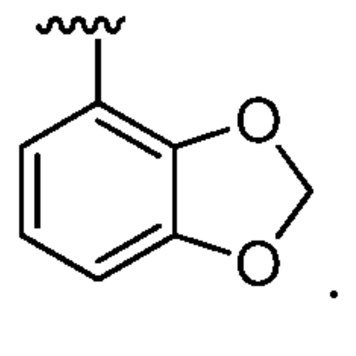
each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -$NR^{14}R^{15}$, -$C(O)R^8$, -SO_2R^{16}, and –NO_2.

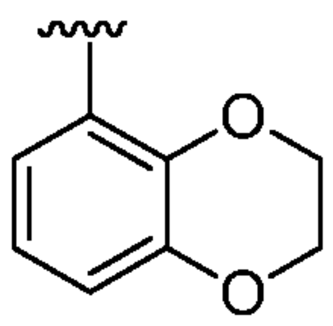
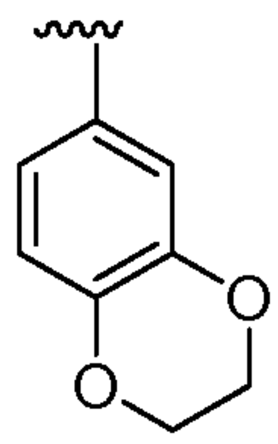
[0111] In some embodiments, R^2 is selected from optionally substituted C_{1-6} alkyl. In some embodiments, R^2 is selected from methyl, ethyl, isopropyl, or trifluoromethyl. In some embodiments, R^2 is methyl.

[0112] Some embodiments disclosed herein with respect to the compounds of formula (II), , R^3 is hydrogen. In some such embodiments, the the compound of formula (II) is selected from the group consisting of compounds **562-565**, **567**, **662** and **663** of Table 1.

[0113] Some embodiments disclosed herein with respect to the compounds of formula (II), R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9. In some embodiments, n is 0.

[0114] In some embodiments, R^3 is selected from -$(CH_2)_n$-(C_{6-10} aryl), optionally substituted with one or more R^9. In some embodiments, R^3 is -$(CH_2)_n$-phenyl optionally substituted with one or more R^9. In some embodiments, R^3 is phenyl, optionally substituted with one or more R^9. In some embodiments, R^3 is unsubstituted phenyl. In some embodiments, R^3 is unsubstituted -$(CH_2)_n$-(C_{6-10} aryl).

[0115] In some embodiments, R^3 is selected from -$(CH_2)_n$-(9 membered heterocyclyl), optionally substituted with one or more R^9. In some embodiments, R^3 is selected from , ,  or , each optionally substituted with one or more R^9. In some such embodiments, R^3 is optionally substituted . In some such embodiments, R^3 is optionally substituted . In some such embodiments, R^3 is optionally substituted . In some such embodiments, R^3 is optionally substituted . In some embodiments, R^3 is unsubstitued.

[0116] In some embodiments, R^3 is selected from -$(CH_2)_n$-(10 membered heterocyclyl), optionally substituted with one or more R^9. In some embodiments, n is 0. In some embodiments, R^3 is selected from  or , each optionally substituted with one or more R^9. In some embodiments, R^3 is unsubstitued.

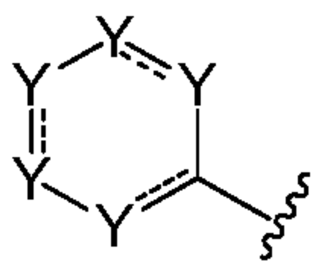
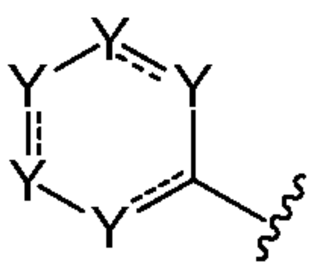
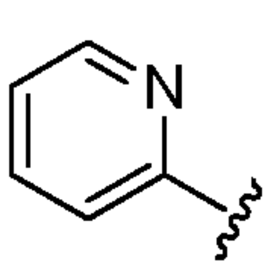
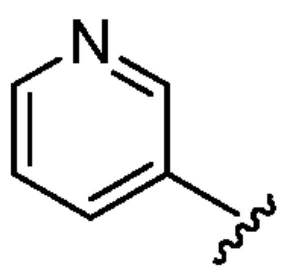
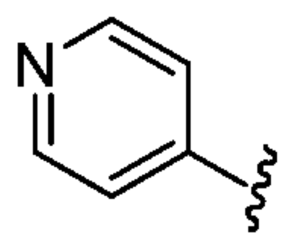
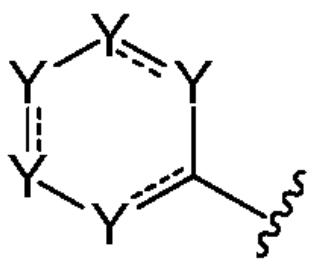
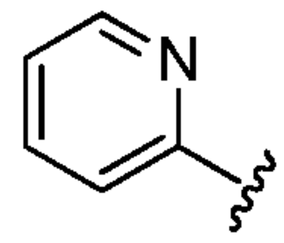
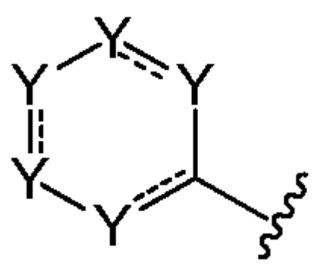
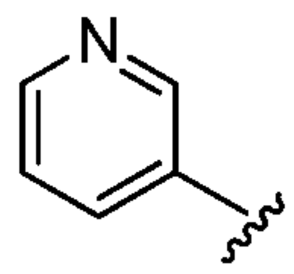
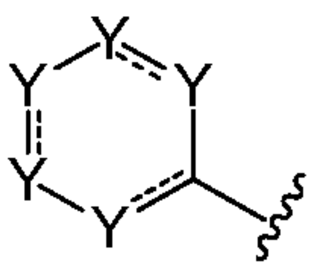
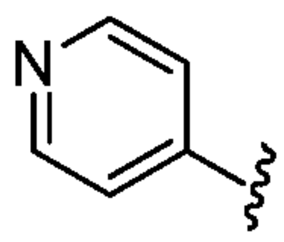
[0117] In any of embodiments of formula (II) described herein, each R^9 is independently selected from halogen, optionally substituted C_{1-6} alkyl, -OR^5, -$NR^{14}R^{15}$ or -$C(O)R^8$. In some embodiments, R^9 is selected from methyl, ethyl, propyl isopropyl, or trifluoromethyl. In some embodiments, R^9 is selected from fluoro or chloro.

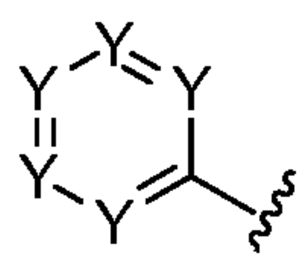
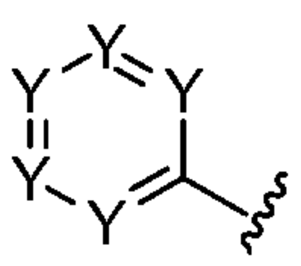
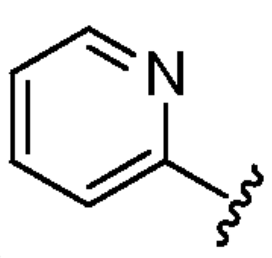
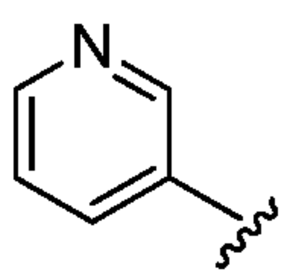
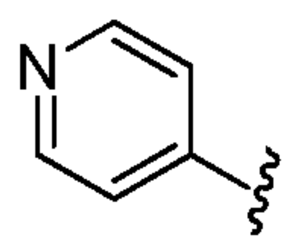
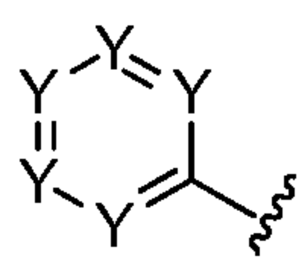
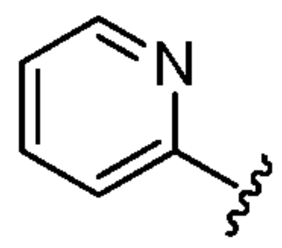
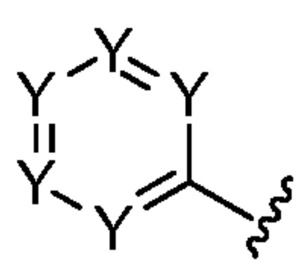
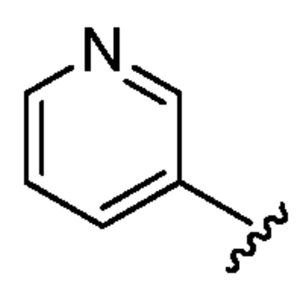
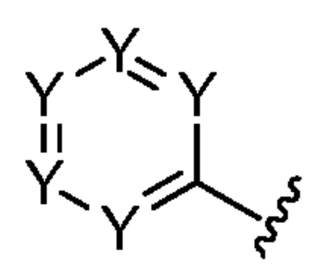
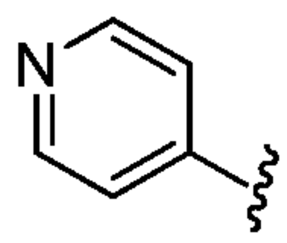
[0118] In some embodiments, R^9 is -OR^5, and wherein R^5 is selected from optionally substituted C_{1-6} alkyl. In some embodiments, R^5 is unsubstituted C_{1-6} alkyl. In some embodiments, R^5 is selected from methyl, ethyl, propyl, isopropyl or trifluoromethyl. In some embodiments, R^5 is methyl. In some other embodiments, R^5 is trifluoromethyl.

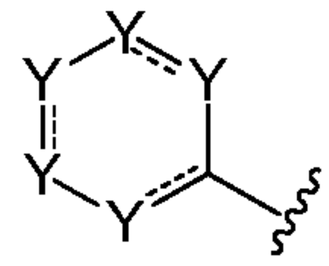
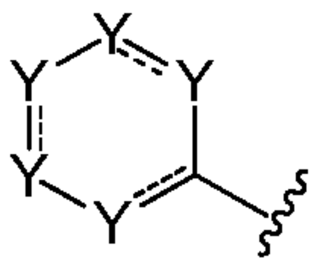
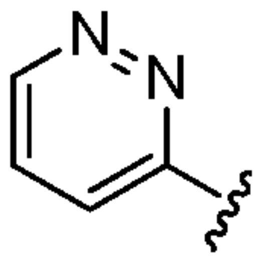
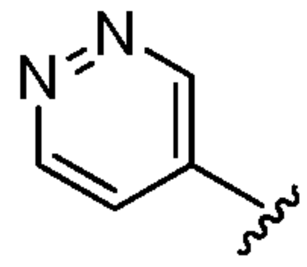
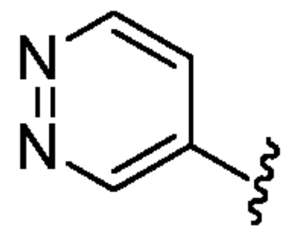
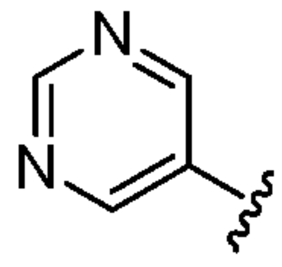
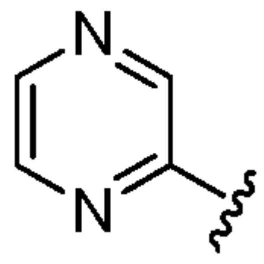
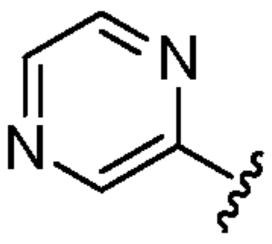
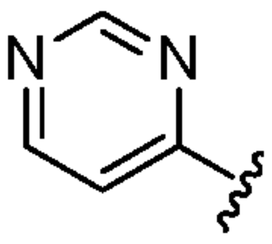
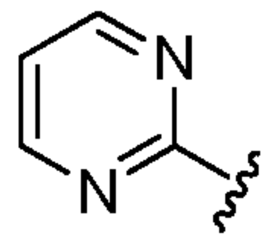
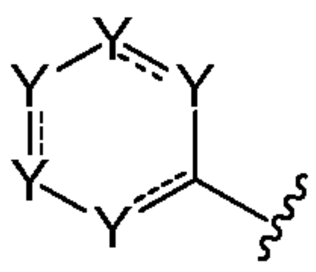
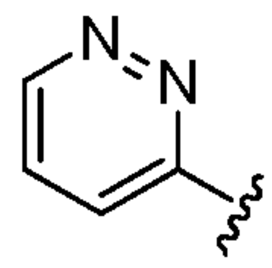
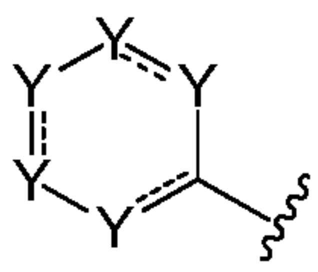
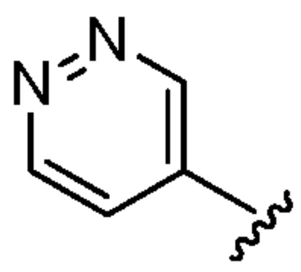
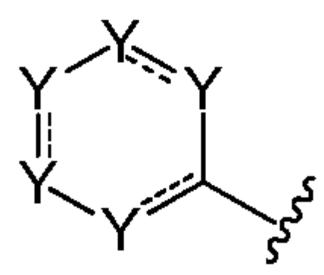
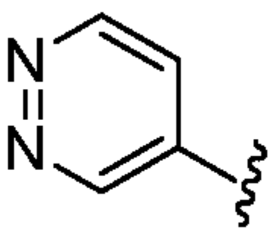
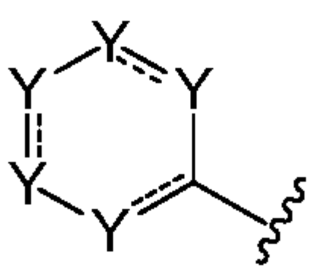
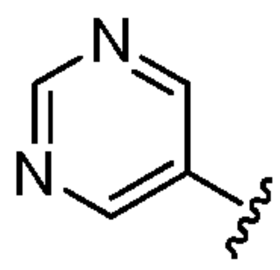
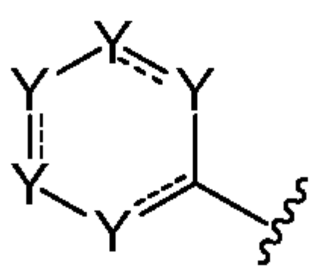
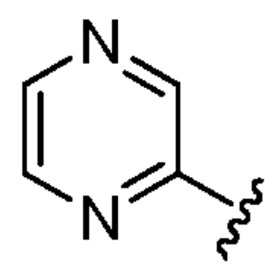
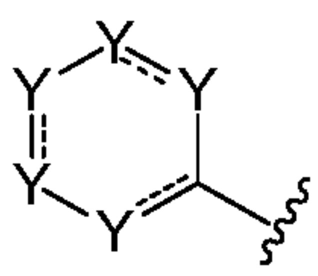
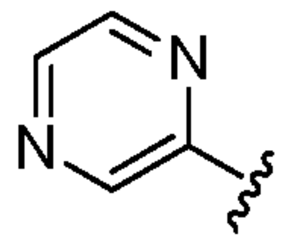
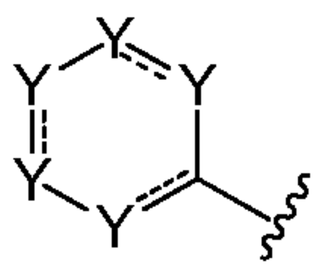
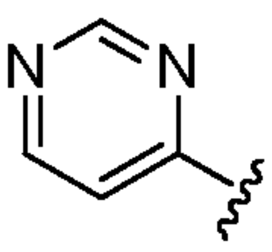
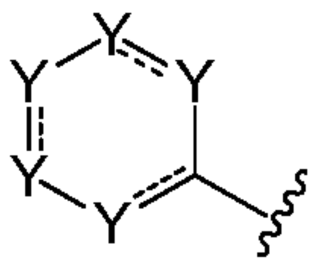
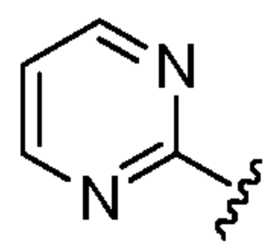
[0119] In some embodiments, R^9 is -$NR^{14}R^{15}$, and wherein each R^{14} and R^{15} is independently selected from hydrogen, C_{1-6} alkyl or -$C(O)R^8$. In some embodiments, R^8 is selected from optionally substituted C_{1-6} alkyl, -OR^5 or -$NR^{12}R^{13}$. In some embodiments, each R^{12} and R^{13} is independently selected from hydrogen or C_{1-6} alkyl. In some embodiments, each R^{12} and R^{13} is independently selected from hydrogen or methyl. In some embodiments, R^5 is selected from hydrogen or C_{1-6} alkyl. In some embodiments, each R^{14} and R^{15} is independently selected from hydrogen, methyl, ethyl, -$C(O)NH_2$, -$C(O)NHCH_3$, -$C(O)N(CH_3)_2$,-$C(O)OH$ or –$C(O)OEt$.

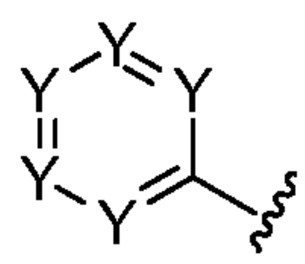
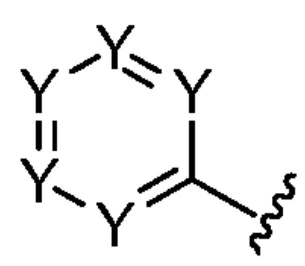
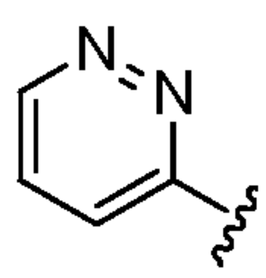
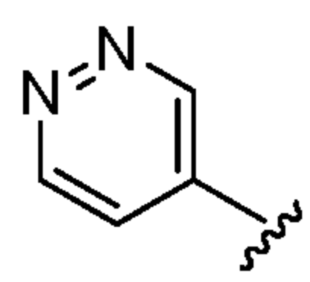
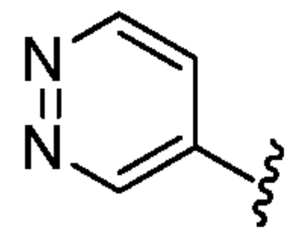
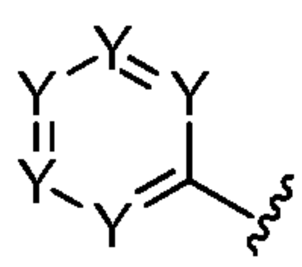
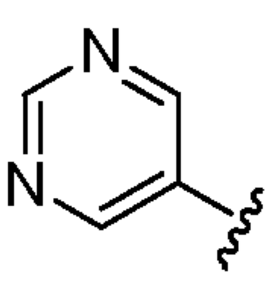
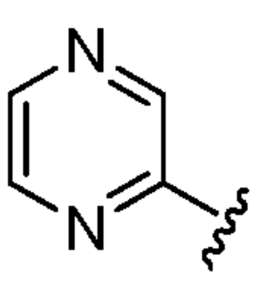
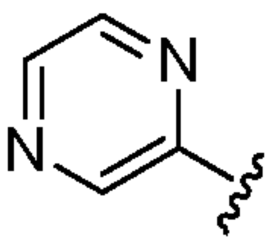
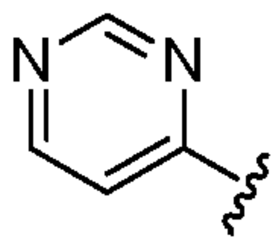
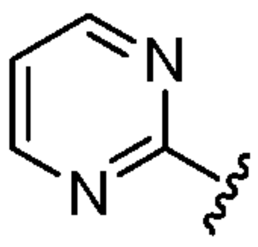
[0120] In some embodiments, R^9 is -C(O)R^8. In some embodiments, R^8 is selected from optionally substituted C_{1-6} alkyl or -$NR^{12}R^{13}$. In some embodiments, R^8 is selected from methyl, -NH_2 or –$NHCH_3$.

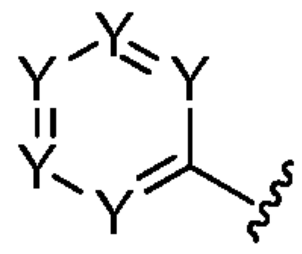
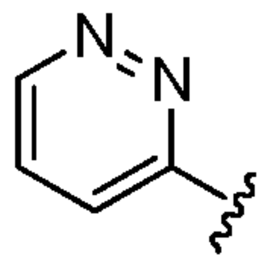
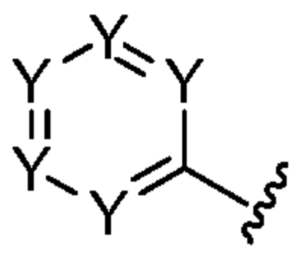
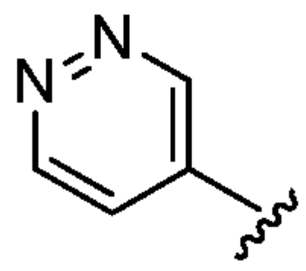
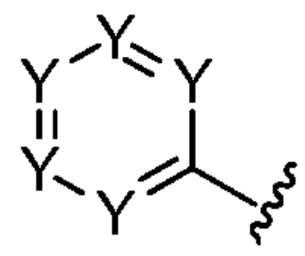
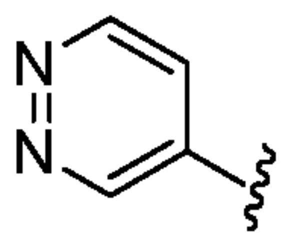
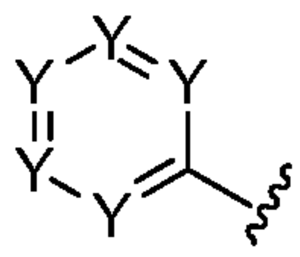
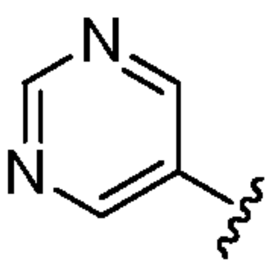
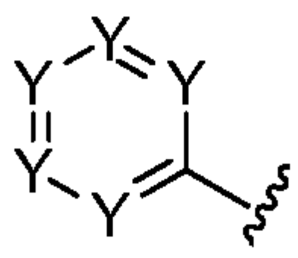
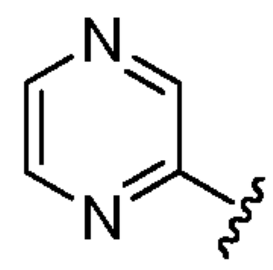
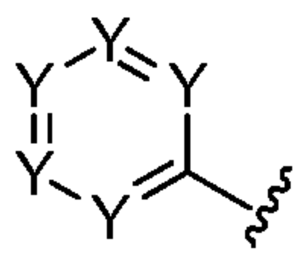
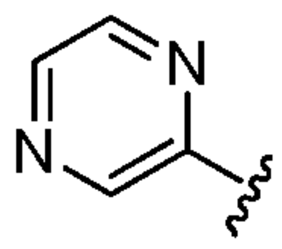
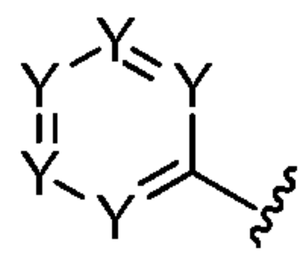
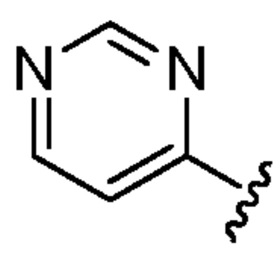
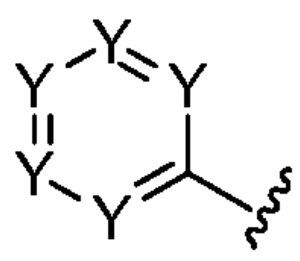
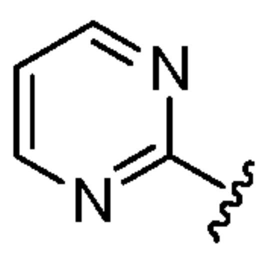
[0121] In some embodiments, all Y is CR^4.

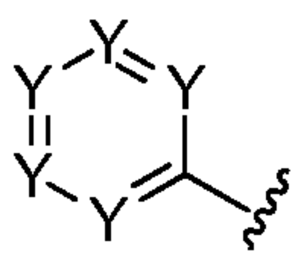
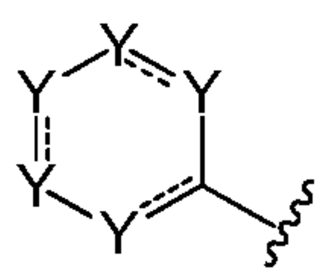
[0122] In some embodiments, at least one Y in  is N. In some embodiments,  is selected from ,  or , each optionally substituted with one to four R^4. In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted .

[0123] In some embodiments, at least one Y in  is N. In some embodiments,  is selected from ,  or , each optionally substituted with one to four R^4. In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted .

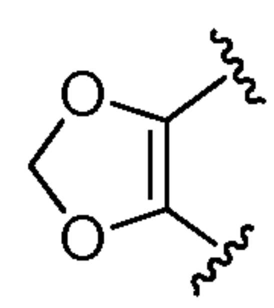
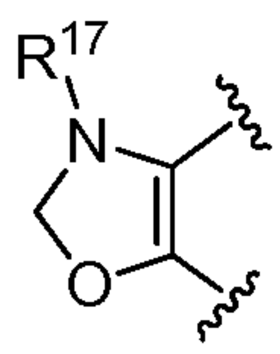
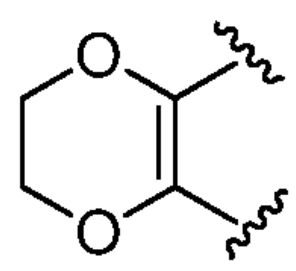
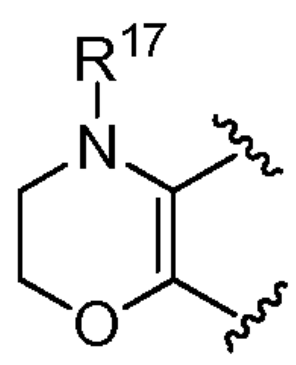
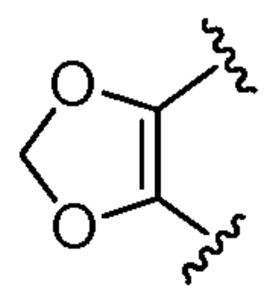
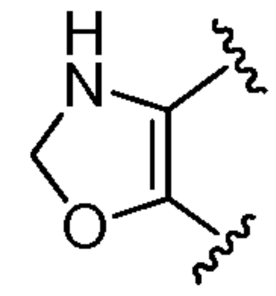
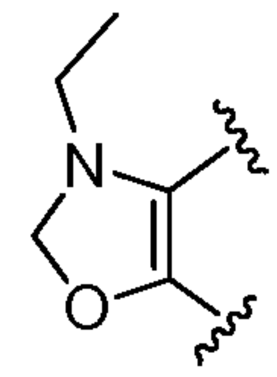
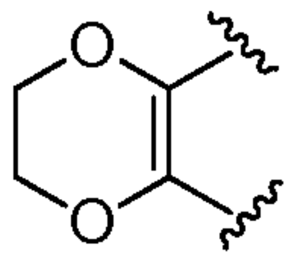
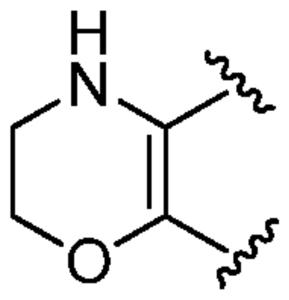
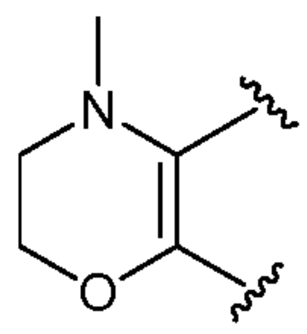
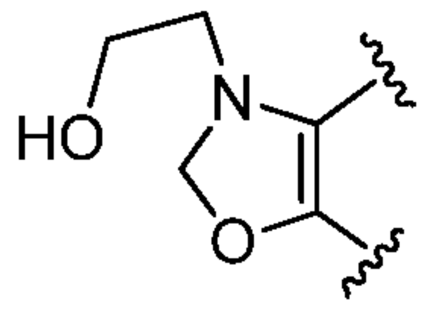
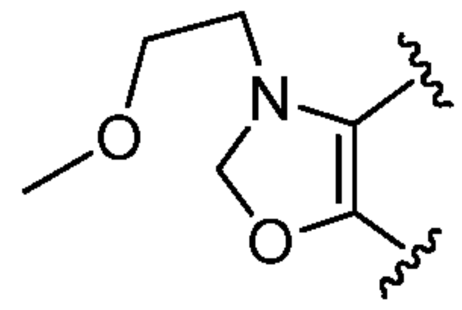
[0124] In some other embodiments, two of Y in  are N. In some embodiments,  is selected from , , , , , ,  or , each optionally substituted with one to three R^4. In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted .

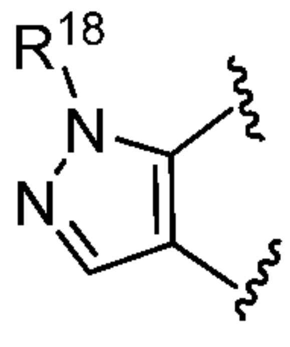
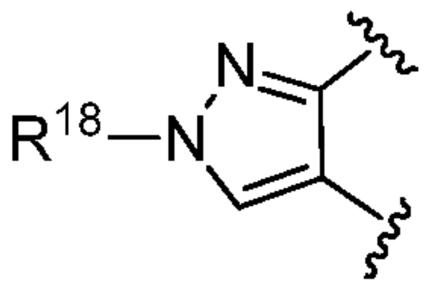
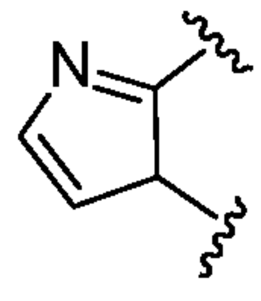
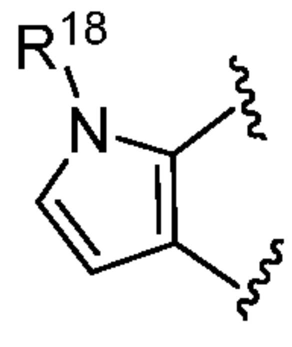
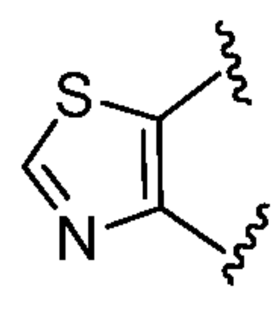
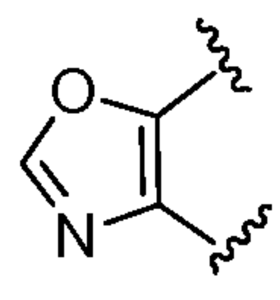
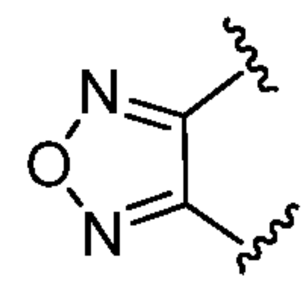
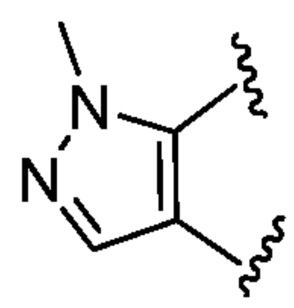
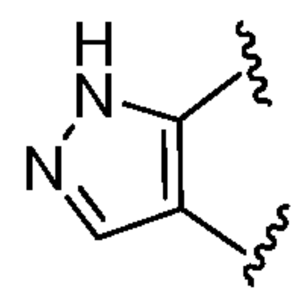
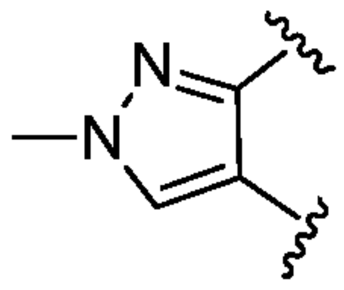
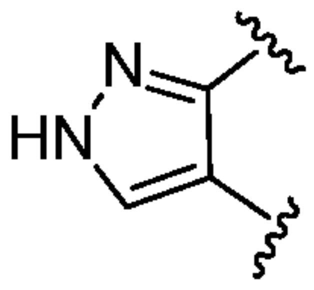
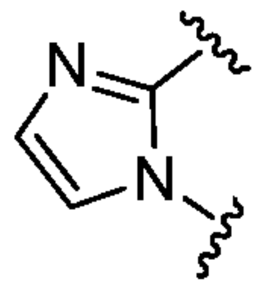
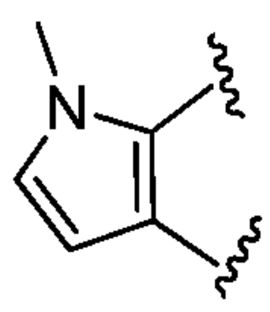
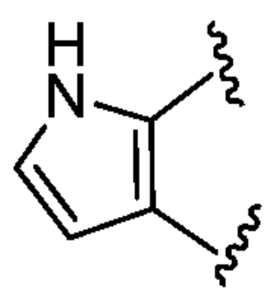
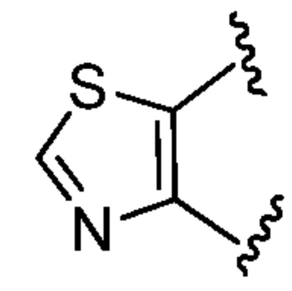
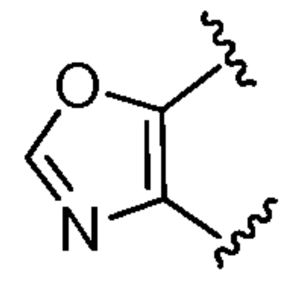
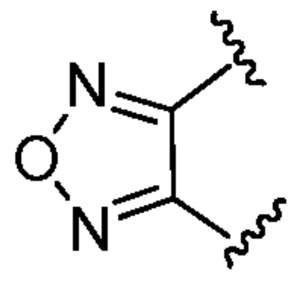
[0125] In some other embodiments, two of Y in  are N. In some such embodiments,  is selected from , , or , each optionally substituted with one to three R^4. In some such further embodiments,  is selected from , , ,  or , each optionally substituted with one to three

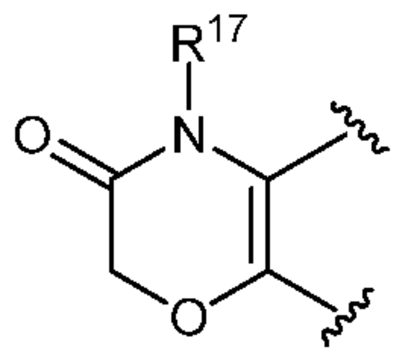
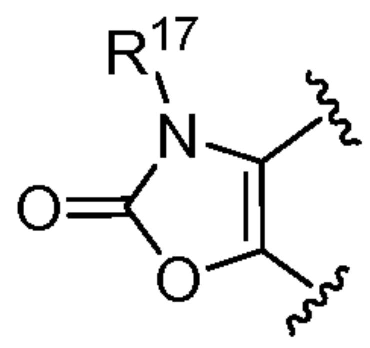
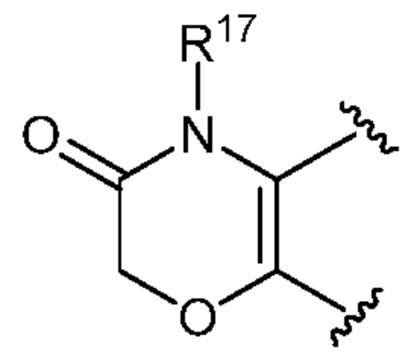
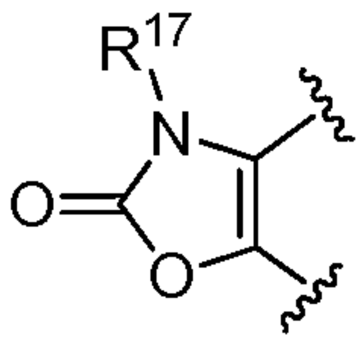
R^4. In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted . In some such embodiments,  is optionally substituted .

[0126] In any of the embodiments of  or  of formula (II) or (IIa) described herein, R^4 is selected from hydrogen, halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy or 5 membered heteroaryl optionally substituted with one or more R^{11}. In some embodiments, R^4 is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or thiazolyl.

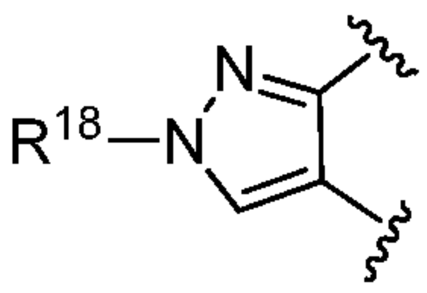
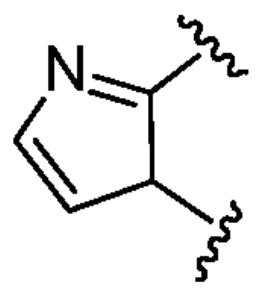
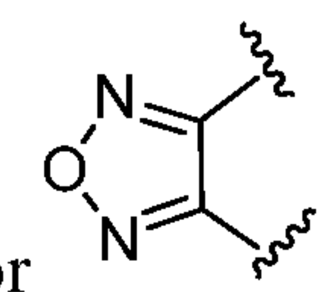
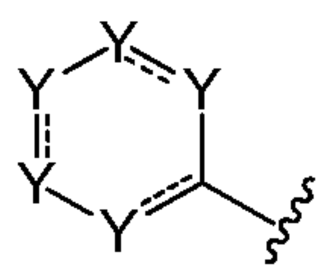
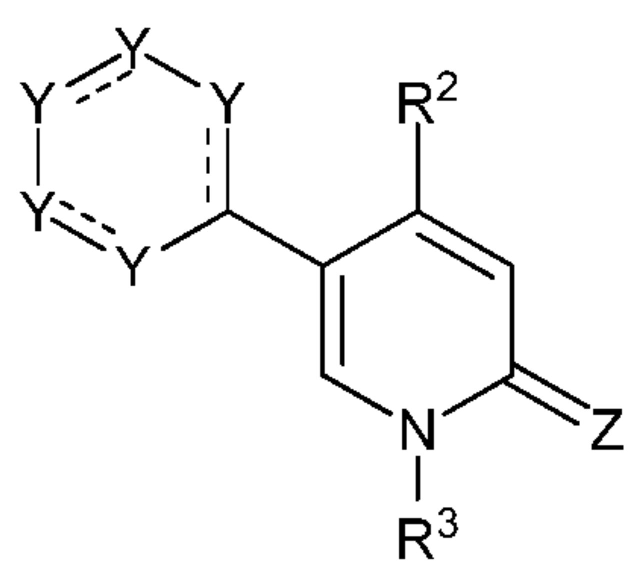
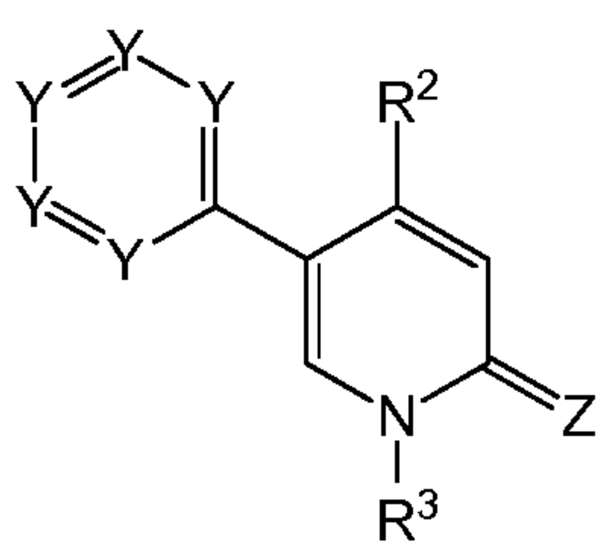
[0127] In some other embodiments, two adjacent R^4 together with the carbon atoms to which they are attached form a fused ring selected from optionally substituted 5 or 6 membered heteroaryl or optionally substituted 5 or 6 membered heterocyclyl.

[0128] In some embodiments, the optionally substituted 5 or 6 membered heterocyclyl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from , , , or , wherein each R^{17} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, or optionally substituted C_{2-8} alkoxyalkyl. In some such embodiments, R^{17} is selected from hydrogen, methyl, ethyl, $-(CH_2)_2OH$ or $-(CH_2)_2OCH_3$. In some futher such embodiments, the optionally substituted 5 or 6 membered heterocyclyl is selected from , , , , , or . In some further such embodiments, the optionally substituted 5 or 6 membered heterocyclyl is selected from  or . In some embodiments, the optionally substituted 5 or 6 membered heterocyclyl is substituted with one or more substituents selected from C_{1-6} alkyl or halogen. In some other embodiments, the 5 or 6 membered heterocyclyl is unsubstituted.

[0129] In some embodiments, the optionally substituted 5 or 6 membered heteroaryl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from , , , , ,  or , wherein each R^{18} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, or optionally substituted C_{2-8} alkoxyalkyl. In some such embodiments, R^{18} is selected from hydrogen or methyl. In some futher such embodiments, the optionally substituted 5 or 6 membered heteroaryl is selected from , , , , , , , ,  or . In some embodiments, the optionally substituted 5 or 6 membered heterocyclyl is substituted with one or more substituents selected from C_{1-6} alkyl or halogen. In some other embodiments, the 5 or 6 membered heterocyclyl is unsubstituted.

[0130] In some embodiments, the substituent on the 5 or 6 membered heteroaryl or 5 or 6 membered heterocyclyl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from C_{1-6} alkyl, C_{1-6} alkoxy, oxo or halogen. In some further embodiments, the substituent is selected from methyl, fluoro, or oxo. In some embodiments, the substituent is oxo. In some such embodiments, the 5 or 6 membered heteroaryl or 5 or 6 membered heterocyclyl are selected from  or . In some embodiments of  or , R^{17} is alkyl.

[0131] In some embodiments, Z is oxygen.

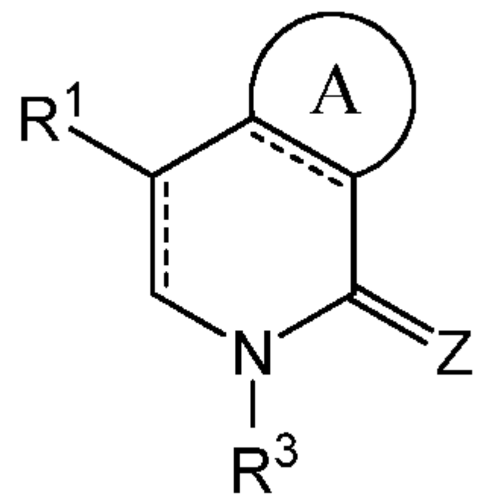
[0132] In some embodiments, the bonds represented by a solid and dashed line are double bonds, provided that when the optionally substituted 5 or 6 membered heteroaryl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from , , or , one of the bonds represented by a solid and dashed line in  is a single bond. In some embodiments, the bonds represented by a solid and dashed line are double bonds in formula (IIa). In some such embodiments, compounds of formula (II) are also represented by . In some such embodiments, compounds of formula (IIa) are also represented by .

[0133] In some embodiments, the compound of formula (II) is selected from the group consisting of **Compounds 163-216**, **241-243**, **245**, **246, 248-252**, **254**, **255**, **258-261**, **263**, **415-430**,

432, **552-567**, **629**, **662** and **663** of Table 1. In some further embodiments, the compound of formula (II) is selected from the group consisting of **Compounds 163-216**, **241-243**, **245**, **246, 248-252**, **254**, **255**, **258-261**, **263**, **415-430**, **432**, **552-561**, **566** and **629** of Table 1.

Formula III

[0134] Some embodiments disclosed herein relate to a compound of formula (III) as described above or a pharmaceutically acceptable salt thereof.



(III)

[0135] Some embodiments disclosed herein with respect to the compounds of formula (III), R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9; and each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -$NR^{14}R^{15}$, -$C(O)R^8$, -SO_2R^{16}, and –NO_2.

[0136] In some embodiments, R^1 is selected from halogen, C_{1-6} alkyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, or 5 to 6-membered heteroaryl optionally substituted with one or more R^4. In some embodiments, R^1 is bromo or fluoro. In some embodiments, R^1 is methyl optionally substituted with one or more R^4. In some embodiments, R^1 is methyl. In some embodiments, R^1 is phenyl optionally substituted with one or more R^4. In some embodiments, R^1 is pyridazinyl optionally substituted with one or more R^4In some embodiments, R^1 is unsubstituted phenyl. In some embodiments, R^1 is pyrazolyl or 1-methyl pyrazolyl optionally substituted with one or more R^4. In some embodiment, R^4 is selected from halogen.

[0137] Some embodiments disclosed herein with respect to the compounds of formula (III), R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9. In some embodiments, n is 0.

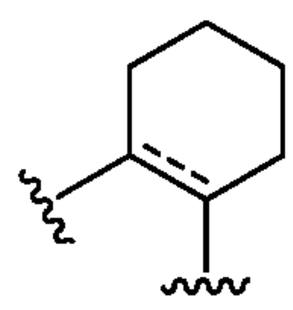
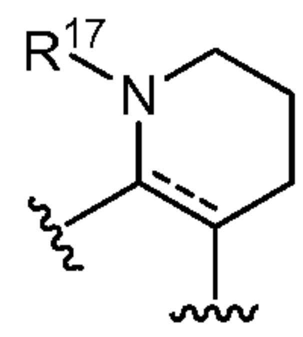
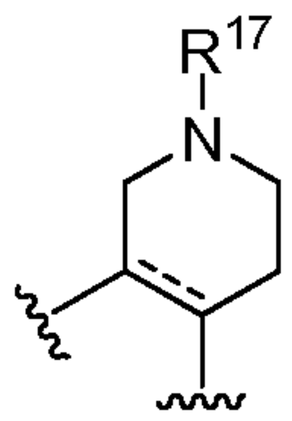
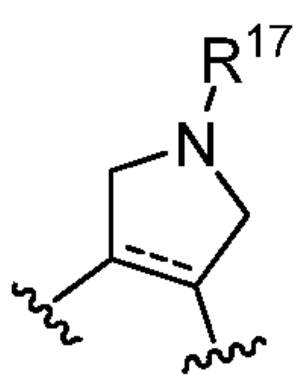
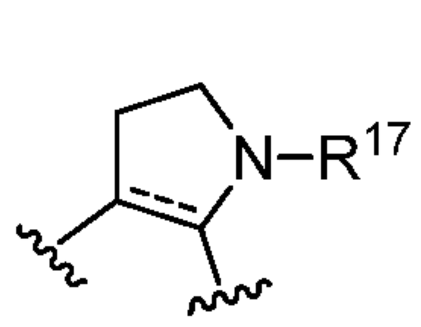
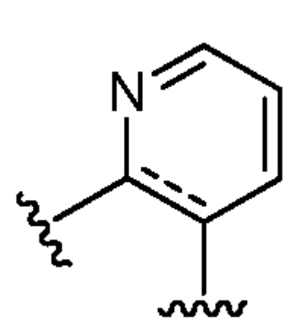
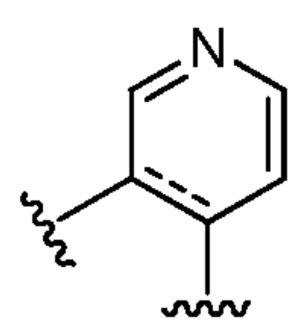
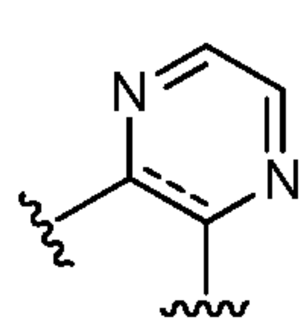
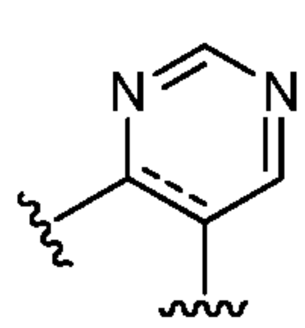
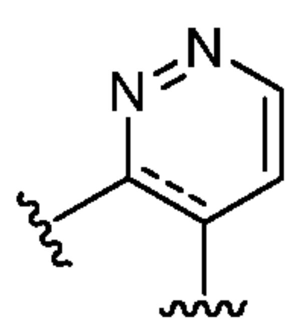
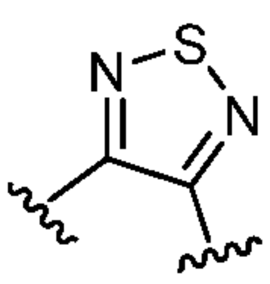
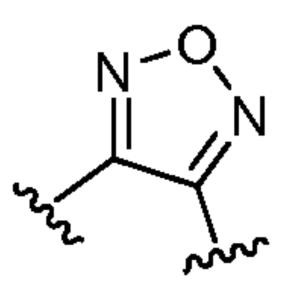
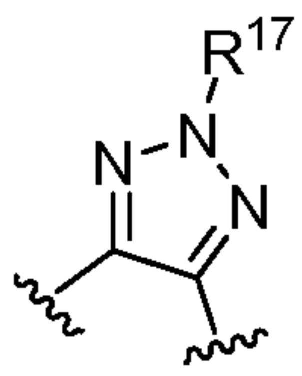
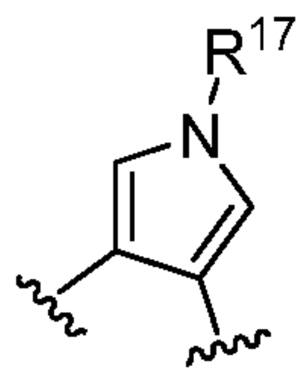
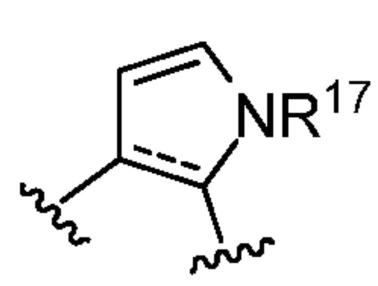
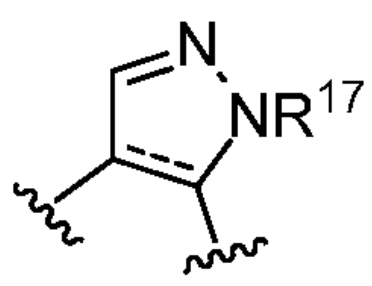
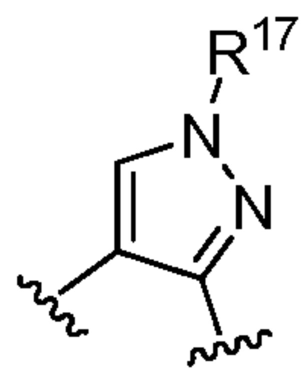
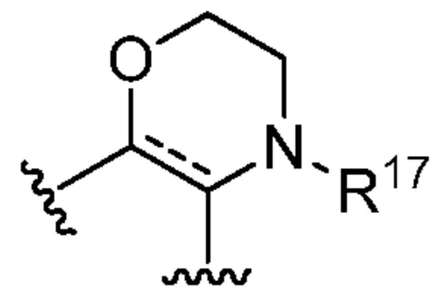
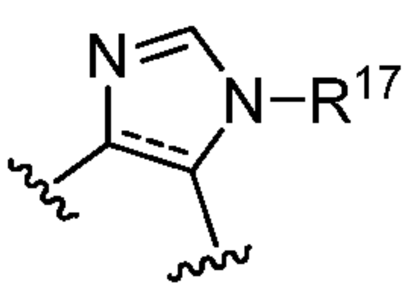
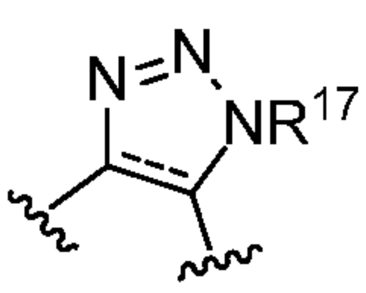
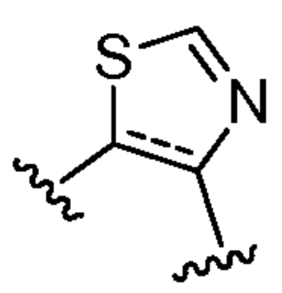
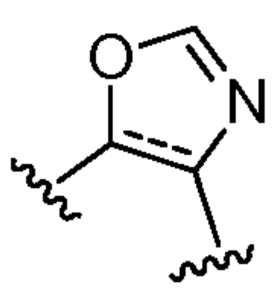
[0138] In some embodiments, R^3 is selected from $-(CH_2)_n-(C_{6-10}$ aryl) optionally substituted with one or more R^9.

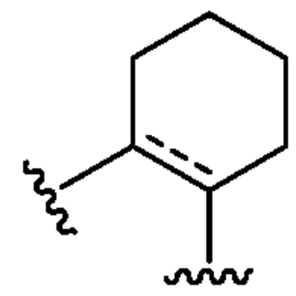
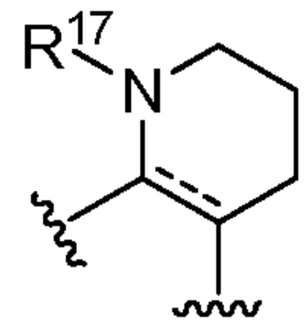
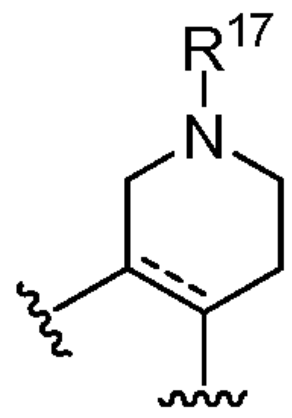
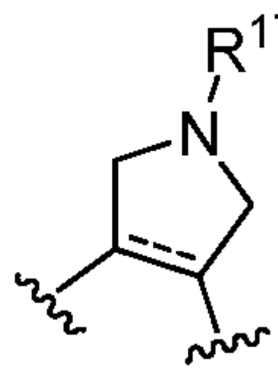
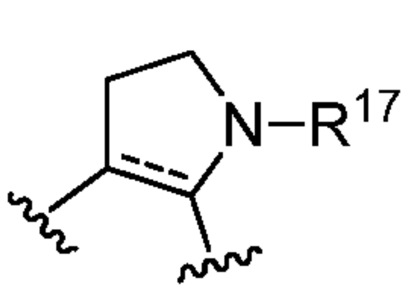
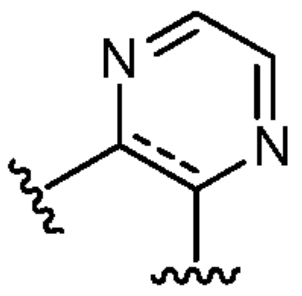
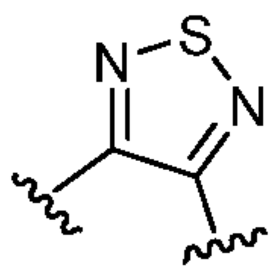
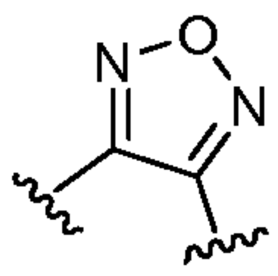
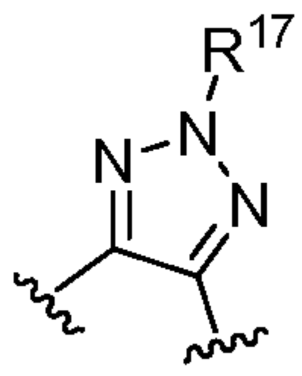
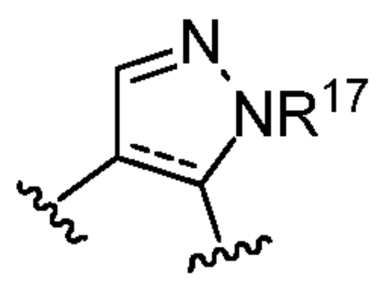
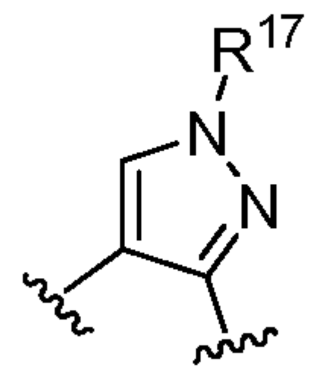
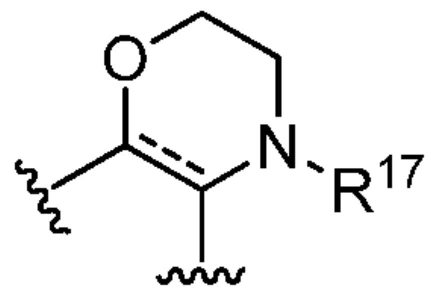
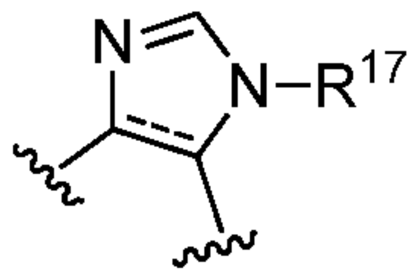
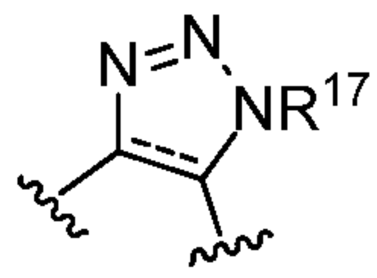
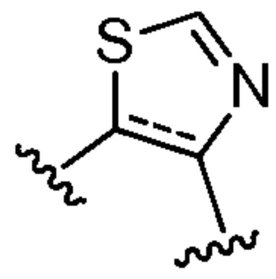
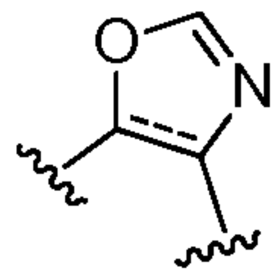
[0139] In some embodiments, R^3 is phenyl, optionally substituted with one or more R^9. In some other embodiments, R^3 is unsubstituted phenyl.

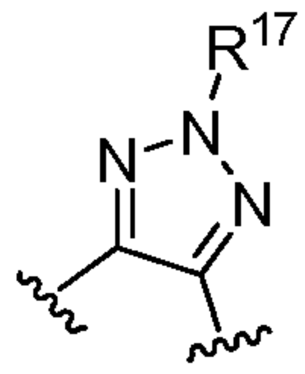
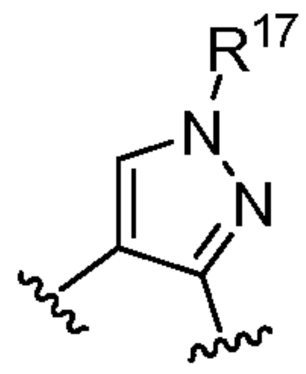
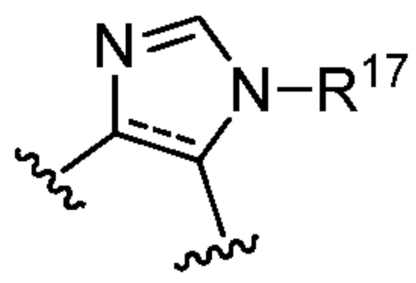
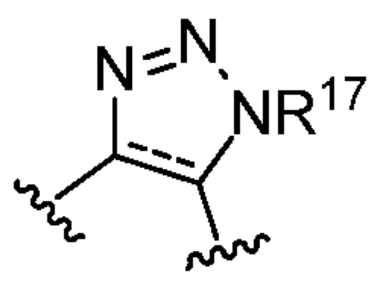
[0140] Some embodiments disclosed herein with respect to the compounds of formula (III), R^3 is hydrogen. In some such embodiments, the the compound of formula (III) is selected from the group consisting of compounds **576, 578, 590, 595, 611-613, 616, 618, 621-623, 637 and 638** of Table 1.

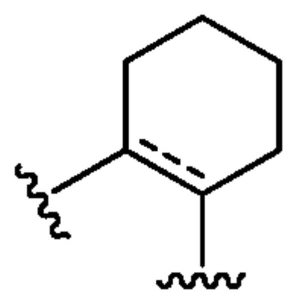
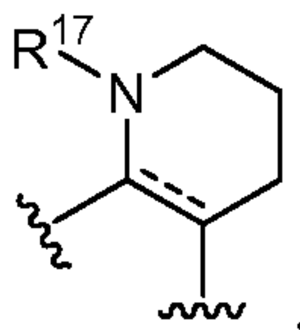
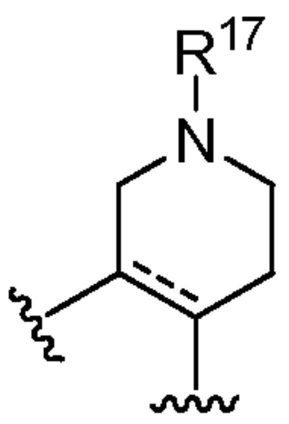
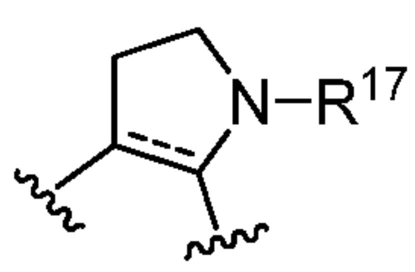
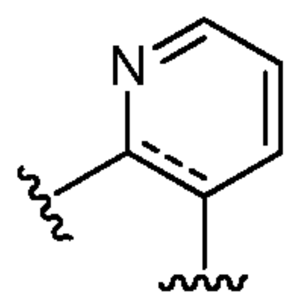
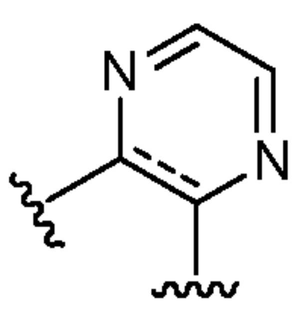
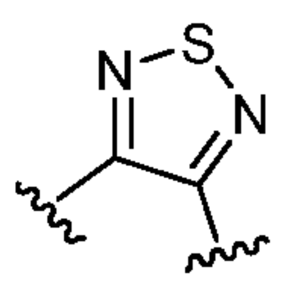
[0141] In any of embodiments of formula (III) described herein, R^9 is selected from cyano, halogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy. In some further embodiments, R^9 is selected from cyano, fluoro, chloro, methyl, ethyl, ethoxy, methoxy, trifluoromethyl or trifluoromethoxy. In some embodiments, R^9 is ethoxy. In some embodiments, R^9 is trifluoromethoxy. In still some other embodiment, R^9 is difluoromethoxy.

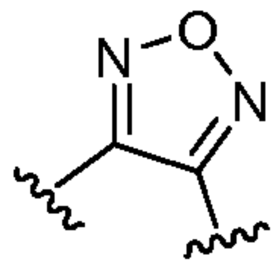
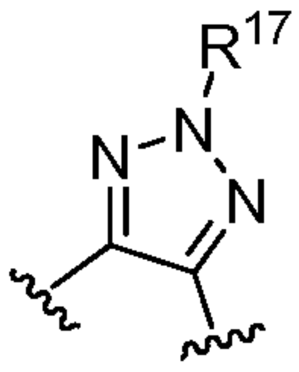
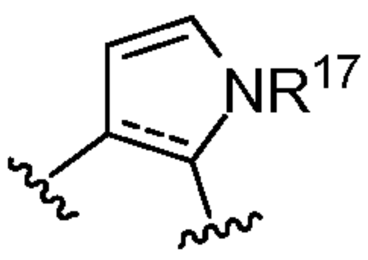
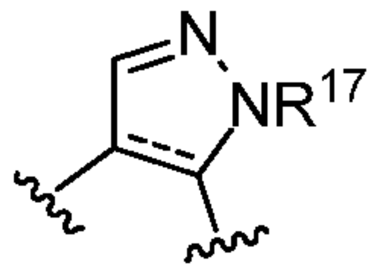
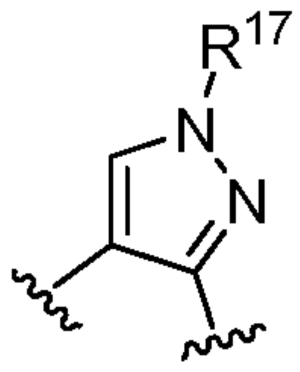
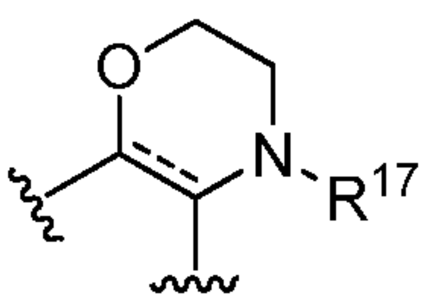
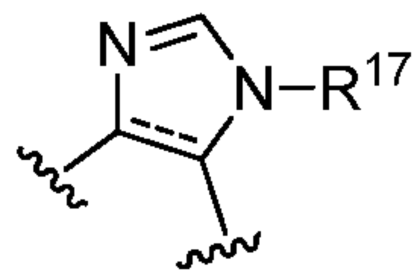
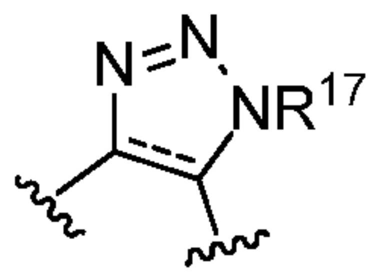
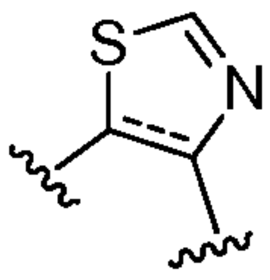
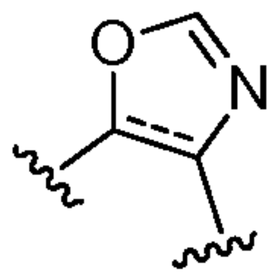
[0142] In any of the embodiments of formula (III) described herein, ring A is selected from 6-membered heteroaryl, 5-membered heterocyclyl or 6-membered heterocyclyl, each optionally substituted with one or more R^4.

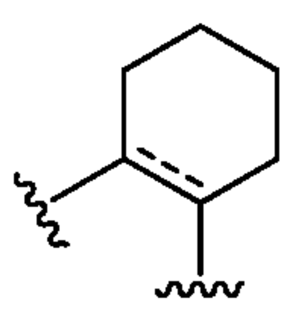
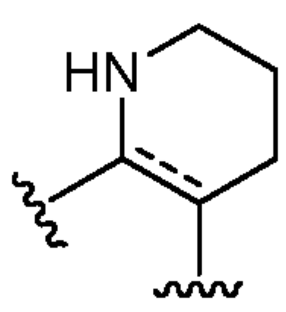
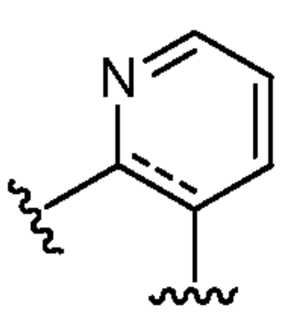
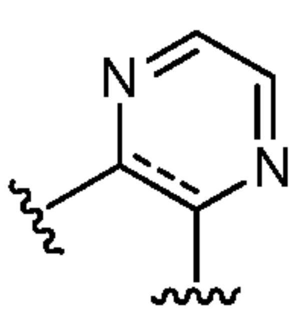
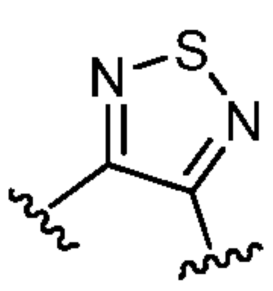
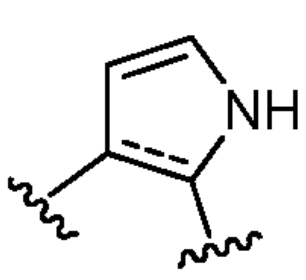
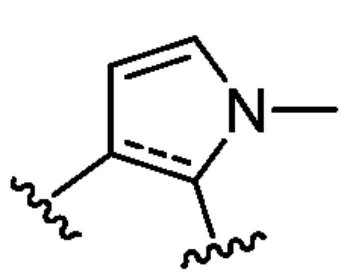
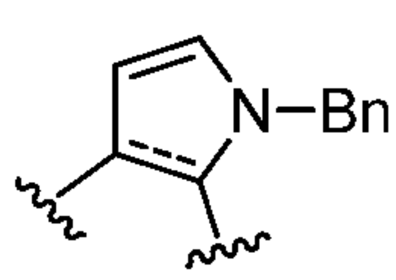
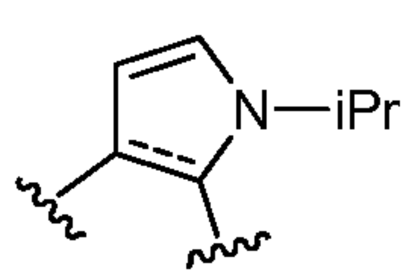
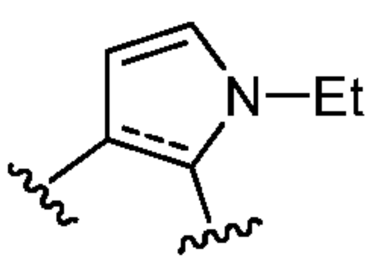
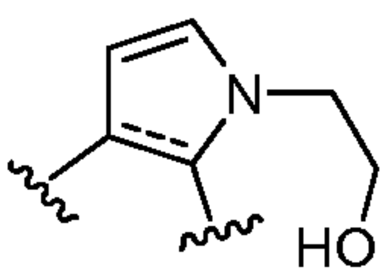
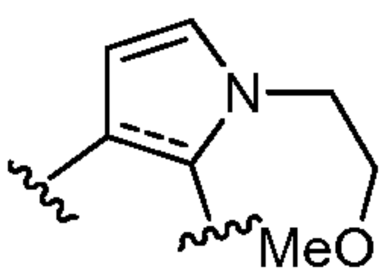
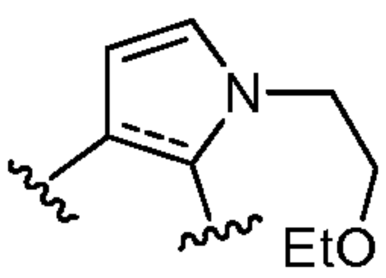
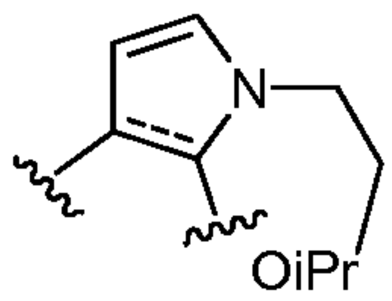
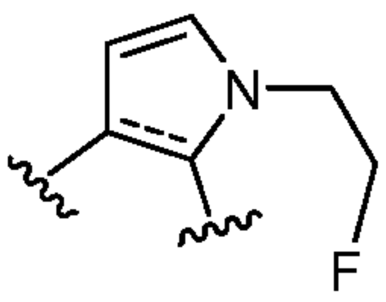
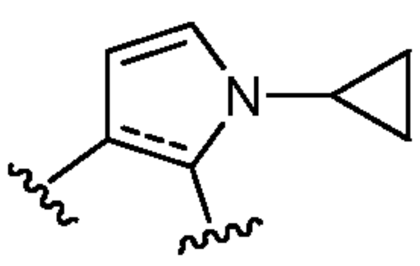
[0143] In some such embodiments, ring A is selected from , , , , , , , , , , , , , , , , , , , ,  or , each optionally substituted with one or more R^4; and wherein each R^{17} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C-carboxy, acyl, C_{6-10} aryl optionally substituted with one or more R^{11}, or C_{7-14} aralkyl optionally substituted with one or more R^{11}.

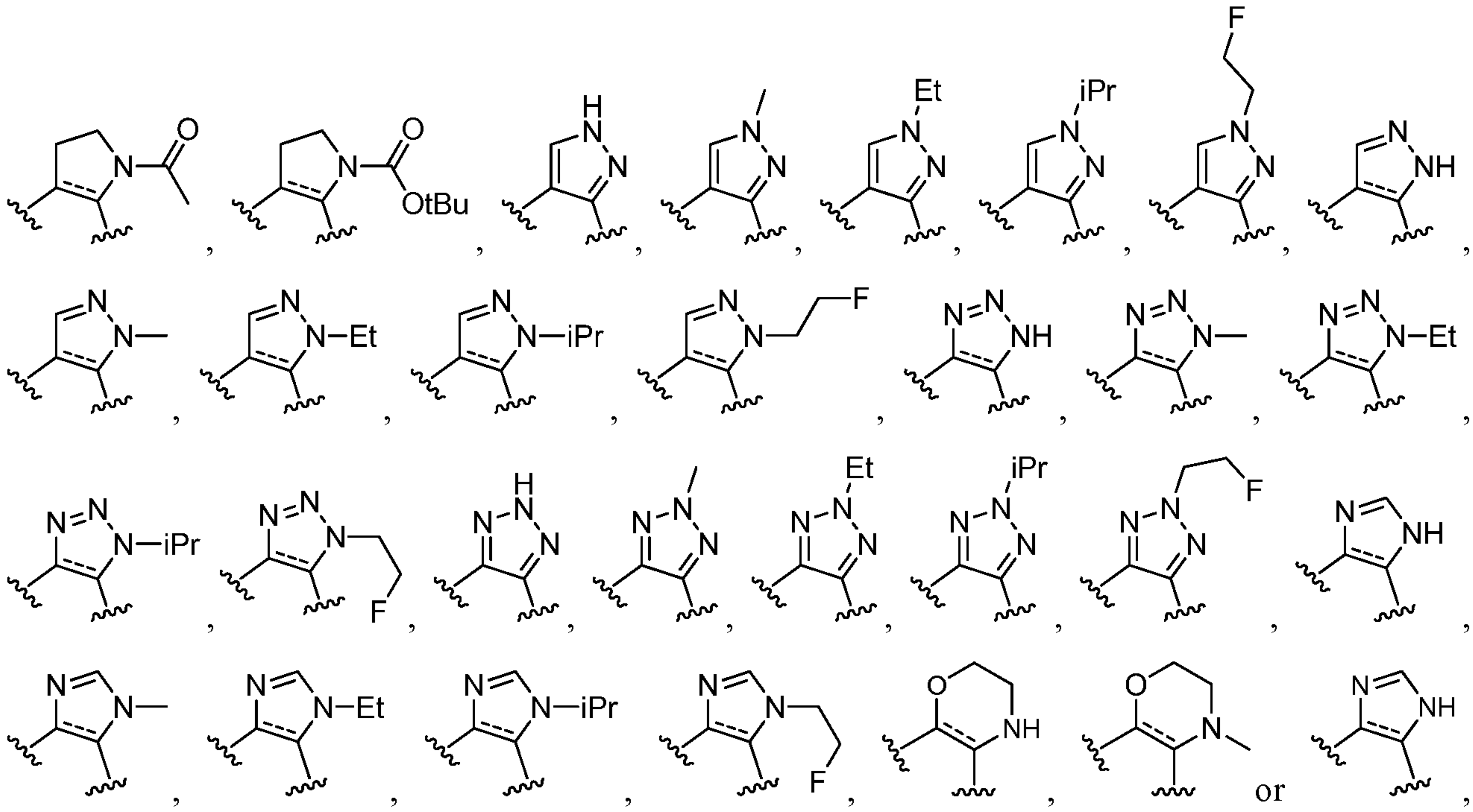
[0144] In some embodiments, ring A is selected from , , , , , , , , , , , , , ,  or , each optionally substituted with one or more R^4.

[0145] In some embodiments, ring A is selected from , ,  or , each optionally substituted with one or more R^4.

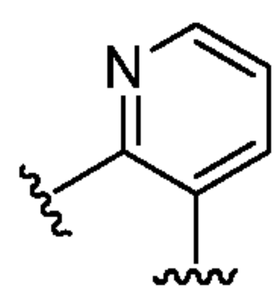
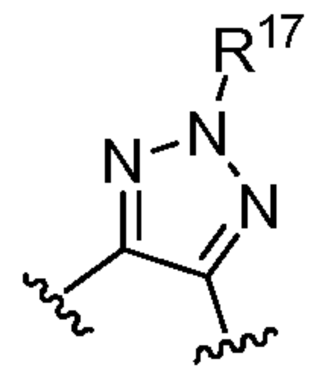
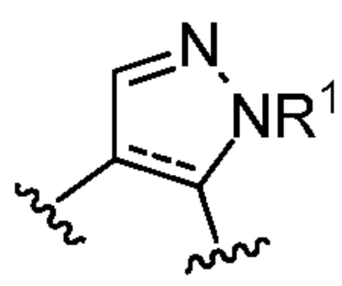
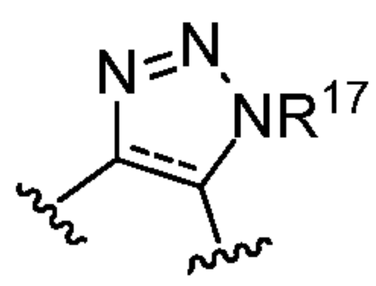
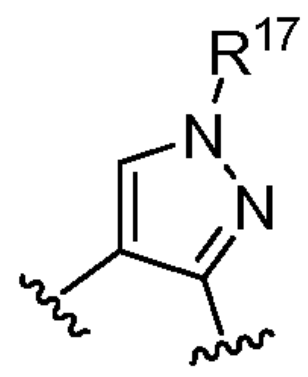
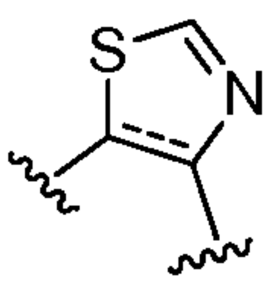
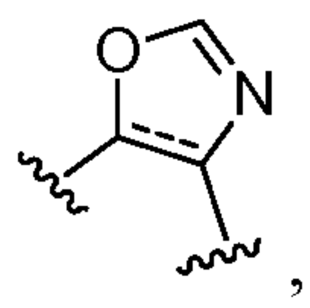
[0146] In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted .

In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In some embodiments, ring A is optionally substituted . In any of embodiments of ring A as described herein in formula (III), R^{17} is selected from hydrogen, methyl, ethyl, isopropyl, cyclopropyl, $-(CH_2)_2F$, $-(CH_2)_2OH$, $-(CH_2)_2OCH_3$, $-(CH_2)_2OC_2H_5$, $-(CH_2)_2OC_3H_7$, $-C(O)O^tBu$, $-C(O)CH_3$ or benzyl.

[0147] In some futher such embodiments, ring A is selected from , , , , , , , , , , , , , , , ,



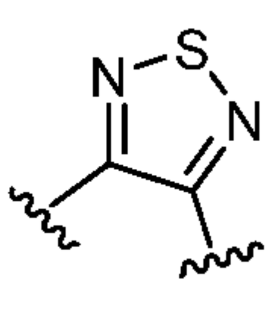
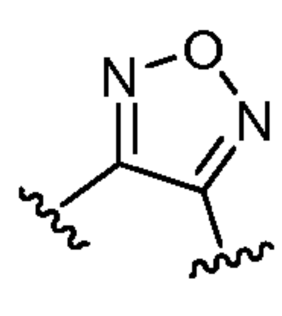
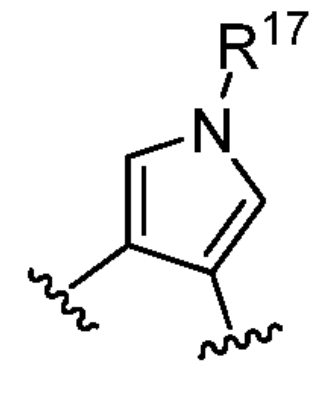
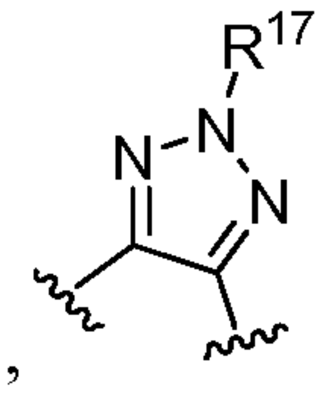
each optionally substituted with one or more R^4.

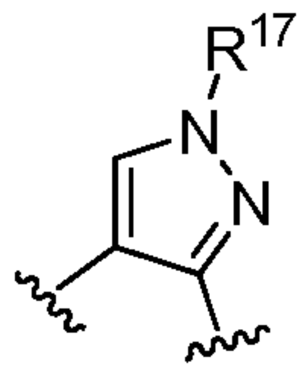
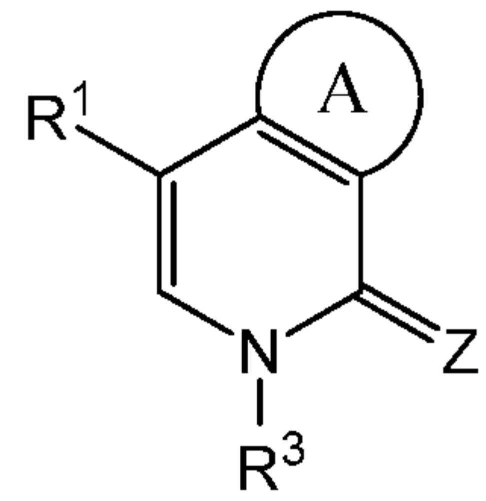
[0148] In some such futher embodiments, ring A is selected from , , , , ,  or , each optionally substituted with one or more R^4.

[0149] In any of the embodiments of formula (III) described herein, R^4 is selected from halogen, optionally substituted C_{1-6} alkyl, or C_{7-14} aralkyl optionally substituted with one or more R^{11}, or two geminal R^4 together are oxo. In some further embodiments, R^4 is selected from fluoro, methyl, trifluoromethyl, or benzyl. In some embodiments, two geminal R^4 together are oxo.

[0150] In some embodiments, ring A is unsubstituted.

[0151] In some embodiments, Z is oxygen.

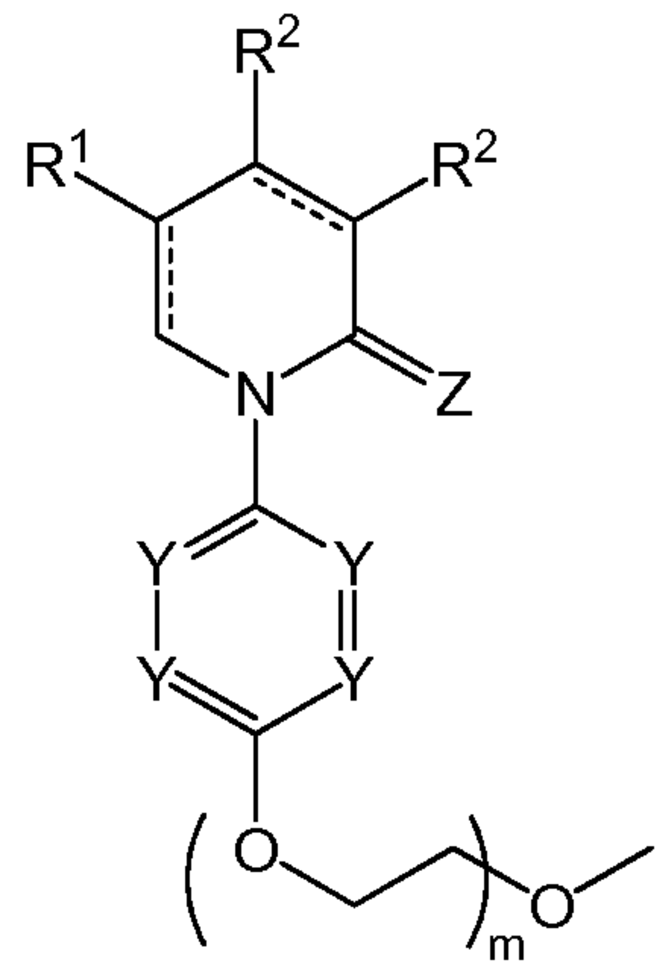
[0152] In some embodiments, the bonds represented by a solid and dashed line are double bonds, provided that when ring A is , , , , or

, one of the bonds represented by a solid and dashed line is a single bond. In some such embodiments, compounds of formula (III) are also represented by .

[0153] In some embodiments, the compound of formula (III) is selected from the group consisting of **Compounds 29-63**, **392-400, 568-628**, **630-661**, and **665** of Table 1. In some futher embodiments, the compound of formula (III) is selected from the group consisting of **Compounds 29-63**, **392-400, 568-574**, **577**, **579-584, 586-589**, **591-594**, **596-608**, **614**, **615**, **617**, **619**, **620**, **624-626**, **631, 634-636**, **640, 642-655, 657-661**, **665**, and **669-695** of Table 1.

Formula IV

[0154] Some embodiments disclosed herein relate to a compound of formula (IV) as described above or a pharmaceutically acceptable salt thereof.



(IV)

[0155] In some embodiments, R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with one or more R^4, or 5-membered heteroaryl optionally substituted with one or more R^4.

[0156] In some embodiments, R^1 is selected from methyl, phenyl, pyrazolyl, or 1-methyl pyrazolyl, each optionally substituted with one or more R^4. In some embodiments, R^1 is methyl. In some embodiments, R^1 is unsubstituted phenyl. In some embodiments, R^1 is unsubstituted pyrazolyl. In yet some other embodiments, R^1 is unsubstituted 1-methyl pyrazolyl.

[0157] In some embodiments, R^2 is selected from hydrogen or optionally substituted C_{1-6} alkyl.

[0158] In some embodiments, all Y are CR^4. In some other embodiment, at least one Y is nitrogen.

[0159] In some embodiments, R^4 is selected from halogen, C_{1-6} alkyl or C_{1-6} alkoxy. In some embodiments, R^4 is selected from fluoro or methyl.

[0160] In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

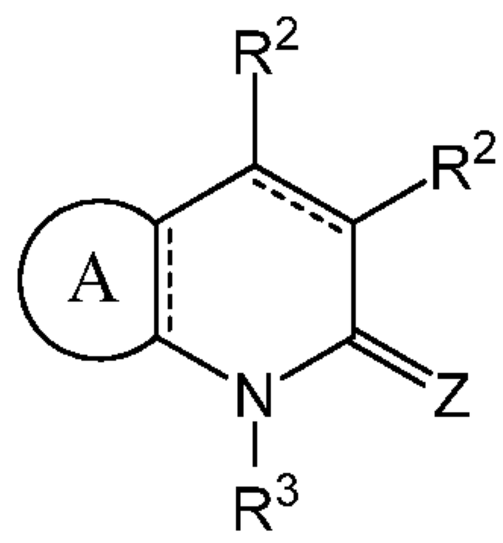
[0161] In some embodiments, Z is oxygen.

[0162] In some embodiments, the bonds represented by a solid and dashed line are double bonds.

[0163] In some embodiments, the compound of formula (IV) is selected from the group consisting of **Compounds 21-26** of Table 1.

Formula V

[0164] Some embodiments disclosed herein relate to a compound of formula (V) as described above or a pharmaceutically acceptable salt thereof.



(V)

[0165] In some embodiments, each R^2 is independently selected from hydrogen, C_{1-6} alkyl or $-OR^5$.

[0166] In some embodiments, each R^2 is hydrogen.

[0167] In some embodiments, R^3 is $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9. In some embodiments, R^3 is phenyl, optionally substituted with one or more R^9. In some other embodiments, R^3 is unsubstituted phenyl.

[0168] In some embodiments, R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, or $-NR^{14}R^{15}$. In some embodiments, R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$. In some embodiments, R^9 is trifluoromethoxy.

[0169] In some embodiments, ring A is a C_5 carbocyclyl optionally substituted with one or more R^4. In some embodiments, ring A is a C_6 carbocyclyl optionally substituted with one or more R^4. In some other embodiments, ring A is unsubstituted.

[0170] In some embodiments, wherein R^4 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, or independently two geminal R^4 together are oxo.

[0171] In some embodiments, ring A is an unsubstituted C_{5-7} carbocyclyl.

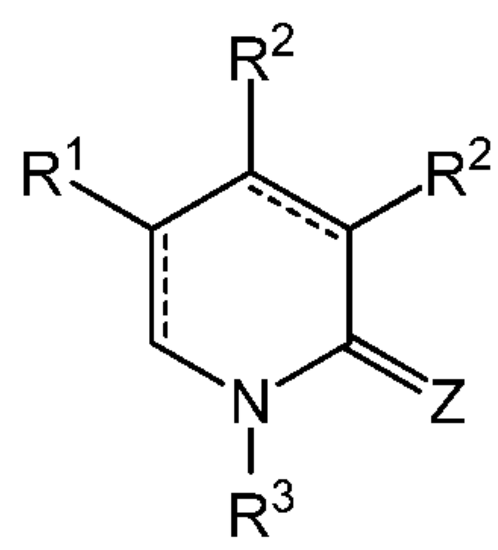
[0172] In some embodiments, Z is oxygen.

[0173] In some embodiments, the bonds represented by a solid and dashed line are double bonds.

[0174] In some embodiments, the compound of formula (V) is selected from the group consisting of **Compounds 27** and **28** of Table 1.

<u>Formula VIa</u>

[0175] Some embodiments disclosed herein relate to a compound of formula (VIa) as described above or a pharmaceutically acceptable salt thereof.



(VIa)

[0176] In some embodiments, R^1 is a C_4 carbocyclyl optionally substituted with one or more R^4.

[0177] In some embodiments, R^1 is a C_5 carbocyclyl optionally substituted with one or more R^4.

[0178] In some embodiments, R^1 is a C_6 carbocyclyl optionally substituted with one or more R^4.

[0179] In some embodiments, R^4 is selected from halogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy. In some embodiments, R^4 is selected from fluoro, chloro, methyl, methoxy, ethoxy, trifluoromethyl, or trifluoromethoxy.

[0180] In some other embodiments, R^1 is unsubstituted.

[0181] In some embodiments, each R^2 is independently selected from hydrogen, halogen, optionally substituted C_{1-6} alkyl, $-OR^5$ or $-NR^6R^7$. In some embodiments, R^2 is hydrogen. In some embodiment, R^2 is halogen.

[0182] In some embodiments, R^2 is optionally substituted C_{1-6} alkyl. In some embodiments, R^2 is methyl. In some other embodiments, R^2 is trifluoromethyl.

[0183] In some embodiments, R^3 is selected from $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9. In some embodiments, R^3 is phenyl, optionally substituted with one or more R^9.

[0184] In some embodiments, R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, or $-NR^{14}R^{15}$. In some embodiments, R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

[0185] In some embodiment, R^3 is unsubstituted phenyl.

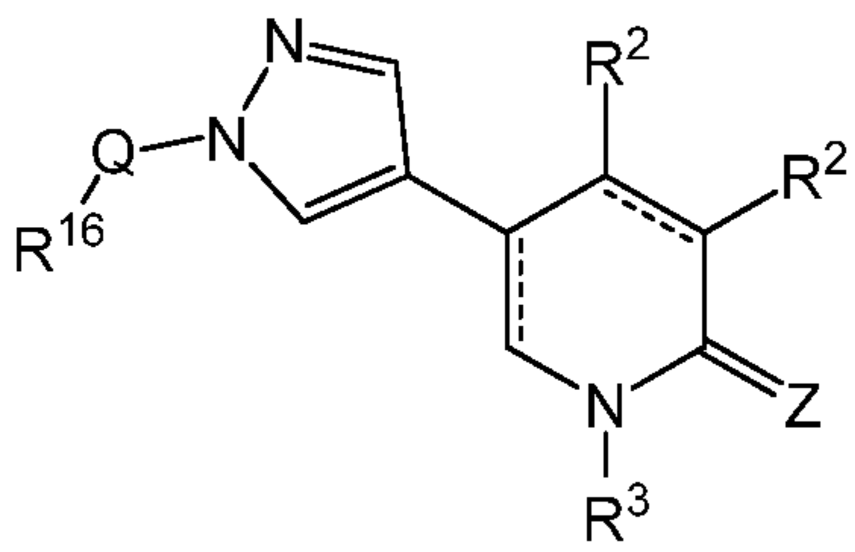
[0186] In some embodiments, Z is oxygen.

[0187] In some embodiments, the bonds represented by a solid and dashed line are double bonds.

[0188] In some embodiments, the compound of formula (VIa) is selected from the group consisting of **Compounds 64-66** of Table 1.

Formula VII

[0189] Some embodiments disclosed herein relate to a compound of formula (VII) as described above or a pharmaceutically acceptable salt thereof.



(VII)

[0190] In some embodiments, each R^2 is independently selected from hydrogen, halogen, optionally substituted C_{1-6} alkyl, $-OR^5$ or $-NR^6R^7$. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is halogen. In some embodiments, R^2 is optionally substituted C_{1-6} alkyl. In some further embodiments, R^2 is methyl or trifluoromethyl.

[0191] In some embodiments, R^3 is selected from $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9. In some embodiments, R^3 is phenyl optionally substituted with one or more R^9.

[0192] In some embodiments, R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, or $-NR^{14}R^{15}$. In some embodiments, R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

[0193] In some embodiments, R^3 is unsubstituted phenyl.

[0194] In some embodiments, Q is C(O). In some other embodiments, Q is $S(O)_t$. In some embodiments, t is 2.

[0195] In some embodiments, R^{16} is selected from optionally substituted C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, or $-OR^5$. In some embodiments, R^{16} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{16} is selected from methyl, ethyl, propyl, isopropyl, or butyl. In some embodiments, R^{16} is phenyl optionally substituted with one or more R^{11}. In some other embodiments, R^{16} is unsubstituted phenyl. In some embodiments, R^{16} is benzyl optionally substituted with one or more R^{11}. In some other embodiments, R^{16} is unsubstituted benzyl. In some embodiments, R^{16} is $-NR^{12}R^{13}$. In some embodiments, each R^{12} and R^{13} is independently selected from hydrogen or optionally substituted C_{1-6} alkyl. In some embodiments, R^{16} is $-OR^5$. In some embodiments, R^5 is selected from hydrogen or optionally substituted C_{1-6} alkyl. In some further embodiments, R^5 is selected from methyl, ethyl, propyl, isopropyl, or butyl.

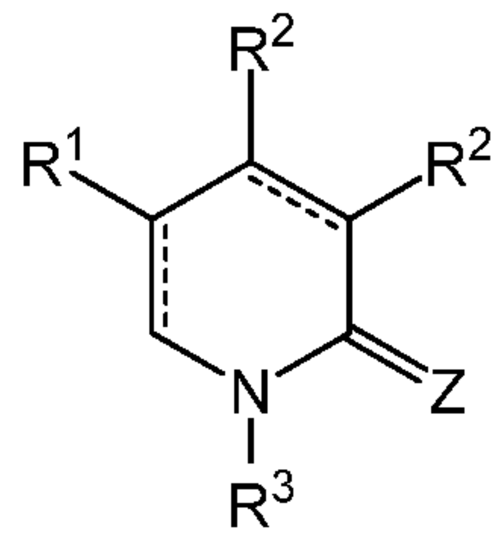
[0196] In some embodiments, Z is oxygen.

[0197] In some embodiments, the bonds represented by a solid and dashed line are double bonds.

[0198] In some embodiments, the compound of formula (VII) is selected from the group consisting of **Compounds 67-76** of Table 1.

<u>Formula VIb</u>

[0199] Some embodiments disclosed herein relate to a compound of formula (VIb) as described above or a pharmaceutically acceptable salt thereof.



(VIb)

[0200] In some embodiments, R^1 is selected from C_{1-6} alkyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, or 5-10 membered heteroaryl optionally substituted with one or more R^4. In some embodiments, R^1 is selected from C_{1-6} alkyl optionally substituted with one or more R^4. In some further embodiments, R^1 is selected from methyl, ethyl, propyl, or isopropyl. In some further embodiments, R^1 is phenyl optionally substituted with one or more R^4. In some embodiments, R^1 is selected from 5 or 6 membered heteroaryl, each optionally substituted with one or more R^4. In some further embodiments, R^1 is selected from pyrazolyl or 1-methyl pyrazolyl, each optionally substituted with one or more R^4. In some other embodiment, R^1 is unsubstituted.

[0201] In some embodiments, R^4 is selected from halogen or optionally substituted C_{1-6} alkyl. In some embodiments, R^4 is fluoro.

[0202] In some embodiments, each R^2 is independently selected from hydrogen, halogen, or optionally substituted C_{1-6} alkyl. In some embodiments, R^2 is hydrogen.

[0203] In some embodiments, R^3 is $-(CH_2)_{1-4}-(C_{6-10}$ aryl), optionally substituted with one or more R^9. In some embodiments, R^3 is $-(CH_2)_{1-4}$-phenyl, optionally substituted with one or more R^9. In some other embodiments, R^3 is unsubstituted. In some embodiments, R^3 is $-(CH_2)$-phenyl, optionally substituted with one or more R^9. In some embodiments, R^3 is $-(CH_2)_2$-phenyl, optionally substituted with one or more R^9. In some other embodiments, R^3 is unsubstituted.

[0204] In some embodiments, R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, $-C(O)R^8$ or $-NR^{14}R^{15}$. In some further embodiments, R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-C(O)CH_3$, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

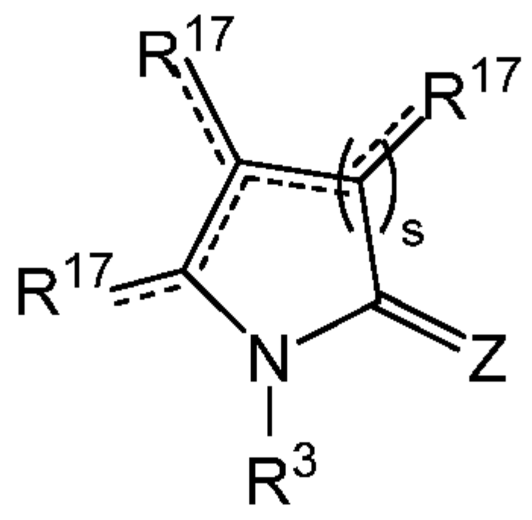
[0205] In some embodiments, Z is oxygen.

[0206] In some embodiments, the bonds represented by a solid and dashed line are double bonds.

[0207] In some embodiments, the compound of formula (VIb) is selected from the group consisting of **Compounds 77-80** of Table 1.

Formula VIII

[0208] Some embodiments disclosed herein relate to a compound of formula (VIII) as described above or a pharmaceutically acceptable salt thereof.



(VIII)

[0209] In some embodiments, R^3 is selected from optionally substituted C_{1-6} alkyl or -$(CH_2)_n$-(C_{6-10} aryl) optionally substituted with one or more R^9. In some embodiments, R^3 is -$(CH_2)_n$-(C_{6-10} aryl) optionally substituted with one or more R^9. In some embodiments, R^3 is phenyl optionally substituted with one or more R^9.

[0210] In some embodiments, R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, -OR^5, -$C(O)R^8$ or -$NR^{14}R^{15}$. In some further embodiments, R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, -$C(O)CH_3$, -$NHCH_3$, -NH_2, or -$NHC(O)CH_3$. In some embodiments, R^9 is trifluoromethoxy.

[0211] In some other embodiments, R^3 is unsubstituted phenyl.

[0212] In some embodiments, R^3 is optionally substituted C_{1-6} alkyl. In some further embodiments, R^3 is C_{1-6} alkyl.

[0213] In some embodiments, each R^{17} is independently selected from hydrogen, halogen, optionally substituted C_{1-6} alkyl or oxo. In some embodiments, each R^{17} is hydrogen.

[0214] In some embodiments, two adjacent R^{17} together with the carbon atoms to which they are attached form a fused phenyl optionally substituted with one or more R^4. In some further embodiments, at least one R^{17} is oxo. In some embodiments, at least one R^{17} is optionally substituted C_{1-6} alkyl. In some embodiments, the fused phenyl is unsubstituted.

[0215] In some embodiments, two adjacent R^{17} together with the carbon atoms to which they are attached form a fused 5-6 membered heteroaryl, optionally substituted with one or more R^4. In some embodiments, at least one R^{17} is oxo. In some embodiments, at least one R^{17} is optionally substituted C_{1-6} alkyl. In some embodiments, the fused 5-6 membered heteroaryl is unsubstituted.

[0216] In some embodiments, R^4 is selected from halogen or optionally substituted C_{1-6} alkyl.

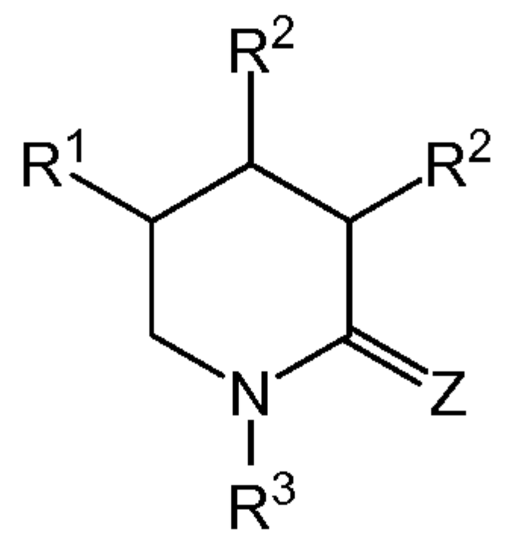
[0217] In some embodiments, n is 0. In some other embodiments, n is 1. In yet some other embodiments, n is 3.

[0218] In some embodiments, Z is oxygen.

[0219] In some embodiments, the compound of formula (VIII) is selected from the group consisting of **Compounds 81**, **82**, and **513-519** of Table 1.

Formula IX

[0220] Some embodiments disclosed herein relate to a compound of formula (IX) as described above or a pharmaceutically acceptable salt thereof.



(IX)

[0221] In some embodiments, R^1 is selected from C_{1-6} alkyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, or 5-10 membered heteroaryl optionally substituted with one or more R^4. In some embodiments, R^1 is C_{1-6} alkyl optionally substituted with one or more R^4. In some embodiments, R^1 is C_{6-10} aryl optionally substituted with one or more R^4.

[0222] In some futher embodiments, R^1 is phenyl optionally substituted with one or more R^4. In some embodiments, R^1 is 5 or 6 membered heteroaryl optionally substituted with one or more R^4. In some further embodiments, R^1 is pyrazolyl or 1-methyl pyrazolyl optionally substituted with one or more R^4.

[0223] In some embodiments, R^4 is selected from halogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy.

[0224] In some embodiments, R^1 is unsubstituted.

[0225] In some embodiments, each R^2 is independently selected from hydrogen, halogen or optionally substituted C_{1-6} alkyl. In some embodiments, R^2 is hydrogen.

[0226] In some embodiments, R^3 is $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9. In some futher embodiments, R^3 is phenyl optionally substituted with one or more R^9. In some other embodiments, R^3 is unsubstituted.

[0227] In some embodiments, R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, $-C(O)R^8$ or $-NR^{14}R^{15}$. In some further embodiments, R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-C(O)CH_3$, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

[0228] In some embodiments, Z is oxygen.

[0229] In some embodiments, the compound of formula (IX) is selected from the group consisting of **Compounds 83**, **84**, **520-522** of Table 1.

[0230] Some embodiments described herein relate to one or more compounds selected from the group consisting of **Compounds 1-20, 217-240, 244, 247, 253, 256, 257, 262, 264-283, 285, 287-339, 341-391, 431, 433, 434, 438-440, 442, 446-512, 546-549, 575, 585, 609, 610, 627, 628, 630, 632, 633, 639, 641, 656, 666-668, 708** and **709** of Table 1.

[0231] In some embodiments, compounds are selected from the following compounds as listed in Table 1.

TABLE 1.

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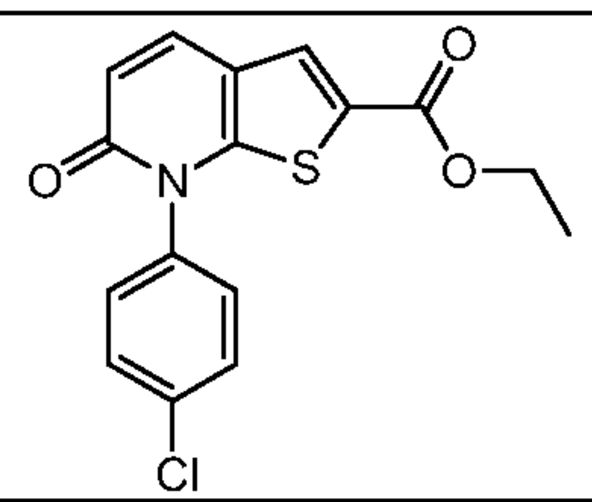
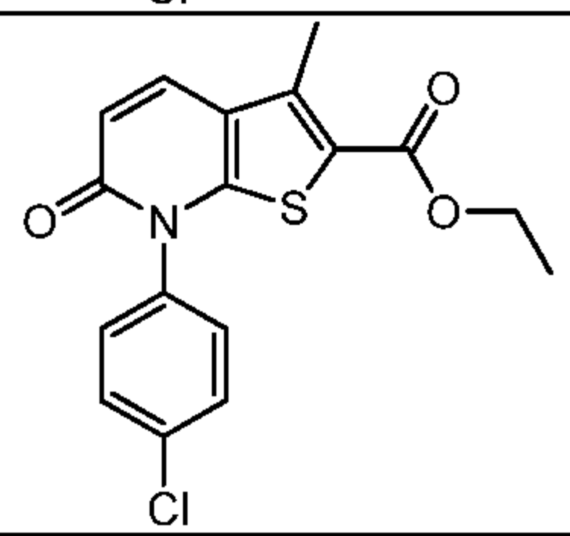
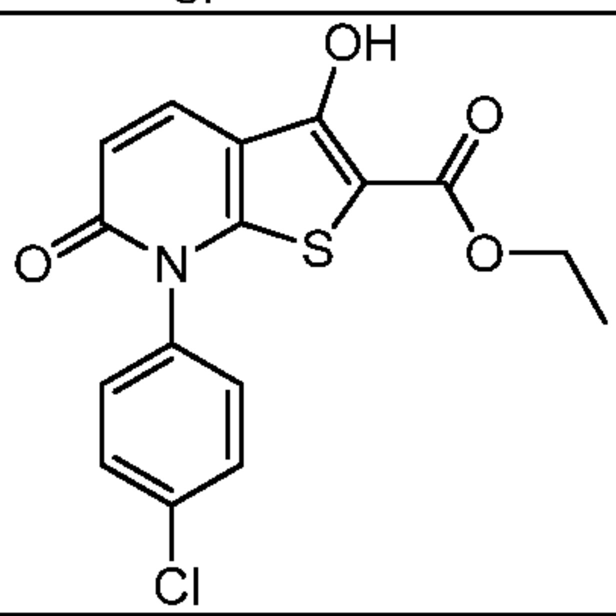
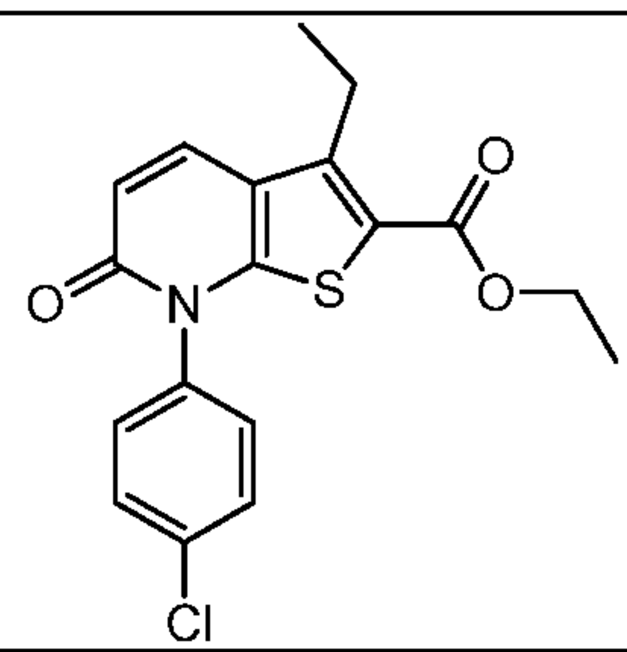
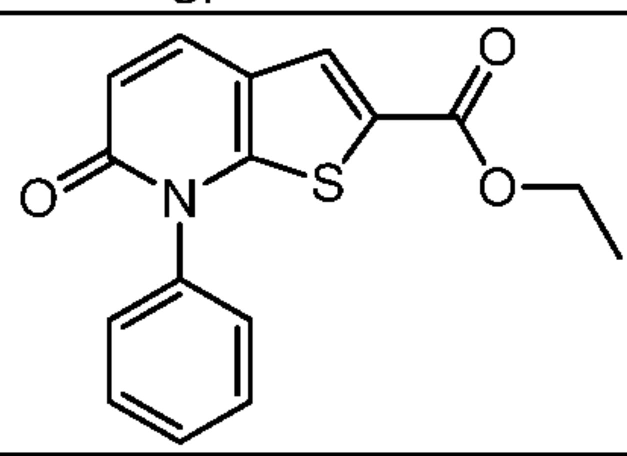
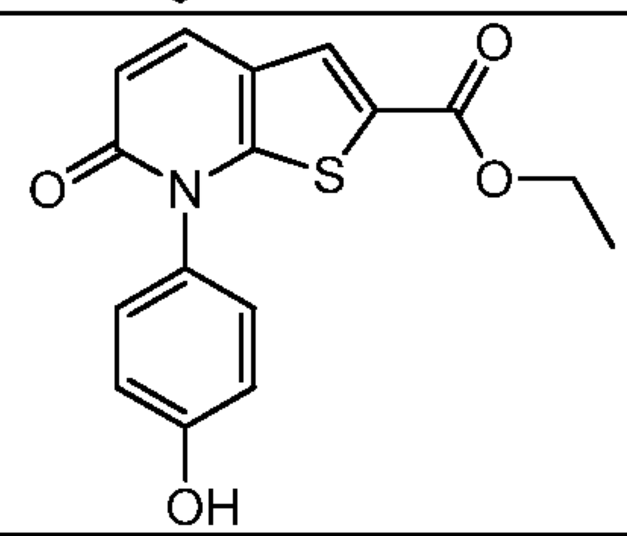
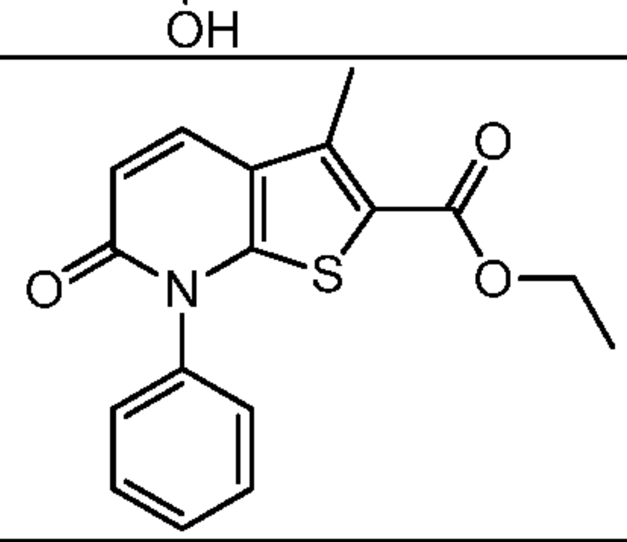
1	
2	
3	
4	
5	
6	
7	

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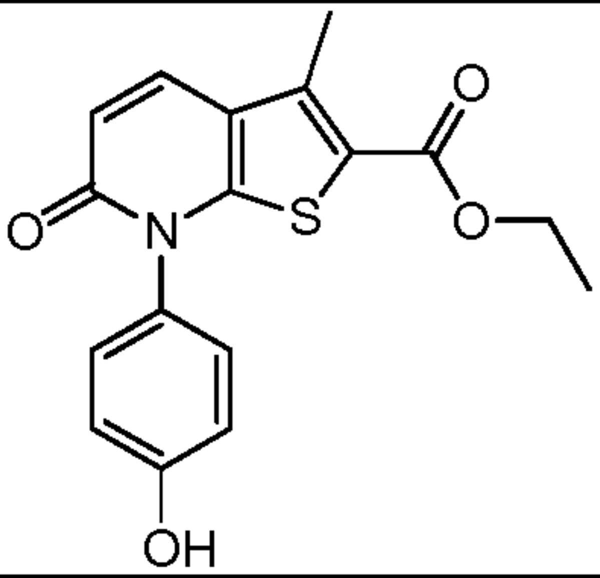
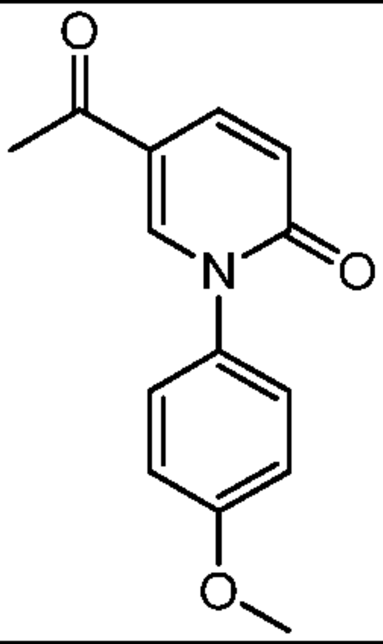
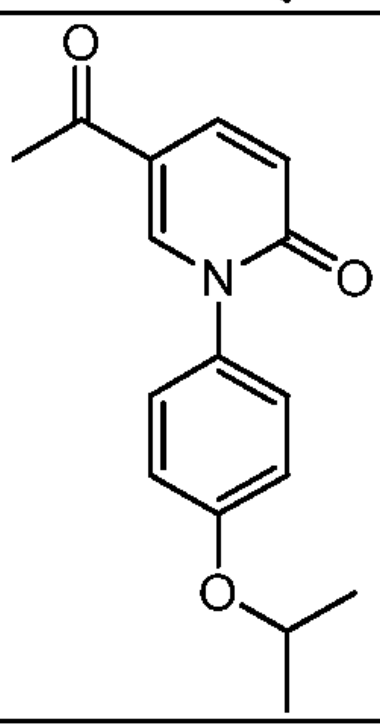
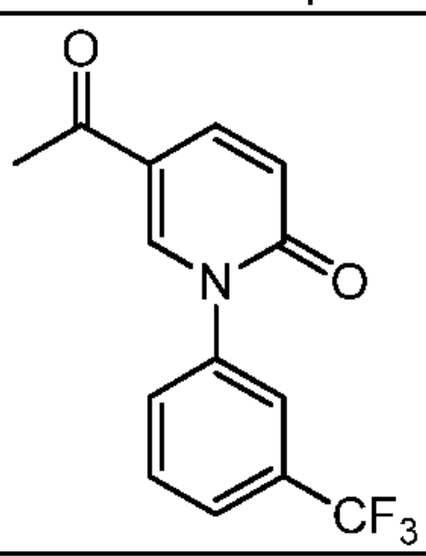
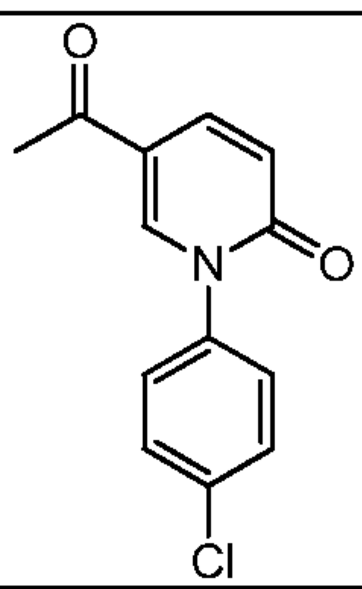
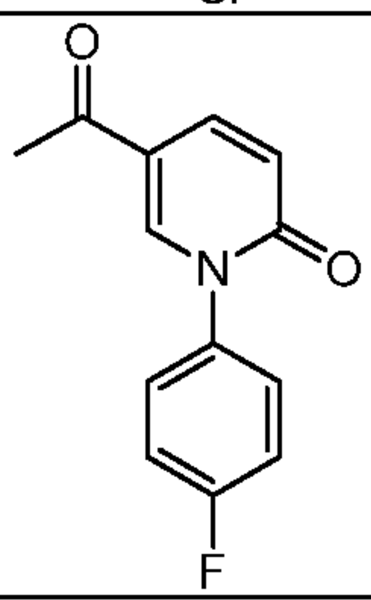
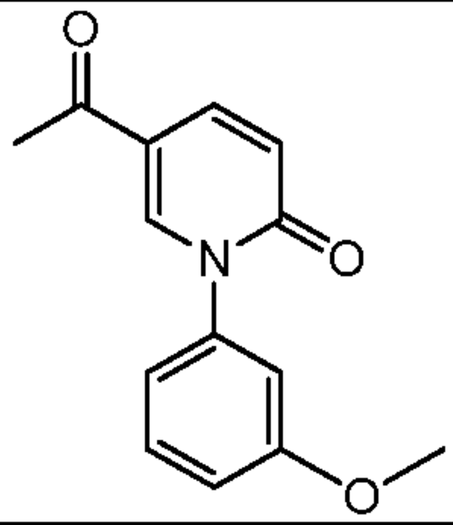
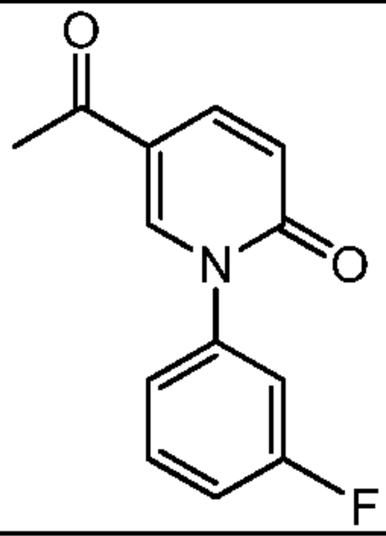
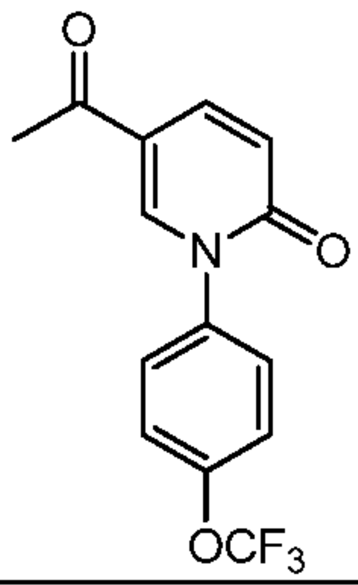
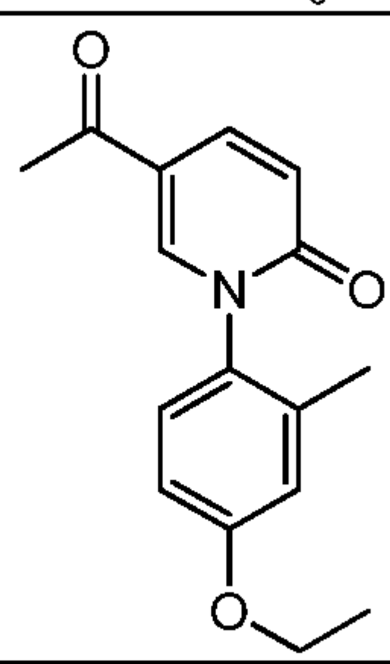
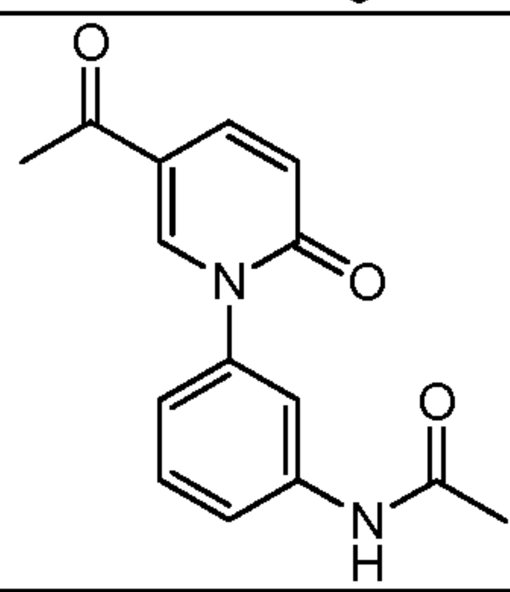
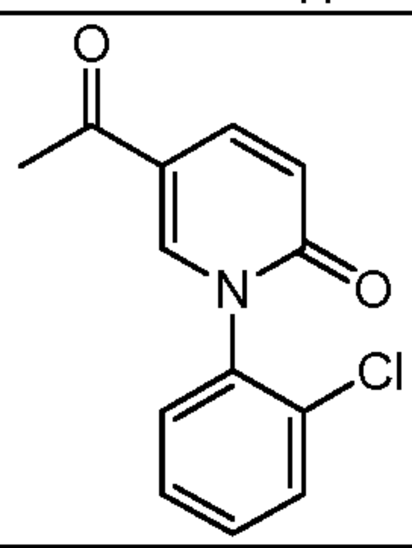
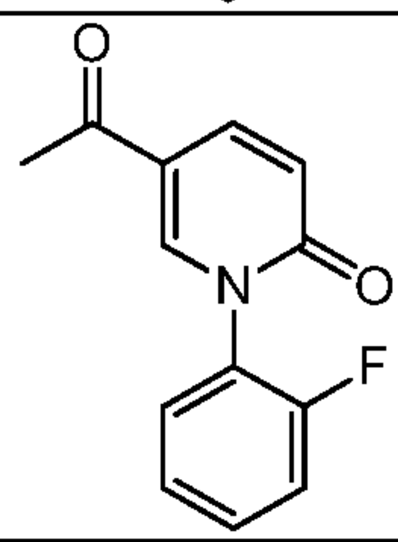
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

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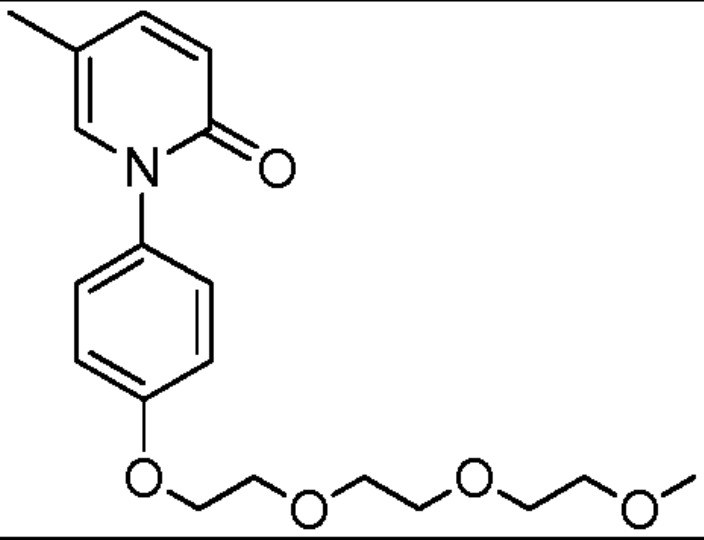
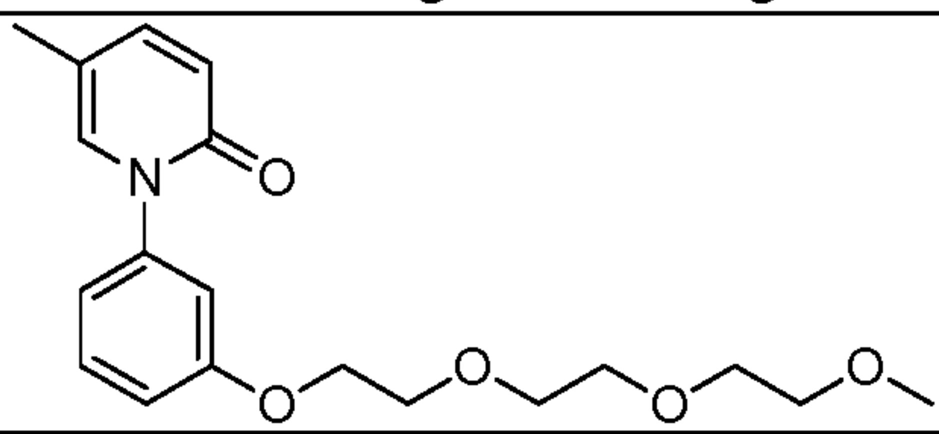
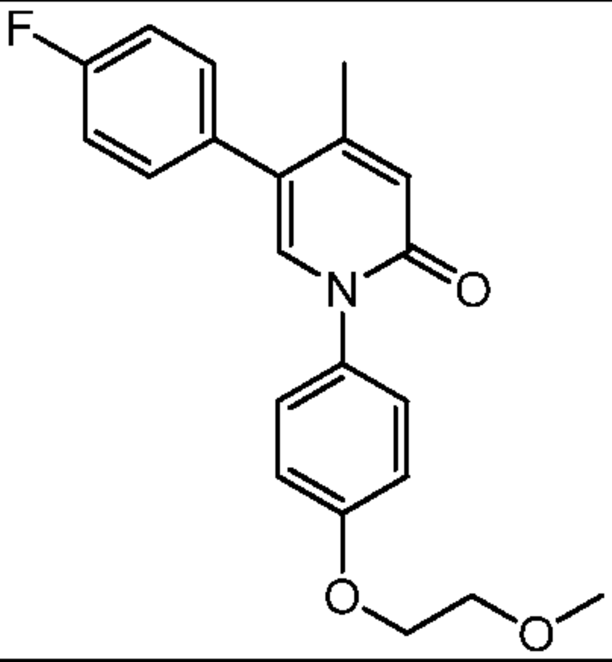
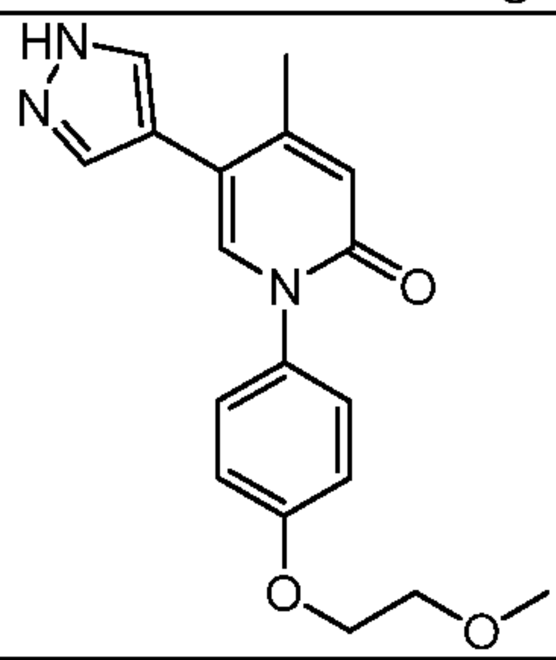
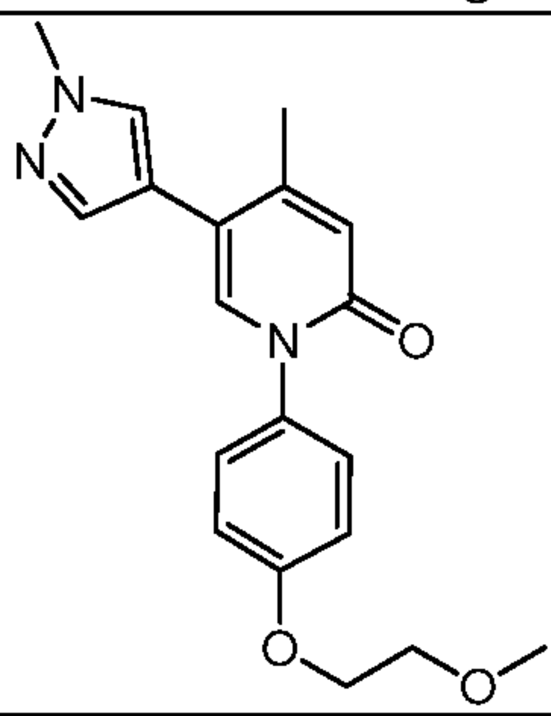
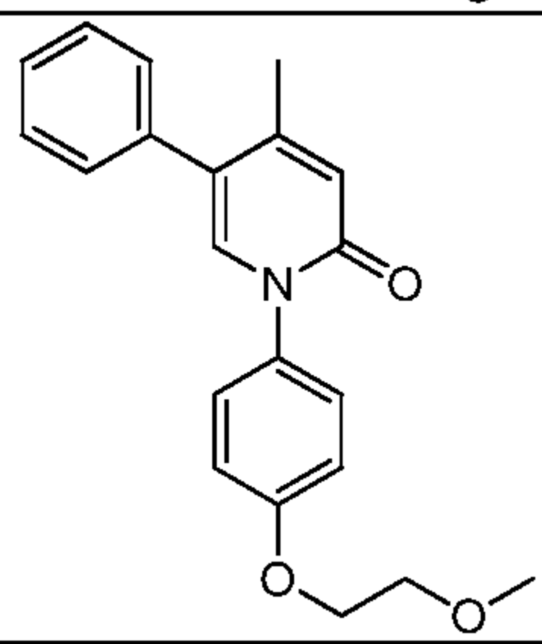
21	
22	
23	
24	
25	
26	

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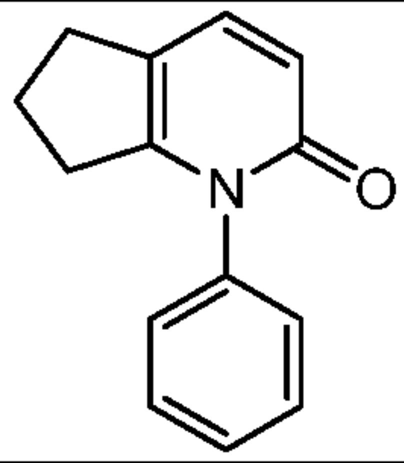
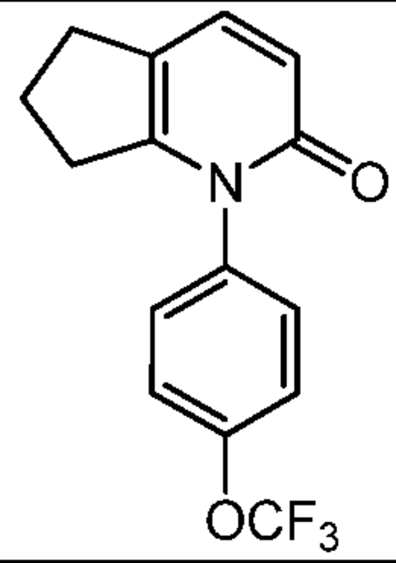
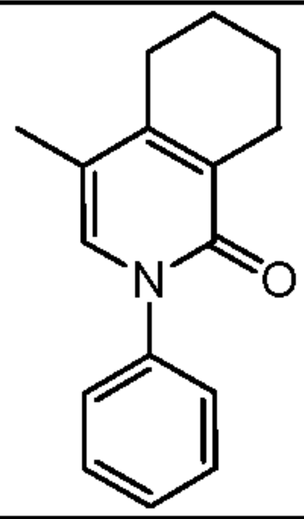
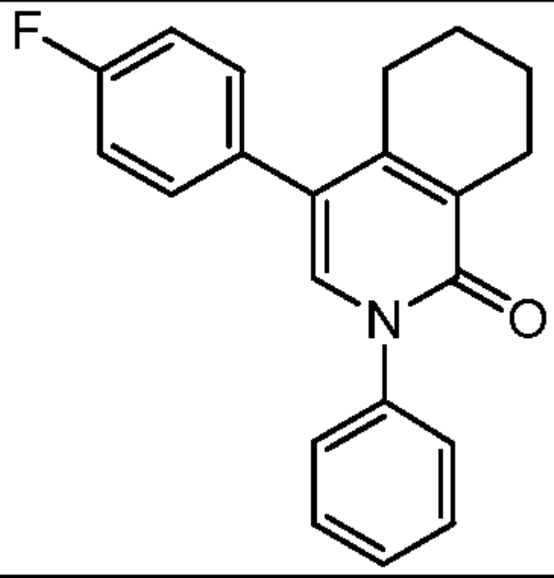
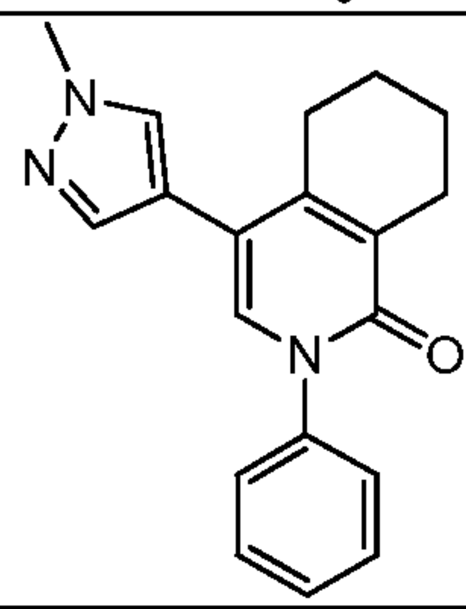
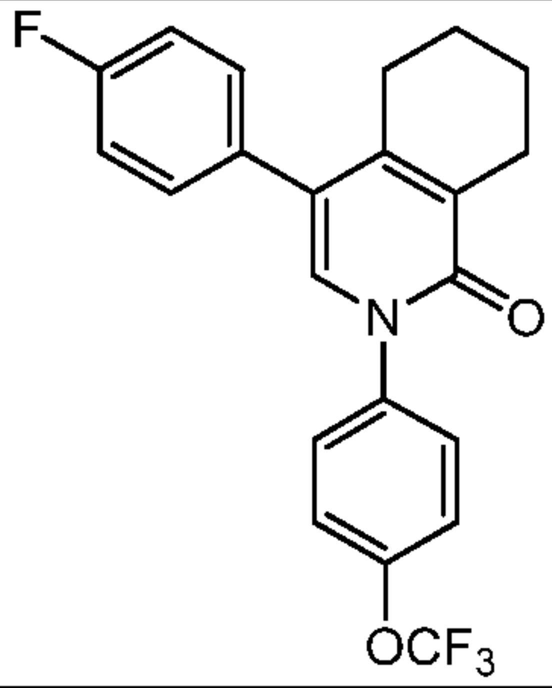
27	
28	
29	
30	
31	
32	

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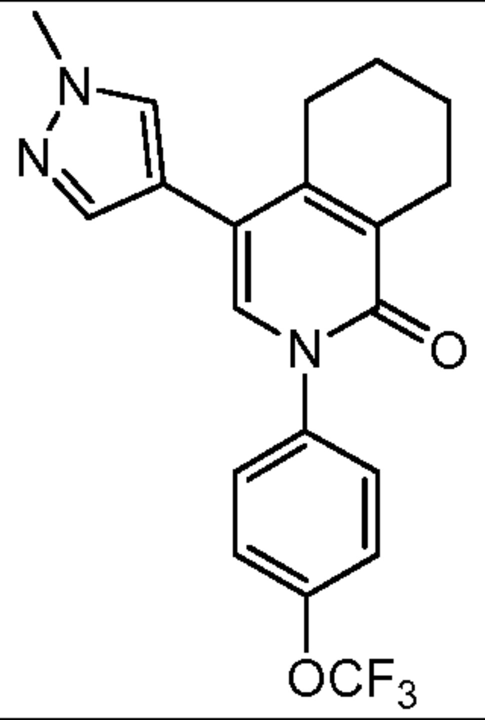
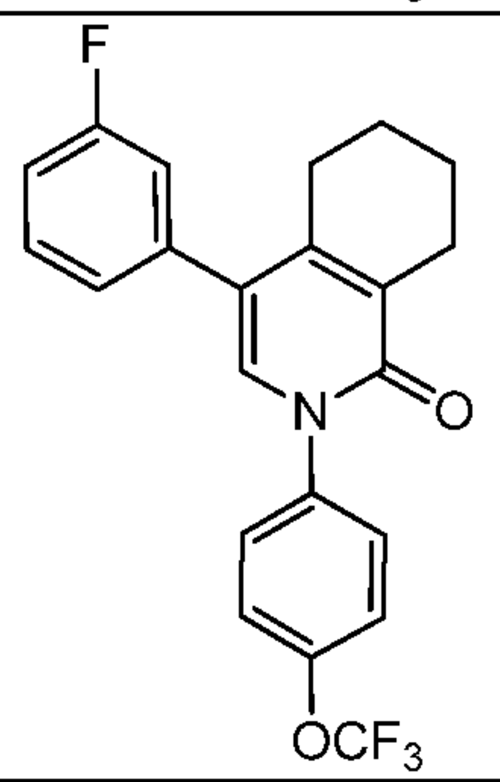
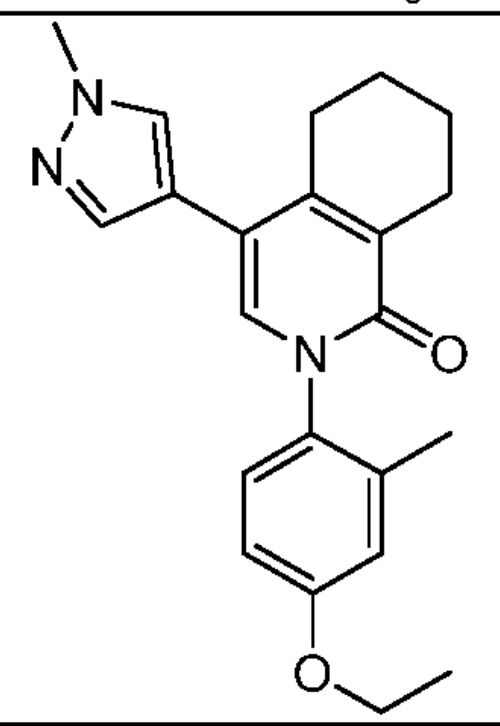
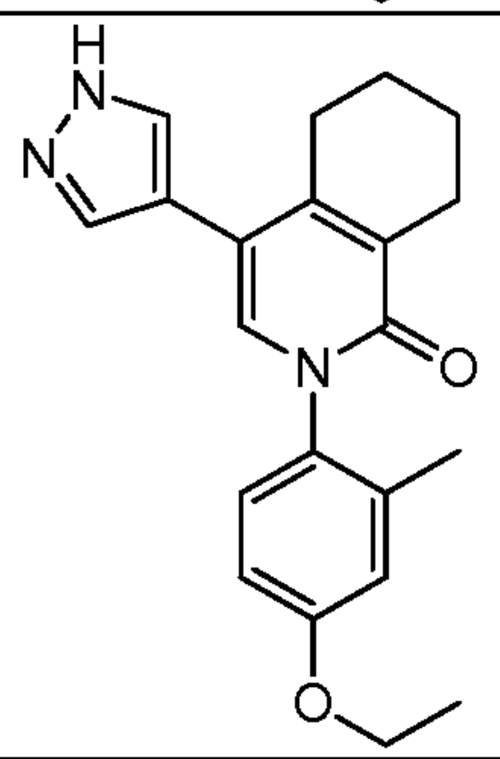
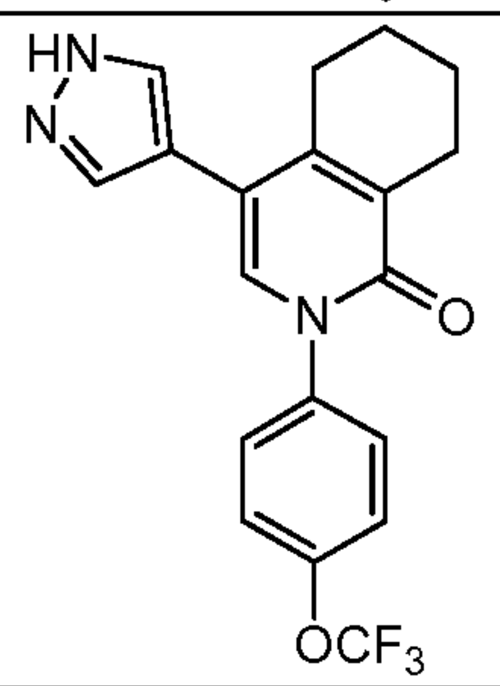
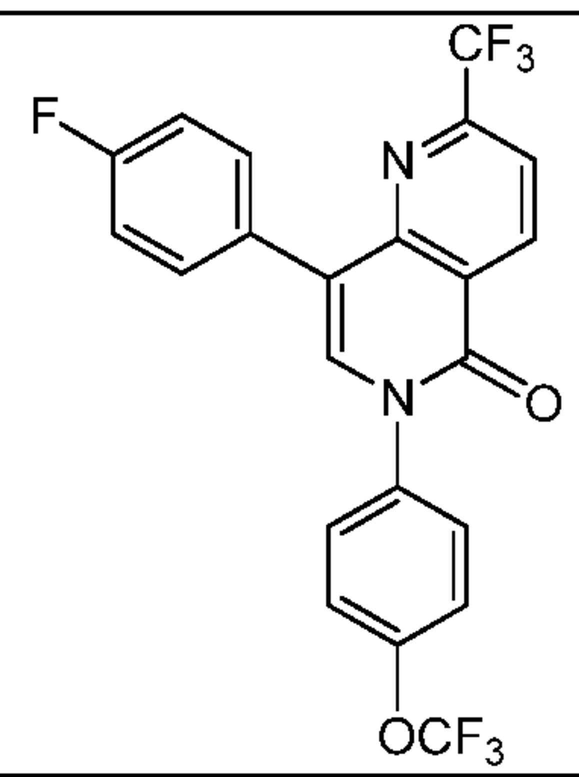
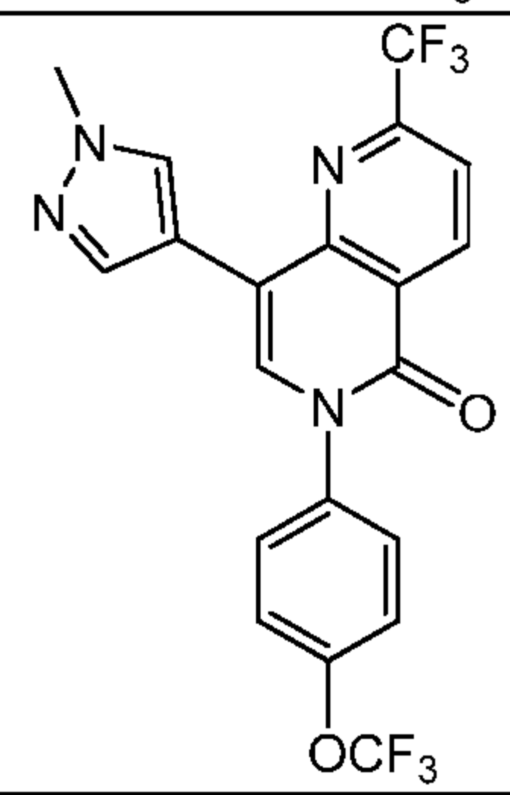
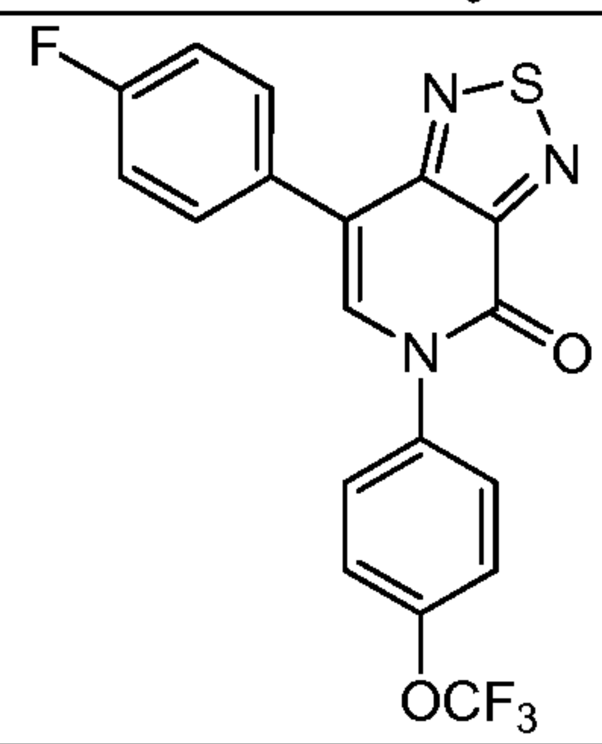
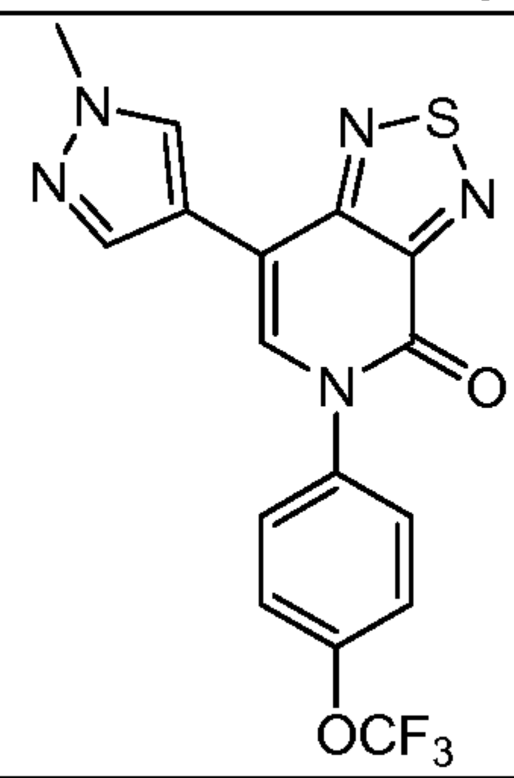
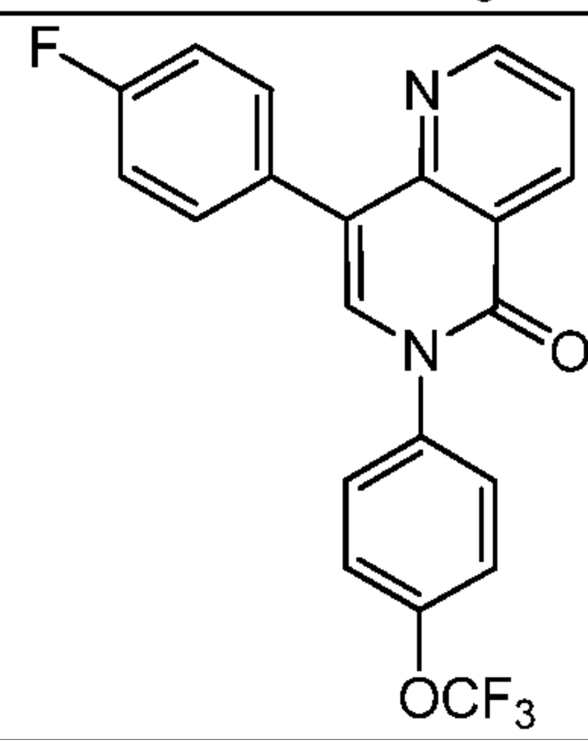
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	

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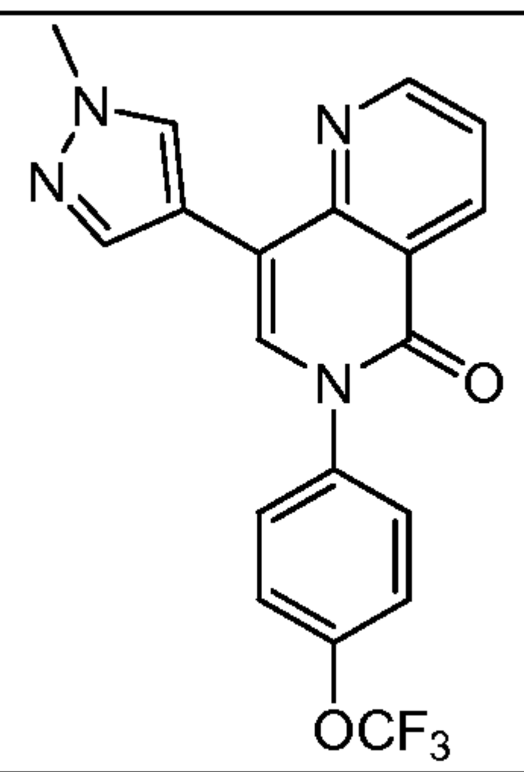
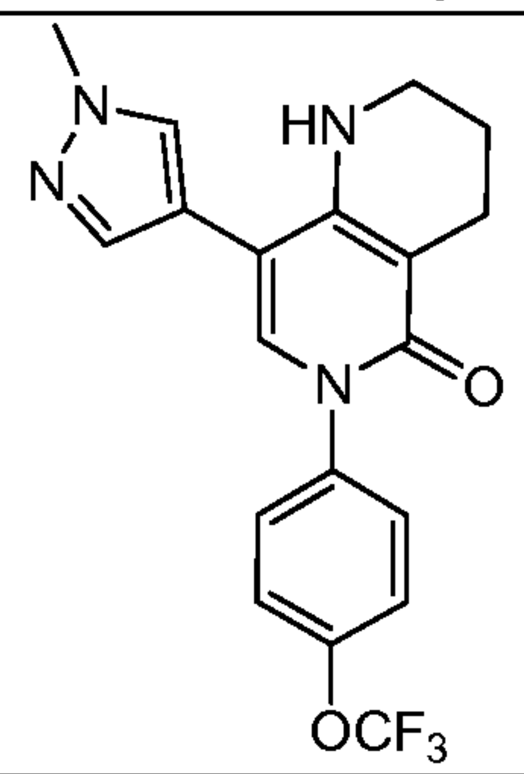
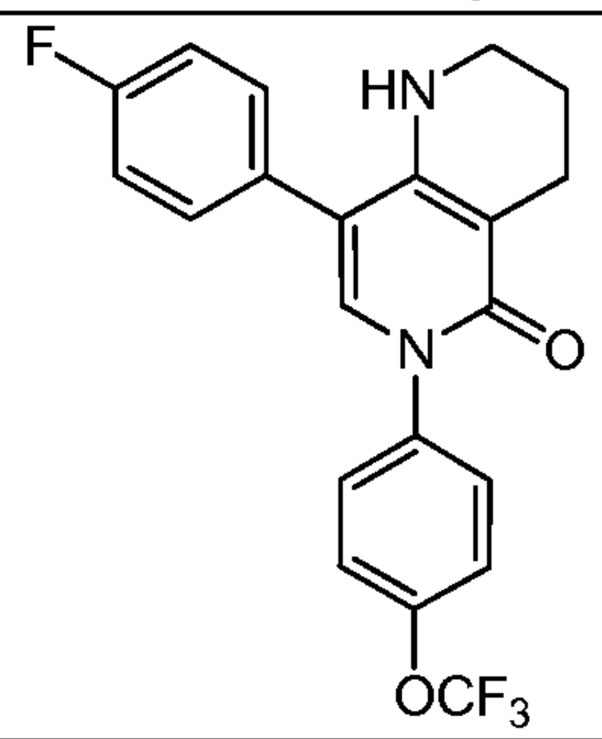
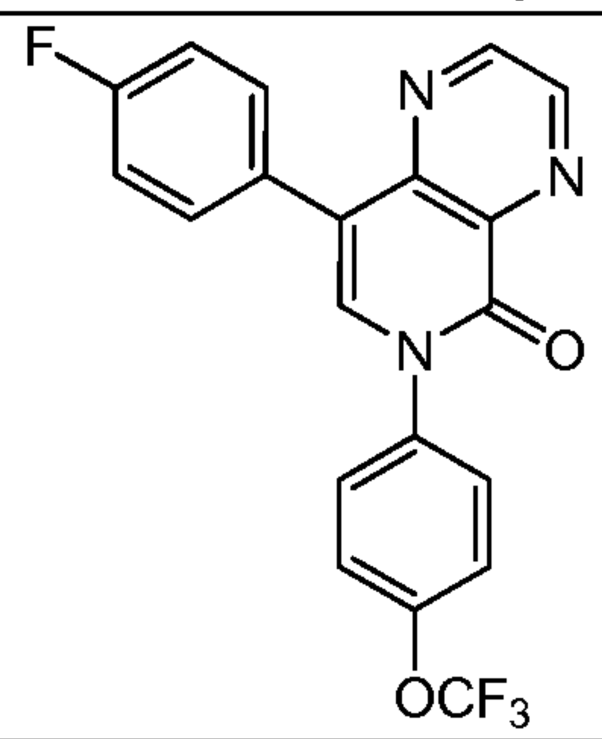
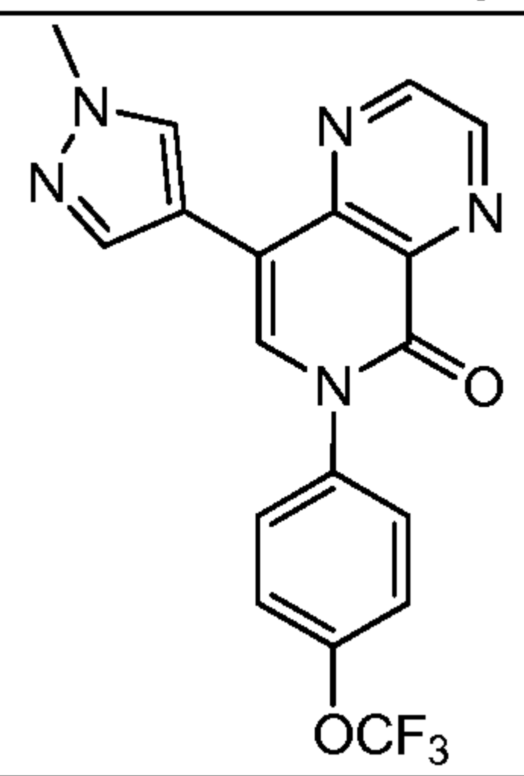
43	
44	
45	
46	
47	

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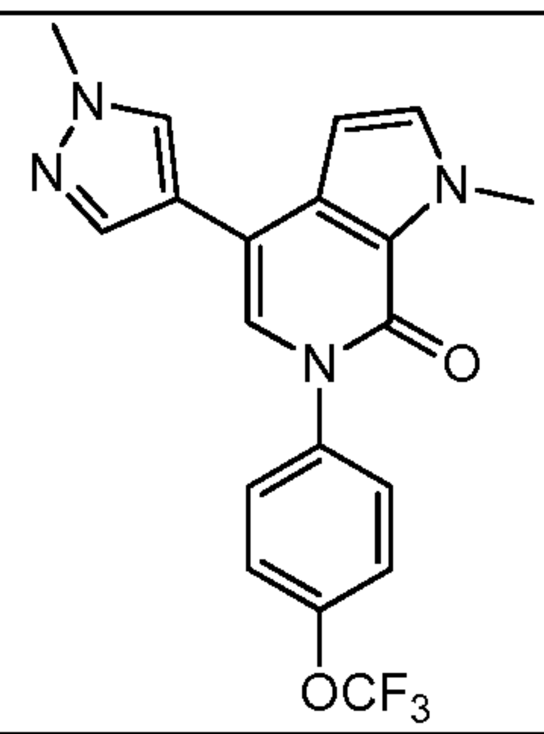
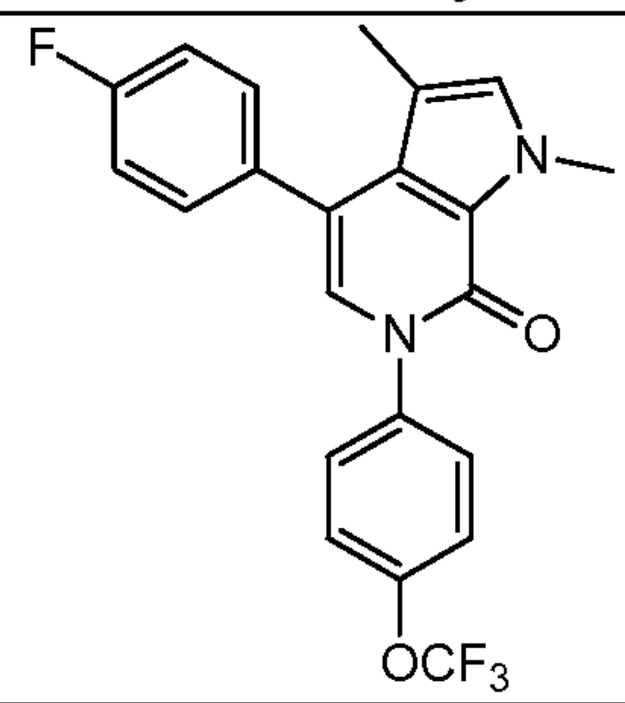
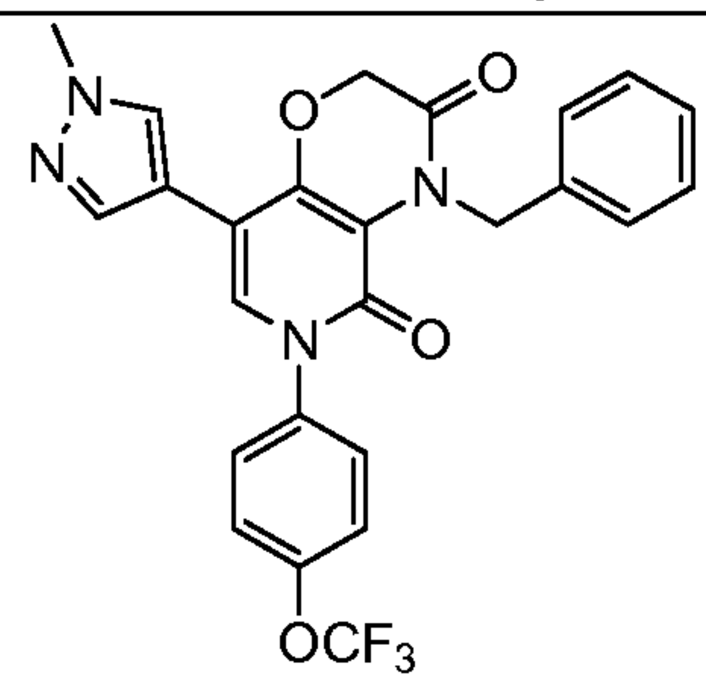
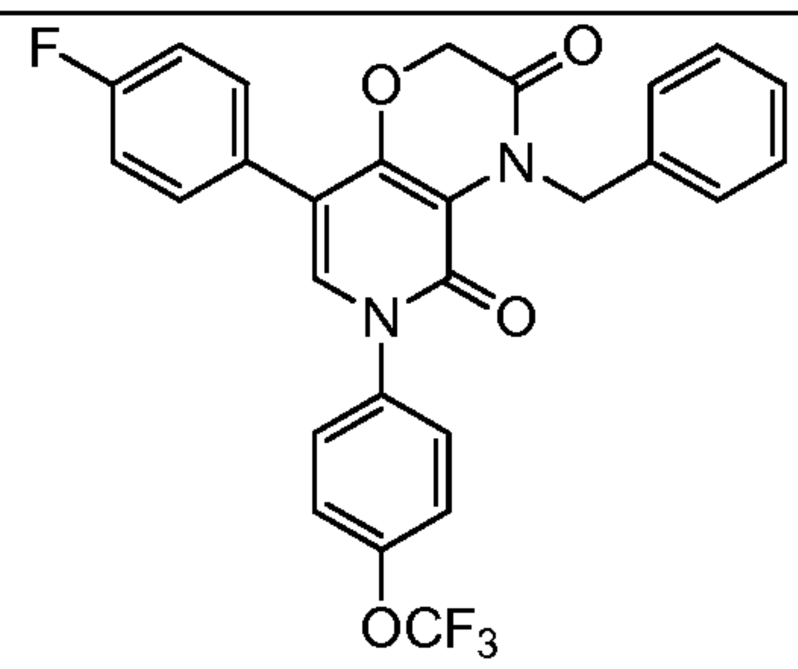
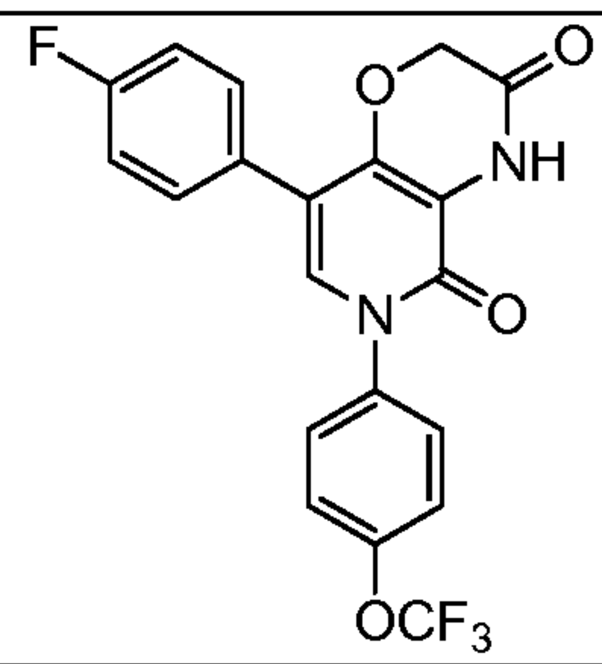
48	
49	
50	
51	
52	

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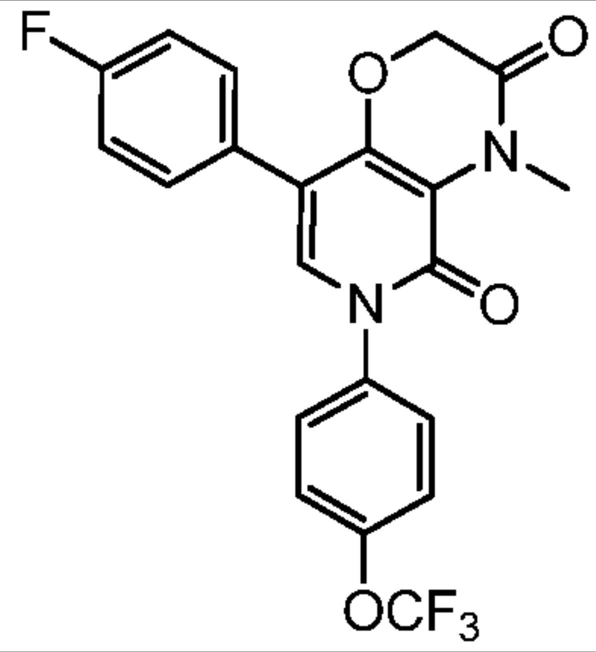
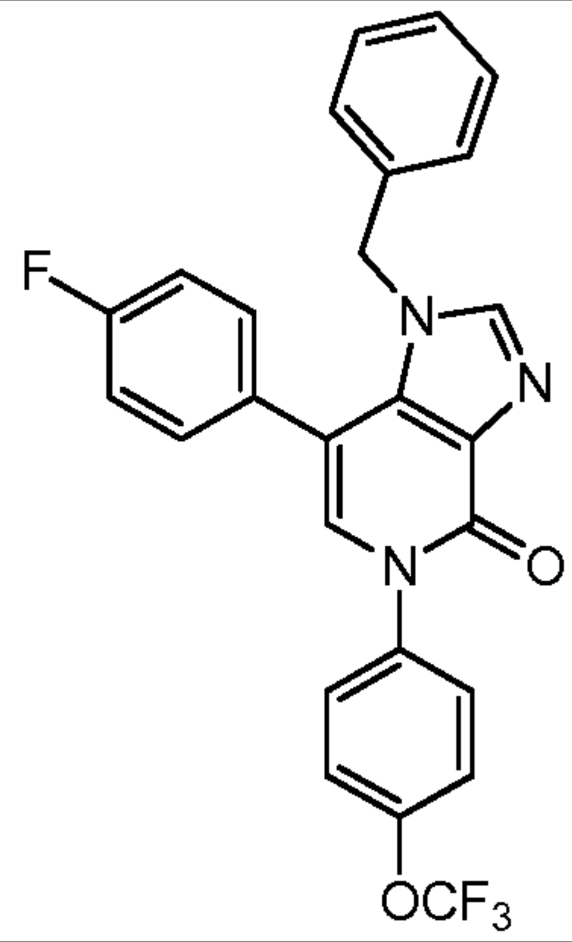
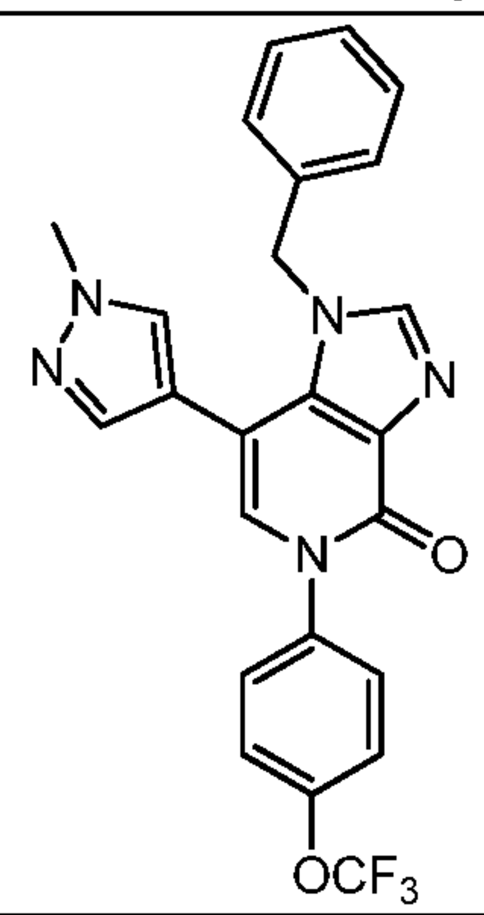
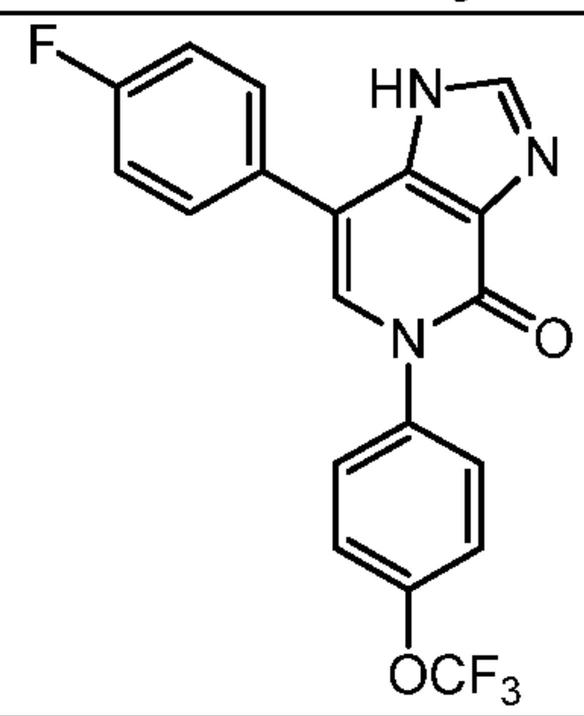
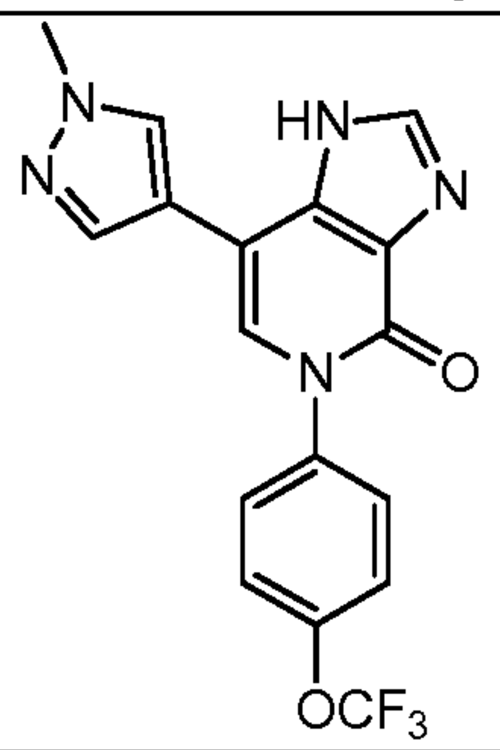
53	
54	
55	
56	
57	

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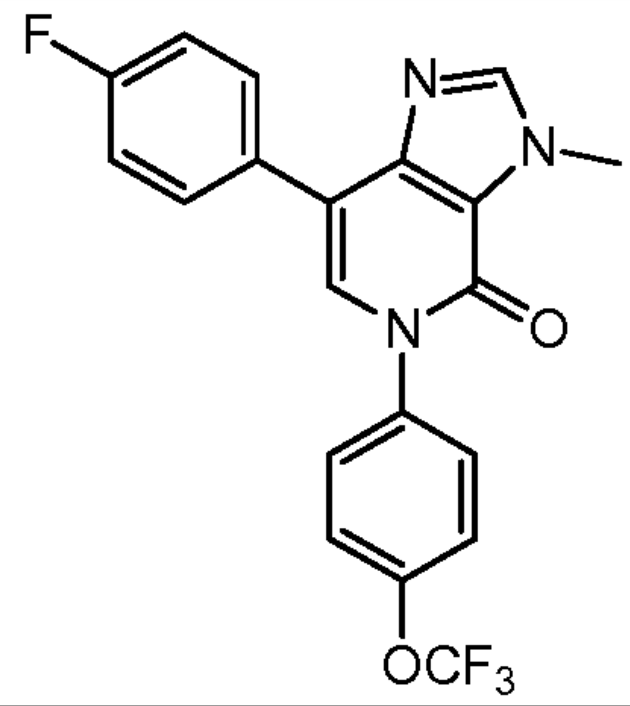
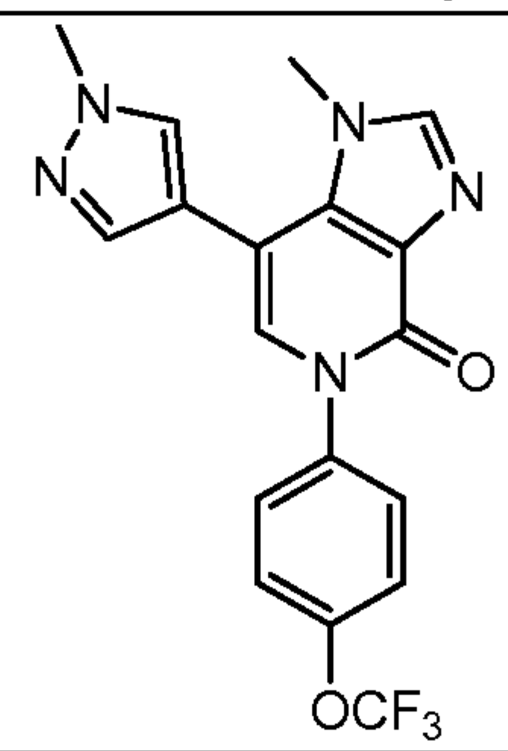
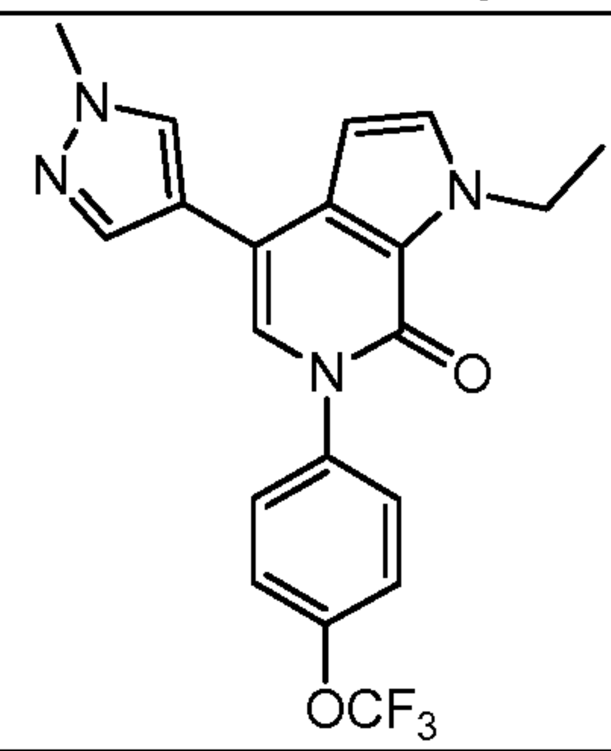
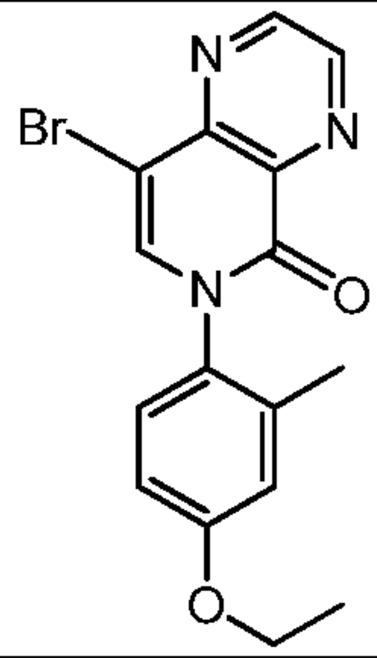
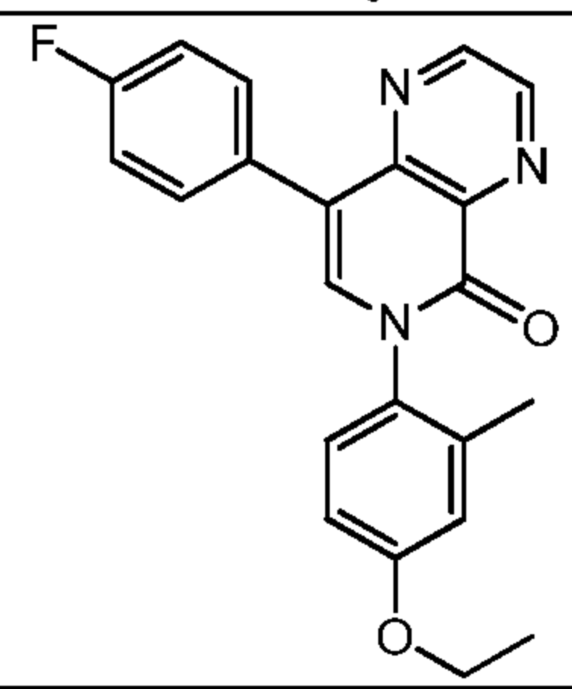
58	
59	
60	
61	
62	

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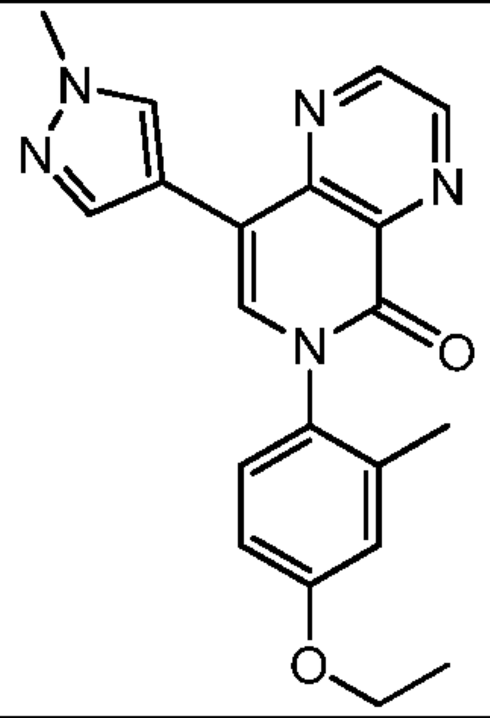
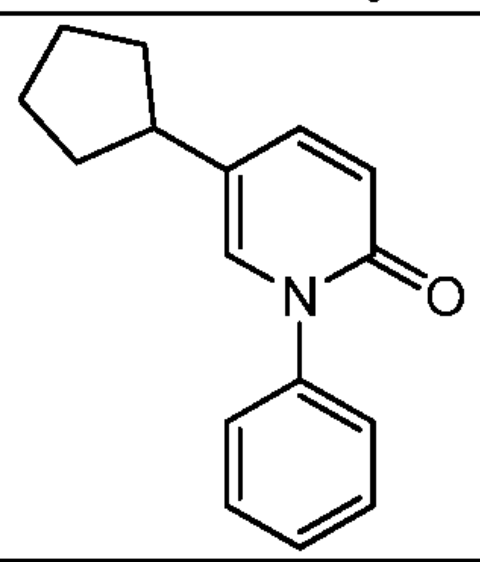
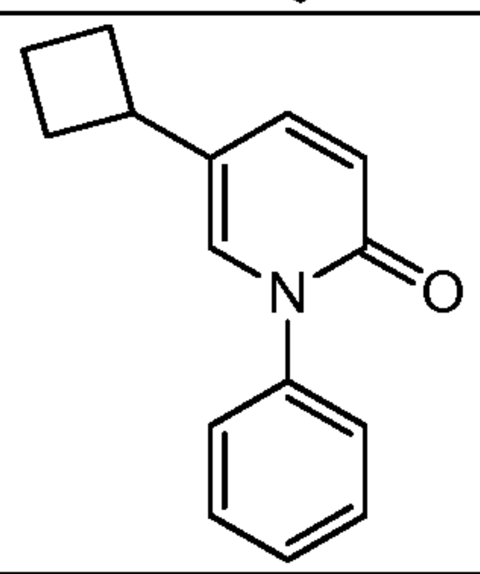
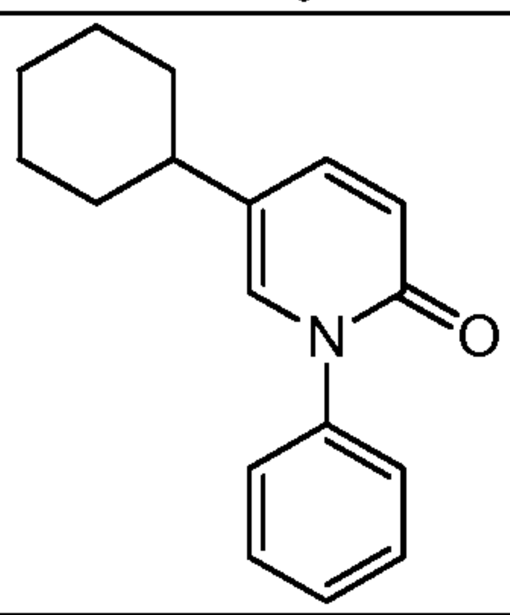
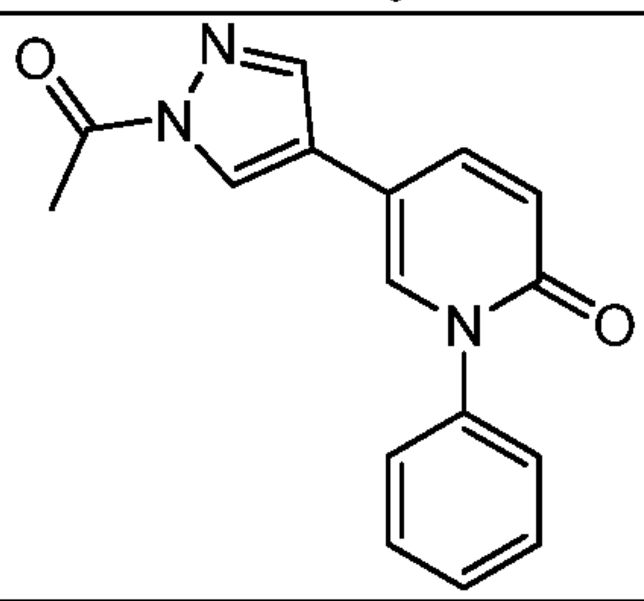
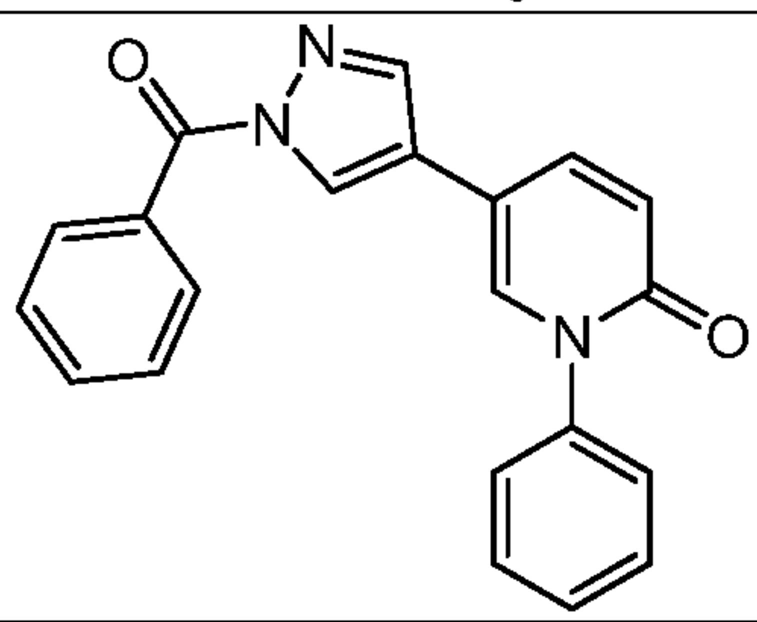
63	
64	
65	
66	
67	
68	

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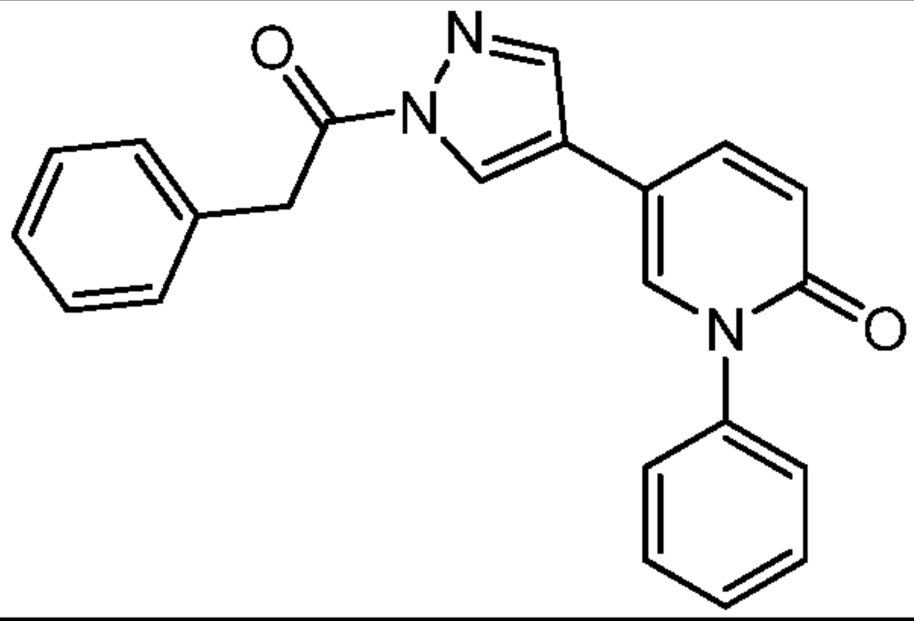
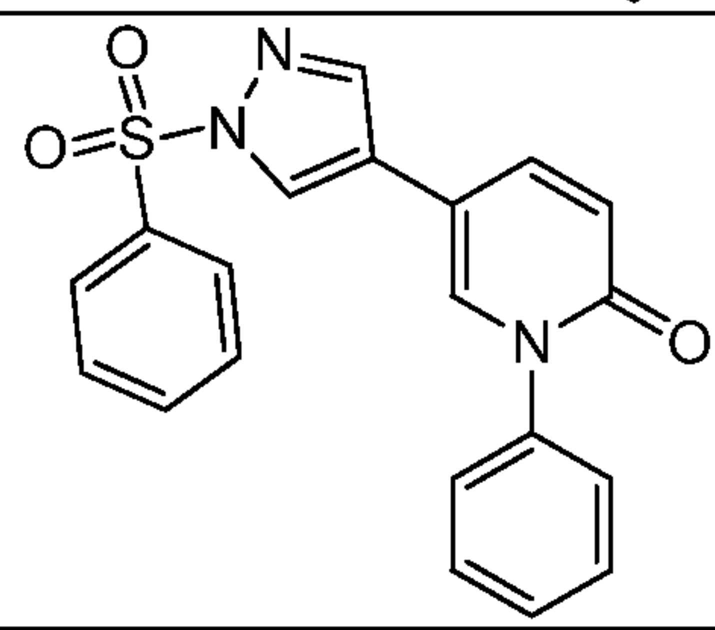
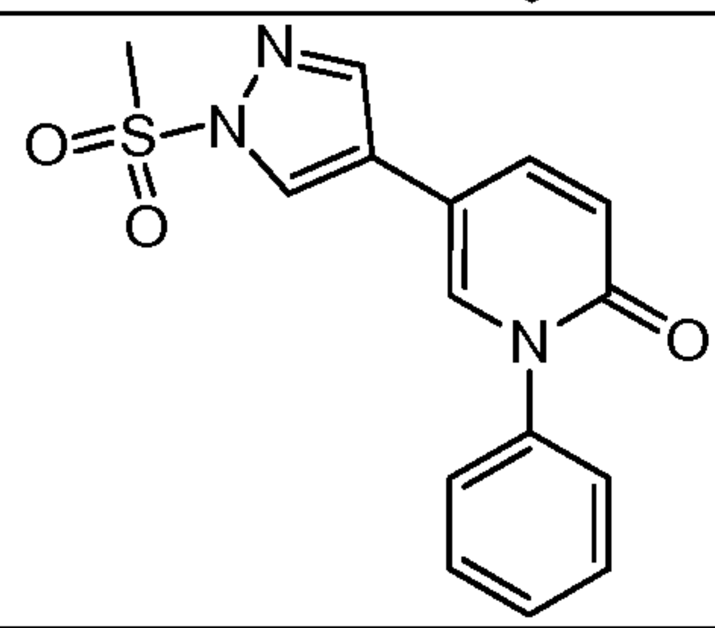
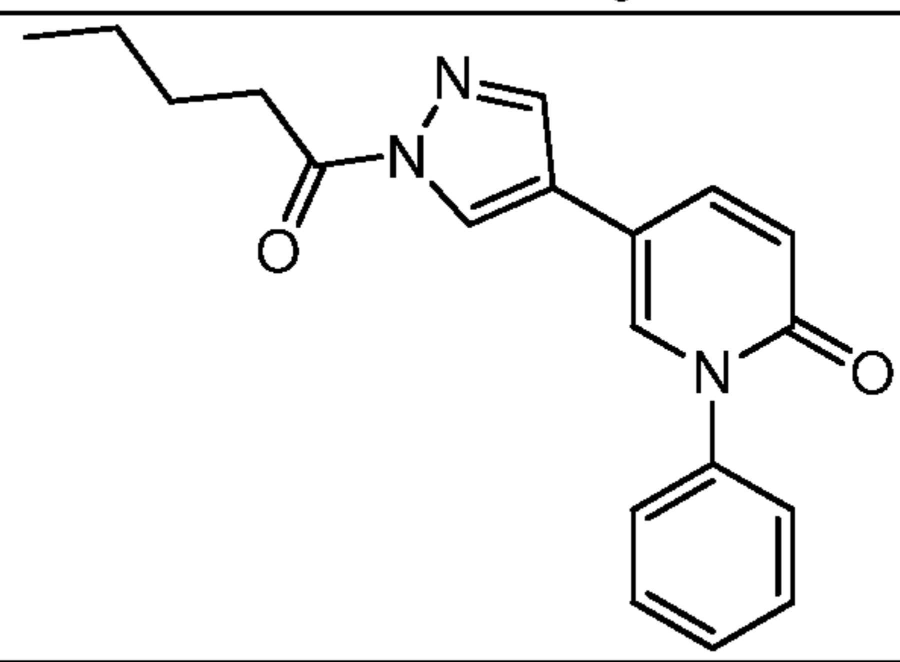
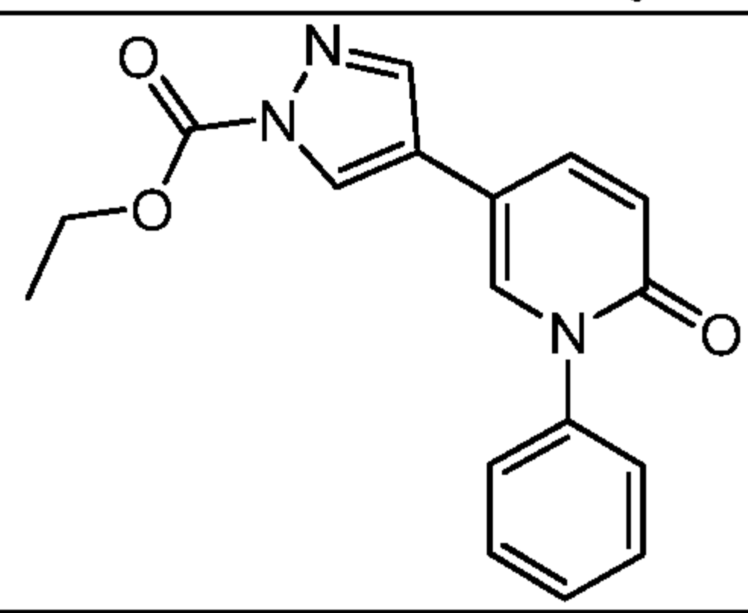
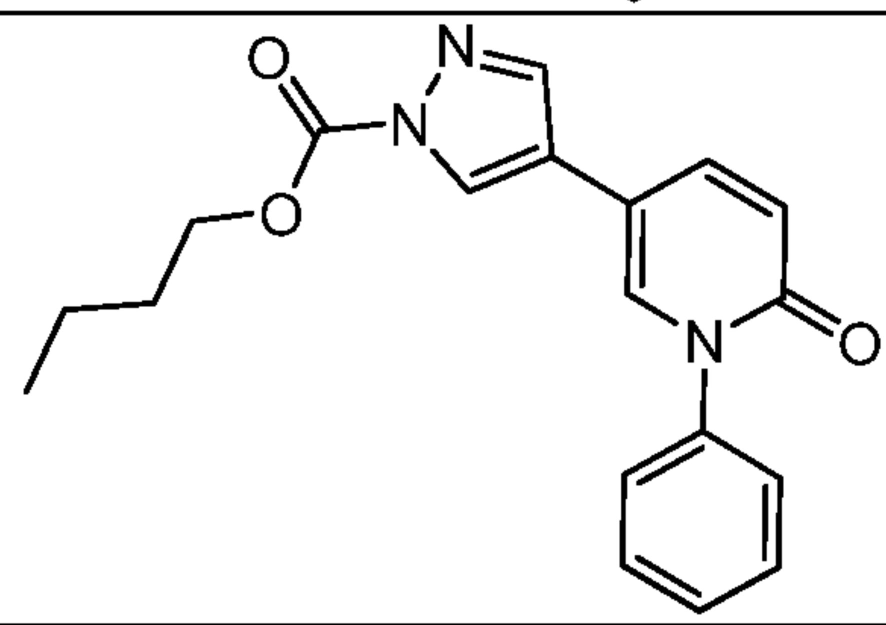
69	
70	
71	
72	
73	
74	

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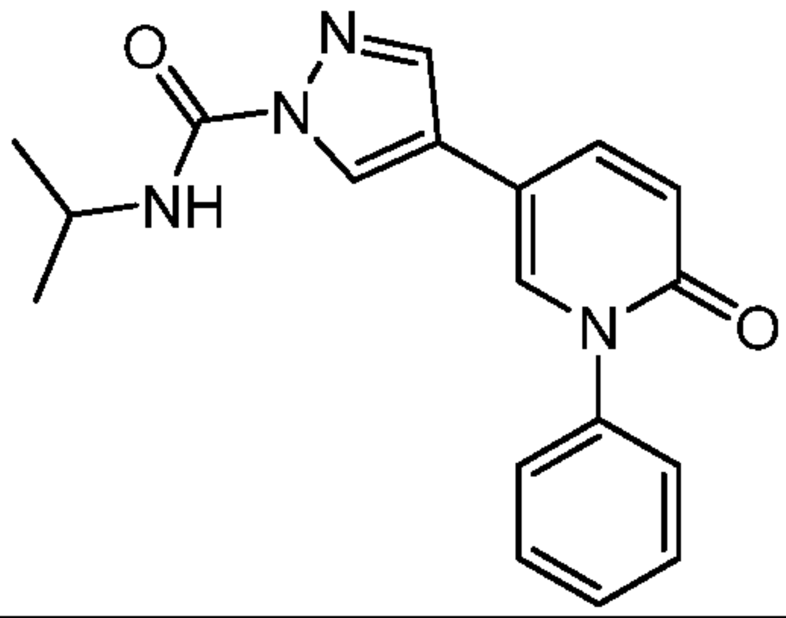
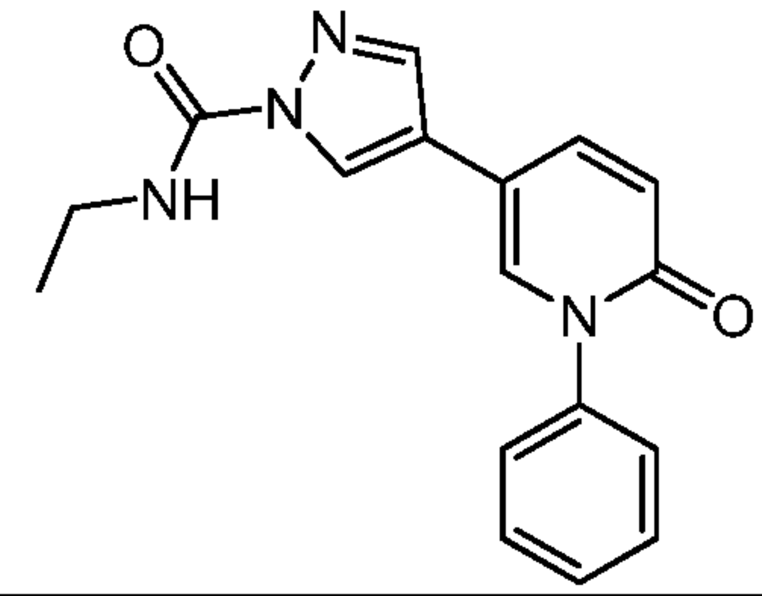
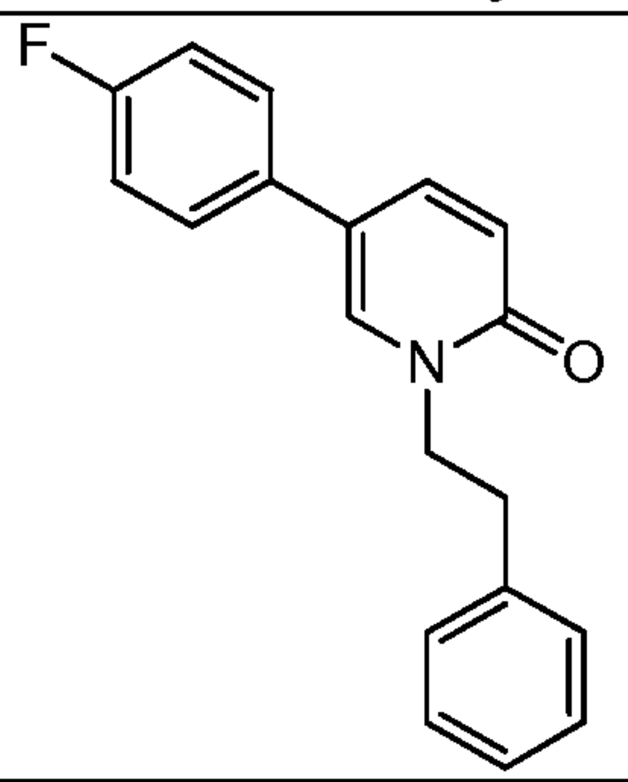
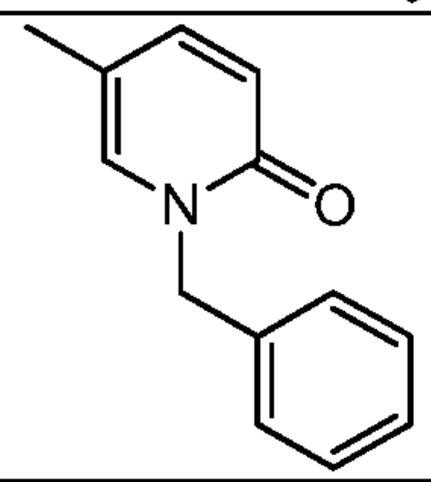
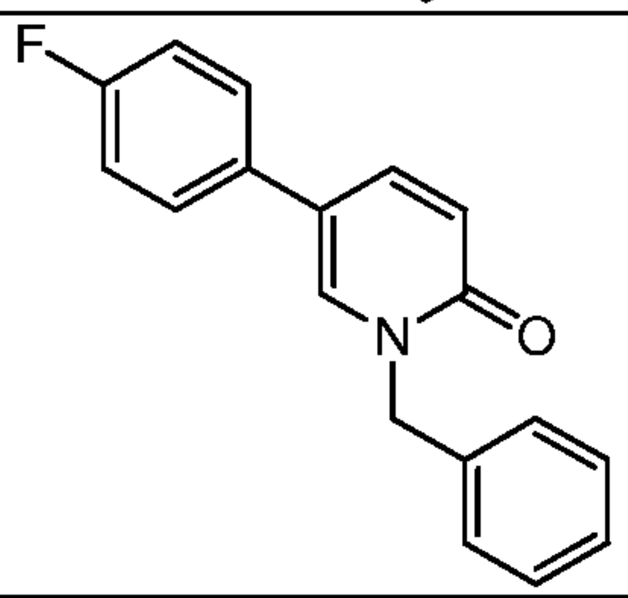
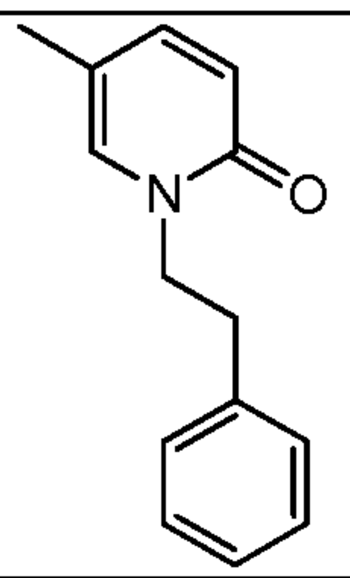
75	
76	
77	
78	
79	
80	

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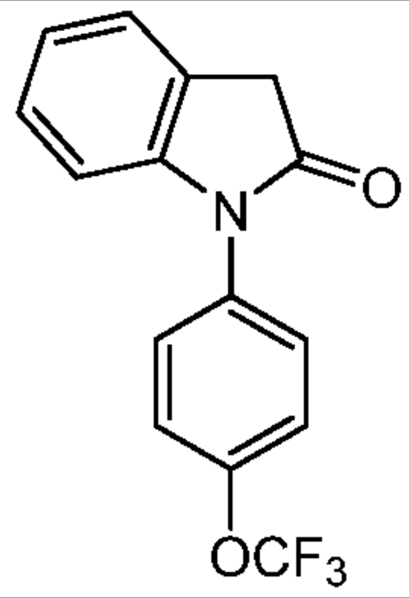
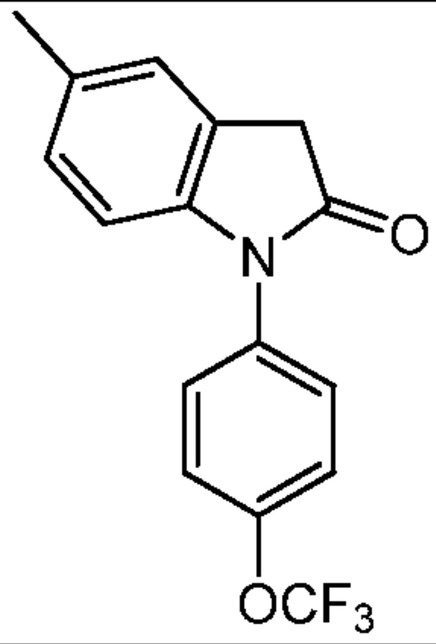
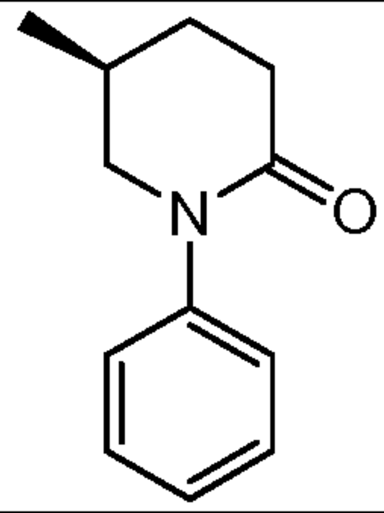
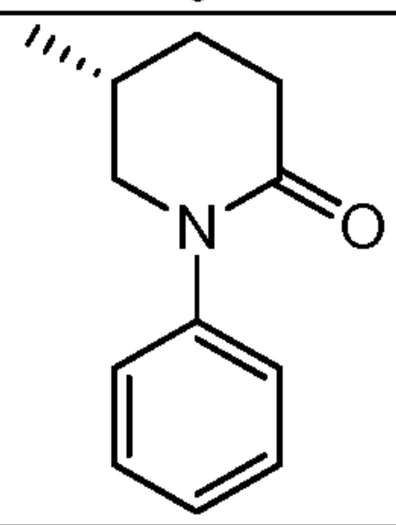
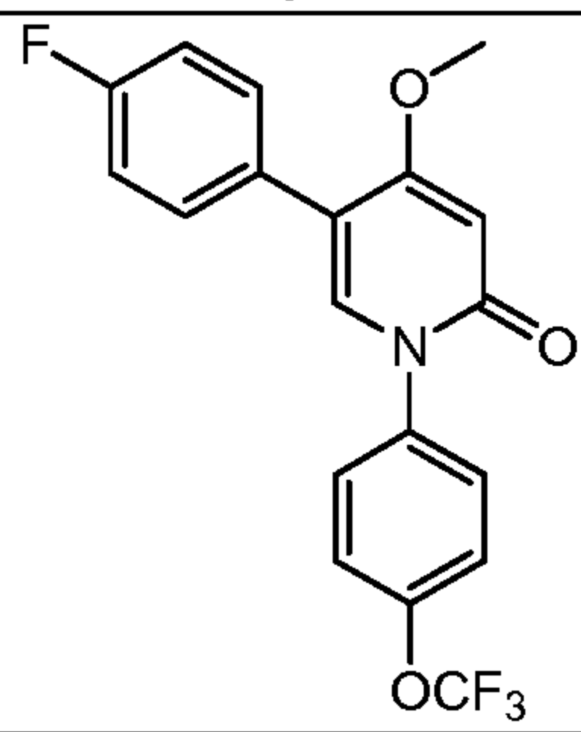
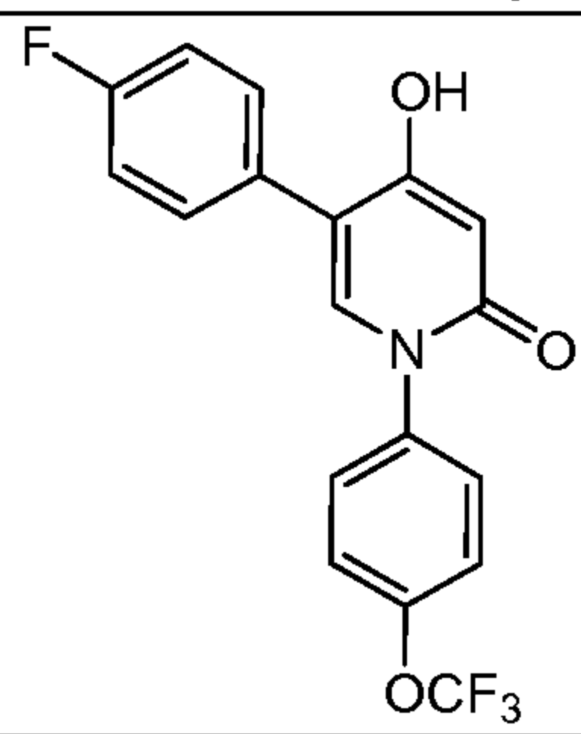
81	
82	
83	
84	
85	
86	

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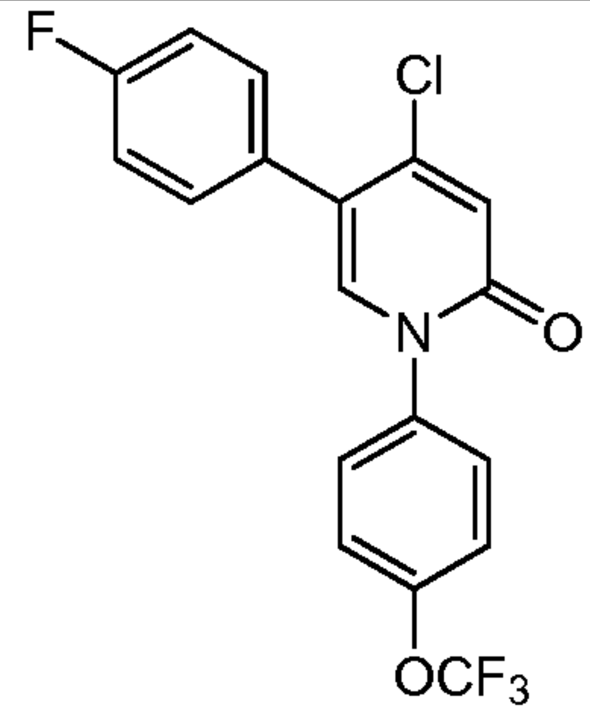
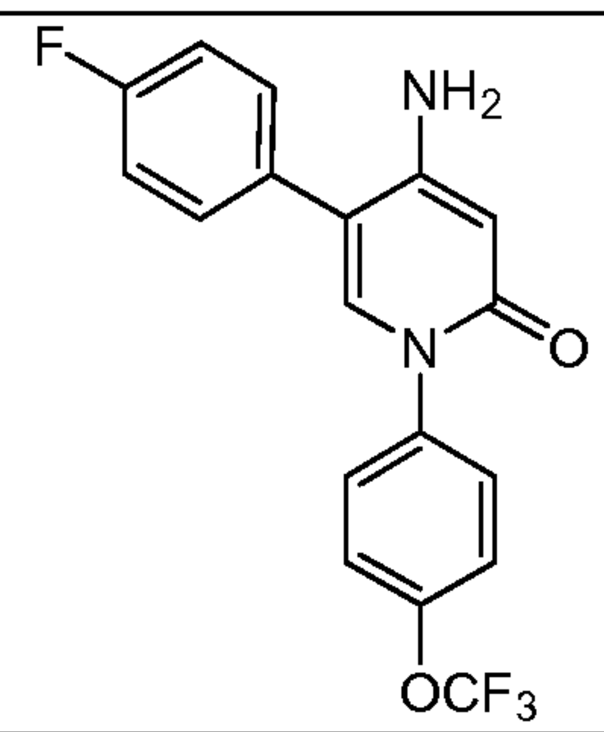
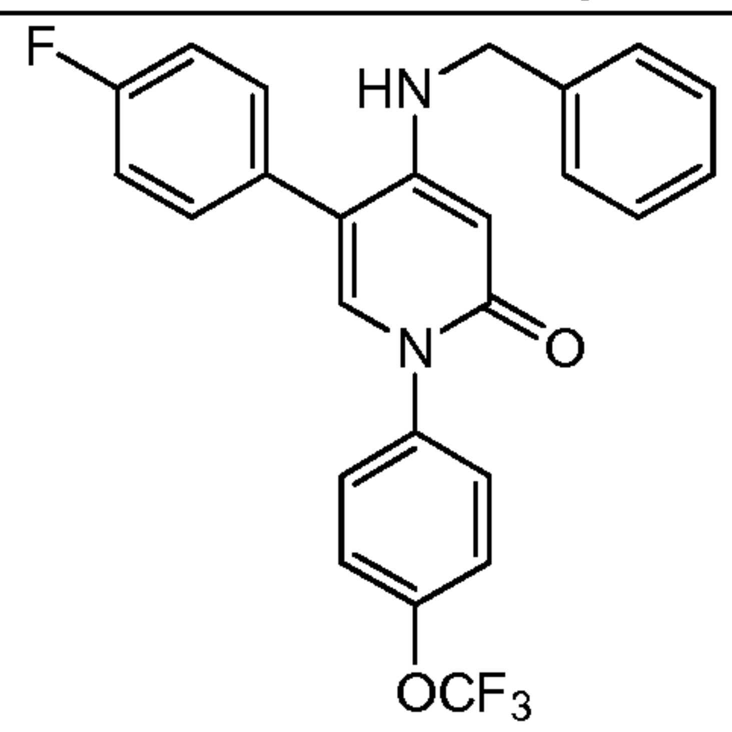
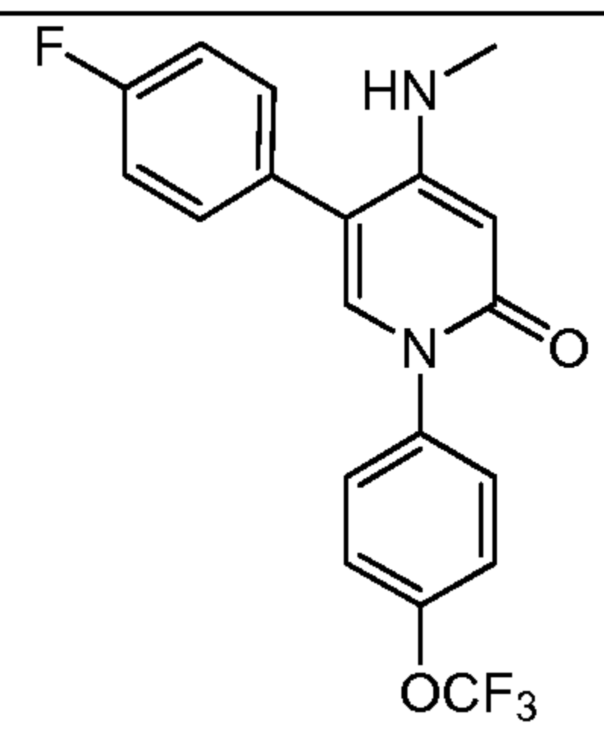
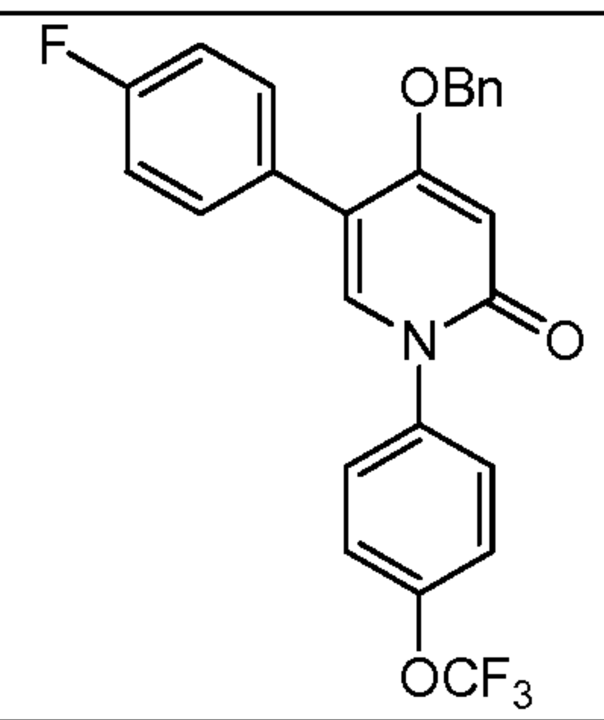
87	
88	
89	
90	
91	

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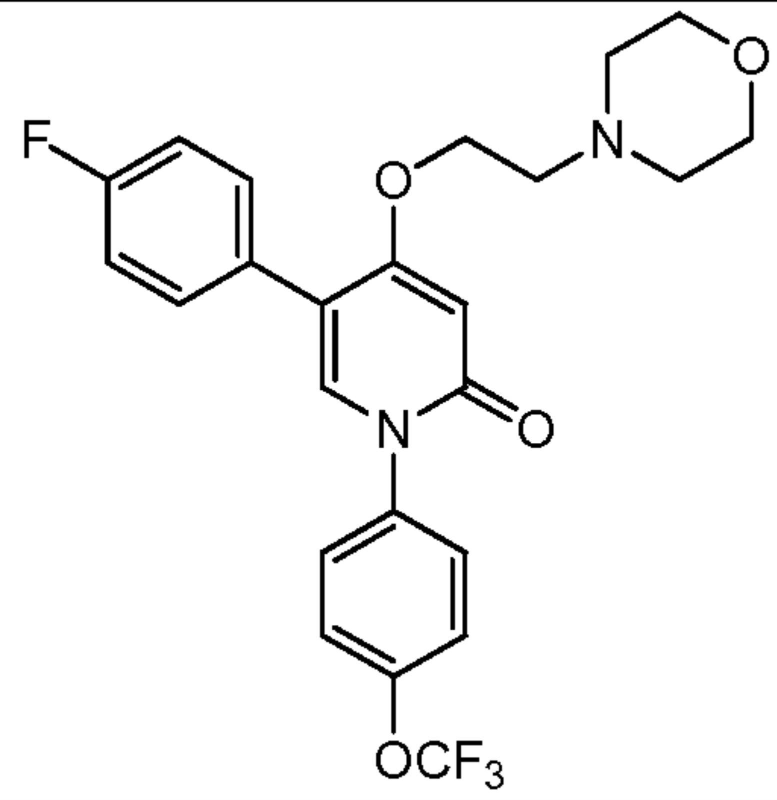
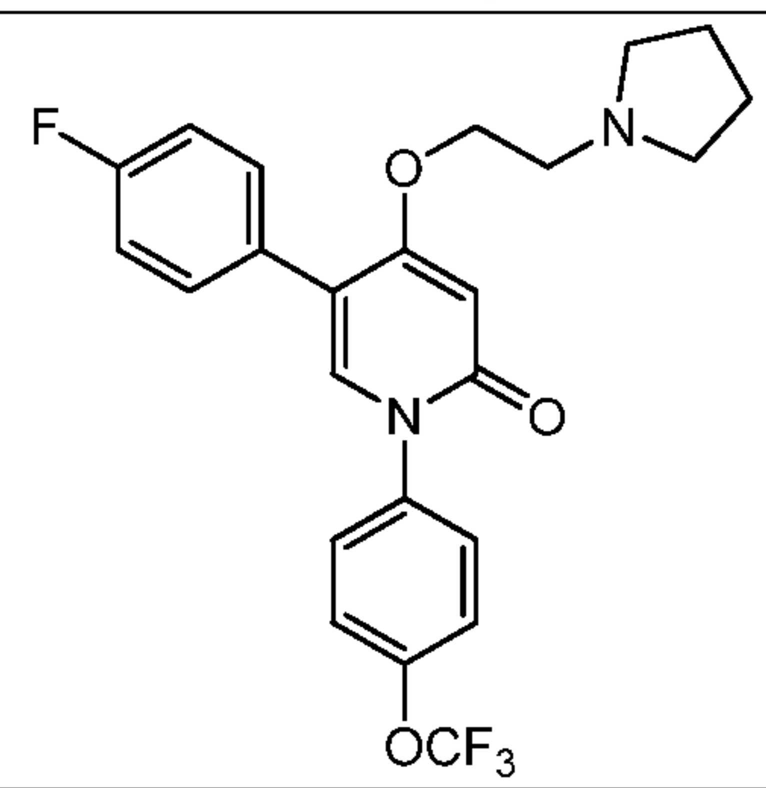
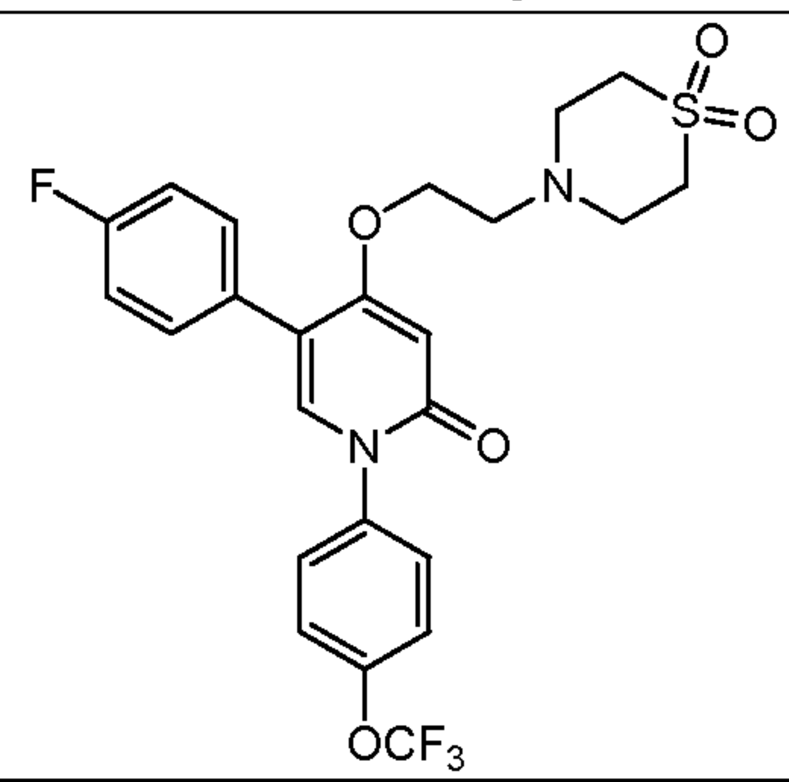
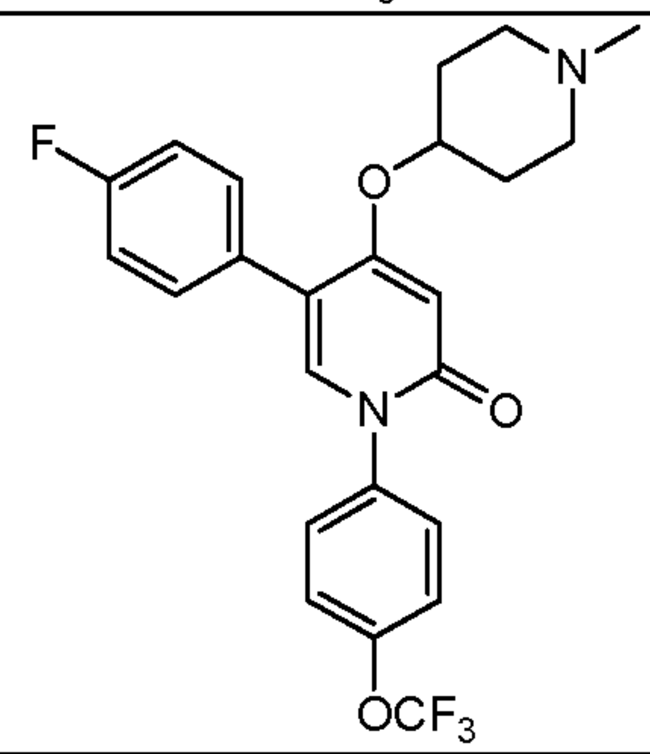
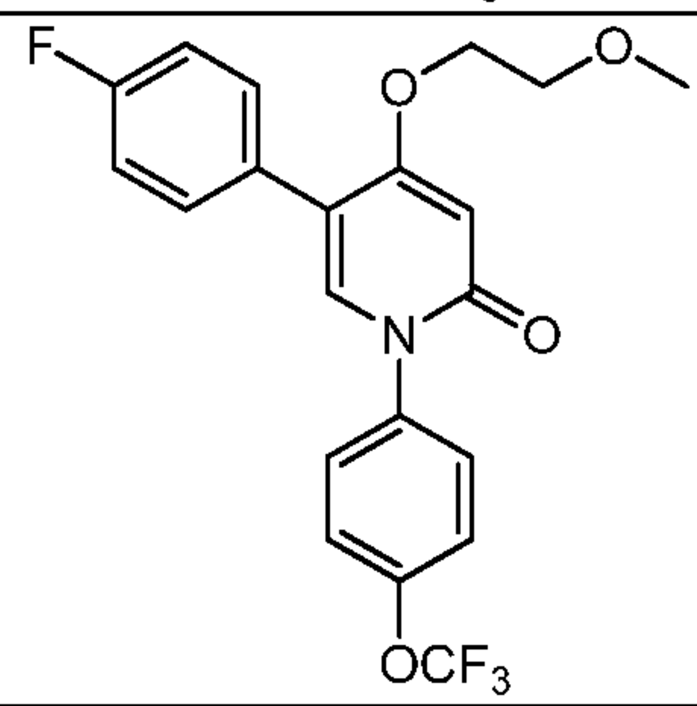
92	
93	
94	
95	
96	

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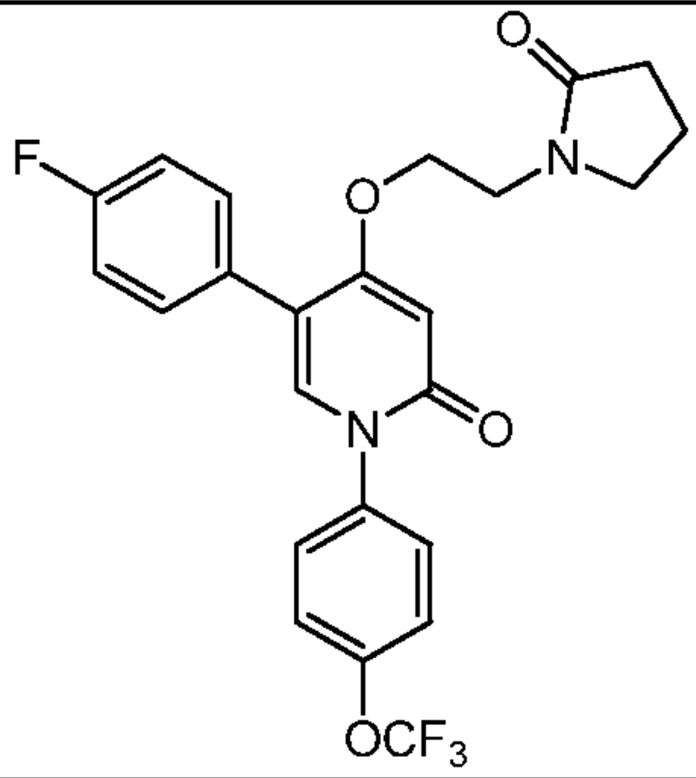
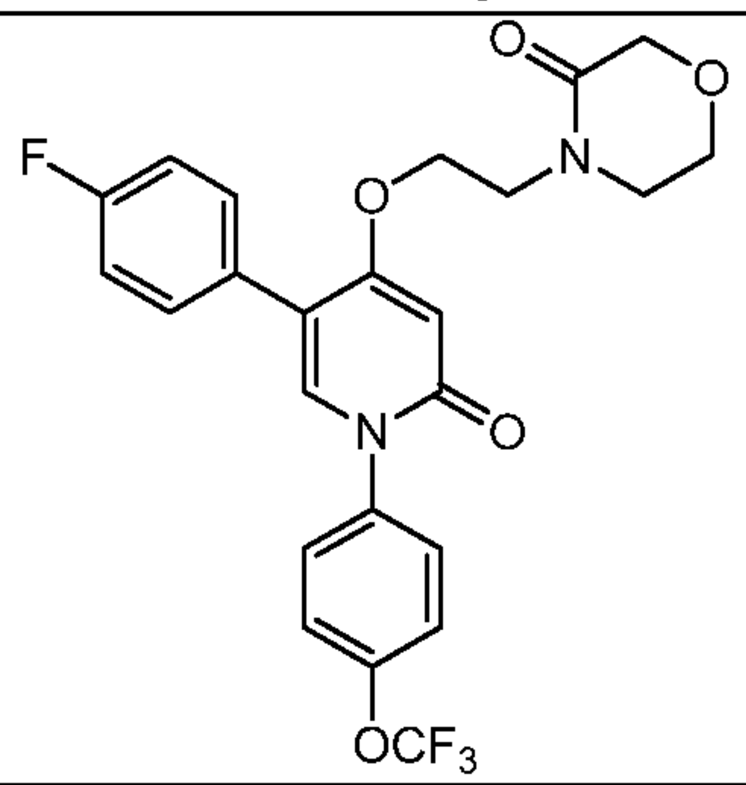
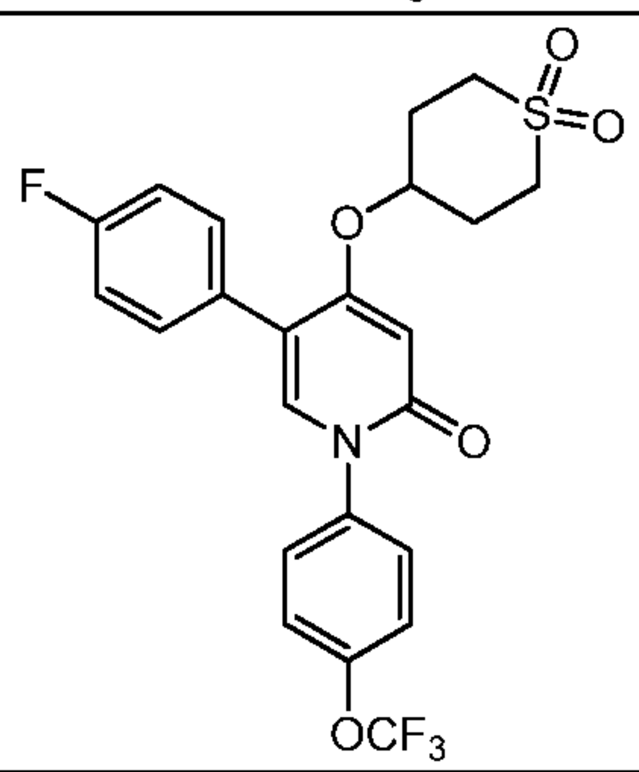
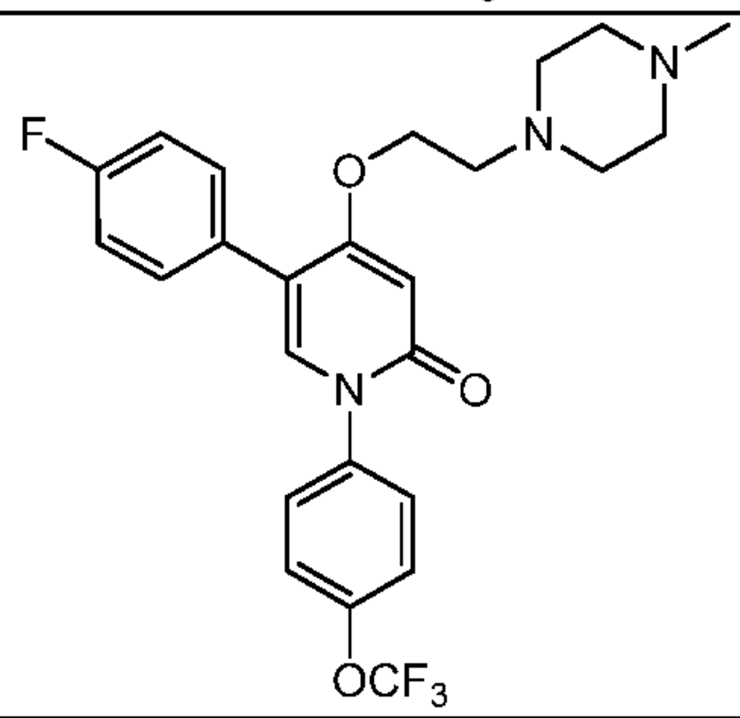
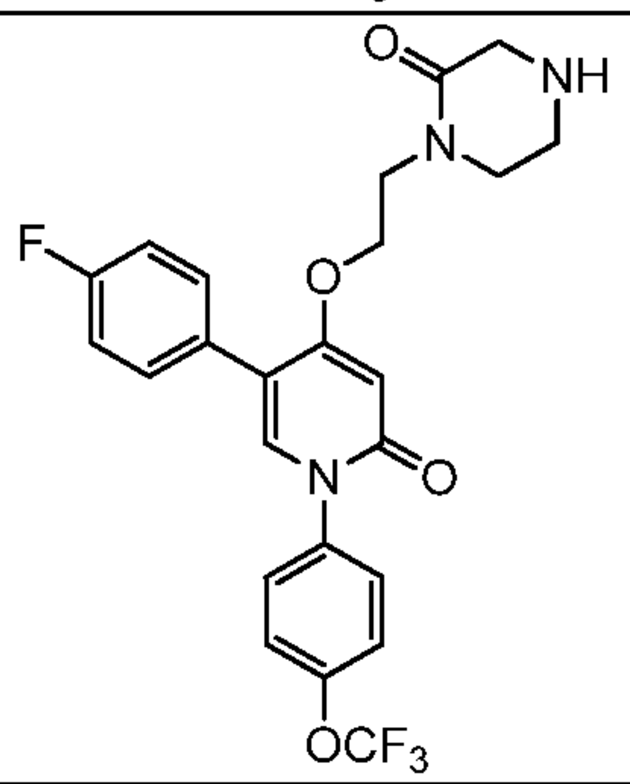
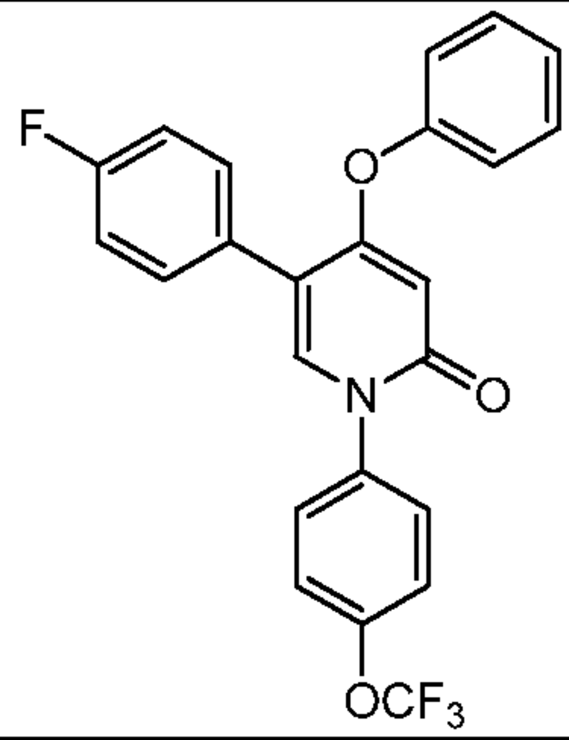
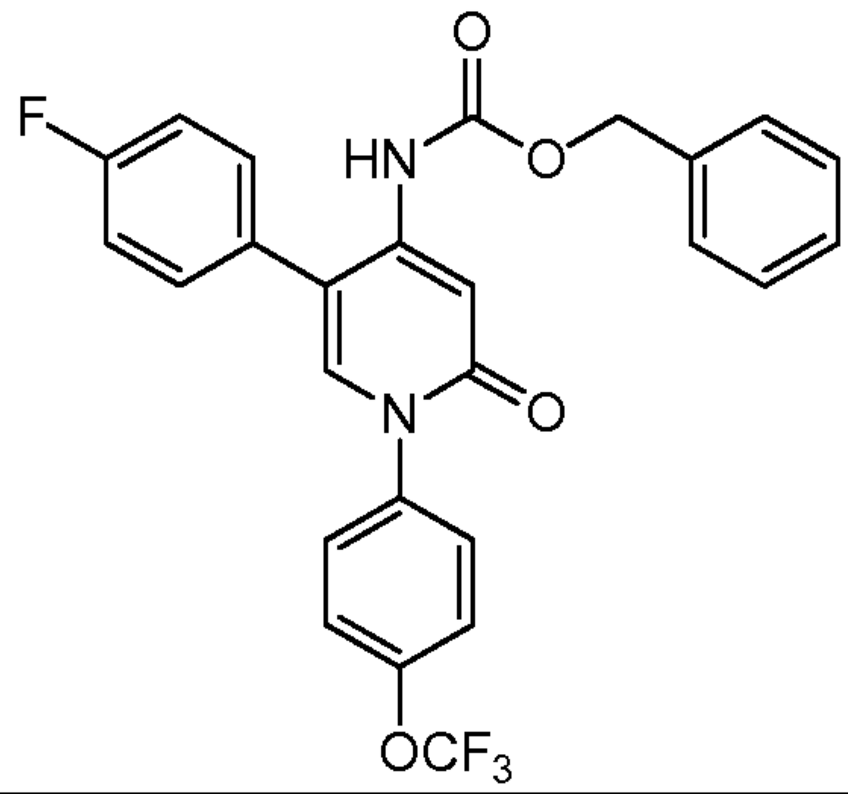
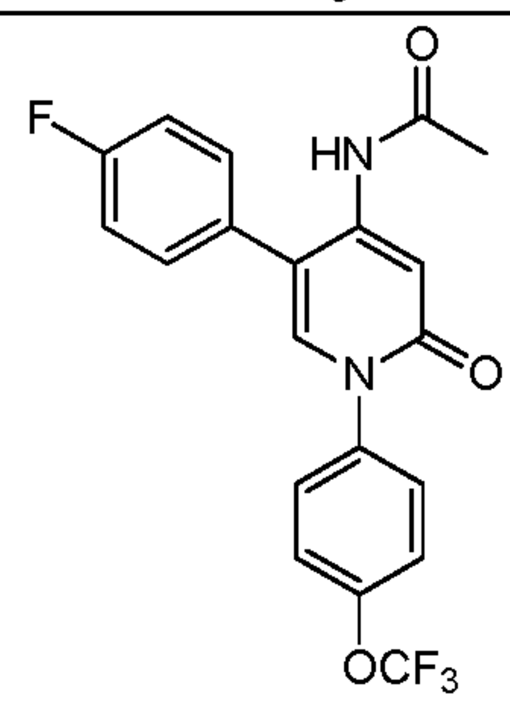
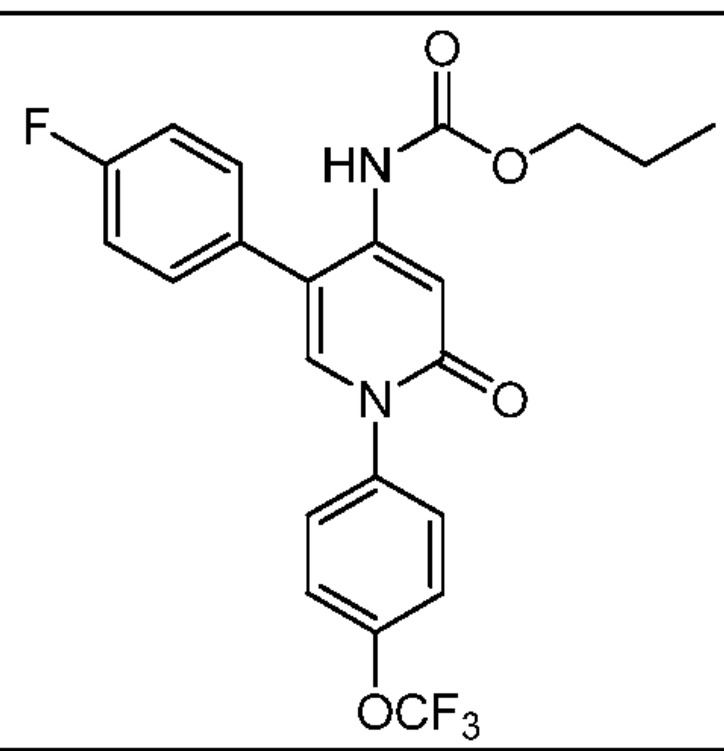
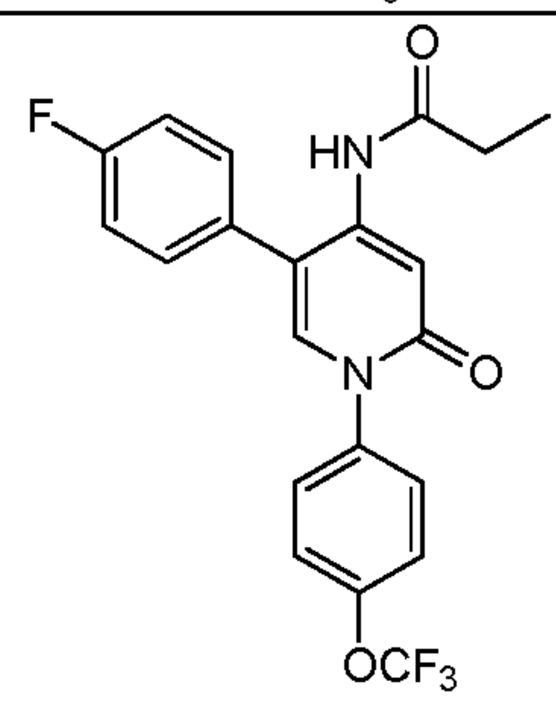
97	
98	
99	
100	
101	
102	
103	
104	
105	
106	

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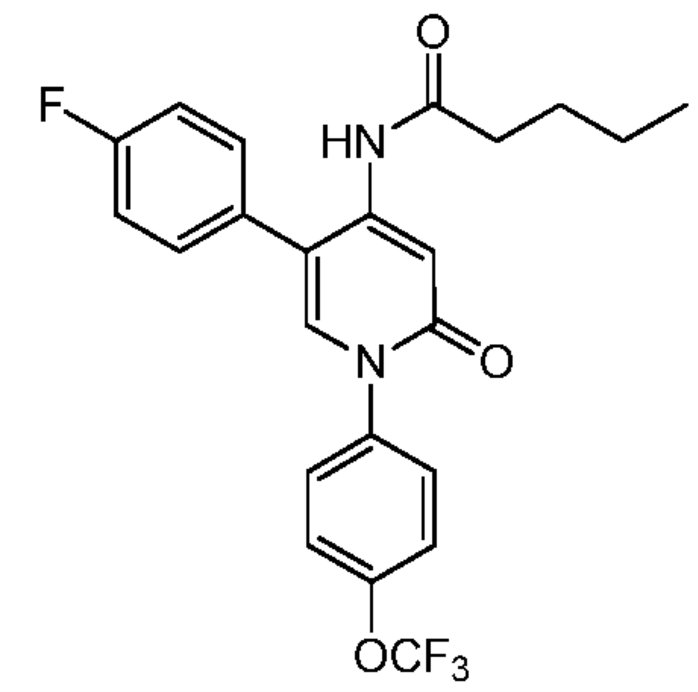
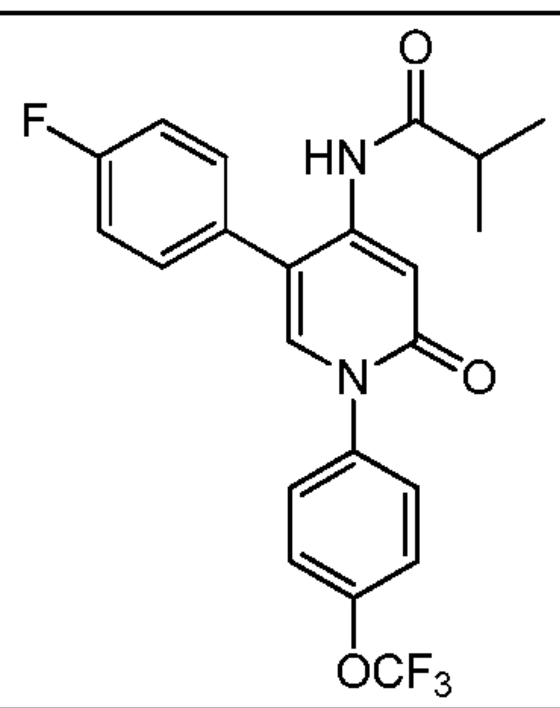
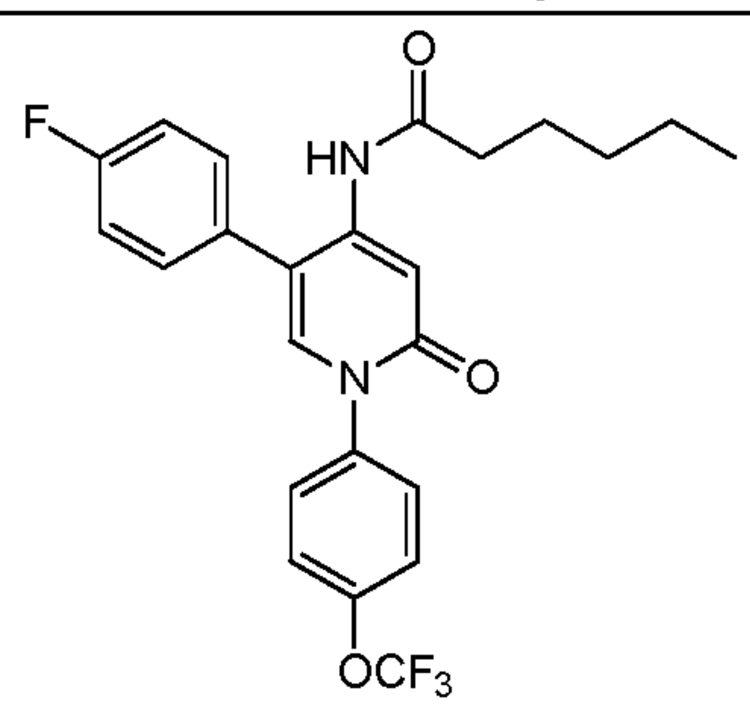
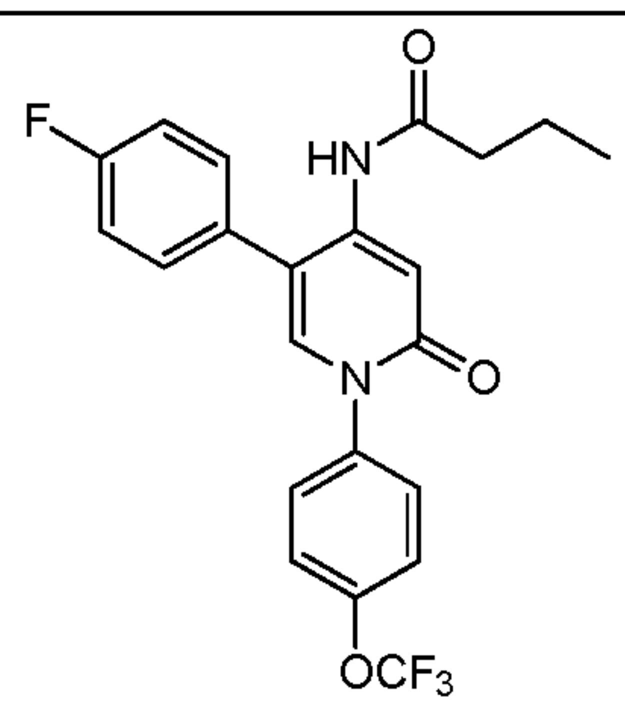
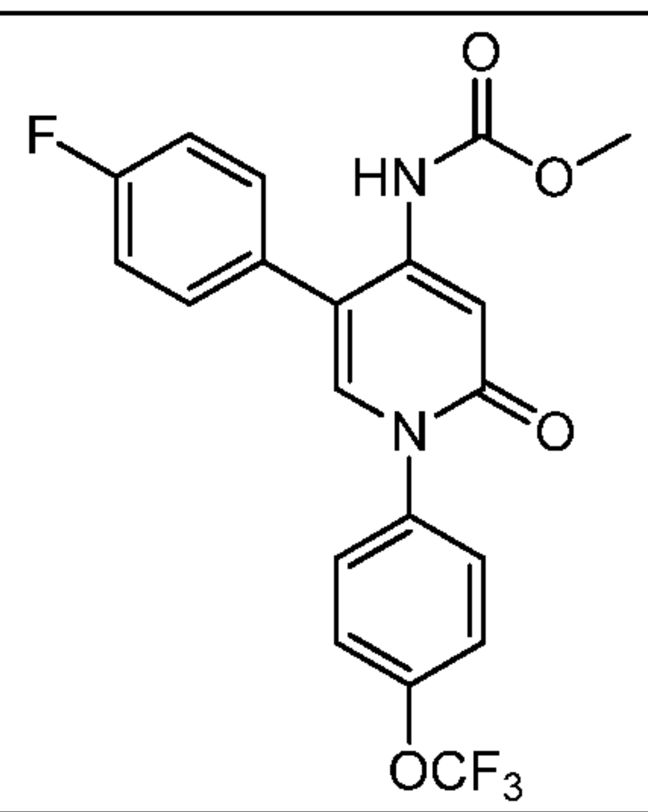
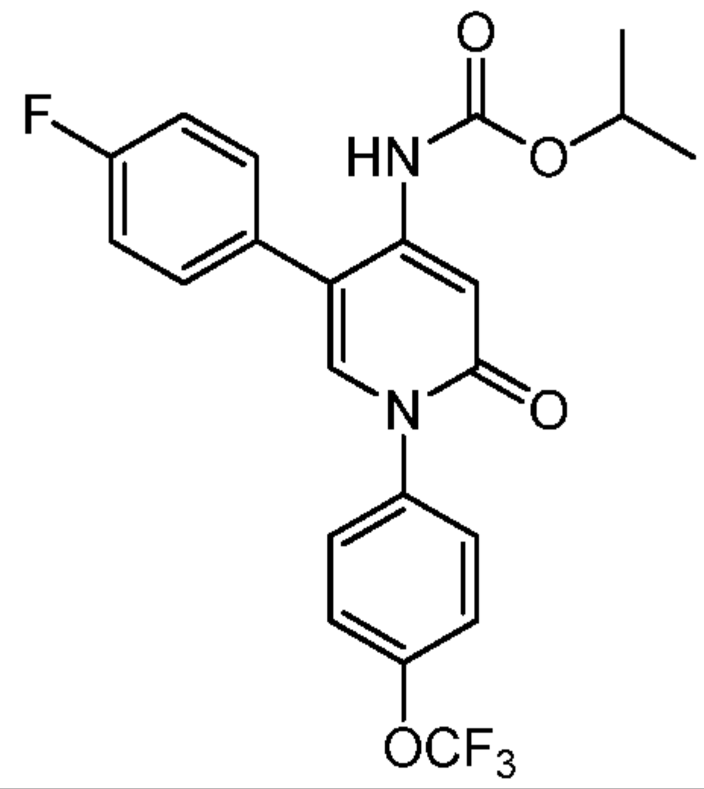
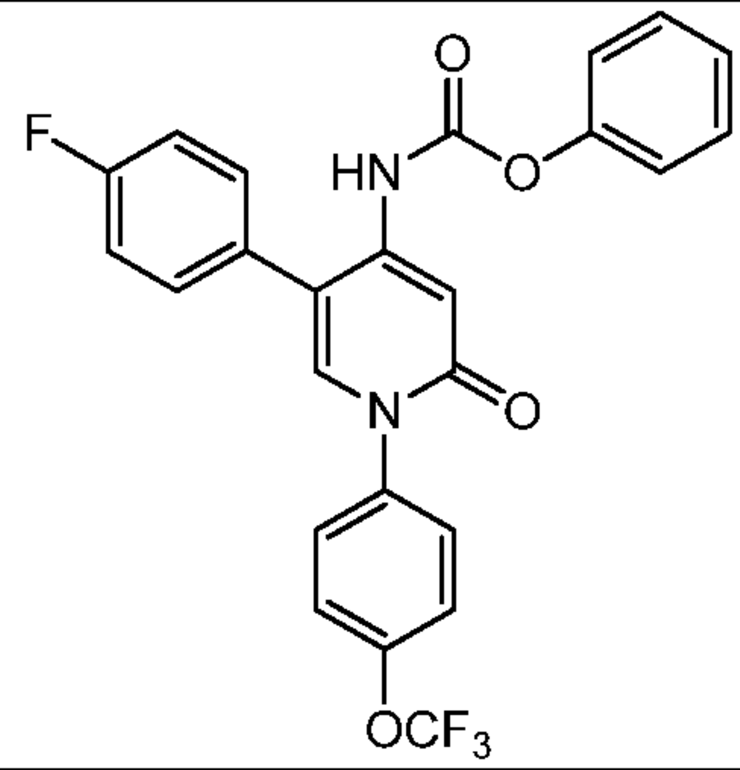
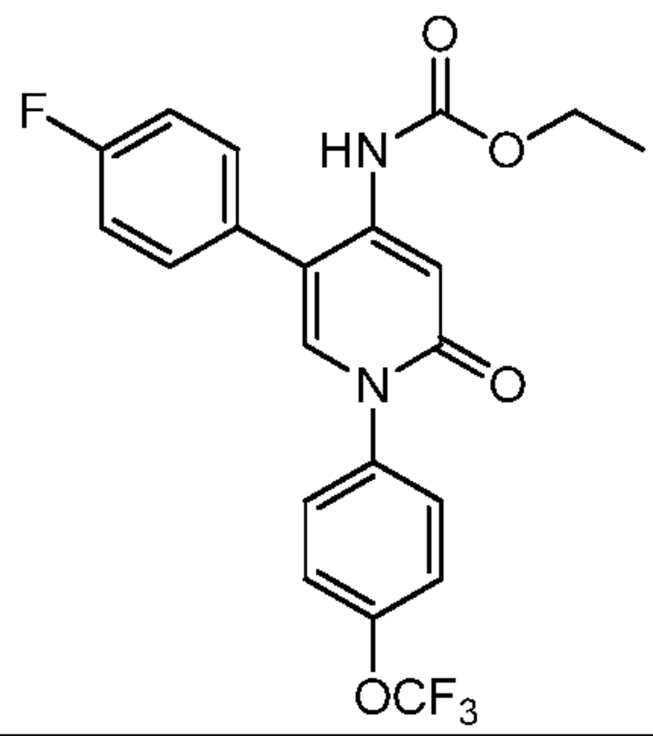
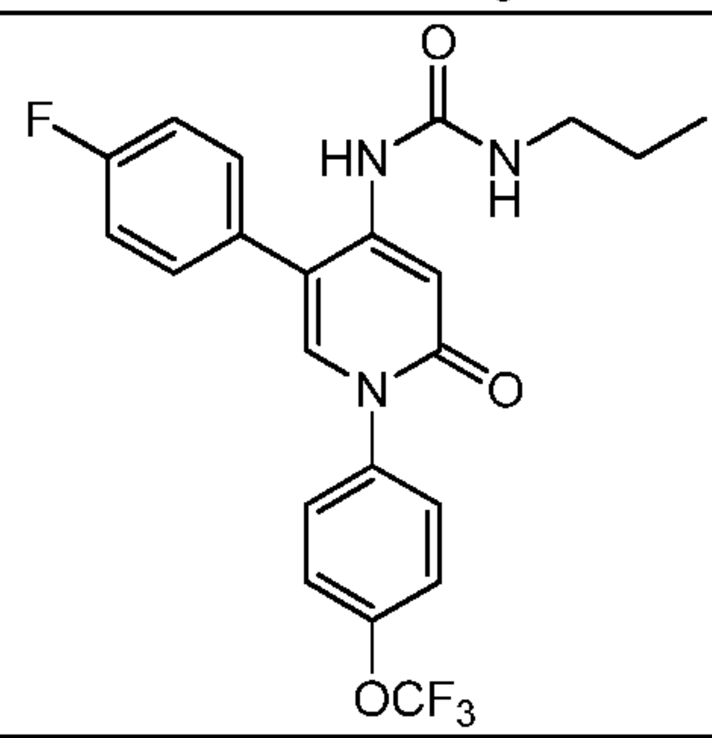
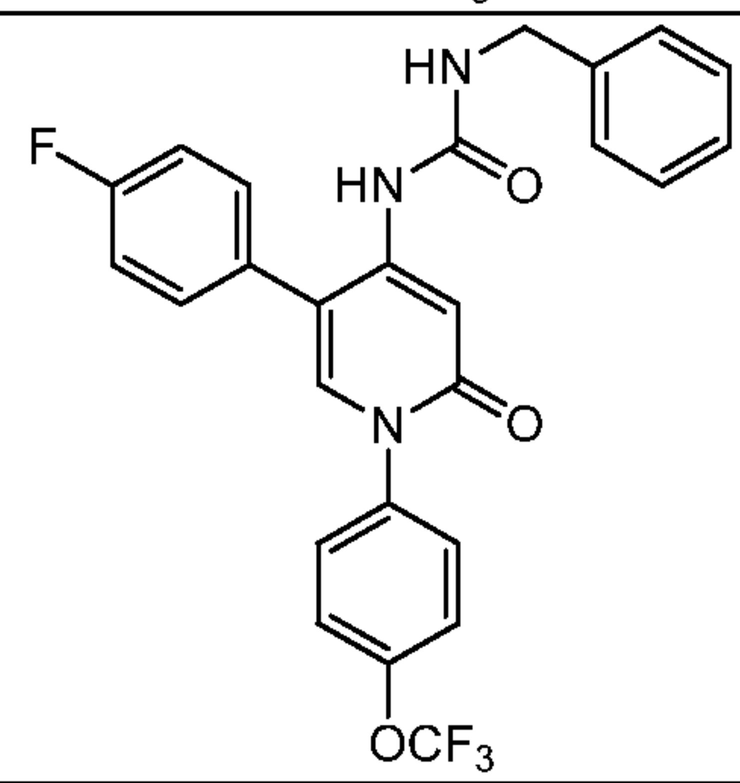
107	
108	
109	
110	
111	
112	
113	
114	
115	
116	

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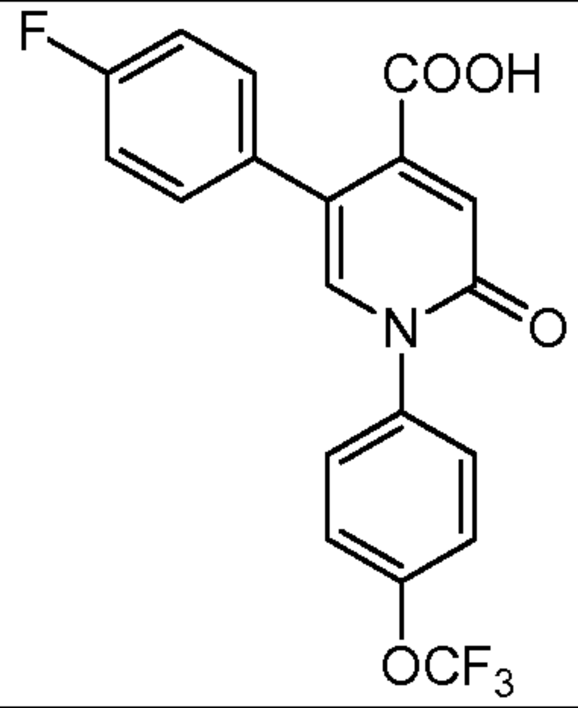
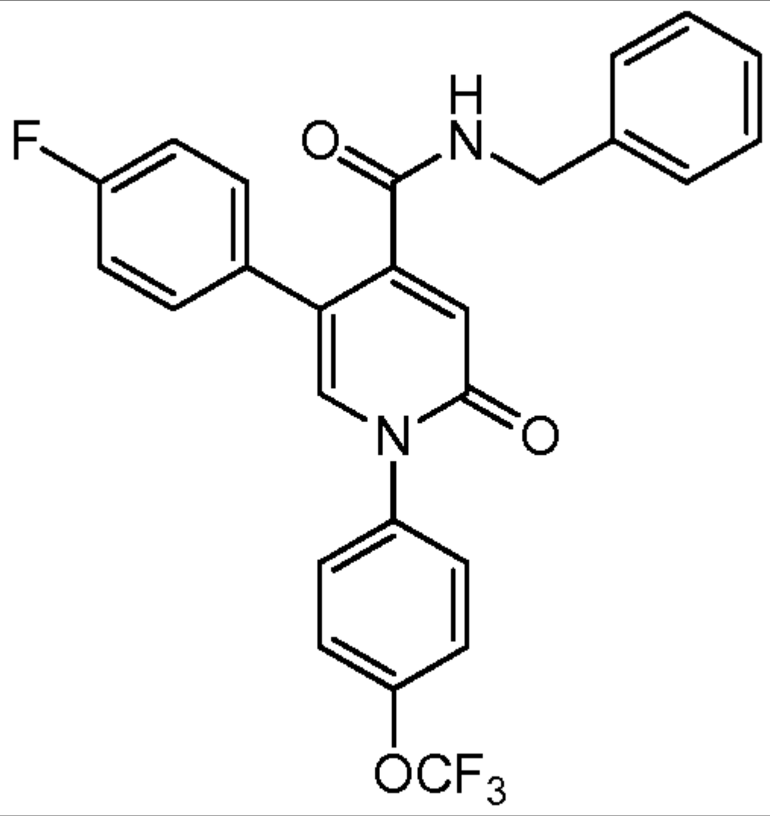
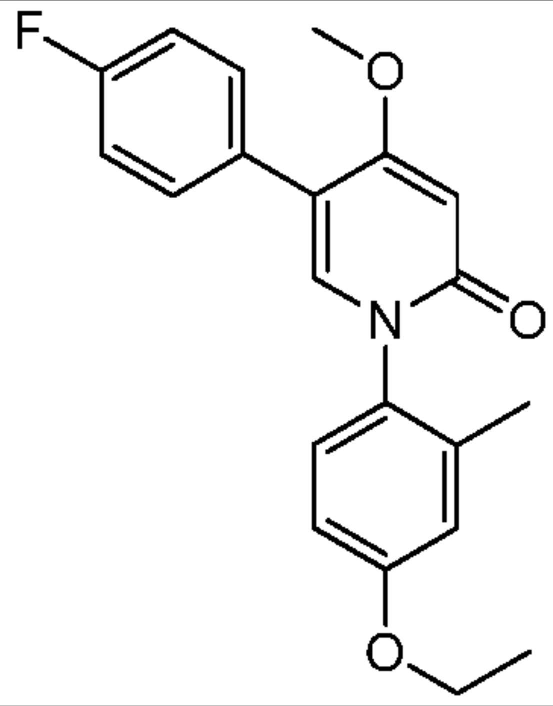
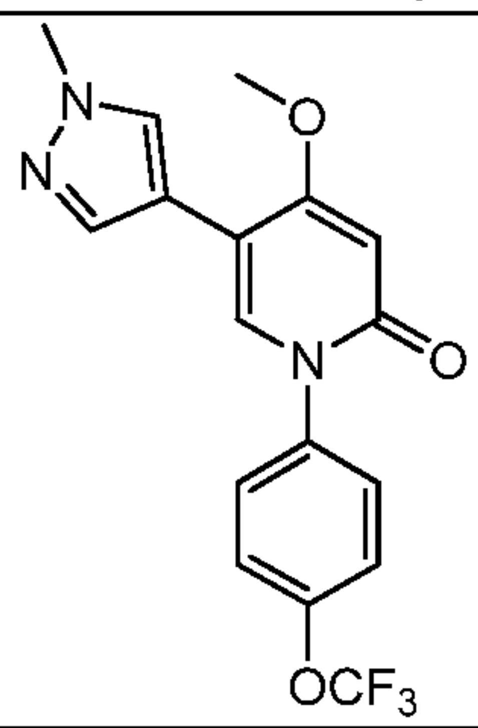
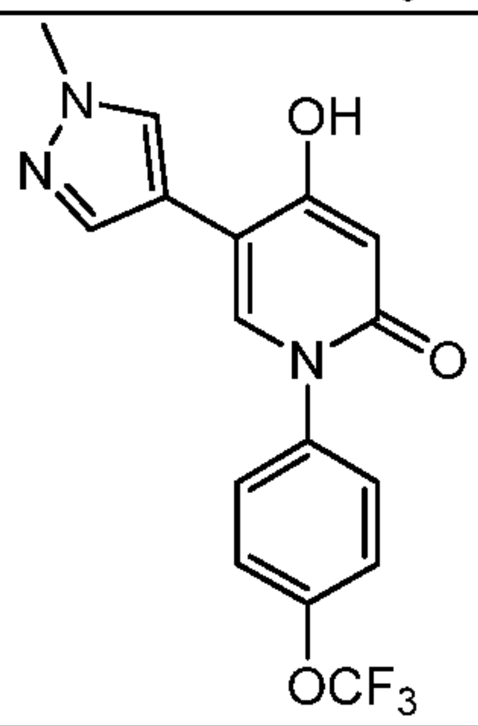
117	
118	
119	
120	
121	

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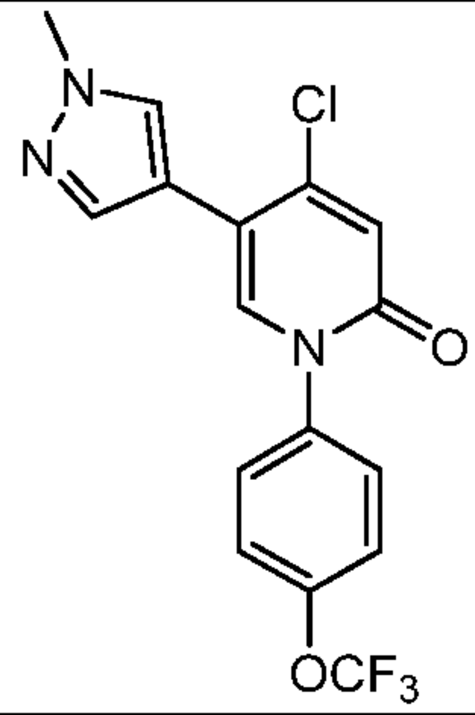
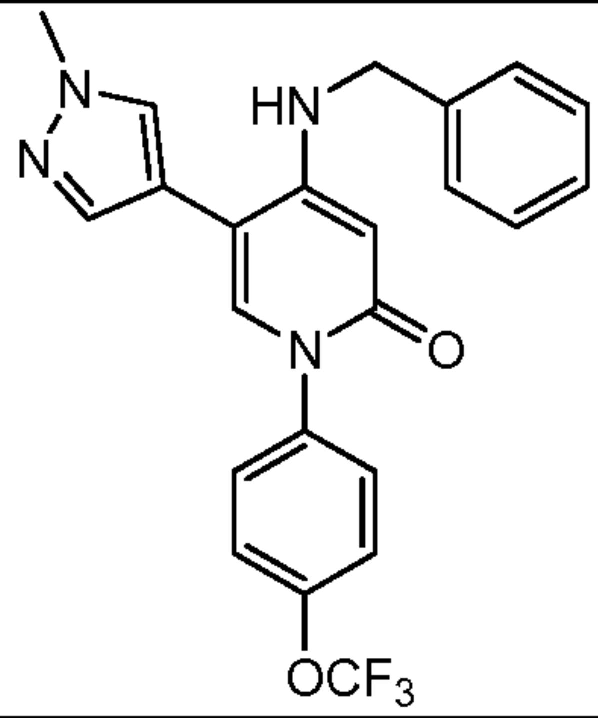
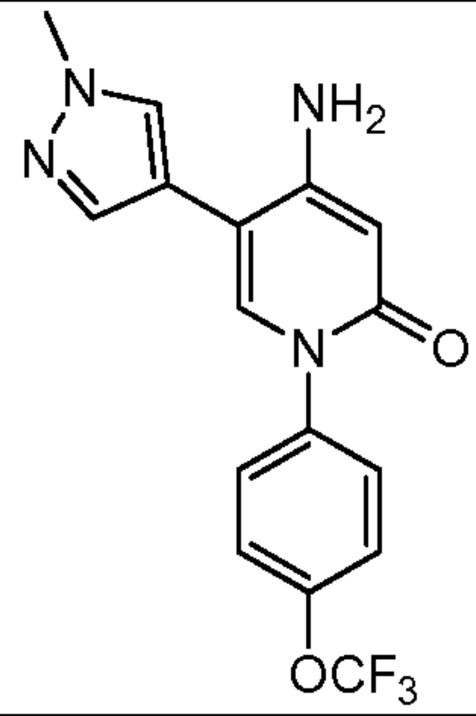
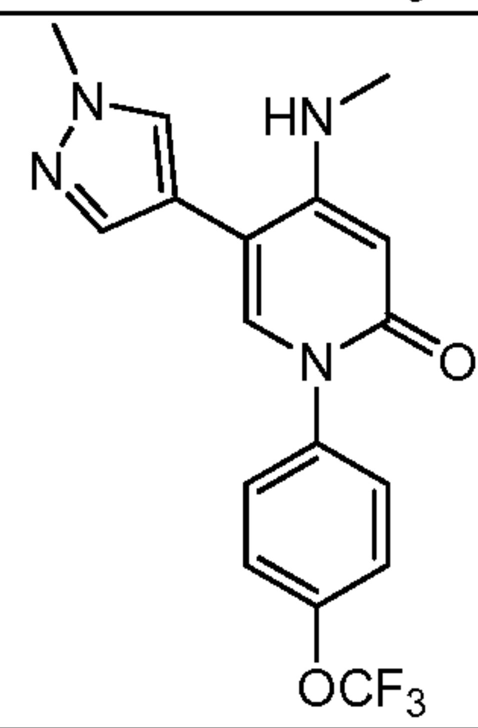
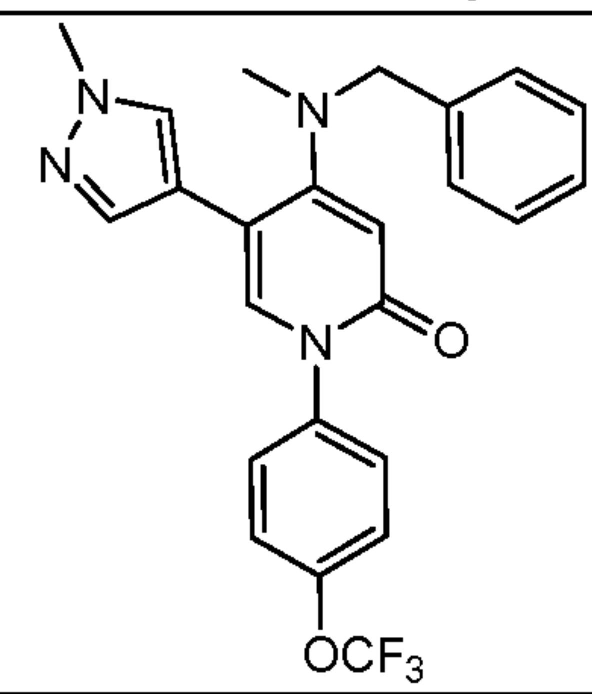
122	
123	
124	
125	
126	

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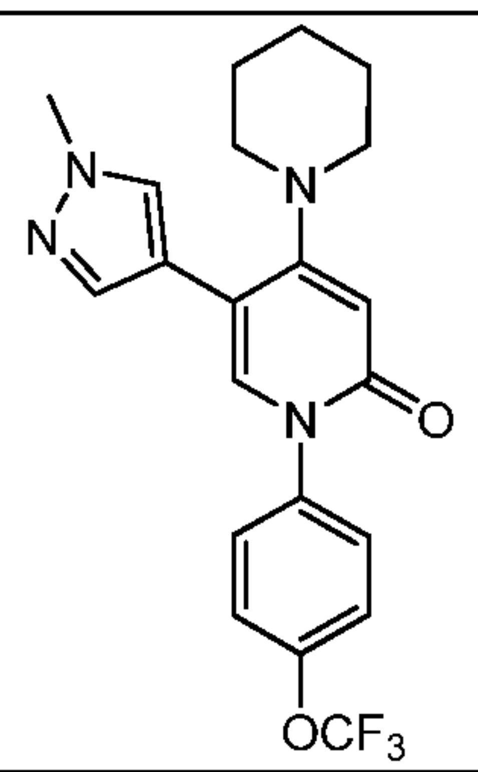
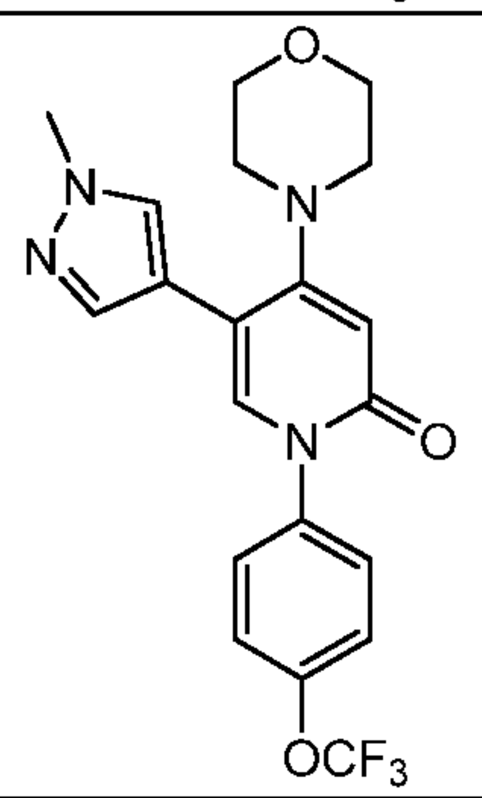
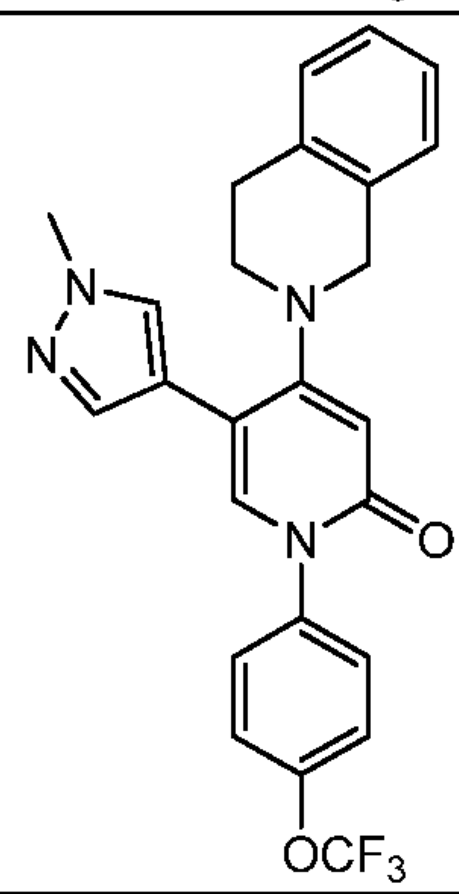
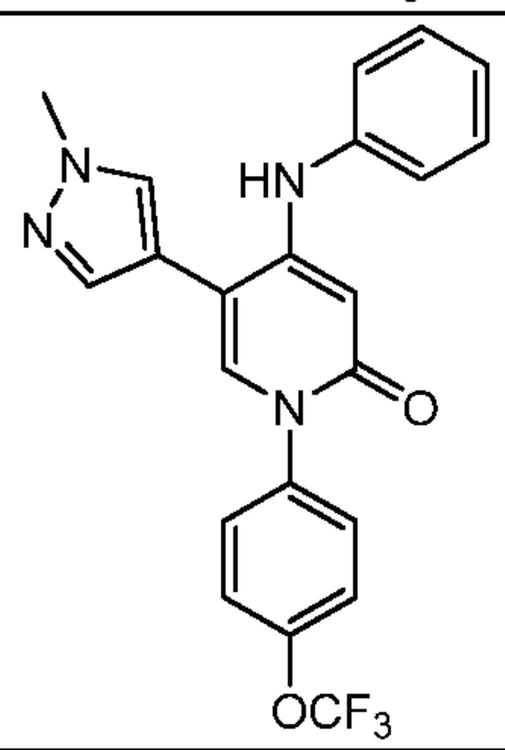
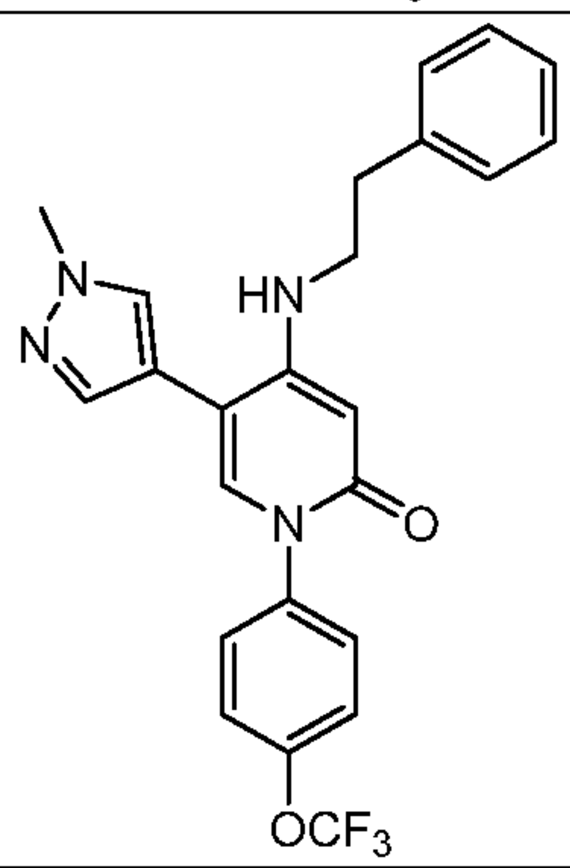
127	
128	
129	
130	
131	

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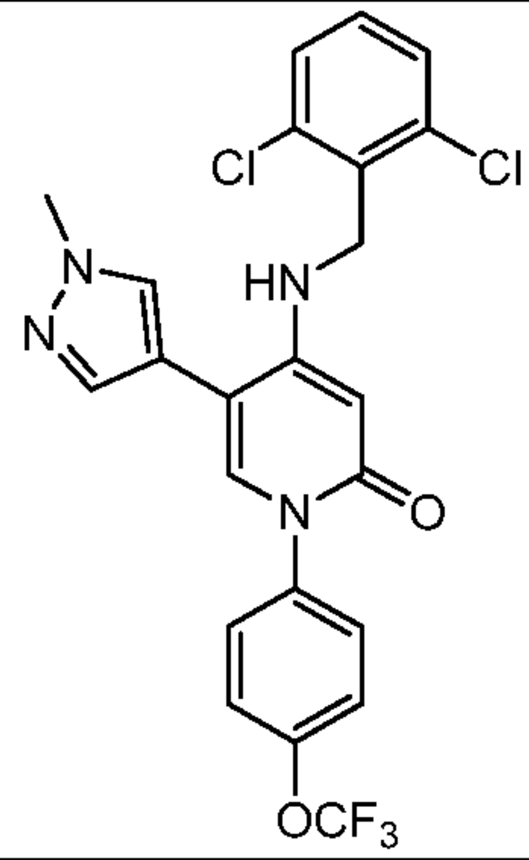
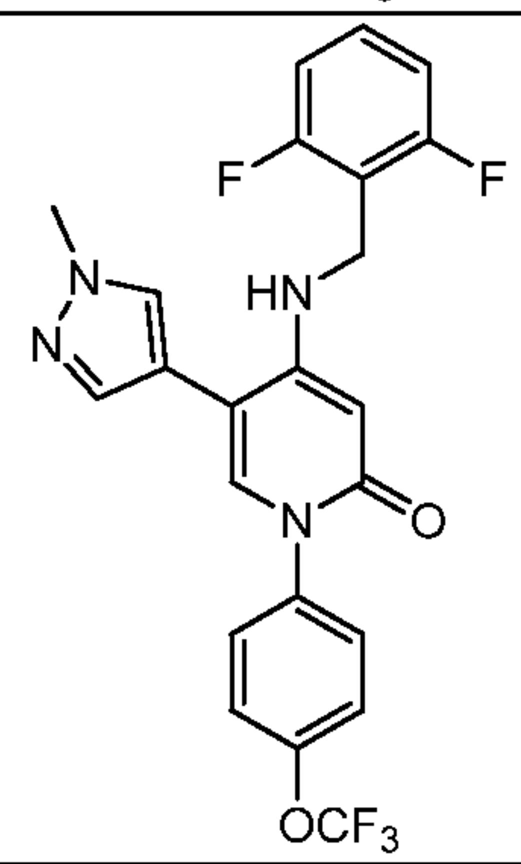
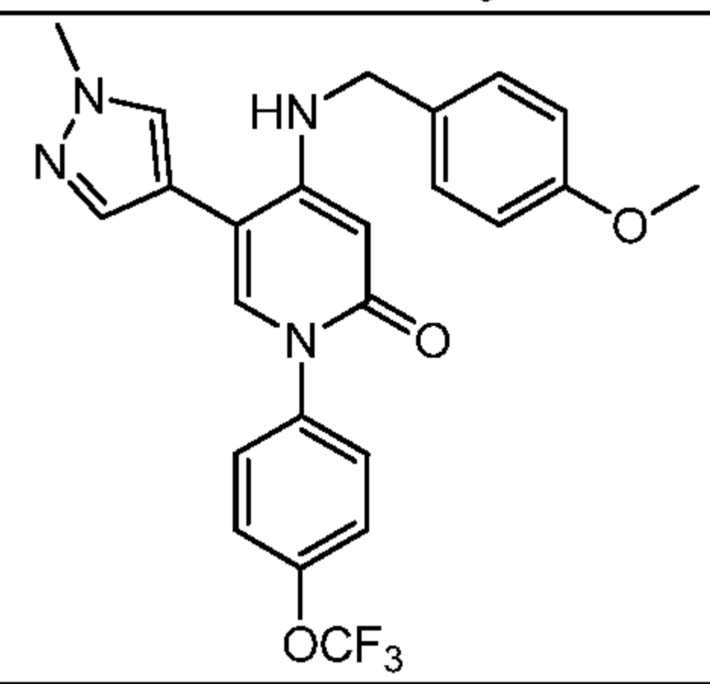
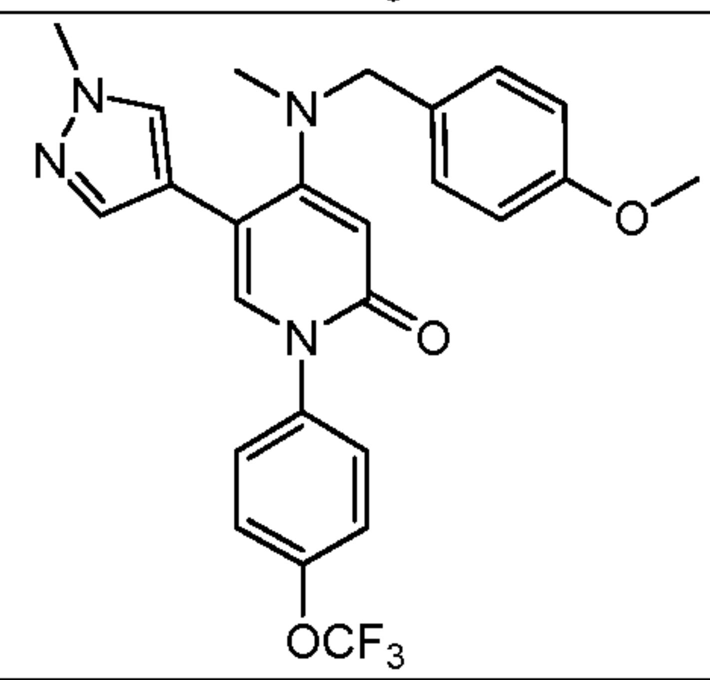
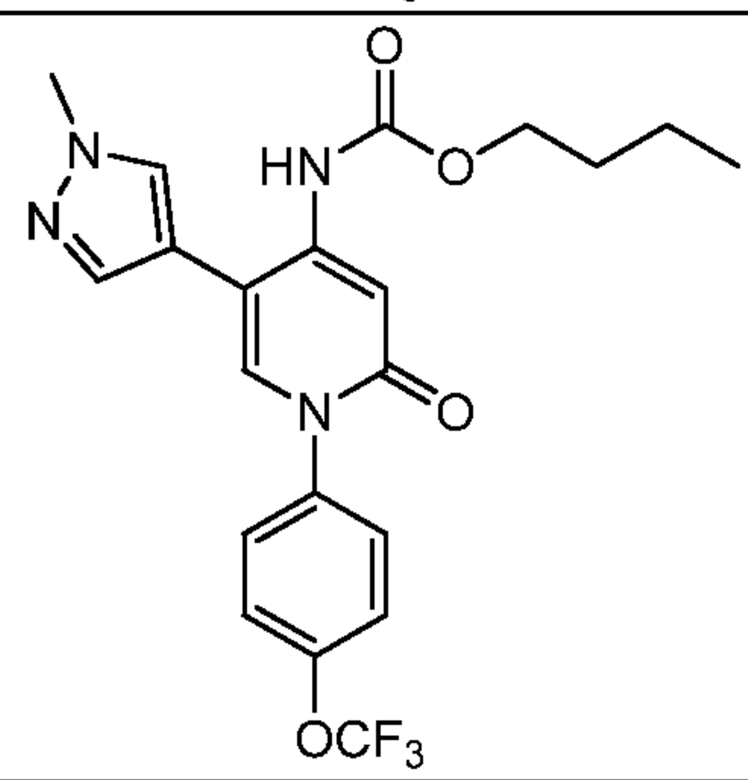
132	
133	
134	
135	
136	

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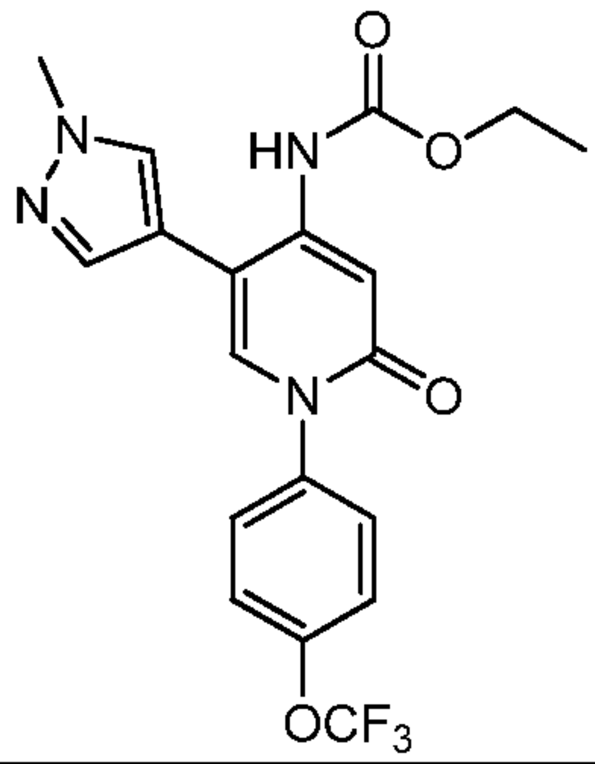
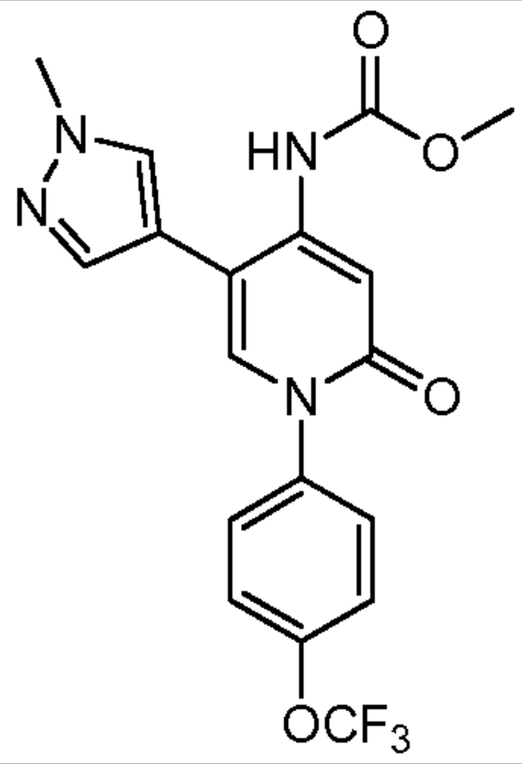
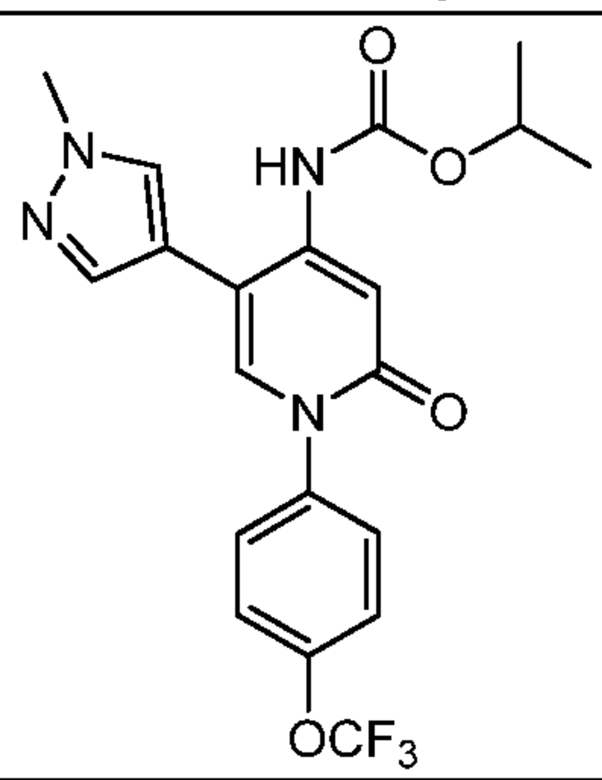
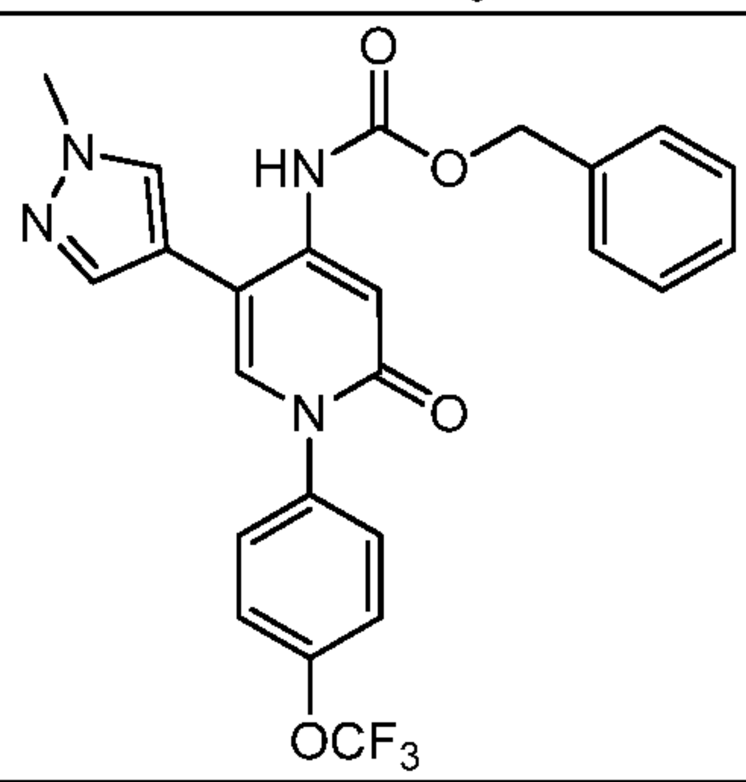
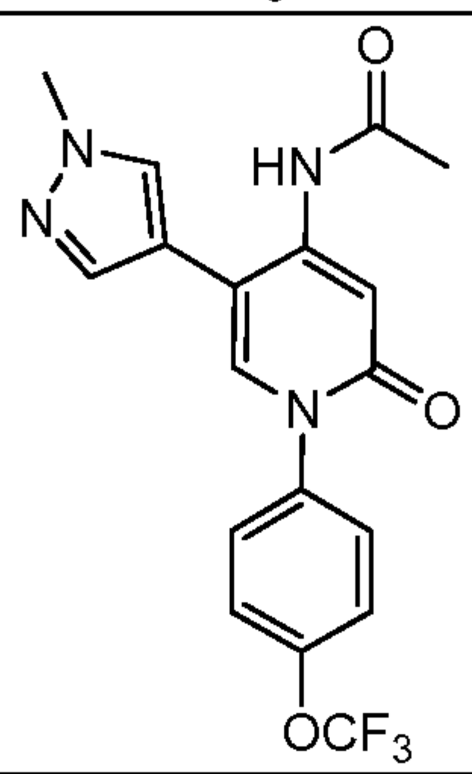
137	
138	
139	
140	
141	

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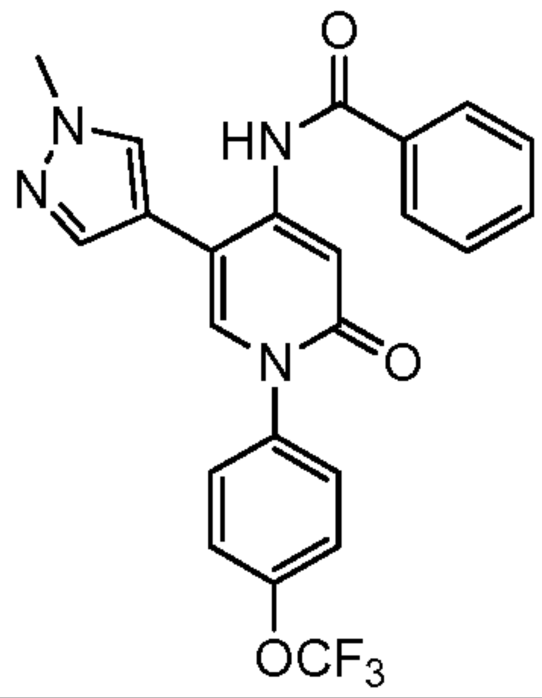
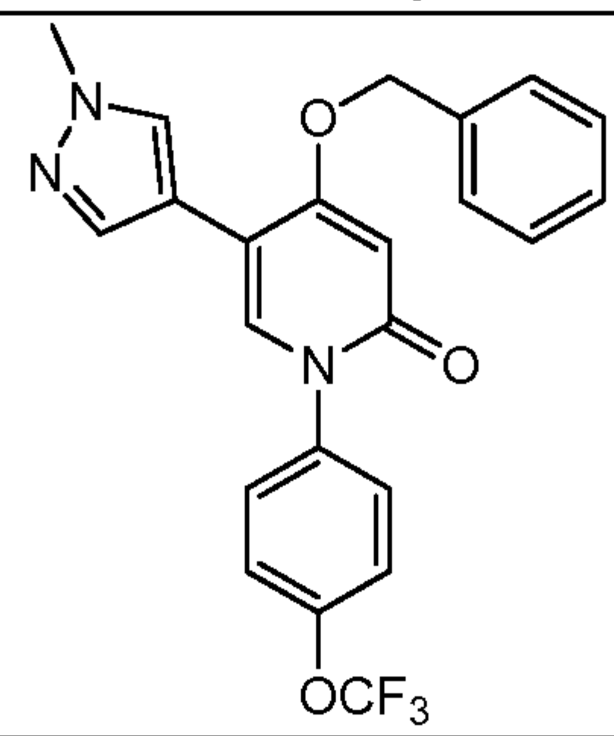
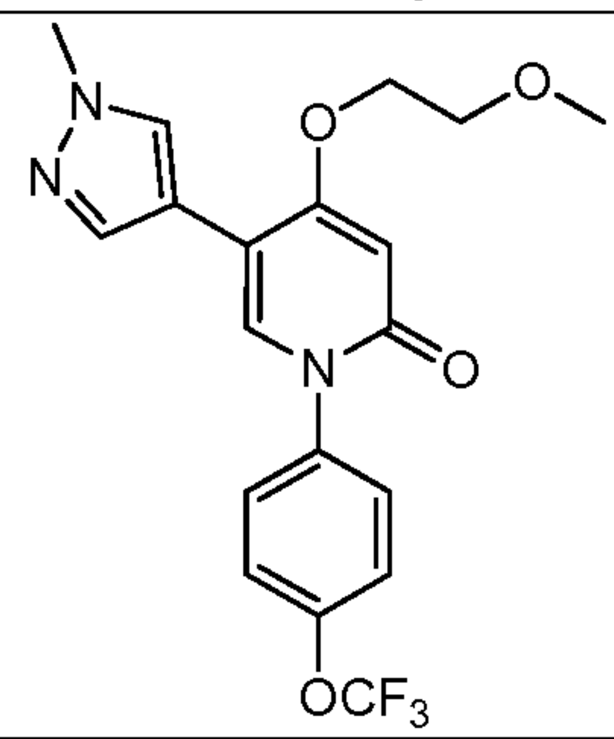
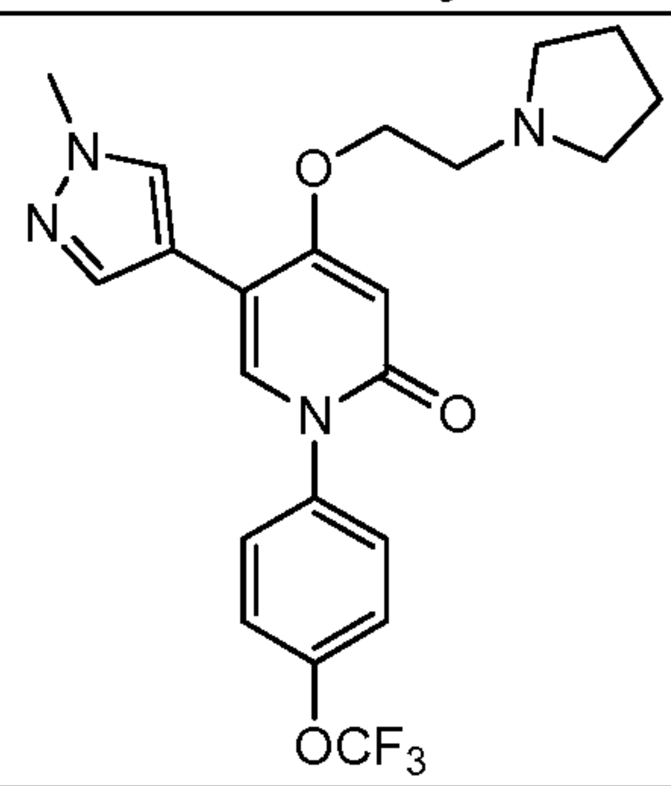
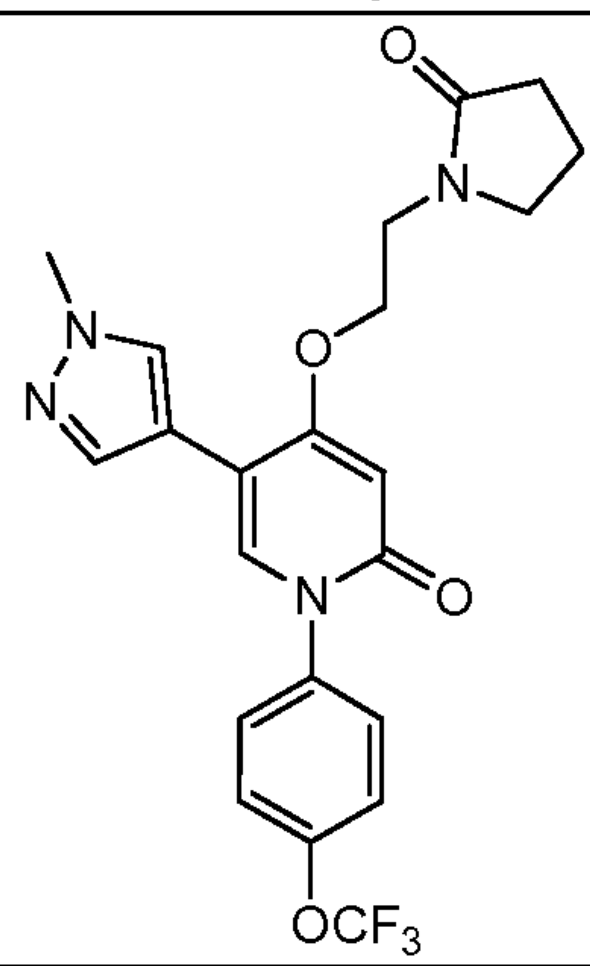
142	
143	
144	
145	
146	

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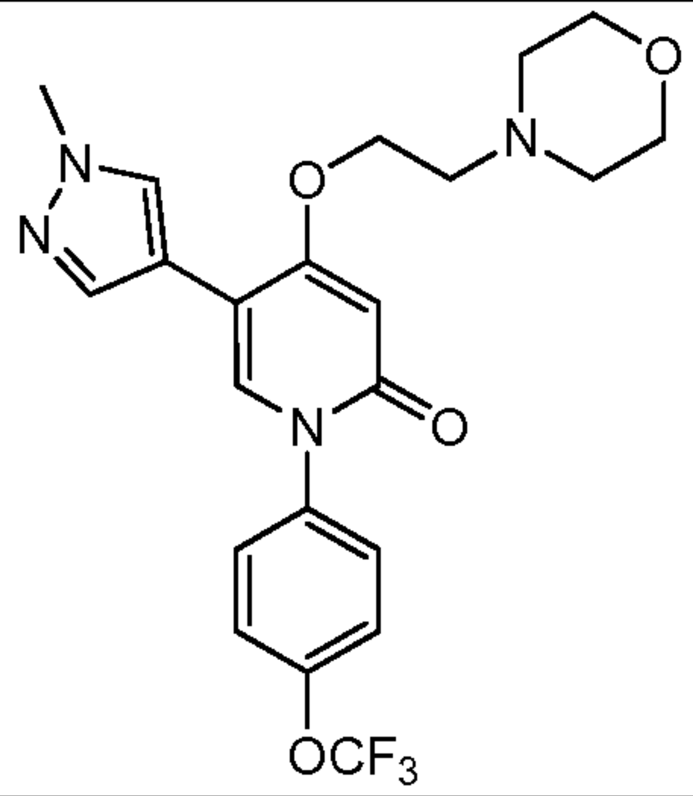
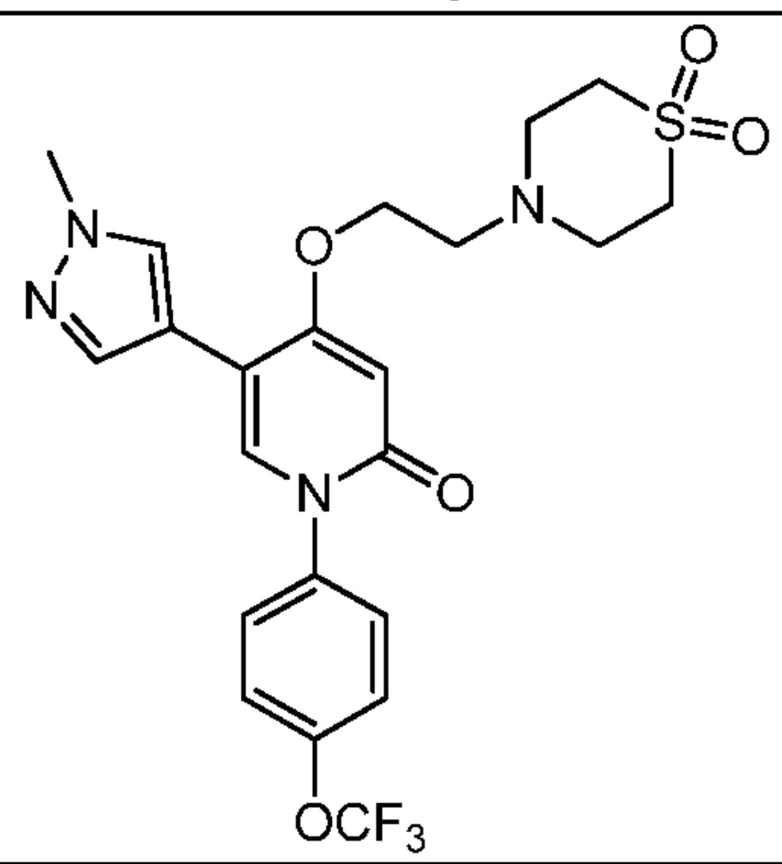
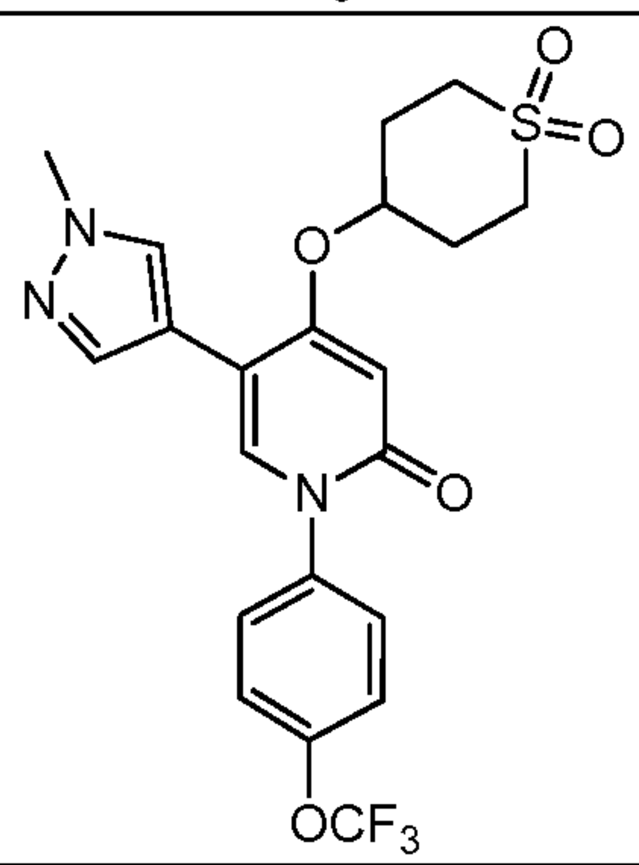
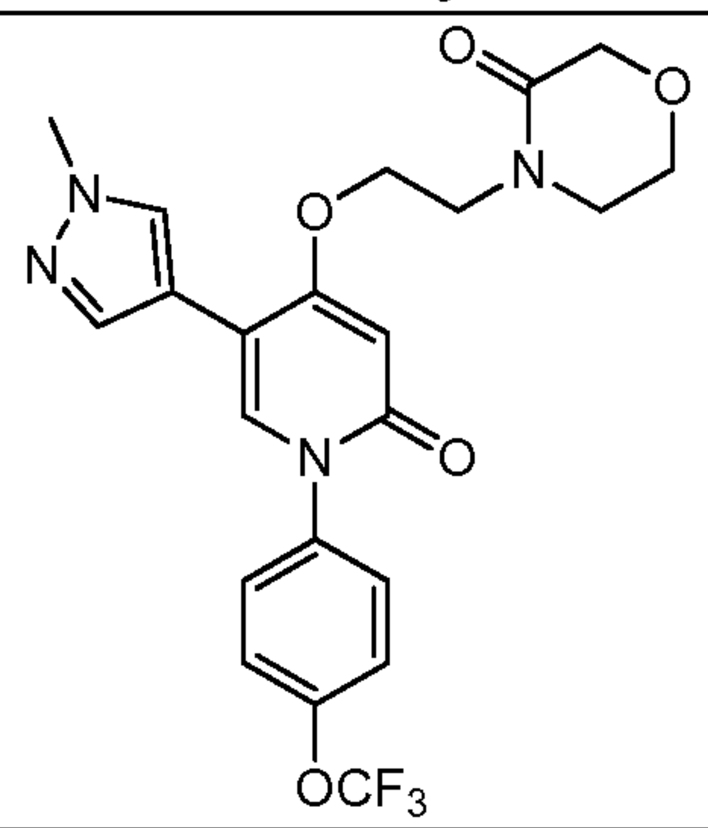
147	
148	
149	
150	

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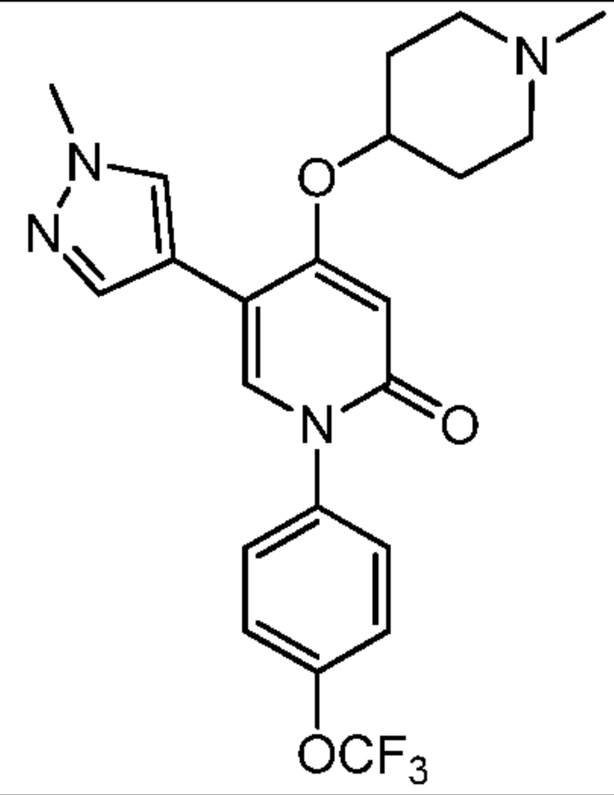
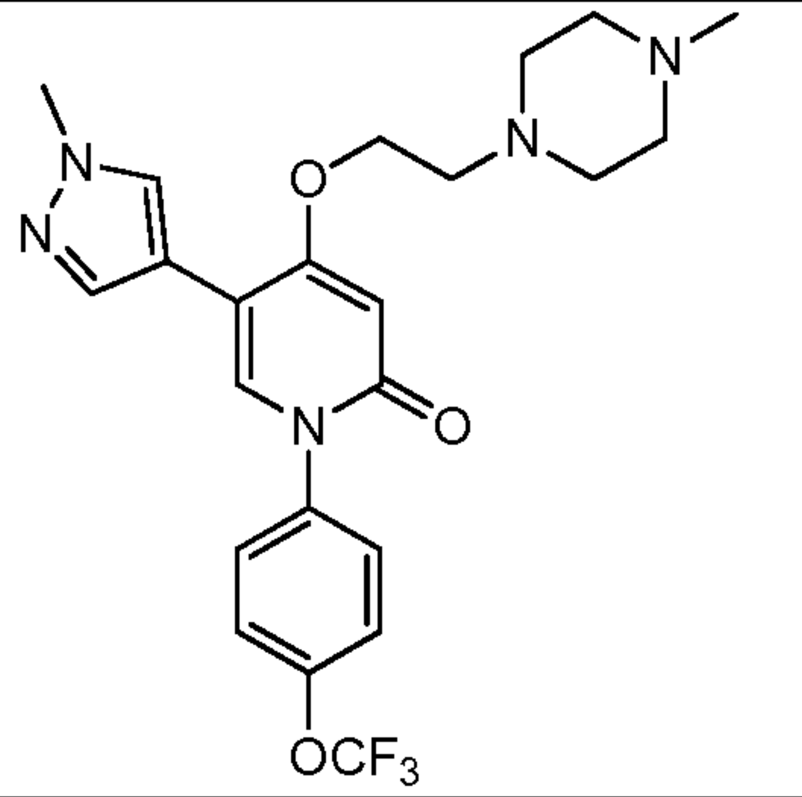
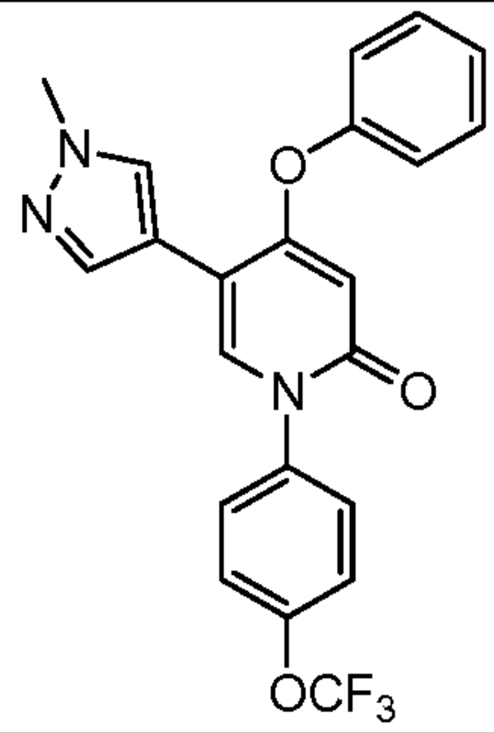
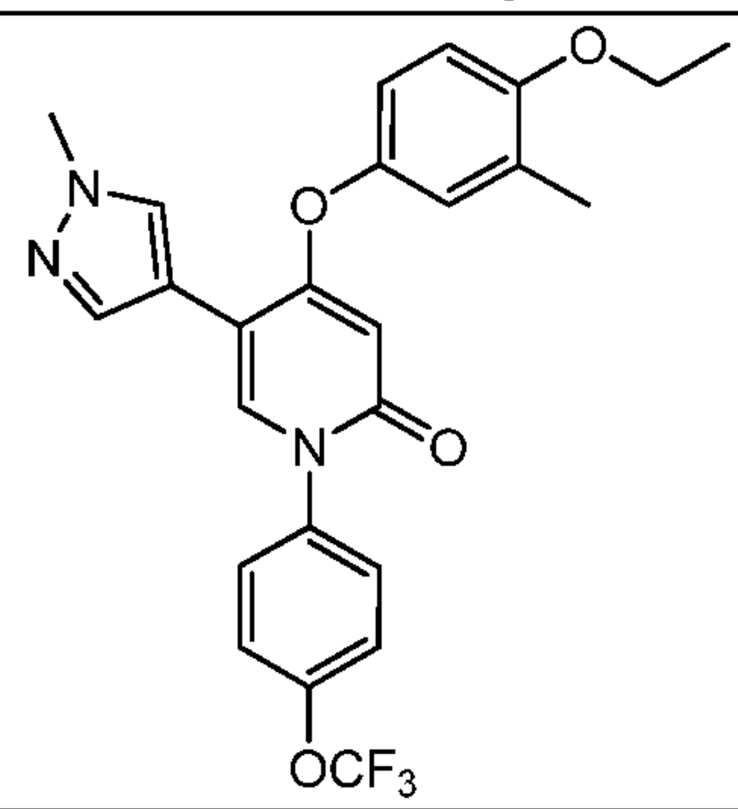
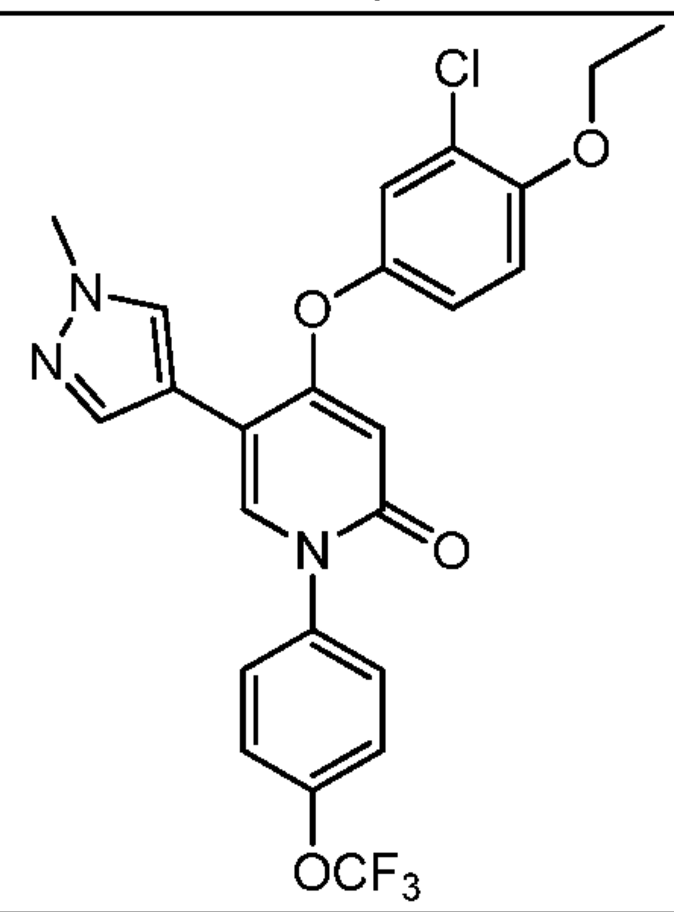
151	
152	
153	
154	
155	

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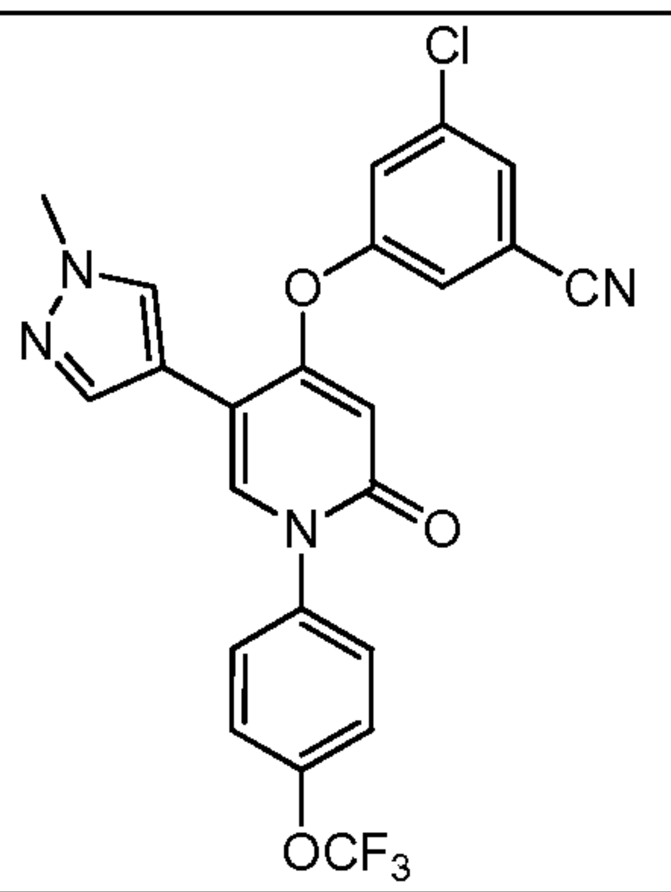
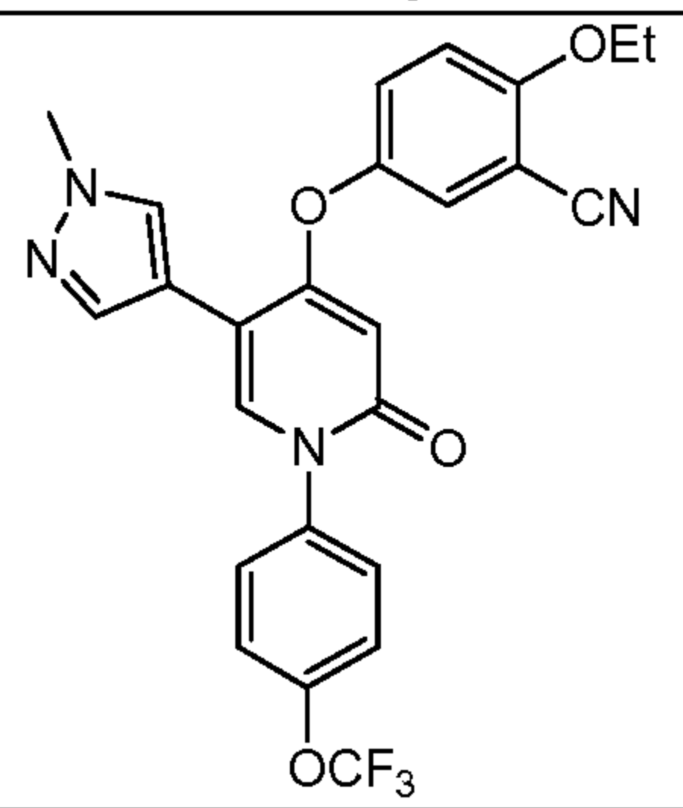
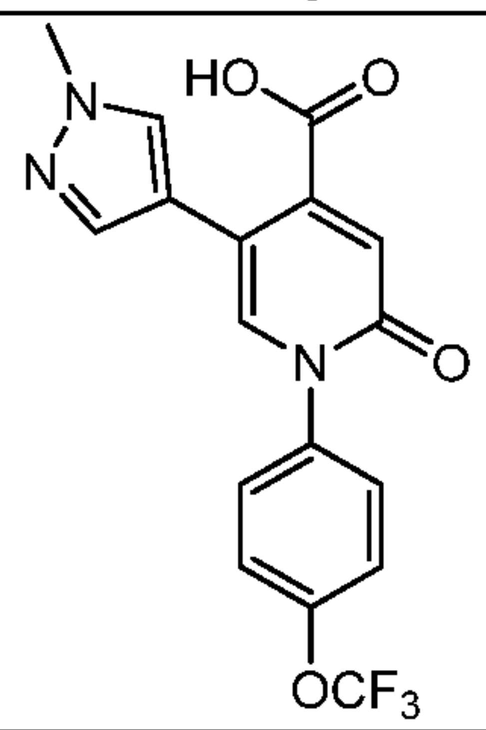
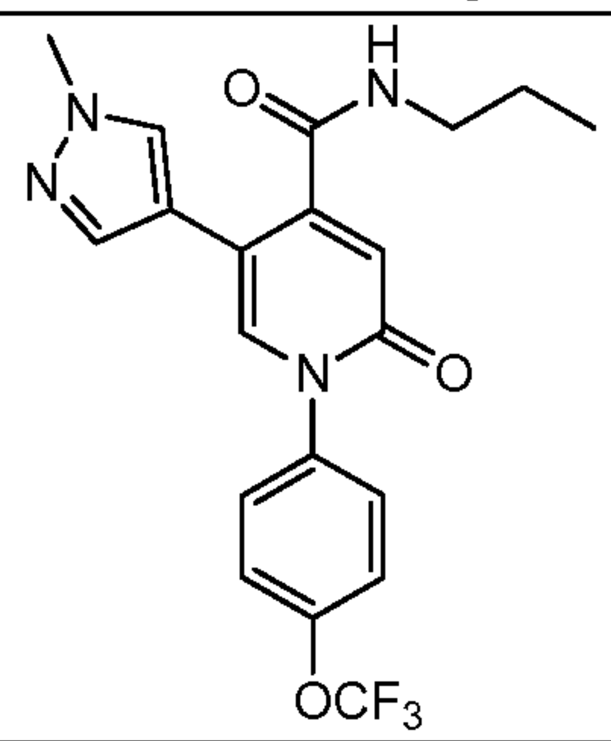
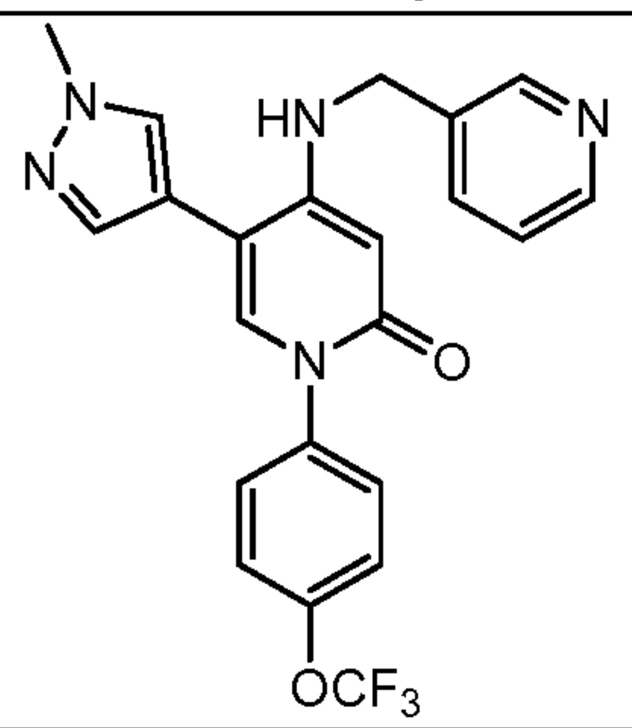
156	
157	
158	
159	
160	

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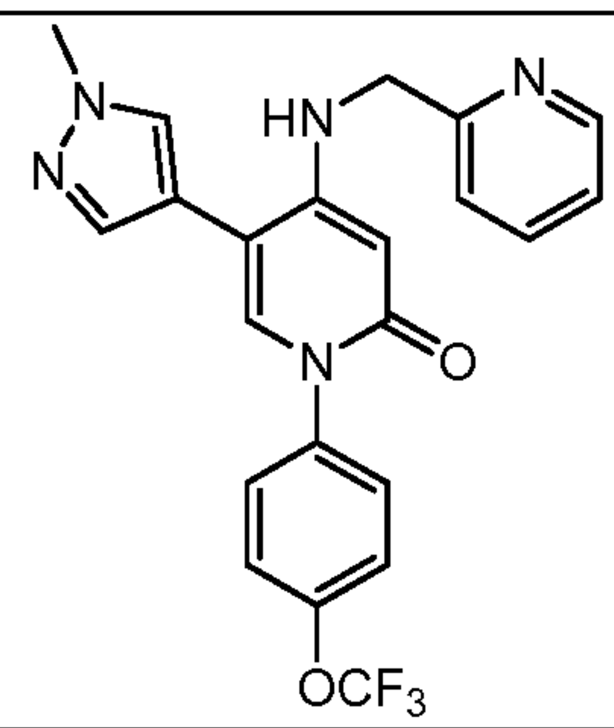
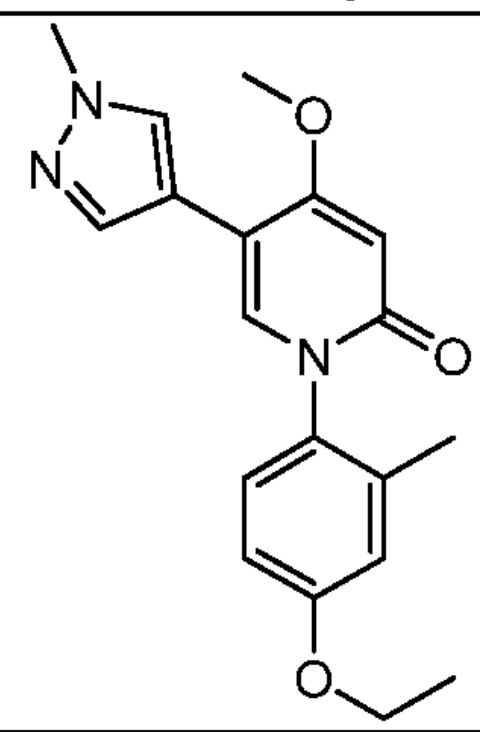
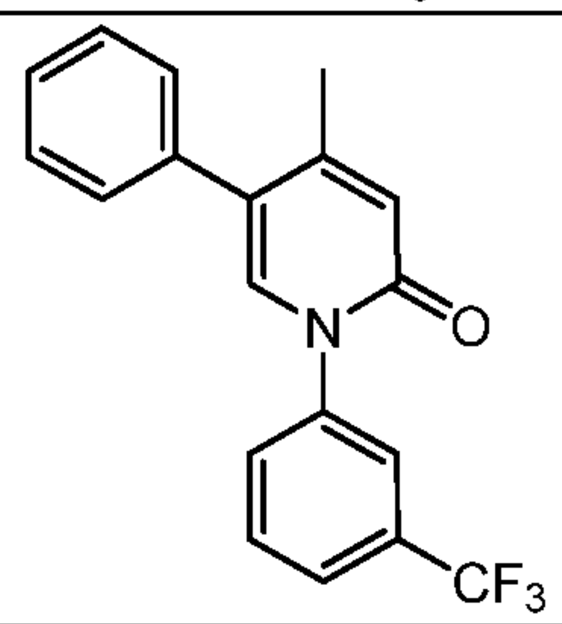
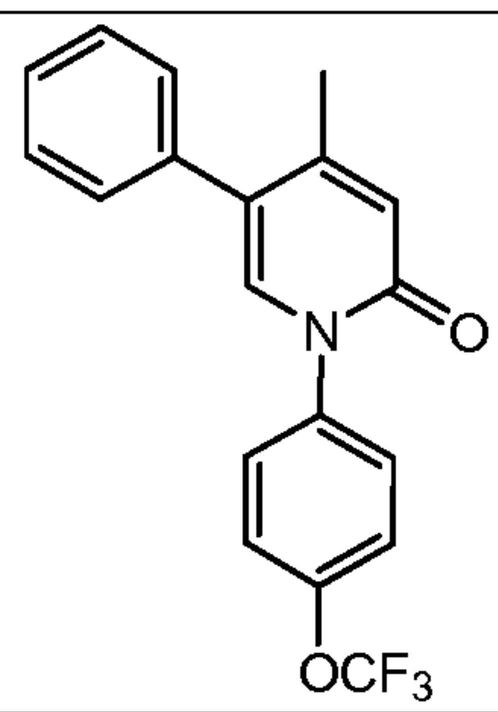
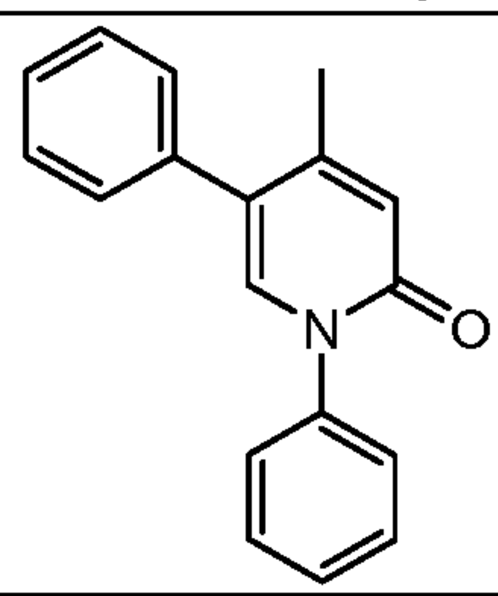
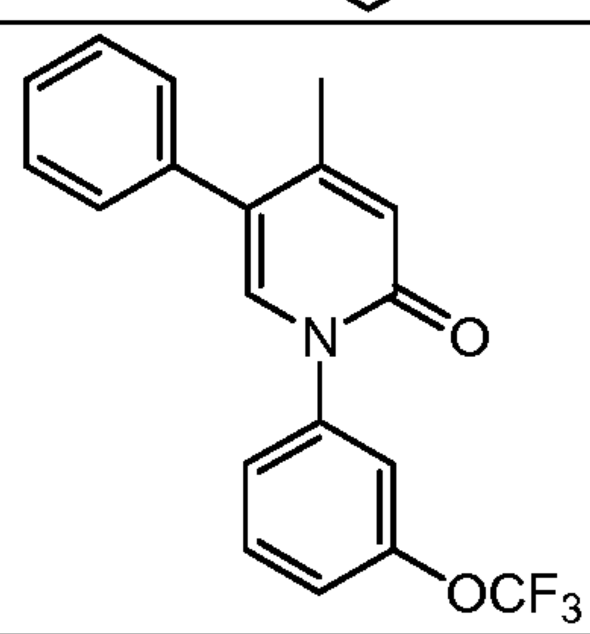
161	
162	
163	
164	
165	
166	

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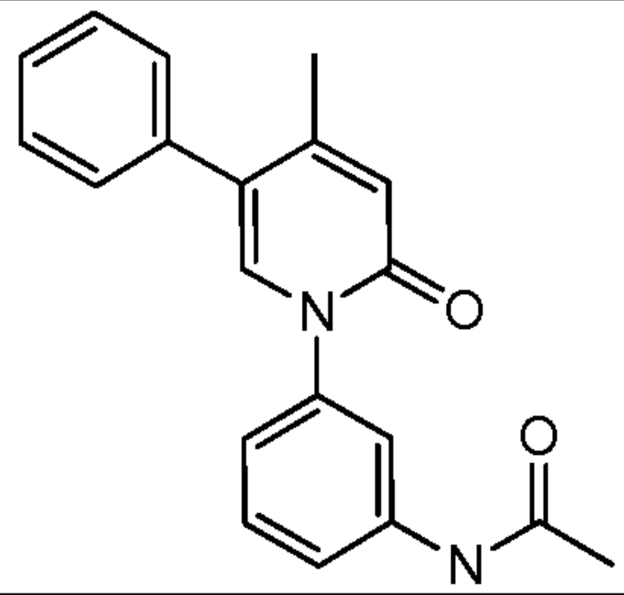
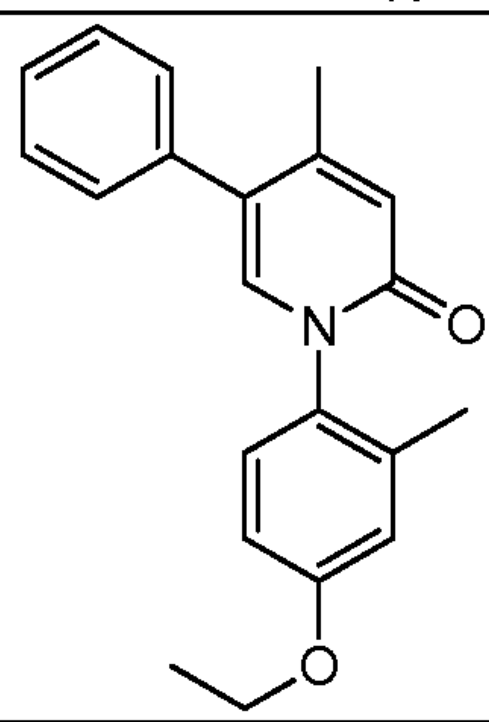
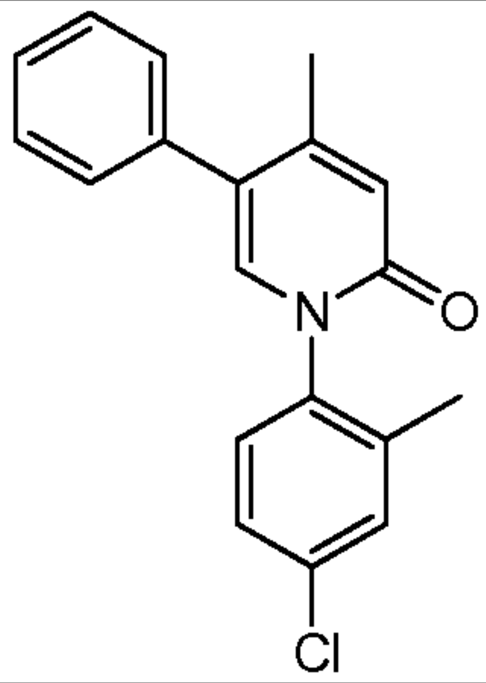
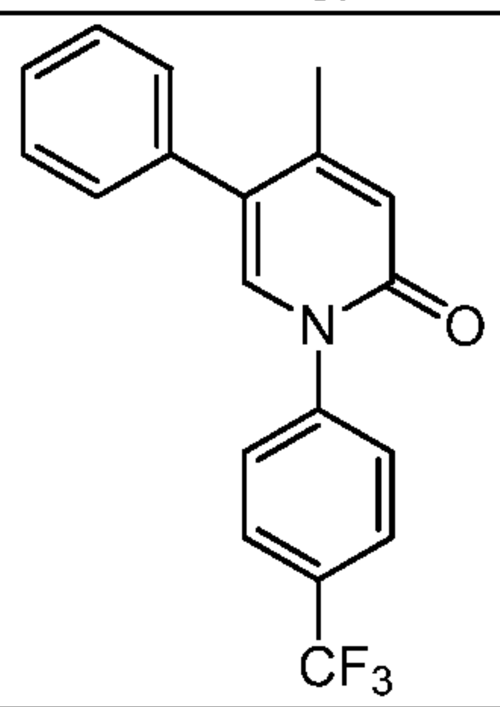
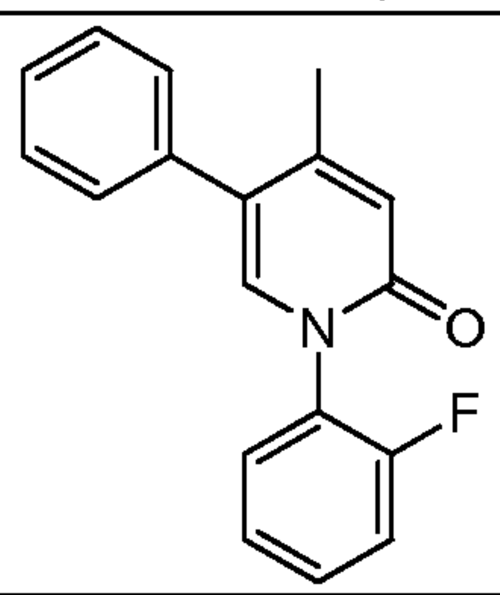
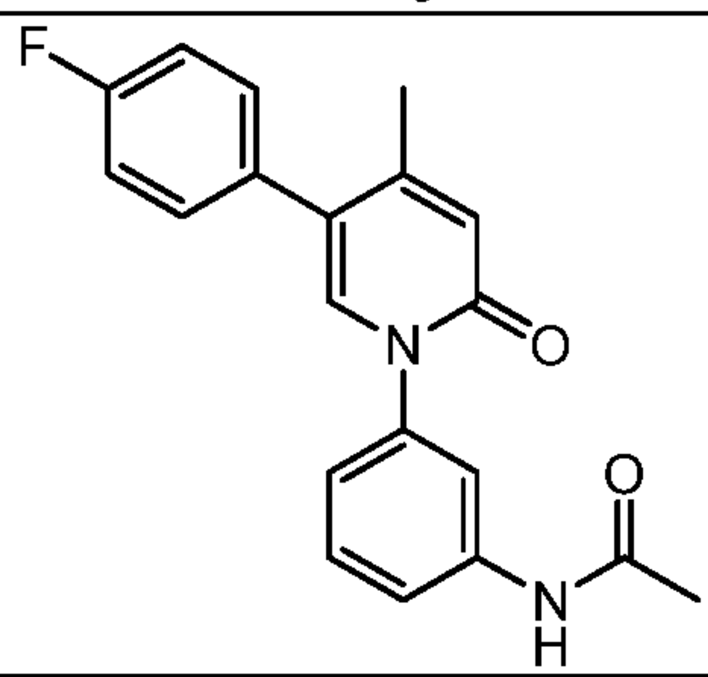
167	
168	
169	
170	
171	
172	

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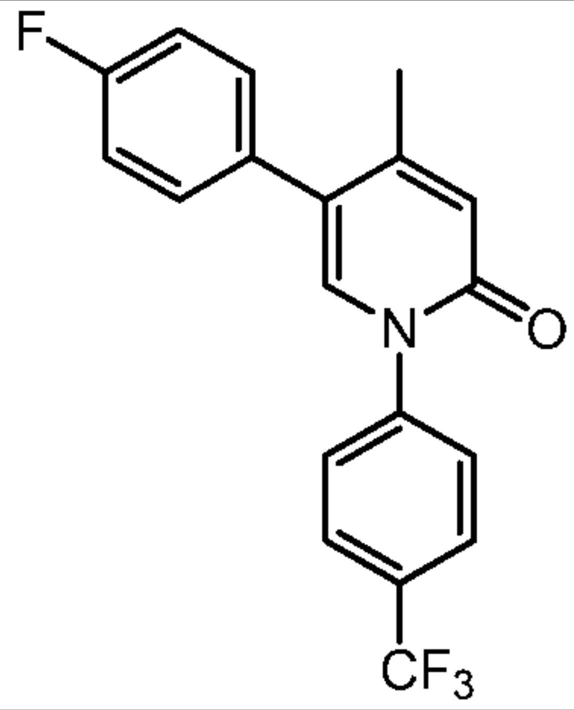
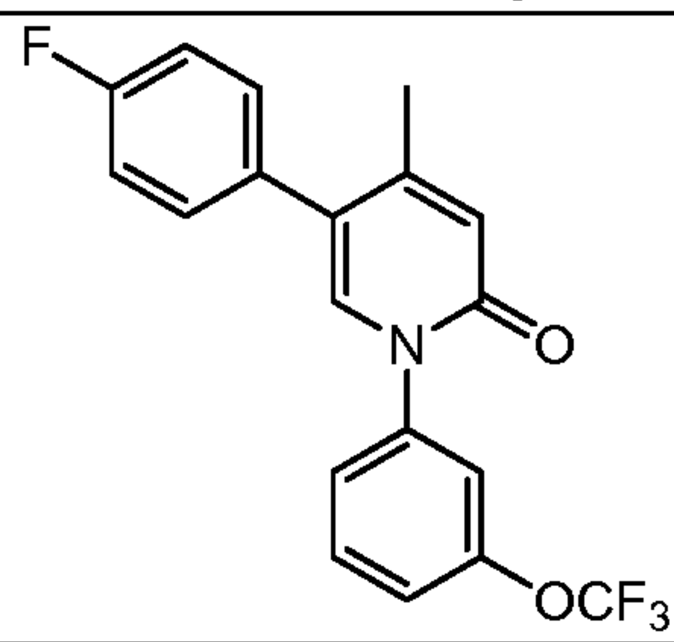
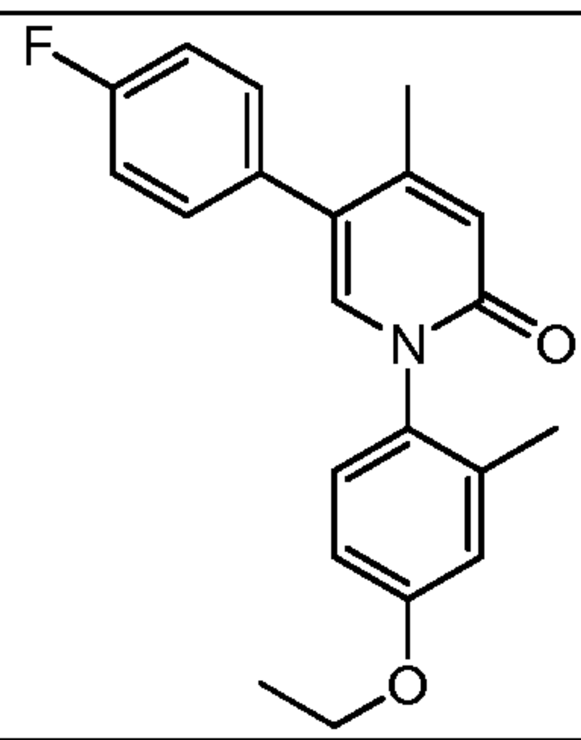
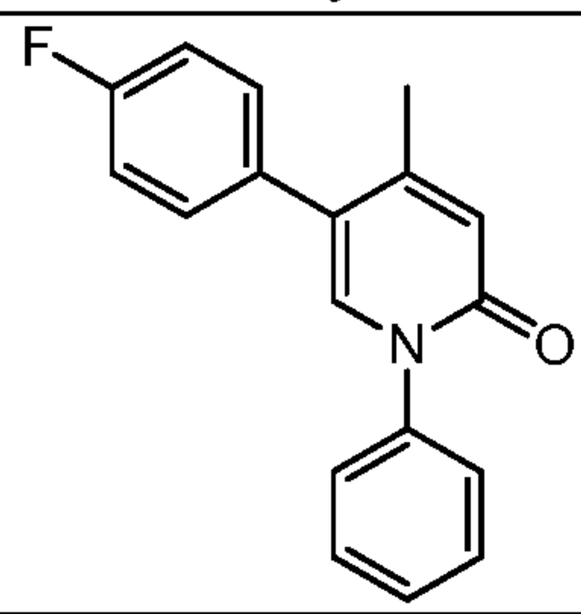
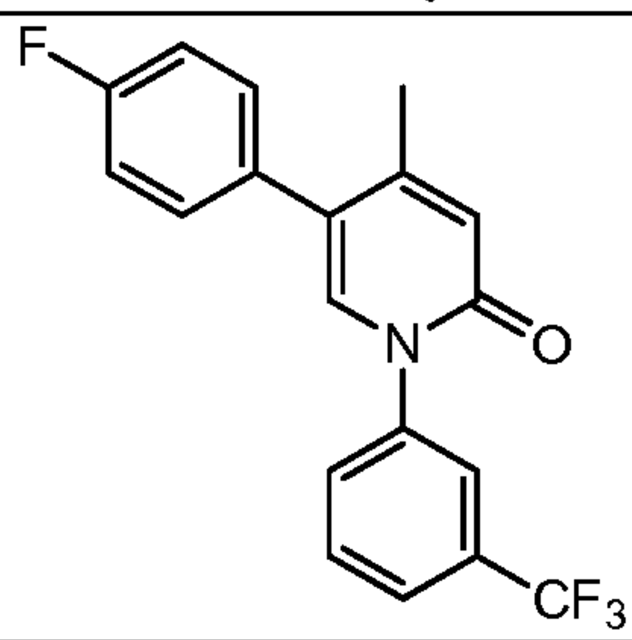
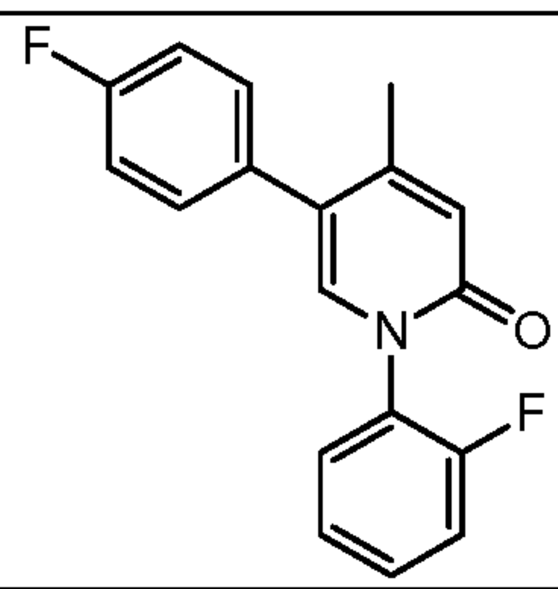
173	
174	
175	
176	
177	
178	

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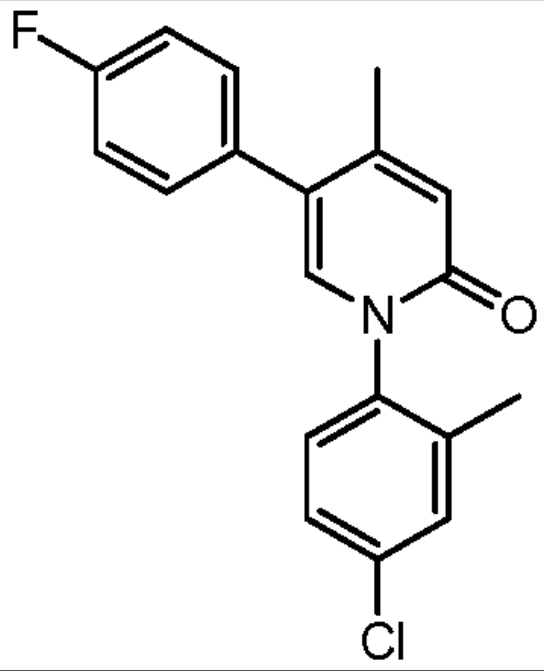
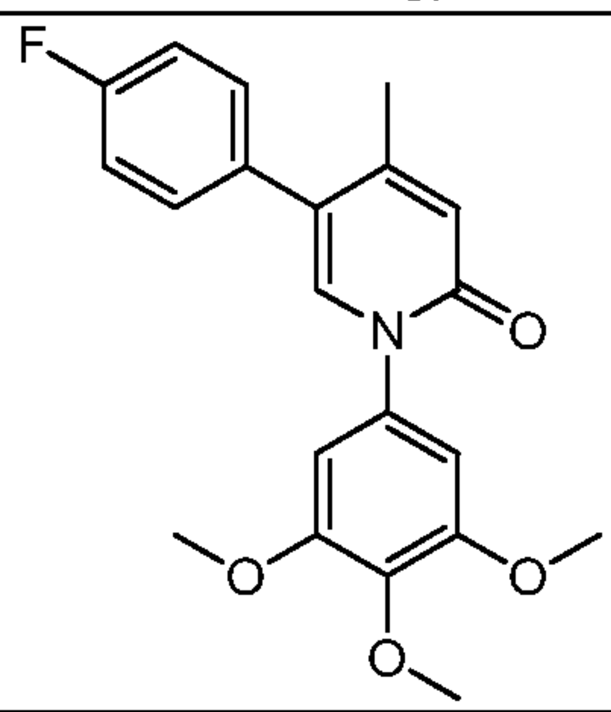
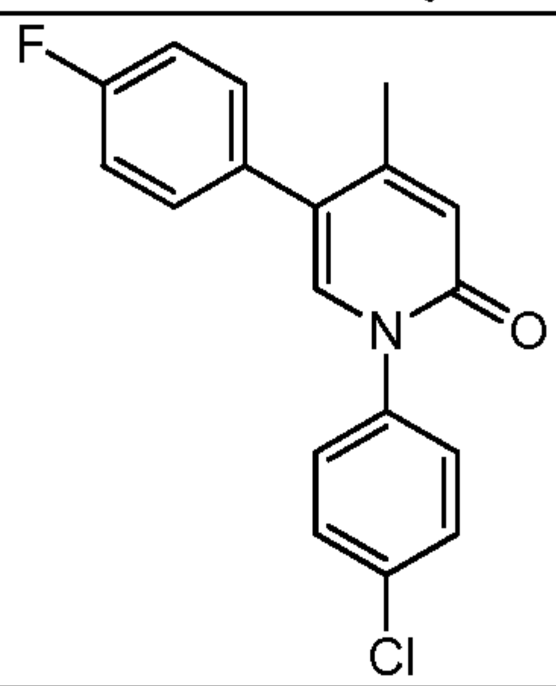
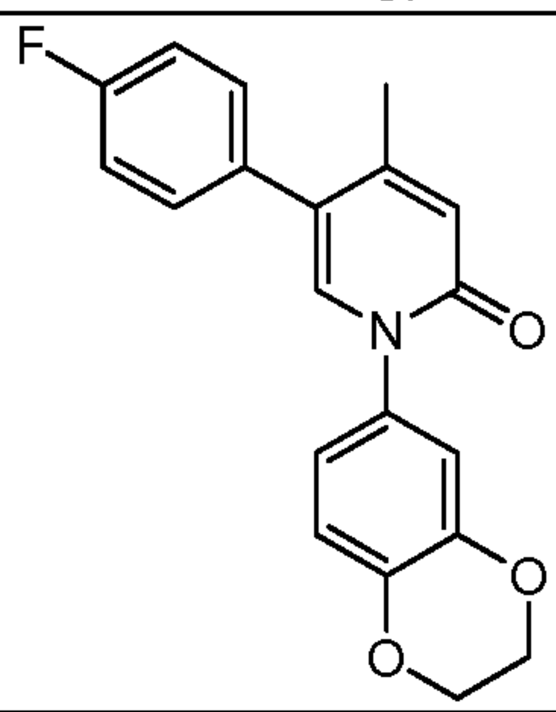
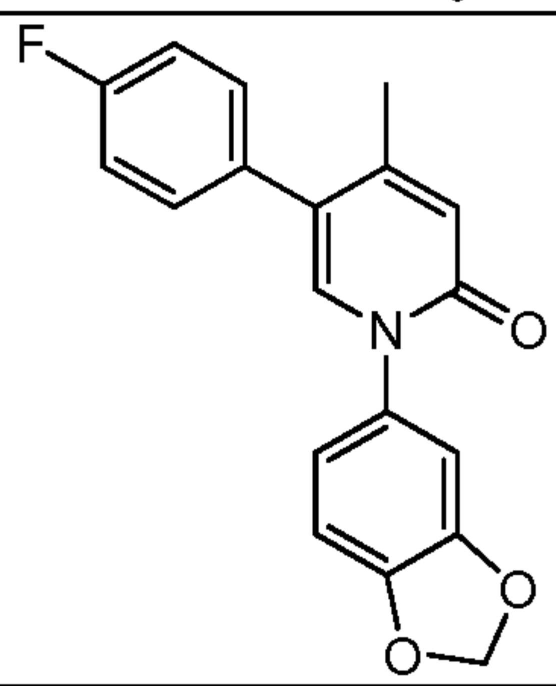
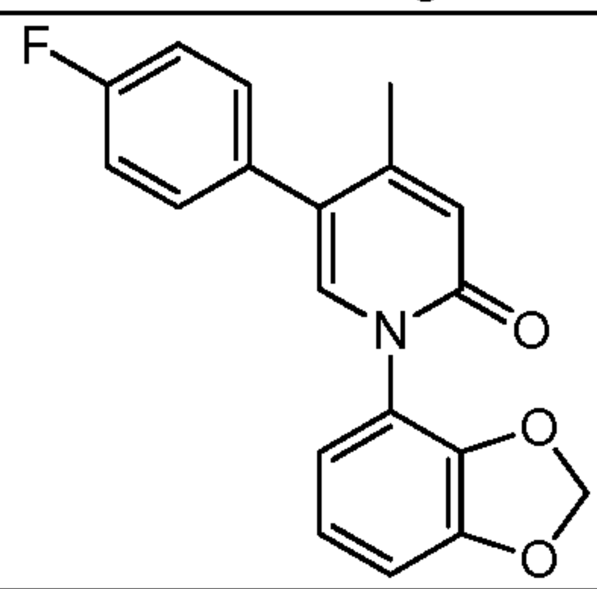
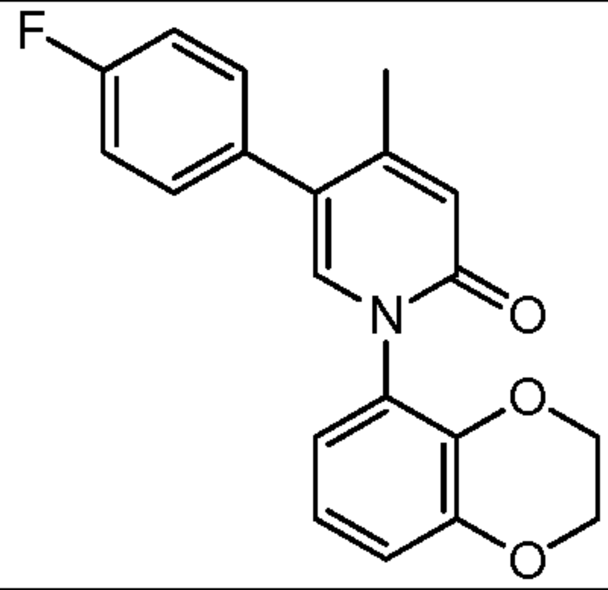
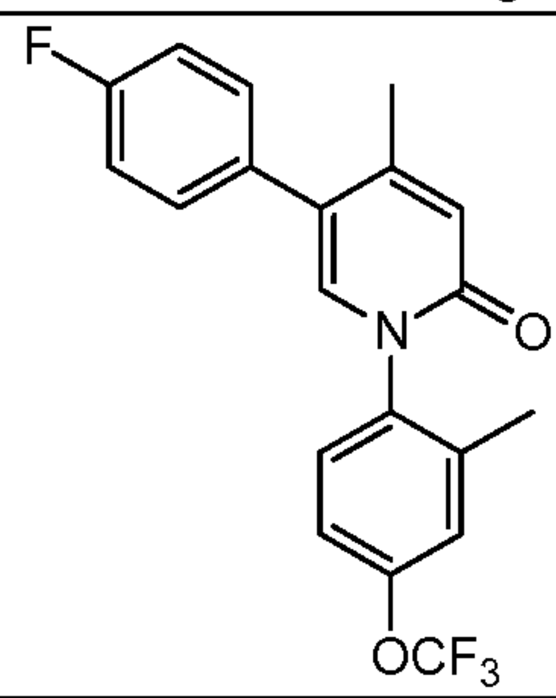
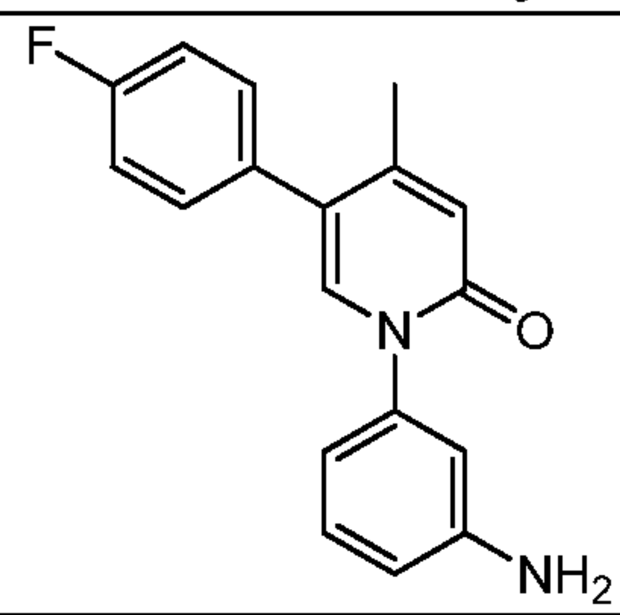
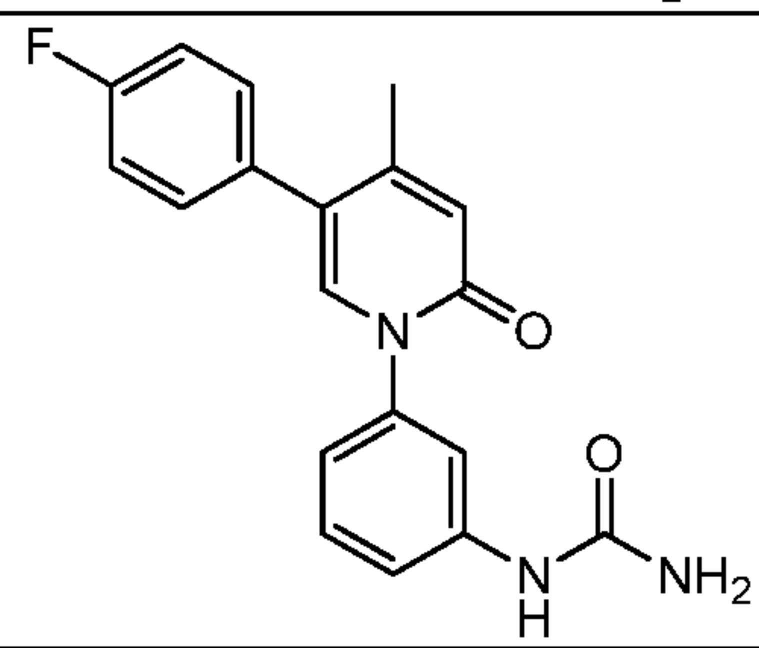
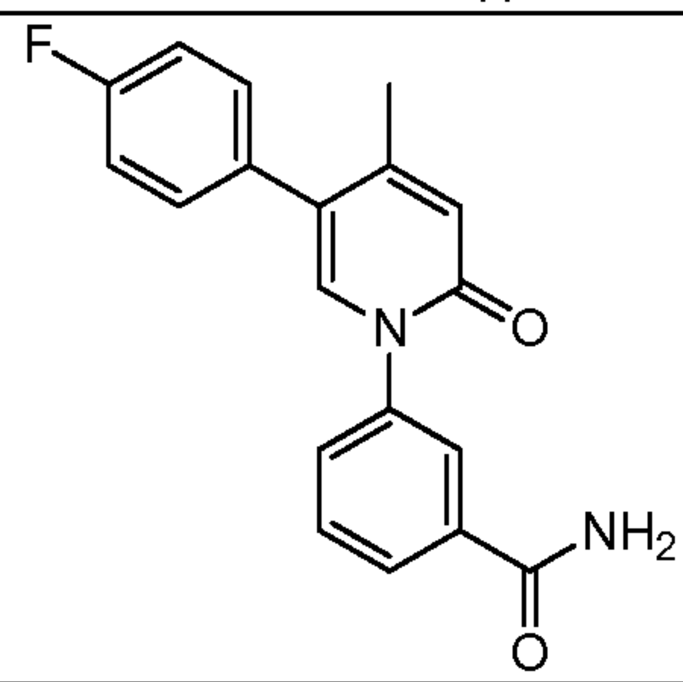
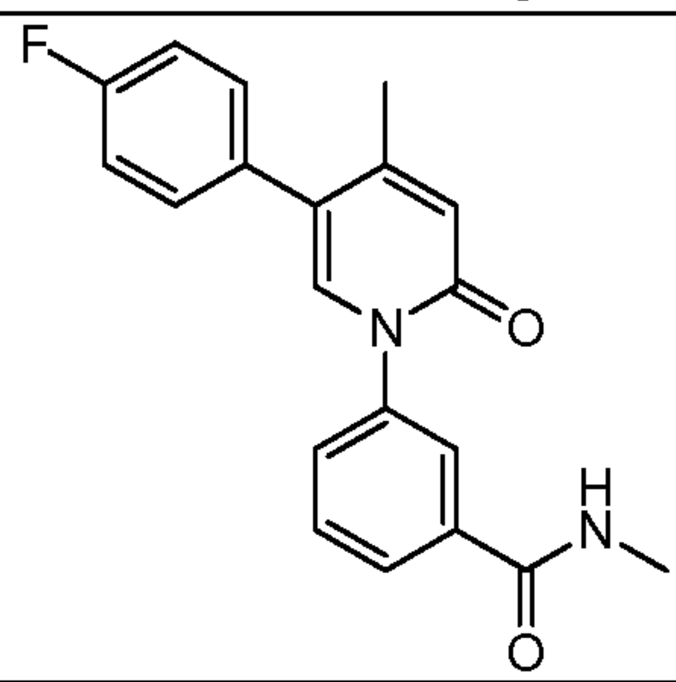
179	
180	
181	
182	
183	
184	
185	
186	
187	
188	
189	
190	

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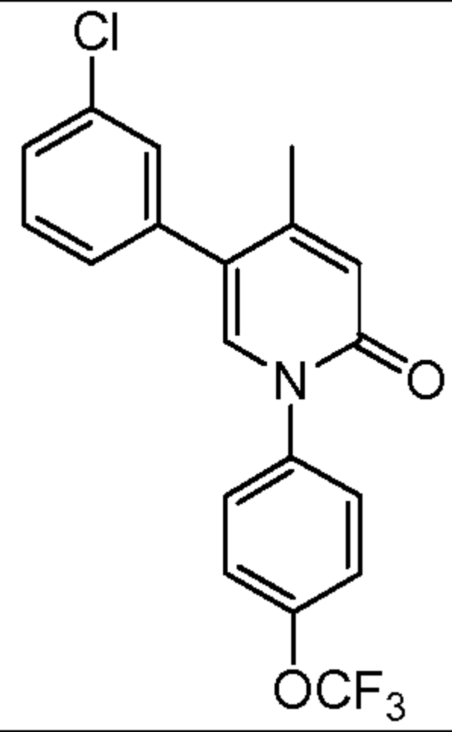
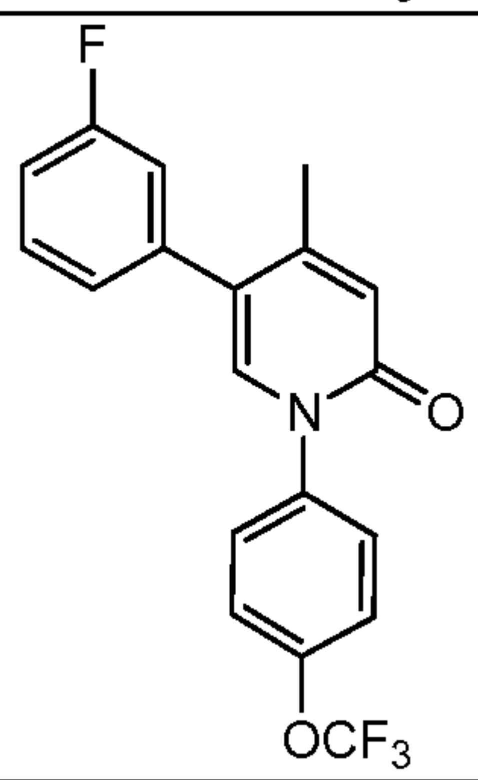
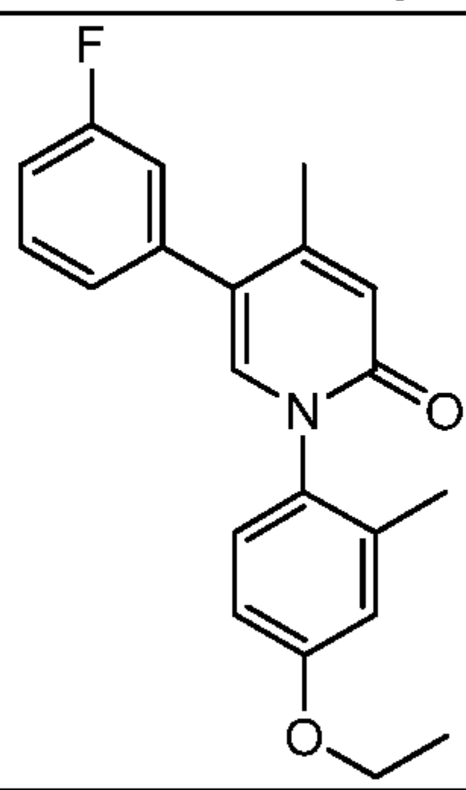
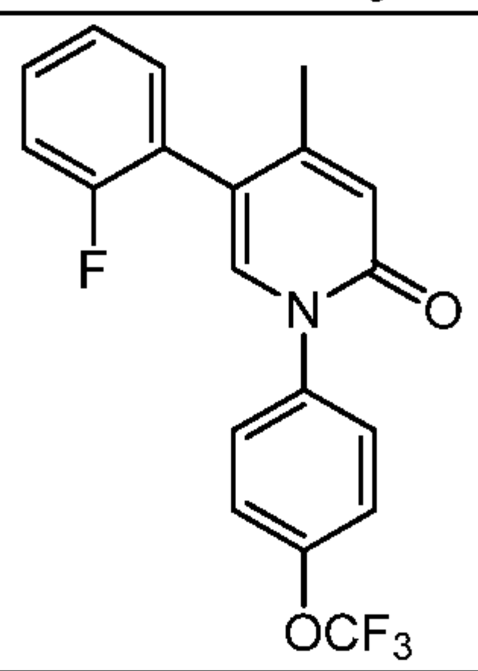
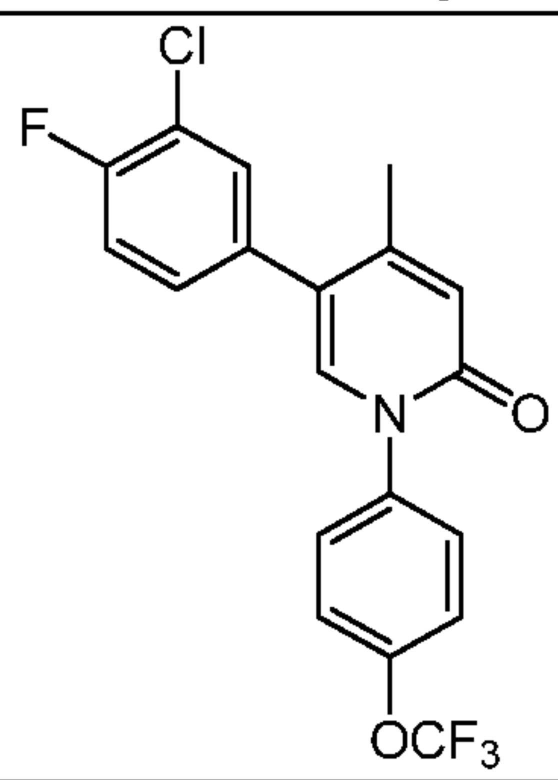
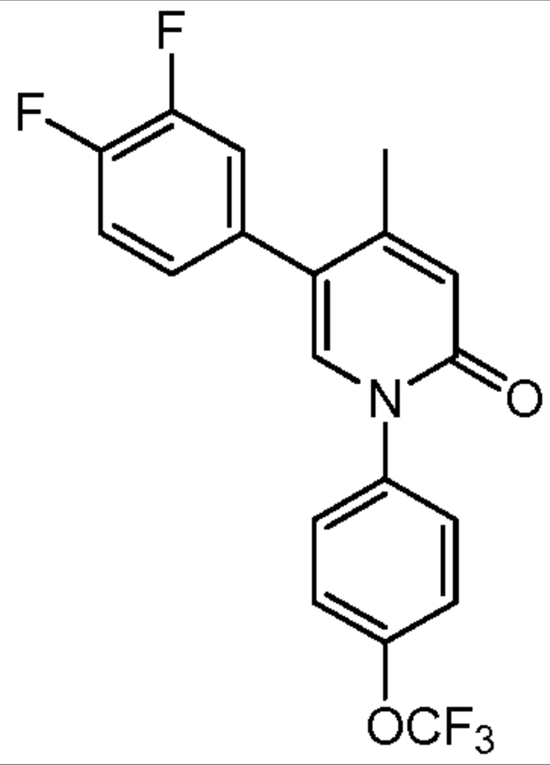
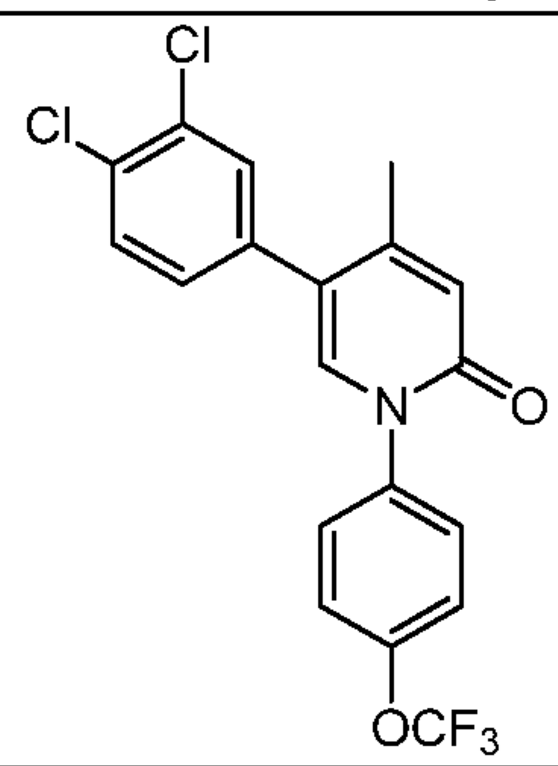
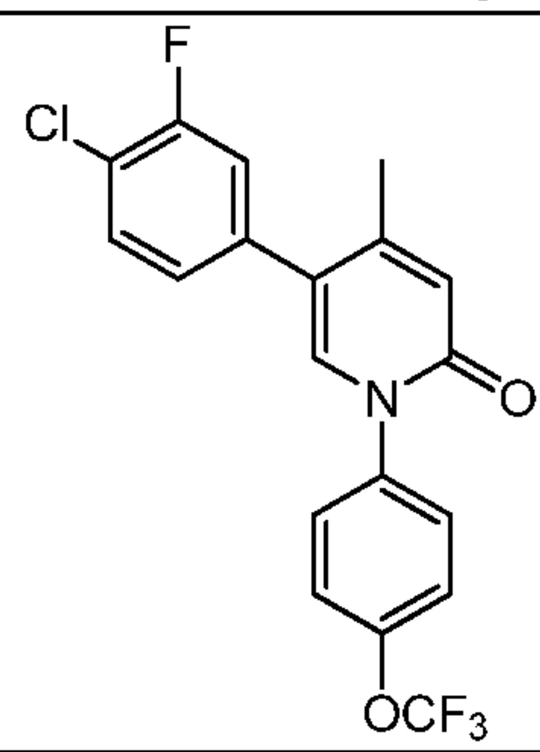
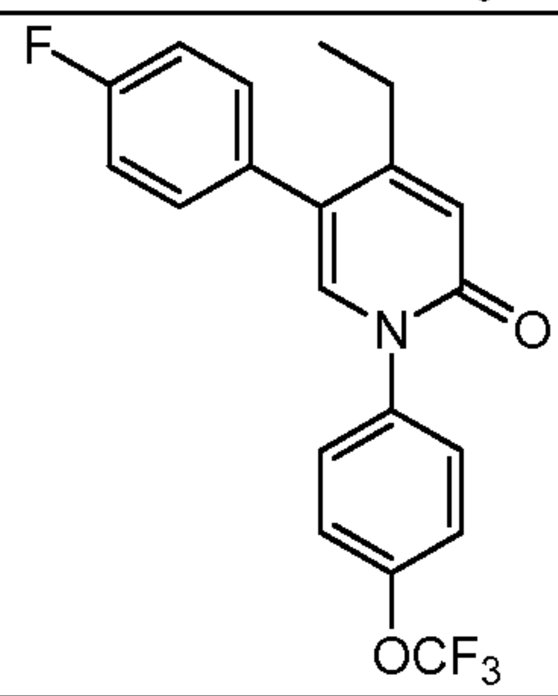
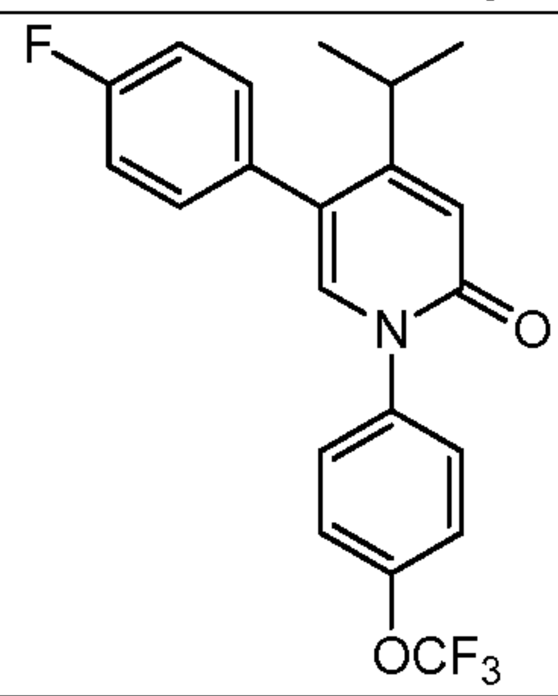
191	
192	
193	
194	
195	
196	
197	
198	
199	
200	

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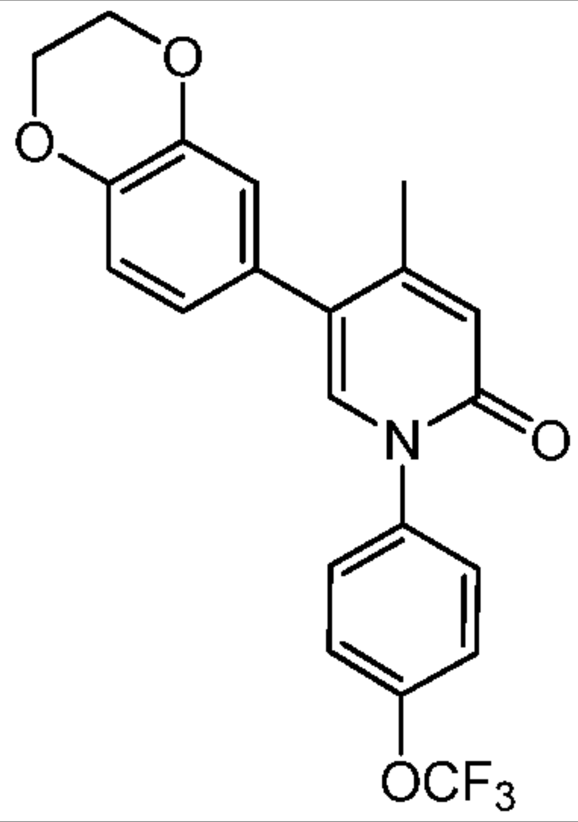
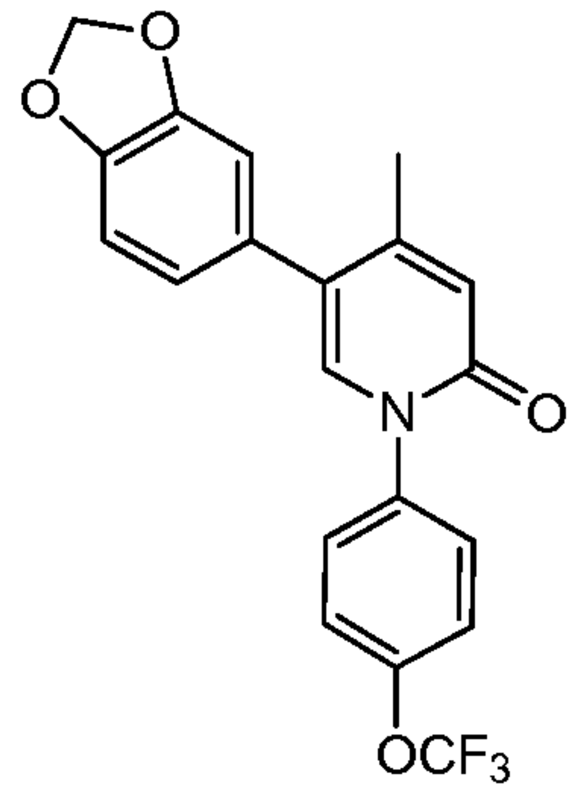
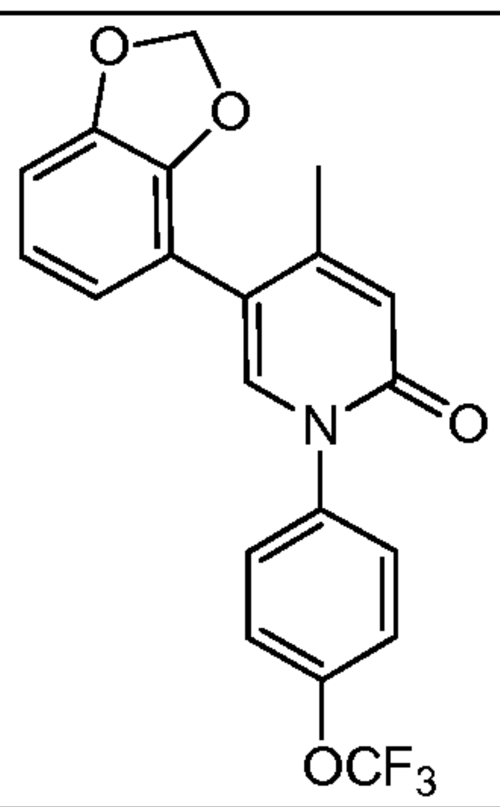
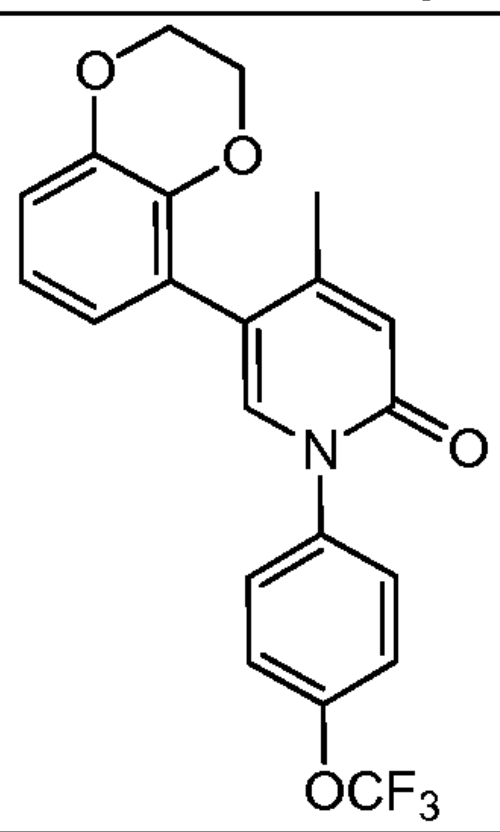
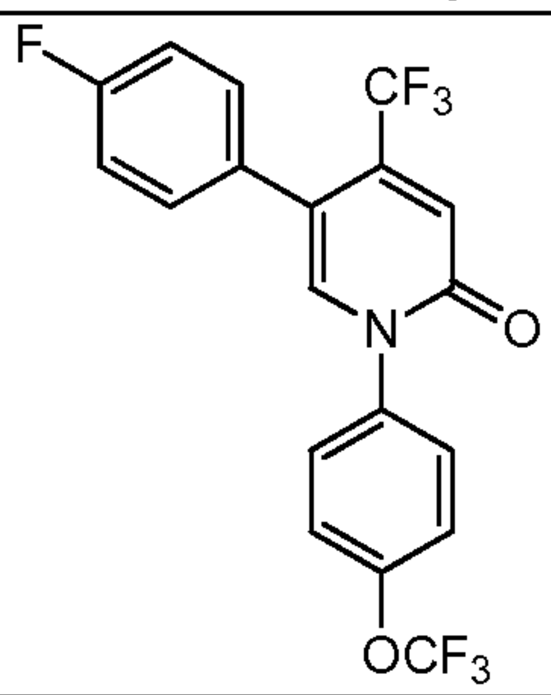
201	
202	
203	
204	
205	

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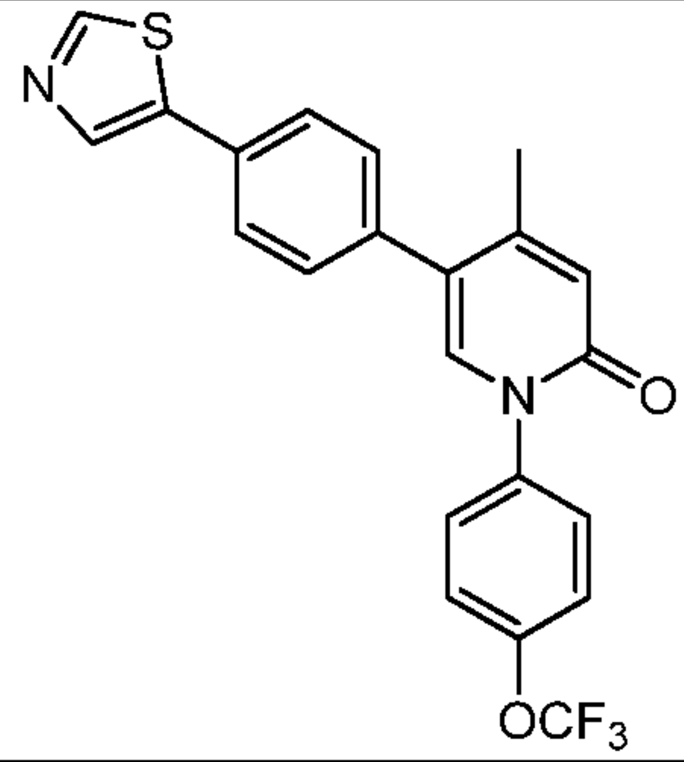
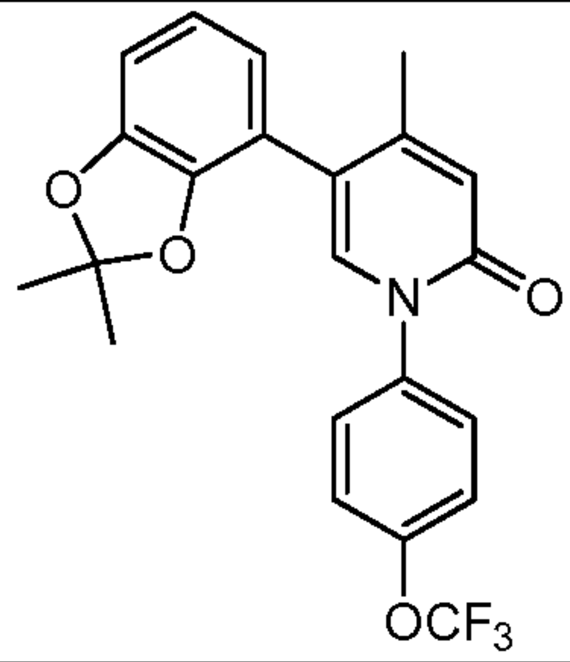
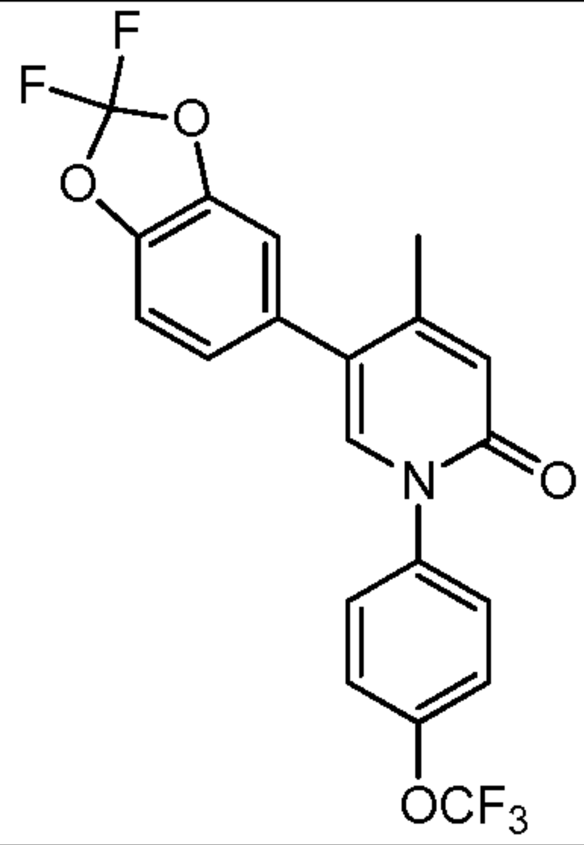
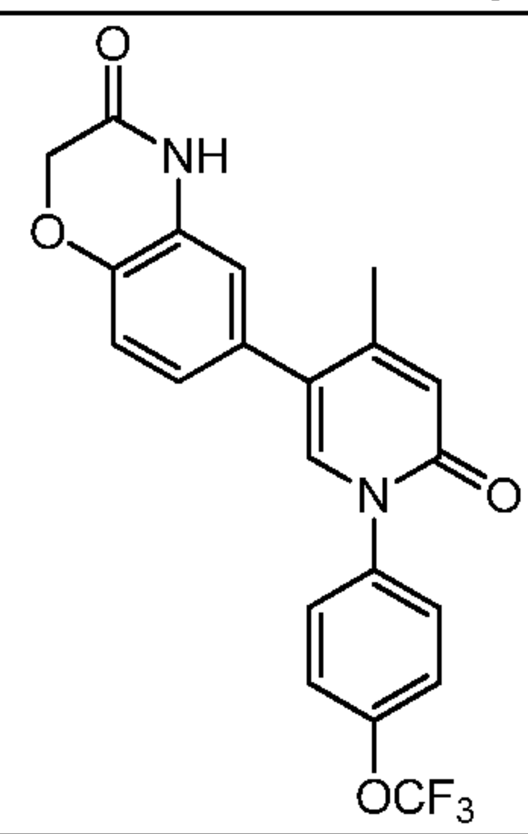
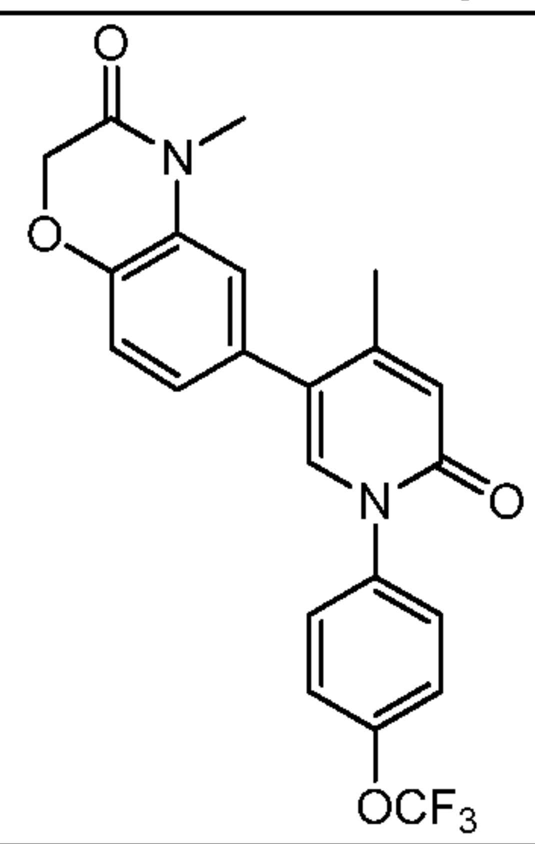
206	
207	
208	
209	
210	

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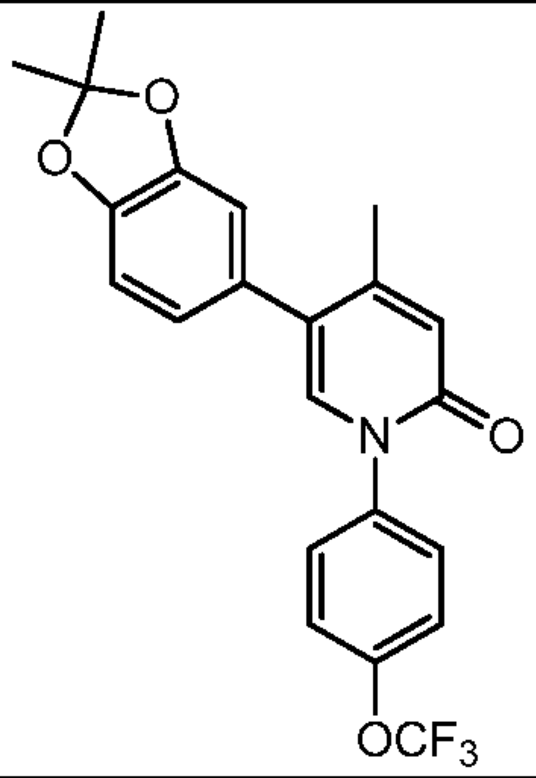
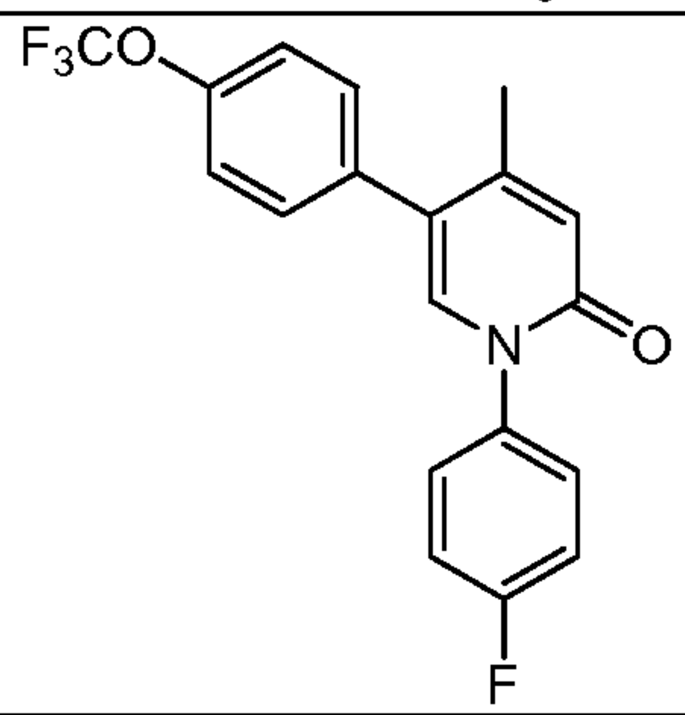
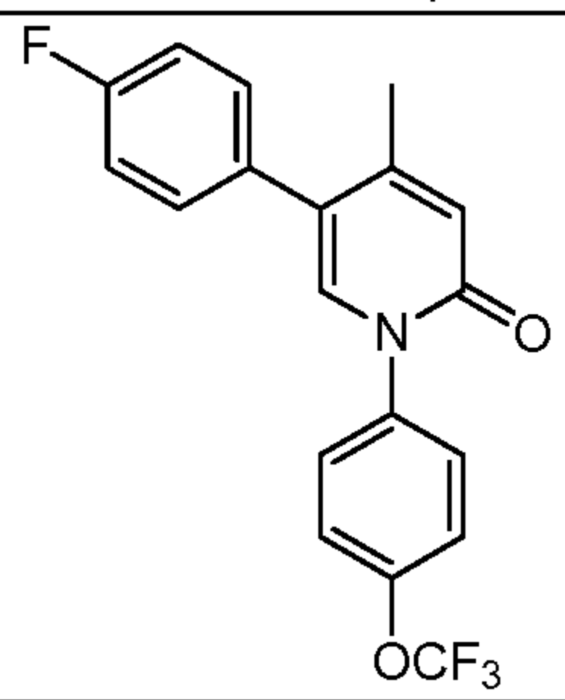
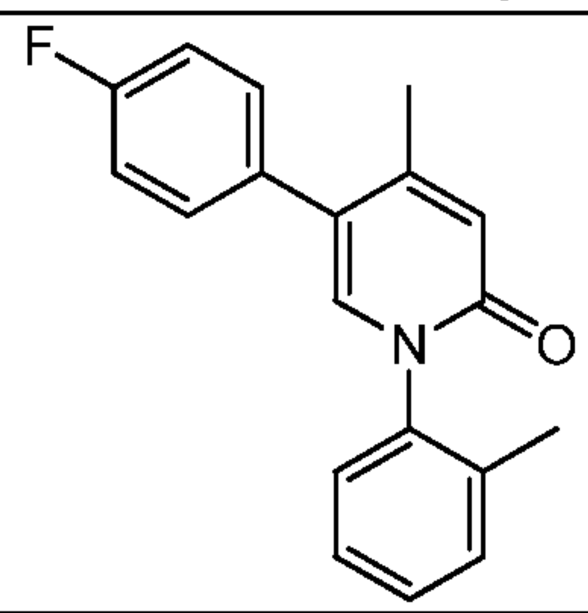
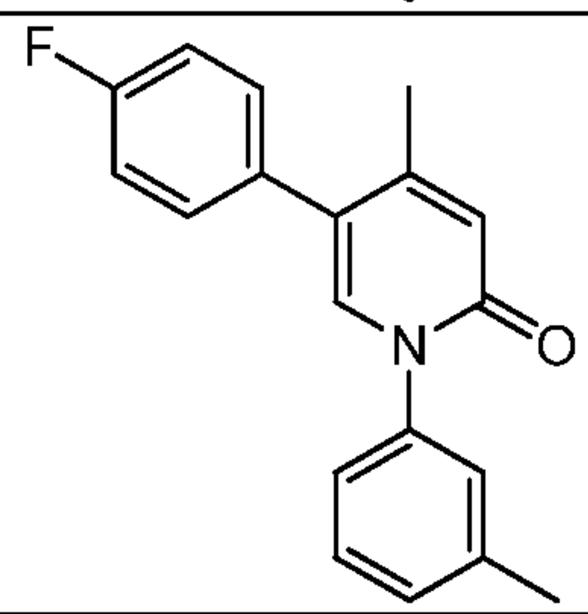
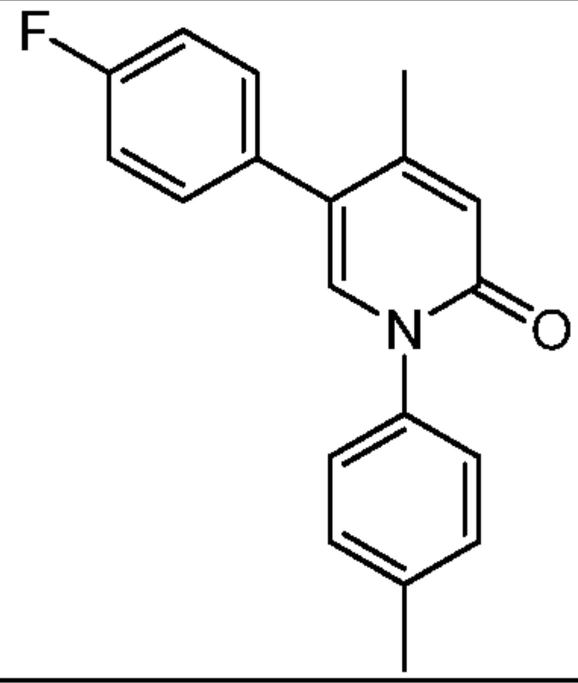
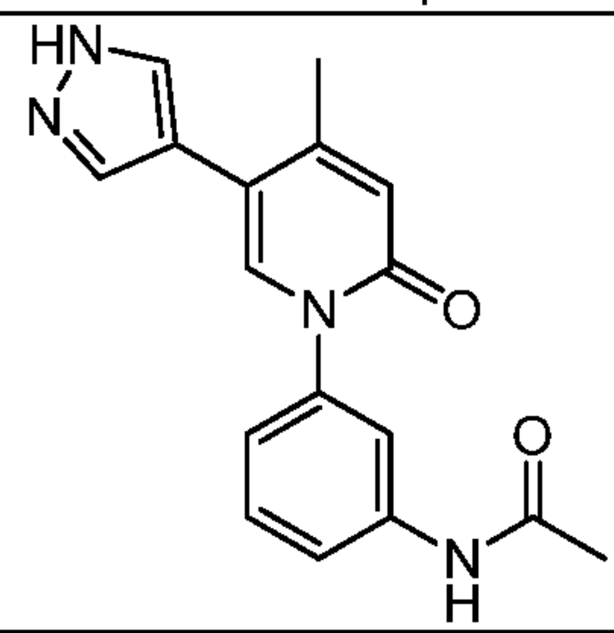
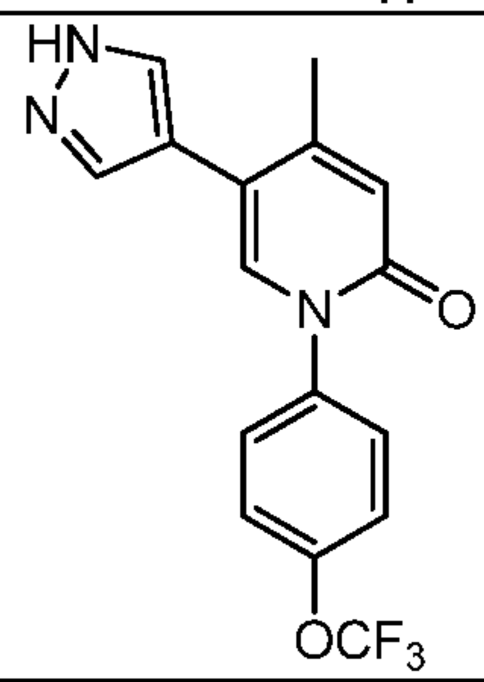
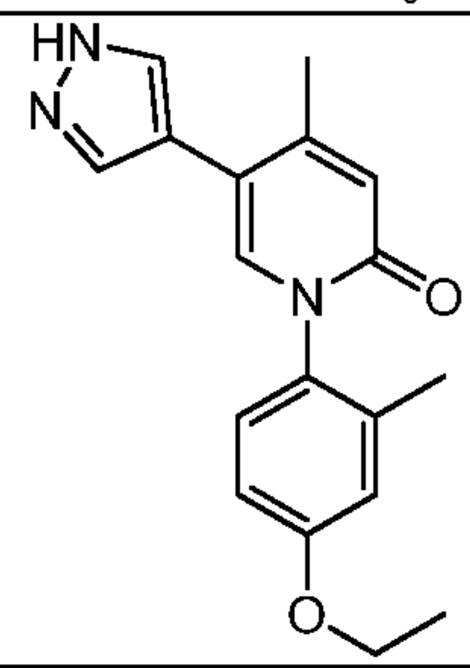
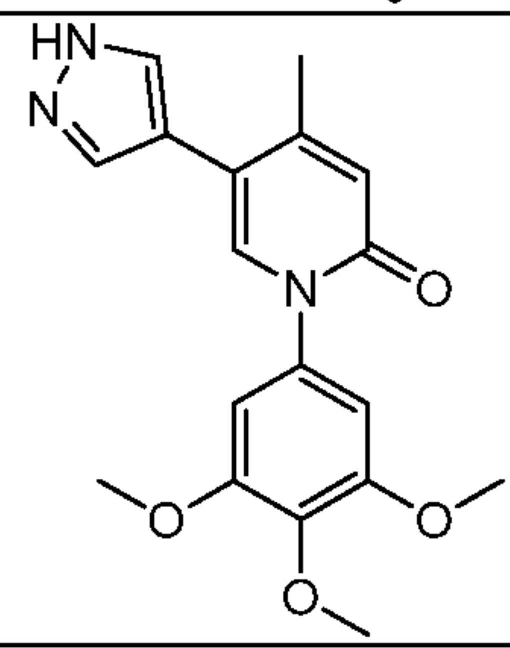
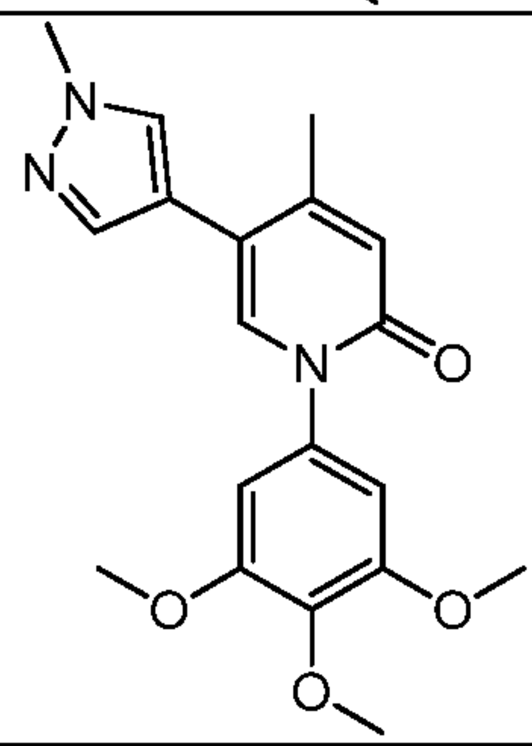
211	
212	
213	
214	
215	
216	
217	
218	
219	
220	
221	

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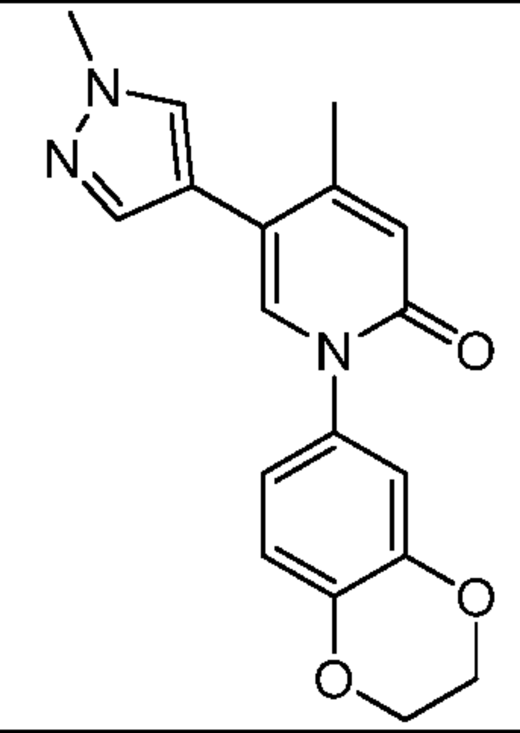
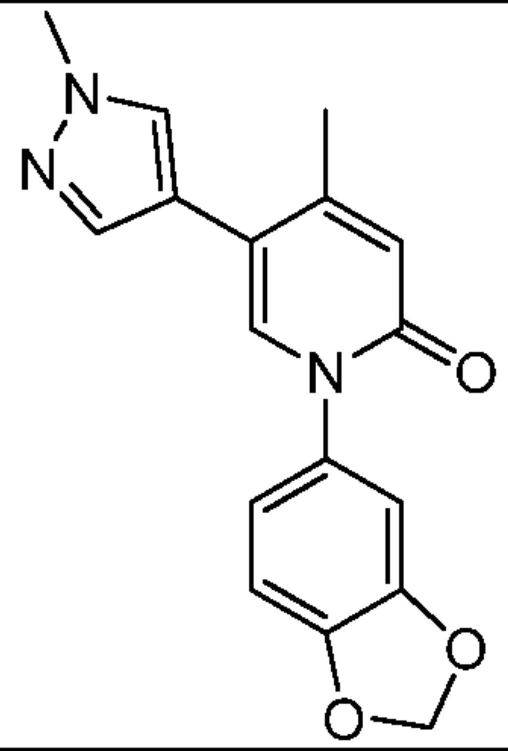
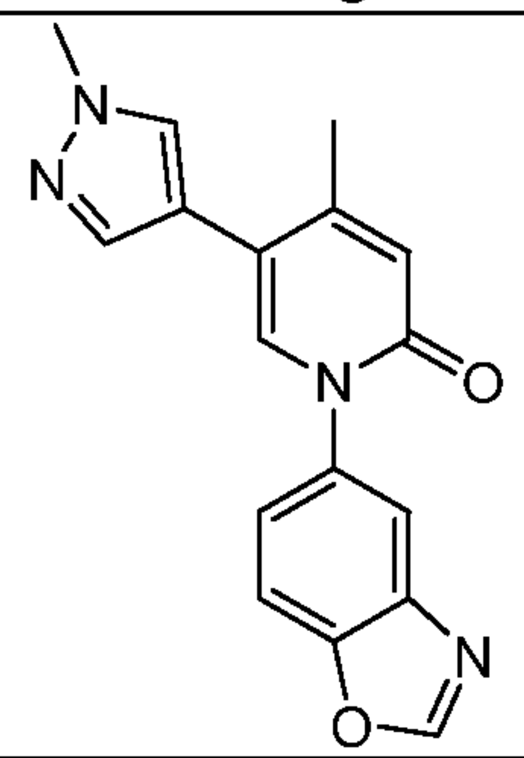
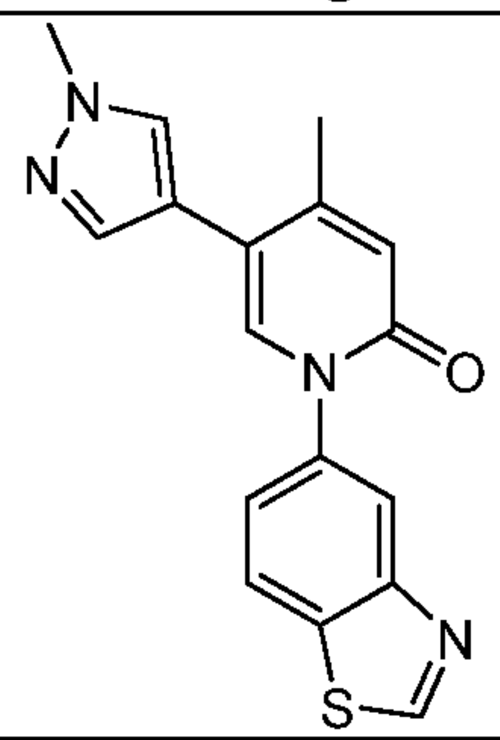
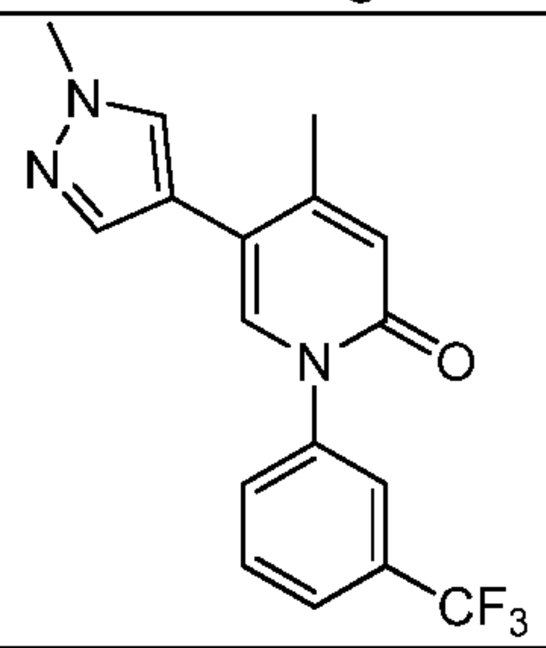
222	
223	
224	
225	
226	

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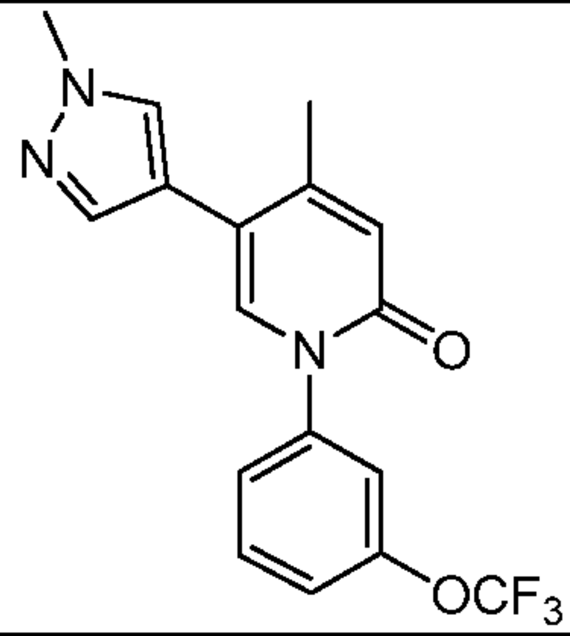
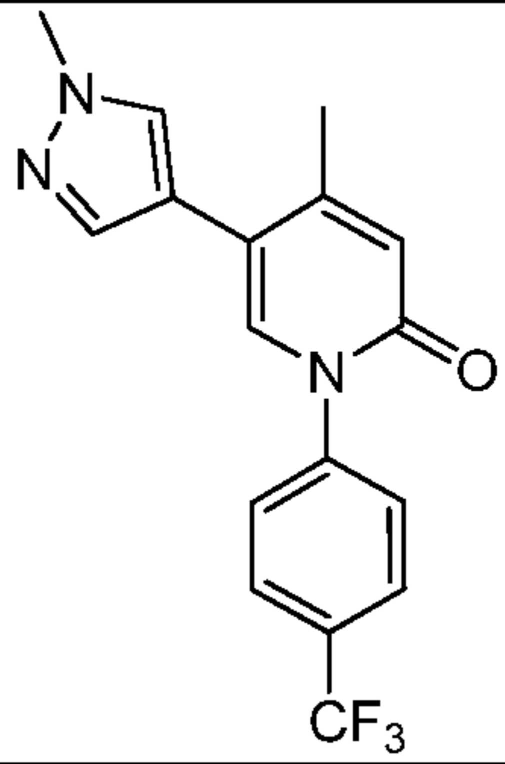
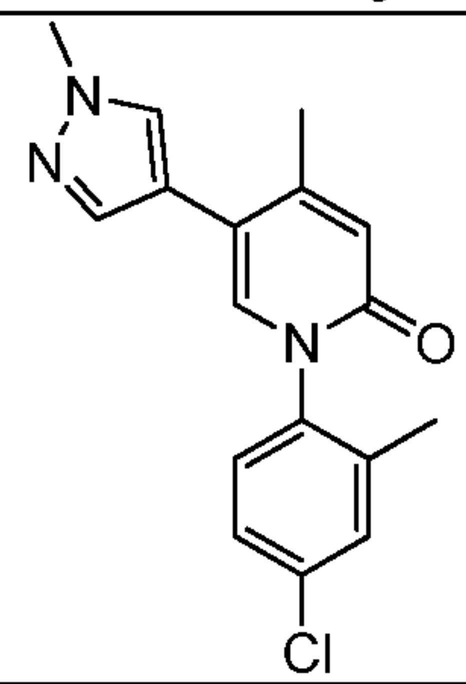
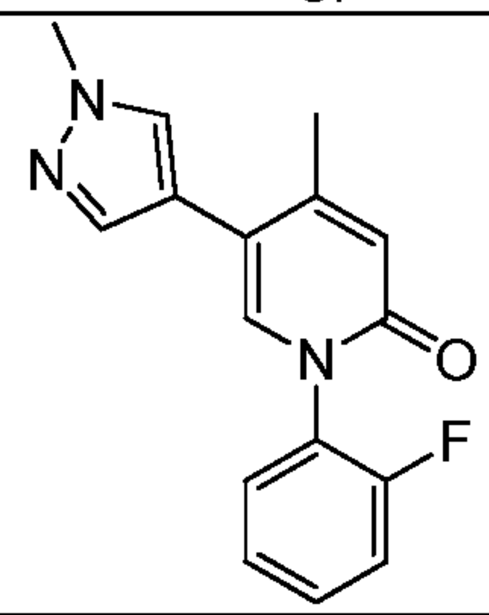
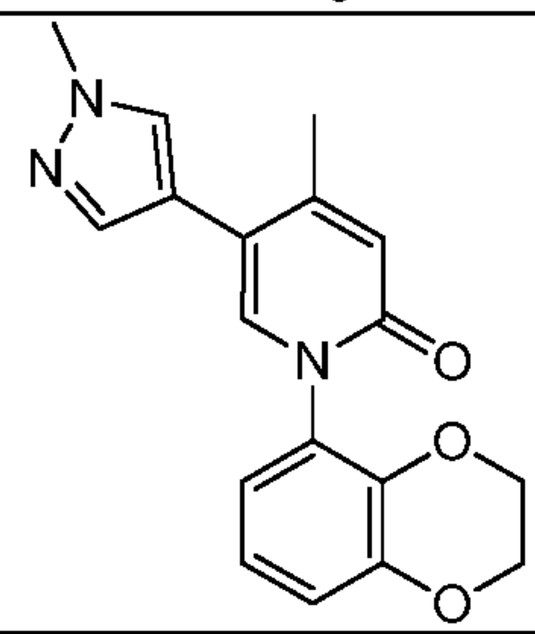
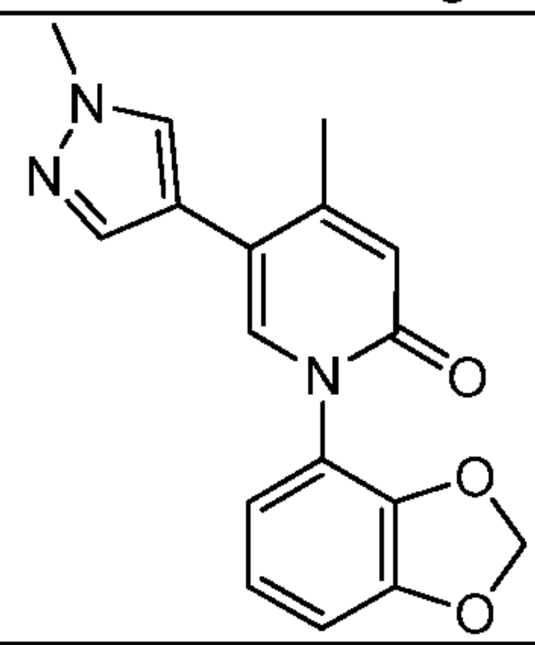
227	
228	
229	
230	
231	
232	

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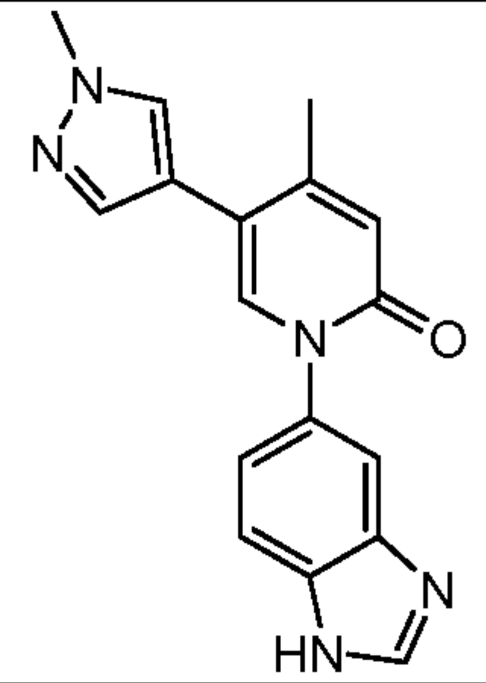
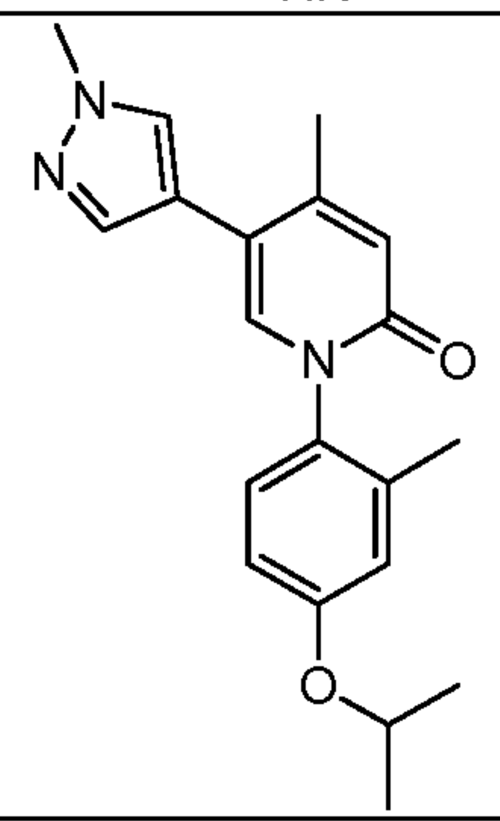
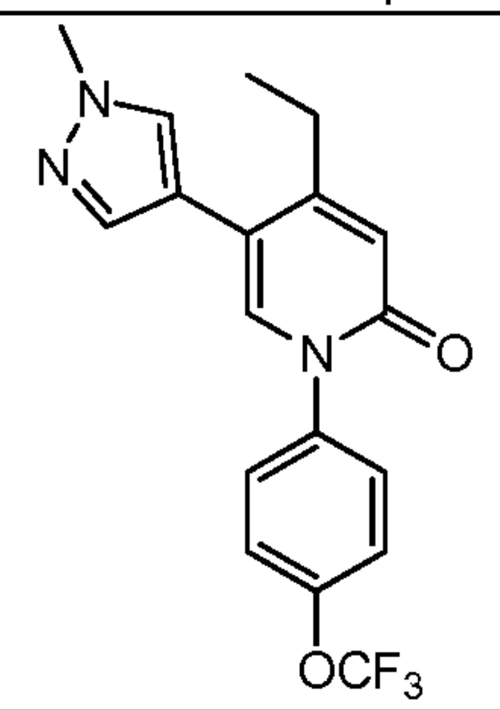
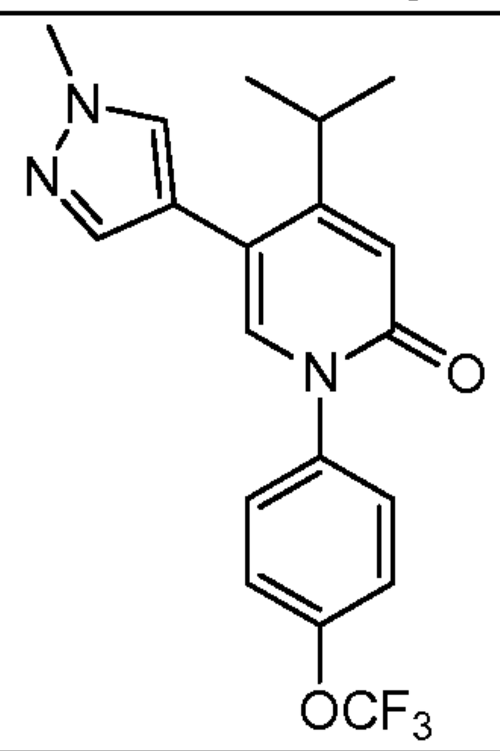
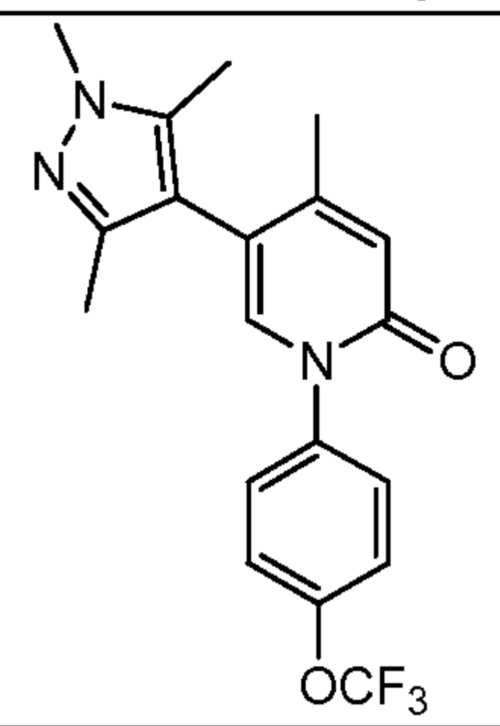
233	
234	
235	
236	
237	

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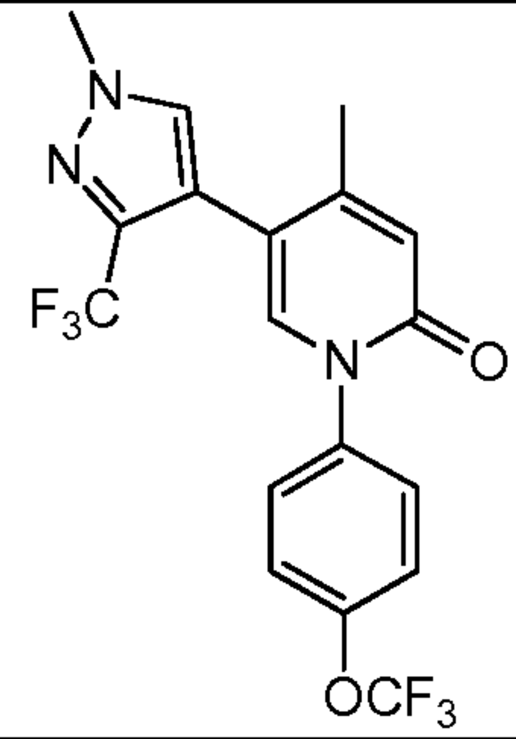
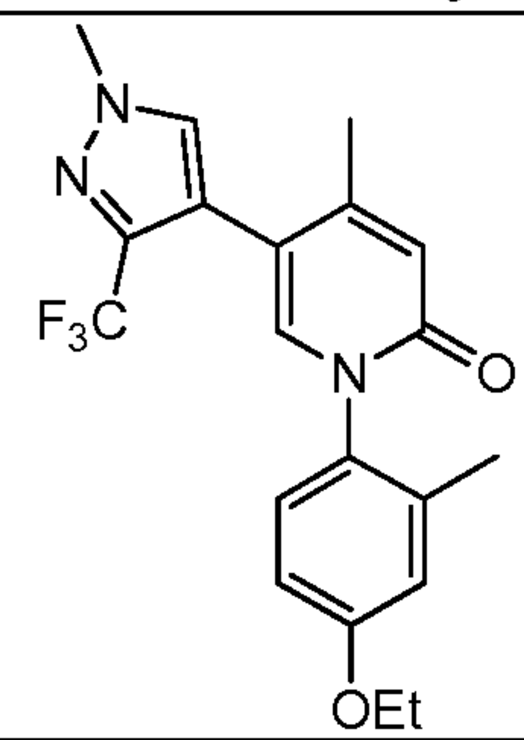
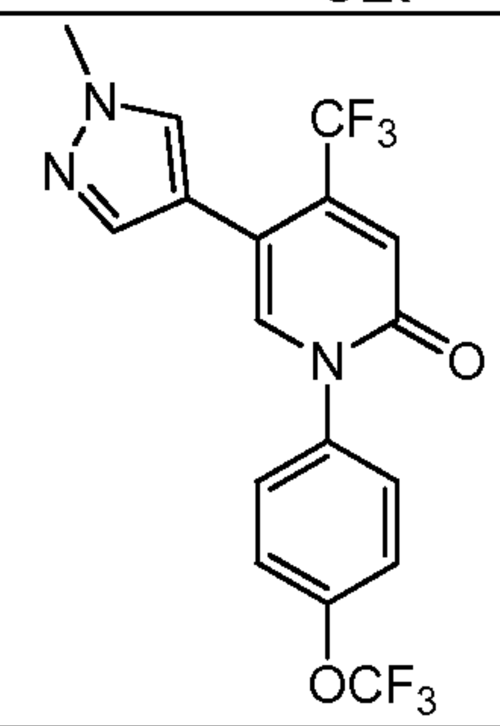
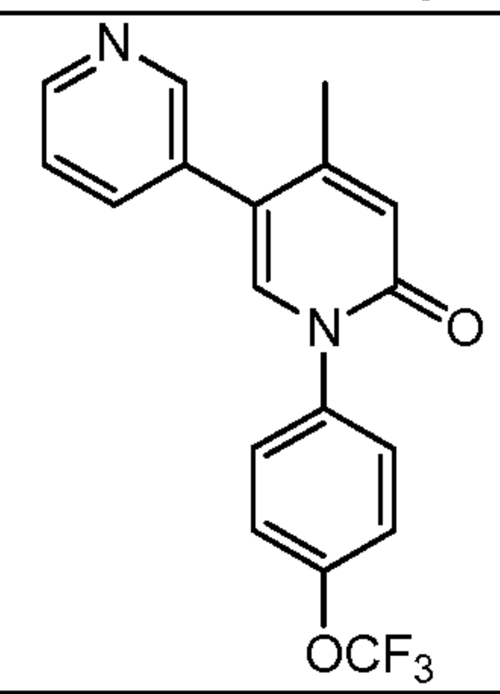
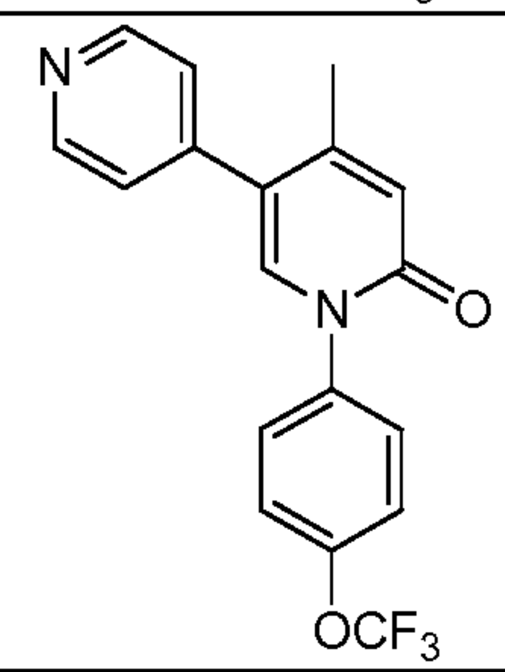
238	
239	
240	
241	
242	

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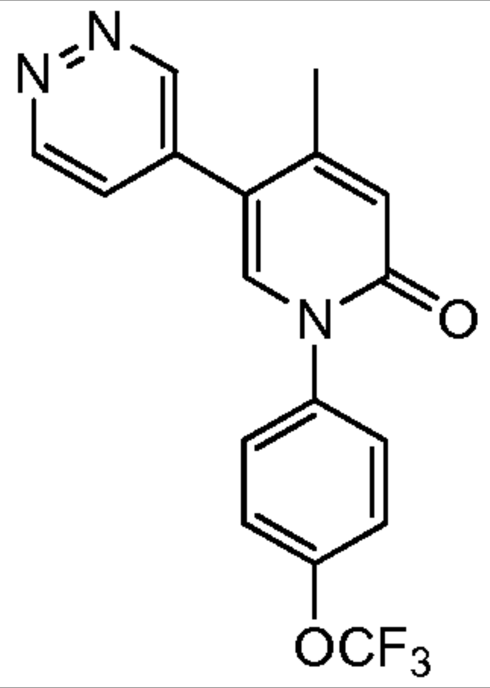
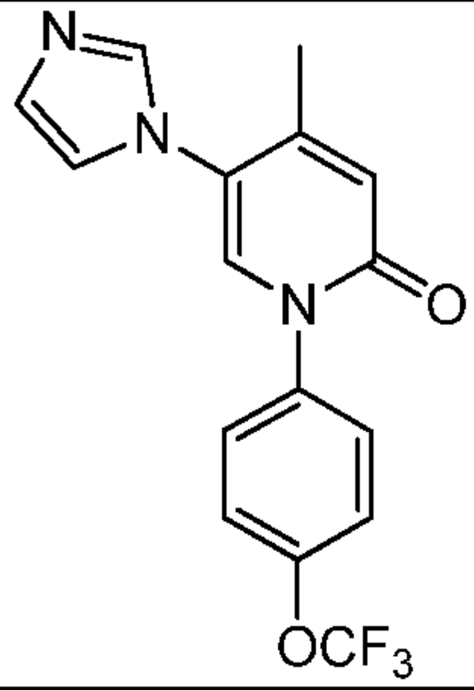
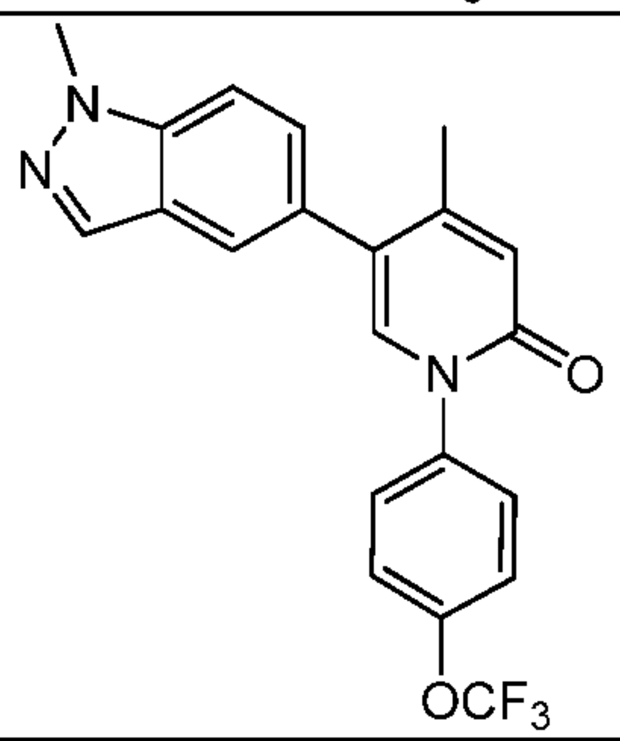
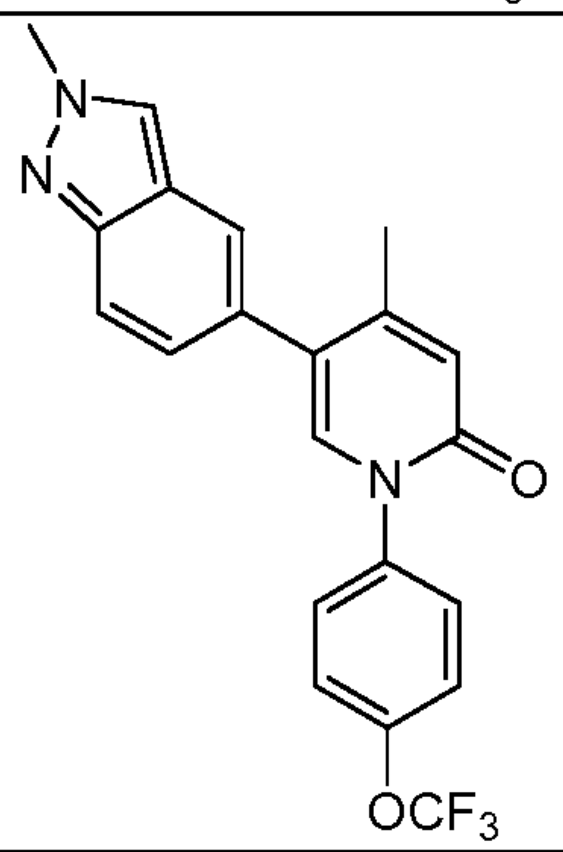
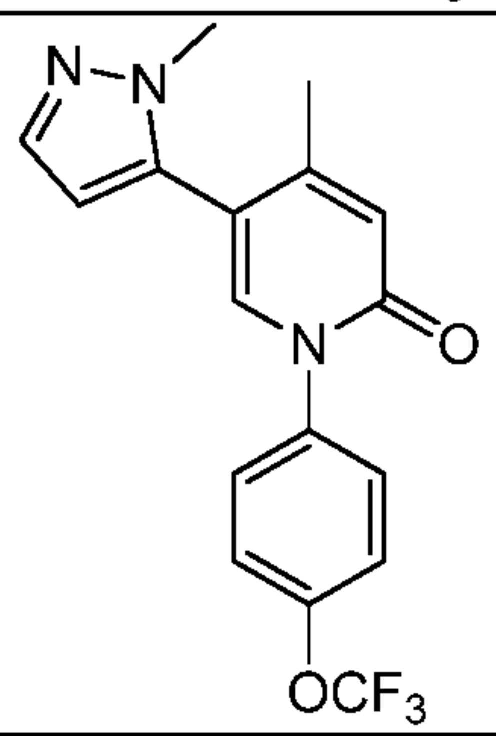
243	
244	
245	
246	
247	

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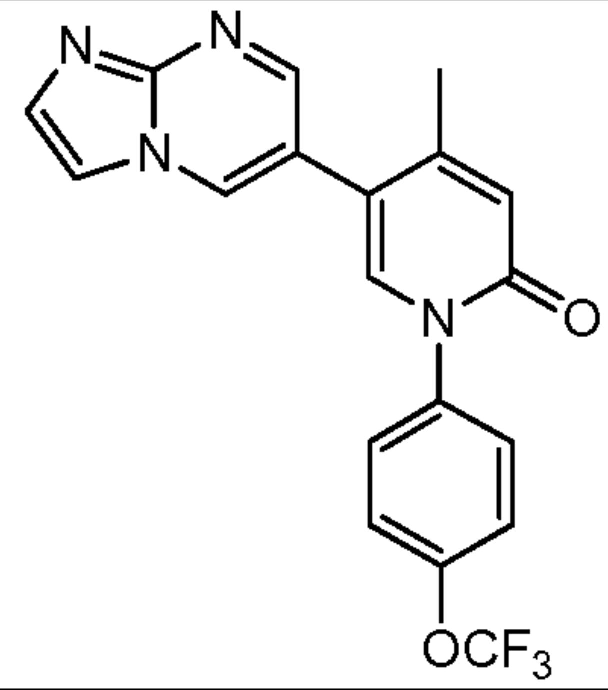
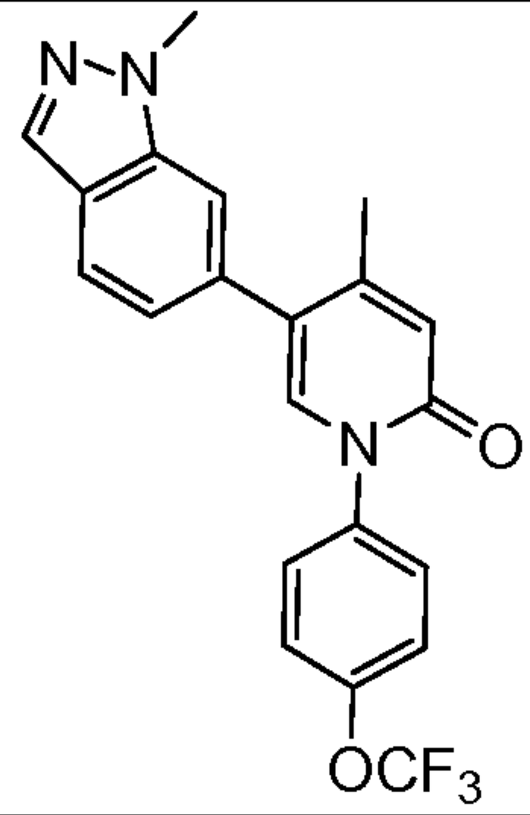
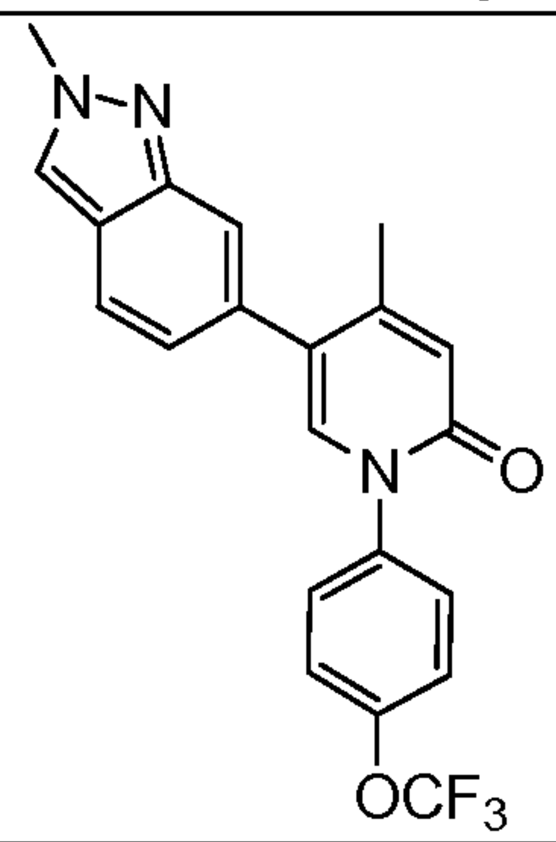
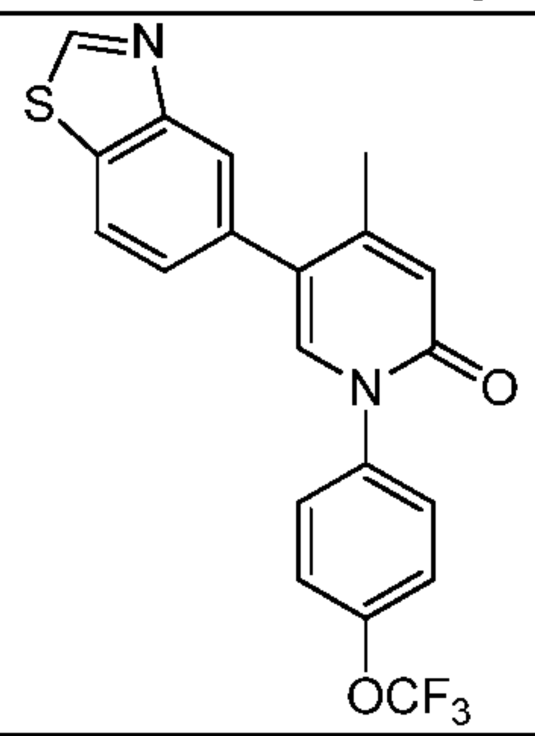
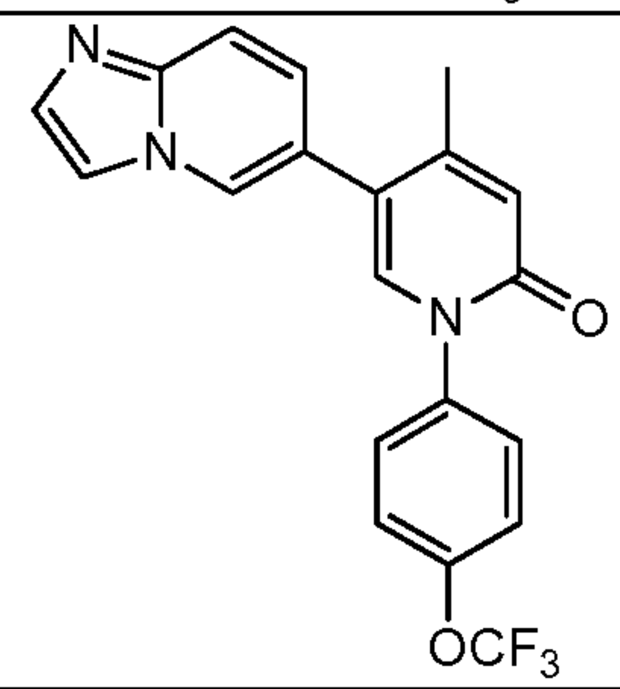
248	
249	
250	
251	
252	

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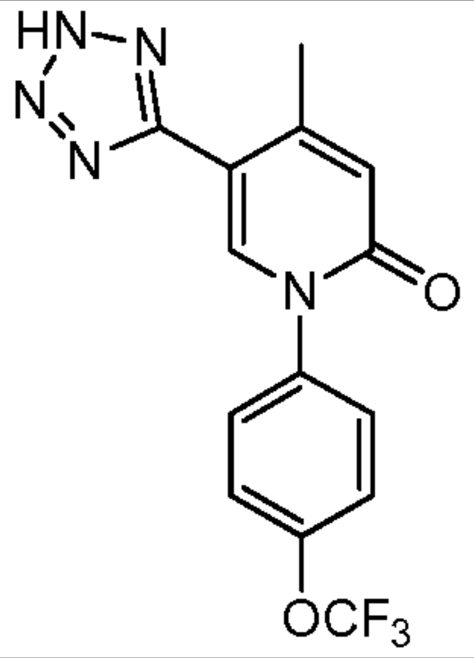
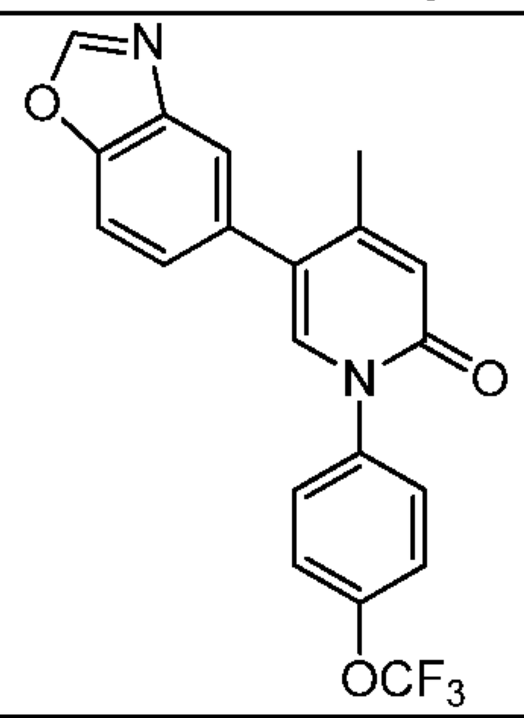
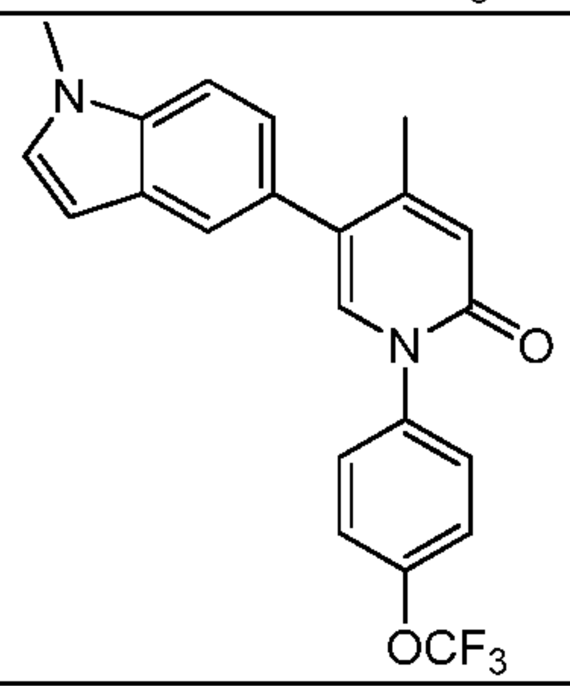
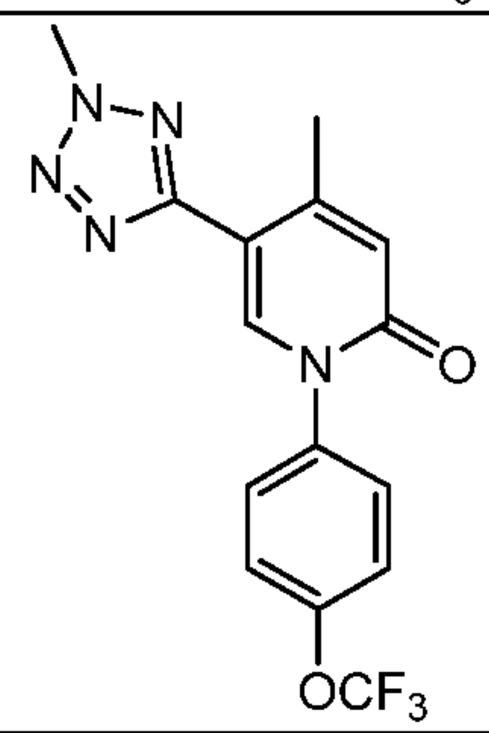
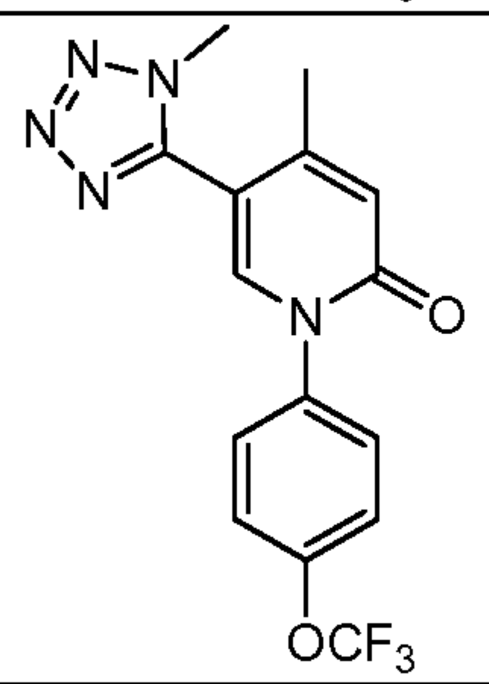
253	
254	
255	
256	
257	

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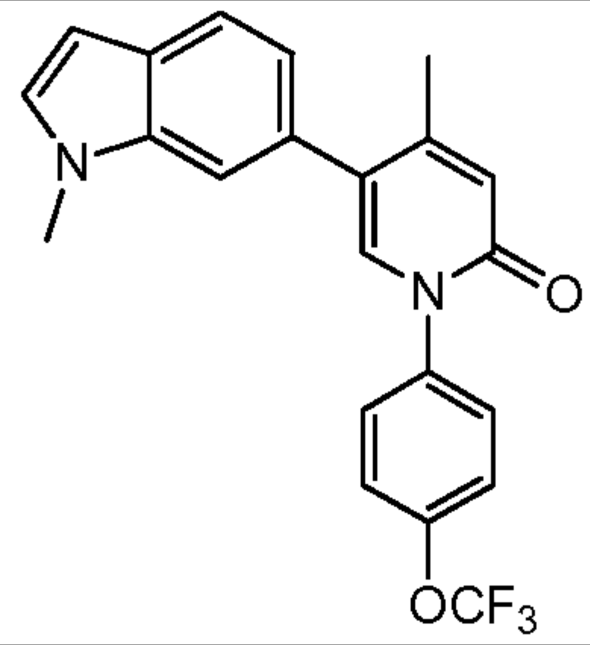
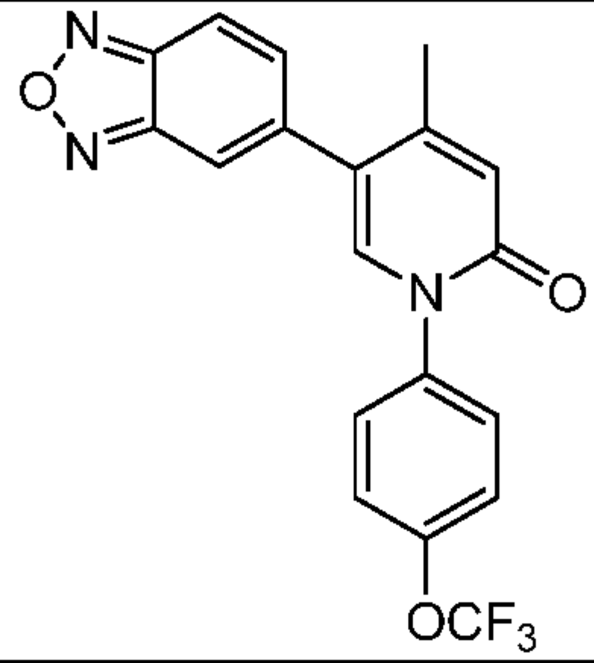
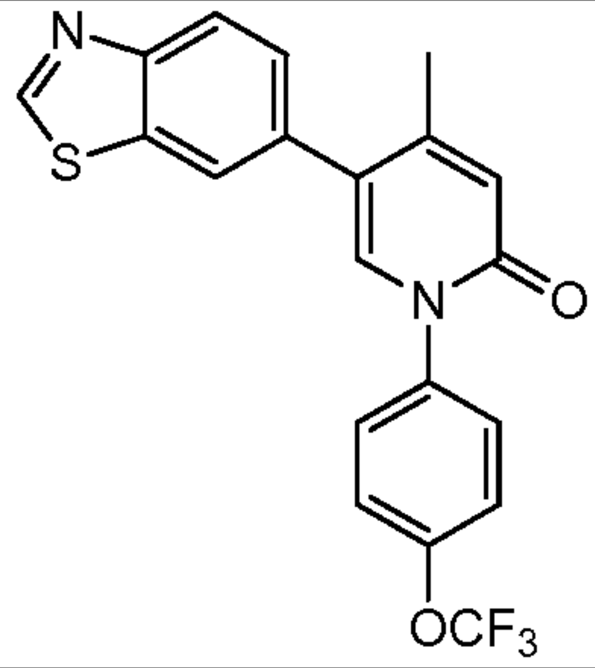
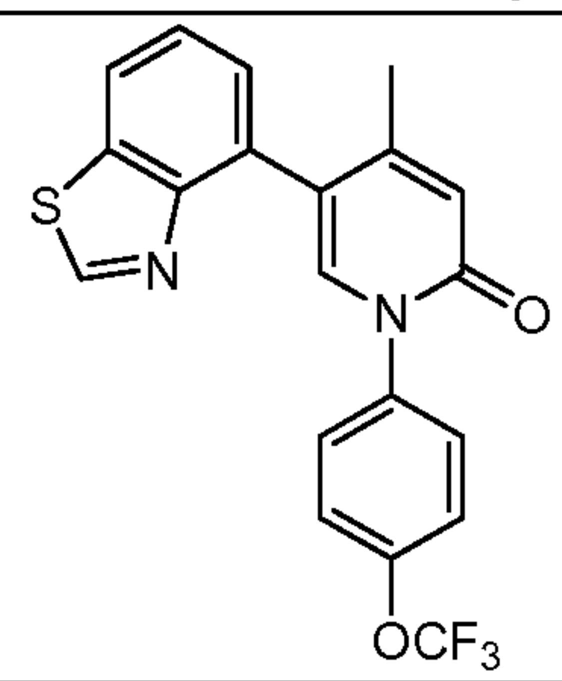
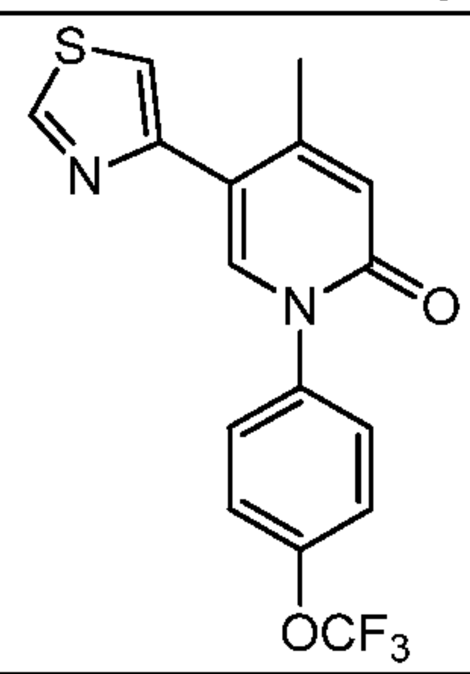
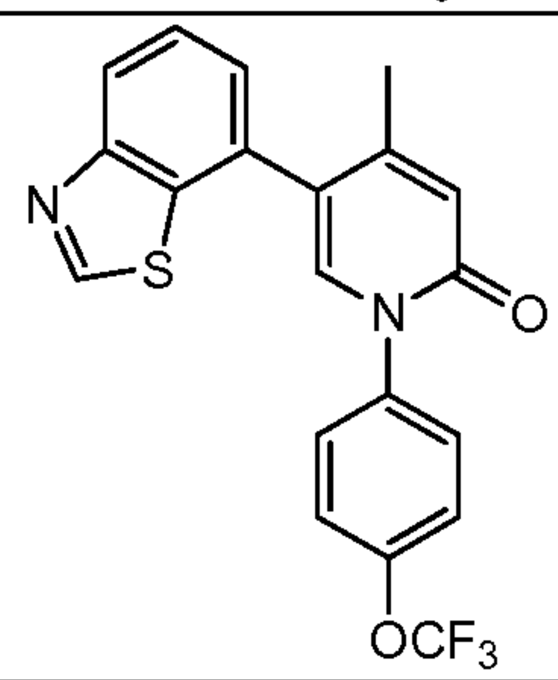
258	
259	
260	
261	
262	
263	

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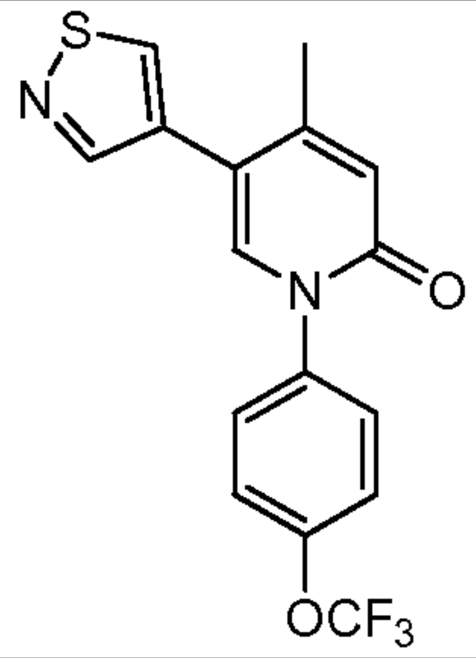
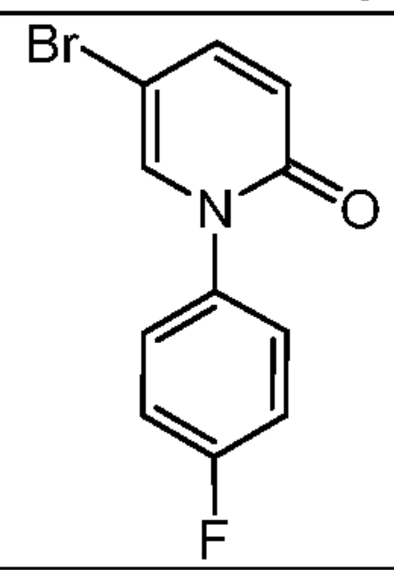
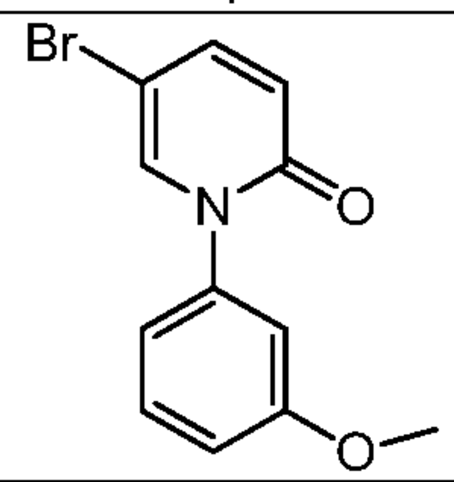
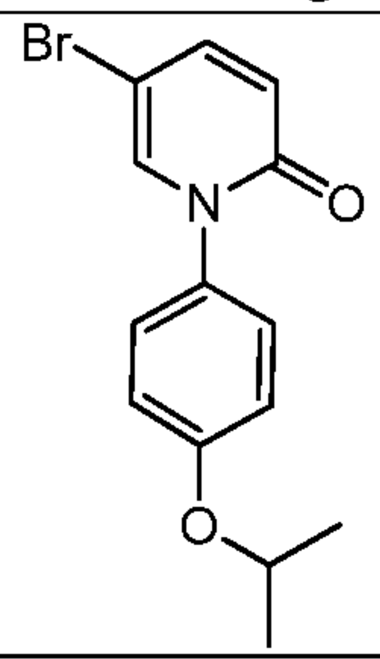
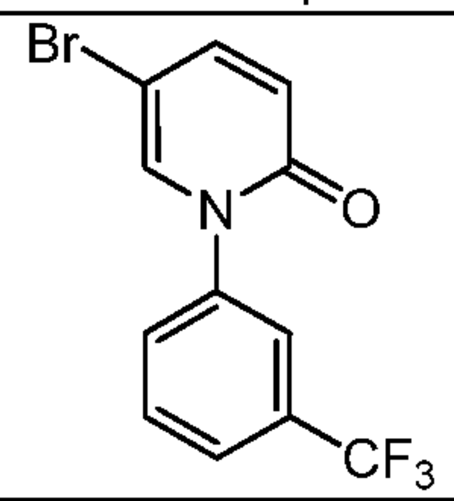
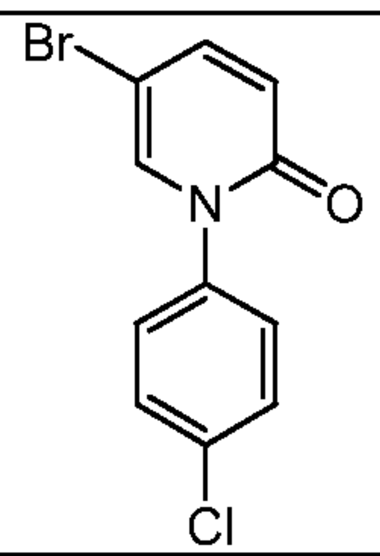
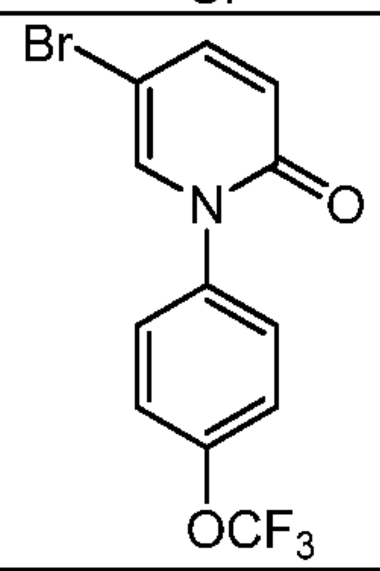
264	
265	
266	
267	
268	
269	
270	

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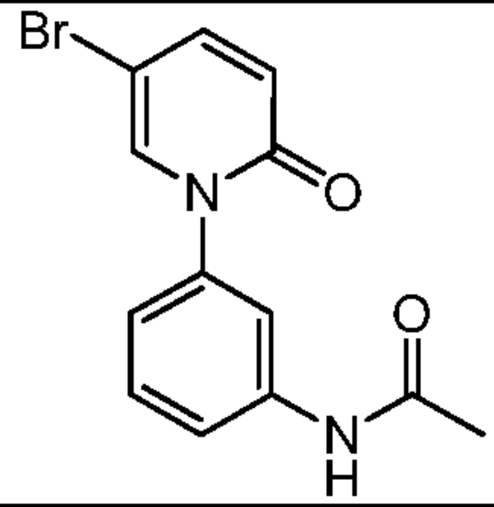
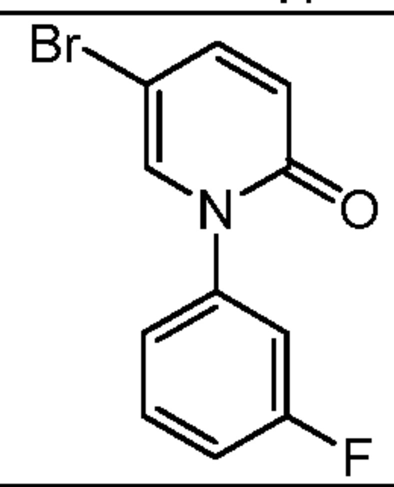
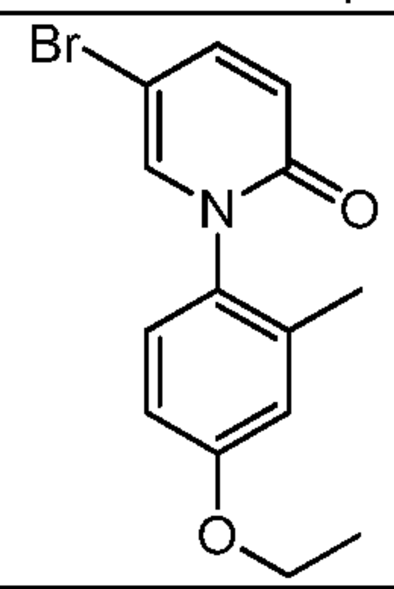
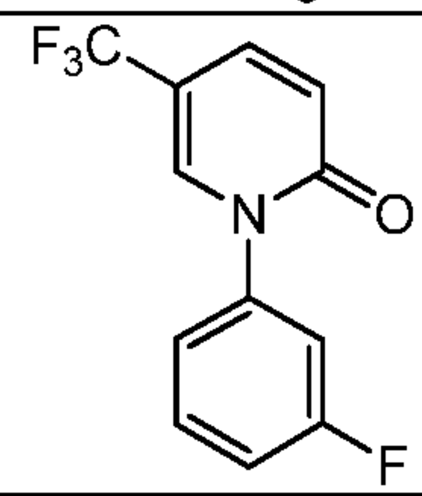
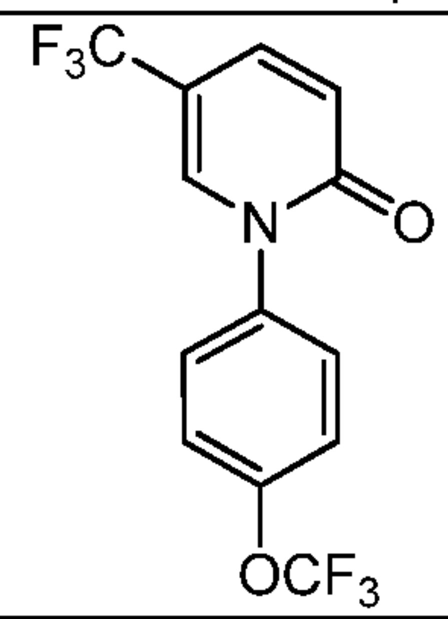
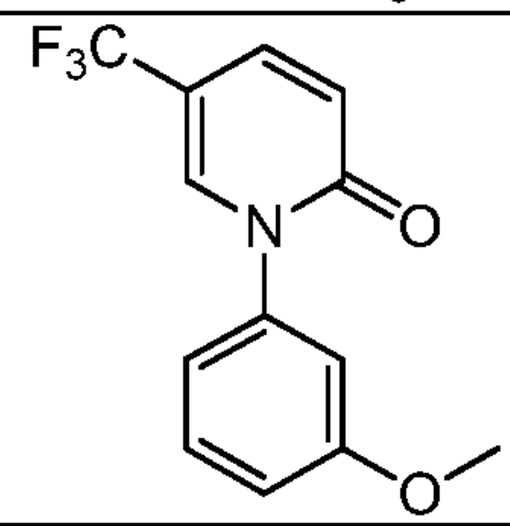
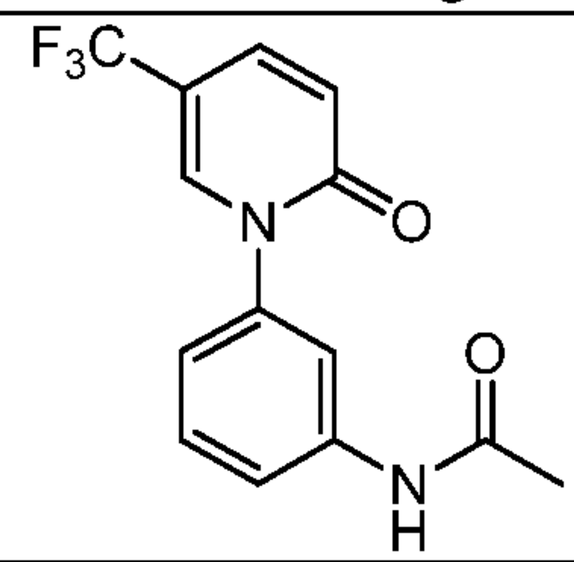
271	
272	
273	
274	
275	
276	
277	

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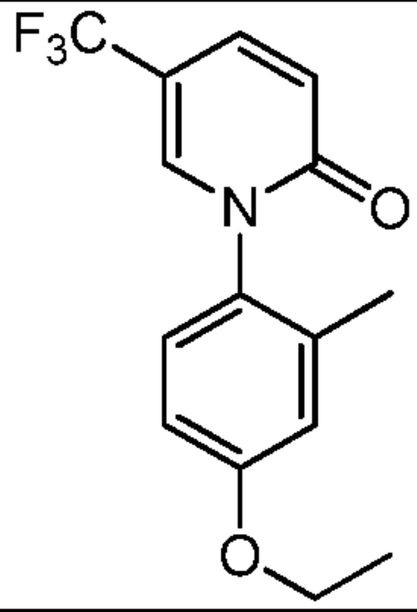
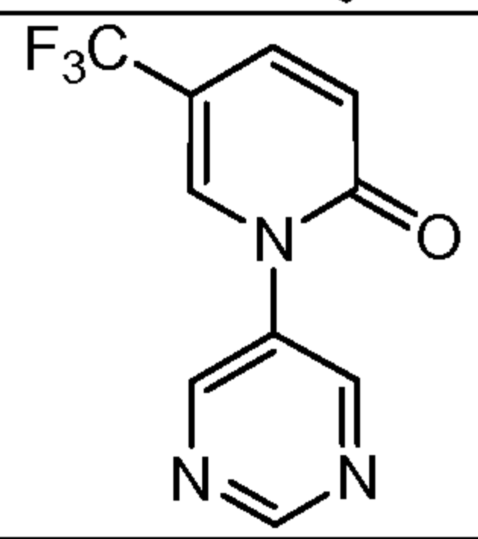
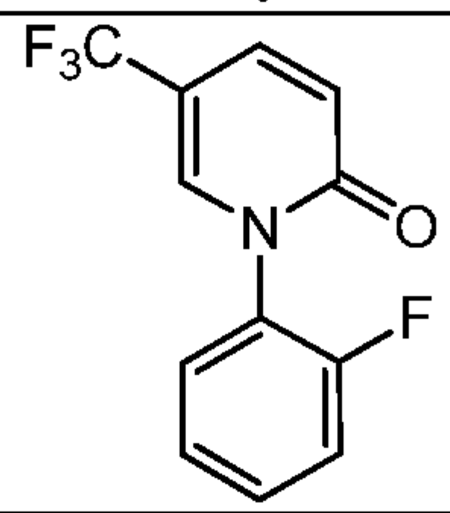
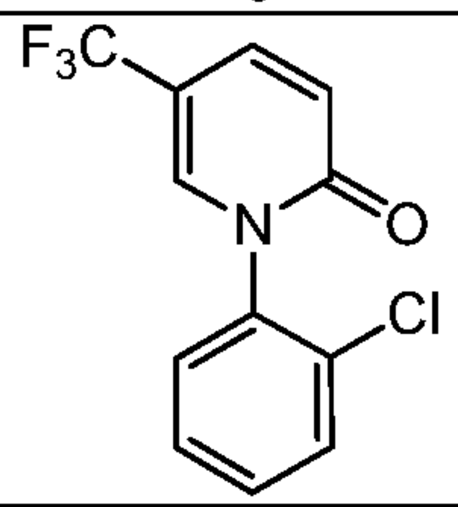
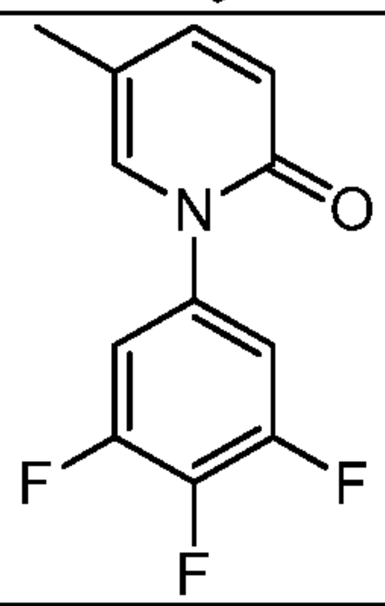
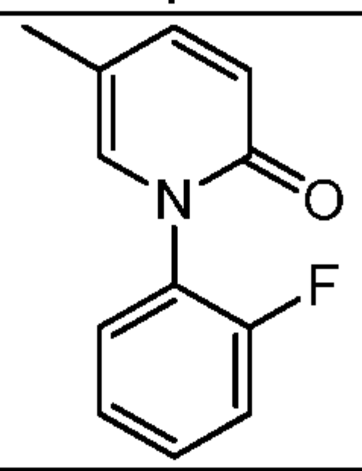
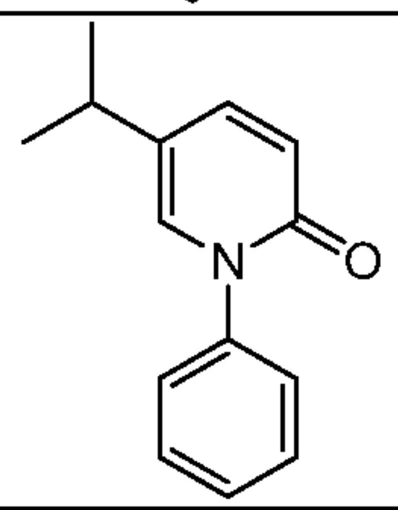
278	
279	
280	
281	
282	
283	
285	

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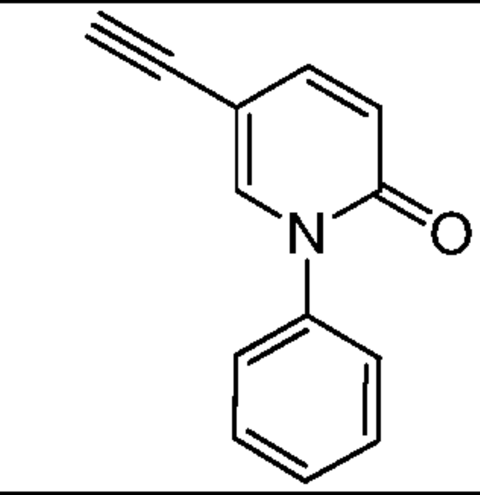
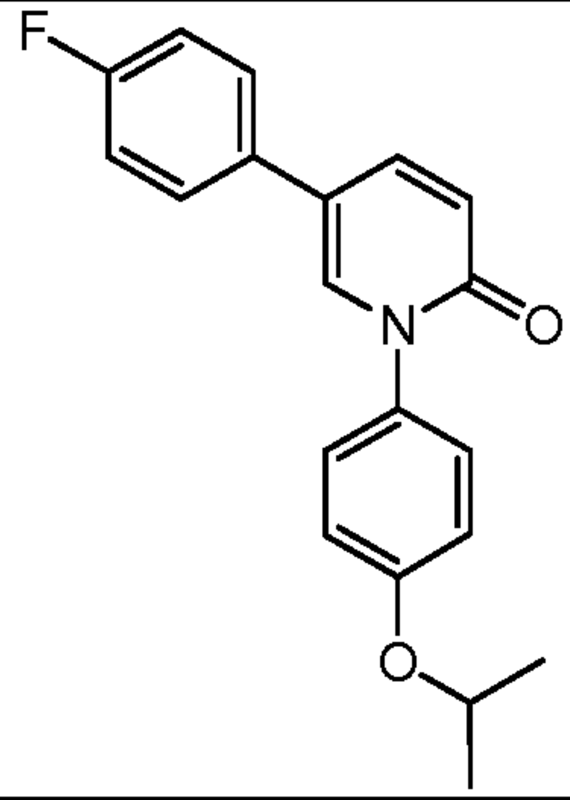
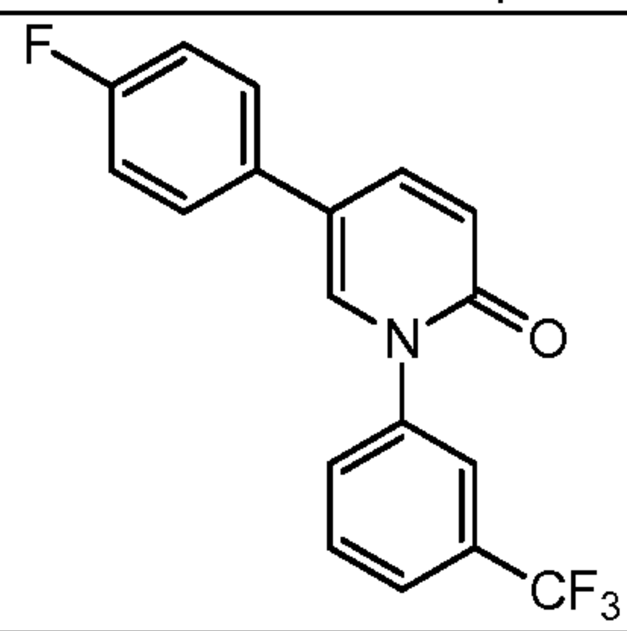
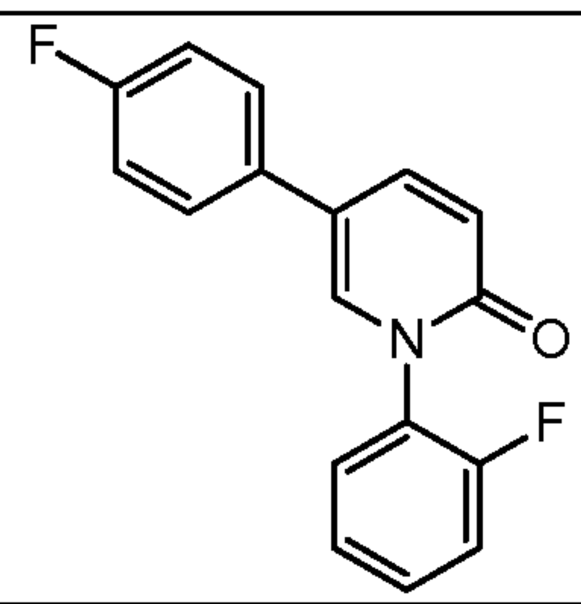
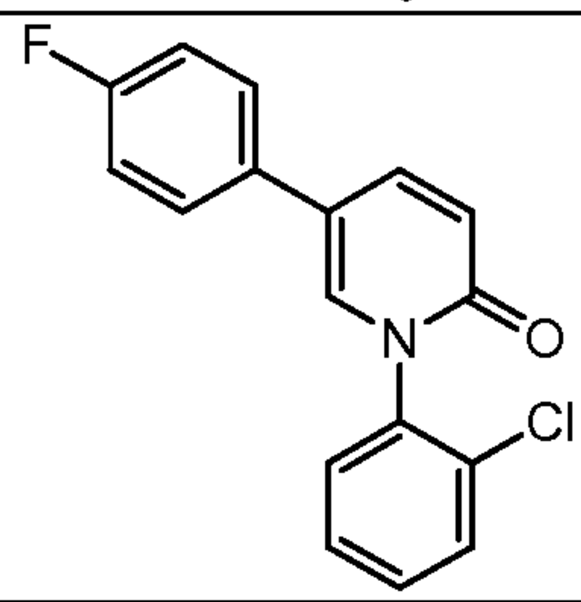
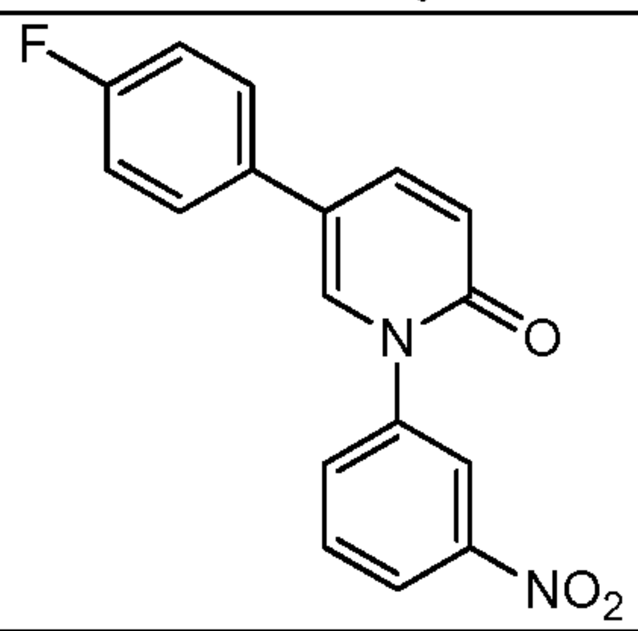
287	
288	
289	
290	
291	
292	

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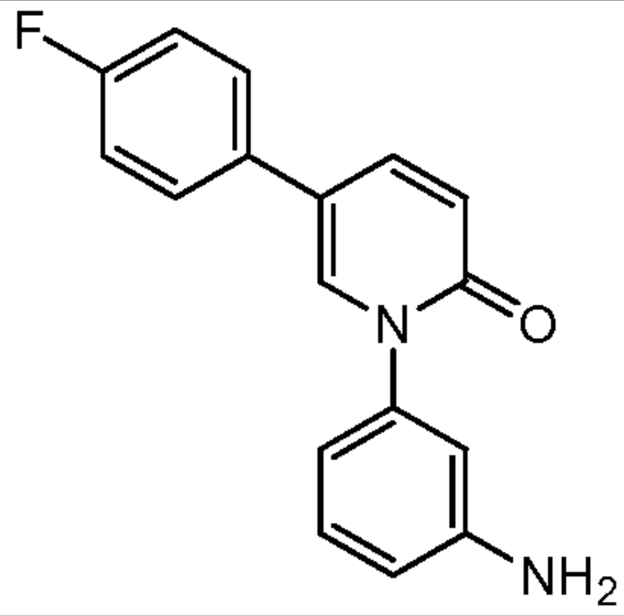
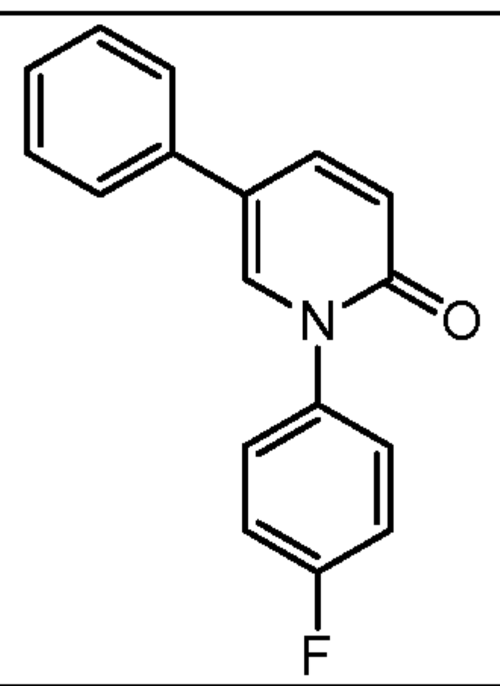
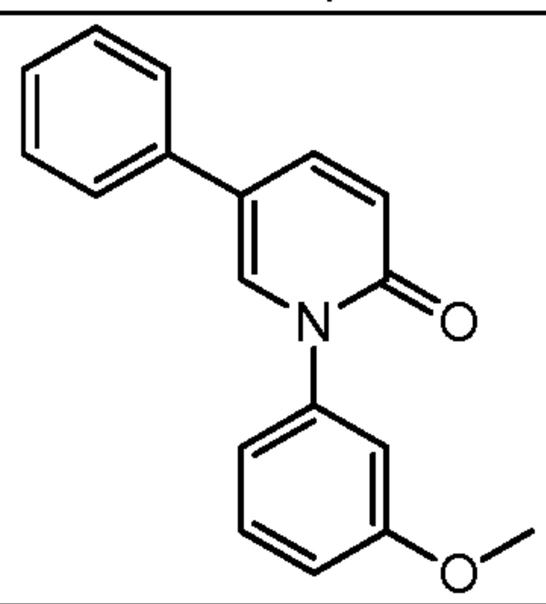
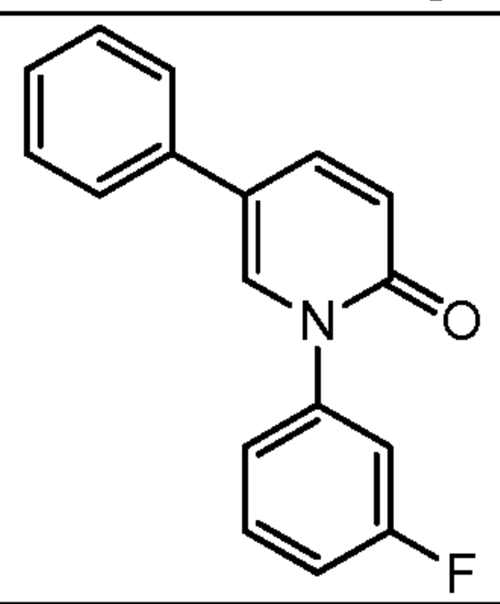
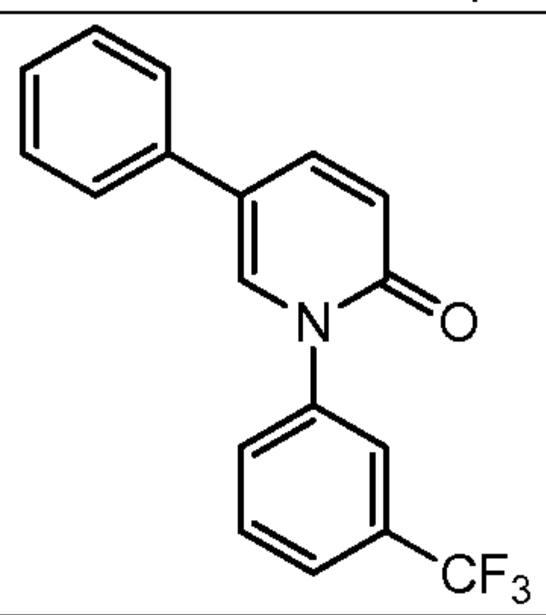
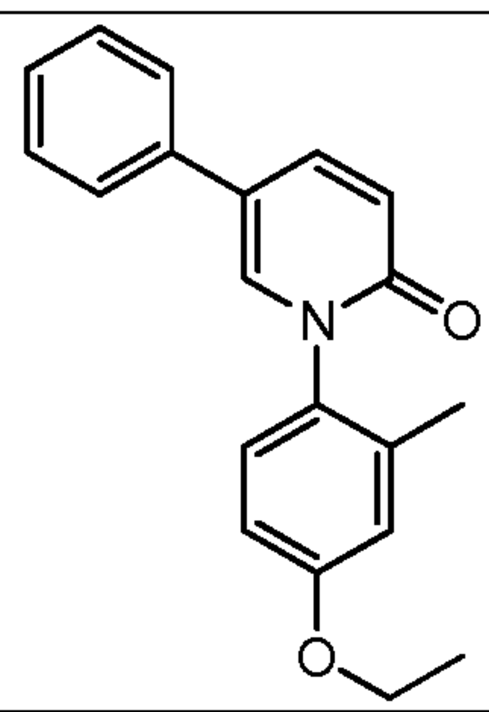
293	
294	
295	
296	
297	
298	

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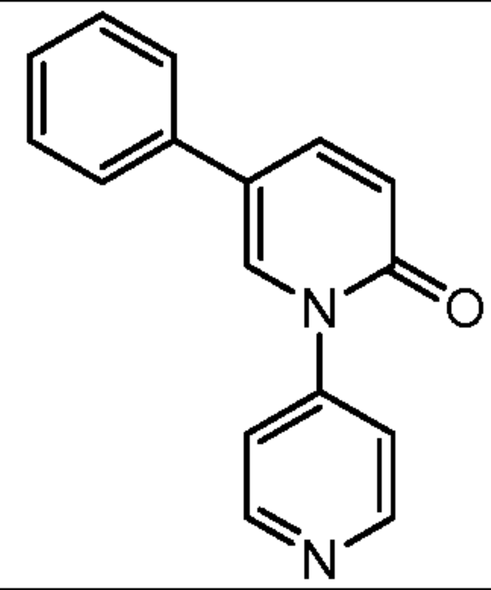
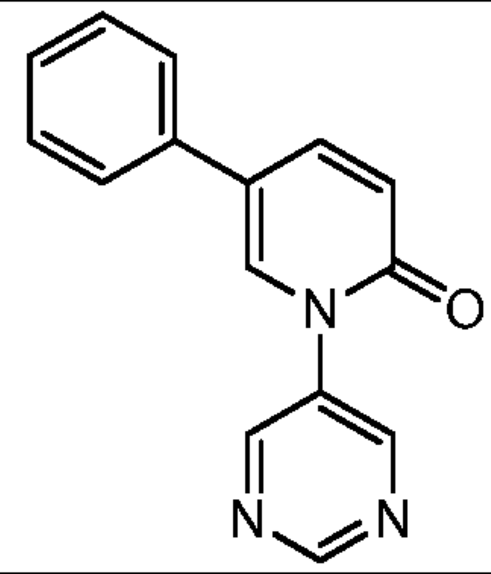
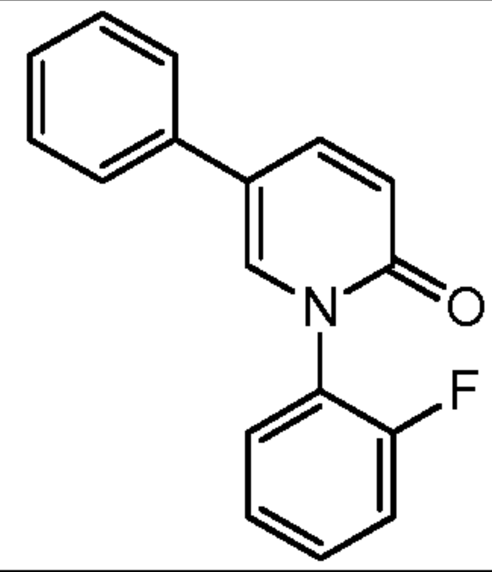
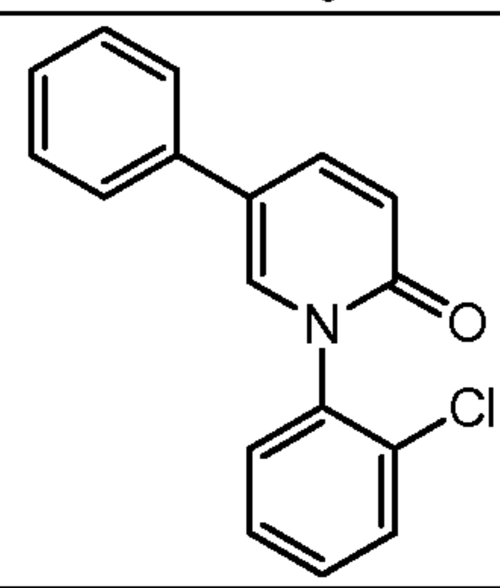
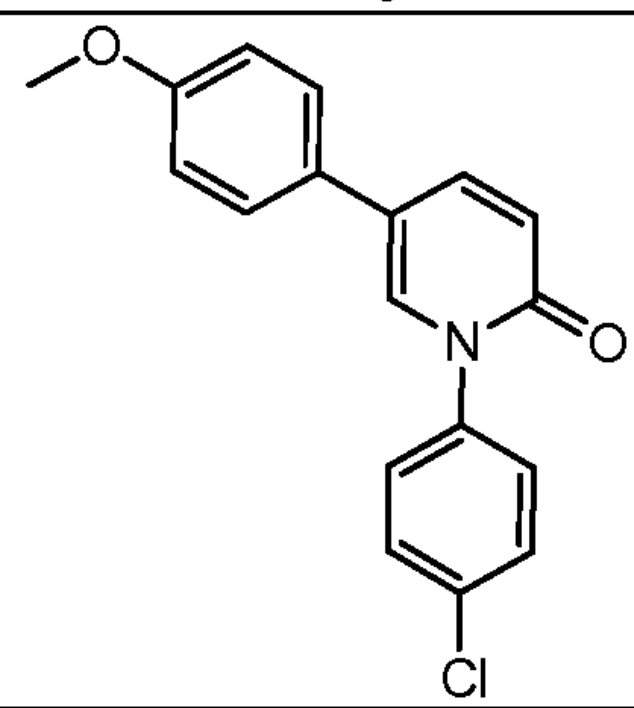
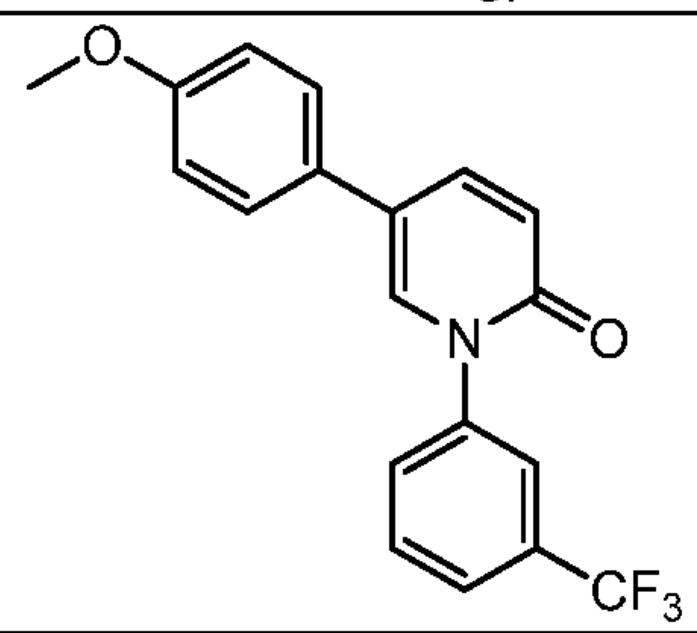
299	
300	
301	
302	
303	
304	

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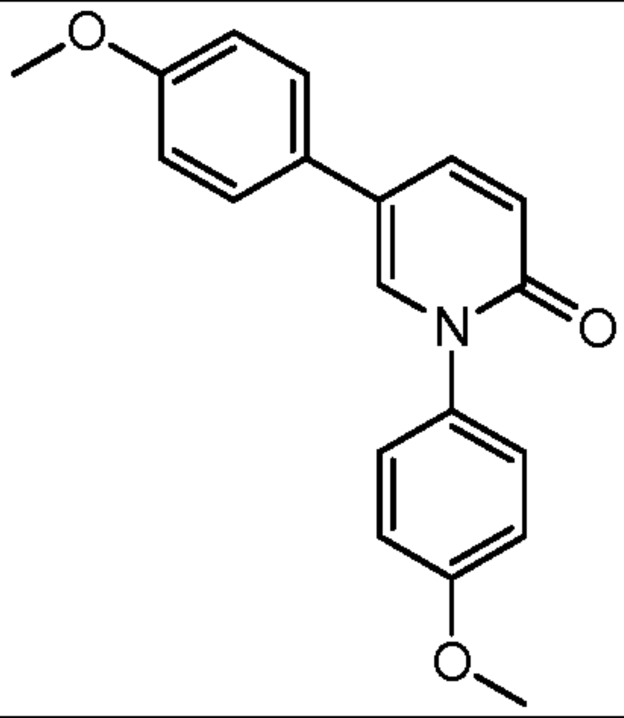
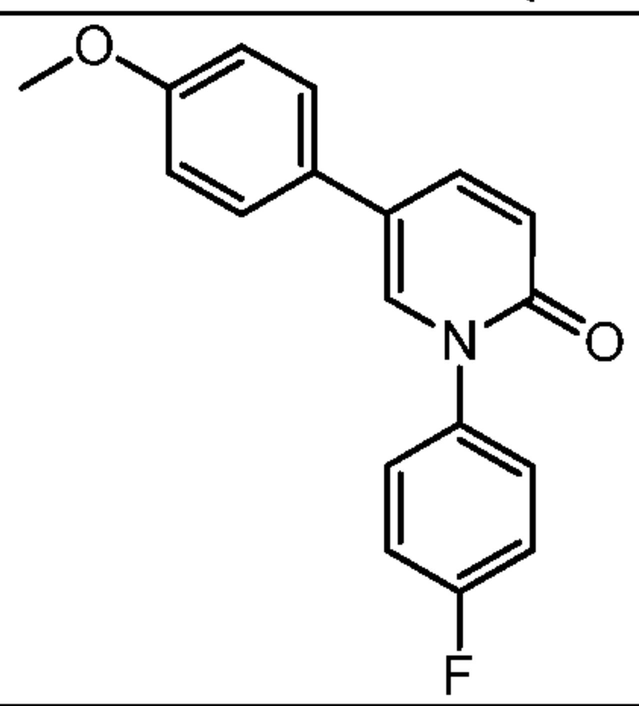
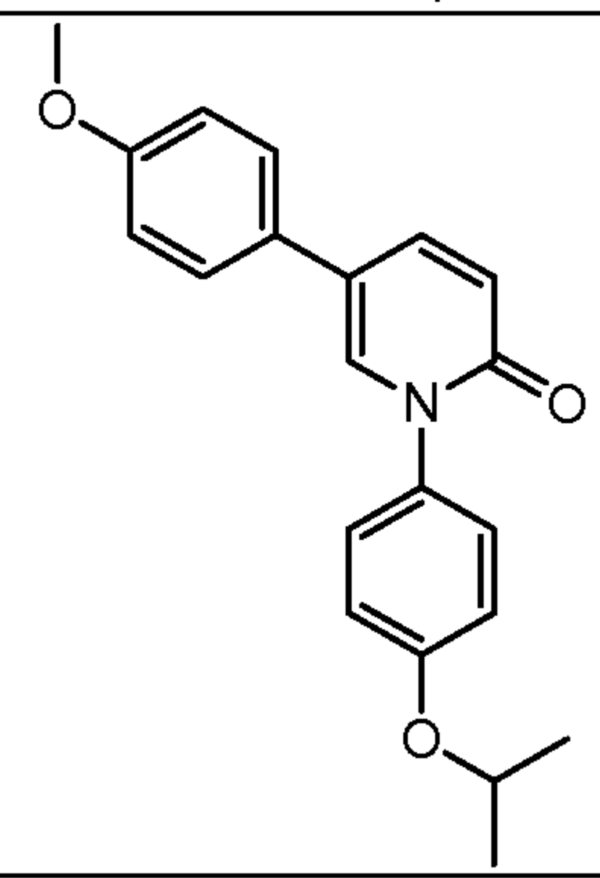
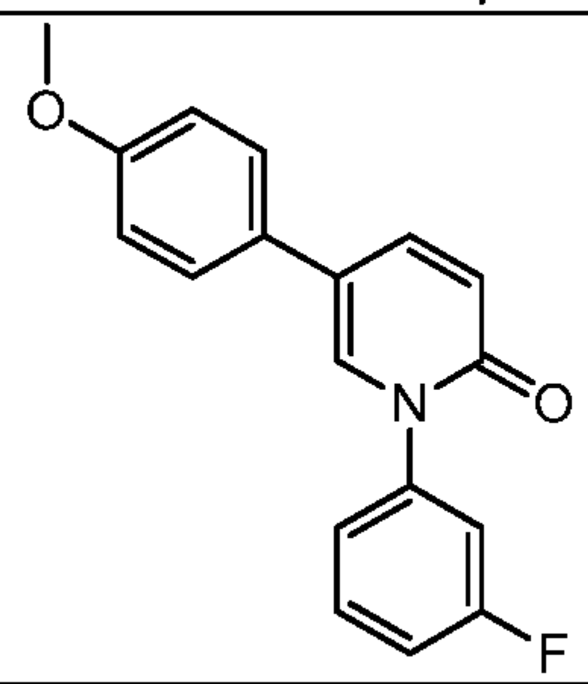
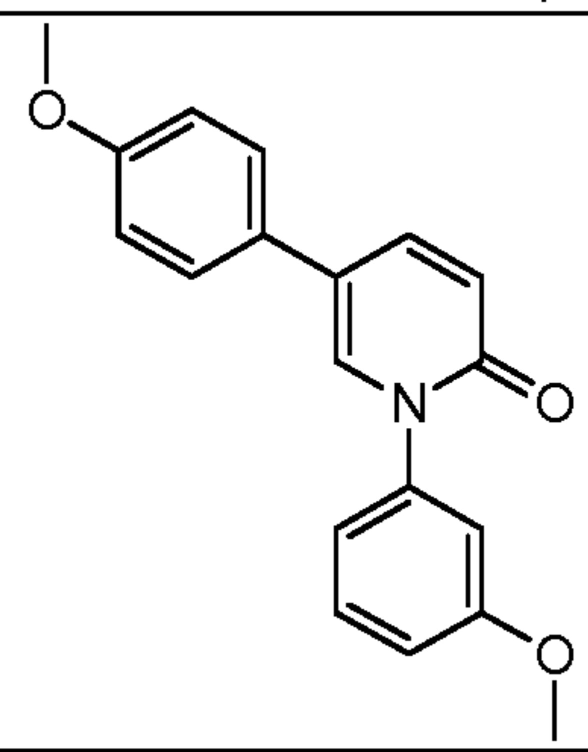
305	
306	
307	
308	
309	

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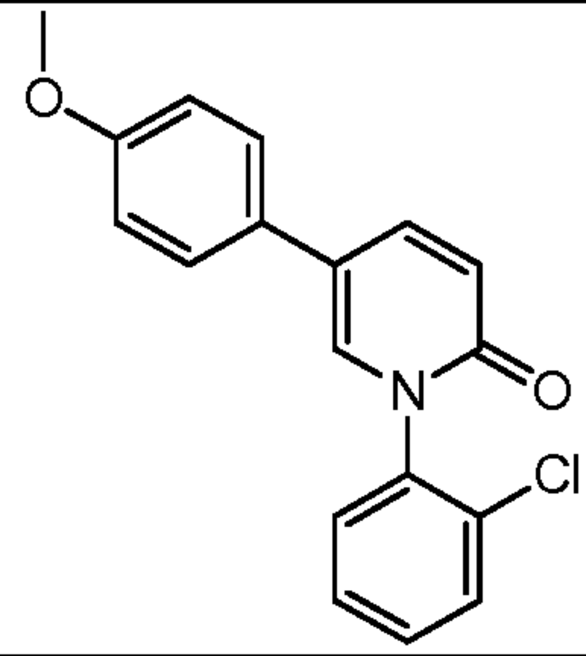
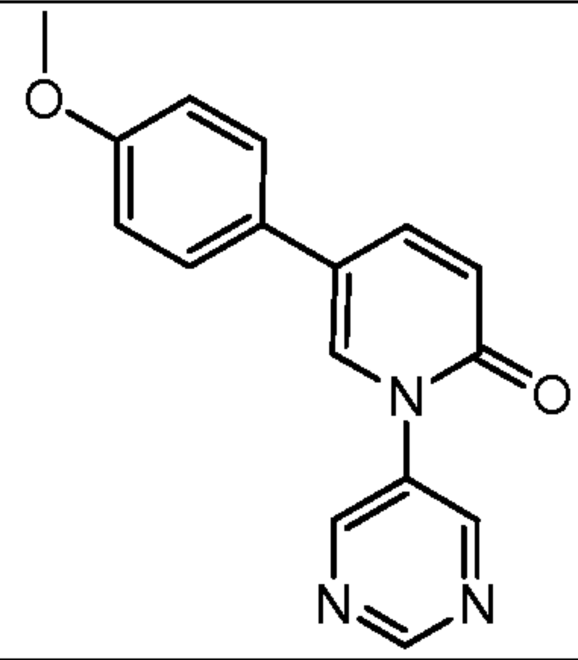
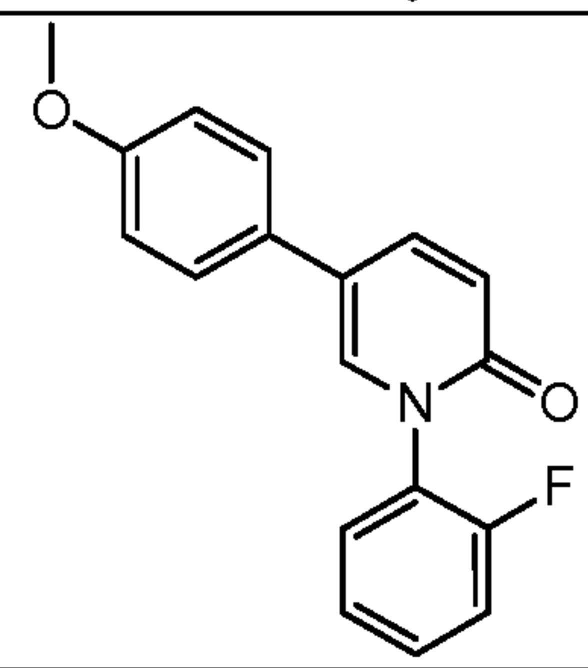
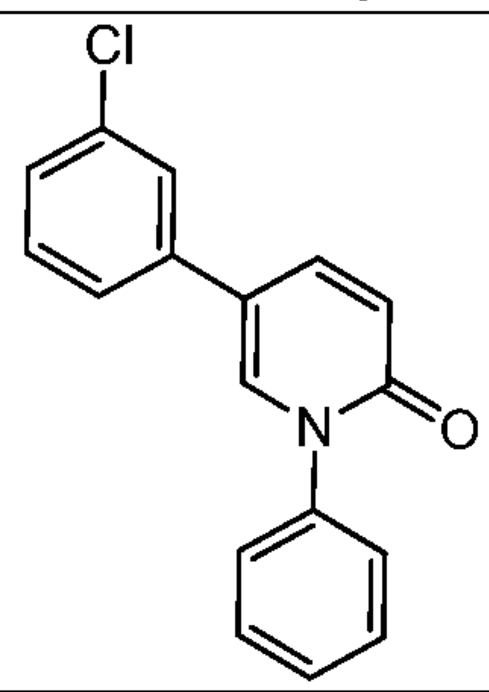
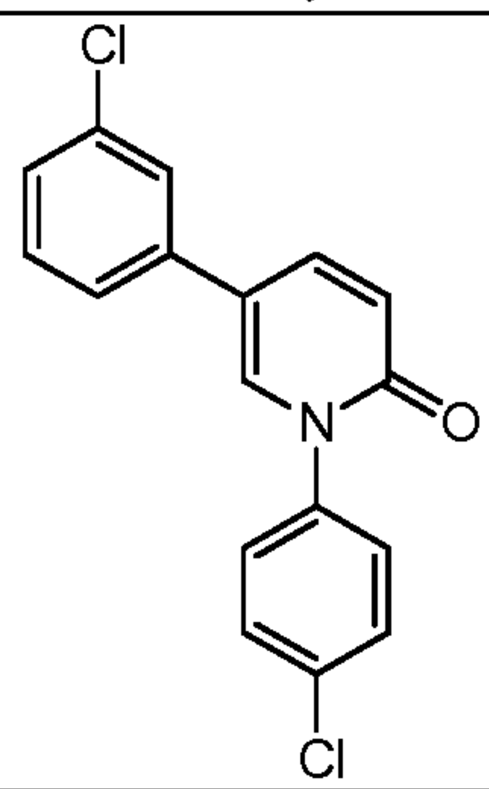
310	
311	
312	
313	
314	

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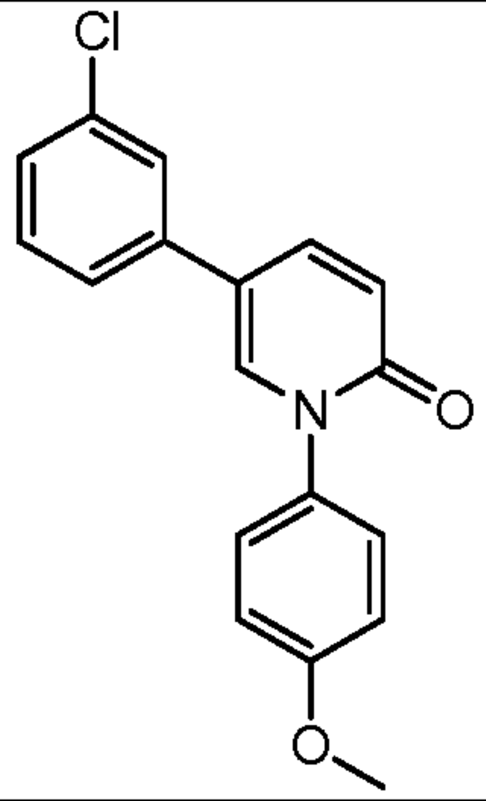
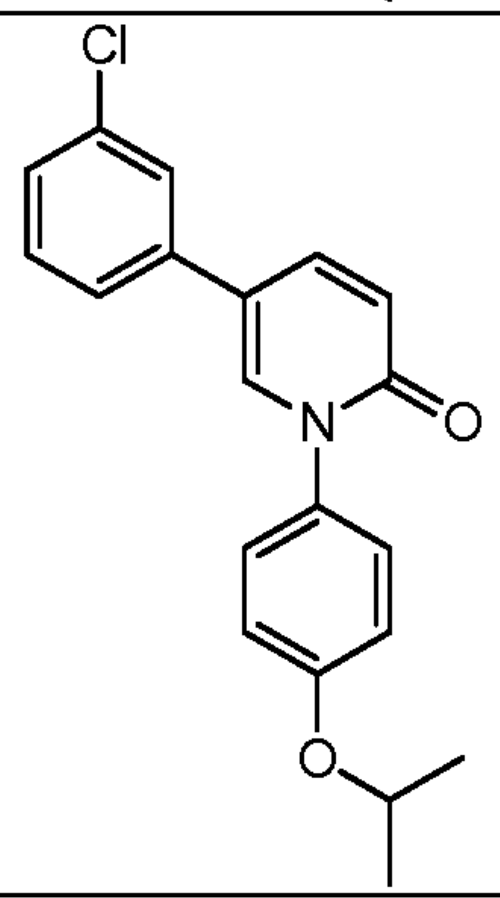
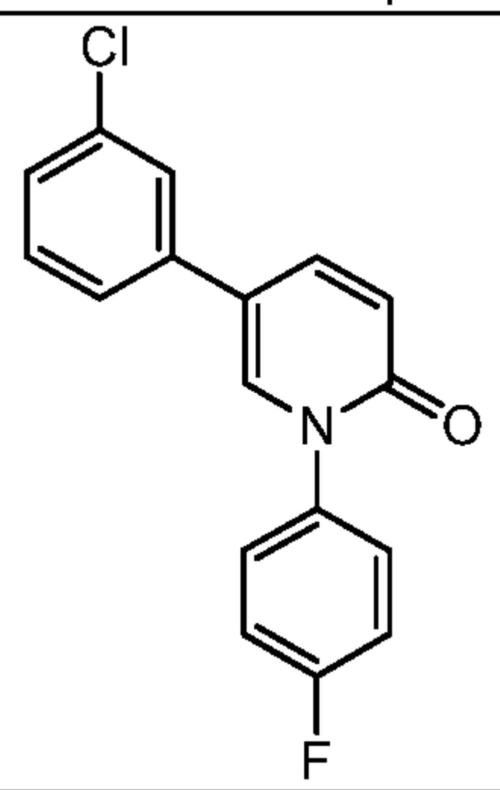
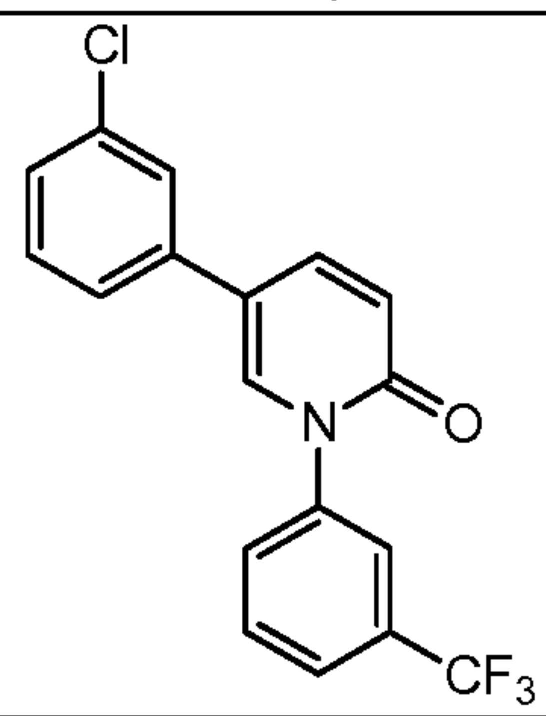
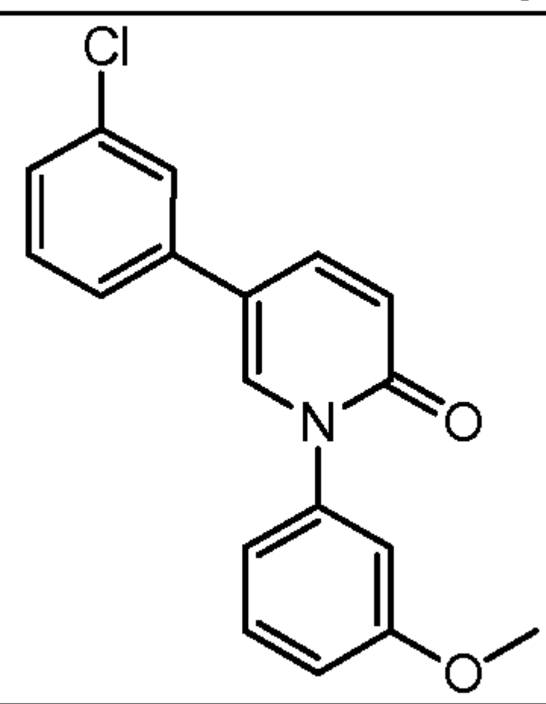
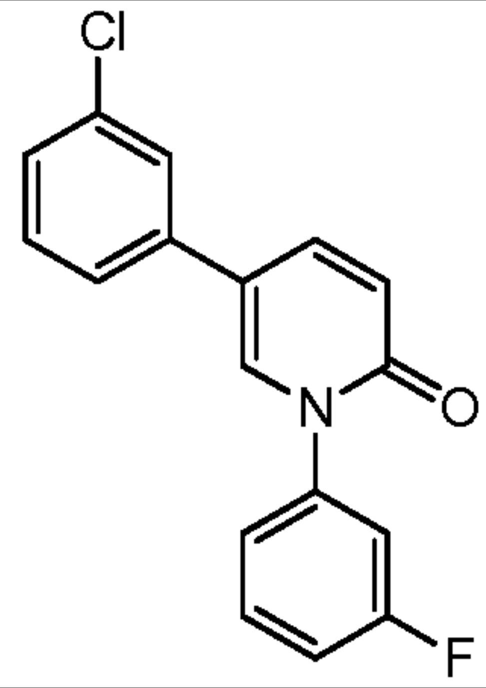
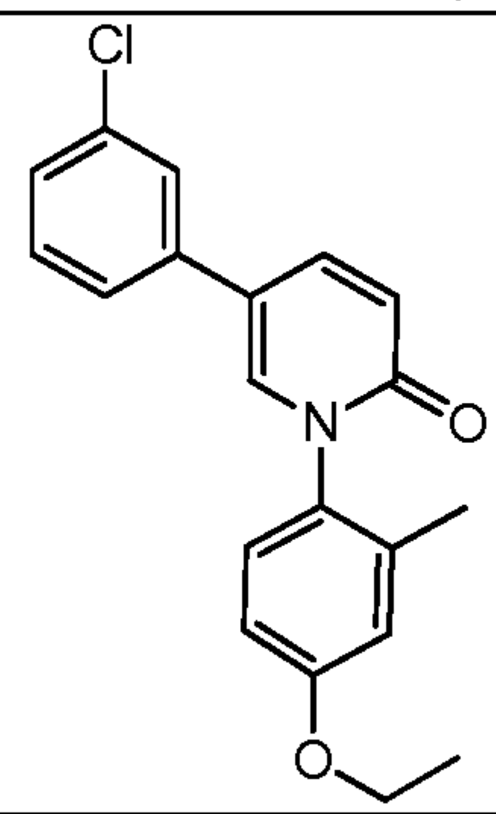
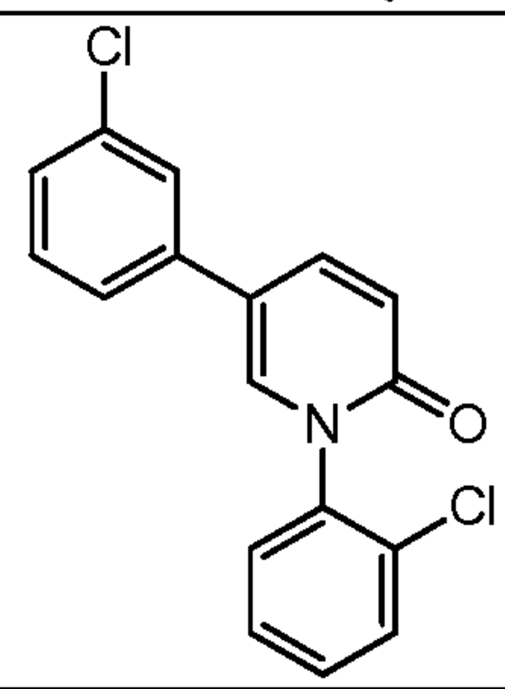
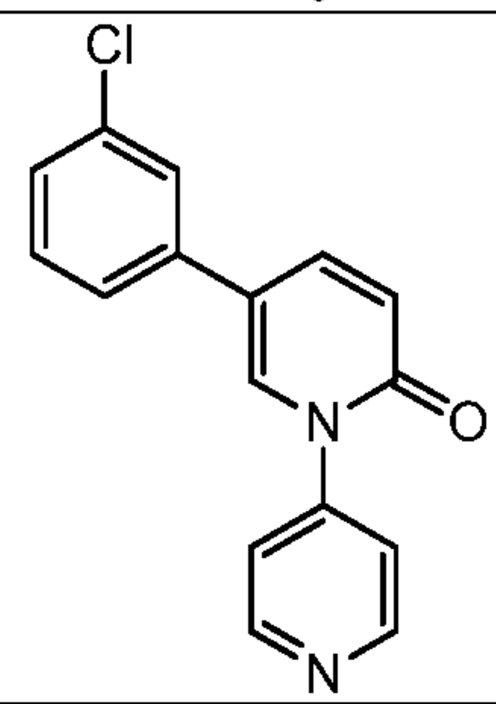
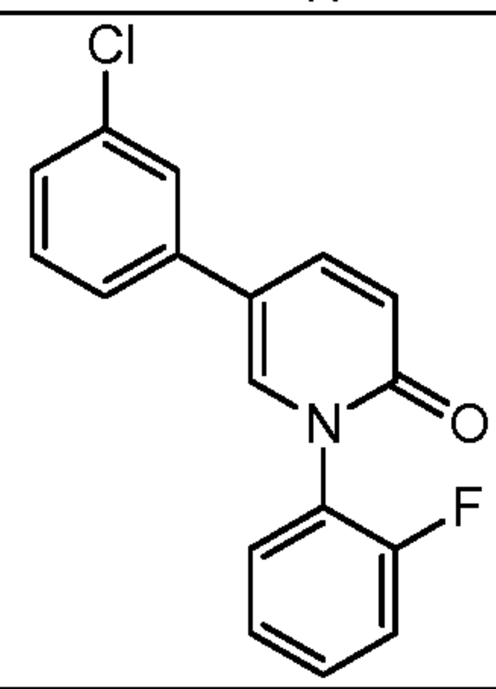
315	
316	
317	
318	
319	
320	
321	
322	
323	
324	

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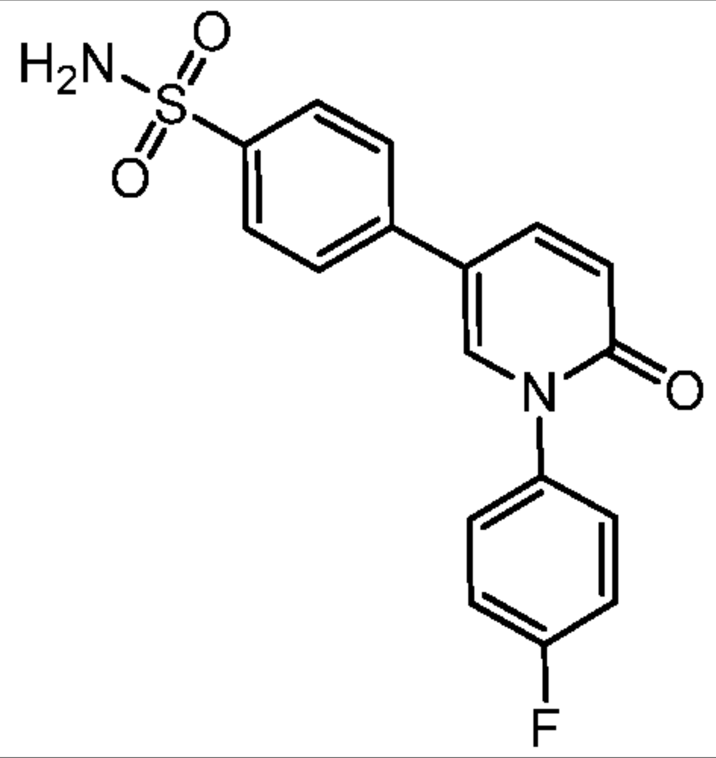
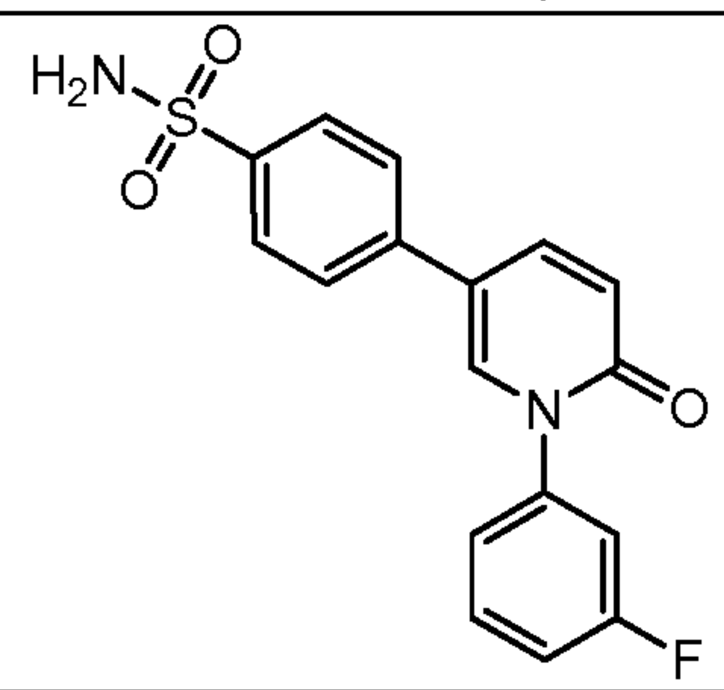
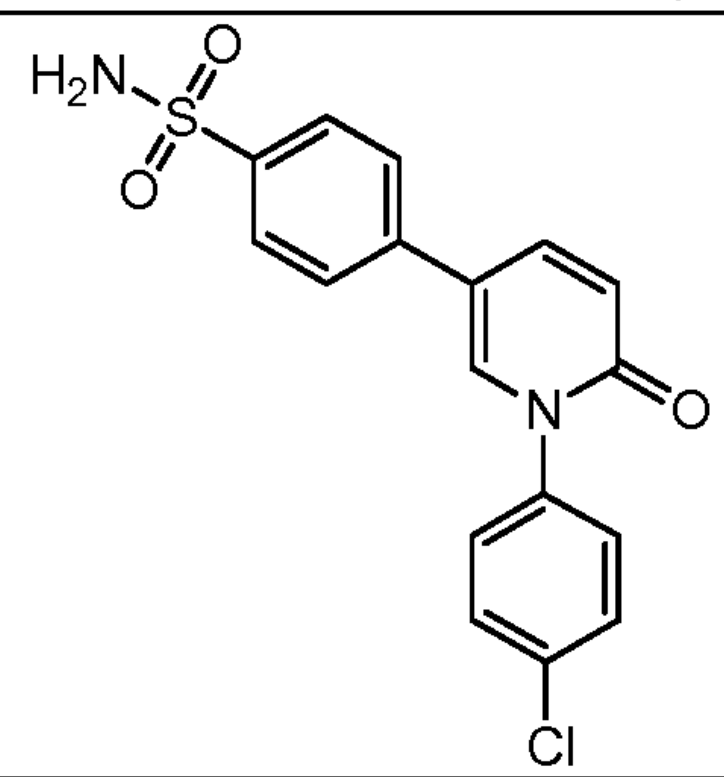
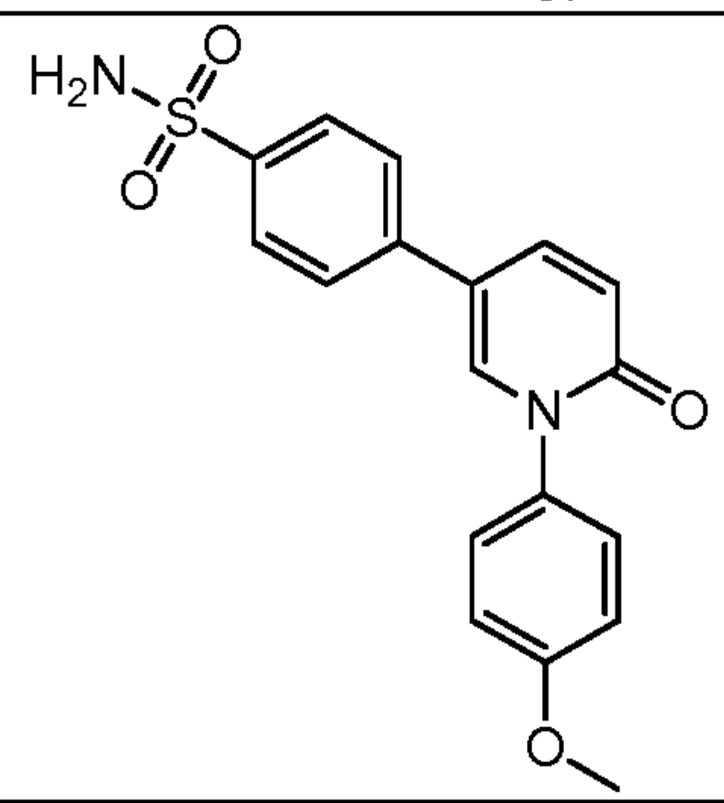
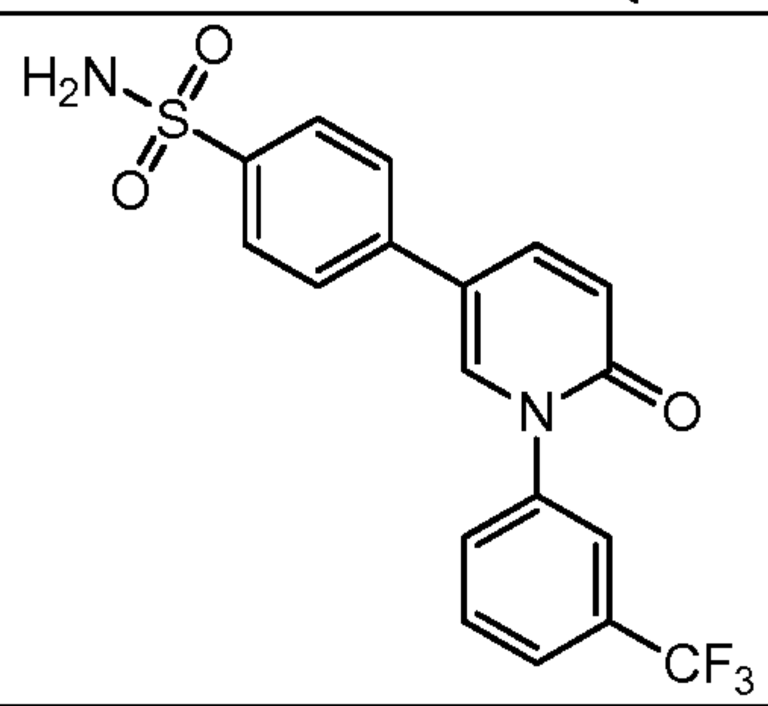
325	
326	
327	
328	
329	

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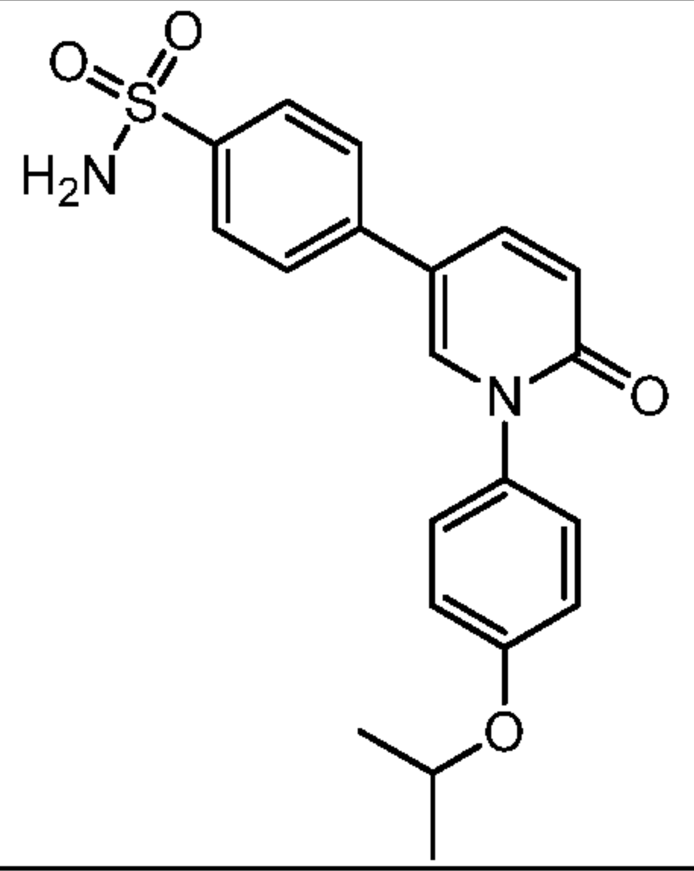
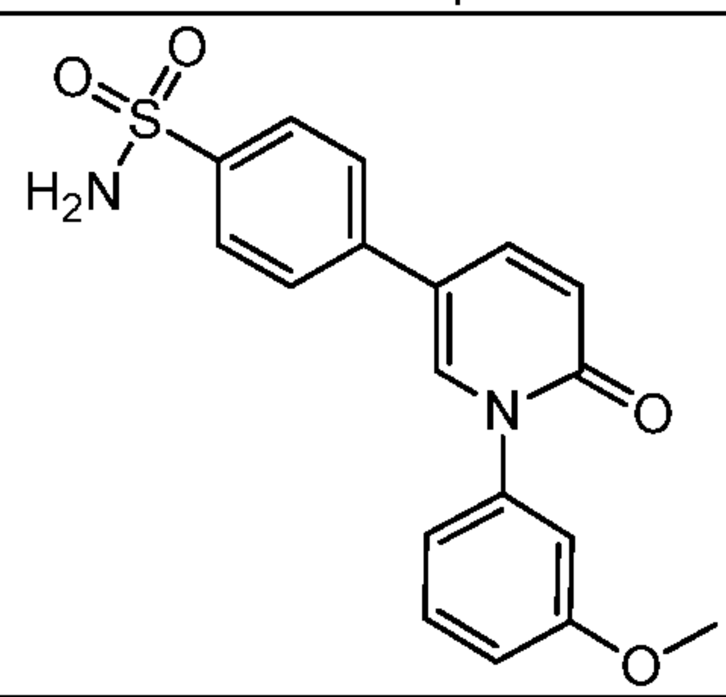
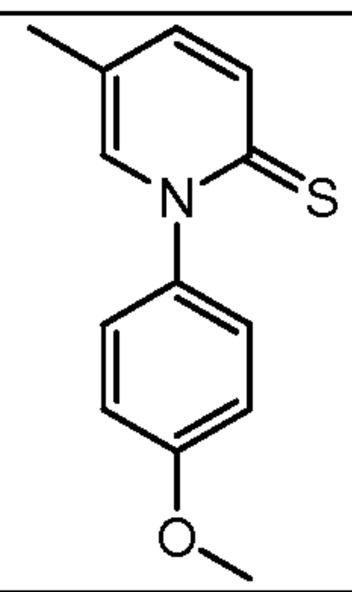
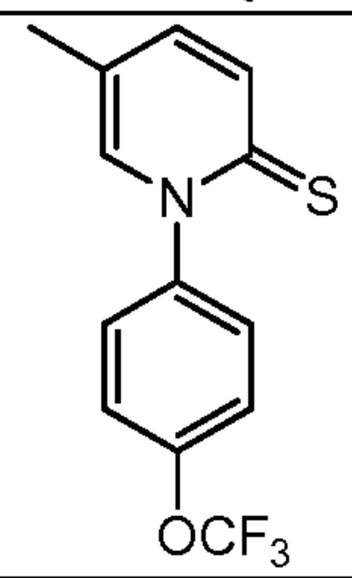
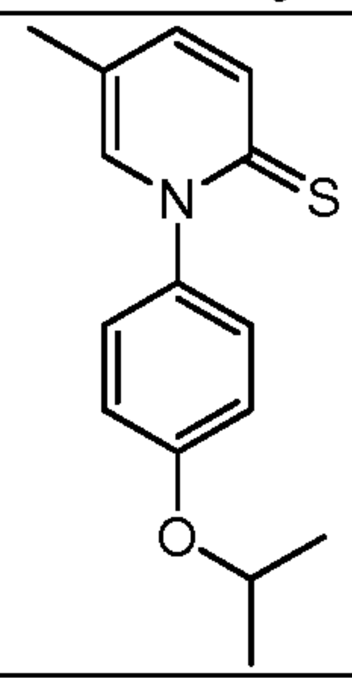
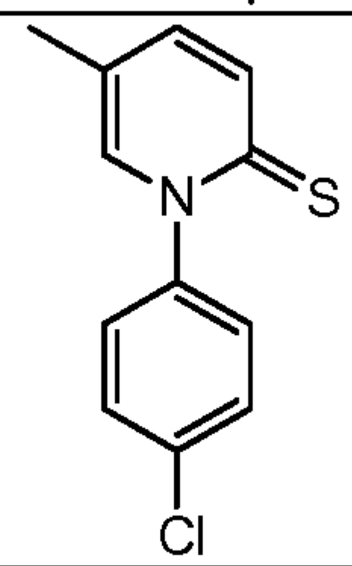
330	
331	
332	
333	
334	
335	

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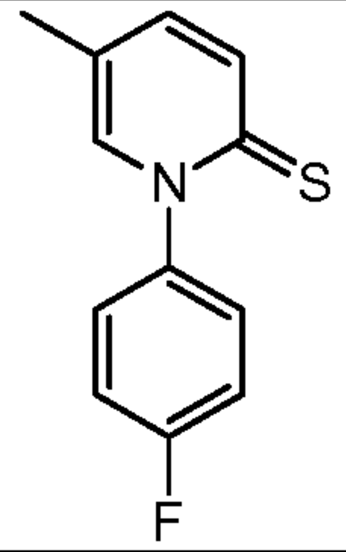
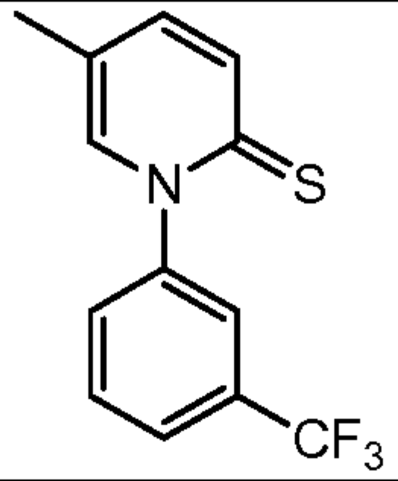
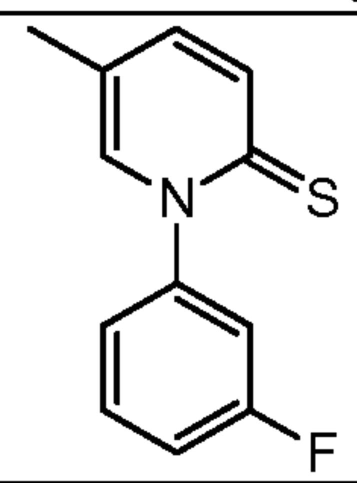
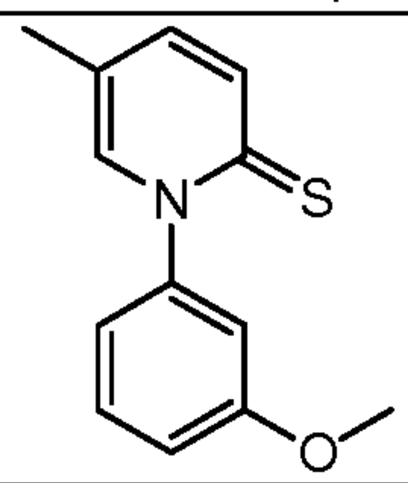
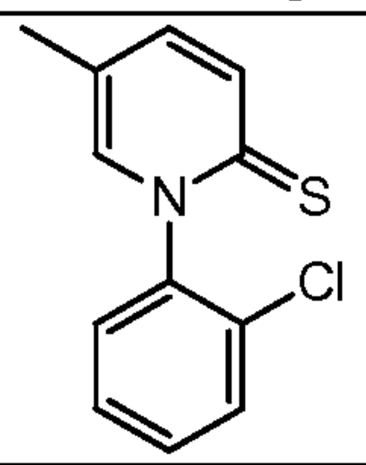
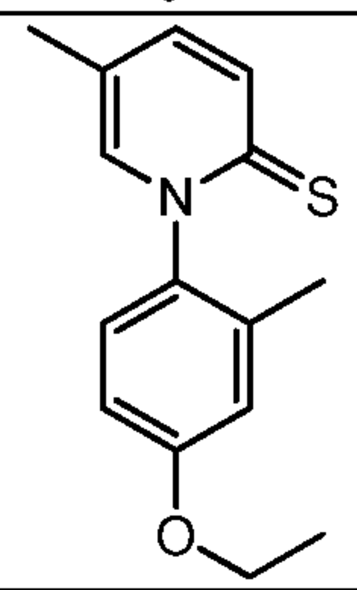
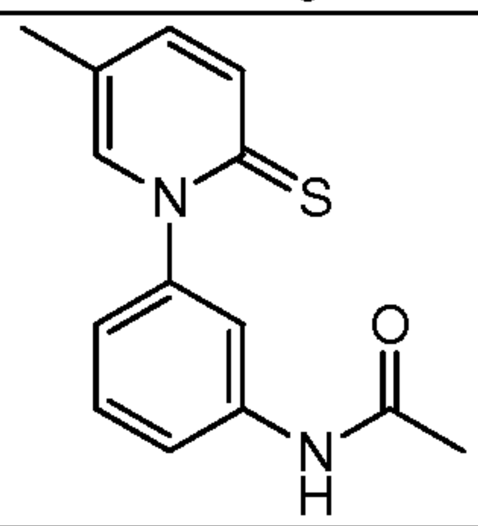
336	
337	
338	
339	
341	
342	
343	

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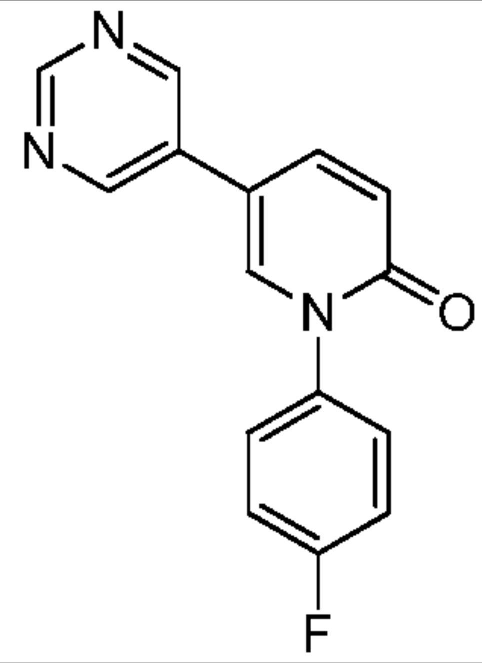
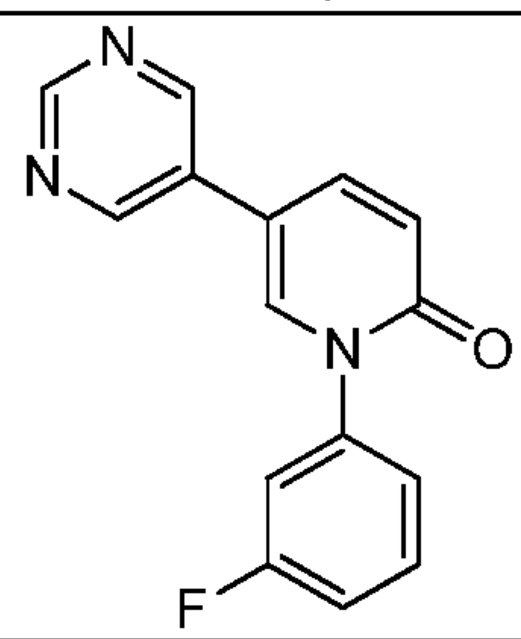
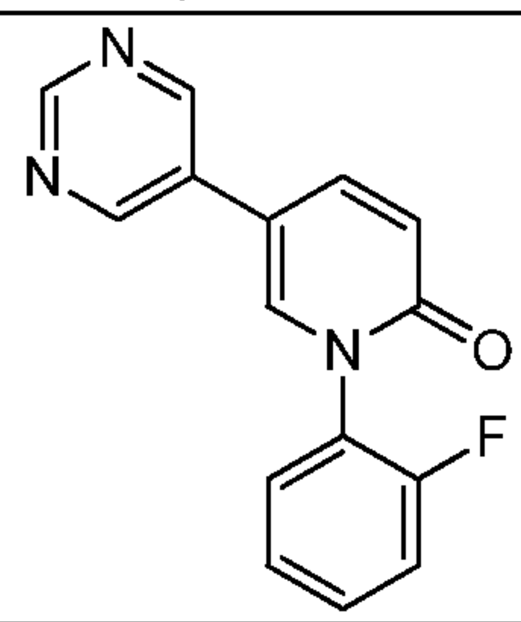
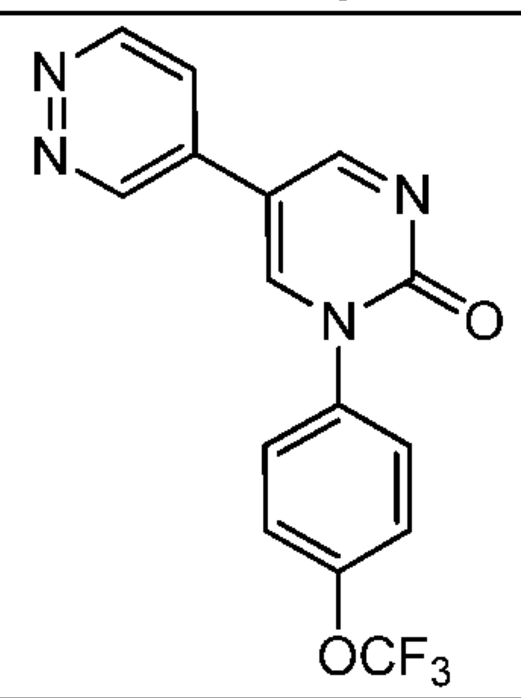
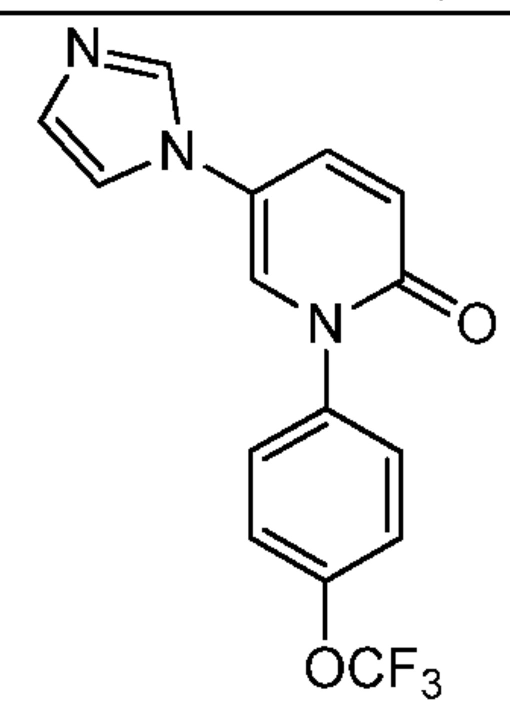
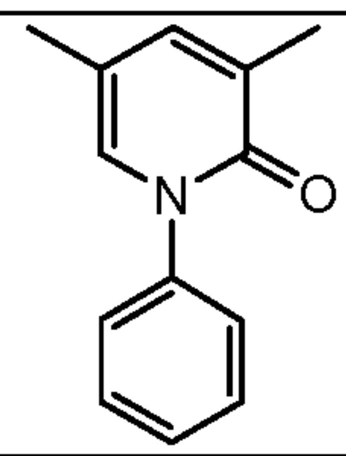
344	
345	
346	
347	
348	
349	

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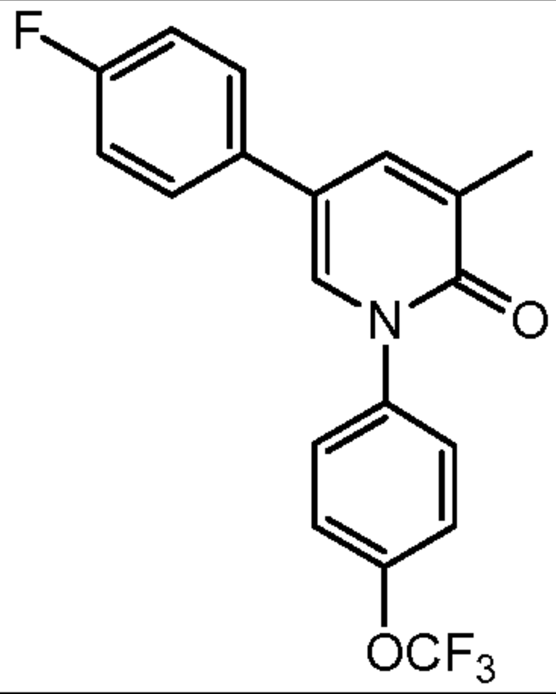
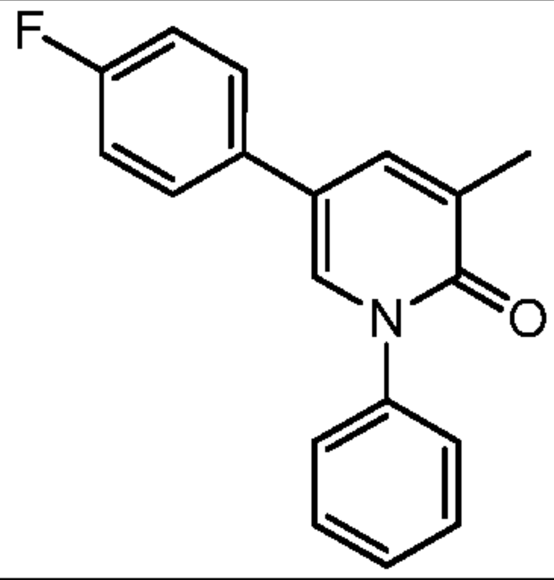
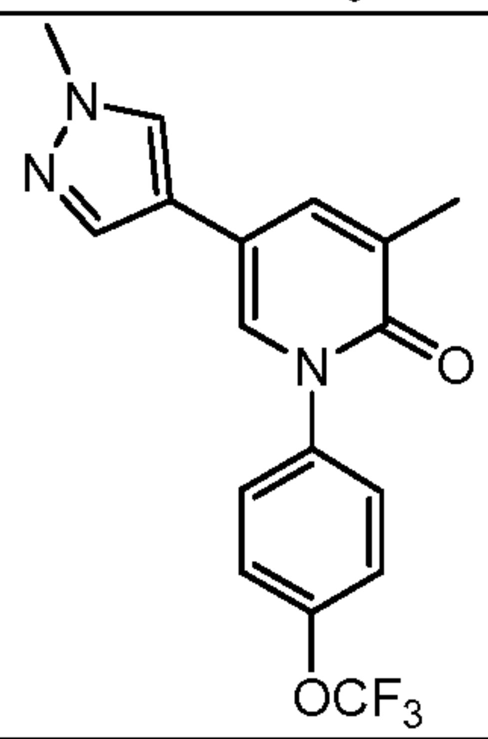
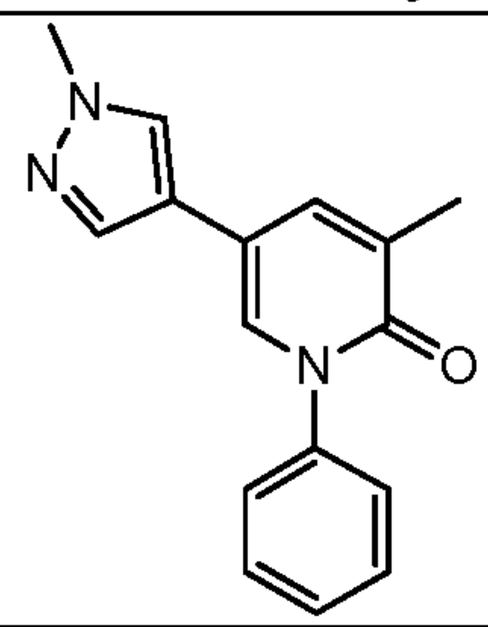
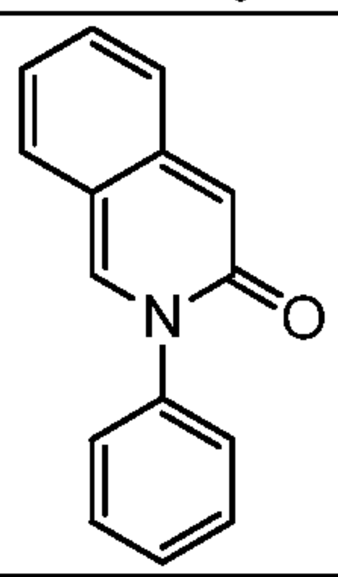
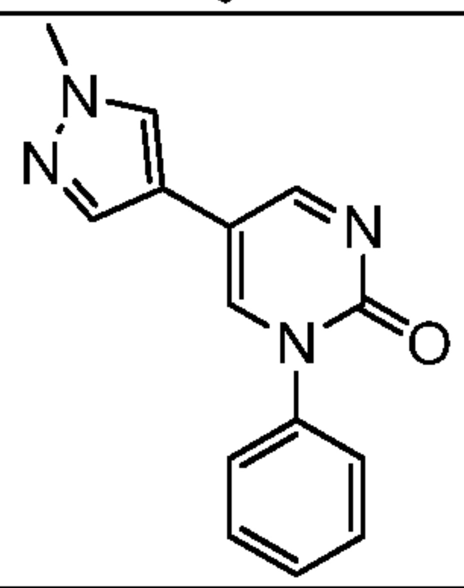
350	
351	
352	
353	
354	
355	

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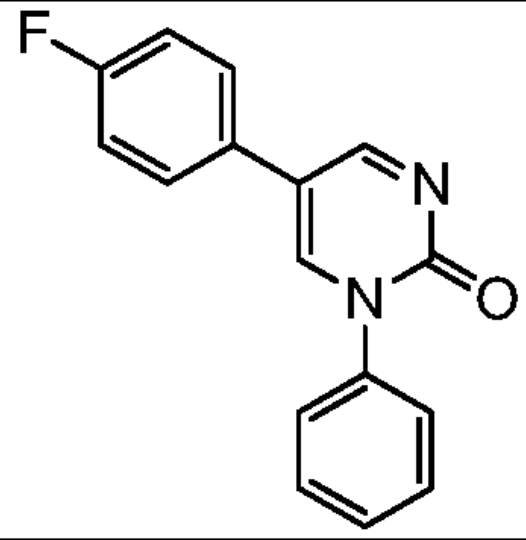
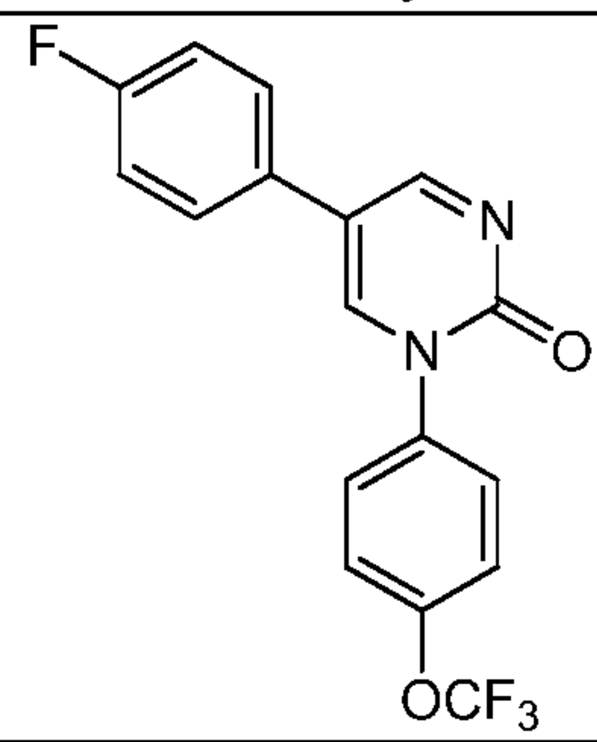
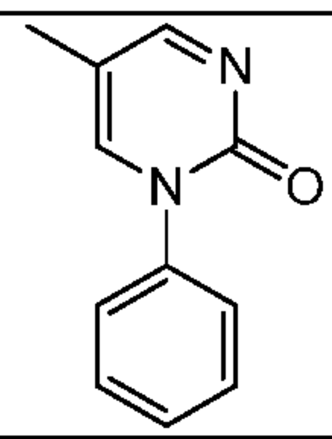
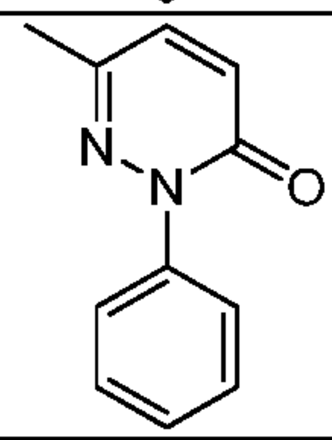
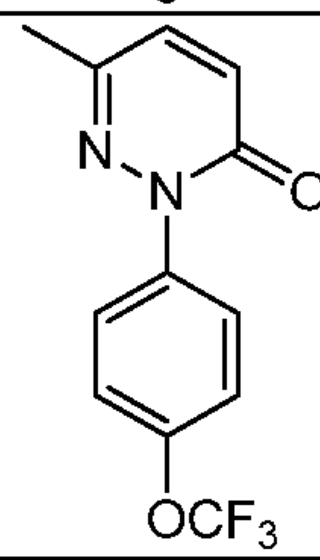
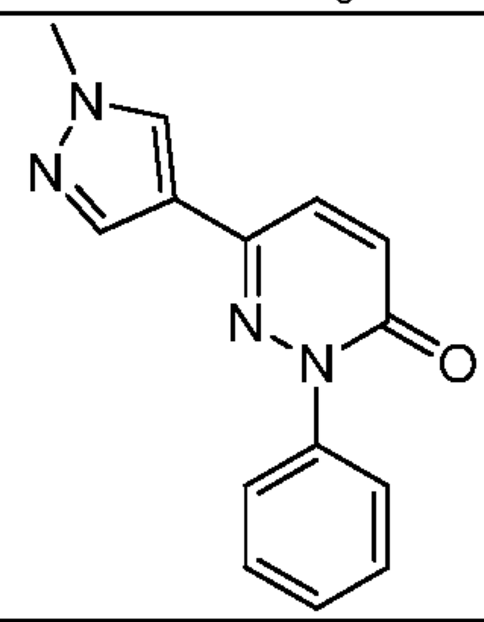
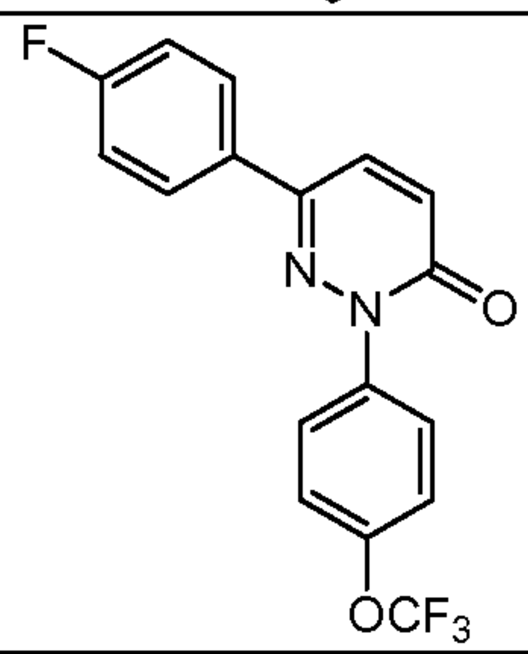
356	
357	
358	
359	
360	
361	
362	

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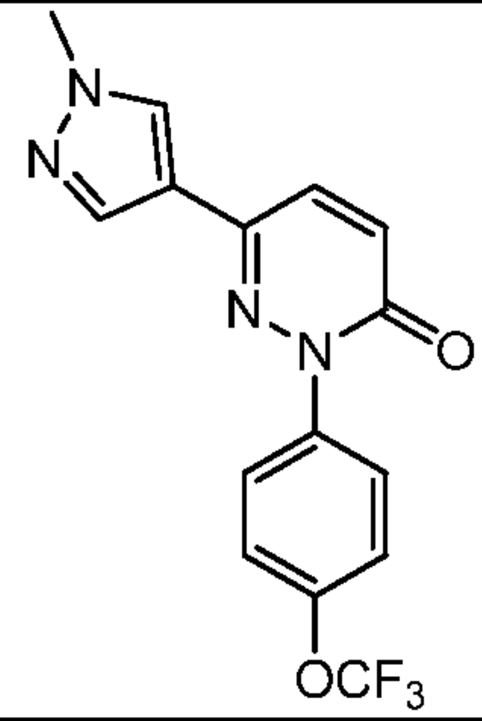
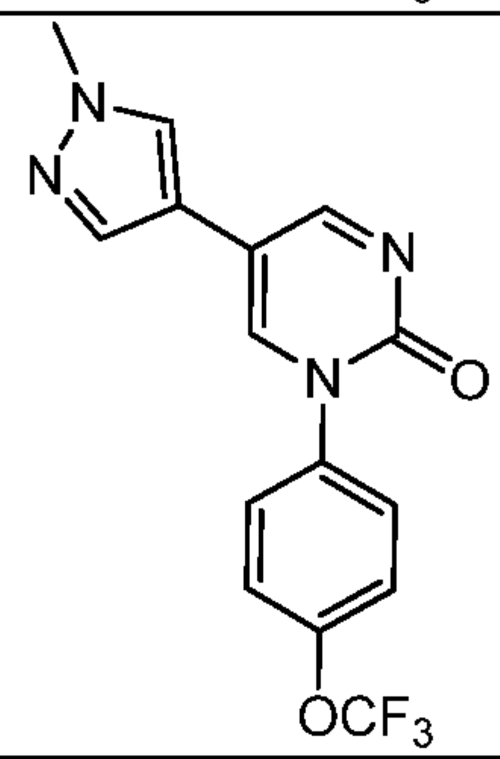
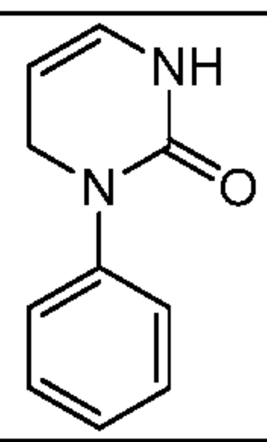
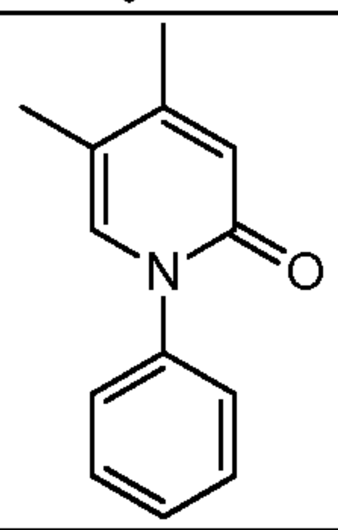
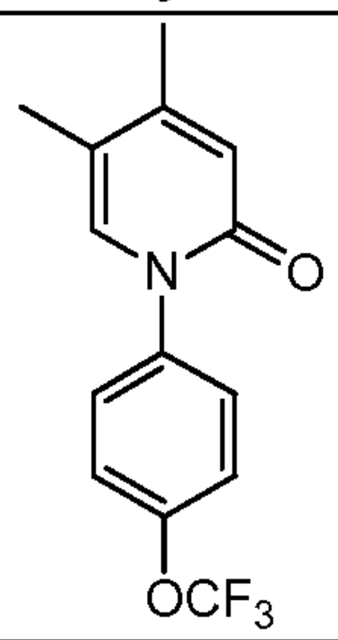
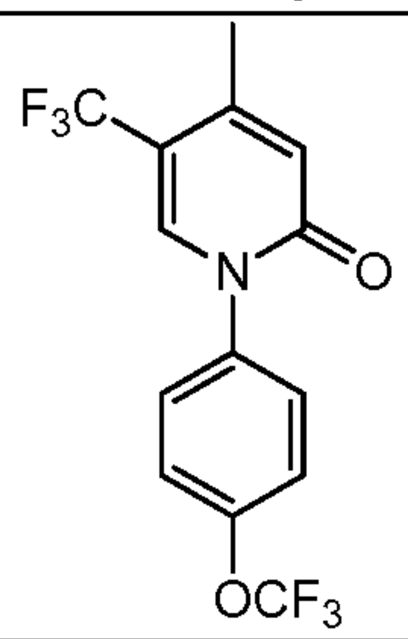
363	
364	
365	
366	
367	
368	

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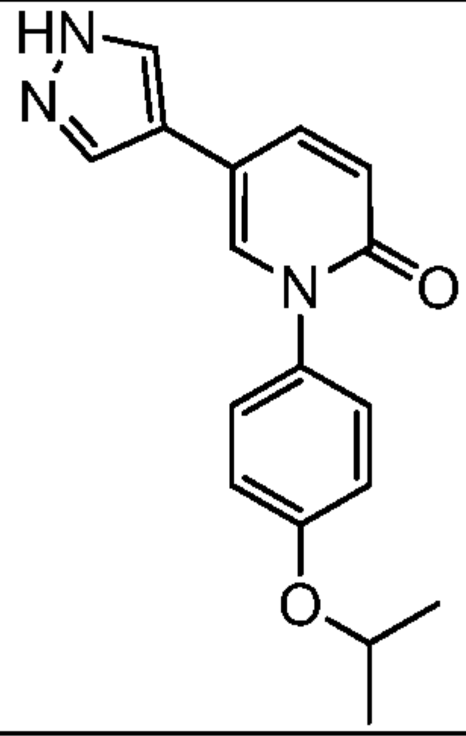
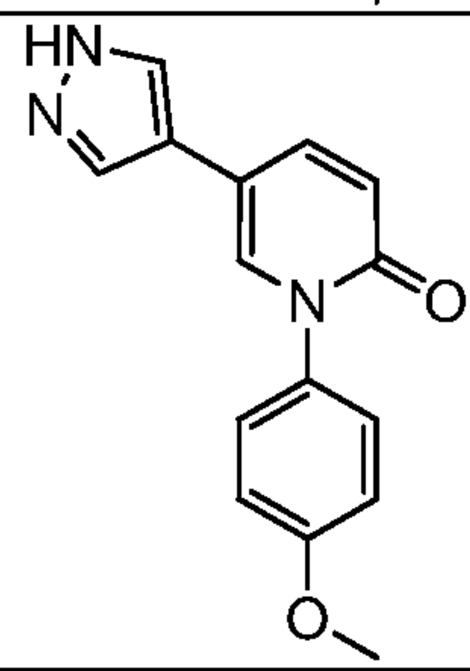
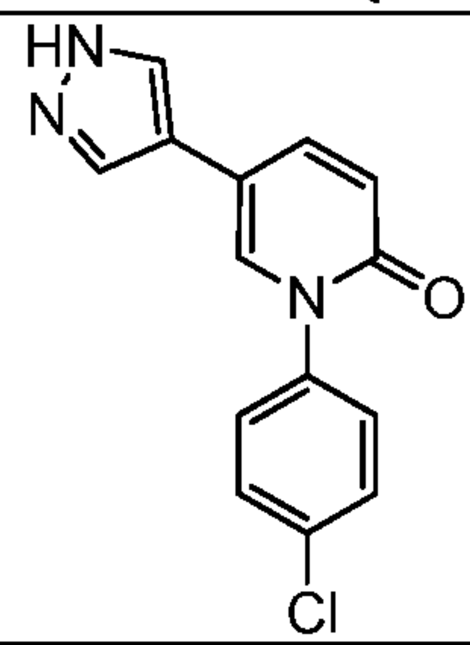
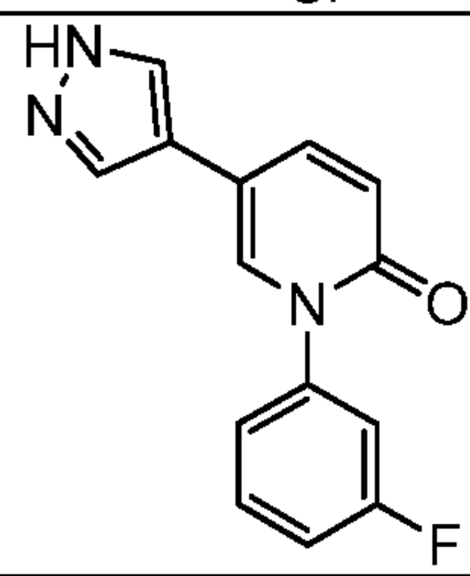
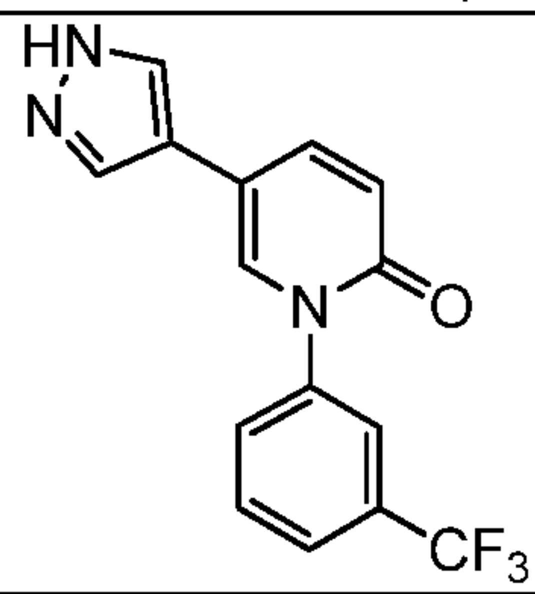
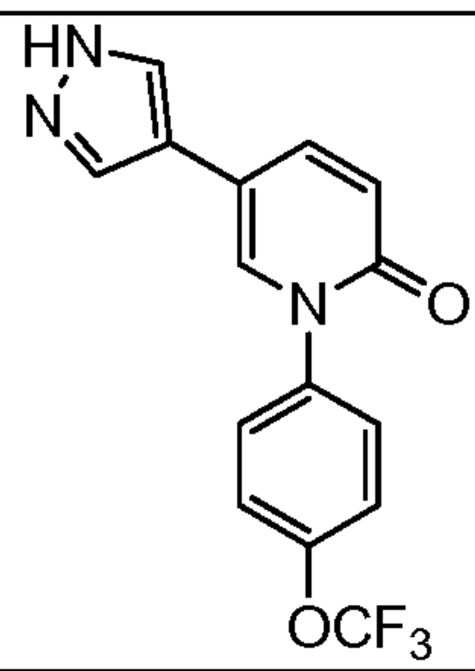
369	
370	
371	
372	
373	
374	

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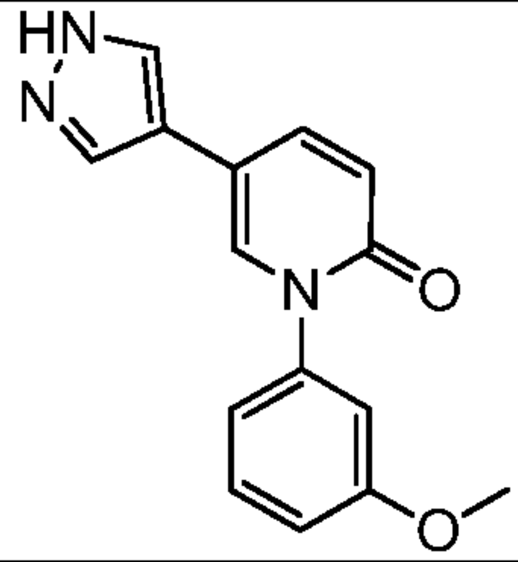
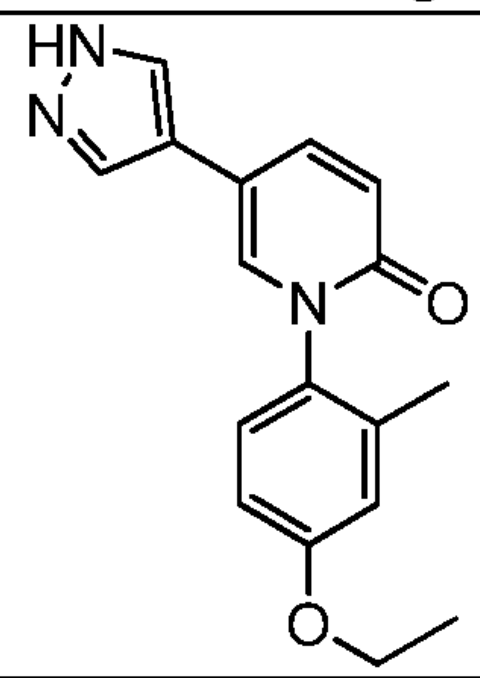
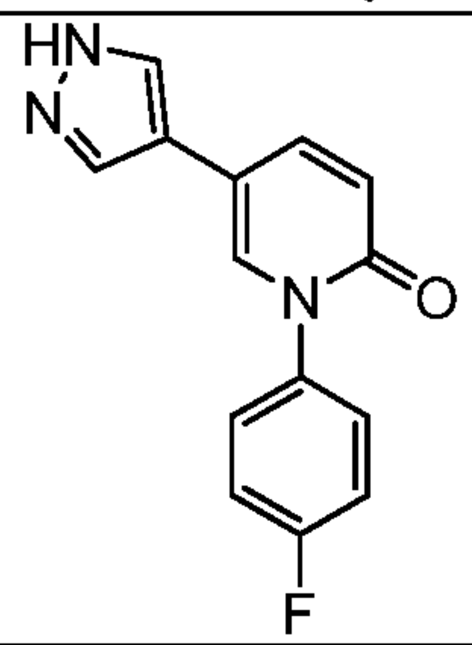
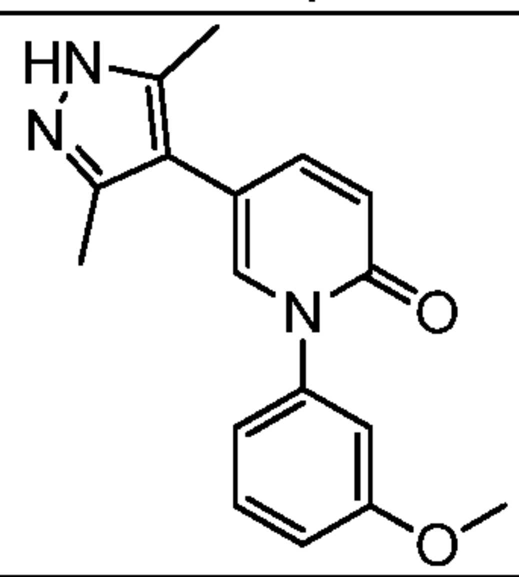
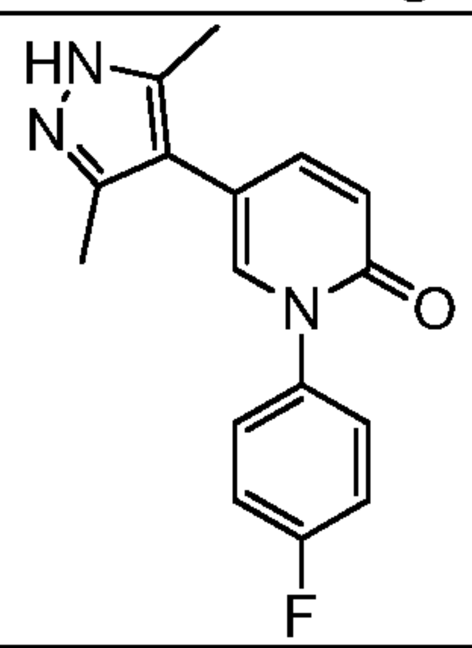
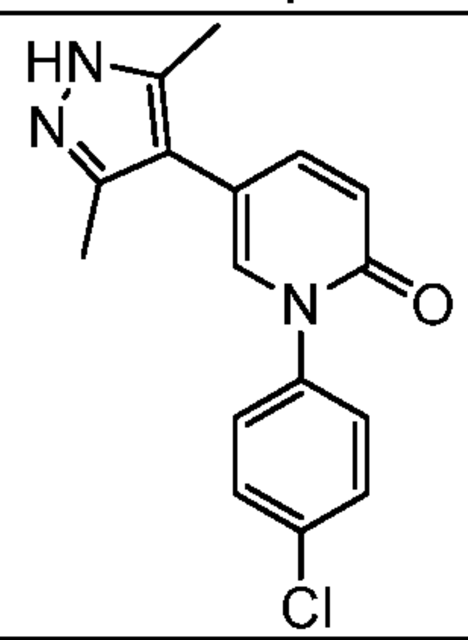
375	
376	
377	
378	
379	
380	

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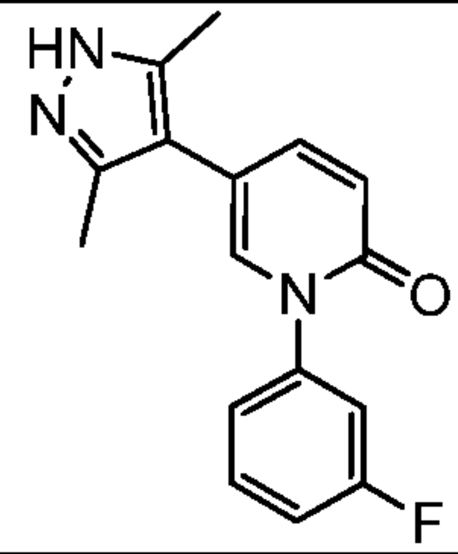
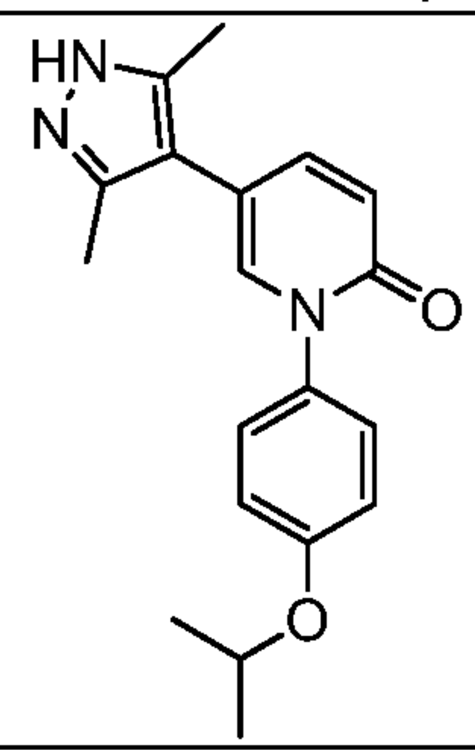
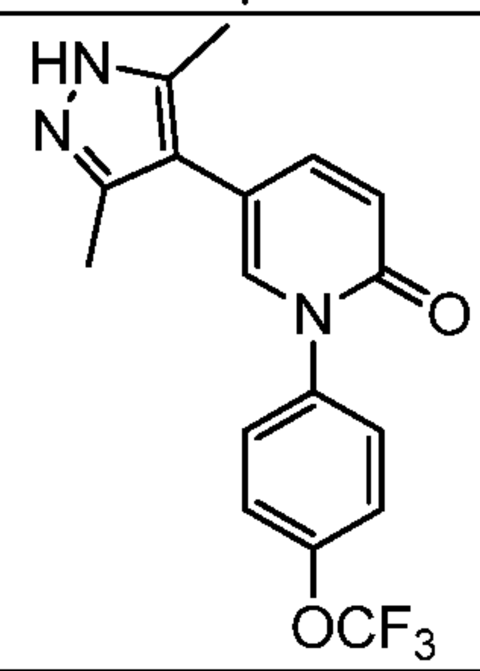
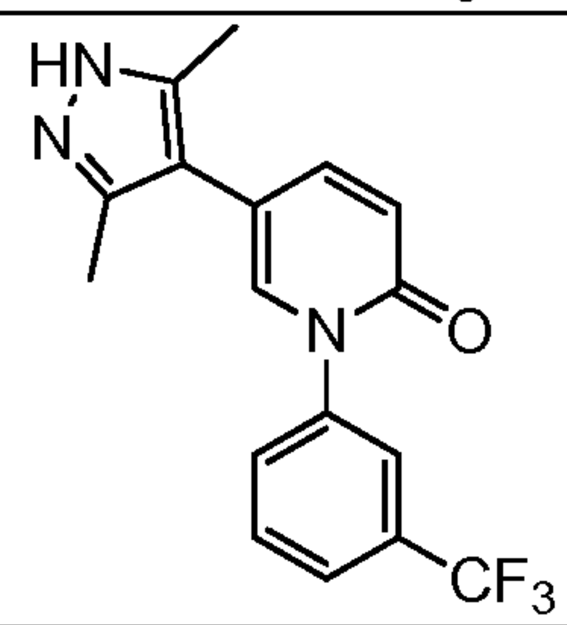
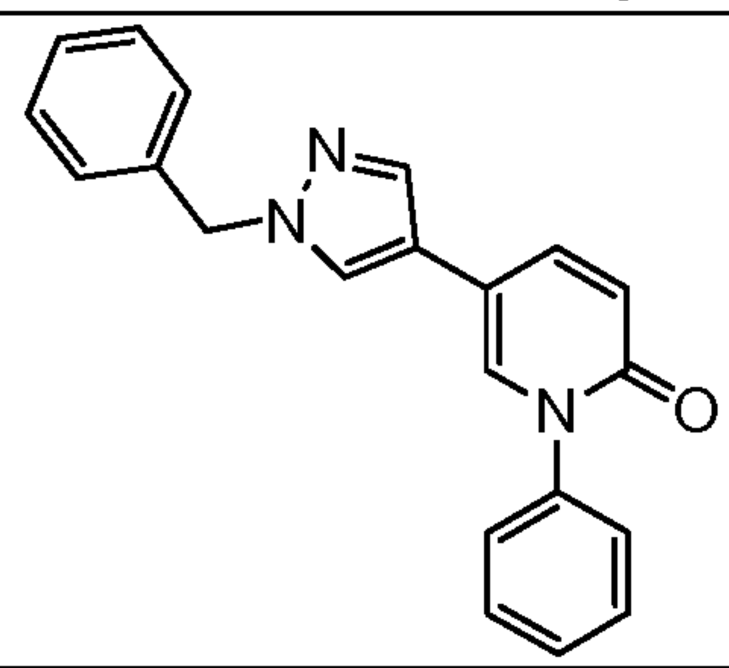
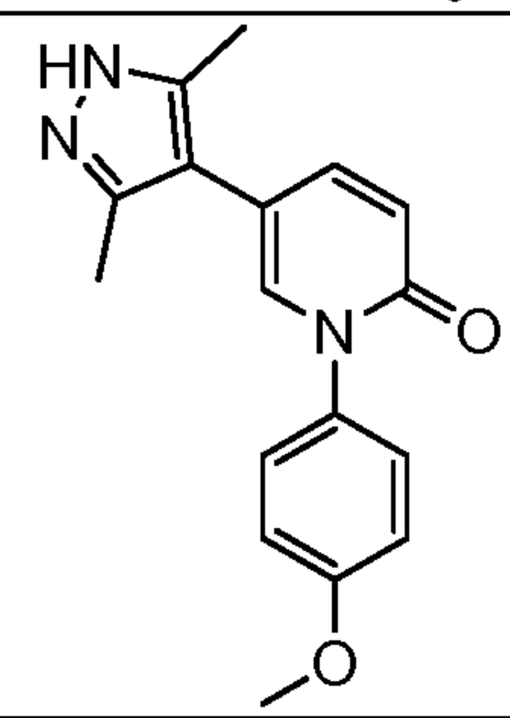
381	
382	
383	
384	
385	
386	

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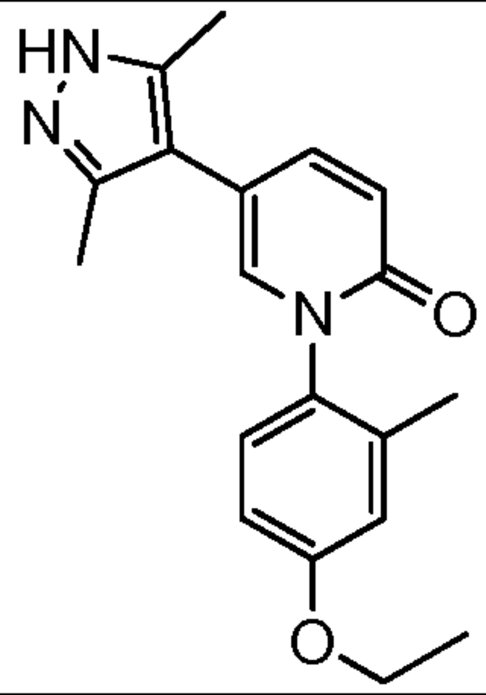
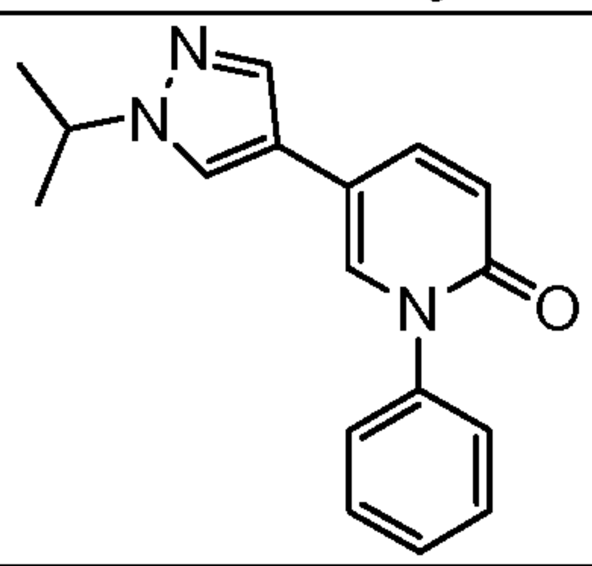
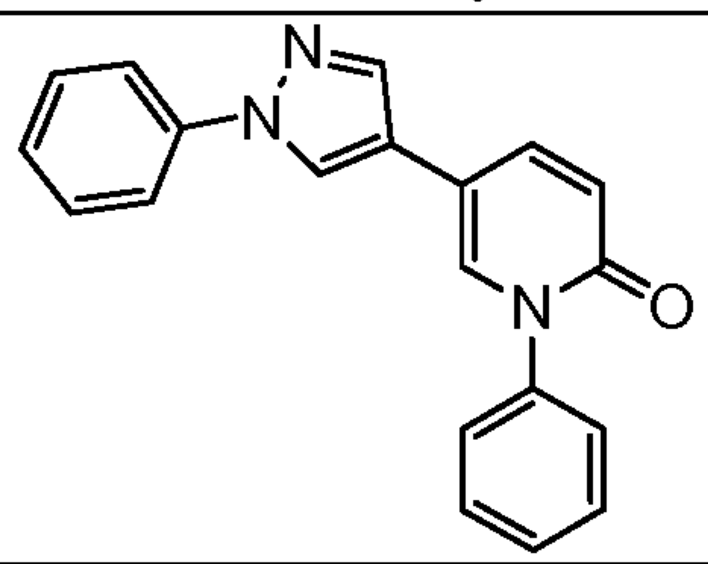
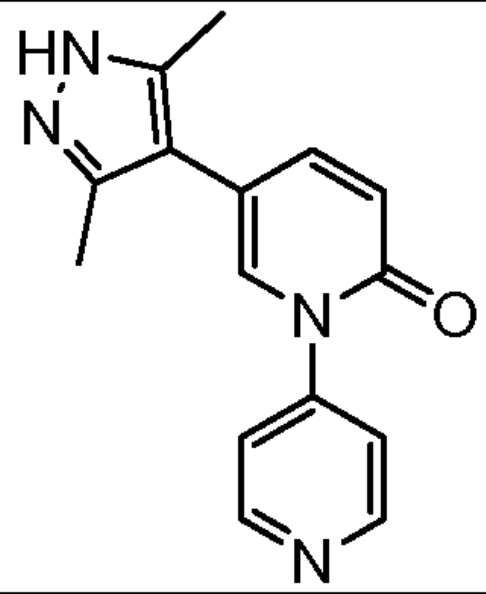
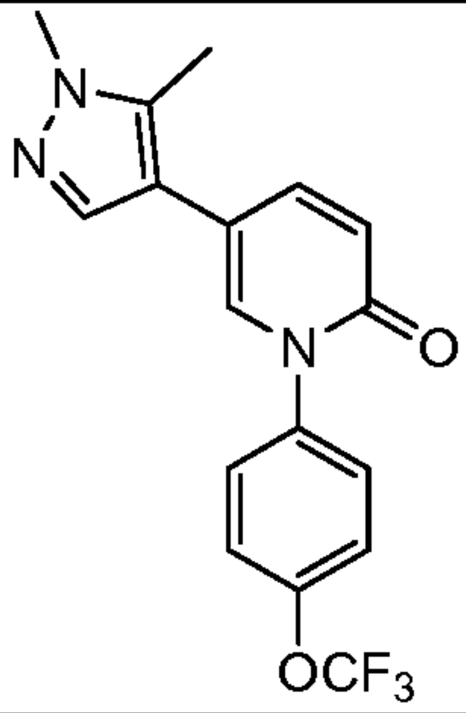
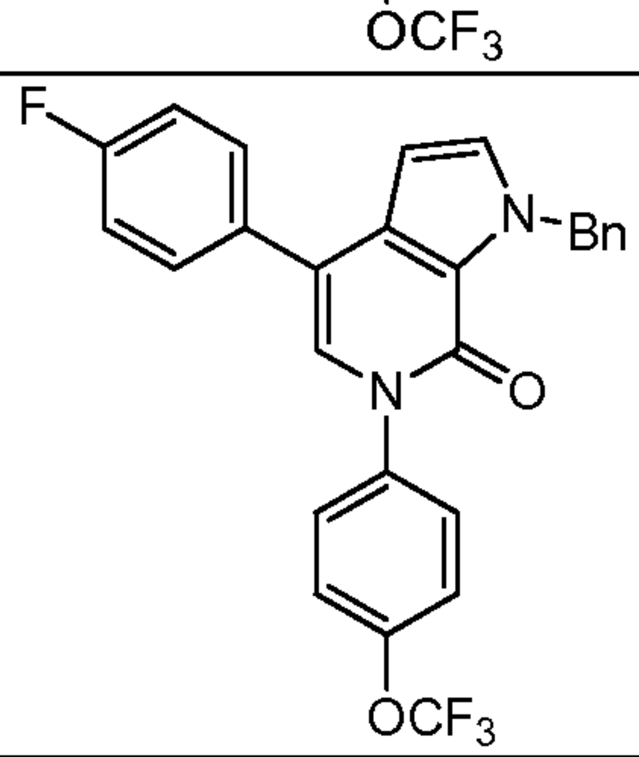
387	
388	
389	
390	
391	
392	

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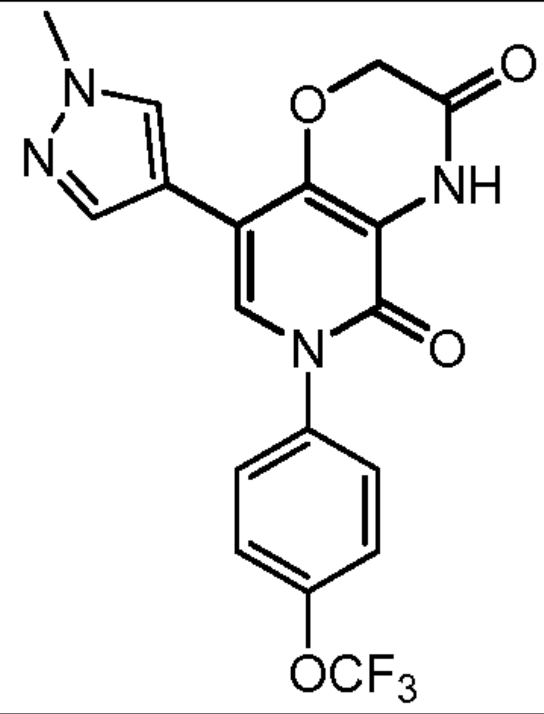
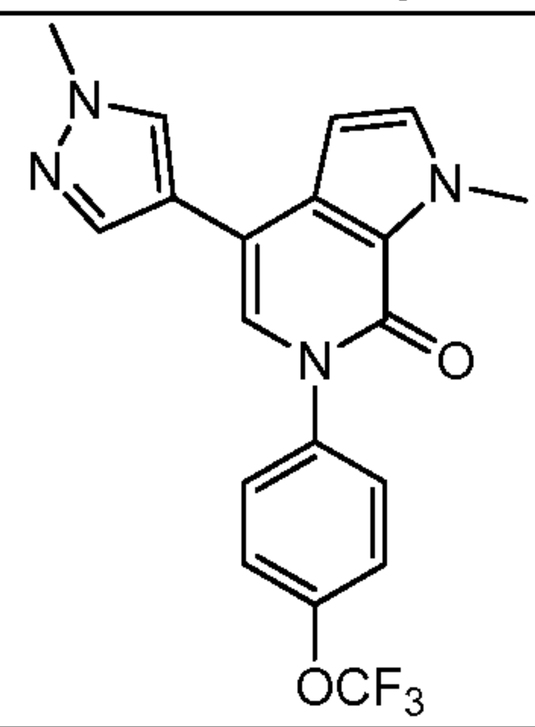
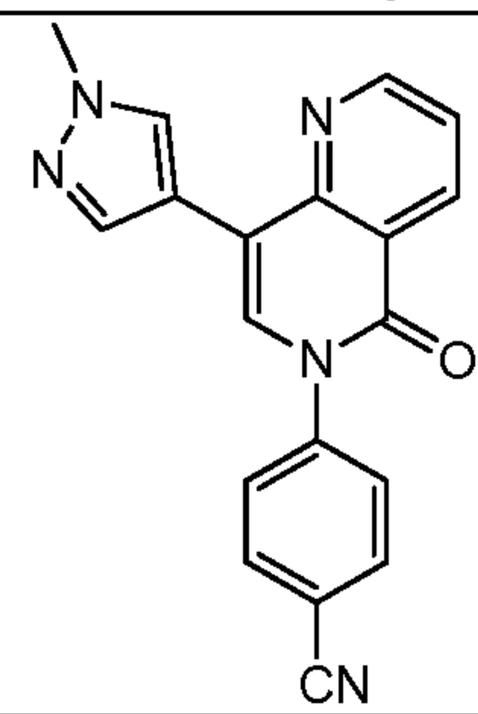
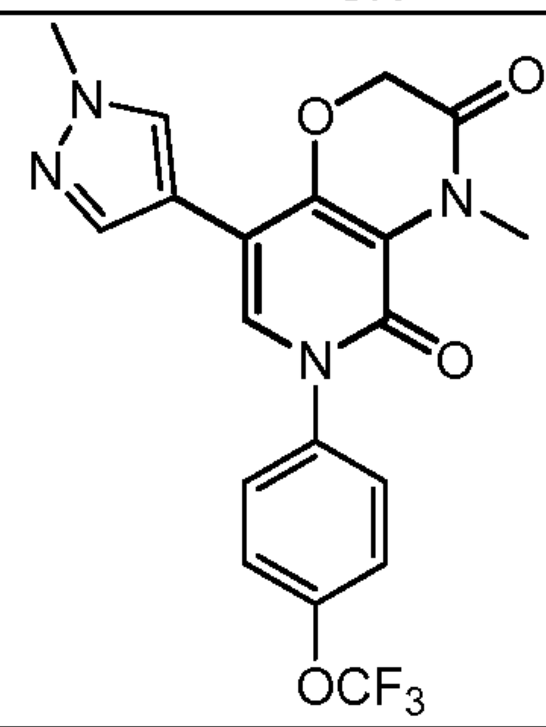
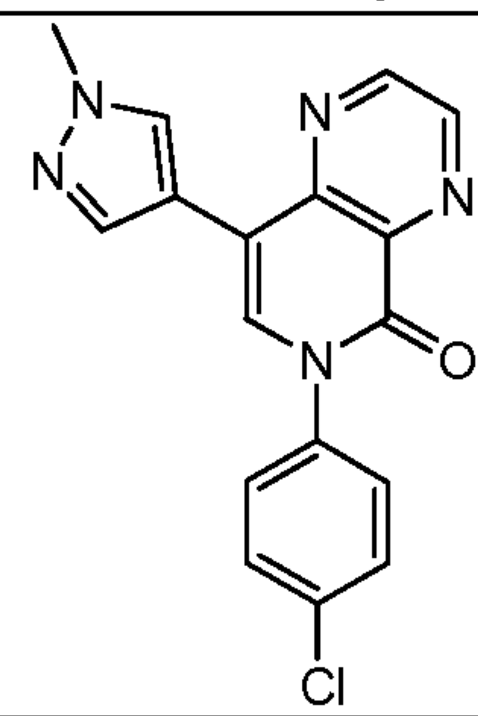
393	
394	
395	
396	
397	

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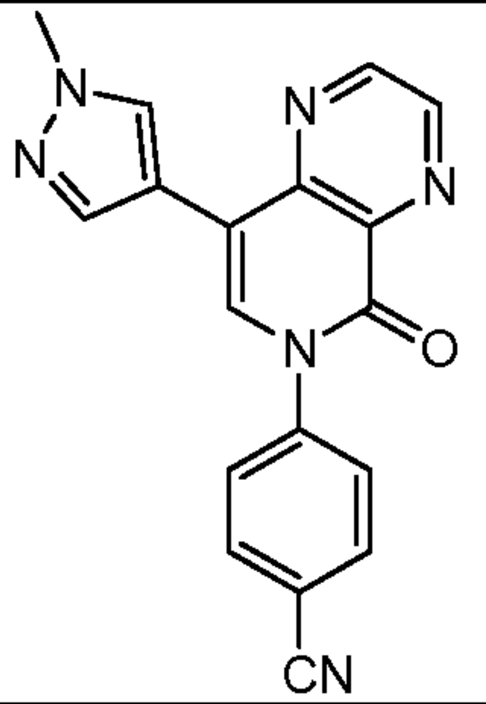
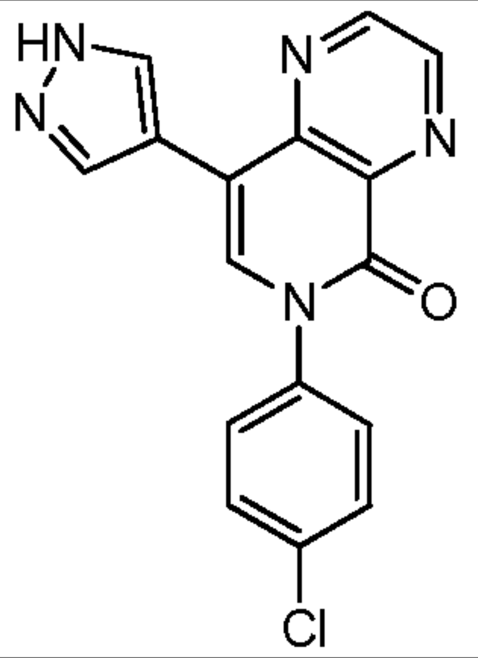
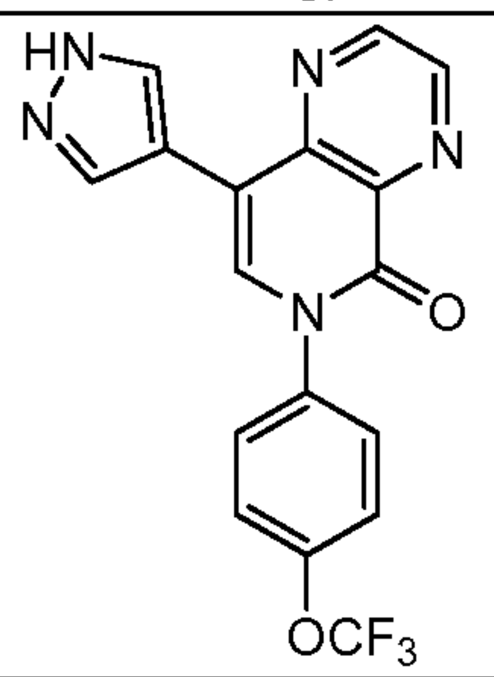
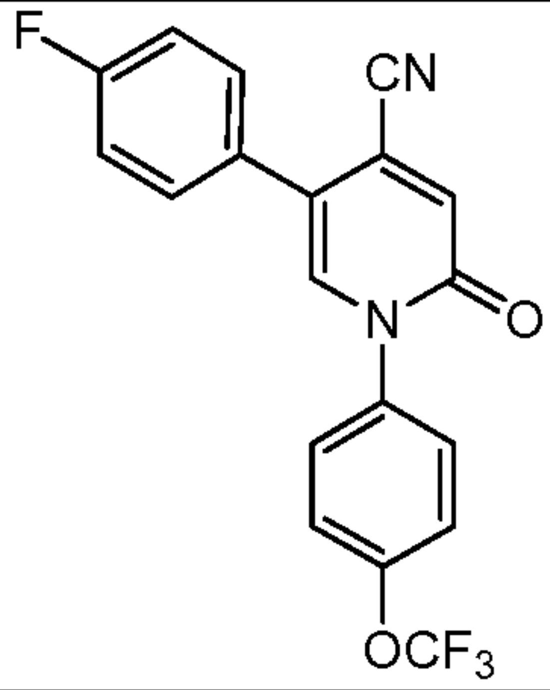
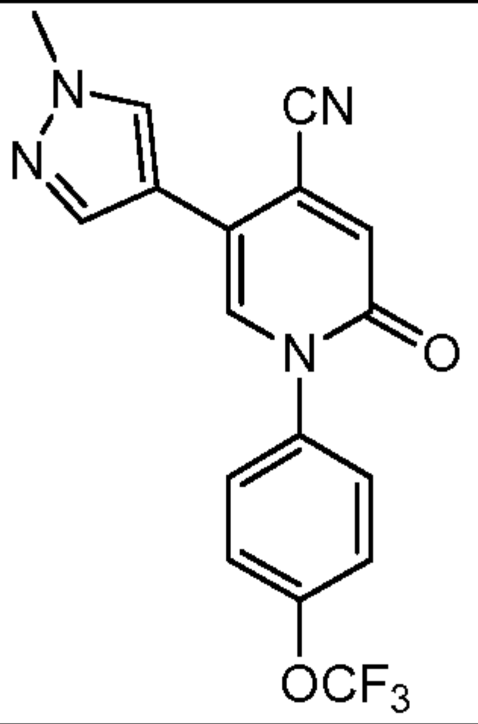
398	
399	
400	
401	
402	

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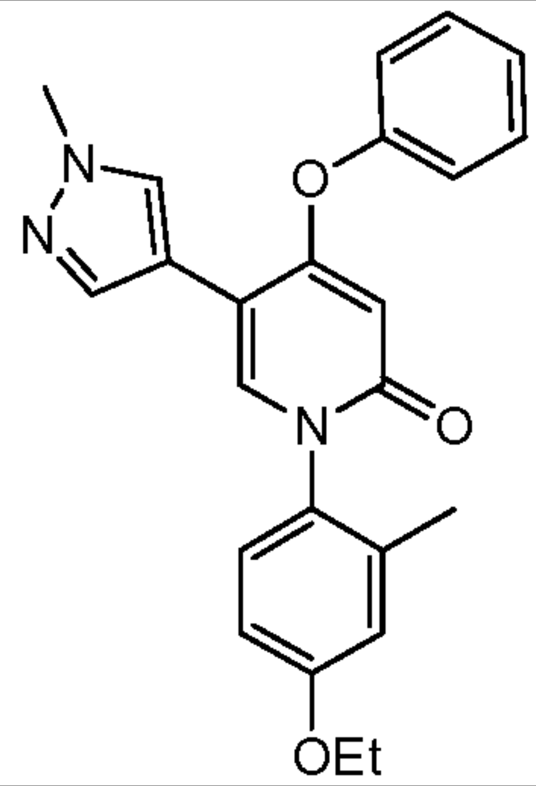
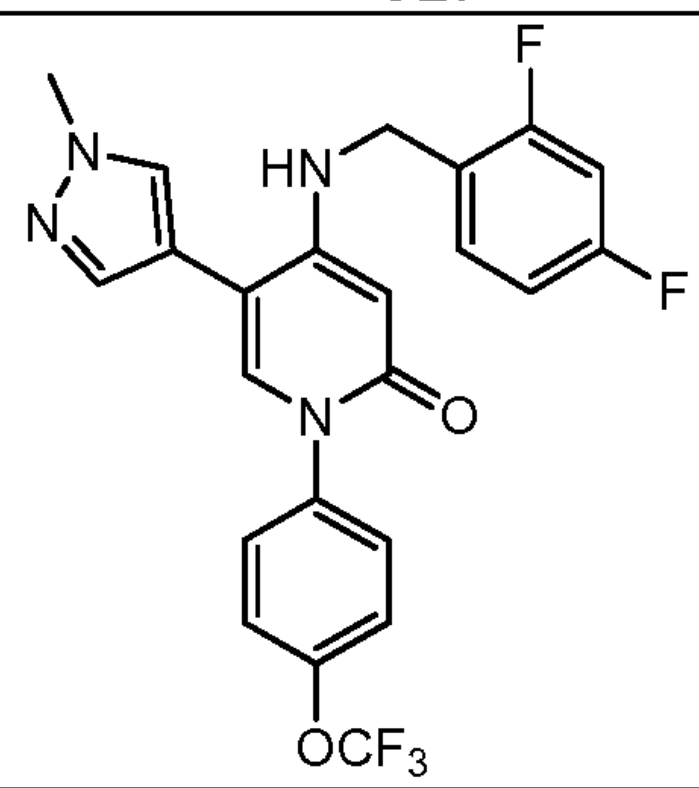
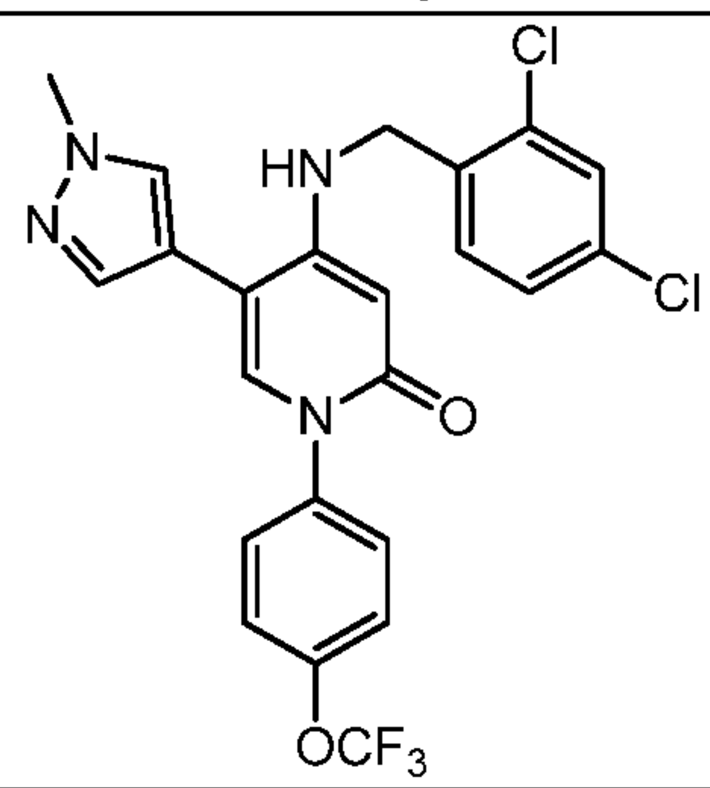
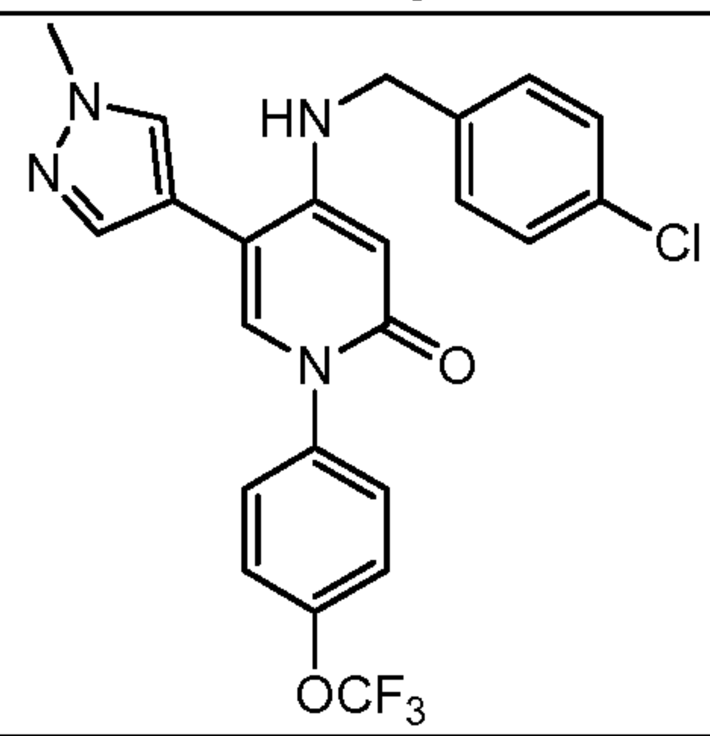
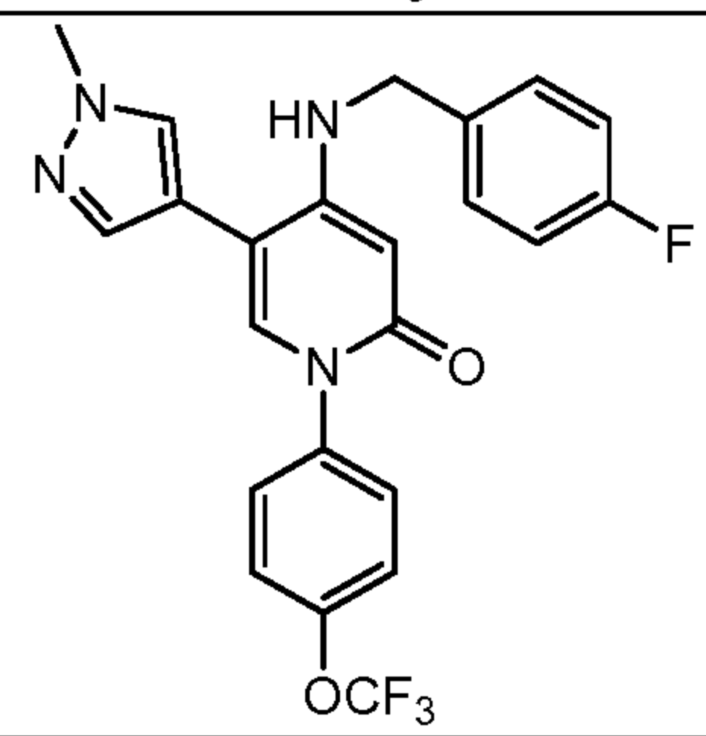
403	
404	
405	
406	
407	

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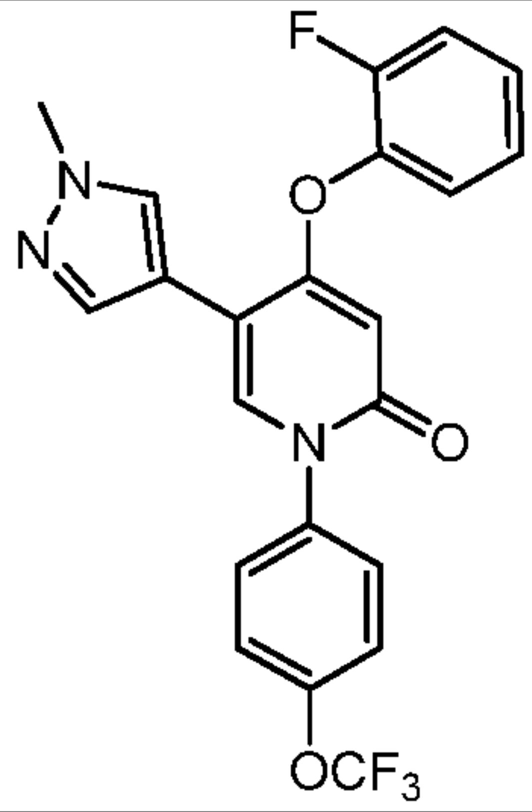
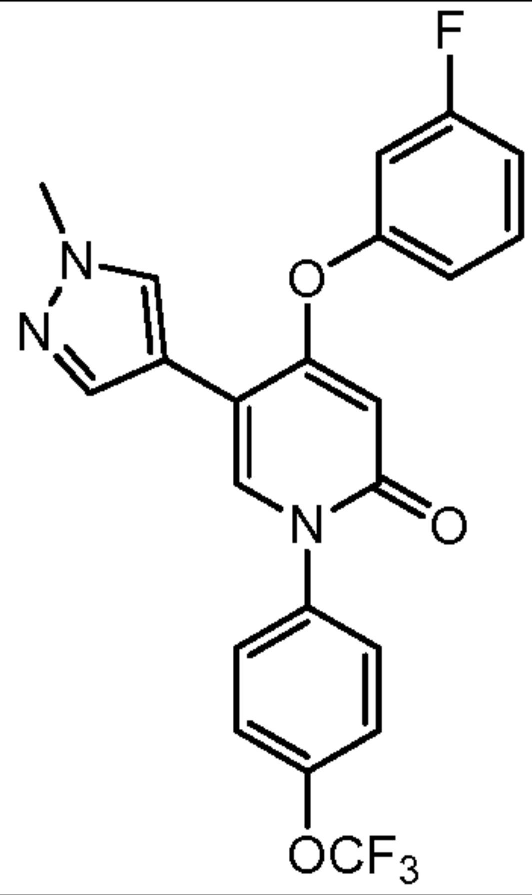
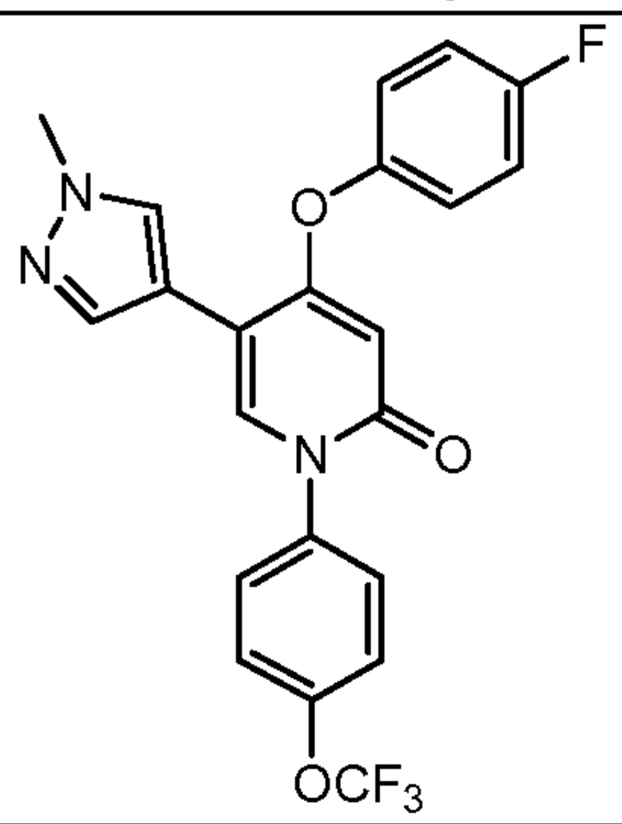
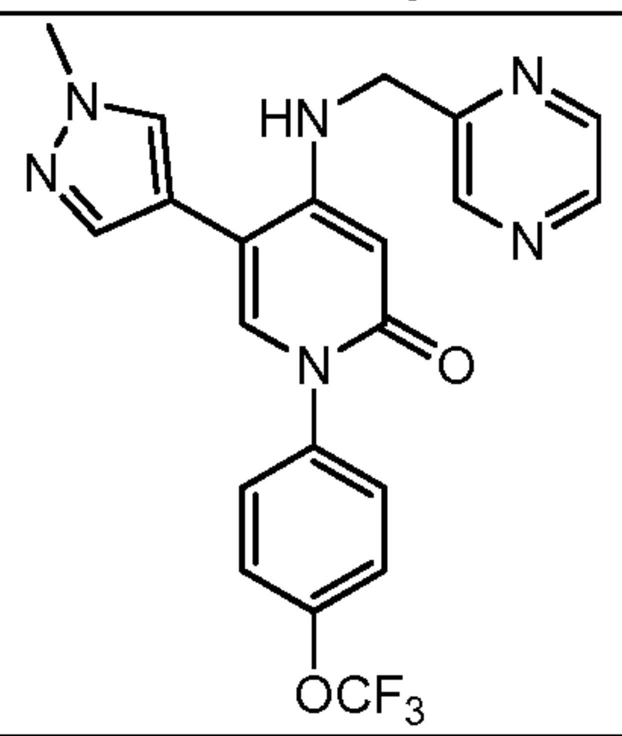
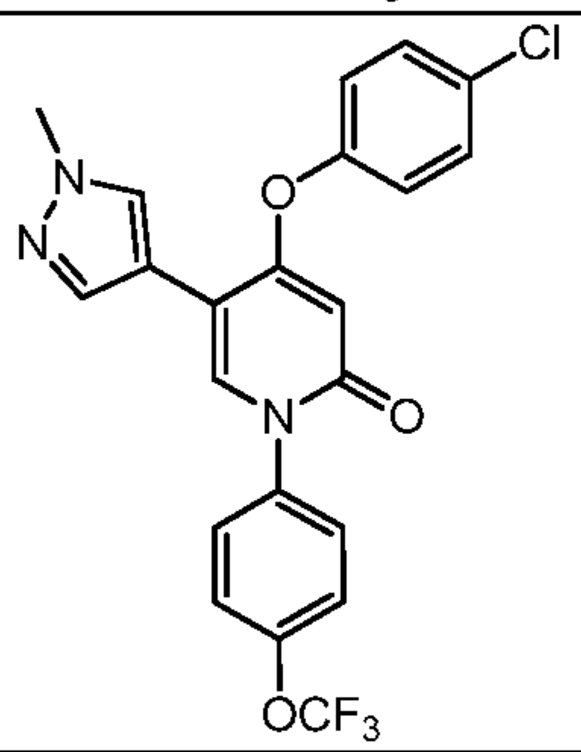
408	
409	
410	
411	
412	

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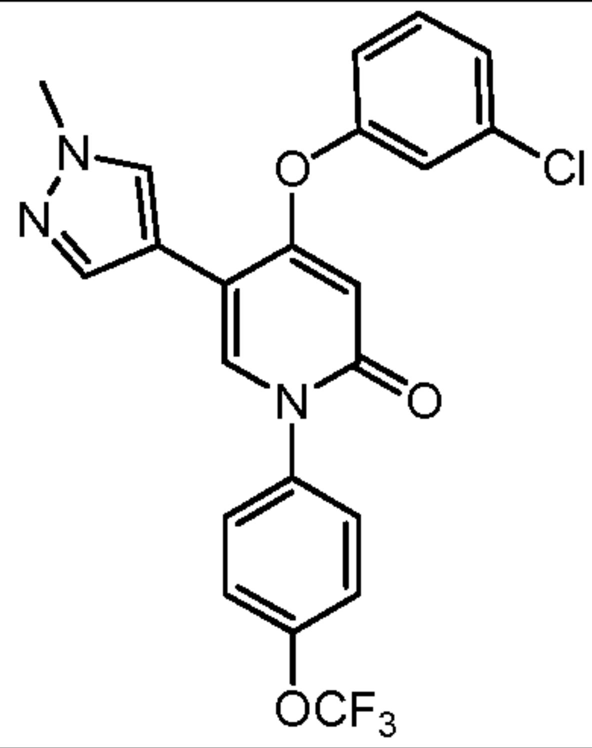
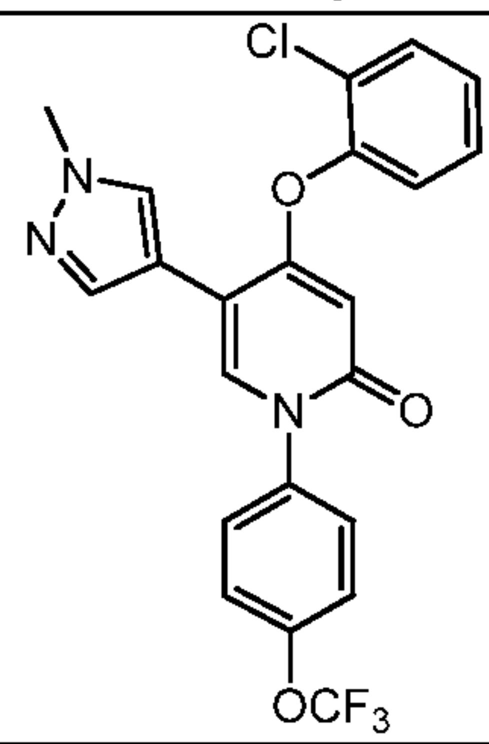
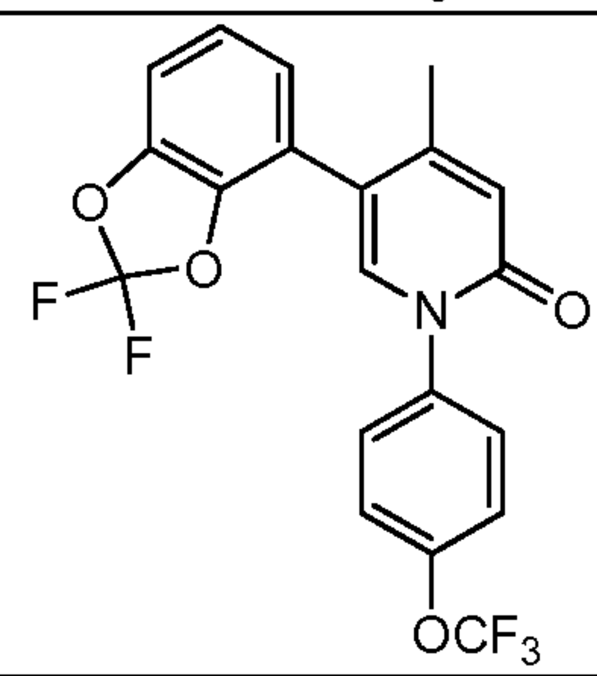
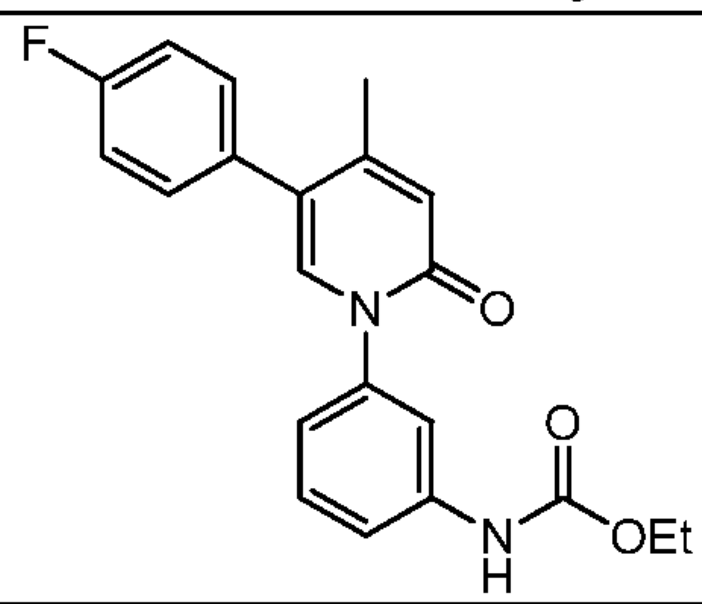
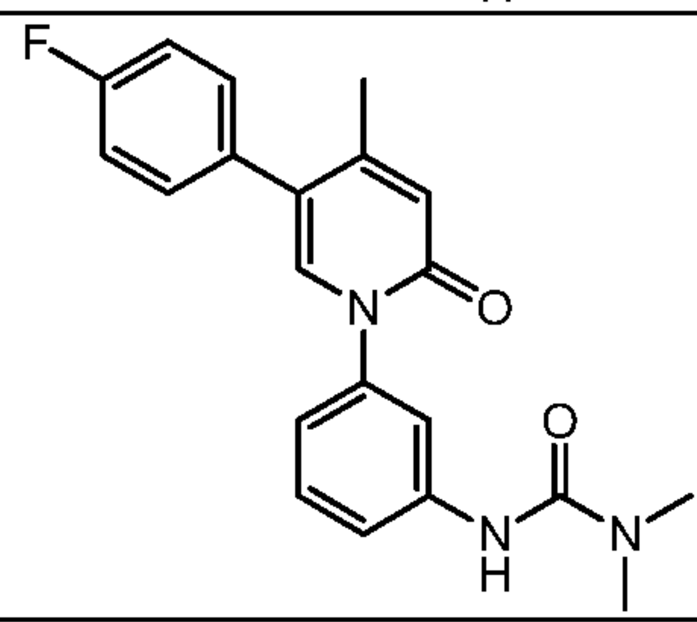
413	
414	
415	
416	
417	

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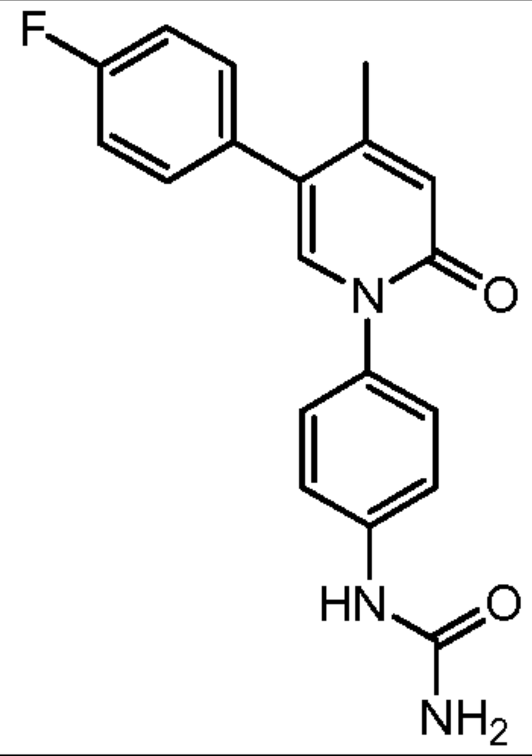
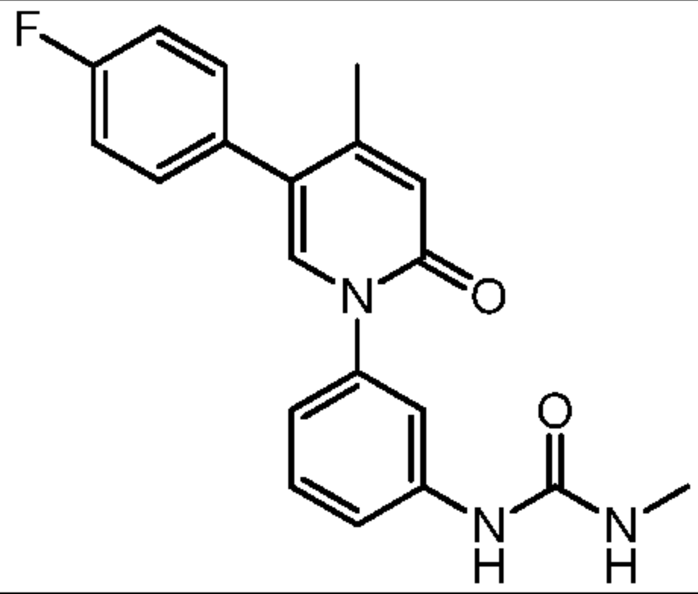
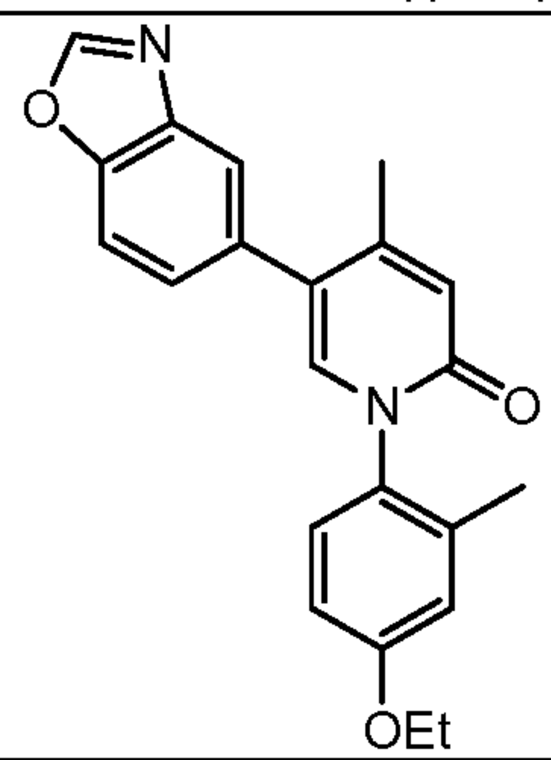
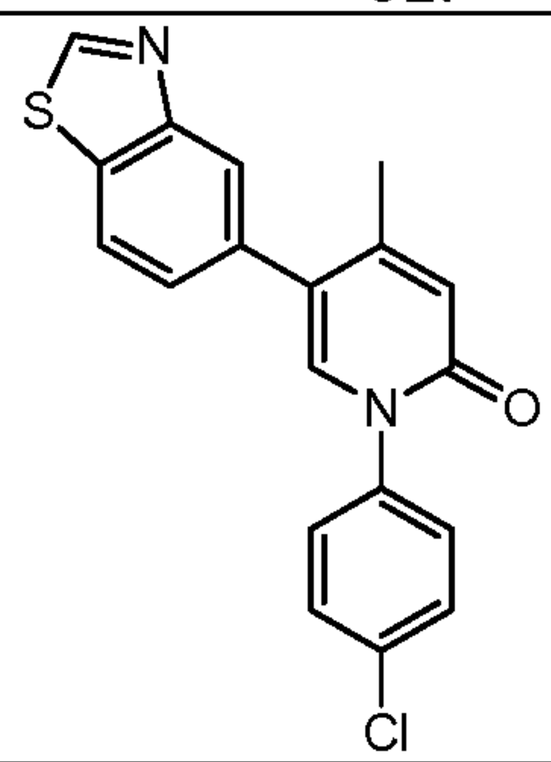
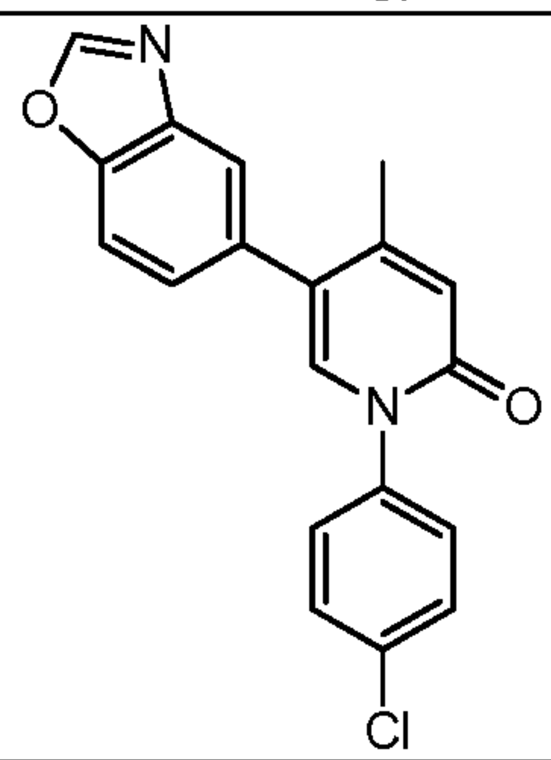
418	
419	
420	
421	
422	

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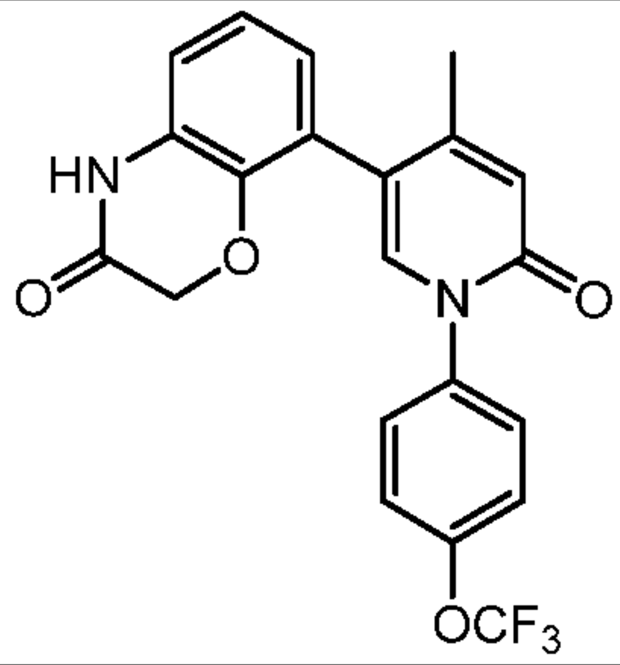
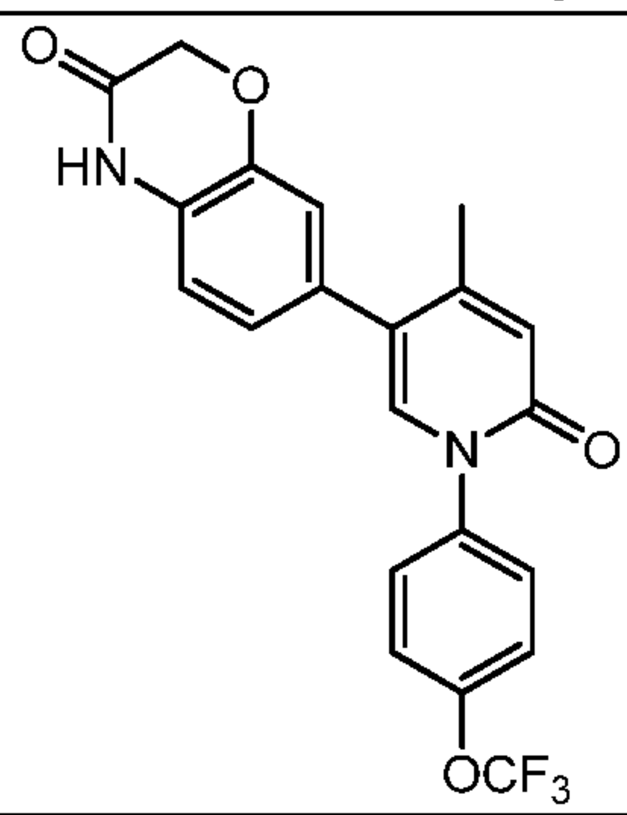
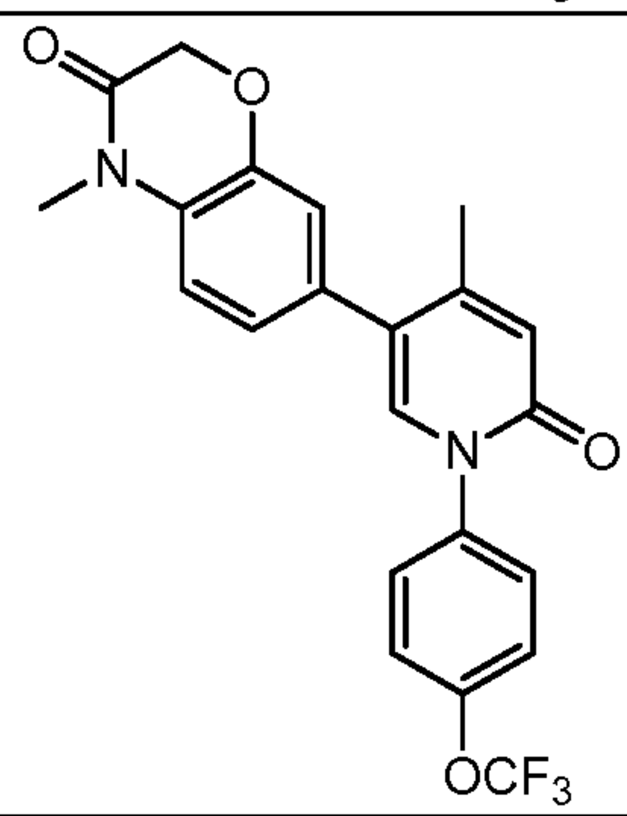
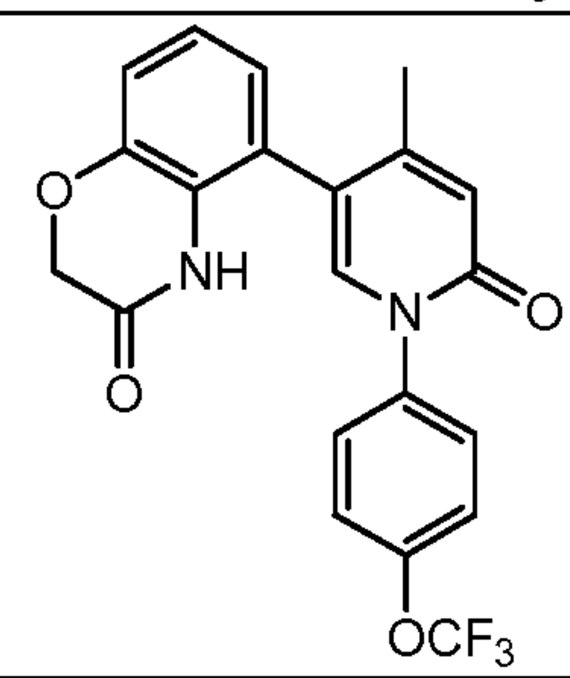
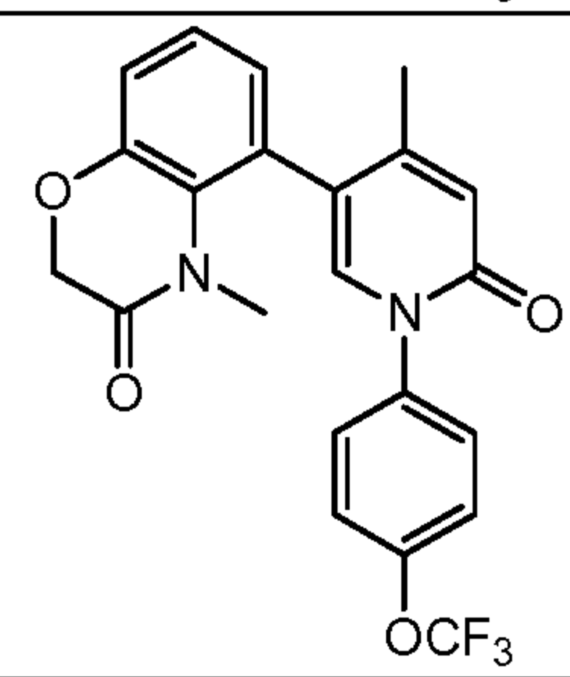
423	
424	
425	
426	
427	

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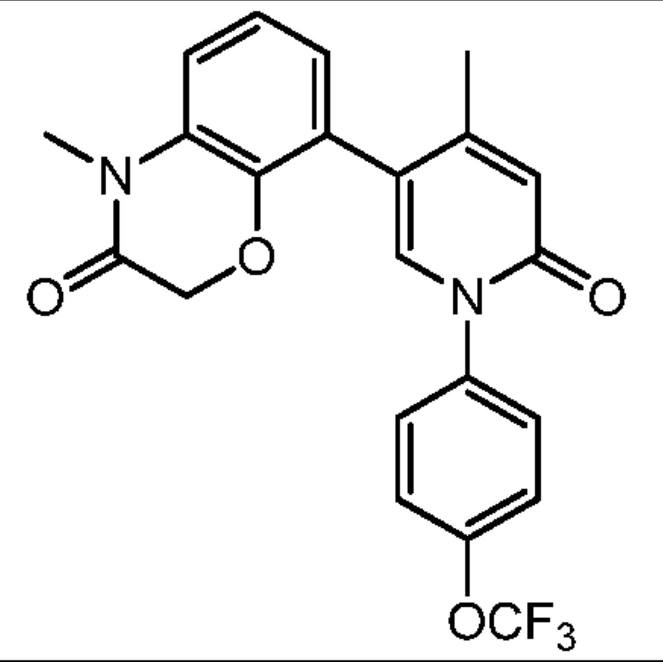
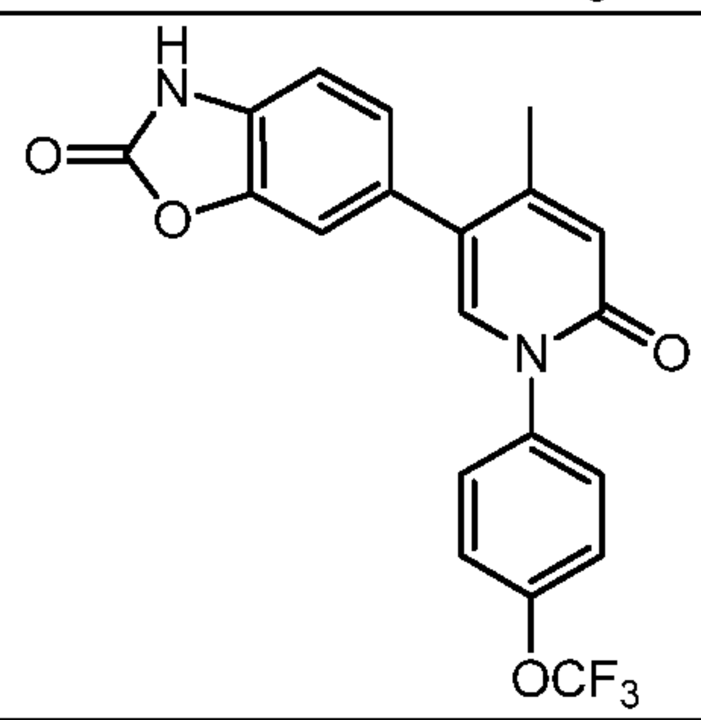
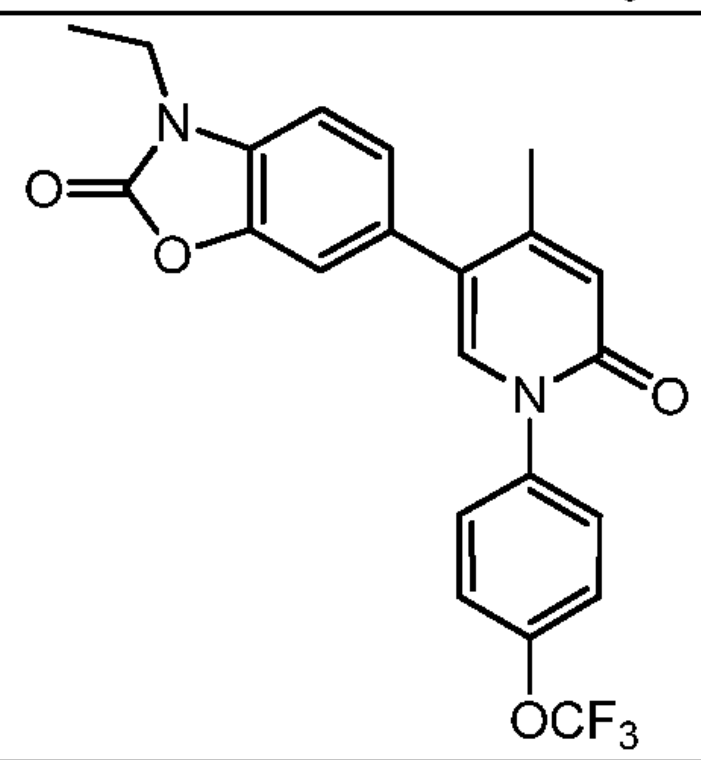
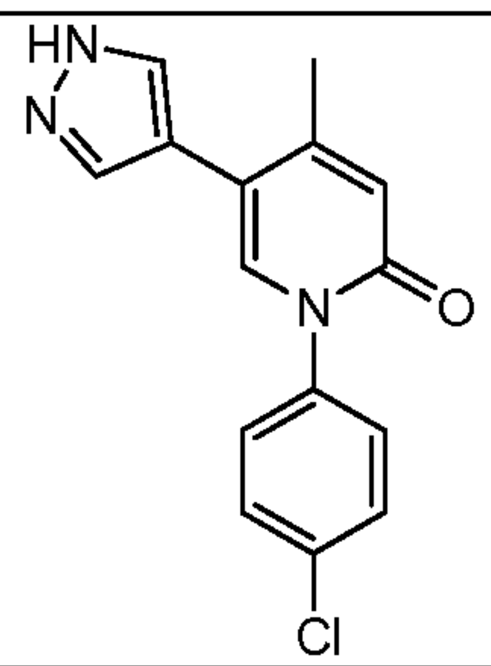
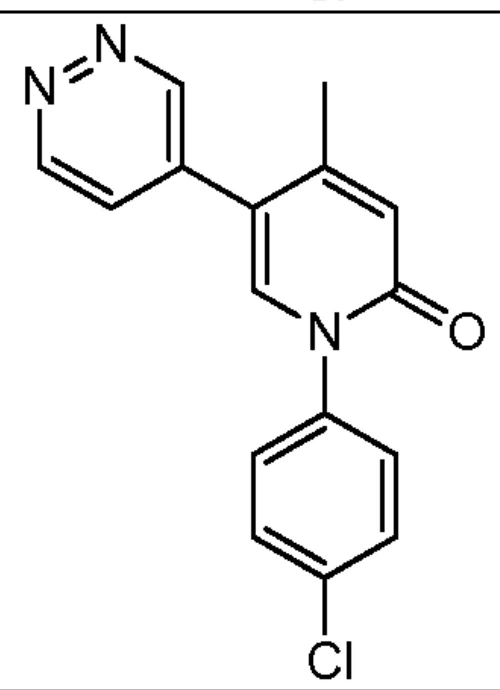
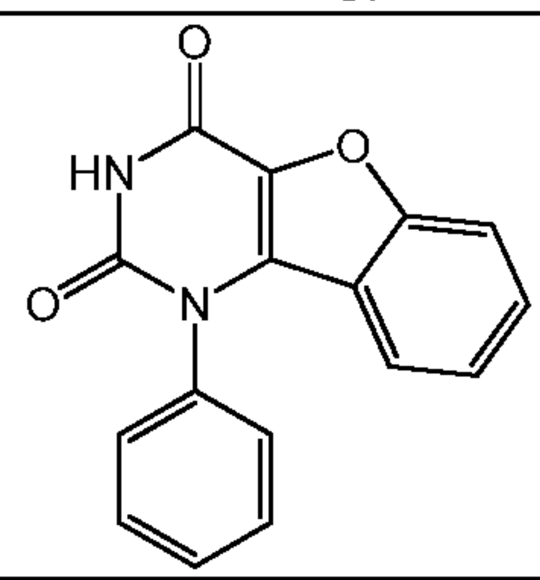
428	
429	
430	
431	
432	
433	

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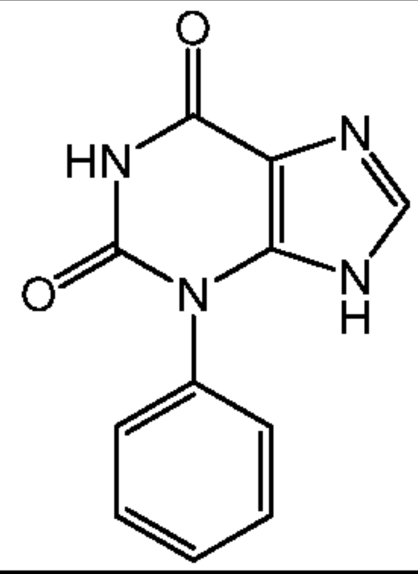
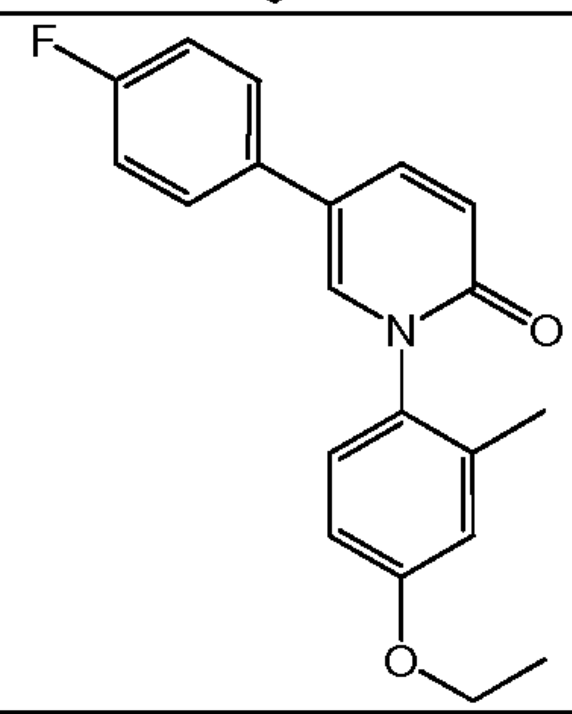
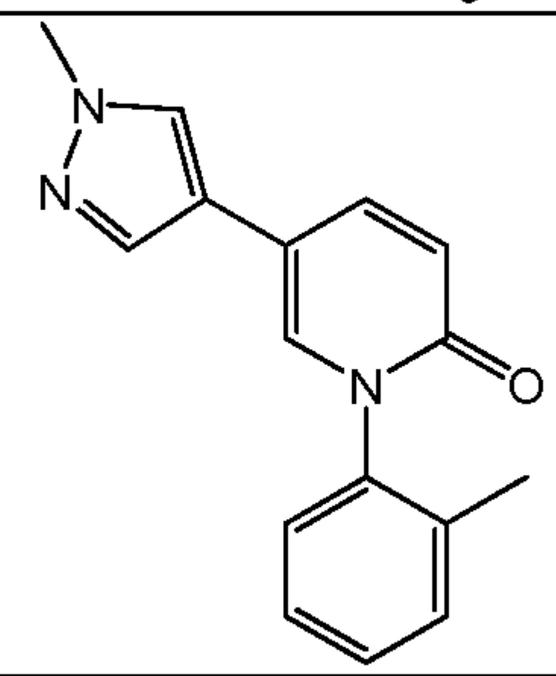
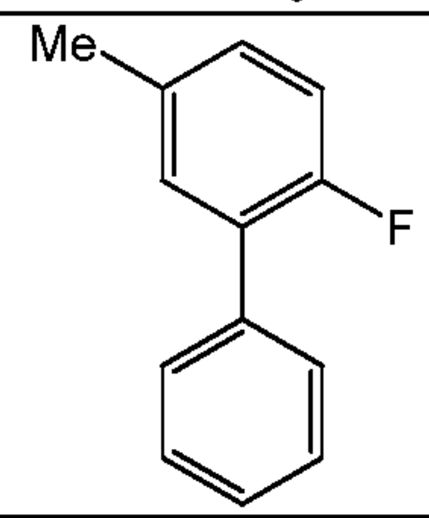
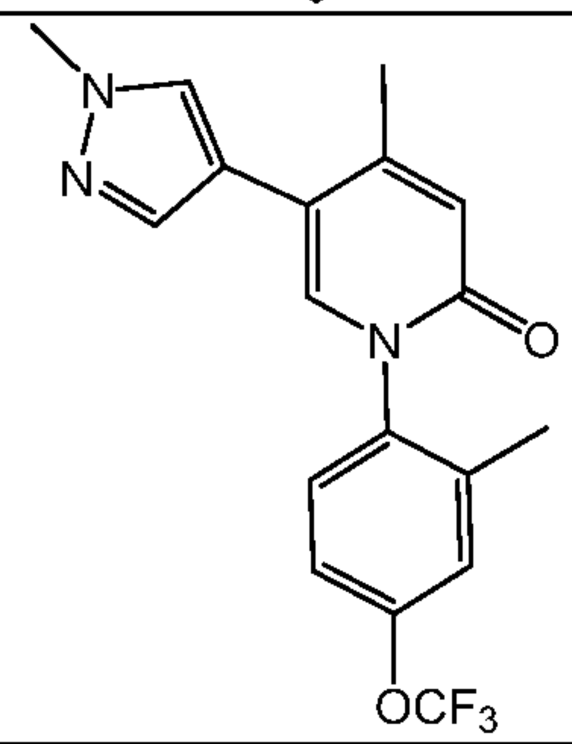
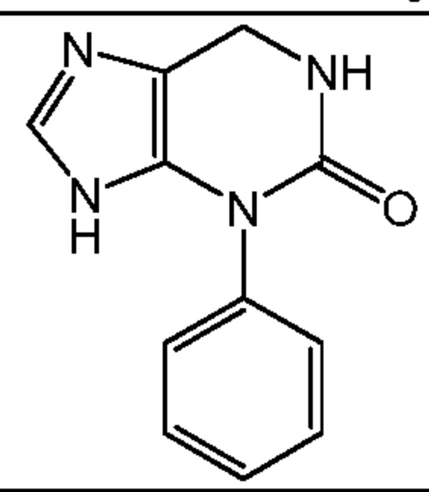
434	
438	
439	
440	
442	
446	

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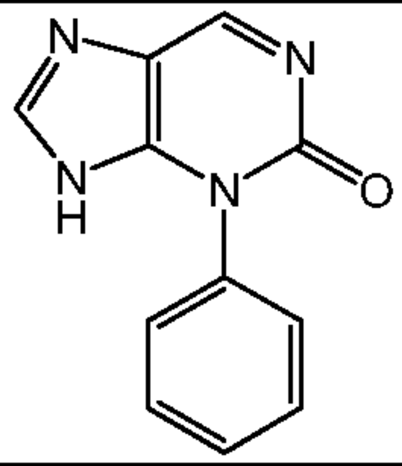
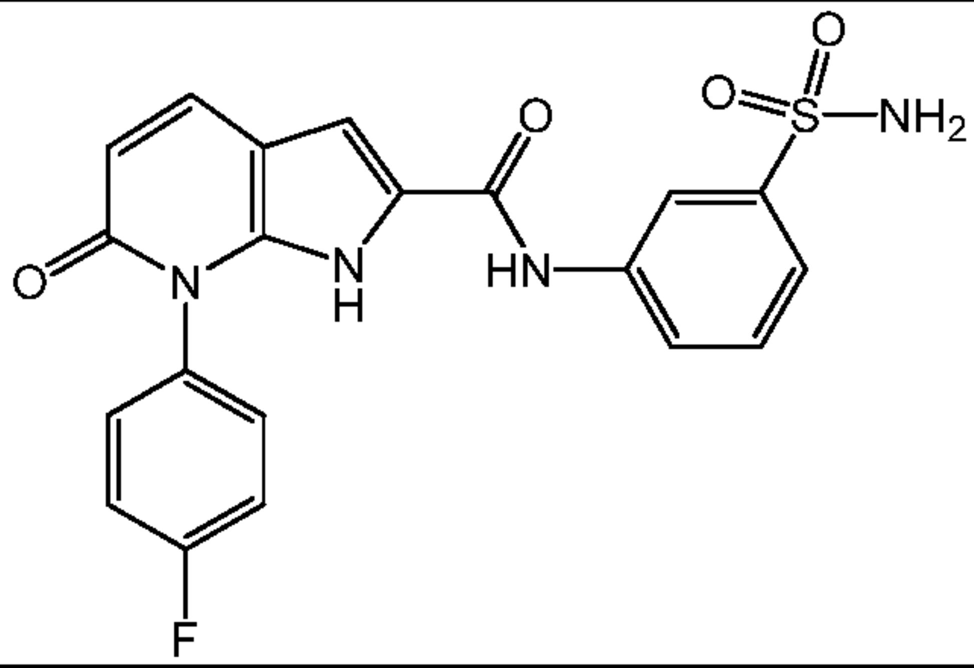
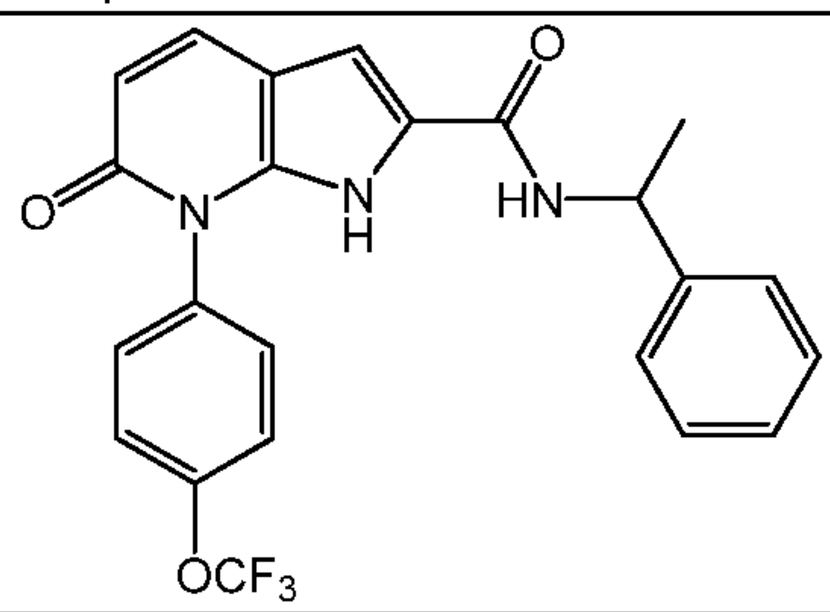
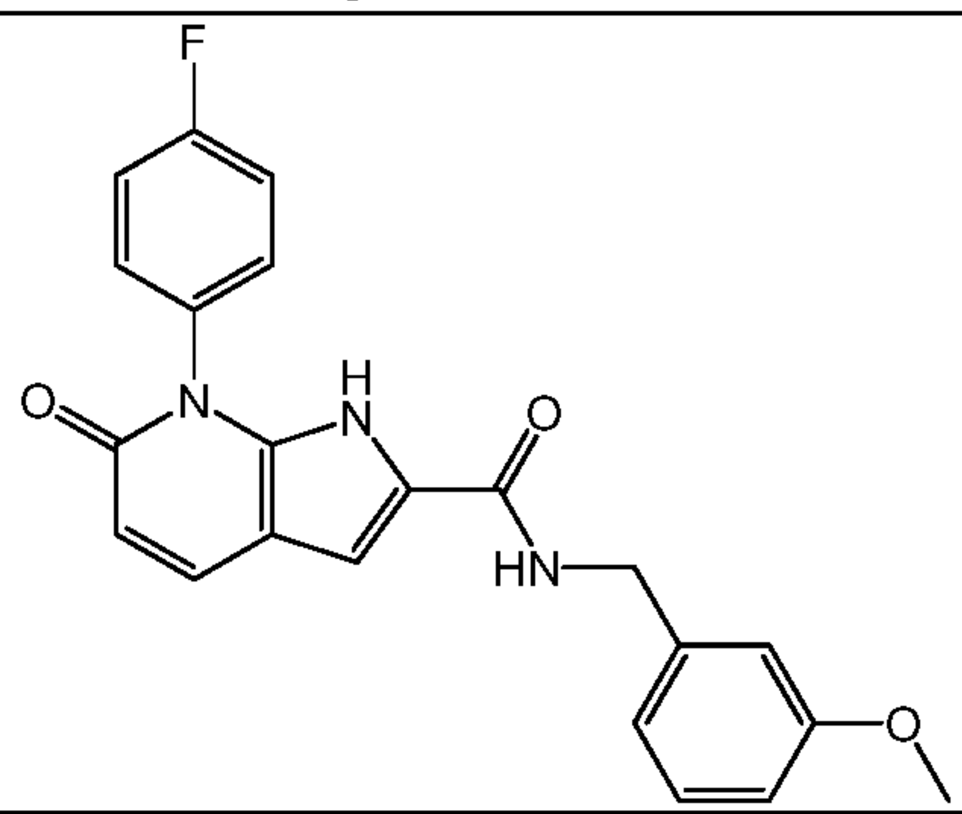
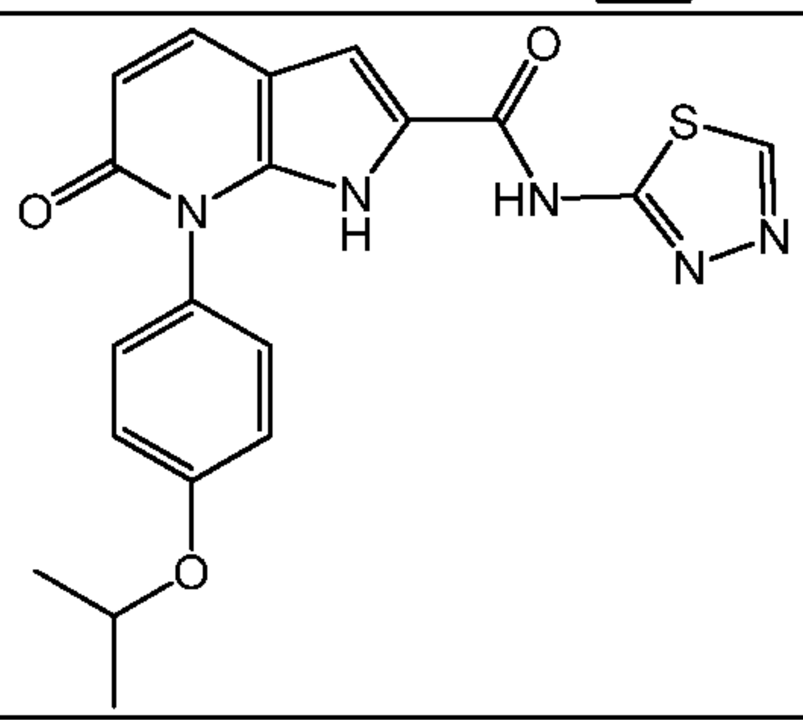
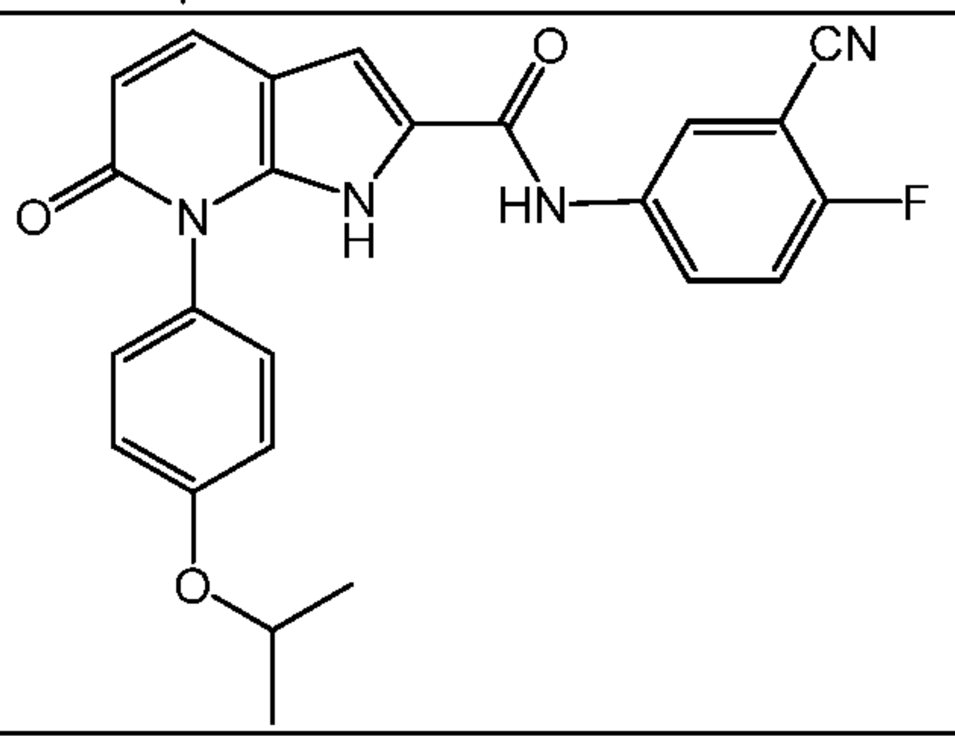
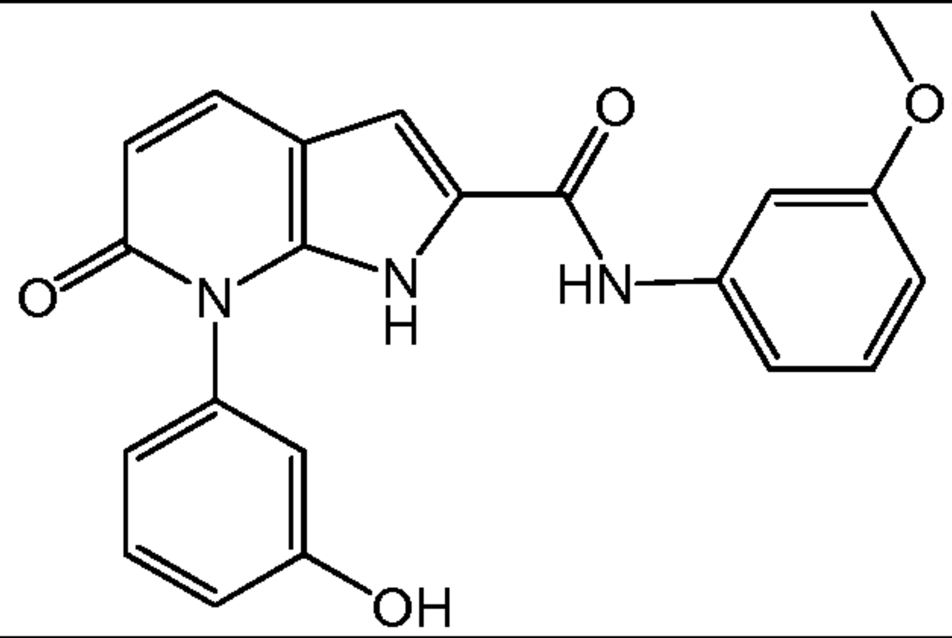
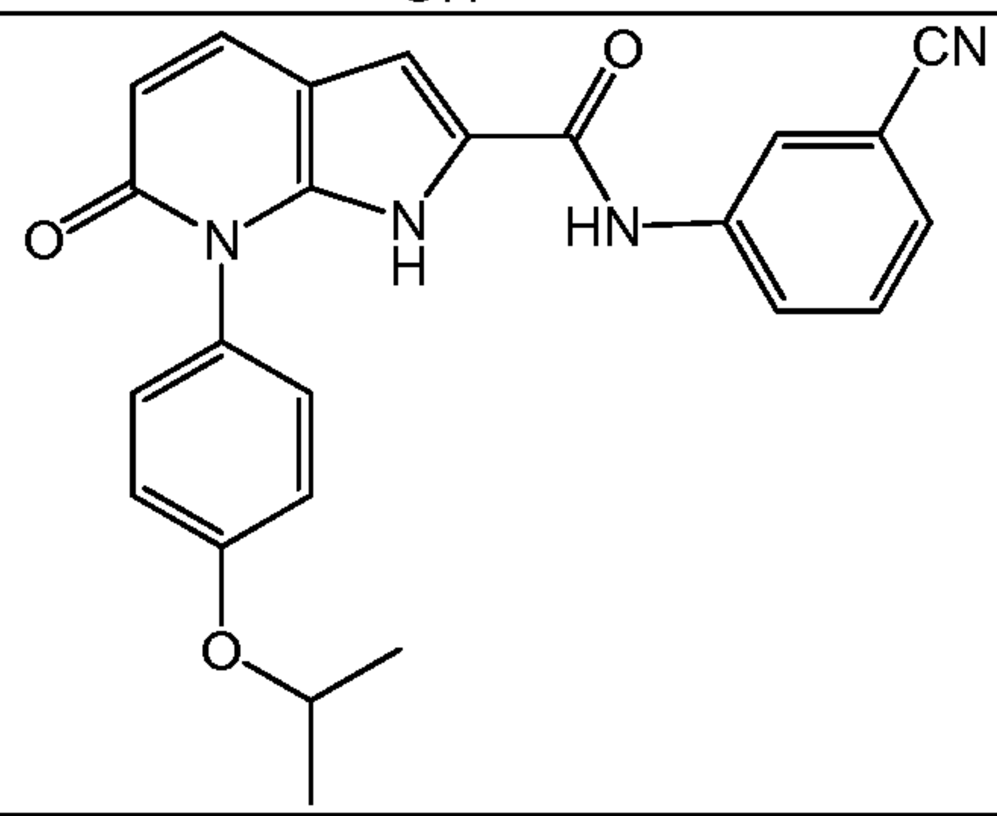
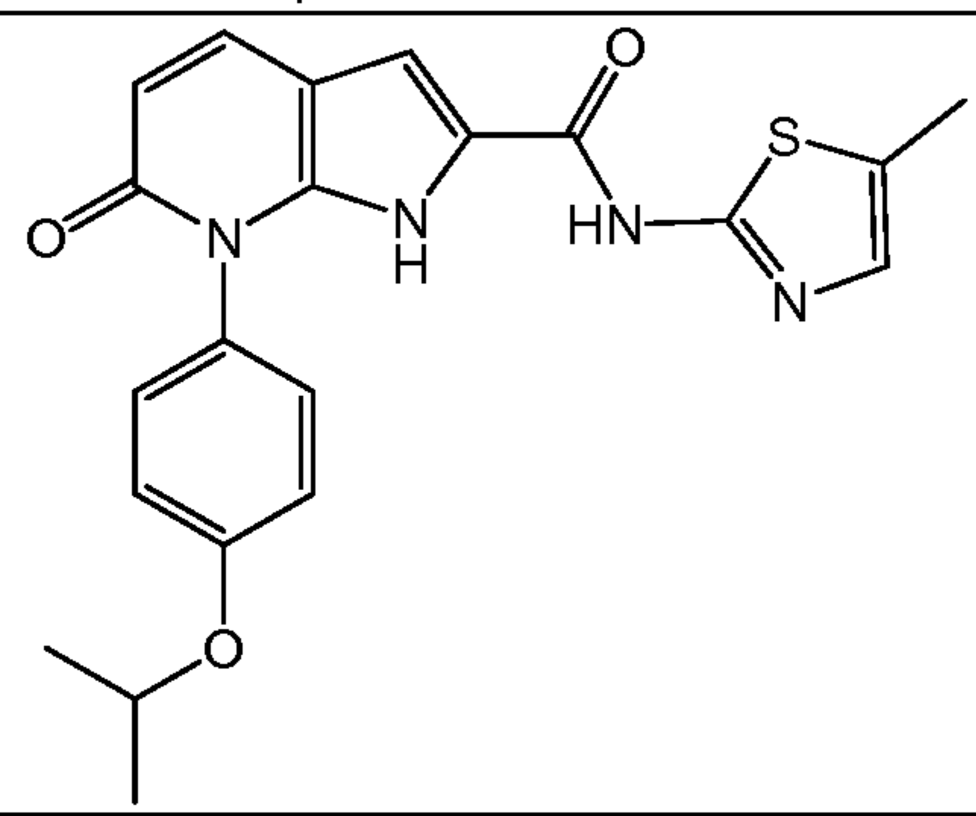
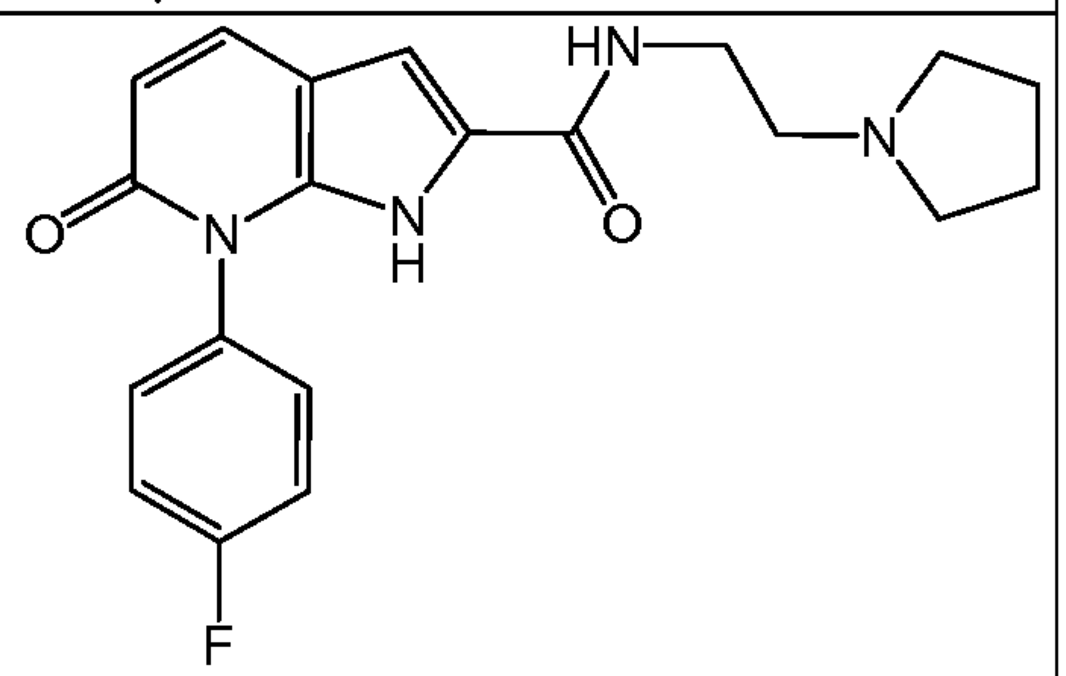
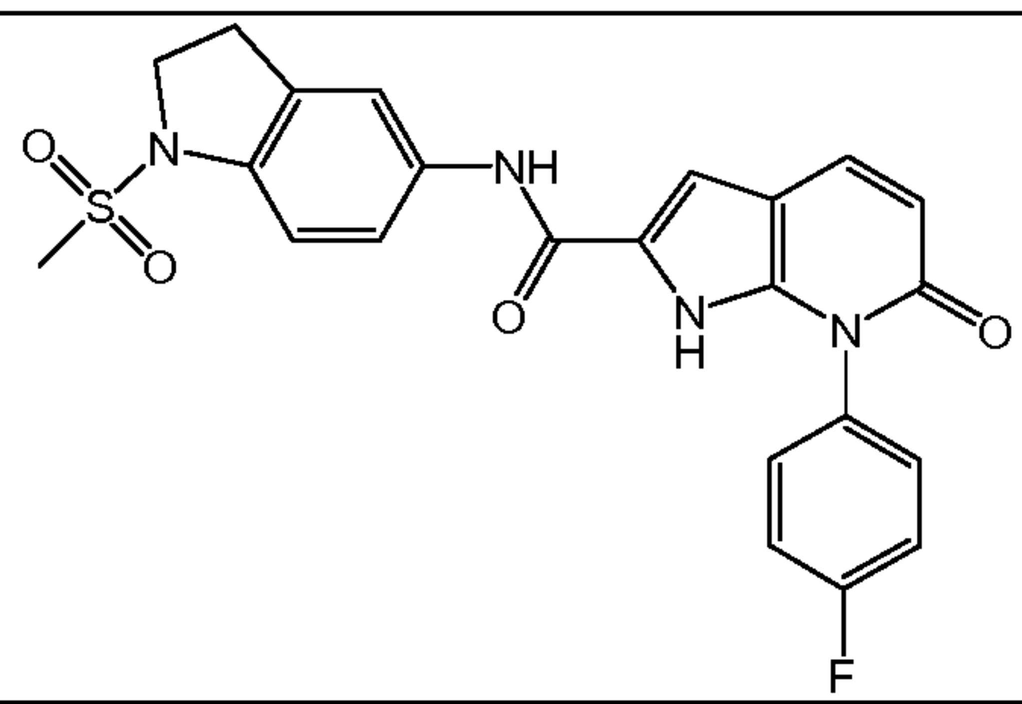
447	
448	
449	
450	
451	
452	
453	
454	
455	
456	
457	

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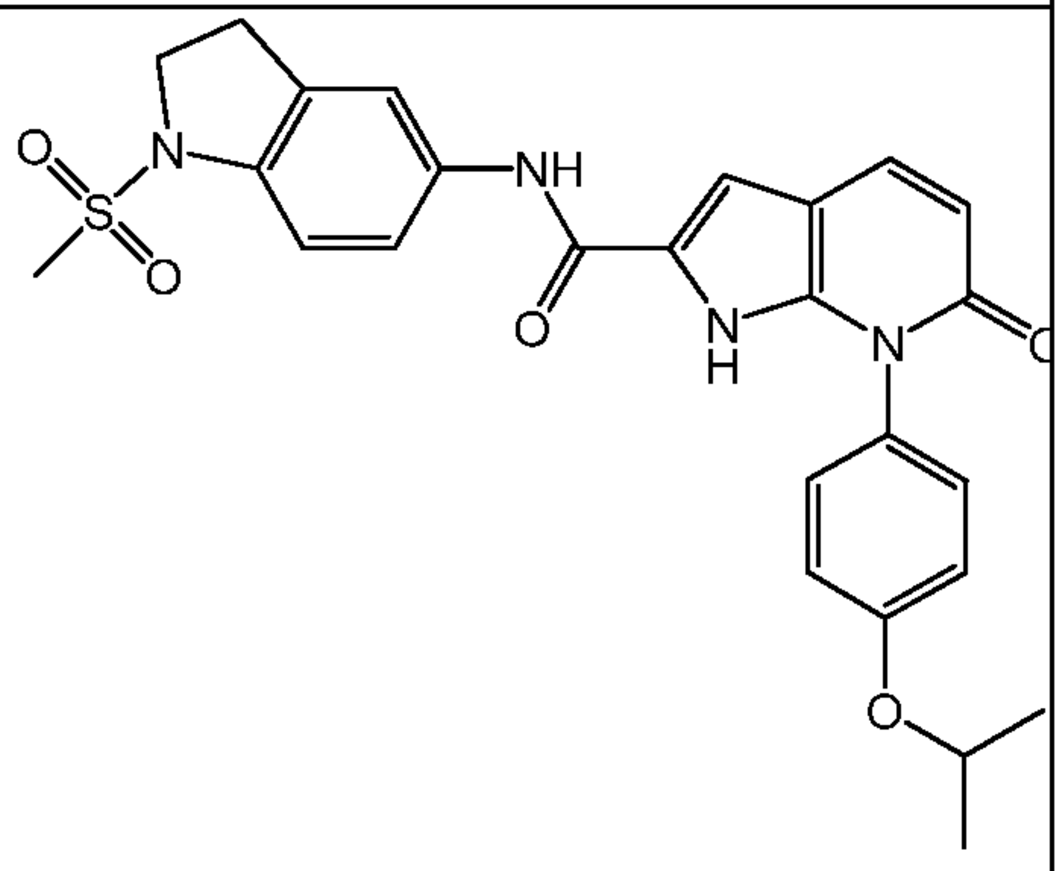
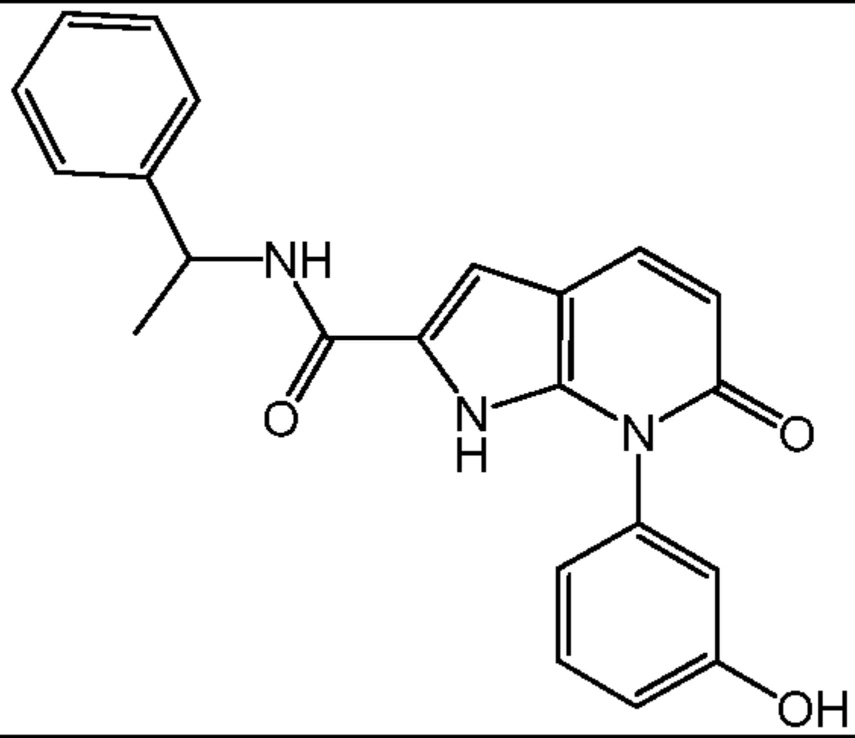
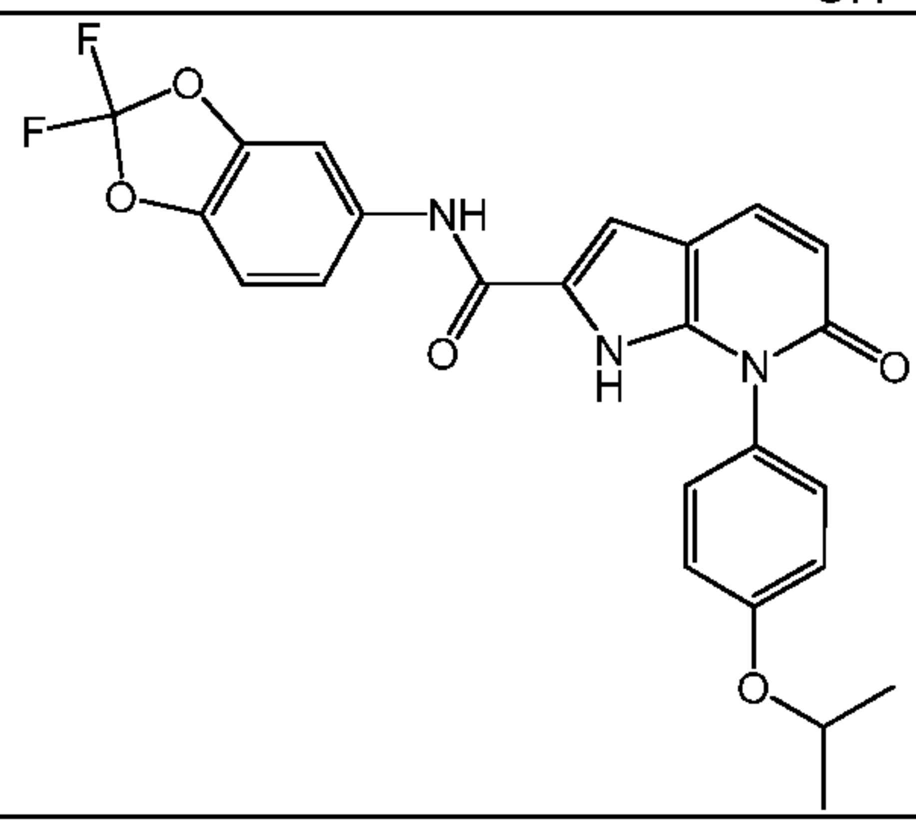
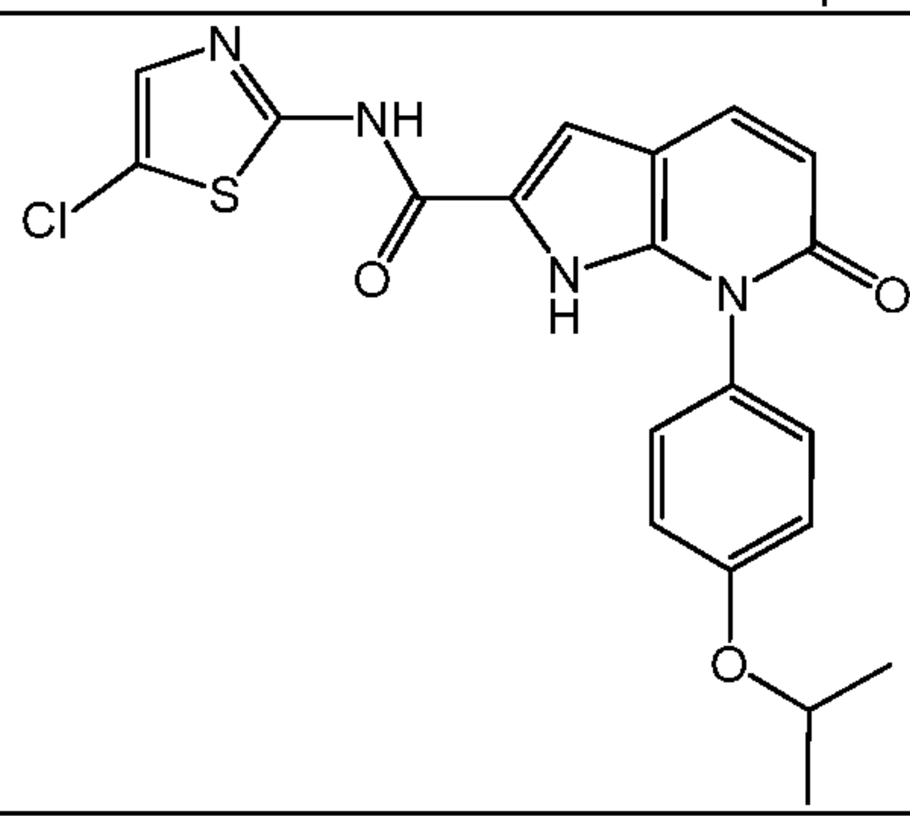
458	
459	
460	
461	

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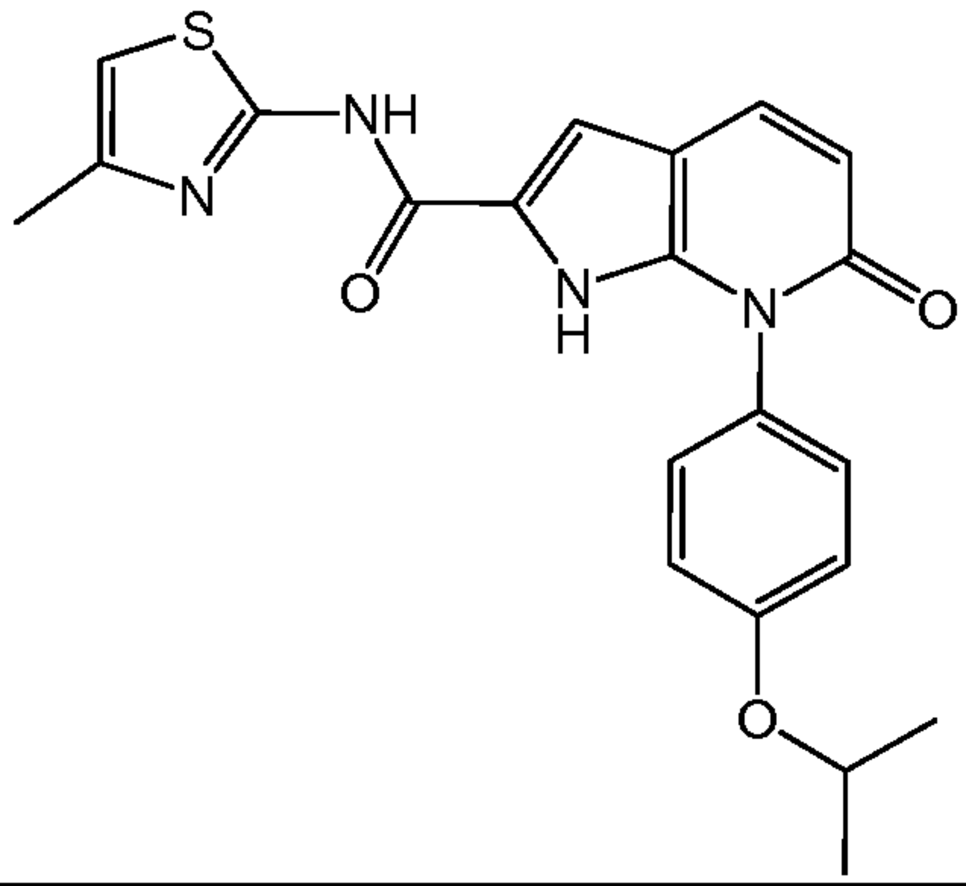
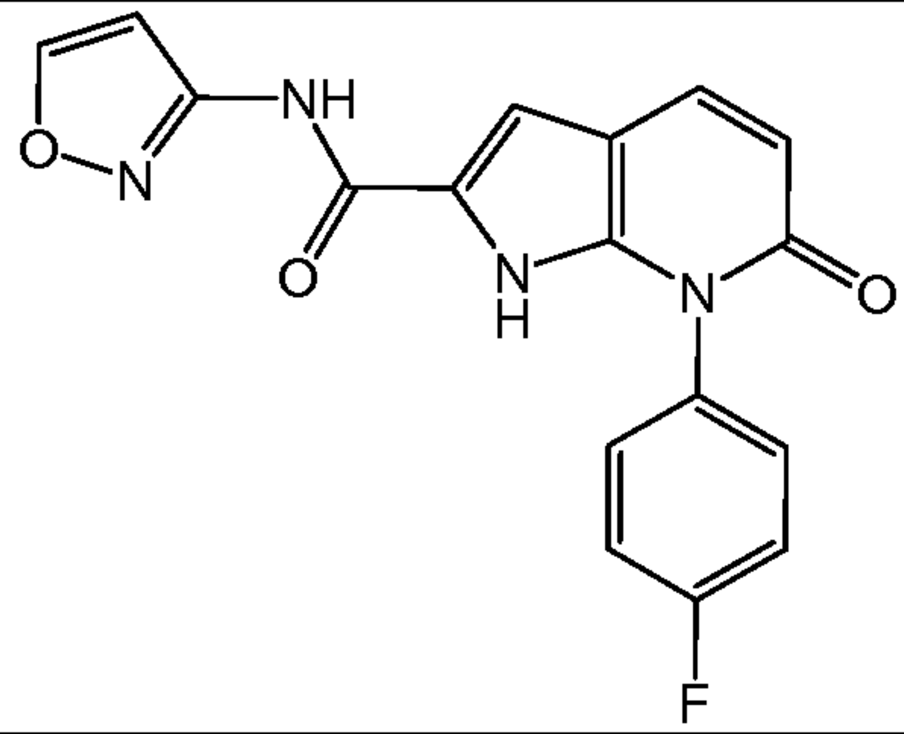
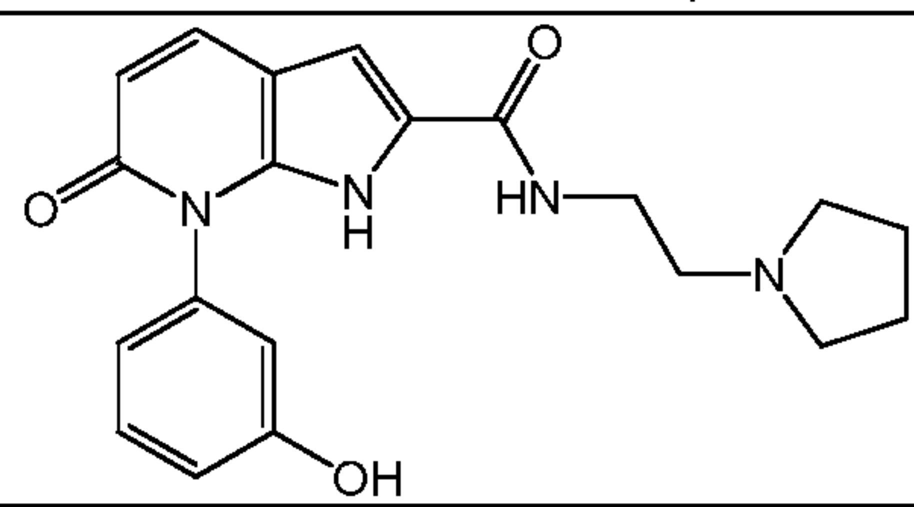
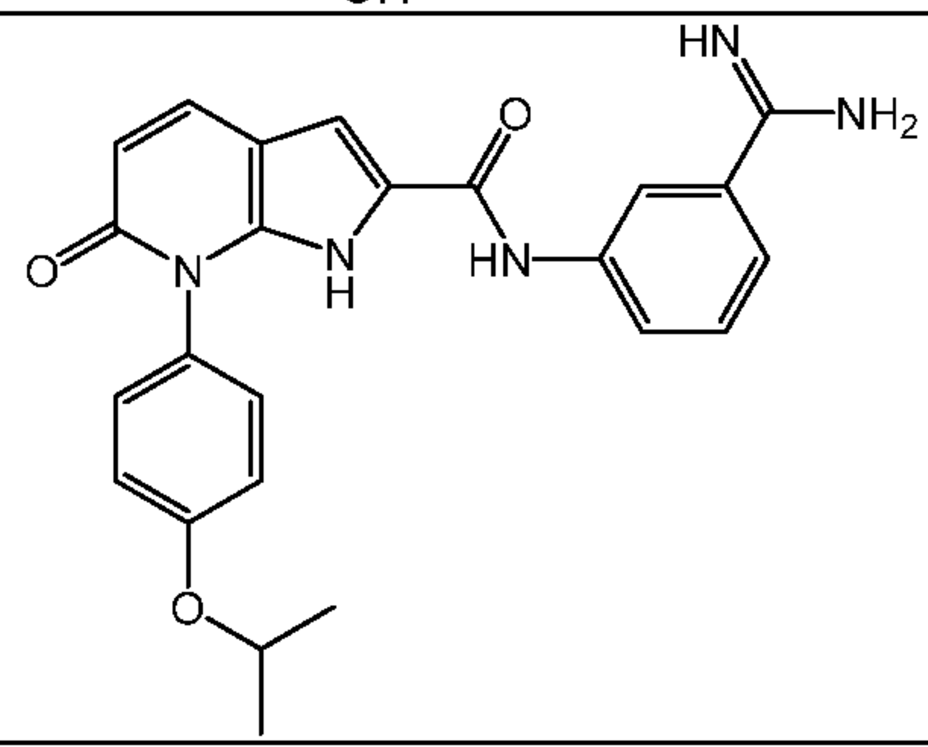
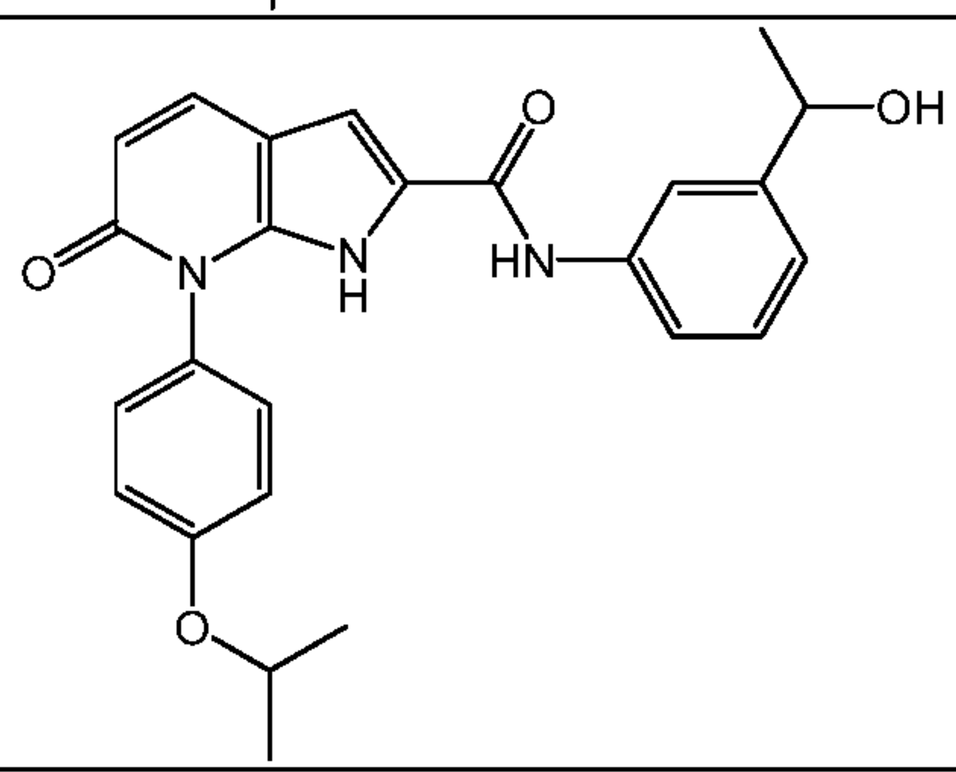
462	
463	
464	
465	
466	

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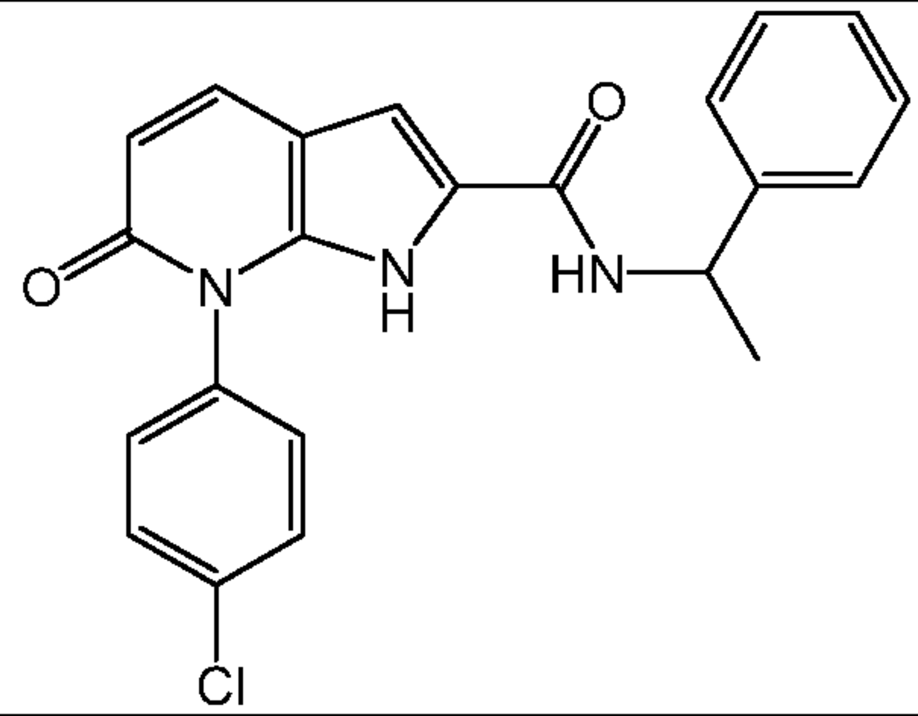
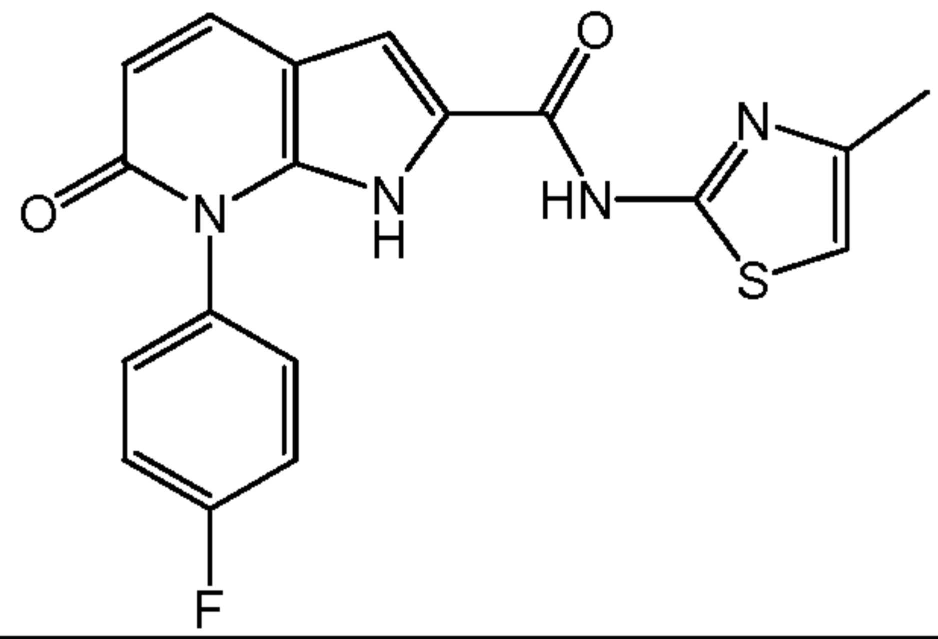
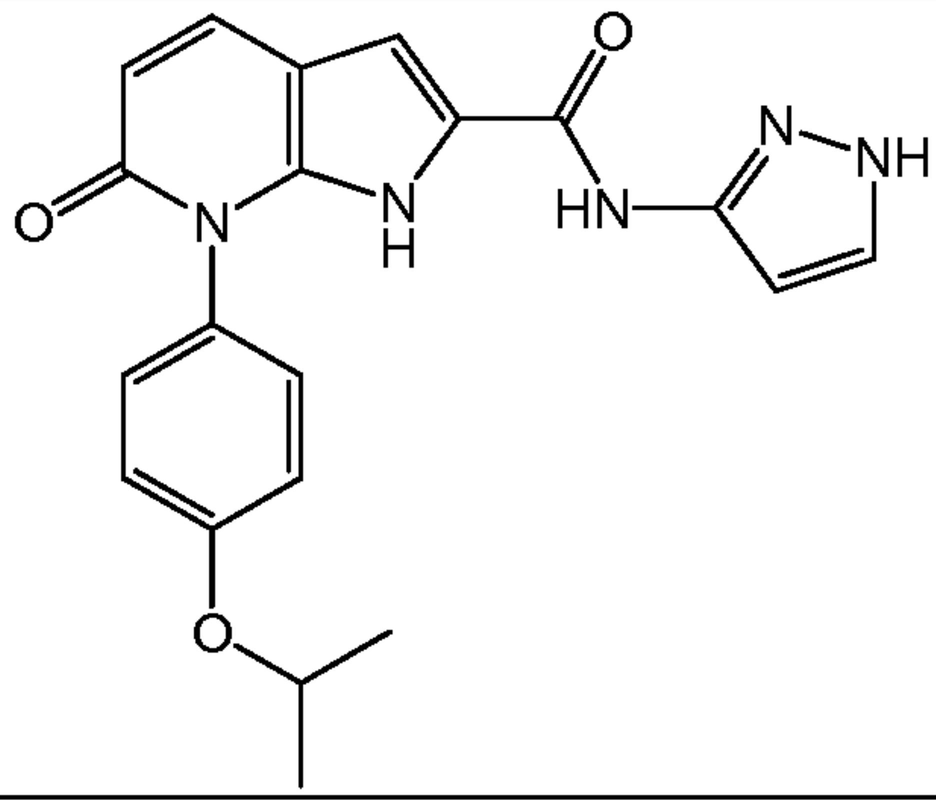
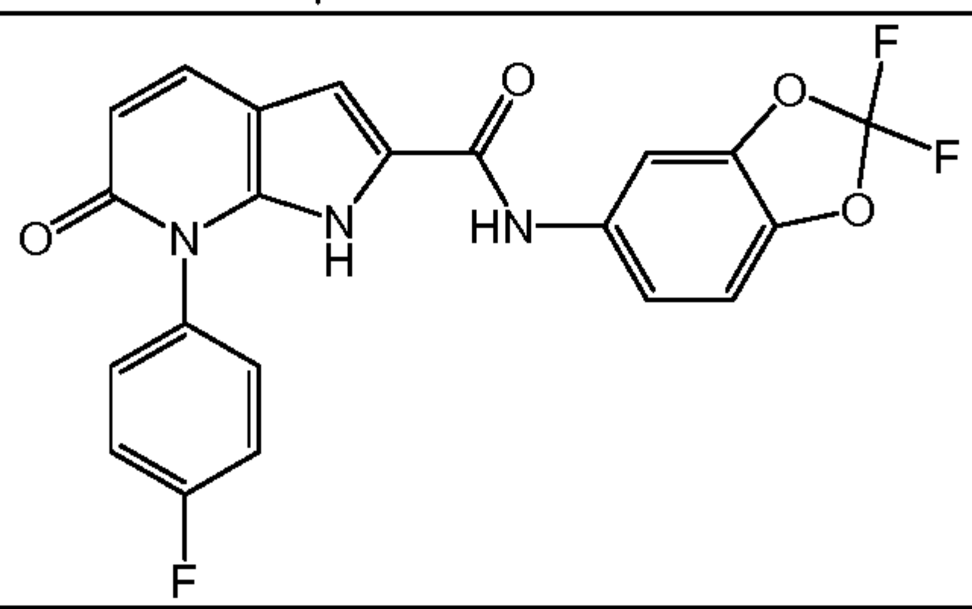
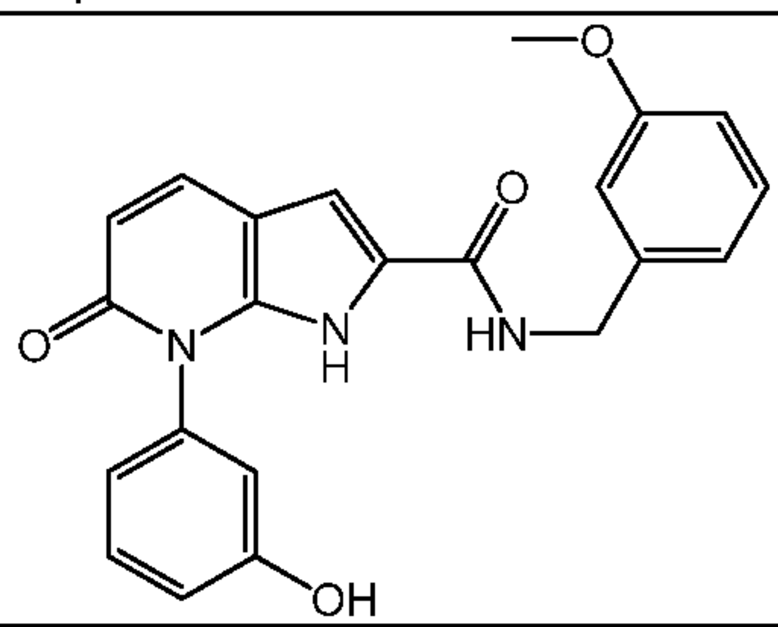
467	
468	
469	
470	
471	

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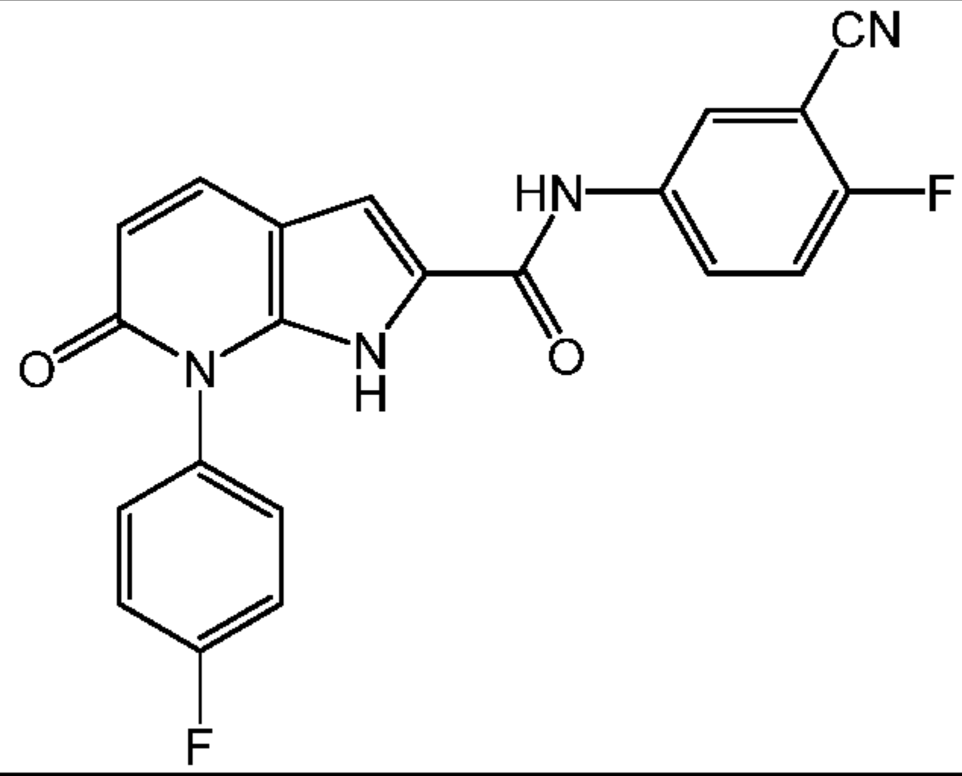
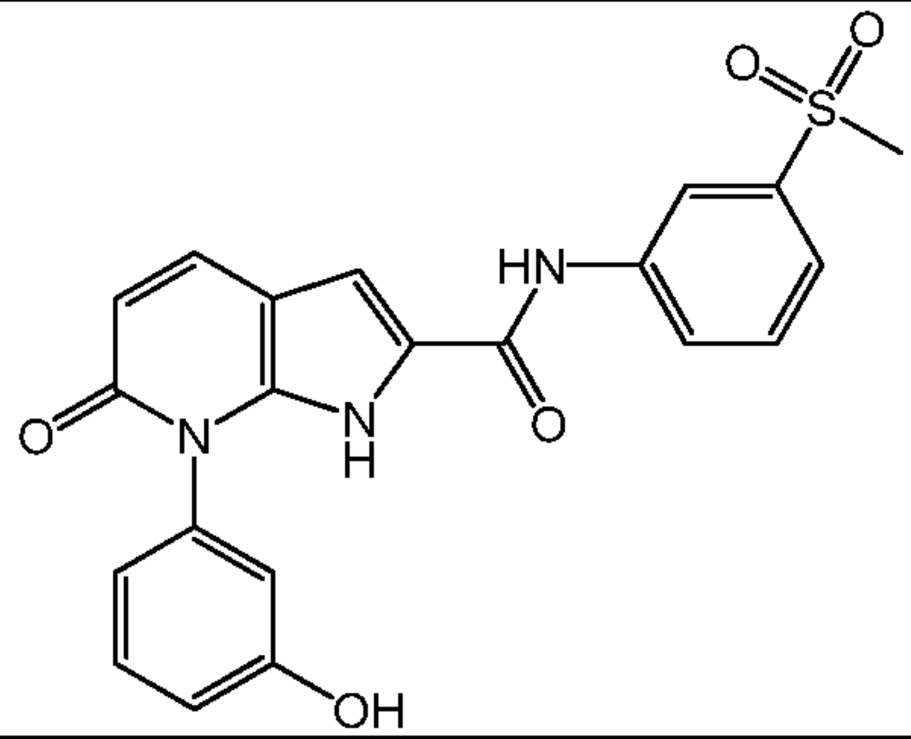
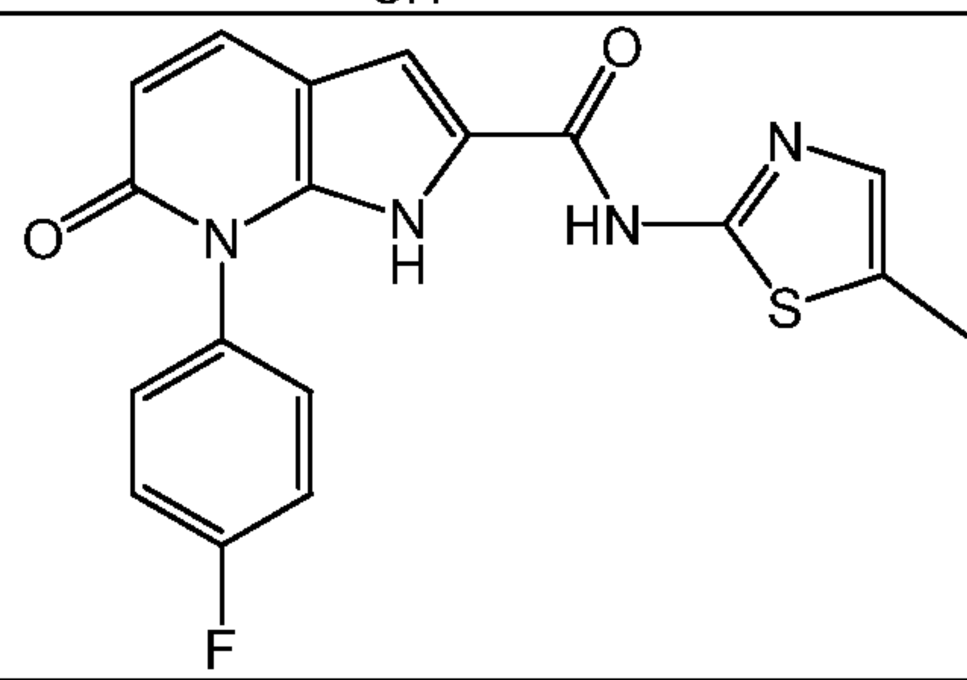
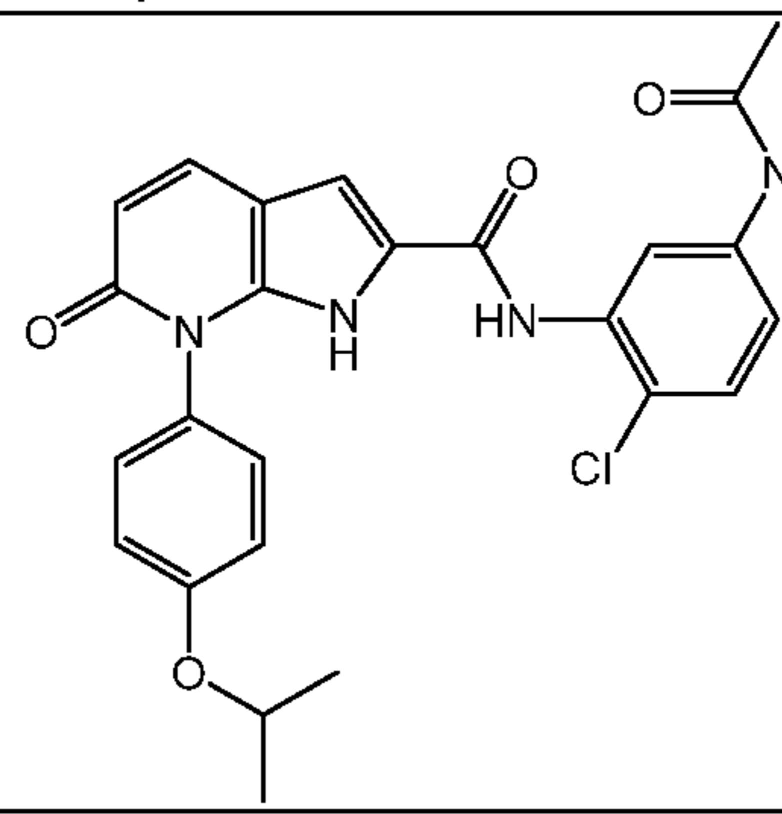
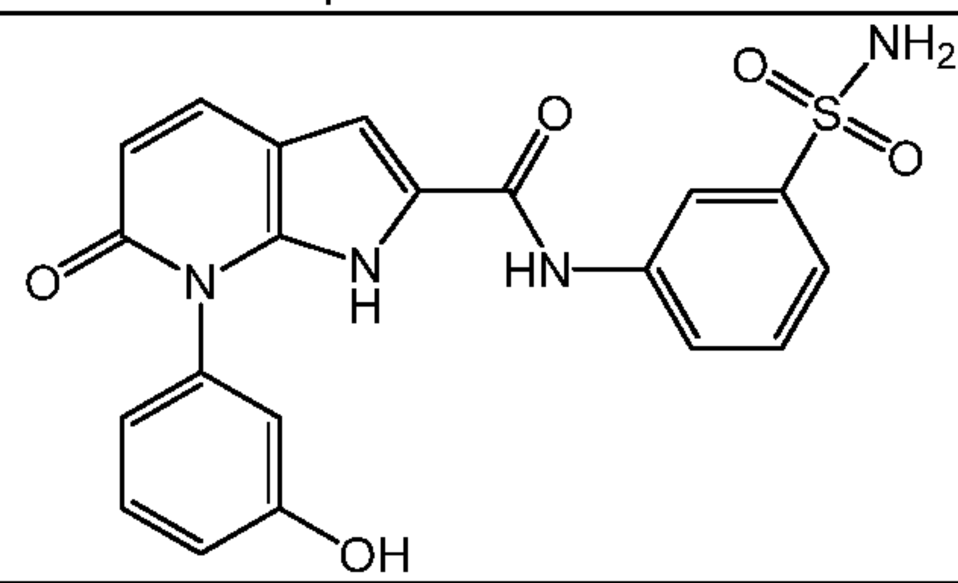
472	
473	
474	
475	
476	

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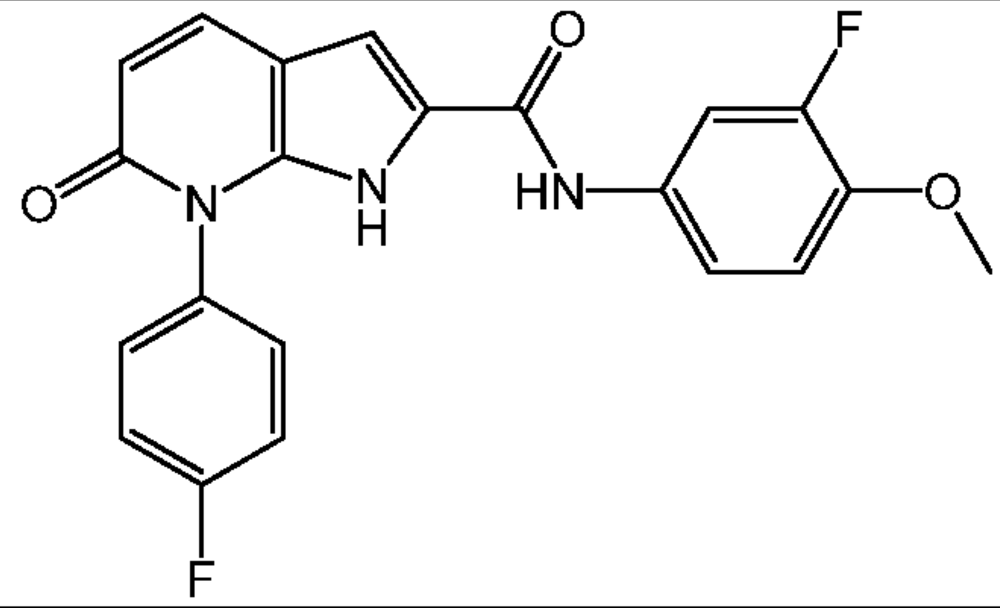
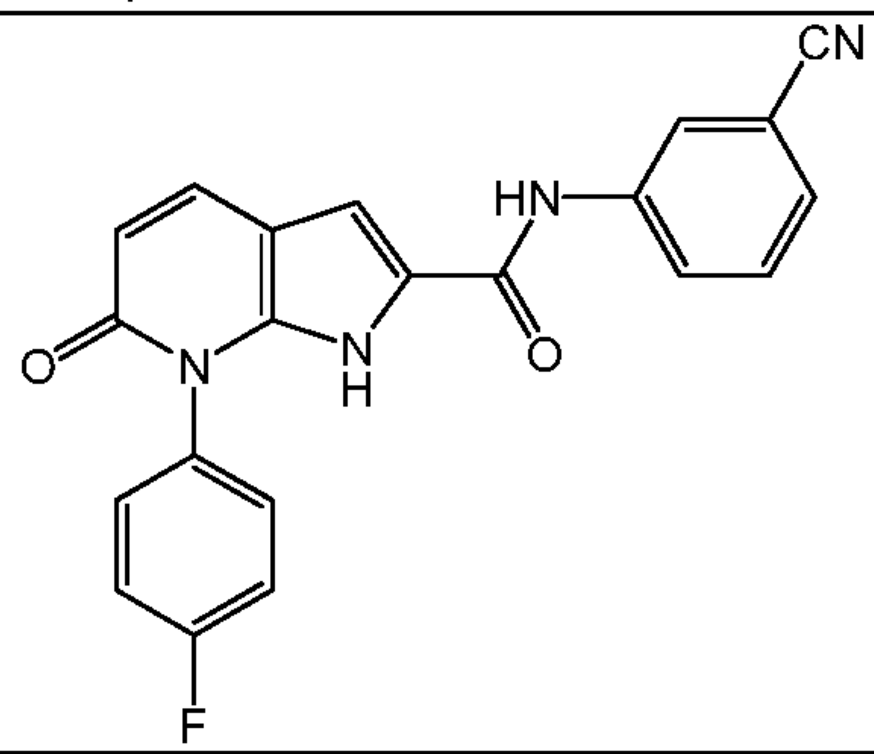
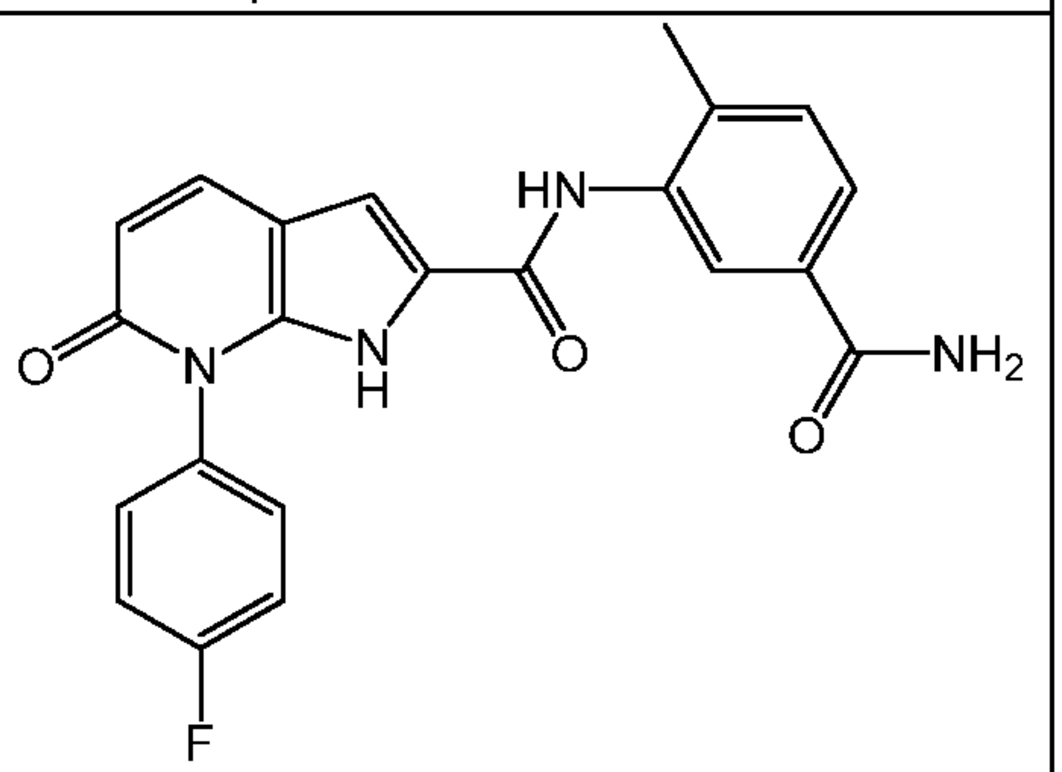
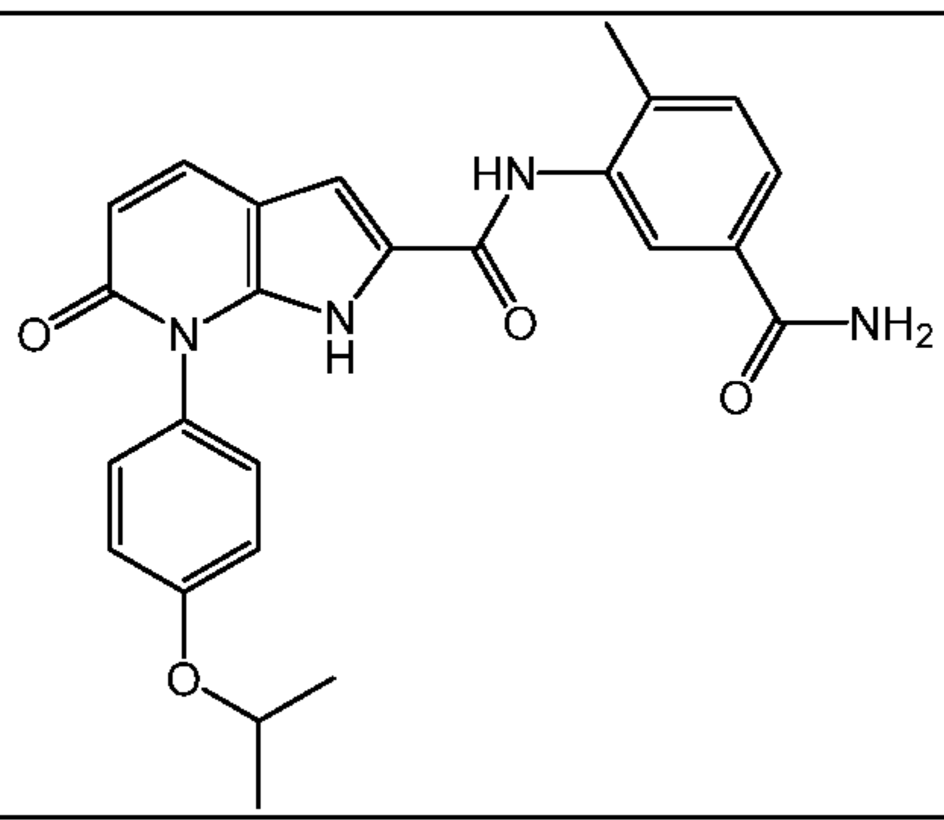
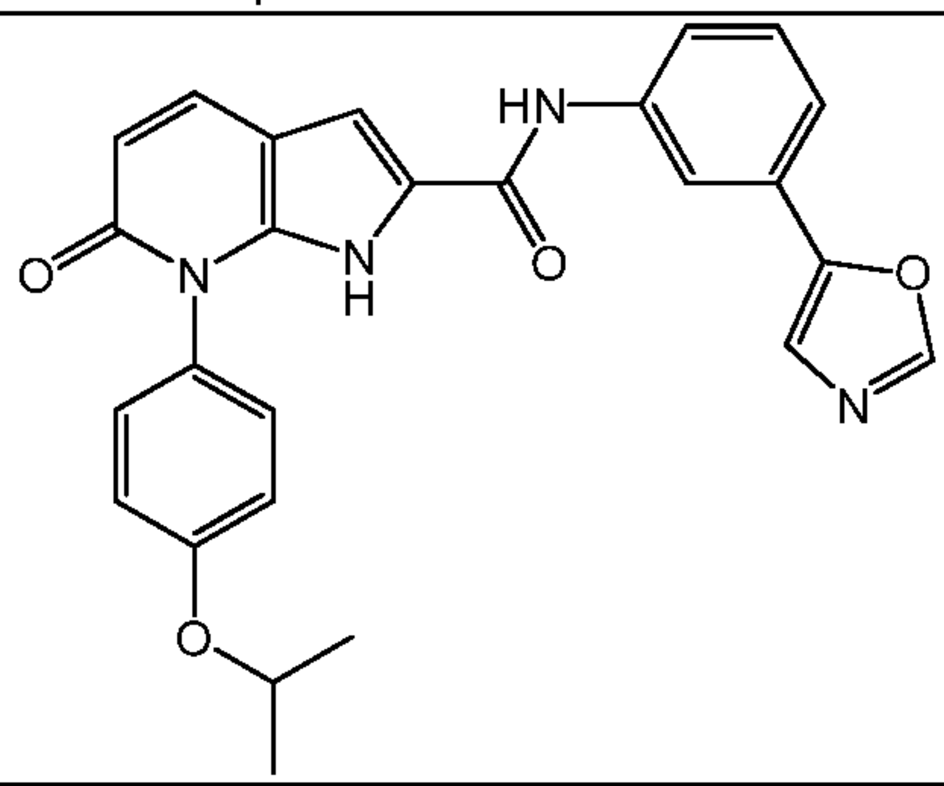
477	
478	
479	
480	
481	

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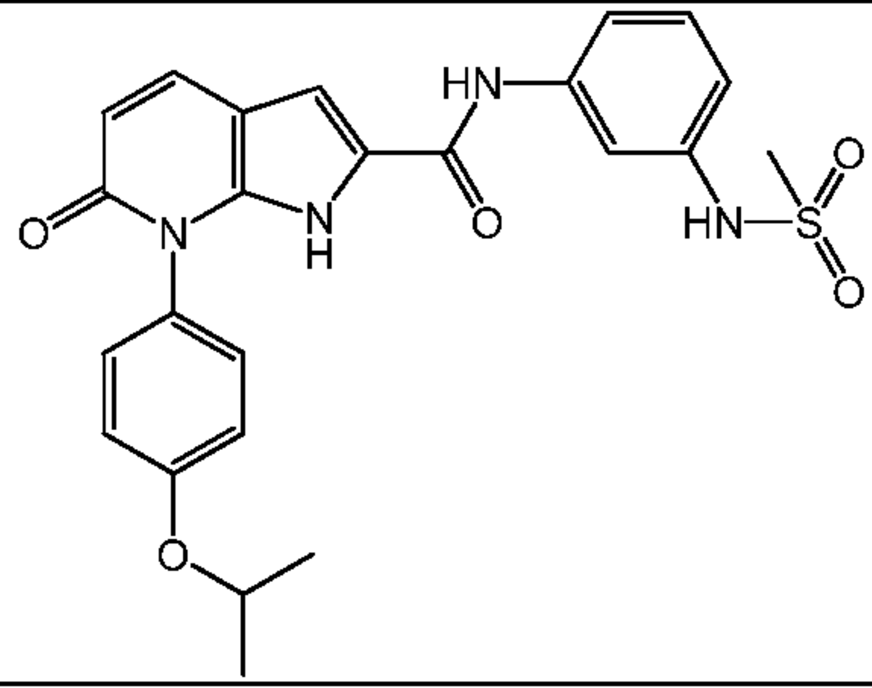
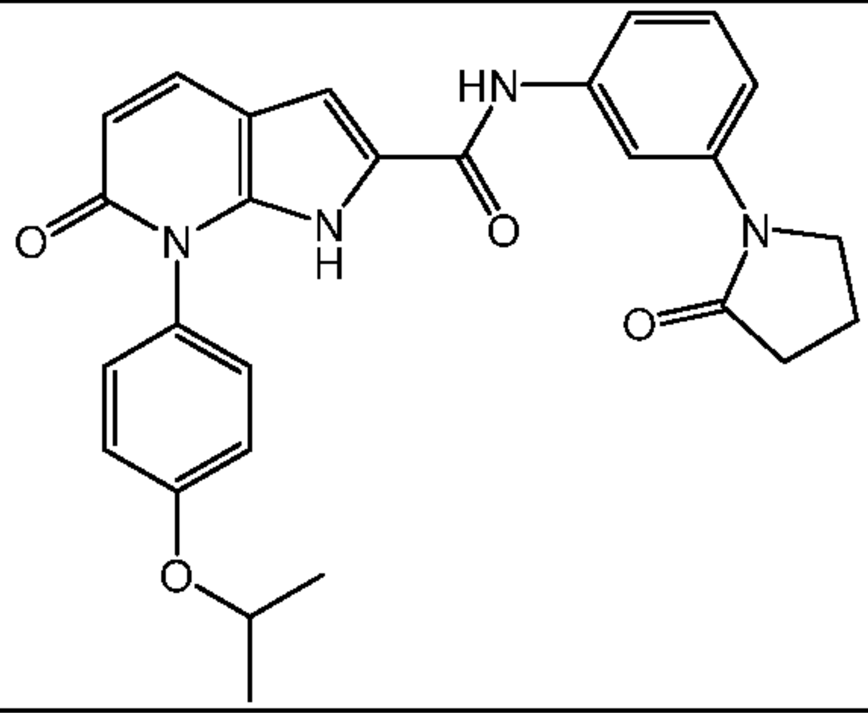
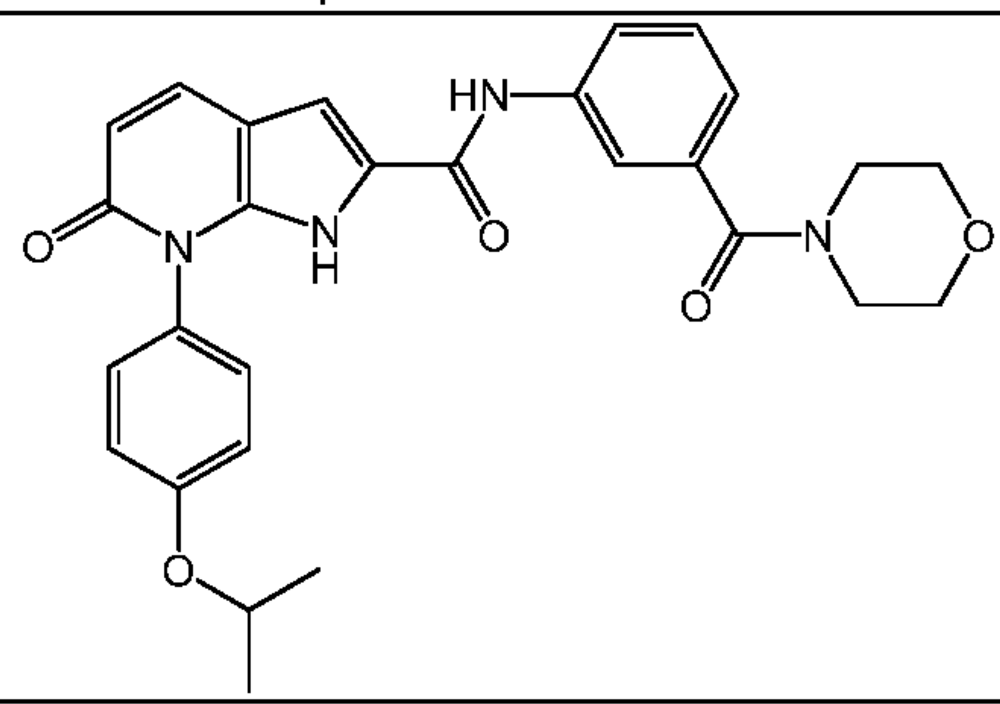
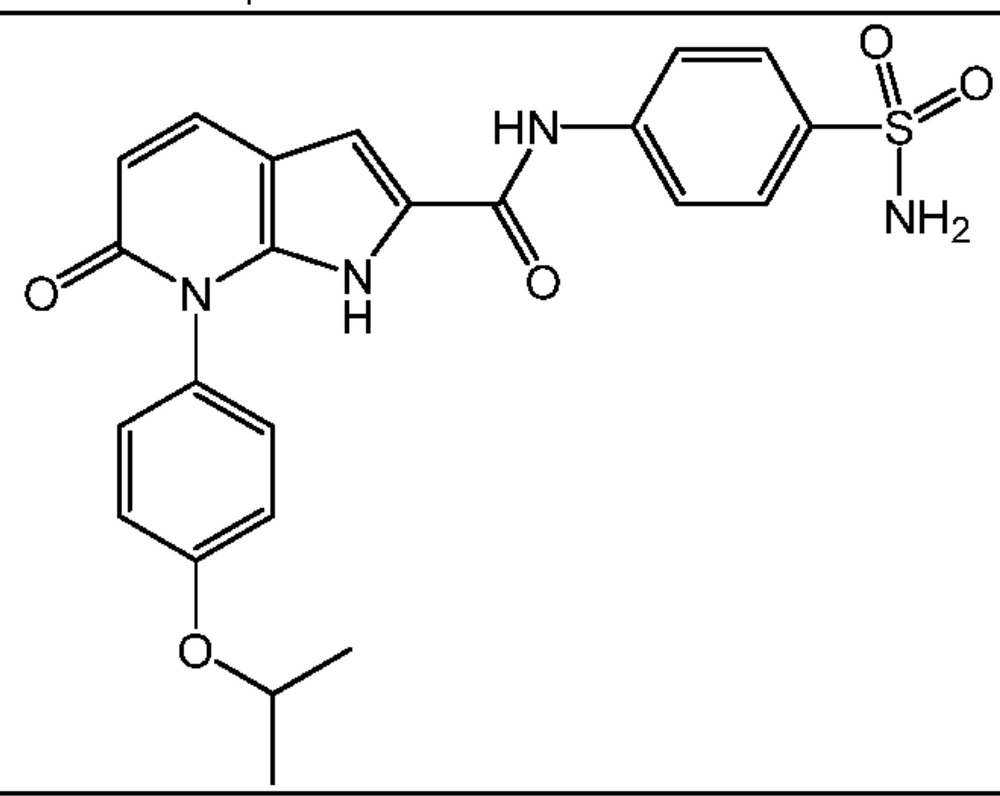
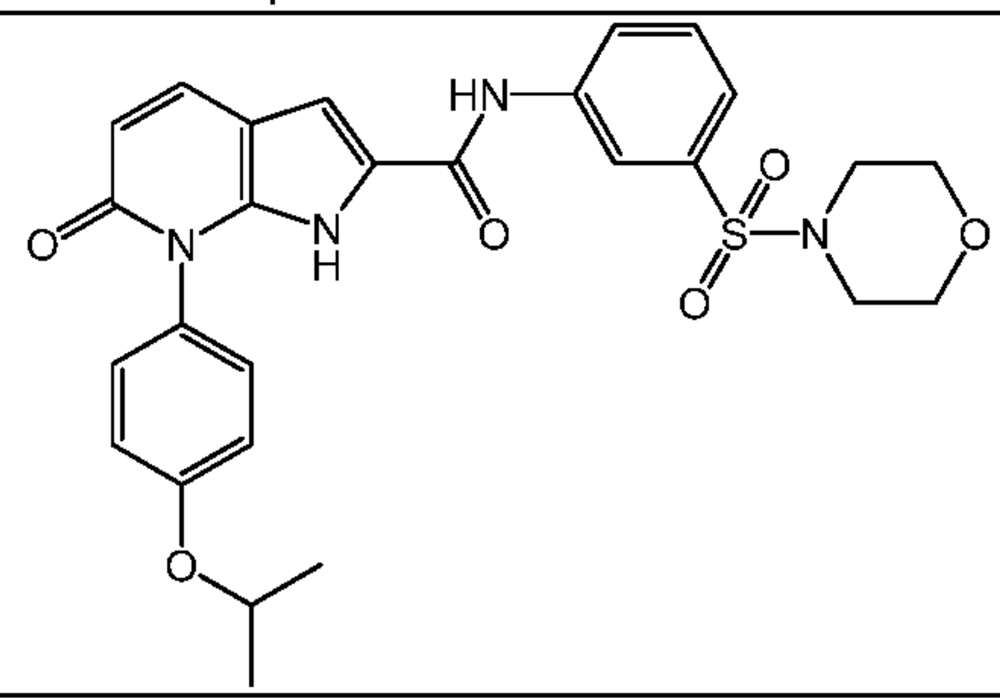
482	
483	
484	
485	
486	

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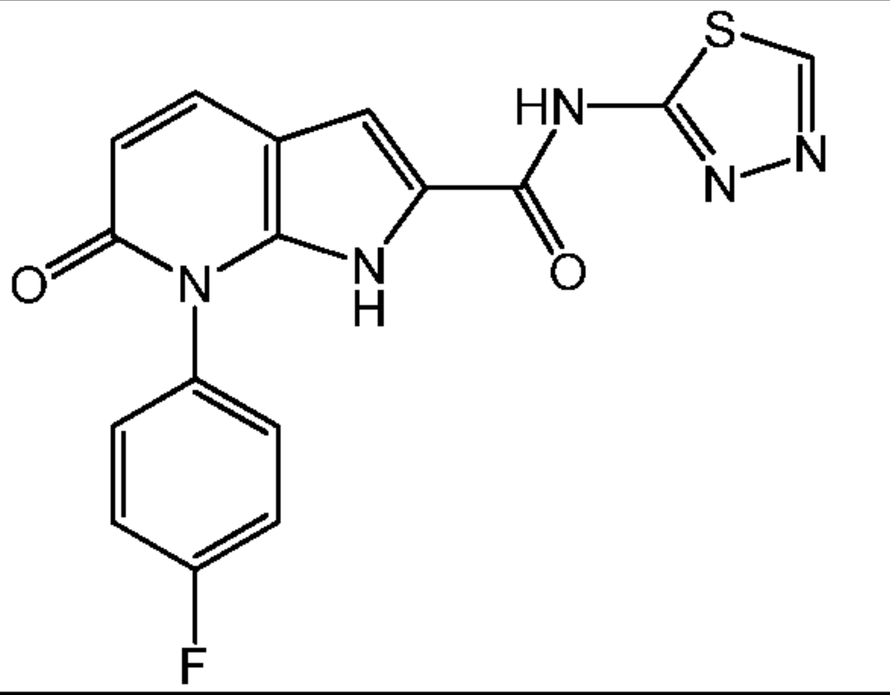
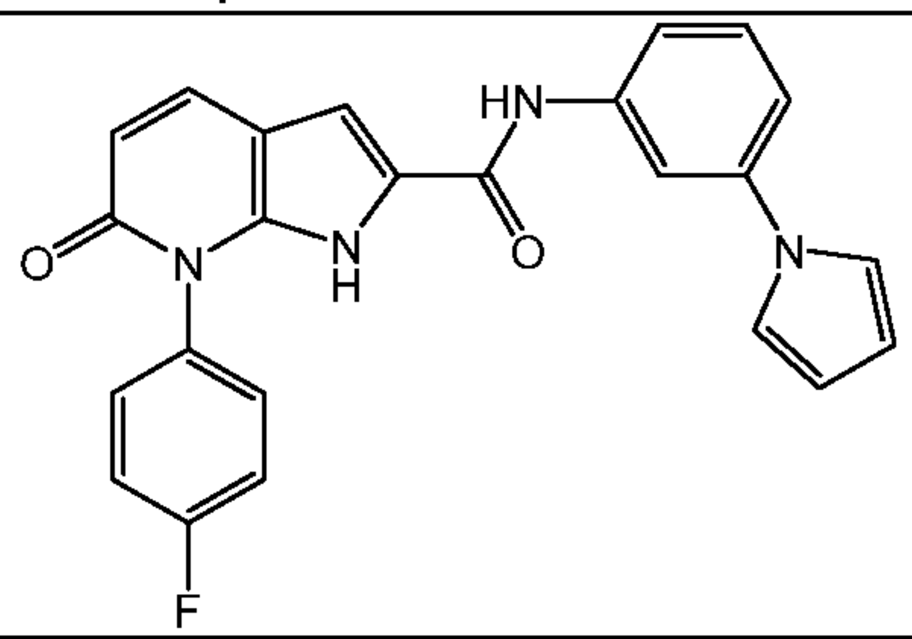
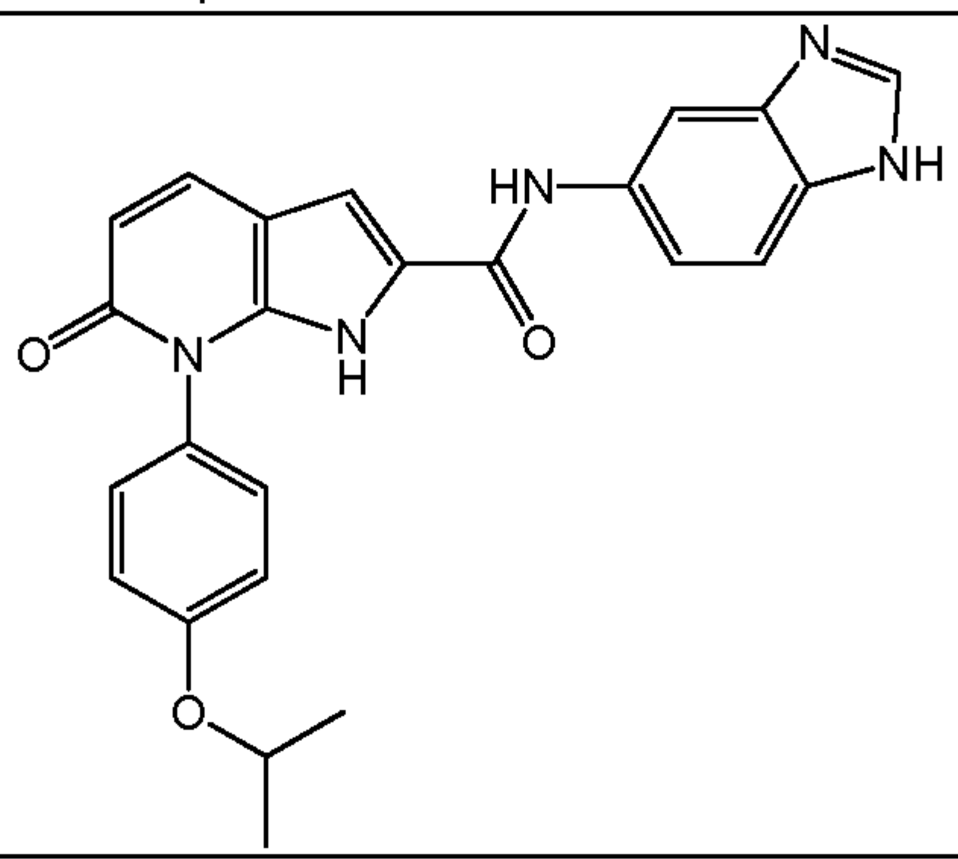
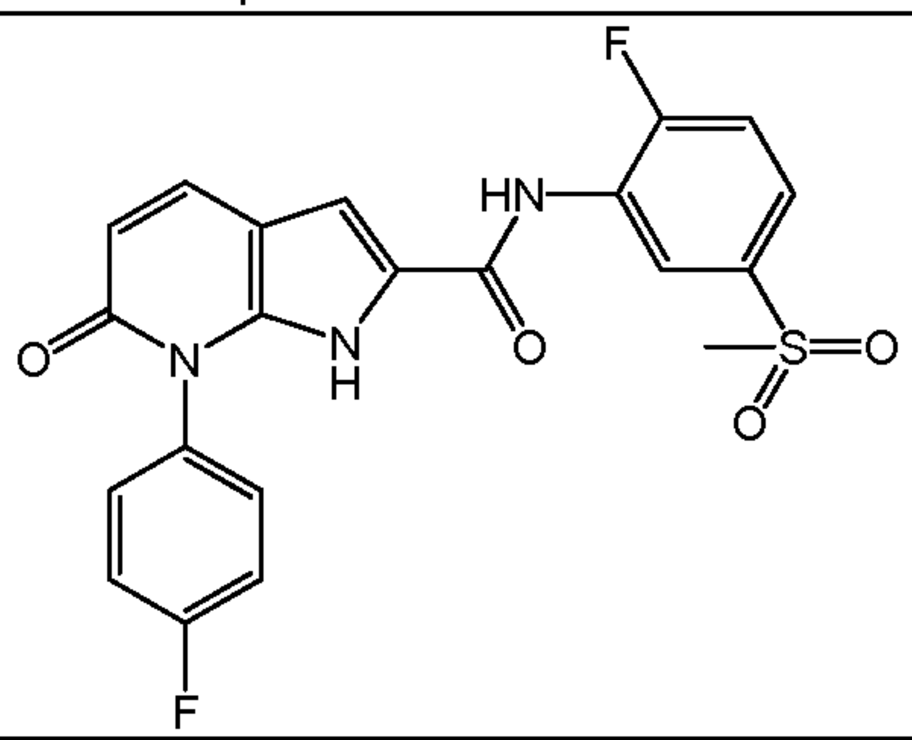
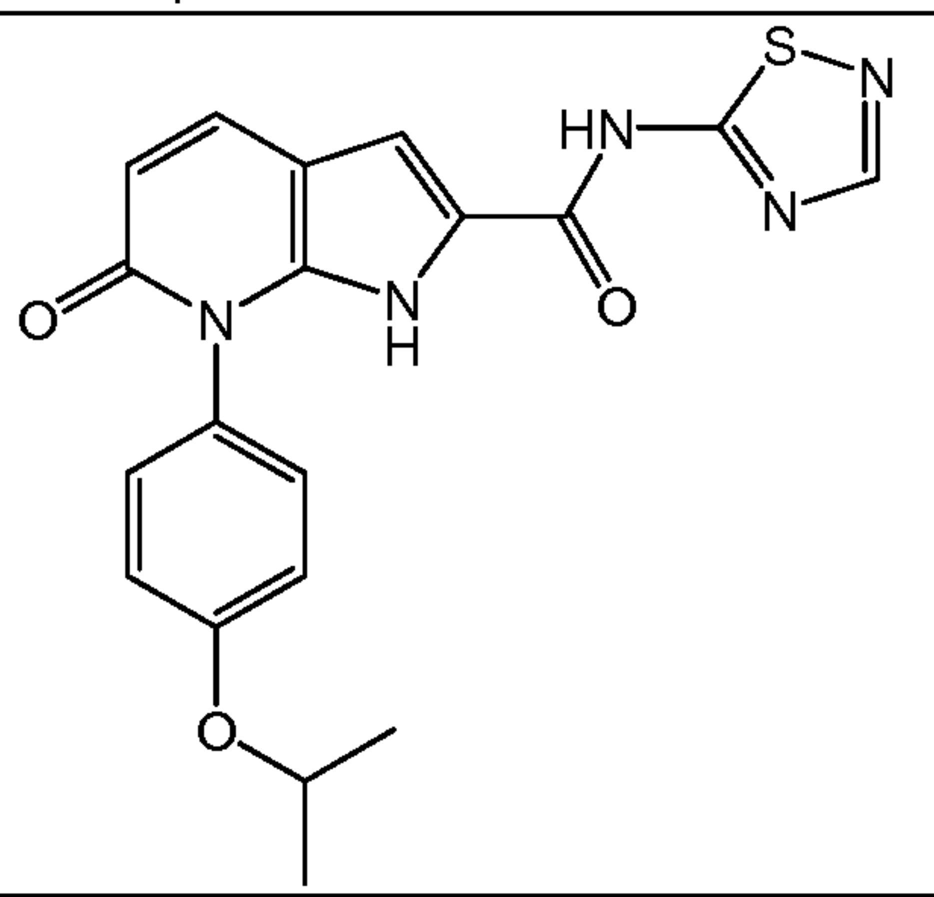
487	
488	
489	
490	
491	

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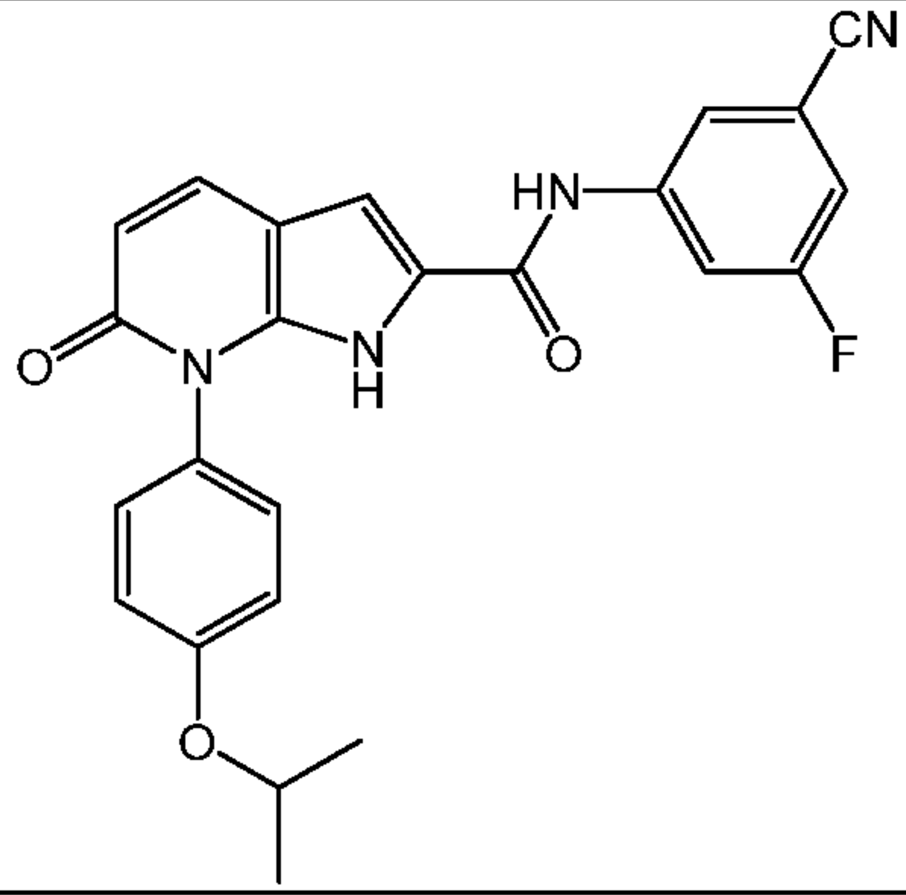
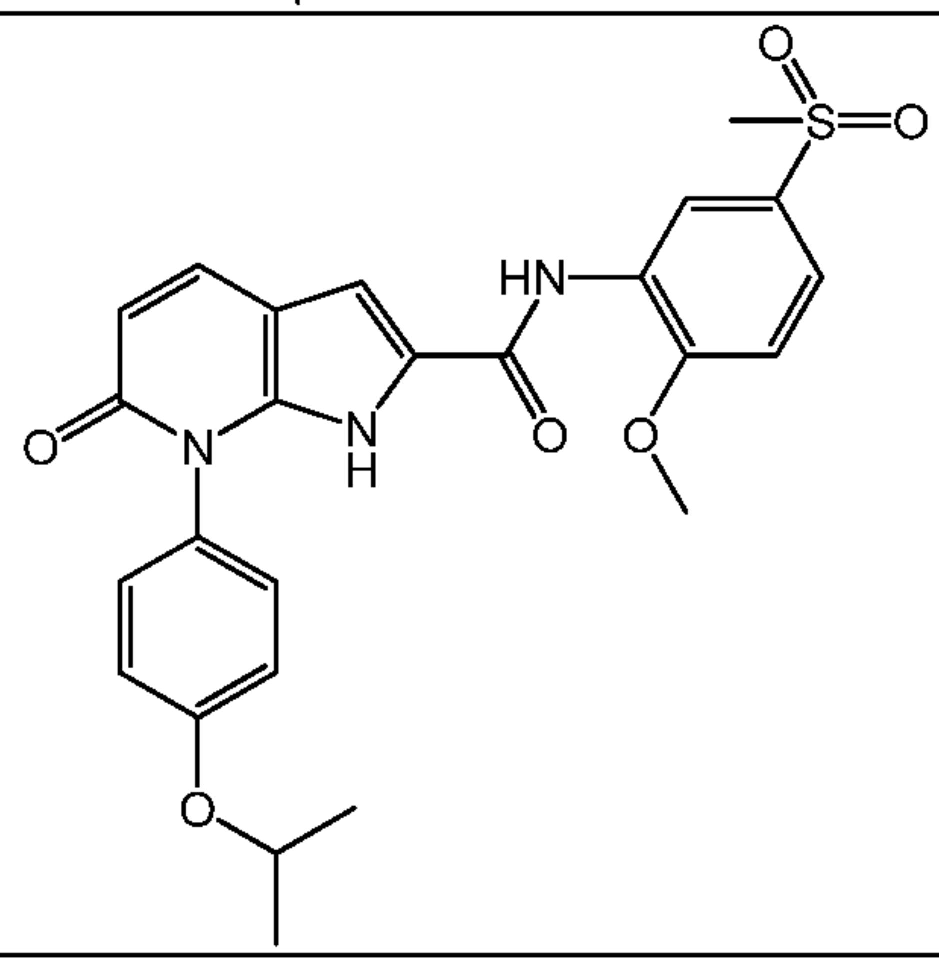
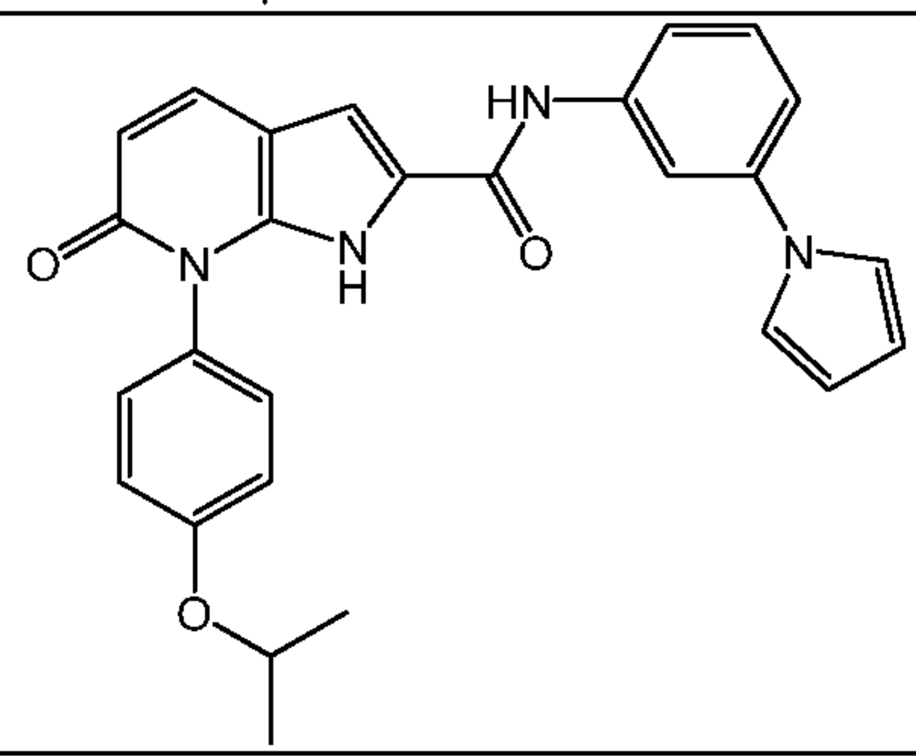
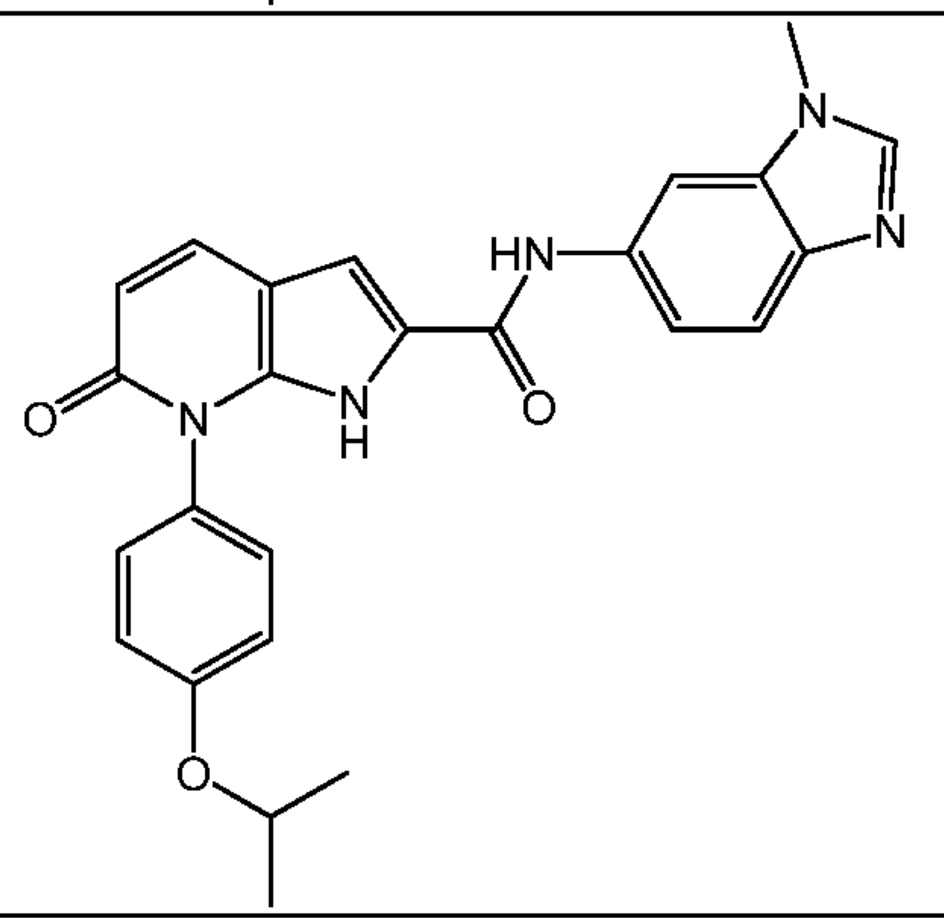
492	
493	
494	
495	

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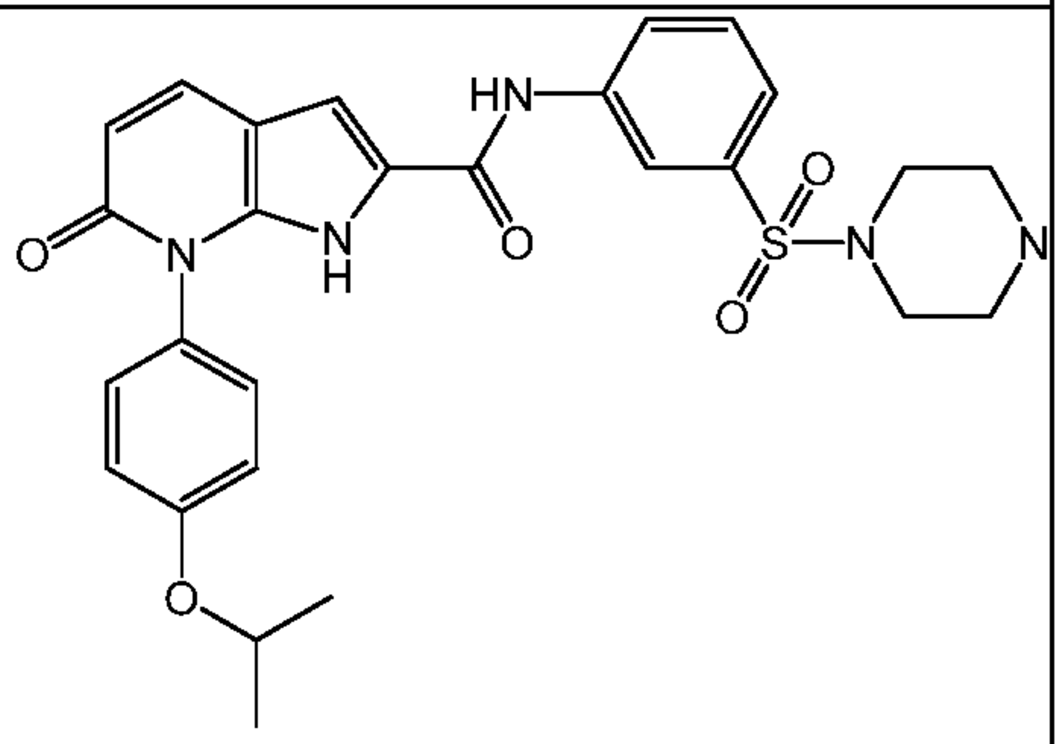
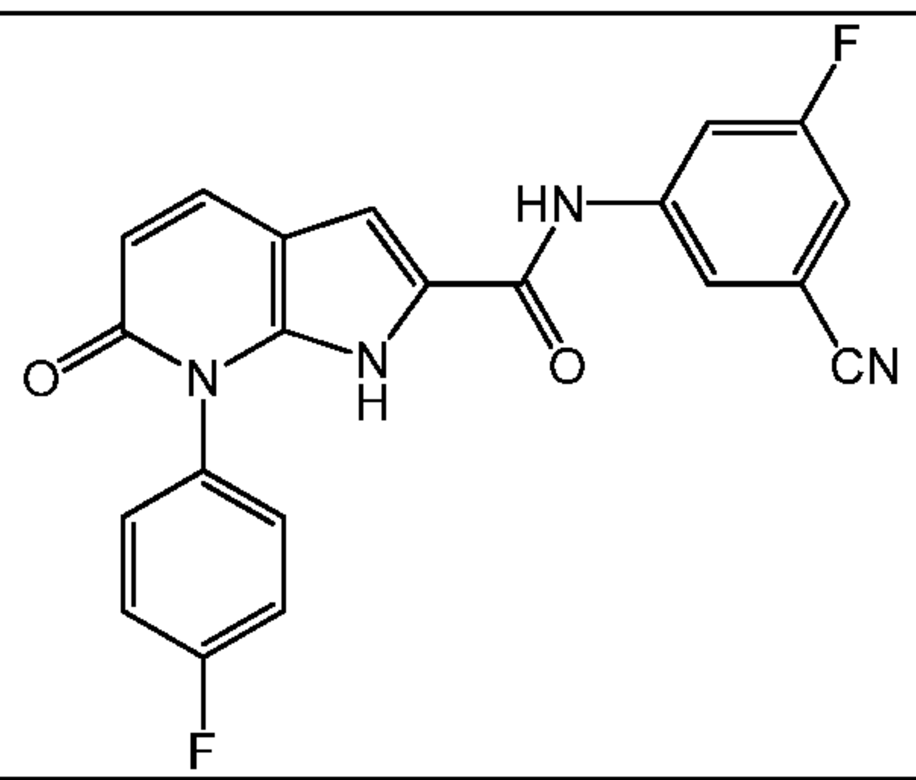
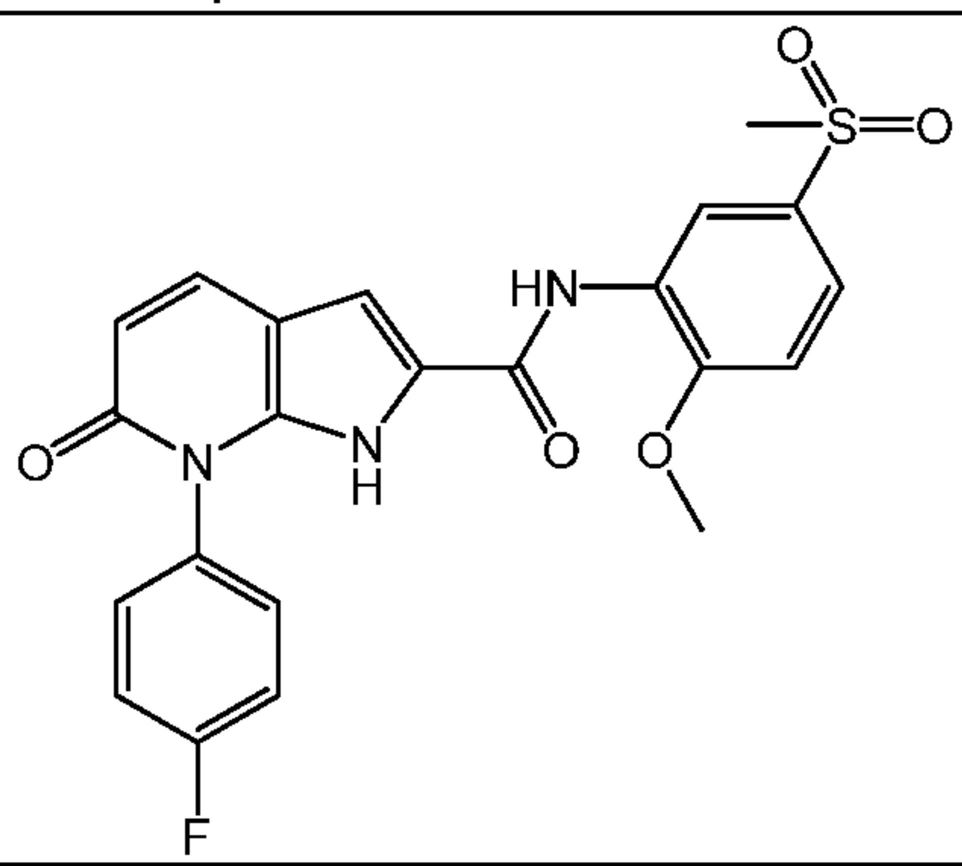
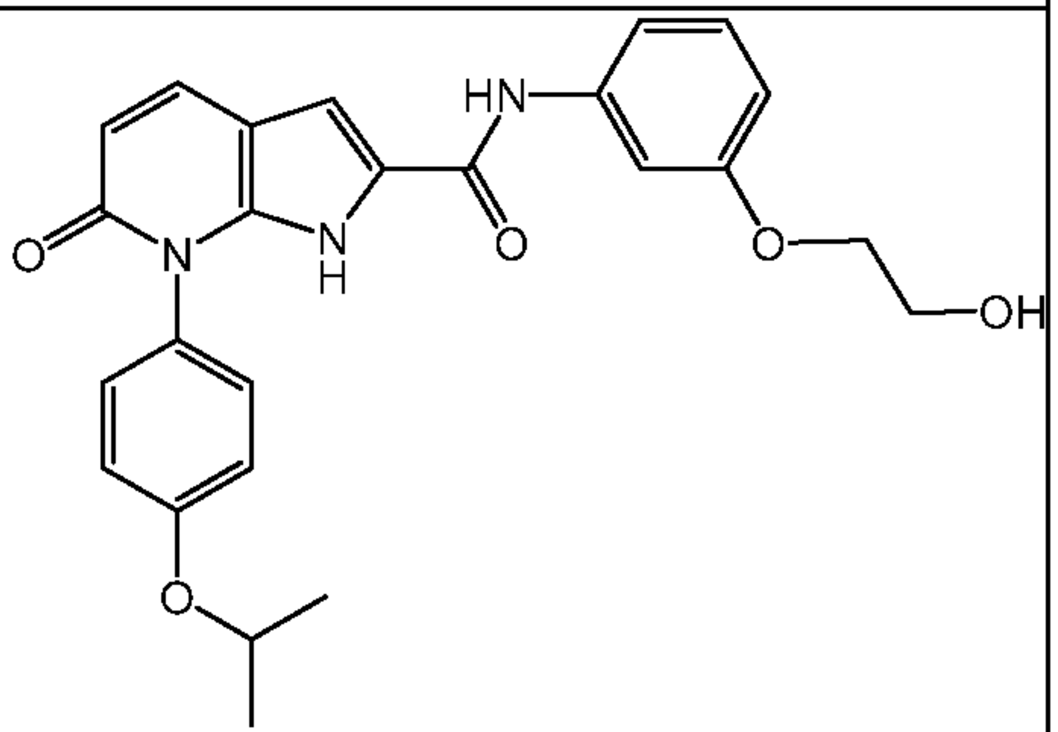
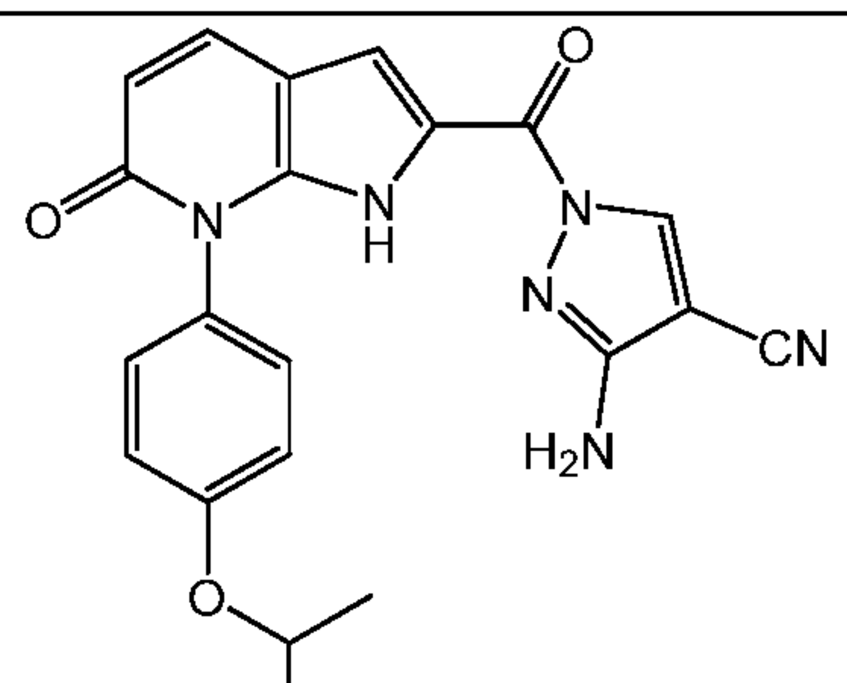
496	
497	
498	
499	
500	

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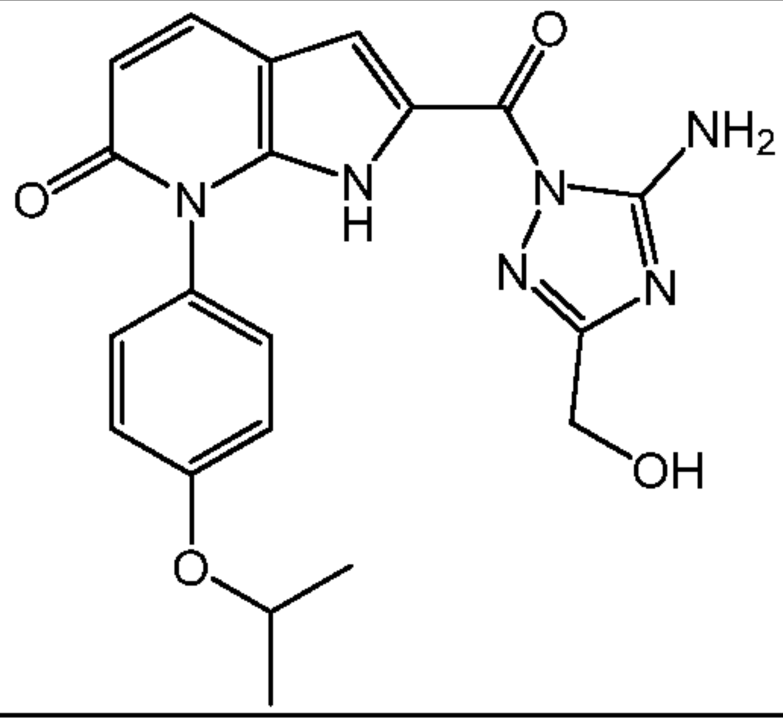
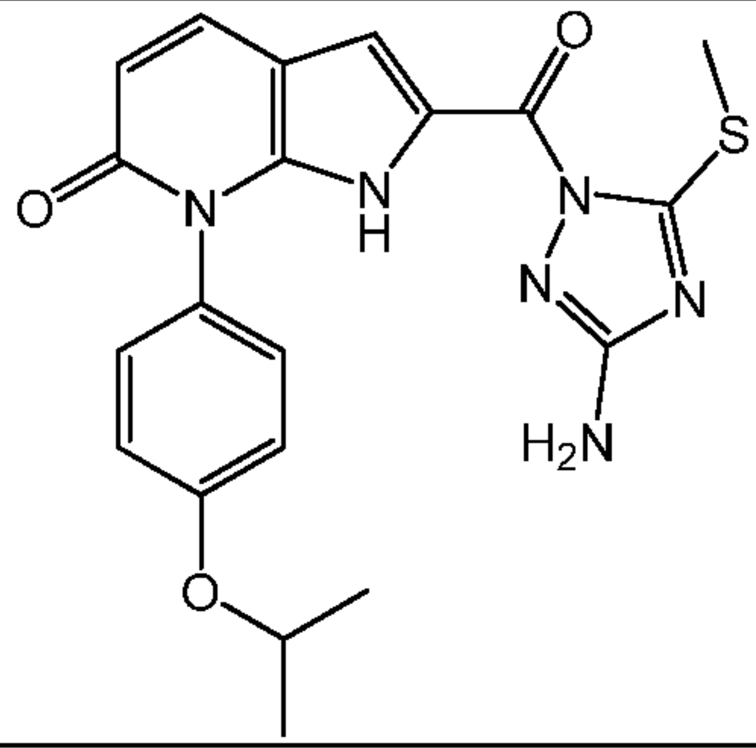
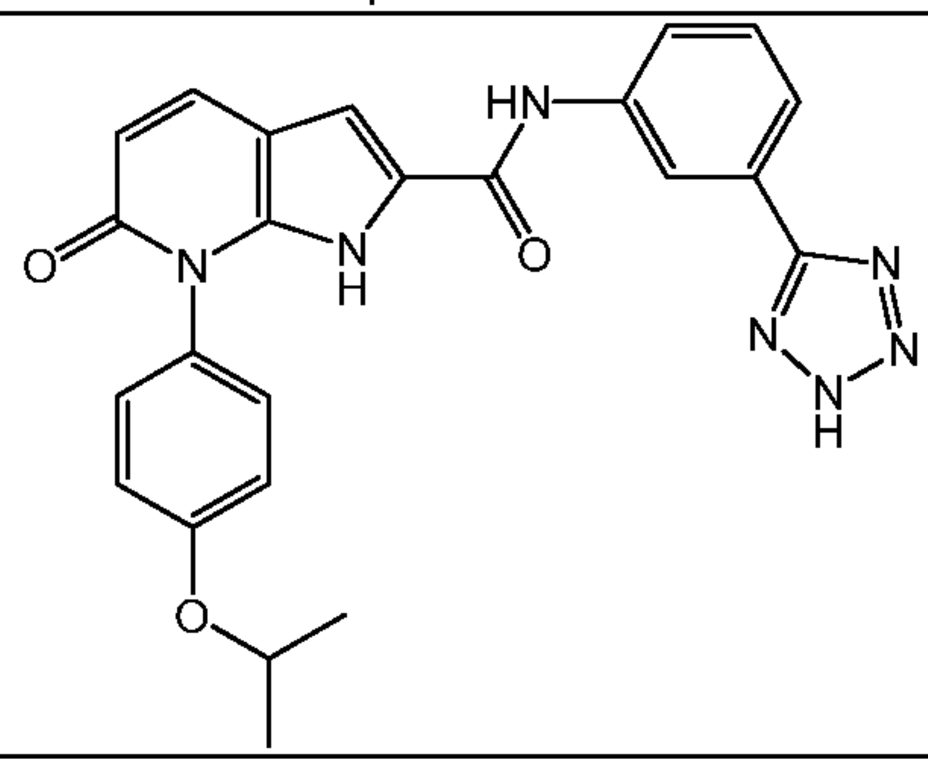
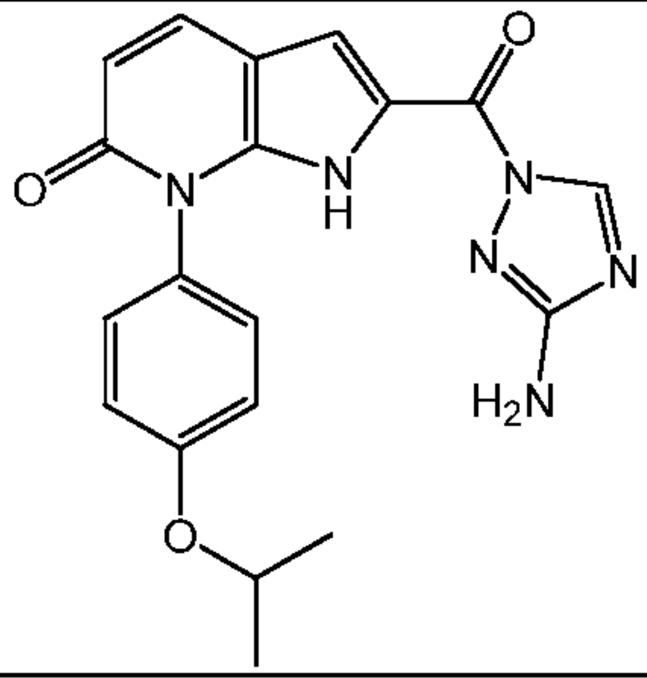
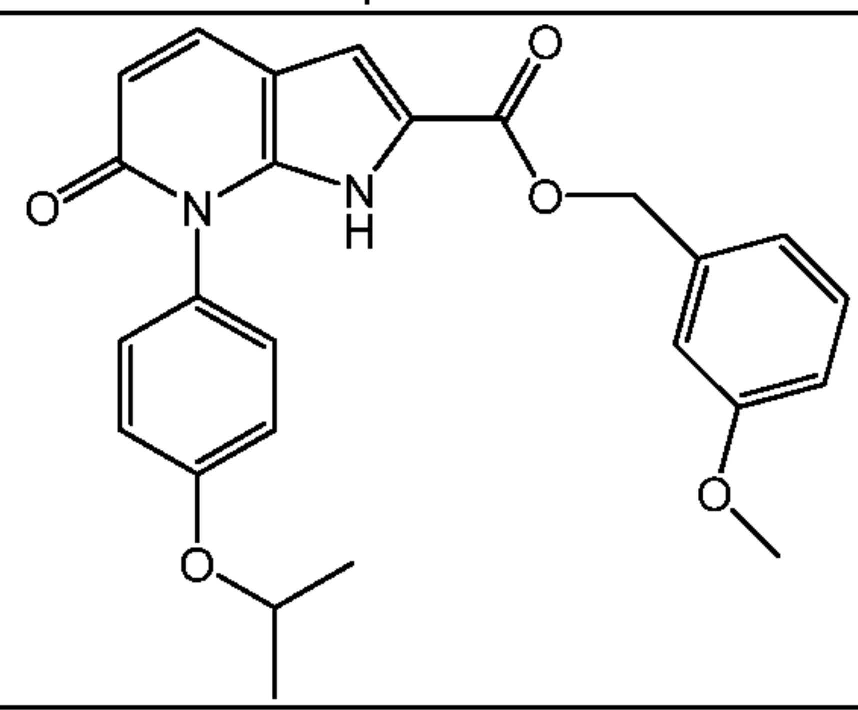
501	
502	
503	
504	
505	

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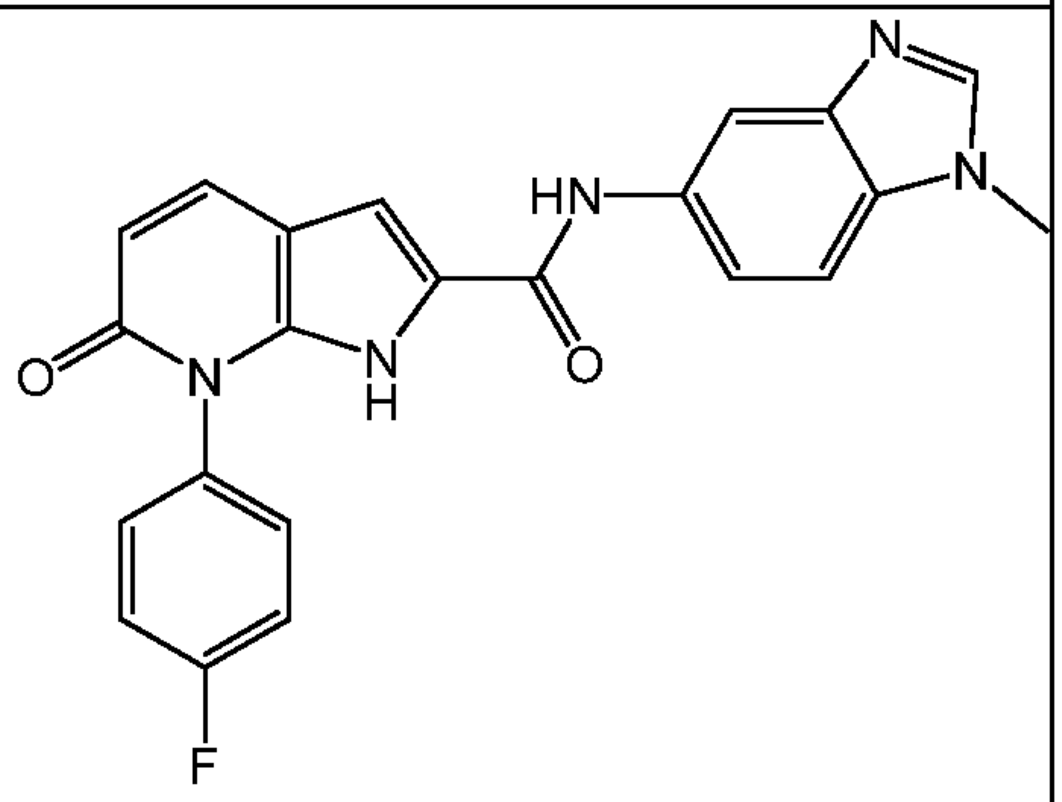
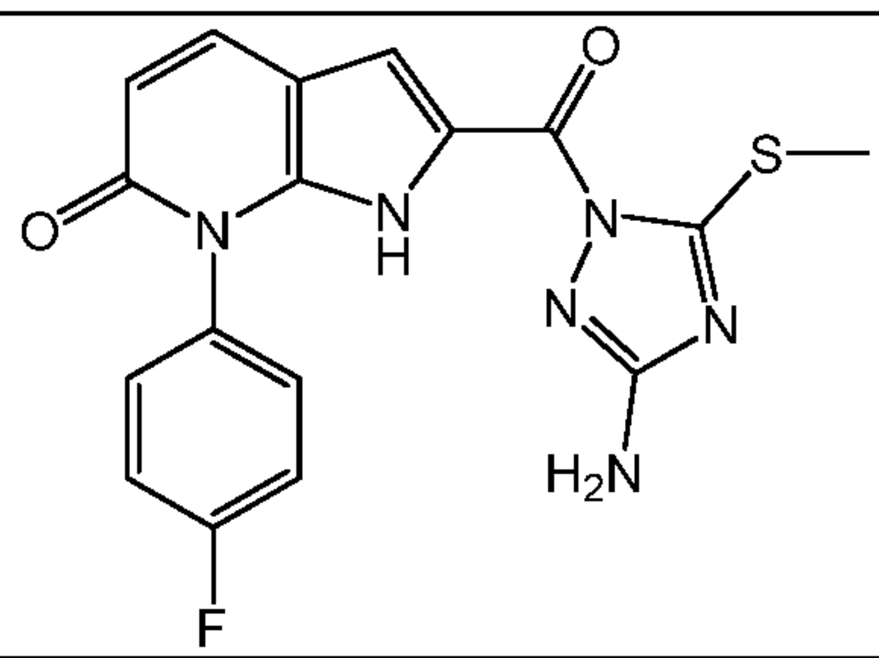
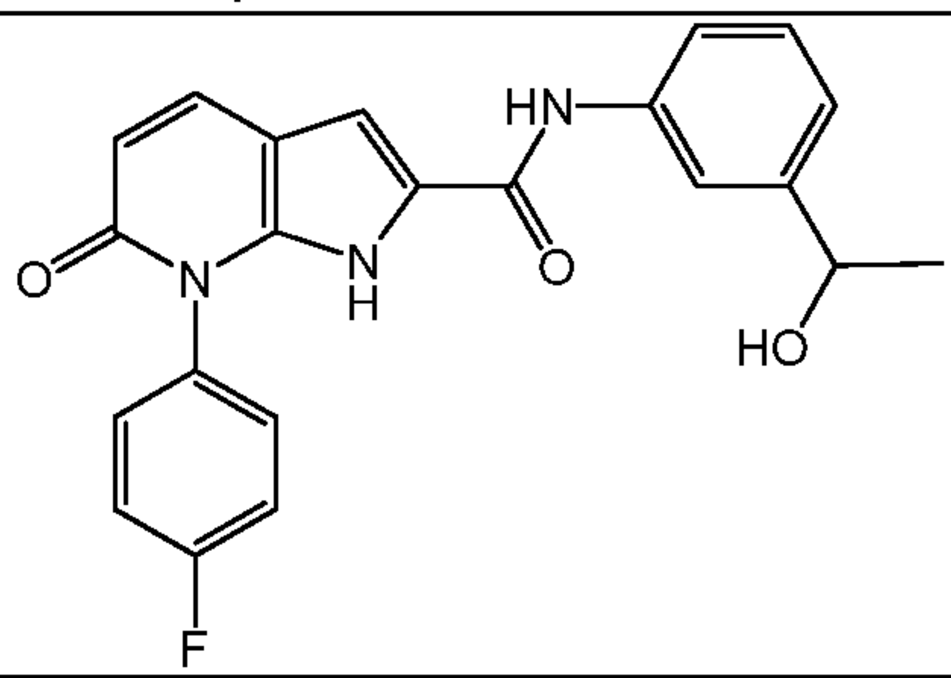
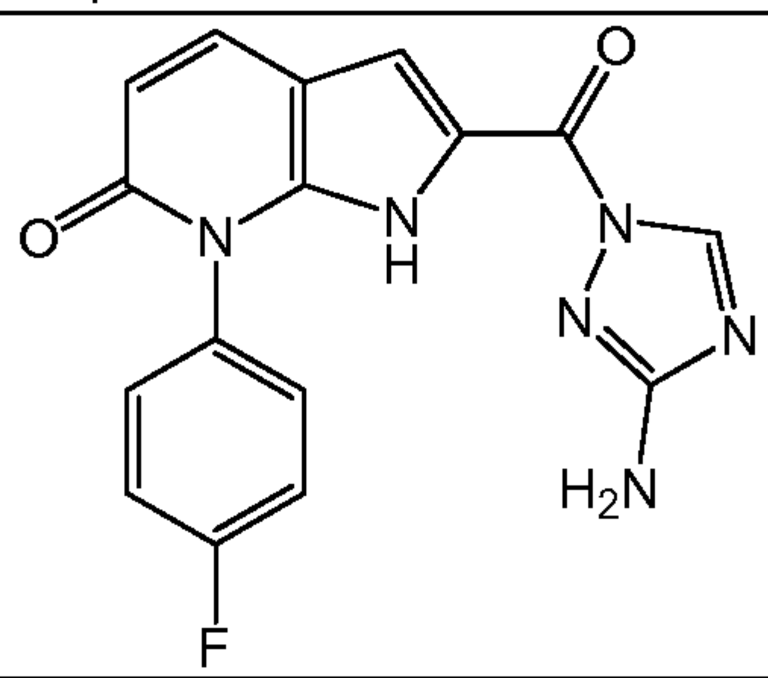
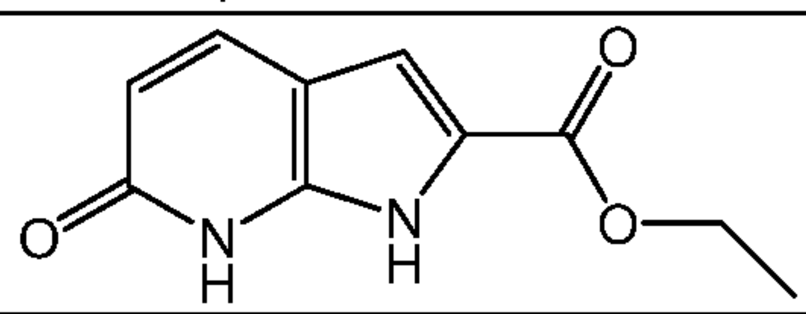
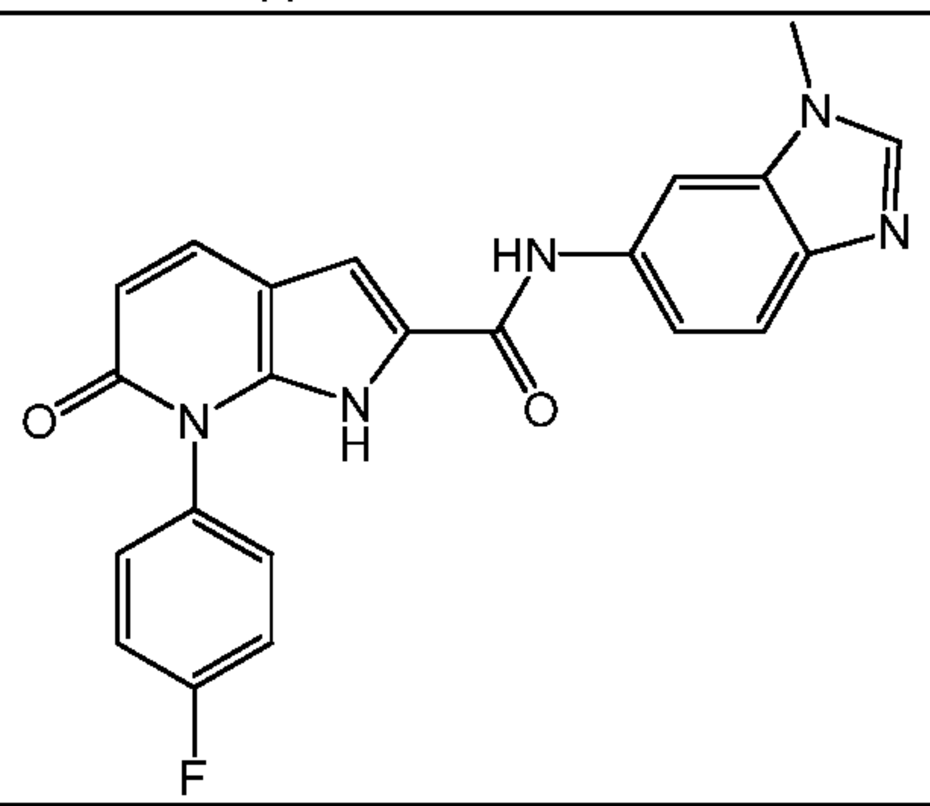
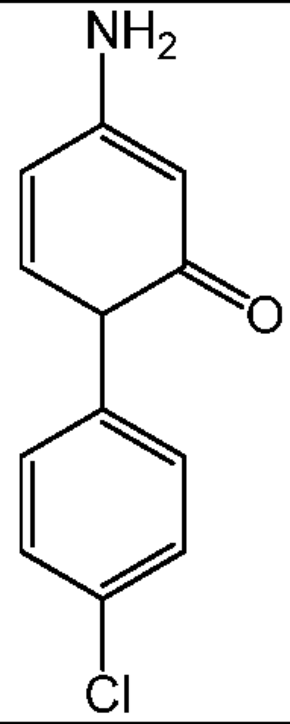
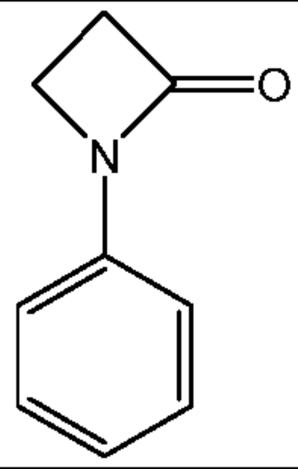
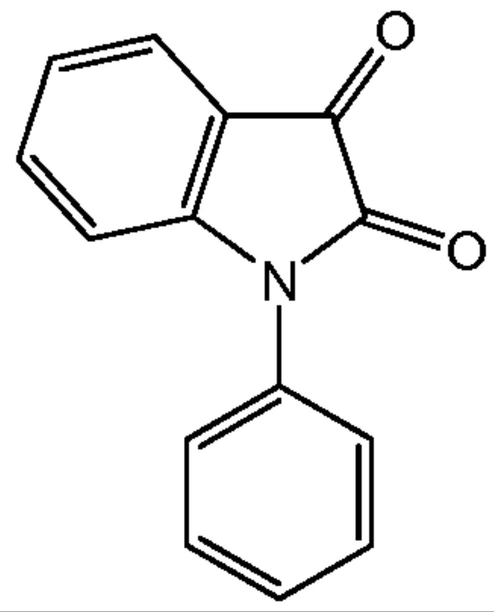
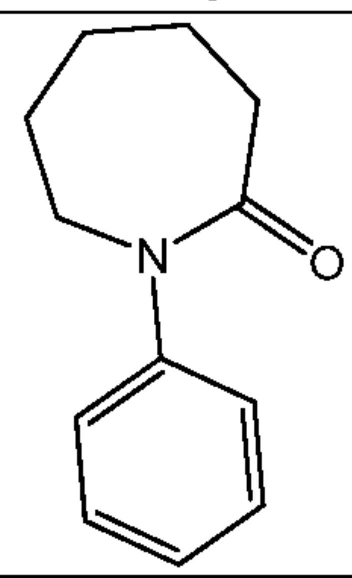
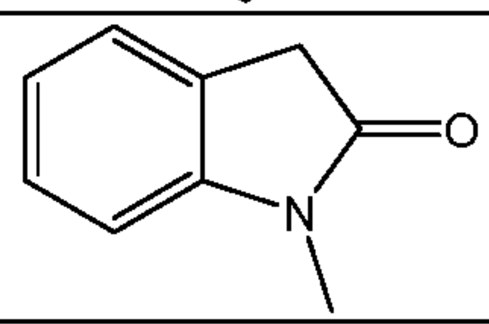
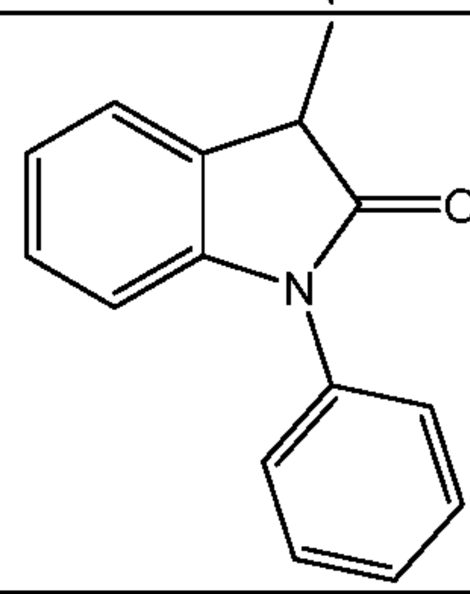
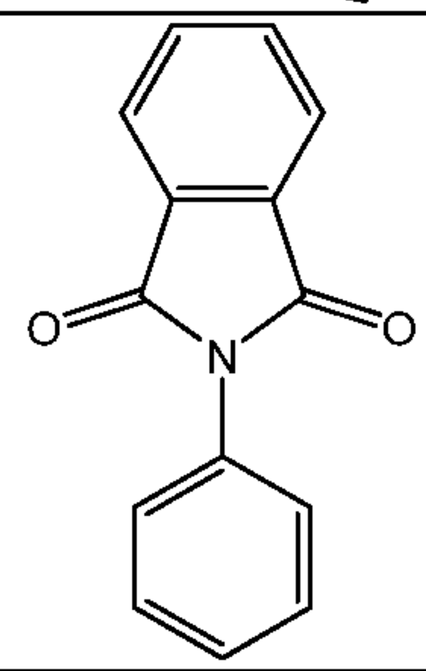
506	
507	
508	
509	
510	
511	
512	
513	
514	
515	
516	
517	
518	

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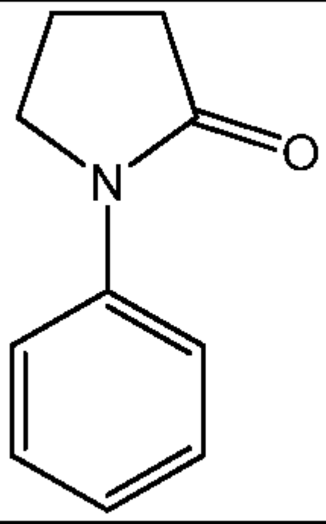
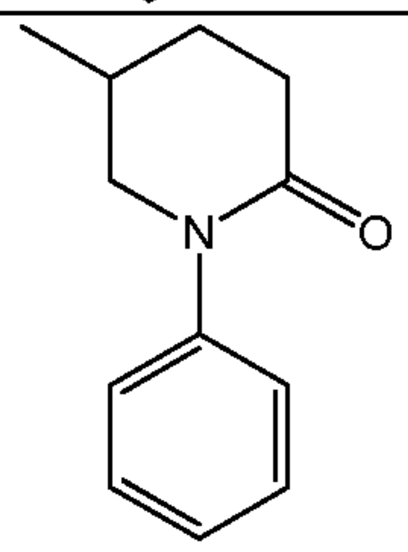
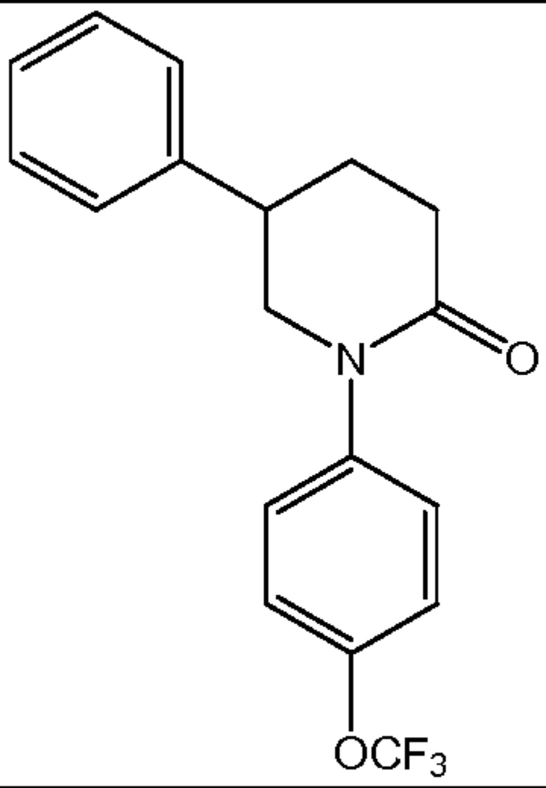
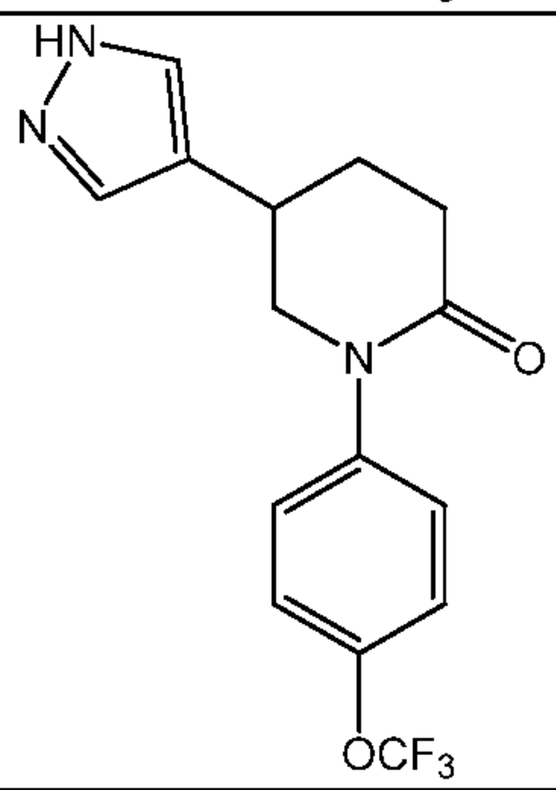
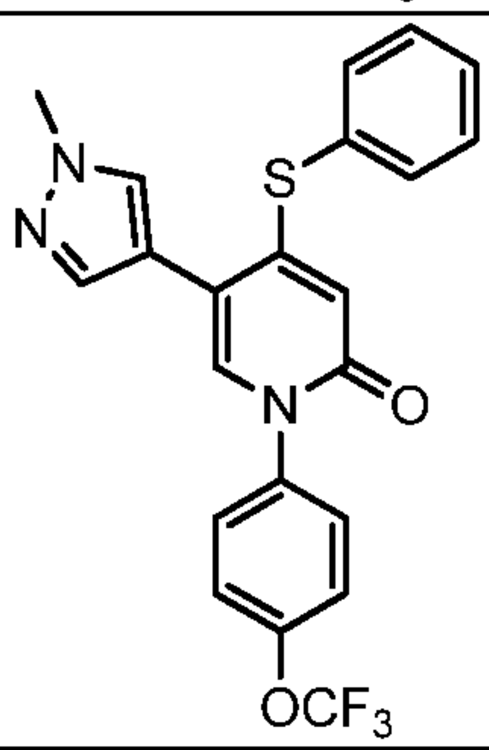
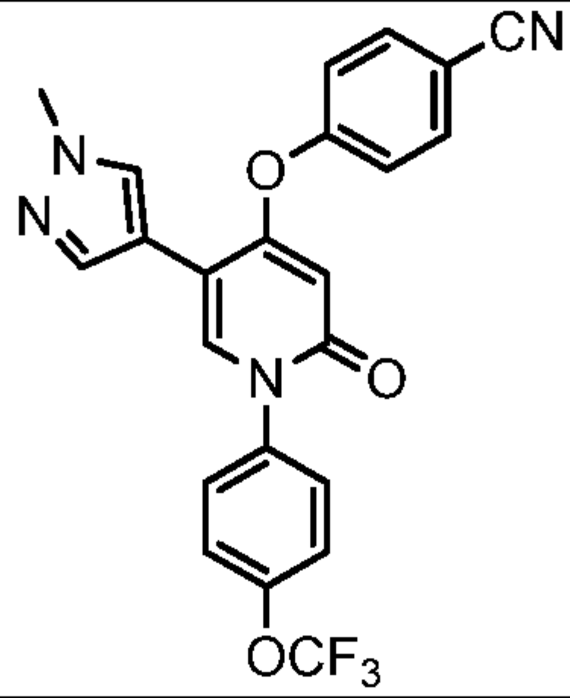
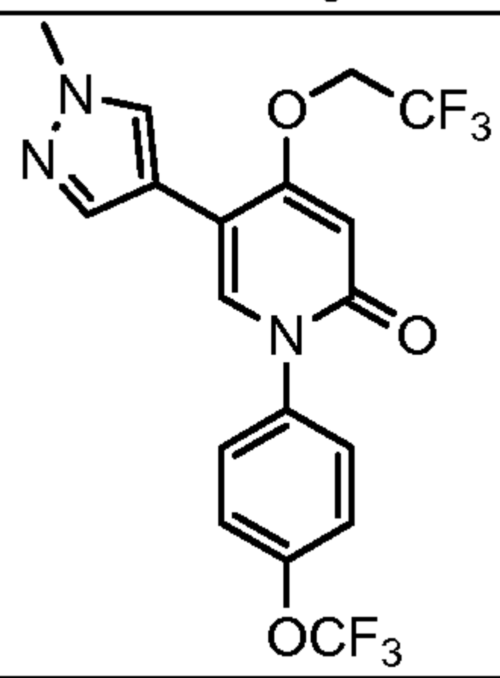
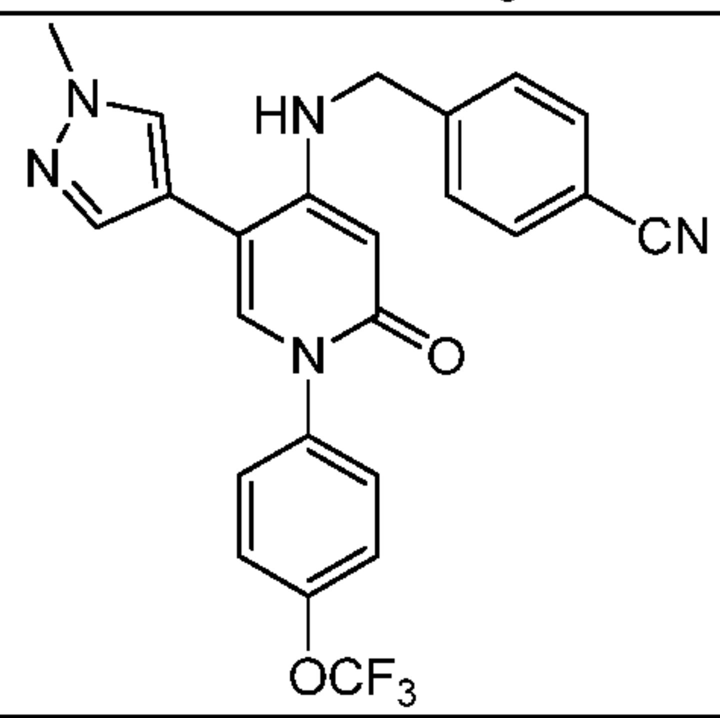
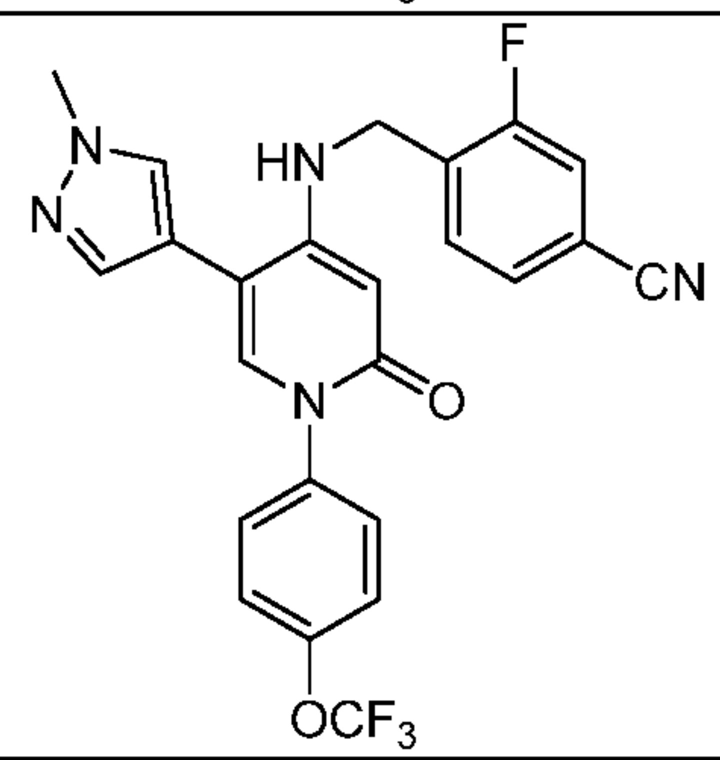
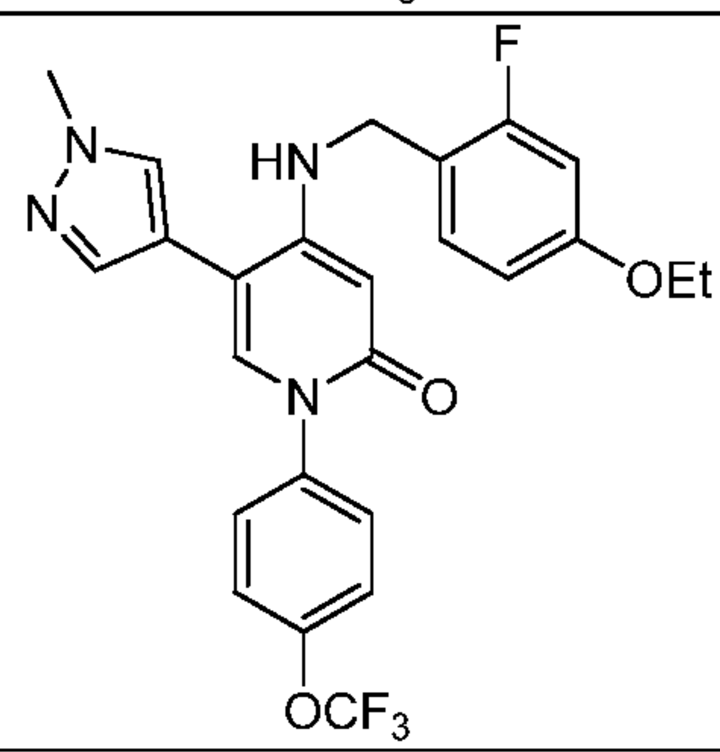
519	
520	 (racemic form of 83/84)
521	
522	
523	
524	
525	
526	
527	
528	

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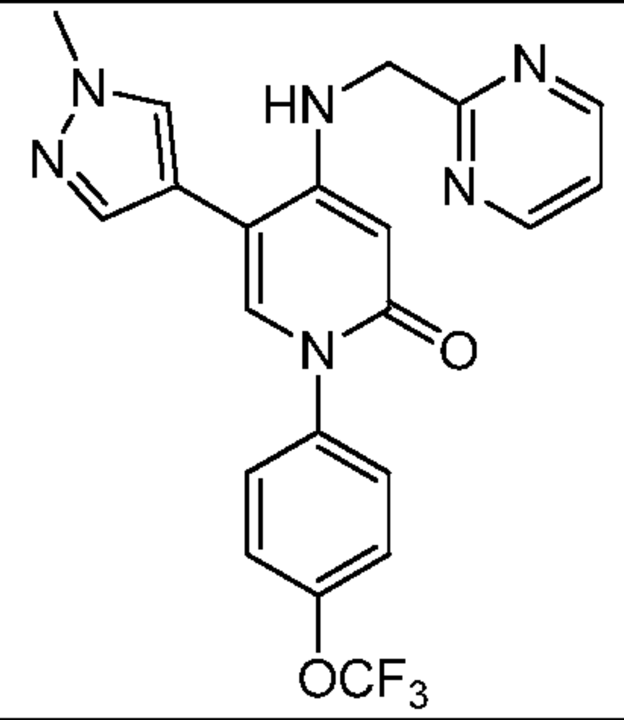
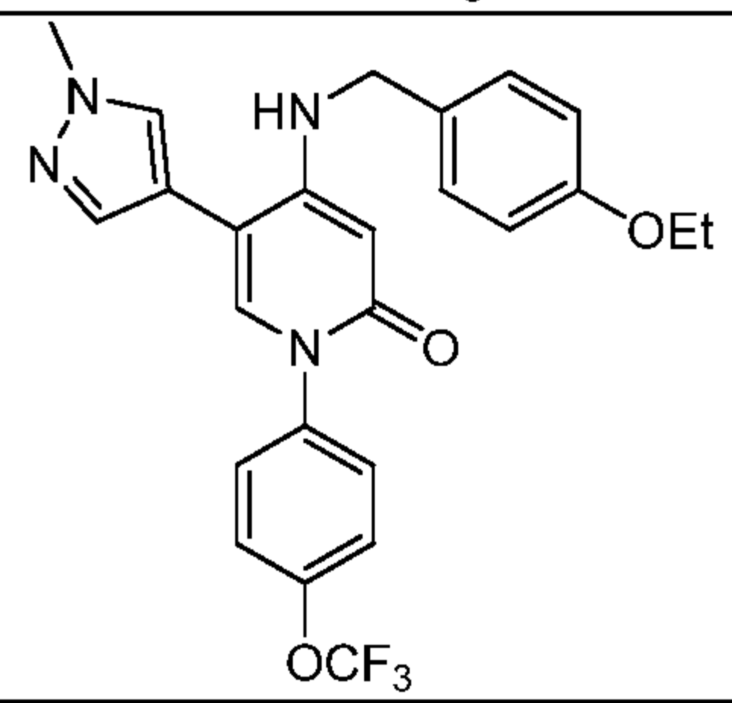
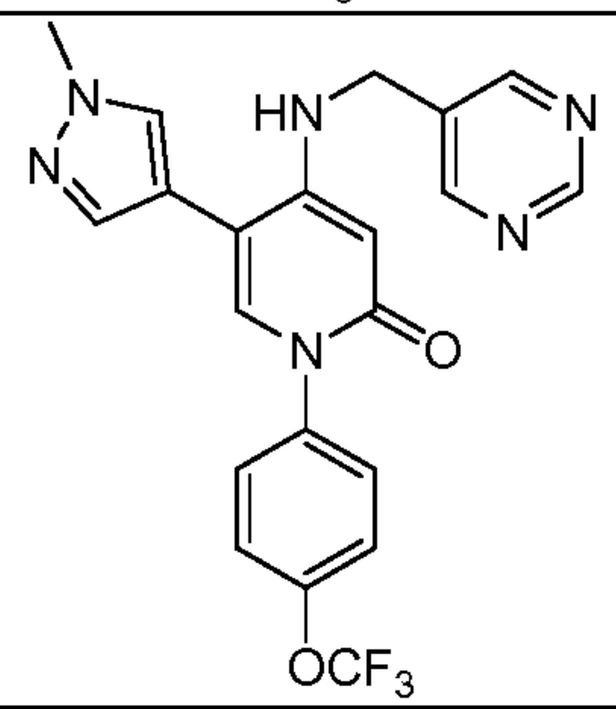
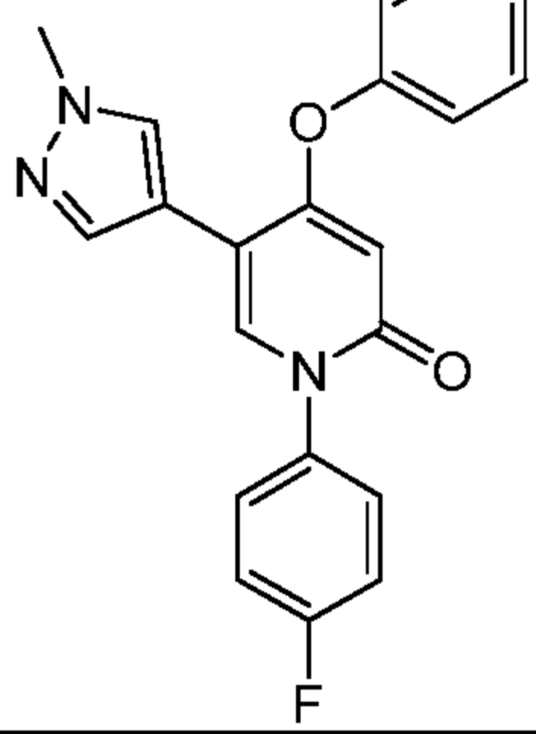
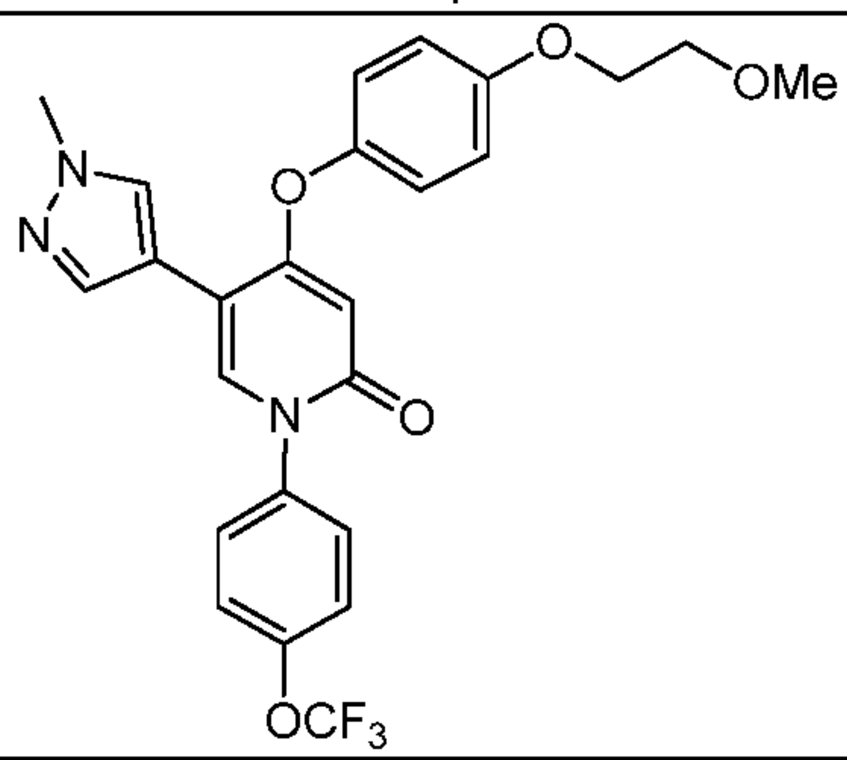
529	
530	
531	
532	
533	

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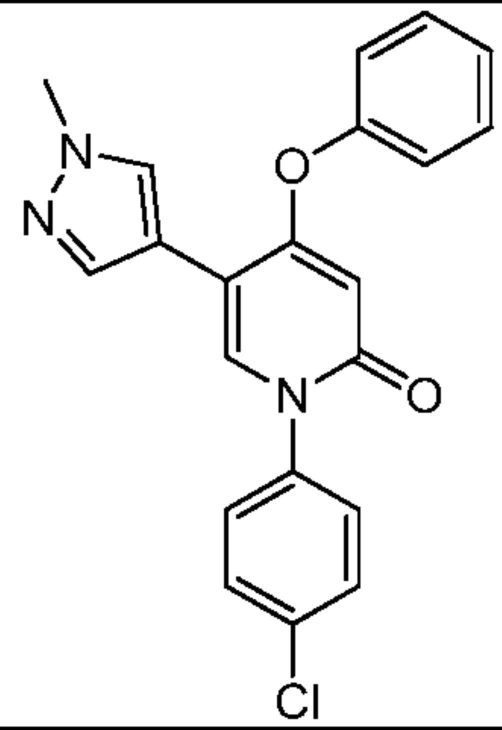
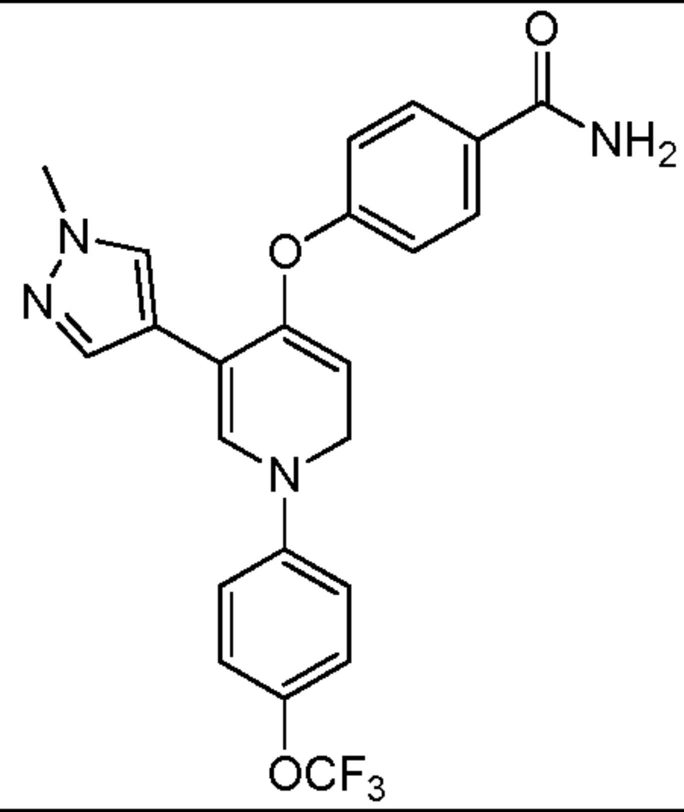
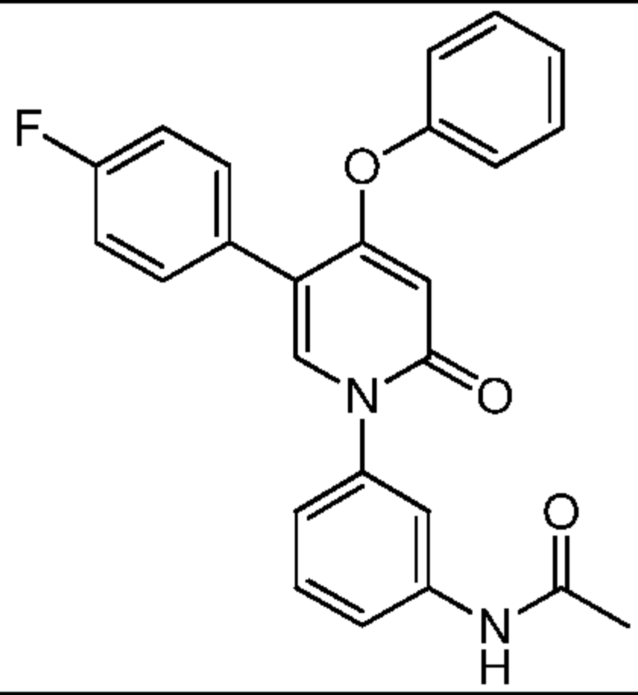
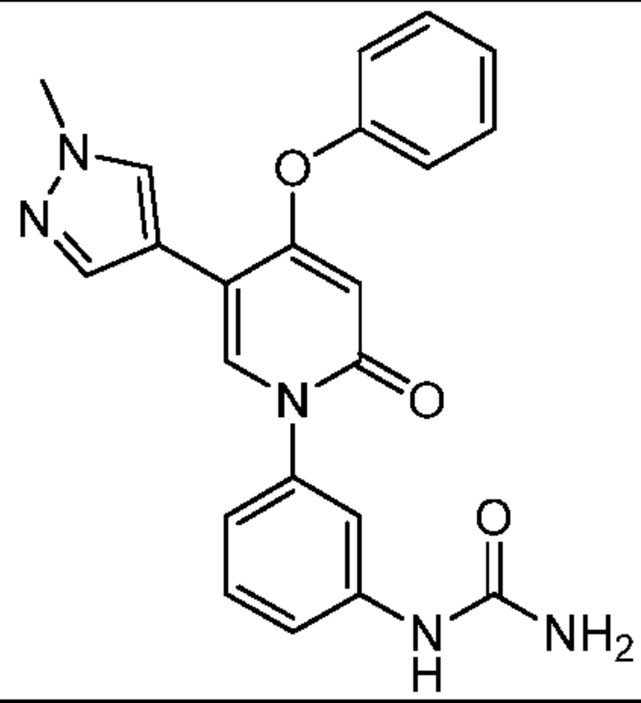
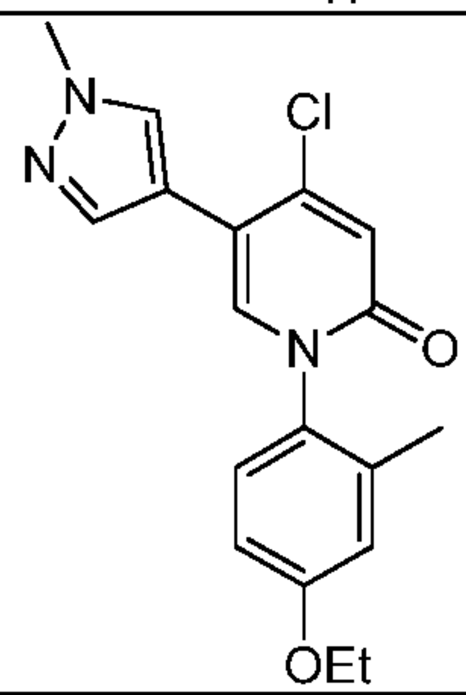
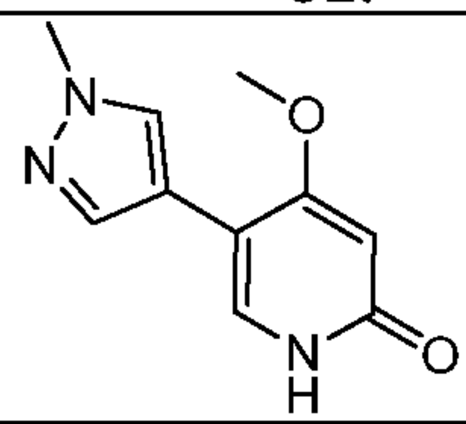
534	
535	
536	
537	
538	
539	

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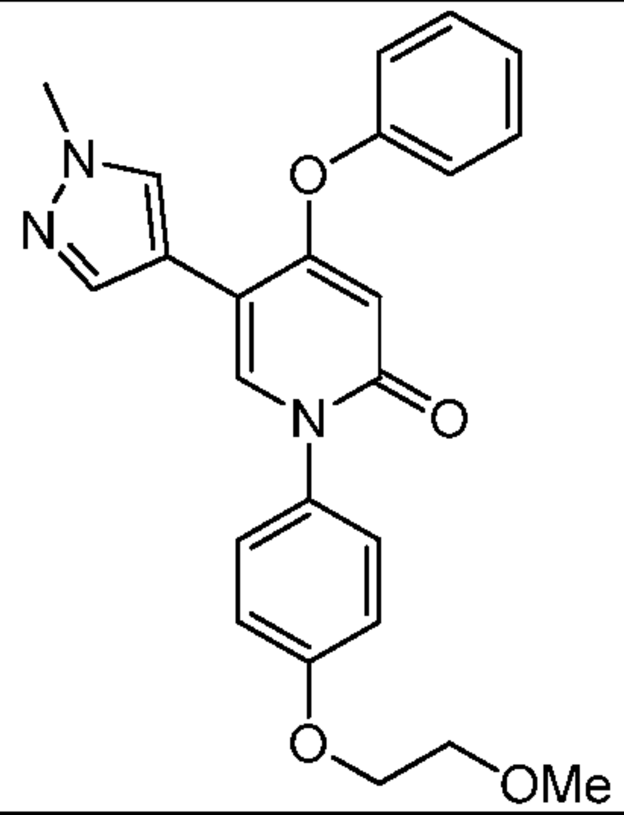
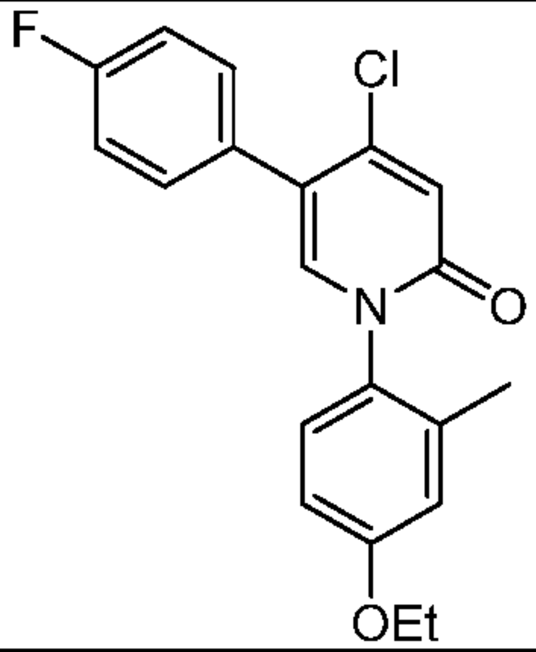
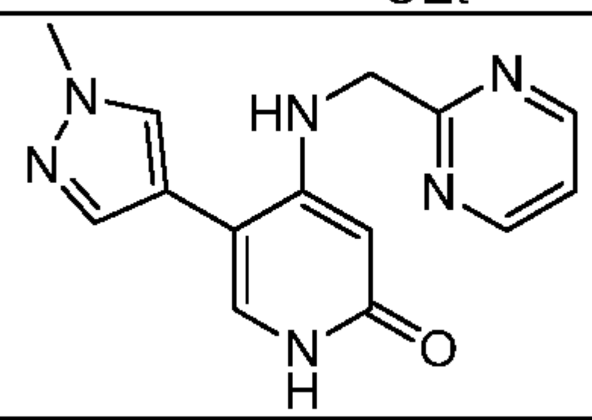
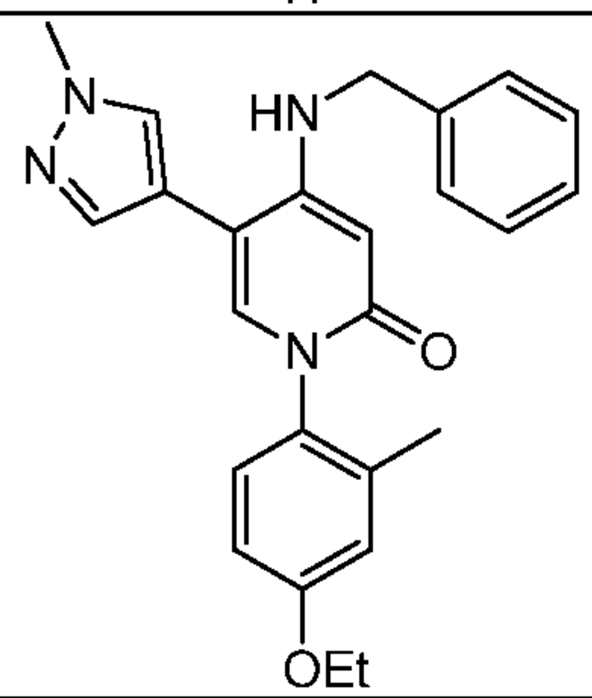
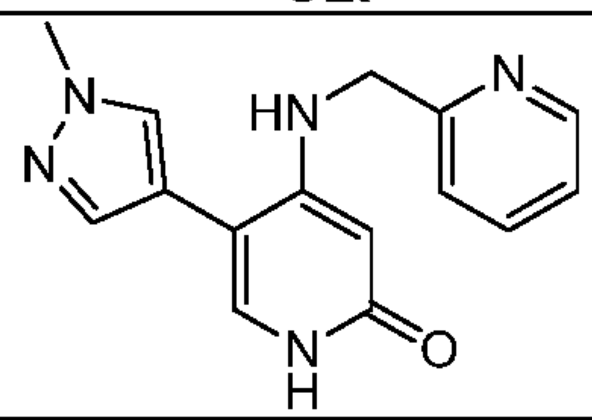
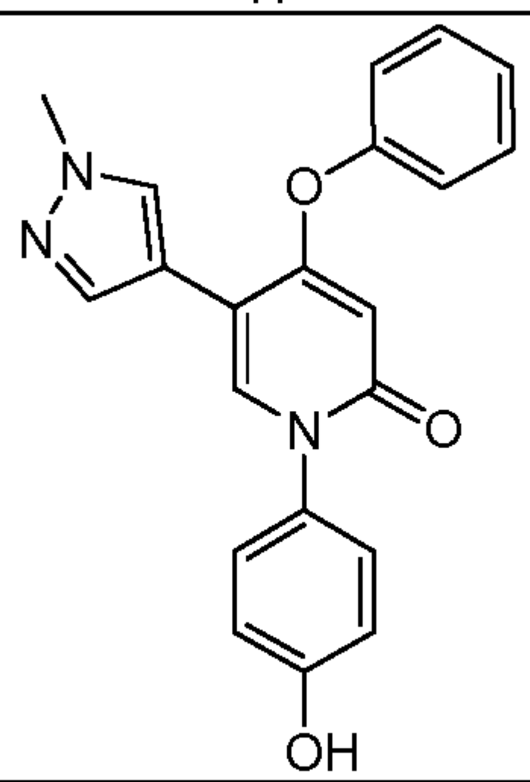
540	
541	
542	
543	
544	
545	

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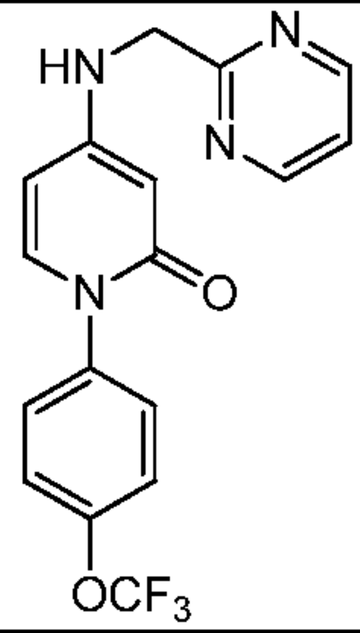
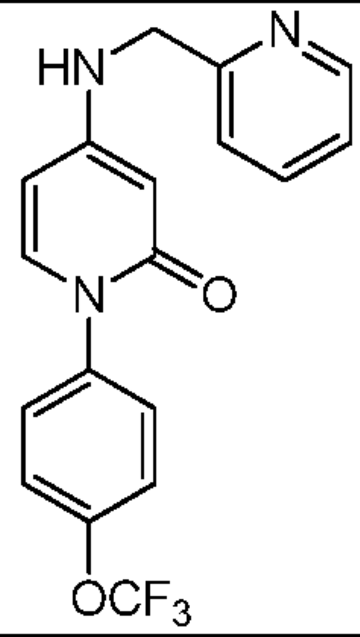
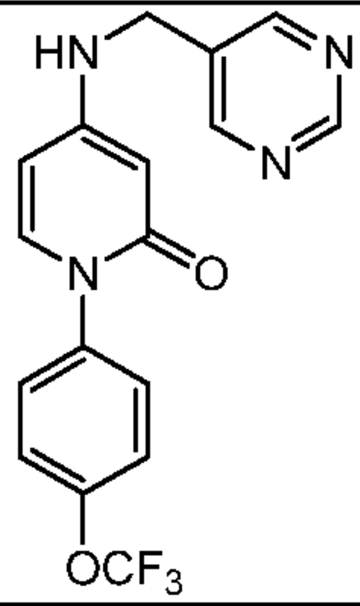
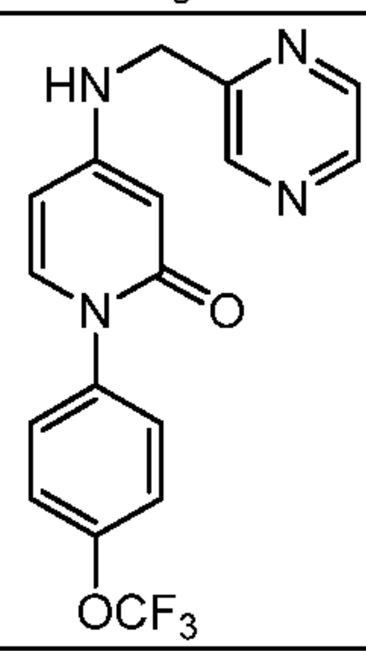
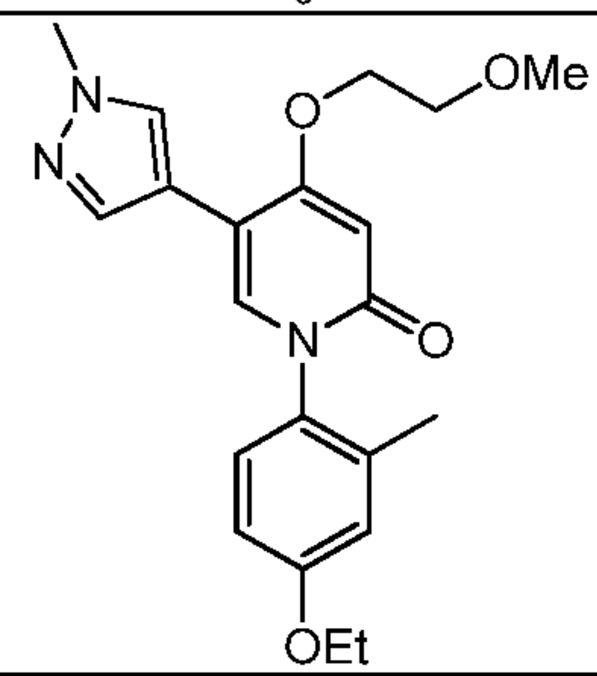
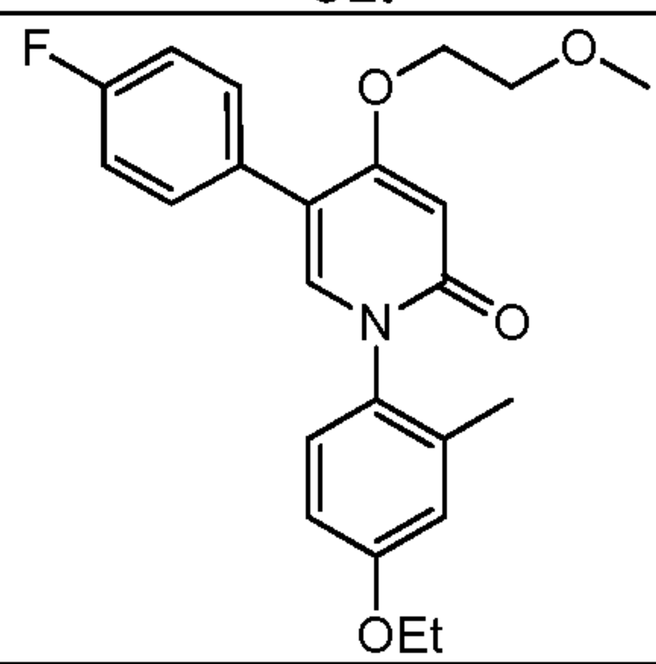
546	
547	
548	
549	
550	
551	

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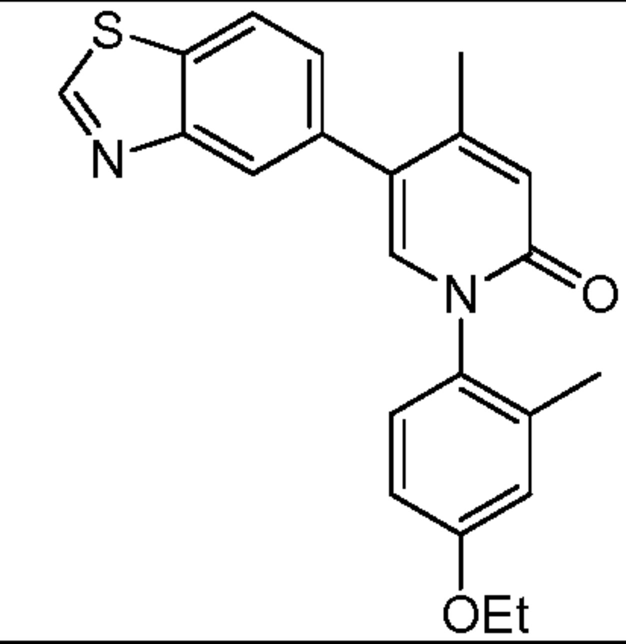
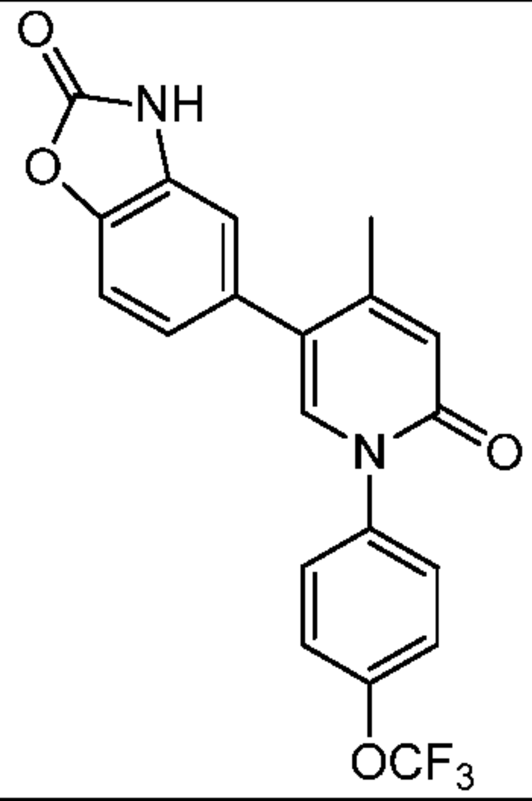
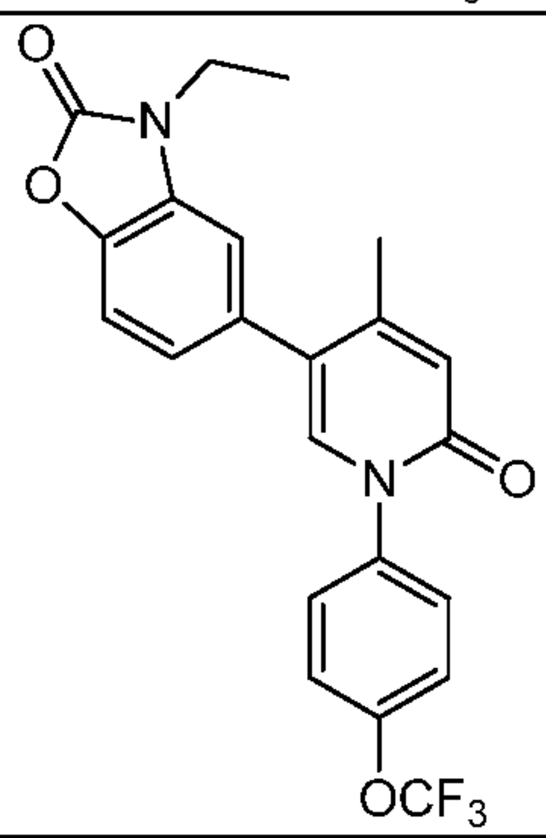
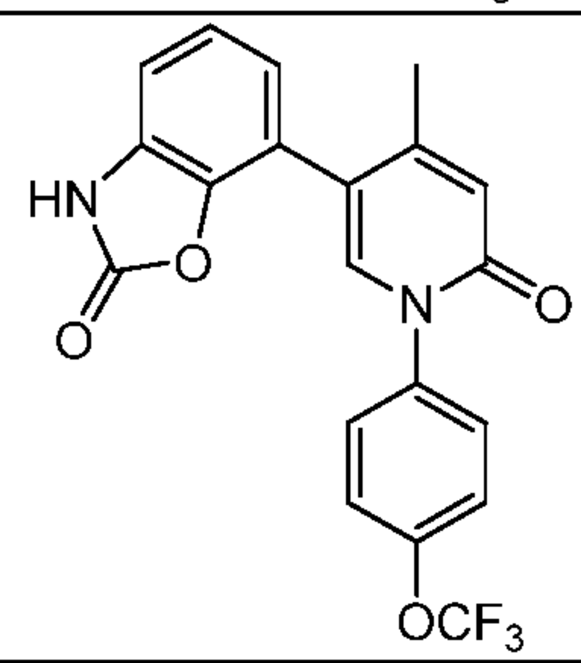
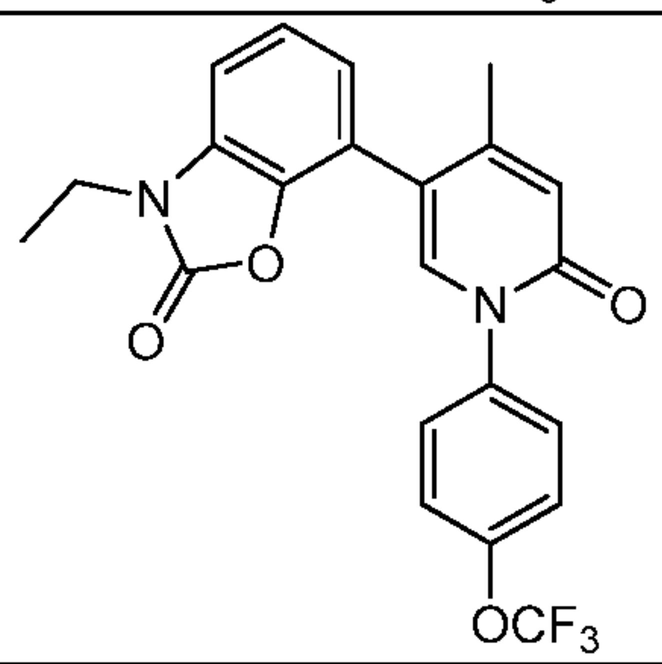
552	
553	
554	
555	
556	

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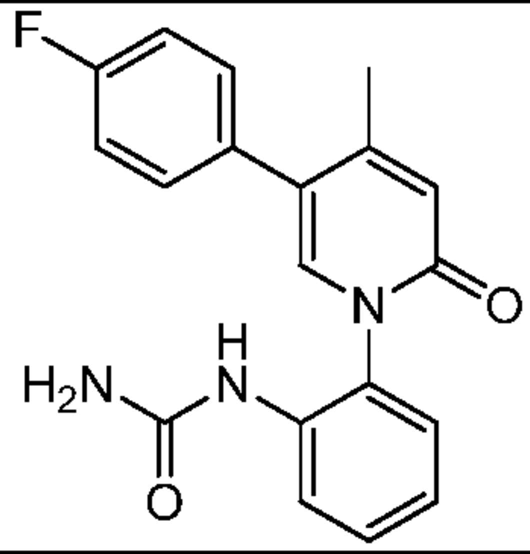
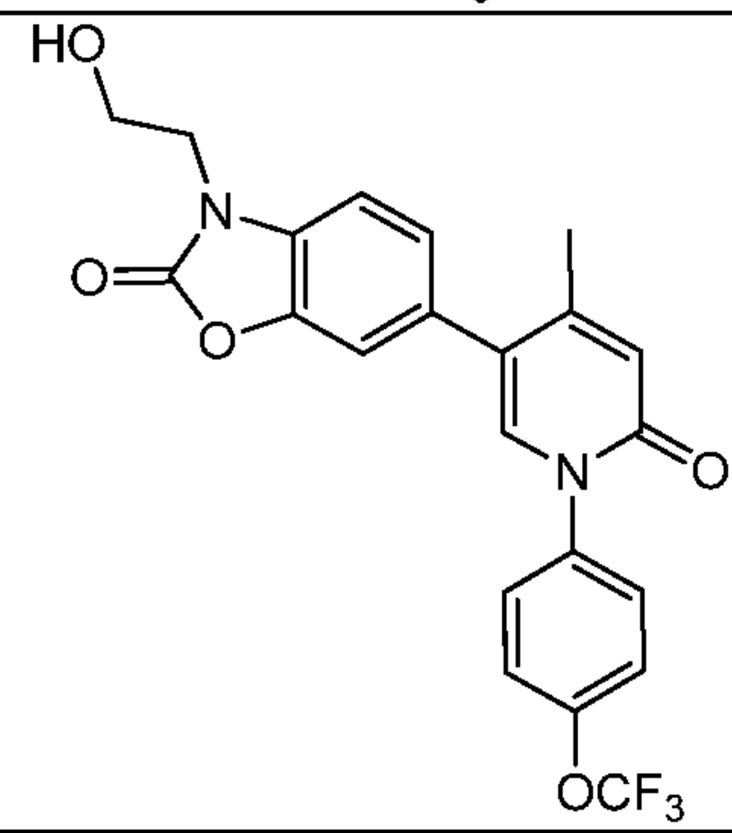
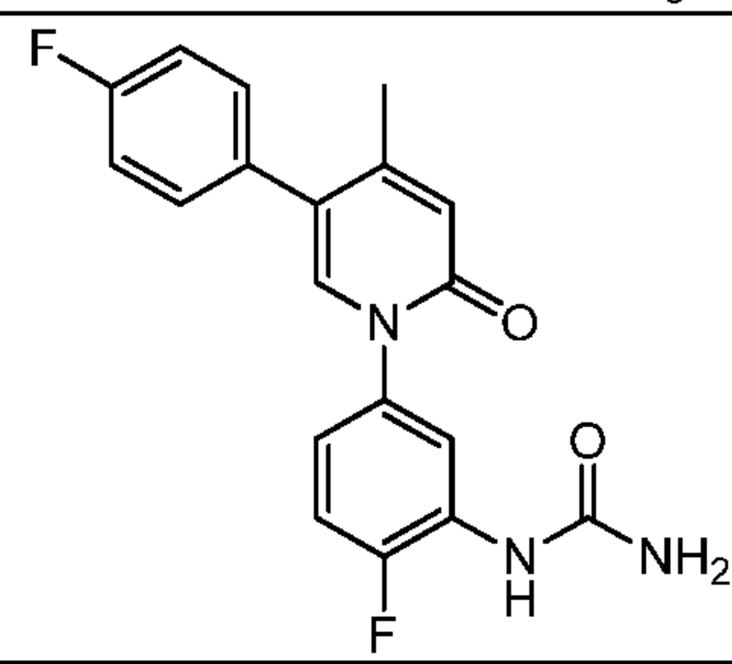
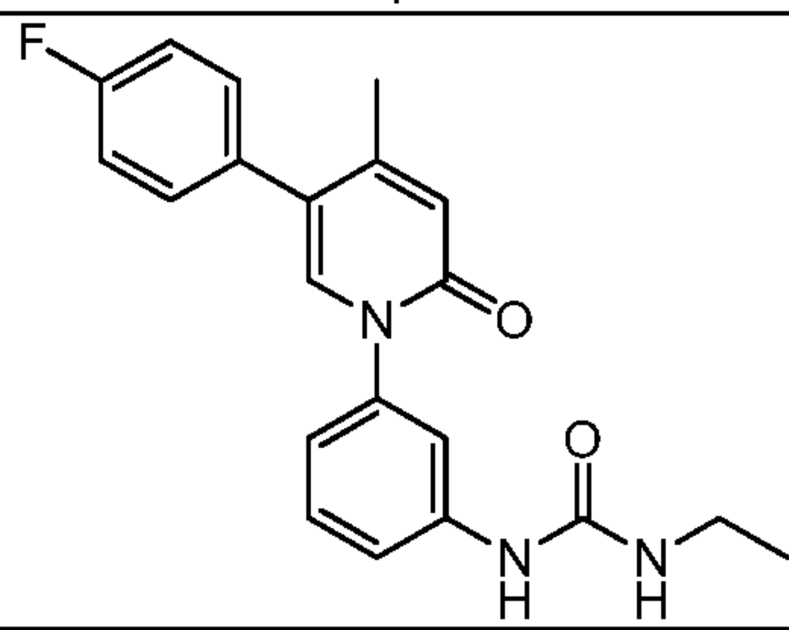
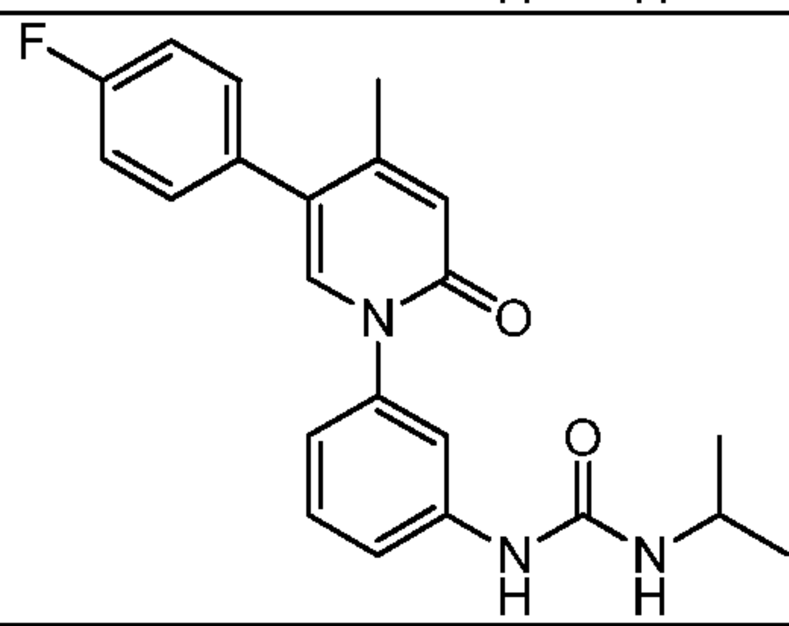
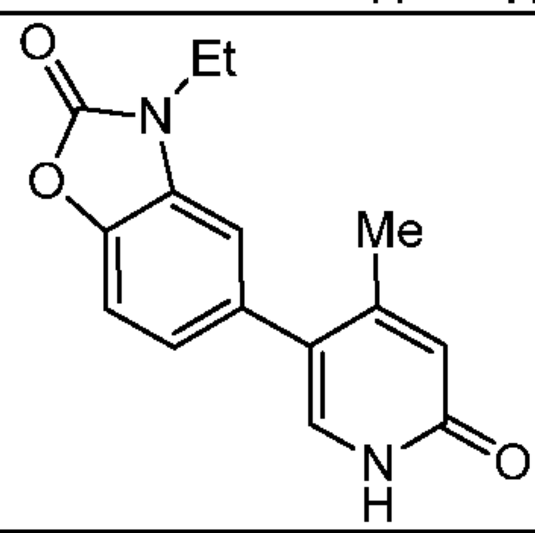
557	
558	
559	
560	
561	
562	

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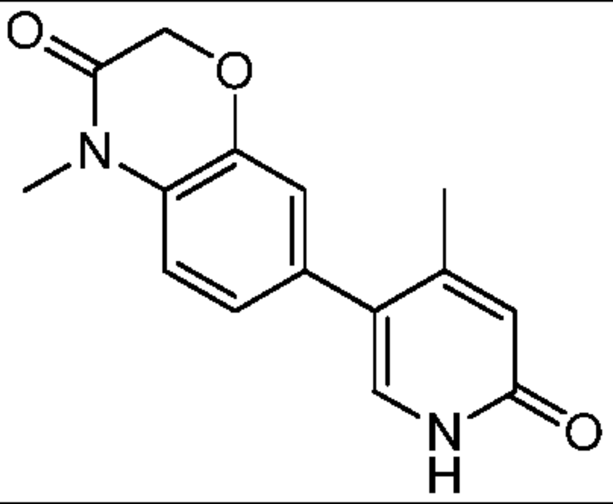
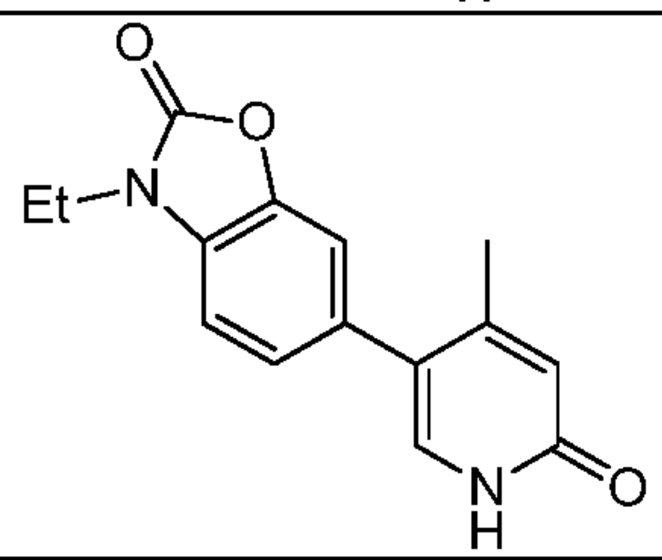
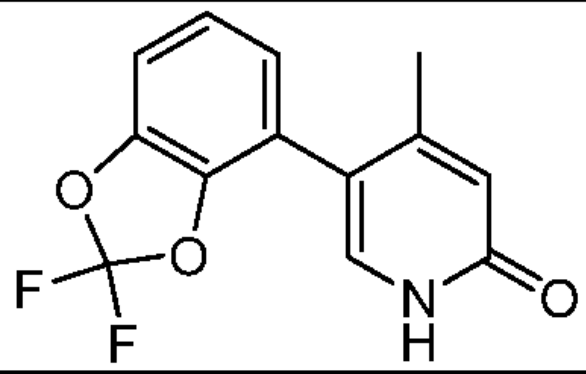
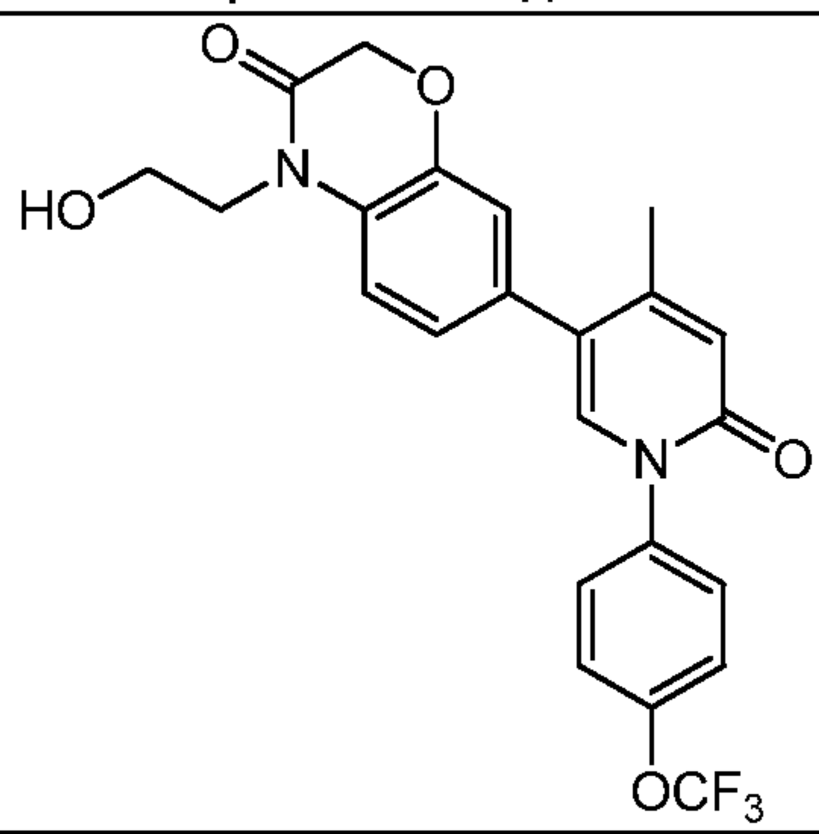
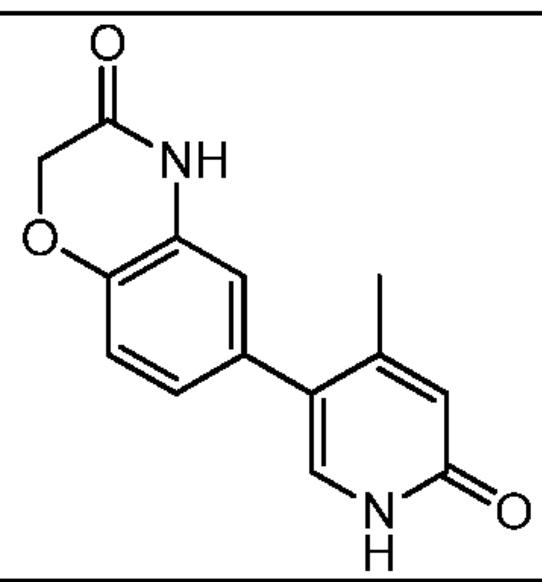
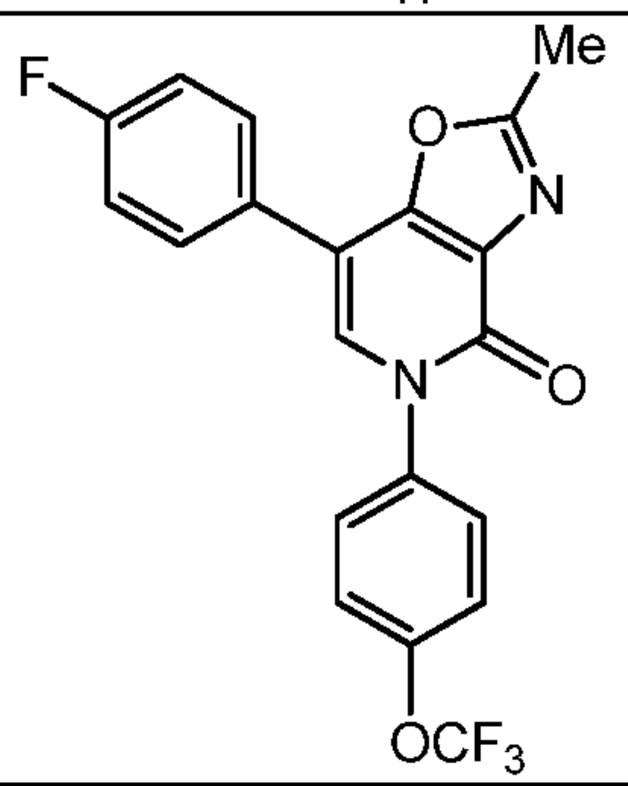
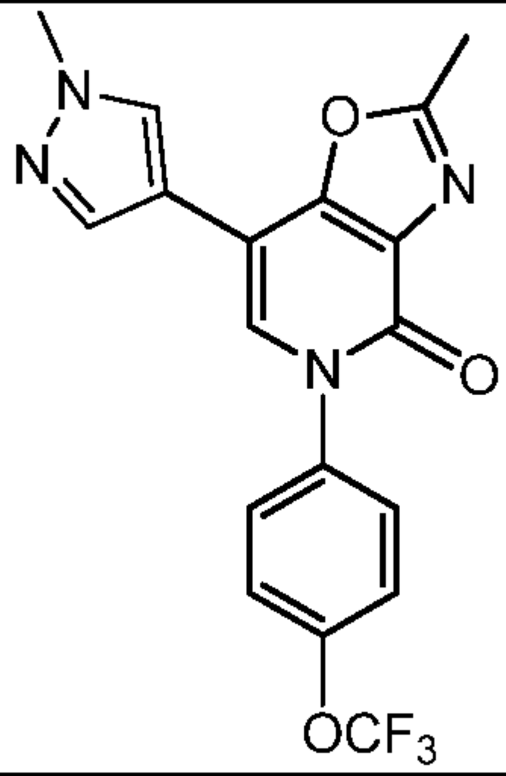
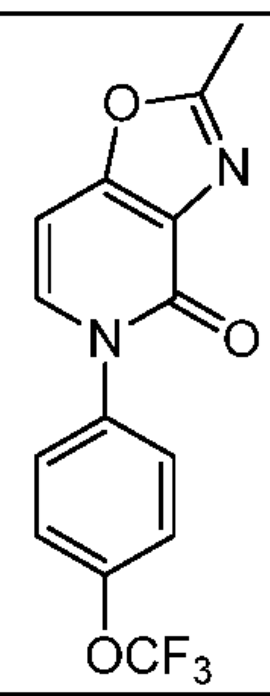
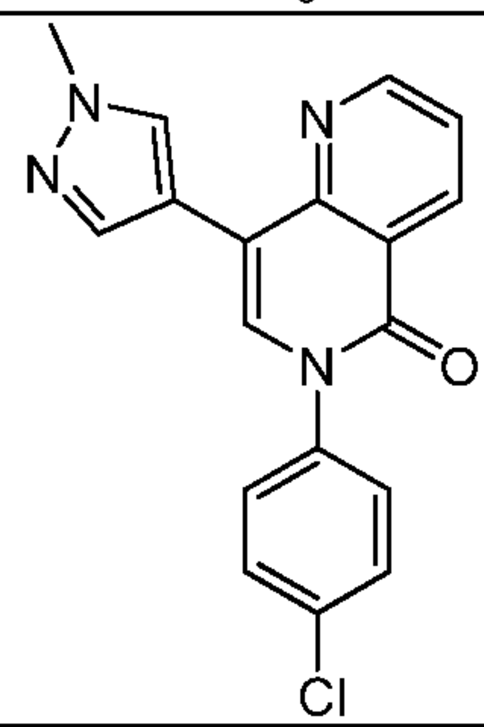
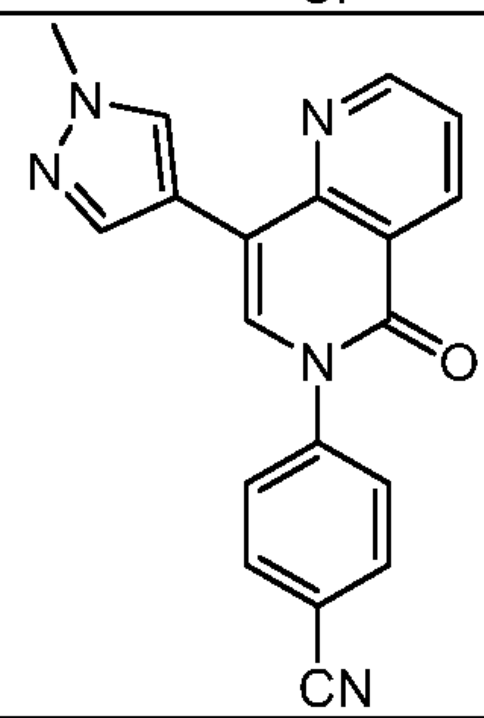
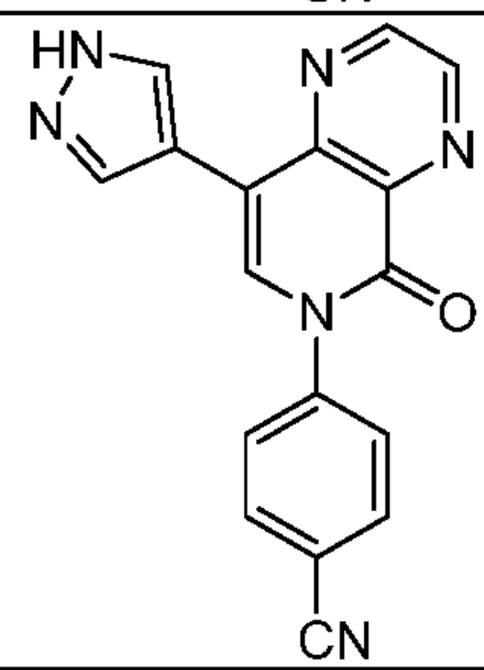
563	
564	
565	
566	
567	
568	
569	
570	
571	
572	
573	

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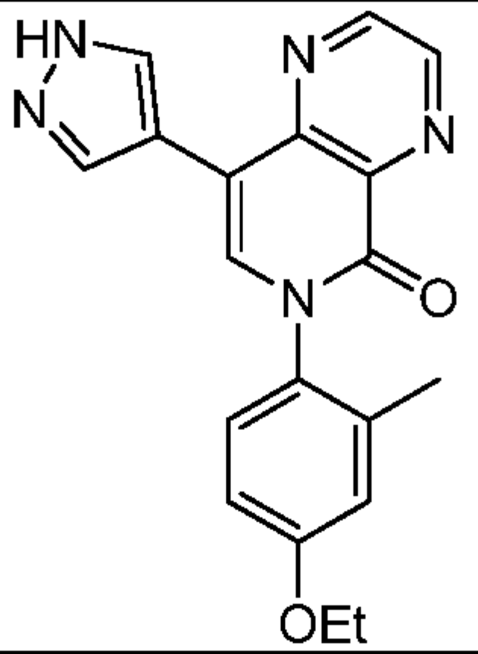
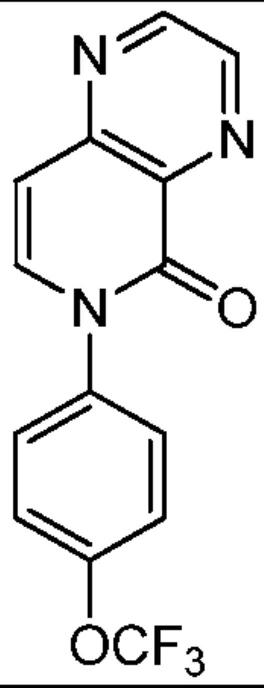
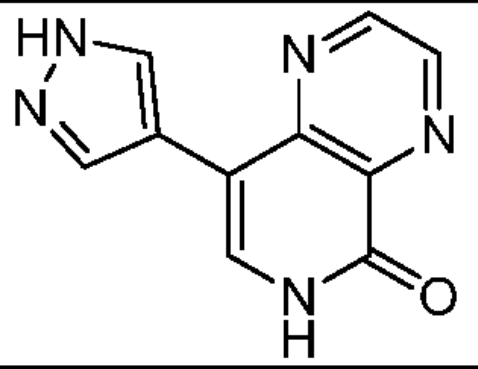
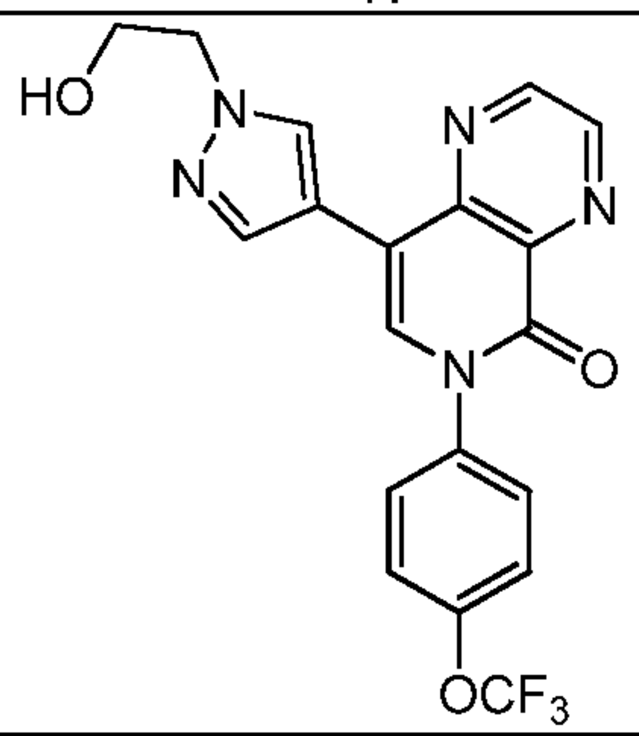
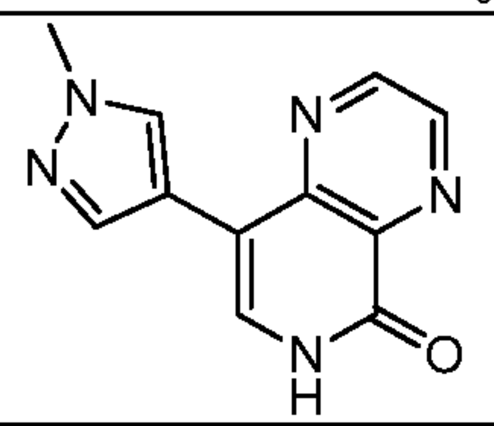
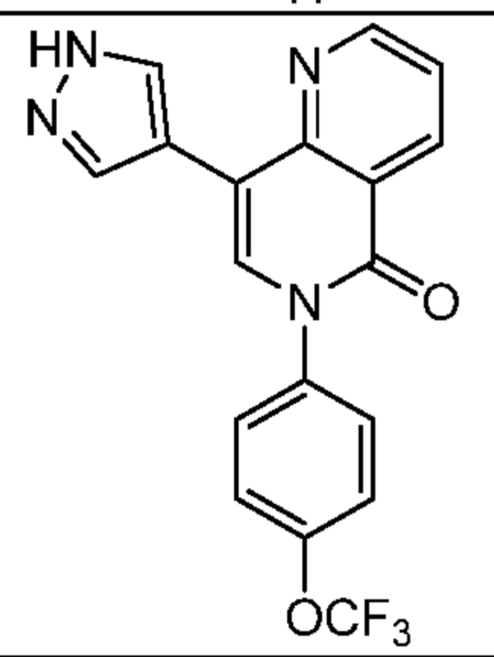
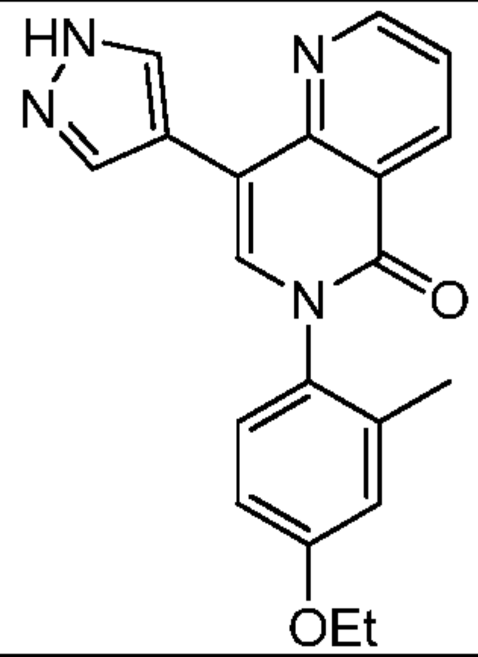
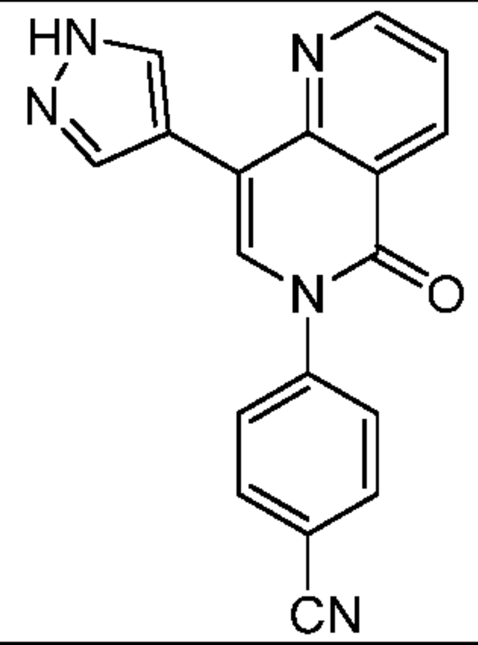
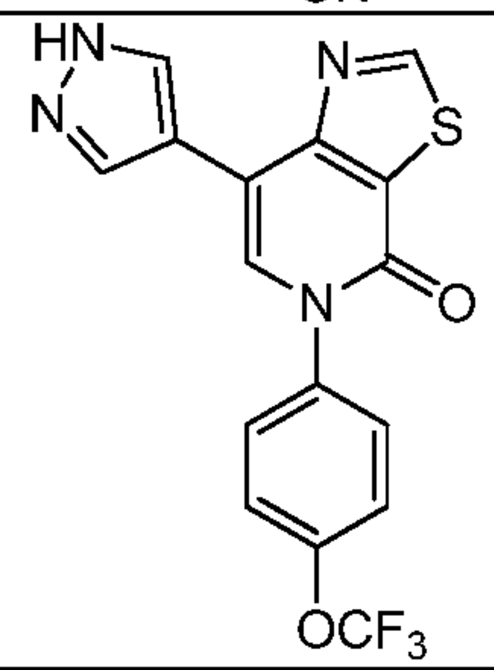
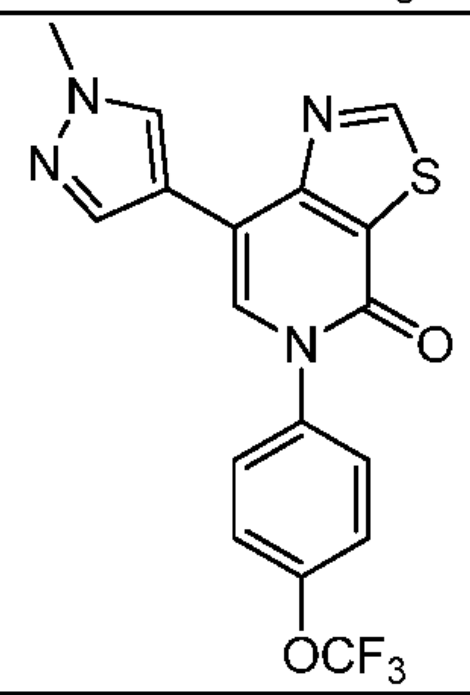
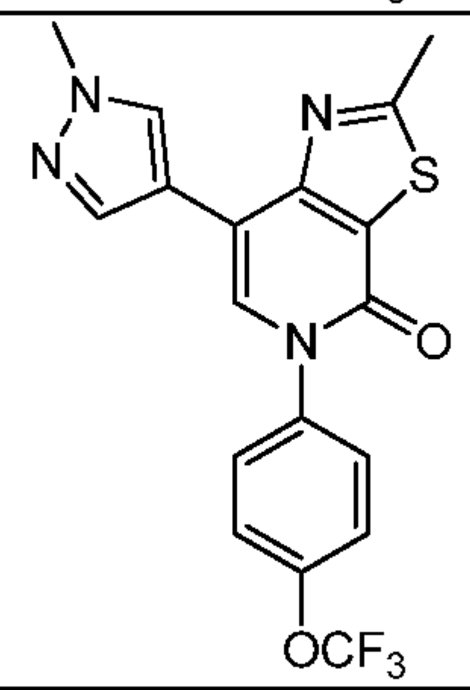
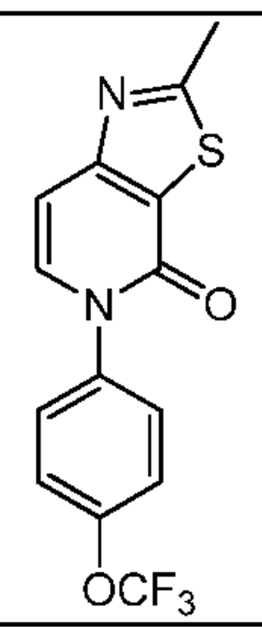
574	
575	
576	
577	
578	
579	
580	
581	
582	
583	
584	
585	

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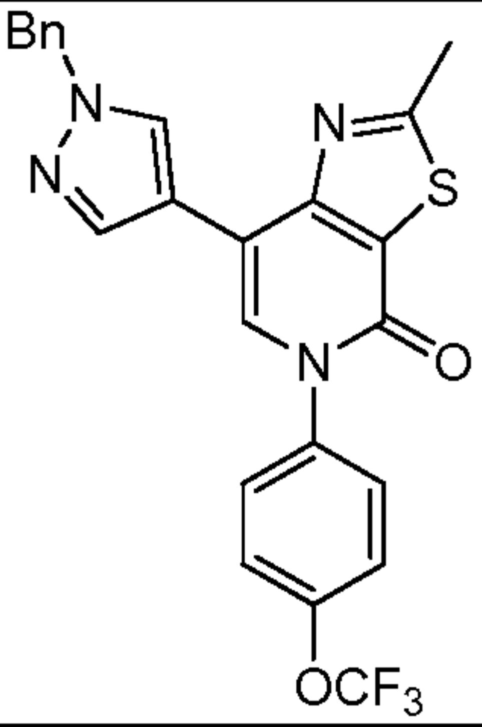
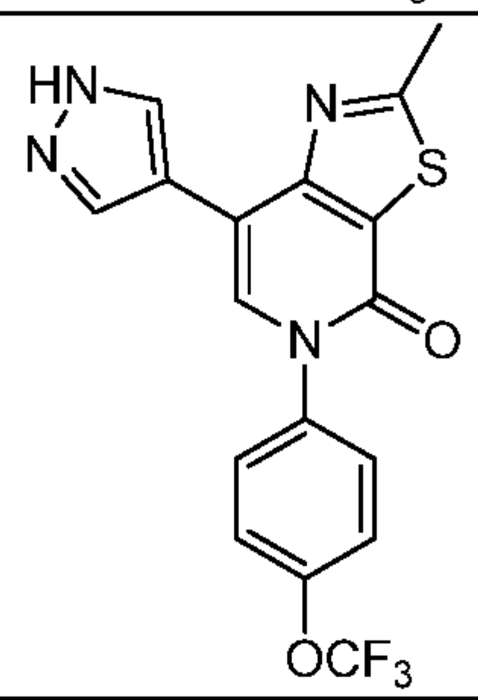
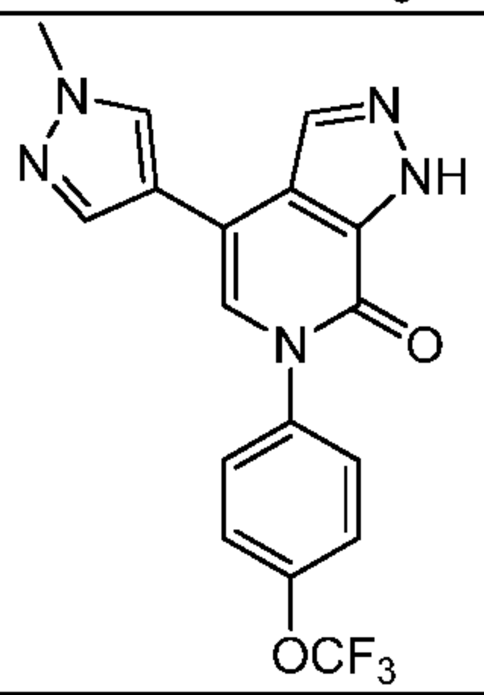
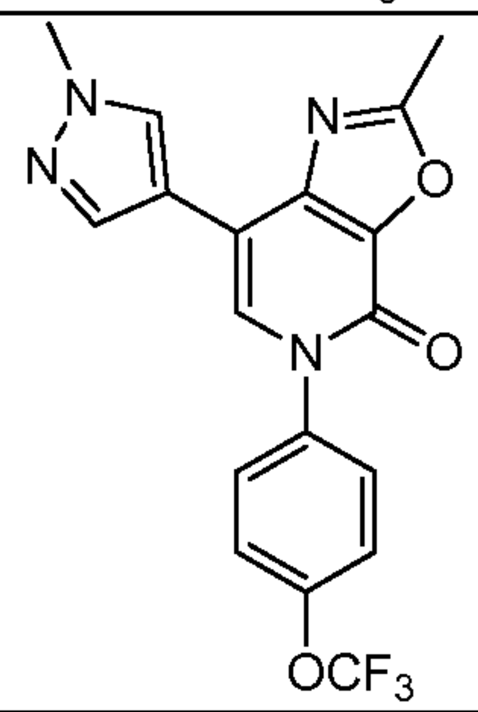
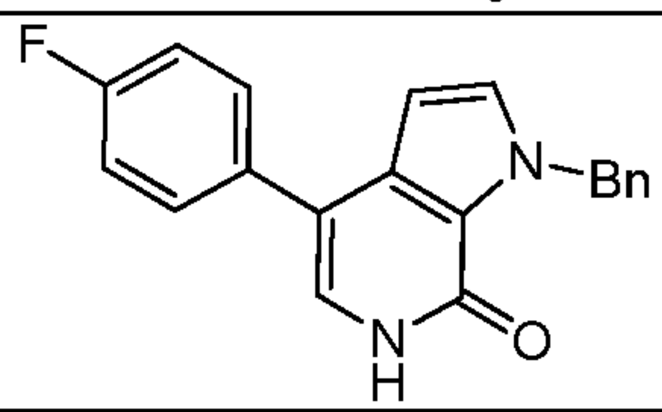
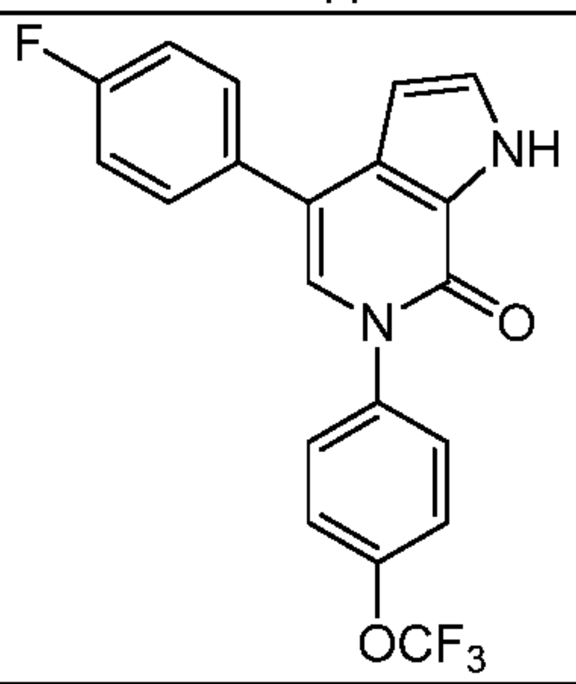
586	
587	
588	
589	
590	
591	

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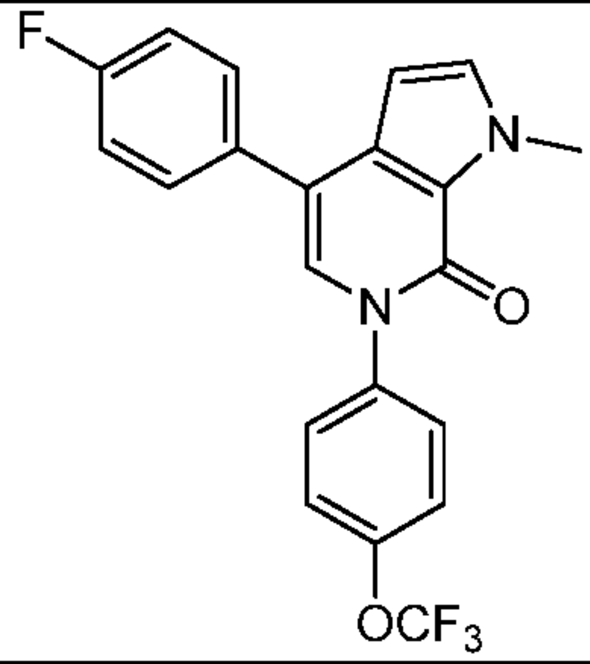
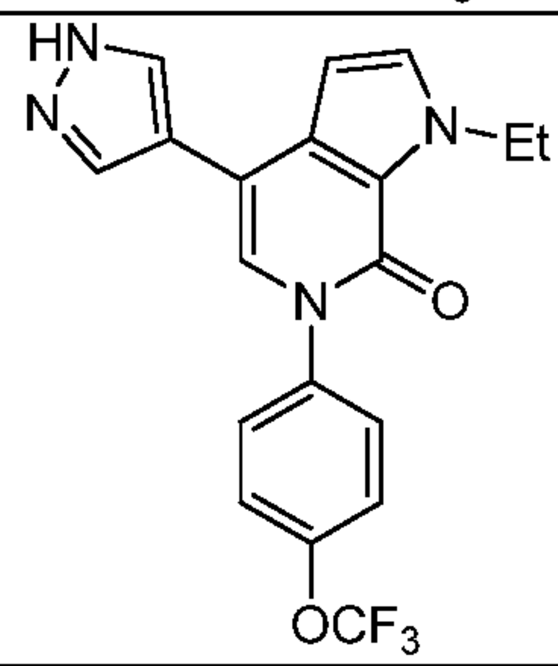
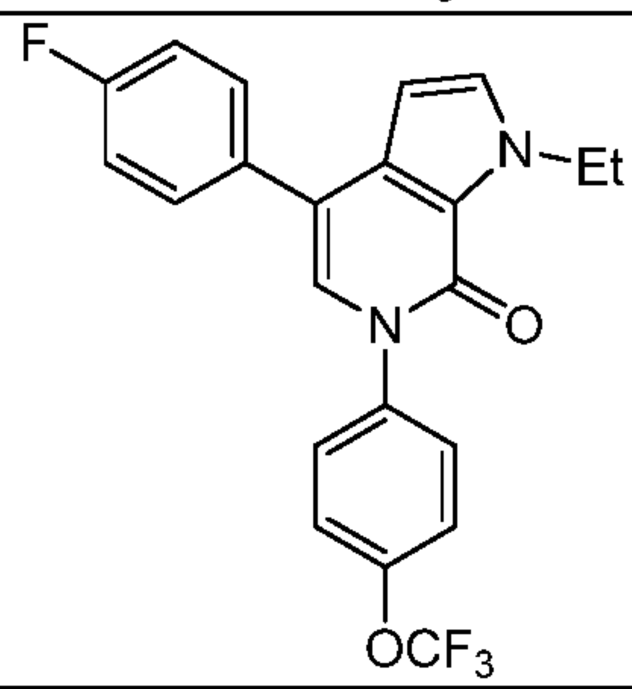
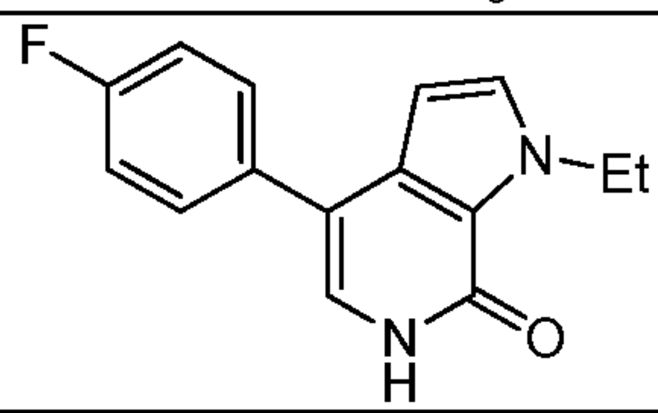
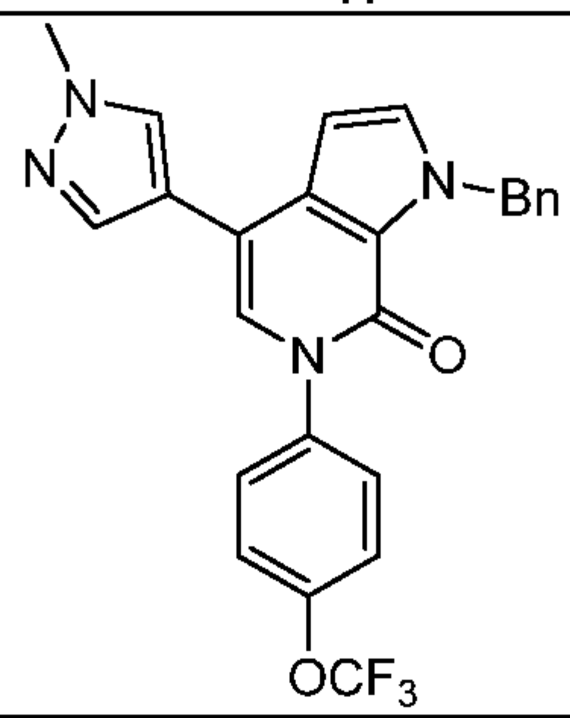
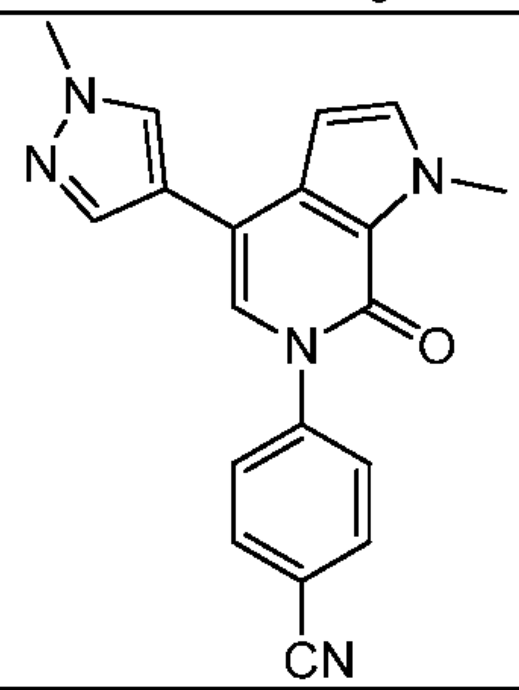
592	
593	
594	
595	
596	
597	

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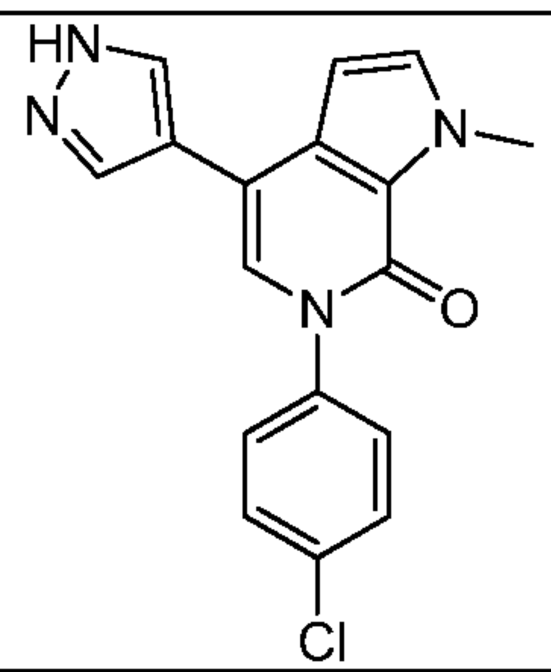
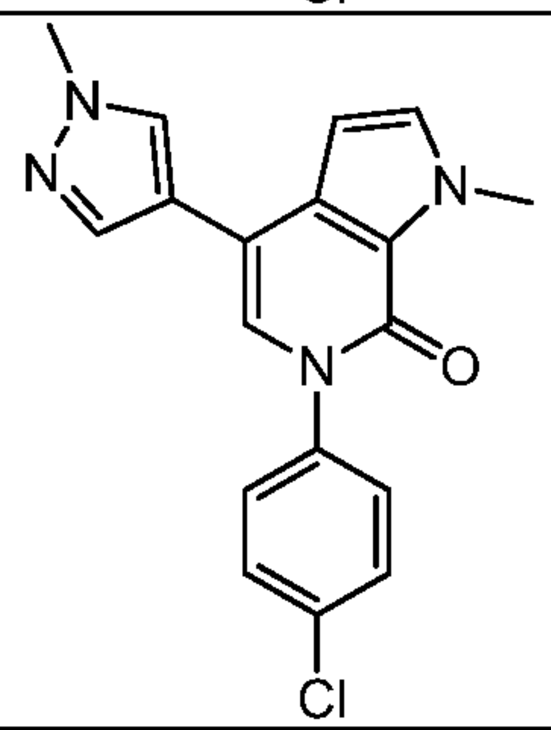
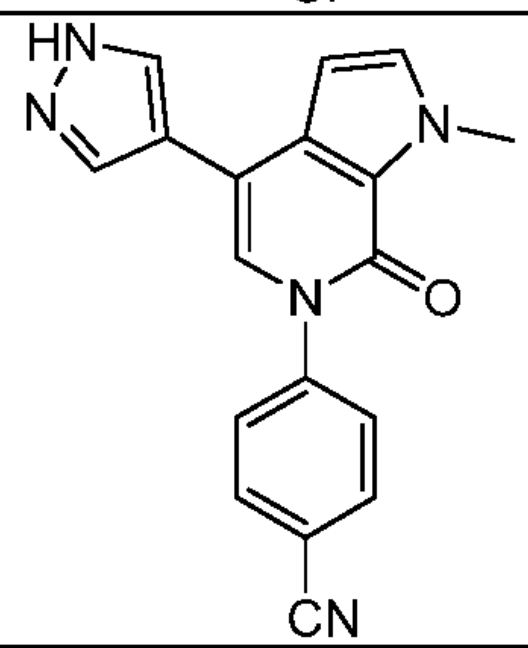
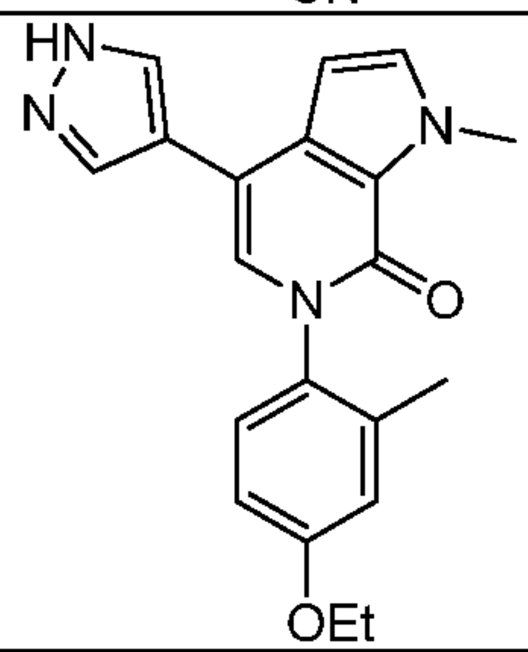
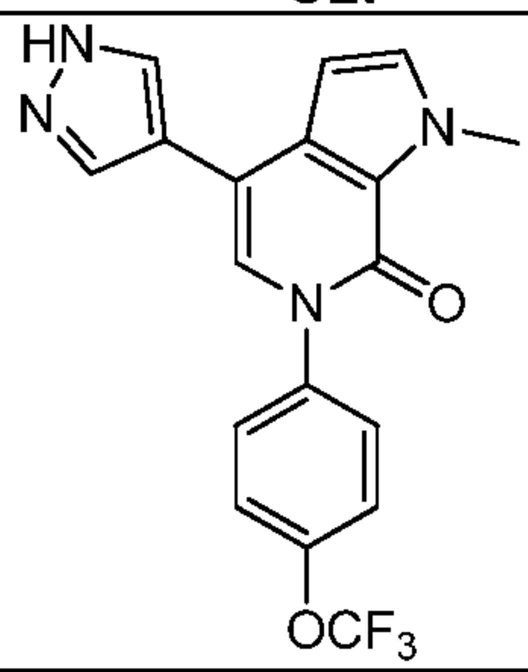
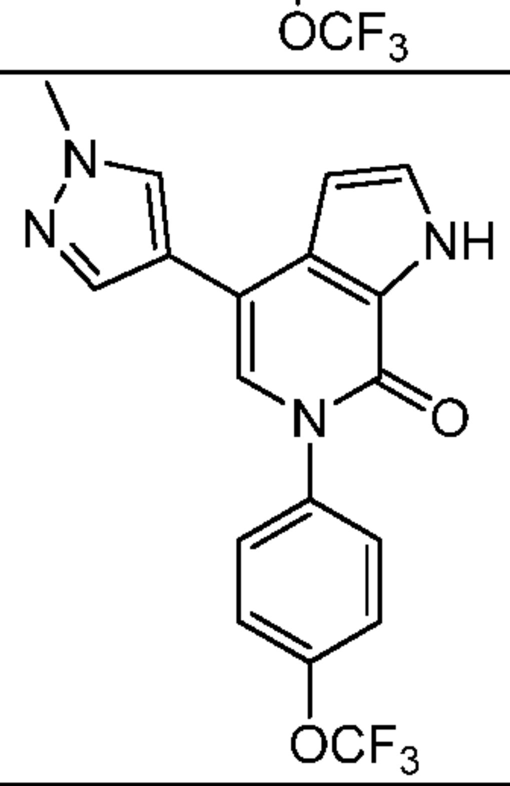
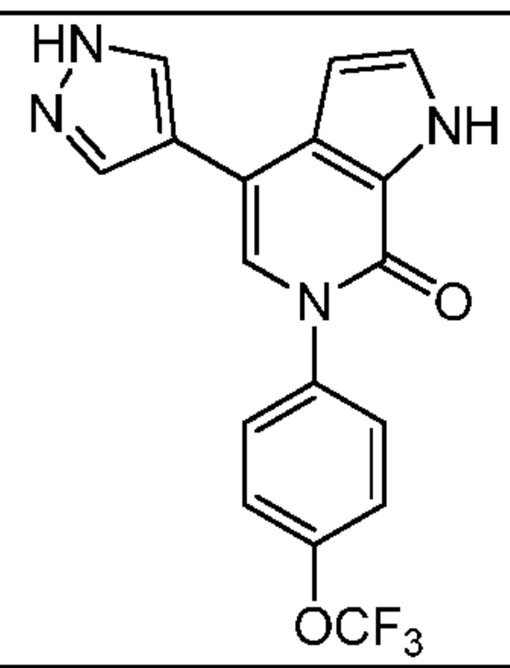
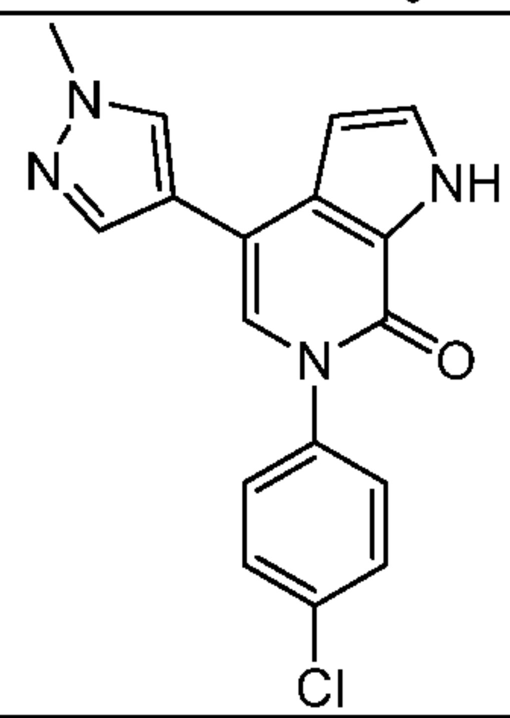
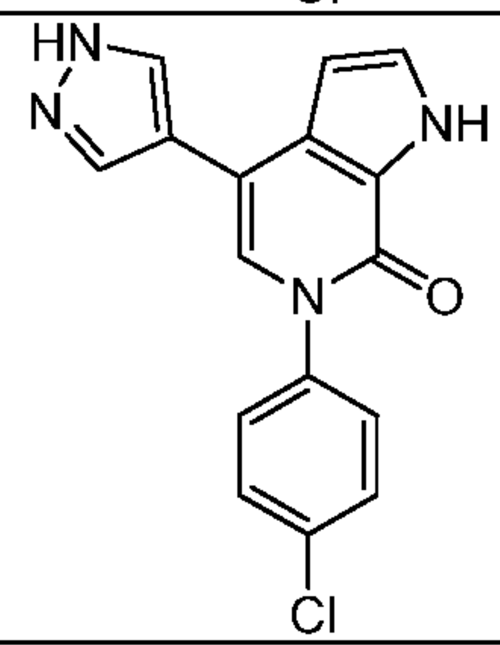
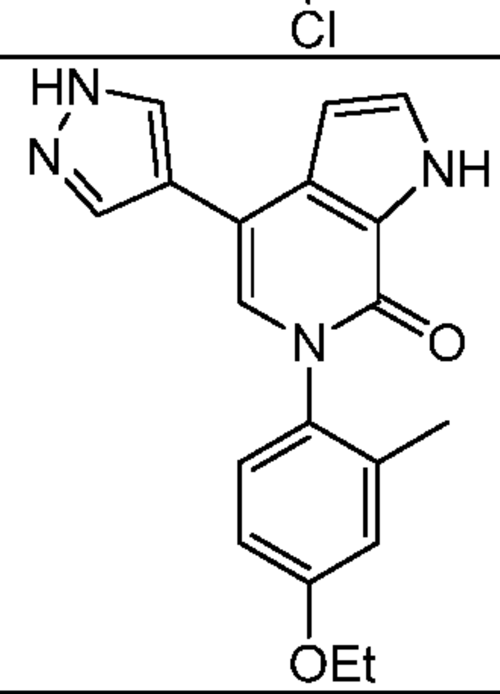
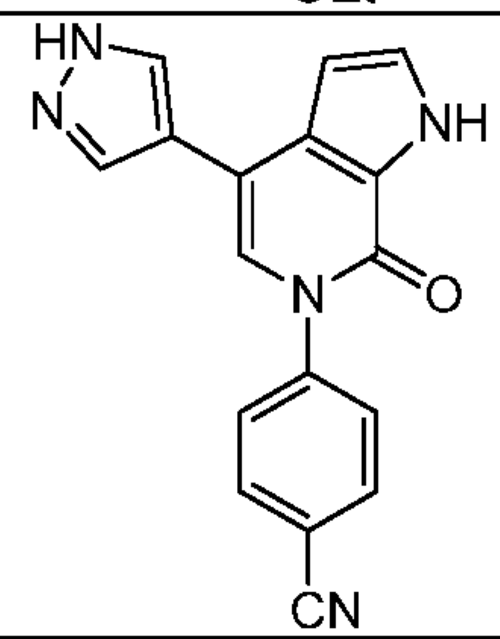
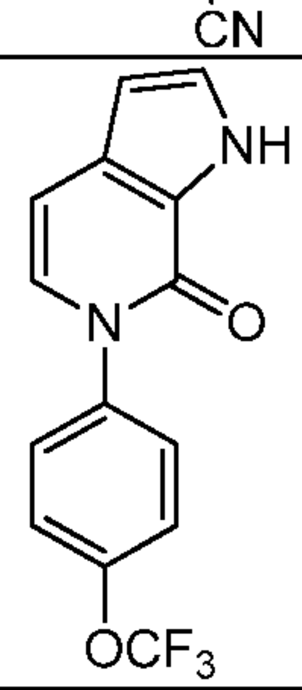
598	
599	
600	
601	
602	
603	
604	
605	
606	
607	
608	
609	

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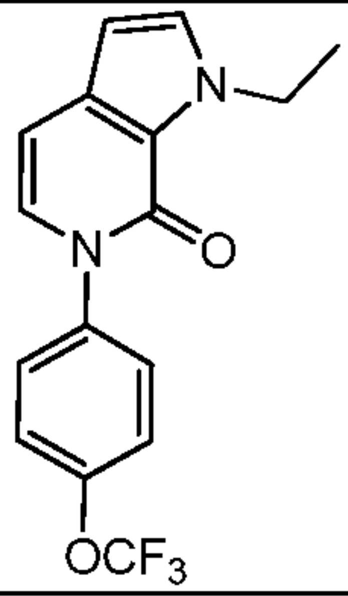
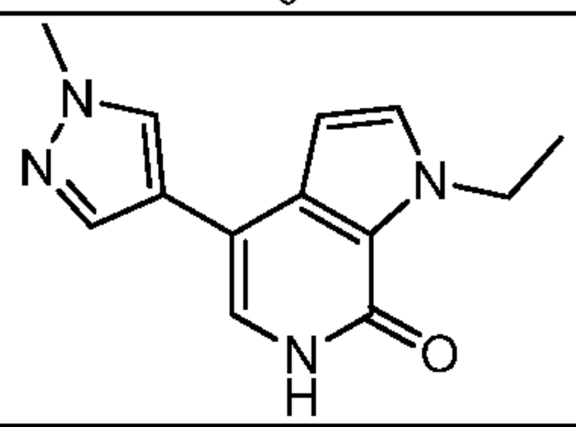
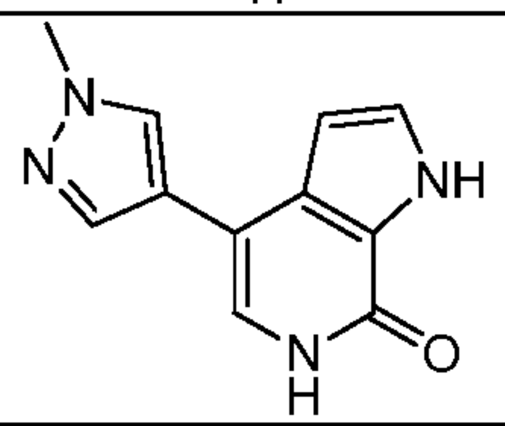
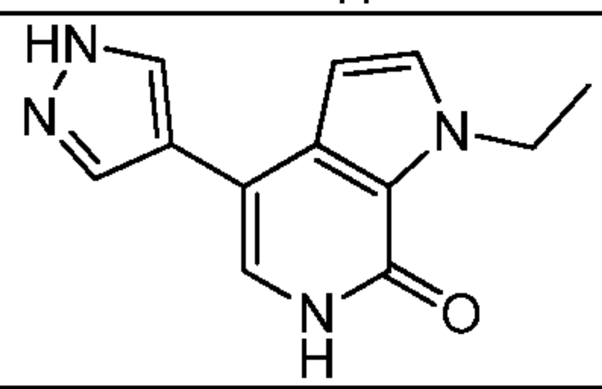
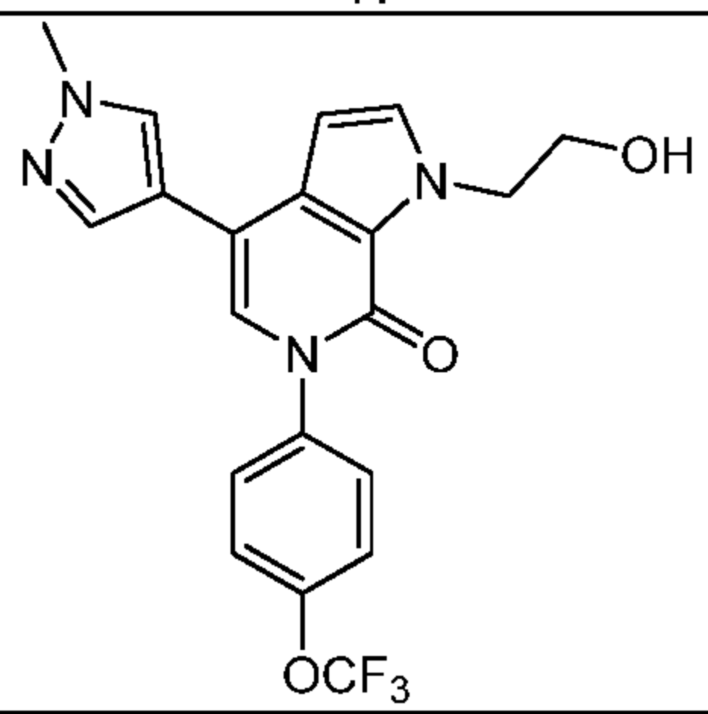
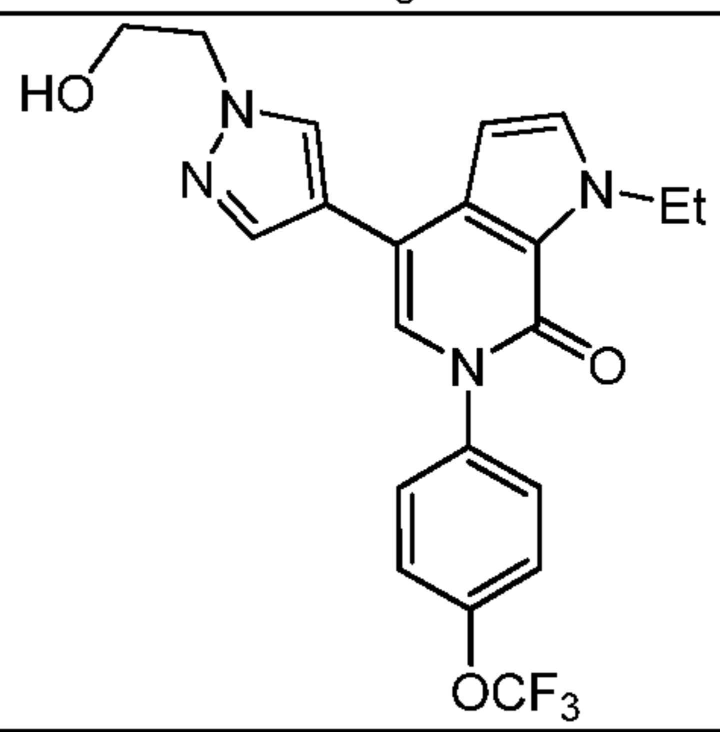
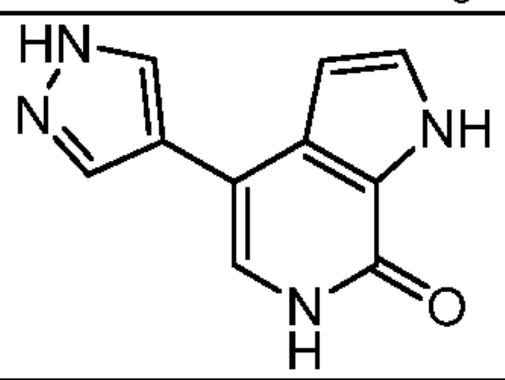
610	
611	
612	
613	
614	
615	
616	

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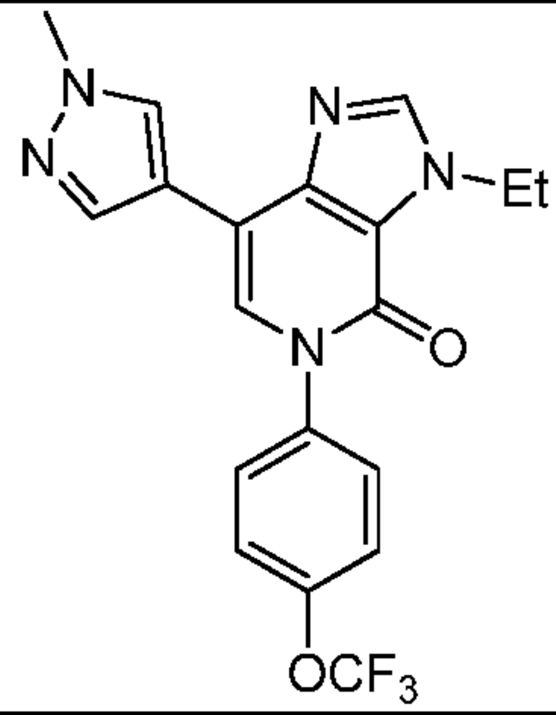
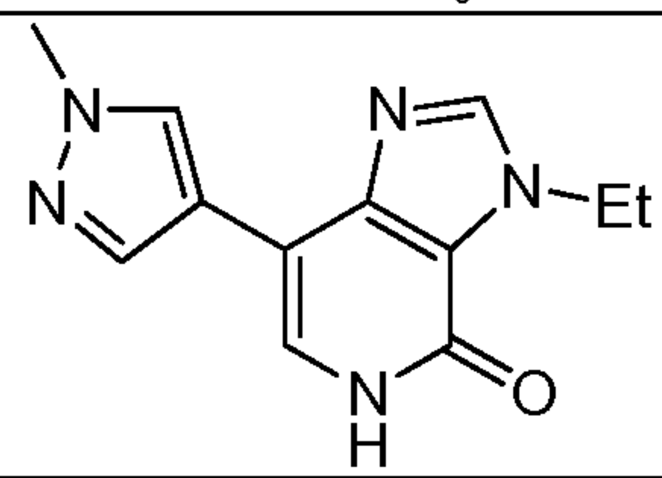
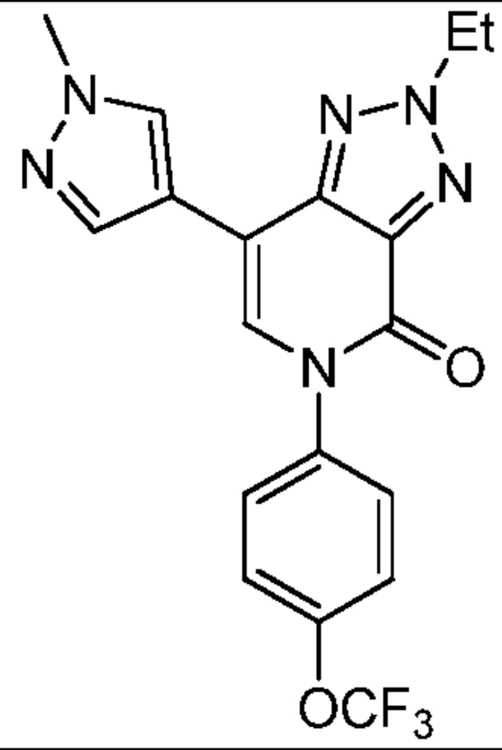
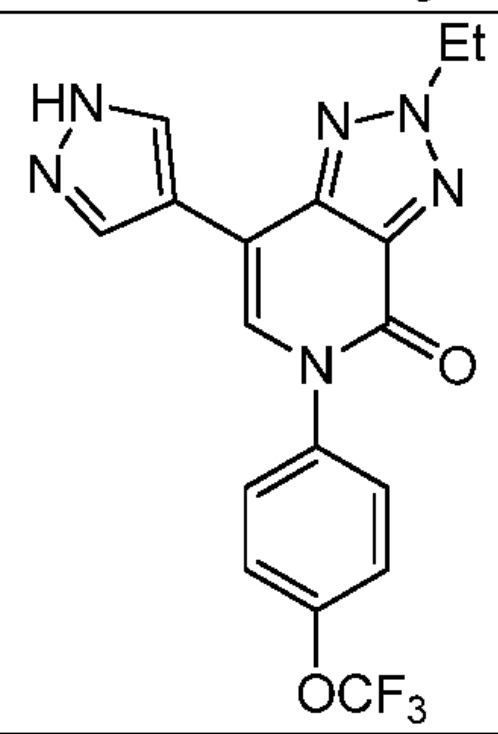
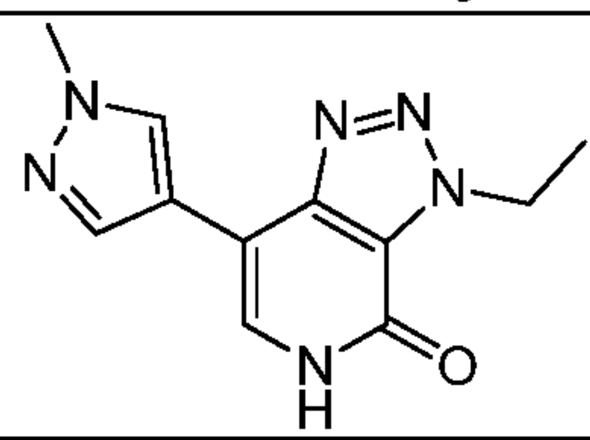
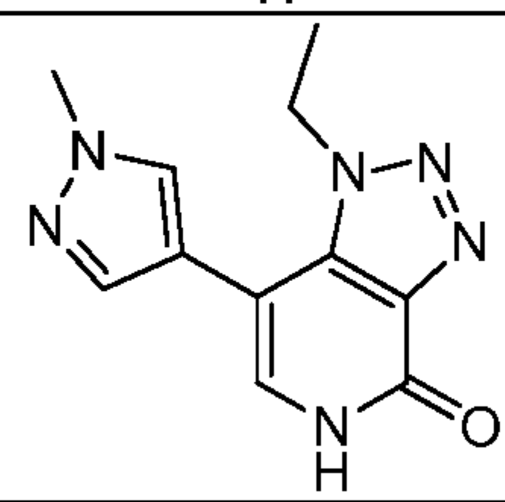
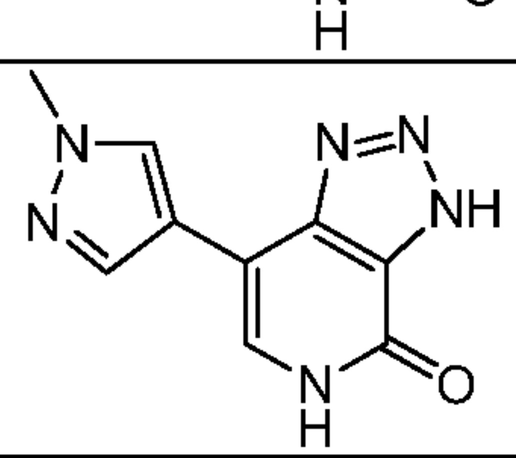
617	
618	
619	
620	
621	
622	
623	

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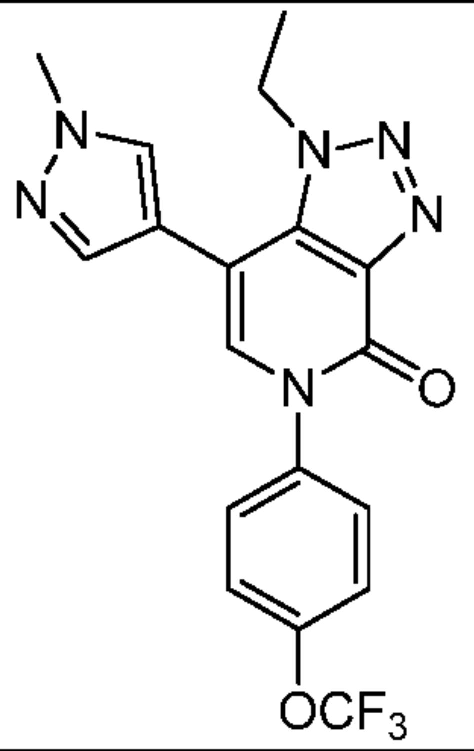
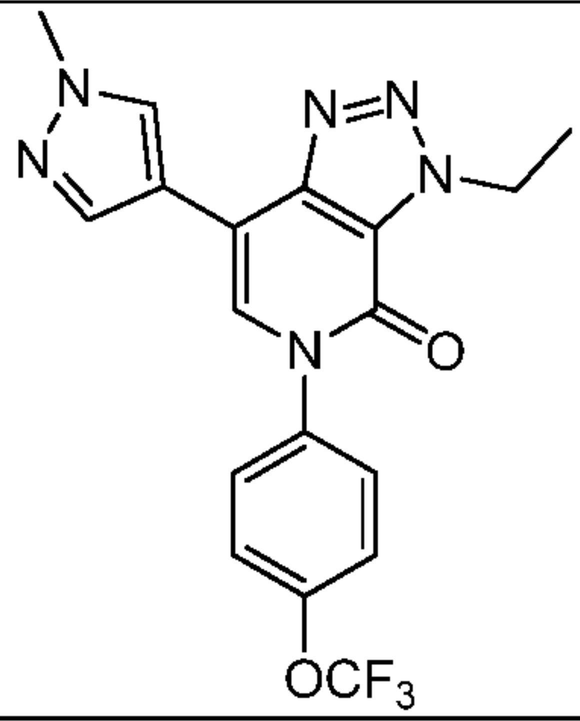
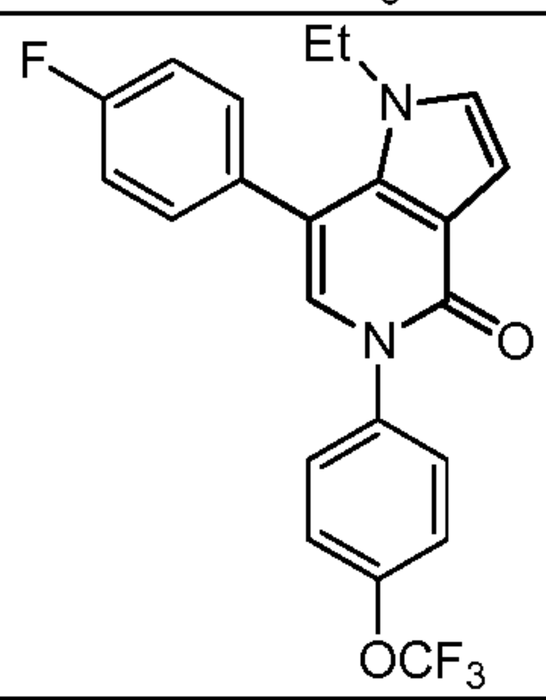
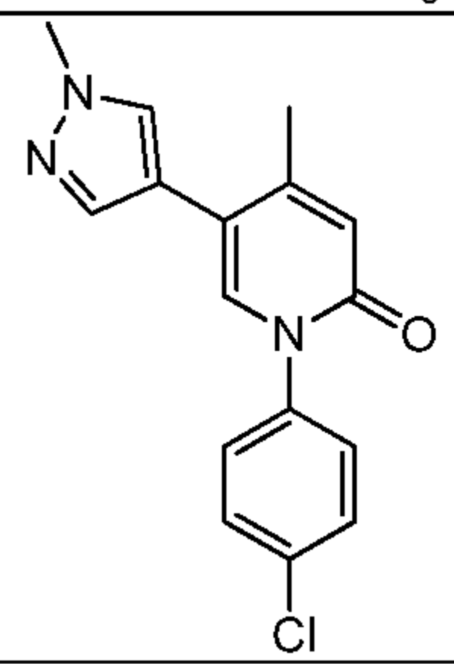
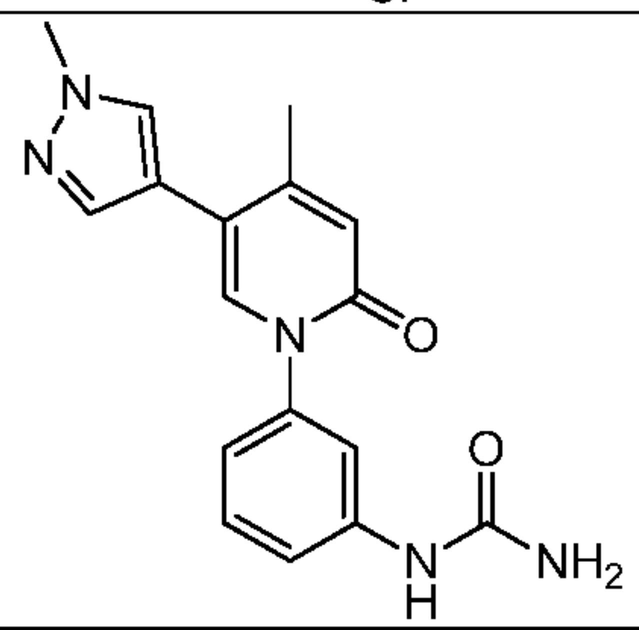
624	
625	
626	
627	
628	

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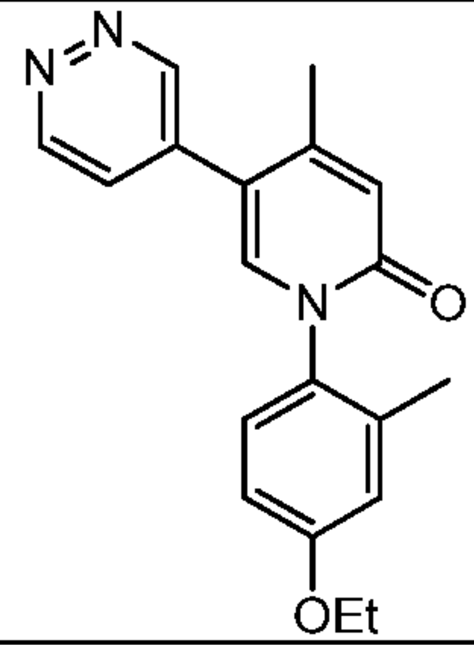
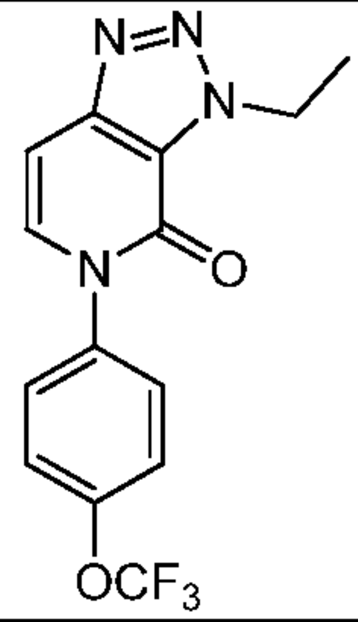
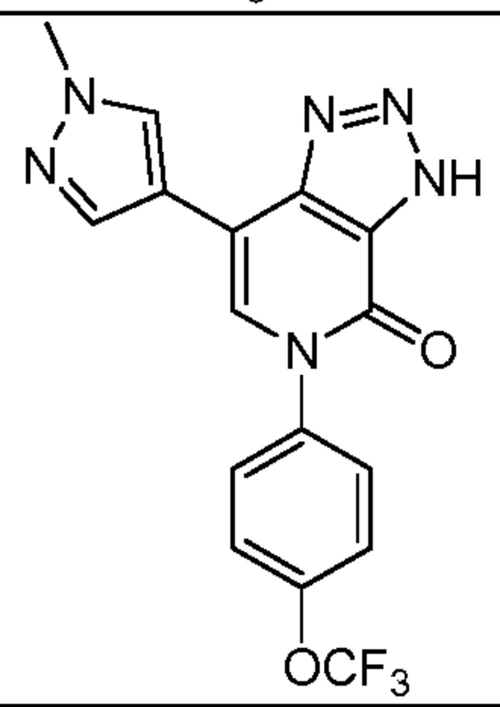
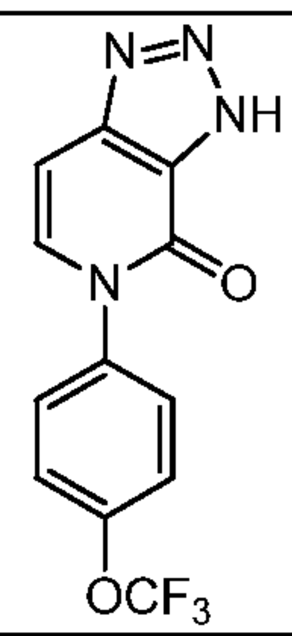
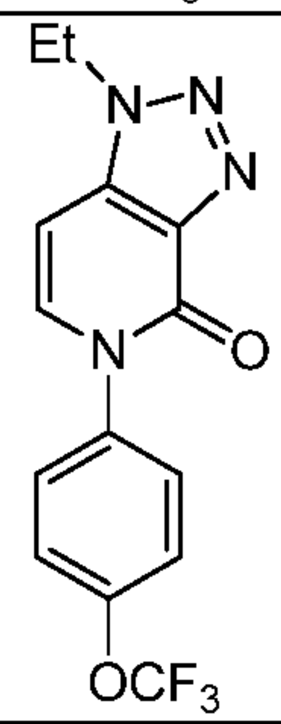
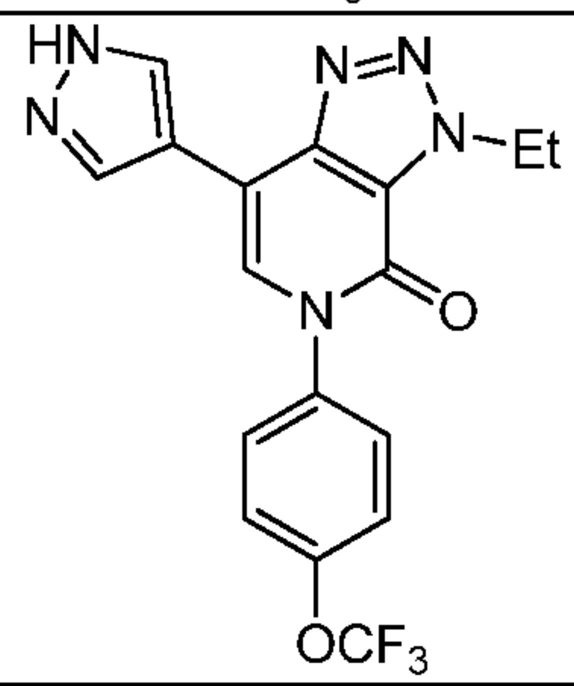
629	
630	
631	
632	
633	
634	

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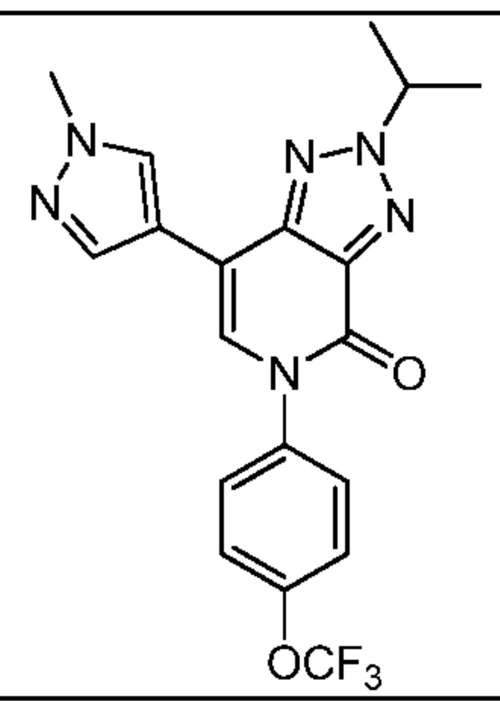
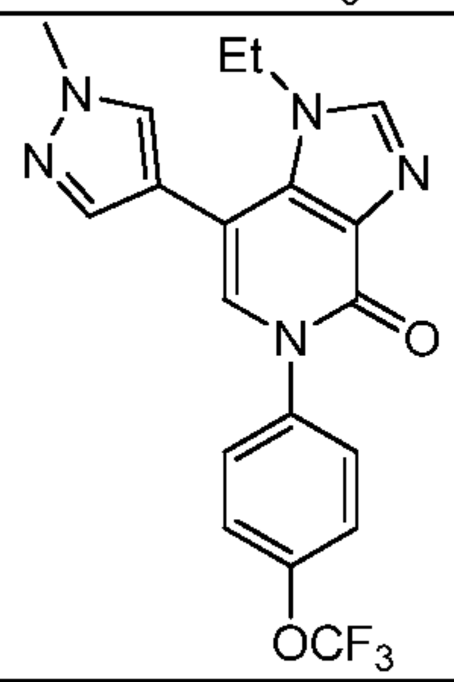
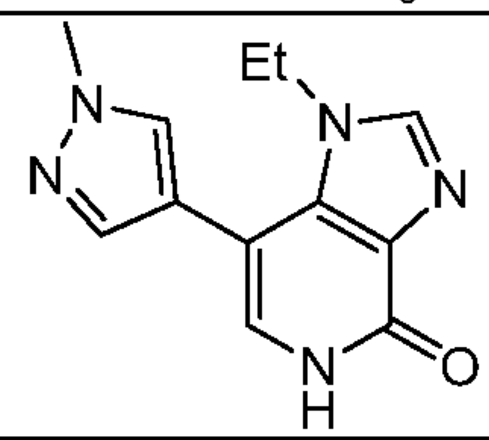
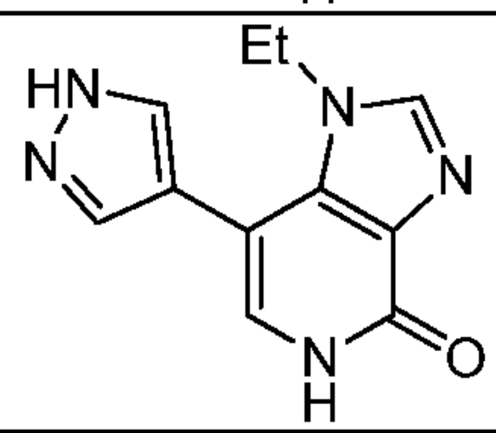
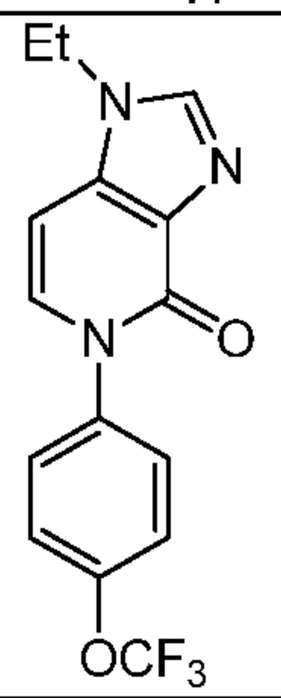
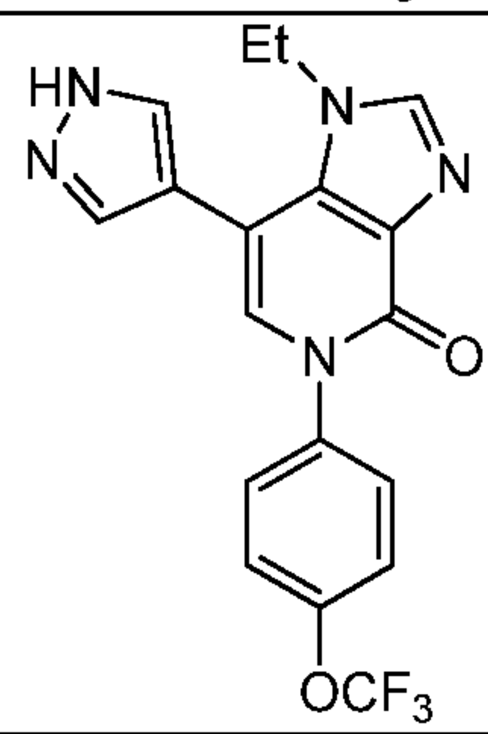
635	
636	
637	
638	
639	
640	

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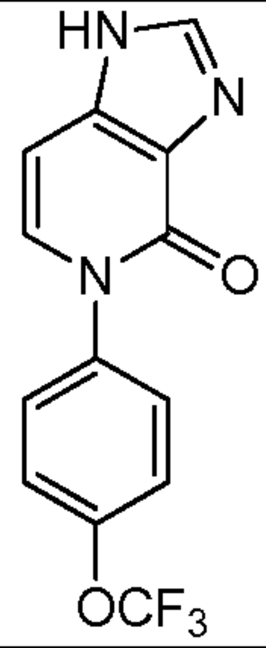
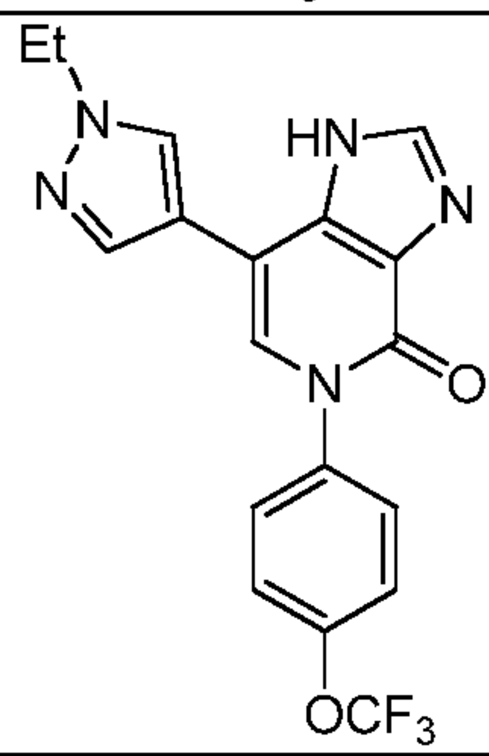
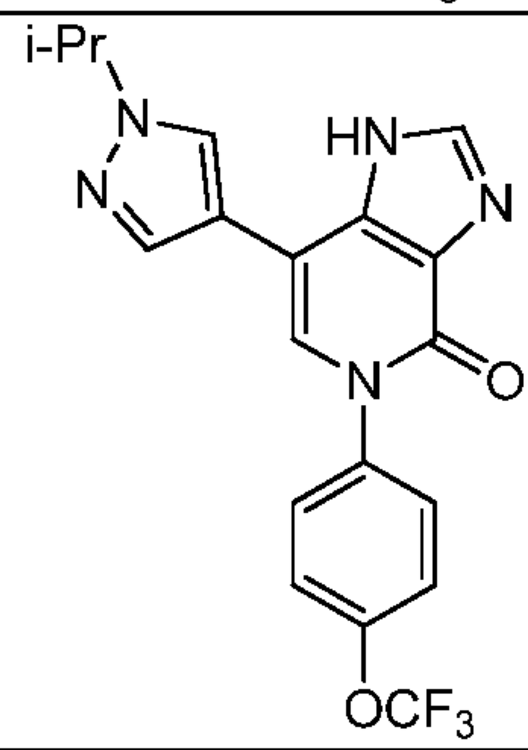
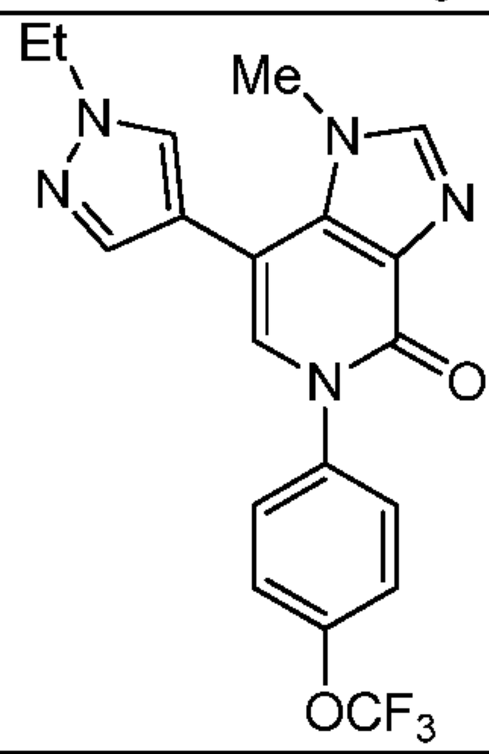
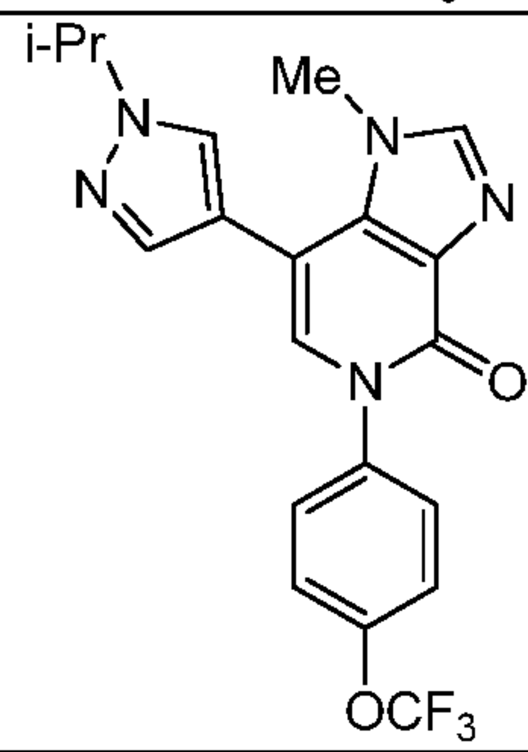
641	
642	
643	
644	
645	

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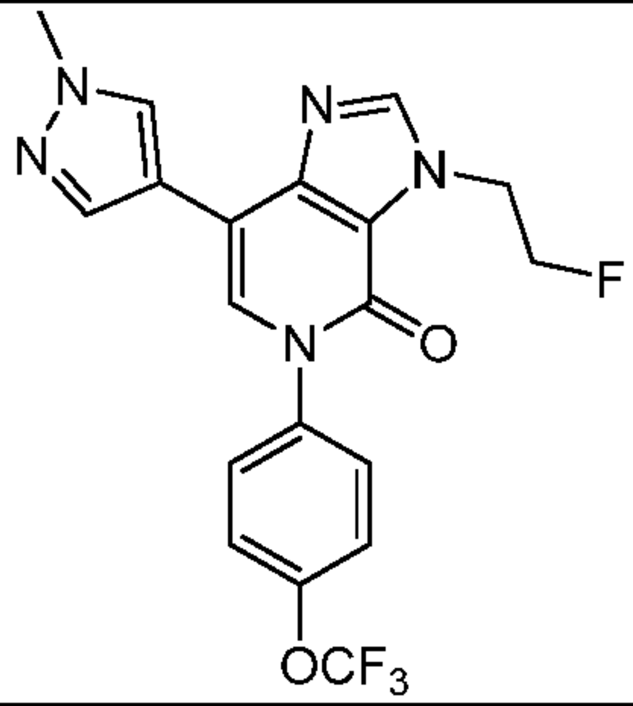
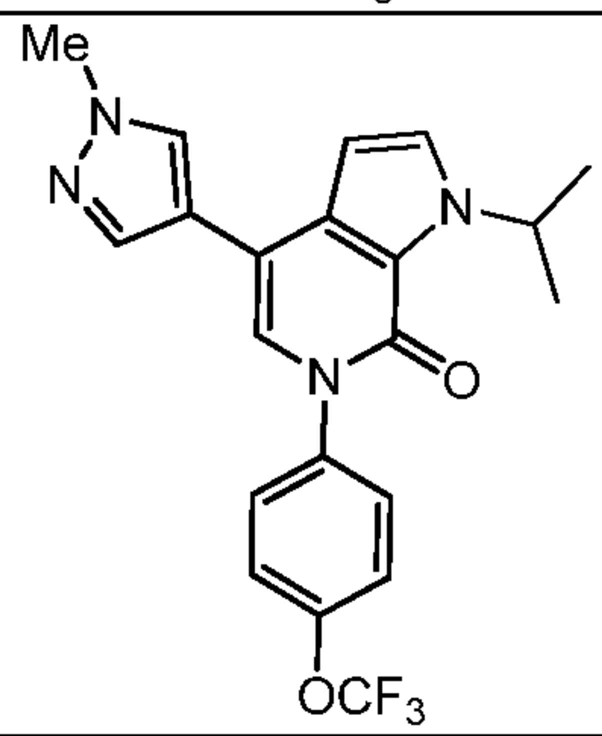
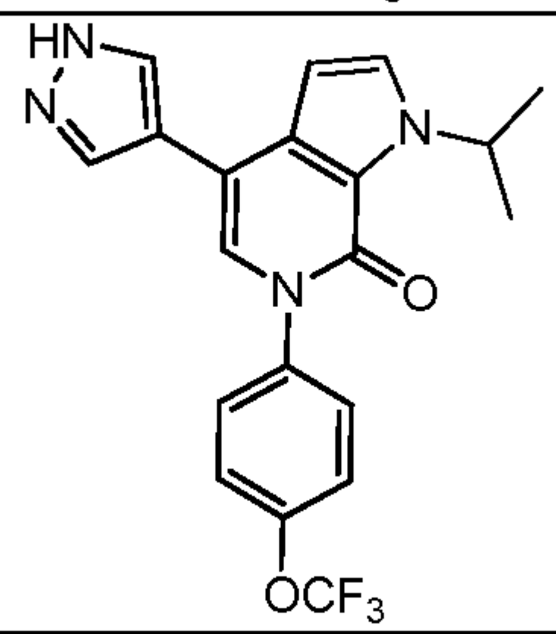
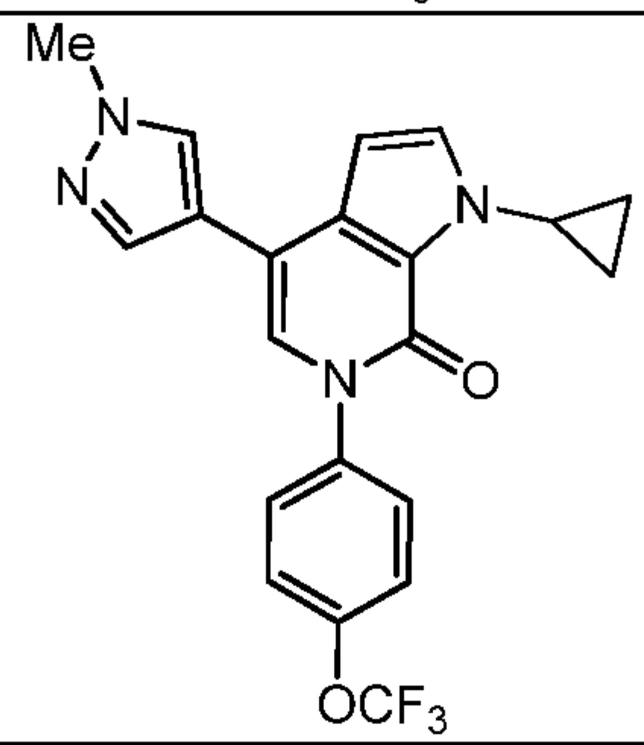
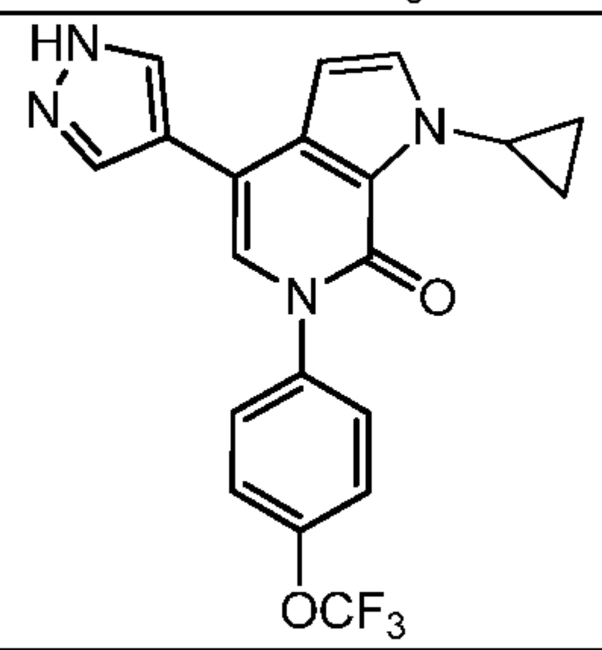
646	
647	
648	
649	
650	

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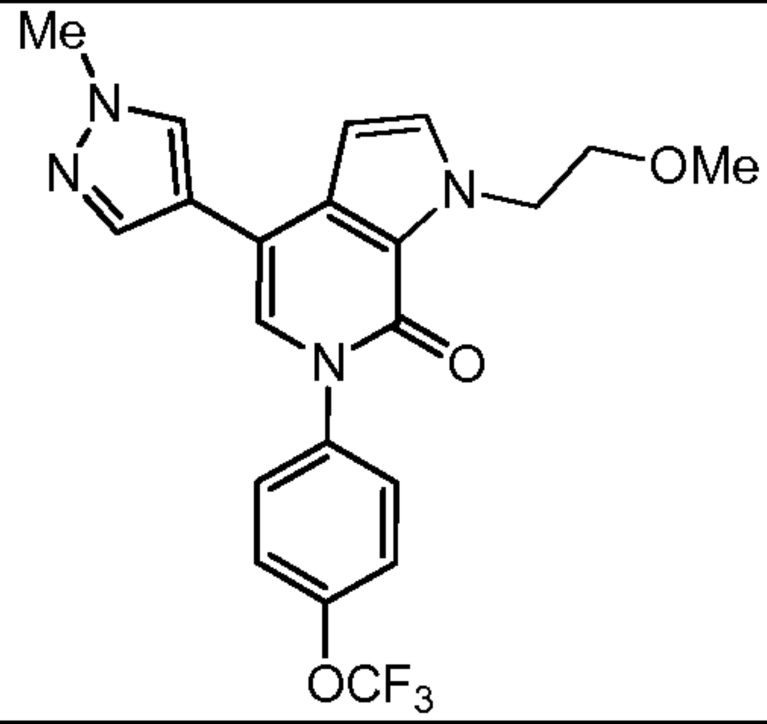
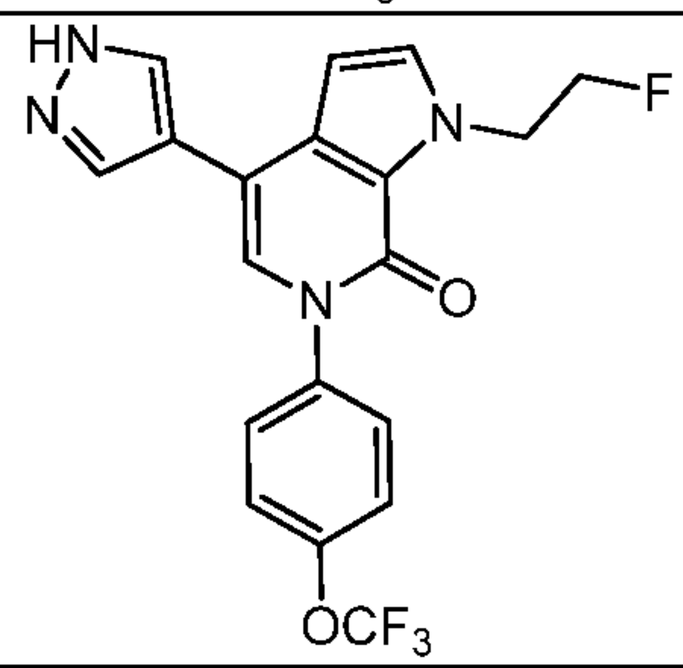
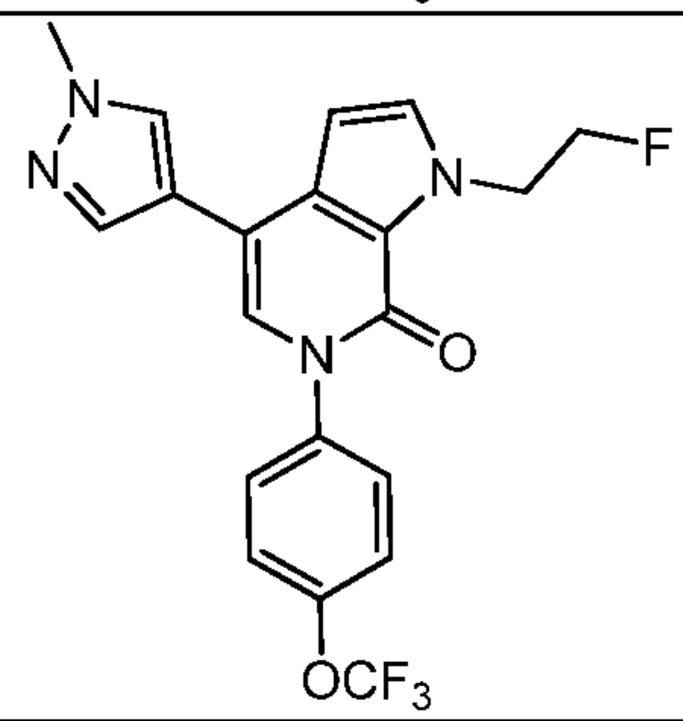
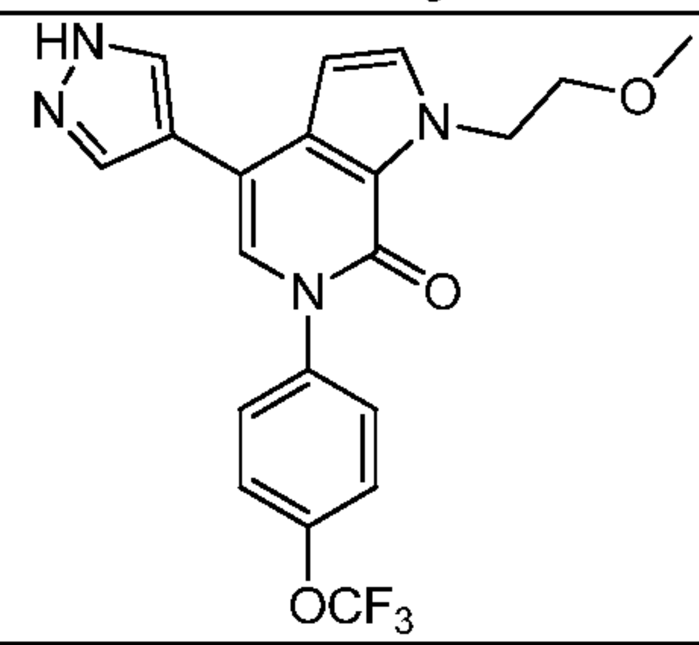
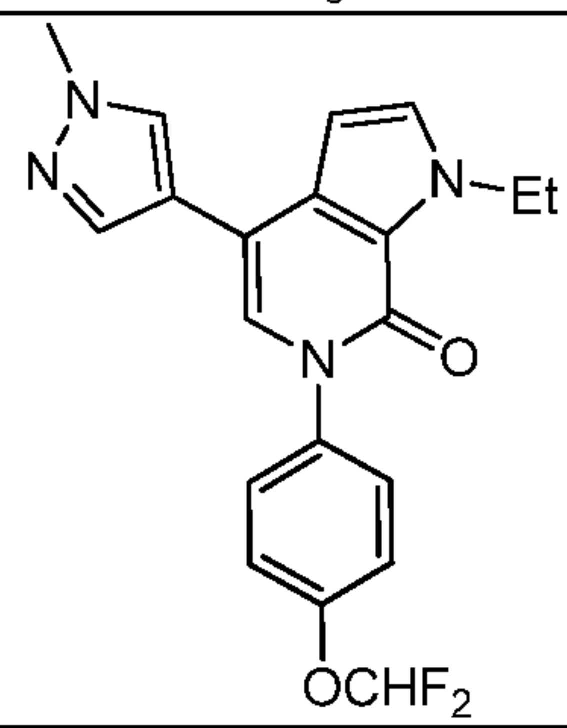
651	
652	
653	
654	
655	

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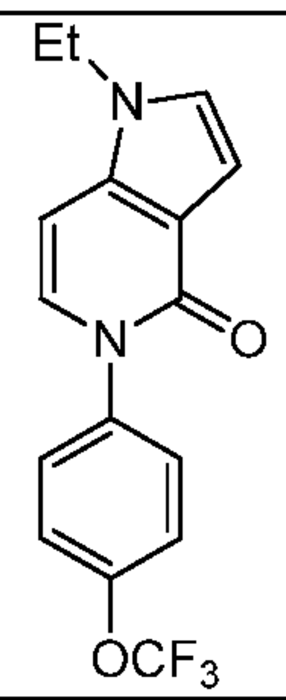
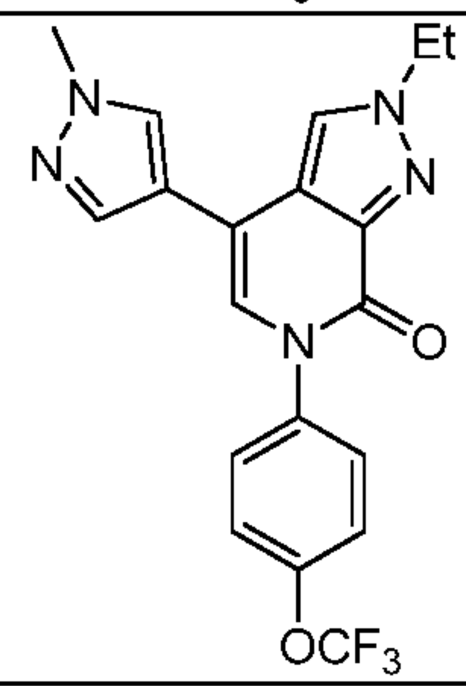
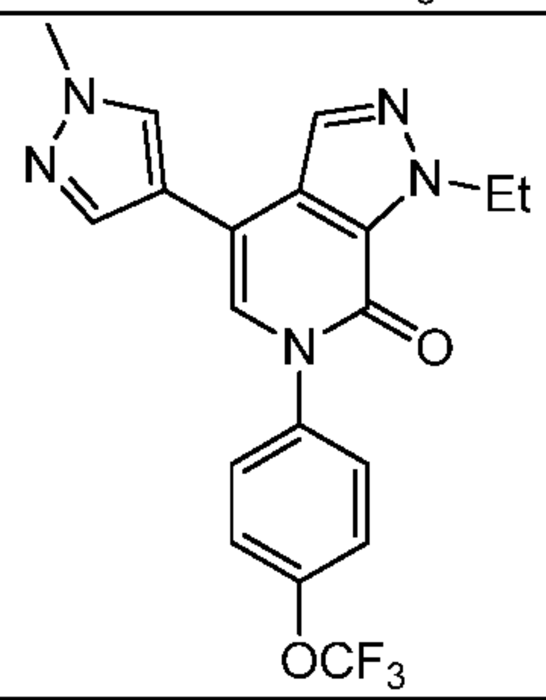
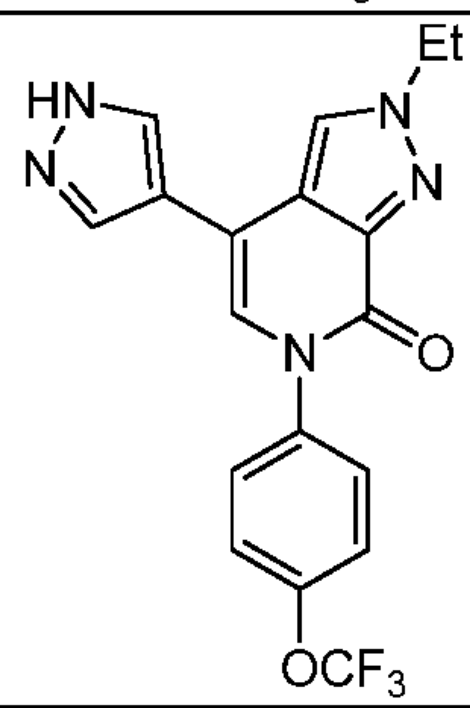
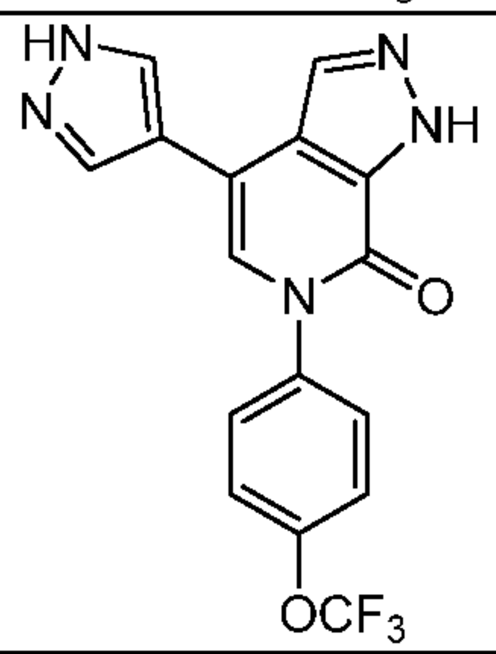
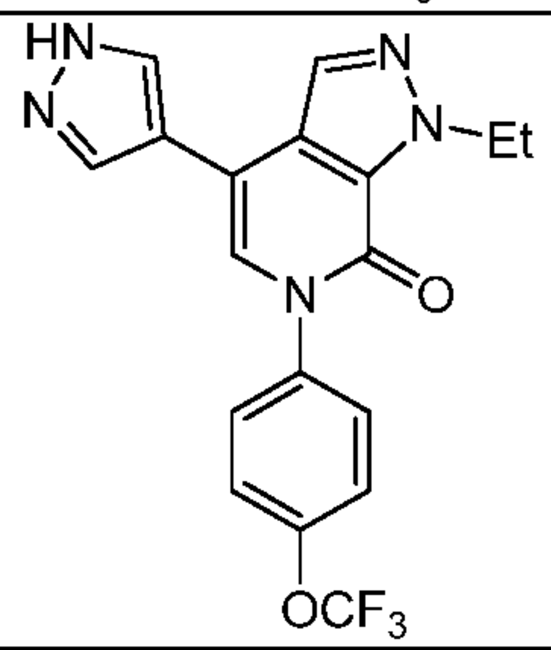
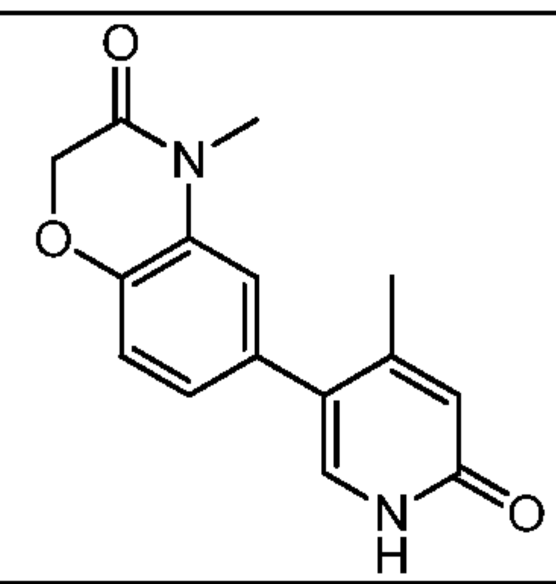
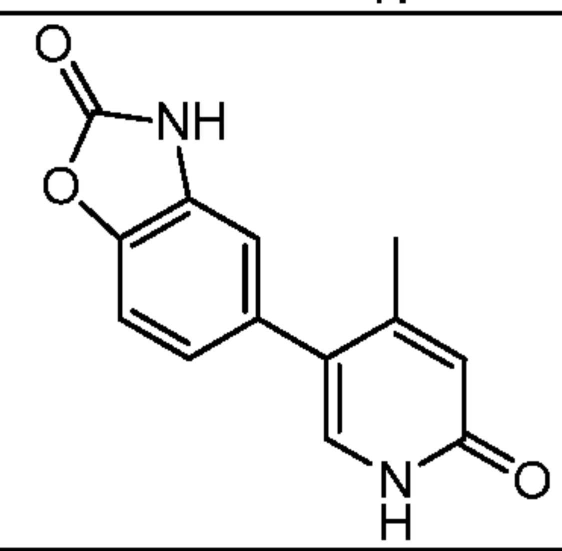
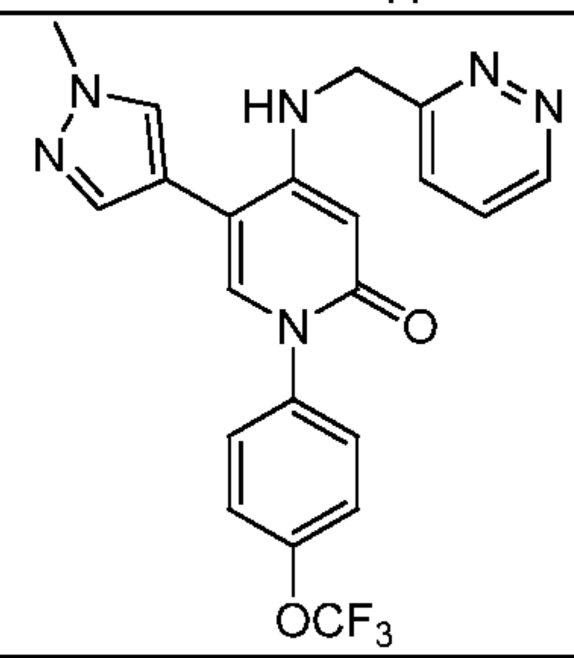
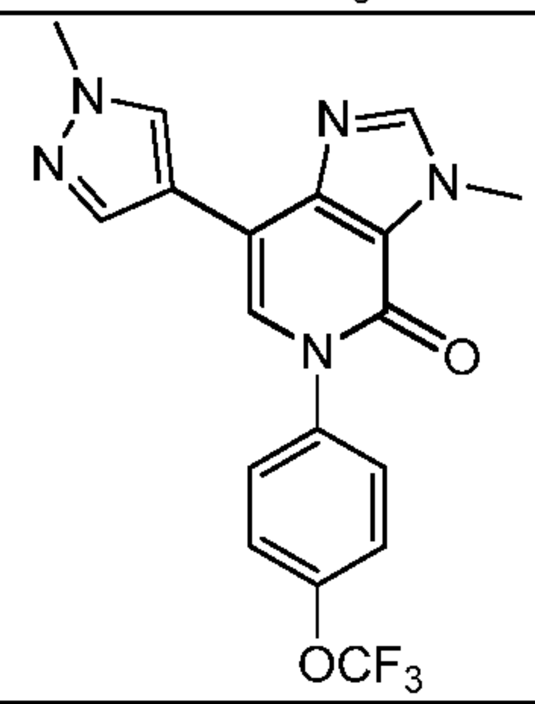
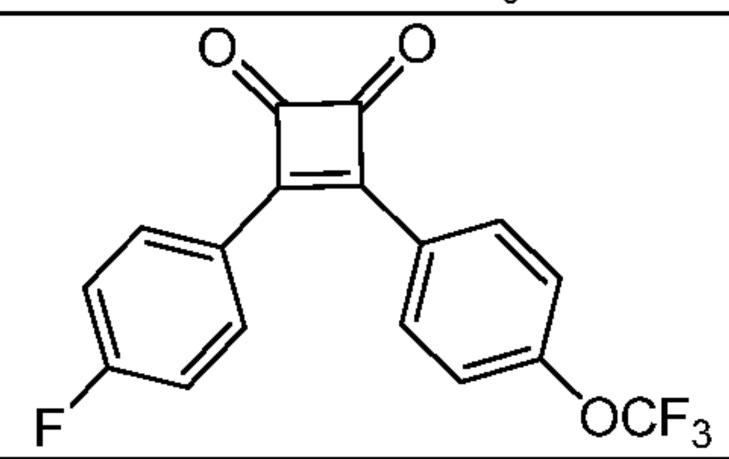
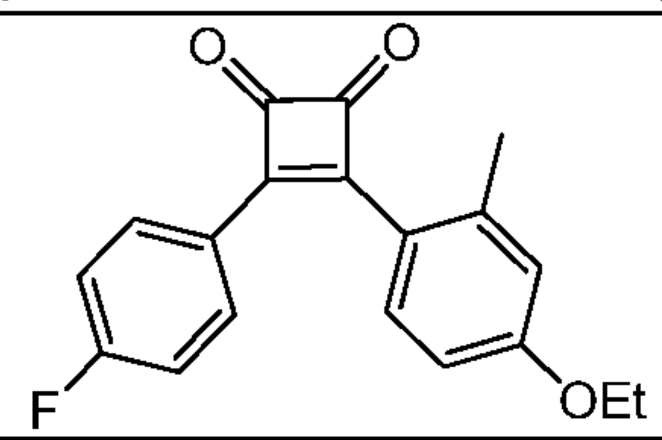
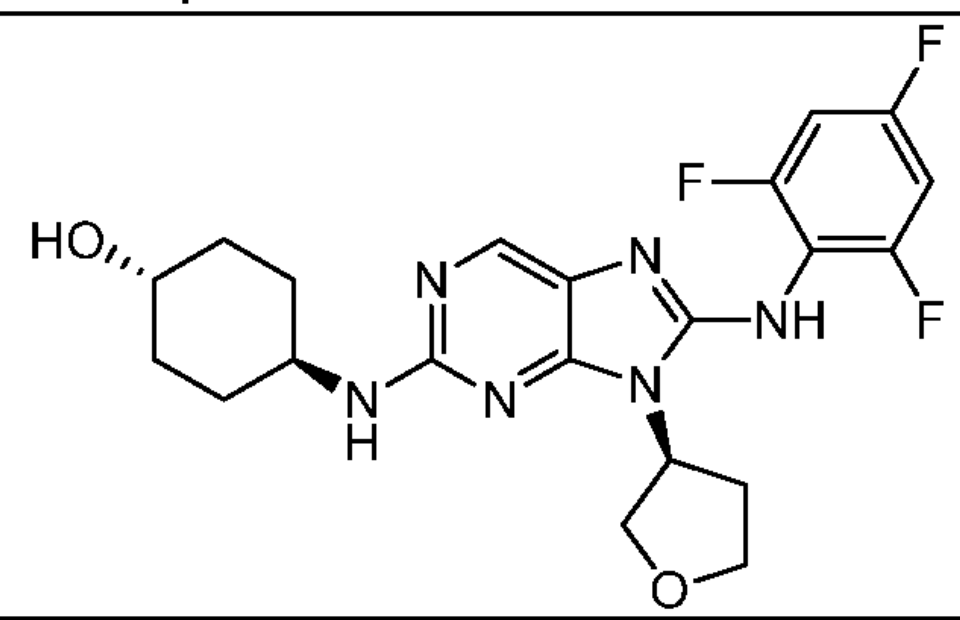
656	
657	
658	
659	
660	
661	
662	
663	
664	
665	
666	
667	
668	

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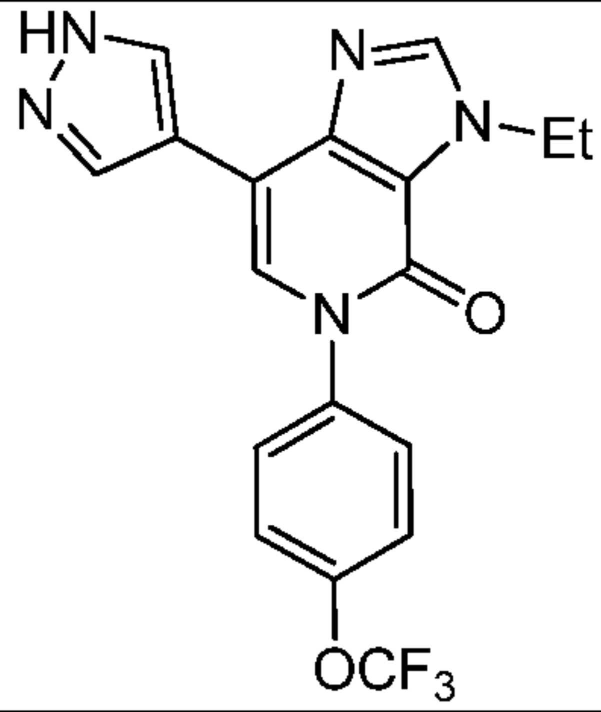
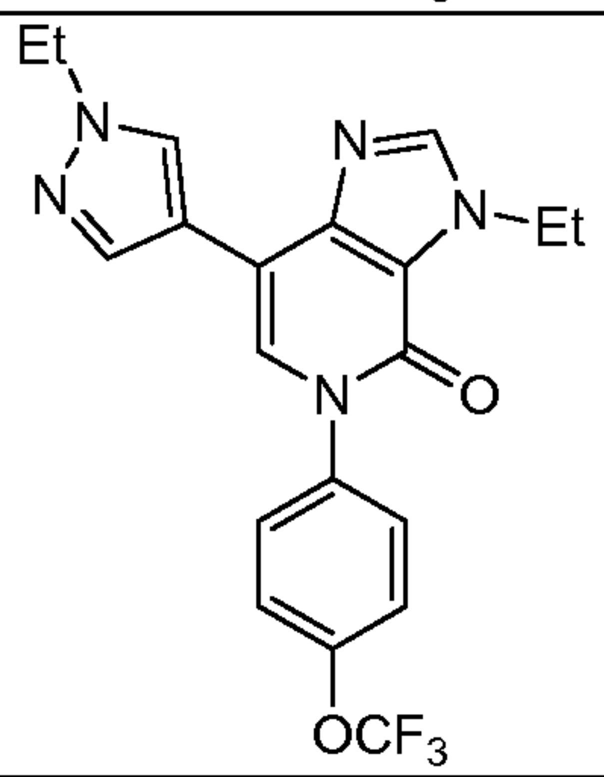
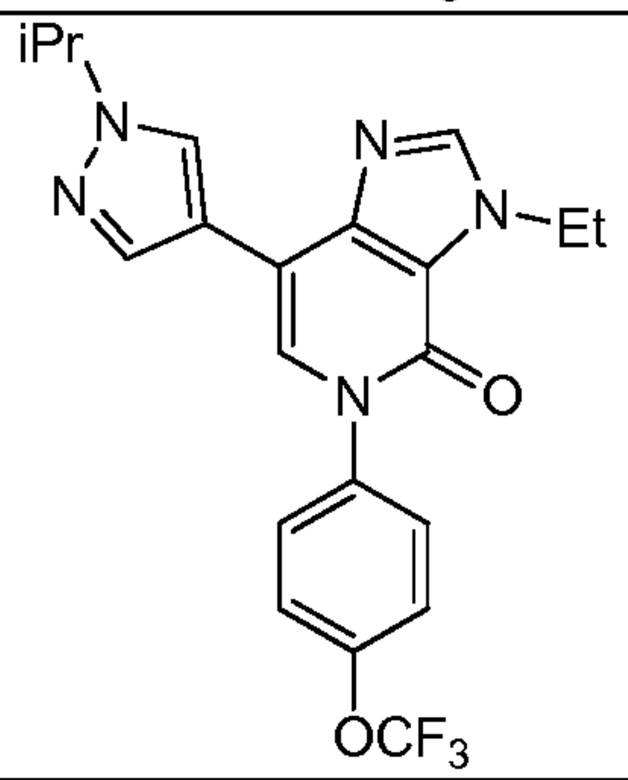
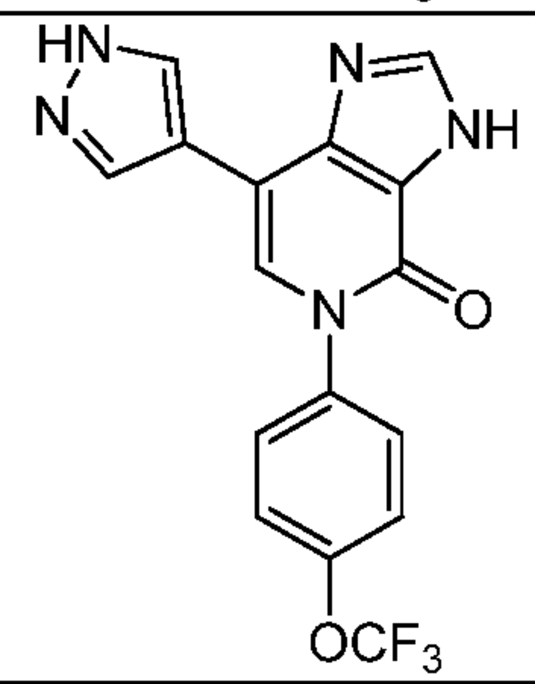
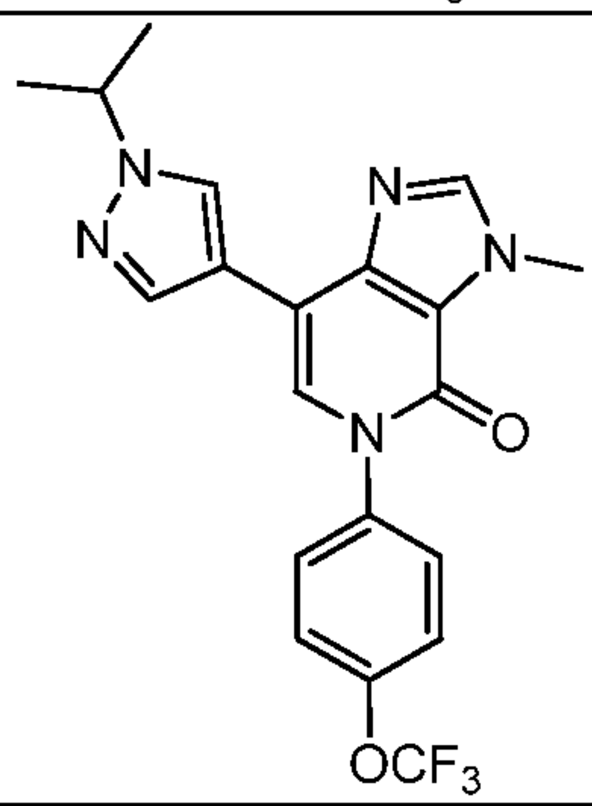
669	
670	
671	
672	
673	

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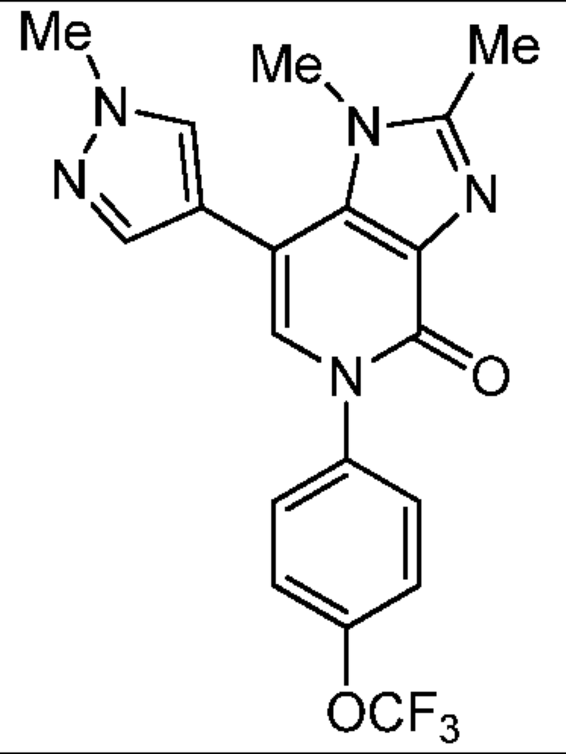
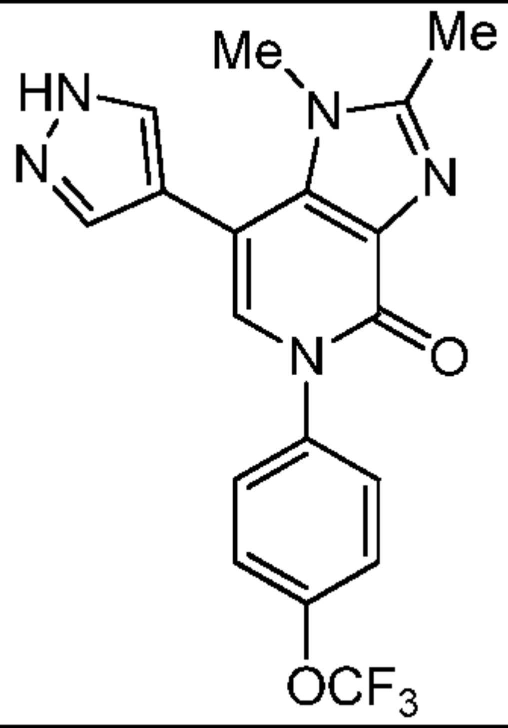
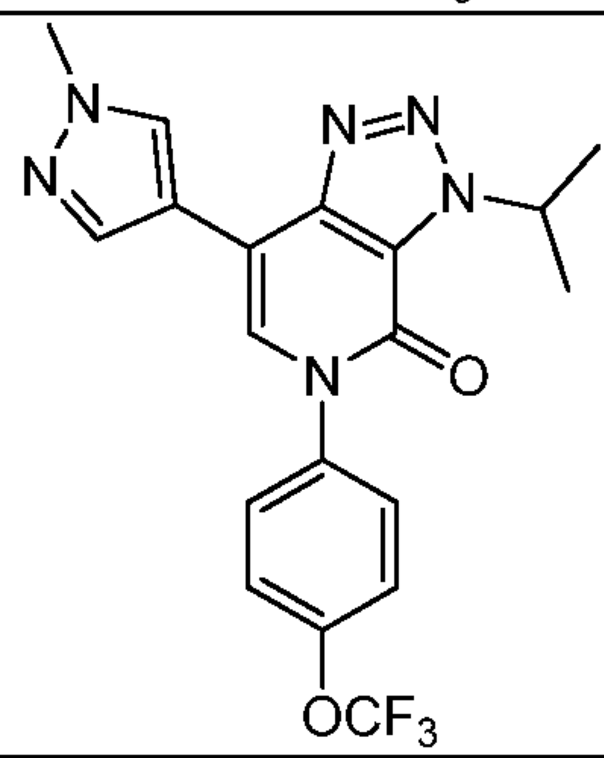
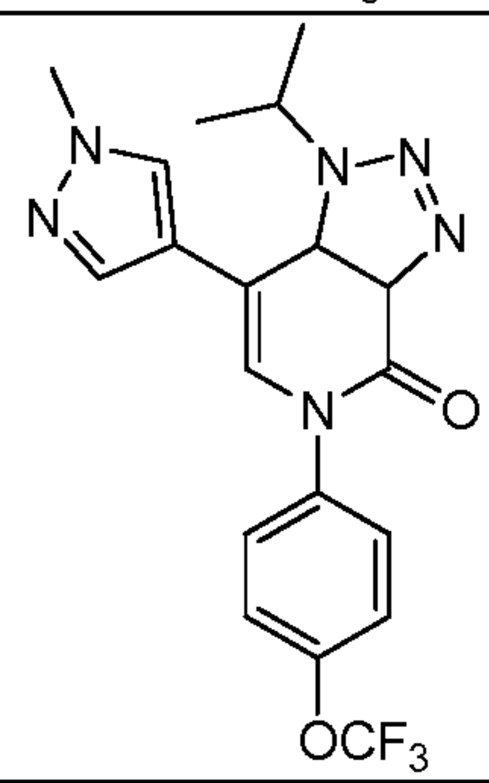
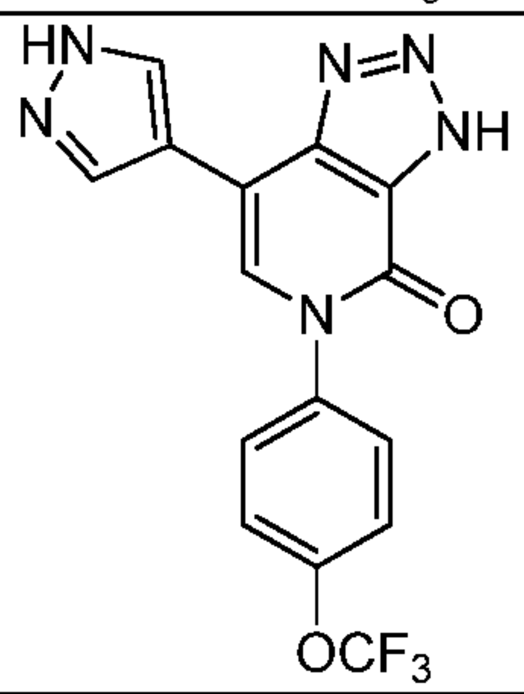
674	
675	
676	
677	
678	

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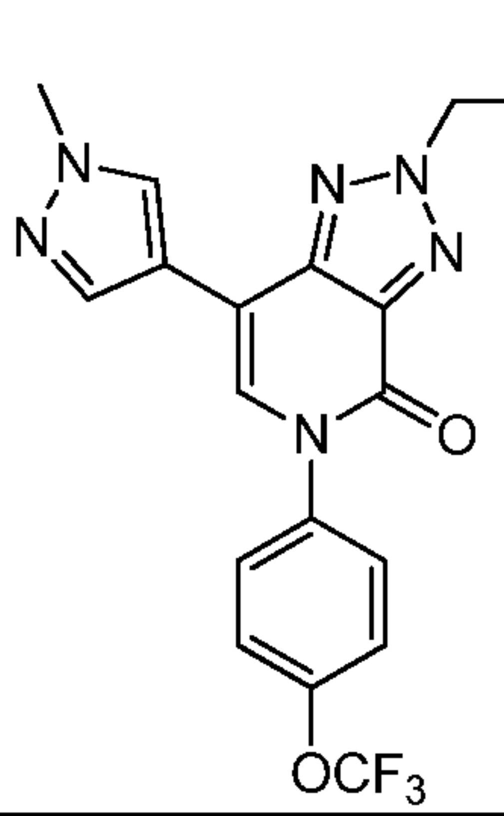
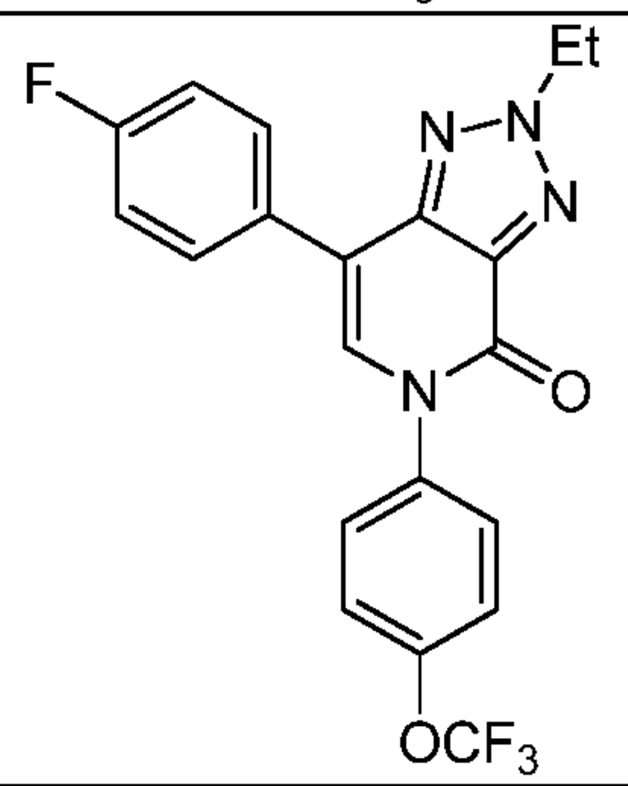
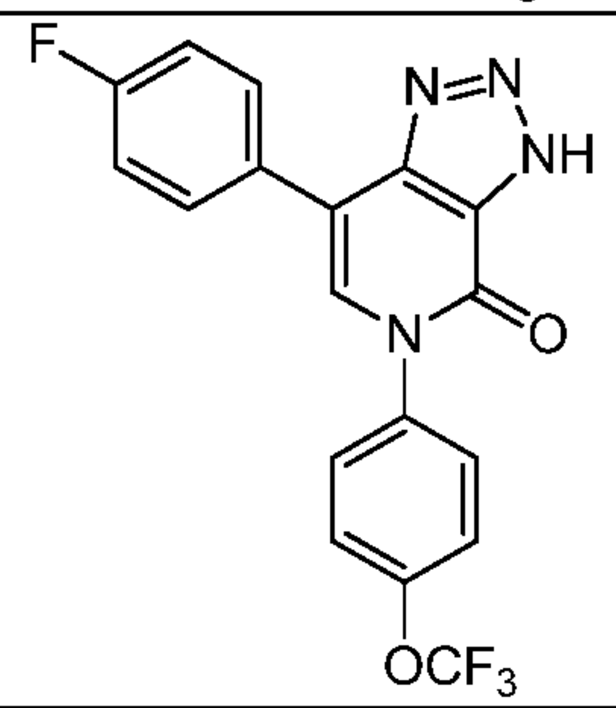
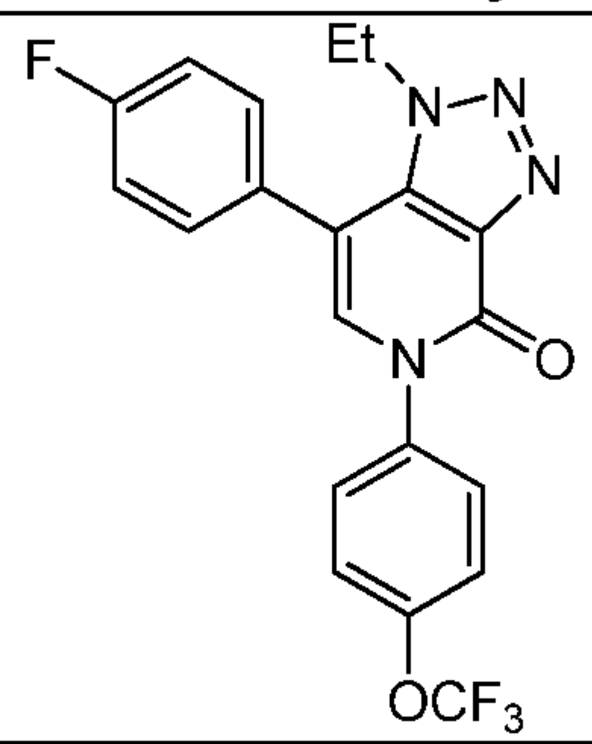
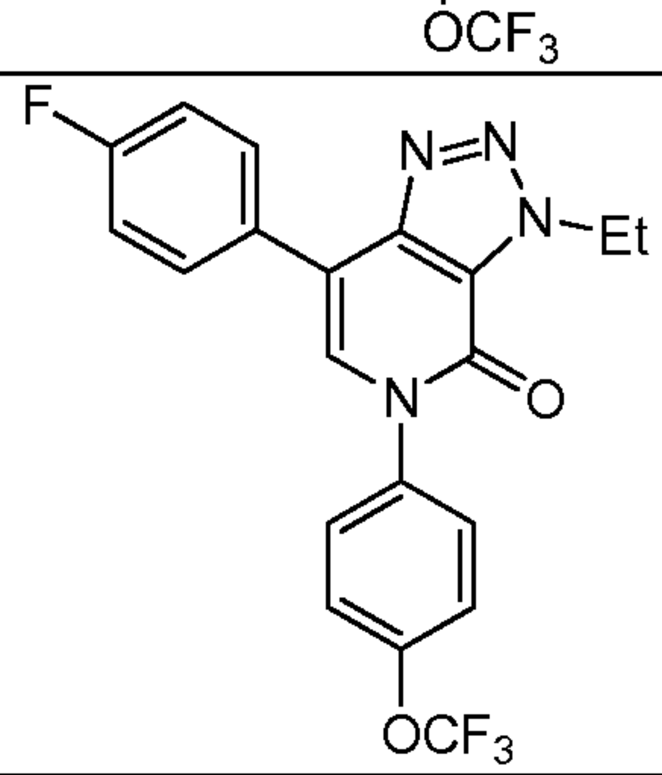
679	
680	
681	
682	
683	

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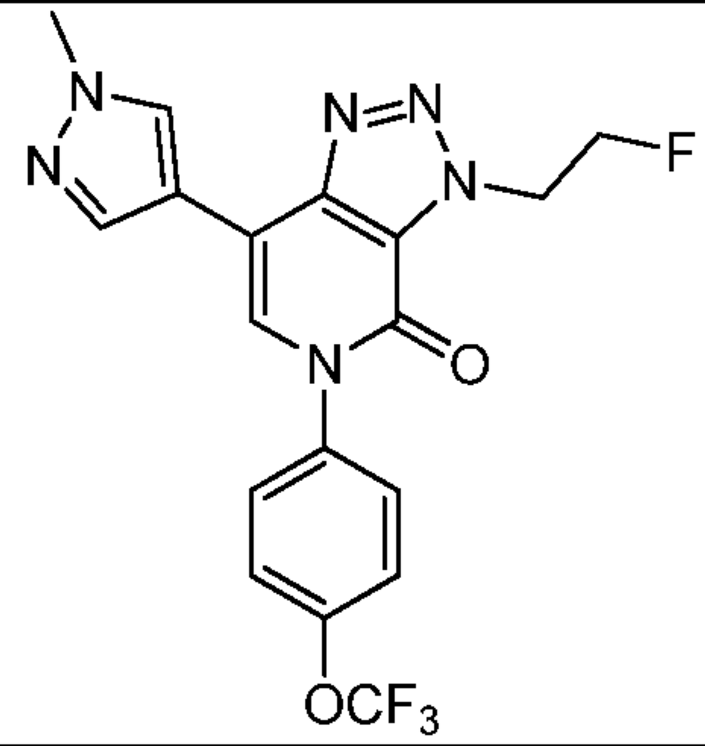
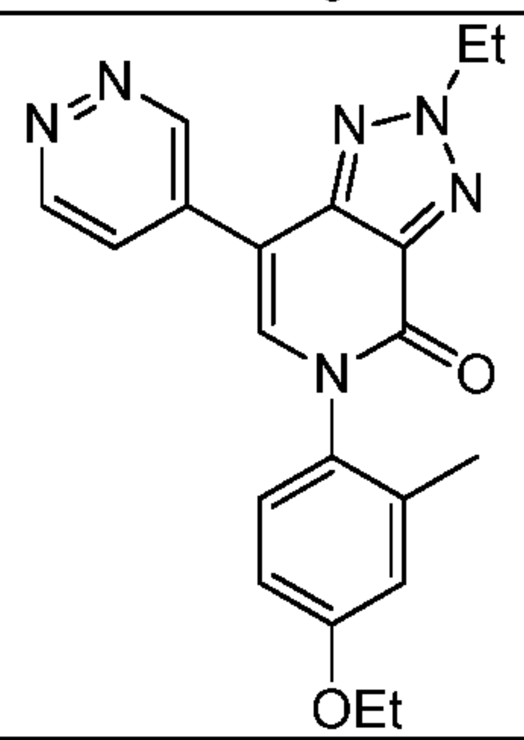
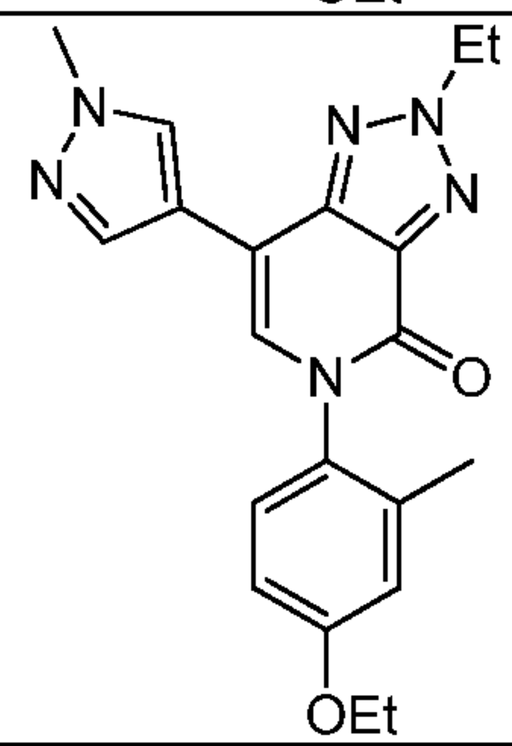
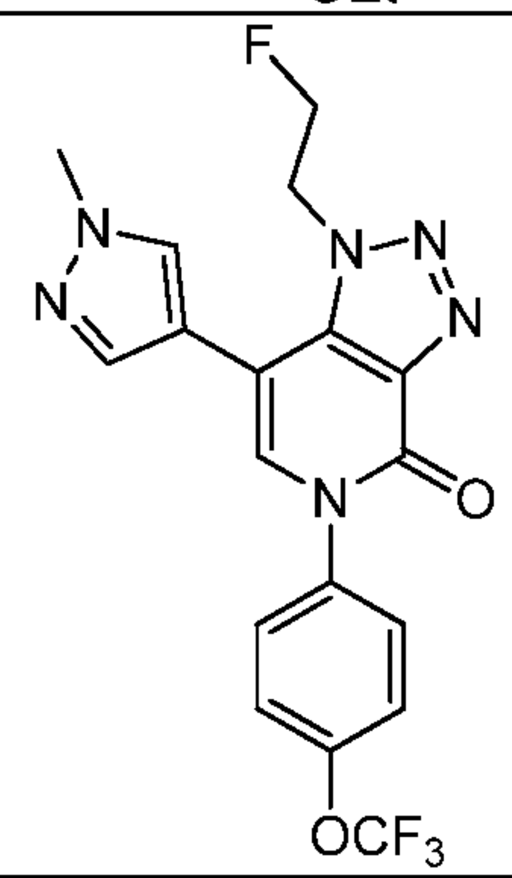
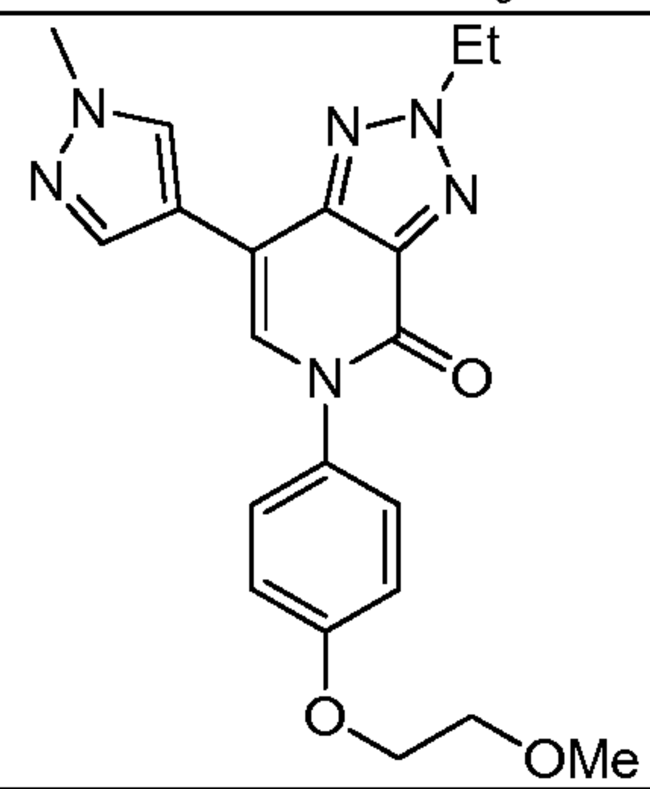
684	
685	
686	
687	
688	

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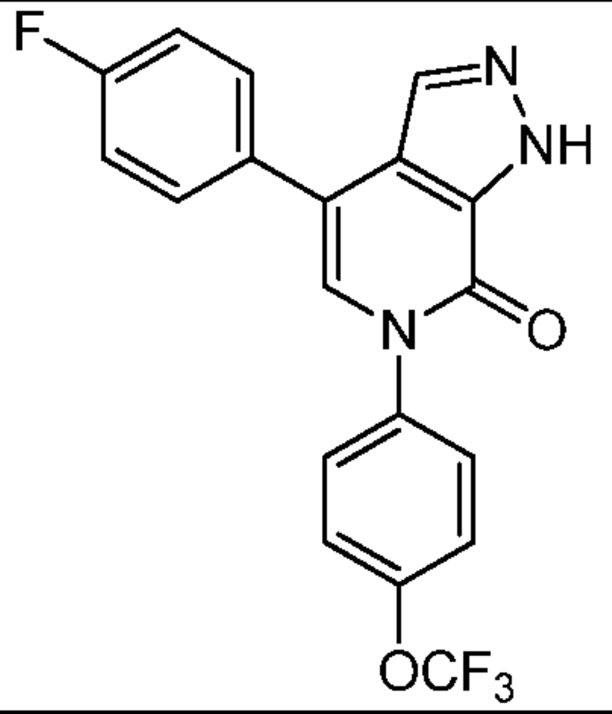
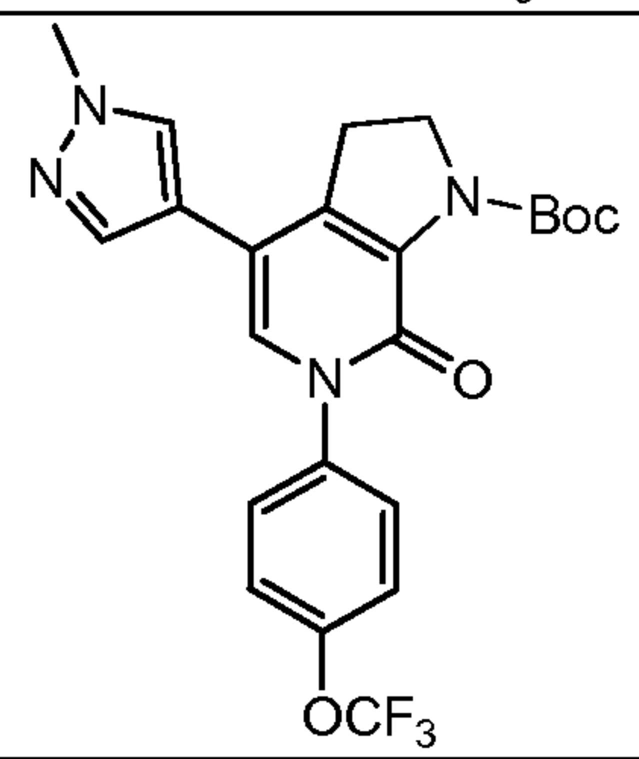
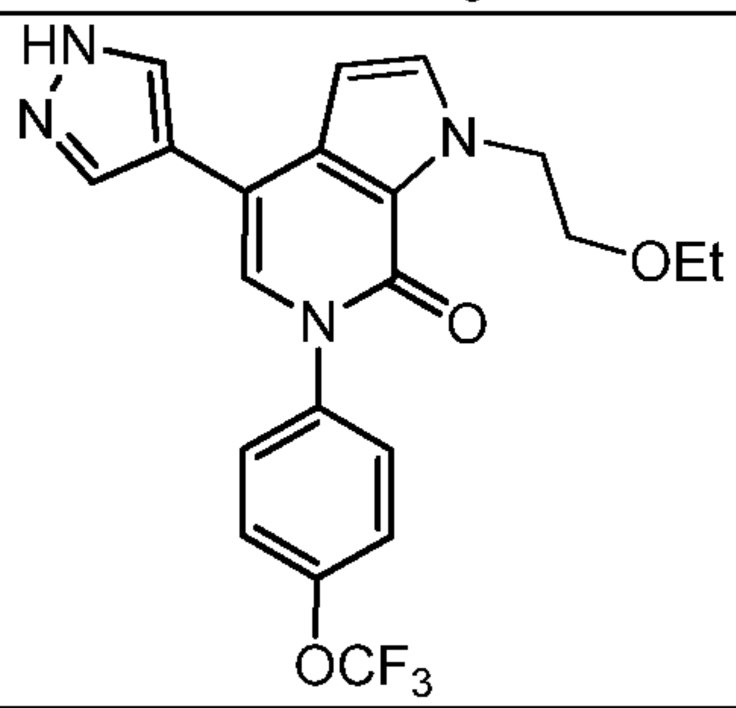
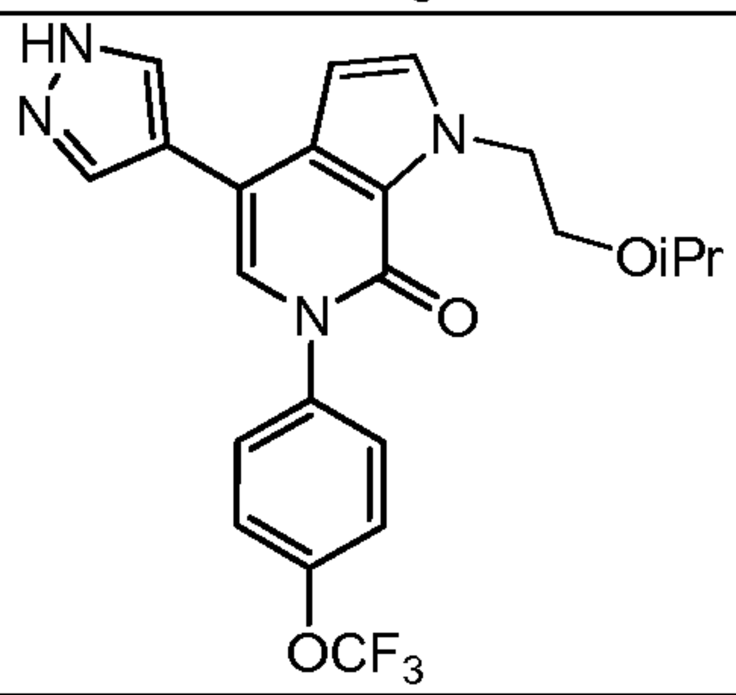
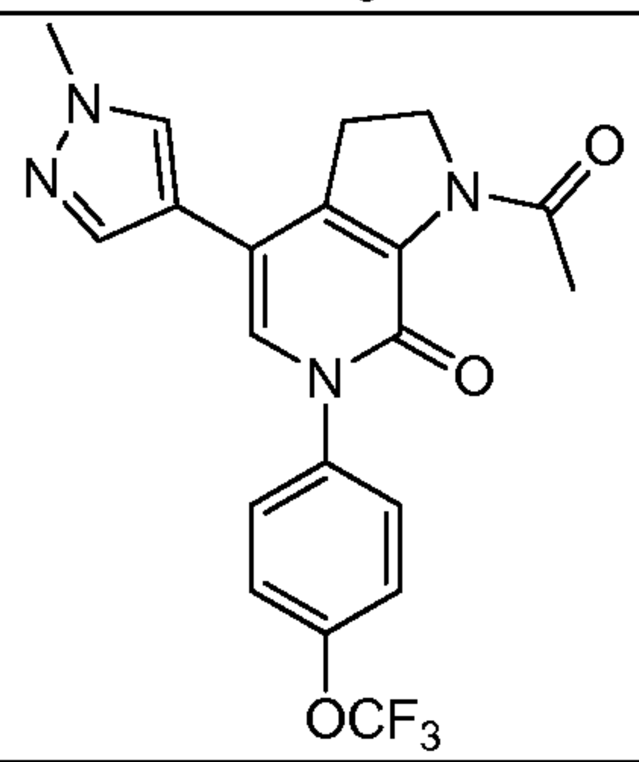
689	
690	
691	
692	
693	

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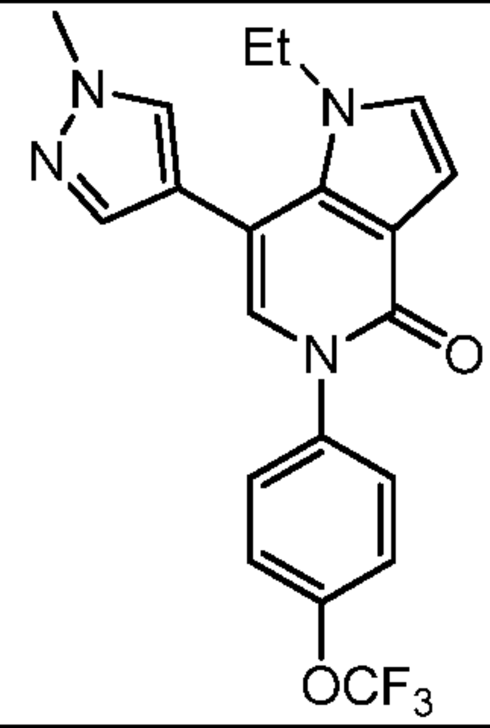
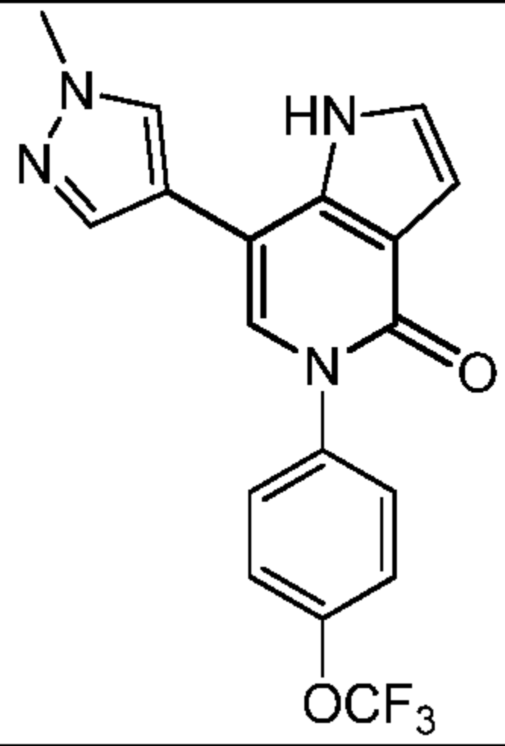
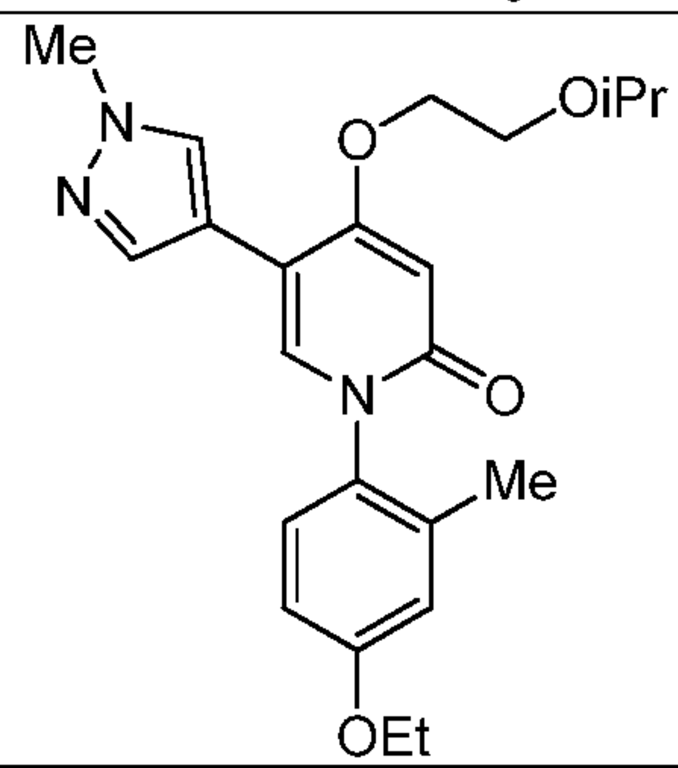
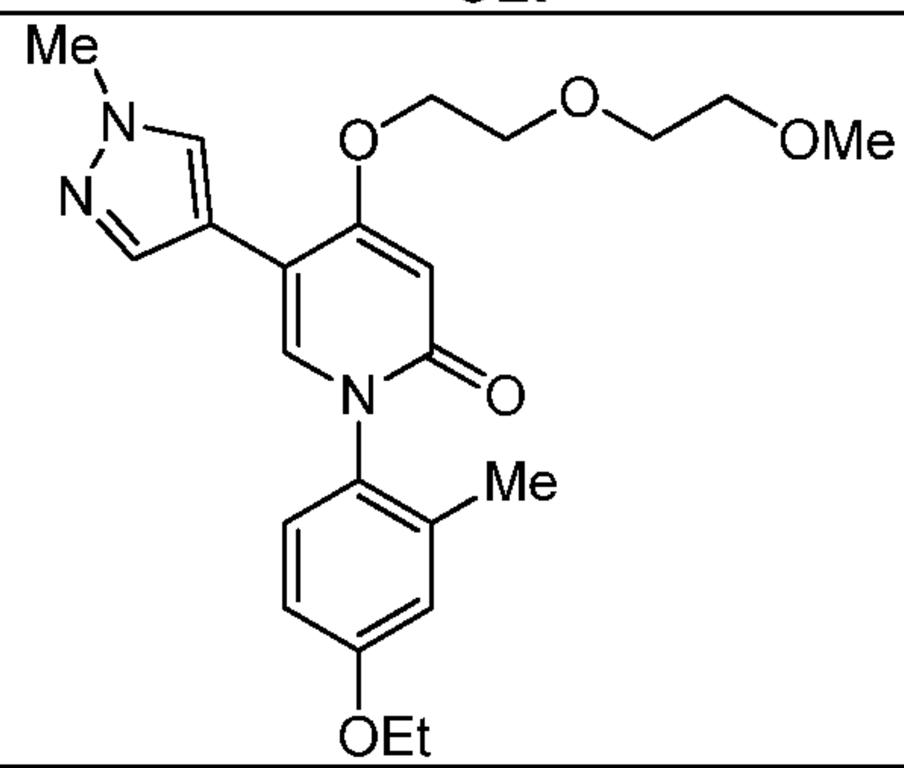
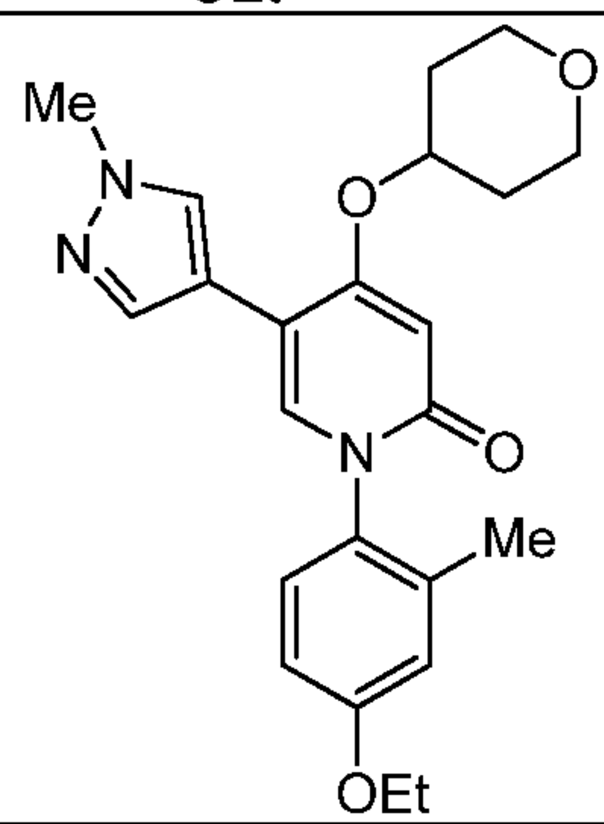
694	
695	
696	
697	
698	

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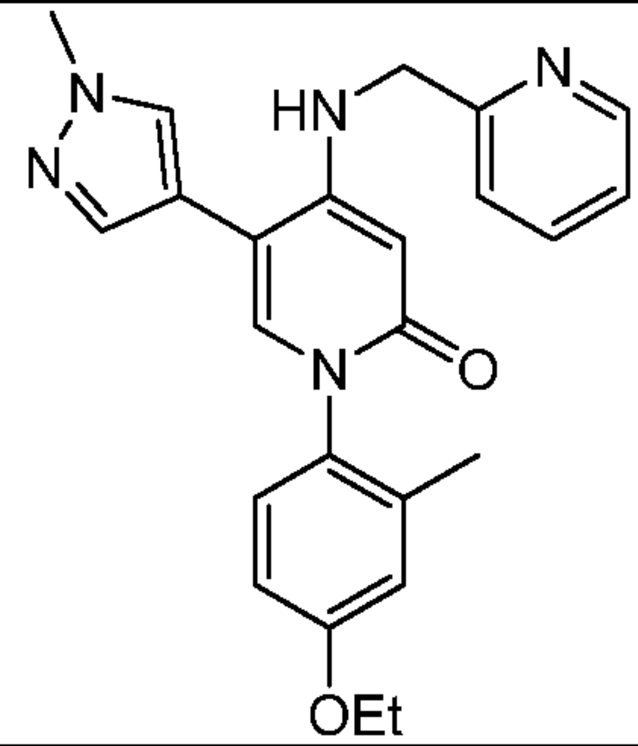
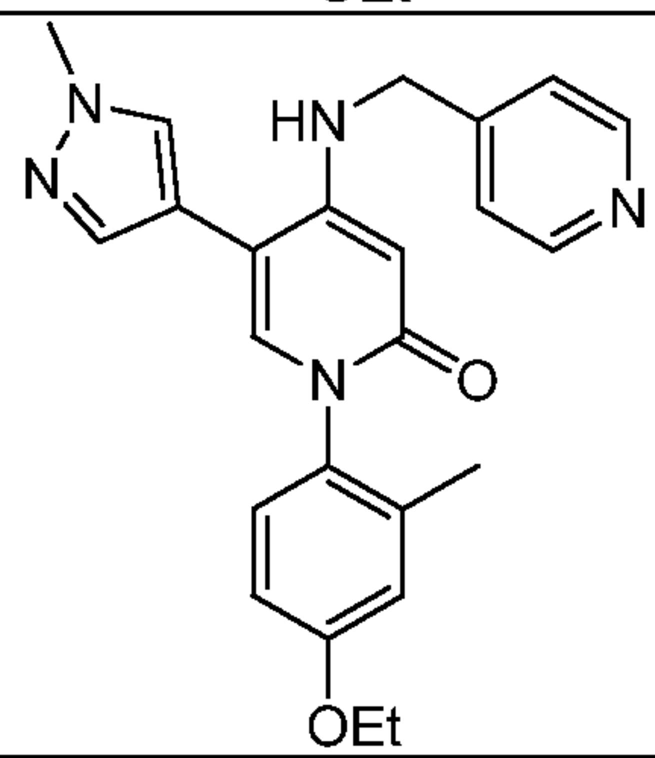
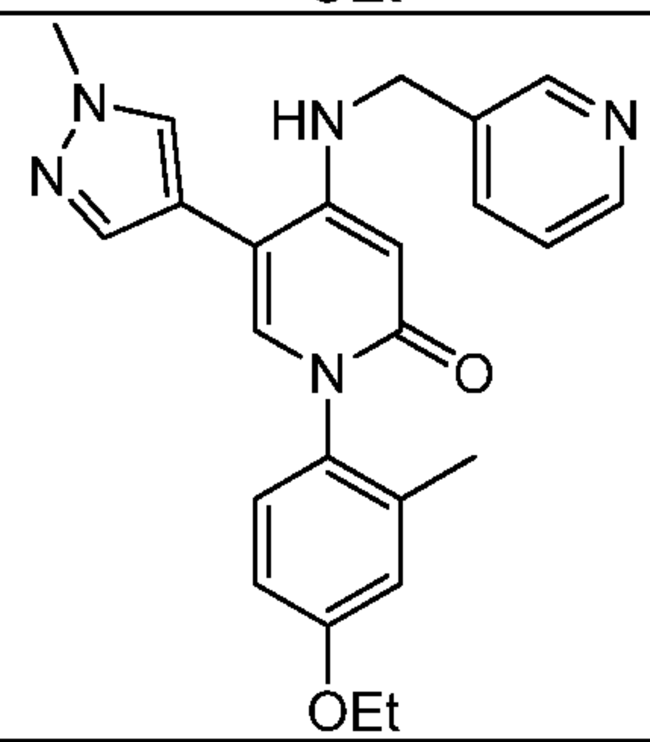
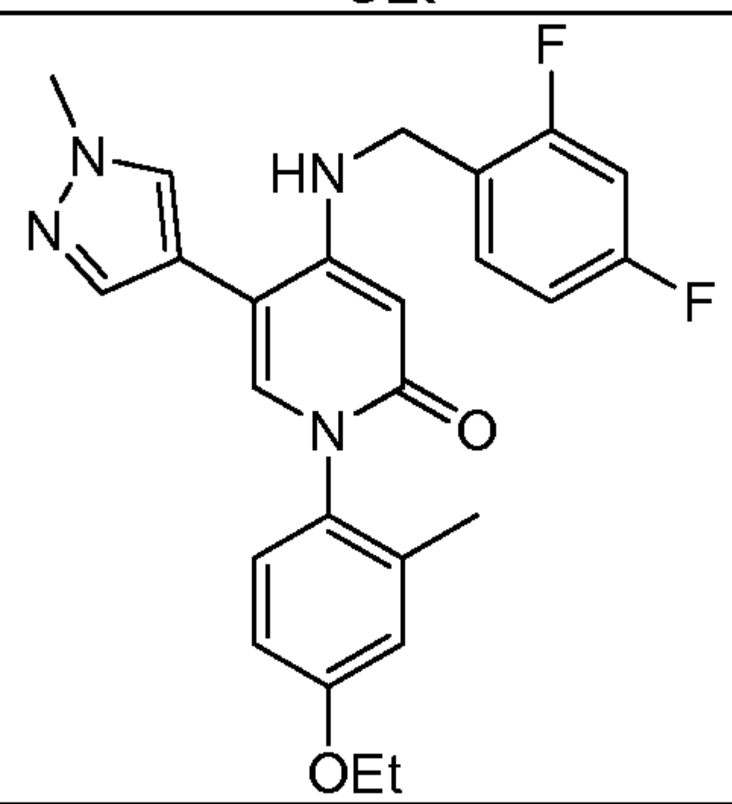
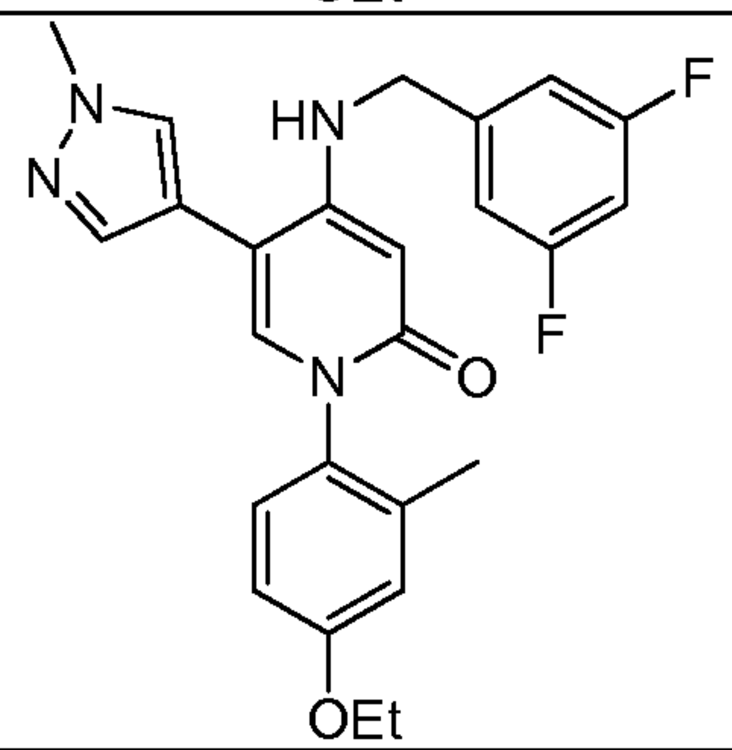
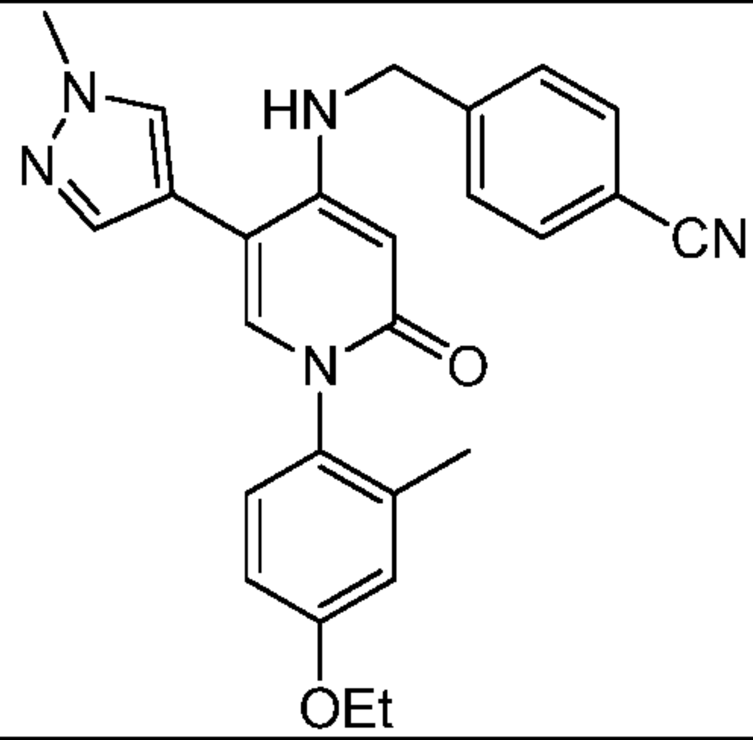
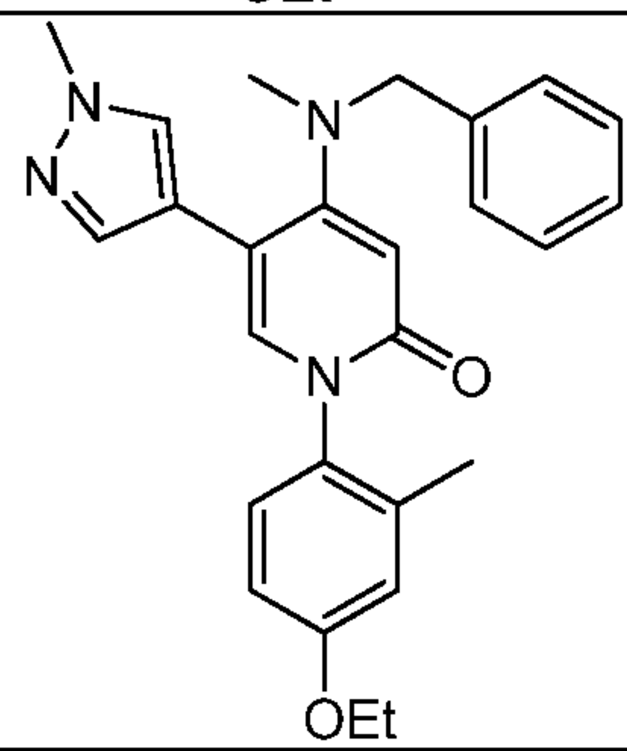
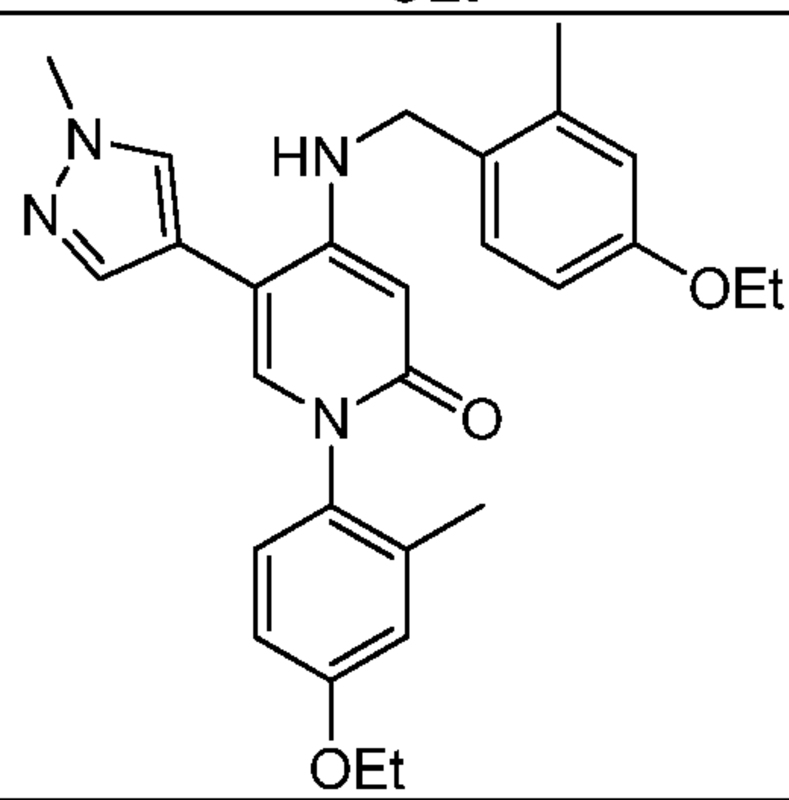
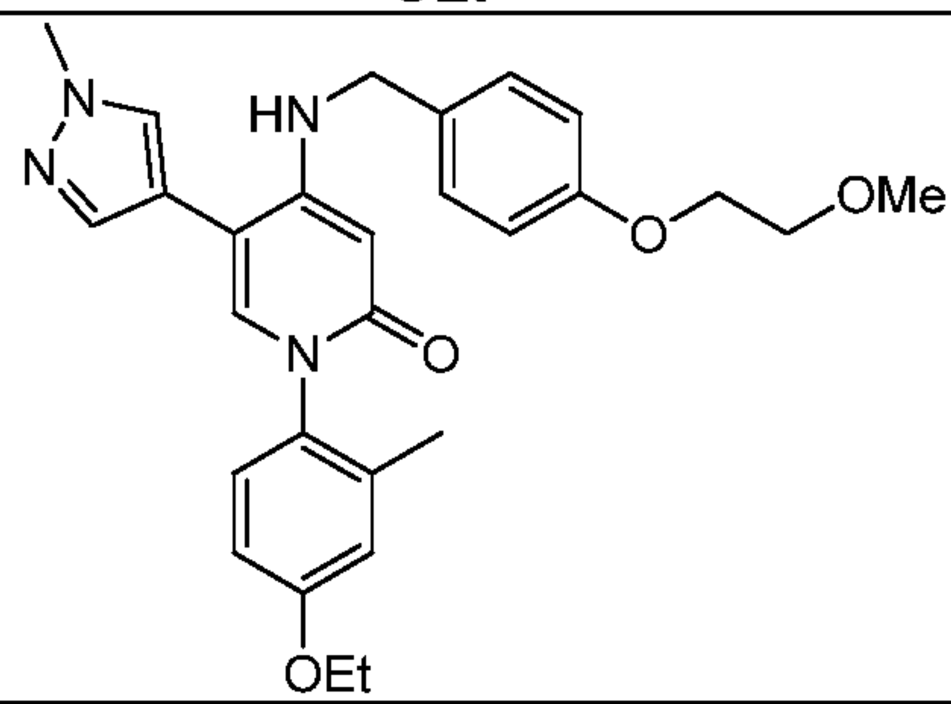
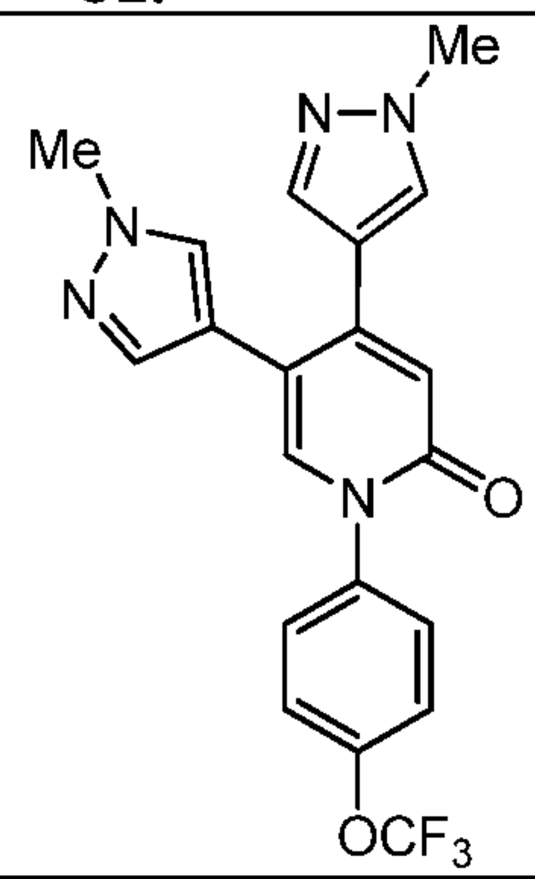
699	
700	
701	
702	
703	
704	
705	
706	
707	
708	

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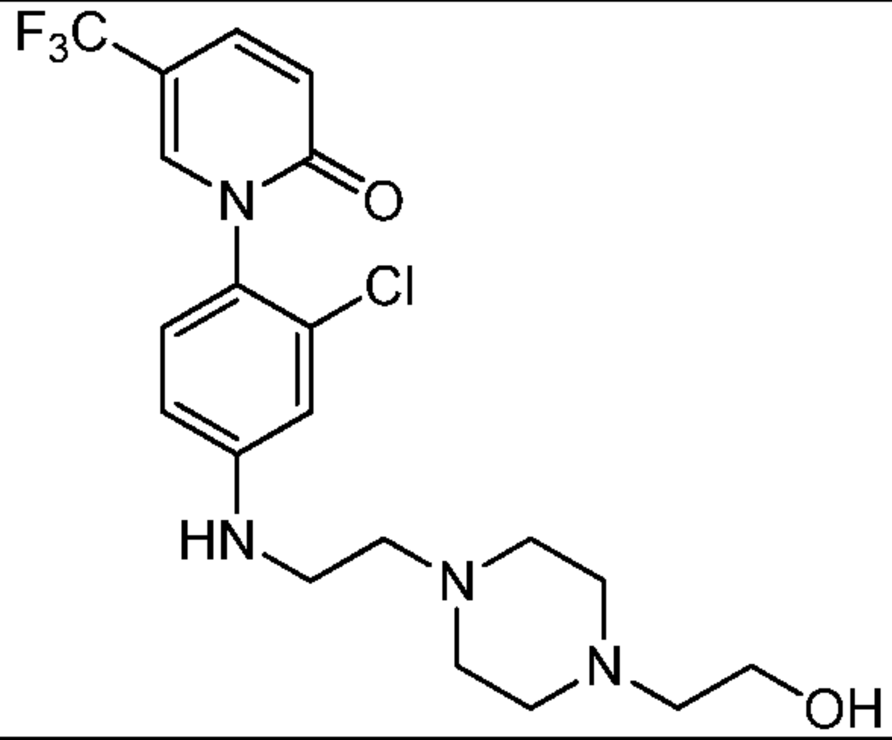
709	

Administration and Pharmaceutical Compositions

[0232] Some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of a compound described herein (including enantiomers, diastereoisomers, tautomers, polymorphs, and solvates thereof), or pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0233] The compounds are administered at a therapeutically effective dosage, e.g., a dosage sufficient to provide treatment for the disease states previously described. While human dosage levels have yet to be optimized for the compounds of the preferred embodiments, generally, a daily dose for most of the compounds described herein is from about 0.25 mg/kg to about 120 mg/kg or more of body weight, from about 0.5 mg/kg or less to about 70 mg/kg, from about 1.0 mg/kg to about 50 mg/kg of body weight, or from about 1.5 mg/kg to about 10 mg/kg of body weight. Thus, for administration to a 70 kg person, the dosage range would be from about 17 mg per day to about 8000 mg per day, from about 35 mg per day or less to about 7000 mg per day or more, from about 70 mg per day to about 6000 mg per day, from about 100 mg per day to about 5000 mg per day, or from about 200 mg to about 3000 mg per day. The amount of active compound administered will, of course, be dependent on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician.

[0234] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly. Oral and parenteral administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0235] The compounds useful as described above can be formulated into pharmaceutical compositions for use in treatment of these conditions. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), incorporated by reference in its entirety.

[0236] In addition to the selected compound useful as described above, come embodiments include compositions containing a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances, which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction, which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal being treated.

[0237] Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0238] The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

[0239] The compositions described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound that is suitable for administration to an animal, preferably mammal subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

[0240] The compositions useful as described above may be in any of a variety of suitable forms for a variety of routes for administration, for example, for oral, nasal, rectal, topical (including transdermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, or other parental routes of administration. The skilled artisan will appreciate that oral and nasal compositions include compositions that are administered by inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes, editors, 2002); Lieberman *et al*., Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0241] Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0242] The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical, and can be readily made by a person skilled in the art.

[0243] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0244] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0245] Compositions described herein may optionally include other drug actives.

[0246] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0247] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use.

Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0248] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0249] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0250] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0251] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0252] In a similar vein, an ophthalmically acceptable antioxidant includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0253] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[0254] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0255] For intravenous administration, the compounds and compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., Compendium of Excipients for Parenteral Formulations, *PDA J Pharm Sci and Tech* **1998**, *52* 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, *PDA J Pharm Sci and Tech* **2011**, *65* 287-332, both of which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0256] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0257] The actual dose of the active compounds described herein depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

<u>Method of Treatment</u>

[0258] Some embodiments described herein relate to a method of treating a fibrotic condition, which can include administering a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject. The methods include identifying a subject at risk for or having a fibrotic condition and administering a compound to the subject in an effective amount for therapeutic treatment or prophylactic treatment of the fibrotic condition.

[0259] A “fibrotic condition,” “fibroproliferative condition,” “fibrotic disease,” “fibroproliferative disease,” “fibrotic disorder,” and “fibroproliferative disorder” are used interchangeably to refer to a condition, disease or disorder that is characterized by dysregulated proliferation or activity of fibroblasts and/or abnormal accumulation of fibronectin and/or pathologic or excessive accumulation of collagenous tissue. Typically, any such disease, disorder or condition is amenable to treatment by administration of a compound having anti-fibrotic activity. Fibrotic disorders include, but are not limited to, pulmonary fibrosis, including idiopathic pulmonary fibrosis (IPF) and pulmonary fibrosis from a known etiology, dermal fibrosis, pancreatic fibrosis, liver fibrosis (e.g., hepatic fibrosis associated with chronic active hepatitis), and renal fibrosis.

[0260] In some embodiments, the subject is a human.

[0261] The terms “therapeutically effective amount,” as used herein, refer to an amount of a compound sufficient to cure, ameliorate, slow progression of, prevent, or reduce the likelihood of onset of the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, the assays disclosed in the following examples. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically and prophylactically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0262] For any compound, the therapeutically or prophylactically effective amount can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

[0263] Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, ED_{50}/LD_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. However, pharmaceutical compositions that exhibit narrow therapeutic indices are also within the scope of the invention. The data obtained from cell culture assays and animal studies may be used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include an ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0264] The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0265] In one aspect, treating a condition described herein results in an increase in average survival time of a population of treated subjects in comparison to a population of untreated subjects. Preferably, the average survival time is increased by more than about 30 days; more preferably, by more than about 60 days; more preferably, by more than about 90 days; and even more preferably by more than about 120 days. An increase in survival time of a population may be measured by any reproducible means. In a preferred aspect, an increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. In an another preferred aspect, an increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0266] In another aspect, treating a condition described herein results in a decrease in the mortality rate of a population of treated subjects in comparison to a population of subjects receiving carrier alone. In another aspect, treating a condition described herein results in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. In a further aspect, treating a condition described herein results a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the embodiments, or a pharmaceutically acceptable salt, metabolite, analog or derivative thereof. Preferably, the mortality rate is decreased by more than about 2%; more preferably, by more than about 5%; more preferably, by more than about 10%; and most preferably, by more than about 25%. In a preferred aspect, a decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means. In another preferred aspect, a decrease in the mortality rate of a population may be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with an active compound. In another preferred aspect, a decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease related deaths per unit time following completion of a first round of treatment with an active compound.

[0267] In another aspect, treating a condition described herein results in a reduction in the rate of cellular proliferation. Preferably, after treatment, the rate of cellular proliferation is reduced by at least about 5%; more preferably, by at least about 10%; more preferably, by at least about 20%; more preferably, by at least about 30%; more preferably, by at least about 40%; more preferably, by at least about 50%; even more preferably, by at least about 60%; and most preferably, by at least about 75%. The rate of cellular proliferation may be measured by any reproducible means of measurement. In a preferred aspect, the rate of cellular proliferation is measured, for example, by measuring the number of dividing cells in a tissue sample per unit time.

[0268] In another aspect, treating a condition described herein results in a reduction in the proportion of proliferating cells. Preferably, after treatment, the proportion of proliferating cells is reduced by at least about 5%; more preferably, by at least about 10%; more preferably, by at least about 20%; more preferably, by at least about 30%; more preferably, by at least about 40%; more preferably, by at least about 50%; even more preferably, by at least about 60%; and most preferably, by at least about 75%. The proportion of proliferating cells may be measured by any reproducible means of measurement. In a preferred aspect, the proportion of proliferating cells is measured, for example, by quantifying the number of dividing cells relative to the number of nondividing cells in a tissue sample. In another preferred aspect, the proportion of proliferating cells is equivalent to the mitotic index.

[0269] In another aspect, treating a condition described herein results in a decrease in size of an area or zone of cellular proliferation. Preferably, after treatment, size of an area or zone of cellular proliferation is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least about 10%; more preferably, reduced by at least about 20%; more preferably, reduced by at least about 30%; more preferably, reduced by at least about 40%; more preferably, reduced by at least about 50%; even more preferably, reduced by at least about 60%; and most preferably, reduced by at least about 75%. Size of an area or zone of cellular proliferation may be measured by any reproducible means of measurement. In a preferred aspect, size of an area or zone of cellular proliferation may be measured as a diameter or width of an area or zone of cellular proliferation.

[0270] The methods described herein may include identifying a subject in need of treatment. In a preferred embodiment, the methods include identifying a mammal in need of treatment. In a highly preferred embodiment, the methods include identifying a human in need of treatment. Identifying a subject in need of treatment may be accomplished by any means that indicates a subject who may benefit from treatment. For example, identifying a subject in need of treatment may occur by clinical diagnosis, laboratory testing, or any other means known to one of skill in the art, including any combination of means for identification.

[0271] As described elsewhere herein, the compounds described herein may be formulated in pharmaceutical compositions, if desired, and can be administered by any route that permits treatment of the disease or condition. A preferred route of administration is oral administration. Administration may take the form of single dose administration, or the compound of the embodiments can be administered over a period of time, either in divided doses or in a continuous-release formulation or administration method (e.g., a pump). However the compounds of the embodiments are administered to the subject, the amounts of compound administered and the route of administration chosen should be selected to permit efficacious treatment of the disease condition.

[0272] Further embodiments include administering a combination of compounds to a subject in need thereof. A combination can include a compound, composition, pharmaceutical composition described herein with an additional medicament.

[0273] Some embodiments include co-administering a compound, composition, and/or pharmaceutical composition described herein, with an additional medicament. By "co-administration," it is meant that the two or more agents may be found in the patient's bloodstream at the same time, regardless of when or how they are actually administered. In some embodiments, the agents are administered simultaneously. In some such such embodiments, administration in combination is accomplished by combining the agents in a single dosage form. In some embodiments, the agents are administered sequentially. In some embodiments the agents are administered through the same route, such as orally. In some other embodiments, the agents are administered through different routes, such as one being administered orally and another being administered i.v. Thus, for example, the combination of active ingredients may be: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by any other combination therapy regimen known in the art. When delivered in alternation therapy, the methods described herein may comprise administering or delivering the active ingredients sequentially, e.g., in separate solution, emulsion, suspension, tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in simultaneous therapy, effective dosages of two or more active ingredients are administered together. Various sequences of intermittent combination therapy may also be used.

Pulmonary Fibrosis

[0274] Pulmonary fibrosis also called idiopathic pulmonary fibrosis (IPF), interstitial diffuse pulmonary fibrosis, inflammatory pulmonary fibrosis, or fibrosing alveolitis, is a lung disorder and a heterogeneous group of conditions characterized by abnormal formation of fibrous tissue between alveoli caused by alveolitis comprising cellular infiltration into the alveolar septae with resulting fibrosis. The effects of IPF are chronic, progressive, and often fatal. The compounds and methods described herein are useful in the treatment of pulmonary fibrosis, such as IPF.

Renal Fibrosis

[0275] Irrespective of the nature of the initial insult, renal fibrosis is considered to be the common final pathway by which kidney disease progresses to end-stage renal failure. The compounds and methods described herein are useful in the treatment of renal fibrosis.

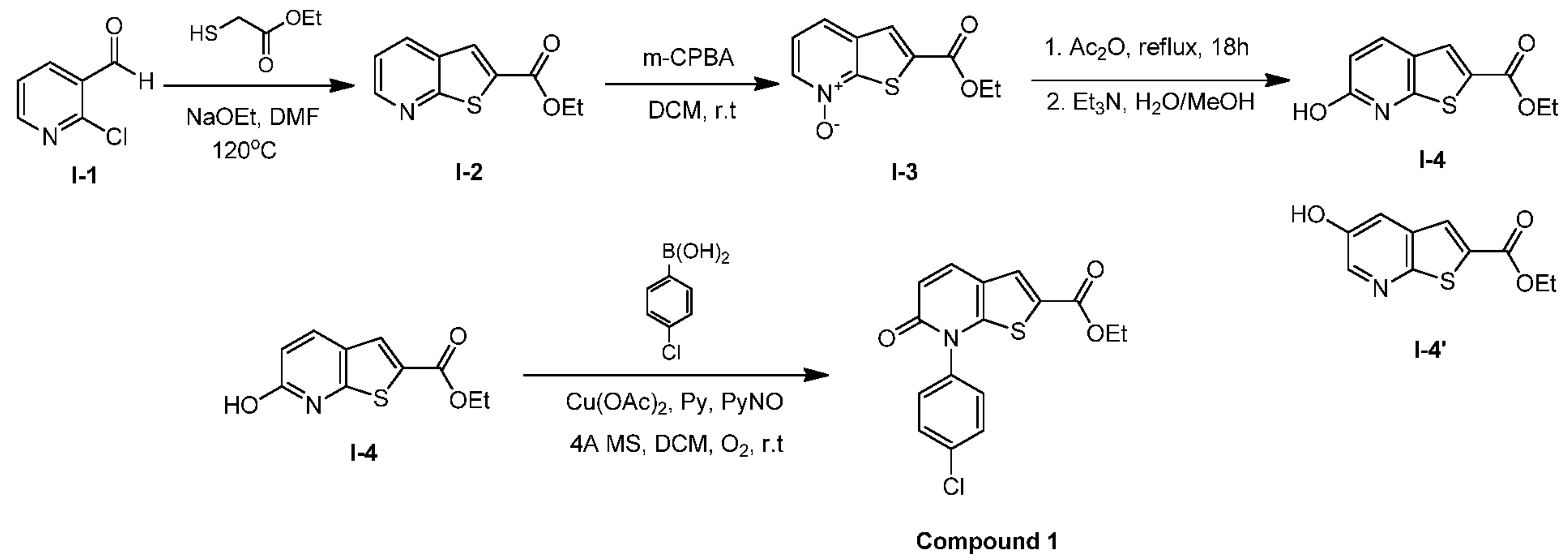
Synthesis

[0276] The compounds disclosed herein may be synthesized by methods described below, or by modification of these methods. Ways of modifying the methodology include, among others, temperature, solvent, reagents etc., known to those skilled in the art. In general, during any of the processes for preparation of the compounds disclosed herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described *in Protective Groups in Organic Chemistry* (ed. J.F.W. McOmie, Plenum Press, 1973); and P.G.M. Green, T.W. Wutts, *Protecting Groups in Organic Synthesis* (3rd ed.) Wiley, New York (1999), which are both hereby incorporated herein by reference in their entirety. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include e.g. those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers, **1989**, or L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, **1995**, which are both hereby incorporated herein by reference in their entirety. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

EXAMPLES

[0277] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

Example 1-A
Synthesis of Compound 1 (Scheme I)



[0278] To a solution of ethyl thioglycolate (11.14 g, 92.8 mmol) in 400 mL of DMF was added NaOEt (14.5 g, 185.7 mmol) by portion wise. The resulting mixture was stirred for 30 min at 0°C. And then **I-1** (10 g, 71.4 mmol) was added to the solution by portion wise. The mixture was stirred at 120 °C overnight. The reaction mixture was cooled to rt., diluted with water (300 mL), extracted with EtOAc (300 mL × 3), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was washed with petroleum ether to afford **I-2** (8.7 g, 59% yield) as a pale brown solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.68 (dd, J = 1.6, 4.4 Hz, 1H), 8.16 (dd, J = 1.6, 8.0 Hz, 1H), 8.00 (s, 1H), 7.36 (m , 1H), 4.43 (q, J = 7.2 Hz, 2 H), 1.42 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 208.0.

[0279] To a solution of **I-2** (7.5 g, 36.2 mmol) in 300 mL of DCM was added *m*-CPBA (12.4 g, 72.4 mmol) by portion wise at 0°C. The resulting solution was stirred at rt overnight, followed by quench with saturated *aq*.$Na_2S_2O_3$. The organic layer was separated, the aqueous layer was extracted with EtOAc (200 mL × 3). The combined organic layers were washed with saturated *aq*. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was washed with petroleum ether to produce **I-3** (7.5 g, 93% yield) as a white solid. **MS (ESI)** ***m/z*** $[M+H]^+$ 224.0.

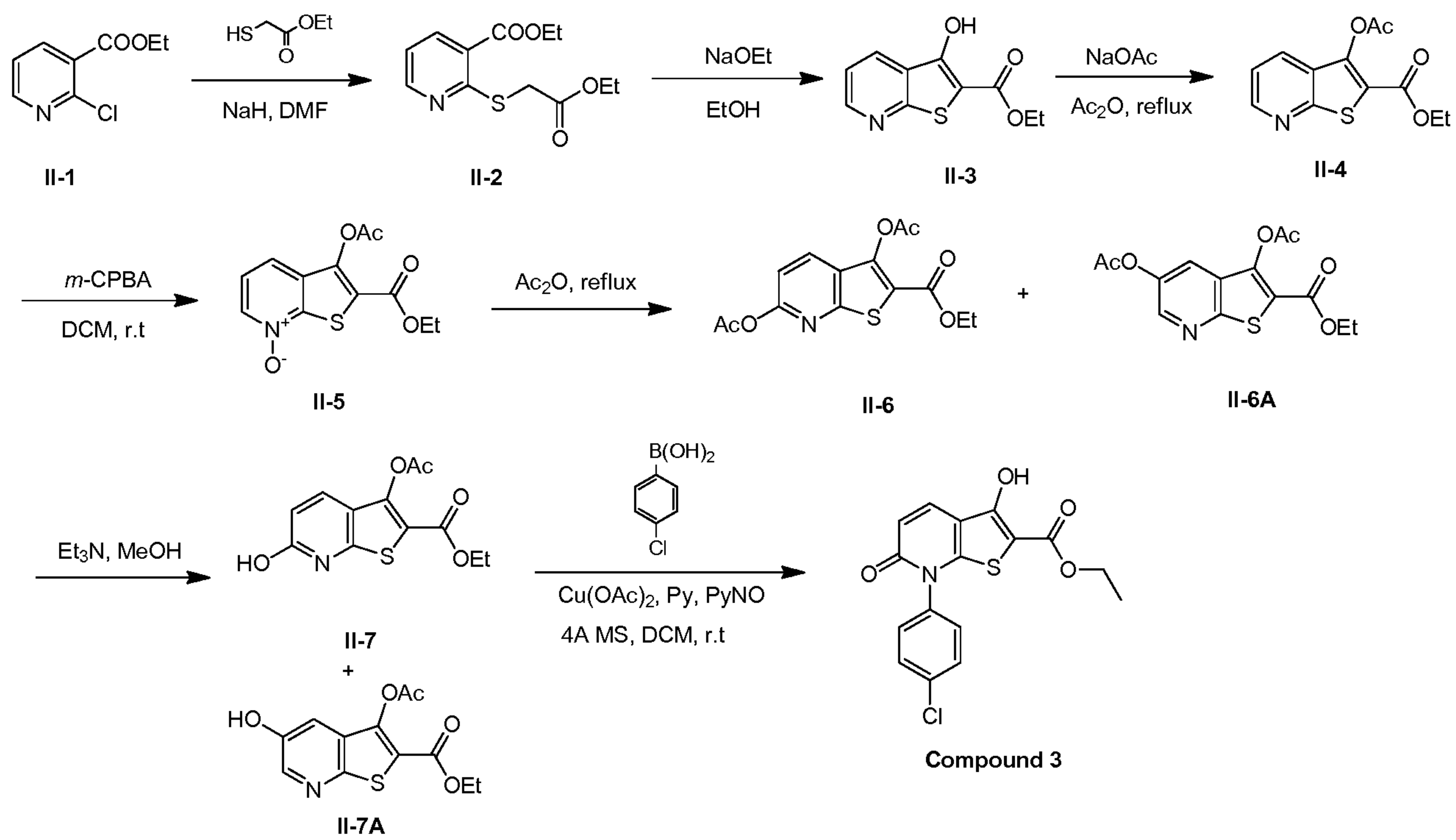
[0280] **I-3** (7.0 g, 31.4 mmol) was added into 60 mL of Ac_2O ,the solution was heated to reflux overnight. The reaction mixture was concentrated, the residue was dissolved with 100 mL of

MeOH, and 6 mL of TEA was added thereto, the mixture was stirred at rt for 4 hours, and then it was concentrated, diluted with EtOAc (500 mL), washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel with petroleum ether/EtOAc (20:1→10:1→5:1→1:1→1:2→1:10) to afford **I-4** (2.8 g, 40% yield) as a brown solid. **MS (ESI)** ***m/z*** $[M+H]^+$ 223.8.

[0281] A flask was charged with **I-4** (1.0 g, 4.48 mmol), 4-chlorophenyl boronic acid (2.11 g, 13.45 mmol), $Cu(OAc)_2$ (4.05 g, 22.4 mmol), pyridine N-oxide (4.26 g, 44.8 mmol), pyridine (2.69 g, 35.8 mmol), 4Å molecular sieve (1.0 g) and 300 mL of anhydrous DCM. The mixture was stirred under oxygen atmosphere at rt. overnight. The reaction was monitored by TLC, when the starting material was consumed, the mixture was concentrated, diluted with water (100 mL), extracted with EtOAc (300 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel with petroleum ether/EtOAc (50:1→30:1→10:1→5:1→2:1) to afford **Compound 1** (900 mg, 60% yield) as a pale yellow solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.04-8.00 (m, 2H), 7.71 (d, *J*=8.4Hz, 2H), 7.60 (d, *J*=8.4Hz, 2H), 6.60 (d, *J*=9.6Hz, 1H), 4.24 (q, *J*=7.2Hz, 2H), 1.24 (t, *J*=7.2Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 333.9.

[0282] **Compound 2** was prepared following the procedure for obtaining **Compound 1** using 1-(2-chloropyridin-3-yl)ethanone in place of **I-1** as a white solid. **^{1}H NMR** (CD_3OD, 400 MHz) δ 8.06 (d, *J*=9.2 Hz, 1H), 7.70-7.67 (m, 2H), 7.50-7.48 (m, 2H), 6.68 (d, *J*=9.6 Hz, 1H), 4.29 (q, *J*=7.2 Hz, 2H), 2.69 (s, 3H), 1.35 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 347.9.

Example 1-B
Synthesis of Compound 3 (Scheme II)



[0283] NaH (1.29 g, 54 mmol) was added to the stirred mixture of **II-1** (5.0 g, 27 mmol) and ethyl thioglycolate (3.9 g, 32.4 mmol) in DMF (50 mL) at 0°C. The reaction mixture was stirred at rt overnight. The reaction was slowly quenched with water (50 mL) and then extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the crude **II-2** (3.7 g, 51% crude yield), which was used for next step directly.

[0284] NaOEt (1.87 g, 27.4 mmol) was added to the mixture of **II-2** (3.7 g, 13.7 mmol) in 30 mL of EtOH, and the reaction mixture was stirred at rt for 2 hours. Then the mixture was adjusted to pH=2 with *aq*. HCl (2 M), the precipitated solid was collect to afford **II-3** (2.4 g, 79% yield), which was used for next step directly.

[0285] A mixture of **II-3** (3 g, 13.4 mmol) and NaOAc (2.2 g, 26.8 mmol) in Ac_2O (50 ml) was stirred at reflux for 2 hours. The mixture was cooled to rt., concentrated *in vacuo*, the mixture was dissolved in EtOAc (100 mL), washed with saturated *aq*. Na_2CO_3 and water. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure to give **II-4** (3 g, 84% yield).

[0286] To a stirring solution of **II-4** (3 g, 11.3 mmol) in anhydrous DCM (60 mL) at 0°C was added *m*-CPBA (5.85 g, 34 mmol). Then the mixture was stirred overnight at rt. After that the mixture was washed with saturated *aq.* Na_2SO_3 solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was re-crystallized from EtOAc to produce **II-5** (2.5 g, 79% yield) as white solid.

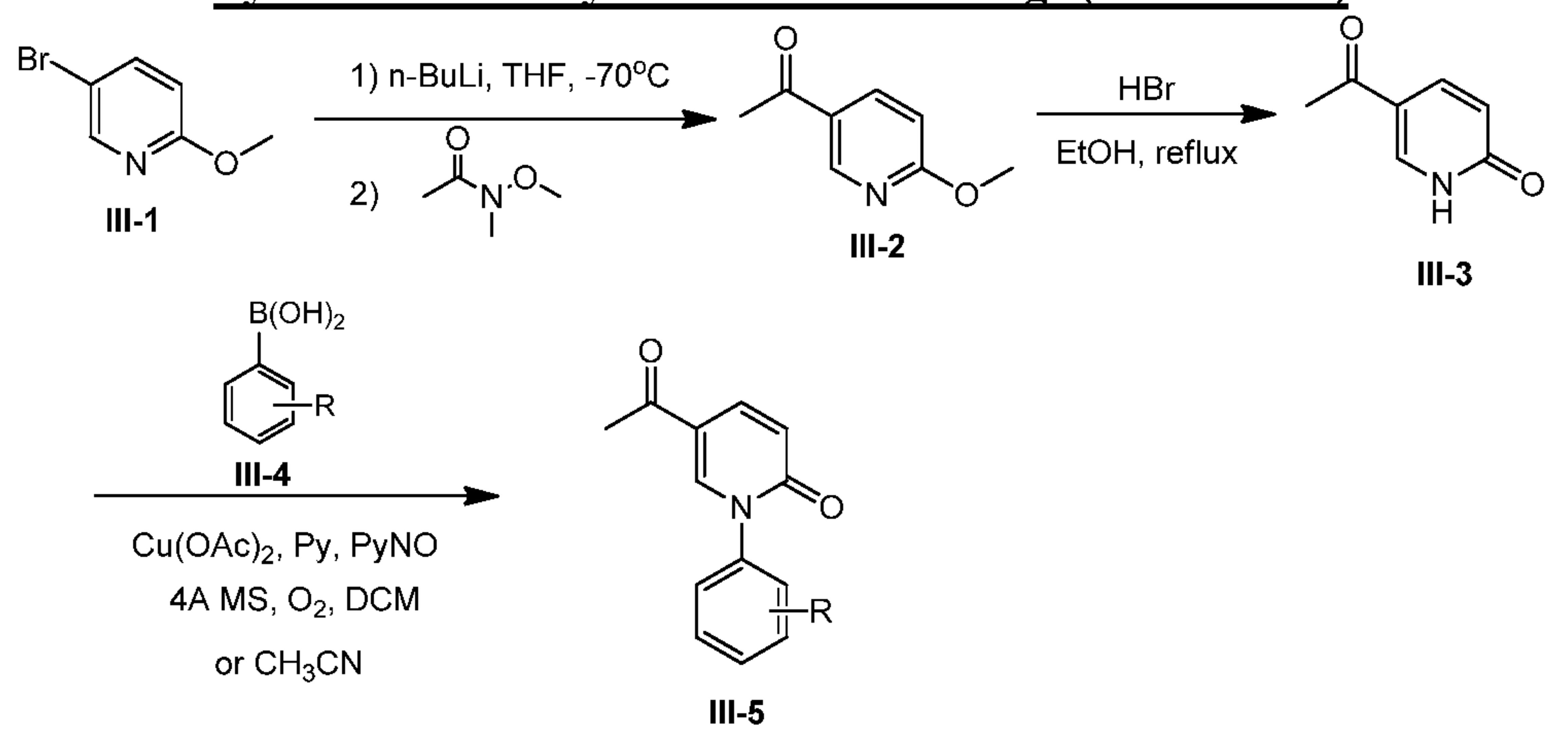
[0287] **II-5** (2.5 g, 8.9 mmol) was dissolved in Ac_2O (30 mL) and the mixture was refluxed at 140°C for 18 hrs. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (20:1) to give a mixture of **II-6** and **II-6A** (1.5 g, 52% yield) as yellow solid.

[0288] To a stirring solution of mixture **II-6** and **II-6A** (1.3 g, 4 mmol) in MeOH (65 mL) was added TEA (10 mL) at rt. Then the mixture was stirred for 1 h at ambient temperature. The mixture was concentrated under reduced pressure to afford a mixture of **II-7** and **II-7A** (1.0 g, 88% crude yield) as yellow solid, which was used directly without further purification.

[0289] A mixture of **II-7** and **II-7A** (500 mg, 1.8 mmol), 4-chlorophenyl boronic acid (842 mg, 5.4 mmol), $Cu(OAc)_2$ (1.63 g, 9 mmol), pyridine-N-oxide (1.71 g, 18 mmol) and pyridine (1.42 g, 18 mmol) in anhydrous DCM (50 mL) was stirred for 80 hours at rt under air. Then the mixture was washed with water and the organic phase was dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by Prep-HPLC to give **Compound 3** (100 mg, 16% yield). **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.96 (d, J = 9.2 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H), 6.43 (d, J = 9.2 Hz, 1H), 4.15 (q, J= 7.2 Hz, 2H), 1.24 (t, J= 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$: 349.9.

[0290] **Compound 4** was prepared following the similar procedure for obtaining **Compound 3** using 1-(2-chloropyridin-3-yl)propan-1-one in place of **II-1**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.3 (brs, 1H), 8.03 (d, J = 9.6 Hz, 1H), 6.53 (d, J = 9.2 Hz, 1H), 4.29 (q, J= 7.2 Hz, 2H), 3.12 (q, J= 7.2 Hz, 2H), 1.33 (t, J= 7.2 Hz, 3H), 1.15 (t, J= 7.2 Hz, 3H).

Example 2
Synthesis of 5-Acyl Pirfenidone Analogs (Scheme III)



[0291] To a solution of **III-1** (30 g, 0.162 mol, 1 eq.) in 300 mL of anhydrous THF was added dropwise a solution of n-BuLi (2.5M in hexane, 77.5 mL, 0.19 mol, 1.2 eq.) at -70°C. After completion of addition, the mixture was stirred at -70°C for 20 min, followed by addition of a solution of N-methoxy-N-methylacetamide (33 g, 0.322 mol, 2 eq.) in 100 mL of anhydrous THF by drop wise, the solution was allowed to warm to rt and stirred for 2 hrs. The reaction was quenched with saturated *aq.* NH_4Cl (100 mL), extracted with EtOAc (300 mL×3), the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with petroleum ether/EtOAc (100:1) to yield **III-2** (14.8 g, 62% yield) as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.81 (d, J = 2.0 Hz, 1H), 8.16 (dd, J = 2.4, 8.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H), 2.55 (s, 3H). **MS (ESI)** *m/z* $[M+H]^+$ 151.6.

[0292] To a solution of **III-2** (5 g, 33 mmol) in 20 mL of EtOH was added *aq.* HBr (48%, 60 mL), the reaction mixture was heated to reflux overnight. After being cooled to rt., the mixture was neutralized by addition of saturated *aq.* $NaHCO_3$, extracted with EtOAc (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to supply crude **III-3** (3 g, 65% yield) as white solid.

[0293] To a solution of **III-3** (1 eq.) in DCM (0.1 mmol/mL) was added boronic acid **III-4** (2 eq.), $Cu(OAc)_2$ (1 eq), Pyridine (10 eq.) and Pyridine-N-Oxide (2 eq.), followed by addition of 4Å molecular sieve (quantity approx. equal to **III-3**). The reaction mixture was stirred at rt under oxygen atmosphere overnight. After completion of the reaction indicated by TLC, the resulting mixture was filtered and washed with , the filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give **III-5.**

[0294] **Compound 10** (61% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.43 (d, J = 2.4 Hz, 1H), 7.90 (dd, J = 9.6, 2.4 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 9.6 Hz, 1H), 3.81 (s, 3H), 2.41 (s, 3H).

[0295] **Compound 11** (67% yield): **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.42 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 9.6, 2.4 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.49 (d, J = 9.6 Hz, 1H), 4.68-4.64 (m, 1H), 3.40 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H).

[0296] **Compound 12** (50% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.57 (d, J = 2.4 Hz, 1H), 7.95-7.92 (m, 2H), 7.87 (d, J = 7.6 Hz, 1H), 7.82-7.79 (m, 2H), 6.56 (d, J = 9.6 Hz, 1H), 2.43 (s, 3H).

[0297] **Compound 13** (78% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.52 (d, J = 2.4 Hz, 1H), 7.95-7.91 (m, 1H), 7.64 (d, J = 8.8Hz, 2H), 7.56 (d, J = 8.8Hz, 2H), 6.56 (d, J = 9.6Hz, 1H), 2.44 (s, 3H).

[0298] **Compound 14** (74% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.49 (d, J = 2.4Hz, 1H), 7.91 (dd, J = 9.6, 2.4 Hz, 1H), 7.56-7.52 (m, 2H), 7.40-7.35 (m, 2H), 6.53 (d, J = 9.6 Hz, 1H), 2.42 (s, 3H).

[0299] **Compound 15** (67% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.45 (d, J = 2.4Hz, 1H), 7.90 (dd, J = 9.6, 2.8 Hz, 1H), 7.46-7.41 (m, 1H), 7.03 (t, 3H), 6.52 (d, J = 9.6Hz, 1H), 3.79 (s, 3H), 2.42 (s, 3H).

[0300] **Compound 16** (74% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.53 (d, J = 2.8Hz, 1H), 7.90 (dd, J = 9.6, 2.4 Hz, 1H), 7.64-7.58 (m, 1H), 7.52-7.48 (m, 1H), 7.41-7.35 (m, 2H), 6.57 (d, J = 9.6 Hz, 2H), 2.45 (s, 3H).

[0301] **Compound 17** (64% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.55 (d, J = 2.4Hz, 1H), 7.92 (dd, J = 9.6, 2.4 Hz, 1H), 7.67-7.63- (m, 2H), 7.55 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 9.6 Hz, 1H), 2.42 (s, 3H).

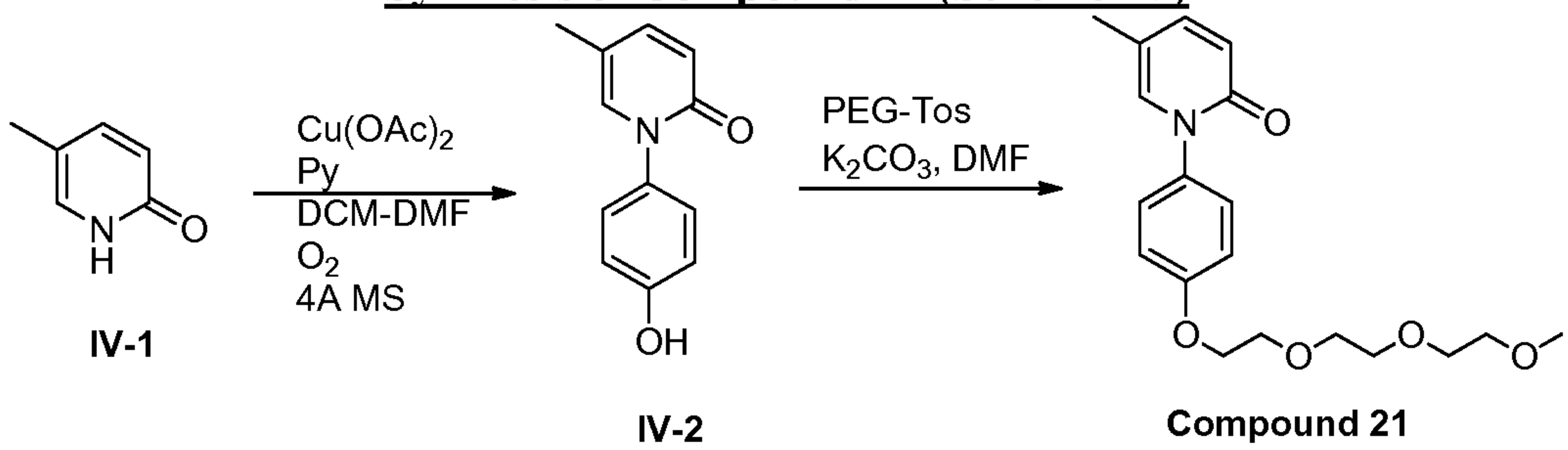
[0302] **Compound 18** (23% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.37 (d, J = 2.4Hz, 1H), 7.92 (dd, J = 9.6, 2.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 6.52 (d, J = 9.6 Hz, 1H), 4.06 (q, J = 6.8 Hz, 2H), 2.40 (s, 3H), 2.00 (s, 3H), 1.34 (t, J = 6.8 Hz, 3H).

[0303] **Compound 19** (40% yield): **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.18 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 7.91 (dd, J = 9.6, 2.4 Hz, 1H), 7.73 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.12 (dd, J = 7.6, 0.8 Hz, 1H), 6.53 (d, J = 9.6 Hz, 1H), 2.41 (s, 3H), 2 .05 (s, 3H).

[0304] **Compound 20** was prepared following the general procedure, except the solvent was changed to acetonitrile (10% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.06 (d, J = 2.4 Hz, 1H), 7.97 (dd, J = 10, 2.4 Hz, 1H), 7.53-7.45 (m, 1H), 7.43-7.36 (m, 1H), 7.34-7.25 (m, 2H), 6.67 (d, J = 10 Hz, 1H), 2.45 (s, 3H). **MS (ESI)** ***m / z*** $(M+H)^+$ 232.0.

Example 3-A

Synthesis of Compound 21 (Scheme IV)



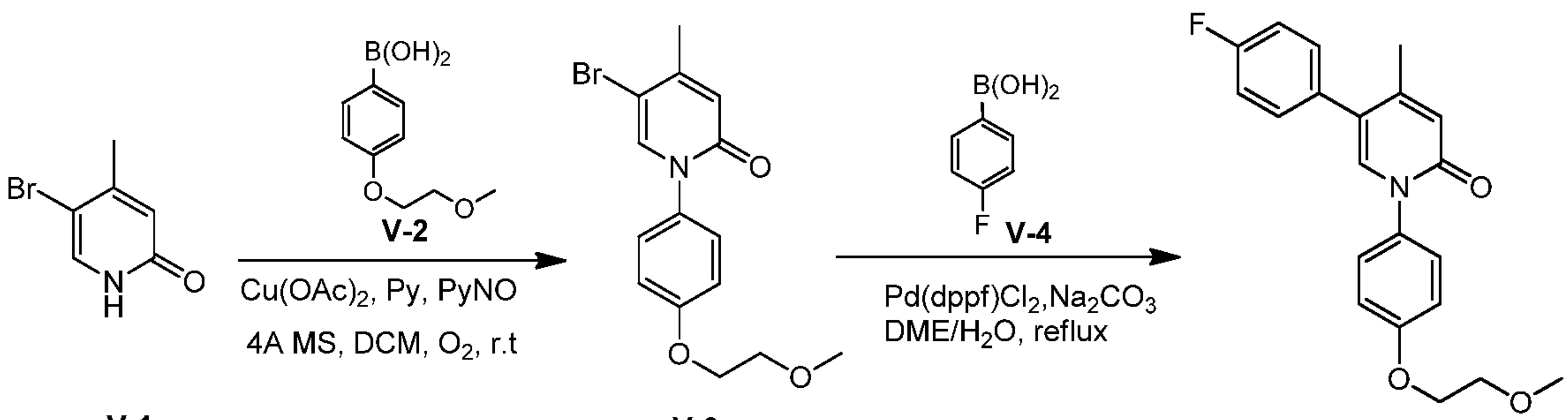
[0305] To a solution of 5-methyl-2-pyridone **IV-1** (643 mg, 5.9 mmol) in DCM (71 mL) and DMF (23.5 mL), $Cu(OAc)_2$ (2.14 g, 11.784 mmol), 4-hydroxy phenyl boronic acid (0.975 g, 7.07 mmol), pyridine (0.95 mL, 11.784 mmol) and activated 4 Å molecular sieves (7.1 g) were added. The mixture was stirred at rt for 24 hours. A concentrated solution of NH_4OH was added, filtered through celite. Filtrate was evaporated under vacuum, and the resulting crude was purified by flash chromatography (SiO_2; DCM/MeOH) to afford **IV-2**, 600 mg (51% yield) of pure product as pale yellow solid. MS: *m/z* 202.2 (M+H).

[0306] To a suspension of **IV-2** (250 mg, 1.24 mmol) in DMF (9 mL) was added PEG-Tos (395 mg, 1.24 mmol), K_2CO_3 (343 mg, 2.48 mmol) and heated at 50°C for 24 hours. Reaction mixture was filtered through a celite pad, washed with MeOH and solvents were removed under vacuum. The crude material was purified by flash chromatography (SiO_2; DCM/MeOH) to afford **Compound 21** (400 mg, 93% yield) of pure product as colorless oil. MS: m/z 348.4 (M+H).

[0307] **Compound 22** was prepared following the similar procedure for obtaining **Compound 21** using 1-(3-hydroxyphenyl)-5-methylpyridin-2(1H)-one in place of **IV-2**. MS: m/z=348.6 (M+H).

Example 3-B

Synthesis of Compound 23 (Scheme V)



V-1 V-3 Compound 23

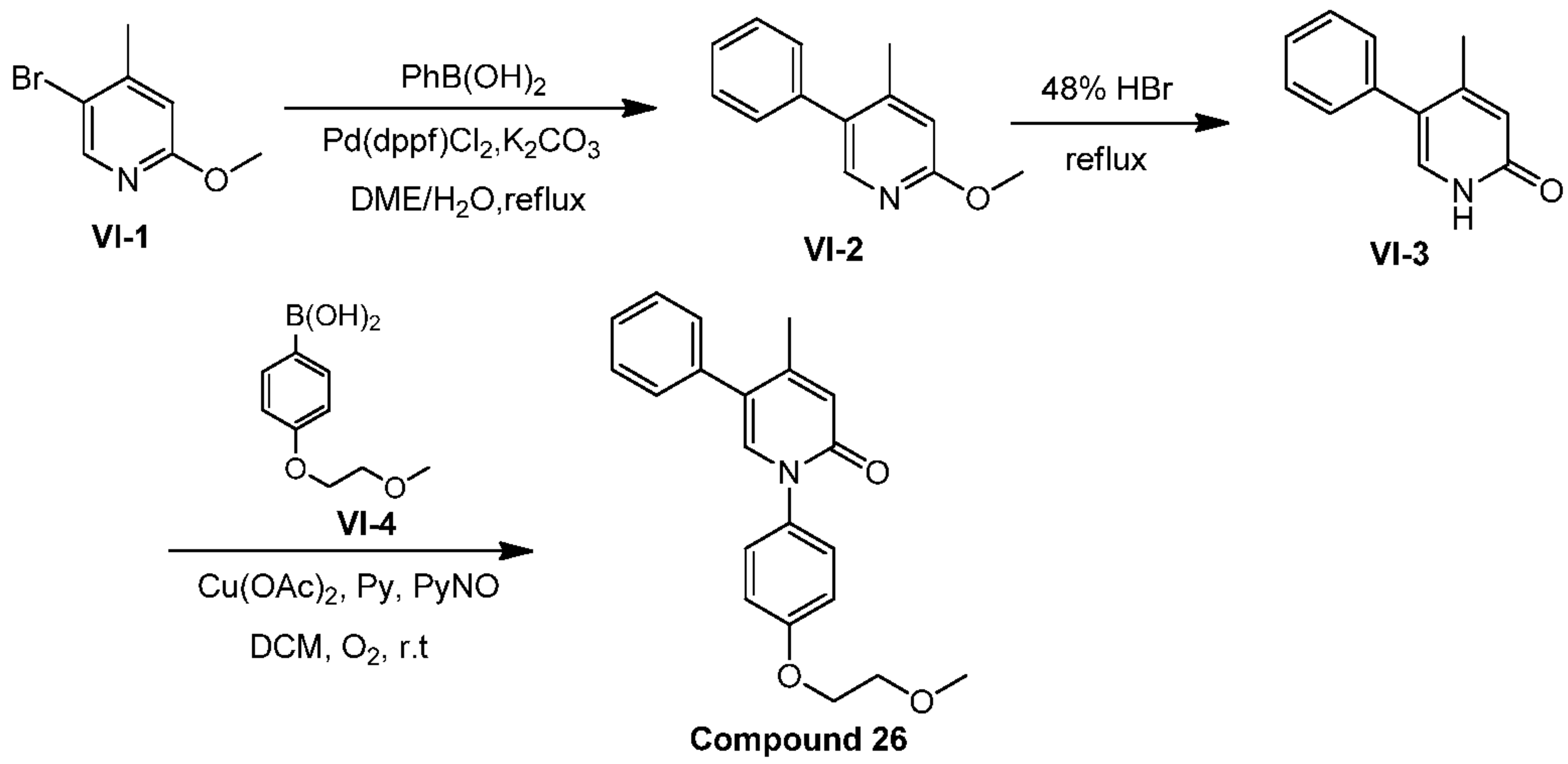
[0308] A mixture of **V-1** (4.3 g, 22 mmol), boronic acid **V-2** (2.75 g, 14 mmol), pyridine (3.58 mL, 43.9 mmol), pyridine N-oxide (4.2 g, 43.9 mmol), 4Å molecular sieve (300 mg) and $Cu(OAc)_2$ (7.95 g, 43.9 mmol) in anhydrous DCM (200 mL) was degassed by purging with O_2. The reaction mixture was stirred at r.t. for 12 hours. The suspension was filtered and filtrate was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with PE/EtOAc (10:1→2:1) to give **V-3** (1.76 g, 36% yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.48 (s, 1H), 7.26-7.23 (m, 2H), 7.01-6.98 (m, 2H), 6.54 (s, 1H), 4.14 (t, J = 4.8 Hz, 2H), 3.76 (t, J = 4.8 Hz, 2H), 3.45 (s, 3H), 2.27 (s, 3H).

[0309] To a solution of **V-3** (510 mg, 1.51 mmol) in 12 mL of DME/H_2O (v/v = 5/1) was added Na_2CO_3 (320 mg, 3.02 mmol), **V-4** (317 mg, 2.26 mmol), Pd(dppf)Cl_2 (110 mg, 0.15 mmol). The mixture was purged with nitrogen and then heated at reflux overnight. The mixture was cooled to r.t., diluted with water (30 mL), extracted with EtOAc (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with PE/EtOAc (10:1→1:1) to produce **Compound 23** (300 mg, 56% yield) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33-7.30 (m, 2H), 7.25-7.23 (m, 2H), 7.17 (s, 1H), 7.11-7.07 (m, 2H), 7.02-7.00 (m, 2H), 6.56 (s, 1H), 4.15 (t, J = 4.8 Hz, 2H), 3.76 (t, J = 4.8 Hz, 2H), 3.45 (s, 3H), 2.12 (s, 3H).

[0310] **Compound 24** was prepared following the similar procedure for obtaining **Compound 23** using *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate in place of **V-4** as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.58 (s, 2H), 7.30 (d, J = 8.8Hz 2H), 7.26 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.58 (s, 1H), 4.15 (t, J = 4.8 Hz, 2H), 3.76 (t, J = 4.8 Hz, 2H), 3.46 (s, 3H), 2.21 (s, 3H).

[0311] **Compound 25** was prepared following the similar procedure for obtaining **Compound 23** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of **V-4** as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 7.36 (s, 1H), 7.31-7.22 (m, 3H), 7.03-6.98 (m, 2H), 6.55 (s, 1H), 4.14 (t, J = 4.8 Hz, 2H), 3.93 (s, 3H), 3.76 (t, J = 4.8 Hz, 2H), 3.46 (s, 3H), 2.21 (s, 3H).

Example 3-C
Synthesis of Compound 26 (Scheme VI)

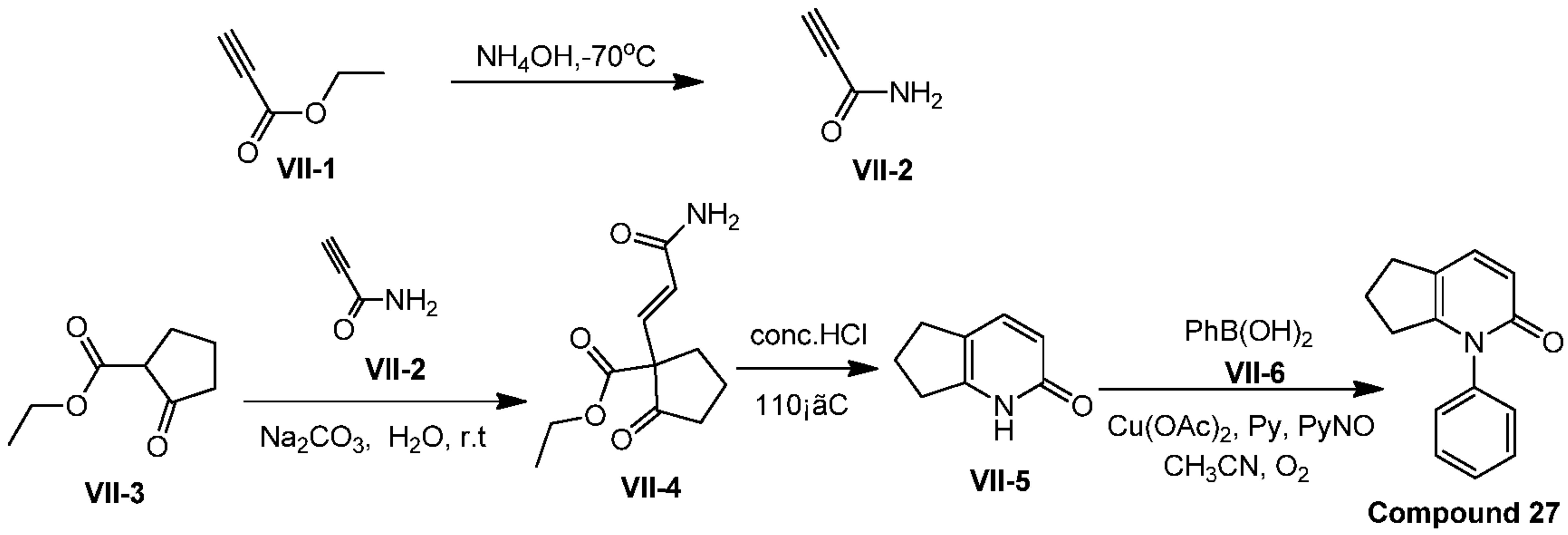


[0312] To a stirred mixture of **VI-1** (600 mg, 2.97 mmol), phenyl boronic acid (435 mg, 3.56 mmol), and K_3CO_3 (409 mg, 8.91 mmol) in DME/H_2O (22 mL, v/v=10/1) was added Pd(dppf)Cl_2 (436 mg, 0.594 mmol). The mixture was purged with nitrogen for three times and then heated at 100°C overnight. The mixture was concentrated to remove DME, diluted with H_2O (50 mL), extracted with EtOAc (100 mL×3). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by prep-TLC (PE/EA=5/1) to give **VI- 2** (226 mg, 38% yield).

[0313] A mixture of **VI-2** (226 mg, 1.13 mmol) with *aq*. HBr (48%, 10 mL) was heated to reflux under nitrogen overnight. After being cooled to r.t., the mixture was neutralized by adding saturated *aq*. $NaHCO_3$, and then extracted with EtOAc (80 mL×3). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford **VI-3** (180 mg, 85% yield).

[0314] To a stirred mixture of **VI-3** (180 mg, 0.972 mmol), boronic acid **VI-4** (285 mg, 1.46 mmol), copper (II) acetate (528 mg, 2.92 mmol) and pyridine (231 mg, 2.92 mmol) in DCM (10 mL) was added pyridine-*N*-oxide (277 mg, 2.92 mmol) in one portion. The solution was stirred at r.t. under oxygen atmosphere overnight. After completion of the reaction indicated by TLC, the resulting mixture was concentrated *in vacuo*. Dissolved the residue in ethyl acetate (100 mL), filtered, and washed the filtrate with brine. The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* to afford a yellowish solid. The crude product was purified by prep-HPLC to give **Compound 26** (48.8 mg, 15% yield) as a yellow solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.42-7.28 (m, 7H), 7.20 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.57 (s, 1H), 4.14 (t, *J* = 4.8 Hz, 2H), 3.76 (t, *J* = 4.8 Hz, 2H), 3.46 (s, 3H), 2.15 (s, 3H).

Example 4
Synthesis of Compound 27 (Scheme VII)



[0315] **VII-1** (2 g, 20 mmol) was added dropwise to ammonia (7 mL) at -70°C. The reaction mixture was stirred at -70°C for 1 hour, and then the reaction mixture was warmed to rt for one additional hour. The organic layer was separated and evaporated to produce **VII-2**, which was used directly for next step.

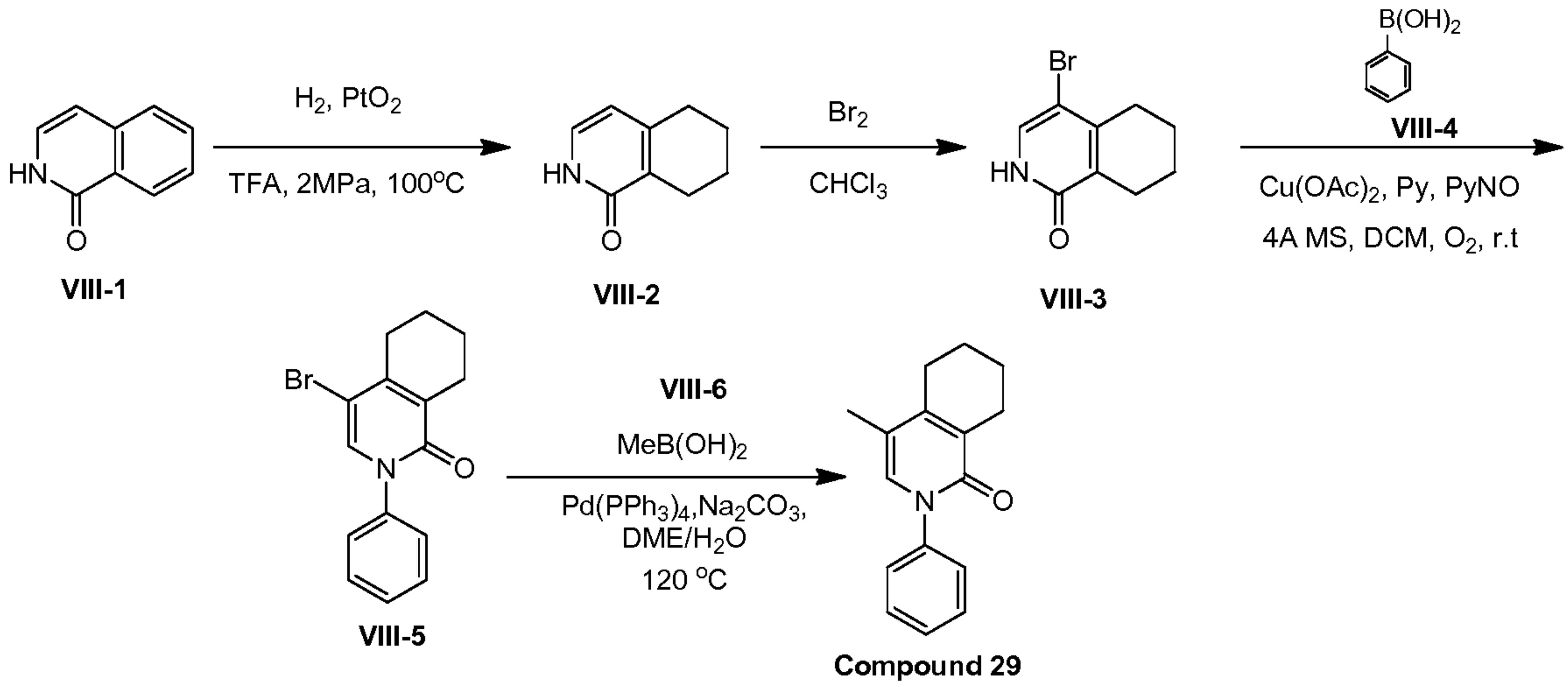
[0316] A mixture of **VII-2** (0.69 g, 10 mmol), **VII-3** (1.56 g, 10 mmol), and Na_2CO_3 (1.06 g, 10 mmol) in water (25 ml) was stirred at rt overnight. And then the mixture was extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel with PE/EtOAc (4/1) to yield **VII-4** (0.55 g, 24% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.13 (s, 1 H), 6.63 (d, J = 10 Hz, 1 H), 5.88 (d, J = 10 Hz, 1 H), 5.39 (brs, 1H), 4.24-4.15 (m, 2H), 2.50-2.42 (m, 1H), 2.33-2.25 (m, 1H), 2.02-1.95 (m, 1H), 1.92-1.80 (m, 2H), 1.76-1.66 (m, 1H), 1.27-1.18 (m, 3H).

[0317] A solution of **VII-4** (1.13 g, 5 mmol) in *conc*. HCl (30 mL) was stirred in a sealed tube at 110°C overnight. The solvent was evaporated under vacuum to yield crude **VII-5** (0.95 g, 111% crude yield). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.85 (d, J = 8.8Hz, 1 H), 6.82 (d, J = 8.8Hz, 1 H), 2.93-2.80 (m, 2H), 2.78-2.72 (m, 2H), 2.13-2.02 (m, 2H).

[0318] To a mixture of **VII-5** (0.513 g, 3 mmol) and phenyl boronic acid **VII-6** (0.732 g, 6 mmol) in acetonitrile (30 mL) was added $Cu(OAc)_2$ (1.64 g, 9 mmol), pyridine (1.42 g, 18 mmol) and pyridine-N-oxide (0.86 g, 9 mmol). The mixture was stirred under oxygen atmosphere at rt overnight. The mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (8:1~ 1: 1) to afford **Compound 27** (0.38 g, 60% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51-7.41 (m, 3 H), 7.33-7.31 (m, 1 H), 7.25-7.22 (m, 2 H), 6.51 (d, J = 9.2 Hz, 1 H), 2.81-2.77 (m, 2H), 2.50-2.46 (m, 2H), 2.07-2.00 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 212.0.

[0319] **Compound 28** was prepared following the similar procedure for obtaining **Compound 27** using (4-(trifluoromethoxy)phenyl)boronic acid in place of phenyl boronic acid (**VII-6**). **^{1}H NMR:** ($CDCl_3$, 400 MHz) δ 7.37-7.26 (m, 5 H), 6.50 (d, J = 9.2 Hz, 1 H), 2.81-2.77 (m, 2H), 2.51-2.47 (m, 2H), 2.09-2.02 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 295.9.

Example 5-A
Synthesis of Compound 29 (Scheme VIII)



[0320] An autoclave was charged with **VIII-1** (4.0 g, 27.6 mmol), PtO_2 (400 mg) and 50 mL of TFA. The mixture was stirred at 110°C under hydrogen (pressure 2.0 MPa) for 1 day, then the solution was filtered, and the solid was washed with MeOH. The filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (10:1→5:1→1:1→1:5→EtOAc) to give **VIII-2** (2.1 g, 51% yield) as white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 12.85 (brs, 1H), 7.16 (d, J = 6.4 Hz, 1H), 6.02 (d, J = 6.4 Hz, 1H), 2.60-2.50 (m, 4 H), 1.81-1.71 (m, 4H). **MS (ESI) *m/z*** $[M+H]^+$ 149.8.

[0321] To a solution of **VIII-2** (1.04 g, 7 mmol) in $CHCl_3$ (20 mL) was added Br_2 (1.12 g, 7 mmol) dropwise at 0°C. The reaction mixture was stirred at rt for 2 hrs. And then the reaction mixture was poured into ice-water, and the solid formed was collected by filtration, the filtrate was extracted with EtOAc (50 mL×3), the solid was re-dissolved in EtOAc (40 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford crude **VIII-3** (1.3 g, 61% yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.44 (s, 1H), 2.62-2.52 (m, 4H), 1.81-1.72 (m, 4H). **MS (ESI) *m/z*** $[M+H]^+$ 227.

[0322] **VIII-3** (500 mg, 2.2 mmol, 1.0 eq.), **VIII-4** (405 mg, 3.3 mmol, 1.5 eq.), $Cu(OAc)_2$ (1.2 g, 6.6 mmol, 3 eq.), pyridine-N-oxide (630 mg, 6.6 mmol, 3 eq.) and pyridine (520 mg, 6.6 mmol, 3 eq.) and 4Å molecular sieve (500 mg) was added into 150 mL of anhydrous DCM. The mixture was stirred under oxygen atmosphere at r.t. overnight. The reaction mixture was filtered; the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was re-crystallized from EtOAc to yield **VIII-5** (550 mg, 83% yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.49-7.30 (m, 6H), 2.64-2.58 (m, 4H), 1.81-1.72 (m, 4H). **MS (ESI) *m/z*** $(M+H)^+$ 303.9.

[0323] A flask was charged with **VIII-5** (300 mg, 1mmol, 1 eq.), $MeB(OH)_2$ (240 mg, 4.0 mmol, 4 eq.), and Na_2CO_3 (418 mg, 3.0 mmol, 3 eq.) in DME/H_2O (24 mL, V/V=5/1). It was purged with N_2, and then $Pd(PPh_3)_4$ (115 mg, 0.1 mmol, 0.1 eq.) was added. The reaction mixture was purged with N_2 again and then stirred at 110°C overnight. The mixture was concentrated under reduced pressure to remove the solvent, and then it was diluted with H_2O (30 mL), extracted with EtOAc (30 mL×3), the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by prep-TLC (PE: EA=2.5:1) to give **Compound 29** (190 mg, 79% yield) as white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.42 (m, 2H), 7.39-7.35 (m, 3H), 6.99 (s, 1H), 2.61-2.58 (m, 2H), 2.52-2.50 (m, 2H), 2.00 (s, 3H), 1.81-1.75 (m, 4H). **MS (ESI) *m/z*** $[M+H]^+$ 240.1.

[0324] **Compound 30** was prepared following the similar procedure for obtaining **Compound 29** using (4-fluorophenyl)boronic acid in place of methyl boronic acid **(VIII-6)** as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.37 (m, 5H), 7.26-7.23 (m, 2H), 7.10-7.06 (m, 3H), 2.68-2.64 (m, 2H), 2.40-2.37 (m, 2H), 1.81-1.77 (m, 2H), 1.72-1.68 (m, 2H). **MS (ESI) *m/z*** $[M+H]^+$ 320.0.

[0325] **Compound 31** was prepared following the similar procedure for obtaining **Compound 29** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of methyl boronic acid (**VIII-6**). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.45 (m, 3H), 7.41-7.39 (m, 3H), 7.34 (s, 1H), 7.15 (s, 1H), 3.93 (s, 3H), 2.65-2.62 (m, 2H), 2.55-2.52 (m, 2H), 1.80-1.72 (m, 4H). **MS (ESI) *m/z*** $[M+H]^+$ 306.2.

[0326] **Compound 32** was prepared following the similar procedure for obtaining **Comound 30** using (4-(trifluoromethoxy)phenyl)boronic acid in place of phenyl boronic acid (**VIII-4**). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.45 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.26-7.22 (m, 2H), 7.11-7.06 (m, 3H), 2.66-2.63 (m, 2H), 2.40-2.37 (m, 2H), 1.81-1.74 (m, 2H),1.72-1.67 (m, 2H). **MS (ESI) *m/z*** $[M+H]^+$ 404.2.

[0327] **Compound 33** was prepared following the similar procedure for obtaining **Compound 31** using (4-(trifluoromethoxy)phenyl)boronic acid in place of phenyl boronic acid (**VIII-4**). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46-7.43 (m, 3H), 7.34-7.30 (m, 3H), 7.17 (s, 1H), 3.94 (s, 3H), 2.64-2.61 (m, 2H), 2.54-2.51 (m, 2H), 1.81-1.72 (m, 4H). **MS (ESI) *m/z*** $[M+H]^+$ 390.2.

[0328] **Compound 34** was prepared following the similar procedure for obtaining **Compound 30** using (4-(trifluoromethoxy)phenyl)boronic acid in place of phenyl boronic acid (**VIII-4**) and (4-fluorophenyl)boronic acid in place of methyl boronic acid (**VIII-6**). **^{1}H NMR**

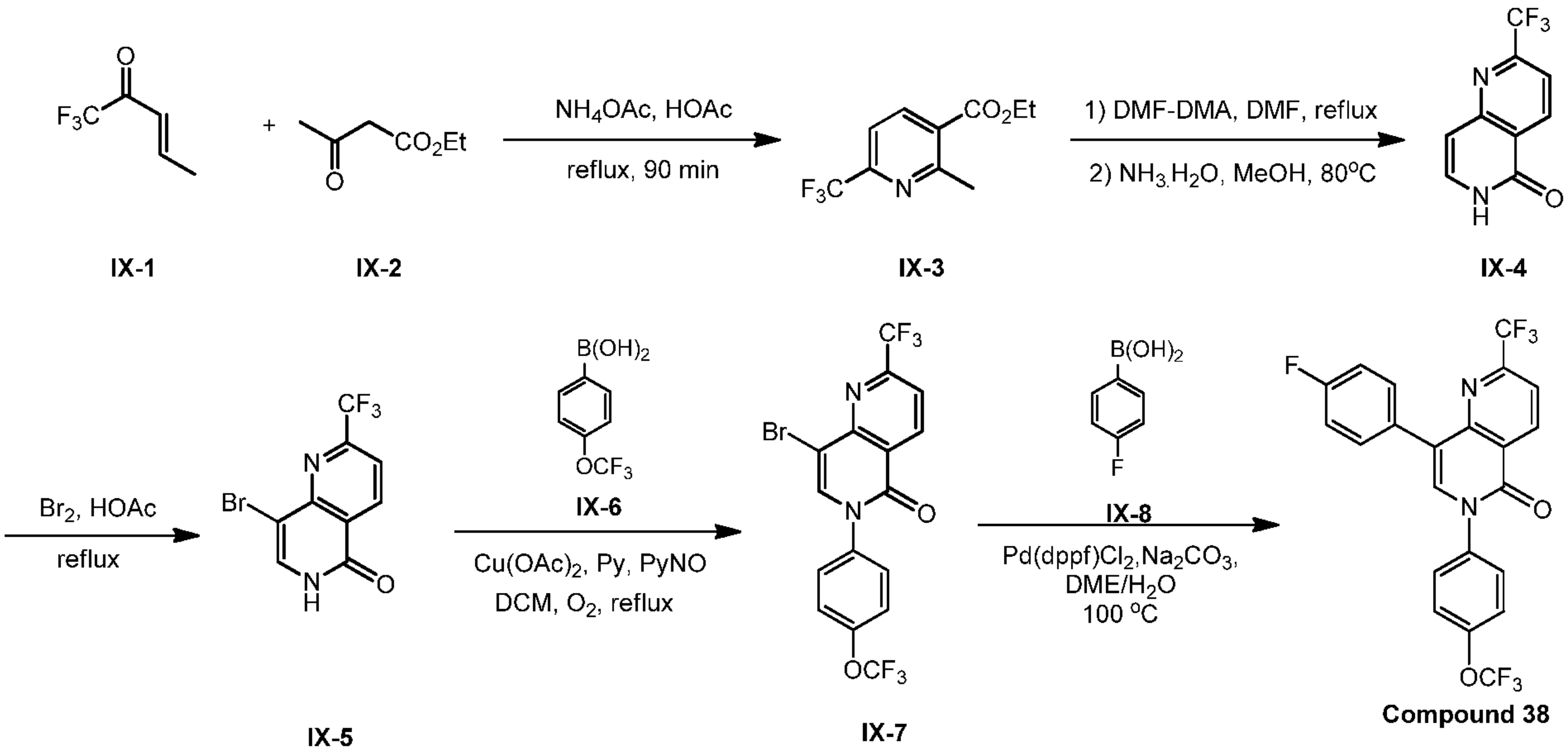
($CDCl_3$, 400 MHz) δ 7.48-7.45 (m, 2H), 7.44-7.30 (m, 3H), 7.10-6.97 (m, 4H), 2.64 (t, J = 6.0 Hz, 2H), 2.41 (t , J = 6.0 Hz, 2H), 1.82-1.76 (m, 2H), 1.72-1.66 (m, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 404.0.

[0329] **Compound 35** was prepared following the similar procedure for obtaining **Compound 29** using (4-ethoxy-2-methylphenyl)boronic acid in place of phenyl boronic acid (**VIII-4**) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of methyl boronic acid (**VIII-6**). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45 (s, 1H), 7.33 (s, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.00 (s, 1H), 6.85-6.77 (m, 2H), 4.04 (q, J = 6.8 Hz, 2H), 3.92 (s, 3H), 2.65-2.61 (m, 2H), 2.57-2.52 (m, 2H), 3.13 (s, 3H), 1.82-1.70 (m, 4H), 1.42 (t, J = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 364.1.

[0330] **Compound 36** was prepared following the similar procedure for obtaining **Compound 29** using (4-ethoxy-2-methylphenyl)boronic acid in place of phenyl boronic acid (**VIII-4**) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate in place of methyl boronic acid (**VIII-6**). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.72 (s, 2H), 7.19 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.92 (s, 1H), 6.85-6.82 (m, 2H), 4.05 (q, J = 6.8 Hz, 2H), 2.65-2.61 (m, 2H), 2.57-2.52 (m, 2H), 2.01 (s, 3H), 1.80-1.70 (m, 4H), 1.35 (t, J = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 350.1.

[0331] **Compound 37** was prepared following the similar procedure for obtaining **Compound 29** using (4-(trifluoromethoxy)phenyl)boronic acid in place of phenyl boronic acid (**VIII-4**) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate in place of methyl boronic acid (**VIII-6**) as white solid. Na_2CO_3 was replaced with K_3PO_4. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.60-7.52 (m, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 2.65-2.62 (m, 2H), 2.52-2.49 (m, 2H), 1.82-1.70 (m, 4H). **MS (ESI)** ***m/z*** $[M+H]^+$ 376.0.

Example 5-B
Synthesis of Compound 38 (Scheme IX)



[0332] A mixture of **IX-1** (14.2 g, 84.6 mmol), **IX-2** (10.0 g, 76.9 mmol), NH_4OAc (12.0 g 153.8 mmol) in HOAc (18.6 g, 307.6 mmol) was heated at reflux for 90 min. The mixture was allowed to cool to rt. Water (30 mL) was added and the reaction mixture was extracted with DCM (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography with petroleum ether/EtOAc (5:1→1:1) to afford **IX-3** (12 g, 67 % yield) as yellow solid. **MS (ESI)** ***m/z*** $[M+H]^+$ 234.1.

[0333] A mixture of **IX-3** (12 g, 52 mmol) and DMF-dimethylacetal (6.2 g, 52 mmol) in DMF (30 mL) was heated to reflux overnight. And then it was allowed to cool to rt. The solvent was removed under reduced pressure and the residue was treated with 18% ammonia in methanol (50 mL) at 80°C for 2 hrs. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography with petroleum ether/EtOAc (2:1→1:2) yield **IX-4** (2.3 g, 21% yield) as a yellow solid. **MS (ESI)** ***m/z*** $[M+H]^+$ 214.9.

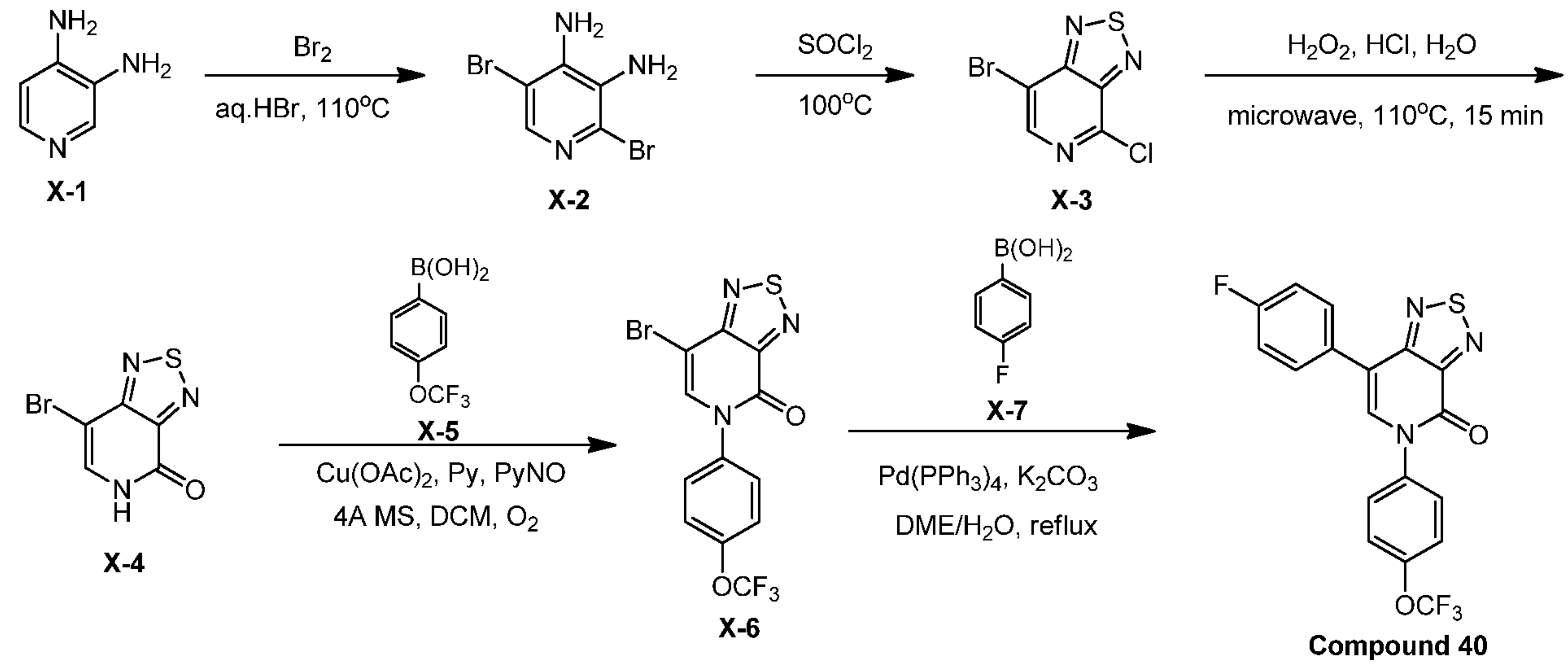
[0334] A solution of Br_2 (747 mg, 4.67 mmol) in HOAc (5 mL) was added dropwise to a stirred solution of **IX-4** (1 g, 4.67 mmol) in HOAc (10 mL). Upon complete addition, the reaction mixture was allowed to stir at rt for 30 min before being heated at reflux for 2 hrs. Once the reaction mixture was cooled to rt, water (20 mL) was added, the resultant precipitate was filtered off and air-dried. The product was then taken up in EtOAc (100 mL), the organic layer was washed with water, saturated aqueous sodium hydrogen carbonate, brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography with petroleum ether/EtOAc (2:1→1:2) to afford **IX-5** (1.3 g, 95 % yield) as solid. **MS (ESI)** ***m/z*** $[M+H]^+$ 293.

[0335] To a stirred solution of **IX-5** (500 mg, 1.7 mmol), **IX-6** (380 mg, 1.88 mmol), $Cu(OAc)_2$ (923 mg, 5.1 mmol) and pyridine (408 mg, 5.1 mmol) in DCM (10 mL) was added pyridine-*N*-oxide (484 mg, 5.1 mmol) in one portion. The solution was refluxed under oxygen atmosphere overnight. After completion of the reaction indicated by TLC, the reaction mixture was concentrated *in vacuo*. Dissolved the residue in ethyl acetate (100 mL), filtered, and washed the filtrate with brine. The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* to afford a yellowish solid. The crude product was purified by flash column chromatography with petroleum ether/EtOAc (5:1→1:1) to afford **IX-7** (600 mg, 78% yield) as a yellow solid. **MS (ESI)** ***m/z*** $[M+H]^+$ 453.

[0336] To a stirred mixture of **IX-7** (250 mg, 0.55 mmol), **IX-8** (116 mg, 0.83 mmol), and Na_2CO_3 (117 mg, 1.1 mmol) in DME/H_2O (5 mL, v:v=5:1) was added Pd(dppf)Cl_2 (41 mg, 0.055 mmol). The mixture was purged with nitrogen for three times and then heated at 100°C overnight. The mixture was concentrated to remove diluted with water (30 mL), extracted with EtOAc (30mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography with PE/EA (5:1→1:1) to give **Compound 38** (176.5 mg, 68% yield) as a yellow solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.94 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.78-7.72 (m, 4H), 7.59-7.55 (m, 2H), 7.31-7.27 (m, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 469.1.

[0337] **Compound 39** was prepared following the similar procedure for obtaining **Compound 38** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in replace of **IX-8**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.91 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 8.09-8.06 (m, 2H), 7.74-7.70 (m, 2H), 7.60-7.57 (m, 2H), 3.87 (s, 3H). **MS (ESI) m / z** $[M+H]^+$ 455.0.

Example 5-C
Synthesis of Compound 40 (Scheme X)



[0338] To the mixture of **X-1** (10.0 g, 10 mmol) dissolved in HBr 48% (200 mL), Br_2 (12.5 mL, 13.4 mmol) was added dropwise under ice-water cooling bath, maintaining the temperature below 40°C. After that, the mixture was heated at 110°C for 5 hrs. The reaction mixture was cooled to rt, filtered and washed with little water. The filter cake is basified to pH 7~8 with saturated *aq*. $NaHCO_3$ and extracted with EtOAc (200 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield **X-2** (17.2 g, 71% yield). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.95 (s, 1H), 5.20 (brs, 4H).

[0339] **X-2** (5.0 g, 18.9 mmol) was dissolved in $SOCl_2$ (50 mL). The mixture was stirred at 100°C for 5 hrs. Removed the excessive solvent, the residue was diluted with EtOAc (200 mL), washed with brine, dried over Na_2SO_4. Filtration, concentration and the residue was **X-3** (4.64 g, 100% yield). Compound **3** was used in next step without further purification. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.55 (s, 1H).

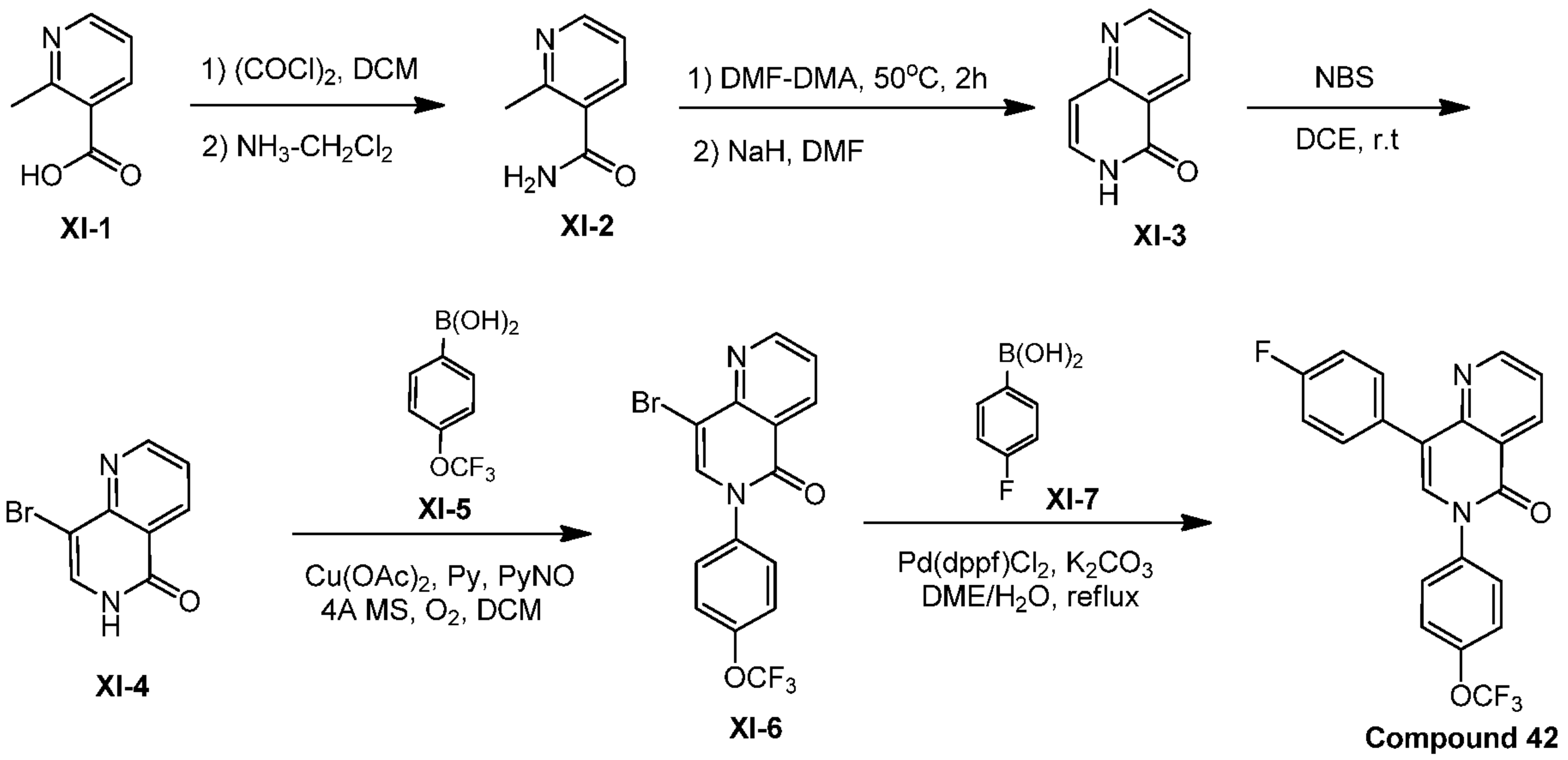
[0340] **X-3** (1.0 g, 4 mmol) was dissolved in water (10 mL), and then two drops H_2O_2 (30%) and 2 drops *conc*. HCl was added. The mixture was stirred at 100°C for 15 min under microwave. After being cooled to rt, the reaction mixture was extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **X-4** (700 mg, 75% yield). **X-4** was used in next step without further purification. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 11.97 (s, 1H), 7.81 (s, 1H).

[0341] To a solution of **X-4** (330 mg , 1.4 mmol) in DCM (30 mL), $Cu(OAc)_2$ (800 mg, 4.4 mmol), **X-5** (500 mg, 2 mmol), pyridine (1 mL), pyridine-N-oxide (400 mg, 4 mmol) and finely ground, activated 4 Å molecular sieves (300 mg) were added. The mixture was stirred at rt for 12 hrs under O_2 atmosphere. The mixture was diluted with EtOAc (100 mL) and filtered, the filtrate was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (PE/EtOAc= 5/1) to give **X-6** (280 mg, 50% yield) as a yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67 (s, 1H), 7.50-7.48 (m, 2H), 7.41-7.39 (m, 2H).

[0342] **X-6** (230 mg, 0.58 mmol), **X-7** (100 mg, 0.71 mmol) and K_2CO_3 (300 mg, 2.17 mmol) were charged into 22 mL of DME/H_2O (v/v=10/1). The reaction mixture was degassed by N_2 for three times and then $Pd(PPh_3)_4$ (60 mg, 0.052 mmol) was added. The reaction mixture was refluxed for 3 hrs. After being cooled to rt, the mixture was diluted with EtOAc (60 mL) and filtered. The filtrate was washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by flash column chromatography (PE/EtOAc= 5/1) to give **Compound 40** (150 mg, 63 % yield) as a yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.77-7.73 (m, 2H), 7.56-7.51 (m, 3H), 7.41 (d, J = 8.0 Hz, 2H), 7.22-7.17 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 407.8.

[0343] **Compound 41** was prepared following the similar procedure for obtaining **Compound 40** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in replace of **X-7.** **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 7.85 (s, 1H), 7.58 (s, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.00 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 393.8.

Example 5-D
Synthesis of Compound 42 (Scheme XI)



[0344] To the solution of **XI-1** (10 g, 73 mmol, 1 eq) in 50 mL of DCM was added 15 mL of oxalyl chloride (adding a drop of DMF). The mixture was stirred for 18 hrs at rt. All the volatiles were removed under reduced pressure. The residue was dried and used directly for the next step (11.3 g, 100% yield). The solid was dissolved in 30 mL of DCM and added into 200 mL of

CH_2Cl_2-NH_3 at -30°C. The mixture was stirred for 18 hrs. LCMS analysis showed the reaction completed. All the volatiles were removed under reduced pressure to afford **XI-2** (7 g, 71% yield), which was used directly for the next step. **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.45 (m, 1H), 7.93 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 7.23 (m, 1H), 2.48 (s, 3H).

[0345] A mixture of **XI-2** (13 g, 95.6 mmol, 1 eq) and 18.2 mL of N,N-dimethylformamide dimethyl acetal was heated at 50°C for 2 hrs. During the second hour, all the volatiles was removed. The residue was cooled to rt., diluted with 100 mL of anhydrous N,N-dimethylformamide, and then treated carefully with batch wise portions of sodium hydride (5 g, 124.3 mmol, 1.3 eq, 60% oil dispersion; caution: vigorous evolution of hydrogen). The mixture was heated at 80°C for 2.5 hrs, and then ice-cooled, treated cautiously with 25 mL of 2-propanol, and then maintained at 0-5°C overnight. The solid were collected, and then dissolved in 10 mL of hot water. The solution was filtered, the filtrate was ice-cooled and then treated dropwise with concentrated hydrochloric acid to pH=~7.0. After storage at 0-5°C for 3 hrs, the precipitated solids were collected, washed with ice-cold water, and dried in vacuum to give **XI-3** (3 g, 32% yield). **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 8.90 (s, 1H), 8.49 (d, J =7.6 Hz, 1H), 7.51-7.43 (m, 2H), 6.61 (d, J =7.6 Hz, 1H).

[0346] A suspension of **XI-3** (2.36 g, 15.7 mmol, 1 eq), N-bromosuccinimide (3.1 g, 17.3 mmol, 1 eq), and 50 mL of 1,2-dichloroethane was stirred at rt for 3.5 hrs. The mixture was filtered; the solids were washed successively with small amounts of chloroform, water, and diethyl ether, and then dried to leave **XI-4** (0.8 g, 23% yield). **MS (ESI) *m/z*** $(M+H)^+$ 226.8.

[0347] A flask was charged with **XI-4** (0.6 g, 2.67 mmol, 1 eq.), **XI-5** (1.1 g, 5.33 mmol, 2 eq.), $Cu(OAc)_2$ (1.45 g, 8 mmol, 3 eq.), pyridine (2.1 g, 26.7 mmol, 10 eq.), pyridine-N-oxide (0.76 g mg, 8.01 mmol, 3 eq.), 200 mg of 4Å molecular sieves and 45 mL of CH_2Cl_2. The mixture was stirred under oxygen atmosphere at rt for 18 hrs. LCMS analysis showed the reaction completed. All the volatiles were removed under reduced pressure. The residue was diluted with water, extracted with ethyl acetate (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a brown oil. Purification by column chromatography on silica gel with petroleum ether/EtOAc (3:1→1:1) to provide **XI-6** (0.5 g, 50% yield). **MS (ESI) *m/z*** $(M+H)^+$ 386.8.

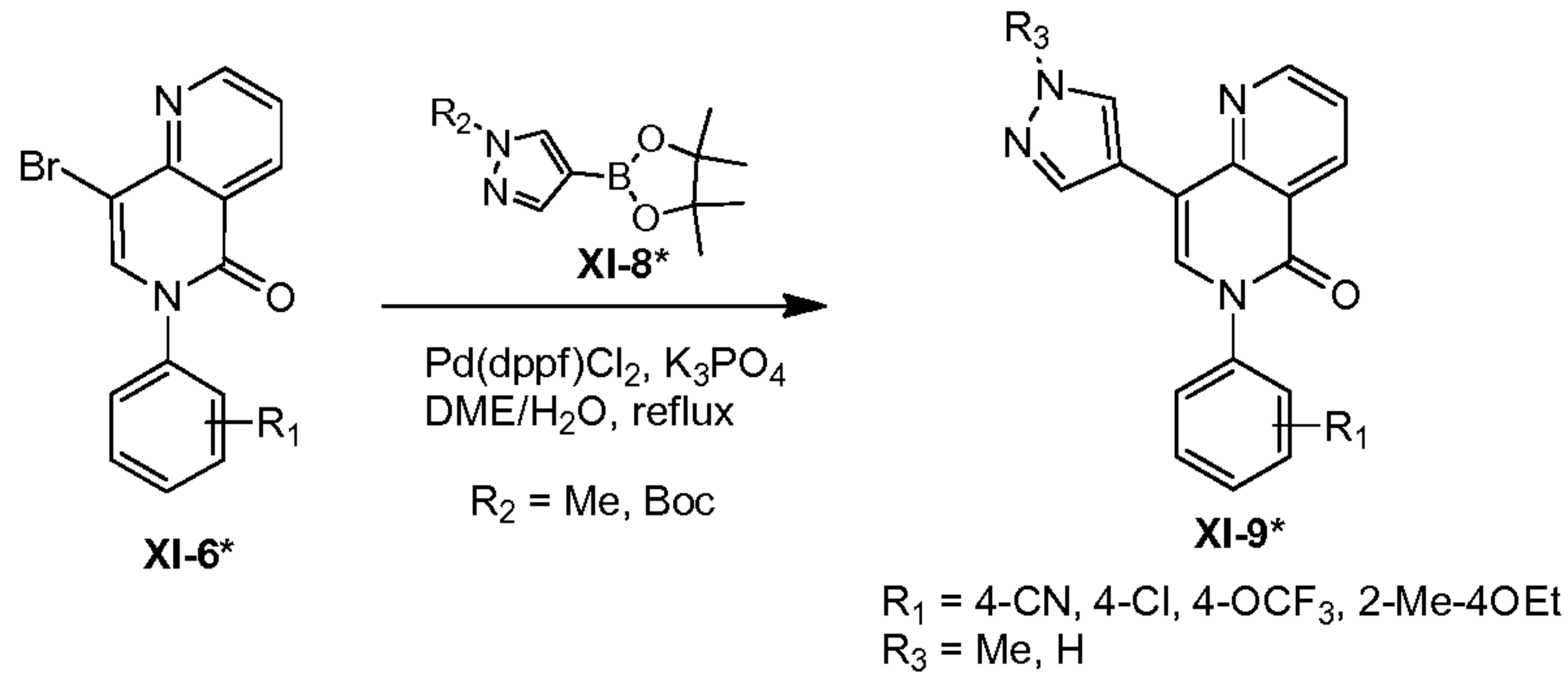
[0348] A flak was charged with **XI-6** (140 mg, 0.36 mmol, 1 eq), **XI-7** (76 mg, 0.54 mmol, 1.5 eq), K_2CO_3 (100 mg, 0.72 mmol, 2 eq), Pd(dppf)Cl_2 (13 mg, 0.018 mmol, 0.05 eq), 10 mL of DME and 2 mL of H_2O, and then it was flushed with nitrogen for three times. The mixture was heated at 100°C for 18 hrs. LCMS analysis showed the reaction completed. All the volatiles were removed under reduced pressure. The residue was diluted with water, extracted with ethyl acetate (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give brown oil. Purification by prep-TLC (PE/EA=2/1) gave **Compound 42** (102.4 mg, 71% yield). **^{1}H NMR** ($CDCl_3$, 300MHz): δ 8.93 (m, 1H), 8.74 (d, *J* =7.8 Hz, 2H), 7.54-7.42 (m, 5H), 7.39-7.31 (m, 3H), 7.09 (t, *J*=9.0 Hz, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 400.9.

[0349] **Compound 43** was prepared following the similar procedure for obtaining **Compound 42** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in replace of **XI-7**. **^{1}H NMR** ($CDCl_3$, 400MHz): δ 9.04 (m, 1H), 8.80 (d, *J* = 8.4Hz, 1H), 8.22 (s, 1H), 7.80 (s, 1H), 7.58 (s, 1H), 7.56-7.51 (m, 3H), 7.40 (d, *J* = 8.4 Hz, 2H), 4.00 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 386.9.

[0350] **Compound 45**: A flask was charged with **Compound 42** (500 mg, 1.25 mmol, 1 eq) and Pd/C (50 mg), 30 mL of MeOH and 3 mL of H_2O. The mixture was stirred for 18 hrs under hydrogen (45 Psi). LCMS analysis showed the reaction completed. The mixture was filtered. The filtrate was concentrated and purified by prep-TLC (PE/EA=2/1) to give **Compound 45** as a white solid (300 mg, 59% yield). **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.36-7.26 (m, 4H), 7.14 (t, *J*=8.8 Hz, 2H), 6.99 (s, 1H), 4.30 (s, 1H), 3.29 (m, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 1.93 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 404.9.

[0351] **Compound 44** was prepared following the similar procedure for obtaining **Compound 45.** **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.41 (s, 1H), 7.36-7.32 (m, 3H), 7.20-7.15 (m, 2H), 6.90 (s, 1H), 4.41 (brs, 1H), 3.85 (s, 3H), 3.20 (m, 2H), 2.54 (m, 2H), 1.82 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 390.9.

[0352] **Compound 395** was prepared following the similar procedure for obtaining Compound **43** using (4-cyanophenyl)boronic acid in place of **XI-5**. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 9.10 (dd, *J* = 1.6 Hz, 4.4 Hz, 1H), 8.79 (dd, *J* = 2.0, 8.0Hz, 1H), 8.21 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.79 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.56-7.52 (m, 2H), 3.99 (s, 3H). **MS (ESI) m / z** $(M+H)^+$ 328.0.



[0353] **XI-6*** with various R^1 groups can be prepared following the similar procedure described in the synthesis of **XI-6**. The last Suzuki-Coupling step was conducted either using Method **1** or Method **2** as described herein. Compounds **571**, **572** and **579-581** were prepared by Suzuki-Coupling of **XI-6*** with the corresponding **XI-8*** using standard procedure described Method **A** using K_3PO_4 in place of K_2CO_3. The HCl salts were prepared by reacting the compounds with *aq*. HCl (1.0M, 1.1 eq) at 0°C in dioxne for 20 mins then concentrated and dried in vacuo.

[0354] **Compound 571**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 9.03 (dd, *J* = 2.0, 5.2 Hz, 1H), 8.79 (dd, *J* =1.6, 8.0Hz, 1H), 8.20 (s, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.53-7.50 (m, 3H), 7.43 (d, *J* =6.8 Hz, 2H), 3.99 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 385.0.

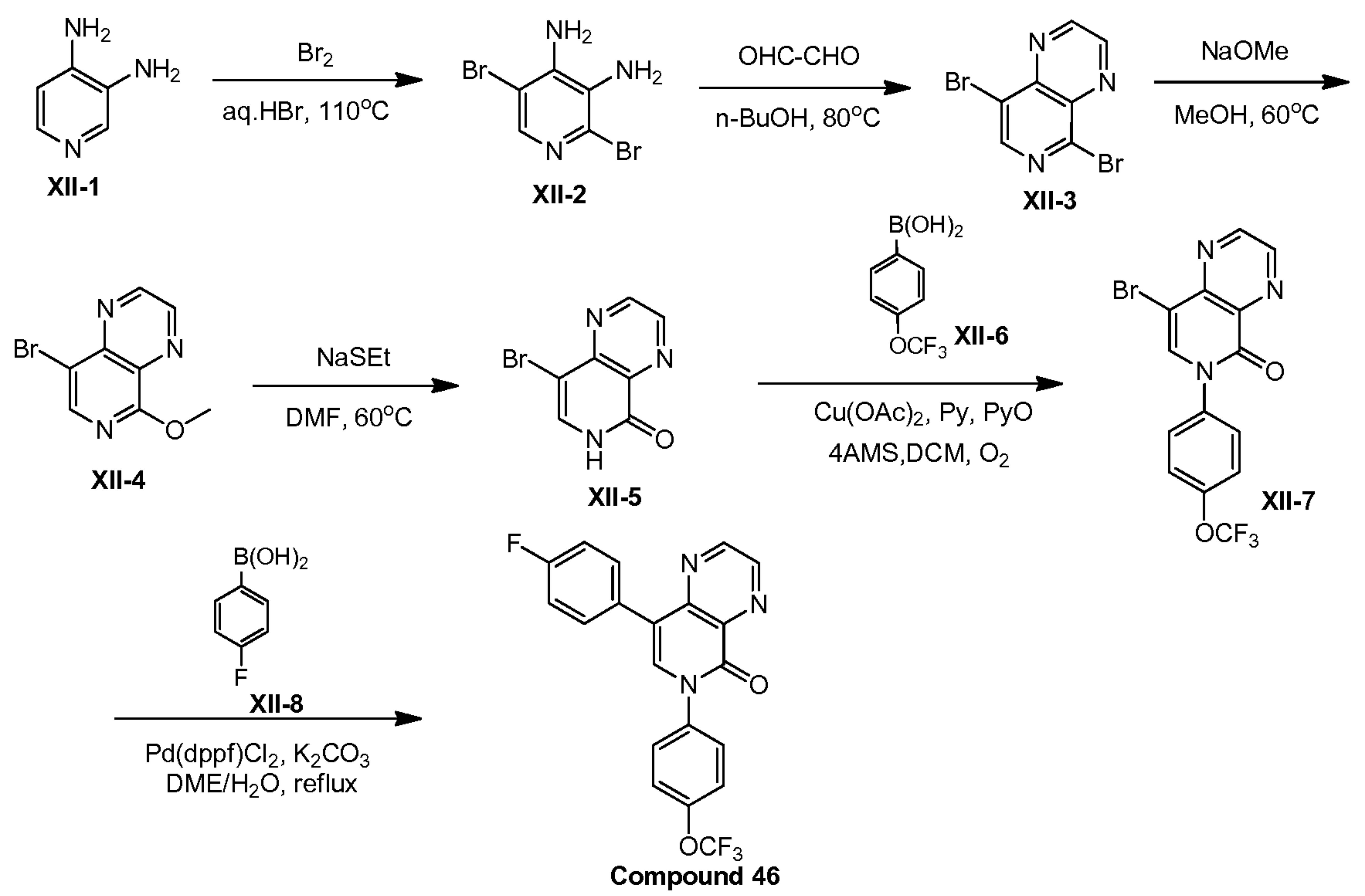
[0355] **Compound 572**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.90 (s, 1H), 9.09 (dd, *J* = 2.0, 4.8 Hz, 1H), 8.65 (dd, *J* =1.6, 8.0Hz, 1H), 8.43 (s, 1H), 8.11 (s, 1H), 8.01 (s, 1H), 7.66-7.63 (m, 5H). **MS (ESI)** ***m/z*** $(M+H)^+$ 322.9.

[0356] **Compound 579**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.88 (s, 1H), 9.09 (dd, *J* =1.6, 4.4 Hz, 1H), 8.64 (dd, *J* =1.6, 8.0Hz, 1H), 8.44 (s, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 7.73 (d, *J* =8.8Hz, 2H), 7.66-7.62 (m, 1H), 7.58 (d, *J* =8.4 Hz, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 373.1.

[0357] **Compound 580**: **^{1}H NMR** (DMSO-d_6, 300MHz) δ 12.86 (s, 1H), 9.09 (dd, *J* = 1.8, 4.5 Hz, 1H), 8.65 (dd, *J* = 1.8, 8.1Hz, 1H), 8.43 (s, 1H), 8.10 (s, 1H), 7.86 (s, 1H), 7.65-7.62 (m, 1H), 7.30-7.23 (m, 1H), 6.99 (d, *J* = 2.4Hz, 1H), 6.93-6.89 (m,1H), 4.09 (q, *J* =7.2Hz, 2H), 2.07 (s, 3H), 1.37 (t, *J* =7.2Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 347.1.

[0358] **Compound 581**: **^{1}H NMR** (DMSO-d_6, 300MHz) δ 12.90 (s, 1H), 9.09 (d, *J* = 3.0 Hz, 1H), 8.66 (d, *J* = 7.2Hz, 1H), 8.34 (s, 1H), 8.08-8.04 (m, 4H), 7.85 (d, *J* = 8.1Hz, 2H), 7.67-7.64 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 314.1.

Example 5-E
Synthesis of Compound 46 (Scheme XII)



[0359] To the mixture of **XII-1** (10.0 g, 10 mmol) dissolved in HBr 48% (200 mL), Br_2 (12.5 mL, 13.4 mmol) was added dropwise under ice-water cooling bath, maintaining the temperature below 40°C. After that, the mixture was heated at 110°C for 5 hrs. The reaction mixture was cooled to rt, filtered and washed with little water. The filter cake is basified to pH 7~8 with saturated *aq.* $NaHCO_3$ and extracted with EtOAc (200 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to yield **XII-2** (17.2 g, 71% yield). ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.95 (s, 1H), 5.20 (brs, 4H).

[0360] **XII-2** (5.0 g, 18.9 mmol) and aqueous glyoxal (40%, 5 mL) was dissolved in *n*-BuOH (15 mL), the mixture was stirred at 80°C for 2 hrs. The reaction mixture was cooled to rt, a solid was precipitated out, filtered, washed with PE and dried in vacuum to afford **XII-3** (5.0 g, 92% yield) as a yellow solid, which was used in next step without further purification. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 9.18 (d, J = 2.0 Hz, 1H), 9.11 (d, J = 2.0 Hz, 1H), 8.84 (s, 1H).

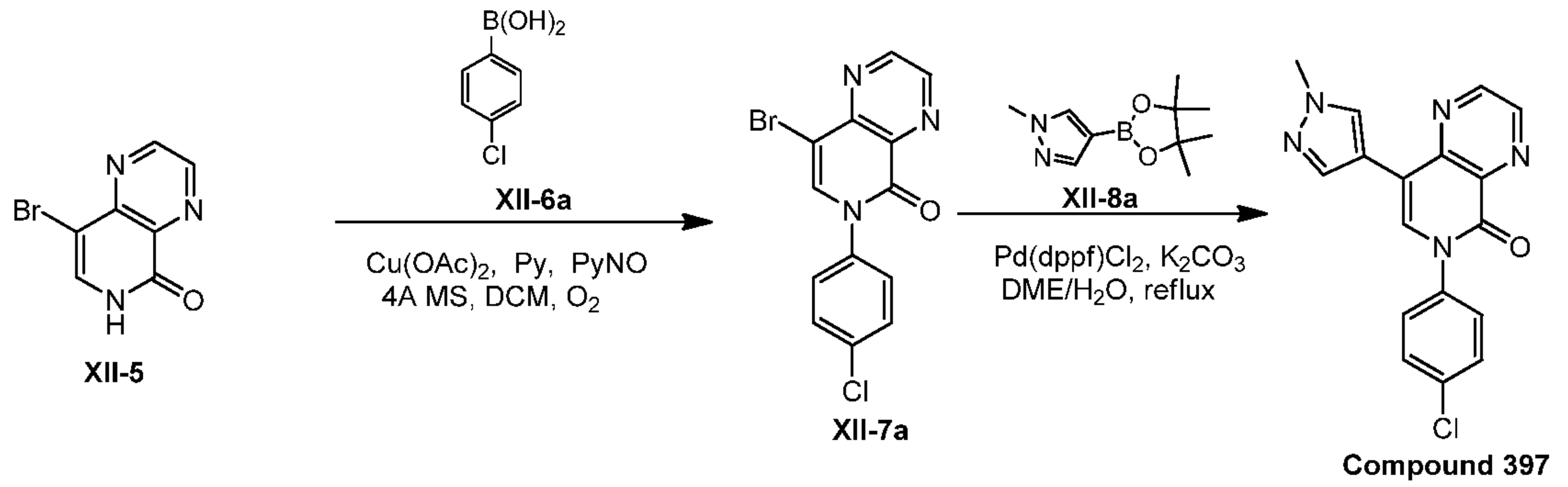
[0361] **XII-3** (5.0 g, 17.3 mmol) and NaOMe (1.4 g, 26 mmol) were dissolved in MeOH (60 mL), and then the mixture was stirred at 60°C for 0.5 h. Removed the solvent, diluted with EtOAc (100 mL), washed with brine, dried over Na_2SO_4 and concentrated to give **XII-4** (3.7 g, 89% yield) as a light yellow solid, which was used in next step without further purification. ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ 9.05 (d, J = 1.8 Hz, 1H), 8.88 (d, J = 1.8 Hz, 1H), 8.46 (s, 1H), 4.17 (s, 3H).

[0362] **XII-4** (2.0 g, 8.4 mmol) and NaSEt (3.2 g, 38 mmol) was dissolved in DMF (30 mL), the mixture was stirred at 60°C for 1.5 hrs. The reaction mixture was cooled to rt, diluted with water (30 mL) and acidified to pH=6~7 with *conc.* HCl. The precipitate was collected by filtration, washed with water and dried in vacuum to afford **XII-5** (1.9 g, 100% yield) as a brown solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.84 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 1.6 Hz, 1H), 7.95 (s, 1H).

[0363] To a solution of **XII-5** (2.0 g, 10 mmol) in DCM (100 mL), copper (II) acetate (3.6 g, 20 mmol), **XII-6** (2.0 g, 12 mmol), pyridine (3 mL), pyridine-N-oxide (1.9 g, 20 mmol) and finely ground, activated 4Å molecular sieves (3.0 g) were added. The mixture was stirred at rt. for 18 hrs under O_2 atmosphere. The solvent was evaporated and the residue was diluted with AcOEt (150 mL) and filtered. The filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel with petroleum ether/EtOAc (1:1~1:2) to yield **XII-7** (400 mg, 12 % yield) as a yellow solid. **MS (ESI)** ***m/z*** $(M+H)^+$ 386.

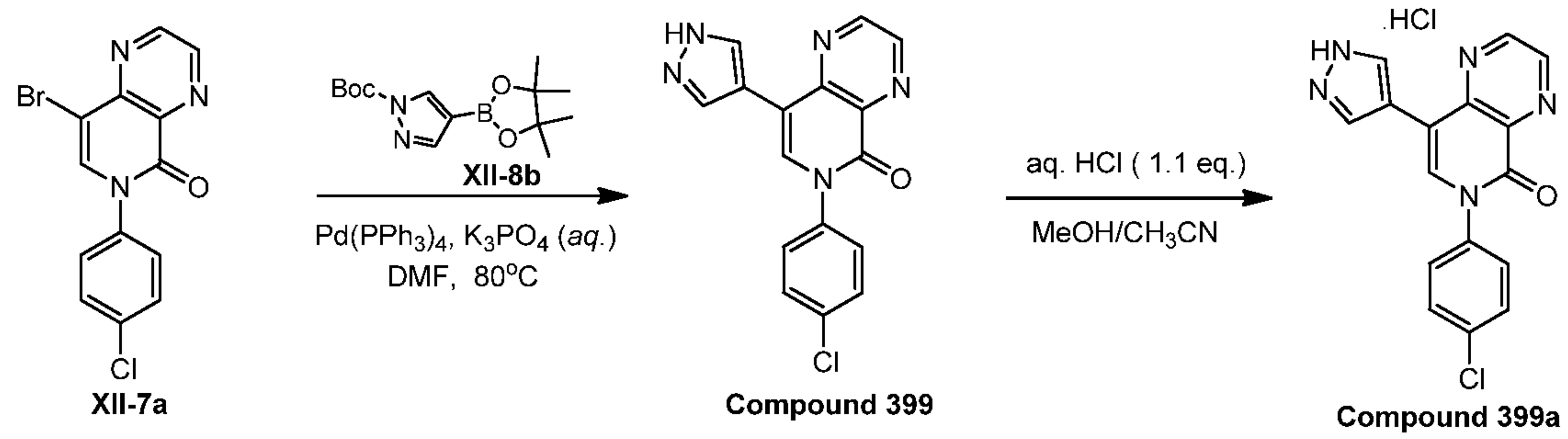
[0364] **Compound 46** was prepared following the similar procedure for obtaining **Compound 42** (75 mg, 72 % yield). **^{1}H NMR** (CD_3OD, 400 MHz) δ 9.01 (d, J = 2.0 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H), 7.83 (s, 1H), 7.73-7.70 (m, 2H), 7.68-7.65 (m, 2H), 7.51 (d, J = 8.0 Hz, 2H),7.21-7.16 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 401.9.

[0365] **Compound 47** was prepared following the similar procedure for obtaining **Compound 46** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in replace of **XII-8**. **^{1}H NMR** (CD_3OD, 400 MHz) δ 9.01 (d, J = 2.0 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.35 (s, 1H), 8.04 (m, 2H), 7.73-7.70 (m, 2H), 7.55-7.50 (m, 2H), 3.97 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 387.9.



[0366] **Compound 397** was prepared following the similar procedure for obtaining Compound **47** using **XII-6a** in place of **XII-6**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.98 (d, J =2.0 Hz, 1H), 8.90 (d, J =2.0 Hz, 1H), 8.13 (s, 1H), 7.80 (s, 1H), 7.64 (s, 1H), 7.55-7.52 (m, 2H), 7.47-7.45 (m, 2H), 4.00 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 337.9.

[0367] **Compound 398** was prepared following the similar procedure for obtaining Compound **397** using (4-cyanophenyl)boronic acid in place of **XII-6a**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.00 (d, J =2.0 Hz, 1H), 8.93 (d, J =2.0 Hz, 1H), 8.14 (s, 1H), 7.89-7.87 (m, 2H), 7.81 (s, 1H), 7.71-7.67 (m, 2H), 7.64 (s, 1H), 4.00 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 328.9.



[0368] To a solution of **XII-7a** (400 mg, 1.2 mmol, 1 eq.) in DMF (4 mL) was added *aq.* K_3PO_4 (2 M, 1.2 mL, 2.4 mmol, 2 eq.), **XII-8b** (425 mg, 1.44 mmol, 1.2 eq.), $Pd(PPh_3)_4$ (67 mg, 0.06 mmol, 0.05 eq.). The mixture was purged with nitrogen and then heated at 80°C for 5 hrs. The mixture was cooled to rt, diluted with water (20 mL), extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash chromatography (PE/EA=1/3) to give **Compound 399** (90 mg, 24% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.99 (d, J =2.0 Hz, 1H), 8.93 (d, J =2.0 Hz, 1H), 8.15 (s, 2H), 7.68 (s, 1H), 7.56-7.52 (m, 2H), 7.48-7.46 (m, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 323.9.

[0369] To the mixture of **Compound 399** (85 mg, 0.365 mmol) in MeOH (5 mL) and CH_3CN (5 mL) was added *aq.*HCl (0.2 M, 2 mL, 0.4 mmol, 1.1 eq.). After stirring for 0.5 h, removed the solvent under reduced pressure, and the residue was dried in vacuum to afford the hydrochloride salt **Compound 399a** as a yellow solid (120 mg, 91% yield). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.12 (d, J =2.0 Hz, 1H), 8.95 (d, J =2.0 Hz, 1H), 8.28 (s, 2H), 8.11 (s, 1H), 7.68-7.62 (m, 4H). **MS (ESI)** ***m/z*** $[M+H]^+$ 323.9.

[0370] **Compound 400** was prepared following the similar procedure for obtaining Comound **399** by reacting **XII-7** with **XII-8b**. **^{1}H NMR** (CD_3OD, 400 MHz) δ 9.09 (d, J =1.6 Hz, 1H), 8.88 (d, J =1.6 Hz, 1H), 8.35-8.20 (m, 2H), 8.05 (s, 1H), 7.71-7.68 (m, 2H), 7.52-7.50 (m, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 374.2.

[0371] The hydrochloride salt of Compound **400** was prepared following the similar procedure for obtaining Compound **399a** as a yellow solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.12 (d, J =2.0 Hz, 1H), 8.95 (d, J =2.0 Hz, 1H), 8.29 (s, 2H), 8.16 (s, 1H), 7.76-7.73 (m, 2H), 7.62-7.59 (m, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 374.0.

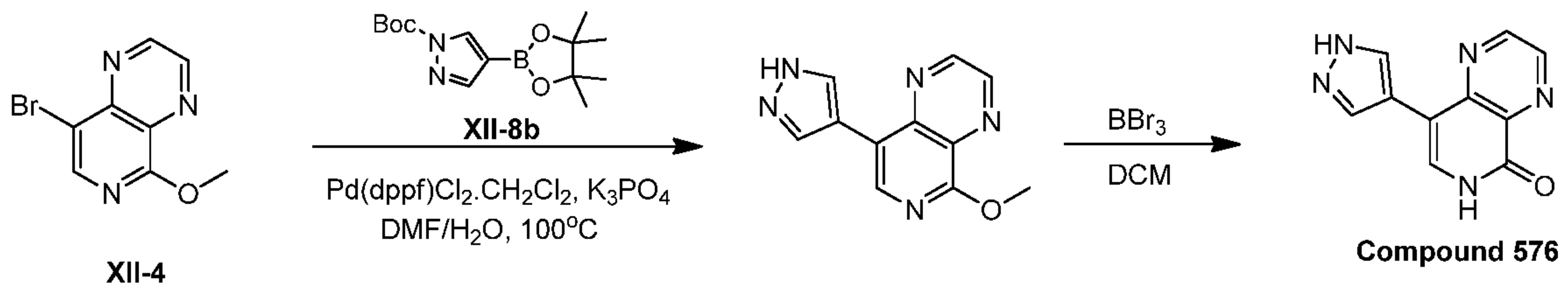
[0372] Compounds **573** and **574** were prepared by following the similar procedure described in the synthesis of **Compound 399**. The corresponding HCl salts were also prepared following the similar procedure described in the synthesis of Compound **399a**.

[0373] **Compounds 573**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.93 (s, 1H), 9.11 (d, *J* =1.6 Hz, 1H), 8.93 (d, *J* =1.6 Hz, 1H), 8.37 (s, 1H), 8.12-8.06 (m, 4H), 7.84-7.82 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 315.0.

[0374] **Compound 574**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.93 (s, 1H), 9.12 (s, 1H), 8.94 (s, 1H), 8.40 (s, 1H), 8.11 (s, 1H), 7.98 (s, 1H), 7.32 (m, 1H), 7.00 (m, 1H), 6.91 (m, 1H), 4.10 (q, *J* =6.8 Hz, 2H), 2.09 (s, 3H), 1.37 (t, *J* =6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 348.1.

[0375] **Compound 575**: To a solution of **XII-7** (300 mg, 0.78 mmol) in DMF (5 mL) was added $Pd(OAc)_2$ (9 mg, 0.039 mmol), Et_3N (240 mg, 2.4 mmol), HCOOH (72 mg, 1.5 mmol) and PPh_3 (20.4 mg, 0.078 mmol). The mixture was purged with nitrogen for three times and then heated at 60°C under nitrogen for 12 hrs. After cooling to rt, the mixture was concentrated, the residue was partitioned between H_2O and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using EA as eluent to afford **Compound 575** (146 mg, 61% yield). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 9.02 (d, *J*=1.5 Hz, 1H), 8.88 (d, *J*=1.8 Hz, 1H), 7.89 (d, *J*=7.5 Hz, 1H), 7.70 (d, *J*=8.7 Hz, 2H), 7.60 (d, *J*=8.4 Hz, 2H), 6.82 (d, *J*=7.5 Hz, 1H).

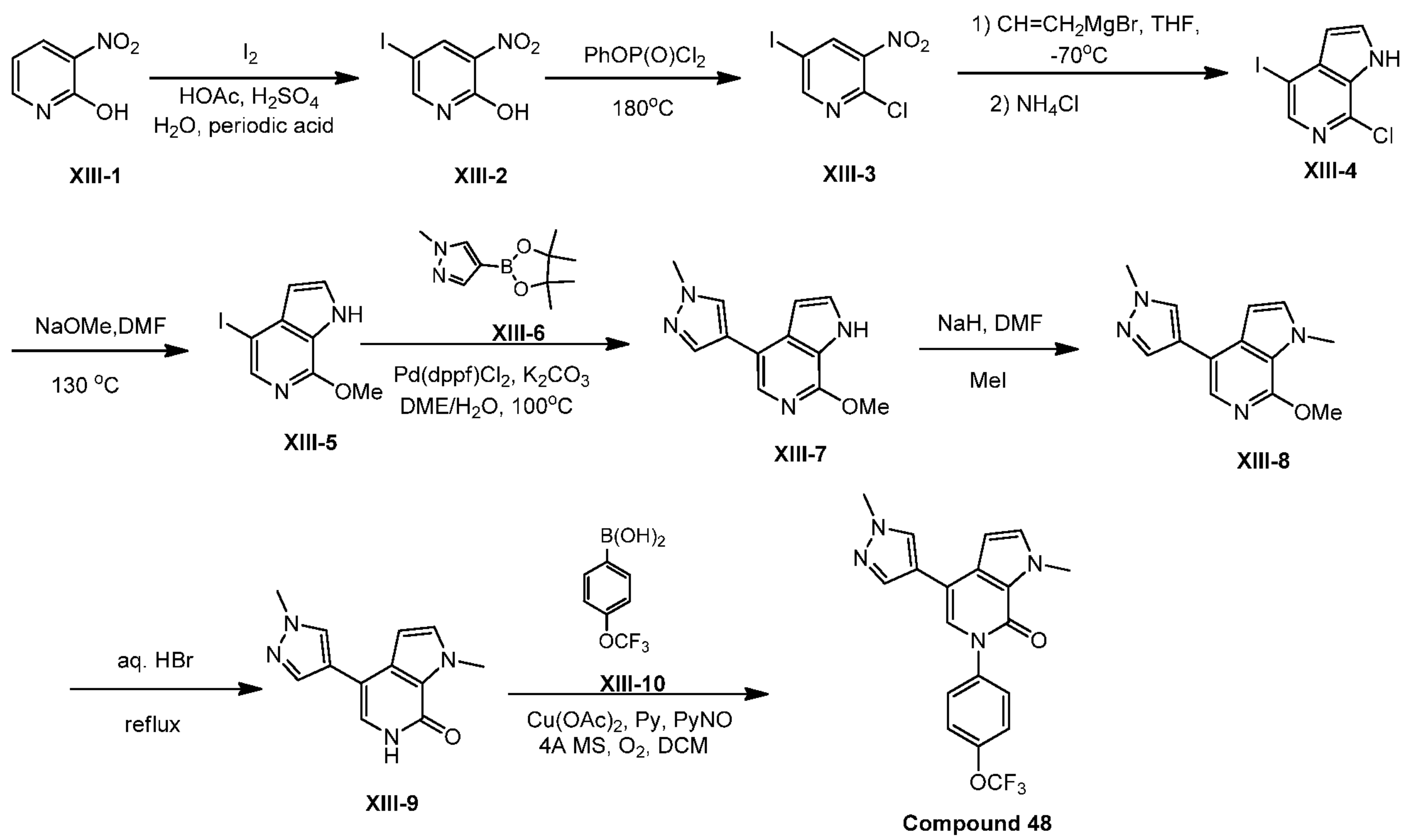
[0376] **Compound 577** was prepared by Suzuki-coupling of **XII-7** with **XII-8b** in DMF/H_2O at 100°C for 12h followed by reacting with 1,3-dioxolan-2-one in the presence of NaOH. **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 9.12 (s, 1H), 8.95 (s, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 8.07 (s, 1H), 7.75 (d, *J*=8.7 Hz, 2H), 7.61 (d, *J*=8.7 Hz, 2H), 4.18 (d, *J*=5.7 Hz, 2H), 3.77 (d, *J*=6.9 Hz, 2H).



[0377] **Compound 576** was prepared by Suzuki-Coupling of **XII-4** and **XII-8b** using the standard procedure described herein followed by reaction with BBr_3 in DCM. **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 12.83 (s, 1H), 9.04 (s, 1H), 8.84 (s, 1H), 8.17 (s, 1H), 7.82 (s, 1H).

[0378] **Compound 578** was prepared following the similar procedure described in the synthesis of Compound 576 using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of **XII-8b**. **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.99 (s, 1H), 8.80 (s, 1H), 8.27 (s, 1H), 7.93 (s, 1H), 7.84 (s, 1H), 3.88 (s, 3H).

Example 5-F
Synthesis of Compound 48 (Scheme XIII)



[0379] A suspension of **XIII-1** (10.3 g, 73.4 mmol, 1 eq) in 46 mL of acetic acid, 20 mL of water, 1.4 mL of concentrated sulfuric acid and periodic acid (3.5 g, 18 mmol, 0.25 eq) was stirred at 90°C for 15 minutes whereby a solution was obtained. Iodine crystals (7.7 g, 30.1 mmol, 0.4 eq) were added portionwise and after 20 minutes a dense yellow precipitate had formed. The mixture was cooled and saturated sodium thiosulphate (50 mL) was added. The solid was filtered and washed with saturated sodium thiosulphate (50 mL) followed by water. The solid was dried under vacuum to afford **XIII-2** (14 g, 72% yield).

[0380] A suspension of **XIII-2** (15 g, 56.4 mmol, 1 eq.) in 35 mL of phenyl dichlorophosphate was heated at 180°C for 30 minutes whereby a brown solution was obtained. TLC analysis (PE:EA=10:1) showed the reaction completed. The solution was allowed to cool then poured onto ice/water, neutralized by a portionwise addition of solid $NaHCO_3$ and extracted with ethyl acetate (150 mL×3), and then washed with *aq*. $NaHCO_3$ (5%, 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give brown solid. The crude product was purified by flash chromatography on silica gel with petroleum ether/EtOAc (5:1→2:1) to give **XIII-3** as yellow solid (14 g, 87% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 284.7.

[0381] To a solution of vinyl magnesium bromide (66 mL, 66 mmol, 3.4 eq, 1.0 M solution in 2-methyl tetrahydrofuran) at -70°C under nitrogen was added a solution of **XIII-3** (5.5 g, 19.3 mmol, 1 eq.) in 120 mL of dry tetrahydrofuran, dropwise over 45 min. After 30 min at -70°C TLC analysis (PE:EA=3:1) showed the starting material was consumed completely. The reaction was quenched with saturated ammonium chloride (50 mL). The mixture was extracted with ethyl acetate (150 mL×3). The combined organic layers was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a brown oil. It was purified by flash chromatography on silica gel with petroleum ether/EtOAc (5:1→2:1) to give **XIII-4** (0.5 g, 9% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 278.8.

[0382] A flask was charged with **XIII-4** (450 mg, 1.6 mmol, 1eq), NaOMe (864 mg, 16 mmol, 10 eq.) and 8 mL of DMF. The mixture was heated at 130ºC for 18 hrs. LCMS analysis showed the reaction completed. The reaction mixture was cooled down to rt, diluted with water, extracted with ethyl acetated (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to yield **XIII-5** (0.2 g, 46% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 274.8.

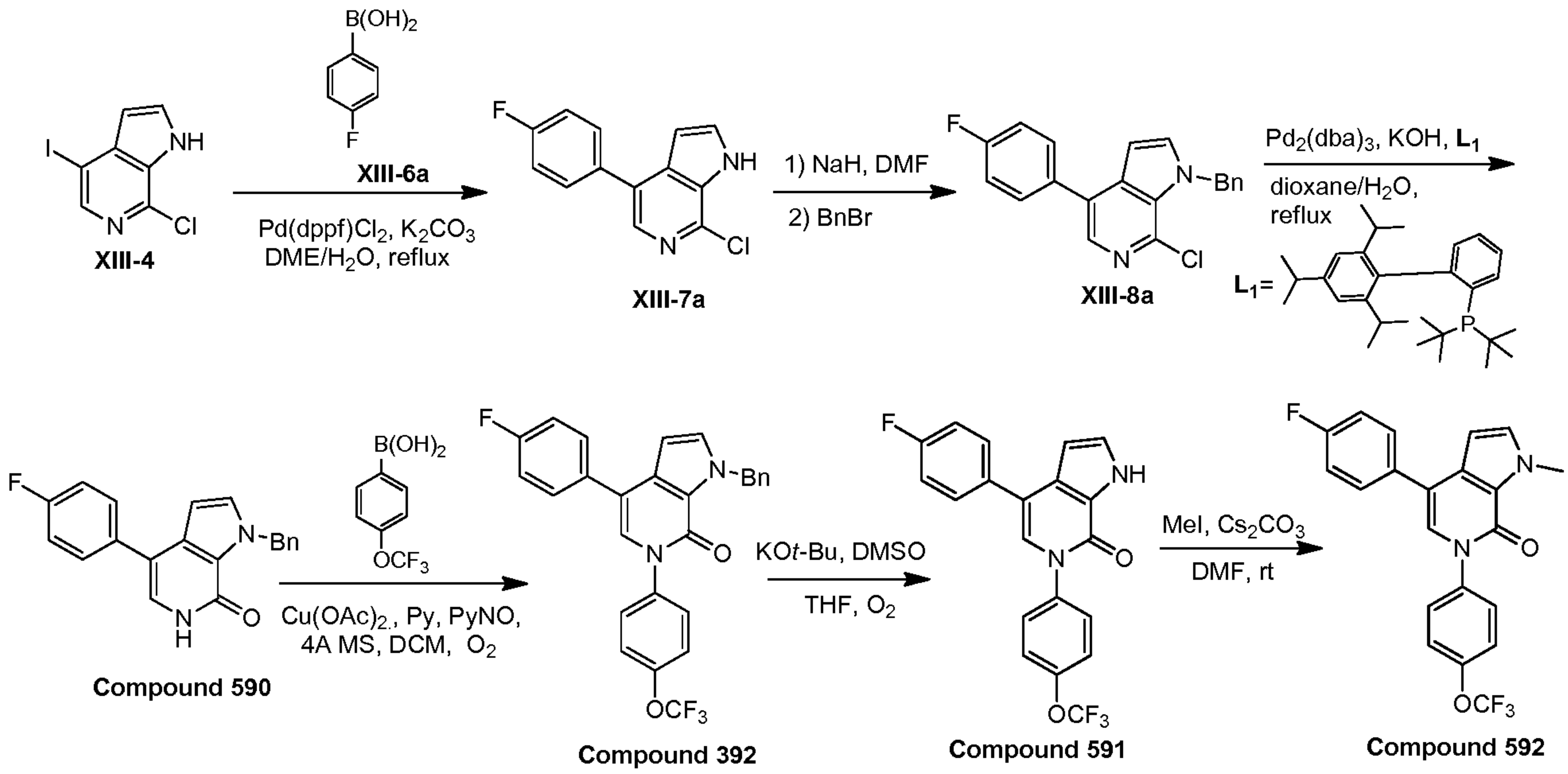
[0383] **XIII-7** was prepared following the similar procedure for obtaining **Compound 42** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (**XIII-6**) in replace of **XI-7**. (150 mg, 51% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 228.9.

[0384] To a solution of **XIII-7** (100 mg, 0.44 mmol, 1 eq.) in DMF (5 mL) was added NaH (60% in mineral oil, 35 mg, 0.88 mmol, 2 eq.). After stirring for 30 min, MeI (75 mg, 0.53 mmol, 1.2 eq.) was added. The mixture was stirred at rt. for 2 hrs. And then it was slowly quenched with water, extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE/EA =1:2) to afford **XIII-8** (90 mg, 85% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 243.0.

[0385] A mixture of **XIII-8** (90 mg, 0.374 mmol) in 10 mL *aq.*HBr (48%) was heated to reflux overnight. After being cooled to rt, the mixture was neutralized by addition of saturated *aq.* $NaHCO_3$, extracted with DCM/*i*-PrOH (30 mL×3, v/v=9/1). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford crude **XIII-9** (70 mg, 82% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 229.0.

[0386] **Compound 48** was prepared following the similar procedure for obtaining **XII-7**. (51.9 mg, 43% yield). **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.63 (s, 1H), 7.53 (s, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 3.0 Hz, 1H), 6.95 (s, 1H), 6.39 (d, J = 3 Hz, 1H), 4.10 (s, 3H), 3.90 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 388.9.

[0387] **Compound 49** was prepared following the similar procedure for obtaining **Compound 48** using 1-propenylmagnesium bromide in place of vinyl magnesium bromide and (4-fluorophenyl)boronic acid in place of **XIII-6**. ^{1}**H NMR** ($CDCl_3$, 300MHz) δ 7.43 (d, J = 8.7 Hz, 2H), 7.32-7.29 (m, 4H), 7.02 (t, J = 8.4 Hz, 2H), 6.77 (s, 1H), 6.71 (s, 1H), 4.08 (s, 3H), 1.69 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.9.



[0388] **XIII-7a** was prepared following the similar procedure for obtaining Compound **42**. **MS (ESI)** ***m/z*** $(M+H)^+$ 246.9.

[0389] To a solution of **XIII-7a** (400 mg, 1.63 mmol, 1 eq.) in 10 mL of DMF was added NaH (60% dispersion in mineral oil, 98 mg, 2.44 mmol, 1.5 eq.) at 0°C. The mixture was stirred at 0°C for 30min. After that, BnBr (417 mg, 2.44 mmol, 1.5 eq.) was added into the flask. The resulting mixture was stirred for 16hrs at rt. TLC (PE/ EA=5/1) analysis showed the reaction completed. The mixture was diluted with water, extracted with EtOA (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a yellow oil. Purification by column chromatography on silica gel (PE/EA=5/1) afford **XIII-8a** (250 mg, 46% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 336.9.

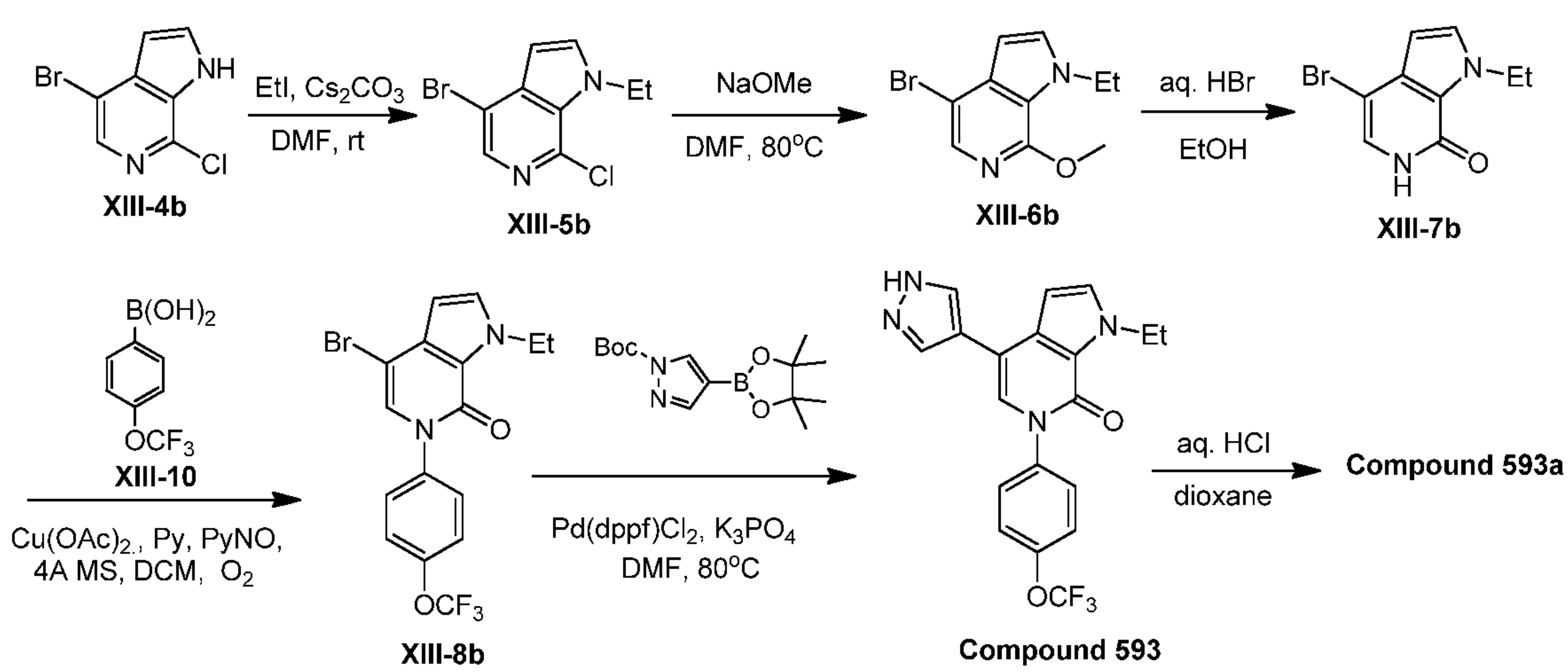
[0390] A flask was charged with **XIII-8a** (250 mg, 0.74 mmol, 1 eq.), KOH (499 mg, 8.9 mmol, 12 eq.), $\mathbf{L_1}$ (97 mg, 0.23 mmol, 0.3 eq.), 10 mL of dioxane and 10 mL of H_2O. The flask was flushed with nitrogen, and then $Pd_2(dba)_3$ (37 mg, 0.04 mmol, 0.05 eq.) was added. The mixture was flushed with nitrogen again, and heated to reflux for 10 hrs. LCMS analysis showed the reaction completed. The mixture was cooled down to rt, diluted with water (20 mL), extracted with ethyl acetate (50 mLx3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by prep-TLC (PE/EA=1/1) gave **Compound 590** (200 mg, 85% yield). **MS (ESI) *m/z*** $(M+H)^+$ 318.9.

[0391] **Compound 392** was prepared by Suzuki Coupling of Compound **590** with **XIII-10** following the similar procedure for obtaining Compound **48** (19% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.53-7.50 (m, 4H), 7.36-7.27 (m, 7H), 7.19 (d, *J* =2.8 Hz, 1H), 7.14 (t, *J* = 8.4 Hz, 2H), 7.01 (s, 1H), 6.46 (d, *J* = 2.8 Hz, 1H), 5.86 (s, 2H). **MS (ESI) *m/z*** $(M+H)^+$ 479.1.

[0392] To a solution of **Compound 392** (220 mg, 0.51 mmol, 1 eq) and DMSO (400 mg, 5.14 mmol, 10 eq) in 20 mL of THF was added KO*t*-Bu (1.15 g, 10.28 mmol, 20 eq) at 0°C. The mixture was stirred for 18h at rt under oxygen. The reaction was quenched with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated and concentrated. Purification by prep-TLC (PE: EA=1:1) gave **Compound 591** as a white solid (140 mg, 70% yield). **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.37 (s, 1H), 7.69-7.65 (m, 4H), 7.51 (d, *J*=8.4 Hz, 2H), 7.44 (t, *J*=2.8 Hz, 1H), 7.29-7.25 (m, 3H), 6.48 (t, *J*=2.4 Hz, 1H). **MS (ESI) *m/z*** $(M+H)^+$ 388.9.

[0393] To a solution of **Compound 591** (200 mg, 0.52 mmol, 1 eq) in 5 mL of DMF was added Cs_2CO_3 (336 mg, 1.03 mmol, 2 eq) at rt. The mixture was stirred for 30min. MeI (146 mg, 1.03 mmol, 2 eq) was added into the flask. The mixture was stirred for 18h at rt. The mixture was diluted with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give yellow solid. Purification by prep-TLC (PE:EA=1:1) gave **Compound 592** as a light yellow solid (90 mg, 43% yield). **^{1}HNMR** (DMSO-d_6, 400MHz) δ 7.68-7.64 (m, 4H), 7.52 (d, *J*=8.0 Hz, 2H), 7.48 (d, *J*=2.8 Hz, 1H), 7.31-7.26 (m, 3H), 6.42 (d, *J*=2.8 Hz, 1H), 4.11 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 403.1.

[0394] **Compound 394** was prepared following the similar procedure for obtaining Compound **392** and using 4-bromo-7-chloro-1H-pyrrolo[2,3-c]pyridine in place of **XIII-4**, **XIII-6** in place of **XIII-6a**, and methyl iodide in place of BnBr. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.70 (s, 1H), 7.60 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J*=2.8 Hz, 1H), 7.02 (s, 1H), 6.46 (d, *J*=2.8 Hz, 1H), 4.20 (s, 3H), 3.97 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 389.0.



[0395] **Compound 593** was prepared following the similar procedure for obtaining **Compound 48** using **XIII-4b** in place of **XIII-4**. The ethylation by EtI and treatment with NaOMe were conducte following the similar procedure described in the synthesis of Compound **592** and **XIII-5**. After HBr hydrolysis, **XIII-7b** was subject to two Suzuki-Coupling reacions to afford **Compound 593** as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.94 (s, 1H), 8.05~7.98 (m, 2H), 7.63~7.61 (m, 2H), 7.52~7.49 (m, 3H), 7.38 (s, 1H), 6.61 (d, J=2.4 Hz, 1H), 4.51 (q, J=7.2 Hz, 2H), 1.33 (t, J=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 389.1.

[0396] HCl salt compound **593a**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.01 (s, 2H), 7.62 (d, J=8.8 Hz, 2H), 7.98 (s, 1H), 7.53~7.50 (m, 3H), 7.38 (s, 1H), 6.61 (d, J=8.8 Hz, 1H), 4.51 (q, J=7.2 Hz, 2H), 1.33 (t, J=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 389.1.

[0397] **Compound 595** was obtained by Suzuki-Coupling of **XIII-4b** with **XIII-6a**, followed by dechlorination following the same procedure described above in the dechlorination of **XIII-8a**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 11.18 (s, 1H), 7.52~7.49 (m, 2H), 7.16~7.11 (m, 3H), 6.97 (s, 1H), 6.41 (d, J=3.2 Hz, 1H), 4.66 (q, J = 7.2 Hz, 2H), 1.52 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 257.1.

[0398] **Compound 594** was obtained by Suzuki Coupling of Compound **595** with **XIII-10** following the same procedure for obtaining Compound **48**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.54~7.51 (m, 2H), 7.35 (d, J=8.4 Hz, 1H), 7.18~7.12 (m, 3H), 7.00 (s, 1H), 6.42 (d, J=2.4 Hz, 1H), 4.62 (q, J=7.2 Hz, 2H), 1.51 (t, J=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 417.2.

[0399] **Compound 615** was obtained as a white solid by reacting Compound **593** with 2-(2-bromoethoxy)tetrahydro-2H-pyran in the presence of Cs_2CO_3 in DMF at 50°C, followed by hydroxy deprotection using TsOH in MeOH at 60°C. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.12 (s, 1H), 7.83 (s, 1H), 7.64 (d, J=8.8Hz, 2H), 7.55-7.51 (m, 3H), 7.38 (s, 1H), 4.92 (t, J=5.2Hz, 1H), 4.57 (q, *J*=7.2Hz, 2H), 4.16 (t, *J*=5.6Hz, 2H), 3.76 (q, *J*=4.6Hz, 2H), 1.35 (t, *J*=7.2Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 433.0.

[0400] **Compound 596** was prepared by following the similar procedure for the preparation of Compound **48**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.13 (s, 1H), 7.82 (s, 1H), 7.66~7.62 (m, 3H), 7.53~7.51 (m, 2H), 7.40 (s, 1H), 7.31~7.25 (m, 5H), 6.68 (d, *J*=2.8 Hz, 1H), 5.77 (s, 2H), 3.87 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 465.1.

[0401] HCl salt compound **596a**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.11 (s, 1H), 7.80 (s, 1H), 7.64~7.60 (m, 3H), 7.51~7.49 (m, 3H), 7.39 (s, 1H), 7.31~7.22 (m, 5H), 6.66 (d, *J*= 2.8 Hz, 1H), 5.76 (s, 2H), 3.85 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 465.1.

[0402] **Compound 614** was obtained by amino deprotection of Compound **596** using KO^{t}Bu, followed by reaction with 2-(2-bromoethoxy)tetrahydro-2H-pyran in the presence of Cs_2CO_3 in DMF, then hydroxy deprotection using TsOH in MeOH. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.12 (s, 1H), 7.82 (s, 1H), 7.63 (d, *J*= 6.8Hz, 2H), 7.52 (d, *J*= 8.4Hz, 2H), 7.47 (s, 1H), 7.38 (s, 1H), 6.60 (d, *J*= 2.8Hz, 1H), 4.54 (t, *J*=6.0Hz, 2H), 3.87 (s, 3H), 3.70 (t, *J*=5.6Hz, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 419.1.

[0403] **Compound 597** was prepared by following the similar procedure for the preparation of Compound **48** using (4-cyanophenyl)boronic acid in place of **XIII-10**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.11 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.80 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 2.8 Hz, 1H), 7.35 (s, 1H), 6.60 (d, *J* = 2.8 Hz, 1H), 4.07 (s, 3H), 3.85 (s, 3H).

[0404] HCl salt compound **597a**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.13 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 2H), 7.78 (m, 3H), 7.48 (s, 1H), 7.37 (s, 1H), 6.62 (s, 1H), 4.09 (s, 3H), 3.86 (s, 3H).

[0405] **Compound 600** was prepared by following the similar procedure for the preparation of Compound **597** using the Boc-protected boronic ester in place of **XIII-6**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.95 (s, 1H), 8.13 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.87 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 2.8 Hz, 1H), 7.37 (s, 1H), 6.61 (d, *J* = 2.8 Hz, 1H), 4.08 (s, 3H).

[0406] HCl salt compound **600a**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.00 (m, 4H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.46 (m, 1H), 7.37 (s, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 4.08 (s, 3H).

[0407] **Compound 599** was obtained by Suzuki-Coupling of 4-bromo-1-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one with (4-chlorophenyl)boronic acid then Suzuki-Coupling with **XIII-6,** following the similar procedure described in the synthesis of **XIII-8b** and Compound **593**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.10 (s, 1H), 7.78 (s, 1H), 7.57 (m, 2H), 7.50 (m, 2H), 7.44 (d, *J* = 2.8 Hz, 1H), 7.30 (s, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 4.07 (s, 3H), 3.85 (s, 3H).

[0408] **Compound 598** was prepared by following the similar procedure for the preparation of Compound **599** using the Boc-protected boronic ester in place of **XIII-6**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.95 (s, 1H), 8.13 (s, 1H), 7.88 (s, 1H), 7.59 (m, 2H), 7.52 (m, 2H), 7.45 (d, J = 2.8 Hz, 1H), 7.34 (s, 1H), 6.62 (d, J = 2.8 Hz, 1H), 4.10 (s, 3H).

[0409] HCl salt compound **598a**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.05 (d, J = 2 Hz, 2H), 7.56 (m, 2H), 7.50 (m, 2H), 7.44 (d, J = 2.8 Hz, 1H), 7.34 (s, 1H), 6.6 (d, J = 2.8 Hz, 1H), 4.07 (s, 3H).

[0410] Compounds **601** and **602** was prepared following the similar procedure described in the synthesis of Compound **598** using the corresponding aromatic boronic acids. Their respective HCl salts compounds **601a** and **602a** were also obtained by reacting with aq. HCl in acetonitrile.

[0411] **Compound 601**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.90 (s, 1H), 8.09 (s, 1H), 7.84 (s, 1H), 7.40 (d, J=2.4 Hz, 1H), 7.14 (d, J=8.0 Hz, 2H), 6.92 (d, J=2.0 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.59 (d, J=2.8 Hz, 1H), 4.07 (m, 5H), 2.02 (s, 3H), 1.34 (t, J=6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 349.0.

[0412] **Compound 601a**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.04 (s, 2H), 7.42 (d, J=2.8 Hz, 1H), 7.15 (d, J=8.4 Hz, 2H), 6.93 (d, J=2.4 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 6.61 (d, J=2.8 Hz, 1H), 4.09-4.05 (m, 5H), 2.04 (s, 3H), 1.35 (t, J=6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 348.9.

[0413] **Compound 602**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.94 (s, 1H), 8.13 (s, 1H), 7.89 (s, 1H), 7.62 (d, J=8.4 Hz, 2H), 7.51 (d, J=8.4 Hz, 2H), 7.45 (d, J=2.4 Hz, 1H), 7.38 (s, 1H), 6.62 (d, J=3.2 Hz, 1H), 4.09 (s, 3H).

[0414] **Compound 602a**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.06 (s, 2H), 7.62 (d, J=8.0 Hz, 2H), 7.51 (d, J=8.0 Hz, 2H), 7.46 (d, J=2.8 Hz, 1H), 7.40 (s, 1H), 6.62 (d, J=2.8 Hz, 1H), 4.09 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 374.9.

[0415] **Compound 603** was prepared by benzyl deprotection of 1-benzyl-4-bromo-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one to form an intermediate 4-bromo-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one, followed by Suzuki-Coupling with **XIII-6** to afford the final product. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.29 (s, 1H), 8.14 (s, 1H), 7.83 (s, 1H), 7.64 (d, J= 8.8Hz, 2H), 7.52 (d, J= 8.8Hz, 2H), 7.43 (m, 1H), 7.38 (s, 1H), 6.66 (m, 1H), 3.86 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 375.0.

[0416] **Compound 604** was prepared by Suzuki-Coupling of 4-bromo-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one with **XII-8b**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.93 (s, 1H), 12.27 (s, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 7.64 (d, J= 8.4Hz, 2H), 7.52 (d, J= 8.4 Hz, 2H), 7.41 (d, J= 8.4 Hz, 2H), 6.67 (d, J= 2.4 Hz, 1H). HCl salt compound **604a**: **^{1}H**

NMR (DMSO-d_6, 400 MHz) δ 12.28 (s, 1H), 8.06 (s, 2H), 7.64 (d, *J*= 8.4Hz, 2H), 7.52 (d, *J*= 8.4 Hz, 2H), 7.42 (m, 2H), 6.67 (d, *J*= 2.4 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 361.0.

[0417] **Compound 609** was obtained by Pd/C hydrogenation of 4-bromo-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.15 (s, 1H), 7.59-7.57 (m, 2H), 7.51-7.49 (m, 2H), 7.35 (t, *J* = 2.6 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.62 (d, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 2.0 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 295.0.

[0418] **Compound 610** was obtained by ethylation of Compound **609** using EtI in the presence of Cs_2CO_3 in DMF. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ7.57-7.55 (m, 2H), 7.50-7.48 (m, 2H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 6.33 (d, *J* = 2.8 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 322.9.

[0419] Other compounds were also prepared using the various procedures described in Example 5-F.

[0420] **Compound 605**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 10.73 (s, 1H), 7.73 (s, 1H), 7.63 (s, 1H), 7.50 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=8.4 Hz, 2H), 7.32 (s, 1H), 7.08 (s, 1H), 6.57 (d, *J* =2.4 Hz, 1H) , 3.98 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 324.9.

[0421] **Compound 606**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.95 (s, 1H), 12.28 (s, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 7.61~7.54 (m, 4H), 7.43 (s, 1H), 7.37 (s, 1H), 6.68 (d, *J* =2.0 Hz, 1H). HCl salt: **MS (ESI)** ***m/z*** $(M+H)^+$ 310.9.

[0422] **Compound 607**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.93 (s, 1H), 12.21 (s, 1H), 8.13~7.89 (m, 2H), 7.42~7.41 (m, 1H), 7.20~7.18 (m, 2H), 6.96~6.86 (m, 2H), 6.68 (d, *J*= 2.4 Hz, 1H), 4.08 (q, *J* =6.8 Hz, 2H), 2.04 (s, 3H), 1.36 (t, *J* =6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 334.9.

[0423] **Compound 608**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.37 (s, 1H), 8.07~8.02 (m, 4H), 7.78 (d, *J*= 8.8 Hz, 2H), 7.45 (d, *J*= 8.8 Hz, 2H), 6.70 (d, *J*= 2.4 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 301.9.

[0424] **Compound 611**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.97 (s, 1H), 8.01 (s, 1H), 7.71 (s, 1H), 7.41 (s, 1H), 6.98 (s, 1H), 6.50 (d, *J* = 2.8 Hz, 1H), 4.51 (q, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 1.33 (t, *J* = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 242.9.

[0425] **Compound 612**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.08 (s, 1H), 11.03 (s, 1H), 8.06 (s, 1H), 7.76 (s, 1H), 7.35 (s, 1H), 7.05 (d, *J* = 5.6 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 3.87 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 215.0.

[0426] **Compound 613**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.91 (s, 1H), 11.00 (d, *J* = 3.6 Hz, 1H), 8.05 (s, 1H), 7.81 (s, 1H), 7.43 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 6.53 (d, *J* = 2.8 Hz, 1H), 4.54 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 229.1.

[0427] **Compound 616**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.93 (s, 1H), 12.08 (s, 1H), 11.05 (s, 1H), 7.96 (brs, 2H), 7.35 (d, J = 2.8 Hz, 1H), 7.07 (s, 1H), 6.60 (d, J = 2.8 Hz, 1H). **MS (ESI)** ***m/z*** $[M+H]^+$ 201.1.

[0428] **Compound 647** was prepared following the similar procedure described in the synthesis of compound **593** using benzyl bromide in place of ethyl bromide in the reaction with **XIII-4b**. After Suzuki-Coupling with **XIII-10**, benzyl was replaced by isopropyl by reaction with KO*t*Bu followed by isopropyl iodide. A second Suzuki-Coupling with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole afforded the final product. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.13 (s, 1H), 7.81 (s, 1H), 7.72 (d, J=3.2 Hz, 1H), 7.63 (d, J=8.8 Hz, 2H), 7.52 (d, J=8.8 Hz, 2H), 7.38 (s, 1H), 6.67 (d, J=3.2 Hz, 1H), 5.77-5.70 (m, 1H), 3.88 (s, 3H), 1.44 (d, J=6.8 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 417.1.

[0429] **Compound 648** was prepared following the similar procedure described in the synthesis of Compound **647** using the Boc-protected boronic ester in the last coupling reaction. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.96 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.71 (d, J=3.2 Hz, 1H), 7.64 (d, J=8.8 Hz, 2H), 7.52 (d, J=8.8 Hz, 2H), 7.39 (s, 1H), 6.67 (d, J=3.2 Hz, 1H), 5.77-5.71 (m, 1H), 1.44 (d, J=6.8 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 403.1.

[0430] **Compounds 649** and **650** were prepared by Suzuki-Coupling of 4-bromo-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one with cyclopropylboronic acid then a second Suzuki Coupling with the corresponding boronic esters. **Compound 649**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.12 (s, 1H), 7.81 (s, 1H), 7.64 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.8 Hz, 2H), 7.46 (d, J=2.8 Hz, 1H), 7.38 (s, 1H), 6.57 (d, J=2.8 Hz, 1H), 4.20-4.15 (m, 1H), 3.86 (s, 3H), 1.07-0.96 (m, 4H). **MS (ESI)** ***m/z*** $(M+H)^+$ 415.0. **Compound 650**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.95 (brs, 1H), 8.13 (s, 1H), 7.88 (s, 1H), 7.64 (d, J=8.8 Hz, 2H), 7.52 (d, J=8.8 Hz, 2H), 7.38 (d, J=3.6 Hz, 1H), 7.40 (s, 1H), 6.58 (d, J=3.6 Hz, 1H), 4.19-4.14 (m, 1H), 1.03-0.97 (m, 4H). **MS (ESI)** ***m/z*** $(M+H)^+$ 401.1.

[0431] **Compounds 651** and **654** were prepared by reacting 4-bromo-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one with 1-chloro-2-methoxyethane in the presence of Cs_2CO_3 in DMF, followed by Suzuki-Coupling with the corresponding boronic esters. **Compound 651**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.13 (s, 1H), 7.82 (s, 1H), 7.64 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.8 Hz, 2H), 7.50 (d, J=3.2 Hz, 1H), 7.39 (s, 1H), 6.61 (d, J=3.2 Hz, 1H), 4.66 (t, J=5.6 Hz, 2H), 3.88 (s, 3H), 3.66 (t, J=5.6 Hz, 2H), 3.23 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 433.1. **Compound 654**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 12.96 (brs, 1H), 8.03 (brs, 2H), 7.63 (d, J=9.0

Hz, 2H), 7.51 (d, *J*=3.0 Hz, 1H), 7.49 (d, *J*=9.0 Hz, 2H), 7.41 (s, 1H), 6.61 (d, *J*=3.0 Hz, 1H), 4.66 (t, *J*=5.4 Hz, 2H), 3.65 (t, *J*=5.4 Hz, 2H), 3.23 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 419.1.

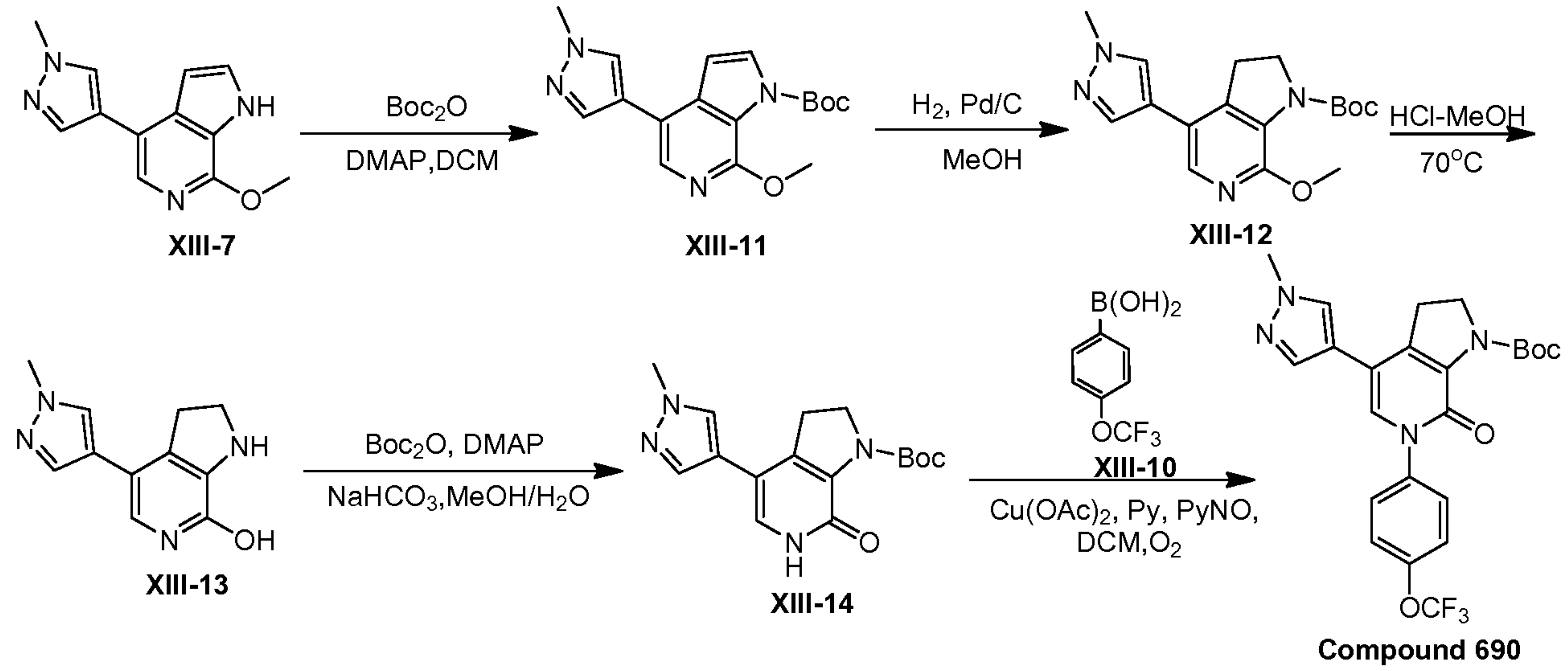
[0432] **Compounds 652** and **653** were prepared by reacting 4-bromo-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one with 1-bromo-2-fluoroethane in the presence of Cs_2CO_3 in DMF, followed by Suzuki-Coupling with the corresponding boronic esters. **Compound 652**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 12.96 (brs, 1H), 8.03 (brs, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.53 (d, *J*=2.8 Hz, 1H), 7.52 (d, *J*=8.8 Hz, 2H), 7.44 (s, 1H), 6.66 (d, *J*=2.8 Hz, 1H), 4.85-4.75 (m, 3H), 4.69 (m, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 407.1. **Compound 653**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 8.14 (s, 1H), 7.83 (s, 1H), 7.64 (d, *J*=8.8 Hz, 2H), 7.53 (d, *J*=2.8 Hz, 1H), 7.52 (d, *J*=8.8 Hz, 2H), 7.42 (s, 1H), 6.65 (d, *J*=2.8 Hz, 1H), 4.84-4.77 (m, 3H), 4.69 (m, 1H), 3.87 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 421.1.

[0433] **Compound 655** was prepared following the similar procedure described in the synthesis of compound **593** where 1-(difluoromethoxy)-4-iodobenzene was used in place of **XIII-10**, and CuI, Cs_2CO_3, and 8-hydroxyquinoline in DMSO/dioxane used as the reaction catalysts. The reaction mixture was purged with N_2 and stirred at 110°C overnight. In the last step coupling reaction, Pd-118 and K_3PO_4 were used in place of $Pd(dppf)Cl_2$ and K_2CO_3. ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 8.10 (s, 1H), 7.79 (s, 1H), 7.54-7.51 (m, 3H), 7.32-7.14 (m, 4H), 6.59 (d, *J*=2.8Hz, 1H), 4.51 (q, *J*=7.2Hz, 2H), 3.85 (s, 3H), 1.33 (t, *J*=7.2Hz, 3H).

[0434] Compound **691** was prepared following the similar procedure described in the synthesis of Compound **593** using 4-bromo-1-(2-ethoxyethyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one in place of **XIII-8b**. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (br. s., 2H), 7.51 (d, *J*=8.5 Hz, 2H), 7.36 (d, *J*=8.5 Hz, 2H), 7.29 (d, *J*=2.5 Hz, 1H), 7.08 (s, 1H), 6.47 (d, *J*=2.3 Hz, 1H), 4.76 (t, *J*=4.9 Hz, 2H), 3.81 (t, *J*=4.9 Hz, 2H), 3.45 (q, *J*=6.9 Hz, 2H), 1.15 (t, *J*=6.9 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 433.1.

[0435] Compound **692** was prepared following the similar procedure described in the synthesis of Compound **593** using 4-bromo-1-(2-isopropoxyethyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one in place of **XIII-8b**. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.85 (br.s., 2H), 7.52 (d, J=8.4 Hz, 2H), 7.36 (d, J=8.4 Hz, 2H), 7.31 (d, J=2.4 Hz, 1H), 7.08 (s, 1H), 6.46 (d, J=2.4 Hz, 1H), 4.74 (t, J=4.8 Hz, 2H), 3.79 (t, J=4.8 Hz, 2H), 3.52~3.45 (m, 1H),1.09 (d, J=6.0 Hz, 6H).

[0436] Compound **693** was prepared by the Suzuki-coupling of 4-bromo-6-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-7(6H)-one with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole catalyzed by Pd-118/K_3PO_4 in dioxane/H_2O mixture; followed by reaction with acetyl chloride to afford the final product. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (s, 1H), 7.49-7.45 (m, 2H), 7.42 (s, 1H), 7.40 - 7.34 (m, 2H), 7.28 (s, 1H), 4.28 (t, J=8.2 Hz, 2H),3.95 (s, 3H), 3.04 (t, J=8.2 Hz, 2H), 2.36 (s, 3H).



[0437] **XIII-7** (2.5 g, 11 mmol) was dissolved in DCM (20 mL), then DMAP (98 mg, 0.66 mmol) and Boc_2O (2.87 g, 13 mmol) was added. The mixture was stirred at 25°C for 1h, then the solvent was removed *in vacuo* to give **XIII-11** (3.3 g, yield 91.6%).

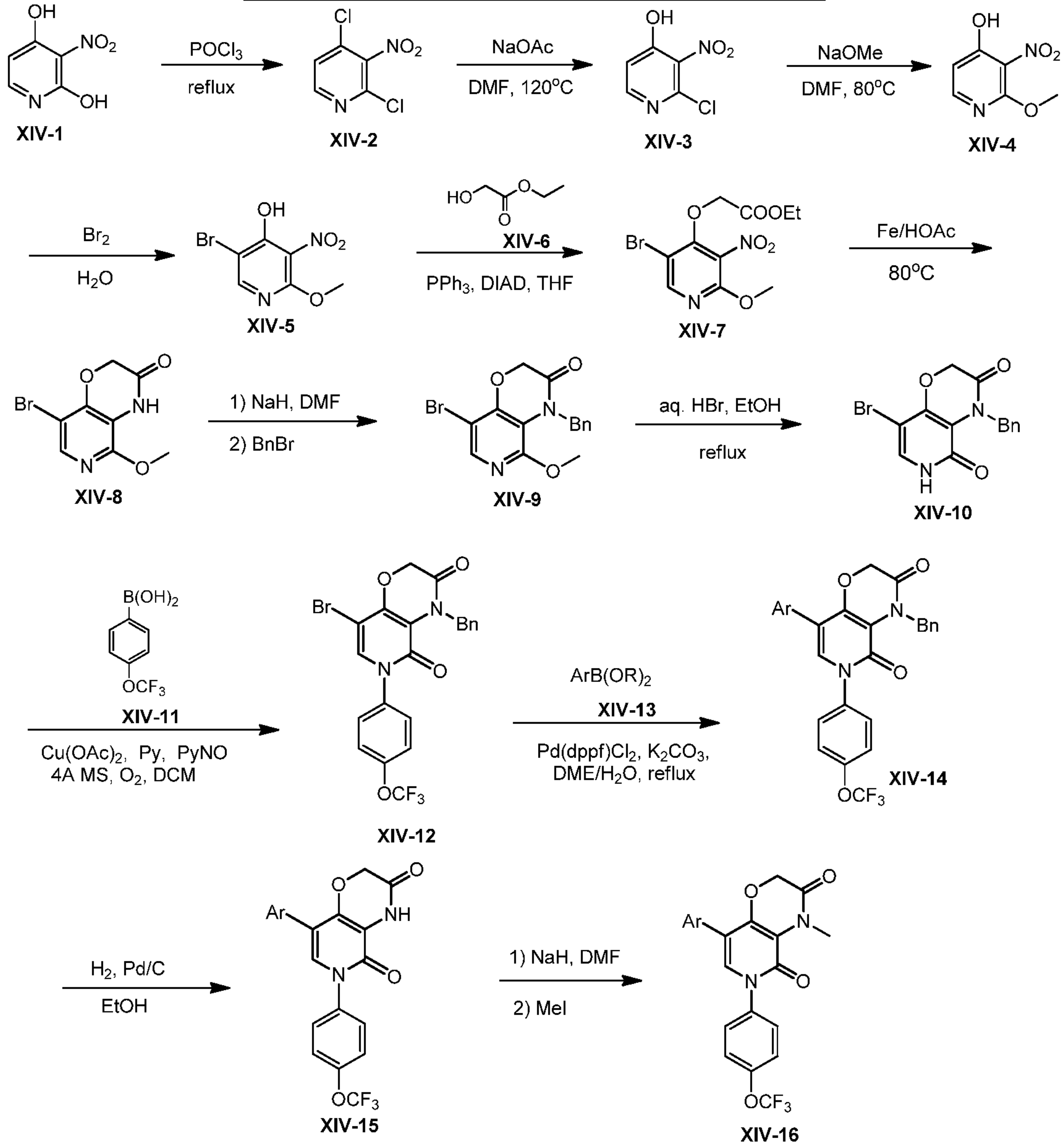
[0438] **XIII-11** (4 g, 12.2 mmol) was dissolved in MeOH (40 mL), then Pd/C (400 mg, 10%) was added. The mixture was purged with hydrogen for three times and then stirreded at 70°C for 40h. Then the solvent was removed in vacuo to give **XIII-12** (3.1 g, yield 77%) as a white solid.

[0439] **XIII-12** (3.3 g, 10.3 mmol) was dissolved in HCl-MeOH (4 M, 30 mL). The mixture was stirreded at 70°C for 2h. Then the solvent was removed in vacuo to give **XIII-13** (2.1 g, yield 97%) as a white solid.

[0440] **XIII-13** (1.5 g, 6.9 mmol) was dissolved in sat. aq. $NaHCO_3$ (20 mL) and MeOH/H_2O (v/v=1/1, 20 mL), then DMAP (102 mg, 0.69 mmol) and Boc_2O (2.27 g, 1.0 mmol) was added. The mixture was stirred at 25°C for 48h. Then the mixture was extracted with EA, the combined organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo to afford a yellowish solid. The crude product was purified to give **XIII-14** (380 mg, 16.8%) as a white solid.

[0441] **XIII-14** was reacted with **XIII-10** following the standard procedure described herein to give Compound **690** (230 mg, 41.7%) as a white solid. **^{1}HNMR** ($CDCl_3$, 400 MHz) δ 7.51 (s, 1H), 7.44 (d, *J*=8.5 Hz, 2H), 7.39 (s, 1H), 7.32 (d, *J*=8.5 Hz, 2H), 7.20 (s, 1H), 4.11 (t, *J*=8.3Hz, 2H), 3.93 (s, 3H), 3.05 (t, *J*=8.3 Hz, 2H), 1.52 (s, 9H). **MS (ESI)** ***m/z*** $(M+H)^+$ 477.2.

Example 5-G
Synthesis of Compounds 50-53 (Scheme XIV)



[0442] **XIV-1** (10 g, 64.1 mmol) was added into $POCl_3$ (20 mL), the reaction mixture was heated at reflux for 2 hrs. The mixture was cooled to rt and poured into saturated aqueous Na_2CO_3, the mixture was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA=10:1) to afford **XIV-2** as a pale yellow solid (10 g, 83% yield). ^{1}**HNMR** ($CDCl_3$, 300MHz) δ 8.45 (d, J = 5.4 Hz, 1 H), 7.48 (d, J = 5.4 Hz, 1H).

[0443] To a solution of **XIV-2** (10 g, 52.1 mmol) in DMF (60 mL) was added NaOAc (10.3 g, 125 mmol), the reaction mixture was stirred at 120°C for 3 hrs. The mixture was cooled to rt and poured into water, extracted with EtOAc. Combined organic phase was washed with brine and concentrated under vacuum to afford the crude product. The residue was purified by column chromatography (PE:EA=1:1) to afford **XIV-3** as a pale yellow solid (5.4 g, 60% yield). **^{1}HNMR** (CD_3OD, 300MHz) δ 8.14 (d, *J*=6.0 Hz, 1H), 6.98 (d, *J*=6.0Hz, 1H).

[0444] To a solution of **XIV-3** (5.4 g, 31.03 mmol) in DMF (30 mL) was added NaOMe (8.4 g, 155.17 mmol), the reaction mixture was stirred at 80°C for 10 hrs. The mixture was cooled to rt and poured into water, extracted with EtOAc. Combined organic phase was washed with brine and concentrated under vacuum to afford the crude product. The residue was purified by column chromatography (PE:EA=1:1) to afford **XIV-4** as a pale yellow solid (4.5 g, 85% yield). **^{1}HNMR** ($CDCl_3$, 300MHz) δ 11.48 (brs, 1H), 8.10 (d, *J* = 5.7 Hz, 1H), 6.71 (d, *J* = 5.7 Hz, 1H), 4.11 (s, 3H).

[0445] To a suspension of **XIV-4** (4.5 g, 26.47 mmol) in water (30 mL) were added drop wise Br_2 (5.3 g, 33.35 mmol) at rt, the reaction mixture was stirred for 30 min then heated at 50°C for 1h. After cooling to rt, the mixture was filtered, washed with water and dried under vacuum to yield **XIV-5** as a pale yellow solid. (3.0 g, 46% yield). **^{1}HNMR** ($CDCl_3$, 400MHz) δ 8.29 (s, 1H), 4.08 (s, 3H).

[0446] A flask was charged with **XIV-5** (2.49 g, 10 mmol, 1 eq.), **XIV-6** (1.25 g, 12 mmol, 1.2 eq.), PPh_3 (3.14 g, 12 mmol, 1.2 eq.) and 30 mL of anhydrous THF, flushed with nitrogen for three times. DIAD (2.42 g, 12 mmol, 1.2 eq.) was added drop wise into the mixture at 0°C. After that, the mixture was warmed to rt and stirred for another 16 hrs. TLC (PE:EA=5:1) analysis showed the reaction completed. The mixture was diluted with water, extracted with EtOAc (100 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a yellow oil. Purification by column chromatography gave **XIV-7** (3 g, yield 89%). **^{1}H NMR** ($CDCl_3$, 300MHz): δ 8.33 (s, 1H), 4.82 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2 H), 4.02 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

[0447] A flask was charged with **XIV-7** (3 g, 8.96 mmol, 1 eq.), Fe powder (2 g, 35.82 mmol, 4 eq.) and 40 mL of AcOH. The mixture was heated at 80°C for 3 hrs. TLC (PE:EA=3:1) analysis showed the reaction completed. The mixture was cooled down to rt, adjusted pH=7-8 with saturated aq. K_3PO_4, extracted with EtOA (100 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a yellow oil. Purification by column chromatography gave **XIV-8** (1.5 g, 65% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 260.8

[0448] To a solution of **XIV-8** (1 g, 3.86 mmol, 1 eq.) in 15 mL of DMF was added NaH (60%, 185 mg, 4.63 mmol, 1.2 eq.) at 0°C. The mixture was stirred at 0°C for 30 min. After that, BnBr (792 mg, 4.63 mmol, 1.2 eq.) was added. The resulting mixture was stirred for 16 hrs at rt. TLC (PE:EA=3:1) analysis showed the reaction completed. The mixture was diluted with water, extracted with EtOA (80 mLx3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give yellow oil. Purification by column chromatography gave **XIV-9** (1.2 g, 89% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 350.9.

[0449] To a solution of **XIV-9** (50 mg, 0.14 mmol, 1 eq.) in 6 mL of EtOH was added 1 mL of *aq*. HBr (40%). The mixture was heated at 100°C for 1 h. TLC (EA) analysis showed the reaction completed. The mixture was cooled down to rt, adjusted pH=7-8 with saturated aq. $NaHCO_3$, extracted with EtOA (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give **XIV-10** (45 mg, 95% yield). **^{1}H NMR** ($CDCl_3$, 400MHz): δ 12.49 (brs, 1H), 7.26-7.22 (m, 6H), 5.64 (s, 2H), 4.73 (s, 2H).

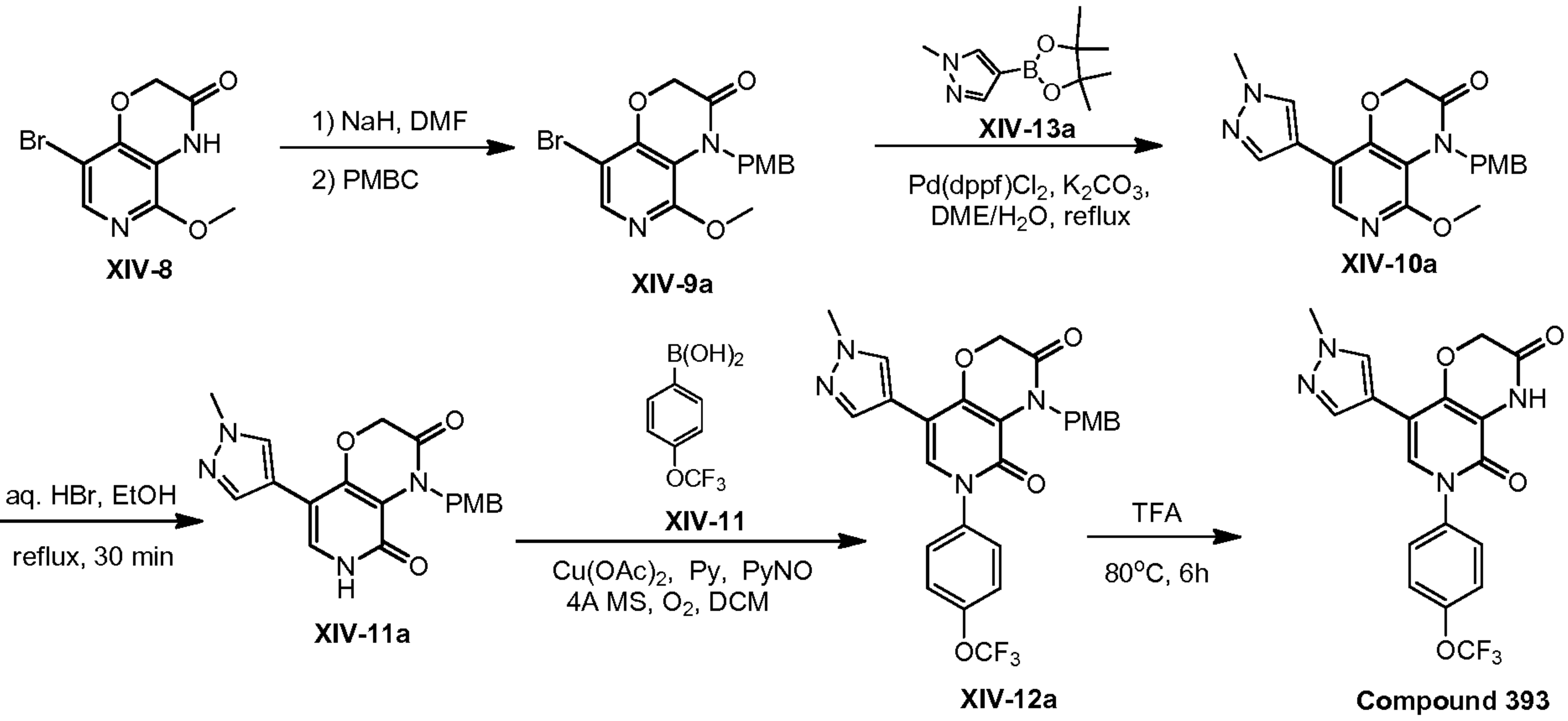
[0450] The preparation of **XIV-12** was followed the general procedure as described in the synthesis of **X-6**.

[0451] **Compound 50** was prepared following the similar procedure for obtaining **Compound 40** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in replace of **X-7**. **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.56 (s, 1H), 7.51 (s, 1H), 7.30-7.17 (m, 11H), 5.58 (s, 2H), 4.65 (s, 2H), 3.86 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 496.9.

[0452] **Compound 51** was prepared following the similar procedure for obtaining **Compound 40**. **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.29-7.19 (m, 11H), 7.05-7.02 (m, 3H), 5.59 (s, 2H), 4.60 (s, 2H). MS (ESI) *m/z* $[M+H]^+$ 511.2.

[0453] **Compound 52**: A flask was charged with **Compound 51** (340 mg, 0.67 mmol), Pd/C (34 mg, 10% mol) and 10 mL of EtOH. The mixture was stirred for 30 hrs under hydrogen (50 psi). TLC (PE: EA=1:1) analysis showed the reaction completed. The mixture was filtered; the filtrate was concentrated to give yellow solid. Purification by prep-TLC gave **Compound 52** (190 mg, 68% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.07 (s, 1H), 7.49 (d, *J*=8.8 Hz, 2H), 7.40-7.38 (m, 4H), 7.12-7.10 (m, 3H), 4.74 (s, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 421.2.

[0454] **Compound 53**: To a solution of **Compound 52** (100 mg, 0.24 mmol, 1 eq.) in 5 mL of DMF was added NaH (14 mg, 0.54 mmol, 1.5 eq.) at 0°C. The mixture was stirred at 0°C for 30 min. After that, MeI (50.7 mg, 0.54 mmol, 1.5 eq.) was added into the flask. The resulting mixture was stirred for 16 hrs at rt. TLC (PE: EA=1:1) analysis showed the reaction completed. The mixture was diluted with water, extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give yellow oil. Purification by prep-TLC gave **Compound 53** (55.5 mg, 54% yield). **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.51-7.48 (m, 2H), 7.42-7.37 (m, 4H), 7.22 (s, 1H), 7.16-7.13 (m, 2H), 4.63 (s, 2H), 3.61 (s, 3H).

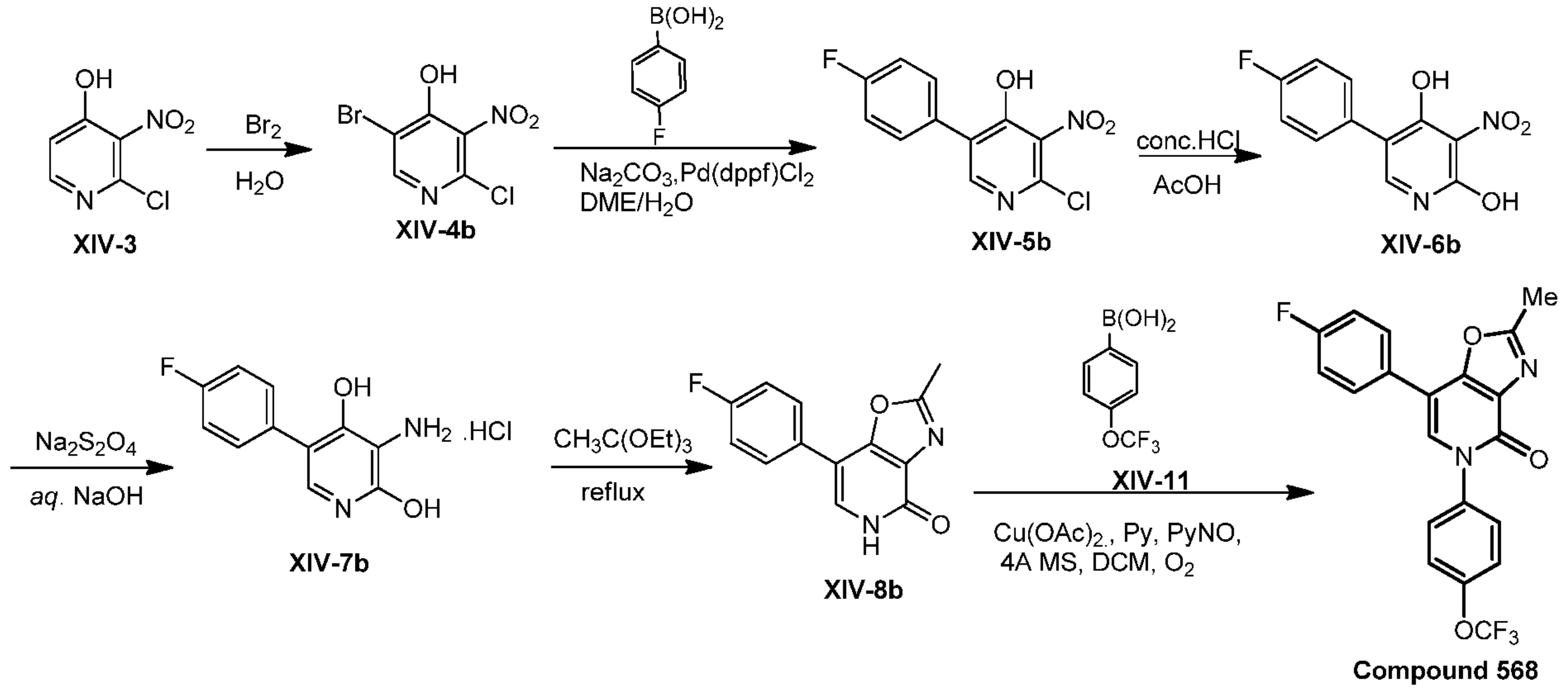


[0455] To a solution of **XIV-8** (200 mg, 0.77 mmol, 1 eq.) in 10 mL of DMF was added NaH (60% dispersion in mineral oil, 60 mg, 1.16 mmol, 1.5 eq.) at 0°C. The mixture was stirred at 0°C for 30 min. After that, PMBC (181 mg, 1.16 mmol, 1.5 eq.) was added into the flask. The resulting mixture was stirred for another 16 hrs at rt. TLC (PE/ EA=3/1) analysis showed the reaction completed. The mixture was diluted with water (20 mL), extracted with EtOA (30 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give yellow oil. Purification by prep-TLC (PE/ EA=3/1) yield **XIV-9a** (245 mg, 85% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 379.0.

[0456] **XIV-12a** was prepared following the scheme illustrated above. **MS (ESI)** ***m/z*** $(M+H)^+$ 526.9.

[0457] The mixture of **XIV-12a** (100 mg, 0.19 mmol) and 5 mL of TFA was heated at 80°C for 6 hrs. TLC (EA) analysis showed the reaction completed. The mixture was cooled down to rt, most of TFA was evaporated, the residue was neutralized with saturated *aq*.$NaHCO_3$, extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated to give a yellow solid. Purification by prep-TLC (EA) gave **Compound 393** (72.3 mg, 93% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.06 (brs, 1H), 7.67 (s, 1H), 7.63 (s, 1H), 7.48-7.45 (m, 2H), 7.38-7.35 (m, 2H), 7.22 (s, 1H), 4.81 (s, 2H), 3.95 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 406.9.

[0458] **Compound 396** was prepared following the similar procedure for obtaining **XIV-12a** using methyl iodide in place of PMBC. **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.64-7.61 (m, 2H), 7.47-7.45 (m, 2H), 7.39-7.37 (m, 2H), 7.31 (s, 1H), 4.67 (s, 2H), 3.95 (s, 3H), 3.58 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 420.9.



[0459] **XIV-5b** was obtained from **XIV-3** in two steps by bromination and Suzuki-Coupling with (4-fluorophenyl)boronic acid using the standard procedure described herein.

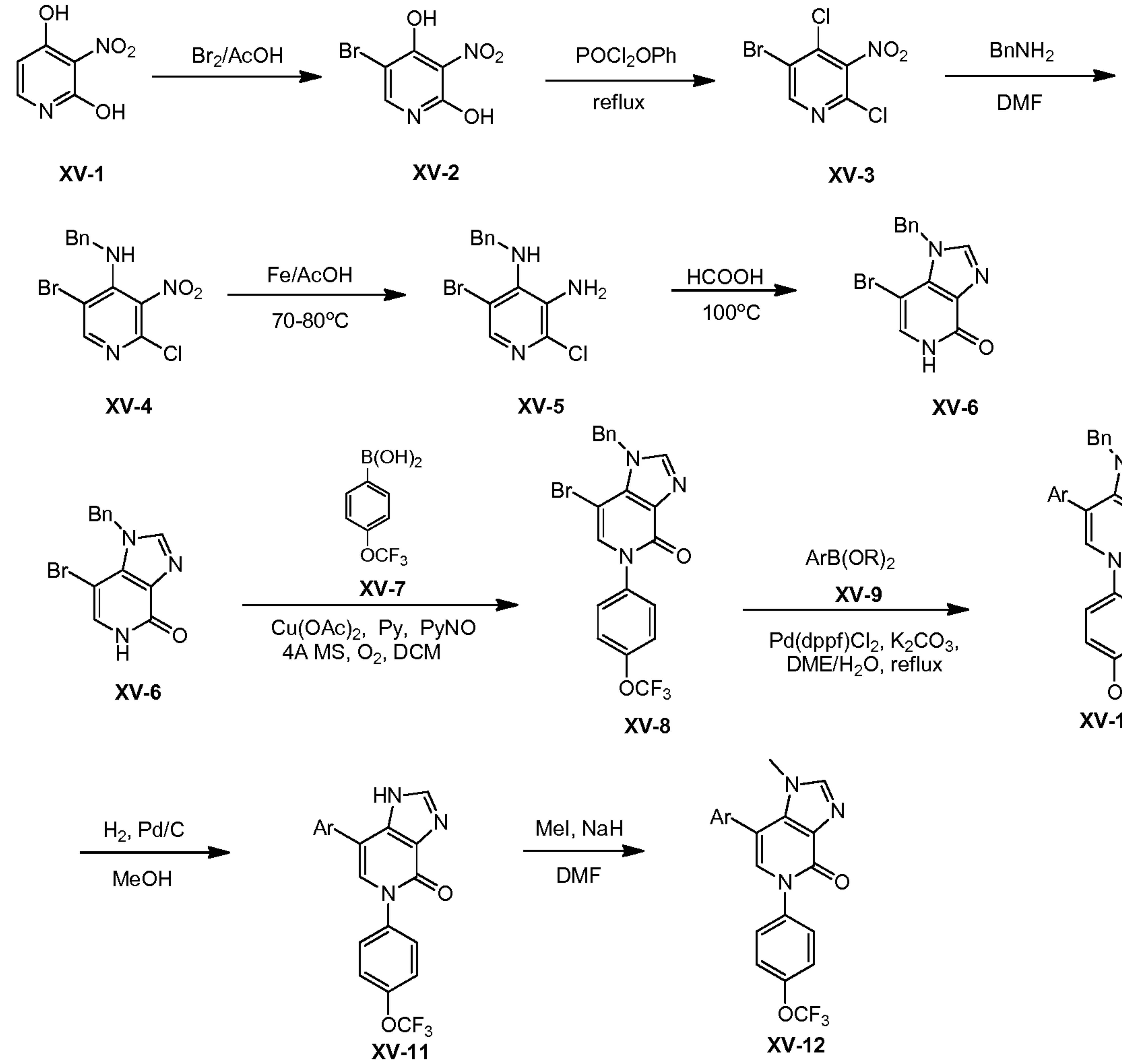
[0460] A solution of **XIV-5b** (1.5 g, 5.6 mmol) in conc.HCl/AcOH (14 mL, v/v= 1/1) was heated at reflux overnight. After cooling to r.t, the mixture was concentrated under reduced pressure to give **XIV-6b** without further purification (1.1 g, 78% yield).

[0461] **XIV-6b** (1.1 g, 4.4 mmol) was added into aq.NaOH (15 mL, 1M). Then $Na_2S_2O_4$ (1.5 g, 8.8 mmol) was added. The mixture was stirred at rt. under dark for 1h. After completion of the reaction indicated by TLC (PE/EA =1:2), the mixture was acidified to pH=5~6, then extrected with EA. The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo to give **XIV-7b** without further purification (0.8 g, 83% yield).

[0462] A mixture of **XIV-7b** (0.8g, 3.6 mmol) in $CH_3C(OEt)_3$ (10 mL) was heated at reflux overnight. After cooling to rt, the mixture was filtered, the filtrate cake was washed with EA/PE (1:1) to give crude **XIV-8b** (340 mg, 39% yield).

[0463] **Compound 568** was obtained by Suzuki-Coupling of **XIV-8b** with **XIV-11** using standard procedure described herein. ^{1}**H NMR** (Methanol-d_4, 300MHz) δ 7.78 (s, 1H), 7.72-7.67 (m, 2H), 7.55-7.51 (m, 2H), 7.41 (d, J=8.4 Hz, 2H), 7.16-7.10 (m, 2H), 2.59 (s, 3H).

Example 5-H
Synthesis of Compounds 54-59 (Scheme XV)



[0464] To a solution of **XV-1** (15 g, 96.2 mmol) in AcOH (120 mL) were added Br_2 (16.7 g, 105.8 mmol). After addition, the reaction mixture was stirred at 70°C for 30min. Then the reaction mixture was poured into ice-water, the resulting precipitate was collected by filtration, washed with water and dried in reduced pressure to afford **XV-2** as a yellow solid (14 g, 60% yield). **^{1}H NMR** (DMSO-d_6, 400MHz) δ 7.85 (s, 1H).

[0465] **XV-2** (2 g, 8.5 mmol) was added into $POCl_2OPh$ (10 mL), and then the reaction mixture was heated at refluxed for 2 hrs. The mixture was cooled to rt and neutralize with saturated *aq*. Na_2CO_3, the mixture was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA=10:1) to afford **XV-3** as a pale yellow solid. (1.5 g, 65% yield). **^{1}HNMR** ($CDCl_3$, 300MHz) δ 8.71 (s, 1 H).

[0466] To a solution of **XV-3** (544 mg, 2 mmol) in 10 mL of DMF was added $BnNH_2$ (268 mg, 2 mmol) at 0°C. The mixture was stirred for 18h at rt. TLC (PE: EA=5:1) analysis showed the reaction completed. The mixture was diluted with water, extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated to give yellow oil. Purification by column chromatography gave **XV-4** as a white solid (400 mg, 58% yield). **MS (ESI)** ***m/z*** $[M+H]^+$ 342.2.

[0467] To a solution of **XV-4** (200 mg, 0.58 mmol, 1 eq.) in 6 mL of AcOH was added Fe powder (131 mg, 2.34 mmol, 4 eq.). The mixture was heated at 70-80°C and stirred for 3 hrs. TLC (PE: EA=5:1) analysis showed the reaction completed. The mixture was cooled down to rt, neutralized with saturated *aq*. K_3PO_4, extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated to give yellow oil. Purification by prep-TLC gave crude **XV-5** (182 mg, 100% crude yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 313.9.

[0468] The mixture of **XV-5** (1.5 g, 4.8 mmol, 1 eq) and 20 mL of formic acid was heated at 100°C for 18 hrs. The reaction mixture was cooled down to rt, neutralized with saturated *aq*. K_3PO_4, extracted with EtOAc (100 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated to give **XV-6** (1.2 g, 82% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 304.0.

[0469] The preparation of **XV-8** followed the similar procedure for obtaining **X-6** (1.1 g, 61% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 465.9.

[0470] **Compound 54** was prepared following the similar procedure for obtaining **Compound 40**. **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.75 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.26-6.90 (m, 10H), 6.55-6.50 (m, 2H), 4.92 (s, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 480.2.

[0471] **Compound 55** was prepared following the similar procedure for obtaining **Compound 40** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in replace of **X-7**. **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.73 (s, 1H), 7.44-7.41 (m, 2H), 7.32-7.19 (m, 6H), 6.92 (s, 1H), 6.73-6.63 (m, 3H), 5.05 (s, 2H), 3.70 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 466.0.

[0472] **XV-11**: A flask was charged with **XV-10**, Pd/C (10% mol) and EtOH. The mixture was stirred for 24 hrs under hydrogen (50 psi). TLC (PE: EA=1:1) analysis showed the reaction completed. The mixture was filtered; the filtrate was concentrated to give a yellow solid. Purification by prep-TLC gave **XV-11**.

[0473] **Compound 56** was prepared from the Pd/C catalytic hydrogenation of **Compound 54**. **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.74 (s, 1H), 8.32 (s, 1H), 8.12-8.09 (m, 2H), 7.73-7.67 (m, 3H), 7.57-7.54 (m, 2H), 7.28-7.23 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 390.0.

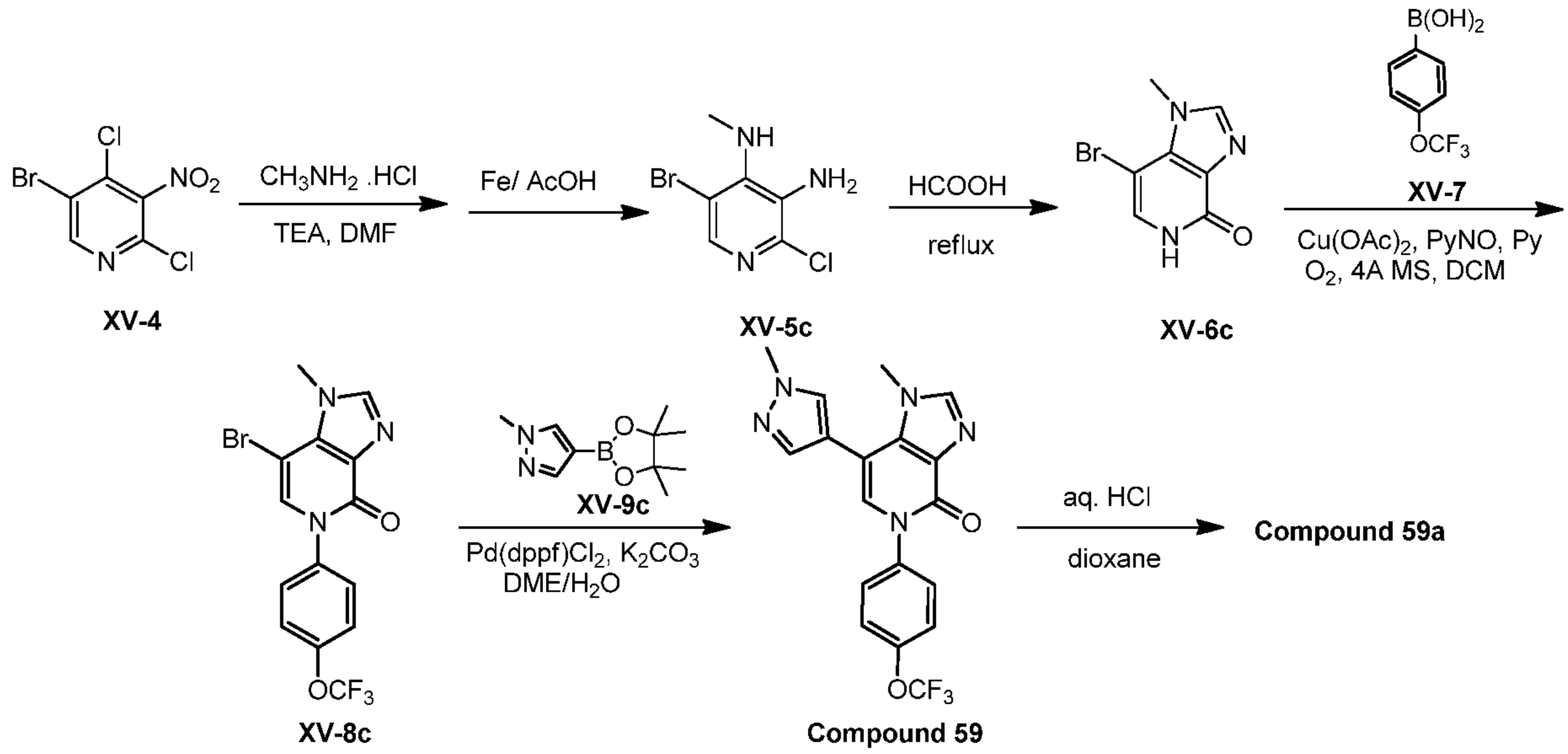
[0474] **Compound 57** was prepared from the catalytic hydrogenation of **Compound 55**. **^{1}H NMR** ($CDCl_3$, 400MHz): δ 12.39 (s, 1H), 8.33 (s, 1H), 8.09 (s, 2H), 7.82 (s, 1H), 7.55 (d, *J*=8.8 Hz, 2H), 7.45-7.41 (m, 2H), 3.99 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 376.0.

[0475] **XV-12**: To a solution of **XV-11** (1 eq.) in DMF was added NaH (1.5 eq.) at 0°C. The mixture was stirred at 0°C for 30 min. After that, MeI (1.5 eq.) was added. The resulting mixture was stirred for 16 hrs at rt. TLC (PE: EA=1:1) analysis showed the reaction completed. The mixture was diluted with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to yield **XV-12**.

[0476] **Compound 58** was prepared by reacting **Compound 56** with NaH in DMF followed by MeI. **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.90-7.75 (m, 3H), 7.56-7.13 (m, 7H), 4.19 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 404.0.

[0477] **Compound 59** was prepared from **Compound 57**. **^{1}H NMR** ($CDCl_3$, 400MHz): δ 8.26 (s, 1H), 7.86 (s, 1H), 7.79 (s, 1H), 7.50 (d, *J*=8.8 Hz, 2H), 7.40-7.33 (m, 3H), 4.17 (s, 3H), 3.97 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 390.1.

Alternative synthesis of Compound 59



[0478] The alternative synthesis of **Compound 59** was performed according to the standard procedure as described herein. HCl salt compound **59a**: **^{1}H NMR** (DMSO-*d*$_6$, 400MHz) δ 8.43 (s, 1H), 7.97 (s, 1H), 7.67 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 3.89 (s, 3H), 3.61 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 390.1.

[0479] **Compound 636** was prepared following a modified synthetic route where **XV-3** was reacted with ethylamine instead of benzy amine, followed by two-step Suzuki-Coupling reactions. Pd-118, K_3PO_4 were used in place of $Pd(dppf)Cl_2$ and K_2CO_3. **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.14 (s, 1H), 7.96 (s, 1H), 7.66 (s, 1H), 7.61 (d, J= 8.4 Hz, 2H), 7.51 (d, J= 8.4 Hz, 2H), 7.26 (s, 1H), 4.01 (q, J= 7.2 Hz, 2H), 3.88 (s, 3H), 1.06 (t, J= 7.2 Hz, 3H).

[0480] **Compound 637** was prepared by Suzuki-Coupling of a modified **XV-5** (where benzyl is replaced by ethyl) with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, followed by reaction with HCOOH. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.2 (s, 1H), 9.17 (s, 1H), 7.96 (s, 1H), 7.63 (s, 1H), 7.19 (s, 1H), 4.04 (q, J=7.2Hz, 2H), 3.91 (s, 3H), 1.11 (t, J=7.2Hz, 3H).

[0481] **Compound 638** was prepared following the same procedure for the synthesis of Compound **637** using the Boc-protected bononic ester. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.41 (s, 1H), 7.94 (s, 2H), 7.38 (s, 1H), 4.16 (q, J=7.2Hz, 2H), 1.28 (t, J=7.2Hz, 3H).

[0482] **Compound 640** was prepared following the same procedure for the synthesis of Compound **636** with a Boc-protected boronic ester in place in the last Suzuki-Coupling reaction. **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 13.07 (brs, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.72 (s, 1H), 7.61 (d, J=8.8 Hz, 2H), 7.51 (d, J=8.8 Hz, 2H), 7.26 (s, 1 H), 3.97 (q, J=7.2 Hz, 2H), 1.02 (t, J=7.2 Hz, 3H). HCl salt **Compound 640a**: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.76 (s, 1H), 7.91 (s, 2H), 7.65 (d, J= 8.8 Hz, 2H), 7.55 (d, J=8.8 Hz, 2H), 7.46 (s, 1H), 4.05 (q, J=6.8Hz, 2H), 1.08 (t, J=6.8Hz, 3H).

[0483] **Compound 641** was prepared by Pd/C hydrogenation (50psi) of **XV-8** in ethanol at 40°C overnight. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.58 (s, 1H), 7.62-7.54 (m, 6H), 6.78 (d, J=7.2Hz, 1H). HCl salt compound **641a**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.01 (s, 1H), 7.68-7.54 (m, 6H), 6.83 (d, J=6.4Hz, 1H).

[0484] **Compound 639** was prepared by Pd/C hydrogenation of a modified **XV-8** (wherein benzyl is replaced by ethyl). **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.14 (s, 1H), 7.55 (m, 5H), 6.83 (d, J=7.6 Hz, 1H), 4.23 (q, J=6.8Hz, 2H), 1.40 (t, J=6.8Hz, 3H). HCl salt **compound 639a**: **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 8.69 (s, 1H), 7.69 (d, J=7.6Hz, 1H), 7.61-7.54 (m, 4H), 6.96 (d, J=7.6Hz, 1H), 4.31 (q, J=7.2Hz, 2H), 1.43 (t, J=7.2Hz, 3H).

[0485] Alternatively, **Compound 639** can be prepared from reacting Compound **641** with NaH followed by reacting with ethyl iodide.

[0486] **Compound 642** was prepared by Suzuki-Coupling of **XV-8** with 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole followed by deprotection of the benzyl group using KOt-Bu in DMSO. **^{1}H NMR** (DMSO-$d6$, 300MHz): δ 8.46 (s, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 7.78 (s, 1H), 7.69 (d, J=8.7 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 4.17 (t, J=7.2 Hz, 2H), 1.41 (t, J=7.2 Hz, 3H).

[0487] **Compound 643** was prepared by Suzuki-Coupling of **XV-8** with 1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole followed by deprotection of the benzyl group using KO*t*-Bu in DMSO. **^{1}H NMR** (DMSO-d_6, 400MHz): δ 13.63 (brs, 1H), 8.46 (s, 1H), 8.30 (s, 1H), 8.12 (s, 1H), 7.77 (s, 1H), 7.67 (d, *J*=8.4 Hz, 2H), 7.57 (d, *J*=8.4 Hz, 2H), 4.52 (m, 2H), 1.44 (d, *J*=6.4 Hz, 6H).

[0488] **Compound 644** was prepared by Suzuki-Coupling of a modified **XV-8** (wherein benzyl is replaced by methyl) with 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using Pd-118 and K_3PO_4 in dioxane/H_2O reluxing for 8h. **^{1}H NMR** (DMSO-d_6, 400MHz): *δ* 8.06 (s, 1 H), 8.00 (s, 1 H), 7.66 (s, 1 H), 7.60 (d, *J*= 8.8 Hz, 2H), 7.51 (d, *J*= 8.8 Hz, 2H), 7.28 (s, 1H), 4.16 (q, *J*= 7.2 Hz, 2H), 3.55 (s, 3H), 1.40 (t, *J*= 8.8 Hz, 3H).

[0489] **Compound 645** was prepared by Suzuki-Coupling of a modified **XV-8** (wherein benzyl is replaced by methyl) with 1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using Pd-118 and K_3PO_4 in dioxane/H_2O reluxing for 8h. **^{1}H NMR** (DMSO-d_6, 400MHz): *δ* 8.04 (d, *J*=7.2 Hz, 2H), 7.65 (s, 1 H), 7.61 (d, *J*=8.8 Hz, 2H), 7.53 (d, *J*=8.8 Hz, 2H) , 7.29 (s, 1H), 4.52 (m, 1 H), 3.55 (s, 3 H), 1.44 (d, *J*=6.8 Hz, 6H).

[0490] **Compound 646** was prepared by Suzuki-Coupling of **XV-8** with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, then KO*t*-Bu deprotecting of the benzyl group, followed by deprotonation with NaH in DMF, then reaction with 1-bromo-2-fluoroethane. **^{1}H NMR** (DMSO-*d6*, 300MHz) δ 8.44 (s, 1H), 8.39 (s, 1H), 8.09 (s, 1H), 7.84 (s, 1H), 7.68 (d, *J*=8.7 Hz, 2H), 7.57 (d, *J*=8.7 Hz, 2H), 4.90 (m, 1H), 4.82 (m, 1H), 4.74 (s, 2H), 3.89 (s, 3H).

[0491] **Compound 665** was prepared by Suzuki-Coupling of **XV-8** with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, then KO*t*-Bu deprotecting of the benzyl group, followed by deprotonation with NaH in DMF, then reacting with MeI. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.43 (s, 1H), 8.30 (s, 1H), 8.08 (s, 1H), 7.78 (s, 1H), 7.64 (d, *J*=8.8 Hz, 2H), 7.55 (d, *J*=8.8 Hz, 2H), 4.05 (s, 3H), 3.88 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 390.1.

[0492] Compound **669** was prepared by reacting 7-bromo-3-ethyl-3H-imidazo[4,5-c]pyridin-4(5H)-one with **XV-7** following the standard copper acetate/pyridine/pyridine-N-oxide catalyzed reaction in DMF at 100°C to form 7-bromo-3-ethyl-5-(4-(trifluoromethoxy)phenyl)-3H-imidazo[4,5-c]pyridin-4(5H)-one, followed by Suzuki-couling with tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate, catalyzed by Pd-118/K_3PO_4 in dioxane/H_2O mixture under reflux condition to provide the final product. **^{1}H NMR** (DMSO-d_6, 400 MHz) *δ* 12.86 (brs, 1H), 8.43 (brs, 1H), 8.36 (s, 1H), 8.17 (brs, 1H), 7.80 (s, 1H), 7.65 (d, *J*=8.4 Hz, 2H), 7.54 (d, *J*=8.4 Hz, 2H), 4.45 (q, *J*=7.2 Hz, 2H), 1.40 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m /z*** $[M+H]^+$ 390.1.

[0493] Compound **670** was prepared by reacting Compound **642** with ethyl iodide with the presence of NaH in DMF solution at rt for 2hrs. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.29 (s, 1H), 7.92 (s, 1H), 7.82 (s, 1H), 7.51 (d, *J*=8.8 Hz, 2H), 7.38 (d, *J*=8.8 Hz, 2H), 7.37 (s, 1H), 4.56 (q, *J*=7.2 Hz, 2H), 4.24 (q, *J*=7.2 Hz, 2H), 1.59-1.51 (m, 6H). **MS (ESI) *m/z*** $[M+H]^+$ 418.1.

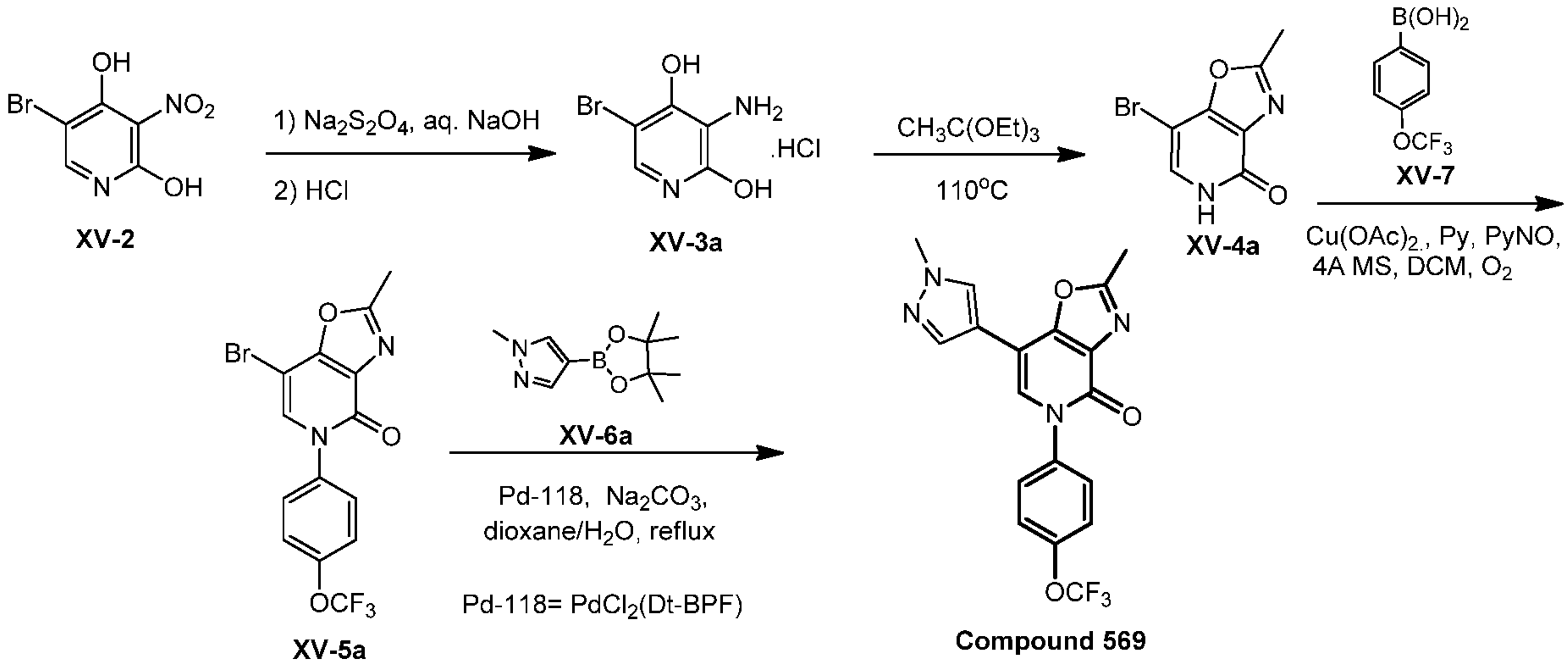
[0494] Compound **671** was prepared by reacting Compound **643** with ethyl iodide in the presence of NaH in DMF solution at rt for 2hrs. **^{1}H NMR** ($CDCl_3$, 300MHz) δ 8.33 (s, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.53 (d, *J*=8.4 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.39 (s, 1H), 4.62-4.55 (m, 3H), 1.60-1.55 (m, 9H). **MS (ESI) *m/z*** $[M+H]^+$ 431.9.

[0495] Compound **673** was prepared by reacting Compound **643** with methyl iodide in the presence of NaH in DMF solution at rt for 2hrs. **^{1}H NMR** ($CDCl_3$, 300MHz): δ 8.29 (s, 1H), 7.84 (d, *J*=10.0 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.49 (d, *J*=9.2 Hz, 2H), 7.38-7.34 (m, 3H), 4.57 - 4.52 (m, 1H), 4.16 (s, 3H), 1.47 (s, 3H), 1.45 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 418.1.

[0496] Compound **672** was prepared by reacting **XV-8** with tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate catalyzed by Pd-118/K_3PO_4 in dioxane/H_2O mixture under reflux condition overnight, followed by removal of the benzyl protecting group using t-BuOK in DMSO/THF at rt for 1h under oxygen atmosphere. **MS (ESI) *m/z*** $[M+H]^+$ 361.9. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 13.66 (brs, 1H), 12.87 (brs, 1H), 8.45 (brs, 1H), 8.31 (brs, 1H), 8.19 (brs., 1H), 7.79 (brs, 1H), 7.66 (d, *J*=8.5Hz, 2H), 7.54 (d, *J*=8.5Hz, 2H).

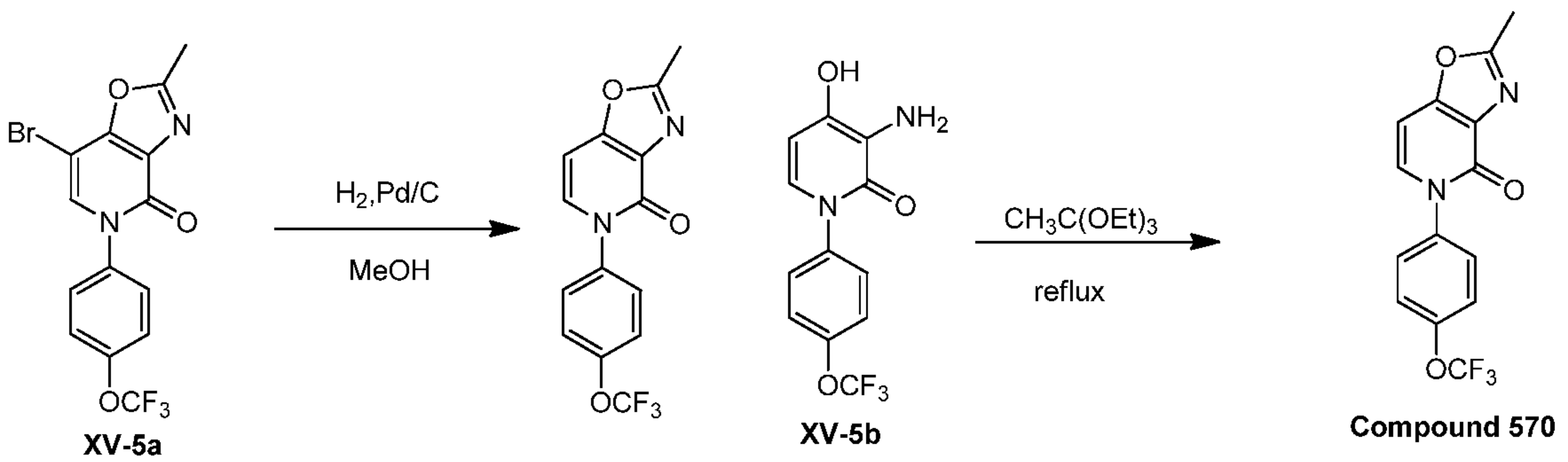
[0497] Compound **674** was prepared by reacting 7-bromo-1,2-dimethyl-1H-imidazo[4,5-c]pyridin-4(5H)-one with **XV-7** following the standard copper acetate/pyridine/pyridine-N-oxide catalyzed reaction in DMF at 100°C to form 7-bromo-1,2-dimethyl-5-(4-(trifluoromethoxy)phenyl)-1H-imidazo[4,5-c]pyridin-4(5H)-one; followed by Suzuki-couling with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, catalyzed by Pd-118/K_3PO_4 in dioxane/H_2O mixture under reflux condition to provide the final product. **^{1}H NMR** (DMSO-d_6, 300MHz): δ 7.56 (s, 1H), 7.51 - 7.45 (m, 3H), 7.31 (d, *J*=8.3 Hz, 2H), 6.99 (s, 1H), 3.99 (s, 3H), 3.44 (s, 3H), 2.55 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 404.1.

[0498] Compound **675** was prepared following the similar procedure for the synthesis of Compound **674** using tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 13.07 (brs, 1H), 7.98 (brs, 1H), 7.69 (brs, 1H), 7.59 (d, *J*=8.0Hz, 2H), 7.50 (d, *J*=8.0Hz, 2H), 7.21 (s, 1H), 3.40 (s, 3H), 2.45 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 390.0.



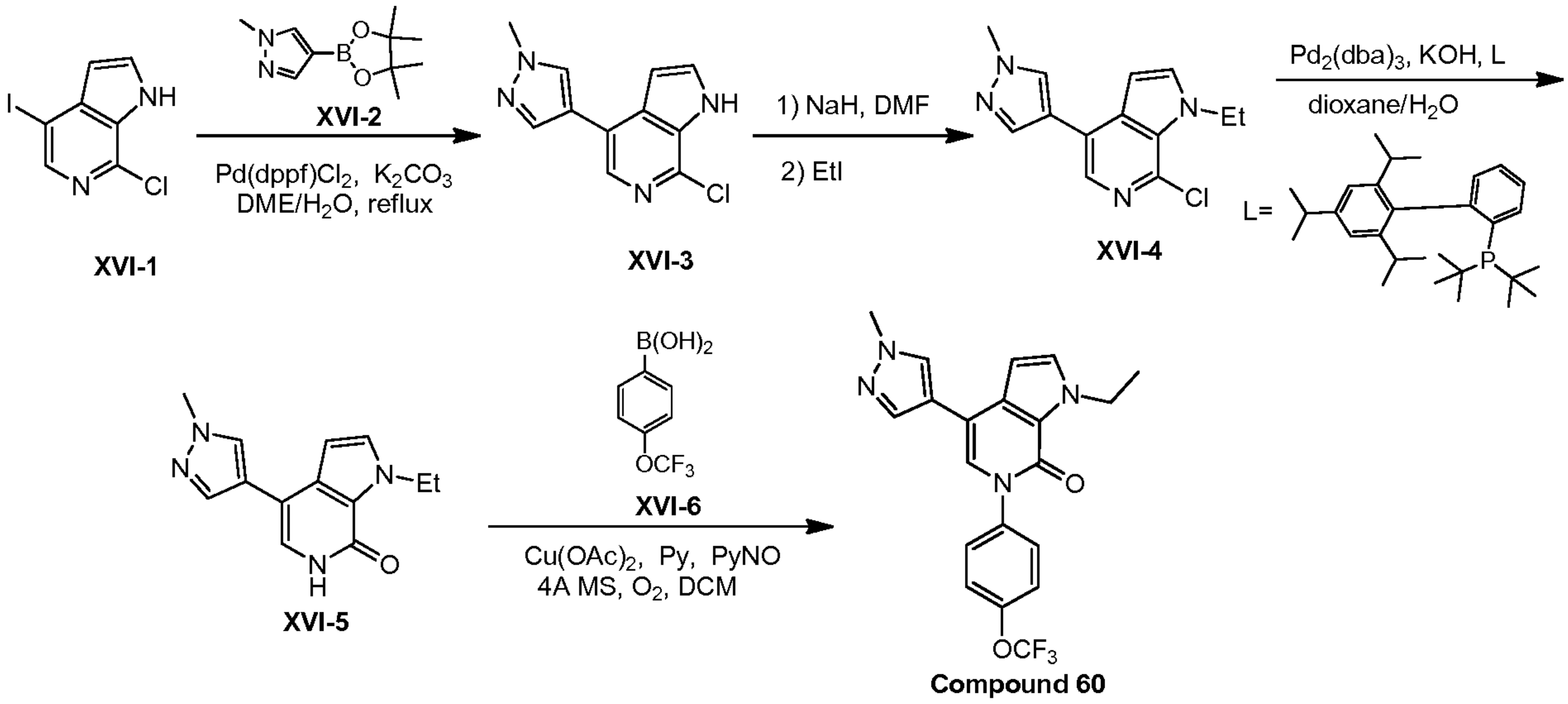
[0499] **XV-4a** was obtained in two steps from **XV-2** following the similar procedure described in the synthesis of **XIV-7b** and **XIV-8b**. **XV-5**a was obtained by Suzuki-Coupling of **XV-4a** and **XV-7** using the standard procedure described herein.

[0500] **Compound 569** was obtained by Suzuki-Coupling of **XV-5a** and **XV-6a** following the similar procedure described in the synthesis of **Compound 209**. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.83 (s, 1H), 7.79 (s, 1H), 7.52-7.47 (m, 3H), 7.40 (d, *J*=8.7Hz, 2H), 4.01 (s, 3H), 2.73 (s, 3H).



[0501] To a solution of **XV-5a** (150 mg, 0.39 mol) in MeOH (10 mL) was added Pd/C (20 mg), the mixture was stirred at rt under H_2 overnight. After completion of the reaction indicated by TLC (EA:PE=1:1), the mixture was filtered, the filtrate was concentrated in vacuo to afford a mixture of Compound **570** and **XV-5b**. The mixture were added into $CH_3C(OEt)_3$ (10 mL). The mixture was heated at reflux overnight. After cooling to rt, the mixture was filtered, the cake was collected and purified by prep-TLC (EA:PE=1:1) to give **Compound 570** (50 mg, 41% yield). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 7.77 (d, *J*=7.5 Hz, 1H), 7.60-7.52 (m, 4H), 6.94 (d, *J*=7.2 Hz, 1H), 2.59 (s, 3H).

Example 5-I
Synthesis of Compounds 60-63 (Scheme XVI)



[0502] **XVI-3** was prepared following the similar procedure for obtaining **XIII-7**. **MS (ESI)** ***m/z*** $(M+H)^+$ 233.0.

[0503] **XVI-4** was prepared following the similar procedure for obtaining **XV-12**, using ethyl iodide in place of methyl iodide. **MS (ESI)** ***m/z*** $(M+H)^+$ 261.1.

[0504] **XVI-5**: A flask was charged with **XVI-4** (150 mg, 0.57 mmol, 1 eq.), $Pd_2(dba)_3$ (285 mg, 0.46 mmol, 0.8 eq.), KOH (383 mg, 6.84 mmol, 12 eq.), Ligand (252 mg, 0.57 mmol, 1 eq.), 10 mL of dioxane and 10 mL of H_2O, flushed with nitrogen for three times. The mixture was heated at 100°C for 10 hrs. LCMS analysis showed the reaction completed. The mixture was cooled down to rt, diluted with water, extracted with ethyl acetate (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated and concentrated. Purification by prep-TLC gave **XVI-5** (130 mg, yield 72%). **MS (ESI)** ***m/z*** $(M+H)^+$ 243.1.

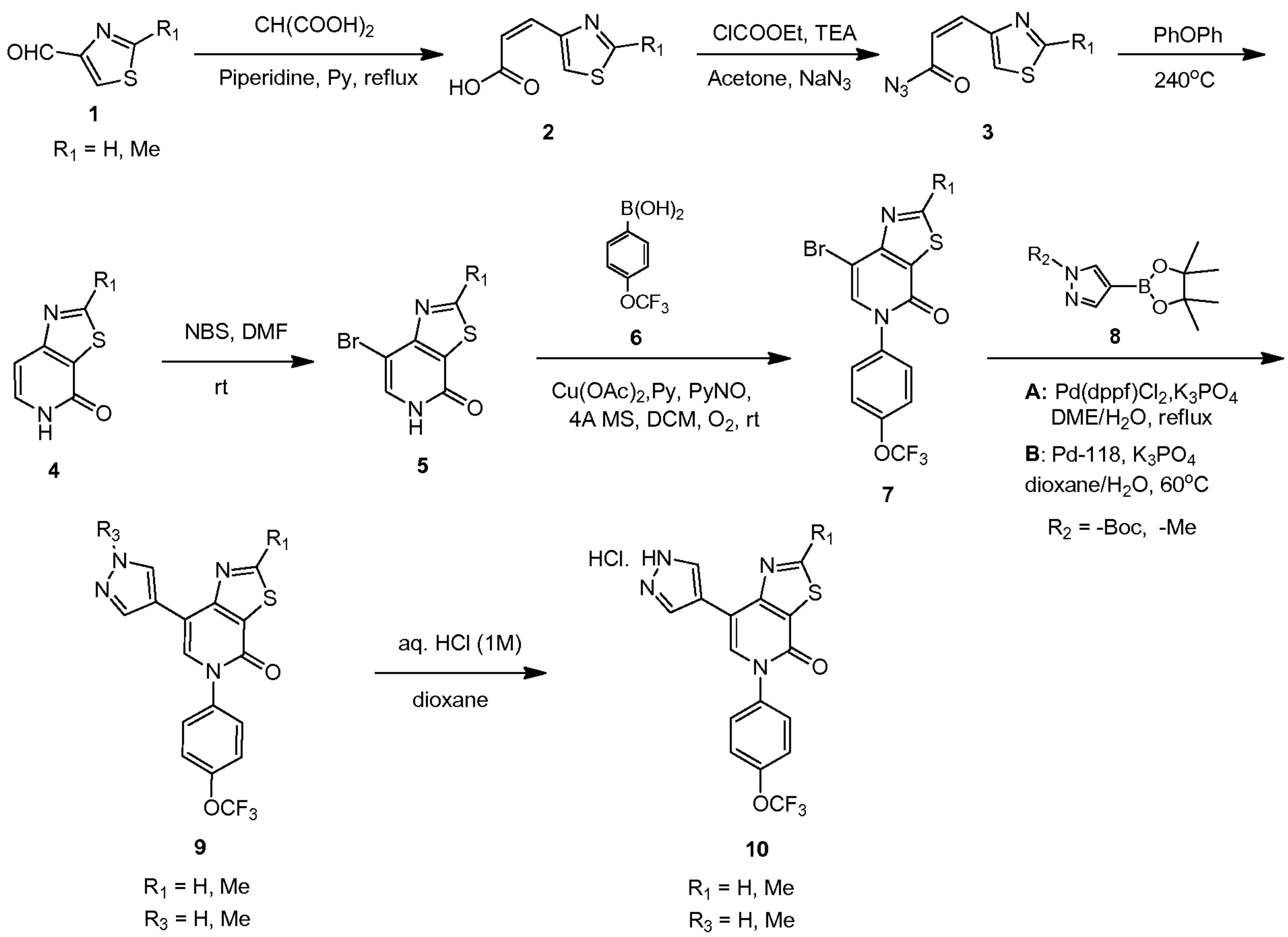
[0505] **Compound 60** was prepared following the similar procedure for obtaining **X-6**. ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.71 (s, 1H), 7.60 (s, 1H), 7.50 (d, *J*=8.4 Hz, 2H), 7.34 (d, *J*=8.4 Hz, 2H), 7.18 (d, *J*=2.8 Hz, 1H), 7.04 (s, 1H), 6.47 (d, *J*=2.8 Hz, 1H), 4.61 (q, *J*=7.2 Hz, 2H), 3.97 (s, 3H), 1.48 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 403.1.

[0506] **Compound 61** was prepared following the similar procedure for obtaining **XII-7** using (4-ethoxy-2-methylphenyl)boronic acid in place of **XII-6**. ^{1}**H NMR** ($CDCl_3$, 300 MHz) *δ* 9.03 (d, *J* = 2.0 Hz, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 7.73 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.89-6.84 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.18 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 359.9.

[0507] **Compound 62** was prepared from **Compound 61** following the similar procedure for obtaining **Compound 46**. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.93 (d, J = 2.0 Hz, 1H), 8.90 (d, J = 2.0 Hz, 1H), 7.57-7.54 (m, 2H), 7.43 (s, 1H), 7.22-7.14 (m, 3H), 6.90-6.84 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 2.22 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 376.0.

[0508] **Compound 63** was prepared from **Compound 61** following the similar procedure for obtaining **Compound 47**. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.93 (d, J = 2.0 Hz, 1H), 8.90 (d, J = 2.0 Hz, 1H), 8.14 (s, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.90-6.85 (m, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 2.19 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 362.0.

Example 5-J
Synthesis of Compounds 582-584 and 586-587



[0509] A flask was charged with compound **1** (3.0 g, 1 eq.), malonic acid (1.2 eq.), pyridine (20 mL), peperidine (1.56 mL). The mixture was stirred under nitrogen atmosphere at 90°C for 2h, cooled, concentrated under reduced pressue, the residue was diluted with water and adjusted pH=~5 by adding aq. HCl, the resulting solid was filtered and washed with water, the solid was dried in vacuo to give compound **2**.

[0510] ClCOOEt (1.2 eq) was added into the solution of compound **2** (1.0 g, 1.0 eq.) and TEA (1.3 eq) in 20 mL of acetone by dropwise at 0°C. The mixture was stirred at 0°C for 1h. The resulting mixture was added into the solution of sodium azide (4 eq.) in 30 mL of acetone and water (v/v=1:1) at 0°C and stirred for 30 mins. The mixture was diluted with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford compound **3**.

[0511] Compound **3** was added into 10 mL of oxydibenzene. The mixture was stirred at 240°C for 2h,cooled the mixture to rt and stirred overnight, filtered the resulting brown solid and washed with EtOAc to give compound **4** as a pale-brown solid.

[0512] A suspension of **4** (1 eq.), N-bromosuccinimide (1.1 eq.) and 50 mL of DMF was stirred at rt for 4h. The mixture was filtered; the solids were washed successively with small amounts of DCM and dried to give compound **5** as a brown solid.

[0513] Compound **7** was prepared from reacting compound **5** with compound **6** using Method **1** as described herein.

[0514] Compound **9** was prepared by Suzuki-coupling of Compound **7** with the corresponding boronic ester **8** using the standard procedure A or B described herein.

[0515] **Compound 582** was prepared following procedure A. **^{1}H NMR** (DMSO-d_6, 300MHz) δ 12.96 (s, 1H), 9.73 (s, 1H), 8.42 (s, 1H), 8.18 (s, 1H), 8.13 (s, 1H), 7.73 (d, *J*=8.7Hz, 2H), 7.58 (d, *J*=8.7Hz, 2H). **MS (ESI) *m/z*** $(M+H)^+$ 378.9.

[0516] **Compound 583** was prepared following procedure A. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 9.72 (s, 1H), 8.40 (s, 1H), 8.10 (d, *J*=9.6Hz, 2H), 7.72 (d, *J* =8.8Hz, 2H), 7.58 (d, *J*=8.4Hz, 2H), 3.89 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 393.0.

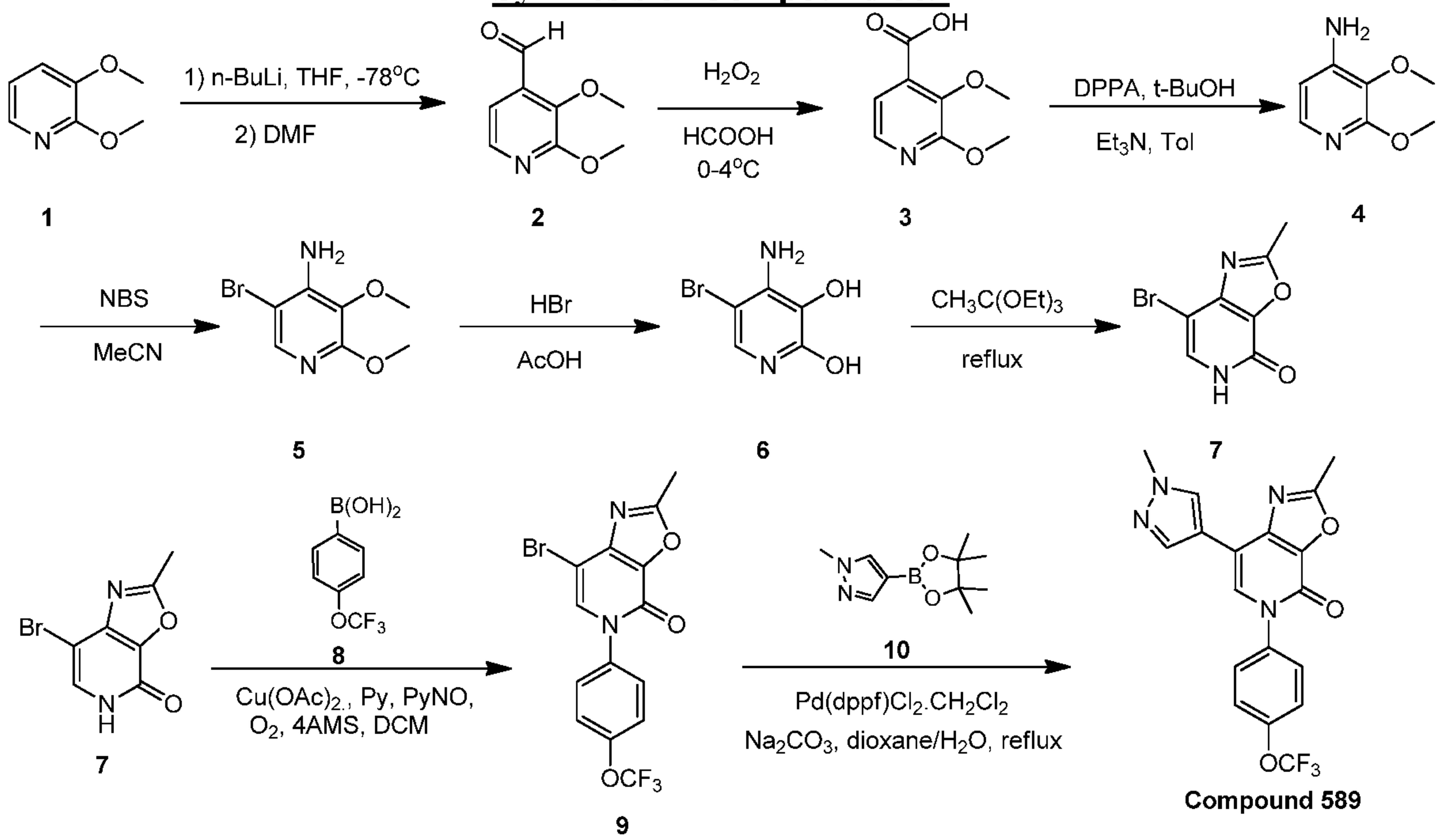
[0517] **Compound 584** was prepared following procedure B. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.18 (s, 1H), 7.80 (s, 1H), 7.52 (d, *J*=9.2Hz, 3H), 7.38 (d, *J*=8.4Hz, 2H), 3.98 (s, 3H), 2.91 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 407.0.

[0518] **Compound 586** was prepared following procedure A. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.51 (s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 7.70 (d, *J*=8.8Hz, 2H), 7.57 (d, *J*=8.4Hz, 2H), 7.35-7.24 (m, 5H), 5.39 (s, 2H), 2.90 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 483.0.

[0519] **Compound 587** was prepared following procedure B. **^{1}H NMR** (DMSO-d_6, 300MHz) δ 12.94 (s, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 8.08 (s, 1H), 7.71 (d, *J*=8.7Hz, 2H), 7.58 (d, *J*=8.7Hz, 2H), 2.91 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 392.7.

[0520] **Compound 585** was prepared by Suzuki-Coupling of 2-methylthiazolo[5,4-c]pyridin-4(5H)-one with (4-(trifluoromethoxy)phenyl)boronic acid using the same method described in the synthesis of Compound **7**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.76 (d, J=7.2Hz, 1H), 7.65 (d, J=9.2Hz, 2H), 7.55 (d, J=8.8Hz, 2H), 6.96 (d, J=7.2Hz, 1H), 2.84 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 326.8.

Example 5-K
Synthesis of Compound 589



[0521] To a solution of compound **1** (5 g, 36 mmol) in THF (50 mL) was added n-BuLi (2.5 M in hexane, 31.5 mL, 79 mmol) at -78°C, then the mixture was stirred at 0°C for 1h. DMF (12 mL, 157.5 mmol) was added at -78°C, and then the mixture was stirred at 0°C for additional 1h. After completion of the reaction, the mixture was quenched with saturated aq. NH_4Cl. The mixture was concentrated in vacuo, the residue was partitioned between H_2O and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (PE:EA=4:1) to afford compound **2** (1.5 g, 25% yield).

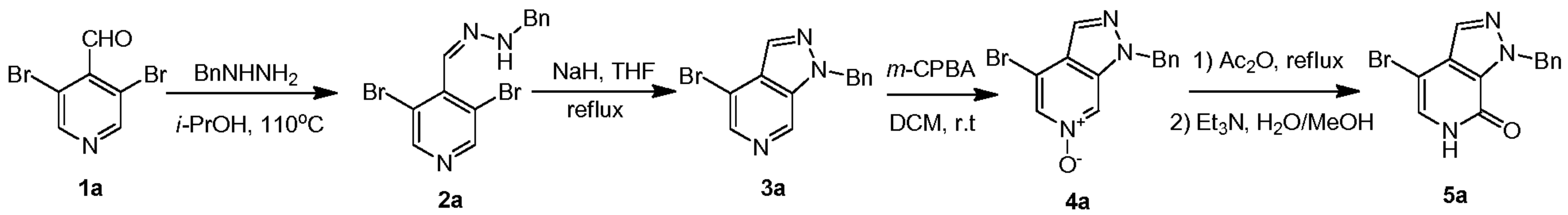
[0522] To a solution of compound **2** (1.5 g, 9.0 mmol) in HCOOH (20 mL) was added H_2O_2 (3.1g, 27 mmol) at 0~4°C. The mixture was stirred at rt overnight. After completion of the reaction, the mixture was quenched with aq. $NaHSO_3$. The mixture was concentrated in vacuo, the residue was partitioned between H_2O and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (PE:EA=1:1) to afford compound **3** (1.5 g, 94% yield).

[0523] To a solution of compound **3** (1.5 g, 8.2 mmol) in toluene (20 mL) was added Et_3N (2.1 g, 20.5 mmol), 4Å molecular sieve (3.0 g). The mixture was purged with nitrogen for three times and then heated to reflux under nitrogen for 0.5h. Then t-BuOH (0.73 g, 9.8 mmol), DPPA (2.4 g, 8.6 mmol) were added in turn. The mixture was stirred at reflux overnight. After cooling to rt, the mixture was filtered, the filtrate was partitioned between H_2O and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (PE:EA=3:1) to afford compound **4** (500 mg, 42% yield).

[0524] Compound **6** was prepared by bromination of compound **4** using NBS followed by HBr hydrolysis. A mixture of comgpound **6** (300 g, 1.5 mmol) in $CH_3C(OEt)_3$ (10 mL) was refluxed overnight. After cooling to rt, the mixture was filtered, the cake was washed with EA/PE (v/v=1/1) to give compound **7** (150 mg, 44% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 230.8.

[0525] **Compound 589** was prepared from compound **7** by two Suzuki coupling steps as indicated in the scheme above. **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.32 (s, 1H), 8.05 (d, J=4.5 Hz, 2H), 7.68 (d, J=8.7 Hz, 2H), 7.59 (d, J=8.7 Hz, 2H), 3.88 (s, 3H), 2.71 (s, 3H).

[0526] Preparation of **Compound 588:**



[0527] The mixture of compound **1a** (16 g, 60.4 mmol, 1 eq.), $BnNHNH_2$ (15 g, 129.3 mmol, 2 eq.) in 100 mL of *i*-PrOH was sealed and heated by microwave at 110°C for 20 min. TLC analysis (PE/EA=5/1) showed the reaction completed. The mixture was cooled to rt. The precipitate was filtered and washed with cool *i*-PrOH to give a light yellow solid Compound **2a**. (16.5 g, 74% yield).

[0528] Compound **2a** (12 g, 32.5 mmol, 1 eq.) was dissolved in 1200 mL of THF, treated with NaH (60% dispersion in mineral oil, 1.56 g, 39.02 mmol, 1.2 eq.). The mixture was heated to reflux for 2h. The mixture was cooled down to rt. The reaction was quenched with water slowly, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give brown oil. Purification by column (PE/EA =20/1~5/1) gave compound **3a** (5.5 g, yield 59%).

[0529] To a solution of compound **3a** (5.5 g, 19.1 mmol, 1 eq.) in 100 mL of DCM was added m-CPBA (6.5 g, 38.2 mmol, 2 eq.). The mixture was stirred for 18h at rt. The reaction was diluted with water, extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give brown oil. Purification by column (PE/EA =5/1~1/1) gave compound **4a** (5.2 g, yield 89%).

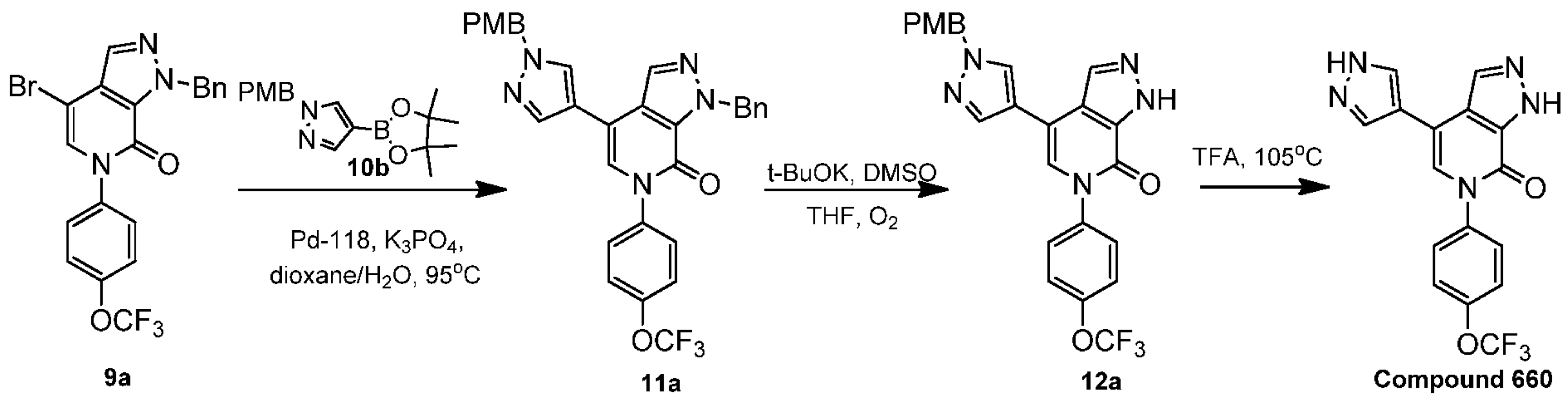
[0530] The solution of compound **4a** (4 g, 13.1 mmol, 1 eq.) in 70 mL of Ac_2O was heated to reflux for 18h. All the volatiles were removed under vacuo. The residue was diluted with MeOH and adjusted pH=7-8 with Et_3N. The mixture was stirred for 4h at rt. The reaction was diluted with water, extracted with EtOAc (150 mLx3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give brown oil. Purification by column chrom (PE/EA =5/1~1/1) gave compound **5a** (0.6 g, yield 15%). **MS (ESI)** ***m/z*** $(M+H)^+$ 305.9.

[0531] **Compound 588** was prepared from compound **5a** in three steps by Suzuki coupling with compound **8** followed by Suzuki coupling with compound **10**, then deprotection of the benzyl group using KO*t*-Bu in DMSO. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 14.37 (s, 1H), 8.33 (s, 1H), 8.28 (s, 1H), 7.94 (s, 1H), 7.68 (d, *J*=8.4 Hz, 2H), 7.57-7.51 (m, 3H), 3.88 (s, 3H).

[0532] HCl salt **Comound 588a**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.38 (s, 1H), 8.28 (s, 1H), 7.94 (s, 1H), 7.69 (d, *J*=8.8 Hz, 2H), 7.57 (d, *J*=8.8 Hz, 2H), 7.50 (s, 1H), 3.88 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 376.0.

[0533] **Compounds 657** and **658** were prepared by reacting Compound **588** with ethyl iodide and NaH in DMF. **Compound 657**: **^{1}H NMR** (DMSO-d_6, 400MHz): δ 8.62 (s, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 7.64 (d, *J*=8.8 Hz, 2H), 7.55 (d, *J*=8.8 Hz, 2H), 7.42 (s, 1H), 4.44 (q, *J*=7.2 Hz, 2H), 3.88 (s, 3H), 1.53 (t, *J*=7.2 Hz, 3H). **Compound 658**: **^{1}H NMR** (DMSO-d_6, 400MHz): δ 8.27 (s, 1H), 8.26 (s, 1H), 7.92 (s, 1H), 7.68 (d, *J*=8.8 Hz, 2H), 7.55 (d, *J*=8.8 Hz, 2H), 7.51 (s, 1H), 4.72 (q, *J*=6.8 Hz, 2H), 3.88 (s, 3H), 1.40 (t, *J*=6.8 Hz, 3H).

[0534] Preparation of **Compound 660**:



[0535] To a solution of compound **9a** (1.8 g, 3.88 mmol, 1 eq.) in dioxane/H_2O (72 mL, v/v=5/1) was added K_3PO_4 (1.6 g, 7.76 mmol, 2 eq.), compound **10b** (1.47 g, 4.66 mmol, 1.2 eq.), Pd-118 (125 mg, 0.19 mmol, 0.05 eq.). The mixture was purged with nitrogen and then heated at 95°C for 8 hrs. The mixture was cooled to rt, diluted with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in* *vacuo*. The residue was purified by column chromatography (PE/EA=1/1) to give **11a** as white solid (1.3 g, 59% yield).

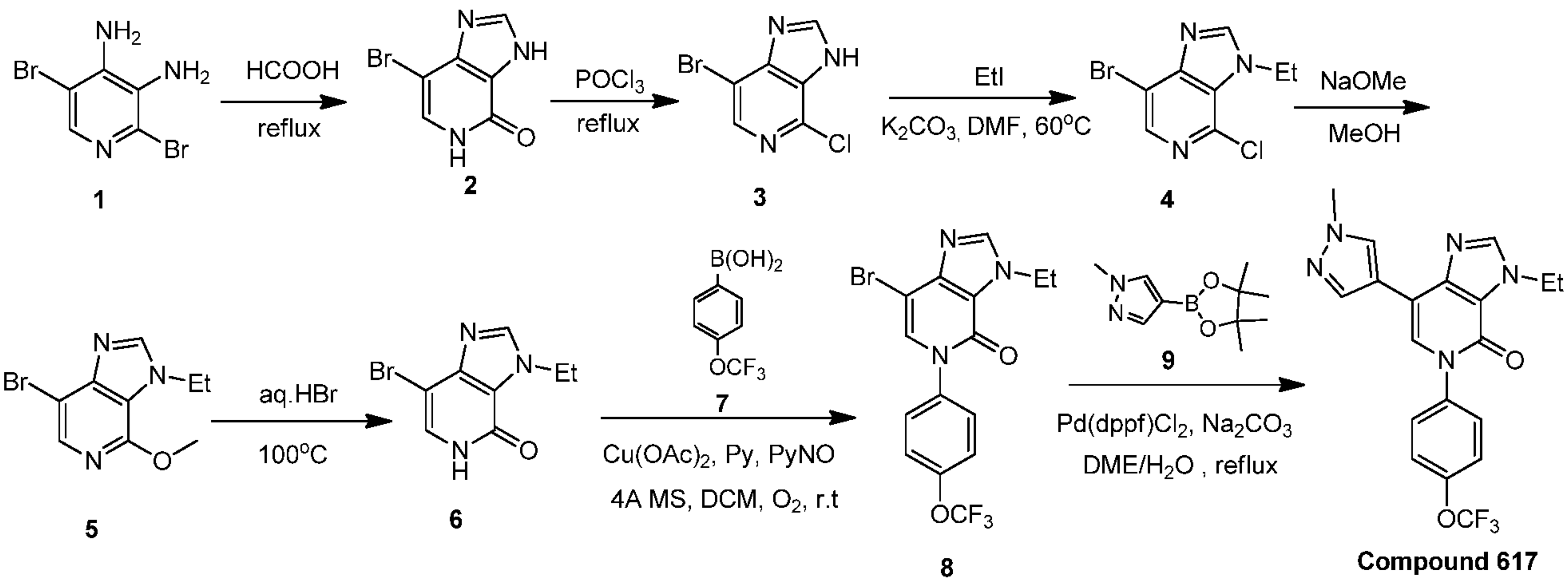
[0536] To a solution of compound **11a** (1.3 g, 2.27 mmol, 1 eq.), DMSO (1.77 g, 22.76 mmol, 10 eq.) in THF (75 mL) was added *t*-BuOK (5.1 g, 45.4 mmol, 20 eq.) at 0°C. The mixture was stirred under oxygen atmosphere at rt for 3h. The reaction was quenched with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EA=1/3) to give crude compound **12a** (1.1 g, 100% yield).

[0537] The solution of compound **12a** (320 mg, 0.66 mmol, 1 eq.) in TFA (5 mL) was heated at 105°C for 3hrs. The mixture was cooled to rt. All the volatiles were removed under reduced pressure. The residue was neutralized with saturated *aq*. $NaHCO_3$, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give brown oil. Purification by column chromatography gave **Compound 660** (180 mg, 75% yield). **^{1}H NMR** (DMSO-d_6, 400MHz): δ 14.27 (brs, 1H), 13.00 (brs, 1H), 8.38 (brs, 1H), 8.25 (brs, 1H), 8.01 (brs, 1H), 7.67 (d, *J*=8.4 Hz, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.50 (s, 1H). **MS (ESI) *m/z*** $(M+Na)^+$ 383.9.

[0538] **Compounds 659** and **661** were prepared by reacting compound **12a** with ethyl iodide and NaH in DMF, separating the two intermediates and then treating each with TFA to affored the final products. **Compound 659**: **^{1}H NMR** (DMSO-d_6, 400MHz): δ 13.01 (brs, 1H), 8.65 (s, 1H), 8.09 (brs, 2H), 7.63 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 2H), 7.43 (s, 1H), 4.43 (q, *J*=7.2 Hz, 2H), 1.51 (t, *J*=7.2 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 389.9. **Compound 661**: **^{1}H NMR** (DMSO-d_6, 400MHz): δ 13.04 (br, 1H), 8.30 (s, 1H), 8.27-8.14 (br, 2H), 7.68 (d, *J*=8.4 Hz, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.53 (s, 1H), 4.72 (q, *J*=7.2 Hz, 2H), 1.40 (t, *J*=7.2 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 389.9.

[0539] Compound **689** was prepared by reacting compound **9a** with (4-fluorophenyl)boronic acid catalyzed by Pd-118/K_3PO_4 in dioxane/H_2O at 90°C, followed by *t*-BuOK deprotecting benzyl group to afford the final product. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.08 (s, 1H), 7.59 - 7.52 (m, 4H), 7.39 (d, J=8.4 Hz, 2H), 7.19 (t, J=8.4 Hz, 2H), 7.08 (s, 1H). **MS (ESI) *m/z*** $[M+H]^+$ 390.0.

Example 5-L
Synthesis of Compound 617



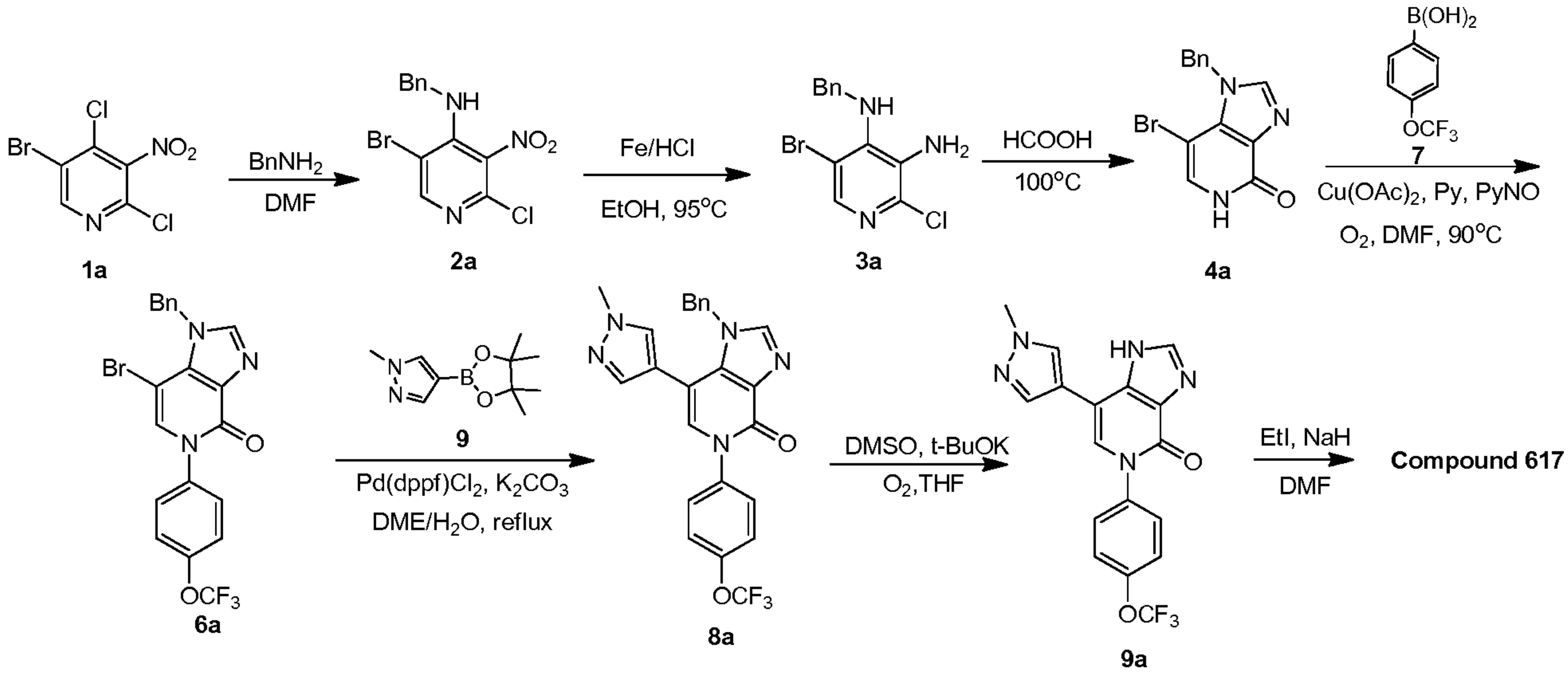
[0540] To a solution of compound **1** (10 g, 37.8 mmol) was added 20 mL of HCOOH. The mixture was refluxed overnight. The mixture was concentrated, purified by column chromatography on silica gel (DCM: MeOH=5:1) to give compound **2** (8 g, yield 99%).

[0541] A mixture of compound **2** (8.0 g, 37.4 mmol) in $POCl_3$ (10 mL) was refluxed for 3h. Cooled down to rt. Then poured into water slowly, adjusted pH=7~8 with saturated aq. $NaHCO_3$, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EA=2:1 to 1:1) to give compound **3** (4.57 g, 53% yield).

[0542] Compounds **4-8** were prepared following the similar procedures described in Example 5-F.

[0543] **Compound 617** was prepared by Suzuki-Coupling of compound **8** with compound **9** following the standard procedure described herein as a white solid.

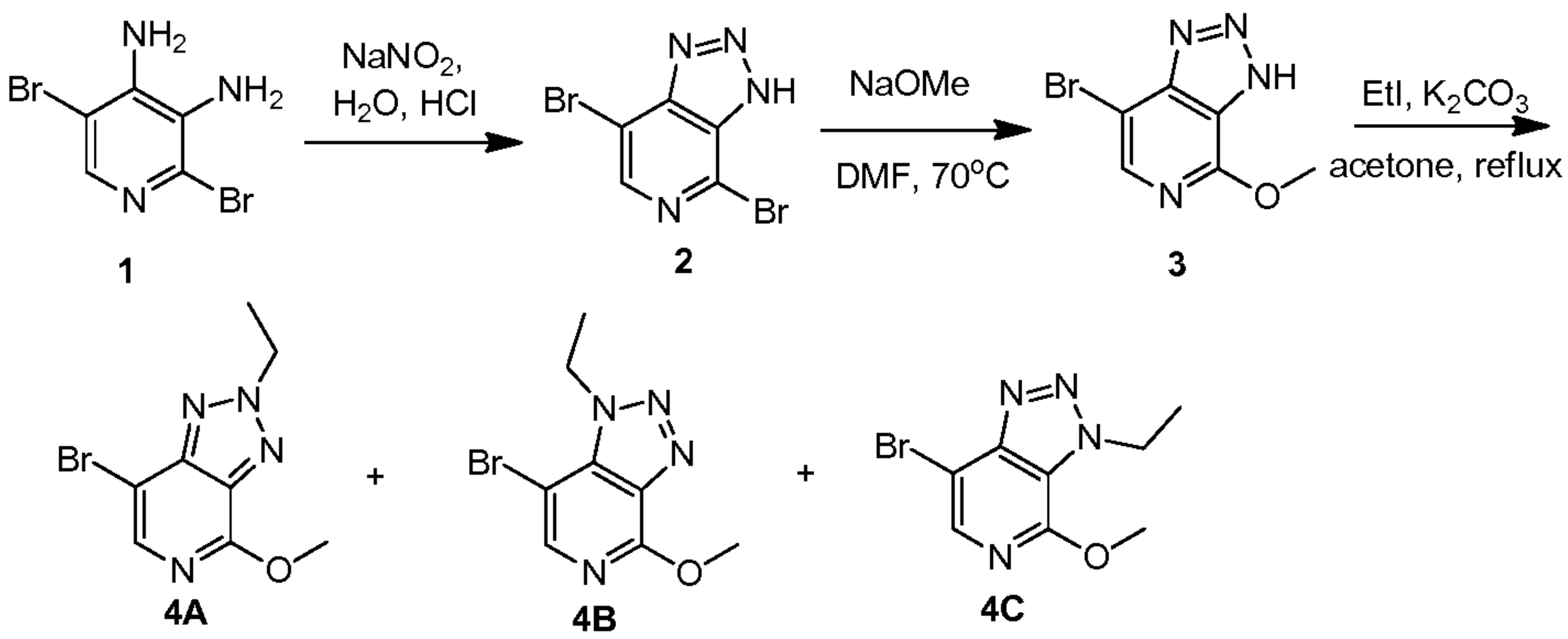
Alternative Synthesis of Compound 617

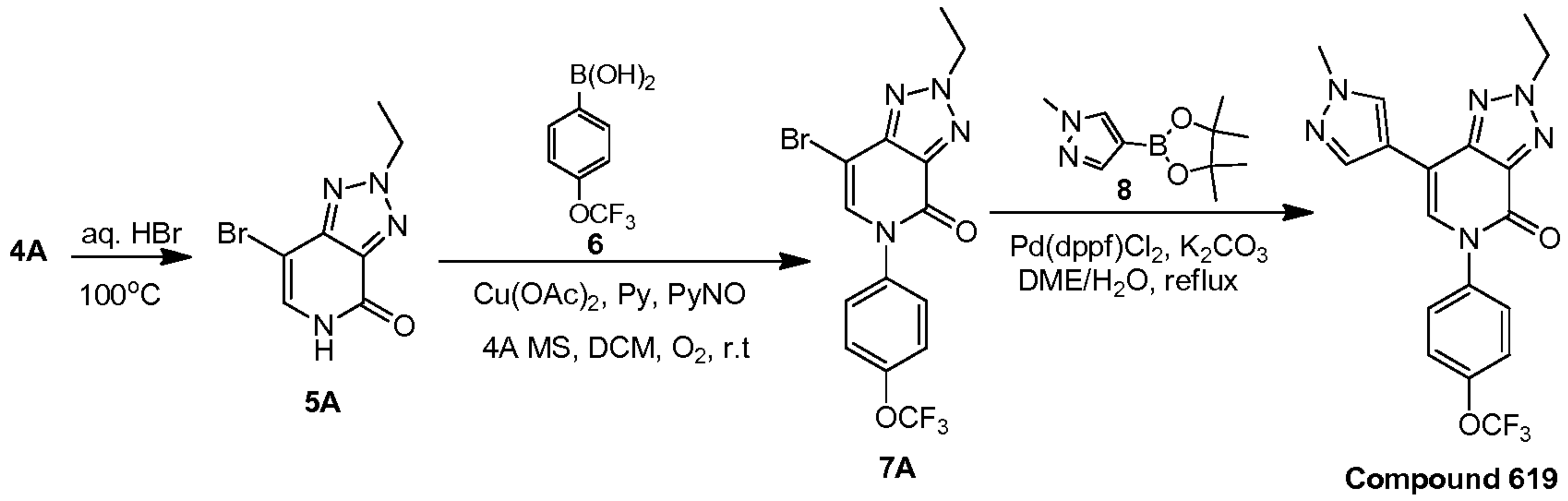


[0544] The detailed synthetic procedure for the alternative synthesis of Compound **617** has been described herein. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.41 (s, 1H), 8.36 (s, 1H), 8.06 (s, 1H), 7.78 (s, 1H), 7.65 (d, J=8.8Hz, 2H), 7.54 (d, J=8.8Hz, 2H), 4.45 (q, J=7.2Hz, 2H), 3.86 (s, 3H), 1.40 (t, J=7.2Hz, 3H).

[0545] **Compound 618** was prepared by Suzuki-Coupling of compound **6** with compound **9**, followed by HBr acid hydrolysis. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.20 (d, J.= 6.4 Hz, 1H), 7.93 (s, 1H), 7.38 (s, 1H), 4.56 (d, J.= 7.2Hz, 2H), 3.95 (s, 3H) ,1.53 (t, J.= 7.2Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 244.1.

Example 5-M
Synthesis of Compound 619





[0546] A solution of $NaNO_2$ (7.8 g, 113.3 mmol) in water (30 mL) was added dropwise into a solution of compound **1** (20 g, 75.5 mmol) in 2N hydrochloric acid (100 mL) at 0°C, and stirred for 1h at 0°C. The precipitate was filtered and wash with ice-water and dried in vacuum to afford compound **2** (17 g, 82% yield) as a yellow brown solid.

[0547] Compounds **3**, **4A-4C**, **5A**, and **7A** were prepared following the similar procedures described in Example 5-F.

[0548] **Compound 619** was prepared by Suzuki-Coupling of compound **7a** with compound **8** following the standard procedure described herein. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.08 (s, 1H), 7.84 (s, 1H), 7.52 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 3H), 4.78 (q, *J*=6.8 Hz, 2H), 3.99 (s, 3H), 1.74 (t, *J*=6.8 Hz, 3H).

[0549] **Compound 620** was prepared following the similar procedure described in the synthesis of Compound **619** using the Boc-protected boronic ester in place of comound **8**. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 12.99 (s, 1H), 8.34 (s, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.65-7.69 (m, 2H), 7.57 (d, *J*=8.4 Hz, 2H), 4.79 (q, *J*=7.2 Hz, 2H), 1.63 (t, *J*=7.2 Hz, 3H).

[0550] **Compound 624** was prepared from compound **4B** following the general procedure described above. **^{1}HNMR** (DMSO-d_6, 400 MHz) δ 8.01 (s, 1H), 7.71 (s, 1H), 7.67-7.65 (m, 2H), 7.55-7.53 (m, 3H), 4.42 (q, *J*=7.2Hz, 2H), 3.90 (s, 3H), 1.20 (t, *J*=7.2Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 405.1.

[0551] **Compound 633** was prepared from compound **4B** following the general procedure described above to form an intermediate compound **7B** followed by Pd/C hydrogenation to affored the final product. **^{1}HNMR** ($CDCl_3$, 400MHz) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.37-7.33 (m, 3H), 6.50 (d, *J*=7.2 Hz, 1H), 4.60 (q, *J*=7.2 Hz, 2H), 1.64 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 324.9.

[0552] **Compound 625** was prepared from compound **4C** following the general procedure described above. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.47 (s, 1H), 8.13 (s, 1H), 7.90 (s, 1H), 7.71-7.69 (m, 2H), 7.59 (d, *J*=8.4Hz, 2H), 4.86 (q, *J*=7.2Hz, 2H), 3.91 (s, 3H), 1.52 (t, *J*=7.2Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 405.1.

[0553] **Compound 630** was prepared from compound **4C** following the general procedure described above to form an intermediate compound **7C** followed by Pd/C hydrogenation to affored the final product. **^{1}HNMR** ($CDCl_3$, 400MHz) δ 7.46 (d, *J*=8.8 Hz, 2H),7.38 (d, *J*=8.8 Hz, 2H), 7.19 (d, *J*=7.2 Hz, 1H), 6.93 (d, *J*=7.2 Hz, 1H), 4.92 (q, *J*=7.2 Hz, 2H), 1.63 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 325.1.

[0554] **Compound 634** was prepared by Suzuki-Coupling of compound **7C** with tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate using Pd-118, K_3PO_4 in dioxane/H_2O. **^{1}HNMR** (DMSO-d_6, 400MHz) δ 13.1 (s, 1H), 8.47 (s, 1H), 8.23 (s, 1H), 7.93 (s, 1H), 7.71 (d, *J*=8.8 Hz, 2H), 7.59 (d, *J*=8.8 Hz, 2H), 4.86 (q, *J*=7.2 Hz, 2H), 1.53 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 391.1.

[0555] HCl salt compound **634a**: **^{1}HNMR** (DMSO-d_6, 400MHz) δ 8.36 (s, 2H), 7.93 (s, 1H), 7.70 (d, *J*=8.4 Hz, 2H), 7.59 (d, *J*=8.4 Hz, 2H), 4.86 (q, *J*=7.2 Hz, 2H), 1.53 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]_+$ 391.0.

[0556] **Compound 621** was prepared by Suzuki-Coupling of compound **4C** with compound **8** followed by HBr hydrolysis. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 11.8 (s, 1H), 8.39 (s, 1H), 8.08 (s, 1H), 7.50 (s, 1H), 4.85 (q, *J*=7.2Hz, 2H), 3.91 (s, 3H), 1.52 (t, *J*=7.2Hz, 3H).

[0557] **Compound 622** was prepared by Suzuki-Coupling of compound **4B** with compound **8** followed by HBr hydrolysis. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 11.66 (s, 1H), 7.96 (s, 1H), 7.64 (s, 1H), 7.13 (s, 1H), 4.31 (q, *J*=7.2Hz, 2H), 3.90 (s, 3H), 1.15 (t, *J*=7.2Hz, 3H).

[0558] **Compound 623** was prepared by amino protection of compound **3** using SEMCl and NaH in DMF, followed by Suzuki-Coupling with comound **8** then HCl hydrolysis in MeOH as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 11.61 (s, 1H), 8.28 (s, 1H), 7.99 (s, 1H), 7.47 (s, 1H), 3.89 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 216.9.

[0559] **Compound 631** was prepared from **Compound 623** by first protecting the triazole hydrogen with Trt-Cl, then Suzuki-Coupling with (4-(trifluoromethoxy)phenyl)boronic acid using standard procedure described herein, followed by deprotecting in HCl/MeOH solution. **^{1}HNMR** (DMSO-d_6, 400 MHz) δ 8.38 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.69 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=8.4 Hz, 2H), 3.90 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 376.9.

[0560] **Compound 632** was prepared by reacting 3-benzyl-7-bromo-3H-[1,2,3]triazolo[4,5-c]pyridin-4(5H)-one with compound **6**, followed by deprotection of the Bz group using Pd/C in hydrogen atmosphere (45 Psi) at rt overnight. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67-7.60 (m, 3H), 7.55 (d, *J*=8.8 Hz, 2H), 6.82 (brs, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 296.9.

[0561] **Compound 635** was prepared following the similar synthetic scheme described in the synthesis of Compound **619** using isopropyl iodide in place of ethyl iodide in the reaction with compound **3**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.08 (s, 1H), 7.85 (s, 1H), 7.51 (d, *J*= 8.8 Hz, 2H), 7.37 (d, *J*= 8.8 Hz, 2H), 7.36 (s, 1H), 5.19-5.12 (m, 1H), 4.00 (s, 3H), 1.75 (d, *J*= 6.8 Hz, 6H).

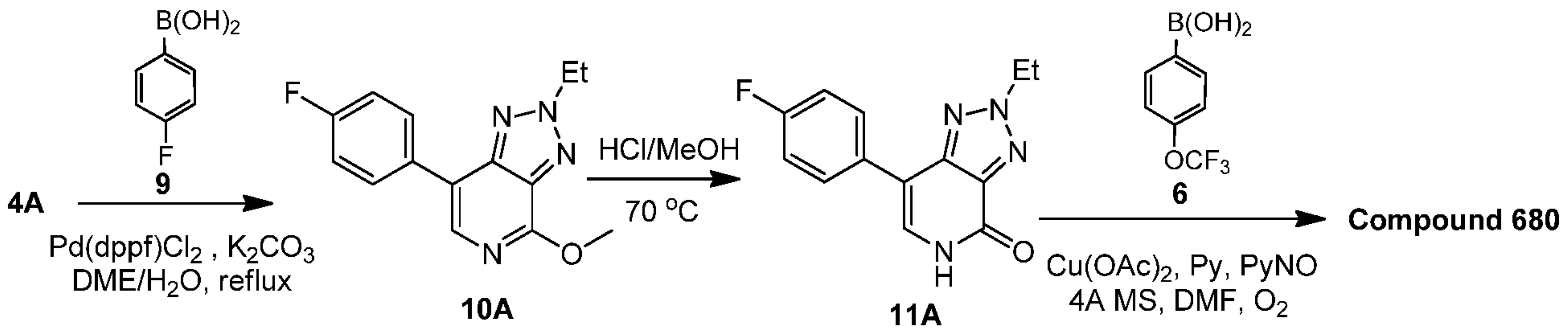
[0562] Compound **676** was prepared following the similar procedure described in the synthesis of Compound **619**. First, 7-bromo-3-isopropyl-4-methoxy-3H-[1,2,3]triazolo[4,5-c]pyridine was formed by reacting compound **3** with isopropyl iodide; followed by $Pd(dppf)Cl_2$ catalyzed Suzuki-coupling with compound **8**, subsequent acid hydrolysis to form 1-isopropyl-7-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-c]pyridin-4(5H)-one. Finally, copper acetate catalyzed coupling with compound **6** provided the final product. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.41 (s, 1H), 7.85 (s, 1H), 7.52 (d, *J*=8.4Hz ,2H), 7.41 (d, J=8.4 Hz, 2H), 7.37 (s, 1H), 5.73~5.66 (m, 1H), 4.00 (s, 3H), 1.75 (d, J=6.8 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 418.9.

[0563] Compound **677** was prepared similarly as Compound **676** using 7-bromo-1-isopropyl-4-methoxy-3H-[1,2,3]triazolo[4,5-c]pyridine as starting material. **^{1}H NMR** (CDCl3, 400 MHz) δ 7.59 (s, 1H), 7.54 (s, 1H), 7.48 (d, J=8.4Hz ,2H), 7.34 (d, J=8.4 Hz, 2H), 7.13 (s, 1H), 4.67~4.57 (m, 1H), 4.01(s, 3H), 1.55 (d, J=6.8 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 418.8.

[0564] Compound **679** was prepared following the similar procedure described in the synthesis of Compound **676** using 7-bromo-2-(2-fluoroethyl)-4-methoxy-2H-[1,2,3]triazolo[4,5-c]pyridine as starting material as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.31 (s, 1H), 8.07 (s, 1H), 7.93 (s, 1H), 7.68 (d, *J*=8.8 Hz, 2H), 7.58 (d, *J*=8.8 Hz, 2H), 5.14 (s, 2H), 5.09 - 5.06 (m, 1H), 5.03-5.01 (m, 1H), 3.89 (s, 3H).

[0565] Compound **684** was prepared following the similar procedure described in the synthesis of Compound **676** using 7-bromo-3-(2-fluoroethyl)-4-methoxy-2H-[1,2,3]triazolo[4,5-c]pyridine as starting material. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.47 (s, 1H), 7.87 (s, 1H), 7.52 (d, *J*=8.8 Hz, 2H), 7.43-7.39 (m, 3H), 5.27 (t, *J*= 4.8 Hz, 1H), 5.22 (t, *J*= 4.8 Hz, 1H), 5.04 (t, *J*= 4.8 Hz, 1H), 4.92 (t, *J*= 4.8 Hz, 1H), 4.01 (s, 3H).

[0566] Compound **687** was prepared following the similar procedure described in the synthesis of Compound **676** using 7-bromo-1-(2-fluoroethyl)-4-methoxy-2H-[1,2,3]triazolo[4,5-c]pyridine as starting material. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.60 (s, 1H), 7.54 (s, 1H), 7.50 (d, *J*=8.8 Hz, 2H), 7.36 (d, *J*=8.8 Hz, 2H), 7.18 (s, 1H), 4.85 (t, *J*=4.8 Hz, 1H), 4.73 (t, *J*=4.8 Hz, 1H), 4.65 (t, *J*=4.8 Hz, 1H), 4.60 (t, *J*=4.8 Hz, 1H), 4.01 (s, 3H).



[0567] A mixture of compound **4A** (1.0 g, 3.906 mmol, 1eq), compound **9** (820 mg, 5.859 mmol, 1.5eq), Pd(dppf)Cl_2 (287 mg , 0.391 mmol , 0.1eq) and K_2CO_3 (1.08 g, 7.812 mmol, 2eq) in DME/H_2O (20 mL, v/v=5/1) was flushed with N_2. And then the mixture was stirred at 80°C under N_2 for 1h. 30 mL of water was added and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified to afford compound **10A** (750 mg, 71% yield).

[0568] A mixture of compound **10A** (650 mg, 2.39 mmol) in HCl/MeOH (4M, 50 mL) was stirred at 70°C overnight. The mixture was concentrated and adjusted to pH =7~8 with saturated aq. $NaHCO_3$. The mixture was filtered and the filter cake was dried in vacuum to afford compound **11A** (570 mg, 92% yield).

[0569] A flask was charged with compound **11A** (250 mg, 0.97 mmol, 1 eq), compound **6** (260 mg, 1.26 mmol, 1.3 eq), $Cu(OAc)_2$ (351 mg, 1.94 mmol, 2 eq), Py (230 mg, 2.91 mmol, 3eq), pyridine N-Oxide (184 mg, 1.94 mmol, 2 eq) and 4Å molecular sieves (150 mg) in DMF. The mixture was stirred under O_2 at rt overnight. The mixture was concentrated and 50 mL of water was added. The mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified to afford **Compound 680** (300 mg, 74% yield) as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.02 (dd, J=5.6, 8.8 Hz, 2H), 7.89 (s, 1H), 7.71 (d, J=8.8 Hz, 2H), 7.57 (d, J=8.4 Hz, 2H), 7.31 (t, J=8.8 Hz, 2H), 4.78 (q, J=7.2 Hz, 2H), 1.59 (t, J=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 419.0.

[0570] Compound **682** was prepared following the similar procedure described in the synthesis of Compound **680** using **4B** as starting material. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (d, J=8.8 Hz, 2H), 7.43 (dd, J=3.2, 8.4 Hz, 2H), 7.36 (d, J=8.4Hz, 2H), 7.25 - 7.19 (m, 3H), 4.23 (q, J=7.2 Hz, 2H), 1.24 (t, J=7.2 Hz, 3H).

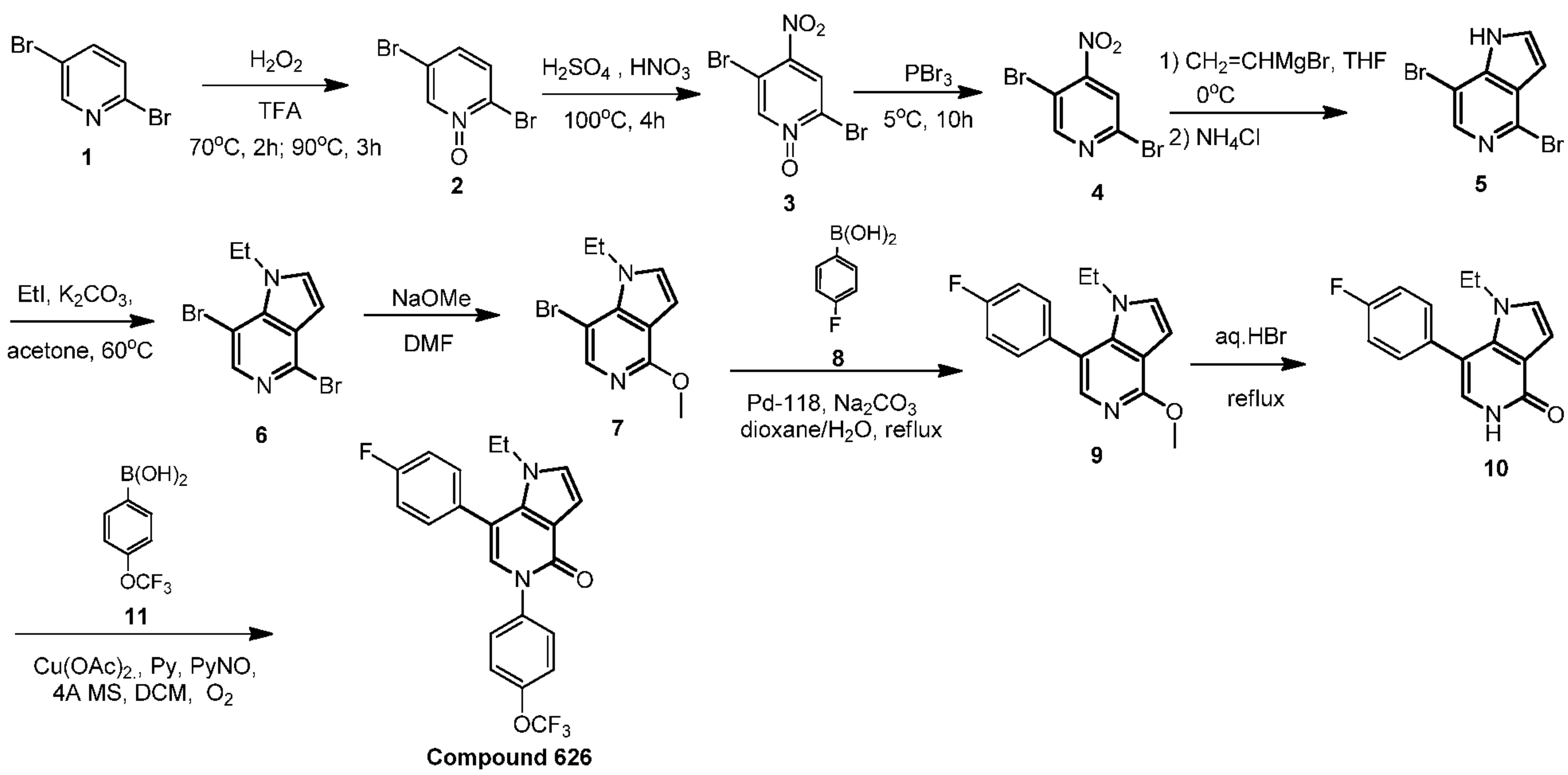
[0571] Compound **683** was prepared following the similar procedure described in the synthesis of Compound **680** using **4C** as starting material. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.93-7.90 (m, 2H), 7.53 (d, J=8.8 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H), 7.34 (s, 1H), 7.19 (t, J=8.8 Hz, 2H), 4.99 (q, J=7.2 Hz, 2H), 1.67 (t, J=7.2 Hz, 3H).

[0572] Compound **685** was prepared following the similar procedure described in the synthesis of Compound **680** using 4-(tributylstannyl)pyridazine in place of compound **9** catalyzed by $Pd(PPh_3)_2Cl_2$ in dioxane refluxed overnight. After HCl hydrolysis, (4-ethoxy-2-methylphenyl)boronic acid was used in place of compound **6** to afford the final product. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.70 (s, 1H), 9.22 (d, *J*=5.2 Hz, 1H), 8.12 (dd, *J*=2.4, 5.4 Hz, 1H), 7.68 (s, 1H), 7.18 (d, *J*=8.4 Hz, 1H),6.91 - 6.83 (m, 2H), 4.80 (q, *J*=7.4 Hz, 2H), 4.08 (q, *J*=6.8 Hz, 2H), 2.17 (s, 3H), 1.76 (t, *J*=7.4 Hz, 3H), 1.45 (t, *J*=7.0 Hz, 3H).

[0573] Compound **686** was prepared following the similar procedure described in the synthesis of Compound **619** using (4-ethoxy-2-methylphenyl)boronic acid in place of compound **6** to afford the final product. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (s, 1H), 7.83 (s, 1H), 7.26 (s, 1H), 7.18 (d, *J*=8.8 Hz, 1H), 6.88 (d, *J*=2.4Hz, 1H), 6.85 (dd, *J*=2.4, 8.8 Hz, 1H), 4.77(q, *J*=7.2 Hz, 2H), 4.08 (q, *J*=7.2 Hz, 2H), 3.99 (s, 3H), 2.16 (s, 3H), 1.75(t, *J*=7.2 Hz, 3H), 1.45 (t, *J*=7.2Hz, 3H).

[0574] Compound **688** was prepared following the similar procedure described in the synthesis of Compound **619** using (4-(2-methoxyethoxy)phenyl)boronic acid in place of compound **6** to afford the final product. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (s, 1H), 7.84 (s, 1H), 7.39 - 7.34 (m, 3H), 7.06 (dd, *J*=2.0, 6.8 Hz, 2H), 4.77 (q, *J*=7.2 Hz, 2H), 4.19 (t, *J*=4.8 Hz, 2H), 3.99 (s, 3H), 3.79 (t, *J*=4.8 Hz, 2H), 3.48 (s, 3H), 1.74 (t, *J*=7.2 Hz, 3H).

Example 5-N
Synthesis of Compound 626



[0575] Hydrogen peroxide (30 %, 35 mL) was added slowly to the solution of compound **1** (40 g, 186.8 mmol) in TFA (200 mL). The resulting mixture was stirred at 70°C for 2h and at 90°C for another 3h. After the mixture was cooled to rt, the mixture was poured over crushed ice. The mixture was extracted with DCM. The combined organic layers were washed with aq. $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford compound **2** (45 g, 96% crude yield), which was used directly for the next step.

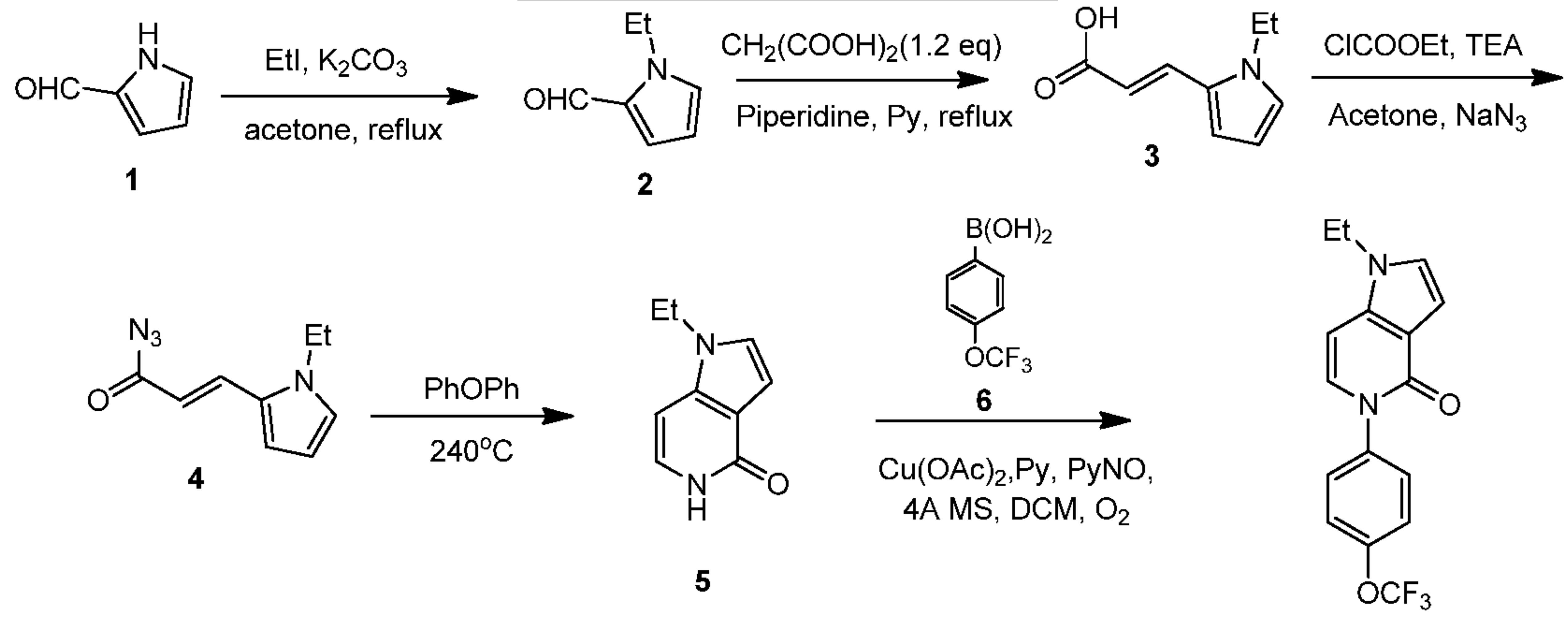
[0576] Compound **2** (45 g, 180 mmol) was added to the mixture of conc. sulfuric acid (200 mL) and fuming nitric acid (150 mL) at rt during stirring. The mixture was heated to 100°C and then stirred for 2h. The reaction mixture was allowed to cool to rt and then poured over crushed ice. The mixture was neutralized with $NH_3.H_2O$ in the ice bath. The precipitate was filtered and washed with PE to give compound **3** (29.6 g, 56% yield).

[0577] Compound **3** (18g, 60.84 mmol) was added into the stirring PBr_3 (46 mL) in portions at 0~5°C. The mixture was stirred at 5°C for about 7h, and then it was poured over crushed ice and extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography (PE:EA=10:1) to give compound **4** (10 g, 59% yield).

[0578] Compounds **5-10** were prepared following the general procedure described in the synthesis of Compound **48**.

[0579] **Compound 626** was prepared by Suzuki-Coupling of compounds **10** and **11**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51 (d, *J*= 8.4 Hz, 2H), 7.44~7.41 (m, 2H), 7.32 (d, *J*= 8.4 Hz, 2H), 7.14 (t, *J*=8.4Hz, 2H), 6.94 (d, *J*=2.8Hz,1H), 6.91~6.89 (m, 2H) , 3.67 (q, *J*=7.2Hz, 2H), 1.10 (t, *J*=7.2Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 417.1.

Example 5-O
Synthesis of Compound 656



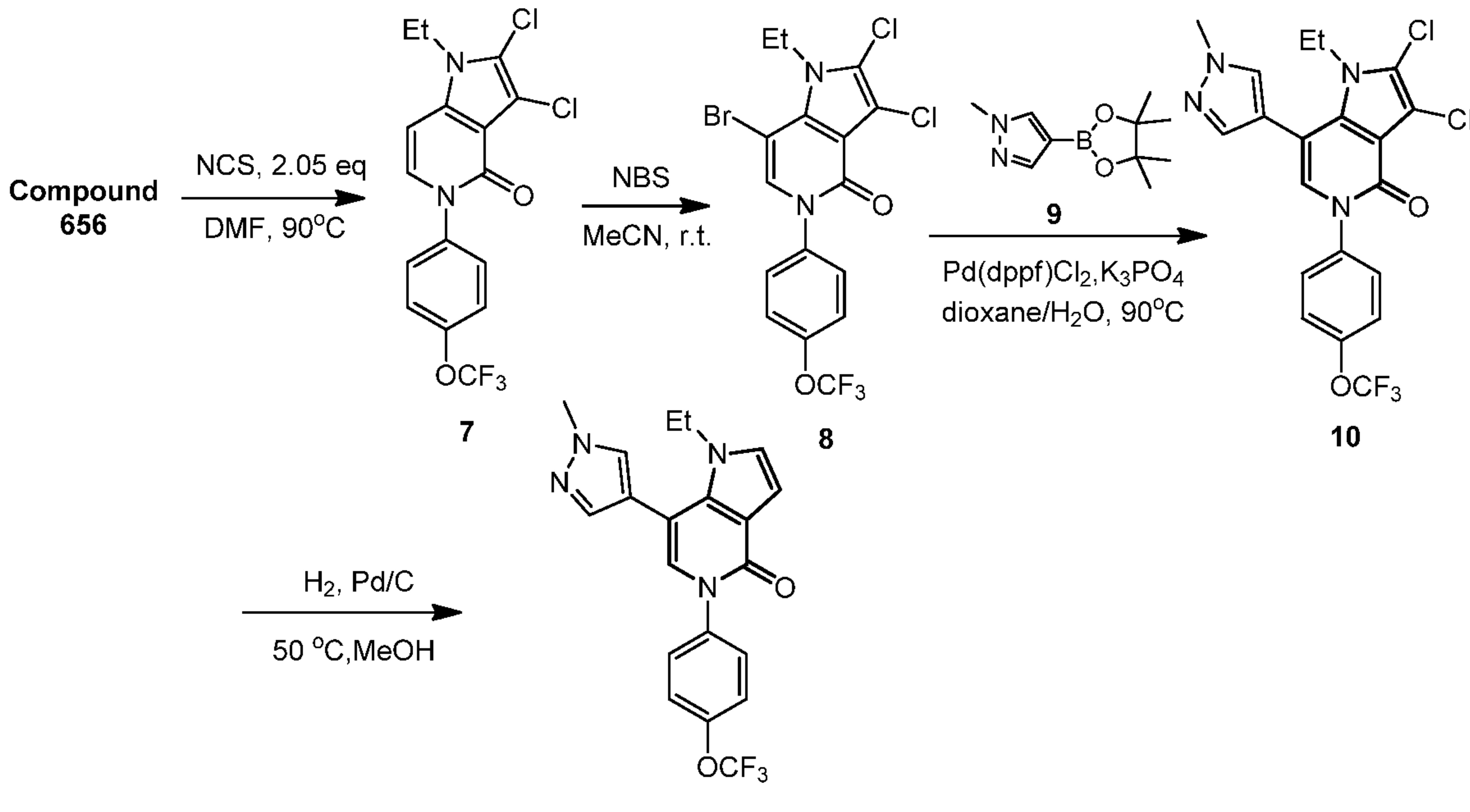
[0580] Cs_2CO_3 (124 g, 0.38 mol) was added to a solution of the compound **1** (60 g, 0.63 mol) in acetone (500 mL). And then iodoethane (118 g, 0.76 mol, 61 mL) was added to the stirring mixture. The mixture was stirred at reflux overnight. The mixture was cooled to rt, filtered and the solvent was evaporated. The residue was purified by column chromatography (PE:EA=200:1 to 100:1) to afford compound **2**(30 g , 39% yield).

[0581] A flask was charged with compound **2** (23 g, 187 mmol), malonic acid (23.3 g, 224 mmol), pyridine (100 mL) and piperidine (22 mL). The mixture was reflux under nitrogen atmosphere overnight. Then the mixture was cooled to rt and concentrated under reduced pressue. The residue was diluted with water and adjusted to pH=~5 by aq. HCl (2 N), the resulting solid was filtered and washed with amount water, the solid was dried *in vacuo* to give compound **3** (26.3 g, 85% yield).

[0582] Ethyl chloroformate (10 g, 87.6 mmol) was added dropwise into the solution of compound **3** (10 g, 73 mmol) and TEA (11.1 g, 109.5 mmol) in 100 mL of acetone at 0°C. The mixture was stirred at 0°C for 1.5h. The resulting mixture was added into the solution of sodium azide (14.3 g, 219 mmol) in 30 mL of acetone and water (V/V=1/1) at 0°C and stirred for 30 min. Then the mixture was warmed to rt and stirred for another 2h. The mixture was poured onto ice-water and the precipitate was collect by filtration. The solid was washed with amount water, dried *in vacuo* to give compound **4** (2.87 g, 21% yield).

[0583] Compound **4** (2.8 g, 15 mmol) was added into 20 mL of diphenyl ether and the mixture was stirred at 240°C for 3h. Then the mixture was cooled to rt and the residue was purified by column chromatography (PE:EA=1:1 to EA:MeOH= 100:1) to afford compound **5** (1.1g, 46 % yield).

[0584] To a solution of compound **5** (200 mg, 1.24 mmol) in DCM (10 mL) was added compound **6** (306.5 mg, 1.49 mmol), $Cu(OAc)_2$ (743 mg, 2.48 mmol), Pyridine (1.17 g, 12.4 mmol, 1.2 mL) and Pyridine-N-Oxide (295 mg, 3.1 mmol), followed by addition of 4Å molecular sieve (100 mg). The reaction mixture was stirred at 30°C under oxygen atmosphere overnight. The resulting mixture was filtered and washed with EtOAc; the filtrate was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE/EA =1:1) to give **Compound 656** (80 mg, 20% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46 (d, *J*=9.2 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.10 (d, *J*=7.6 Hz, 1H), 6.93 (d, *J*=3.2 Hz, 1H), 6.84 (d, *J*=3.2 Hz, 1H), 6.45 (d, *J*=7.2 Hz, 1H), 4.10 (q, *J*=7.2 Hz, 2H), 1.48 (t, *J*=7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 323.0.



Compound 694

[0585] To a solution of compound **656** (1.8 g, 5.6 mmol) in DMF\` (20 mL) was added NCS (1.53 g, 11.5 mmol). The mixture was heated at 90°C for 2 hrs. Then the mixture was washed with water, exteacted with EA. The organic layer was washed with brine, dried under Na_2SO_4, concentrated in vacuo. The crude residue was purified to afford compound **7** (1.6 g, 73% yield).

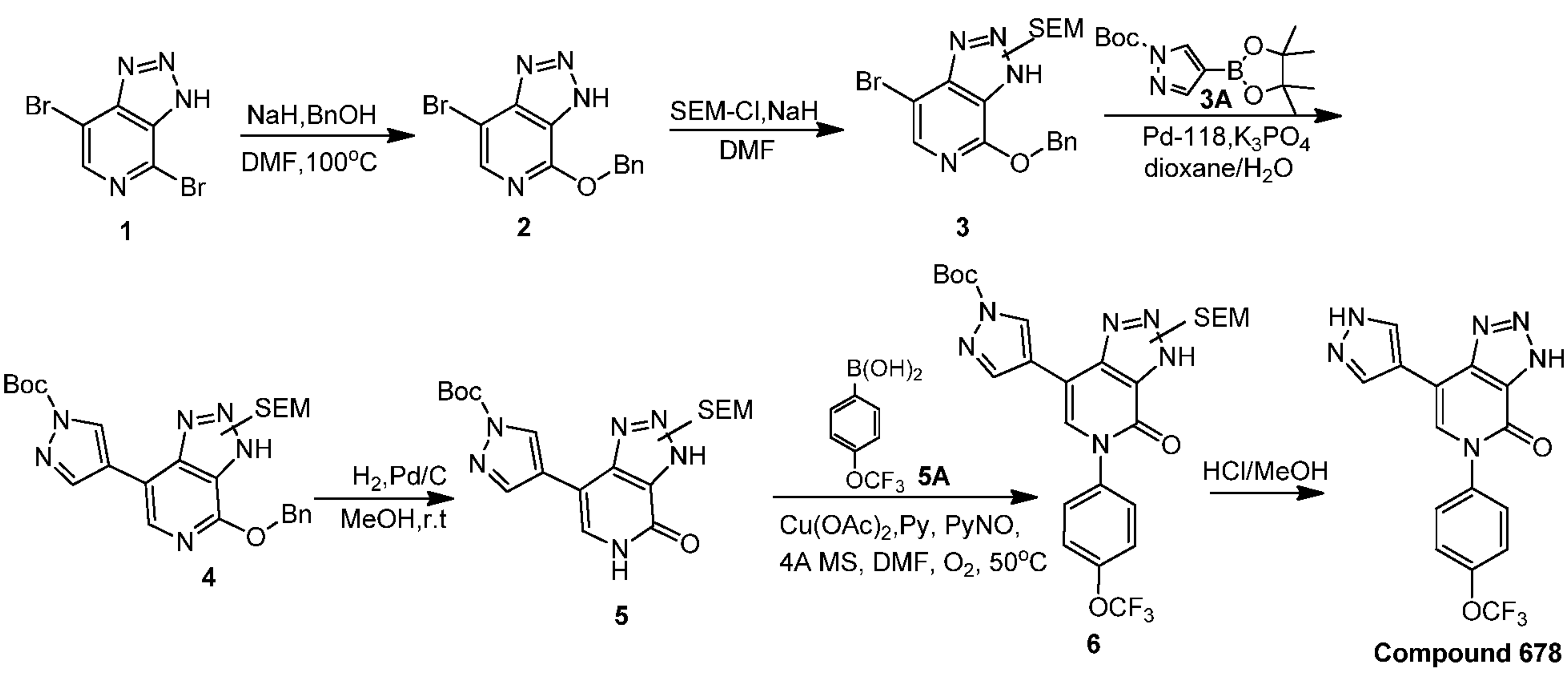
[0586] To a solution of compound **7** (1.0 g, 2.56 mmol) in MeCN (20 mL) was added NBS (543 mg, 3.07 mmol) at 0~5°C. The mixture was stirred at rt overnight. Then the mixture was concentrated in vacuo. The crude residue was purified to afford compound **8** (0.5 g, 42% yield).

[0587] To a stirred mixture of compound **8** (800 mg, 1.7 mmol), and **9** (530 mg, 2.55 mmol) in dioxane/H_2O (30 mL,V:V=5:1) was added K_3PO_4 (720 mg, 3.4 mmol), $Pd(dppf)Cl_2$ (125 mg, 0.17 mmol) under N_2 protection. The reaction mixture was heated at 90°C overnight. The mixture was poured into water, extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*, the residue was purified to afford compound **10** (310 mg, yield: 38.8%).

[0588] Compound **10** (250 mg, 0.53 mmol) was dissolved in MeOH (20 mL), Pd/C (30 mg) was added under N_2 protect, the reaction was stirred overnight at H_2 balloon at 50°C. The suspention was filtered through a pad of celite. The filter cake was washed with MeOH, the combined filtrate was concentrated in vacuo, the crude product was purified to afford **Compound 694** (95 mg, 45% yield). **^{1}H NMR** (400MHz,$CDCl_3$) δ 7.57 (s, 1H), 7.49 - 7.42 (m, 3H), 7.29 (d, J=8.4 Hz, 2H), 6.93 - 6.90 (m, 1H), 6.89 - 6.84 (m, 2H), 3.96 (s, 3H), 3.86 (q, J=7.2 Hz, 2H), 1.18 (t, J=7.2 Hz, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 403.1.

[0589] Compound **695** was prepared following the similar procedure described in the synthesis of Compound **694** using 1-benzyl-5-(4-(trifluoromethoxy)phenyl)-1H-pyrrolo[3,2-c]pyridin-4(5H)-one as starting material. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 11.5 (s, 1H), 8.16 (s, 1H), 7.83 (s, 1H), 7.61 (d, *J*=8.8 Hz, 2H), 7.51 (d, *J*=8.8 Hz, 2H), 7.42 (s, 1H), 7.19 (s, 1H), 6.66 (s, 1H), 3.89 (s, 3H).

Example 5-P
Synthesis of Compound 678



[0590] To a solution of BnOH (2.3 g, 21.7 mmol) in DMF (50 mL) was added NaH (60% dispersion in mineral oil, 1.5 g, 36.2 mmol) at 0°C, the mixture was stirred for 30 mins at rt, compound **1** (5 g, 18.1 mmol) was added, the solution was heated to 100°C for 3-4 hours, then quenched with aq. HCl (1N), extracted with EA, the combined organic layer was washed with brine and concentrated to give crude product, which was purified to afford compound **2** (4 g, yield 72%).

[0591] To a solution of compound **2** (4 g, 13.2 mmol) in DMF (50 mL) was added NaH (60% dispersion in mineral oil, 1 g, 26.4 mmol) at 0°C, the mixture was stirred for 30 mintues at rt, and then SEM-Cl (3.3 g, 19.8 mmol) was added, the reaction was stirred for 12 hours at rt. The mixture was quenched with water, extracted with EA, the combined organic layer was washed with brine and concentrated to give crude product, the residue was purified to afford compound **3** (3.7 g, yield 65%).

[0592] To a stirred mixture of compound **3** (4 g, 9.2mmol), and **3A** (4.2g, 18.4 mmol) in dioxane/H_2O (100 mL, V/V=5/1) was added K_3PO_4 (3.9g, 18.4 mmol), Pd-118 (600 mg, 0.92 mmol) under N_2 protection. The reaction mixture was heated to 60-70°C overnight. The mixture was poured into water, extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*, the residue was purified by column chromatography on silica gel (PE/EA =5:1) to afford compound **4** (3 g, yield 62.5%).

[0593] To a solution of compound **4** (3 g, 5.7 mmol) in MeOH (50 mL) was added Pd/C (600 mg) under N_2 protection, the reaction was stirred overnight under H_2 balloon at rt, then the mixture was filtered through a pad of celite. The filter cake was washed with MeOH (50 mL), the combined filtrates was concentrated *in vacuo*, the crude product was purified to afford compound **5** (1.2 g, 48% yield).

[0594] To a solution of compound **5** (400 mg, 0.93 mmol) in DMF (20 mL) was added compound **5A** (288 mg, 1.4 mmol), and $Cu(OAc)_2$ (336.7 mg, 1.86 mmol), Py (367.4 mg, 4.65 mmol), pyridine N-Oxide (176.7 mg, 1.86 mmol). The reaction mixture was stirred at 50°C overnight, and then it was poured into water, extracted with EA, the combined organic layer was washed with brine and concentrated to give crude product. The residue was purified to afford compound **6** (300 mg, yield 54%).

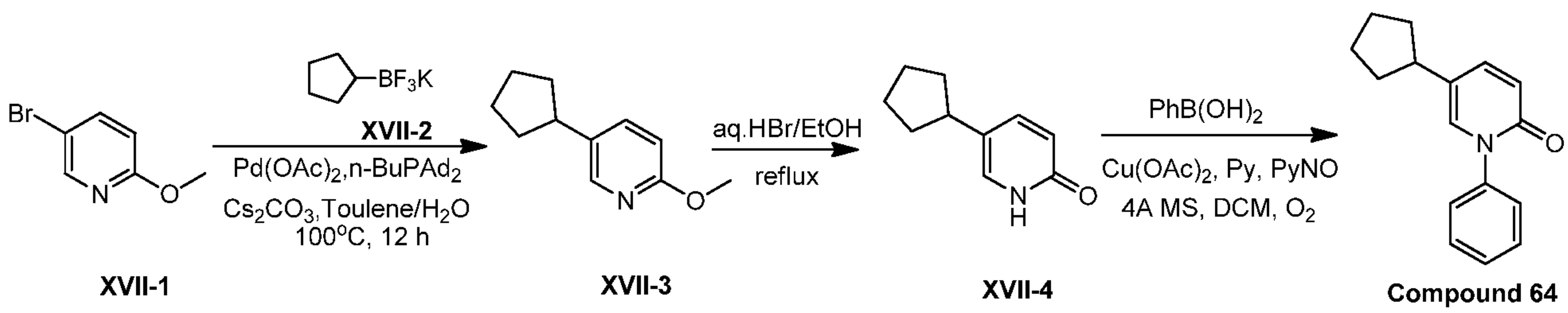
[0595] Compound **6** (700 mg, 1.18 mmol) was dissolved in HCl/MeOH (4M, 20 mL), the reaction was stirred for 1-2 hours at rt, and then the solvents were evaporated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with EA. The combined organic layer was concentrated in *vacuo*, and the crude product was washed with EA to afford **Compound 678** (260 mg, 61%yield).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.28 (brs, 2H), 7.92 (s, 1H), 7.69 (d, *J*=8.4Hz, 2H), 7.57 (d, *J*=8.0Hz, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 362.9.

[0596] Compound **681** was prepared following the similar procedure described in the synthesis of Compound **678** using (4-fluorophenyl)boronic acid in place of compound **3A**. **^{1}H NMR**

(CD_3OD, 400 MHz) δ 7.84-7.80 (m, 2H), 7.70-7.64 (m, 3H), 7.49 (d, J=8.4Hz, 2H), 7.25-7.20 (m, 2H). **MS (ESI)** ***m/z*** [M+H]+ 391.0.

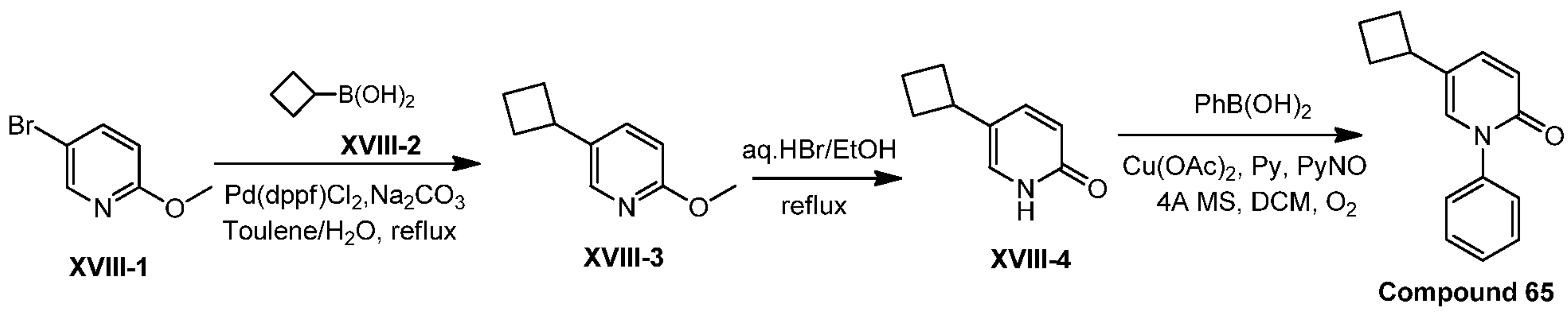
Example 6-A
Synthesis of Compound 64 (Scheme XVII)



[0597] A mixture of **XVII-1** (1.57 g, 8.35 mmol), **XVII-2** (1.61 g, 9.19 mmol), $Pd(OAc)_2$ (0.187 g, 0.835 mmol), n-$BuPAd_2$ (0.298 g, 0.835 mmol) and Cs_2CO_3 (8.17 g, 25.05 mmol) in toluene/H_2O (50 mL/10 mL) was degassed by purging with nitrogen. The mixture was heated at 100°C for 12 hrs. After being cooled to rt, the mixture was diluted with water (30 mL), extracted with EtOAc (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (PE/EA =100:1→40:1) to produce **XVII-3** as a yellow oil (0.8 g, 54% yield).

[0598] **Compound 64**: **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.50-7.47 (m, 2H), 7.42-7.34 (m, 4H), 7.12 (d, J = 2.1Hz, 1H), 6.64 (d, J = 6.9Hz, 1H), 2.72-2.80 (m, 1H), 2.05-1.96 (m, 2H), 1.80-1.63 (m, 4H), 1.52-1.47 (m, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 240.1.

Example 6-B
Synthesis of Compound 65 (Scheme XVIII)



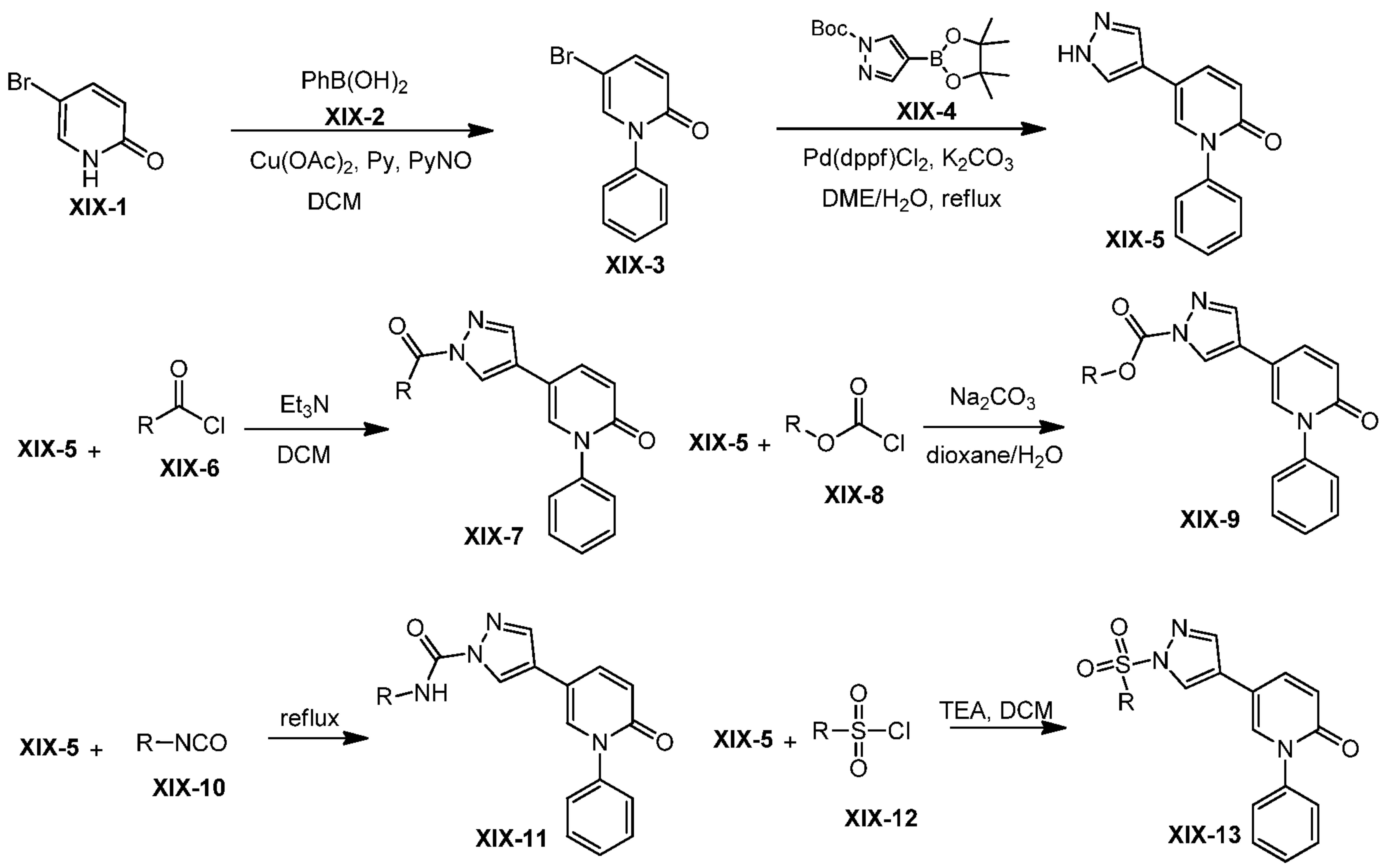
[0599] To a solution of **XVIII-1** (2.1 g, 10.9 mmol) in toulene/H_2O (60 mL, v/v=5/1) was added Na_2CO_3 (1.4 g, 14.71 mmol), **XVIII-2** (1.2 g, 11.99 mmol), followed by $Pd(dppf)Cl_2$ (812 mg, 1.11 mmol). The mixture was purged with nitrogen and then heated at reflux overnight. The mixture was cooled to rt., diluted with water (50 mL), extracted with EtOAc (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (PE/EA 100:1→40:1) to give

XVIII-3 as a yellow oil (0.4 g, 24% yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.97 (d, J = 2.4Hz, 1H), 7.46 (dd, J = 8.4, 2.4Hz, 1H), 6.68 (d, J = 8.4Hz, 1H), 3.90 (s, 3H), 3.51-3.40 (m, 1H), 2.37-2.30 (m, 2H), 2.28-1.99 (m, 3H), 1.96-1.82 (m, 1H).

[0600] **Compound 65**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51-7.47 (m, 2H), 7.46-7.36 (m, 4H), 7.08 (d, J = 2.8Hz, 1H), 6.65 (d, J = 9.2Hz, 1H), 3.35-3.26 (m, 1H), 2.31-2.23 (m, 2H), 2.09-1.96 (m, 3H),1.87-1.83 (m, 1H). **MS (ESI)** ***m/z*** $[M+H]^+$ 226.0.

[0601] **Compound 66** was prepared following the similar procedure for obtaining **Compound 64**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51-7.46 (m, 2H), 7.43-7.33 (m, 4H), 7.09 (d, J = 2.4Hz, 1H), 6.63 (d, J = 9.6Hz, 1H), 2.32-2.25 (m, 1H), 1.87-1.82 (m, 4H), 1.76-1.72 (m, 1H), 1.41-1.18 (m, 5H). **MS (ESI)** ***m/z*** $[M+H]^+$ 254.1.

Example 7
Synthesis of Compounds 67-76 (Scheme XIX)



[0602] **XIX-3** was prepared following the similar procedure for obtaining **V-3** using **XIX-2** in place of **V-2** as a yellow solid.

[0603] **XIX-5** was prepared following the similar procedure for obtaining **Compound 23** using **XIX-4** in place of **V-4.**

[0604] **XIX-7:** To a stirring solution of **XIX-5** (1.0 eq) and TEA (3 eq.) in DCM was added acyl chloride (2.0 eq) dropwise at 0°C. The mixture was stirred for 1h at rt. then it was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by prep-TLC (EtOAc) to afford **XIX-7**.

[0605] **Compound 67**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.34 (s, 1 H), 7.82 (s, 1 H), 7.59-7.41(m, 7 H), 6.77-6.74 (m, 1 H), 2.72 (s, 3H).

[0606] **Compound 68**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.54 (s, 1 H), 8.13 (d, J = 7.2 Hz, 2 H), 7.91 (s, 1 H), 7.66-7.43 (m, 10 H), 6.78 (d, J = 9.6 Hz, 1 H).

[0607] **Compound 69**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.34 (s, 1 H), 7.86 (s, 1 H), 7.59-7.28 (m, 12 H), 6.75 (d, J = 8.8 Hz, 1 H), 4.45 (s, 2 H).

[0608] **Compound 72**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.34 (s, 1 H), 7.80 (s, 1 H), 7.60-7.40 (m, 7 H), 6.74 (d, J = 8.8 Hz, 1 H), 3.15-3.10 (m, 2 H), 1.81-1.72 (m, 2 H), 1.481-1.40 (m, 2 H), 0.98-0.93 (m, 3 H).

[0609] **XIX-9**: To a solution of **XIX-5** (1.0 eq) in dioxane/H_2O (v/v=10:1) was added Na_2CO_3 (1.5 eq) with stirring at 0°C for 10 min. Then **XIX-8** (1.2 eq) was added dropwise. The mixture was stirred at rt for 5 hours. The reaction was concentrated. The residue was partitioned between EtOAc and H_2O. The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated. The crude product was purified by prep-TLC (EtOAc) to give **XIX-9**.

[0610] **Compound 73**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.80 (s, 1H), 8.33 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.01 (dd, J = 2.4, 9.6 Hz, 1H), 7.57-7.52 (m, 2H), 7.49-7.45 (m, 3H), 6.58 (d, J = 9.6 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2Hz, 3H).

[0611] **Compound 74**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.78 (s, 1H), 8.33 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.00 (dd, J = 2.8, 9.6 Hz, 1H), 7.57-7.53 (m, 2H), 7.49-7.46 (m, 3H), 6.58 (d, J = 9.6 Hz, 1H), 4.40 (t, J = 6.4 Hz, 2H), 1.74-1.70 (m, 2H), 1.46-1.39 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H).

[0612] **XIX-11**: A mixture of **XIX-5** (1 eq.) and **XIX-10** (0.5 mmol/mL) was stirred at 90-100°C under N_2 overnight. The mixture was concentrated. The residue was purified by prep-TLC (PE: EtOAc = 1:1) to give **XIX-11**.

[0613] **Compound 75**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.70 (s, 1H), 8.24-8.21 (m, 2H), 8.14 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 9.3, 2.4 Hz, 1H), 7.53-7.42 (m, 5H), 6.53 (d, J = 9.3 Hz, 1H), 3.99-3.92 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H).

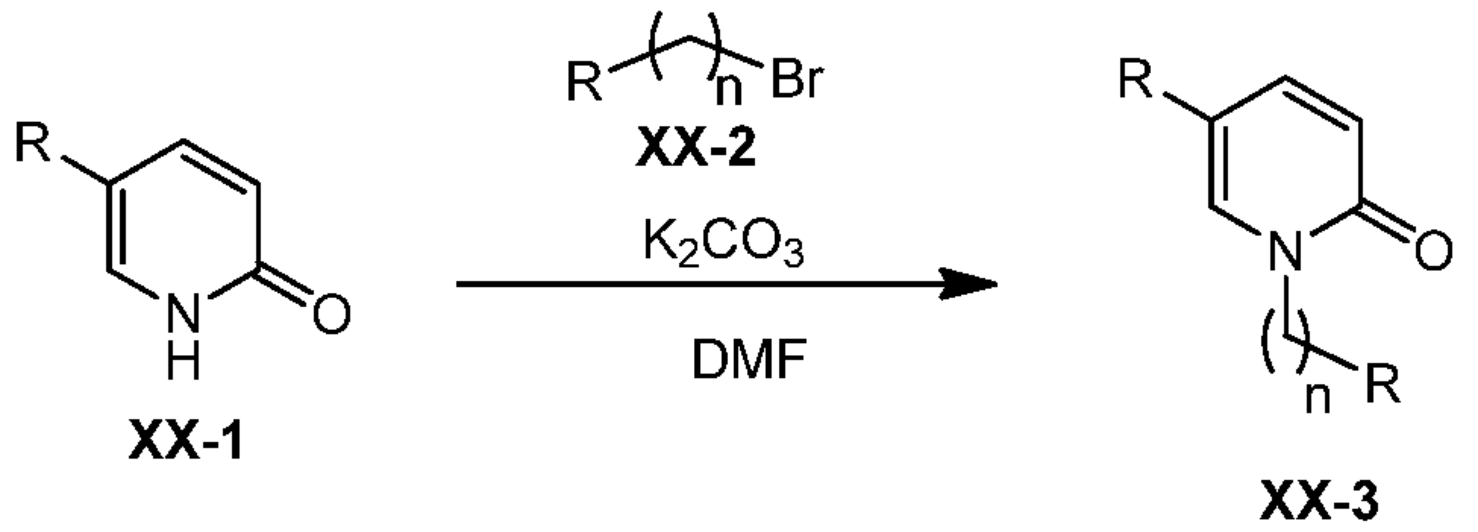
[0614] **Compound 76**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.70 (s, 1H), 8.51 (t, J = 6.0 Hz, 1H), 8.20 (d, J = 0.6 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 9.6, 2.7 Hz, 1H), 7.51-7.42 (m, 5H), 6.53 (d, J = 9.3 Hz, 1H), 3.31-3.24 (m, 2H), 1.12-1.07 (m, 3H).

[0615] **XIX-13**: To a solution of **XIX-5** (1 eq.) in DCM (0.16 mmol/mL) was added **XIX-12** (1.25 eq.) and TEA (3 eq.) at 0°C. Then the mixture was stirred at rt. overnight. The mixture was concentrated, diluted with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by prep-TLC (PE: EA = 1:2) to give **XIX-13**.

[0616] **Compound 70**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.19 (s, 1H), 8.04-8.02 (m, 2H), 7.82 (s, 1H), 7.69-7.65 (m, 1H), 7.58-7.49 (m, 6H), 7.47-7.45 (m, 1H), 7.39-7.37 (m, 2H), 6.72 (d, *J* = 9.2 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 378.1.

[0617] **Compound 71**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.11 (s, 1H), 7.91 (s, 1H), 7.55-7.39 (m, 7H), 6.75 (d, *J* = 9.6 Hz, 1H), 3.35 (s, 3H). **MS (ESI)** ***m/z*** $(M+Na)^+$ 338.0.

Example 8
Synthesis of Compounds 77-80 (Scheme XX)



[0618] **XX-3**: **XX-1** (1 eq.), **XX-2** (1.2 eq.) and K_2CO_3 (1.5 eq.) were dissolved in DMF. The solution was stirred at 50°C for 6 hrs under N_2 atmosphere. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give crude product, it was purified by prep-TLC (PE:EA= 1:1) to yield **XX-3**.

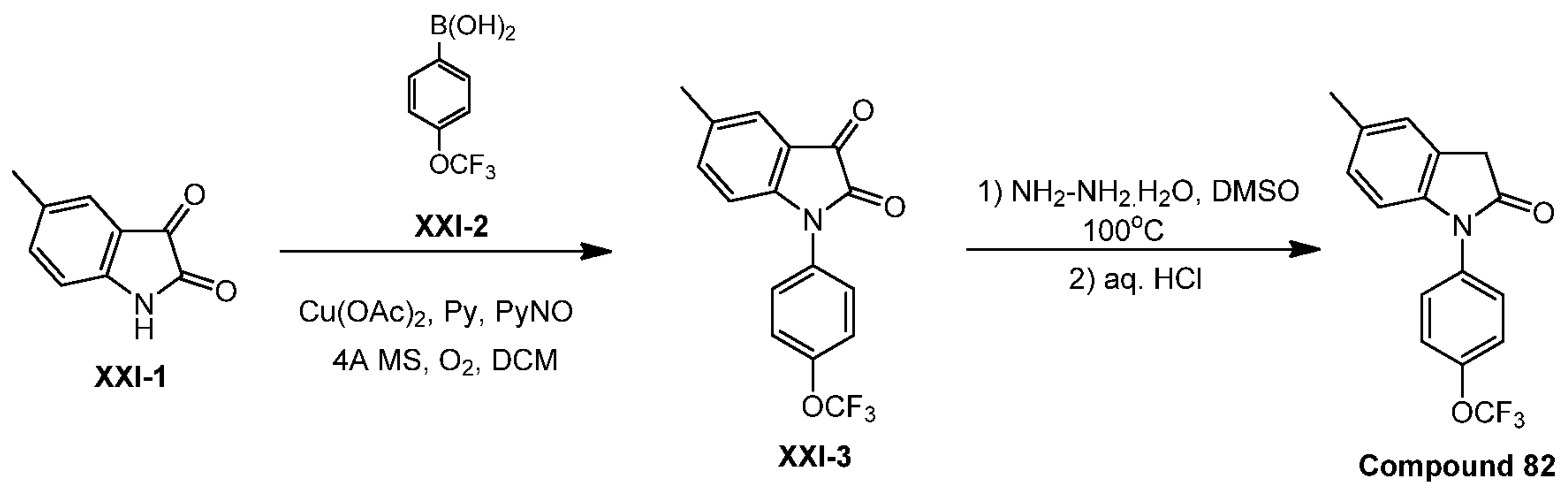
[0619] **Compound 77** was prepared by reacting 5-(4-fluorophenyl)pyridin-2(1H)-one with (2-bromoethyl)benzene following the general procedure described above. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (m, 1H), 7.33-7.24 (m, 3H), 7.18-7.16 (d, *J* = 6.8 Hz, 2H), 7.09-7.00 (m, 4H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.68-6.66 (d, *J* = 9.6 Hz, 1H), 4.23-4.20 (m, 2H), 3.12-3.09 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 293.9.

[0620] **Compound 79** was prepared by reacting 5-(4-fluorophenyl)pyridin-2(1H)-one with (bromomethyl)benzene following the general procedure described above. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.57-7.55 (m, 1H), 7.42-7.41 (d, *J* = 2.8 Hz, 1H), 7.38-7.28 (m, 7H), 7.10-7.05 (m, 2H), 6.72-6.70 (d, *J* = 9.2 Hz, 1H), 5.22 (s, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 280.1.

[0621] **Compound 78** was prepared by reacting 5-methylpyridin-2(1H)-one with (bromomethyl)benzene following the general procedure described above. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36-7.27 (m, 5H), 7.19-7.16 (m, 1H), 7.02 (s, 1H), 6.58-6.56 (d, *J* = 7.2 Hz, 1H), 5.12 (s, 2H), 2.03 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 199.8.

[0622] **Compound 80** was prepared by reacting 5-methylpyridin-2(1H)-one with (2-bromoethyl)benzene following the general procedure described above. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31-7.21 (m, 3H), 7.18-7.15 (m, 3H), 6.70 (s, 1H), 6.54-6.52 (d, J = 9.2 Hz, 1H), 4.16-4.08 (m, 2H), 3.06-3.02 (m, 2H), 1.96 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 213.9.

Example 9
Synthesis of Compound 82 (Scheme XXI)

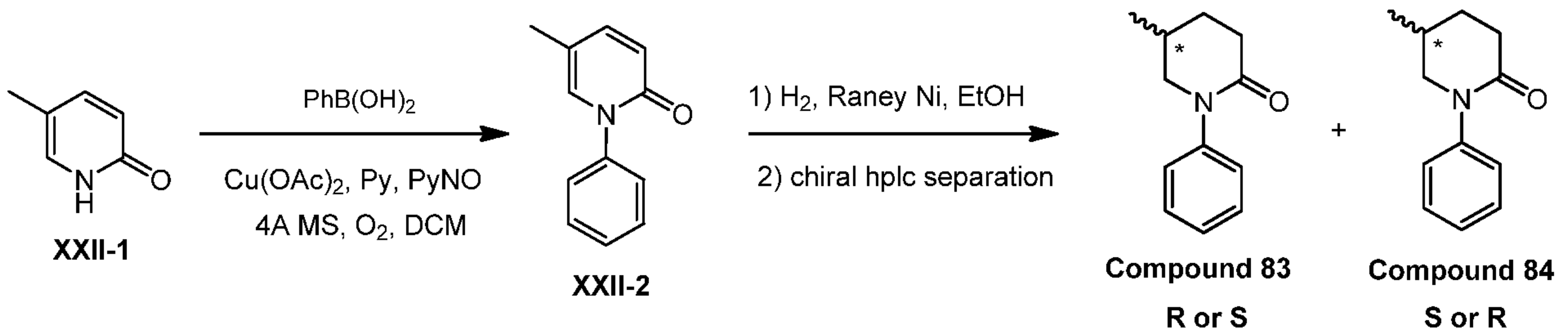


[0623] **XXI-3** was obtained following the similar procedure for obtaining **X-6** as a red solid. **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.52-7.35 (m, 5H), 7.26 (s, 1H), 6.82 (d, J = 8.1 Hz, 1H), 2.37 (s, 3H).

[0624] To the solution of **XXI-3** (500 mg, 1.56 mmol) in 10 mL of DMSO was added hydrazine hydrate (1 mL) at 0°C, The mixture was stirred at 100°C for 2 hrs. After being cooled, the mixture was quenched with *aq*. HCl (1M) and stirred for 1 h, extracted with EA (50 mL×3).The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE/EA=20/1) to afford **Comopund 82** (50 mg, 11% yield) as a white solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.48 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.69 (s, 2 H), 2.35 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 308.1.

[0625] **Compound 81** was obtained by reacting indolin-2-one with (4-(trifluoromethoxy)phenyl)boronic acid refluxing in anhydrous DCM under oxygen atmosphere overnight in the presence of $Cu(OAc)_2$ and 4Å molecular sieve as a white solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.47 (d, J = 8.0 Hz, 2H), 7.38-7.32 (m, 3H), 7.23 (t, J= 7.6 Hz, 1H),7.11 (t, J= 7.6 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 3.73 (s, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 294.0.

Example 10
Synthesis of Compounds 83 and 84 (Scheme XXII)



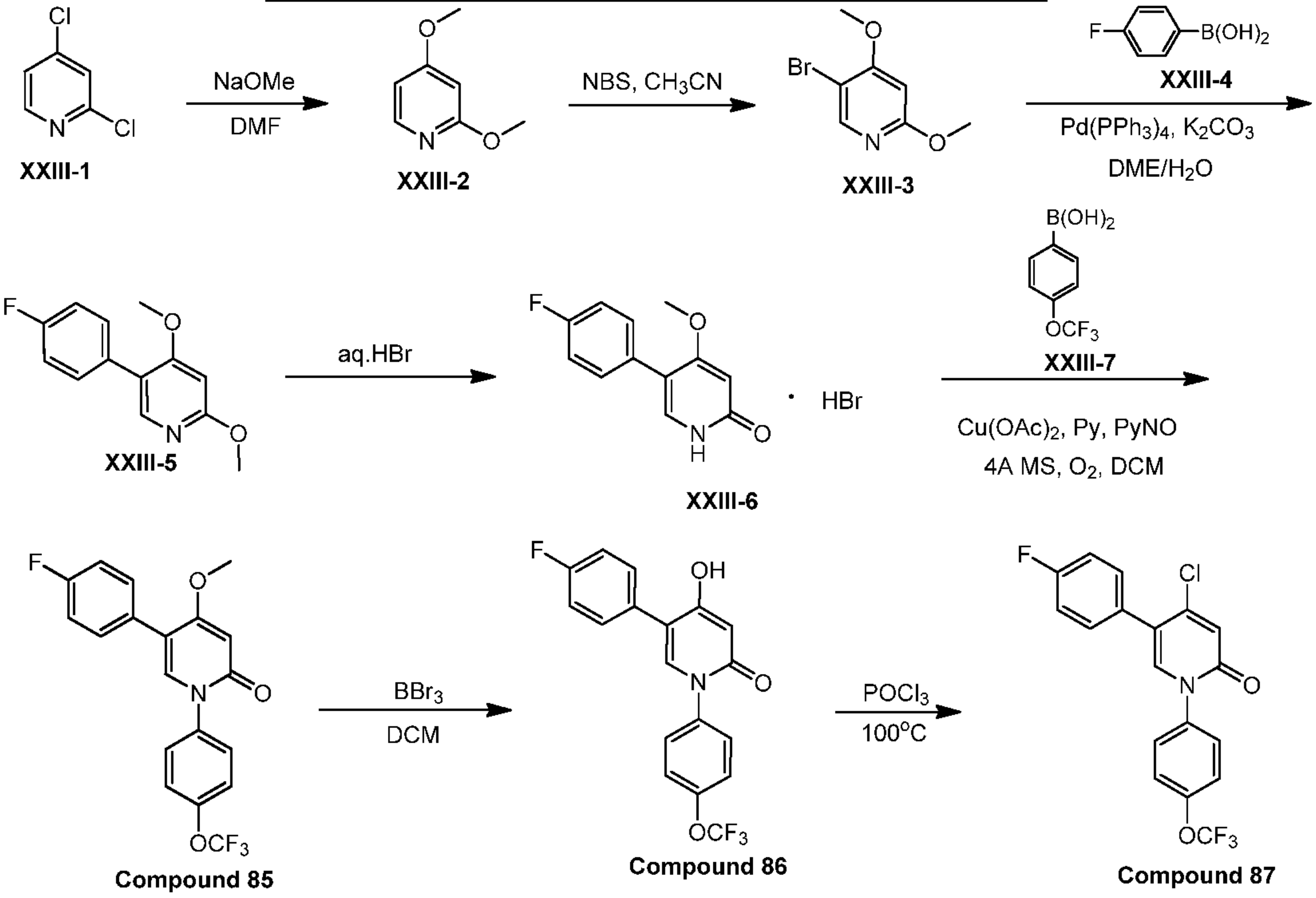
[0626] **XXII-2** was prepared following the similar procedure for obtaining **XIX-3** as a white solid.

[0627] **XXII-2** (500 mg, 2.7 mmol) was dissolved in EtOH, the solution was degassed with Ar for three times and then Raney Ni was added. The mixture was degassed by Ar and H_2 in turn for three times. The mixture was stirred at rt for 24 hrs under H_2 (15~20 psi). The reaction was detected by LCMS and TLC .The reaction mixture was filtrated and washed with EA, the filtrate was concentrated and the residue was purified by column chromatography (PE/EA=3/1) and then separated by chiral prep–HPLC to give the two pure optical enantiomer: **Compound 83** (149 mg, 30% yield) and **Compound 84** (30.3 mg, 6% yield). The absolute chirality of the two compounds was not identified.

[0628] **Compound 83: ^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41-7.37 (m, 2H), 7.27-7.23 (m, 3H), 3.59-3.54 (m, 1H), 3.36-3.30 (m, 1H), 2.66-2.50 (m, 2H), 2.19-2.10 (m, 1H), 2.00-1.94 (m, 1H), 1.67-1.57 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H) . **MS (ESI)** ***m/z*** $(M+H)^+$ 190.0. RT (SFC)=3.99.

[0629] **Compound 84: ^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41-7.37 (m, 2H), 7.27-7.23 (m, 3H), 3.59-3.55 (m, 1H), 3.36-3.31 (m, 1H), 2.66-2.50 (m, 2H), 2.19-2.10 (m, 1H), 2.00-1.94 (m, 1H), 1.67-1.57 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 190.0. RT (SFC)=4.18.

Example 11-A
Synthesis of Compounds 85-87 (Scheme XXIII)



[0630] **XXIII-1** (15 g, 0.1 mol) was dissolved in anhydrous DMF (80 mL), and then freshly prepared sodium methoxide (24 g, 0.44 mol) was added. The resulting mixture was stirred at 110 - 120 °C for 12 hrs under N_2. Cooled to rt, diluted with EA (800 mL) and washed with water and brine, dried over Na_2SO_4, concentrated. The residue was purified by flash column chromatography (PE/EA = 10:1) to give **XXIII-2** (7.5 g, 54% yield) as a colorless oil.

[0631] The mixture of **XXIII-2** (7.4 g, 53 mmol) and N-bromosuccinimide (9.3 g, 52 mmol) in anhydrous CH_3CN (250 mg) was stirred at 70-85°C for 12 hrs in dark. Cooled to rt, the mixture was concentrated and the residue was purified by flash column chromatography (PE/EA=50/1) to give **XXIII-3** (8.3 g, 72% yield) as a white solid.

[0632] **XXIII-3** (16.0 g, 38.2 mmol), **XXIII-4** (13.4 g, 95.9 mmol) and K_2CO_3 (36.6 g, 265.3 mmol) were dissolved in a mixture of DME/H_2O (250 mL /25 mL). The solution was degassed by N_2 for three times and then $Pd(PPh_3)_4$ (8.5 g, 7.37 mmol) was added. The reaction mixture was stirred at 90-100°C for 10h under N_2 and then cooled to rt, diluted with AcOEt and filtered, the filtrate was washed with brine. The separated organic phase was dried over Na_2SO_4, concentrated. The residue was purified by flash column chromatography (PE/EA = 20:1~5:1) to give **XXIII-5** (16.0 g, 93 % yield).

[0633] A solution of **XXIII-5** (15.0 g, 64.4 mmol) in *aq.*HBr (48%, 250 mL) was stirred at 100°C for 7h. Then the mixture was cooled to rt, the formed precipitate was filtrated, washed with water to give **XXIII-6** (17.6 g, yield 91%) as a white solid, which would be utilized in next step without any further purification.

[0634] To a solutin of **XXIII-6** (4.6 g, 21 mmol) in DCM (180 mL), copper (II) acetate (7.42 g, 41 mmol), **XXIII-7** (8.65 g, 42 mmol), pyridine (10 mL), pyridine-N-oxide (7.8 g, 82 mmol) and 4 Å molecular sieves (3.0 g) were added. The mixture was stirred at rt for 38 hrs under O_2 atmosphere. The mixture was filtered; the filtrate was washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by flash column chromatography (PE/EA=1/1) to give **Compound 85** (3.7 g, 46% yield) as a white solid. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.57-7.55 (m, 3H), 7.47-7.44 (m, 4H), 7.13-7.09 (m, 2H), 6.12 (s, 1H), 3.90 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 380.0.

[0635] To a solution of **Compound 85** (2.0 g, 5.26 mmol) in dry DCM (25 mL) was added BBr_3 (2.63 g, 10.52 mmol) dropwise at -65 °C~-70°C. After addition, the mixture was stirred at 5~8 °C for 12 h, but the starting material still remained. More BBr_3 (5.26 g, 21 mmol) was added dropwise at -65 °C~-70 °C, after that, the mixture was stirred at 25~30°C for 24 hrs. And then the mixture was cooled to 0 °C under ice-water bath, quenched with methanol by dropwise addition until no smoke appeared. Then the mixture was concentrated, the residue was basified to pH 8~9 with saturated *aq.*$NaHCO_3$, extracted with EA (50 mL×3), washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by flash column chromatography (PE/EtOAc= 1/2) to give **Compound 86** (1.2 g, 52 % yield) as a white solid. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.58-7.49 (m, 5H), 7.45-7.43 (m, 2H), 7.13-7.09 (m, 2H), 6.01 (s, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 366.0.

[0636] To a solution of **Compound 86** (3.3 g, 9.0 mmol) in $POCl_3$ (60 mL) was added *N*, *N* – Dimethylaniline (1.5 g, 12.4 mmol). The resulting mixture was stirred at 100 °C for 2 hrs, cooled to rt, distilled most of $POCl_3$, quenched with ice-water, and then basified to pH 7-8 with saturated *aq.* $NaHCO_3$, and extracted with EA (50 mL×3). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (PE:EA=5:1) to give **Compound 87** (2.0 g, 58% yield) as a light yellow solid. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.72 (s, 1H), 7.61-7.58 (m, 2H), 7.48-7.44 (m, 4H), 7.19-7.15 (m, 2H), 6.85 (s, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 384.0.

[0637] **Compound 88**: Compound **87** was dissolved in 4-methoxybenzylamine (2 mL), the mixture was stirred at 180°C for 2.5h under N_2. After being cooled to rt, the mixture was diluted with EA (60 mL), washed with *aq.*HCl (2 M) with brine, dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE:EA=1:2) to give an intermediate (47 mg, 50% yield) which was further dissolved in TFA (2 mL) and stirred at rt for 3h. Then it was diluted with water and basified to pH 8-9 with saturated *aq.* $NaHCO_3$, extracted with EA (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE/EA=1/3) to give **Compound 88** (30 mg, 79% yield). **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.53-7.51 (m, 2H), 7.45-7.40 (m, 4H), 7.32 (s, 1H), 7.19 (t, J = 8.8 Hz, 2H), 5.78 (s, 1H).

[0638] **Compound 89**: A mixture of **Compound 87** (75 mg , 0.2 mmol) in benzylamine (1 mL) was stirred at 180°C for 4 hrs, then it was cooled to rt and purified by flash column chromatography (PE:AE=1:1) to give **Compound 89** (80 mg, 90% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.47-7.44 (m, 2H), 7.38-7.34 (m, 4H), 7.31-7.27 (m, 5H), 7.16-7.12 (m, 2H), 7.06 (s, 1H), 5.70 (s, 1H), 4.59 (t, J = 5.2 Hz, 1H), 4.34 (d, J = 5.2 Hz, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 455.3.

[0639] **Compound 90** was prepared following the similar procedure for obtaining **Compound 88** using 1-(4-methoxyphenyl)-N-methylmethanamine in place of 4-methoxybenzylamine. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.45 (m, 2H), 7.34-7.28 (m, 4H), 7.17-7.12 (m, 2H), 7.03 (s, 1H), 5.65 (s, 1H), 4.28 (m, 1H), 2.83 (d, J = 4.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 379.0.

[0640] **Compounds 104** and **107-110** were prepared by the reaction of **Compound 88** (1 eq.) with the relevant acyl chloride (1.1 eq.) in DCM and pyridine (5 eq.). The mixture was stirred at rt overnight.

[0641] **Compound 104**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.76 (s, 1H), 7.47 (d, J = 8.8Hz, 2H), 7.36-7.30 (m, 4H), 7.23-7.19 (m, 3H), 6.96 (s, 1H), 2.06 (s, 3H).

[0642] **Compound 107**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.78 (s, 1H), 7.47 (d, J = 8.8Hz, 2H), 7.35-7.31 (m, 4H), 7.24-7.19 (m, 3H), 6.95 (s, 1H), 2.22 (t, J = 7.6Hz, 2H), 1.59-1.51 (m, 2H), 1.36-1.26 (m, 2H), 0.89 (t, J = 7.2Hz, 3H) .

[0643] **Compound 108**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.79 (s, 1H), 7.47 (d, J = 8.8Hz, 2H), 7.36-7.31 (m, 4H), 7.25-7.20 (m, 3H), 7.02 (s, 1H), 2.39-2.32 (m, 1H), 1.12 (d, J = 6.8Hz, 2H).

[0644] **Compound 109**: **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.81 (s, 1H), 7.50-7.46 (m, 2H), 7.38-7.33 (m, 4H), 7.25-7.21 (m, 3H), 6.97 (s, 1H), 2.24 (t, J = 7.5Hz, 2H), 1.59 (t, J = 6.9Hz, 2H), 1.32-1.26 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H).

[0645] **Compound 110**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.78 (s, 1H), 7.47 (d, J = 8.8Hz, 2H), 7.35-7.31 (m, 4H), 7.24-7.20 (m, 3H), 6.94 (s, 1H), 2.20 (t, J = 7.6Hz, 2H), 0.93 (t, J = 7.6Hz, 3H).

[0646] **Compound 106**: To a solution of **Compound 88** (120 mg, 0.33 mmol) in toluene (3 mL) was added propionic anhydride (50 mg, 0.38 mmol). The mixture was heated to reflux overnight. The reaction was concentrated to remove toluene. The residue was purified by prep-

HPLC to give **Compound 106** (38.2 mg, 28% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.78 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.36-7.31 (m, 4H), 7.24-7.20 (m, 3H), 6.96 (s, 1H), 2.27 (q, *J* = 7.6 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H).

[0647] Compounds **105**, **112** and **113** were prepared by reacting **Compound 88** with the relevant chloroformate in LiHMDS and THF.

[0648] **Compound 105**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.48-7.45 (m, 3H), 7.34-7.30 (m, 4H), 7.23-7.17 (m, 3H), 6.46 (s, 1H), 4.12 (d, *J* = 6.8 Hz, 2H), 1.70-1.63 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H).

[0649] **Compound 112**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.49-7.41 (m, 3H), 7.34-7.30 (m, 4H), 7.23-7.16 (m, 3H), 6.41 (s, 1H), 5.05-4.98 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 6H).

[0650] **Compound 113**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.53 (s, 1H), 7.49 (d, *J* = 9.2Hz, 4H), 7.41-7.37 (m, 4H), 7.34 (d, *J* = 8.4Hz, 2H), 7.28-7.14 (m, 3H), 7.15-7.12 (m, 2H), 6.81 (s, 1H).

[0651] **Compound 91**: To a solution of Compound **86** (250 mg, 0.7 mmol) in dry DMF (5 mL) was added BnBr (128 mg, 0.77 mmol) and Na_2CO_3 (112 mg, 1.1 mmol), the reaction mixture was stirred at rt overnight. And then it was diluted with water (10 mL), extracted by ethyl acetate (30 mL×3). The combined extract was washed with brine and water, dried over Na_2SO4, concentrated to give crude product. The crude product was purified by flash chromatography (PE/EA=5/1) to give **Compound 91** (60 mg, 19% yield). **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.59-7.56 (m, 3H), 7.53-7.49 (m, 2H), 7.46 (d, *J* =8.4 Hz, 2H), 7.40-7.33 (m, 5H), 7.14-7.09 (m, 2H), 6.23 (s, 1H), 5.23 (s, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 456.1.

[0652] Compounds **92-100** were prepared by reacting **Compound 87** with the relevant alcohol (1 eq.) in DMF and NAH (1.5 eq.) at rt for 2 hrs. After the reaction mixture was quenched with water and extract with EA, the the organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purification by prep-TLC to give the final product.

[0653] **Compound 92**: **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.47-7.45 (m, 2H), 7.41-7.37 (m, 2H), 7.35-7.33 (m, 2H), 7.24 (m, 1H), 7.08-7.04 (m, 2H), 6.06 (s, 1H), 4.15-4.12 (m, 2H), 3.69-3.66 (m, 4H), 2.76-2.74 (m, 2H), 2.47-2.45 (m, 4H). **MS (ESI)** ***m/z*** $(M+H)^+$ 479.2.

[0654] **Compound 93**: **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.47-7.45 (m, 2H), 7.38-7.32 (m, 4H), 7.23 (s, 1H), 7.09-7.05 (m, 2H), 6.06 (s, 1H), 4.30 (m, 2H), 3.06 (m, 2H), 2.70 (m, 4H), 1.84(m, 4H). **MS (ESI)** ***m/z*** $(M+H)^+$ 463.1.

[0655] **Compound 94**: **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.47-7.45 (m, 2H), 7.36-7.32 (m, 4H), 7.24 (m, 1H), 7.09-7.05 (m, 2H), 6.04 (s, 1H), 4.11-4.09 (m, 2H), 2.98-2.93 (m, 10H). **MS (ESI)** ***m/z*** $(M+H)^+$ 527.0.

[0656] **Compound 95**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.45 (m, 2H), 7.37-7.32 (m, 4H), 7.26 (s, 1H), 7.11-7.07 (m, 2H), 6.06 (s, 1H), 4.58 (m, 1H), 2.62 (m, 4H), 2.42 (s, 3H), 2.27 (m, 2H), 2.02 (m, 2H). **MS (ESI) *m/z*** $(M+H)^+$ 463.1.

[0657] **Compound 96**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.45 (m, 2H), 7.42-7.39 (m, 2H), 7.35-7.33 (m, 2H), 7.25 (s, 1H), 7.09-7.05 (m, 2H), 6.06 (s, 1H), 4.15 (t, J = 4.4 Hz, 2H), 3.72 (t, J = 4.4 Hz, 2H), 3.37 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 424.1.

[0658] **Compound 97**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.45 (m, 2H), 7.36-7.32 (m, 4H), 7.23 (s, 1H), 7.10-7.06 (m, 2H), 6.04 (s, 1H), 4.15-4.12 (m, 2H), 3.65-3.62 (m, 2H), 3.17-3.13 (m, 2H), 2.32-2.28 (m, 2H), 2.91-1.84 (m, 2H). **MS (ESI) *m/z*** $(M+H)^+$ 477.1.

[0659] **Compound 98**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.44 (m, 2H), 7.35-7.32 (m, 4H), 7.23 (s, 1H), 7.10-7.06 (m, 2H), 6.04 (s, 1H), 4.22-4.19 (m, 2H), 4.10 (s, 2H), 3.73-3.71 (m, 2H), 3.62-3.59 (m, 2H), 3.11-3.08 (m, 2H). **MS (ESI) *m/z*** $(M+H)^+$ 492.9.

[0660] **Compound 99**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.44 (m, 2H), 7.36-7.29 (m, 5H), 7.14-7.10 (m, 2H), 6.06 (s, 1H), 4.72 (s, 1H), 3.05-2.91 (m, 4H), 2.53-2.39 (m, 4H). **MS (ESI) *m/z*** $(M+H)^+$ 498.0.

[0661] **Compound 100**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.45 (m, 2H), 7.39-7.32 (m, 4H), 7.24 (s, 1H), 7.09-7.04 (m, 2H), 6.05 (s, 1H), 4.14-4.11 (m, 2H), 2.83-2.80 (m, 2H), 2.69 (brm, 4H), 2.49 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 492.1.

[0662] **Compound 102**: To a stirred mixture of **Compound 87** (200 mg, 0.521 mmol), phenol (59 mg, 0.625 mmol), and K_3PO_4 (331 mg, 1.56 mmol) in THF (5 mL) was added $Pd_2(dba)_3$ (96 mg, 0.104 mmol). The mixture was purged with nitrogen for three times and then heated to reflux overnight. The mixture was concentrated to remove THF, diluted with H_2O, extracted with EtOAc (30 mL×3), the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the crude product was purified by prep-HPLC to give **Compound 102** (158 mg, 69% yield) as a yellow solid. **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 7.53-7.42 (m, 6H), 7.35-7.33 (m, 3H), 7.30-7.26 (m, 1H), 7.14-7.09 (m, 4H), 5.82 (s, 1H).

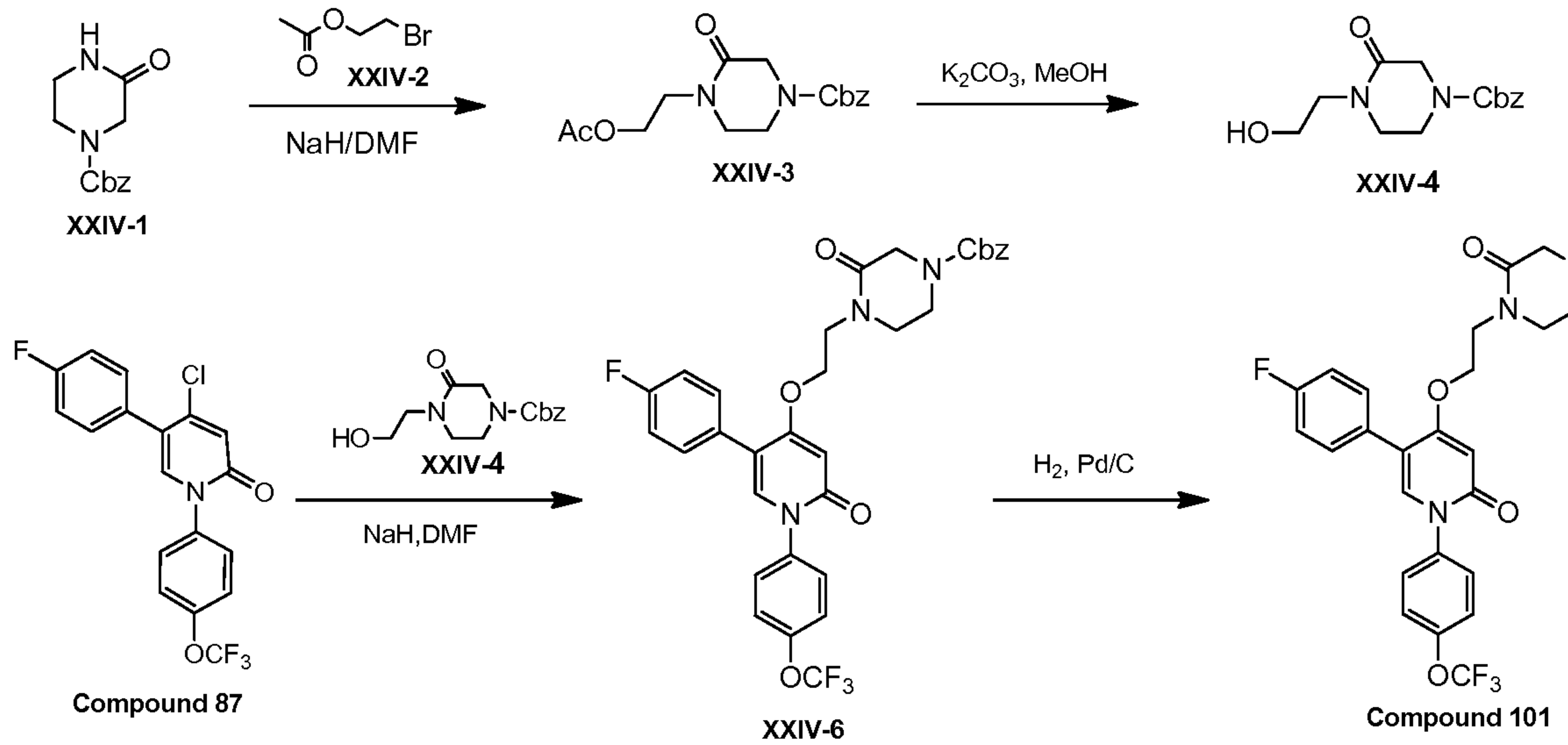
[0663] **Compound 541** was prepared following the similar procedure described in the synthesis of **Compound 85** by reacting 4-chloro-5-(4-fluorophenyl)pyridin-2(1H)-one with 2-methyl-4-ethoxy boronic acid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.66 (s, 1H), 7.49 (m, 2H), 7.28-7.20 (m, 3H), 6.93 (s, 1H), 6.93-6.87 (m, 1H), 6.81 (s, 1H), 4.05 (q, J =6.8 Hz, 2H), 2.06 (s, 3H), 1.33 (t, J = 6.8 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 358.0.

[0664] **Compound 551** was prepared by reacting Compound **541** with 2-methoxyethanol in DMF and KOH at 150°C overnight. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45-7.39 (m, 2H), 7.14-7.02

(m, 4H), 6.85-6.80 (m, 2H), 6.07 (s, 1H), 4.14 (t, *J* =4.4 Hz, 2H), 4.04 (q, *J* =7.2 Hz, 2H), 3.72 (t, *J* =4.4 Hz, 2H), 3.38 (s, 3H), 2.16 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 398.2.

[0665] **Compound 550** was prepared following the similar procedure for the synthesis of Compound **551** using 4-chloro-2-methoxy-5-(1-methyl-1H-pyrazol-4-yl)pyridine in place of **XXIII-5**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (s, 1H), 7.63 (s, 1H), 7.29 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 1 H), 6.85-7.96 (m, 2H), 6.05 (s, 1H), 4.18 (t, *J* = 4.4 Hz, 2H), 4.06 (q, *J* =6.8 Hz, 2 H), 3.91 (s, 3H), 3.82 (t, *J* = 4.4 Hz, 2H), 3.48 (s, 3H), 2.14 (s, 3H), 1.42 (t, *J* = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 384.1.

Example 11-B
Synthesis of Compound 101 (Scheme XXIV)



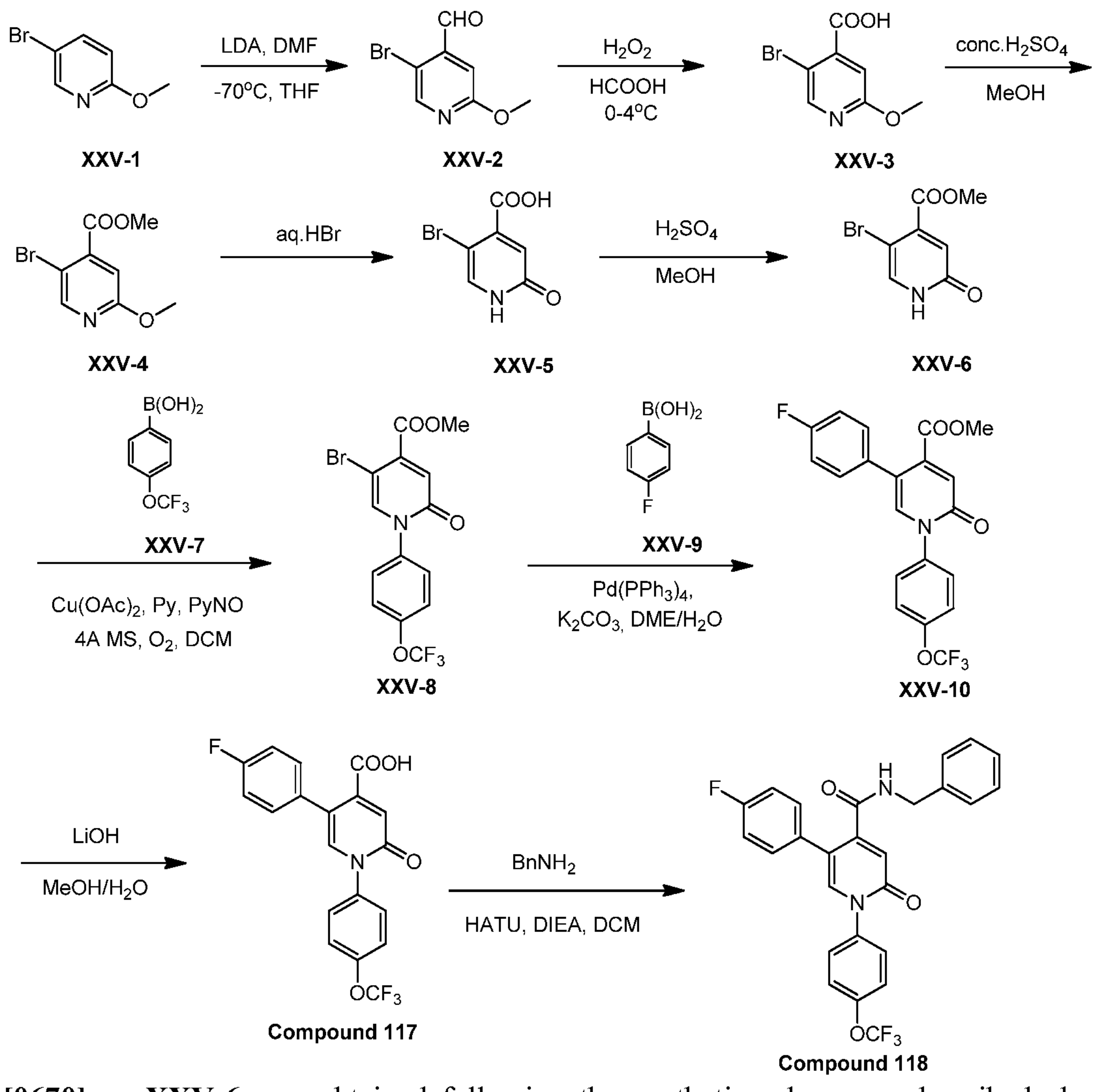
[0666] To the solution of **XXIV-1** (20 g, 85.5 mmol) in DMF (100 mL) was added NaH (60%, 4.1 g, 103 mmol) in portions. The mixture was stirred at rt for 30 min. Then **XXIV-2** (14.3 g, 85.5 mmol) was added. The reaction was stirred at rt overnight. The reaction was quenched with ice-water carefully, and then extracted with EtOAc (100 mL×2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was used for next step directly (40 g, 140% crude yield).

[0667] To the solution of **XXIV-3** (6.8 g, 21.25 mmol) in MeOH (50 mL) was added K_2CO_3 (8.8 g, 64 mmol). The mixture was stirred at rt for 2hrs. Then concentrated, diluted with H_2O, extracted with EtOAc (100 mL×2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was used directly (3.0 g, 51% yield).

[0668] To the solution of **XXIV-4** (900 mg, 3.24 mmol) in DMF (10 mL) was added NaH (60%, 160 mg, 3.9 mmol). The mixture was stirred at rt for 30 min. Then **Compound 87** (1.25 g, 3.24 mmol) was added. The reaction was stirred at rt overnight. LCMS showed the reaction was completed. The reaction was quenched with ice-water carefully, and then extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give **XXIV-6** (140 mg, 22% yield).

[0669] A mixture of **XXIV-6** (140 mg, 0.224 mmol) and Pd/C in ethanol (5 mL) was stirred under H_2 at rt for 4 hours. Filtered the reaction, and concentrated. The residue was purified by prep-HPLC to afford **Compound 101** (30.9 mg, 28% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.45-7.40 (m, 2H), 7.36-7.31 (m, 4H), 7.26 (m, 1H), 7.11-7.07 (m, 2H), 6.14 (s, 1H), 4.18 (m, 2H), 3.75-3.70 (m, 4H), 3.30 (m, 2H), 3.07 (m, 2H).

Example 11-C
Synthesis of Compounds 117 and 118 (Scheme XXV)



[0670] **XXV-6** was obtained following the synthetic scheme as described above. **MS (ESI)** *m/z* $(M+H)^+$ 231.95.

[0671] **XXV-10** was prepared following the similar procedure for obtaining **Compound 40**. **^{1}HNMR** ($CDCl_3$, 400MHz) δ 7.50-7.42 (m, 2H), 7.40-7.31 (m, 4H), 7.26-7.20 (m, 1H), 7.10-7.03 (m, 3H), 3.73 (s, 3H).

[0672] **Compound 117**: The mixture of **XXV-10** (1.0 g, 2.5 mmol), $LiOH.H_2O$ (1.0 g, 24 mmol) in $MeOH/H_2O$ (15 mL/3 mL) was stirred at rt overnight. The mixture was evaporated and then acidified with *aq.* HCl (2 M) to pH=4~5, extracted with EtOAc (30 mLx3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give **Compound 117** (806 mg, 83% yield) as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) *δ* 7.80 (s, 1H), 7.72-7.67 (m, 2H), 7.57-7.53 (m, 2H), 7.43-7.38 (m, 2H), 7.25-7.20 (m, 2H), 6.75 (s, 1H). **MS (ESI) *m/z*** $[M+H]^+$ 394.0.

[0673] **Compound 118**: To a solution of **Compound 117** (98.2 mg, 0.25 mmol) in dry DCM (40 mL) was added benzyl amine (29 mg, 0.28 mmol), followed by adding HATU (105 mg, 0.28 mmol) and DIEA (65 mg, 0.5 mmol). The reaction mixture was stirred at rt overnight. The resulting mixture was concentrated to remove solvent, diluted with EtOAc (50 mL), washed with 5% citric acid, sat. *aq.* $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated to give crude product. The crude product was purified by prep-TLC (PE: EA=5:1) to yield **Compound 118** (10 mg, 8.3% yield) as a yellow solid. **^{1}HNMR** (CD_3OD, 400 MHz) δ 7.69 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.34-7.26 (m, 5H), 7.12-7.10 (m, 2H), 7.02-6.98 (m, 2H), 6.69 (s, 1H), 4.38 (s, 2H). **MS (ESI) *m/z*** $(M+H)^+$ 483.1.

[0674] General procedure for preparing Compounds **103, 111,** and **114**: To a mixture of **Compound 117** (1 eq.) in toluene was added TEA (2.6 eq.) and 4Å molecular sieve. The mixture was stirred at 100°C for 1h, then DPPA (1.05 eq.) and the relevant alcohol (1.2 eq.) was added under N_2 protection. The reaction mixture was stirred at 110°C overnight. The mixture was concentrated, diluted with H_2O, extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the residue was purified by prep-TLC (PE:EA=2:1) to give the final product.

[0675] **Compound 103**: **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.52 (s, 1H), 7.49-7.45 (m, 2H), 7.44-7.26 (m, 9H), 7.22-7.15 (m, 3H), 6.53 (s, 1H), 5.18 (s, 2H). **MS (ESI) *m/z*** $[M+H]^+$ 499.0.

[0676] **Compound 111**: **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.47-7.45 (m, 3H), 7.33-7.30 (m, 4H), 7.21-7.17 (m, 3H), 6.50 (s, 1H), 3.76 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 422.0.

[0677] **Compound 114**: **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.50-7.45 (m, 3H), 7.35-7.30 (m, 4H), 7.22-7.17 (m, 3H), 6.46 (s,1H), 4.21 (q, *J* = 6.8 Hz, 2 H), 1.28 (t, *J* = 6.8 Hz, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 436.1.

[0678] General procedure for preparing Compounds **115** and **116**: To the solution of **Compound 117** (1 eq.) in toluene was added TEA (2.5 eq) and 4Å molecular sieve (100 mg). The mixture was heated to 100°C for 30 minutes.Then cooled to 80°C, the relevant amine (1.2 eq.) and DPPA (1.2 eq) were added. The mixture was heated to 110°C for 3 hrs. The mixture was filtered, diluted with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to give the final product.

[0679] **Compound 115**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.35-7.30 (m, 5H), 7.20-7.15 (m, 3H), 6.09 (s, 1H), 4.77 (s, 1H), 3.13 (d, J=6.0 Hz, 2H), 1.51 (m, 2H), 0.90 (t, J =7.2 Hz, 3H).

[0680] **Compound 116**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33 (s, 2H), 7.26-7.22 (m, 5H), 7.21-7.17 (m, 6H), 7.03-6.97 (m, 3H), 6.90 (brs, 1H), 4.24 (d, J =5.2 Hz, 2H).

[0681] **Compound 119** was prepared following the similar procedure for obtaining **Compound 85** using (4-ethoxy-2-methylphenyl)boronic acid in place of **XXIII-7**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38-7.34 (m, 2H), 7.13-7.11 (m, 2H), 7.08-7.04 (m, 2H), 6.84-6.78 (m, 2H), 6.10 (s, 1H), 4.04 (q, J = 7.2 Hz, 2 H), 3.85 (s, 3H), 2.17 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H). **MS (ESI)** *m/z* $(M+H)^+$ 353.9.

[0682] **Compound 120** was prepared following the similar procedure for obtaining **Compound 85** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of **XXIII-4** as a white solid. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.61 (m, 2H), 7.47-7.43 (m, 2H), 7.38-7.33 (m, 3H), 6.07 (s, 1H), 3.93 (s, 3H), 3.91(s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 365.9.

[0683] **Compound 121** was prepared following the similar procedure for obtaining **Compound 86**. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 7.97 (s, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 7.55-7.53 (m, 2H), 7.48-7.46 (m, 2H), 6.00 (s, 1H), 3.89 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 352.0.

[0684] **Compound 122** was prepared following the similar procedure for obtaining **Compound 87**. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.88 (s, 1H), 7.81 (s, 1H), 7.68 (s, 1H), 7.59-7.57 (m, 2H), 7.48-7.46 (m, 2H), 6.84 (s, 1H), 4.90 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 370.1.

[0685] General procedure for preparing Compounds **123, 126-129, 131-135, 160** and **161**: A mixture of **Compound 122** (200 mg, 0.542 mmol) in the relevant amine (1 mL) was stirred at 130~160 °C for 4 hrs. After being cooled to rt, the mixture was diluted with H_2O, extracted with EtOAc, the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the crude product was purified by flash column chromatography (PE:AE=1:3) to give the final product.

[0686] **Compound 123**: **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.82 (s, 1H), 7.64 (s, 1H), 7.51-7.47 (m, 2H), 7.42-7.38 (m, 2H), 7.36-7.35 (m, 5H), 7.28-7.25 (m, 1H), 5.53 (s, 1H), 4.45 (d, J = 4.4 Hz, 2H), 3.97 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 441.1.

[0687] **Compound 126**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55 (s, 1H), 7.50-7.45 (m, 2H), 7.40 (s, 1H), 7.33-7.28 (m, 4H), 7.25 (m, 1H), 7.13-7.09 (m, 3H), 6.00 (s, 1H), 4.16 (s, 2H), 3.81 (s, 3H), 2.65 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 455.

[0688] **Compound 127**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.61 (s, 1H), 7.55 (s, 1H), 7.46-7.42 (m, 2H), 7.32-7.28 (m, 2H), 7.12 (s, 1H), 6.05 (s, 1H), 3.93 (s, 3H), 2.91 (m, 4H), 1.56 (m, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 419.

[0689] **Compound 128**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 7.52 (s, 1H), 7.45-7.41 (m, 2H), 7.32-7.28 (m, 2H), 7.12 (s, 1H), 6.06 (s, 1H), 3.92 (s, 3H), 3.70 (m, 4H), 2.96 (m, 4H). **MS (ESI)** ***m/z*** $(M+H)^+$ 421.1.

[0690] **Compound 129**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.60 (s, 1H), 7.51 (s, 1H), 7.48-7.45 (m, 2H), 7.33-7.30 (m, 2H), 7.20-7.17 (m, 3H), 7.13-7.11 (m, 1H), 7.08-7.05 (m, 1H), 6.23 (s, 1H), 4.23 (s, 2H), 3.89 (s, 3H), 3.28 (t, J = 6.0 Hz, 2H), 2.77 (t, J = 6.0 Hz, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 467.1.

[0691] **Compound 131**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45-7.41 (m, 2H), 7.37-7.26 (m, 6H), 7.18-7.16 (m, 2H), 7.08 (s, 1H), 7.02 (s, 1H), 5.70 (s, 1H), 4.43 (t, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.42 (q, J = 6.4 Hz, 2H), 2.93 (t, J = 6.4 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 454.0.

[0692] **Compound 132**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49 (s, 1H), 7.45-7.42 (m, 2H), 7.39-7.33 (m, 3H), 7.31-7.24 (m, 3H), 7.05 (s, 1H), 5.90 (s, 1H), 4.61-4.55 (m, 3H), 3.91 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 508.0.

[0693] **Compound 133**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49 (s, 1H), 7.44-7.39 (m, 3H), 7.30-7.26 (m, 3H), 7.04 (s, 1H), 6.95-6.90 (m, 2H), 5.81 (s, 1H), 4.79 (t, J = 6.0 Hz, 1H), 4.41 (d, J = 6.0 Hz, 2H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 477.1.

[0694] **Compound 134**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51 (s, 1H), 7.45-7.39 (m, 3H), 7.30-7.25 (m, 2H), 7.22-7.20 (m, 2H), 7.06 (s, 1H), 6.90-6.87 (m, 2H), 5.70 (s, 1H), 4.70 (t, J = 5.2 Hz, 1H) , 4.25 (d, J = 5.2 Hz, 2H), 3.93 (s, 3H), 3.81 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 471.2.

[0695] **Compound 135**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56 (s, 1H), 7.48-7.42 (m, 3H), 7.32-7.30 (m, 2H), 7.13 (s, 1H), 7.03-7.00 (m, 2H), 6.85-6.81 (m, 2H), 5.98 (s, 1H), 4.08 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.59 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 485.0.

[0696] **Compound 160**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.56-8.55 (m, 2H), 7.61 (d, J =8.0 Hz, 1H), 7.52 (s, 1H), 7.43-7.41 (m, 3H), 7.31-7.28 (m, 3H), 7.08 (s, 1H), 5.64 (s, 1H), 4.82 (t, J = 5.6 Hz, 1H), 4.37 (d, J = 5.6 Hz, 2H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 442.0.

[0697] **Compound 161**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.53 (d, J = 4.4 Hz, 1H), 7.71-7.67 (m, 1H), 7.61 (s, 1H), 7.54 (s, 1H), 7.46-7.44 (m, 2H), 7.30-7.27 (m, 3H), 7.23-7.20 (m, 1H), 7.11 (s, 1H), 6.10 (t, J = 4.4 Hz, 1H), 5.67 (s, 1H), 4.44 (d, J = 4.4 Hz, 2H), 3.98 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 442.0.

[0698] **Compound 124**: **Compound 134** (200 mg, 0.42 mmol) was dissolved in TFA (3 mL). The solution was stirred at rt for 3 days under N_2. After the material was consumed, most of TFA was evaporated, the remaining mixture was diluted with water and neutralized with saturated *aq*. $NaHCO_3$, extracted with EA (30 mL×3), the organic phase was washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by prep-TLC (PE/EA =1/3) to give **Compound 124** (50 mg, 34% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.54 (s, 1H), 7.45-7.43 (m, 3H), 7.31-7.29 (m, 2H), 7.12 (s, 1H), 5.80 (s, 1H), 4.39 (brs, 2H), 3.96 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 350.9.

[0699] **Compound 125** was prepared from **Compound 135** following the similar procedure for obtaining **Compound 124**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50 (s, 1H), 7.45~7.41 (m, 3H), 7.30~7.28 (m, 2H), 7.04 (s, 1H), 5.63 (s, 1H), 4.50 (t, J = 4.8 Hz, 1H), 3.95 (s, 3H), 2.83 (d, J = 4.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 364.9.

[0700] **Compound 130**: To a stirred mixture of **Compound 122** (100 mg, 0.271 mmol, 1 eq.), aniline (76 mg, 0.81 mmol, 3.0 eq), Xantphos (8 mg, 0.0135 mmol, 0.05 eq.), and K_3PO_4 (57 mg, 0.271 mmol, 1.0 eq.) in DMF (2 mL) was added $Pd_2(dba)_3$ (12 mg, 0.0135 mmol, 0.05 eq.). The mixture was purged with nitrogen for three times and then heated at 100°C under nitrogen overnight. After being cooled to rt, the mixture was diluted with H_2O (10 mL), extracted with EtOAc (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by Prep-HPLC to afford **Compound 130** (20 mg, 18% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.62 (s, 1H), 7.53 (s, 1H), 7.47-7.44 (m, 2H), 7.38 (t, J =7.6 Hz, 2H), 7.32 (d, J =8.4 Hz, 2H), 7.22-7.18 (m, 4H), 6.20 (s, 1H), 6.12 (s, 1H), 3.99 (s, 3H).

[0701] **Compound 158** was prepared following the similar procedure for obtaining **Compound 117** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of **XXV-9** as a white solid. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.71 (m, 2H), 7.61-7.58 (m, 2H), 7.55 (s, 1H), 7.48-7.46 (m, 2H), 6.83 (s, 1H), 3.88 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 380.1.

[0702] **Compound 159** was prepared following the similar procedure for obtaining **Compound 118** using propan-1-amine in place of benzyl amine as a white solid. **^{1}H NMR** (400

MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.46 (s, 1H), 7.35-7.32 (m, 3H), 7.29-7.26 (m, 2H), 6.85 (t, J = 4.8 Hz, 1H), 6.59 (s, 1H), 3.86 (s, 3H), 3.22 (q, J = 6.4 Hz, 2H), 1.45 (q, J = 7.2 Hz, 2H), 0.82 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 420.1.

[0703] **Compounds 136-140** were prepared from **Compound 158** following the similar procedure for obtaining **Compound 103**.

[0704] **Compound 136**: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.45-7.41 (m, 4H), 7.32-7.29 (m, 2H), 7.17 (s, 1H), 6.71 (s, 1H), 4.18-4.14 (m, 2H), 3.98 (s, 3H), 1.67-1.59 (m, 2H), 1.42-1.23 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 450.1.

[0705] **Compound 137**: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.45 (s, 1H), 7.43-7.41 (m, 3H), 7.29-7.27 (m, 2H), 7.16 (s, 1H), 6.72 (s, 1H), 4.22-4.17 (m, 2H), 3.96 (s, 3H), 1.28-1.25 (m, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 422.1.

[0706] **Compound 138**: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.45-7.43 (m, 4H), 7.33-7.30 (m, 2H), 7.18 (s, 1H), 6.75 (s, 1H), 3.98 (s, 3H), 3.77 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 408.1.

[0707] **Compound 139**: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.47-7.43 (m, 4H), 7.33-7.30 (m, 2H), 7.17 (s, 1H), 6.65 (s, 1H), 5.05-5.00 (m, 1H), 3.98 (s, 3H), 1.28 (d, J = 6.0 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 436.1.

[0708] **Compound 140**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.49 (s, 2H), 7.44-7.40 (m, 3H), 7.38 (m, 5H), 7.33-7.30 (m, 2H), 7.29 (s, 1H), 7.16 (s, 1H), 6.77 (s, 1H), 5.18 (s, 2H), 3.95 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 484.14.

[0709] **Compound 141**: **Compound 124** (150 mg, 0.43 mmol) was dissolved in 6 mL of DCM/pyridine (v/v=1/1), and then acetyl chloride (36 mg, 0.46 mmol) was added. The mixture was stirred at rt overnight. Then the mixture was diluted with DCM (50 mL), washed with water and brine, dried over Na_2SO_4, concentrated *in vacuo* to give the crude product. The crude product was purification by prep-TLC (PE/EA =1/1) to afford **Compound 141** (70 mg, 42% yield). ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.73 (s, 1H), 7.54 (s, 1H), 7.45-7.43 (m, 3H), 7.32-7.30 (m, 2H), 7.22-7.19 (m, 2H), 3.99 (s, 3H), 2.12 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 392.9.

[0710] **Compound 142** was prepared following the similar procedure for obtaining **Compound 141** using bezoyl chloride in place of acetyl chloride. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (s, 1H), 7.94 (s, 1H), 7.68-7.64 (m, 3H), 7.58-7.55 (m, 1H), 7.49-7.44 (m, 5H), 7.34-7.32 (m, 2H), 7.25 (s, 1H), 4.00 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 455.

[0711] **Compound 143** was prepared from **Compound 121** following the similar procedure for obtaining **Compound 91**. ^{1}**H NMR** (CD_3OD, 400 MHz) δ 7.83 (s, 2H), 7.73 (s, 1H), 7.56 (d, J = 6.4 Hz, 2H), 7.54-7.37 (m, 7H), 6.20 (s, 1H), 5.27 (s, 2H), 3.84 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 442.1.

[0712] Compounds **144-152** were prepared by reacting **Compound 121** with the relevant alcohol (1 eq.) in DMF and NAH (1.5 eq.) at rt for 2 hrs. After the reaction mixture was quenched with water and extract with EA, the the organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purification by prep-TLC to give the final product.

[0713] **Compound 144**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.94 (s, 1H), 7.87 (s, 1H), 7. 78 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 5.99 (s, 1H), 4.20-4.18 (m, 2H), 3.80 (s, 3H), 3.75-3.73 (m, 2H), 3.35 (s, 3H).

[0714] **Compound 145**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.80 (s, 1H), 7.63 (s, 1H), 7. 46-7.44 (m, 2H), 7.38 (s, 1H), 7.33-7.26 (m, 2H), 6.05 (s, 1H), 4.18 (m, 2H), 3.91 (s, 3H), 2.97-3.00 (m, 2H), 2.62 (m, 4H), 1.82 (m, 4H).

[0715] **Compound 146**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.80 (s, 1H), 7.55 (s, 1H), 7. 42-7.46 (m, 3H), 7.33-7.35 (m, 2H), 6.04 (s, 1H), 4.15 (t, J =5.2 Hz, 2H), 3.95 (s, 3H), 3.83 (t, J =5.2 Hz, 2H), 3.39 (t, J =6.8 Hz, 2H), 2.36 (t, J =8.0 Hz, 2H), 2.05-1.98 (m, 2H).

[0716] **Compound 147**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H), 7.67 (s, 1H), 7.45-7.43 (m, 2H), 7.39 (s, 1H), 7.33-7.26 (m, 2H), 6.05 (s, 1H), 4.16 (t, J =5.2 Hz, 2H), 3.92 (s, 3H), 3.74 (m, 4H,), 2.85 (t, J =5.2 Hz, 2H), 2.56 (m, 4H).

[0717] **Compound 148**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65 (s, 1H), 7.56 (s, 1H), 7.46-7.44 (m, 2H), 7.36-7.34 (m, 3H), 6.05 (s, 1H), 4.17-4.14 (m, 2H), 3.93 (s, 3H), 3.11-3.03 (m, 10H). **MS (ESI)** ***m/z*** $(M+H)^+$ 513.1.

[0718] **Compound 149**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55 (s, 1H), 7.43 (m, 3H), 7. 35 (m, 3H,), 6.06 (s, 1H), 4.73 (m, 1H), 3.95 (s, 3H), 3.21-3.14 (m, 2H), 3.03-2.09 (m, 2H), 2.59-2.45 (m, 4H).

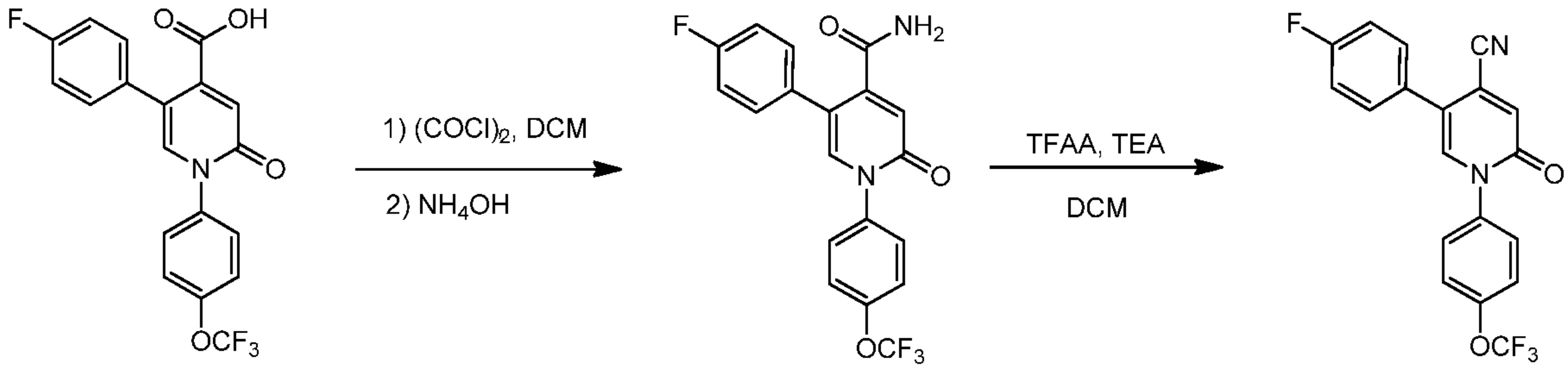
[0719] **Compound 150**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (s, 1H), 7.56 (s, 1H), 7.46-7.44 (m, 2H), 7.38-7.33 (m, 3H), 6.05 (s, 1H), 4.24-4.21 (m, 2H), 4.16 (s, 2H), 3.93-3.91 (m, 5H), 3.84-3.81 (m, 2H), 3.39-3.37 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 479.1.

[0720] **Compound 151**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.59 (s, 1H), 7.54 (s, 1H), 7.46-7.43 (m, 2H), 7.37-7.34 (m, 3H), 6.06 (s, 1H), 4.61-4.58 (m, 1H), 3.94 (s, 3H), 2.90 (m, 2H), 2.55 (m, 3H), 2.18-2.08 (m, 2H), 1.80-1.67 (m, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 449.0.

[0721] **Compound 152**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.82 (s, 1H), 7.65 (s, 1H), 7.46-7.44 (m, 2H), 7.40 (s, 1H), 7.39-7.32 (m, 2H), 6.04 (s, 1H), 4.16 (t, J = 5.6 Hz, 2H), 3.95 (s, 3H), 2.87 (t, J = 5.6 Hz, 2H), 2.61-2.49 (m, 8H), 2.31 (s, 3H).

[0722] **Compound 153**: **Compound 122** (1.5 g, 4.06 mmol), phenol (763 mg, 8.12 mmol) and K_3PO_4 (2.6 g, 12.2 mmol) were added into DMF (15 mL). The solution was degassed by N_2 for three times and then $Pd_2(dba)_3$ (570 mg, 0.81 mmol) was added. The reaction mixture was stirred at 110°C for 14 hrs under N_2. After being cooled to rt, the mixture was diluted with EA (80 mL) and filtered; the filterate was washed with brine. The separated organic phase was dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash column chromatography (PE/EA =1/1) to give **Compound 153** (848 mg, 49 % yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H), 7.69 (s, 1H), 7.50-7.44 (m, 5H), 7.36-7.26 (m, 3H), 7.16 (m, 2H), 5.79 (s, 1H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 428.

[0723] **Compound 156** was prepared following the similar procedure for obtaining **Compound 153** using 3-chloro-5-hydroxybenzonitrile in place of phenol. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.64-7.59 (m, 3H), 7.52 (s, 1H), 7.48-7.44 (m, 3H), 7.39-7.36 (m, 3H), 5.82 (s, 1H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 486.9.



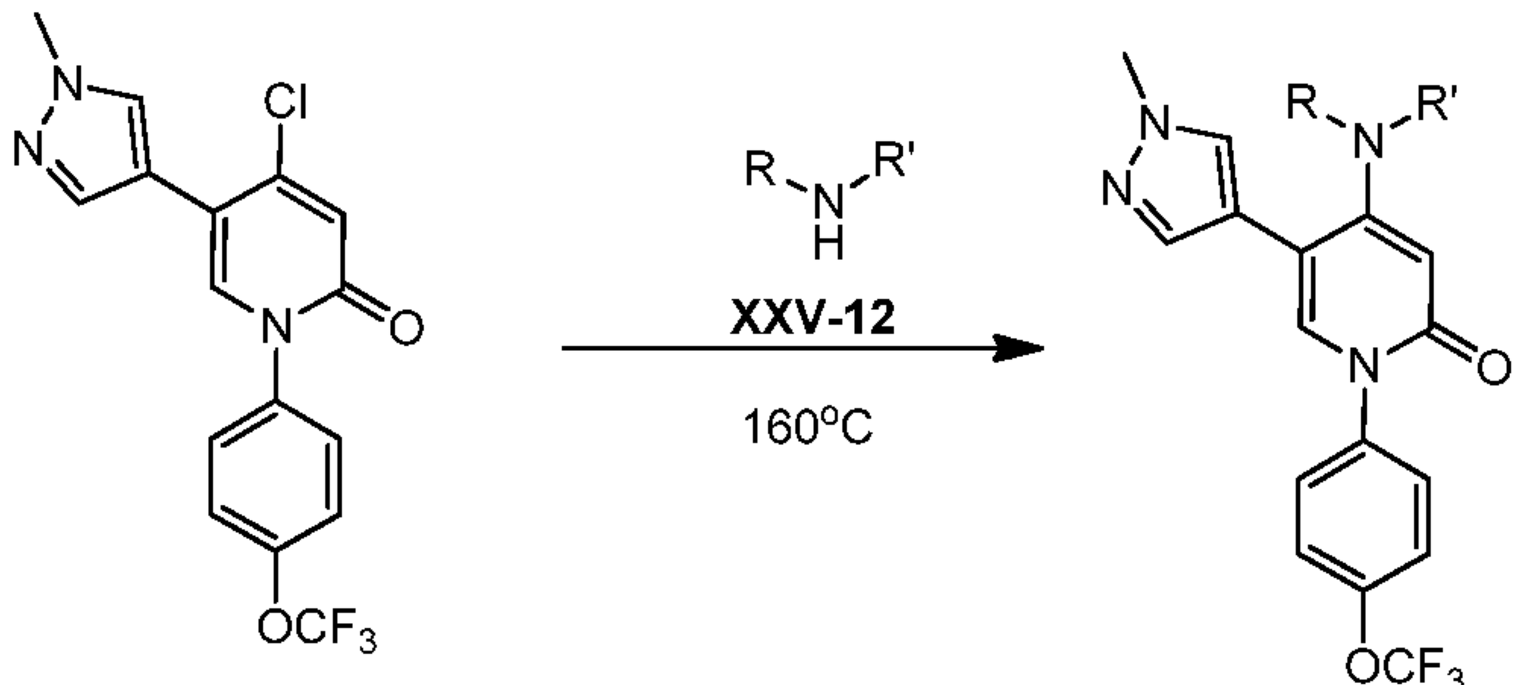
Compound 117 XXV-11 Compound 401

[0724] To a stirred mixture of **Compound 117** (350 mg, 0.89 mmol) in 10 mL of DCM was added oxalyl chloride (335 mg, 2.63 mmol) at 0°C. The mixture was stirred for 2hrs, and then the mixture was concentrated under reduced pressure. The residue was re-dissoloved in DCM (10 mL) and the mixture was added to the well-stirred ammonia (5 mL) at 0°C. After the mixture was stirred at 0°C for 30 min, the reaction mixture was extracted with EA (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (CH_2Cl_2/MeOH= 20/1) to give **XXV-11** (220 mg, 63% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 393.1.

[0725] To a solution of **XXV-11** (220 mg, 0.56 mmol) in 10 mL of DCM was added TEA (85.3 mg, 0.84 mmol) and TFAA (81.6 mg, 0.84 mmol). The reaction mixture was stirred at rt under N_2 for 3 hrs and then diluted with DCM (30 mL) and filtered. The filtrate was washed with brine, dried over Na_2SO_4, the residue was purified by prep-HPLC to give **Compound 401** (180 mg, 86% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.37 (m, 7H), 7.19-7.14 (m, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 375.1.

[0726] **Compound 402** was prepared following the similar procedure for obtaining Compound **401** using Comound **158** in place of Compound **117**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H), 7.76 (d, J = 9.6 Hz, 1H), 7.61 (s, 3H), 7.39 (m, 2H), 7.12 (d, J = 9.6 Hz, 1H), 3.97 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 361.1.

[0727] **Compound 403** was prepared following the similar procedure for obtaining Compound **153** using 4-chloro-1-(4-ethoxy-2-methylphenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2(1H)-one in place of Compound **122**. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.74 (s, 1H), 7.67 (s, 1H), 7.47-7.43 (m, 2H), 7.39 (s, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.17 (d, J = 3.6 Hz, 2H), 7.12 (d, J = 3.6 Hz, 2H), 6.85-6.80 (m, 2H), 5.80 (s, 1H), 4.04 (q, J = 7.2 Hz, 2 H), 3.92 (s, 3H), 2.15 (s, 3H), 1.32 (t, J = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 402.2.



Compound 122

XXV-13

[0728] A mixture of **Compound 122** in the relevant amine (1 mmol/1 mL) was stirred at 160°C for 4 hrs. After being cooled to rt, the mixture was diluted with H_2O, extracted with EtOAc, the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the crude product was purified by column chromatography (PE/EtOAc =1/1) to give the final products.

[0729] Alternatively, a solution of Compound **122** (1.355 mmol) in toluene (20 mL) were added the relevant amine (2.71 mmol), NaOtBu (520 mg, 5.42 mmol), Xphos (64.9 mg, 0.136 mmol), $Pd(OAc)_2$ (30.5 mg, 0.136 mmol). The mixture was degassed under in vacuum and purged with N_2 three times. The reaction mixture was heated to 100°C or to reflux overnight. The mixture was cooled to rt, diluted with water, extracted with EA. The combined organic layer was dried over Na_2SO_4, concentrated in vacuum. The residual was purified by silica gel chromatography eluted with DCM:MeOH (50:1-10:1) to give the final product.

[0730] Compounds **404-407**, **411, 526-531**, and **546-549** were prepared following the general scheme as illustrated above.

[0731] **Compound 404**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.50 (s, 1H), 7.43-7.39 (m, 3H), 7.30-7.25 (m, 3H), 7.06 (s, 1H), 6.88-6.80 (m, 2H), 5.64 (s, 1H), 4.85 (t, *J* = 6.0 Hz, 1H), 4.34 (d, *J* = 6.0 Hz, 2H), 3.93 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 477.1.

[0732] **Compound 405**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.54 (s, 1H), 7.45-7.40 (m, 4H), 7.30-7.24 (m, 4H), 7.08 (s, 1H), 5.59 (s, 1H), 4.92 (t, *J* = 6.0 Hz, 1H), 4.38 (d, *J* = 6.0 Hz, 2H), 3.95 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 510.1.

[0733] **Compound 406**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.52 (s, 1H), 7.47-7.40 (m, 3H), 7.35-7.20 (m, 5H), 7.11 (s, 1H), 5.91 (s, 1H), 4.97 (t, *J* = 6.0 Hz, 1H), 4.34 (d, *J* = 6.0 Hz, 2H), 3.95 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 475.1.

[0734] **Compound 407**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.52 (s, 1H), 7.46-7.41 (m, 3H), 7.32-7.25 (m, 4H), 7.08-7.03 (m, 3H), 5.65 (s, 1H), 4.77 (t, *J* = 5.6 Hz, 1H), 4.30 (d, *J* = 5.6 Hz, 2H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 458.9.

[0735] **Compound 411**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.62 (s, 1H), 8.53 (s, 2H), 7.60 (s, 1H), 7.50 (s, 1H), 7.45-7.43 (m, 2H), 7.31-7.29 (m, 2H), 7.12 (s, 1H), 5.74 (t, *J* = 5.2 Hz, 1H), 5.68 (s, 1H), 4.52 (d, *J* = 5.2 Hz, 2H), 3.98(s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 443.0.

[0736] **Compound 526**: **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.58 (d, *J* = 8.1Hz, 2H), 7.48 (s, 1H), 7.33-7.38 (m, 5H), 6.59 (s, 1H), 7.21 (d, *J* = 8.1Hz, 2H), 7.03 (s, 1H), 5.48 (s, 1H), 4.87 (t, *J* = 5.7Hz, 1H), 4.36 (d, *J* = 5.7Hz, 2H), 3.89 (s, 3H).

[0737] **Compound 527**: **^{1}H NMR** (Methanol-d_4, 300 MHz) δ 7.75 (s, 1H), 7.55 (d, *J*=5.7Hz, 2H), 7.50-7.41 (m, 5H), 7.34 (d, *J*=8.7Hz, 2H), 5.52 (s, 1H), 4.51 (s, 2H), 3.86 (s, 3H).

[0738] **Compound 528**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 7.89 (s, 1H), 7.57 (s, 1H), 7.52 (d, *J* = 8.4Hz, 2H), 7.44 (d, *J* = 8.4Hz, 2H), 7.40 (s, 1H), 7.25 (t, *J* = 8.8Hz, 1H), 6.80-6.83 (dd, J_1=2.4Hz, J_2=12.4Hz), 6.74-6.77 (dd, J_1=2.4Hz, J_2=8.8Hz), 6.63 (t, *J* = 5.6Hz, 1H), 5.35 (s, 1H), 4.32 (d, *J* = 5.6Hz, 2H), 4.00 (q, *J* = 6.8Hz, 2H), 3.86 (s, 3H), 1.29 (t, *J* = 6.8Hz, 3H).

[0739] **Compound 529**: **^{1}H NMR** ($CDCl_3$, 300MHz) δ 8.65 (d, *J* = 5.1Hz, 2H), 7.58 (s, 1H), 7.47 (s, 1H), 7.35-7.40 (m, 3H), 7.16-7.24 (m, 2H), 7.05 (s, 1H), 6.10 (t, *J* = 4.5Hz ,1H), 5.65 (s, 1H), 4.50 (d, *J* = 4.5Hz, 2H), 3.92 (s, 3H).

[0740] **Compound 530**: **MS (ESI)** ***m/z*** $[M+H]^+$ 485.0. Hydrogen chloride salt: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.91 (s, H), 7.58 (s, H), 7.54-7.50 (m, 2H), 7.48-7.43 (m, 2H), 7.33 (m, 1H), 7.26 (d, *J*.= 8.4 Hz, 2H), 6.89 (d,*J*.= 8.4 Hz, 2H), 6.51 (m, 1H), 5.27 (s, 1H), 4.28 (d, *J*.= 6.0 Hz, 2H), 3.99 (q, *J*.= 6.8 Hz, 2H), 3.88 (s, 3H) , 1.31 (t, *J*.= 7.2 Hz, 3H)

[0741] **Compound 531**: **^{1}H NMR** ($CDCl_3$, 300MHz) δ 9.11 (s, 1H), 8.62 (s, 2H), 7.46 (s, 1H), 7.35 (d, J = 9.3Hz, 3H), 7.24 (s, 1H), 7.20 (d, J = 4.2Hz, 1H), 7.03 (s, 1H), 5.53 (s, 1H), 4.80 (t, J = 5.7Hz, 1H), 4.34 (d, J = 5.7Hz, 2H), 3.88 (s, 3H). **MS (ESI) m / z** $[M+H]^+$ 443.0.

[0742] Preparation of various salts of **Compound 531**: Compound **531** was dissolved in MeOH, followed by addition of aquesou salt solution. The mixture was sttired at rt for 1h. The reaction mixture was concentrated to dryness. The residual aqueous solution was lyophilized to give the final corresponding salt of Compound **531**.

[0743] Hydrogen chloride salt: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 9.10 (s, 1H), 8.82 (s, 2H), 7.95 (s, 1H), 7.60 (s, 1H), 7.52 (d, J = 9.2Hz, 2H), 7.43 (d, J = 8.4Hz, 2H), 7.40 (s, 1H), 6.80 (t, J = 5.6Hz, 1H), 5.43 (s, 1H), 4.45 (d, J = 5.6Hz, 1H), 3.87 (s, 3H).

[0744] Citrate salt: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.22 (brs, 1H), 9.08 (s, 1H), 9.08 (s, 1H), 8.80 (s, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 7.49 (d, J = 8.8Hz, 2H), 7.41 (d, J = 8.8Hz, 2H), 7.31 (s, 1H), 6.56 (t, J = 6Hz, 1H), 5.28 (s, 1H), 4.41 (d, J = 6Hz, 2H), 3.86 (s, 3H), 2.74 (d, J = 15.6Hz, 2H), 2.65 (d, J = 15.6Hz, 2H).

[0745] p-TsOH salt: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 9.11 (s, 1H), 8.82 (s, 2H), 7.97 (s, 1H), 7.61 (s, 1H), 7.45-7.56 (m, 7H), 7.10 (d, J = 8Hz, 2H), 6.94 (s, 1H), 5.48 (s, 1H), 4.47 (d, J = 5.2Hz, 2H), 3.87 (s, 3H), 2.27 (s, 3H).

[0746] Acetic acid salt: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 9.18 (s, 1H), 8.70 (s, 2H), 7.53 (s, 1H), 7.44 (s, 1H), 7.42 (d, J = 8.8Hz, 2H), 7.29 (d, J = 8.8Hz, 2H), 7.10 (s, 1H), 4.87 (t, J = 5.6Hz, 1H), 4.41 (d, J = 5.6Hz, 2H), 3.95 (s, 3H), 2.06 (s, 1H).

[0747] Compounds **546-549** were prepared by reacting 4-bromo-1-(4-(trifluoromethoxy)phenyl)pyridin-2(1H)-one with the corresponding amines.

[0748] **Compound 546**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.83 (d, J=5.1Hz, 2H), 7.49-7.44 (m, 6H), 7.37 (d, J=7.5Hz, 1H), 6.01 (dd, J=1.8, 7.5 Hz, 1H), 5.17 (s, 1H), 4.49 (d, J=5.7Hz, 2H).

[0749] **Compound 547**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.55 (d, J=4.2Hz, 1H), 7.82 (d, J=7.5Hz, 1H), 7.66 (d, J=5.1Hz, 1H),7.44-7.43 (m, 7H), 6.02 (t, J=7.5 Hz, 1H), 5.14 (s, 1H), 4.38 (d, J=5.7Hz, 2H).

[0750] **Compound 548**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 9.12 (s, 1H), 8.80 (s, 2H), 7.45-7.37 (m, 6H), 6.90 (t, J=7.5 Hz, 1H), 5.30 (s, 1H), 4.39 (d, J=5.7Hz, 2H).

[0751] **Compound 549**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 8.68-8.63 (m, 2H), 8.58 (s, 1H), 7.51-7.36 (m, 6H), 5.98 (d, J=7.5 Hz, 1H), 5.23 (s, 1H), 4.48 (d, J=5.1Hz, 2H).

[0752] **Compound 538** was prepared from **Compound 403** in three steps: first, Compound **403** (3.6 g, 11 mmol) was stirred in HBr aqueous solution (40%, 30 mL) at 90°C for 12hrs. After standard workup, the resulting intermediate was redissolved in $POCl_3$ (20 mL) and refluxed for 2h to afford the corresponding chloride (520 mg, 18% yield). Subsequently, acetone (10 mL), K_2CO_3 (342 mg, 2.48 mmol) and iodomethane (387 mg, 2.48 mmol) were added in portions. The mixture was stirred at 60°C overnight. The mixture was cooled to rt and filtered. The filtrate was concentrated and purified by flash column chromatography (PE:EA=2:1) to give **Compound 538** (252 mg, 43%) .**^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.96 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.18~7.16 (d, J = 8 Hz,1H), 6.92 (s, 1H), 6.85-6.83 (m, 1H) , 6.76 (s, 1H), 4.05 (q, J = 6.8 Hz, 2H), 3.82 (s, 3H), 2.01 (s, 3H) , 1.33 (t, J = 6.8 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 344.1.

[0753] **Compound 543**: **Compound 538** (100 mg, 0.29 mmol) was dissolved in $BnNH_2$ (5 mL), the mixture was stirred at 160°C for 3h under N_2. After cooled to rt, the mixture was diluted with water and extracted with EtOAc. Following standard workup and purification, Compound **543** was obtained (53 mg, yield 44 %). **MS (ESI) *m/z*** $(M+H)^+$ 414.9.

[0754] Alternative way to prepare **Compound 543**: first, 5-bromo-4-chloro-2-methoxypyridine was reacted with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole under the standard Suzuki-Coupling condition to form 4-chloro-2-methoxy-5-(1-methyl-1H-pyrazol-4-yl)pyridine; then it was subject to HBr hydrolysis, followed by a second Suzuki-Coupling with (4-ethoxy-2-methylphenyl)boronic acid, then reaction with $BnNH_2$ as described herein. Hydrogen chloride salt: **^{1}H NMR** (DMSO-d_6, 400 MHz) **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.01 (s, 1H), 7.64 (s, 1H), 7.46 (s, 1H), 7.41-7.35 (m, 5H), 7.28 (m, 1H), 7.18 (d, J = 8.8Hz, 1H), 6.93 (s, 1H), 6.83 (d, J = 8.8Hz, 1H), 5.87 (s, 1H), 4.45 (s, 2H), 4.04 (q, J = 6.8Hz, 2H), 3.89 (s, 3H), 2.00 (s, 3H), 1.32 (t, J = 6.8Hz, 3H).

[0755] Compounds **699-704** and **706** were prepared by reacting 4-chloro-1-(4-ethoxy-2-methylphenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2(1H)-one with the corresponding amines followin the similar procedure described above. The HCl salts thereof were also prepared following the similar procedure above.

[0756] Compound **699**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.54 (d, J=4.0 Hz, 1H), 7.90 (s, 1H), 7.80 (dt, J=1.8, 7.7 Hz, 1H), 7.58 (s, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.29 (dd, J_1=5.3, J_2=6.8Hz, 1H), 7.08 (s, 1H), 7.04 (d, J=8.5 Hz, 1H), 6.86 (d, J=2.8 Hz, 1H), 6.78 (dd, J_1=2.9, J_2=8.7 Hz, 1H), 6.49 (t, J=5.5 Hz, 1H), 5.75 (s, 1H), 5.22 (s, 1H), 4.42 (d, J=5.5 Hz, 2H), 4.03 (q, J=6.9 Hz, 2H), 3.87 (s, 3H), 2.00 (s, 3H), 1.32 (t, J=7.0 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 416.2.

[0757] HCl salt of Compound **699**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.74 (d, J=4.5 Hz, 1H), 8.23 (t, J=7.2 Hz, 1H), 7.99 (s, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.71-7.65 (m, 1H), 7.64 (d, J=0.8Hz, 1H), 7.25 (s, 1H), 7.08 (d, J=8.5 Hz, 1H), 6.88 (d, J=2.8 Hz, 1H), 6.85-6.77 (m, 2H), 5.46 (s, 1H), 4.65 (d, J=4.5 Hz, 2H), 4.07-4.01 (m, 2H), 3.88 (s,3H), 2.00 (s, 3H), 1.32 (t, J=6.9 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.2.

[0758] Compound **700**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.56-8.50 (m, 2H), 7.91 (s, 1H), 7.58 (s, 1H), 7.37 (d, J=5.8 Hz, 2H), 7.08-7.01 (m, 2H), 6.85 (d, J=2.5 Hz, 1H), 6.77(dd, J_1=2.8, J_2=8.5 Hz, 1H), 6.46 (t, J=6.1 Hz, 1H), 5.75 (s, 1H), 5.09 (s, 1H), 4.38 (d, J=6.0 Hz, 2H), 4.02 (q, J=6.9 Hz, 2H), 3.87 (s, 3H), 1.99 (s, 3H), 1.32 (t, J=6.9 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.2.

[0759] HCl salt of Compound **700**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.85 (d, J=6.5 Hz, 2H), 7.98 (d, J=6.3 Hz, 2H), 7.96 (s, 1H), 7.63 (s, 1H), 7.17 (s, 1H), 7.04 (d, J=8.8 Hz, 1H), 6.86 (d, J=2.8 Hz, 1H), 6.78 (dd, J_1=2.8, J_2=8.5 Hz, 1H), 6.73 (t, J=6.1 Hz, 1H), 5.20 (s, 1H), 4.66 (d, J=6.0 Hz, 2H), 4.03 (d, J=7.0 Hz, 2H), 3.88 (s, 3H), 2.00-1.98 (m,3H), 1.32 (t, J=6.9 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.2.

[0760] Compound **701**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.59 (d, J=1.8 Hz, 1H), 8.47 (dd, J_1=1.6, J_2=4.9 Hz, 1H), 7.89 (s, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.56 (s, 1H), 7.38 (dd, J_1=4.8, J_2=7.8 Hz, 1H), 7.06-7.01 (m, 2H), 6.85 (d, J=2.5 Hz, 1H), 6.77 (dd, J_1=2.8, J_2=8.5 Hz, 1H), 6.42 (t, J=6.1 Hz, 1H), 5.75 (s, 1H), 5.20 (s, 1H), 4.38 (d, J=6.0 Hz,2H), 4.02 (q, J=7.0 Hz, 2H), 3.86 (s, 3H), 1.99 (s, 3H), 1.32 (t, J=7.0 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.2.

[0761] HCl salt of Compound **701**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.90 (s, 1H), 8.78 (d, J=5.3 Hz, 1H), 8.46 (d, J=8.0 Hz, 1H), 8.00-7.91 (m, 2H), 7.61 (s, 1H), 7.17 (s, 1H), 7.05 (d, J=8.5Hz, 1H), 6.87 (d, J=2.5 Hz, 1H), 6.78 (dd, J_1=2.5, J_2=8.5 Hz, 1H), 6.74 (t, J=6.0 Hz, 1H), 5.39 (s, 1H), 4.56 (d, J=5.8 Hz, 2H), 4.06-4.01 (m, 2H), 3.87 (s, 3H),1.99 (s, 3H), 1.32 (t, J=6.9 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.2.

[0762] Compound **702**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.87 (s., 1H), 7.55 (s, 1H), 7.45~7.40 (m, 1H), 7.30~7.20 (m, 1H), 7.10~7.02 (m, 3H), 6.85 (d, J=2.4 Hz, 1H), 6.79~6.76 (m, 1H), 6.35~6.31 (m, 1H), 5.18 (s, 1H), 4.35 (d, J=5.6 Hz, 2H), 4.02 (q, J=7.2 Hz, 2H), 3.86 (s, 3H), 2.00 (s, 3H), 1.32 (t, J=7.2 Hz, 3H).

[0763] HCl salt of Compound **702**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.91 (s, 1H), 7.58 (s, 1H), 7.47~7.43 (m, 1H), 7.30~7.24 (m, 2H), 7.10 (d, J=8.4 Hz, 2H), 6.88 (s., 1H), 6.81 (d, J=8.4 Hz, 1H), 6.73 (s, 1H), 5.42 (s, 1H), 4.39 (d, J=4.8 Hz, 2H), 4.03 (q, J=6.8 Hz, 2H), 3.87 (s, 3H), 2.00 (s, 3H), 1.32 (t, J=6.8 Hz, 3H).

[0764] Compound **703**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.92 (s., 1H), 7.57 (s, 1H), 7.12~7.03 (m, 5H), 6.85 (d, *J*=2.4 Hz, 1H), 6.78 (d, *J*=2.4 Hz, 1H), 6.46 (t, *J*=6.0 Hz, 1H), 5.15 (s, 1H), 4.36 (d, *J*=6.0 Hz, 2H), 4.02 (q, *J*=7.2 Hz, 2H), 3.87 (s, 3H), 2.00 (s, 3H) , 1.32 (t, *J*=7.2 Hz, 3H).

[0765] HCl salt of Compound **703**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.98 (s, 1H), 7.61 (s, 1H), 7.26 (s, 1H), 7.13~7.10 (m, 4H), 6.88 (brs, 2H), 6.80 (d, *J*=8.4Hz, 1H), 5.42 (s, 1H), 4.41 (d, *J*=4.8 Hz, 2H), 4.03 (q, *J*=6.8 Hz, 2H), 3.88 (s, 3H), 2.0 (s, 3H), 1.32 (t, *J*=6.8 Hz, 3H).

[0766] Compound **704**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.91 (s, 1H), 7.83 (d, *J*=8.0 Hz, 2H), 7.61 - 7.52 (m, 3H), 7.06 (s, 1H), 7.03 (d, *J*=8.8 Hz, 1H), 6.85 (d, *J*=2.8 Hz, 1H), 6.78 (dd, *J*=2.8, 8.4 Hz, 1H), 6.50 (t, *J*=6.0 Hz, 1H), 5.76 (s, 1H), 5.10 (s, 1H), 4.44 (d, *J*=6.0 Hz, 2H), 4.03 (q, *J*=7.2 Hz, 2H), 3.87 (s, 3H), 1.99 (s, 3H), 1.32 (t, *J*=7.2 Hz, 3H).

[0767] HCl salt of Compound **704**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.95 (s, 1H), 7.83 (d, J=8.0 Hz, 2H), 7.61 (s, 1H), 7.56 (d, J=8.0 Hz, 2H), 7.27 (s, 1H), 7.09 (d, J=8.8 Hz, 1H), 6.99 (t, J=5.8 Hz, 1H), 6.87 (d, J=2.8 Hz, 1H), 6.79 (dd, J=2.8, 8.8 Hz, 1H), 5.41 (s, 1H), 4.48 (d, J=5.6 Hz, 2H), 4.02 (q, J=7.2 Hz, 2H), 3.87 (s, 3H), 1.98 (s, 3H), 1.31 (t, J=7.2Hz, 3H).

[0768] Compound **705**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.84 (s, 1H), 7.58 (s, 1H), 7.33-7.21 (m, 4H), 7.16 (d, *J*=7.2Hz, 2H), 7.16 (d, *J*=7.2Hz, 1H), 7.07 (s, 1H), 6.87 (d, *J*=2.8Hz, 1H), 5.69 (s, 1H), 4.11 (d, *J*=8.8Hz, 2H), 4.02 (q, *J*=7.2Hz, 2H), 3.75 (s, 3H), 2.52 (s, 3H), 2.00 (s, 3H), 1.31 (t, *J*= 7.2Hz, 3H).

[0769] HCl salt of Compound **705**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.87 (s, 1H), 7.60 (s, 1H), 7.37-7.24 (m, 4H), 7.19 (d, *J*=7.0 Hz, 2H), 7.14 (d, *J*=8.8 Hz, 1H), 6.91 (d, *J*=2.5 Hz, 1H), 6.83 (dd, *J*=2.8, 8.5Hz, 1H), 5.83 (s, 1H), 4.26-4.13 (m, 2H), 4.05 (q, *J*=7.0 Hz, 2H), 3.78 (s, 3H), 2.58 (s, 3H), 2.03 (s, 3H), 1.34 (t, *J*=7.0 Hz, 3H).

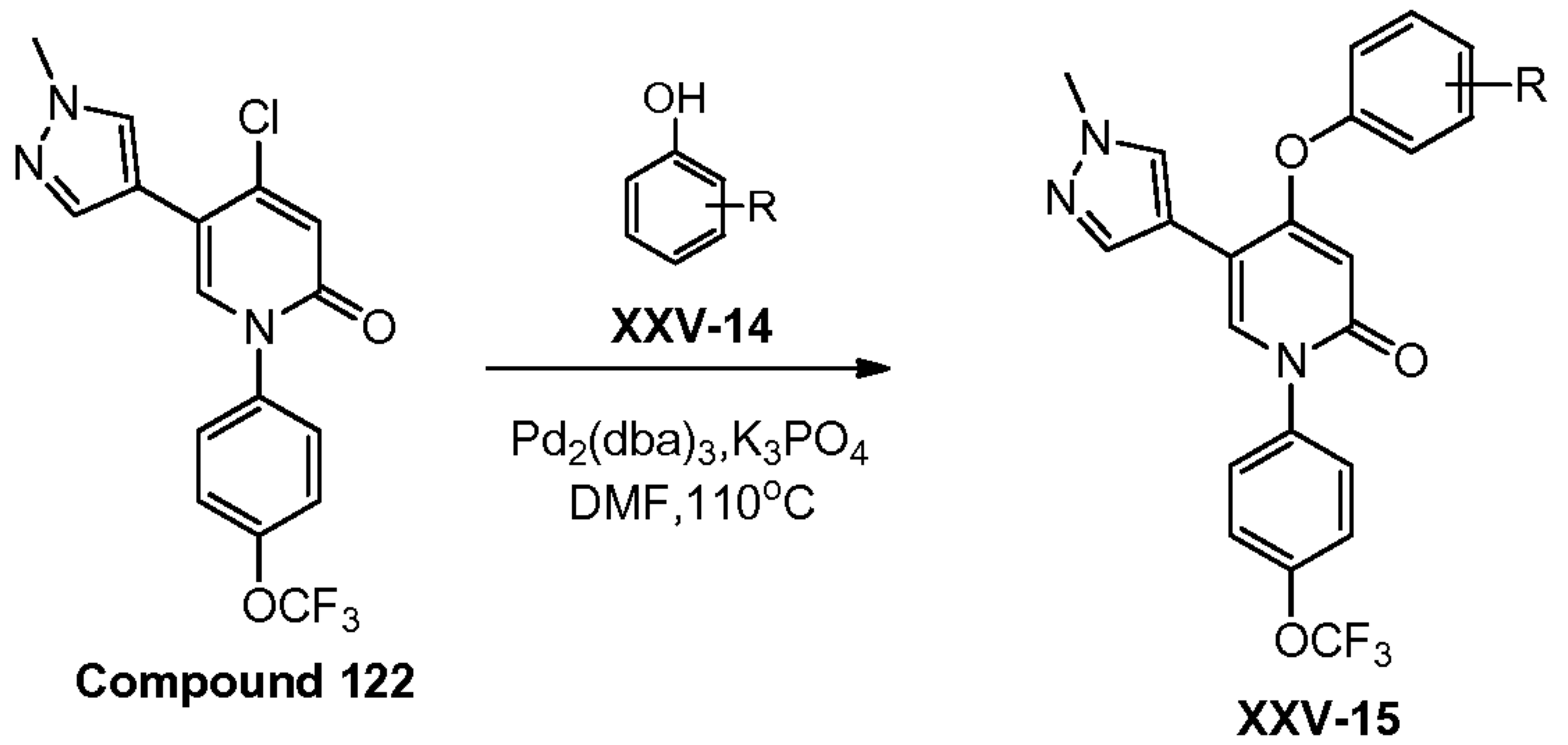
[0770] Compound **706**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.86 (s, 1H), 7.54 (s, 1H), 7.41 (s, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 7.05 (d, *J*=6.8 Hz, 1H), 6.86 (d, *J*=2.8Hz, 1H), 6.80-6.72 (m, 3H), 5.97 (t, *J*=5.6 Hz, 1H), 5.15 (s, 1H), 4.22 (d, *J*=5.2 Hz, 2H), 4.06-3.98 (m, 4H), 3.85 (s, 3H), 2.29 (s, 3H), 2.01 (s, 3H), 1.35-1.29 (m, 6H).

[0771] HCl salt of Compound **706**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.97 (s, 1H), 7.62 (s, 1H), 7.41 (s, 1H), 7.16 (dd, *J*=8.5, 17.3 Hz, 2H), 6.98-6.90 (m, 2H), 6.84 (dd, *J*=2.8, 8.5 Hz, 1H), 6.80 (s, 1H), 6.74 (dd, *J*=2.6, 8.4 Hz, 1H), 5.66 (br. s., 1H), 4.31 (d, *J*=5.3 Hz, 2H), 4.10-3.91 (m, 4H), 3.88 (s, 3H), 2.32 (s, 3H), 2.02 (s, 3H), 1.35-1.29 (m, 6H).

[0772] Compound **707**: ^{1}H **NMR** (DMSO-d_6, 400 MHz) δ 7.85 (s, 1H), 7.53 (s, 1H), 7.26 (d, *J*=8.4 Hz, 2H), 7.01 (t, *J*=2.4 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 6.83 (d, *J*=2.8 Hz, 1H), 6.76 (t, *J*=5.6Hz, 1H), 5.18 (s,1H), 4.24 (d, *J*=5.6 Hz, 2H), 4.06-4.00 (m, 4H), 3.84 (s, 3H), 3.63 (t, *J*=4.8, 2H), 3.29 (s, 3H), 1.97 (s, 3H), 1.31 (t, *J*=6.8 Hz, 3H).

[0773] HCl salt of Compound **707**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.97 (s, 1H), 7.61 (s, 1H), 7.36 (d, *J*=2.5Hz, 1H), 7.31 (d, *J*=8.5Hz, 2H), 7.18 -7.06 (m, 2H), 6.96 - 6.89 (m, 3H), 6.84-6.81 (m, 1H), 5.71 (brs, 1H), 4.34 (brs, 2H), 4.09-4.02 (m, 4H), 3.89 (s, 3H), 3.66-3.64 (m, 2H), 3.30 (s, 3H), 2.00 (s, 3H), 1.33 (t, *J*=7.0 Hz, 3H).

[0774] Compound **708** was prepared by HBr hydrolysis of 2-methoxy-4,5-bis(1-methyl-1H-pyrazol-4-yl)pyridine, followed by standard copper acetate/pyridine/pyridine-N-oxide catalyzed reaction in DMF at 90°C to afford the final product. ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.71 (s, 1H), 7.65-7.63 (m, 3H), 7.56 (s, 1H), 7.52 (d, *J* =8.0 Hz, 2H), 7.33 (s, 1H), 7.28 (s, 1H), 6.60 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H).



[0775] **Compound 122** (1 eq.), phenol (**XXV-14,** 2 eq.) and K_3PO_4 (3 eq.) were added into DMF. The solution was degassed by nitrogen for three times and then $Pd_2(dba)_3$ (0.2 eq.) was added. The reaction mixture was stirred at 110°C for 14 hrs under N_2. After being cooled to rt, the mixture was diluted with EA and filtered; the filtrate was washed with brine. The separated organic phase was dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (PE/EA =1/1) to give the final product.

[0776] Compounds **408-410** and **412-414** were prepared following the general scheme as illustrated above.

[0777] **Compound 408**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (s, 1H), 7.68 (s, 1H), 7.49-7.45 (m, 3H), 7.37-7.33 (m, 2H), 7.30-7.22 (m, 4H), 5.79 (s, 1H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 446.1.

[0778] **Compound 409**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), 7.67 (s, 1H), 7.50 (s, 1H), 7.47-7.42 (m, 3H), 7.37-7.33 (m, 2H), 7.05-7.00 (m, 1H), 6.98-6.96 (m, 1H), 6.94-6.90 (m, 1H), 5.84 (s, 1H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 445.9.

[0779] **Compound 410**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.72 (s, 1H), 7.68 (s, 1H), 7.49-7.44 (m, 3H), 7.36-7.34 (m, 2H), 7.17-7.14 (m, 4H), 5.76 (s, 1H), 3.94 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 445.9.

[0780] **Compound 412**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.70 (s, 1H), 7.67 (s, 1H), 7.49-7.42 (m, 5H), 7.36-7.34 (m, 2H), 7.12-7.10 (m, 2H), 5.78 (s, 1H), 3.94 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 462.1.

[0781] **Compound 413**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.70 (s, 1H), 7.67 (s, 1H), 7.50 (s, 1H), 7.47-7.35 (m, 5H), 7.32~7.29 (m, 1H), 7.20-7.19 (m, 1H), 7.10-7.06 (m, 1H), 5.82 (s, 1H), 3.94 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 462.1.

[0782] **Compound 414**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H), 7.79 (s, 1H), 7.55-7.45 (m, 4H), 7.40-7.34 (m, 3H), 7.31-7.29 (m, 1H), 7.24-7.21 (m, 1H), 5.74 (s, 1H), 3.97 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 462.1.

[0783] **Compounds 533** and **535** were prepared by reacting Compound **122** with the corresponding substituted phenol in DMF and KOH at 130°C overnight.

[0784] **Compound 533**: **^{1}HNMR** ($CDCl_3$, 400 MHz) δ 7.75 (s, 1H), 7.68 (s, 1H), 7.48-7.43 (m, 3H), 7.34 (d, *J*=8.4 Hz, 2H), 7.06 (d, *J*=9.2 Hz, 2H), 6.69 (d, *J*=9.2 Hz, 2H), 5.78 (s, 1H), 4.15 (t, *J*=4.8 Hz, 1H), 3.94 (s, 3H), 3.78 (t, *J*=4.8 Hz, 2H), 3.48 (s, 3H).

[0785] **Compound 535**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.05~8.01 (m, 5H), 7.84 (s, 1H), 7.61 (d, J= 8.8 Hz, 2H), 7.53 (d, J= 8.4 Hz, 2H), 7.45 (s, 1H) , 7.37 (s, 1H), 7.35 (s, 1H) , 5.46 (s, 1H) , 3.84 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 457.2.

[0786] Preparation of **Compound 664**: To a solution of Compound **122** (210 mg, 0.569 mmol) in dioxane (20 mL) were added pyridazin-3-ylmethanamine hydrochloride (165 mg, 1.14 mmol), NaOtBu (218 mg, 2.28 mmol), Xphos (27.2 mg, 0.057 mmol), precatalyst 13 (44.8 mg, 0.057 mmol). The mixture was degassed under in vacuum and purged with N_2 three times. The reaction mixture was stirred at 100°C for 14h. The mixture was cooled to rt. The mixture was diluted with water and extracted with EA. The combined organic layer was dried over Na_2SO_4, concentrated in vacuum. The residue was purified by column chromatography on silica gel eluted with DCM:MeOH (50:1-10:1) to give **Compound 664** (50 mg, 20% yield) as a pale yellow solid. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 9.15 (s, 1H), 7.91 (s, 1H), 7.67 (s, 2H), 7.60 (s, 1H), 7.49 (d, *J*=8.8Hz, 2H), 7.42 (d, *J*=8.8Hz, 2H), 7.33 (s, 1H), 6.67 (t, 1H), 5.25 (s, 1H), 4.62 (t, *J*=5.6Hz, 1H), 3.87 (s, 3H).

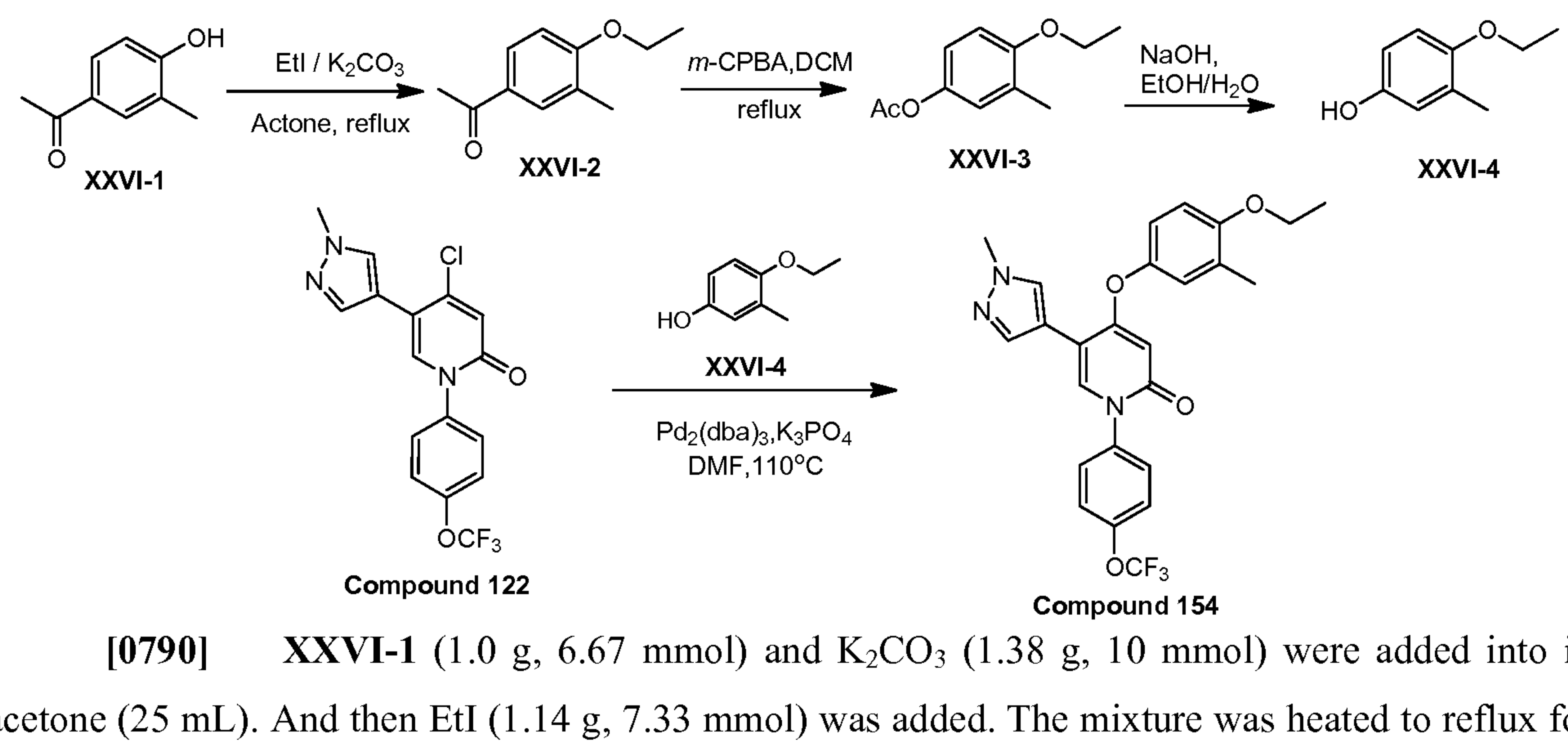
[0787] Compound **696** was prepared by reacting 4-chloro-1-(4-ethoxy-2-methylphenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2(1H)-one with 2-isopropoxyethanol in the presence of NaH in

DMF solution at rt for 12hrs to afford the final product as a yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.78 (s, 1H), 7.66 (s, 1H), 7.32 (s, 1H), 7.15 - 7.12 (m, 1H), 6.89 - 6.81 (m, 2H), 6.08 (s, 1H), 4.22 - 4.18 (m, 2H), 4.10-4.05 (q, *J*=6.9 Hz, 2H), 3.93 (s, 3H), 3.87-3.85 (dd, *J*=3.6, 5.6 Hz, 2H), 3.77-3.74 (td, *J*=6.1, 12.2 Hz, 1H), 2.16 (s, 3H),1.45 (t, *J*=6.9 Hz, 3H), 1.27 (d, *J*=6.3 Hz, 6H). **MS (ESI) *m/z*** ($M+H^+$) 412.3.

[0788] Compound **697** was prepared by reacting 4-chloro-1-(4-ethoxy-2-methylphenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2(1H)-one with 2-(2-methoxyethoxy)ethanol in the presence of NaH in DMF solution at rt for 12 hrs to afford the final product as a light yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.79 (s, 1H), 7.64 (s, 1H), 7.31 (s, 1H), 7.13 (d, *J*=8.5 Hz, 1H), 6.89 - 6.81 (m, 2H), 6.07 (s, 1H), 4.25 - 4.20 (m, 2H), 4.11 - 4.03 (q, *J*=6.9 Hz, 2H), 3.96 - 3.90 (m, 5H), 3.78 - 3.72 (m, 2H), 3.66- 3.60 (m, 2H), 3.45 - 3.40 (m, 3H), 2.16 (s, 3H), 1.45 (t, *J*=6.9 Hz, 3H). **MS (ESI) *m/z*** ($M+H^+$) 428.3.

[0789] Compound **698** was prepared by reacting 4-chloro-1-(4-ethoxy-2-methylphenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2(1H)-one with tetrahydro-2H-pyran-4-ol in the presence of NaH in DMF solution at rt for 16 hrs to afford the final product as a light yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 7.60 (s, 1H), 7.31 (s, 1H), 7.13 (d, *J*=8.5 Hz, 1H), 6.89 - 6.81 (m, 2H), 6.10 (s, 1H), 4.64 (t t, *J*=3.9, 8.0 Hz, 1H), 4.07 (q, *J*=6.9 Hz, 2H), 4.04 - 3.96 (m, 2H), 3.95 (s, 3H), 3.64 (dt, *J*=1.8, 8.8 Hz, 2H), 2.21 - 2.12 (m, 5H), 1.91 (ttd, *J*=4.0, 8.4, 12.8 Hz, 2H), 1.45 (t, *J*=7.0 Hz, 3H). **MS (ESI) *m/z*** ($M+H^+$) 410.2.

Example 11-D
Synthesis of Compound 154 (Scheme XXVI)



[0790] **XXVI-1** (1.0 g, 6.67 mmol) and K_2CO_3 (1.38 g, 10 mmol) were added into in acetone (25 mL). And then EtI (1.14 g, 7.33 mmol) was added. The mixture was heated to reflux for

24 hrs. The mixture was cooled to rt and removed the solvent. Then the crude product was diluted with EA (100 mL), washed with water and brine, dried over Na_2SO_4, concentrated *in vacuo* to give **XXVI-2** (870 mg, 73% yield), which was used directly without further purification.

[0791] A mixture of **XXVI-2** (1.2 g, 6.74 mmol) and *m*-CPBA (1.5 g, 8.76 mmol) in DCM (30 mL) was refluxed for 48 hrs. The reaction mixture was cooled to rt, diluted with DCM (100 mL), washed with saturated *aq.*$Na_2S_2O_3$ and *aq.* K_2CO_3, dried over Na_2SO_4. Concentrated *in vacuo* to give **XXVI-3** (1.0 g, 77% crude yield), which was used directly without further purification.

[0792] **XXVI-3** (1 g, 5 mmol) was dissolved in ethanol (10 mL), then treated with a solution of NaOH (2.6 g) in H_2O (3 mL) slowly. The resultant mixture was stirred at rt for 4 hrs. The resultant mixture was concentrated and residue was diluted with water (10 mL). The mixture was made acidic with diluted HCl (*aq.*) and extrated with EA (50 mL×3). The organic phases were combined, washed with brine, dried over Na_2SO_4, concentrated under reduced presssure to give the crude product. The residue was purification by flash chromatography on silica gel (PE/EA=5:1→2:1) to give **XXVI-4** (800 mg, ~100% yield).

[0793] **Compound 154** was prepared by following the similar procedure described in synthesis of **Compound 153** (101 mg, 20 % yield). ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H), 7.68 (s, 1H), 7.47-7.44 (m, 3H), 7.36-7.34 (m, 2H), 6.93-6.84 (m, 3H), 5.80 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 2.24 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 486.

[0794] **Compound 155** was prepared by following the similar procedure for obtaining **Compound 154** using 3-chloro-4-ethoxyphenol in place of **XXVI-4**. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.71 (s, 1H), 7.67 (s, 1H), 7.48~7.44 (m, 3H), 7.36~7.34 (m, 2H), 7.21 (s, 1H), 7.03~6.96 (m, 2H), 5.80 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 505.9.

[0795] **Comound 157** was prepared by following the similar procedure for obtaining **Compound 154** using 2-ethoxy-5-hydroxybenzonitrile in place of **XXVI-4**. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 7.6 Hz, 2H), 7.50-7.44 (m, 3H), 7.39-7.31 (m, 4H), 7.03 (d, J = 9.2 Hz, 1H), 5.73 (s, 1H), 4.19 (q, J = 6.8 Hz, 2H), 3.94 (s, 3H), 1.52 (t, J = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 497.

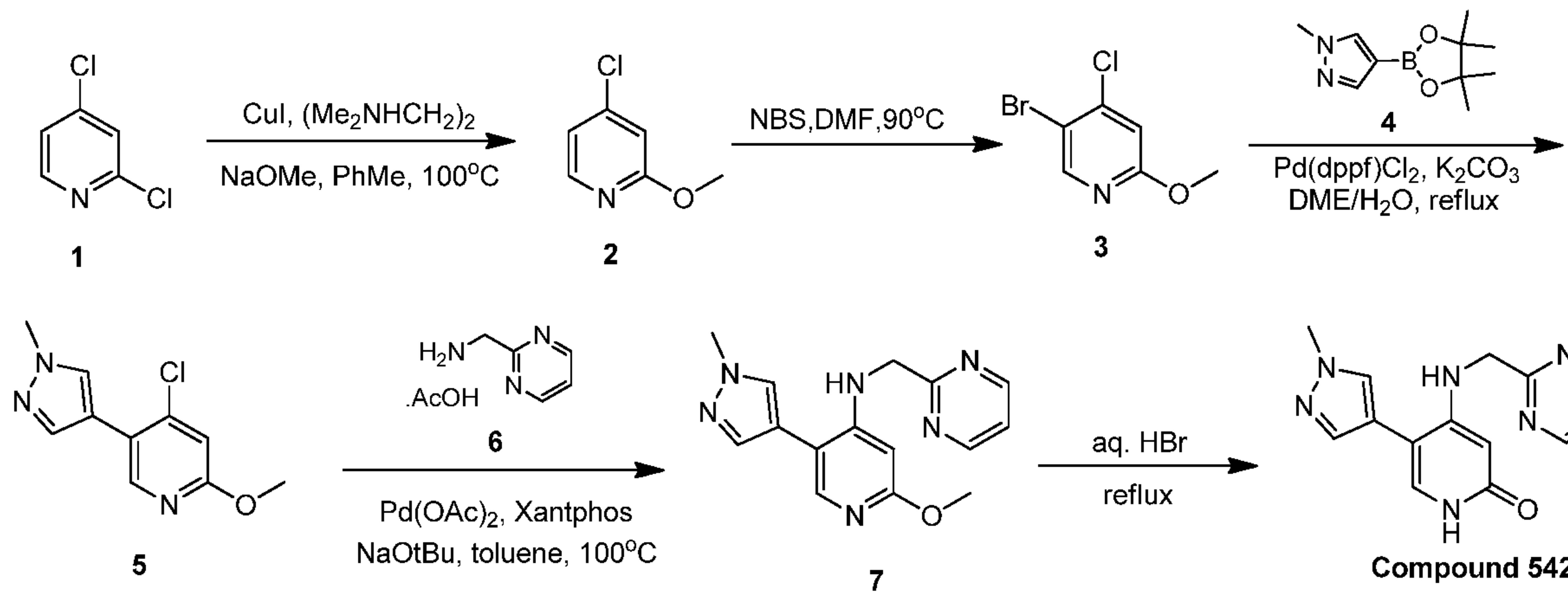
[0796] **Compound 162** was prepared following the similar procedure for obtaining **Compound 85** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of **XXIII-4** and using (4-ethoxy-2-methylphenyl)boronic acid in place of **XXIII-7**. ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.93 (s, 1H), 7.71 (s, 1H), 7.64 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.90 (d, J =

2.8 Hz, 1H), 6.84-6.81 (m, 1H), 5.95 (s, 1H), 4.04 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 2.00 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 340.1.

[0797] **Compound 532** was prepared following the similar procedure for obtaining **Compound 154** using 4-chloro-1-(4-fluorophenyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2(1H)-one in place of **Compound 122** and using phenol in place of **XXIV-4**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.75 (s, 1H), 7.68 (s, 1H), 7.49-7.44 (m, 3H), 7.39-7.36 (m, 2H), 7.32-7.20 (m, 1H), 7.18-7.14 (m, 4H), 5.79 (s, 1H), 3.93 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 362.1

[0798] **Compound 534** was prepared following the similar procedure for the synthesis of **Compound 532**. **^{1}H NMR** (Methanol-d_4, 400 MHz) δ 8.02 (s, 1H), 7.93 (s, 1H), 7.85 (s, 1H), 7.58~7.54 (m, 4H), 7.45 (d, J= 8.8 Hz, 2H), 7.41~7.37 (m, 1H) , 7.27 (d, J= 8.8 Hz, 2H), 5.67 (s, 1H), 3.93 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 378.1.

Example 11-E
Synthesis of Compound 542



[0799] To a mixture of compound **1** (68 g, 0.465 mol) in toluene (250 mL) was added CuI (17.9 g, 0.093mol), $(Me_2NHCH_2)_2$ (36.8 g, 0.418 mol) and NaOMe (50.2 g 0.93 mol). The mixture was purged with nitrogen for three times and then heated at 100°C for 8 hours. The mixture was concentrated to remove toluene, diluted with H_2O and extracted with EtOAc. After standard workup, the crude product was chromatographed on silica gel (PE) to give compound **2** (39.5 g, 60% yield).

[0800] To a solution of compound **2** (28.7 g. 0.2 mol) in DMF (50 mL) was added NBS (35.5 g, 0.2 mol). The mixture was heated at 90°C for 8 hours. The crude compound **3** was collected by filtration. (22 g, 50% yield).

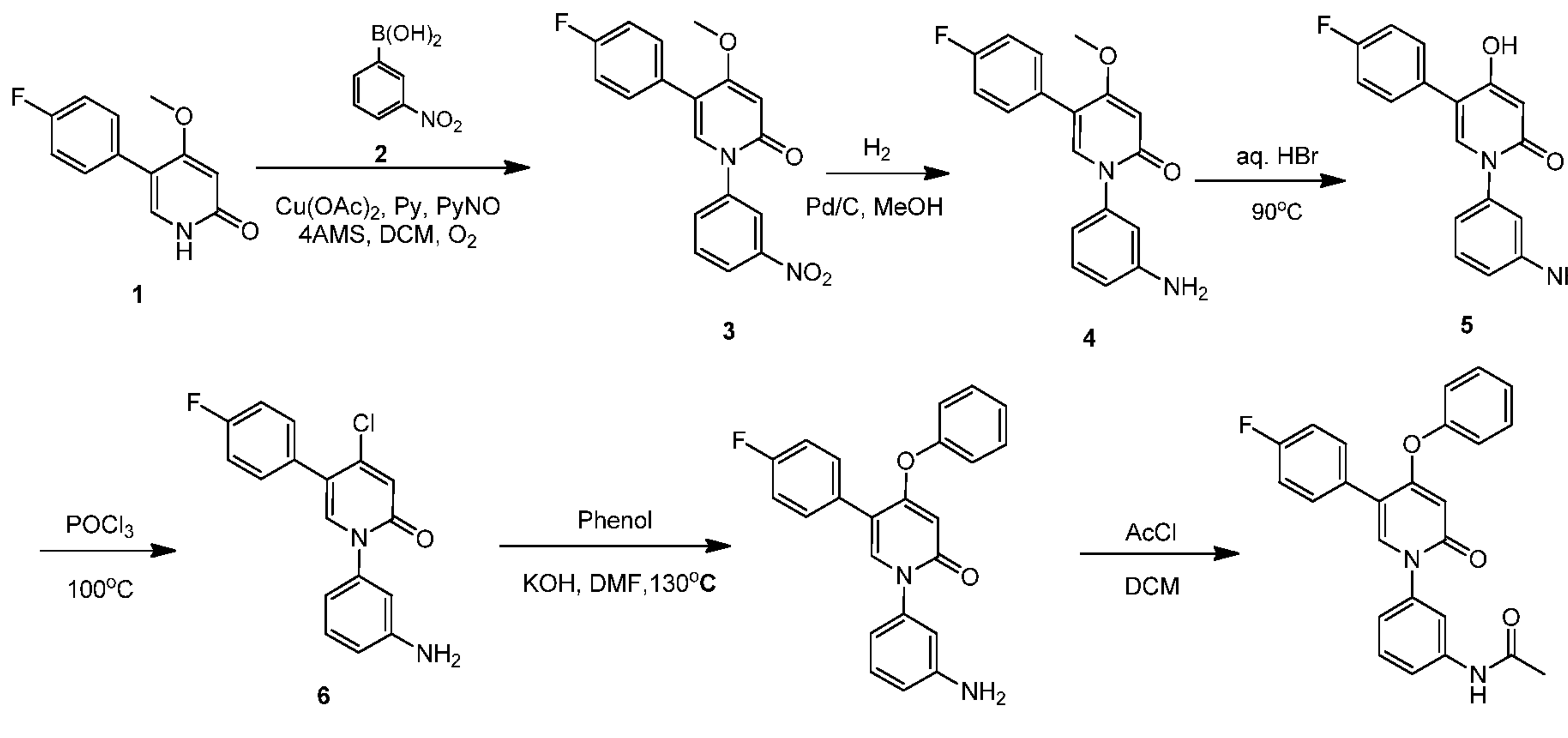
[0801] To a stirred mixture of compound **3** (4 g, 18.1 mmol), compound **4** (4.52 g 21.72 mmol), and K_2CO_3 (5 g, 36.2 mmol) in DME/H_2O (48 mL,v/v=5/1) was added Pd(dppf)Cl_2 (668 mg, 0.91 mmol) under N_2 protection. The reaction mixture was degassed with nitrogen again and refluxed overnight. The mixture was concentrated, diluted with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EA=2/1) to give compound **5** (2.8g, 69% yield) as a pale yellow solid.

[0802] To a solution of compound **5** (500 mg, 2.24 mmol) in toluene (20 mL) were added compound **6** (757.1 mg, 4.48 mmol), NaOtBu (860.2 mg, 8.96 mmol), Xantphos (129.5 mg, 0.224 mmol), $Pd(OAc)_2$ (50.2 mg, 0.224 mmol). The mixture was degassed under in vacuum and purged with N_2 three times. The reaction mixture was stirred at 100°C for 14h. The mixture was cooled to rt, diluted with water and extracted with EA. The combined organic layer was dried over Na_2SO_4, concentrated in vacuum. The residue was purified by silica gel chromatography eluted with DCM:MeOH (50:1-10:1) to afford compound **7** (300 mg, 45%) as a pale yellow solid.

[0803] Compound **7** (300 mg, 1.01 mmol) was dissolved in *aq.* HBr (40%, 15 mL), the mixture was heated to reflux overnight. After cooling to rt, the mixture was adjusted with *aq.* NaOH (1 M) to pH=4-5, the resulting precipitate was collected by filtration and dried *in vacuo* to give **Compound 542** (40 mg, 14% yield). **^{1}H NMR** (DMSO-d_6, 400MHz) δ 10.60 (s, 1H), 8.81 (d, J = 4.8Hz, 2H), 7.85 (s, 1H), 7.55 (s, 1H), 7.43 (t, J = 4.8Hz, 2H), 6.99 (s, 1H), 6.33 (t, J = 5.2Hz, 1H), 5.16 (s, 1H), 4.47 (d, J = 5.2Hz, 1H), 3.89 (s, 3H).

[0804] **Compound 544** was prepared following the similar procedure for the synthesis of **Compound 542** using pyridin-2-ylmethanamine in place of compound **6**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.56 (s, 1H), 8.52-8.51 (m, 1H), 7.85 (s, 1H), 7.90-7.56 (m, 1H), 7.53 (s, 1H), 7.33 (d, J =8.0 Hz, 1H), 7.29-7.26 (m, 1H), 6.95 (s, 1H), 6.33 (t, J=5.6 Hz, 1H), 5.05 (s, 1H), 4.37-4.35 (d, J=5.6 Hz, 2H), 3.88 (s, 3H).

Example 11-E
Synthesis of Compound 536



Compound 536

[0805] Preparation of compound **3** was followed the general procedure. A mixture of compound **3** (2.9 g, 8.5 mmol) and Pd/C (0.29 g) in methanol (20 mL) was stirred under H_2 at rt for 3 hours. The mixture was filtered and concentrated to give compound **4** (2.7 g, 98% yield).

[0806] A mixture of compound **4** (2.5 g, 8 mmol) in *aq.* HBr (40%, 20 mL) was stirred at 90°C for 12 hrs. After being cooled to rt, the mixture was poured into water, neutralized with $NaHCO_3$, and then extracted with DCM/i-PrOH. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford crude compound **5** (2.05 g, 86% yield).

[0807] Compound **5** (2.4 g, 0.008 mol) in $POCl_3$ (20 mL) was stirred at 100°C for 2h. After completion, the residue was diluted with H_2O and extracted with EtOAc. Following general workup procedure, the residue was purified by flash chromatography (PE:EA=1:1) to give compound **6** (560 mg, 22% yield).

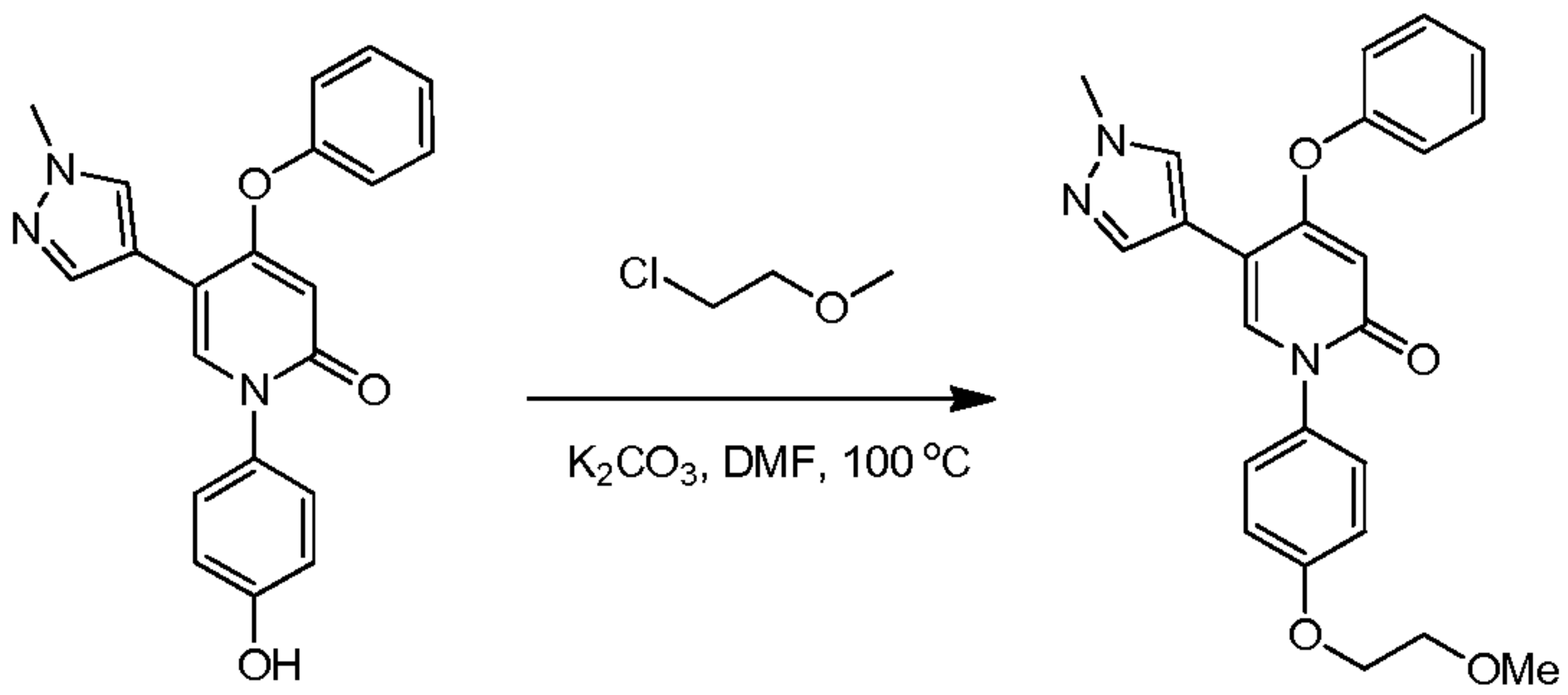
[0808] A mixture of compound **6** (300 mg, 0.95 mmol), KOH (107 mg, 1.91 mmol) in DMF (20 mL) was added phenol (134 mg, 1.4 mmol). The mixture was stirred at 130°C for 2h. After cooled to rt, the mixture was diluted with H_2O and extracted with EtOAc. After general workup procedure, the residue was purified by prep-HPLC to give compound **7** (232 mg, 65% yield).

[0809] To a solution of compound **7** (240 mg, 0.62 mmol) in DCM (20 mL) was added AcCl (0.8 mL, 0.93 mmol). The mixture was stirred at rt for 2 h, and the mixture was diluted with DCM (100 mL), the organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated, the residue was purified by prep.TLC (PE/EA=3/1) to give **Compound 536** (132 mg, 52% yield). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.12 (s, 1H), 7.72 (m, 2H), 7.67-7.63 (m, 2H), 7.54-

7.48 (m, 3H), 7.41-7.37 (m, 1H), 7.34-7.33 (m, 1H), 7.29-7.26 (m, 2H), 7.23-7.21 (m, 2H), 7.11-7.09 (m, 1H), 5.35 (s, 1H), 2.03 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 415.1.

[0810] **Compound 537** was prepared following the similar procedure for the synthesis of **Compound 536**, using **Compound 539** in place of Compound **1**. The hydrogenation step was conducted after the substitution of phenol. TMS-NCO was used in place of AcCl. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.86 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.84 (s, 1H), 7.57-7.53 (m, 3H), 7.39-7.30 (m, 5H), 6.93-6.91 (m, 1H), 5.98 (s, 2H), 5.35 (s, 1H), 3.84 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 402.0.

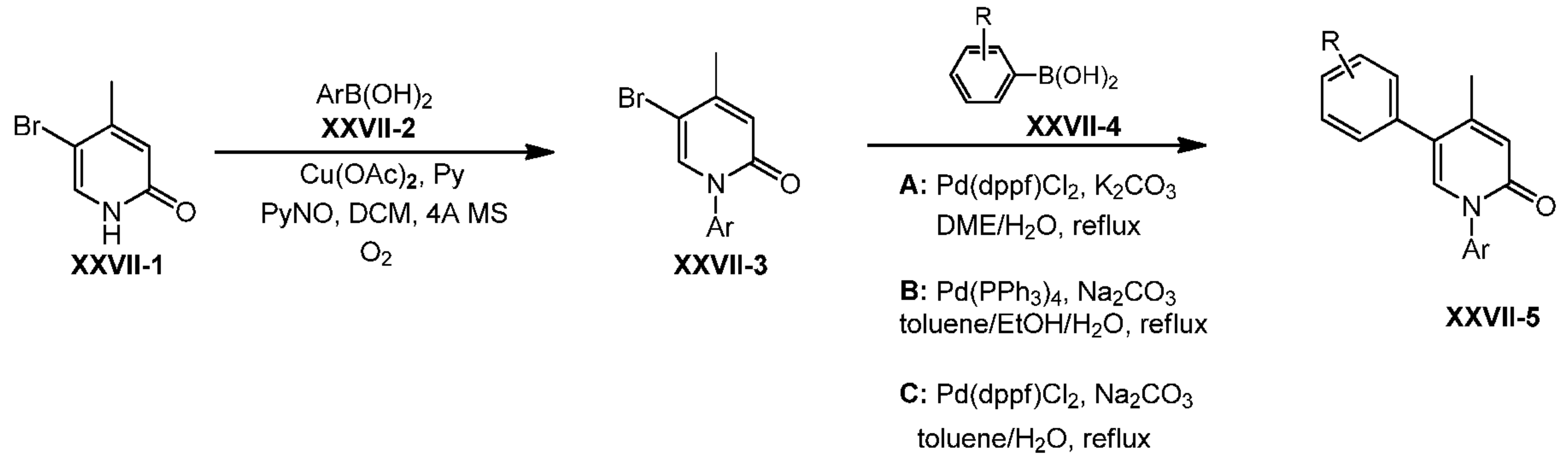
[0811] **Compound 545** was prepared following the similar procedure for the synthesis of Compound 536 using (4-methoxyphenyl)boronic acid in place of Compound **1**. The hydrogenation and reaction with AcCl steps were eliminated.



Compound 545 Compound 540

[0812] **Compound 540**: To a solution of **Compound 545** (200 mg, 0.56 mmol) in DMF (5 mL), 1-chloro-2-methoxyethane (68mg, 0.72mmol) and K_2CO_3 (155mg, 1.12mmol) was added. The mixture was stirred at 100°C overnight, then diluted with water and extracted with EA. After standard workup procedure, the residue was purified by prep-TLC (PE:EA=1:1) to give **Compound 540** (100 mg, yield 43%) **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (s, 1H), 7.68 (s, 1H), 7.51 (s, 1H), 7.45 (t, *J*=8.0 Hz, 2H), 7.30 (d, *J*= 8.8 Hz, 2H), 7.26 (s, 1H) , 7.16 (d, *J*= 8.0 Hz, 2H), 7.03 (d, *J*= 8.8 Hz, 2H), 5.79 (s, 1H), 4.16 (t, *J*=4.8 Hz, 2H), 3.93 (s, 3H), 3.77 (t, *J*= 4.8 Hz, 2H), 3.46 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 418.1.

Example 12-A
Synthesis of 4-Methyl, 5-Phenyl Pirfenidone Analogs (Scheme XXVII)



[0813] **XXVII-3**: To a solution of **XXVII-1** (1 eq.) in DCM (0.1 mmol/mL) was added the relevant boronic acid **XXVII-2** (1.5~2 eq.), $Cu(OAc)_2$ (1~3 eq), Pyridine (10 eq.) and Pyridine-N-Oxide (2~3 eq.), followed by addition of 4Å molecular sieve (200~500 mg). The reaction mixture was stirred at rt under oxygen atmosphere overnight. After completion of the reaction indicated by TLC, the resulting mixture was filtered and washed with ethyl acetate; the filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give the final product.

[0814] Three general procedures for the preparation of **XXVII-5**:

[0815] **Method A**: To a mixture of **XXVII-3** (1 eq.), the relevant boronic acid **XXVII-4** (1.2 eq.) and K_2CO_3 (2 eq.) in DME /H_2O (v/v=6/1) was added Pd(dppf)Cl_2 (0.1 eq.). The reaction mixture was degassed by purging with nitrogen and then was heated to reflux overnight. After the completion of the reaction, the mixture was cooled to rt, concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the final product.

[0816] **Method B**: To a mixture of **XXVII-3** (1 eq.), the relevant boronic acid **XXVII-4** (1.2 eq.) and Na_2CO_3 (2 eq.) in toluene/EtOH/H_2O (v/v/v=5/2/1) was added $Pd(PPh_3)_4$ (0.1 eq.). The reaction mixture was degassed by purging with nitrogen and then was heated to reflux overnight. After the completion of the reaction, the mixture was cooled to rt, concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the final product.

[0817] **Method C**: To a mixture of **XXVII-3** (1 eq.), boronic acid **XXVII-4** (1.2 eq.) and Na_2CO_3 (2 eq.) in toluene/H_2O (v/v=5/1) was added Pd(dppf)Cl_2 (0.1 eq.). The reaction mixture was degassed by purging with nitrogen and then was heated to reflux overnight. After the completion of the reaction, the mixture was cooled to rt, concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the final product.

[0818] Compounds **163-171, 191, 194, 201-205**, **552** were prepared following the Method **A** as described above. Compounds **172-177** were prepared following the Method B as described above. Compounds **195-198** were prepared following the Method C as described above.

[0819] **Compound 163**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69-7.60 (m, 4H), 7.44-7.35 (m, 3H), 7.30-7.26 (m, 2H), 7.20 (s, 1H), 6.60 (s, 1H), 2.16 (s, 3H).

[0820] **Compound 164**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50-7.47 (m, 2H), 7.43-7.38 (m, 3H), 7.35-7.31 (m, 2H), 7.30-7.26 (m, 2H), 7.21 (s, 1H), 6.60 (s, 1H), 2.16 (s, 3H).

[0821] **Compound 165**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.50-7.35 (m, 8H), 7.30-7.26 (m, 2H), 7.22 (s, 1H), 6.59 (s, 1H), 2.16 (s, 3H).

[0822] **Compound 166**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.53-7.49 (m, 1H), 7.44-7.37 (m, 4H), 7.34 (s, 1H), 7.30-7.19 (m, 3H), 7.19 (s, 1H), 6.59 (s, 1H), 2.16 (s, 3H).

[0823] **Compound 167**: **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 8.67 (s, 1H), 7.69 (s, 1H), 7.44-7.27 (m, 8H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.66 (s, 1H), 2.21 (s, 3H), 2.01 (s, 3H).

[0824] **Compound 168**: **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 7.43-7.35 (m, 3H), 7.32-7.28 (m, 2H), 7.17 (s, 1H), 7.13 (d, *J* = 8.8Hz, 1H), 6.84-6.78 (m, 3H), 4.04 (q, *J* = 7.6 Hz, 2H), 2.22 (s, 3H), 2.15 (s, 3H), 1.42 (t, *J* = 7.6 Hz, 3H).

[0825] **Compound 169**: **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 7.98 (s, 1H), 7.44-7.35 (m, 3H), 7.29-7.25 (m, 3H), 7.22-7.18 (m, 1H), 7.03 (d, *J* = 8.4Hz, 1H), 6.79 (s, 1H), 2.28 (s, 3H), 2.20 (s, 3H).

[0826] **Compound 170**: **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.45-7.38 (m, 3H), 7.30-7.27 (m, 3H), 6.77 (s, 1H), 2.21 (s, 3H).

[0827] **Compound 171**: **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 7.50-7.41 (m, 5H), 7.31-7.25 (m, 5H), 6.87 (s, 1H), 2.24 (s, 3H).

[0828] **Compound 172**: **^{1}H NMR** ($CDCl_3$, 400MHz) *δ* 9.07 (s, 1H), 7.67 (s, 1H), 7.29-7.21 (m, 5H), 7.12-7.07 (m, 2H), 6.95-6.93 (m, 1H), 6.60 (s, 1H), 2.17 (s, 3H), 1.95 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 337.0.

[0829] **Compound 173**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.75 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.27-7.24 (m, 2H), 7.18 (s, 1H), 7.13-7.09 (m, 2H), 6.59 (s, 1H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 348.0.

[0830] **Compound 174**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.54-7.50 (m, 1H), 7.41-7.38 (m, 1H), 7.33 (s, 1H), 7.29-7.24 (m, 3H), 7.17 (s, 1H), 7.10 (t, J=8.4 Hz, 2H), 6.58 (s, 1H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 364.0.

[0831] **Compound 175**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.26-7.22 (m, 2H), 7.13-7.06 (m, 4H), 6.84-6.78 (m, 2H), 6.58 (s, 1H), 4.04 (q, J = 6.8 Hz, 2H), 2.16 (m, 3H), 2.14 (m, 3H), 1.42 (t, J = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 338.2.

[0832] **Compound 176**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.50-7.46 (m, 2H), 7.43-7.41 (m, 3H), 7.26-7.23 (m, 2H), 7.20 (s, 1H), 7.12-7.07 (m, 2H), 6.58 (s, 1H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 280.1.

[0833] **Compound 177**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.77-7.68 (m, 4H), 7.35-7.31 (m, 2H), 7.26-7.17 (m, 3H), 6.67 (s, 1H), 2.21 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 348.1.

[0834] **Compound 191**: ^{1}**H NMR** (CD_3OD, 400 MHz) δ 7.61-7.57 (m, 2H), 7.52 (s, 1H), 7.46-7.41 (m, 5H), 7.32-7.30 (m, 1H), 6.59 (s, 1H), 2.22 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 380.0.

[0835] **Compound 194**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.51-7.48 (m , 2H), 7.41-7.32 (m , 3H), 7.27-7.13 (m , 4H), 6.60 (s, 1H), 2.11 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 364.1.

[0836] **Compound 195**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.50-7.45 (m, 3H), 7.36-7.32 (m, 2H), 7.24-7.19 (m, 2H), 7.15-7.10 (m, 1H), 6.58 (s, 1H), 2.13 (s, 3H).

[0837] **Compound 196**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.45 (m, 2H), 7.36-7.32 (m, 2H), 7.24-7.19 (m, 2H), 7.15-7.10 (m, 1H), 7.03-6.99 (m, 1H), 6.58 (s, 1H), 2.13 (s, 3H).

[0838] **Compound 197**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.50-7.47 (m, 3H), 7.40 (s, 1H), 7.37-7.32 (m, 2H), 7.18 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.60 (s, 1H), 2.15 (s, 3H).

[0839] **Compound 198**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.48-7.42 (m, 3H), 7.36-7.32 (m, 2H), 7.20 (s, 1H), 7.10 (m, 1H), 7.02 (m, 1H), 6.59 (s, 1H), 2.15 (s, 3H).

[0840] **Compound 201**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.46 (m , 2H), 7.35-7.30 (m , 2H), 7.16 (s, 1H), 6.90-6.88 (m , 1H), 6.78 (s, 1H), 6.75-6.71 (m , 1H), 6.56 (s, 1H), 4.29 (s, 4H), 2.16 (s, 3H). MS (ESI) *m/z* $(M+H)^+$ 404.0.

[0841] **Compound 202**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.50-7.47 (m , 2H), 7.35-7.31 (m , 2H), 7.17 (s, 1H), 6.85-6.82 (m , 1H), 6.75-6.70 (m , 2H), 6.56 (s, 1H), 6.00 (s, 2H), 2.15 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 389.9.

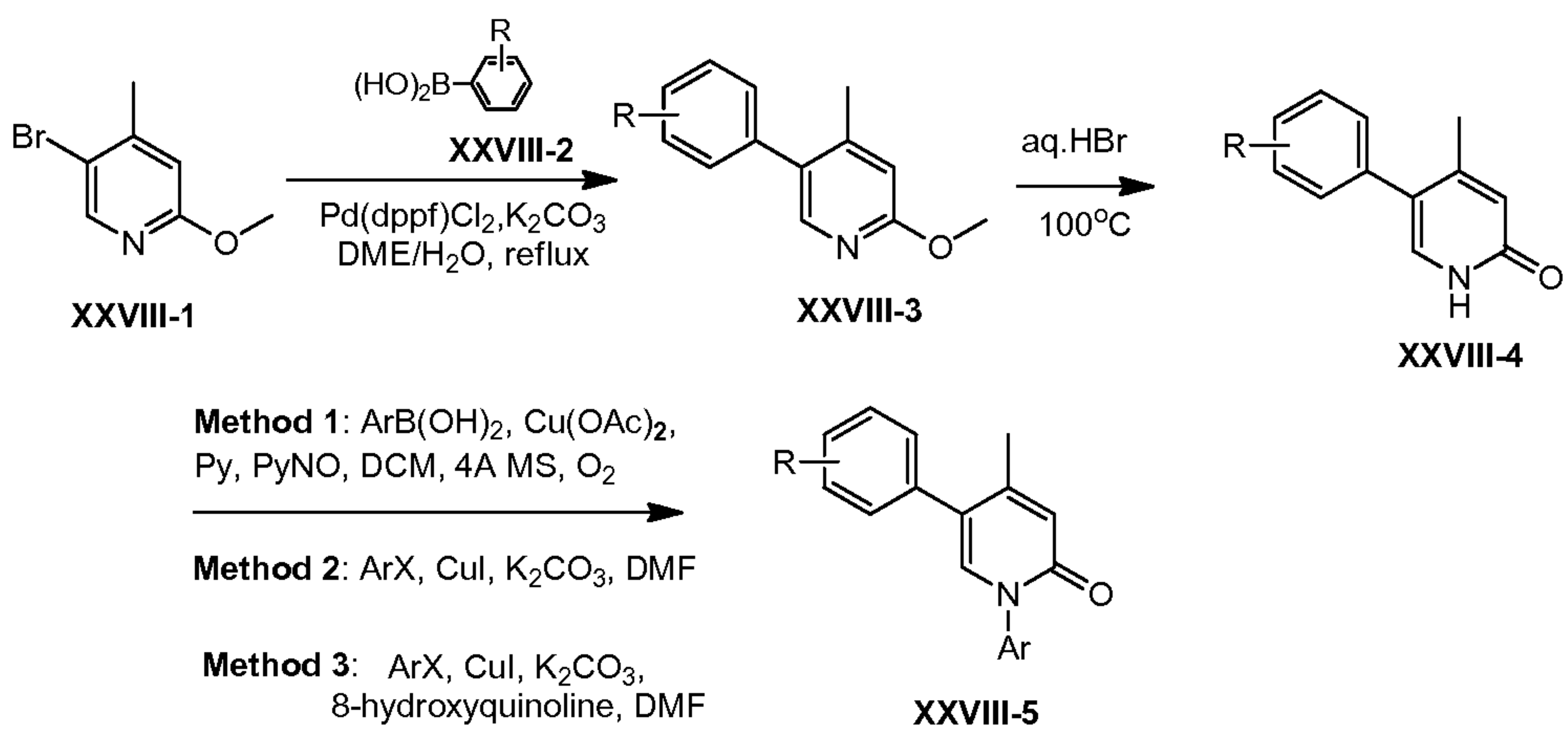
[0842] **Compound 203**: Na_2CO_3 was used instead of K_2CO_3. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.47 (m, 2H), 7.34-7.30 (m, 2H), 6.90-6.86 (m, 2H), 6.72-6.70 (m, 2H), 6.60 (s, 1H), 5.99 (s, 2H), 2.19 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 390.1.

[0843] **Compound 204**: $Pd(PPh_3)_4$ was used instead of $Pd(dppf)Cl_2$, and Na_2CO_3 was used instead of K_2CO_3. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.51-7.49 (m, 2H), 7.34-7.30 (m, 2H), 7.18 (s, 1H), 6.93-6.84 (m, 2H), 6.72-6.70 (m, 1H), 6.56 (s, 1H), 4.28 (s, 4H), 2.09 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 403.9.

[0844] **Compound 205**: 5-bromo-4-(trifluoromethyl)pyridin-2(1H)-one was used instead of **XXVII-1**. Na_2CO_3 was used instead of K_2CO_3. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50-7.48 (m, 2H), 7.37 (d, J = 8.4Hz, 2H), 7.32-7.26 (m, 3H), 7.11-7.07 (m, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 417.8.

[0845] **Compound 552**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.04 (s, 1H), 8.05 (s, 1H), 7.98 (d, J = 8.4Hz, 1H), 7.39-7.36 (m , 1H), 7.17-7.13 (m , 2H), 6.84 (s, 1H), 6.80 (dd, J=1.6, 4.4 Hz, 1H), 8.16 (dd, J=2.4, 8.4Hz, 1H), 6.62 (s, 1H), 4.04 (q, J = 7.2Hz, 2 H), 2.20 (s, 3H), 2.19 (s, 3H), 1.41 (t, J= 7.2 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 377.1.

Example 12-B
Synthesis of 4-Methyl, 5-Phenyl Pirfenidone Analogs (Scheme XXVIII)



[0846] **XXVIII-3** was prepared following Method **A** for obtaining **XXVII-5**.

[0847] **XXVIII-4**: A mixture of **XXVIII-3** in *aq.* HBr (48%) was stirred at 100°C overnight. After being cooled to rt, the mixture was concentrated in vacuo. The remaining mixture was neutralized with saturated *aq.*$NaHCO_3$, and extracted with EtOAc (30 mL×3). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford the crude **XXVIII-4**.

[0848] Three general procedures for the preparation of **XXVIII-5**:

[0849] **Method 1**: To a solution of **XXVIII-4** (1 eq.) in DCM (0.1 mmol/mL) was added the relevant boronic acid **XXVIII-2** (1.5~2 eq.), $Cu(OAc)_2$ (1~3 eq), pyridine (10 eq.) and Pyridine-

N-Oxide (2~3 eq.), followed by addition of 4Å molecular sieve (200~500 mg). The reaction mixture was stirred at rt under oxygen atmosphere overnight. After completion of the reaction indicated by TLC, the resulting mixture was filtered and washed with ethyl acetate; the filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give the title compound. Compounds **181-183, 178-180, 192** and **193** were prepared following Method **1**.

[0850] **Compound 178**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.43-7.39 (m, 2H), 7.28-7.23 (m, 5H), 7.12-7.08 (m, 3H), 6.60 (s, 1H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 298.0.

[0851] **Compound 179**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.34 (s, 1H), 7.30-7.21 (m, 3H), 7.16 (d, J = 8.4 Hz 1H), 7.12-7.07 (m, 2H), 7.02 (s, 1H), 6.59 (s, 1H), 2.19 (s, 3H), 2.15 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 327.9.

[0852] **Compound 180**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38-7.33 (m, 2H), 7.18 (s, 1H), 7.09 (t, J = 8.8Hz, 2H), 6.60 (s, 2H), 6.57 (s, 1H), 3.85 (s, 9H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 370.1.

[0853] **Compound 192**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.49-7.46 (m, 2H), 7.45-7.32 (m, 3H), 7.20 (s, 1H), 7.09-7.00 (m, 2H), 6.98 (m, 1H), 6.58 (s, 1H), 2.16 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 364.0.

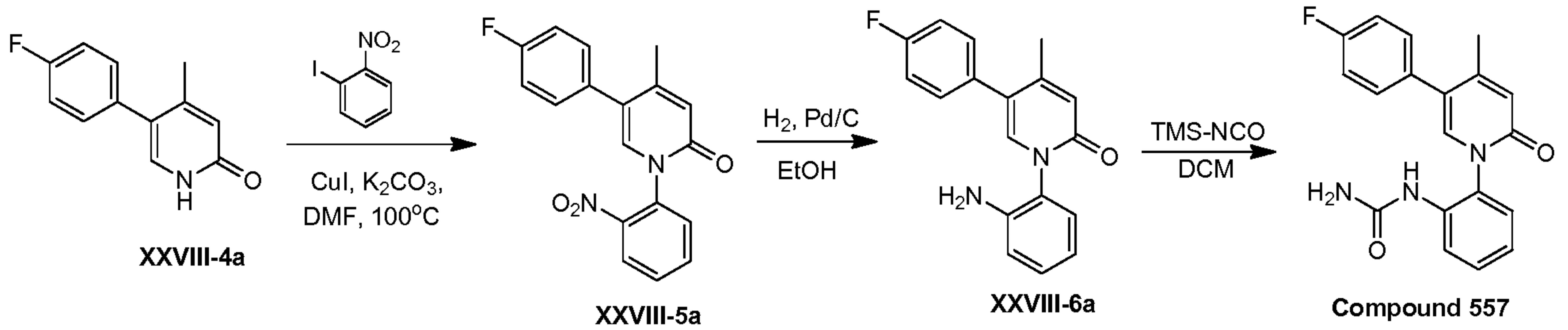
[0854] **Compound 193**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38-7.34 (m, 1H), 7.33-6.98 (m, 5H), 6.84-6.78 (m, 2H), 6.58 (s, 1H), 4.04 (q, J = 7.2 Hz, 2 H), 2.17 (s, 6H), 1.42 (t, J = 7.2 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 338.1.

[0855] **Compound 181**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.50 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8Hz, 2H), 7.28-7.23 (m, 3H), 7.13 (t, J = 8.4 Hz, 2H), 6.86 (s, 1H), 2.21 (s, 3H).

[0856] **Compound 182**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.25-7.21 (m, 2H), 7.16 (s, 1H), 7.08 (t, J = 8.4Hz, 2H), 6.95-9.92 (m, 2H), 6.88-6.85 (m, 1H), 6.56 (s, 1H), 4.28 (s, 4H). 2.11 (s, 3H).

[0857] **Compound 183**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.26-7.22 (m, 2H), 7.16 (s, 1H), 7.09 (t, J = 8.4 Hz, 2H), 6.92 (s, 1H), 6.88-6.80 (m, 2H), 6.56 (s, 1H). 6.02 (s, 2H), 2.12 (s, 3H).

[0858] **Method 2**: To a stirred mixture of 5-(4-fluorophenyl)-4-methylpyridin-2(1H)-one (203 mg, 1 mmol, 1.0 eq.), 1-bromo-2-methyl-4-(trifluoromethoxy)benzene (382 mg, 1.5 mmol, 1.5 eq.), and K_2CO_3 (276 mg, 2 mmol, 2.0 eq.) in DMF (5 mL) was added CuI (19 mg, 0.1 mmol, 0.1 eq.). The reaction mixture was stirred at 140°C for 3 days under N_2 protection. The mixture was cooled to rt, diluted with EA (50 mL), washed with water and brine, concentrated. The residue was purified by flash chromatography on silica gel (PE: EA=5:1→1:1) to give **Compound 186** (40 mg, 11% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.27-7.17 (m, 8H), 7.12-7.07 (m, 1H), 6.60 (s, 1H), 2.23 (s, 3H), 2.15 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 378.0.



[0859] **XXVIII-5a** was prepared from **XXVIII-4a** following Method **2** as described above. **XXVIII-6a** was prepared by hydrogenation (50Psi) of **XXVIII-5a** in ethanol at rt for 4h. **Compound 557** was obtained from reacting **XXVIII-6a** with TMS-NCO. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.21 (d, J=8 Hz, 1H), 7.99 (s, 1H), 7.93 (s, 1H), 7.42-7.39 (m, 2H), 7.30-7.26 (m, 2H), 7.09 (t, J=7.6 Hz, 1H), 7.01 (m, 2H), 6.93 (m, 1H), 6.17 (s, 2H), 2.26 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 338.0.

[0860] **Method 3**: To a stirred mixture of 5-(4-fluorophenyl)-4-methylpyridin-2(1H)-one (2.04 g, 10 mmol, 1.0 eq.), 4-bromobenzo[*d*][1,3]dioxole (3.0 g, 15 mmol, 1.5 eq.), and K_2CO_3 (2.76 g, 20 mmol, 2eq.) in DMF (50 mL) was added CuI (191 mg, 1 mmol, 0.1 eq.) and 8-hydroxyquinoline (140 mg, 1 mmol, 0.1 eq.). The reaction mixture was stirred at 140°C for 3 days under N_2 protection. The mixture was cooled to rt, diluted with EA (250 mL), washed with water and brine, concentrated. The residue was purified by flash chromatography on silica gel (PE:EA=5:1→1:1) to yield **Compound 184** (680 mg, 21% yield) as white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35-7.32 (m, 2H), 7.26 (s, 1H), 7.18 (t, J=8.8Hz, 2H), 7.02-6.94 (m, 3H), 6.67 (s, 1H), 6.13 (s, 2H), 2.21 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 323.8.

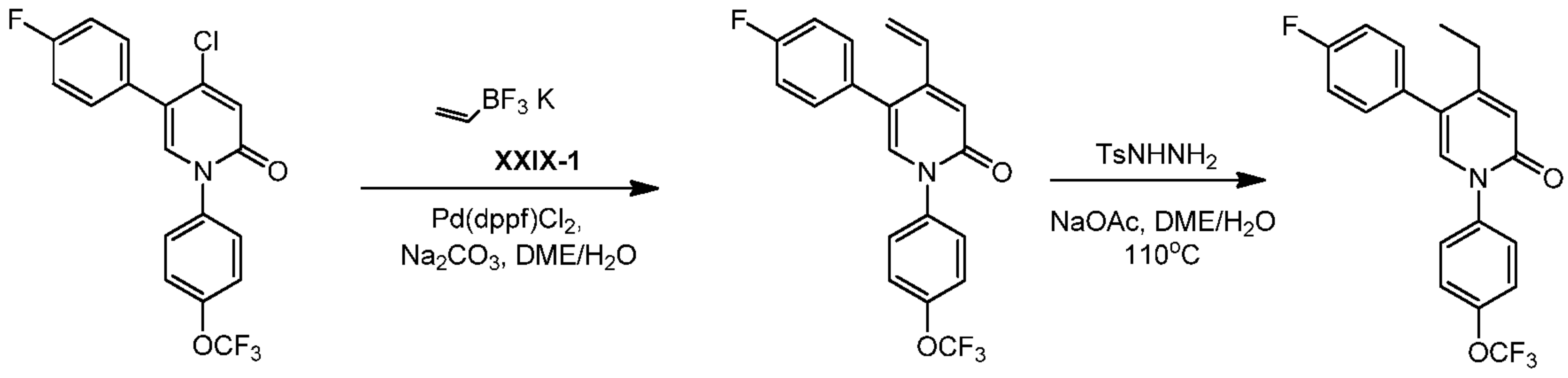
[0861] **Compound 185** was prepared following the similar procedure for obtaining **Compound 184** using 5-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine in place of 4-bromobenzo[*d*][1,3]dioxole. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28-7.24 (m, 3H), 7.11-7.06 (m, 3H), 6.94-6.88 (m, 3H), 6.57 (s, 1H), 4.30-4.28 (m, 4H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 338.1.

[0862] **Compound 187**: To the solution of **Compound 172** (378 mg, 1.12 mmol) in EtOH/H_2O (10 mL, v/v=2/1) was added *aq.*H_2SO_4 (6 M, 2 mL). The mixture was heated to reflux overnight. LCMS showed the reaction was completed. The mixture was concentrated, extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE/EA=3/1) to give **Compound 187** (200 mg, 60% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.26-7.21 (m, 3H), 7.18 (s, 1H), 7.11-7.06 (m, 2H), 6.75-6.68 (m, 3H), 6.56 (s, 1H), 2.12 (s, 3H).

[0863] **Compound 188**: To the solution of **Compound 187** (80 mg, 0.102 mmol) in THF/H_2O (2 mL, v/v=4/1) was added KOCN (10 mg, 0.112 mmol) and AcOH (one drop). The mixture was heated to reflux overnight. LCMS showed the reaction was completed. The mixture was concentrated, diluted with EtOAc (50 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to give **Compound 188** (62.2 mg, 67% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.12 (s, 1H), 7.62 (s, 1H), 7.24-7.21 (m, 3H), 7.13-7.08 (m, 2H), 6.88 (d, *J* = 8.8Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.60 (s, 1H), 4.84 (s, 2H), 2.18 (s, 3H).

[0864] **Compound 559** was prepared reacting **XXVIII-4a** with 2-fluoro-5-iodoaniline using Method **3** as described above, followed by reacting with TMS-NCO. **^{1}H NMR** (DMSO-d_6, 400 MHz) *δ* 8.53 (s, 1H), 8.19 (d, *J*=6.0Hz, 1H), 7.44-7.40 (m, 3H), 7.29-7.20 (m, 3H), 6.97 (m, 1H), 6.43 (s, 1H), 6.27 (s, 2H), 2.08 (s, 3H).

Example 12-C
Synthesis of Compound 199 (Scheme XXIX)

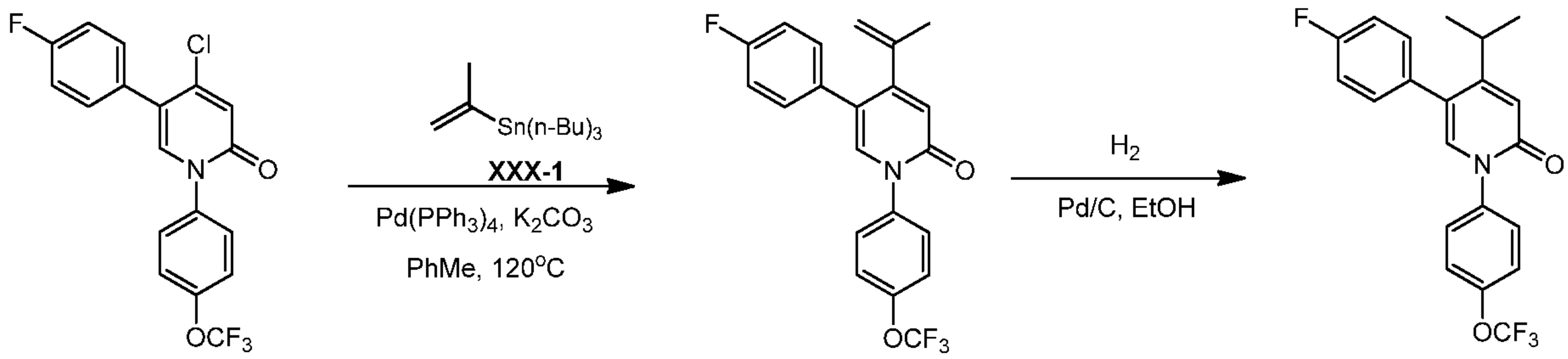


[0865] To a stirred mixture of **Compound 87** (200 mg, 0.52 mmol), **XXIX-1** (92 mg, 0.68 mmol), and Na_2CO_3 (60 mg, 1.4 mmol) in DME/H_2O (18 mL, V/V=8/1) was added Pd(dppf)Cl_2 (140 mg, 0.99 mmol) under N_2 protection. The reaction mixture was stirred at 110°C overnight. The mixture was concentrated to remove DME , diluted with H_2O, extracted with EtOAc (30 mL×3), the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*, the residue was purified by prep-TLC (PE:EA=2.5:1) to give **XXIX-2** (112 mg, yield: 57%) as a white solid. **MS (ESI)** ***m/z*** $[M+H]^+$ 376.09.

[0866] **XXIX-2** (170 mg, 0.45 mmol), $TsNHNH_2$ (338 mg, 1.81 mmol), and NaOAc (371 mg, 4.53 mmol) were added into DME/H_2O (20 mL, v/v=5/1). The reaction mixture was stirred at 110°C overnight. The mixture was concentrated to remove DME , diluted with H_2O, extracted with EtOAc (30 mL×3), the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the residue was purified by prep-HPLC to afford **Compound 199** (107 mg, yield 64%) as white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.49-7.46 (m, 2H), 7.33-7.31

(m, 2H), 7.26-7.22 (m, 2H), 7.14 (s, 1H), 7.11-7.06 (m, 2H), 6.60 (s, 1H), 2.46-2.41(m, 2H), 1.12-1.07 (m, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 378.10.

Example 12-D
Synthesis of Compound 200 (Scheme XXX)



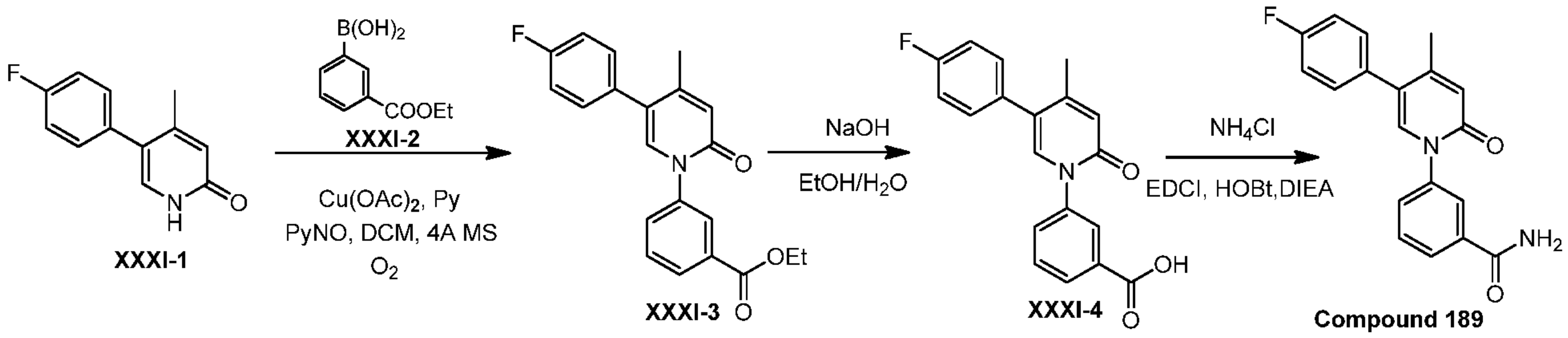
Compound 87 XXX-2 Compound 200

[0867] To a stirred mixture of **Compound 87** (150 mg, 0.270 mmol), **XXX-1** (135 mg, 0.4 mmol), and K_2CO_3 (186 mg, 1.35 mmol) in toluene (5 mL) was added $Pd(PPh_3)_4$ (30 mg, 0.0270 mmol). The mixture was purged with nitrogen for three times and then heated at 120°C overnight. And then the mixture was concentrated, diluted with H_2O, extracted with EtOAc (30 mL×3), the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by prep-TLC (PE:EA=5:1) to yield **XXX-2** (135 mg, 88% yield).

[0868] A mixture of **XXX-2** (100 mg, 0.259 mmol) and dry Pd/C in ethanol (5 mL) was stirred under H_2 at rt for 1h. Filtered the reaction, and concentrated the organic layer to give **Compound 200** (61.6 mg, 61% yield). ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.49 (d, *J* = 8.8Hz, 2H), 7.34 (d, *J* = 8.4Hz, 2H), 7.25-7.23 (m, 2H), 7.14-7.08 (m, 3H), 6.65 (s, 1H), 2.85-2.77 (m, 1H), 1.14 (d, *J* = 6.8Hz, 6H).

[0869] **Compound 629**: To a mixture of 5-bromo-1-(4-ethoxy-2-methylphenyl)-4-methylpyridin-2(1H)-one (1.5 g, 4.66 mmol) and 4-(tributylstannyl)pyridazine (3.44 g, 9.31 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_2Cl_2$ (0.163 g, 0.233 mmol) under N_2 at rt. The mixture was refluxed overnight. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic layer were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (PE/EA=1:2→EA) to produce **Compound 629** as a yellow solid (0.806 g, 54% yield). ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 9.33 (d, *J*=2.4 Hz, 1H), 9.21 (d, *J*=5.6 Hz, 1H), 7.78 (dd, *J*=2.4, 5.2 Hz, 1H), 7.70 (s, 1H), 7.18 (d, *J*=8.8 Hz, 1H), 6.92 (d, *J*=2.4 Hz, 1H), 6.85 (dd, *J*=2.4, 8.4 Hz, 1H), 6.50 (s, 1H), 4.07 (q, *J*=6.8 Hz, 2H), 2.21 (s, 3H), 2.04 (s, 3H), 1.32 (t, *J*=6.8 Hz, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 322.0.

Example 12-D
Synthesis of Compound 189 (Scheme XXXI)



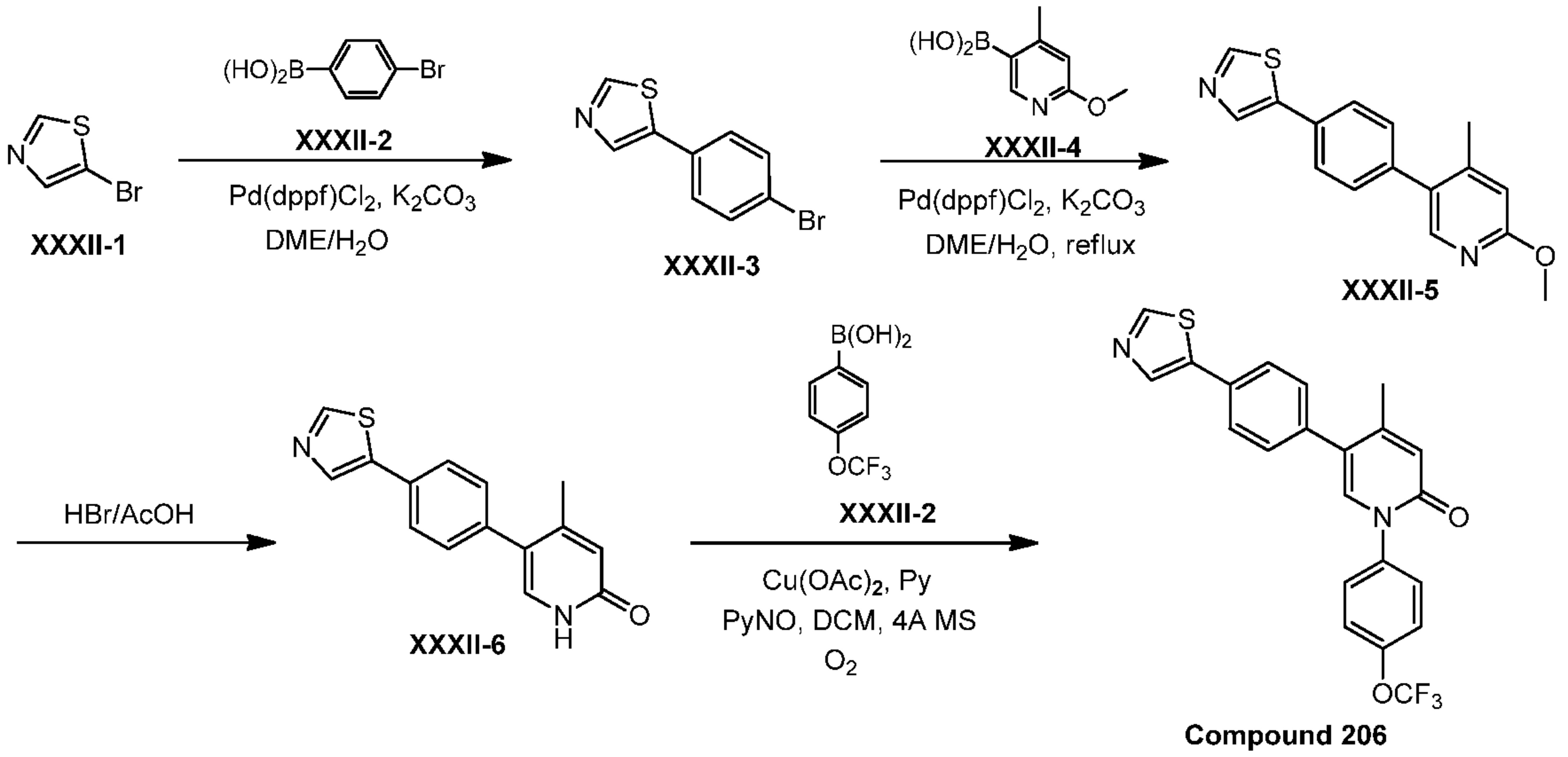
[0870] **XXXI-3** was obtained following the similar procedure for obtaining **XXVII-3**.

[0871] To a solution of **XXXI-3** (300 mg, 0.854 mmol) in EtOH (10 mL) was added a solution of NaOH (102 mg, 2.56 mmol) in water (8 mL). The reaction mixture was heated to 100°C for 4 hrs. After concentration in *vacuo*, the mixture was acidified with *aq.* HCl (1N). Then the mixture was extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was used for next step directly without further purification (200 mg, 72% yield). **MS (ESI)** ***m/z*** $[M+H]^+$ 324.0.

[0872] **XXXI-4** (150 mg, 0.464 mmol), HOBT (70 mg, 0.51 mmol), EDC·HCl (100 mg, 0.51 mmol) and DIEA (260 mg, 2 mmol) were charged into dry DCM (5 mL), followed by NH_4Cl (75 mg, 1.4 mmol). The reaction mixture was stirred at rt overnight. The mixture was diluted with water (10 mL), extracted with EtOAc (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC to afford **Compound 189** as a pale yellow solid (21.8 mg, 17% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.89 (s, 1H), 7.84 (m, 1H), 7.59-7.53 (m, 2H), 7.27-7.22 (m, 3H), 7.13-6.99 (m, 2 H), 6.56 (s, 1H), 2.14 (s, 3H). **MS (ESI)** ***m/z*** $(M+Na)^+$ 344.9.

[0873] **Compound 190:** To a solution of **XXXI-4** (250 mg, 0.77 mmol), HATU (350 mg, 0.92 mmol), and DIEA (300 mg, 2.3 mmol) in dry DCM (8 mL) was added the methylamine hydrochloride (78 mg, 1.16 mmol). The reaction mixture was stirred at rt overnight. The mixture was diluted with water (20 mL), extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-TLC (DCM:MeOH=10:1) to produce **Compound 190** as a white solid (159.3 mg, 61% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.75 (m, 1H), 7.52-7.46 (m, 2H), 7.27-7.21 (m, 3H), 7.13-7.08 (m, 2 H), 6.70 (brs, 1H), 6.57 (s, 1H), 2.96 (d, J = 4.8 Hz, 3H), 2.14 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$336.9.

Example 12-E
Synthesis of Compound 206 (Scheme XXXII)



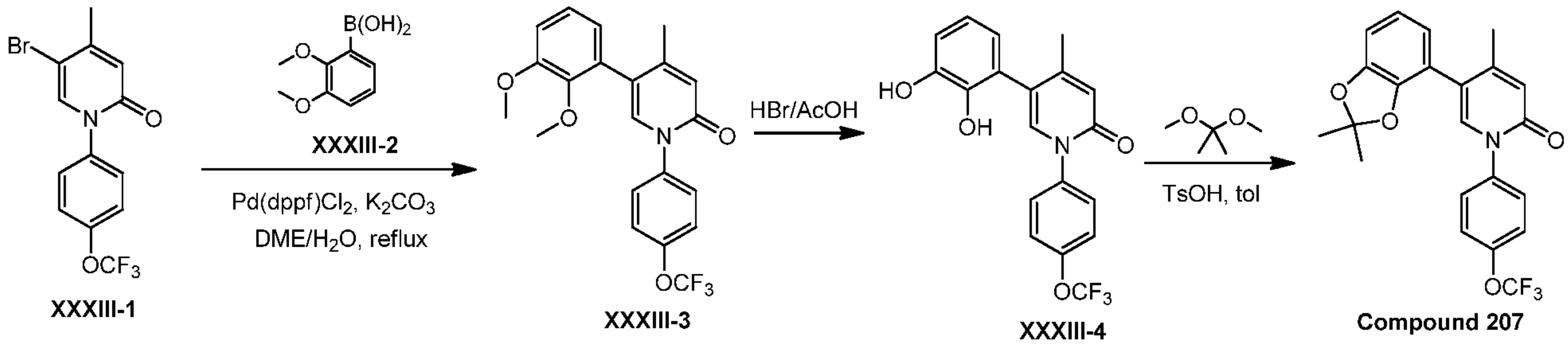
[0874] To a stirred mixture of **XXXII-1** (1.5 g, 9.15 mmol), **XXXII-2** (1.83 g, 9.15 mmol), and K_2CO_3 (3.79 g, 27.45 mmol) in DME/H_2O (50 mL, v:v=5:1) was added Pd(dppf)Cl_2 (1.34 g, 1.83 mmol) under N_2 protection. The reaction mixture was heated to reflux overnight. The mixture was poured into water, extracted with EtOAc (150 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (PE:EA=10:1→5:1→3:1) to afford **XXXII-3** (600 mg, 21% yield).

[0875] To a stirred mixture of **XXXII-3** (400 mg, 1.7 mmol), **XXXII-4** (425.8 mg, 2.55 mmol), and K_2CO_3 (703.8 mg, 5.1 mmol) in DME/H_2O (50 mL, v:v=5:1) was added Pd(dppf)Cl_2 (120 mg, 0.17 mmol) under N_2 protection. The reaction mixture was heated to reflux for 4 hours, then the mixture was poured into water, extracted with EtOAc (30 mL×3), the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE:EA=3:1→1:1) to afford **XXXII-5** (220 mg, 46% yield). **MS (ESI)** ***m/z*** $[M+H]^+$ 283.

[0876] A mixture of **XXXII-5** (100 mg, 0.35 mmol) in AcOH (5 mL) and *aq.* HBr (40%, 5 mL) was heated to reflux overnight. And then it was neutralized with *aq.* NaOH (1 M), extracted with EA (30 mLx3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give **XXXII-6** (80 mg, 85% yield). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 9.12 (s, 1H), 8.36 (s, 1H), 7.73-7.70 (d, J = 7.8 Hz, 2H), 7.41-7.39 (d, J =8.1Hz, 2H), 7.25 (s, 1H), 6.30 (s, 1H), 1.90 (s, 3H).

[0877] **Compound 206** was prepared by following the similar procedure for obtaining **XXVII-3** (150 mg, 58% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.79 (s, 1H), 8.12 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.34 (m, 4H), 7.23 (s, 1H), 6.61 (s, 1H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 429.1.

Example 12-F
Synthesis of Compound 207 (Scheme XXXIII)

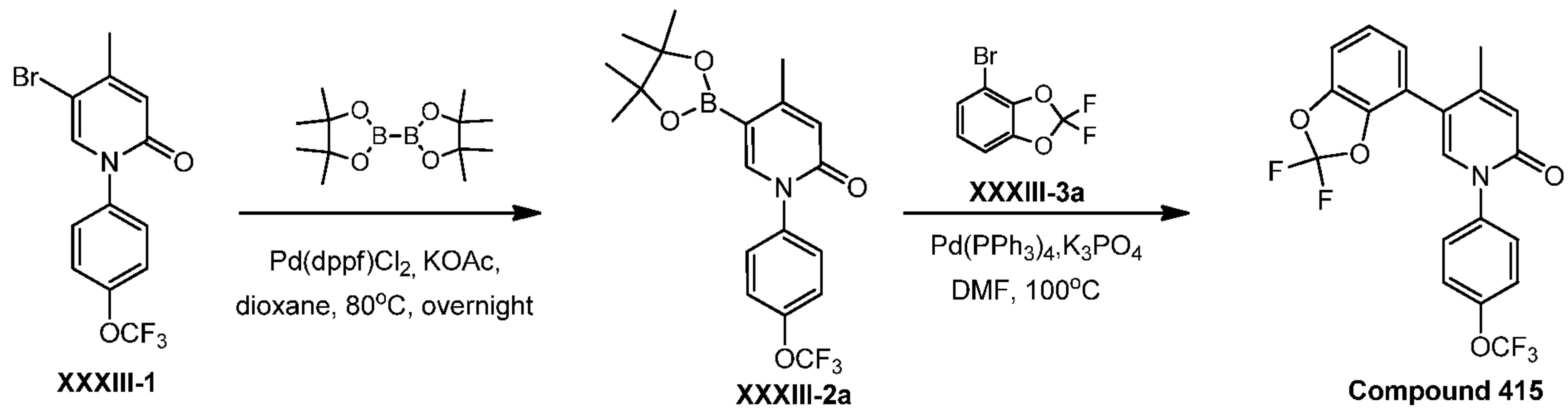


[0878] **XXXIII-3** was prepared following the similar procedure for obtaining **XXXII-5**.

[0879] **XXXIII-4** was prepared following the similar procedure for obtaining **XXXII-6**.

[0880] To a solution of **XXXIII-3** (450 mg, 1.2 mmol) in toluene (50 mL) was added 2,2-dimethoxypropane (9 mL) and TsOH (45.6 mg, 0.24 mmol), the mixture was heated to reflux overnight. The mixture was poured into water, extracted with EA (50 mLx3). The combined organic layer was washed with brine and concentrated to give crude product, which was purified by prep-HPLC to give **Compound 207** (200 mg, 41% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.47 (m, 2H), 7.33-7.31 (d, J = 8.4Hz, 2H), 7.24 (s, 1H), 6.83-6.79 (m, 1H), 6.77-6.75 (m, 1H), 6.64-6.62 (m, 1H), 6.57 (s, 1H), 2.18 (s, 3H), 1.70 (s, 6H). **MS (ESI)** ***m/z*** [M+H]+ 418.

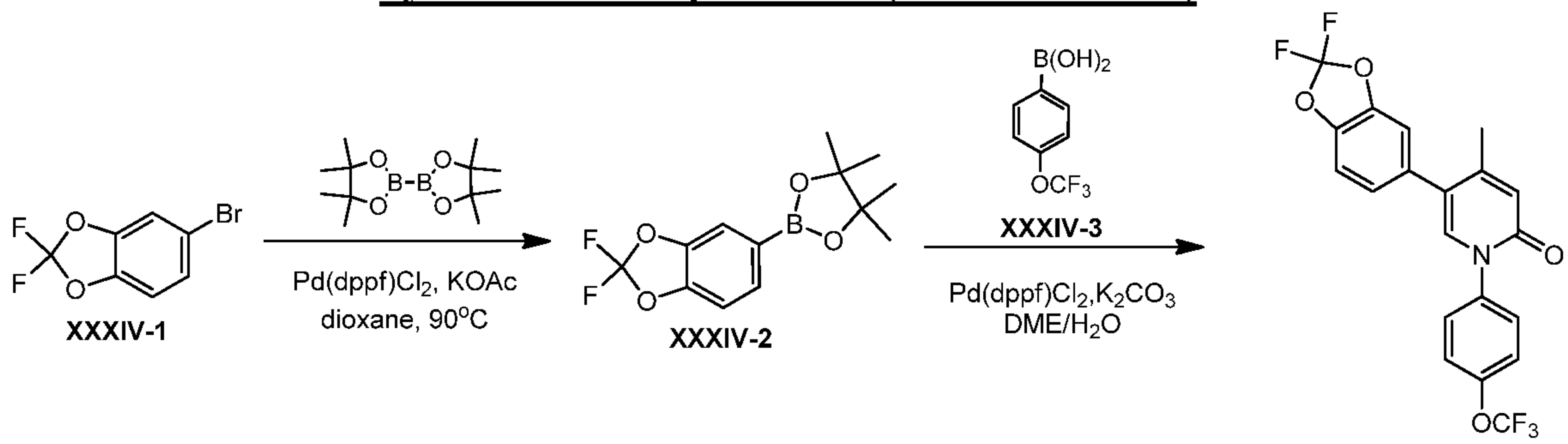
[0881] **Compound 211** was prepared following the similar procedure for obtaining **Compound 207** using (3,4-dimethoxyphenyl)boronic acid in place of **XXXIII-2**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.46 (m, 2H), 7.34-7.31 (m, 2H), 7.16 (s, 1H), 6.75-6.73 (d, J = 7.6 Hz, 1H), 6.67-6.64 (m, 2H), 6.56 (s, 1H), 2.16 (s, 3H), 1.70 (s, 6H). **MS (ESI)** ***m/z*** [M+H]+ 417.9.



[0882] **XXXIII-2a** was prepared by following the similar procedure for obtaining **XXXIII-3** using bis (pinacolato)diboron in place of **XXXIII-2** as a white solid.

[0883] **Compound 415**: To a solution of **XXXIII-2a** (200 mg, 1.06 mmol) in DMF (4 mL) was added K_3PO_4 (476 mg 2.11 mmol), **XXXIII-3a** (500 mg, 3.16 mmol), $Pd(PPh_3)_4$ (122 mg, 0.106 mmol.). The mixture was purged with nitrogen and then heated at 100°C overnight. The mixture was cooled to rt, diluted with water (20 mL), extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by prep-TLC (PE/EA =10/1) to give **Compound 415** (128 mg, 36% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.50 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.29 (s, 1H), 7.15-7.08 (m, 2H), 6.98-6.96 (m, 1H), 6.62 (s, 1H), 2.17 (s, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 425.9.

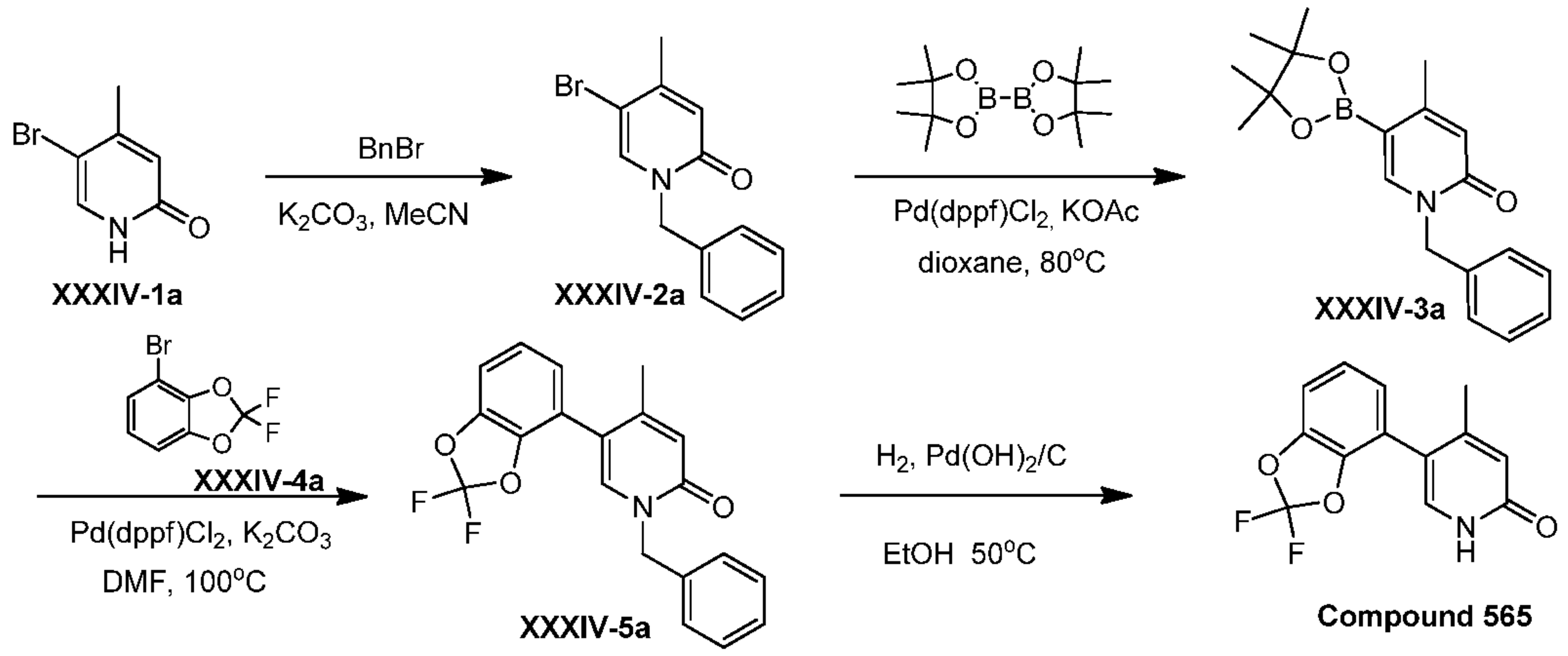
Example 12-G
Synthesis of Compound 208 (Scheme XXXIV)



Compound 208

[0884] A flask was charged with **XXXIV-2** (1 g, 4.2 mmol), bis (pinacolato)diboron (1.27 g, 5 mmol) and KOAc (0.5 g, 5 mmol) in 1,4-dioxane (30 mL). The flask was purged with nitrogen for three times. And then $Pd(dppf)Cl_2$ (150 mg, 0.21 mmol) was added thereto and then the mixture was purged with nitrogen again. The mixture was stirred at 90°C for 12 hrs. After the starting material was consumed, the mixture was cooled to rt, the solvent was evaporated *in vacuo*. The residue was diluted with water (30 mL), extracted with EA (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE:EA=10:1 to 5:1) to provide **XXXIV-2** (800 mg, 67% yield) as a white solid.

[0885] **Comound 208** was obtaining following the similar procedure for obtaining **XXXII-5**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.45 (m, 2H), 7.33 (d, J = 8.4Hz, 2H), 7.18 (s, 1H), 7.11-7.09 (m, 1H), 7.02-6.97 (m, 2H), 6.59 (s, 1H), 2.14 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 425.9.

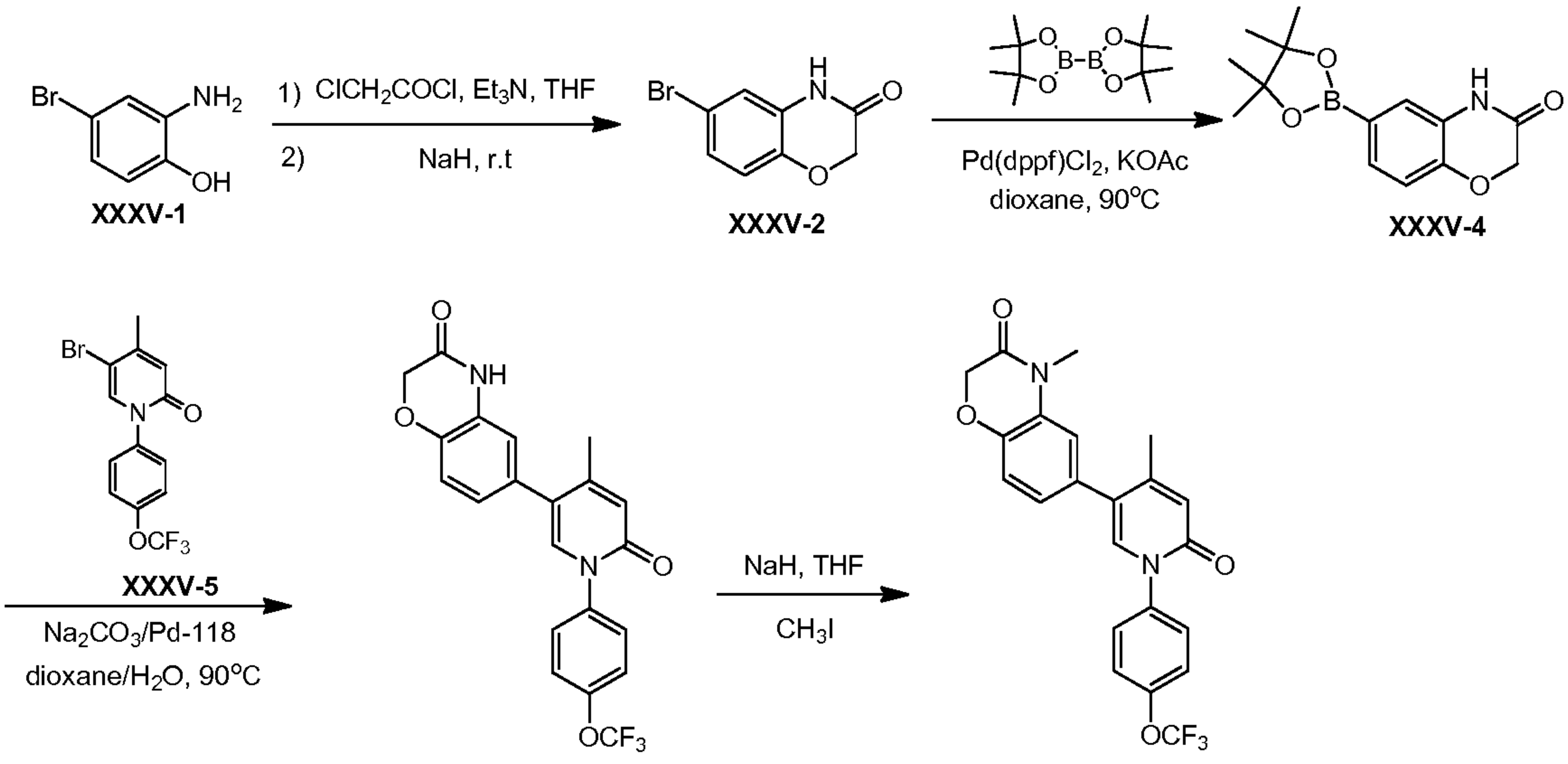


[0886] To a mixture of **XXXIV-1** (700 mg, 3.763 mmol) in MeCN (20 mL) was added BnBr (954 mg, 15.465 mmol) and K_2CO_3 (1.349 g, 7.523 mmol). The mixture was stirred at rt overnight, and then it was concentrated to remove MeCN, diluted with H_2O, extracted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude product was chromatographed on silica gel (PE:EA=1:1) to give **XXXIV-2** (600 mg, yield 58 %). **MS (ESI)** ***m/z*** $[M+H]^+$ 278.2.

[0887] **XXXIV-3a** was prepared from Suzuki-Coupling of **XXXIV-2a** and bis (pinacolato)diboron following the standard procedure described above. **XXXIV-5a** was prepared by Suzuki-Coupling of **XXXIV-3a** with **XXXIV-4a** following the standard procedure described above.

[0888] A mixture of **XXXIV-5a** (250 mg, 0.704 mmol) and $Pd(OH)_2/C$ (25 mg) in EtOH (10 mL) was stirred under 1 atm of H_2 at 50°C overnight. After completion of the reaction, the mixture was filtered and concentrated, the residue was purified by prep-TLC (PE/EA=5/1) to afford **Compound 565** (40 mg, 22% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35 (s, 1H), 7.16-7.06 (m , 2H), 6.92 (d, J = 7.6 Hz, 1 H), 6.52 (s, 1H), 2.16 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 266.1.

Example 12-H
Synthesis of Compound 209 (Scheme XXXV)



Compound 209 Compound 210

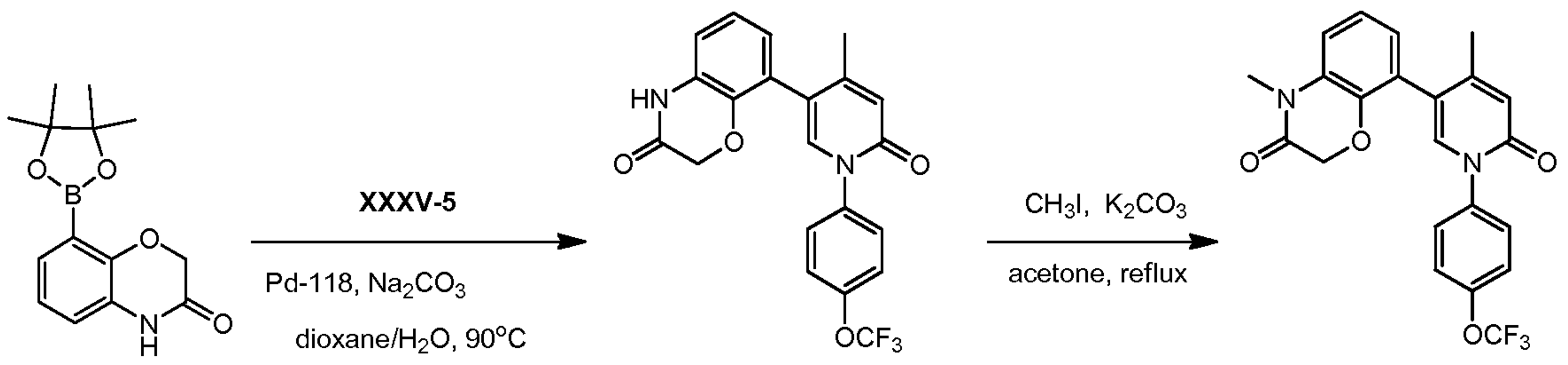
[0889] TEA (4.06 g, 0.04 mmol) was added to a solution of **XXXV-1** (5 g, 27 mmol) in THF (150 mL). And then 2-chloroacetyl chloride (3.33 g, 0.03 mmol) was added in portions at 0°C. After 20 minutes, the mixture was stirred at rt for 2 hrs. The reaction mixture was cooled to 0°C and NaH (60%, 2.2 g, 54 mmol) was added in portions. The reaction mixture was stirred at 0°C for 20 minutes then at rt for 2h before being quenched with water. The solvent was removed *in vacuo* and the resulting mixture diluted with water. The precipitate was filtered, washed with water and dried *in vacuo* to give **XXXV-2** (5.5 g, 89% yield).

[0890] To the solution of **XXXV-2** (2.3 g, 10 mmol) in dioxane (20 mL), bis (pinacolato)diboron (3.05 g , 12 mmol), potassium acetate (2 g , 20 mmol) and Pd(dppf)Cl_2 (730 mg, 1 mmol) was added. The mixture was purged with nitrogen and sitirred at 90°C overnight. Then the mixture was diluted with EA (200 mL) and filtrated. The organic phase was washed with brine, dried over Na_2SO_4, concentrated *in vacuo* to give the crude product. The residue was purification by column chromatography on silica gel (PE:EA=3:1 to 1:1) to give **XXXV-4** (1.9 g, 69% yield) .

[0891] To the solution of **XXXV-4** (1.4 g, 5.1 mmol) in dioxane/H_2O (15 mL/3 mL), **XXXV-5** (1.47 g, 4.2 mmol), Na_2CO_3 (890 mg, 8.4 mmol) and Pd-118 (137 mg , 6.21 mmol) were added. The mixture was purged with nitrogen and stirred at 90°C overnight. Then the mixture was diluted with EA (100 mL) and filtrated. The organic phase was washed with brine, dried over Na_2SO_4, concentrated *in vacuo* to give the crude product. The residue was purified by column chromatography on silica gel (PE:EA=2:1 to 1:1) to afford **Compound 209** (1.36 g, 64% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.05 (s, 1H), 7.49-7.45 (m, 2H), 7.35-7.32 (m, 2H), 7.16 (s, 1H), 7.03-

7.00 (m, 1H), 6.89-6.87 (m, 1H) ,6.74 (s, 1H), 6.58 (s, 1H), 4.65 (s, 2H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.9.

[0892] **Compound 210**: **Compound 209** (400 mg, 0.96 mmol) was dissolved in THF (2 mL), NaH (60%, 60 mg, 1.2 mmol) was added in portions under stirring at 0°C. After about 30 minutes, iodomethane (2.1 g, 14.6 mmol) was added; the mixture was stirred at rt for 14 hrs. Then diluted with water and extracted with EA (30 mL×3). The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated *in vacuo* to give the crude product, which was purified by prep-TLC (PE:EA= 2:1) to provide **Compound 210** (262 mg, 63% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50-7.48 (m, 2H), 7.36-7.31 (m, 2H), 7.19 (s, 1H), 7.03-7.00 (m, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.87 (s, 1H), 6.59 (s, 1H), 4.66 (s, 2H), 3.38 (s, 3H), 2.15 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 431.0.



XXXV-4a Compound 423 Compound 428

[0893] **XXXV-4a** was prepared by following the similar procedure for obtaining **XXXV-4** using 2-amino-6-bromophenol in place of **XXXV-1**.

[0894] To the solution of **XXV-4a** (450 mg, 1.64 mmol) in dioxane/H_2O (10 mL / 2 mL), **XXV-5** (516 mg, 1.49 mmol), Na_2CO_3 (316 mg, 2.98 mmol) and Pd-118 (50 mg , 0.08 mmol) was added. The mixture was purged with nitrogen and sitirred at 90°C overnight. Then the mixture was diluted with EA (100 mL) and filtered. The organic phase was washed with brine, dried over Na_2SO_4, concentrated in *vacuo* to give the crude product. The residue was purified by column chromatography (PE/EA=2/1) to produce **Compound 423** (440 mg, 65% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.59 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H), 7.02-6.98 (m, 1H), 6.88-6.85 (m, 2H) , 6.58 (s, 1H), 4.62 (s, 2H), 2.09 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.9.

[0895] To the stirring mixture of **Compound 423** (370 mg, 0.89 mmol) in acetone (5 mL), K_2CO_3 (180 mg, 1.33 mmol) and iodomethane (139 mg, 0.98 mmol) were added in portions. The mixture was refluxed overnight. The mixture was cooled to rt and filtered. The filtrate was concentrated in *vacuo* to give the crude product. The residue was purified by column chromatography (PE/EA=2/1) to give **Compound 428** (230 mg, 60% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.17 (s, 1H), 7.11-7.07 (m, 1H), 7.04-7.02

(m, 1H), 6.91-6.89 (m, 1H) , 6.58 (s, 1H), 4.62 (s, 2H), 3.40 (s, 3H), 2.08 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 431.0.

[0896] Compounds **424** and **425** were prepared following the similar procedure for obtaining Compounds **423** and **428** using 2-amino-5-bromophenol as starting material.

[0897] **Compound 424**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.49 (s, 1H), 7.50-7.46 (m, 2H), 7.35-7.31 (m, 2H), 7.18 (s, 1H), 6.91 (s, 1H), 6.89-6.83 (m, 2H), 6.59 (s, 1H) , 4.65 (s, 2H), 2.16 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.9.

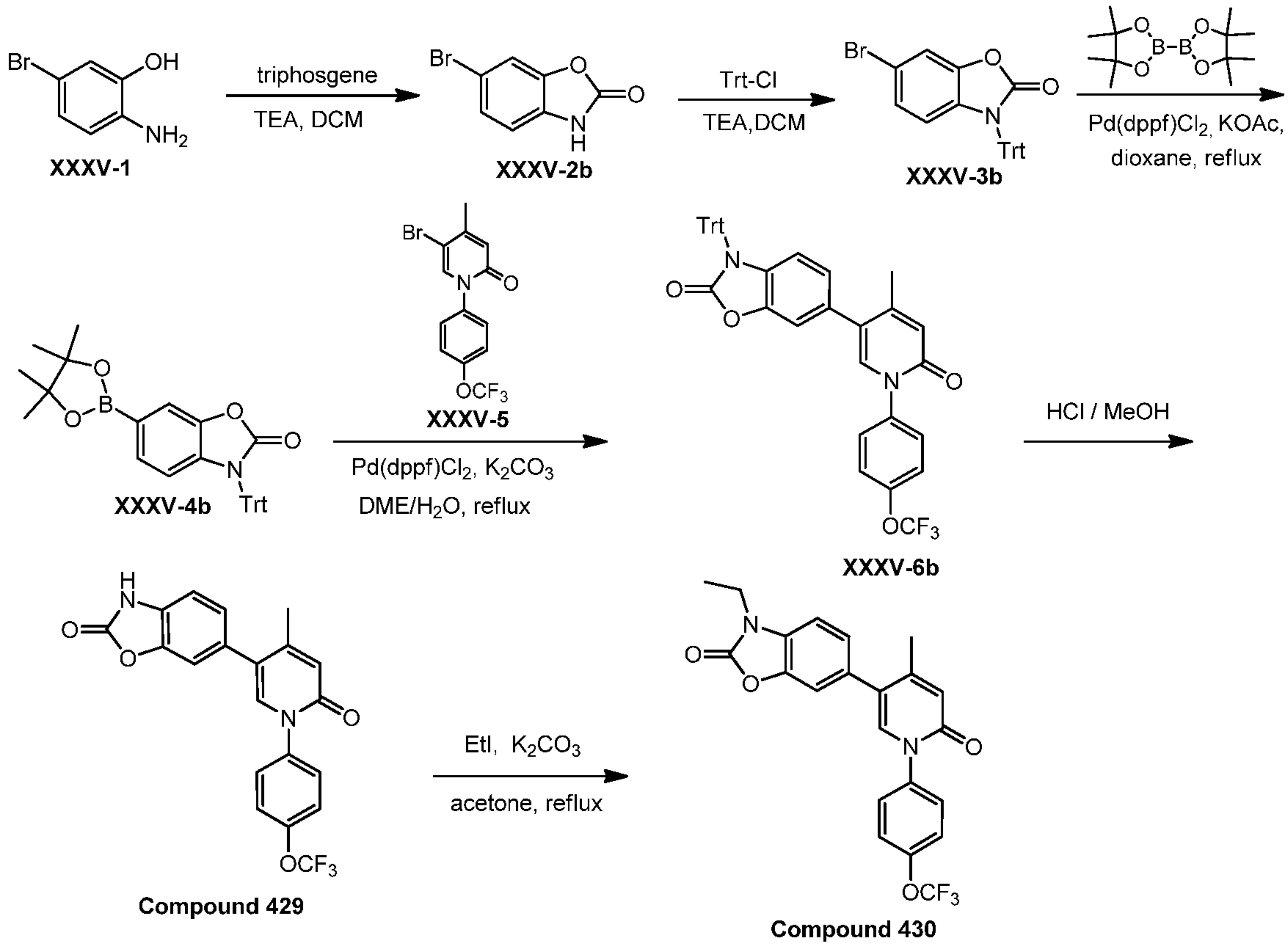
[0898] **Compound 425**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.19 (s, 1H), 7.01-6.92 (m, 3H), 6.58 (s, 1H), 4.65 (s, 2H), 3.39 (s, 3H), 2.17 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 431.0.

[0899] Compounds **426** and **427** were prepared following the similar procedure for obtaining Compounds **423** and **428** using 2-amino-3-bromophenol as starting material.

[0900] **Compound 426**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.23 (s, 1H), 7.02 (d, J = 4.8 Hz, 2H), 6.85-6.83 (m, 1H) , 6.59 (s, 1H), 4.58 (s, 2H), 1.97 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 416.9.

[0901] **Compound 427**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.46 (d, J = 9.2 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 7.10-7.08 (m, 2H), 6.91-6.89 (m, 1H), 6.63 (s, 1H), 4.61-4.50 (m, 2H), 3.04 (s, 3H), 2.07 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 431.0.

[0902] **Compound 566** was obtained by reacting **Compound 424** with 2-(2-bromoethoxy)tetrahydro-2H-pyran in DMF with the presence of Cs_2CO_3, followed by hydroxy group deprotection using TsOH. H_2O. ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ 7.47 (d, J= 9.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.18~7.13 (m, 2H), 6.94 (d, J = 7.2 Hz, 2H), 6.58 (s, 1H), 4.67 (s, 2H), 4.16 (t, J = 5.4 Hz, 2H), 3.98 (m, 2H), 2.16 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 461.0.



[0903] To a solution of **XXXV-1** (3 g, 16 mmol) in dry DCM (50 mL) was added TEA (3.2 g, 32 mmol). The reaction mixture was cooled to 0°C, triphosgene (1.6 g, 5.3 mmol) was added slowly. The mixture was stirred overnight at rt, then quenched with water, extracted with DCM (80 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (PE/EA=10/1) to afford **XXXV-2b** (2.7g, 79% yield).

[0904] To a solution of **XXXV-2b** (500 mg, 2.97 mmol) in dry DCM (20 mL) was added TEA (360 mg, 3.56 mmol) and Trt-Cl (992 mg, 3.56 mmol). The mixture was stirred overnight at rt, then poured into water, extracted with DCM (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (PE/EA=10/1) to afford **XXXV-3b** (1.2 g, 89% yield).

[0905] **XXXV-4b** was prepared following the similar procedure for obtaining **XXXV-4**. **MS (ESI)** ***m/z*** $(M+H)^+$ 503.9.

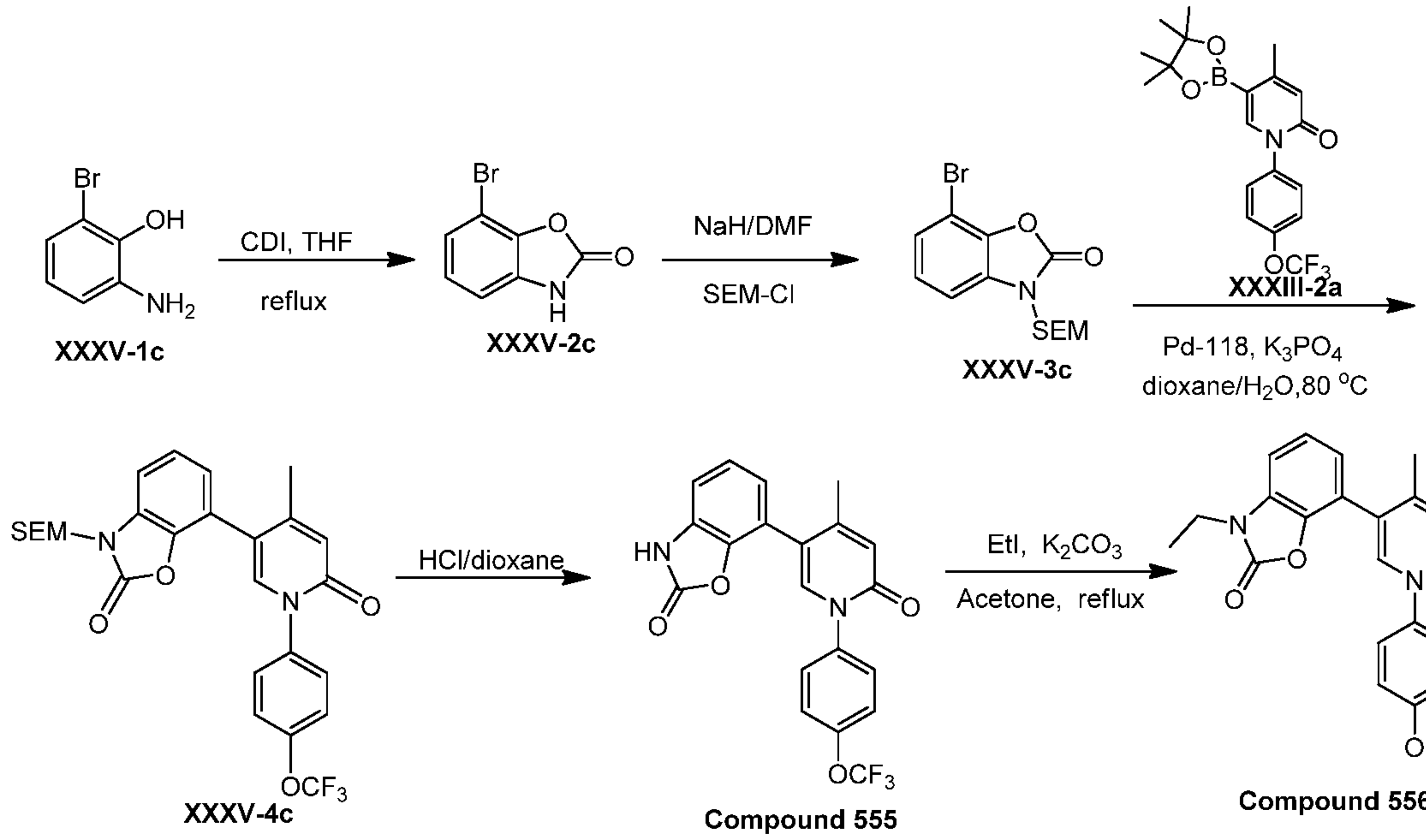
[0906] **XXXV-6b** was prepared following the similar procedure described in Method **A**. **MS (ESI)** ***m/z*** $(M+H)^+$ 645.1.

[0907] **Compound 429**: **XXXV-6b** (800 mg, 1.24 mmol) was dissolved in a solution of HCl/MeOH (4 M, 50 mL), the mixture was stirred overnight at 70°C. And then the mixture was concentrated, the residue was diluted with water (20 mL) and adjusted to pH= 7~8 with saturated *aq.* $NaHCO_3$, extracted with EtOAc (80 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (PE/EA=10/1→5/1) to afford **Compound 429** (370 mg, 74% yield).

[0908] **Compound 430** was prepared following the similar procedure for obtaining **Compound 428** using ethyl iodide instead of methyl iodide. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.46 (m, 2H), 7.34-7.32 (m, 2H), 7.18 (s, 1H), 7.14 (s, 1H), 7.11-7.08 (m, 1H), 7.02-7.00 (m, 1H), 6.59 (s, 1H), 3.92 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 431.1.

[0909] **Compound 553** was prepared following the similar procedure described in the synthesis of Compound **429** using 2-amino-4-bromophenol in place of **XXXV-1**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.64 (d, J=6.8Hz, 2H), 7.53-7.49 (m, 3H), 7.32 (d, J=8.0Hz, 1H), 7.10 (d, J=8.4Hz, 2H), 6.48 (s, 1H), 2.13 (s, 3H). **MS (ESI) *m/z*** [M+H]+ 403.0.

[0910] **Compound 554** was prepared following the similar procedure described in the synthesis of Compound **430**. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.66-7.63 (m, 2H), 7.58 (s, 1H), 7.53-7.51 (m, 2H), 7.40-7.37 (m, 2H), 7.18-7.15 (m, 1H), 6.50 (s, 1H), 3.86 (q, J=6.8Hz, 2H), 2.16 (s, 3H), 1.26 (t, J=6.8Hz, 3H). **MS (ESI) *m/z*** [M+H]+ 431.1.



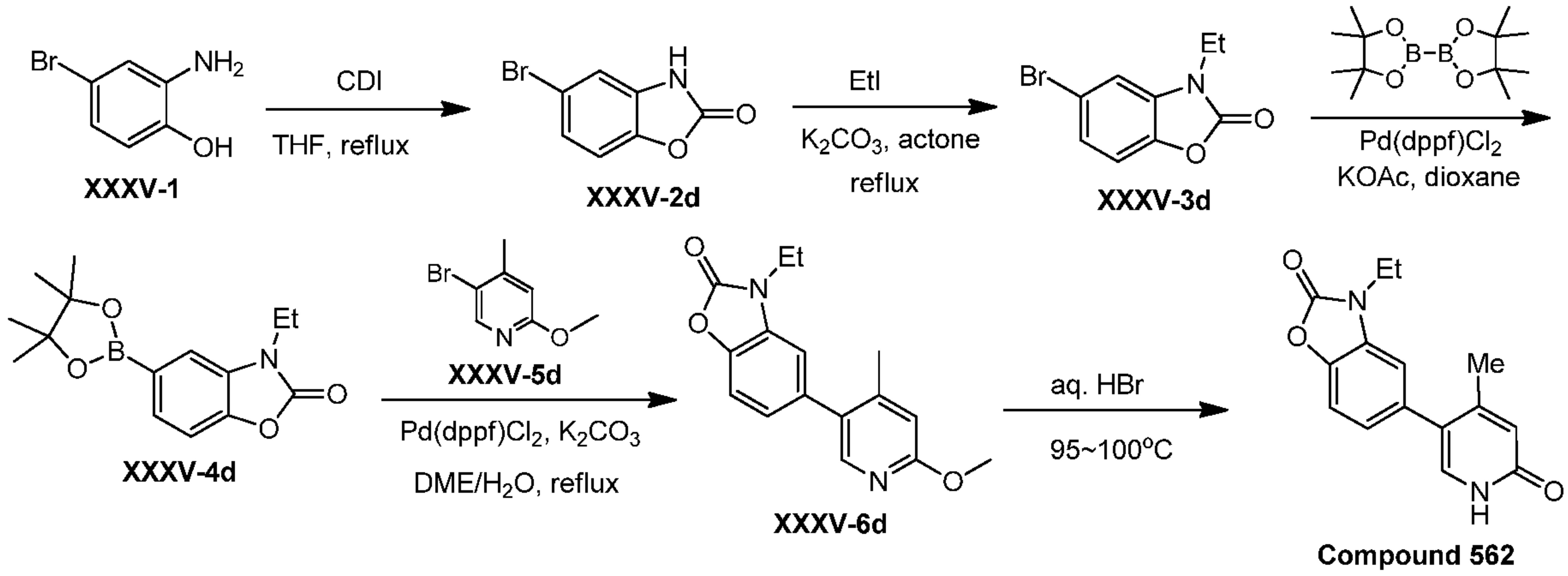
[0911] To a solution of **XXXV-1c** (200 mg, 1.08 mmol) in dry THF(15 ml) was added CDI (262 mg, 1.62mmol). The reaction mixture was heated to reflux overnight, then quenched with water, extracted with EA, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by chromatography on silica gel (PE:EA=10:1) to afford **XXXV-2c** (160 mg, yield 70%).

[0912] To a solution of **XXXV-2c** (5.3 g, 25 mmol) in DMF (20 mL) was added NaH (60% dispersion in mineral oil, 1.5 g, 37.5 mmol) at 0 °C, The mixture was stirred for 30 mins at rt, then SEM-Cl (6.2 g, 37.5 mmol) was added slowly, and then the reaction mixture was stirred overnight at rt. The mixture was poured into water, extracted with EA, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (PE:EA=15:1→5:1) to afford **XXXV-3c** (2.7 g, yield 31%).

[0913] **XXXV-4c** was prepared following the similar procedure described in the synthesis of Compound **423**. **Compound 555** was prepared by acid hydrolysis of **XXXV-4c**. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.62-7.57 (m, 3H), 7.45 (d, *J*=8.4Hz, 2H), 7.22 (d, *J*=8.0Hz,1H), 7.13-7.06 (m, 2H), 6.62 (s, 1H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 403.1.

[0914] **Compound 556** was prepared following the similar procedure described in the synthesis of Compound **430**. **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.63-7.57 (m, 3H), 7.46-7.44 (d, *J*= 8.4Hz, 2H), 7.31-7.26 (m, 2H), 7.13-7.11 (d, *J*=7.6Hz, 1H), 6.62 (s, 1H), 3.94 (q, *J*=7.2Hz, 2H), 2.18 (s, 3H), 1.36 (t, d=7.2 Hz, 3H). **MS (ESI)** ***m/z*** [M+H]+ 431.0.

[0915] **Compound 558** was prepared by reacting **Compound 429** with (2-bromoethoxy)(tert-butyl)dimethylsilane in acetone with the presence of K_2CO_3, followed by deprotection of the TBDMS protecting group using TBAF. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.19 (s,1H), 7.47 (d, *J*=8.8Hz, 2H), 7.33 (d, *J*=8.4Hz, 2H), 7.19 (s, 1H), 7.05 (d, *J*=8.4Hz, 1H), 7.00 (s, 1H), 6.88 (d, *J*=2.0Hz, 1H), 6.57 (s, 1H), 4.67 (t, *J*=8.0Hz, 2H), 4.19 (t, *J*=8.0Hz, 2H), 2.17 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 447.2

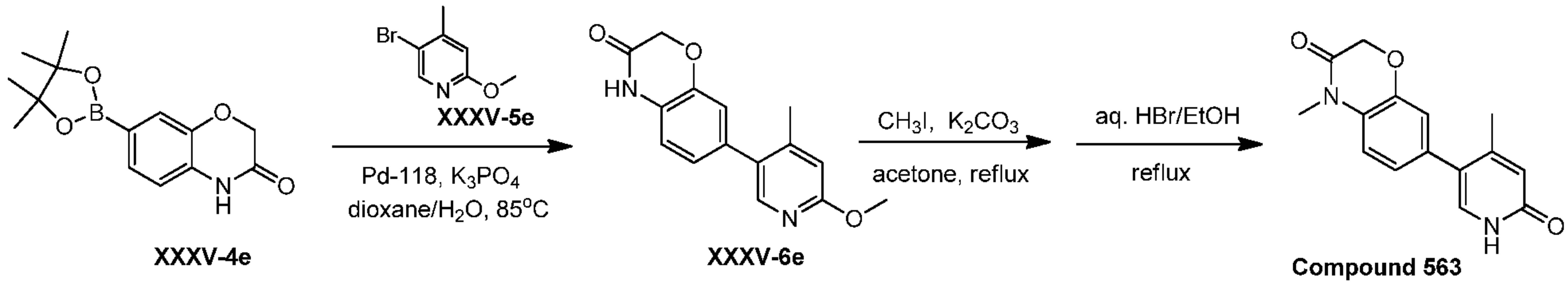


[0916] **XXXV-2d** was prepared following the similar procedure described in the synthesis of **XXXV-2c**. **XXXV-4d** was prepared by reacting **XXXV-2d** with ethyl iodide followed by Suzuki-coupling using the standard procedure described in the synthesis of **XXXV-4b**.

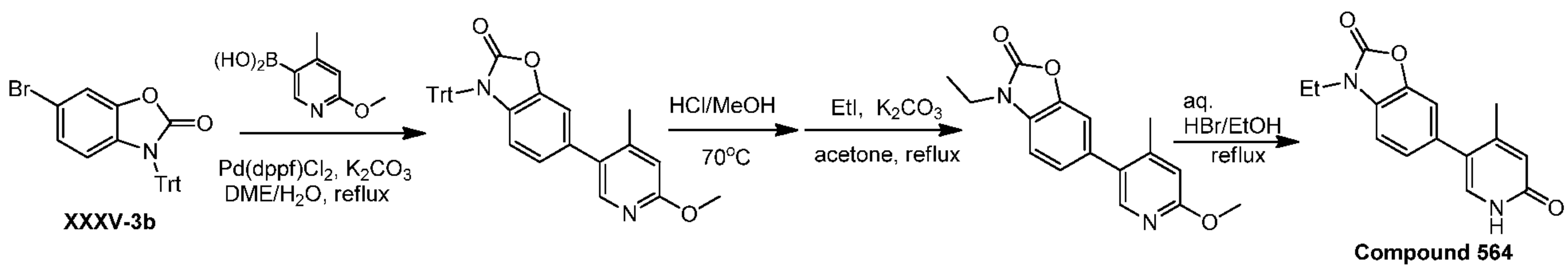
[0917] **XXXV-6d** was prepared by reacting **XXXV-4d** with **XXXV-5d** using Method **A** as described herein. Compound 562 was obtained from acid hydrolysis of XXXV-6d. 1H NMR (DMSO-d_6, 300 MHz) δ 11.65 (s, 1H), 7.35~7.39 (m, 2H), 7.29 (s, 1H), 7.12 (d, J=7.8 Hz, 1H), 6.35 (s, 1H), 3.95 (t, J=6.6Hz, 2H) , 2.14 (s, 3H) , 1.32 (t, J=6.6 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 270.9.

[0918] **Compound 662** was prepared following the similar procedure described in the synthesis of **Compound 562** using $ClCH_2COCl$ in place of CDI in the reaction with **XXXV-1**. The subsequent reaction with EtI was eliminated. After the second Suzuki-Coupling reaction, methyl iodide was used to methylate the proton on the benzo[b][1,4]oxazin-3(4H)-one moiety before performing the HBr hydrolysis. ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 7.21 (s, 1H), 7.08 (s, 1H), 7.02 (d, J= 8.0 Hz, 1H), 6.96 (d, J= 8.0 Hz, 1H), 6.27 (s, 1H), 4.67 (s, 2H), 3.29 (s, 3H), 2.07 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 270.9.

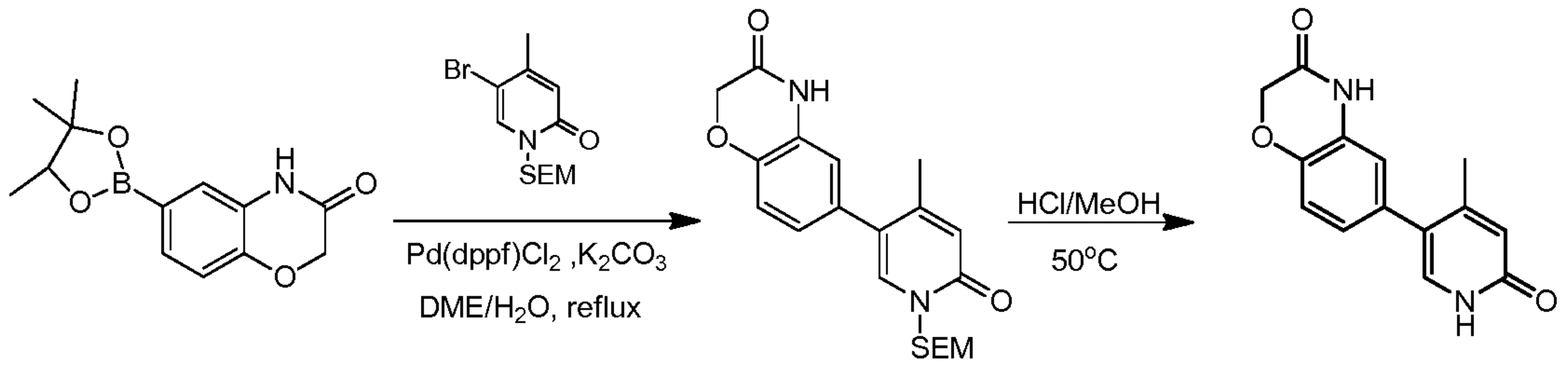
[0919] **Compound 663** was prepared following the similar procedure described in the synthesis of **Compound 562** using Trt-Cl in place of EtI in the reaction with **XXXV-2d** and 5-bromo-4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)pyridin-2(1H)-one was used in place of **XXXV-5d**. Finally, the trityl group was removed by HCl in MeOH solution. ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 11.73 (s, 1H), 7.31 (d, J=8.4 Hz, 1H), 7.25 (s, 1H) , 7.01 (s, 1H) , 7.00 (d, J=6.8 Hz, 1H) , 6.33 (s, 1H) , 2.05 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 243.1.



[0920] **XXXV-4e** was prepared by following the similar procedure for obtaining **XXXV-4** using 2-amino-5-bromophenol in place of **XXXV-1**. **XXXV-6e** was obtained by reacting **XXXV-4e** with **XXXV-5e** following the similar procedure described in the synthesis of **Compound 423**. **Compound 563** was obtained by methylation of **XXXV-6e** followed by HBr hydrolysis. ^{1}**H NMR** (DMSO-d_6, 400MHz) δ 11.54 (s, 1H), 7.17-7.15 (m, 2H), 6.99-6.95 (m, 2H), 6.24 (s, 1H), 4.65 (s, 2H), 3.27 (s, 3H), 2.04 (s, 3H).



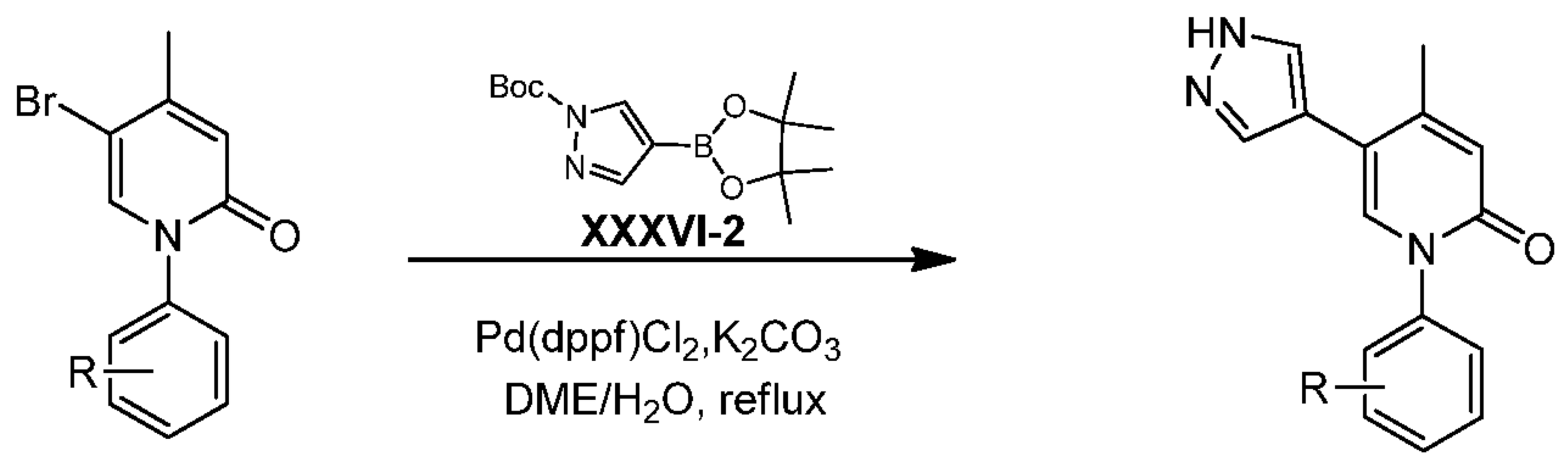
[0921] **Compound 564** was prepared from **XXXV-3b** following the synthetic scheme described above. **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.26-7.23 (m, 1H), 7.10 (s, 1H), 7.06-7.00 (m, 2H), 6.49 (s, 1H), 3.92 (q, J=7.2Hz, 2H), 2.13 (s, 3H), 1.42 (t, J=7.2Hz, 3H). **MS (ESI)** ***m/z*** [M+H]+ 270.9



XXXV-4 Compound 567

[0922] **Compound 567** was prepared by Suzuki-Coupling of **XXXV-4** with SEM-protected 5-bromo-4-methylpyridin-2(1H)-one, followed by HCl hydrolysis. **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 11.54 (s, 1H), 10.74 (s, 1H), 7.14 (s, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 6.0 Hz, 1H), 6.78 (s, 1H), 6.27 (s, 1H), 4.64 (s,2H), 2.04 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 257.0.

Example 13-A
Synthesis of 4-Methyl, 5-Pyrazole analogs (Scheme XXXVI)



XXXVI-1 XXXVI-3

[0923] To a solution of **XXXVI-1** (1 eq.) in DME/H_2O (v/v=10/1) was added K_2CO_3 (2 eq.), **XXXVI-2** (1.5 eq.), $Pd(dppf)Cl_2$ (0.1 eq.). The mixture was purged with nitrogen and then heated at reflux overnight. The mixture was cooled to rt, diluted with water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography to give the final product.

[0924] **Compound 217**: **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.85-7.65 (m, 3H), 7.59-7.55 (m, 2H), 7.48-7.45 (m, 1H), 7.17-7.14 (m, 1H), 6.57 (s, 1H), 2.31 (s, 3H), 2.13 (s, 3H).

[0925] **Compound 218**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.60 (s, 2H), 7.47 (d, J = 8.0Hz, 2H), 7.34 (d, J = 8.0Hz, 2H), 7.24 (s, 1H), 6.59 (s, 1H), 2.22 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 336.0.

[0926] **Compound 219**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.58 (s, 2H), 7.16-7.10 (m, 2H), 6.84-6.79 (m, 2H), 6.60 (s, 1H), 4.04 (q, J = 6.8Hz, 2H), 2.23 (s, 3H), 2.16 (s, 3H), 1.42 (t, J = 6.8Hz, 3H).

[0927] **Compound 220**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.59 (s, 2H), 7.26 (s, 2H), 6.60 (s, 3H), 3.86 (s, 9H), 2.23 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 342.1.

[0928] The 4-methyl, 5-(1-Me) pyrazole analogs were prepared following the same prodecure for obtaining **XXXVI-3** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of **XXXVI-2**.

[0929] **Compound 221**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.50 (s, 1H), 7.26 (s, 1H), 6.59-6.55 (m, 4H), 3.86 (s, 12H), 2.30 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 356.0.

[0930] **Compound 226**: **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.81-7.71 (m, 5H), 7.59-7.57 (m, 2H), 6.57 (s, 1H), 3.91 (s, 3H), 2.31 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 334.1.

[0931] **Compound 227**: **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.51-7.47 (m, 2H), 7.38-7.37 (m, 2H), 7.30-7.25 (m, 2H), 7.21 (s, 1H), 6.56 (s, 1H), 3.94 (s, 3H), 2.22 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 350.1.

[0932] **Compound 228**: **^{1}H NMR** (CD_3OD, 400 MHz) δ 7.86-7.84 (m, 2H), 7.71 (s, 1H), 7.67-7.65 (m, 2H), 7.61-7.58 (m, 2H), 6.58 (s, 1H), 3.92 (s, 3H), 2.31 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 334.1.

[0933] Compounds **225**, **229** and **230** were prepared following Method **1** as described in Example 12-B.

[0934] **Compound 225**: **^{1}H NMR** (CD_3OD, 400 MHz) δ 9.08 (s, 1H), 8.13 (d, J = 2.0 Hz, 1 H), 8.08-8.04 (m, 1H), 7.58-7.55 (m, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 7.33 (s, 1H), 6.61 (s, 1H), 3.94 (s, 3H), 2.25 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 322.9.

[0935] **Compound 229**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.45 (s, 1H), 7.36-7.32 (m, 2H), 7.28-7.25 (m, 1H), 7.14 (d, J = 8.0Hz, 1H), 7.05 (s, 1H), 6.57 (s, 1H), 3.93 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H). **MS (ESI)** ***m/z*** $(M+Na)^+$ 314.1.

[0936] **Compound 230**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.47 (s, 1H), 7.46-7.37 (m, 3H), 7.28-7.23 (m, 1H), 7.15 (s, 1H), 6.58 (s, 1H), 3.93 (s, 3H), 2.22 (s, 3H). **MS (ESI)** ***m/z*** $(M+Na)^+$ 283.9.

[0937] **Compound 222** was prepared following a modified Method **1** procedure, using DMSO in place of DCM and the molecular sieve was not used. **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.45 (s, 1H), 7.34 (s, 1H), 7.19 (s, 1H), 6.94-6.91 (m, 2H), 6.85-6.81 (m, 1H), 6.50 (s, 1H), 4.26 (s, 4H), 3.92 (s, 3H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 324.

[0938] Compounds **223** and **224** were prepared following the similar procedure as described in the synthesis of Compound **222**. **Compound 223**: **^{1}H NMR** ($CDCl_3$, 300MHz) δ 7.40 (s, 1H), 7.29 (s, 1H), 7.14 (s, 1H), 6.83-6.79 (m, 2H), 6.74-6.71 (m, 1H), 6.48 (s, 1H), 5.96 (s, 2H), 3.87 (s, 3H), 2.15 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 310.0. **Compound 224: ^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.17 (s, 1H) 7.81 (s, 1H), 7.70-7.67 (d, J = 8.8Hz, 1H), 7.48-7.45 (m, 2H), 7.38 (s, 1H), 7.28 (s, 1H), 6.59 (s, 1H), 3.94 (s, 3H), 2.24 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 307.1.

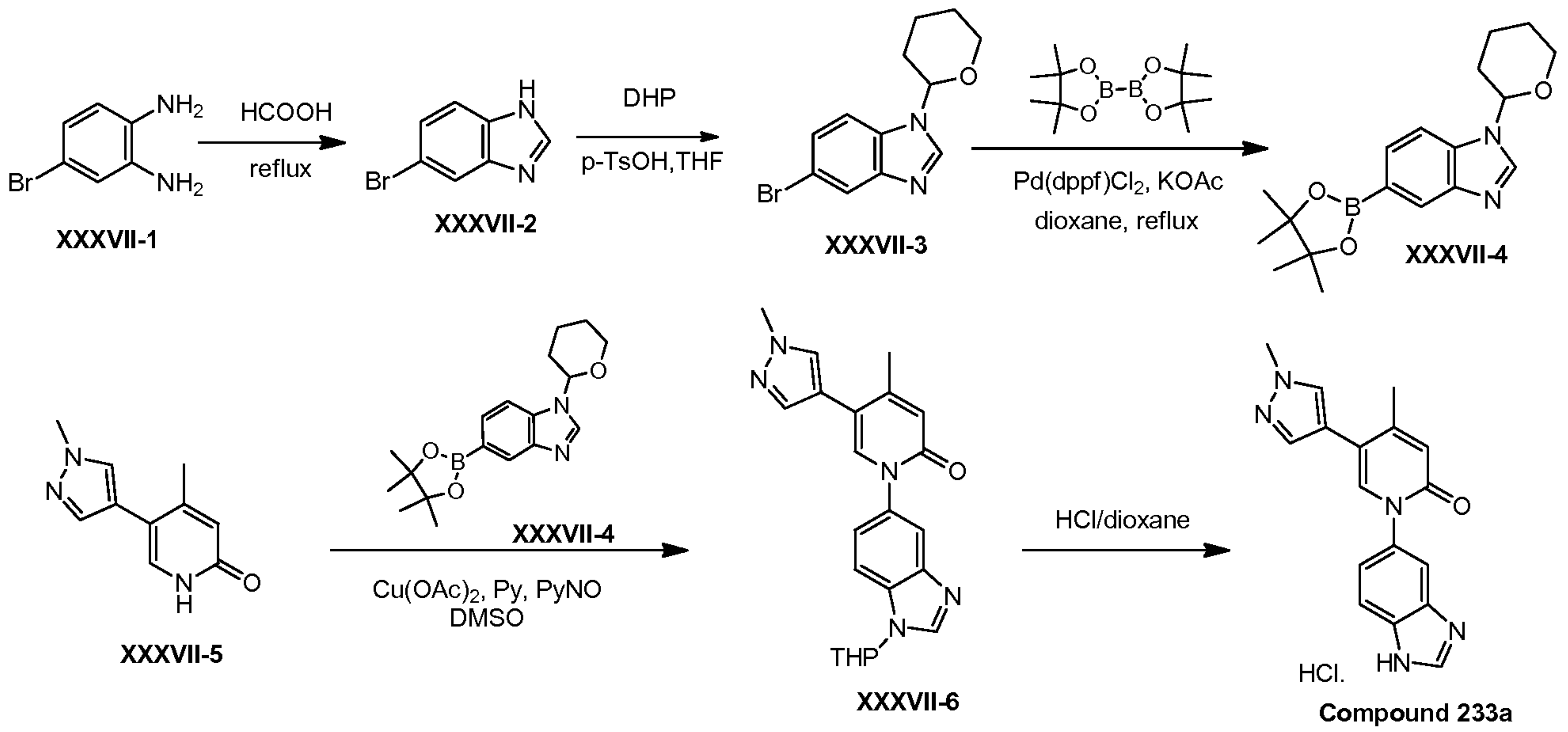
[0939] Compounds **231** and **232** were prepared following Method **3** as described in Example 12-B.

[0940] **Compound 231**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.06 (s, 1H), 7.57 (s, 1H), 7.43 (s, 1H), 6.87-6.72 (m, 4H), 4.28-4.22 (m, 4H), 3.96 (s, 1H), 2.37 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 323.9.

[0941] **Compound 232**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.47 (s, 1H), 7.36 (s, 1H), 7.21 (s, 1H), 6.93-6.85 (m, 3H), 6.57 (s, 1H), 6.04 (s, 2H), 3.94 (s, 3H), 2.21 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 309.8.

[0942] **Compound 431** was prepared following the similar procedure for obtaining **XXXVI-3** using Pd-118 and K_3PO_4 instead of $Pd(dppf)Cl_2$ and K_2CO_3. The Boc protecting group was subsequently removed in HCl/MeOH solution at rt. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.59 (s, 2H), 7.47-7.45 (m, 2H), 7.38-7.35 (m, 2H), 7.23 (s, 1H), 6.59 (s, 1H), 2.22 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 285.9.

Example 13-B
Synthesis of Compound 233 (Scheme XXXVII)



[0943] A solution of **XXXVII-1** (10 g, 53.4 mmol) in HCOOH (50 mL) was heated at reflux for 2 hours, after cooled to rt, aq.NaOH (10%) was added slowly until the mixture was basic.

Then extracted with EtOAc (100 mL×3), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give **XXXVII-2** (9 g, 85% yield).

[0944] To a solution of **XXXVII-2** (5 g, 25.4 mmol) in THF (35 mL) was added *p*-TsOH (1.3 g, 7.6 mmol), DHP (35ml). The reaction mixture was stirred at 60°C overnight. The reaction mixture was poured into ice-water, and the aqueous was extracted with EA (50 mL×3), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give crude **XXXVII-3** (4.8 g, 67% yield).

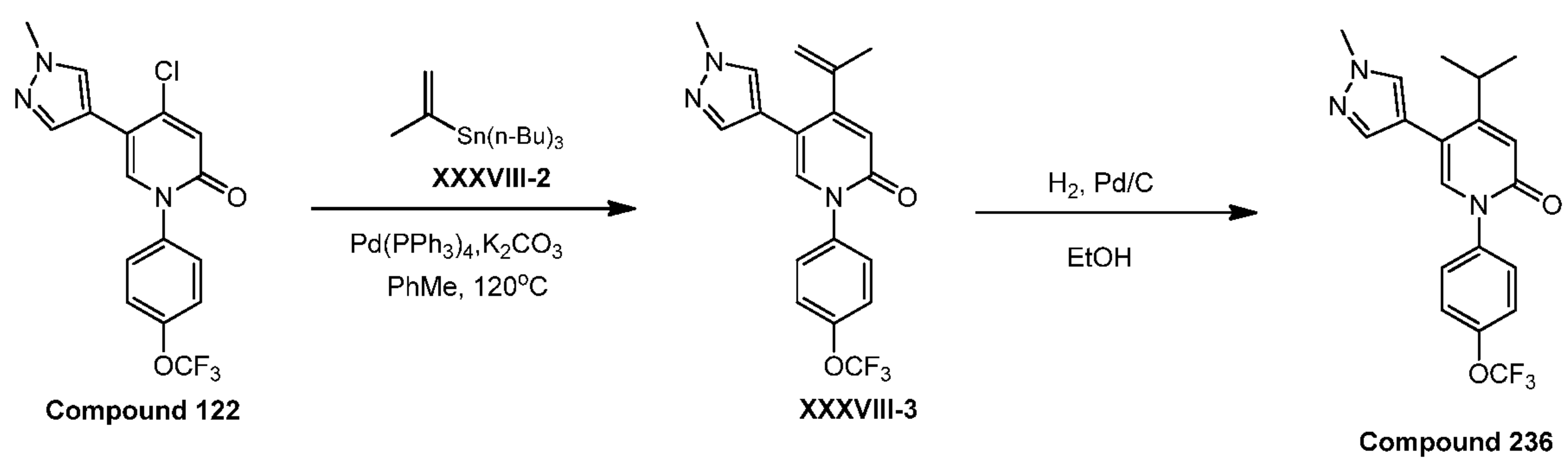
[0945] To a solution of **XXXVII-3** (1 g, 3.5 mmol) in dioxane (20 mL) was added KOAc (0.69 g, 7 mmol), bis(pinacolato)diboron (0.95 g 3.67 mmol), Pd(dppf)Cl_2 (0.25 g, 0.035 mmol) under N_2 protection. The reaction mixture was degassed with nitrogen, and then heated to reflux overnight. The reaction mixture was poured into ice-water, and the aqueous was extracted with EA (60 mL×3), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give crude **XXXVII-4** (0.8 g, 70% yield).

[0946] **XXXVII-6** was prepared following the procedure described in the synthesis of Compound **222**. **MS (ESI)** ***m/z*** $[M+H]^+$ 390.1.

[0947] **XXXVII-6** (200 mg, 0.5 mmol) was dissolved in a solution of HCl/dioxane (4 M, 50 mL), the mixture was stirred overnight at rt, the mixture was concentrated to yield the hydrochloride salt **Compound 233a** (120 mg, 79% yield). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.66 (s, 1H), 7.99-7.94 (m, 2H), 7.90 (s, 1H), 7.64-7.60 (m, 3H), 6.48 (s, 1H), 3.84 (s, 3H), 2.55 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 305.9.

[0948] **Compound 235** was prepared from Compound **122** following the similar procedure for obtaining Compound **199**. **^{1}HNMR** (CD_3OD, 400 MHz) δ 7.76 (s, 1H), 7.59-7.54 (m, 4H), 7.48 (d, *J* = 8.4 Hz, 2H), 6.58 (s, 1H), 3.94 (s, 3H), 2.65 (q, *J* = 7.6 Hz, 2 H), 1.19 (t, *J* = 7.6 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 364.0.

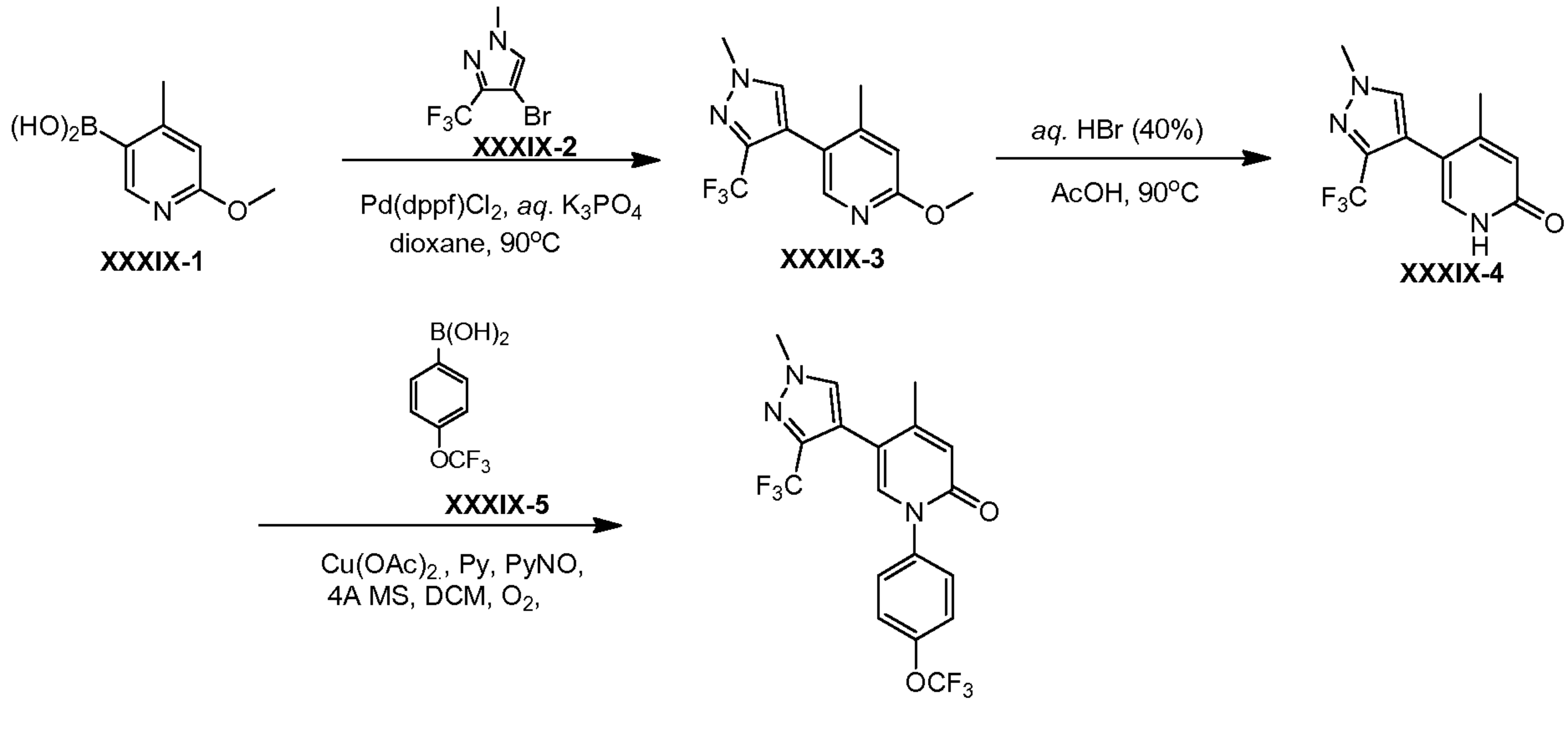
Example 13-C
Synthesis of Compound 236 (Scheme XXXVIII)



[0949] To a stirred mixture of **Compound 122** (200 mg, 0.54 mmol), **XXXVIII-2** (270 mg, 0.81 mmol), and K_3CO_3 (150 mg, 1.08 mmol) in toluene (6 mL) was added $Pd(PPh_3)_4$ (60 mg, 0.054 mmol). The mixture was purged with nitrogen for three times and then heated at 120°C overnight. The mixture was concentrated to remove solvent, diluted with H_2O (10 mL), extracted with EtOAc (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by prep-HPLC to give **XXXVIII-3** (130 mg, 64% yield).

[0950] A mixture of **XXXVIII-3** (130 mg, 0.259 mmol) and Pd/C in ethanol (5 mL) was stirred under H_2 at rt for 1 hour. Filtered the mixture, and concentrated to give **Compound 236** (86.2 mg, 66% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.48-7.45 (m, 3H), 7.36-7.31 (m, 3H), 7.17 (s, 1H), 6.63 (s, 1H), 3.95 (s, 3H), 2.97-2.90 (m, 1H), 1.17 (d, J = 6.8 Hz, 6H). **MS (ESI) *m/z*** $(M+H)^+$ 378.1.

Example 13-D
Synthesis of Compound 238 (Scheme XXXIX)



[0951] To a stirred mixture of **XXXIX-1** (400 mg, 2.4 mmol), **XXXIX-2** (500 mg, 2.18 mmol), and K_3PO_4 (2 M, 1.1 mL, 2.2 mmol) in dioxane (20 mL) was added $Pd(dppf)Cl_2$ (160 mg, 0.218 mmol) under N_2 protection. The reaction mixture was degassed with nitrogen again and stirred at 90°C overnight. The mixture was concentrated, diluted with H_2O (20 mL), extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EA=2/1) to give **XXXIX-3** (400 mg, 67% yield).

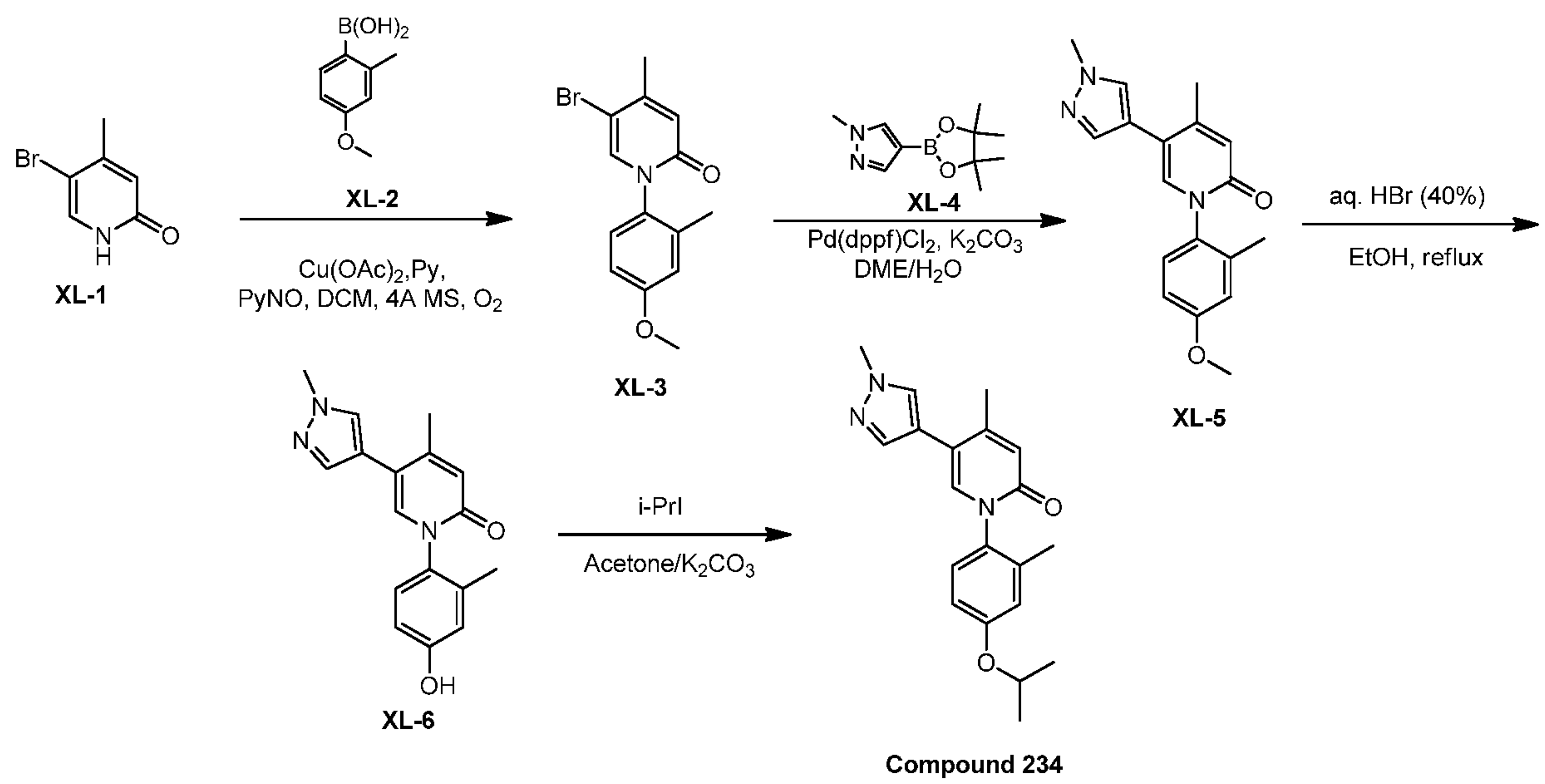
[0952] A mixture of **XXXIX-3** (400 mg, 1.48 mmol) in *aq*. HBr (40%, 10 mL) and HOAc (5 mL) was stirred at 90°C for 12 hrs. After being cooled to rt, the mixture was poured into water (20 mL), neutralized with Na_2CO_3, and then extracted with DCM/i-PrOH (30 mLx3, v/v=9/1). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford crude **XXXIX-4** (220 mg, 58% yield) as light yellow oil. **MS (ESI)** ***m/z*** $(M+H)^+$ 257.9.

[0953] **Compound 238** was prepared following the general procedure described in Method 1 as pale yellow solid (80 mg, 24% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.46-7.40 (m, 3H), 7.34-7.30 (m, 2H), 7.19 (s, 1H), 6.56 (s, 1H), 3.99 (s, 3H), 2.05 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 418.0.

[0954] **Compound 237** was prepared following the similar procedure for obtaining Compound **238** using (1,3,5-trimethyl-1H-pyrazol-4-yl)boronic acid in place of **XXXIX-1** and 5-bromo-2-methoxy-4-methylpyridine in place of **XXXIX-2**. **^{1}H NMR** ($CDCl_3$, 400MHz) *δ* 7.45-7.41 (m, 2H), 7.31-7.26 (m, 2H), 7.04 (s, 1H), 6.54 (s, 1H), 3.73 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.96 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 378.2.

[0955] **Compound 239** was prepared following the similar procedure for obtaining Compound **238** using (4-ethoxy-2-methylphenyl)boronic acid in place of **XXXIX-5** as a pale yellow solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.40 (s, 1H), 7.10-7.05 (m, 2H), 6.85-6.75 (m, 2H), 6.55 (s, 1H), 4.02 (q, *J* = 6.8 Hz, 2 H), 3.97 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H), 1.40 (t, *J* = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 392.1.

Example 13-E
Synthesis of Compound 234 (Scheme XL)

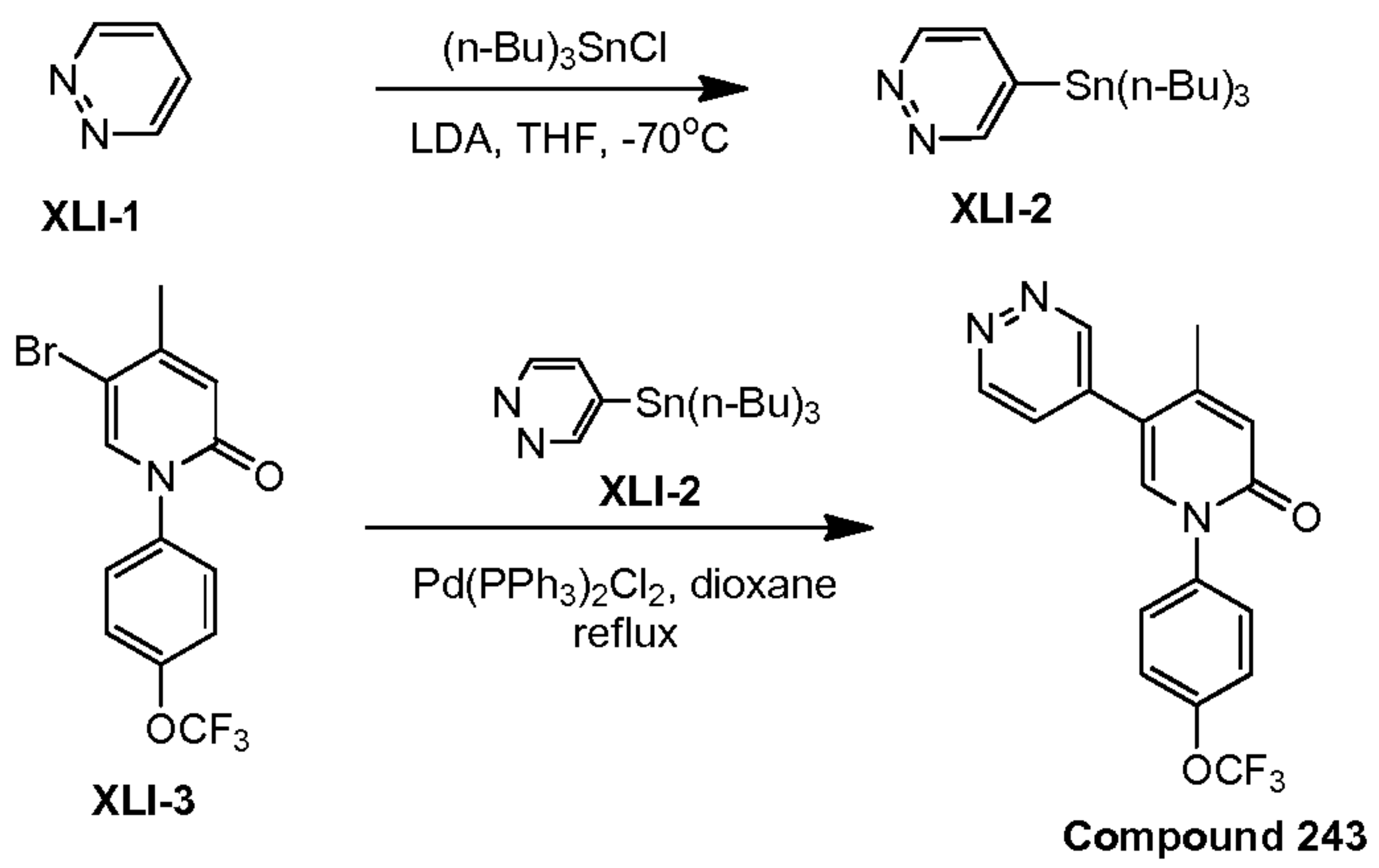


[0956] **XL-6** was prepared following the synthesis scheme described herewith.

[0957] To a solution of **XL-6** (100 mg, 0.34 mmol) in acetone (10 mL) was added compound 2-iodopropane (83.7 mg, 0.51 mmol), and K_2CO_3 (84 mg, 0.68 mmol). The reaction mixture was heated to reflux overnight. After cooling to rt, the mixture was poured into ice-water, extracted with EA (50mL×3). The combined organic layer was washed with brine and concentrated to give crude product. The residue was purified by prep-HPLC to give **Compound 234** (50 mg, 44% yield) as a white solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.46 (s, 1H), 7.35 (s, 1H), 6.98 (s, 1H), 7.10-7.07 (m, 2H), 6.8 (s, 1H), 6.78-6.76 (m, 1H), 6.56 (s, 1H), 4.57-4.51 (m, 1H), 3.92 (s, 3H), 2.23 (s, 3H), 2.13 (s, 3H), 1.34 (d, J = 6 Hz, 6H). **MS (ESI)** ***m/z*** $[M+H]^+$ 337.9.

[0958] **Compound 240** was prepared following the similar procedure for obtaining Compound 234 using 5-bromo-4-(trifluoromethyl)pyridin-2(1H)-one in place of **XL-1** and (4-(trifluoromethoxy)phenyl)boronic acid in place of **XL-2**. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.48-7.46 (m, 3H), 7.42 (s, 1H), 7.38-7.25 (m, 3H), 7.07 (s, 1H), 3.94 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 403.9.

Example 14-A
Synthesis of Compound 243 (Scheme XLI)



[0959] A solution of LDA (1 M in THF, 10 mL, 10 mmol) was added dropwise to a solution of **XLI-1** (0.8 g, 10 mmol) and $(n\text{-}Bu)_3SnCl$ (3.7 g, 11 mmol) in THF (10 mL) at -70°C under N_2. The reaction mixture was stirred at -70°C for 1 hour. The reaction was quenched with saturated *aq*. NH_4Cl (50 mL) and extracted with EA (50 mL×3), the organic layer dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA=1/1) to give **XLI-2** (1 g, 27% yield).

[0960] To a mixture of **XLI-3** (0.2 g, 0.58 mmol) and **XLI-2** (0.43 g, 1.2 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_2Cl_2$ (0.04 g, 0.058 mmol) under N_2 at rt. The mixture was stirred at reflux overnight. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with EA) to afford **Compound 243** (0.16 g, 80% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.25-9.20 (m, 2H), 7.47-7.33 (m, 3H), 7.38-7.34 (m, 2H), 7.31 (s, 1 H), 6.65 (s, 1 H), 2.23 (s, 3 H). **MS (ESI)** ***m/z*** $(M+H)^+$ 348.0.

[0961] **Compound 241**: To a stirred mixture of **XLI-3** (300 mg, 0.86 mmol), pyridin-3-ylboronic acid (160 mg, 1.04 mmol), and K_3PO_4 (0.86 ml, 1.72 mmol) in DMF (10 mL) was added $Pd(PPh_3)_4$ (100 mg, 0.086 mmol) under N_2 protection. The reaction mixture was stirred at 110°C overnight. The mixture was concentrated, diluted with H_2O, extracted with EtOAc (30 mL×3), the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the residue was purified by prep-HPLC to give **Compound 241** (122 mg, 41% yield) as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.63 (s, 1H), 8.57-8.56 (m, 1H), 7.90-7.85 (m, 1H), 7.70-7.64 (m, 3H), 7.53-7.51 (m, 2H), 7.48-7.45 (m, 1H) , 6.52 (s, 1H), 2.14 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 347.1.

[0962] **Compound 242** was prepared follow the similar procedure for obtaining **Compound 241** using pyridin-4-ylboronic acid in place of pyridin-3-ylboronic acid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.60 (d, J =4.8 Hz, 2H), 7.71 (s, 1H), 7.66-7.64 (m, 2H), 7.53-7.47 (m, 4H), 6.52 (s, 1H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 347.1.

[0963] **Compound 247** was prepared according to **Method 4**: To a solution of **XLI-3** (900 mg, 2.59 mmol) in dioxane/H_2O (12 mL, v/v=5/1) was added K_2CO_3 (720 mg, 5.18 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (600 mg, 2.85 mmol), $Pd(dppf)Cl_2$ (180 mg, 0.26 mmol). The mixture was purged with nitrogen and then heated at 100°C by microwave for 40 min. The mixture was cooled to rt, diluted with water, extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (PE: EA= 10:1→1:1) to give **Compound 247** as a yellow solid (175 mg, 20 % yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (s, 1H), 7.48-7.45 (m, 2H), 7.36-7.32 (m, 2H), 7.26 (m, 1H), 6.60 (s, 1H), 6.23(s, 1H), 3.76 (s, 3H), 2.03 (s, 3H).

[0964] **Compound 254** was prepared following the similar procedure for obtaining **XL-5** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole in place of **XL-4** and using 5-**XLI-3** in place of **XL-3** as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.71 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.52-7.48 (m, 2H), 7.35-7.29 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 2.15 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 387.0.

[0965] **Compound 255** was prepared following the similar procedure for obtaining Compound **254** using (1-methyl-1H-indol-5-yl)boronic acid and Na_2CO_3 instead of K_2CO_3 as a yellow solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.65-7.63 (m, 2H), 7.54-7.45 (m, 5H), 7.35 (d, J =

2.8Hz, 1H), 7.16 (dd, *J* = 1.6, 8.4 Hz, 2H), 6.47 (s, 1H), 6.20 (d, *J* = 2.8 Hz, 1H), 3.81 (s, 3H), 2.13 (s, 3H).

[0966] **Compound 259** was prepared following the similar procedure for obtaining Compound **255** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[c][1,2,5]oxadiazole. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.90 (dd, *J* = 1.2, 9.6Hz, 1H), 7.75 (s, 1H), 7.50-7.48 (m, 2H), 7.39-7.34 (m, 4H), 6.64 (s, 1H), 2.22 (s, 3H).

[0967] **Compound 251** was prepared following the similar procedure for obtaining Compound **255** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.06 (s, 1H), 8.06 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.52-7.49 (m, 2H), 7.39-7.32 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.63 (s, 1H), 2.19 (s, 3H).

[0968] **Compound 244** was prepared following the similar procedure for obtaining **XL-3** by reacting 5-(1H-imidazol-1-yl)-4-methylpyridin-2(1H)-one with (4-(trifluoromethoxy)phenyl) boronic acid. **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.60 (s, 1H), 7.57-7.50 (m, 4H), 7.37-7.33 (m, 2H), 7.25 (m, 1H), 6.58 (s, 1H), 2.01 (s, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 336.1.

[0969] **Compound 245** was prepared following the similar procedure for obtaining **XL-5** by reacting **XLI-3** with 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.99 (s, 1H), 7.62 (s, 1H), 7.51 (d, *J* = 9.2Hz, 2H), 7.45 (d, *J* = 8.8Hz, 1H), 7.34-7.23 (m, 4H), 6.61 (s, 1H), 4.11 (s, 3H), 2.15 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 400.1.

[0970] **Compound 246** was prepared following the similar procedure for obtaining **XL-5** by reacting **XLI-3** with 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.97 (s, 1H), 7.80 (d, *J* = 8.8Hz, 1H), 7.56 (s, 1H), 7.51 (d, *J* = 9.2Hz, 2H), 7.36 (m, 3H), 7.25 (m, 1H), 6.81 (s, 1H), 4.29 (s, 3H). 2.22 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 400.1.

[0971] **Compound 249** was prepared prepared following the similar procedure for obtaining **XL-5** by reacting **XLI-3** with 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole. **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 8.02 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.52~7.50 (m, 2H), 7.35~7.33 (m, 2H), 7.29~7.28 (m, 2H) ,7.07 (d, *J* = 8.0 Hz, 1H), 6.62 (s, 1H), 4.09 (s, 3H), 2.18 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 400.0.

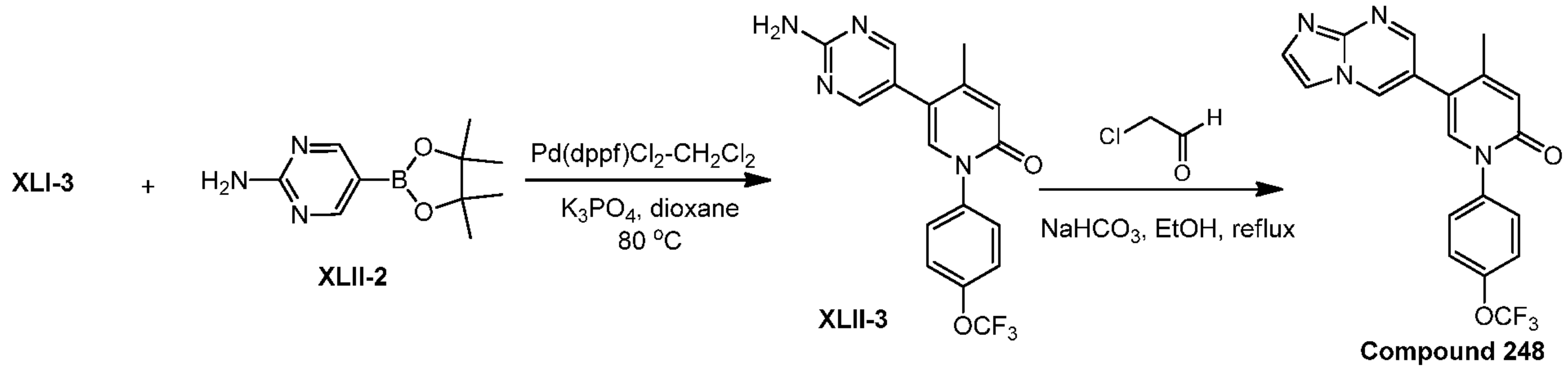
[0972] **Compound 250** prepared following the similar procedure for obtaining **XL-5** by reacting **XLI-3** with 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole. **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.94 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.53~7.50 (m, 2H), 7.34~7.32 (m, 2H), 7.27 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H) , 4.25 (s, 3H), 2.19 (s, 3H) . **MS (ESI)** ***m/z*** $(M+H)^+$ 400.0.

[0973] **Compound 258** was prepared following the similar procedure for obtaining **XL-5** using 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole in place of **XL-4** and using **XLI-3** in place of **XL-3** as a yellow solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.66-7.62 (m, 1H), 7.56-7.48 (m, 4H), 7.44 (s, 1H), 7.33 (s, 1H), 7.02 (d, J = 8.0Hz, 1H), 6.48 (s, 1H), 6.42 (m, 1H), 3.78 (s, 3H), 2.15 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 398.9.

[0974] **Compound 260** was prepared following the similar procedure for obtaining **XL-5** using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole in place of **XL-4** and using **XLI-3** in place of **XL-3**. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 9.05 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.52-7.43 (m, 3H), 7.37-7.32 (m, 2H), 7.28-7.26 (m, 1H), 6.63 (s, 1H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 403.0.

[0975] **Compound 432** was prepared following the similar procedure for obtaining compound **243** using Pd-118 and K_3PO_4 instead of Pd(dppf)Cl_2 and K_2CO_3. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 9.25 (d, J = 5.2 Hz, 1H), 9.20 (s, 1H), 7.50-7.47 (m, 2H), 7.44-7.42 (m, 1H), 7.38-7.35 (m, 2H), 7.30 (s, 1H), 6.64 (s, 1H), 2.22 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 297.9.

Example 14-B
Synthesis of Compound 248 (Scheme XLII)



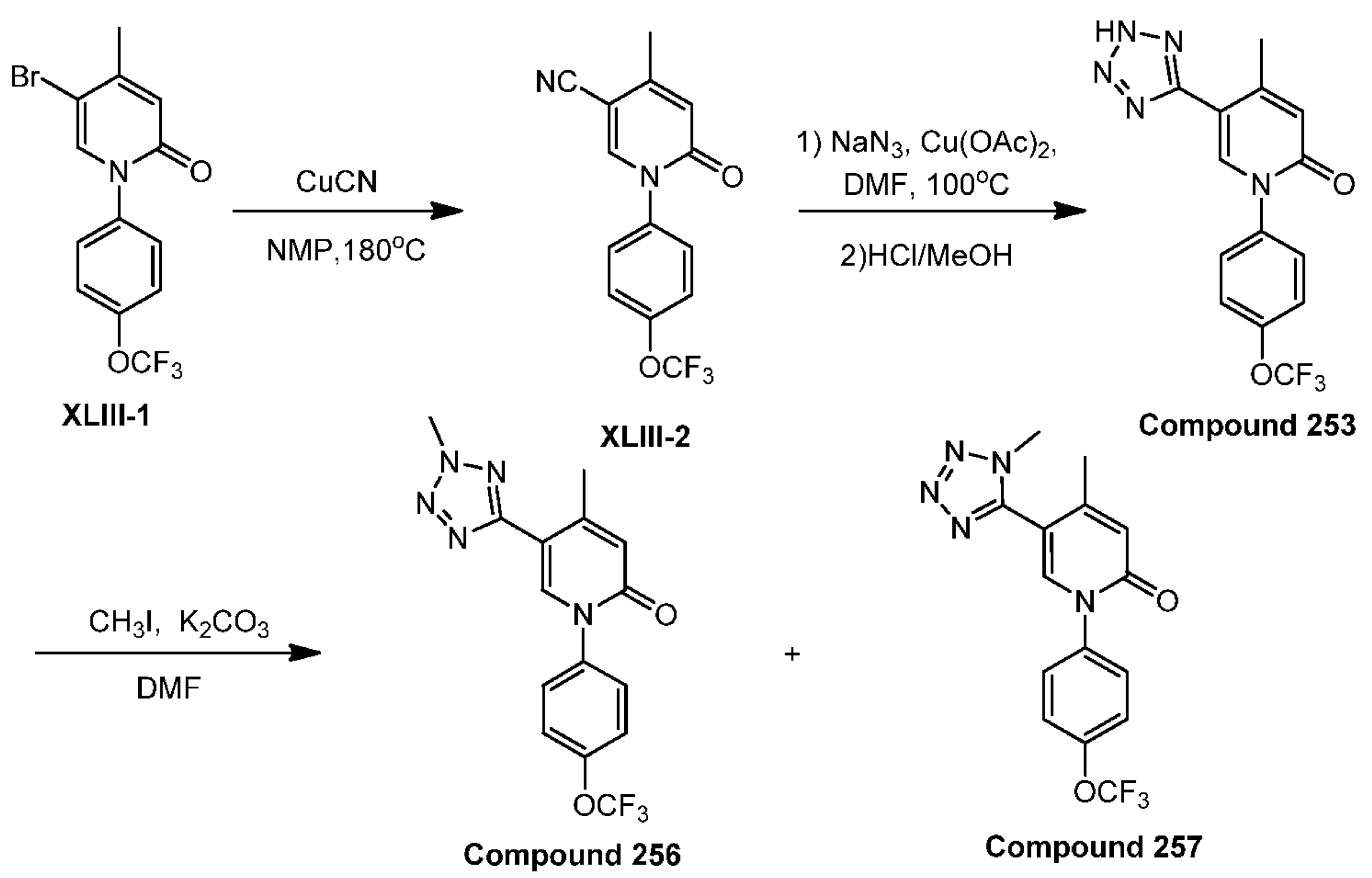
[0976] A flask was charged with **XLI-3** (0.8 g, 2.30 mmol, 1 eq), **XLII-2** (1.02 g, 4.60 mmol, 2 eq), Pd(dppf)Cl_2-CH_2Cl_2 (0.094 g, 0.11 mmol, 0.05 eq), K_3PO_4 (1.22 g, 4.60 mmol, 2 eq) and 50 mL of dioxane, flushed with nitrogen for three times. The mixture was heated at 80°C for 8 hrs. LCMS analysis showed the reaction completed. The reaction mixture was cooled down to rt, diluted with water, extracted with ethyl acetate (80 mL×3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give brown oil. Recrystallization from EA gave offwhite solid **XLII-3** (0.4 g, 48% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 362.9.

[0977] A flask was charged with **XLII-3** (300 mg, 0.83 mmol, 1 eq), $NaHCO_3$ (139 mg, 1.66 mmol, 2 eq), *aq.* 2-chloroacetaldehyde (40%, 1.6 g, 8.3 mmol, 10 eq) and 20 mL of EtOH. The mixture was heated to reflux for 18 hrs. LCMS analysis showed the reaction completed. The reaction mixture was cooled down to rt, diluted with water, extracted with ethyl acetate (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a brown oil. Purification by prep-TLC (PE/EA=2/1) gave **Compound 248** as a brown solid (145.5 mg, 45% yield). **MS (ESI)** ***m/z*** $(M+H)^+$ 386.9. ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 9.05 (d, J = 2.4 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H), 7.90 (s, 1H), 7.84 (s, 1H), 7.76 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 6.55 (s, 1H), 2.22 (s, 3H).

[0978] **Compound 252** was prepared following the similar procedure for obtaining Compound **248** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine in place of **XLII-2**. **MS (ESI)** ***m/z*** $(M+H)^+$ 386.9. ^{1}**H NMR** (DMSO-d_6, 300 MHz): δ 8.62 (s, 1H), 7.92 (s, 1H), 7.72 (s, 1H), 7.66-7.53 (m, 6H), 7.33 (d, J = 6.8 Hz, 1H), 6.52 (s, 1H), 2.19 (s, 3H).

Example 14-C

Synthesis of Compound 253, 256 and 257 (Scheme XLIII)



[0979] To the solution of **XLIII-1** (600 mg, 1.7 mmol) in 5 mL of NMP was added CuCN (462 mg, 5.1 mmol). The mixture was heated to 180 °C for 3 hrs. The mixture was diluted with H_2O, extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the residue was purified by column chromatography on silica gel (PE/EA=5/1) to give **XLIII-2** (400 mg, 80 % yield) as a white solid.

[0980] To the solution of **XLIII-2** (300 mg, 1 mmol) in 3 mL of DMF was added NaN_3 (130 mg, 2 mmol).and $Cu(OAc)_2$ (360 mg, 2 mmol). The mixture was heated to 100°C under microwave for 20 minutes. And then the mixture was filtered at 70°C, the filtrate was cooled to rt, the mixture was filtered again. The residual solid was dissolved in HCl/MeOH (4 M), stirred at rt for 1 h. The mixture was concentrated to give **Compound 253** (50 mg, 14.5 % yield) as black solid. ^{1}**H**

NMR (DMSO-d_6, 400 MHz) δ 8.17 (s, 1H), 7.60 (m, 2H), 7.51 (m, 2H), 6.51 (s, 1H), 2.36 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 338.0.

[0981] To the solution of **Compound 253** (200 mg, 0.59 mmol) in 2 mL of DMF was added CH_3I (100 mg, 0.7 mmol).and K_2CO_3 (170 mg, 1.2 mmol). The mixture was stirred at rt for 3hrs. The mixture was diluted with H_2O, extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, the residue was purified by prep-TLC (PE/EA=1/1) to give **Compound 256** (130 mg, 62% yield) and **Compound 257** (40 mg, 19% yield). ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.60 (s, 1H), 4.38 (s, 3H), 2.55 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 351.9. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.44 (m, 3H), 7.35 (d, J = 8.8 Hz, 2H), 6.65 (s, 1H), 4.05 (s, 3H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 351.9.

[0982] Compounds **261-264** were also prepared following the general procedure as described herein.

[0983] **Compound 261**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 9.04 (s, 1H), 8.03-8.00 (m, 1H), 7.53-7.47 (m, 3H), 7.42-7.28 (m, 4H), 6.65 (s, 1H), 2.07 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 402.8.

[0984] **Compound 262**: **MS (ESI)** ***m/z*** $[M+H]^+$ 352.8. ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.87 (m, 1H), 7.70 (s, 1H), 7.51-7.47 (m, 2H), 7.35-7.27 (m, 3H), 6.60 (s, 1H), 2.36 (s, 3H).

[0985] **Compound 263**: ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 9.42 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.64-7.59 (m, 3H), 7.51-7.45 (m, 3H), 6.55 (s, 1H), 1.98 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 402.9.

[0986] **Compound 264**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.54 (s, 1H), 8.48 (s, 1H), 7.49-7.45 (m, 2H), 7.37-7.32 (m, 2H), 7.29 (s, 1H), 6.61 (s, 1H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 353.1.

Example 15
5-Bromo Pyridone Analogs

[0987] Compounds **265-273** were prepared following Method **1** in Example **12-B** using 5-bromopyridin-2(1H)-one reacting with the relevant boronic acids.

[0988] **Compound 265**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.97 (s, 1H), 7.63 (d, J = 9.6 Hz, 1 H), 7.52-7.48 (m, 2H), 7.37-7.32 (m, 2H), 6.48 (d, J = 9.6 Hz, 1 H). **MS (ESI)** ***m/z*** $(M+H)^+$ 268.1.

[0989] **Compound 266**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 8.34 (s, 1H), 8.02 (d, J = 9.6 Hz, 1 H), 7.85-7.81 (m, 1H)，7.46-7.38 (m, 3H), 6.88 (d, J = 9.6 Hz, 1 H), 4.21 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 280.0.

[0990] **Compound 267**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.92 (d, *J*=2.8 Hz, 1H), 7.60 (dd, *J* = 9.6, 2.8 Hz, 1 H), 7.32-7.29 (m, 2H), 7.02-6.99 (m, 2H), 6.45 (d, *J* = 9.6 Hz, 1H), 4.70-4.63 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 310.0.

[0991] **Compound 268**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 8.07 (d, *J* = 2.8 Hz, 1H), 7.91 (s, 1H), 7.85-7.82 (m, 1H), 7.80-7.73 (m, 2H), 7.65 (dd, *J* = 9.6, 2.8 Hz, 1 H), 6.51 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 319.9.

[0992] **Compound 269**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.98 (d, *J* = 2.8 Hz, 1H), 7.63 (dd, *J* = 9.6, 2.8 Hz, 1 H), 7.60-7.56 (m, 2H), 7.50-7.47 (m, 2H), 6.48 (d, *J* =9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 285.8.

[0993] **Compound 270**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 8.03 (d, *J* = 2.8 Hz, 1H), 7.66-7.59 (m, 3H), 7.53-7.50 (m, 2H), 6.50 (d, *J* = 10 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 335.9.

[0994] **Compound 271**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 10.17 (s, 1H), 7.96 (d, *J* = 2.8 Hz, 1H), 7.70 (s, 1H), 7.67-7.58 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.10-7.07 (m, 1H), 6.49 (d, *J* = 10 Hz, 1H), 2.07 (s, 3H). **MS (ESI)** ***m/z*** $(M+Na)^+$ 328.9.

[0995] **Compound 272**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.98 (d, *J* = 2.8 Hz, 1H), 7.62 (dd, *J* = 9.6, 2.8 Hz, 1 H), 7.58-7.50 (m, 1H), 7.42-7.39 (m, 1H), 7.33-7.27 (m, 2H), 6.47 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 267.8.

[0996] **Compound 273**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.83 (d, *J* = 2.8 Hz, 1H), 7.63 (dd, *J* = 9.6, 2.8 Hz, 1 H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.86-6.83 (m, 1H), 6.47 (d, *J* = 9.6 Hz, 1H), 4.07 (q, *J* = 6.8 Hz, 2H), 2.01 (s, 3H), 1.35 (t, *J* = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 307.9.

Example 16
5-substituted Pyridone Analogs

[0997] Compounds **274-278, 280** and **281** were prepared following Method **1** in Example **12-B** by reacting 5-trifluoromethyl pyridin-2(1H)-one reacting with the relevant boronic acids.

[0998] **Compound 274**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) *δ* 7.73 (s, 1H), 7.58-7.49 (m, 2H), 7.22-7.15 (m, 3H), 6.74 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 257.9.

[0999] **Compound 275**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) *δ* 7.73 (s, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.48-7.42 (m, 2H), 7.38-7.36 (m, 2H), 6.73 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 324.1.

[1000] **Compound 276**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) *δ* 7.74 (s, 1H), 7.54-7.50 (m, 1H), 7.45-7.40 (m, 1H), 7.03-6.99 (m, 1H), 6.94-6.90 (m, 2H), 6.72 (d, *J* = 9.6 Hz, 1H), 3.85 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 270.1.

[1001] **Compound 277**: **^{1}HNMR** (DMSO-d_6, 400MHz) δ 10.18 (s, 1H), 8.25 (s, 1H), 7.79-7.75 (m, 1H), 7.71 (s, 1H), 7.63-7.61 (m, 1H), 7.48-7.43 (m, 1H), 7.14-7.11 (m, 1H), 6.66 (d, J = 9.6 Hz, 1H), 2.07 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 296.9.

[1002] **Compound 278**: **^{1}HNMR** (DMSO-d_6, 400MHz) δ 8.13 (m, 1H), 7.76-7.72 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.91 (s, 1H), 6.84-6.81 (m, 1H), 6.61 (d, J = 9.6 Hz, 1H), 4.04 (q, J=6.8 Hz, 2H), 1.97 (s, 3H), 1.31 (t, J=6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 298.1.

[1003] **Compound 280**: **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 7.67 (s, 1H), 7.55-7.48 (m, 2H), 7.40-7.35 (m, 1H), 7.32-7.28 (m, 2H), 6.75 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 258.1.

[1004] **Compound 281**: **^{1}H NMR:** ($CDCl_3$, 400MHz) δ 7.61-7.53 (m, 3H), 7.47-7.37 (m, 3H), 6.76 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 273.9.

[1005] **Compound 279** were prepared following Method **2** in Example **12-B** by reacting 5-trifluoromethyl pyridin-2(1H)-one with 5-bromopyridine. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 9.31 (s, 1H), 8.89 (s, 2H), 7.72 (s, 1H), 7.59 (d, J = 9.6 Hz, 1H), 6.78 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 242.0.

[1006] **Compound 282** was prepared following Method **1** in Example **12-B** by reacting 5-methyl pyridine-2(1H)-one with (3,4,5-triflurophenyl)boronic acid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 2.4 Hz, 1H), 7.10-7.03 (m, 3H), 6.59 (d, J = 9.6 Hz, 1H), 2.10 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 239.9.

[1007] **Compound 283** was prepared following Method **2** by reacting 5-methyl pyridine-2(1H)-one with 1-fluoro-2-iodobenzene. **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 7.42-7.31 (m, 2H), 7.30-7.21 (m, 3H), 7.01 (s, 1H), 6.62 (d, J = 9.6 Hz, 1H), 2.09 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 204.1.

[1008] **Compound 285** was prepared following the general methods described herein. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50-7.47 (m, 2H), 7.43-7.35 (m, 4H), 7.10 (d, J = 2.4Hz, 1H), 6.64 (d, J = 9.6Hz, 1H), 2.73-2.65 (m, 1H), 1.20 (d, J = 6.8Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 214.2.

[1009] **Compound 287**: To a mixture of 5-bromo-1-phenylpyridin-2(1H)-one (0.25 g, 1 mmol) and ethynyltrimethylsilane (5 mL) in DMF (10 mL) and TEA (2 mL) was added CuI (0.02 g, 0.1 mmol) and $Pd(PPh_3)_2Cl_2$ (0.07 g, 0.1 mmol). The mixture was purged with nitrogen for 5 minutes and stirred under N_2 at 100°C overnight. The reaction mixture was worked up to afford an intermediate product (0.16 g, 60% yield), which was mixed with TBAF (0.16 g, 0.6 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 3 hours. The organic layer was concentrated and the residue was purified by column chromatography (PE/EA = 10/1) to yield **Compound 287** (0.08 g, 68% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.6 (d, J = 2.4Hz, 1 H), 7.54-7.35 (m, 6H), 6.63 (d, J = 9.6Hz, 1H), 3.03 (s, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 196.1.

Example 17
5-Phenyl Pyridone Analogs

[1010] Compounds **288** through **331** were prepared following the similar procedures described herein in Method **A** through **C** and Method **1** through **4**.

[1011] **Compound 288**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.91-7.87 (m, 2H), 7.68-7.64 (m, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.22 (t, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 9.2 Hz, 1H), 4.70-4.64 (m, 1H), 1.30 (d, J = 6.0 Hz, 6H). **MS (ESI)** ***m/z*** $[M+H]^+$ 324.1.

[1012] **Compound 289**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.05 (d, J =2.4 Hz, 1H), 7.96-7.93 (m, 2H), 7.86-7.84 (m, 2H), 7.79-7.77 (m, 1H), 7.72-7.68 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 6.62 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $[M+H]^+$ 333.9.

[1013] **Compound 290**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.02-7.94 (m, 2H), 7.69-7.66 (m, 2H), 7.61-7.53 (m, 2H), 7.46-7.37 (m, 2H), 7.36-7.22 (m, 2H), 6.62 (d, J =9.6Hz, 1H). **MS (ESI)** ***m/z*** $[M+H]^+$ 284.0.

[1014] **Compound 291**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (dd, J =2.4, 9.6 Hz, 1H), 7.61-7.58 (m, 1H), 7.48-7.35 (m, 6H), 7.08 (t, J =8.4 Hz, 2H), 6.78 (d, J =9.6 Hz, 1H). **MS (ESI)** ***m/z*** $[M+H]^+$ 300.1.

[1015] **Compound 294**: **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.72-7.70 (m, 1H), 7.53 (s, 1H), 7.46-7.39 (m, 6H), 7.37-7.32 (m, 1H), 7.22-7.17 (m, 2H), 6.74 (d, J =9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 266.0.

[1016] **Compound 295**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.73-7.70 (m, 1H), 7.57 (s, 1H), 7.46-7.39 (m, 5H), 7.36-7.32 (m, 1H), 7.02-6.97 (m, 3H), 6.75 (d, J =9.6 Hz, 1H), 3.84 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 277.9.

[1017] **Compound 296**: **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.73-7.70 (m, 1H), 7.52-7.40 (m, 6H), 7.36-7.32 (m, 1H), 7.24-7.14 (m, 3H), 6.75 (d, J =9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 266.1.

[1018] **Compound 297**: **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.76-7.65 (m, 5H), 7.55 (s, 1H), 7.46-7.40 (m, 4H), 7.38-7.32 (m, 1H), 6.77 (d, J =9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 315.2.

[1019] **Compound 298**: **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.76-7.73 (m, 1H), 7.47-7.40 (m, 5H), 7.35-7.31 (m, 1H), 7.15 (d, J =8.4 Hz, 1H), 6.88-6.82 (m, 2H), 6.77 (d, J =9.2 Hz, 1H), 4.06 (q, J =6.8 Hz, 2H), 2.17 (s, 3H), 1.44 (t, J =6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 305.9.

[1020] **Compound 308**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.69-7.66 (m, 1H), 7.49-7.45 (m, 2H), 7.35 (d, J = 8Hz, 2H), 7.25-7.15 (m, 3H), 6.97-6.93 (m, 2H), 6.75 (d, J = 9.6 Hz, 1H), 3.83 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 296.0.

[1021] **Compound 309**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.68-7.65 (m, 1H), 7.35 (d, J = 2.4Hz, 1H), 7.43-7.33 (m, 3H), 7.01-6.93 (m, 5H), 6.75 (d, J = 9.2Hz, 1H), 3.83 (s, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 308.0.

[1022] **Compound 310**: ^{1}**H NMR** ($CDCl_3$, 300MHz) δ 7.72-7.69 (m, 1H), 7.60-7.57 (m, 1H), 7.43-7.41 (m, 3H), 7.37-7.33 (m, 3H), 6.96-6.93 (m, 2H), 6.77 (d, J = 9.6 Hz, 1H), 3.83 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 311.9.

[1023] **Compound 314**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.68 (dd, J=2.8, 9.6 Hz, 1H), 7.52-7.49 (m, 3H), 7.41-7.29(m, 6H), 6.75 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 315.9.

[1024] **Compound 315**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.68-7.65 (m, 1H), 7.56 (d, J = 4.0Hz, 1H), 7.42-7.28 (m, 6H), 7.04-7.00 (m, 2H), 6.76 (d, J = 9.2 Hz, 1H), 3.86 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 312.0.

[1025] **Compound 316**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) δ 7.67-7.64 (m, 1H), 7.56 (s, 1H), 7.42 (s, 1H), 7.34-7.28 (m, 5H), 7.00-6.97 (m, 2H), 6.76 (d, J = 9.2 Hz, 1H), 4.63-4.55 (m, 1H), 1.38 (s, 3H), 1.36 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 340.1.

[1026] **Compound 317**: ^{1}**H NMR:** (DMSO-d_6, 400 MHz) δ 8.09 (m, 1 H), 7.96 (dd, J=2.8, 9.6 Hz, 1H), 7.75 (s, 1H), 7.62-7.53 (m, 3H), 7.43-7.33 (m, 4H), 6.59 (d, J = 9.6 Hz, 1 H). **MS (ESI)** ***m/z*** $(M+H)^+$ 299.9.

[1027] **Compound 318**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) δ 7.73-7.66 (m, 5H), 7.54 (s, 1H), 7.43-7.30 (m, 4H), 6.78 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 349.9.

[1028] **Compound 319**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) δ 7.68-7.65 (m, 1H), 7.56 (s, 1H), 7.43-7.39 (m, 2H), 7.34-7.28 (m, 3H), 7.01-6.96 (m, 3H), 6.75 (d, J = 9.6 Hz, 1H), 3.84 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 311.9.

[1029] **Compound 320**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) δ 8.11 (s, 1H), 7.97-7.94 (m, 1H), 7.78 (s, 1H), 7.61-7.32 (m, 7H), 6.60 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 299.9

[1030] **Compound 321**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) δ 7.42 (d, J = 4.0Hz, 1H), 7.43-7.38 (m, 2H), 7.29-7.27 (m, 3H), 7.12 (d, J = 8.0Hz, 1H), 6.84-6.80 (m, 2H), 6.75 (d, J = 9.6Hz, 1H), 4.03 (q, J = 6.8Hz, 2H), 2.13 (s, 3H), 1.41 (t, J = 6.8Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 340.1

[1031] **Compound 322**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) δ 7.73-7.69 (m, 1H), 7.60-7.58 (m, 1H), 7.46-7.29 (m, 8H), 6.79 (d, J = 9.6Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 316.0.

[1032] **Compound 292**: ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.36-8.31 (m, 2H), 7.86-7.85 (m, 1H), 7.74-7.68 (m, 2H), 7.50 (s, 1H), 7.42-7.38 (m, 2H), 7.15-7.11 (m, 2H), 6.78 (d, J = 9.2 Hz, 1H). **MS (ESI)** ***m/z*** $[M+H]^+$ 310.8.

[1033] **Compound 299**: ^{1}**HNMR** ($CDCl_3$, 400MHz) δ 8.77 (brs, 2H), 7.73-7.68 (m, 1H), 7.51-7.32 (m, 8H), 6.77-6.72 (m, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 249.2.

[1034] **Compound 302**: ^{1}**HNMR** ($CDCl_3$, 400MHz) *δ* 7.78-7.75 (m, 1H), 7.62-7.58 (m, 1H), 7.47-7.40 (m, 8H), 7.35-7.32 (m, 1H), 6.79 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 282.2.

[1035] **Compound 300**: ^{1}**HNMR** ($CDCl_3$, 400MHz) *δ* 9.27 (s, 1H), 8.95 (s, 2H), 7.80-7.75 (m, 1H), 7.51-7.35 (m, 6H), 6.79 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 250.0.

[1036] **Compound 301**: ^{1}**HNMR** ($CDCl_3$, 400MHz) δ 7.76-7.72 (m, 1H), 7.50-7.39 (m, 7H), 7.38-7.27 (m, 3H), 6.78 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 265.9.

[1037] **Compound 311**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 9.26 (s, 1H), 8.94 (s, 2H), 7.72 (dd, *J* = 2.8, 9.6 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.35-7.33 (m, 2H), 6.97-6.95 (m, 2H), 6.77 (d, *J* = 9.6 Hz, 1H), 3.84 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 279.9.

[1038] **Compound 323**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) *δ* 8.82 (brs, 2H), 7.72-7.68 (m, 1H), 7.52 (d, *J* = 2.4Hz, 1H), 7.47-7.42 (m, 2H), 7.39-7.30 (m, 4H), 6.79 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 283.1.

[1039] **Compound 312**: ^{1}**H NMR** ($CDCl_3$, 400MHz) δ 7.71-7.68 (m, 1H), 7.48-7.39 (m, 3H), 7.37-7.27 (m, 4H), 6.96-6.93 (m, 2H), 6.76 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 296.0.

[1040] **Compound 324**: ^{1}**H NMR:** ($CDCl_3$, 400MHz) δ 7.70-7.67 (m, 1H), 7.48-7.41 (m, 4H), 7.37-7.28 (m, 5H), 6.79 (d, *J* = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 300.1.

[1041] **Compound 303**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.90-7.86 (m, 2H), 7.59-7.51 (m, 6H), 6.97-6.94 (m, 2H), 6.59 (d, *J* = 9.6 Hz, 1H), 3.76 (s, 3H). **MS (ESI)** ***m/z*** **z** $(M+H)^+$ 312.0.

[1042] **Compound 304**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.95-7.76 (m, 6H), 7.59-7.54 (m, 2H), 6.98-6.95 (m, 2H), 6.60 (d, *J* = 9.6 Hz, 1H), 3.76 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 345.9.

[1043] **Compound 305**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.89-7.82 (m, 2H), 7.66-7.54 (m, 4H), 7.43-7.39 (m, 2H), 7.08-7.03 (m, 2H), 6.98-6.96 (m, 2H), 6.56 (d, *J* = 9.2 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 308.0.

[1044] **Compound 306**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.91-7.87 (m, 2H), 7.59-7.53 (m, 4H), 7.39-7.33 (m, 2H), 6.99-6.96 (m, 2H), 6.59 (d, *J* = 9.2 Hz, 1H), 3.78 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 296.1.

[1045] **Compound 307**: ^{1}**HNMR** (DMSO-d_6, 400MHz) δ 7.88-7.82 (m, 2H), 7.56-7.54 (m, 2H), 7.39-7.36 (m, 2H), 7.04-6.95 (m, 4H), 6.56 (d, *J*=9.2 Hz, 1H), 4.71-4.66 (m, 1H), 3.78 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 336.1.

[1046] **Compound 313**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.69-7.66 (m, 1H), 7.58-7.51 (m, 3H), 7.49-7.42 (m, 4H), 7.36-7.29 (m, 3H), 6.77 (d, J = 9.6 Hz, 1H). **MS (ESI) *m/z*** $(M+H)^+$ 281.9.

[1047] **Compound 293**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.90-7.87 (m, 2H), 7.68-7.64 (m, 2H), 7.26-7.13 (m, 3H), 6.65-6.54 (m, 4H), 5.40 (brs, 2H). **MS (ESI) *m/z*** $[M+H]^+$ 280.9.

[1048] **Compound 325**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.13 (d, J = 2.8 Hz, 1H), 8.02-7.99 (m, 1H), 7.86-7.81 (m, 4H), 7.60-7.56 (m, 2H), 7.40-7.35 (m, 4H), 6.64 (d, J = 9.6 Hz, 1H). **MS (ESI) *m/z*** $(M+H)^+$ 344.9.

[1049] **Compound 326**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.88 (d, J = 2.4 Hz, 1H), 7.75-7.72 (m, 1H), 7.60-7.54 (m, 4H), 7.34-7.29 (m, 1H), 7.25-7.22 (m, 1H), 7.13-7.05 (m, 4H), 6.37 (d, J = 9.6 Hz, 1H). **MS (ESI) *m/z*** $(M+H)^+$ 345.2.

[1050] **Compound 327**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.15 (d, J = 2.8 Hz, 1H), 8.04-8.01 (m, 1H), 7.87-7.82 (m, 4H), 7.64-7.57 (m, 4H), 7.38 (s, 2H), 6.65 (d, J = 9.6 Hz, 1H). **MS (ESI) *m/z*** $(M+H)^+$ 360.9.

[1051] **Compound 328**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.09 (d, J = 2.8 Hz, 1H), 8.00-7.97 (m, 1H), 7.85-7.80 (m, 4H), 7.44-7.41 (m, 2H), 7.37 (s, 2H), 7.08-7.02 (m, 2H), 6.62 (d, J = 9.6 Hz, 1H), 3.82 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 356.9.

[1052] **Compound 329**: **^{1}HNMR** (DMSO-d_6, 400 MHz) δ 8.21 (s, 1H), 8.02 (dd, J = 2.4, 9.6 Hz, 1H), 7.96 (s, 1H), 7.87-7.65 (m, 7H), 7.40 (s, 2H), 6.65 (d, J = 9.6 Hz, 1H). **MS (ESI) *m/z*** $(M+H)^+$ 394.9.

[1053] **Compound 330**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.08 (d, J = 2.8 Hz, 1H), 7.98-7.95 (m, 1H), 7.84-7.76 (m, 4H), 7.39-7.36 (m, 4H), 7.02 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 9.6 Hz, 1H), 4.70-4.64 (m, 1H), 1.29 (d, J = 6.0 Hz, 6H). **MS (ESI) *m/z*** $(M+H)^+$ 384.8.

[1054] **Compound 331**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.11 (d, J = 2.4 Hz, 1H), 8.03-8.00 (m, 1H), 7.87-7.81 (m, 4H), 7.49-7.42 (m, 1H), 7.39 (s, 2H), 7.11-7.04 (m, 3H), 6.63 (d, J = 9.6 Hz, 1H), 3.81 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 356.9.

Example 18
2(1H)-Thione Analogs

[1055] Compounds **332-339** and **341-343** were prepared according to the general procecure: To a solution of Pirfenidone analog (1 eq.) in toluene was added Lawesson reagent (0.6 eq.). The reaction mixture was refluxed under nitrogen overnight. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluenting with petroleum ether/EtOAc) to provide final thione analogs.

[1056] **Compound 332**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.83 (s, 1H), 7.47-7.44 (m, 1H), 7.32-7.25 (m, 3H), 7.08-7.04 (m, 2H), 3.82 (s, 3H), 2.13 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 231.9.

[1057] **Compound 333**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 8.7 Hz, 1 H), 7.41-7.38 (m, 5H), 7.15 (d, J = 9.0 Hz, 1H), 2.17 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 285.9.

[1058] **Compound 334**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 9.0 Hz, 1 H), 7.41 (s, 1H), 7.25-7.20 (m, 2H), 7.09 (d, J = 9.0 Hz, 1 H), 6.96 (d, J = 9.0 Hz, 2 H), 4.60-4.52 (m, 1H), 2.15 (s, 3H), 1.35 (d, J = 6.0 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 259.9.

[1059] **Compound 335**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.68 (d, J = 9.0 Hz, 1H), 7.51-7.47 (m, 2H), 7.37 (s, 1H), 7.30 (d, J = 1.8 Hz, 1H), 7.28 (s, 1H), 7.12 (dd, J = 2.1, 9.0 Hz, 1H), 2.18 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 236.2.

[1060] **Compound 336**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 7.37-7.10 (m, 5H), 2.17 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 219.9.

[1061] **Compound 337**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.75-7.57 (m, 5H), 7.37 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), 2.17 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 270.0.

[1062] **Compound 338**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 9.0 Hz, 1H), 7.53-7.48 (m, 1H), 7.39 (s, 1H), 7.21-7.08 (m, 4H), 2.17 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 219.9.

[1063] **Compound 339**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 9.0 Hz, 1H), 7.42-7.40 (m, 2H), 7.11 (d, J = 8.7 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 6.86-6.84 (m, 1H), 3.82 (s, 3H), 2.17 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 231.9.

[1064] **Compound 341**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.84 (s, 1H), 7.69-7.67 (m, 1H), 7.54-7.38 (m, 4H), 7.37 (dd, J = 2.0, 9.2 Hz, 1H), 2.14 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 236.1.

[1065] **Compound 342**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.73 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.30 (dd, J =2.0, 8.8 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.84 (dd, J = 2.8, 8.4 Hz, 1H), 4.04 (q, J = 6.8 Hz, 2H), 2.11 (s, 3H), 1.94 (s, 3H), 1.33 (t, J = 6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 260.1.

[1066] **Compound 343**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.17 (s, 1H), 7.83 (s, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45-7.41 (m, 2H), 7.31 (dd, J = 2.0, 8.8 Hz, 1H), 6.96 (t, J = 6.4 Hz, 1H), 2.11 (s, 3H), 2.05 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 258.9.

Example 19
5-Heterocycle Substituted Analogs

[1067] Compounds **344-346** were prepared following the similar procedure in Scheme **XXVIII**, Method **1**.

[1068] **Compound 344**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.11-9.09 (m, 3H), 8.26 (m, 1H), 8.05-8.02 (m, 1H), 7.58-7.55 (m, 2H), 7.39-7.35 (m, 2H), 6.64 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 267.8.

[1069] **Compound 345**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.13 (m, 3H), 8.31 (m, 1H), 8.08-8.05 (m, 1H), 7.61-7.57 (m, 1H), 7.54-7.50 (m, 1H), 7.42-7.36 (m, 2H), 6.68 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 267.7.

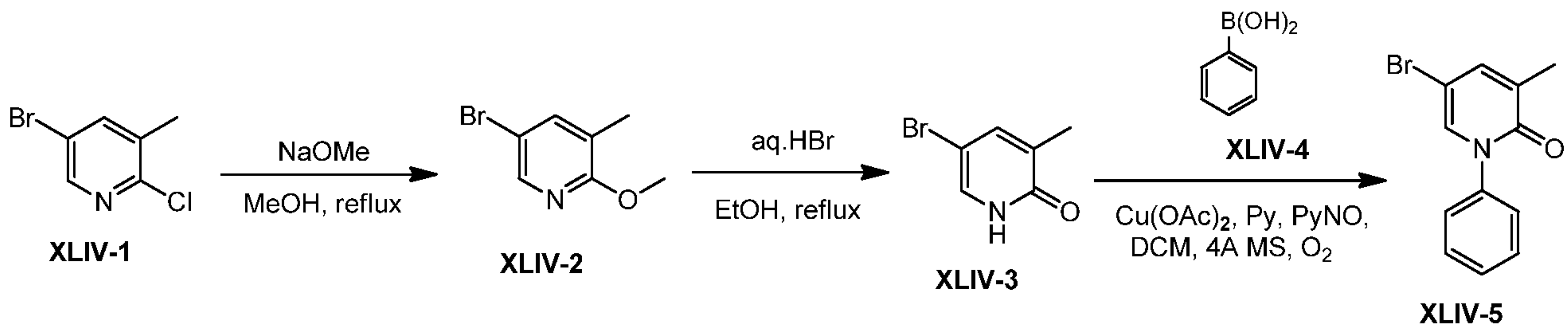
[1070] **Compound 346**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H), 8.86 (s, 2H), 7.70-7.67 (m, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.52-7.43 (m, 2H), 7.34-7.29 (m, 2H), 6.86 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 289.9.

[1071] **Compound 347** was prepared following the similar synthetic procedure for obtaining Compound 243: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.34 (d, J = 2.4 Hz, 1H), 9.20 (d, J = 5.6 Hz, 1H), 7.79-7.74 (m, 2H), 7.52-7.49 (m, 2H), 7.41-7.39 (m, 2H), 6.85 (d, J = 9.6 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 334.9.

[1072] **Compound 348** was prepared following the similar procedure in Scheme **XXVIII**, Method **1**, except that the first step intermediate was formed by reacting imidazole with 5-bromo-2-methoxypyridine in DMSO with the presence of L-proline ,CuI, K_2CO_3 and 4Å molecular sieve. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.53-7.47 (m, 4H), 7.39-7.36 (m, 2H), 7.21 (s, 1H), 7.11 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 321.9.

Example 20

3-Methyl Substituted Analogs (Scheme XLIV)



[1073] To a solution of NaOMe (5.29 g, 98 mmol) in MeOH (500 mL) was added **XLIV-1** (10 g, 49 mmol) by portionwise. The reaction mixture was heated to reflux overnight. The solution was cooled, quenched with water slowly, extracted with PE (100 mL ×3). The combined organic layer was washed with brine and concentrated to give **XLIV-2** (8.0 g, 81% yield) as a white solid.

[1074] **XLIV-5** was prepared following the similar procedure in Method **1** for obtaining **XXVIII**-5. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.51-7.35 (m, 7H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 265.8.

[1075] Compounds **349**, **351** and **353** were prepared by reacting **XLIV-5** with the relevant boronic acid or ester following the similar procedure described in Method **A**.

[1076] **Compound 349**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68-7.52 (m, 2H), 7.48-7.35 (m, 3H), 7.20-7.16 (m, 1H), 6.96 (s, 1H), 2.17 (s, 3H), 2.08 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 200.0.

[1077] **Compound 351**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 7.80 (m, 2H), 7.78-7.62 (m, 2H), 7.52-7.44 (m, 5H), 7.23-7.17 (m, 2H), 2.09 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 280.1.

[1078] **Compound 353**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 7.99 (s, 1H), 7.74-7.68 (m, 3H), 7.49-7.39 (m, 5H), 3.78 (s, 3H), 2.06 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 265.9.

[1079] **Compound 350**: To a mixture of 5-bromo-3-methyl-1-(4-(trifluoromethoxy)phenyl)pyridin-2(1H)-one (300 mg, 0.86 mmol, 1 eq.) in 12 mL of toluene/EtOH/H_2O (v/v/v=4/1/1) were added (4-fluorophenyl)boronic acid (242 mg, 1.73 mmol, 2 eq.) and K_2CO_3 (357 mg, 2.59 mmol, 3 eq.). The mixture was degassed by N_2 for three times and then $Pd(PPh_3)_4$ (100 mg, 0.08 mmol, 0.1 eq.) was added. The reaction vessel was sealed and heated in microwave at 100°C for 1h. After being cooled to rt, the mixture was diluted with EA (100 mL), washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by prep-TLC (PE/EA=3/2) to afford **Compound 350** (210 mg, 67% yield) as a white solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.55 (s, 1H), 7.51-7.47 (m, 2H), 7.41-7.34 (m, 5H), 7.11 (t, J = 8.8 Hz, 2H), 2.27 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 364.0.

[1080] **Compound 352** was prepared by following the similar procedure for obtaining Compound **350** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in place of (4-fluorophenyl)boronic acid as a white solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.58 (s, 1H), 7.48-7.43 (m, 4H), 7.36-7.32 (m, 3H), 3.93 (s, 3H), 2.24 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 350.1.

Example 21
Pirfenidone Analogs with Heterocyclic Core

[1081] **Compound 354** was prepared following the similar procedure described in Method **1** by reacting isoquinolin-3(2H)-one with phenyl boronic acid. **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.75 (s, 1H), 7.60-7.50 (m, 6H), 7.35-7.28 (m, 2H), 6.92-6.88 (m, 1H), 6.59 (s, 1H). **MS (ESI) *m/z*** $(M+H)^+$ 222.0.

[1082] Compounds **355** and **356** were prepared following the similar procedure described in Scheme **XXVII** and Method **A** using 5-bromopyrimidin-2(1H)-one in place of **XXVII-1** and $Pd(PPh_3)_4$ in place of $Pd(dppf)Cl_2$.

[1083] **Compound 355**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.83 (d, J =3.6 Hz, 1H), 7.77 (d, J =3.6 Hz, 1H), 7.61 (s, 1H), 7.56-7.44 (m, 6H), 3.96 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 253.0.

[1084] **Compound 356**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.95 (d, J =3.2 Hz, 1H), 7.85 (d, J =3.6 Hz, 1H), 7.57-7.40 (m, 7H), 7.17 (t, J =8.4 Hz, 2H). **MS (ESI)** ***m/z*** $[M+H]^+$ 267.0.

[1085] **Compound 357** was prepared following the similar procedure described in Scheme **XXVIII** and Method **A** using 5-bromo-2-methoxypyrimidine in place of **XXVIII-1** and $Pd(PPh_3)_4$ in place of Pd(dppf)Cl_2. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.11 (d, J = 2.8 Hz, 1H), 8.58 (d, J = 3.6 Hz, 1H), 7.79-7.74 (m, 4H), 7.58 (d, J = 8.4 Hz, 2 H), 7.30 (t, J = 8.4 Hz, 2 H).

[1086] Compound **358** was prepared following the general procedure described in Method **1** by reacting 5-methylpyrimidin-2(1H)-one with phenyl boronic acid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.60 (brs, 1H), 7.52-7.40 (m, 6H), 2.16 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 187.1.

[1087] Compounds **359** and **360** were prepared following the general procedure described in Method **1** by reacting 6-methylpyridazin-3(2H)-one with the relevant boronic acid.

[1088] **Compound 359**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.58 (d, J = 7.8 Hz, 2H), 7.49-7.44 (m, 2H), 7.39-7.34 (m, 1H), 7.11 (d, J = 9.6 Hz, 1H), 6.68 (d, J = 9.3 Hz, 1H), 2.38 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 187.1.

[1089] **Compound 360**: **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 7.66 (d, J = 9.0 Hz, 2H), 7.47-7.40 (m, 3H), 6.99 (d, J = 9.6Hz, 1H), 2 .28 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 271.1.

[1090] **Compound 361** was prepared following the general procedure described in Method **A** by reacting 6-chloro-2-phenylpyridazin-3(2H)-one with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.25 (s, 1H), 7.90-7.85 (m, 2H), 7.60-7.59 (m, 2H), 7.51-7.50 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 10.0 Hz, 1H), 3.86 (s, 3H). **MS (ESI)** ***m/z*** $[M+H]^+$ 252.8. Compounds **362** and **363** were prepared similarly starting with 6-chloro-2-(4-(trifluoromethoxy)phenyl)pyridazin-3(2H)-one.

[1091] **Compound 362**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.82-7.71 (m, 5H), 7.35 (d, J = 8.0Hz, 2H), 7.18-7.14 (m, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 351.0.

[1092] **Compound 363**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.84 (s, 1H), 7.78 (s, 1H), 7.75 (d, J = 6.8 Hz, 2H), 7.49 (d, J=10 Hz, 1H), 7.34-7.31 (m, 2H), 7.08 (d, J = 9.6 Hz, 1H), 3.96 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 337.1.

[1093] **Compound 364** was prepared following the similar procedure for obtaining Compound **355** using (4-(trifluoromethoxy)phenyl)boronic acid in place of phenyl boronic acid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 7.75 (s, 1H), 7.60-7.52 (m, 4H), 7.40-7.35 (m, 2H), 3.97 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 337.2.

[1094] **Compound 365**: To a solution of 1-phenylpyrimidin-2(1H)-one (250 mg, 1.45 mmol) in dry THF (20 mL) was added a solution of $NaBH_4$ (58 mg, 1.5 mmol) in 20 mL MeOH by dropwise at 0°C. The reaction mixture was stirred at rt for 1h. The mixture was concentrated to remove DCM, the residue was purified by SFC to give 1-phenyl-3,4-dihydropyrimidin-2(1H)-one and **Compound 365** (74.8 mg, 30% yield) as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41-7.33 (m, 4H), 7.23-7.21 (m, 1H), 6.53 (brs, 1H), 6.14-6.11 (m, 1H), 4.88-4.84 (m, 1H), 4.32-4.31 (m, 2H). **MS (ESI) *m/z*** $[M+H]^+$ 174.9.

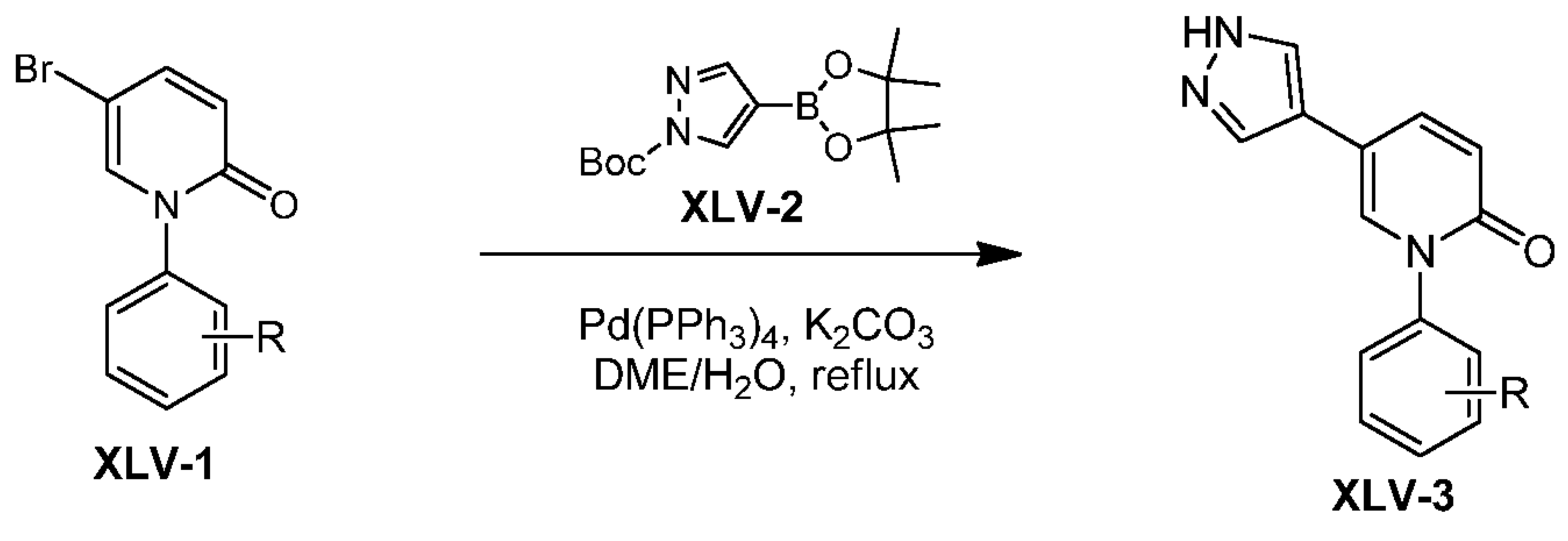
Example 22
4-Methyl Substituted Analogs

[1095] **Compound 366**: To a stirred mixture of 5-bromo-4-methyl-1-phenylpyridin-2(1H)-one (300 mg, 1.15 mmol) and Pd(dppf)Cl_2 (83 mg, 0.1 mmol) in 10 mL of anhydrous dioxane was added $Zn(Me)_2$ (1.2 M in toluene, 3.8 mL, 4.56 mmol) under N_2 protection. The reaction mixture was refluxed overnight. After being cooled to rt, the mixture was filtered, concentrated. The resulting residue was diluted with H_2O (30 mL), extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The residue was purified by prep-TLC (PE/EA=3/1) to produce **Compound 366** (60 mg, 26% yield) as a white solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.49-7.45 (m, 2H), 7.41-7.36 (m, 3H), 7.07 (s, 1H), 6.49 (s, 1H), 2.18 (s, 3H), 2.03 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 200.1.

[1096] **Compound 367** was prepared following the similar procedure for obtaining Comound 366 using 5-bromo-4-methyl-1-(4-(trifluoromethoxy)phenyl)pyridin-2(1H)-one instead of 5-bromo-4-methyl-1-phenylpyridin-2(1H)-one. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42-7.39 (m, 2H), 7.33-7.30 (m, 2H), 7.03 (s, 1H), 6.48 (s, 1H), 2.17 (s, 3H), 2.03 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 284.1.

[1097] **Compound 368** was prepared following the similar procedure described in Method **1** by reacting 4-methyl-5-(trifluoromethyl)pyridin-2(1H)-one with (4-(trifluoromethoxy)phenyl)boronic acid as a yellow solid. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.70 (s, 1H), 7.44-7.41 (m, 2H), 7.39-7.36 (m, 2H), 6.61 (s, 1H), 2.38 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 337.9.

Example 23
5-Pyrazole Substituted Analogs (Scheme XLV)



[1098] To a mixture of **XLV-1** (1 eq.), **XLV-2** (1.3 eq.) and K_2CO_3 (2 eq.) in DME/H_2O (v/v=6/1) was added $Pd(PPh_3)_4$ (0.1 eq.). The reaction mixture was degassed by purging with nitrogen and then was heated to reflux overnight. After the completion of the reaction, the mixture was cooled to rt, diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EA=1/1 to EA) to afford **XLV-3**. Compounds **369-377** were prepared following the general procedure discussed above.

[1099] **Compound 369**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.8 (brs, 1H), 8.09-8.01 (m, 1H), 7.90-7.78 (m, 2H), 7.33 (d, J = 8.8 Hz, 1 H), 7.01 (d, J = 8.8Hz, 1 H), 6.50 (d, J = 9.6 Hz, 1 H), 4.68-4.62 (m, 1H), 1.28 (d, J = 6.0 Hz, 6H).

[1100] **Compound 370**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67 (s, 2H), 7.58-7.55 (m, 1H), 7.48 (s, 1H), 7.33 (d, J = 8.8Hz, 2 H), 7.00 (d, J = 8.8Hz, 2 H), 6.73 (d, J = 9.2Hz, 1 H), 3.85 (s, 3H).

[1101] **Compound 371**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.10 (brs, 1H), 7.91 (s, 1H), 7.86-7.82 (m, 2H), 7.60-7.57 (m, 2H), 7.60-7.57 (m, 2H), 6.54 (d, J = 9.2Hz, 1 H).

[1102] **Compound 372**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.11 (brs, 1H), 7.96 (s, 1H), 7.89-7.85 (m, 2H), 7.61-7.57 (m, 1H), 7.46 (d, J = 8.0 Hz, 1 H), 7.37-7.31 (m, 2H), 6.58 (d, J = 8.0 Hz, 1 H).

[1103] **Compound 373**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.87 (brs, 1H), 8.10 (brs, 1H), 7.99 (s, 1H), 7.90-7.77 (m, 6H), 6.58 (d, J = 8.4 Hz, 1H).

[1104] **Compound 374**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.87 (brs, 1H), 8.10 (brs, 1H), 7.99 (s, 1H), 7.87 (d, J = 8.4 Hz, 2 H), 7.63-7.60 (m, 2H), 7.54-7.50 (m, 2H), 6.55 (d, J = 9.6 Hz, 1 H).

[1105] **Compound 375**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.86 (brs, 1H), 8.10 (brs, 1H), 7.90-7.80 (m, 3H), 7.44-7.39 (m, 1H), 7.03-6.98 (m, 3H), 6.53 (d, J = 9.2 Hz, 1H), 3.78 (s, 3H).

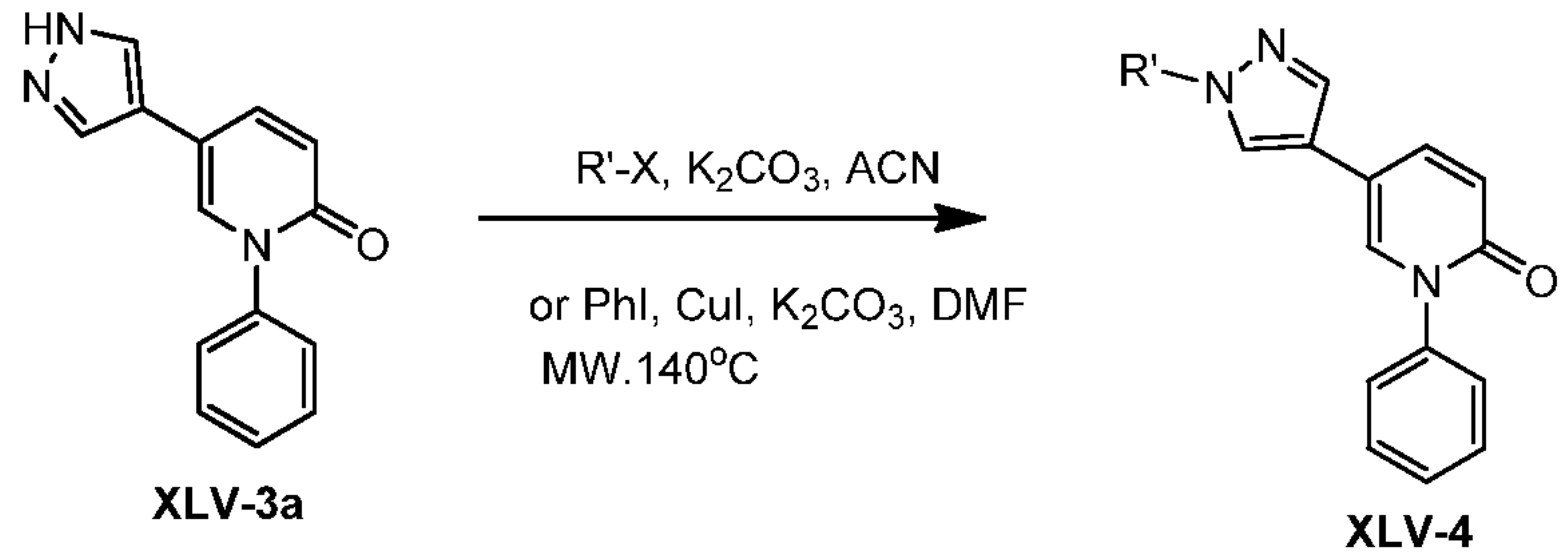
[1106] **Compound 376**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.86 (brs, 1H), 8.10 (s, 1H), 7.87-7.79 (m, 3H), 7.18 (d, J=8.8 Hz, 1H), 6.95-6.86 (m, 2H), 6.55 (d, J =7.2 Hz, 1H), 4.07 (q, J =6.8 Hz, 2H), 2.03 (s, 3H), 1.35 (t, J =6.8 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 295.9.

[1107] **Compound 377**: **^{1}H NMR** (DMSO-d_6, 400MHz) δ 12.86 (brs, 1H), 8.09 (brs, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.85-7.82 (m, 2 H), 7.53-7.49 (m, 2H), 7.37-7.33 (m, 2H), 6.53 (d, J = 9.6 Hz, 1H).

[1108] **Compound 627** was obtained from the corresponding non-Boc protected boronic ester following the general procedure described in Method **A**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45-

7.39 (m, 3H), 7.37-7.30 (m, 3H), 7.18 (s, 1H), 6.51 (s, 1H), 3.91 (s, 3H), 2.19 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 300.1.

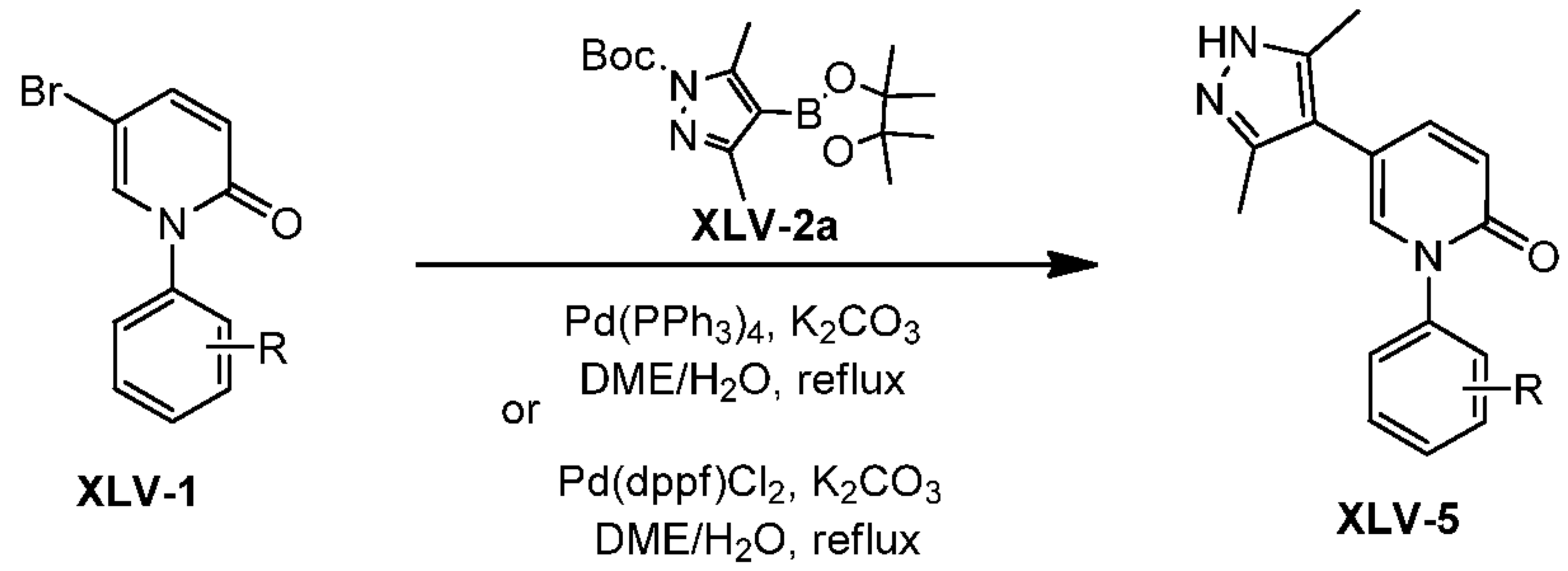
[1109] **Compound 628**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.83 (s, 1H), 7.87 (s, 1H), 7.57 (s, 1H), 7.55 (m, 1H), 7.46 (s, 1H), 7.34-7.31 (m, 2H), 6.93-6.89 (m, 1H), 6.40 (s, 1H), 5.95 (s, 2H), 3.81 (s, 3H), 2.21 (s, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 324.1.



[1110] **Compound 385**: To a solution of **XLV-3a** (0.2 g, 0.8 mmol) in CH_3CN (15 mL) was added K_2CO_3 (0.5 g, 3.6 mmol), benzyl chloride (0.37 g, 2.9 mmol). The mixture was purged with nitrogen and then heated to reflux overnight. The mixture was cooled to rt, diluted with water, extracted with EtOAc (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE:EA=1:2) to give **Compound 385** (112.8 mg, 46% yield). **^{1}H NMR** (DMSO-d_6, 400MHz) δ 8.18 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.85 (s, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.53-7.42 (m, 5H), 7.33-7.21 (m, 5H), 6.53 (d, J=9.6 Hz, 1H), 5.28 (s, 2H). **MS (ESI)** ***m/z*** $(M+H)^+$ 328.2.

[1111] **Compound 388** was prepared following the similar procedure for obtaining Compound **385** using isopropyl iodide in place of benzyl chloride. **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.58-7.50 (m, 5H), 7.47-7.40 (m, 4H), 6.72 (d, J = 9.6 Hz, 1H), 4.54-4.48 (m, 1H), 1.52 (d, J = 6.8 Hz, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 280.0.

[1112] **Compound 389**: To a stirred mixture of **XLV-3a** (0.2 g, 0.8 mmol), iodobenzene (2 g, 9.8 mmol), and K_2CO_3 (0.89 g, 6.4 mmol) in DMF (2 mL) was added CuI (0.12 g, 0.8 mmol). The mixture was purged with nitrogen for three times and then heated at 140°C under microwave for 2 hrs. The mixture was diluted with H_2O, extracted with EtOAc (20 mL×3). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was chromatographed on silica gel (PE: EA = 1:2) to give **Compound 389** (50.3 mg, 25% yield). **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.01 (s, 1H), 7.81 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.63-7.60 (m, 1H), 7.55-7.42 (m, 8H), 7.33-7.29 (m, 1H), 6.76 (d, J = 8.0 Hz, 1H). **MS (ESI)** ***m/z*** $(M+H)^+$ 314.2.



[1113] Compounds **378, 379, 381, 387** and **390** were prepared following the similar procedure for obtaining **XLV-3** using **XLV-2a** in place of **XLV-2**.

[1114] **Compound 378**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.30 (brs, 1H), 7.54-7.51 (m, 1H), 7.44-7.40 (m, 2H), 7.03-7.00 (m, 3H), 6.54 (d, J = 9.2, 1H), 3.80 (s, 3H), 2.18 (s, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 295.9.

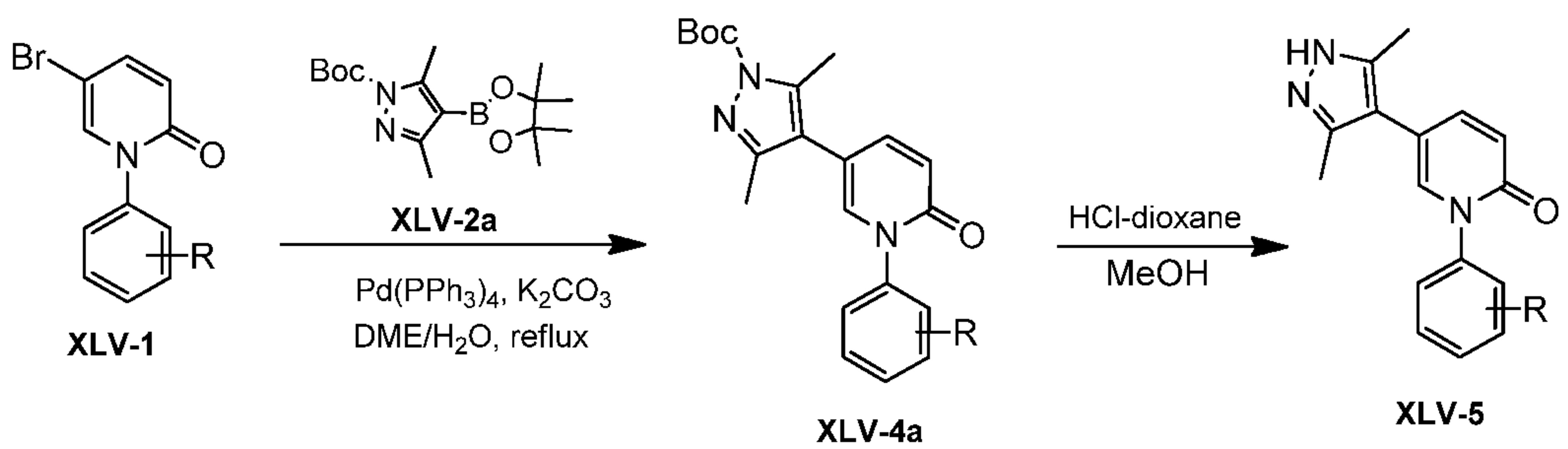
[1115] **Compound 379**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.30 (brs, 1H), 7.44-7.36 (m, 3H), 7.21-7.17 (m, 3H), 6.72 (d, J = 9.6 Hz, 1H), 2.27 (s, 6H).

[1116] **Compound 381**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 7.50-7.43 (m, 1H), 7.40-7.36 (m, 1H), 7.23-7.10 (m, 4H), 6.73 (d, J=9.6 Hz, 1H), 2.27 (s, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 283.1.

[1117] **Compound 387**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 7.53 (d, J = 9.2 Hz, 1H), 7.32 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.87-6.84 (m, 1H), 6.54 (d, J = 9.2 Hz, 1H), 4.05 (q, J =6.8 Hz, 2H), 2.17 (s, 6H), 2.05 (s, 3H), 1.35 (t, J =6.8 Hz, 3H). **MS (ESI)** ***m/z*** $(M+H)^+$ 323.4.

[1118] **Compound 390**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.79-8.78 (m, 2H), 7.46-7.45 (m, 2H), 7.40-7.38 (m, 1H), 7.18 (s, 1H), 6.74 (d, J = 9.6 Hz, 1H), 2.28 (s, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 267.1.

[1119] **Compound 380** were prepared following the similar procedure for obtaining **XLV-3** using **XLV-2a** in place of **XLV-2** and using $Pd(dppf)Cl_2$ in place of $Pd(PPh_3)_4$. **^{1}H NMR** (DMSO-d_6, 400MHz): δ 12.25 (s, 1H), 7.60-7.47 (m, 6H), 6.51 (d, J=9.2 Hz, 1H), 2.16 (s, 6H). **MS (ESI)** ***m/z*** $(M+H)^+$ 299.8.



[1120] Additonal Boc-deprotection procedure: To a solution of **XLV-4a** (1 eq.) in MeOH (0.1-0.2 mmol/mL) was added a solution of HCl (gas) in dioxane (4 M, volume was two times of

MeOH). The mixture was stirred at rt for 1h. After the completion of the reaction, the mixture was concentrated *in vacuo*. The crude product was purified by prep-HPLC to yield **XLV-5**. The prepration of Comounds **382-384** and **386** followed the above deprotection procedure.

[1121] **Compound 382**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.28 (s, 1H), 7.50 (dd, J = 9.6, 2.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.33 (dd, J = 6.8, 2.0 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 5.52 (d, J = 9.2 Hz, 1H), 4.70-4.64 (m, 1H), 2.17 (s, 6H),1.30 (s, 6H).

[1122] **Compound 383**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.27 (s, 1H), 7.61 (dd, J = 6.8, 2.4 Hz, 1H), 7.54-7.50 (m, 5H), 6.55 (dd, J = 8.8, 1.2 Hz, 1H),2.16 (s, 6H).

[1123] **Compound 384**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.27 (s, 1H), 7.88 (s, 1H), 7.82-7.73 (m, 3H), 7.55-7.52 (m, 2H), 6.56 (dd, J = 8.8, 0.8 Hz, 1H), 2.16 (s, 6H).

[1124] **Compound 386**: **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 12.27 (s, 1H), 7.88 (s, 1H), 7.49 (dd, J = 9.6, 2.8 Hz, 1H), 7.40-7.34 (m, 3H), 7.04-7.02 (m, 2H), 6.50 (d, J = 9.2 Hz, 1H), 3.79 (s, 3H), 2.15 (s, 6H).

[1125] **Compound 391** was prepared by following the similar procedure for obtaining Compound **238** (Scheme XXXIX) by using 4-bromo-1,5-dimethyl-1H-pyrazole in place of **XXXIX-2**. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.42 (m, 4H), 7.38-7.33 (m, 2H), 7.26-7.24 (m, 1H), 6.71 (d, J = 9.2 Hz, 1H), 3.83 (s, 3H), 2.32 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 349.9.

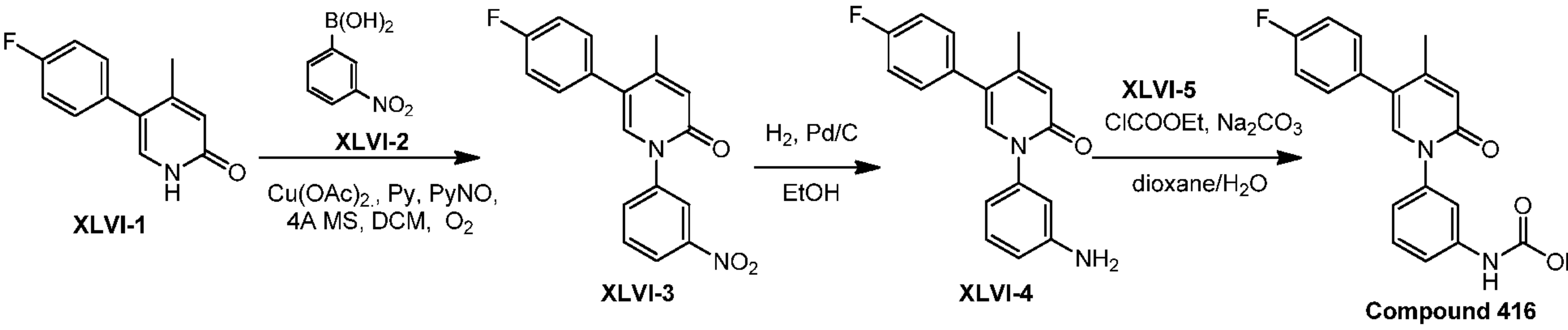
[1126] Compounds **420-422** were prepared following Scheme **XLV** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole or 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole as **XLV-2** and 5-bromo-1-(4-ethoxy-2-methylphenyl)-4-methylpyridin-2(1H)-one or 5-bromo-1-(4-chlorophenyl)-4-methylpyridin-2(1H)-one as **XLV-1**.

[1127] **Compound 420**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.14 (s, 1H), 7.70 (s, 1H), 7.62-7.59 (m, 1H), 7.32-7.30 (m, 1H), 7.15-7.12 (m, 2H), 6.85-6.79 (m, 2H), 6.61 (s, 1H), 4.03 (q, J = 6.8 Hz, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 361.1.

[1128] **Compound 421**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 9.07 (s, 1H), 8.05 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.48-7.43 (m, 2H), 7.42-7.37 (m, 3H), 7.26 (s, 1H), 6.62 (s, 1H), 2.18 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 352.9.

[1129] **Compound 422**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.16 (s, 1H), 7.70 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48-7.43 (m, 2H), 7.41-7.38 (m, 2H), 7.32-7.28 (m, 2H), 6.60 (s, 1H), 2.14 (s, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 337.2.

Example 24
5-Phenyl, 4-Alkyl Substituted Analogs (Scheme XLVI)



[1130] **XLVI-3** was prepared following the general procedure described in Method **1**. **MS (ESI) *m/z*** $(M+H)^+$ 325.1.

[1131] A mixture of **XLVI-3** (2.3 g, 7.08 mmol) and Pd/C (~0.2 g) in ethanol (30 mL) was stirred under H_2 at rt overnight. Filtered the mixture, and concentrated the filtrate to give **XLVI-4** (1.6 g, 77% yield.). **MS (ESI) *m/z*** $(M+H)^+$ 294.9.

[1132] To a solution of **XLVI-4** (400 mg, 1.36 mmol) in dioxane/H_2O (11 mL, v/v=10:1) was added Na_2CO_3 (288 mg, 2.72 mmol) with stirring at 0°C. Then ethyl chloroformate **(XLVI-5)** (443 mg, 4.08 mmol) was added dropwise. The mixture was stirred at rt for 5 hours. The reaction was evaporated to dryness. The residue was diluted with water (20 mL), extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude was purified by prep-TLC (PE/EA=1/1) to give **Compound 416** (389 mg, 78% yield) as a white solid. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.81 (s, 1H), 7.54 (s, 1H), 7.47-7.34 (m, 5H), 7.24-7.20 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.08 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 366.9.

[1133] **Compound 417**: To the solution of **XLVI-4** (500 mg, 1.7 mmol) in Py (2 mL) was added dimethylcarbamic chloride (365 mg, 3.4 mmol)**.** The mixture was stirred at rt overnight. The reaction was partitioned between EA (100 mL) and H_2O (20 mL). The organic layer was separated, washed with *aq*. HCl (2N) and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE/EA=1/3) to give **Compound 417** (160 mg, 26% yield).**^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.46 (s, 1H), 7.57 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.44-7.41 (m, 2H), 7.39 (s, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 8.8 Hz, 2H), 7.00-6.98 (m, 1H), 6.44 (s, 1H), 2.91 (s, 6H), 2.09 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 365.9.

[1134] **Compound 419**: To the solution of **XLVI-4** (500 mg, 1.7 mmol) in Py (2 mL) was added methylcarbamic chloride (317 mg, 3.4 mmol)**.** The mixture was stirred at rt overnight. The reaction was partitioned between EA (100 mL) and H_2O (20 mL). The organic layer was separated, washed with *aq*. HCl (2N) and brine, dried over anhydrous Na_2SO_4 and concentrated.

The residue was purified by prep-TLC (PE/EA=1/3) to give **Compound 419** (209 mg, 35% yield). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.73 (s, 1H), 7.57 (s, 1H), 7.47-7.42 (m, 3H), 7.38-7.30 (m, 2H), 7.27-7.22 (m, 2H), 6.96 (d, J = 7.2Hz, 1H), 6.46 (s, 1H), 6.11-6.07 (m, 1H), 2.64 (d, J = 4.8Hz, 3H), 2.11 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 351.9.

[1135] **XLVI-4a** was prepared following the similar procedure for obtaining **XLVI-4** by using (4-nitrophenyl)boronic acid in place of **XLVI-2**. **MS (ESI) *m/z*** $(M+H)^+$ 294.9.

[1136] **Compound 418**: To the solution of **XLVI-4a** (500 mg, 1.7 mmol) in DCM (15 mL) was added TMSNCO (978 mg, 8.5 mmol). The mixture was stirred at rt overnight. LCMS showed the reaction was completed. The mixture was filtered and concentrated. The residue was purified by prep-TLC (PE/EA=1/3) to afford **Compound 418** (101 mg, 18% yield). **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.70 (s, 1H), 7.48-7.39 (m, 5H), 7.28-7.20 (m, 4H), 6.41 (s, 1H), 5.89 (s, 2H), 2.08 (s, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 337.9.

[1137] **Compound 560** was prepared by reacting **XLVI-4** with isocyanatoethane in DCM at rt overnight. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.50 (s, 1H), 7.58 (s, 1H), 7.46-7.41 (m, 3H), 7.33-7.24 (m, 4H), 6.95 (d, J=7.2Hz, 1H), 6.45 (s, 1H), 6.08 (d, J=7.2 Hz, 1H), 3.74 (m, 1H), 2.11 (s, 3H), 1.10 (d, J=6.4 Hz, 6H).

[1138] **Compound 561** was prepared by reacting **XLVI-4** with 2-isocyanatopropane in DCM at rt overnight. **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.62 (s, 1H), 7.56 (s, 1H), 7.44-7.39 (m, 3H), 7.32-7.30 (m, 2H), 7.22 (t, J=8.8 Hz, 2H), 6.94-6.92 (m, 1H), 6.43 (s, 1H), 6.15 (t, J=5.6 Hz, 1H), 3.11-3.04 (m, 2H), 2.08 (s, 3H), 7.02 (t, J=7.2 Hz, 3H).

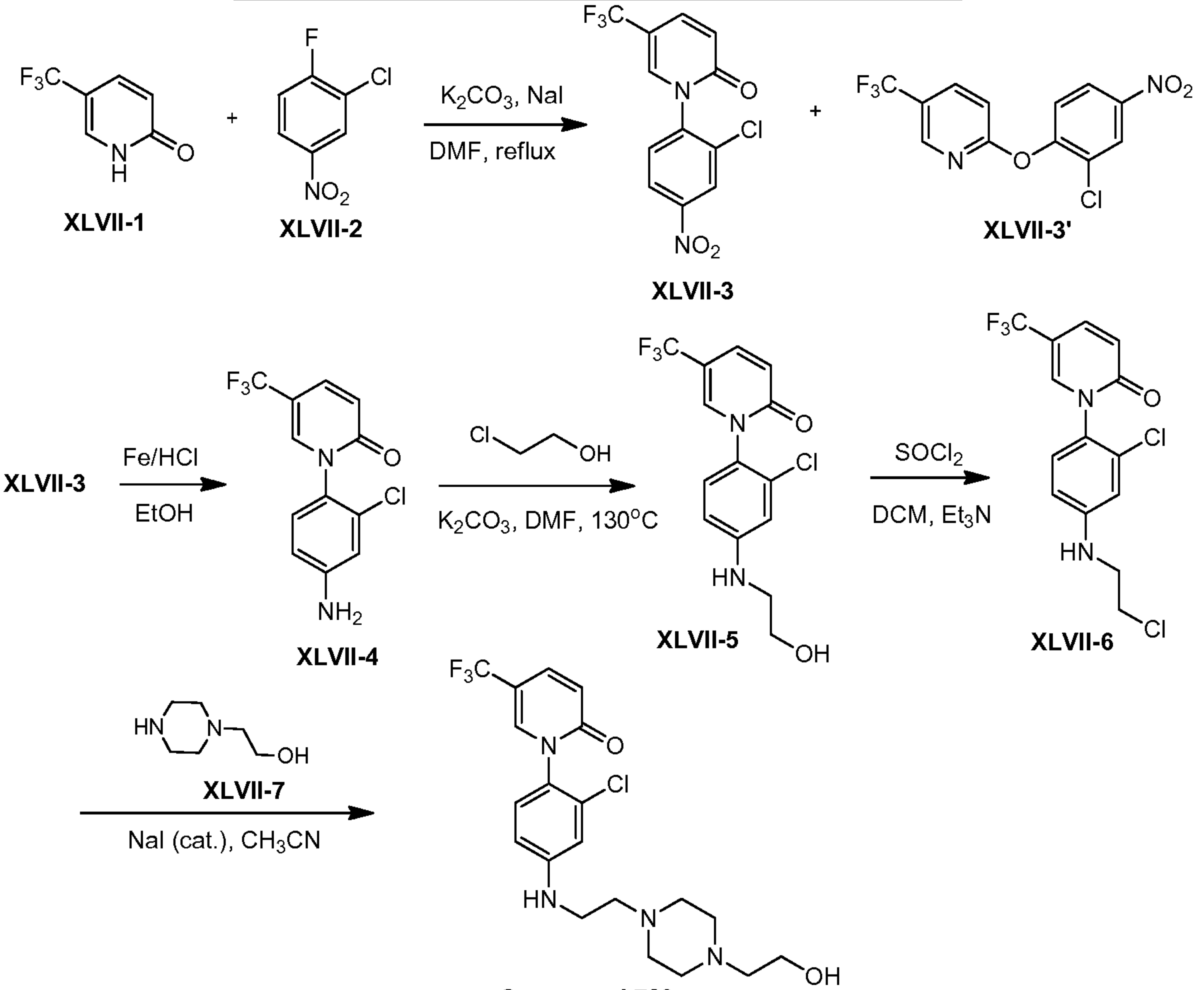
[1139] Additional compounds as shown in Table 1 were also prepared. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein.

[1140] **Compound 666**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.20~8.10 (m, 4H), 7.42~7.40 (m, 2H), 7.27 (m, 2H). **MS (ESI) *m/z*** $[M+H]^+$ 337.0.

[1141] **Compound 667**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.04~8.00 (m, 2H), 7.51~7.49 (m, 1H), 7.20~7.15 (m, 2H), 6.90~6.85 (m, 2H), 4.14~4.09 (q, J = 7.2 Hz, 2H), 2.30 (s, 3H), 1.48~1.44 (t, J = 7.2 Hz, 3H). **MS (ESI) *m/z*** $[M+H]^+$ 311.0.

[1142] **Compound 668**: **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.26 (s, 1H),7.90 (s, 1H), 6.79 (t, J= 8.0Hz, 2H), 5.40 (s, 1H), 4.72 (d, J= 8.0Hz, 1H), 4.49-4.38 (m, 2H), 3.94-3.90 (q, J= 6.4Hz, 1H), 3.81-3.66 (m, 4H), 2.75-2.65 (m, 1H), 2.28-2.16 (m, 4H), 2.05-1.97 (m, 2H), 1.52-1.44 (m, 3H), 1.31-1.25 (m, 3H). **MS (ESI) *m/z*** $(M+H)^+$ 449.1. EE%: 95.5%.

Example 25
5-Haloalkyl Substituted Analogs (Scheme XLVII)


Compound 709

[1143] To a mixture of **XLVII-1** (8.2 g, 50 mmol, 1 eq) in DMF (60 mL) was added **XLVII-2** (13.1 g, 75 mmol, 1.5 eq), K_2CO_3 (11.0 g, 80 mmol, 1.6 eq) and NaI (1.4 g, 9.3 mmol, 0.18 eq). The resulting mixture was refluxed for 4 h under N_2. Then the mixture was cooled to rt and diluted with H_2O and extracted with EA. The combined organic phase was washed with brine, dried over Na_2SO_4, and filtrated. EA was evaporated to allow solid precipitate out. The solid was filtered, and the filter cake was washed with PE to give the pure **XLVII-3** (11.2 g, 70%) as a brown solid. The filtrate was concentrated and purified by flash column chromatography (PE:EA=10:1~1:1) to afford the **XLVII-3'**(1.7 g, 10.6%) as a yellow oil.

[1144] The mixture of **XLVII-3** (9.85 g, 31 mmol, 1 eq) and reductive iron power (5.2 g, 93 mmol, 3 eq) in 80 mL of 50% EtOH was heated to reflux, *conc*.HCl (0.34 mL, 4 mmol) was added dropwise, then the mixture was refluxed for 4h. Then the mixture was cooled to rt, filtered, washed the filter cake with EA, the filtrate was washed with brine, dried over Na_2SO_4, and concentrated to afford **XLVII-4** (8.9 g, crude yield 100%).

[1145] The mixture of **XLVII-4** (6.0 g, 20.8 mmol, 1 eq), chloroethanol (20 mL, 300 mmol, 14.4 eq) and K_2CO_3 (5.75 g, 41.6 mmol, 2 eq) in DMF (50 mL) was stirred at 130°C for 28h. After the mixture was cooled to rt, diluted with H_2O, and extracted with EA, the filtrate was concentrated and the residue was purified to afford **XLVII-5** (2.5 g, 36 %) as a yellow solid.

[1146] The mixture of **XLVII-5** (2.0 g, 6 mmol, 1 eq), $SOCl_2$ (0.65 mL, 9 mmol, 1.5 eq) and Et_3N (1.3 mL, 9 mmol, 1.5 eq) in DCM (50 mL) was stirred at rt for 28h under N_2. The reaction was then quenched with H_2O, extracted with EA, the filtrate was concentrated and the residue was purified to produce **XLVII-6** (1.5 g, 71%) as a yellow solid.

[1147] The mixture of **XLVII-6** (900 mg, 2.6 mmol, 1 eq), **XLVII-7** (1.2 g, 7.8 mmol, 3 eq) and NaI (30 mg, catalytic amount) in CH_3CN (50 mL) was refluxed for 16h under N_2. The solvent was then removed and the resulting residue was purified to give **Compound 709** (420 mg, 37%) as a yellow colloid substance. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.61 (s, 1H), 7.51 (dd, J =2.6, 9.7 Hz, 1H), 7.11 (d, J =8.5 Hz, 1H), 6.76 - 6.70 (m, 2H), 6.58 (dd, J =2.6, 8.7 Hz, 1H), 4.74 (t, J =4.5 Hz, 1H), 3.66 - 3.60 (m, 2H), 3.16 (q, J =5.3 Hz, 2H), 2.72 - 2.44 (m, 12H). **MS (ESI)** ***m/z*** ($M+H^+$) 445.1.

Example 26
ET-1 Assay

Assay of Inhibitory Effect on TGF-b induced Endothelin-1 Production

[1148] Fibroblasts (primary human lung and dermal, HFL-1, 3T3 etc) are seeded in 96-well plates at ~15000 cells/well and serum starved for 0-48 hours. After media exchange, compounds serially diluted in DMSO are added to the cells. After a brief incubation of ~30 min, stimulants (TGFb, serum, LPA etc) are added followed by further incubation for 16-48 hours. Media is then harvested and stored frozen in plate format for later endothelin-1 (ET-1) determination by ELISA. Toxicity measurements are made using the ATPlite kit (Perkin-Elmer). ET-1 is quantified using an ELISA kit (R&D Systems). The amount of ET-1 produced in the assay wells are back-calculated using the ELISA standard. The ability of a compound to inhibit ET-1 production is typically analyzed by fitting dose-response curves to a 4-parameter logistic function to obtain an EC50 value. A measure of cytotoxicity (CC50) is likewise reported from the same experiment using the ATPlite data.

Assay Data for Compounds

[1149] Compounds of some embodiments were prepared according to synthetic methods described herein and assay data obtained for EC_{50} against ET-1. The assay data obtained is presented in Table 2, in which A= less than 50 μM, B = greater than or equal to 50 μM and less than or equal to 200 μM; and C = greater than 200 μM.

TABLE 2.

Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1
10	C	59	A	107	C	154	C
11	C	60	A	108	C	156	C
12	C	61	A	110	C	157	A
13	C	62	C	111	C	158	C
14	C	63	A	112	C	159	C
15	C	64	B	113	C	160	B
17	C	65	C	114	C	161	A
18	C	66	B	115	C	162	A
19	B	67	C	116	C	163	A
21	C	68	C	118	C	164	A
22	C	71	C	119	A	165	B
23	B	73	A	120	A	166	A
24	C	74	B	121	C	167	C
25	C	75	B	122	C	168	B
26	A	77	B	123	A	169	B
27	C	78	C	124	C	170	A
28	B	79	A	125	C	171	B
29	B	80	B	126	A	172	C
31	A	81	B	127	C	173	C
32	C	82	C	128	A	174	A
33	A	83	C	129	B	175	B
34	A	84	C	130	C	176	B
35	A	85	C	131	C	177	B
36	A	86	B	132	C	178	B
37	B	87	A	133	B	180	B
38	C	88	B	134	A	181	C
39	A	89	C	135	B	182	C
40	C	90	C	136	B	183	C
42	C	91	C	137	C	184	B
43	A	92	B	138	C	185	B
44	C	93	A	139	C	186	A
45	C	94	C	140	B	187	B
46	A	95	A	141	C	188	A
47	A	96	C	143	C	189	C
49	A	97	C	144	C	190	B
50	C	98	B	145	B	191	B
51	C	99	A	146	C	192	A
52	C	100	A	147	C	193	B
53	C	101	C	148	C	194	A
54	C	102	C	149	B	195	A
55	C	103	C	150	B	196	B
56	C	104	C	151	A	197	B
57	C	105	C	152	B	198	B
58	A	106	C	153	A	199	B

Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1
200	B	255	C	319	A	380	C
201	B	256	C	320	A	381	C
202	B	257	C	321	A	382	B
203	A	258	A	322	A	383	B
204	A	259	B	323	C	384	B
205	B	260	B	324	B	385	B
206	B	261	C	327	C	387	B
207	B	262	B	328	C	388	C
208	B	263	A	329	C	390	C
209	A	264	C	330	C	391	A
210	A	265	C	331	C	392	C
211	C	266	C	332	C	393	C
212	B	267	C	333	B	394	A
213	C	268	C	334	C	395	B
214	B	269	C	336	C	396	C
216	B	270	C	338	C	397	C
217	C	271	C	344	C	398	C
218	A	272	C	345	C	399	C
219	B	273	C	346	C	400	A
220	C	274	C	347	B	401	C
221	C	275	C	349	C	402	A
222	C	276	C	350	B	403	A
223	C	277	C	351	A	404	A
224	C	278	B	352	B	405	A
225	C	279	C	353	B	406	B
226	C	281	C	354	B	407	A
227	C	282	C	355	C	408	C
228	B	283	C	356	B	409	A
229	B	285	C	357	C	410	A
230	C	287	C	359	C	411	B
231	B	288	B	360	A	412	C
232	C	289	B	361	C	413	A
233	C	290	B	362	C	414	A
234	C	291	C	363	C	415	A
235	B	294	B	364	C	416	A
236	B	296	C	365	C	417	A
237	B	298	B	366	C	418	B
238	B	299	C	367	C	419	B
240	C	300	C	368	C	420	B
241	C	302	B	369	B	421	B
242	C	303	B	370	C	422	C
243	B	309	B	371	C	423	C
244	C	310	B	372	C	424	B
247	C	311	C	373	C	425	A
248	C	312	C	374	A	426	C
250	B	313	B	375	C	427	C
251	A	314	A	376	A	429	C
252	B	315	A	377	B	430	A
253	C	316	A	378	B	431	C
254	A	318	A	379	C	432	C

Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1	Compd. #	EC_{50} ET-1
438	C	566	C	609	A	676	A
439	C	568	C	610	A	677	B
440	C	569	A	611	A	678	B
442	C	570	C	612	A	679	A
526	C	571	C	614	A	680	C
527	A	573	C	615	A	681	B
528	A	574	A	617	A	682	A
529	C	575	A	618	B	683	A
530	A	577	B	619	A	684	B
531	A	579	C	620	A	685	A
532	A	580	A	622	C	686	B
533	B	581	C	623	C	687	A
534	A	582	A	624	A	688	B
535	A	583	A	625	A	689	A
536	A	584	A	626	A	690	A
537	A	585	C	628	A	691	A
540	A	586	A	629	A	692	A
541	C	587	A	631	A	693	B
542	A	588	C	634	A	694	A
543	A	591	A	636	C	695	A
544	B	593	A	647	A	696	B
545	C	594	A	648	A	697	B
546	C	595	A	649	A	698	B
547	A	596	A	650	A	699	B
550	A	597	C	651	A	700	B
552	C	598	A	657	A	701	A
553	A	599	A	665	A	702	A
554	C	600	A	666	A	703	A
555	C	601	A	667	A	704	A
556	C	602	A	669	A	705	A
557	A	603	A	670	A	706	A
558	B	604	A	671	A	707	A
559	A	605	A	672	A	708	B
562	A	606	A	673	A	709	B
563	A	607	A	674	B		
565	A	608	B	675	A		

Example 27
Cell Proliferation Assay

Assay of Inhibitory Effect on Cell Proliferation (BrdU Incorporation)

[1150] Fibroblasts (primary human lung and dermal, HFL-1, 3T3 etc) were plated on a 96-well plate and serum starved for 24-48 hours. The media were then exchanged for media containing stimulants (LPA, TGFb, serum etc) and cultured further for 16-24 hours before BrdU addition. After culturing for another 8 hours, cells were washed with PBS and the amount of BrdU incorporated into the cells was assayed by absorbance at 450 nm using the Cell proliferation ELISA system (RPN250, Amersham LIFE SCIENCE). The difference between the amount of BrdU incorporated in the stimulant-added well and the amount of BrdU incorporated in the well containing no stimulant represented the amount of BrdU incorporation accelerated by stimulant. The increase of BrdU incorporation without the addition of test compounds was set as 100% and the concentration of compound with 50% inhibition in the increase of BrdU incorporation (IC_{50} value) was determined. The test compounds were added 0-30 min before stimulant addition.

Assay Data for Compounds

[1151] Compounds of some embodiments were prepared according to synthetic methods described herein and assay data obtained for IC_{50} for BrdU inhibition. The assay data obtained is presented in Table 3, in which A= less than 50 µM, B = greater than or equal to 50 µM and less than or equal to 200 µM; and C = greater than 200 µM.

TABLE 3.

Compd. #	IC_{50} BRDU	Compd. #	IC_{50} BRDU	Compd. #	IC_{50} BRDU	Compd. #	IC_{50} BRDU
13	C	126	A	219	C	383	B
21	C	133	B	229	A	385	A
28	B	134	A	234	C	387	B
29	C	153	A	237	A	391	B
31	B	155	A	238	A	394	A
41	A	157	C	239	A	395	B
43	C	160	A	243	C	399	A
46	A	161	A	251	A	400	A
47	A	162	A	252	B	402	C
49	A	175	A	254	A	403	A
50	A	180	A	258	A	404	A
51	C	184	A	259	A	405	A
52	C	185	A	260	A	406	A
53	C	188	A	261	A	407	A
58	A	189	C	262	A	410	A
59	A	192	A	263	A	411	A
60	A	195	A	276	C	413	A
61	A	196	A	278	B	414	A
63	A	198	A	282	C	415	A
68	C	201	A	285	C	416	A
71	C	202	A	290	C	417	A
73	C	203	A	300	C	418	B
75	B	204	A	316	A	419	B
80	C	206	A	333	C	424	A
86	A	207	A	350	B	425	A
87	A	208	B	351	B	430	A
101	B	209	A	353	C	431	B
119	A	210	C	360	B	432	B
120	A	216	A	374	B	531	A
123	A	218	A	376	C	535	A

Compd. #	IC_{50} BRDU	Compd. #	IC_{50} BRDU	Compd. #	IC_{50} BRDU	Compd. #	IC_{50} BRDU
538	B	575	A	610	A	650	A
542	A	583	A	615	A	651	A
543	A	584	A	617	B	657	A
544	A	588	A	618	B	658	C
547	A	591	C	619	A	662	C
550	A	594	A	620	A	664	A
551	A	595	B	624	A	665	B
553	A	600	C	625	A	681	A
557	A	601	A	626	A	682	A
562	A	602	A	629	C	683	A
563	A	603	A	631	C	684	A
564	A	604	A	636	C	685	A
565	A	605	A	640	C	686	A
569	A	606	A	647	A	687	A
570	C	607	A	648	A	688	B
574	A	609	A	649	B	689	A

[1152] While the disclosure has been illustrated and described in detail in the foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive. The disclosure is not limited to the disclosed embodiments. Variations to the disclosed embodiments can be understood and effected by those skilled in the art in practicing the claimed disclosure, from a study of the drawings, the disclosure and the appended claims.

[1153] All references cited herein are incorporated herein by reference in their entirety. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[1154] Unless otherwise defined, all terms (including technical and scientific terms) are to be given their ordinary and customary meaning to a person of ordinary skill in the art, and are not to be limited to a special or customized meaning unless expressly so defined herein. It should be noted that the use of particular terminology when describing certain features or aspects of the disclosure should not be taken to imply that the terminology is being re-defined herein to be restricted to include any specific characteristics of the features or aspects of the disclosure with which that terminology is associated.

[1155] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[1156] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term ‘including’ should be read to mean ‘including, without limitation,’ ‘including but not limited to,’ or the like; the term ‘comprising’ as used herein is synonymous with ‘including,’ ‘containing,’ or ‘characterized by,’ and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term ‘having’ should be interpreted as ‘having at least;’ the term ‘includes’ should be interpreted as ‘includes but is not limited to;’ the term ‘example’ is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; adjectives such as ‘known’, ‘normal’, ‘standard’, and terms of similar meaning should not be construed as limiting the item described to a given time period or to an item available as of a given time, but instead should be read to encompass known, normal, or standard technologies that may be available or known now or at any time in the future; and use of terms like ‘preferably,’ ‘preferred,’ ‘desired,’ or ‘desirable,’ and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function of the invention, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the invention. Likewise, a group of items linked with the conjunction 'and' should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as 'and/or' unless expressly stated otherwise. Similarly, a group of items linked with the conjunction 'or' should not be read as requiring mutual exclusivity among that group, but rather should be read as 'and/or' unless expressly stated otherwise.

[1157] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. A single processor or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[1158] It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (*e.g.,* "a" and/or "an" should typically be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation *is* explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean *at least* the recited number (*e.g.,* the bare recitation of "two recitations," without other modifiers, typically means *at least* two recitations, or *two or more* recitations). Furthermore, in those instances where a convention analogous to "at least one of

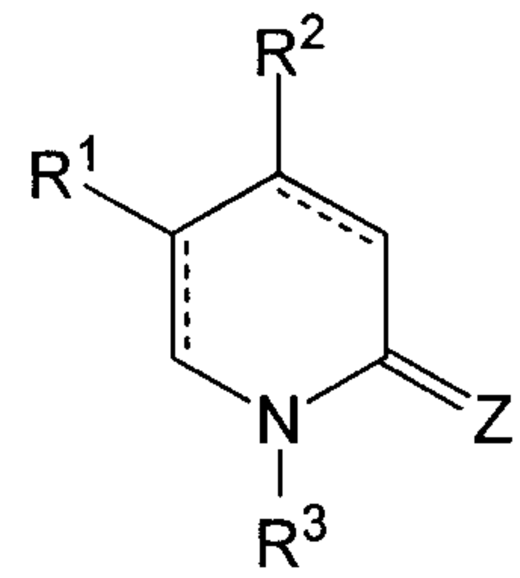
A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g.,* "a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g.,* "a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

[1159] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term 'about.' Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[1160] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it is apparent to those skilled in the art that certain changes and modifications may be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention to the specific embodiments and examples described herein, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. A compound having the structure of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of halogen, -CN, -C(O)R^8, -SO_2R^{16}, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

R^2 is selected from the group consisting of halogen, -CN, -OR^5, -SR^5, -NR^6R^7, and -C(O)R^8;

R^3 is selected from the group consisting of hydrogen, phenyl, -$(CH_2)_n$-(5-10 membered heteroaryl), -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more

R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form a 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^9 is independently selected from the group consisting of hydroxy, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -N$R^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, -CN, and –NO_2;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -O-$(CH_2)_n$-C_{1-8} alkoxy, -C(O)R^8, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond, provided that

when R^3 is H, then R^1 is selected from C_{6-10} aryl optionally substituted with one or more R^4, or 5-10 membered heteroaryl optionally substituted with one or more R^4;

when R^3 is a phenyl; R^2 is OR^5 or NR^6R^7; then R^1 is not triazolyl;

when R^3 is 4-methyl phenyl, R^2 is morpholinyl, and Z is O; then R^1 is not methyl; and

when R^3 is 4-methyl phenyl, R^2 is $-N(CH_3)_2$, Z is O; then R^1 is not methyl.

2. The compound of Claim 1, wherein

R^2 is selected from the group consisting of halogen, $-OR^5$, $-NR^6R^7$, and $-C(O)R^8$;

R^3 is selected from the group consisting of phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), $-(CH_2)_n-(C_{3-10}$ carbocyclyl), and $-(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$; and

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy.

3. The compound of Claim 1 or 2, wherein R^1 is a C_{6-10} aryl optionally substituted with one or more R^4.

4. The compound of Claim 3, wherein R^1 is a phenyl optionally substituted with one or more R^4.

5. The compound of Claim 1 or 2, wherein R^1 is a 5-10 membered heteroaryl optionally substituted with one or more R^4.

6. The compound of Claim 5, wherein R^1 is a pyrazolyl or 1-methyl pyrazolyl optionally substituted with one or more R^4.

7. The compound of any one of Claims 1 to 6, wherein each R^4 is independently selected from halogen, or optionally substituted C_{1-6} alkyl.

8. The compound of Claim 7, wherein R^4 is fluoro.

9. The compound of Claims 7, wherein R^4 is methyl.

10. The compound of any one of Claims 1 to 9, wherein R^2 is halogen.

11. The compound of Claim 10, wherein R^2 is selected from bromo or chloro.

12. The compound of any one of Claims 1 to 9, wherein R^2 is –CN.

13. The compound of any one of Claims 1 to 9, wherein R^2 is $-OR^5$.

14. The compound of Claim 13, wherein R^5 is selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, C_{7-14} aralkyl optionally

substituted with one or more R^{11}, C_{6-10} aryl optionally substituted with one or more R^{11}, and $-(CH_2)_n-$(3-10 membered heterocyclyl) optionally substituted with one or more R^{10}.

15. The compound of Claim 14, wherein R^5 is hydrogen.

16. The compound of Claim 14, wherein R^5 is optionally substituted C_{1-6} alkyl.

17. The compound of Claim 16, wherein R^5 is methyl or halogen substituted ethyl.

18. The compound of Claim 14, wherein R^5 is C_{6-10} aryl optionally substituted with one or more R^{11}.

19. The compound of Claim 18, wherein R^5 is phenyl optionally substituted with one or more R^{11}.

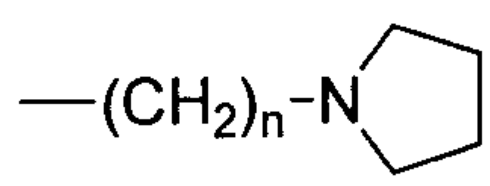
20. The compound of Claim 14, wherein R^5 is C_{7-14} aralkyl optionally substituted with one or more R^{11}.

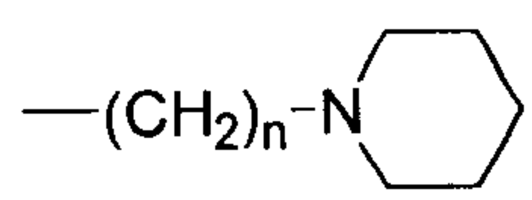
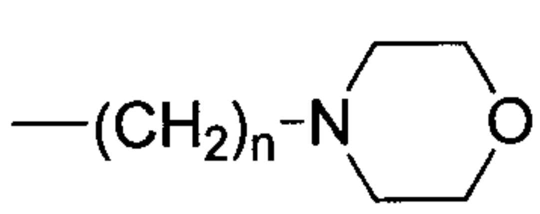
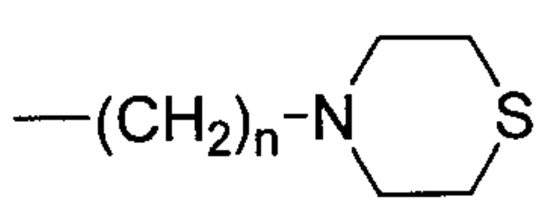
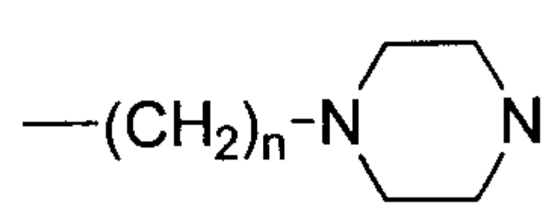
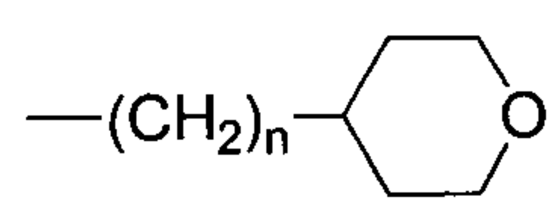
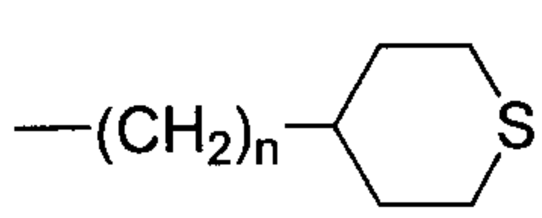
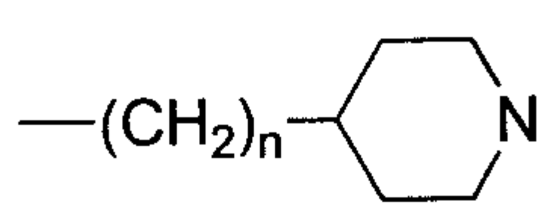
21. The compound of Claim 20, wherein R^5 is benzyl optionally substituted with one or more R^{11}.

22. The compound of Claim 14, wherein R^5 is optionally substituted C_{2-8} alkoxyalkyl.

23. The compound of Claim 22, wherein R^5 is selected from $-(CH_2)_2OCH_3$, $-(CH_2)_2OC_3H_7$ or $-(CH_2)_2O(CH_2)OCH_3$.

24. The compound of Claim 14, wherein R^5 is $-(CH_2)_n-$(5 or 6 membered heterocyclyl) optionally substituted with one or more R^{10}.

25. The compound of Claim 24, wherein R^5 is  optionally substituted with one or more R^{10}.

26. The compound of Claim 24, wherein R^5 is selected from , , , or , , , or , each optionally substituted with one or more R^{10}.

27. The compound of any one of Claims 1 to 9, wherein R^2 is $-NR^6R^7$.

28. The compound of Claim 27, wherein each R^6 and R^7 is independently selected from hydrogen, C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl

optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, or -C(O)OR^5.

29. The compound of Claim 28, wherein R^6 is hydrogen or C_{1-6} alkyl.

30. The compound of Claim 28 or 29, wherein R^7 is hydrogen.

31. The compound of Claim 28 or 29, wherein R^7 is C_{1-6} alkyl.

32. The compound of Claim 28 or 29, wherein R^7 is C_{6-10} aryl optionally substituted with one or more R^{11}.

33. The compound of Claim 32, wherein R^7 is phenyl optionally substituted with one or more R^{11}.

34. The compound of Claim 32, wherein R^7 is unsubstituted phenyl.

35. The compound of Claim 28 or 29, wherein R^7 is C_{7-14} aralkyl optionally substituted with one or more R^{11}.

36. The compound of Claim 35, wherein R^7 is benzyl or –$(CH_2)_2$Ph, each optionally substituted with one or more R^{11}.

37. The compound of Claim 35, wherein R^7 is unsubstituted benzyl or unsubstituted -$(CH_2)_2$Ph.

38. The compound of Claim 28 or 29, wherein R^7 is (6 membered heteroaryl)alkyl optionally substituted with one or more R^{11}.

39. The compound of Claim 38, wherein R^7 is –CH_2-pyridyl, –CH_2-pyrazinyl, or -CH_2-pyrimidinyl, each optionally substituted with one or more R^{11}.

40. The compound of Claim 38, wherein R^7 is –CH_2-pyridyl, –CH_2-pyrazinyl or - CH_2-pyrimidinyl, each unsubstituted.

41. The compound of Claim 28 or 29, wherein R^7 is -C(O)R^8.

42. The compound of Claim 41, wherein R^8 is selected from C_{1-6} alkyl, C_{6-10} aryl, or -N$R^{12}R^{13}$.

43. The compound of Claim 42, wherein R^8 is selected from methyl, ethyl, propyl, isopropyl, butyl, pentyl or phenyl.

44. The compound of Claim 42, wherein R^8 is -N$R^{12}R^{13}$.

45. The compound of Claim 44, wherein each R^{12} and R^{13} is independently selected from hydrogen, C_{1-6} alkyl, or benzyl.

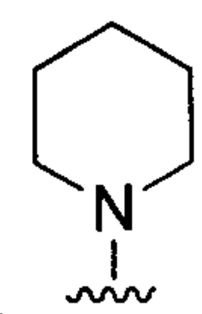
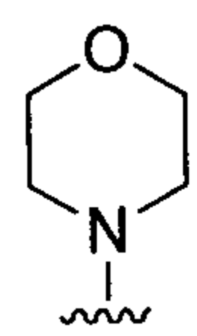
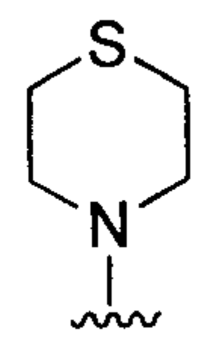
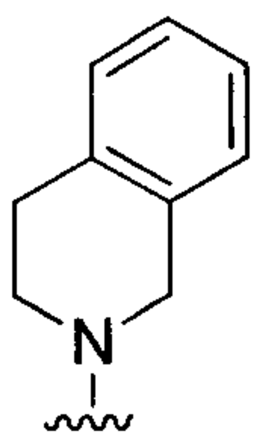
46. The compound of Claim 28 or 29, wherein R^7 is -C(O)OR^5.

47. The compound of Claim 46, wherein R^5 is selected from hydrogen, C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, or C_{7-14} aralkyl optionally substituted with one or more R^{11}.

48. The compound of Claim 47, wherein R^5 is selected from methyl, ethyl, isopropyl, butyl.

49. The compound of Claim 47, wherein R^5 is selected from phenyl or benzyl, each optionally substituted with one or more R^{11}.

50. The compound of Claim 27, wherein R^6 and R^7 together with the nitrogen to which they are attached form a 6-10 membered heterocyclyl optionally substituted with one or more R^{10}.

51. The compound of Claim 50, wherein the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached is selected from  ,  ,  , or  , each optionally substituted with one or more R^{10}.

52. The compound of Claim 50 or 51, wherein the heterocyclyl formed by R^6 and R^7 together with the nitrogen to which they are attached is unsubstituted.

53. The compound of any one of Claims 1 to 52, wherein R^{10} is C_{1-6} alkyl.

54. The compound of any one of Claims 1 to 52, wherein two geminal R^{10} together are oxo.

55. The compound of any one of Claims 1 to 9, wherein R^2 is -SR^5.

56. The compound of Claim 55, wherein R^5 is C_{6-10} aryl optionally substituted with one or more R^{11}.

57. The compound of Claim 55 or 56, wherein R^5 is optionally substituted phenyl.

58. The compound of any one of Claims 1 to 9, wherein R^2 is -C(O)R^8.

59. The compound of Claim 58, wherein R^8 is selected from -NR^{12}R^{13}.

60. The compound of Claim 59, wherein each R^{12} and R^{13} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, or C_{7-14} aralkyl optionally substituted with one or more R^{11}.

61. The compound of Claim 60, wherein each R^{12} and R^{13} is independently selected from hydrogen, C_{1-6} alkyl, phenyl optionally substituted with one or more R^{11}, or benzyl optionally substituted with one or more R^{11}.

62. The compound of Claim 61, wherein the phenyl or benzyl is unsubstituted.

63. The compound of any one of Claims 1 to 9, wherein R^2 is -C(O)OR^5.

64. The compound of Claim 63, wherein R^5 is hydrogen or C_{1-6} alkyl.

65. The compound of any one of Claims 1 to 64, wherein each R^{11} is independently selected from –CN, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, -O-$(CH_2)_n$-C_{1-8} alkoxy, or -C(O) $NR^{12}R^{13}$.

66. The compound of Claim 65, wherein R^{11} is selected from -CN, -Cl, -F, $-CH_3$, $-OCH_3$, $-OC_2H_5$, $-CF_3$, $-OCF_3$, -O-$(CH_2)_2$-OCH_3, or -C(O)NH_2.

67. The compound of any one of Claims 1 to 66, wherein R^3 is phenyl optionally substituted with one or more R^9.

68. The compound of Claim 67 , wherein R^9 is selected from hydroxy, halogen, optionally substituted C_{1-6} alkyl, –OR^5, or -NR^{14}R^{15}.

69. The compound of Claim 68, wherein R^9 is selected from hydroxy, fluoro, chloro, methyl, ethyl, or trifluoromethyl.

70. The compound of Claim 68, wherein R^9 is –OR^5.

71. The compound of Claim 70, wherein R^5 is selected from hydrogen, C_{1-6} alkyl, halo substituted C_{1-6} alkyl, or C_{2-8} alkoxyalkyl.

72. The compound of Claim 71, wherein R^5 is selected from trifluoromethyl, ethyl or $-(CH_2)_2OCH_3$.

73. The compound of Claim 68, wherein R^9 is -NH-C(O)R^8.

74. The compound of Claim 73, wherein R^9 is selected from -NH-C(O)-C_{1-6} alkyl, or -NH-C(O)-NH_2.

75. The compound of Claims 67 , wherein R^3 is unsubstituted.

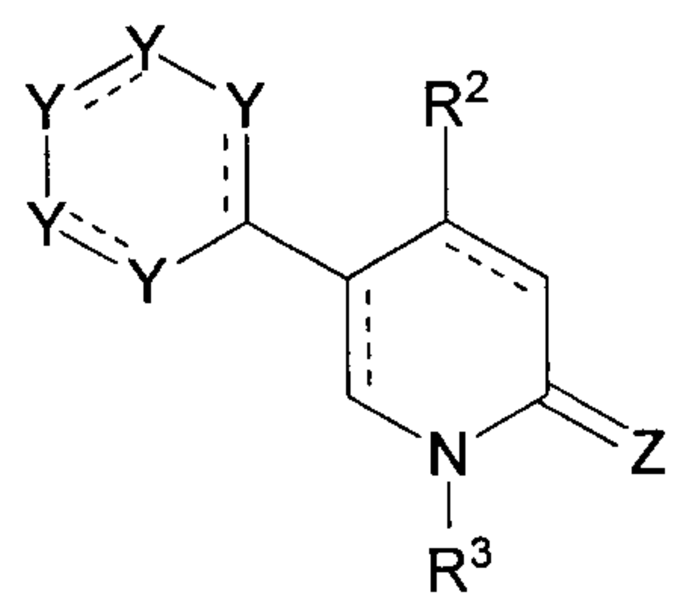
76. The compound of any one of Claims 1 and 3 to 66, wherein R^3 is hydrogen.

77. The compound of any one of Claims 1 to 75, wherein Z is oxygen.

78. The compound of any one of Claims 1 to 77, wherein the bonds represented by a solid and dashed line are double bonds.

79. The compound of Claim 1, wherein the compound is selected from the group consisting of **Compounds 85-162, 401-414, 523-545, 550, 551, 664** and **696-707** of Table 1, or pharmaceutically acceptable salts thereof.

80. A compound having the structure of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^2 is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl;

R^3 is selected from the group consisting of hydrogen, $-(CH_2)_n-(C_{6-10}$ aryl), $-(CH_2)_n-$(5-10 membered heteroaryl), $-(CH_2)_n-(C_{3-10}$ carbocyclyl), and $-(CH_2)_n-$(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

Y is selected from N and CR^4;

each R^4 is independently selected from the group consisting of hydrogen, halogen, -CN, -OH, $-C(O)R^8$, $-SO_2R^{16}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11},

or independently two adjacent R^4 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl, optionally substituted C_{3-7} carbocyclyl, and optionally substituted 3-7 membered heterocyclyl;

each R^9 is independently selected from the group consisting of hydroxy, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, -CN, and $-NO_2$;

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and $-(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

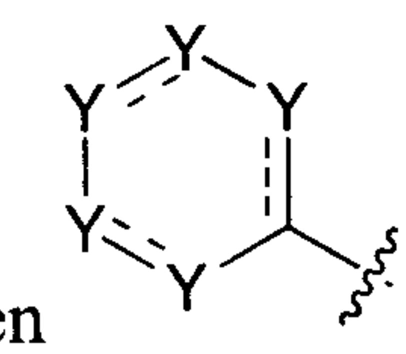
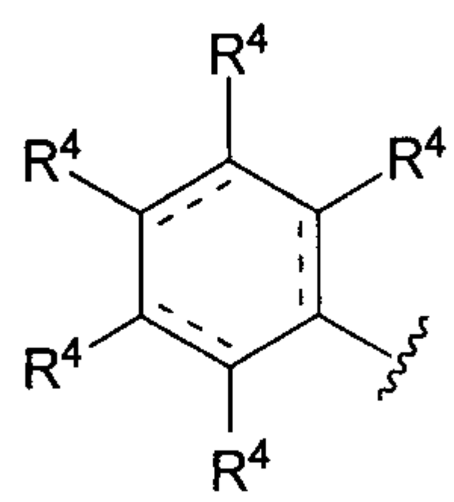
each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

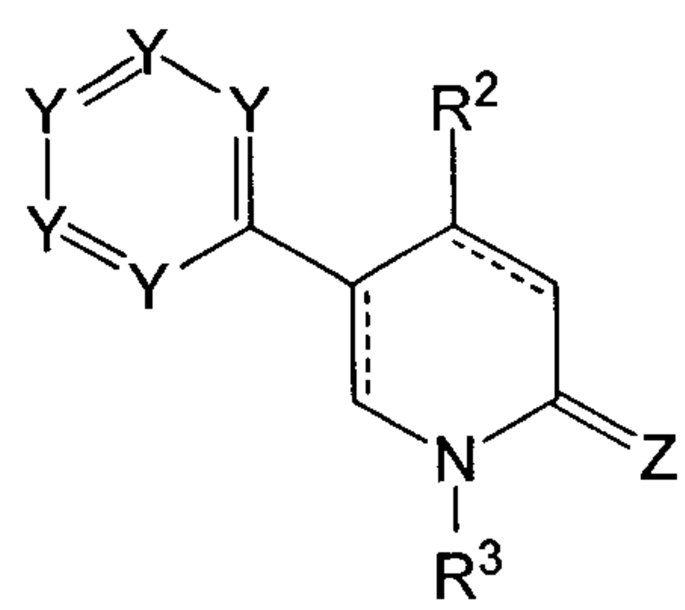
Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

81. The compound of Claim 80, wherein if R^3 is hydrogen, then  is , and the two adjacent R^4 together with the carbon atoms to which they are attached form a fused ring selected from optionally substituted 5 or 6 membered heteroaryl or optionally substituted 5 or 6 membered heterocyclyl.

82. The compound of Claim 80, wherein formula (II) is also represented by formula (IIa):



(IIa)

R^3 is selected from the group consisting of $-(CH_2)_n-(C_{6-10}$ aryl), $-(CH_2)_n-$(5-10 membered heteroaryl), $-(CH_2)_n-(C_{3-10}$ carbocyclyl), and $-(CH_2)_n-$(3-10 membered heterocyclyl), each optionally substituted with one or more R^9; and each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$.

83. The compound of any one of Claims 80 to 82, wherein R^2 is selected from optionally substituted C_{1-6} alkyl.

84. The compound of Claim 83, wherein R^2 is selected from methyl, ethyl, isopropyl, or trifluoromethyl.

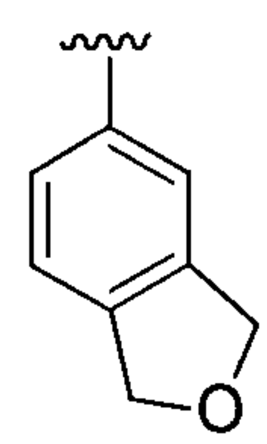
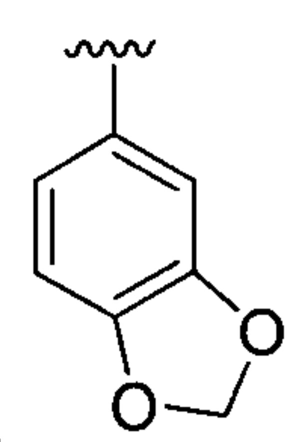
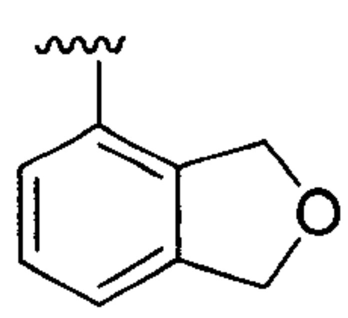
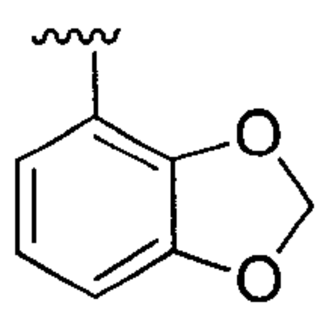
85. The compound of Claim 84, wherein R^2 is methyl.

86. The compound of any one of Claims 80, 81, and 83 to 85, wherein R^3 is hydrogen.

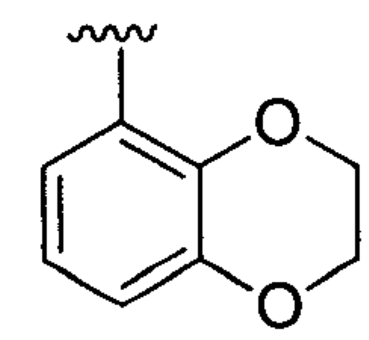
87. The compound of any one of Claims 80 to 85, wherein R^3 is selected from $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9.

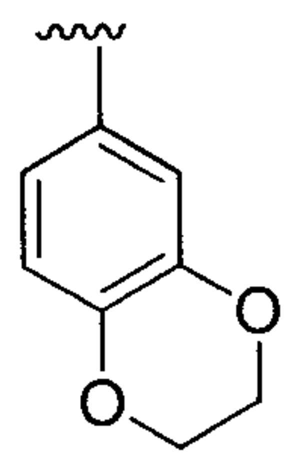
88. The compound of Claim 87, wherein R^3 is $-(CH_2)_n$-phenyl optionally substituted with one or more R^9.

89. The compound of any one of Claims 80 and 82 to 85, wherein R^3 is selected from $-(CH_2)_n$-(9 membered heterocyclyl), optionally substituted with one or more R^9.

90. The compound of Claim 89, wherein R^3 is selected from , ,  or , each optionally substituted with one or more R^9.

91. The compound of any one of Claims 80 and 82 to 85, wherein R^3 is selected from $-(CH_2)_n$-(10 membered heterocyclyl), optionally substituted with one or more R^9.

92. The compound of Claim 91, wherein R^3 is selected from  or



, each optionally substituted with one or more R^9.

93. The compound of any one of Claims 87 to 92, wherein n is 0.

94. The compound of any one of Claims 80 to 93, wherein each R^9 is independently selected from cyano, halogen, optionally substituted C_{1-6} alkyl, $-OR^5$, $-NR^{14}R^{15}$ or $-C(O)R^8$.

95. The compound of Claim 94, wherein R^9 is selected from methyl, ethyl, propyl isopropyl, or trifluoromethyl.

96. The compound of Claim 94, wherein R^9 is selected from fluoro or chloro.

97. The compound of Claim 94, wherein R^9 is $-OR^5$, and wherein R^5 is selected from optionally substituted C_{1-6} alkyl.

98. The compound of Claim 94 or 97, wherein R^5 is selected from methyl, ethyl, propyl, isopropyl or trifluoromethyl.

99. The compound of Claim 94, wherein R^9 is $-NR^{14}R^{15}$, and wherein each R^{14} and R^{15} is independently selected from hydrogen, C_{1-6} alkyl or $-C(O)R^8$.

100. The compound of Claim 99, wherein R^8 is selected from optionally substituted C_{1-6} alkyl, $-OR^5$ or $-NR^{12}R^{13}$.

101. The compound of Claim 100, wherein each R^{12} and R^{13} is independently selected from hydrogen or C_{1-6} alkyl.

102. The compound of Claim 100, wherein R^5 is selected from hydrogen or C_{1-6} alkyl.

103. The compound of any one of Claims 94 and 99 to 101, wherein each R^{14} and R^{15} is independently selected from hydrogen, methyl, ethyl, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)OH$ or $-C(O)OEt$.

104. The compound of Claim 94, wherein R^9 is $-C(O)R^8$.

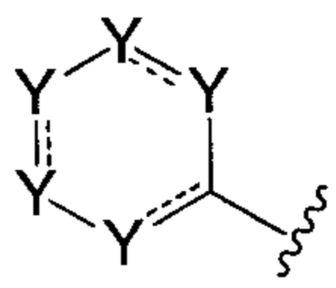
105. The compound of Claim 94 or 104, wherein R^8 is selected from optionally substituted C_{1-6} alkyl or $-NR^{12}R^{13}$.

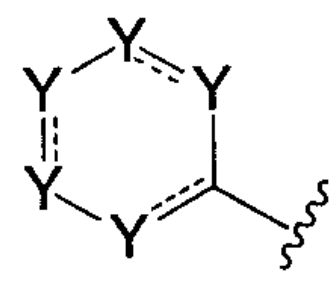
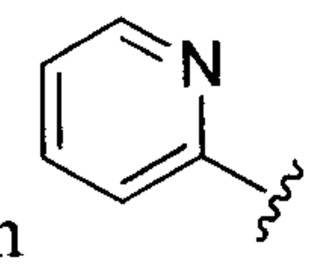
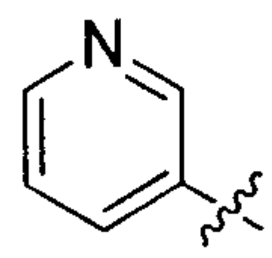
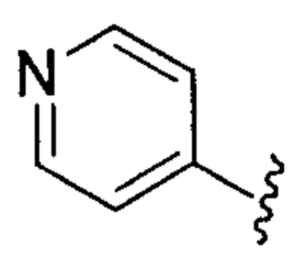
106. The compound of Claim 105, wherein each of R^{12} or R^{13} is independently selected from hydrogen or C_{1-6} alkyl.

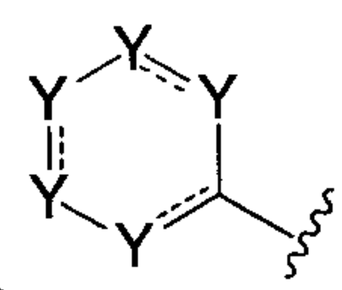
107. The compound of any one of Claims 87 to 93, wherein R^3 is unsubstituted.

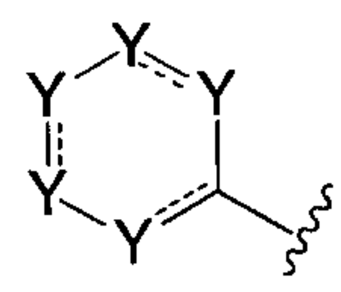
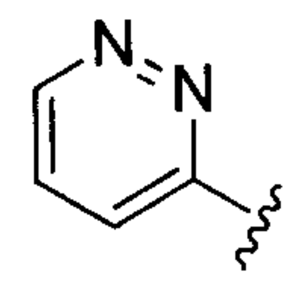
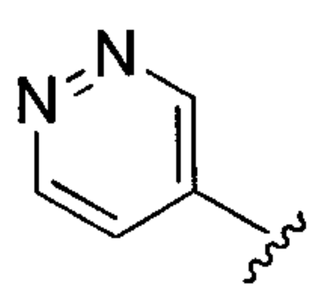
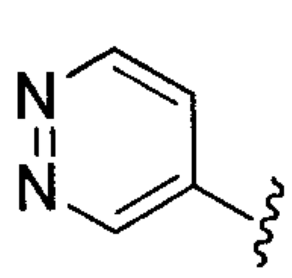
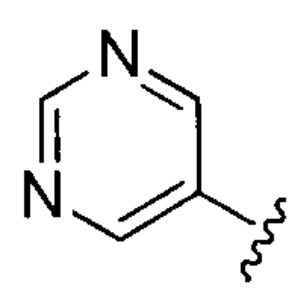
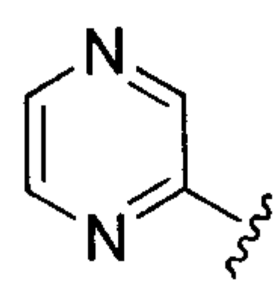
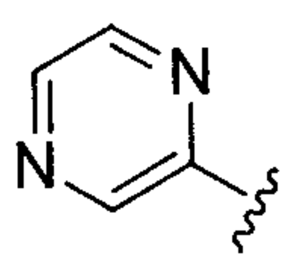
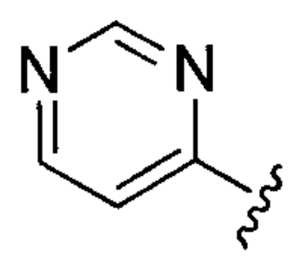
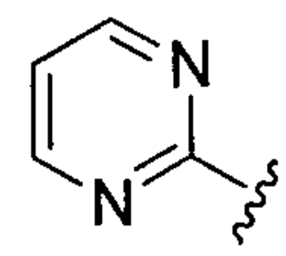
108. The compound of any one of Claims 80 to 107, wherein all Y is CR^4.

109. The compound of any one of Claims 80 to 107, wherein at least one Y in

 is N.

110. The compound of Claim 109, wherein  is selected from , , or , each optionally substituted with one to four R^4.

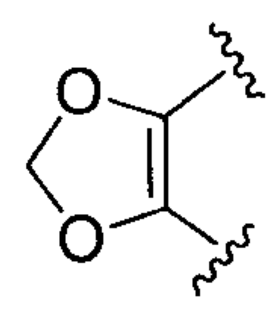
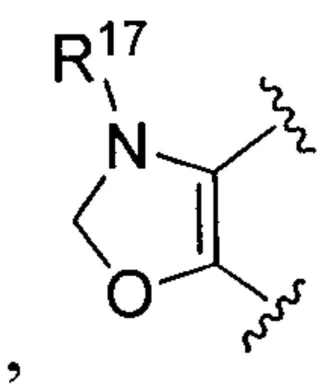
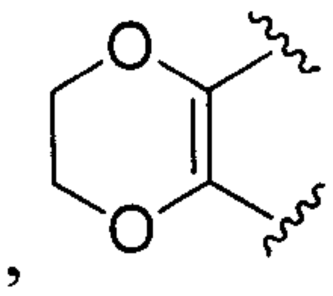
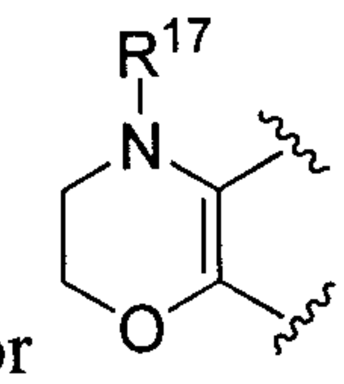
111. The compound of Claim 109, wherein two of Y in  are N.

112. The compound of Claim 111, wherein  is selected from , , , , , ,  or , each optionally substituted with one to three R^4.

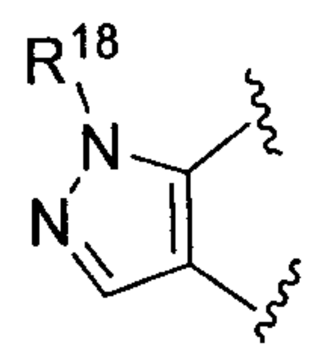
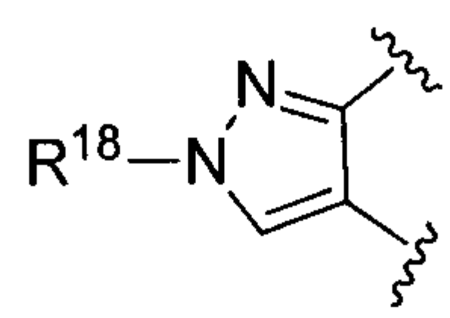
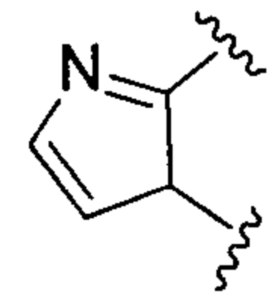
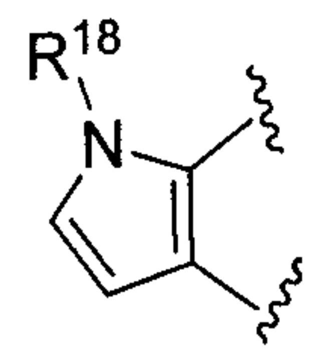
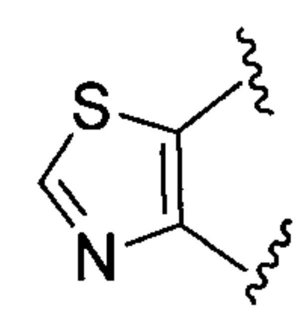
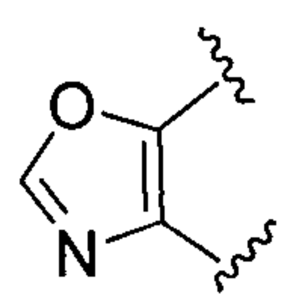
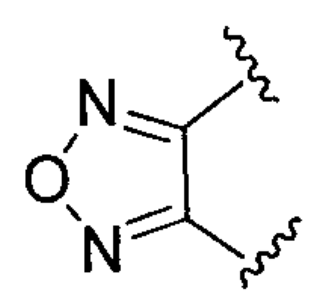
113. The compound of any one of Claims 80 to 112, wherein R^4 is selected from hydrogen, halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy or 5 membered heteroaryl optionally substituted with one or more R^{11}.

114. The compound of Claim 113, wherein R^4 is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or thiazolyl.

115. The compound of any one of Claims 80 to 112, wherein two adjacent R^4 together with the carbon atoms to which they are attached form a fused ring selected from optionally substituted 5 or 6 membered heteroaryl or optionally substituted 5 or 6 membered heterocyclyl.

116. The compound of Claim 115, wherein the optionally substituted 5 or 6 membered heterocyclyl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from , , , or , wherein each R^{17} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, or optionally substituted C_{2-8} alkoxyalkyl.

117. The compound of Claim 116, wherein R^{17} is selected from hydrogen, methyl, ethyl, $-(CH_2)_2OH$ or $-(CH_2)_2OCH_3$.

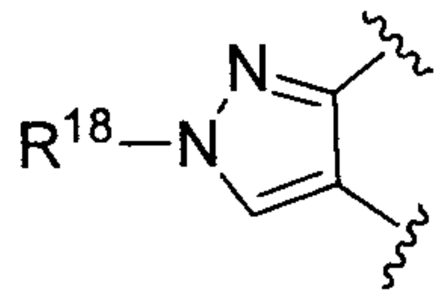
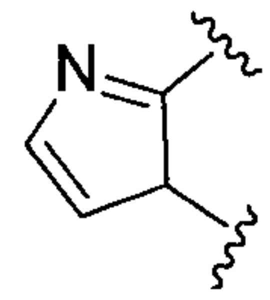
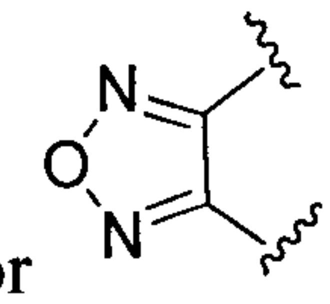
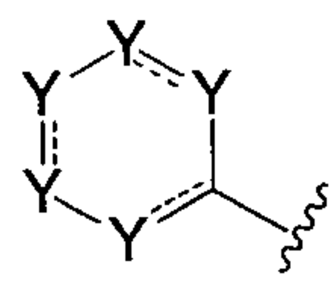
118. The compound of Claim 115, wherein the optionally substituted 5 or 6 membered heteroaryl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from , , , , ,  or , wherein each R^{18} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, or optionally substituted C_{2-8} alkoxyalkyl.

119. The compound of Claim 118, wherein R^{18} is selected from hydrogen or methyl.

120. The compound of any one of Claims 115 to 119, wherein the substituent on the 5 or 6 membered heteroaryl or 5 or 6 membered heterocyclyl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from C_{1-6} alkyl, C_{1-6} alkoxy, oxo or halogen.

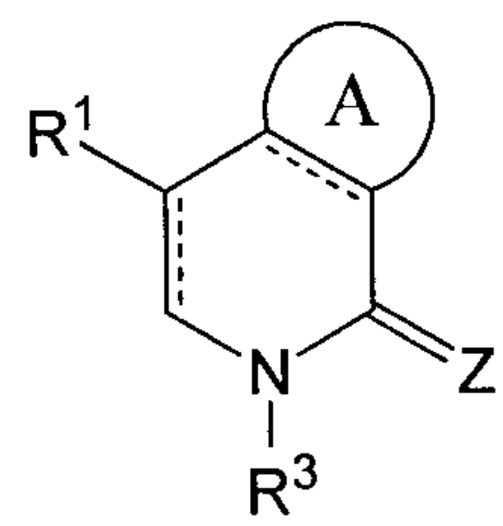
121. The compound of Claim 120, wherein the substituent on the 5 or 6 membered heteroaryl or 5 or 6 membered heterocyclyl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from methyl, fluoro, or oxo.

122. The compound of any one of Claims 80 to 121, wherein Z is oxygen.

123. The compound of any one of Claims 80, 81 and 83 to 122, wherein the bonds represented by a solid and dashed line are double bonds, provided that when the optionally substituted 5 or 6 membered heteroaryl formed by two adjacent R^4 together with the carbon atoms to which they are attached is selected from , , or , one of the bonds represented by a solid and dashed line in  is a single bond.

124. The compound of Claim 80, wherein the compound is selected from the group consisting of **Compounds 163-216, 241-243, 245, 246, 248-252, 254, 255, 258-261, 263, 415-430, 552-561, 566** and **629** of Table 1, or pharmaceutically acceptable salts thereof.

125. A compound having the structure of formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of bromo, chloro, fluoro, -CN, $-C(O)R^8$, $-SO_2R^{16}$, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5 to 6 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

R^3 is selected from the group consisting of hydrogen, phenyl, $-(CH_2)_n$-(5-10 membered heteroaryl), and 3-10 membered heterocyclyl, each optionally substituted with one or more R^9;

ring A is selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^9 is independently selected from the group consisting of hydroxy, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -$NR^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, -CN, and –NO_2;

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -$NR^{12}R^{13}$, and -OR^5;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and $-(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond, provided that

when R^3 is hydrogen, then R^1 is selected from C_{6-10} aryl optionally substituted with one or more R^4, or 5 to 6 membered heteroaryl optionally substituted with one or more R^4;

when R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then ring A cannot be optionally substituted phenyl;

when ring A is selected from cyclopentenyl, optionally substituted pyrrolyl or optionally substituted dihydropyrrolidinyl, R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then R^1 is not bromo, chloro, fluoro, 3-methoxy phenyl or 3,5-dimethoxy phenyl;

when ring A is pyridyl, R^1 is optionally substituted phenyl, and Z is O; then n in R^3 is zero and R^3 is not halogen substituted phenyl;

when ring A is optionally substituted pyrimidyl, R^3 is phenyl or benzyl, and Z is O; then R^1 is not methyl or benzyl;

when ring A is optionally substituted furanyl, R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then R^1 is not fluoro;

when ring A is optionally substituted pyrrolyl, R^3 is phenyl optionally substituted with one or more R^9, and Z is O; then R^1 is not methyl;

when ring A is tetrahydrofuranyl, R^3 is phenyl, and Z is O; then R^1 is not methyl or phenyl; and

when ring A is pyradizinyl, R^3 is 4-NO_2-phenyl, and Z is O; then R^1 is not methyl.

126. The compound of Claim 125, wherein

R^3 is selected from the group consisting of phenyl, -$(CH_2)_n$-(5-10 membered heteroaryl), and 3-10 membered heterocyclyl, each optionally substituted with one or more R^9; and

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -$NR^{14}R^{15}$, -$C(O)R^8$, -SO_2R^{16}, and –NO_2.

127. The compound of Claim 125, wherein R^1 is selected from bromo, chloro, fluoro, C_{1-6} alkyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, or 5 to 6 membered heteroaryl optionally substituted with one or more R^4.

128. The compound of Claim 127, wherein R^1 is bromo or fluoro.

129. The compound of Claim 127, wherein R^1 is methyl optionally substituted with one or more R^4.

130. The compound of Claim 127, wherein R^1 is phenyl optionally substituted with one or more R^4.

131. The compound of Claim 127, wherein R^1 is pyridazinyl optionally substituted with one or more R^4.

132. The compound of Claim 127, wherein R^1 is pyrazolyl or 1-methyl pyrazolyl optionally substituted with one or more R^4.

133. The compound of any one of Claims 125 to 132, wherein R^3 is hydrogen.

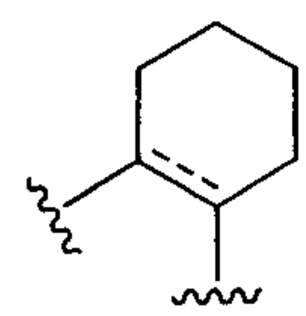
134. The compound of any one of Claims 125 to 132, wherein R^3 is selected from phenyl optionally substituted with one or more R^9.

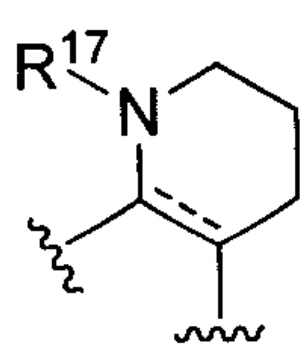
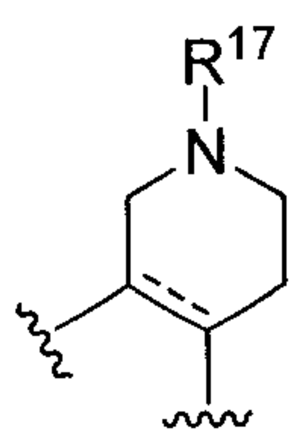
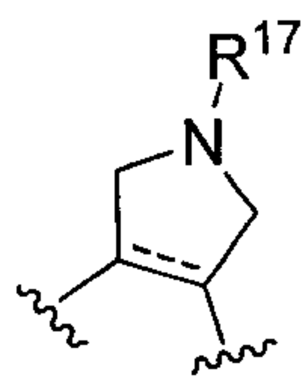
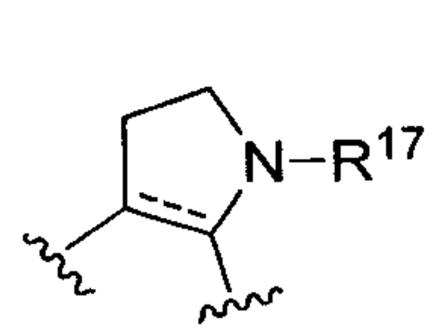
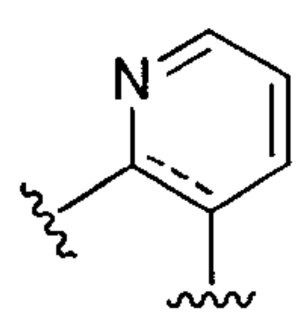
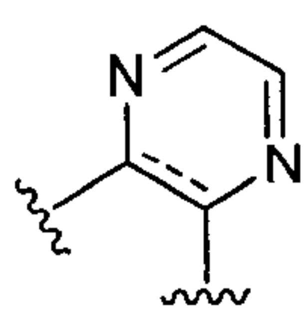
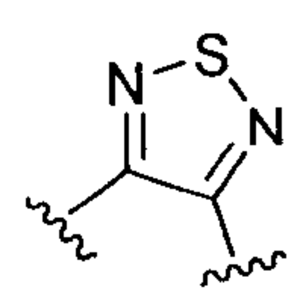
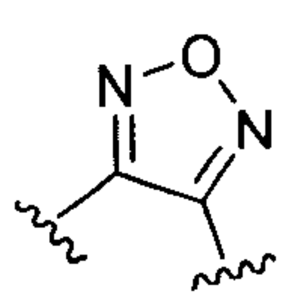
135. The compound of Claim 134, wherein R^3 is unsubstituted.

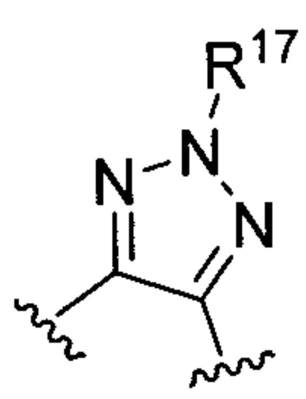
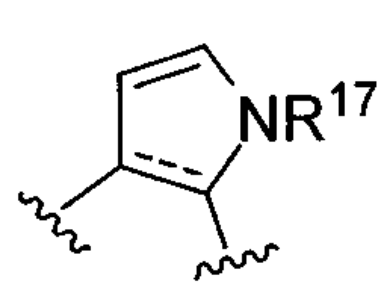
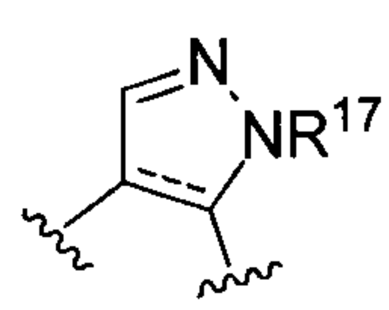
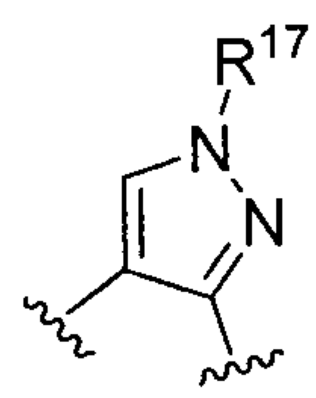
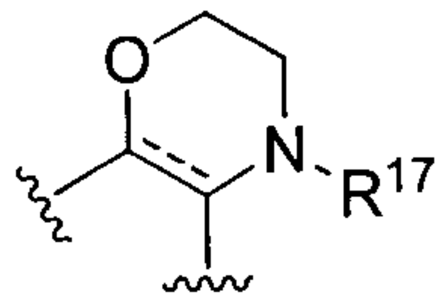
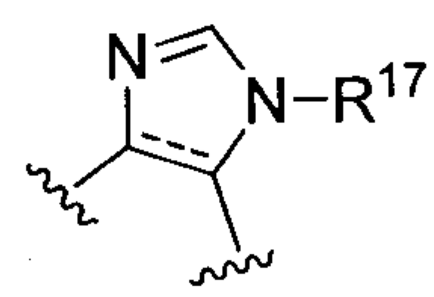
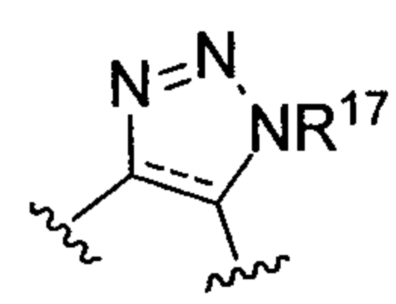
136. The compound of Claim 134, wherein R^9 is selected from cyano, halogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy.

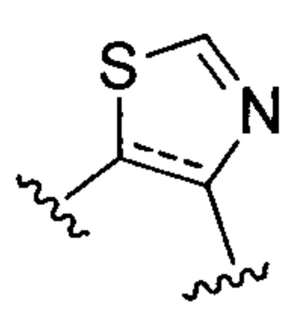
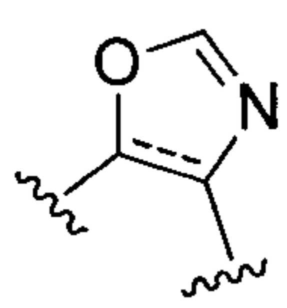
137. The compound of Claim 136, wherein R^9 is selected from cyano, fluoro, chloro, methyl, ethyl, ethoxy, methoxy, trifluoromethyl, trifluoromethoxy or difluoromethoxy.

138. The compound of any one of Claims 125 to 137, wherein ring A is selected from C_{3-10} carbocyclyl, 5-membered heteroaryl, 6-membered heteroaryl, 5-membered heterocyclyl or 6-membered heterocyclyl, each optionally substituted with one or more R^4.

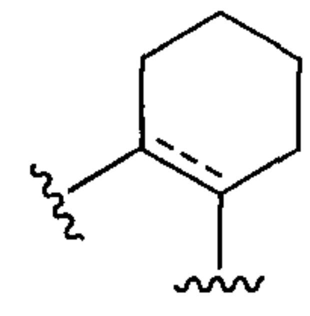
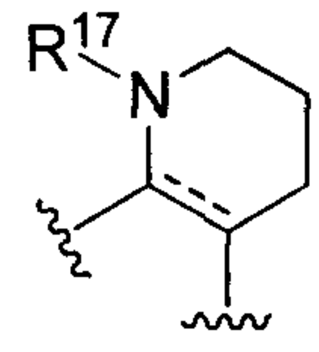
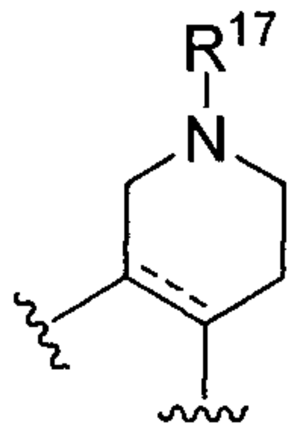
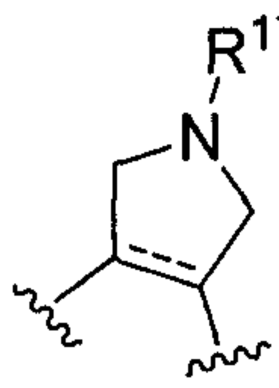
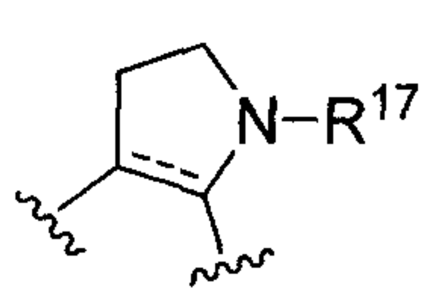
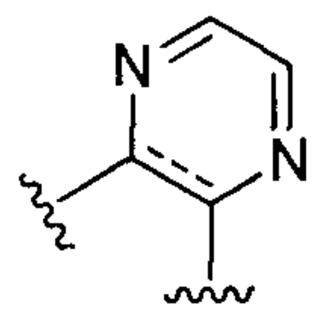
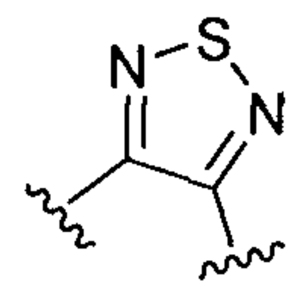
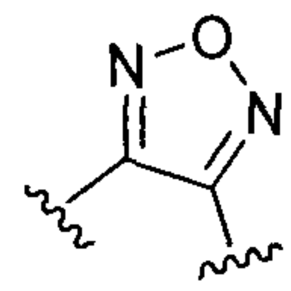
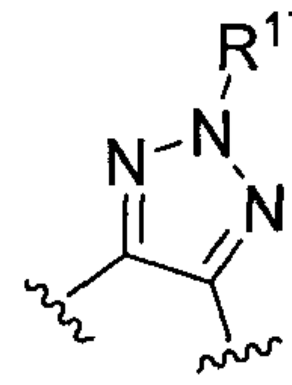
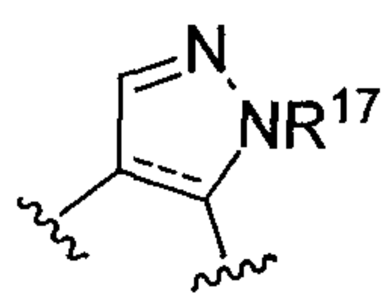
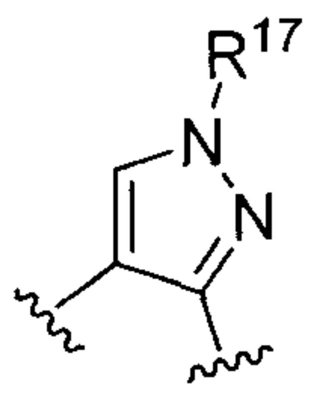
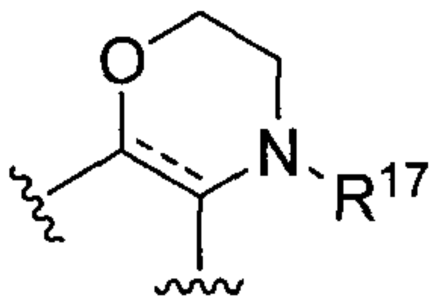
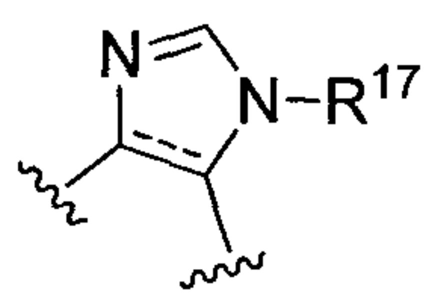
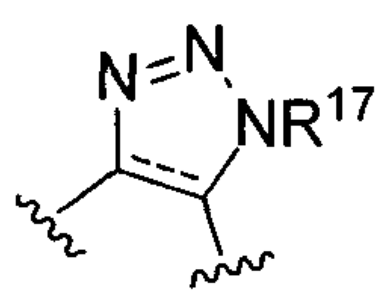
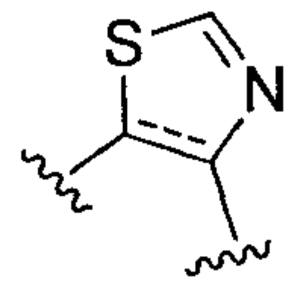
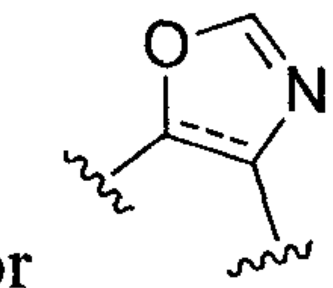
139. The compound of Claim 138, wherein ring A is selected from ,

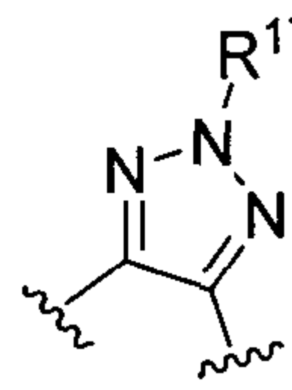
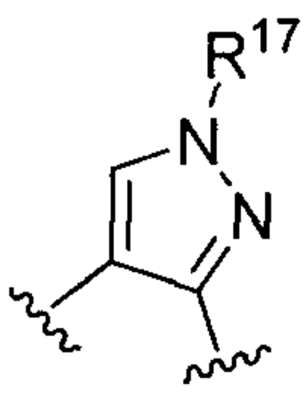
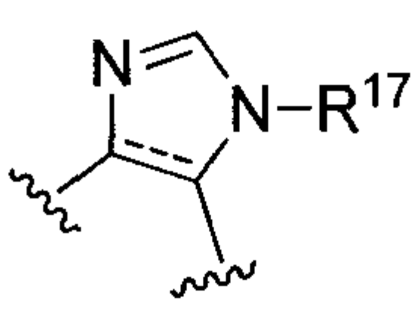
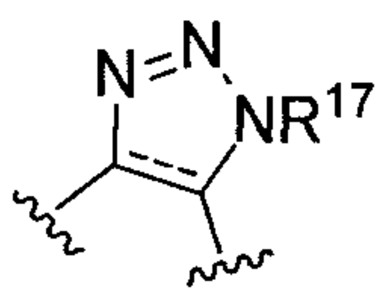
, , , , , , , ,

, , , , , , ,

 or , each optionally substituted with one or more R^4; and wherein each R^{17} is independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally

substituted C_{3-6} cycloalkyl, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C-carboxy, acyl, C_{6-10} aryl optionally substituted with one or more R^{11}, or C_{7-14} aralkyl optionally substituted with one or more R^{11}.

140. The compound of Claim 139, ring A is selected from , , , , , , , , , , , , , ,  or , each optionally substituted with one or more R^4.

141. The compound of Claim 139 or 140, wherein ring A is selected from , ,  or , each optionally substituted with one or more R^4.

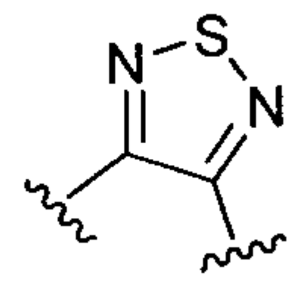
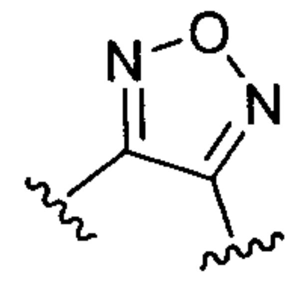
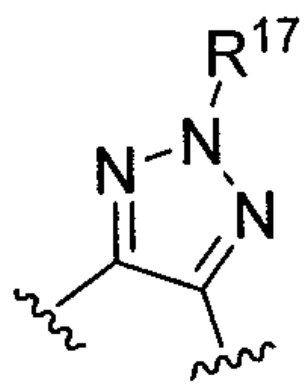
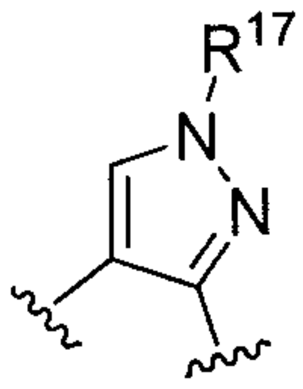
142. The compound of any one of Claims 139 to 141, wherein R^{17} is selected from hydrogen, methyl, ethyl, isopropyl, cyclopropyl, $-(CH_2)_2F$, $-(CH_2)_2OH$, $-(CH_2)_2OCH_3$, $-(CH_2)_2OC_2H_5$, $-(CH_2)_2OC_3H_7$, -C(O)O-*t*-Bu, $-C(O)CH_3$ or benzyl.

143. The compound of any one of Claims 125 to 142, wherein R^4 is selected from halogen, optionally substituted C_{1-6} alkyl, or C_{7-14} aralkyl optionally substituted with one or more R^{11}, or two geminal R^4 together are oxo.

144. The compound of Claim 143, wherein R^4 is selected from fluoro, methyl, trifluoromethyl, $-(CH_2)_2OH$, benzyl, or two geminal R^4 together are oxo.

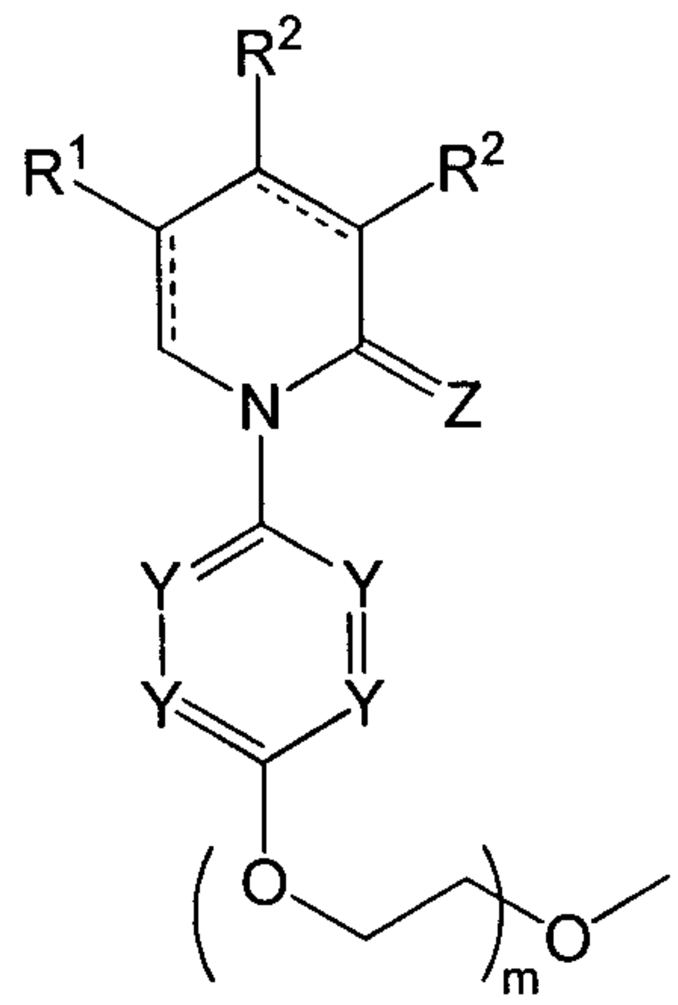
145. The compound of any one of Claim 138 to 142, wherein ring A is unsubstituted.

146. The compound of any one of Claims 125 to 145, wherein Z is oxygen.

147. The compound of any one of Claims 125 to 146, wherein the bonds represented by a solid and dashed line are double bonds, provided that when ring A is , , , or , one of the bonds represented by a solid and dashed line is a single bond.

148. The compound of Claim 125, wherein the compound is selected from the group consisting of **Compounds 29-63**, **392-400**, **568, 569, 571-574, 576-584, 586-608, 611-626, 631, 634-638, 640, 642-655, 657-661**, **665**, and **669-695** of Table 1, or pharmaceutically acceptable salts thereof.

149. A compound having the structure of formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -$C(O)R^8$,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10}, and -$(CH_2)_n$-(C_{6-10} aryl) optionally substituted with one or more R^{11};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -$C(O)R^8$, and -$C(O)OR^5$;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -$C(O)R^8$, and -$C(O)OR^5$;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-NR^{12}R^{13}$, and $-OR^5$;

each Y is independently N or CR^9;

each R^9 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, and $-NR^{14}R^{15}$,

or independently two adjacent R^9 together with the ring atoms to which they are attached form a fused optionally substituted 3-10 membered heterocyclyl or a fused optionally substituted 5-10 membered heteroaryl;

each R^{10} is independently selected from the group consisting of oxo, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

Z is selected from oxygen and sulfur;

n is an integer from 0 to 4;

m is an integer from 1 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

150. The compound of Claim 149, wherein R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with one or more R^4, or 5-membered heteroaryl optionally substituted with one or more R^4.

151. The compound of Claim 150, wherein R^1 is selected from methyl, phenyl, pyrazolyl, or 1-methyl pyrazolyl, each optionally substituted with one or more R^4.

152. The compound of Claim 151, wherein R^1 is unsubstituted.

153. The compound of any one of Claims 149 to 151, wherein R^2 is selected from hydrogen or optionally substituted C_{1-6} alkyl.

154. The compound of any one of Claims 149 to 153, wherein all Y are CR^9.

155. The compound of any one of Claims 149 to 153, wherein at least one Y is N.

156. The compound of any one of Claims 149 to 155, wherein R^4 is selected from halogen, C_{1-6} alkyl or C_{1-6} alkoxy.

157. The compound of Claim 156, wherein R^4 is selected from fluoro or methyl.

158. The compound of any one of Claims 149 to 157, wherein m is 1.

159. The compound of any one of Claims 149 to 157, wherein m is 2.

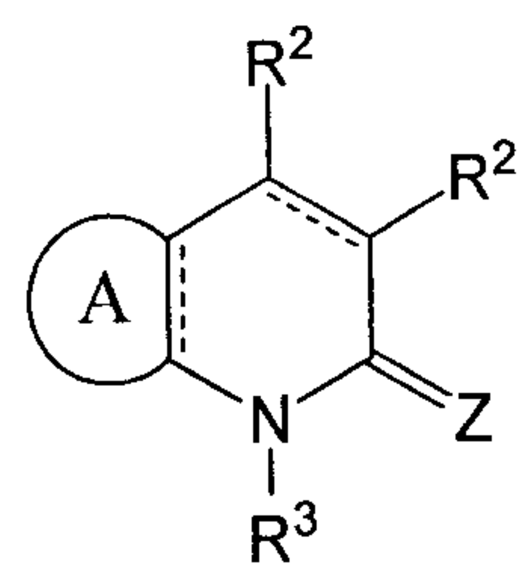
160. The compound of any one of Claims 149 to 157, wherein m is 3.

161. The compound of any one of Claims 149 to 160, wherein Z is oxygen.

162. The compound of any one of Claims 149 to 161, wherein the bonds represented by a solid and dashed line are double bonds.

163. The compound of Claim 149, wherein the compound is selected from the group consisting of **Compounds 21-26** of Table 1, or pharmaceutically acceptable salts thereof.

164. A compound having the structure of formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

A is a C_{5-7} carbocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -C(O)R^8,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of phenyl, -$(CH_2)_n$-(5-10 membered heteroaryl), and -$(CH_2)_n$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, $-C(O)R^8$, and $-C(O)OR^5$;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

165. The compound of Claim 164, wherein each R^2 is independently selected from hydrogen, C_{1-6} alkyl or $-OR^5$.

166. The compound of Claim 165, wherein R^2 is hydrogen.

167. The compound of any one of Claims 164 to 166, wherein R^3 is phenyl, optionally substituted with one or more R^9.

168. The compound of Claim 167, wherein R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, or $-NR^{14}R^{15}$.

169. The compound of Claim 168, wherein R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

170. The compound of Claim 169, wherein R^9 is trifluoromethoxy.

171. The compound of any one of Claims 164 to 170, wherein ring A is a C_5 carbocyclyl optionally substituted with one or more R^4.

172. The compound of any one of Claims 164 to 170, wherein ring A is a C_6 carbocyclyl optionally substituted with one or more R^4.

173. The compound of any one of Claims 164 to 172, wherein R^4 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, or independently two geminal R^4 together are oxo.

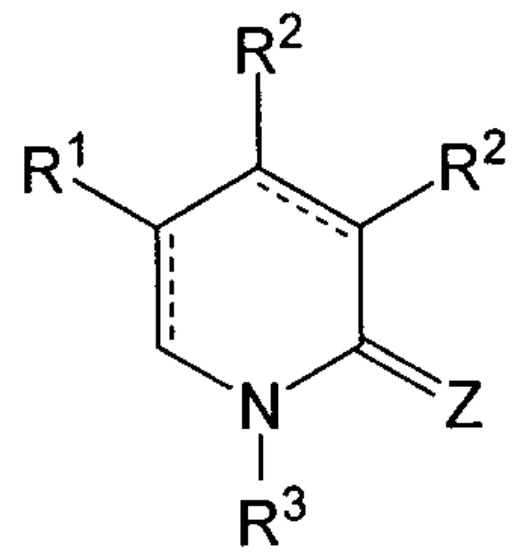
174. The compound of any one of Claims 164, 171 and 172, wherein ring A is unsubstituted.

175. The compound of any one of Claims 164 to 174, wherein Z is oxygen.

176. The compound of any one of Claims 164 to 175, wherein the bonds represented by a solid and dashed line are double bonds.

177. The compound of Claim 164, wherein the compound is selected from the group consisting of **Compounds 27** and **28** of Table 1, or pharmaceutically acceptable salts thereof.

178. A compound having the structure of formula (VIa):



(VIa)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is a C_{4-7} carbocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, $-OR^5$, $-NR^6R^7$, and $-C(O)R^8$,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of $-(CH_2)_n-(C_{6-10}$ aryl), $-(CH_2)_n-$(5-10 membered heteroaryl), $-(CH_2)_n-(C_{3-10}$ carbocyclyl), and $-(CH_2)_n-$(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, $-C(O)R^8$, $-SO_2R^{16}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -N$R^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, and –NO_2;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

179. The compound of Claim 178, wherein R^1 is a C_4 carbocyclyl optionally substituted with one or more R^4.

180. The compound of Claim 178, wherein R^1 is a C_5 carbocyclyl optionally substituted with one or more R^4.

181. The compound of Claim 178, wherein R^1 is a C_6 carbocyclyl optionally substituted with one or more R^4.

182. The compound of any one of Claims 178 to 181, wherein R^4 is selected from halogen, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkoxy.

183. The compound of Claim 182, wherein R^4 is selected from fluoro, chloro, methyl, methoxy, ethoxy, trifluoromethyl, or trifluoromethoxy.

184. The compound of Claim 178, wherein R^1 is unsubstituted.

185. The compound of any one of Claims 178 to 184, wherein each R^2 is independently selected from hydrogen, halogen, optionally substituted C_{1-6} alkyl, $-OR^5$ or $-NR^6R^7$.

186. The compound of Claim 185, wherein R^2 is hydrogen.

187. The compound of Claim 185, wherein R^2 is halogen.

188. The compound of Claim 185, wherein R^2 is optionally substituted C_{1-6} alkyl.

189. The compound of Claim 188, wherein R^2 is selected from methyl or trifluoromethyl.

190. The compound of any one of Claims 178 to 189, wherein R^3 is selected from $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9.

191. The compound of Claim 190, wherein R^3 is phenyl, optionally substituted with one or more R^9.

192. The compound of Claim 191, wherein R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, or $-NR^{14}R^{15}$.

193. The compound of Claim 192, wherein R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

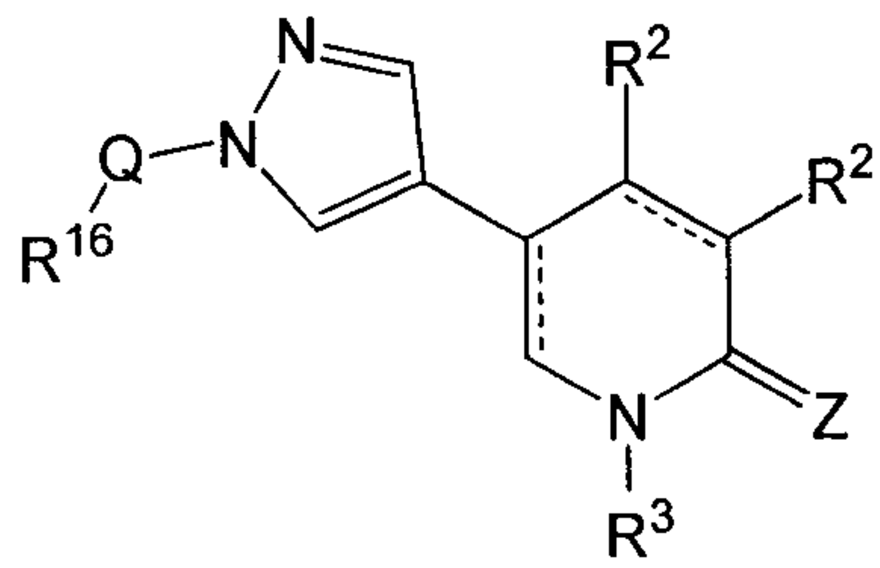
194. The compound of Claim 191, wherein R^3 is unsubstituted phenyl.

195. The compound of any one of Claims 178 to 194, wherein Z is oxygen.

196. The compound of any one of Claims 178 to 195, wherein the bonds represented by a solid and dashed line are double bonds.

197. The compound of Claim 178, wherein the compound is selected from the group consisting of **Compounds 64-66** of Table 1, or pharmaceutically acceptable salts thereof.

198. A compound having the structure of formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof, wherein

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, $-OR^5$, $-NR^6R^7$, and $-C(O)R^8$,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of phenyl, 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of $-(CH_2)_n-(C_{6-10}$ aryl), $-(CH_2)_n-$(5-10 membered heteroaryl), $-(CH_2)_n-(C_{3-10}$ carbocyclyl), and $-(CH_2)_n-$(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, $-C(O)R^8$, $-SO_2R^{16}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and $-(CH_2)_n-$(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -N$R^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, and –NO_2;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

Q is selected from C(O) and $S(O)_t$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4;

t is 1 or 2; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

199. The compound of Claim 198, wherein each R^2 is independently selected from hydrogen, halogen, optionally substituted C_{1-6} alkyl, $-OR^5$ or $-NR^6R^7$.

200. The compound of Claim 199, wherein R^2 is hydrogen.

201. The compound of Claim 199, wherein R^2 is halogen.

202. The compound of Claim 199, wherein R^2 is optionally substituted C_{1-6} alkyl.

203. The compound of Claim 202, wherein R^2 is methyl or trifluoromethyl.

204. The compound of any one of Claims 198 to 203, wherein R^3 is selected from $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9.

205. The compound of Claim 204, wherein R^3 is phenyl optionally substituted with one or more R^9.

206. The compound of Claim 205, wherein R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, or $-NR^{14}R^{15}$.

207. The compound of Claim 206, wherein R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

208. The compound of Claim 205, wherein R^3 is unsubstituted phenyl.

209. The compound of any one of Claims 198 to 208, wherein Q is C(O).

210. The compound of any one of Claims 198 to 208, wherein Q is $S(O)_t$.

211. The compound of Claim 210, wherein t is 2.

212. The compound of any one of Claims 198 to 211, wherein R^{16} is selected from optionally substituted C_{1-6} alkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, or $-OR^5$.

213. The compound of Claim 212, wherein R^{16} is optionally substituted C_{1-6} alkyl.

214. The compound of Claim 213, wherein R^{16} is selected from methyl, ethyl, propyl, isopropyl, or butyl.

215. The compound of Claim 212, wherein R^{16} is phenyl optionally substituted with one or more R^{11}.

216. The compound of Claim 215, wherein R^{16} is unsubstituted phenyl.

217. The compound of Claim 212, wherein R^{16} is benzyl optionally substituted with one or more R^{11}.

218. The compound of Claim 217, wherein R^{16} is unsubstituted benzyl.

219. The compound of Claim 212, wherein R^{16} is $-NR^{12}R^{13}$.

220. The compound of Claim 219, wherein each R^{12} and R^{13} is independently selected from hydrogen or optionally substituted C_{1-6} alkyl.

221. The compound of Claim 212, wherein R^{16} is $-OR^5$.

222. The compound of Claim 221, wherein R^5 is selected from hydrogen or optionally substituted C_{1-6} alkyl.

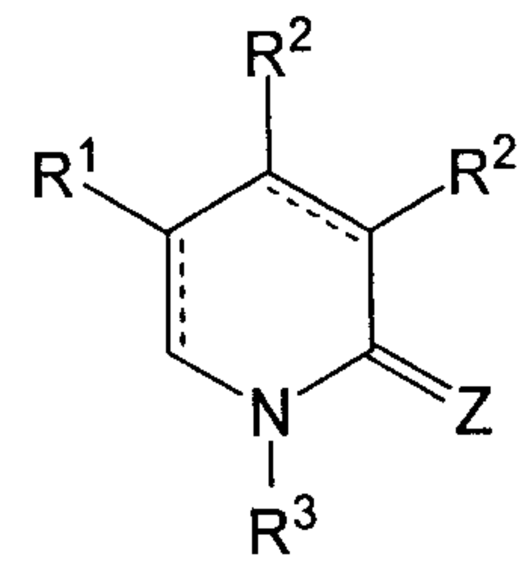
223. The compound of Claim 222, wherein R^5 is selected from methyl, ethyl, propyl, isopropyl, or butyl.

224. The compound of any one of Claims 198 to 223, wherein Z is oxygen.

225. The compound of any one of Claims 198 to 224, wherein the bonds represented by a solid and dashed line are double bonds.

226. The compound of Claim 198, wherein the compound is selected from the group consisting of **Compounds 67-76** of Table 1, or pharmaceutically acceptable salts thereof.

227. A compound having the structure of formula (VIb):



(VIb)

R^1 is selected from the group consisting of bromo, chloro, fluoro, -CN, -C(O)R^8, -SO_2R^{16}, C_{1-6} alkyl, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5 to 6 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -C(O)R^8,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of 5-6 membered heteroaryl, C_{3-7} carbocyclyl, and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of -$(CH_2)_{1-4}$-(C_{6-10} aryl), -$(CH_2)_{1-4}$-(5-10 membered heteroaryl), -$(CH_2)_{1-4}$-(C_{3-10} carbocyclyl), and -$(CH_2)_{1-4}$-(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-}

$_{14}$ aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11};

each R^5 is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, -OR^5, -N$R^{14}R^{15}$, -C(O)R^8, -SO_2R^{16}, and –NO_2;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond; provided that

when R^1 is selected from the group consisting of optionally substituted C_{6-10} aryl, optionally substituted 5 to 6 membered heteroaryl, optionally substituted 6 to 10 membered heterocyclyl, optionally substituted hexyl, C_{1-6}alkyl, optionally substituted C_{2-6} alkenyl; each of R^2 is hydrogen or one of R^2 is hydrogen and the other R^2 is methyl;

and Z is O; then R^3 is not -CH_2-phenyl substituted with one or more halogen atoms; and provided that

R^1 is not 4-methoxy phenyl.

228. The compound of Claim 227, wherein R^1 is selected from C_{1-6} alkyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, or 5to 6 membered heteroaryl optionally substituted with one or more R^4.

229. The compound of Claim 228, wherein R^1 is selected from C_{1-6} alkyl.

230. The compound of Claim 229, wherein R^1 is selected from methyl, ethyl, propyl, or isopropyl.

231. The compound of Claim 228, wherein R^1 is phenyl optionally substituted with one or more R^4.

232. The compound of Claim 228, wherein R^1 is selected from 5 or 6 membered heteroaryl, each optionally substituted with one or more R^4.

233. The compound of Claim 232, wherein R^1 is selected from pyrazolyl or 1-methyl pyrazolyl, each optionally substituted with one or more R^4.

234. The compound of any one of Claims 227 to 233, wherein R^4 is selected from halogen or optionally substituted C_{1-6} alkyl.

235. The compound of Claim 234, wherein R^4 is fluoro.

236. The compound of any one of Claims 227 to 233, wherein R^1 is unsubstituted.

237. The compound of any one of Claims 227 to 236, wherein each R^2 is independently selected from hydrogen, halogen, or optionally substituted C_{1-6} alkyl.

238. The compound of Claim 237, wherein R^2 is hydrogen.

239. The compound of any one of Claims 227 to 238, wherein R^3 is -$(CH_2)_{1-4}$-(C_{6-10} aryl), optionally substituted with one or more R^9.

240. The compound of Claim 239, wherein R^3 is -$(CH_2)_{1-4}$-phenyl, optionally substituted with one or more R^9.

241. The compound of Claim 240, wherein R^3 is -(CH_2)-phenyl, optionally substituted with one or more R^9.

242. The compound of Claim 240, wherein R^3 is -$(CH_2)_2$-phenyl, optionally substituted with one or more R^9.

243. The compound of any one of Claims 227 to 242, wherein R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, $-C(O)R^8$ or $-NR^{14}R^{15}$.

244. The compound of Claim 243, wherein R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-C(O)CH_3$, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

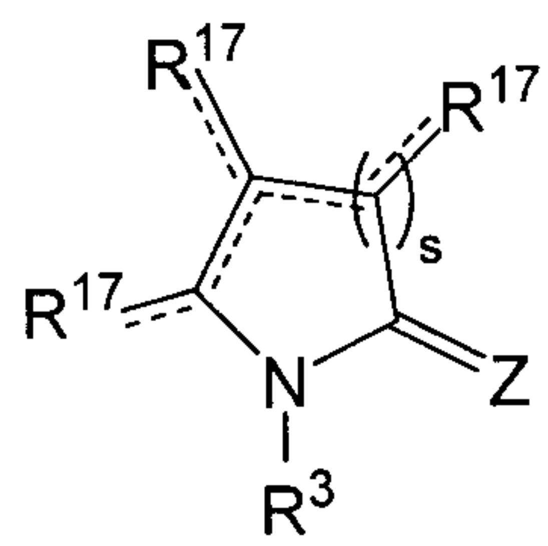
245. The compound of any one of Claims 239 to 242, wherein R^3 is unsubstituted.

246. The compound of any one of Claims 227 to 245, wherein Z is oxygen.

247. The compound of any one of Claims 227 to 246, wherein the bonds represented by a solid and dashed line are double bonds.

248. The compound of Claim 227, wherein the compound is selected from the group consisting of **Compounds 77-80** of Table 1, or pharmaceutically acceptable salts thereof.

249. A compound having the structure of formula (VIII):



(VIII)

R^3 is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-(CH_2)_n-(C_{6-10}$ aryl) optionally substituted with one or more R^9, $-(CH_2)_n-$(5-10 membered heteroaryl) optionally substituted with one or more R^9, $-(CH_2)_n-(C_{3-10}$ carbocyclyl) optionally substituted with one or more R^9, and $-(CH_2)_n-$(3-10 membered heterocyclyl) optionally substituted with one or more R^9;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8} alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$;

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and -C(O)R^8;

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{17} is independently selected from the group consisting of hydrogen, oxo, halogen, -CN, -C(O)R^8, -SO_2R^{16}, C_{1-6} alkyl optionally substituted with one or more R^4,

C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4,

or independently two adjacent R^{17} together with the carbon atoms to which they are attached form a fused phenyl or 5-6 membered heteroaryl, each optionally substituted with one or more R^4;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -$NR^{12}R^{13}$, and -OR^5;

Z is selected from oxygen and sulfur;

each n is independently an integer from 0 to 4;

s is 0, 1,or 3; and

the bonds represented by a solid and dashed line are independently selected from the group consisting of a single bond and a double bond.

250. The compound of Claim 249, wherein R^3 is selected from optionally substituted C_{1-6} alkyl or -$(CH_2)_n$-(C_{6-10} aryl) optionally substituted with one or more R^9.

251. The compound of Claim 250, wherein R^3 is -$(CH_2)_n$-(C_{6-10} aryl) optionally substituted with one or more R^9.

252. The compound of Claim 251, wherein R^3 is phenyl optionally substituted with one or more R^9.

253. The compound of any one of Claims 249 to 252, wherein R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, $-C(O)R^8$ or $-NR^{14}R^{15}$.

254. The compound of Claim 253, wherein R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-C(O)CH_3$, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

255. The compound of Claim 252, wherein R^3 is unsubstituted phenyl.

256. The compound of Claim 250, wherein R^3 is optionally substituted C_{1-6} alkyl.

257. The compound of any one of Claims 249 to 256, wherein each R^{17} is independently selected from hydrogen, halogen, optionally substituted C_{1-6} alkyl or oxo.

258. The compound of Claim 257, wherein each R^{17} is hydrogen.

259. The compound of any one of Claims 249 to 256, wherein two adjacent R^{17} together with the carbon atoms to which they are attached form a fused phenyl optionally substituted with one or more R^4.

260. The compound of Claim 259, wherein at least one R^{17} is oxo.

261. The compound of Claim 259, wherein at least one R^{17} is optionally substituted C_{1-6} alkyl.

262. The compound of any one of Claims 259 to 261, wherein the fused phenyl is unsubstituted.

263. The compound of any one of Claims 249 to 256, wherein two adjacent R^{17} together with the carbon atoms to which they are attached form a fused 5-6 membered heteroaryl, optionally substituted with one or more R^4.

264. The compound of Claim 263, wherein at least one R^{17} is oxo.

265. The compound of Claim 263, wherein at least one R^{17} is optionally substituted C_{1-6} alkyl.

266. The compound of any one of Claims 263 to 265, wherein the fused 5-6 membered heteroaryl is unsubstituted.

267. The compound of any one of Claim 259 to 261 and 263 to 265, wherein R^4 is selected from halogen or optionally substituted C_{1-6} alkyl.

268. The compound of any one of Claims 249 to 267, wherein n is 0.

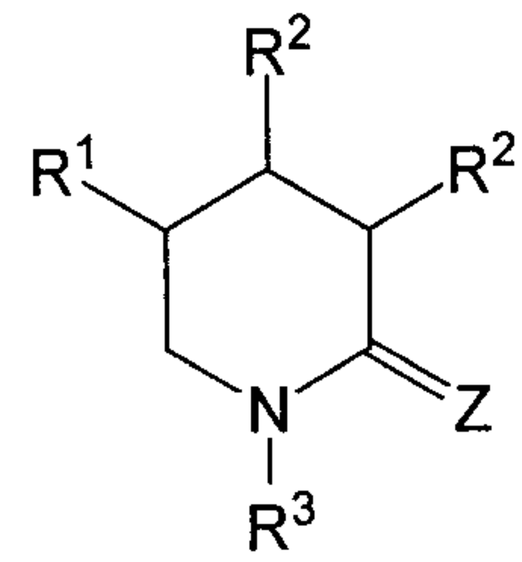
269. The compound of any one of Claims 249 to 267, wherein n is 1.

270. The compound of any one of Claims 249 to 267, wherein n is 3.

271. The compound of any one of Claims 249 to 270, wherein Z is oxygen.

272. The compound of Claim 249, wherein the compound is selected from the group consisting of **Compounds 81**, **82**, and **513-519** of Table 1.

273. A compound having the structure of formula (IX):



(IX)

R^1 is selected from the group consisting of hydrogen, halogen, -CN, -C(O)R^8, -SO_2R^{16}, C_{1-6} alkyl optionally substituted with one or more R^4, C_{2-6} alkenyl optionally substituted with one or more R^4, C_{2-6} alkynyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, 5-10 membered heteroaryl optionally substituted with one or more R^4, C_{3-10} carbocyclyl optionally substituted with one or more R^4, and 3-10 membered heterocyclyl optionally substituted with one or more R^4;

each R^2 is independently selected from the group consisting of hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -OR^5, -NR^6R^7, and -C(O)R^8,

or both R^2 together with the carbon atoms to which they are attached form a fused ring selected from the group consisting of C_{3-7} carbocyclyl and 3-7 membered heterocyclyl, each optionally substituted with one or more R^4;

R^3 is selected from the group consisting of -$(CH_2)_n$-(C_{6-10} aryl), 5-10 membered heteroaryl, -$(CH_2)_n$-(C_{3-10} carbocyclyl), and -$(CH_2)_n$ -(3-10 membered heterocyclyl), each optionally substituted with one or more R^9;

each R^4 is independently selected from the group consisting of halogen, -CN, -OH, -C(O)R^8, -SO_2R^{16}, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6}

alkoxy, optionally substituted C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, 5-10 membered heteroaryl optionally substituted with one or more R^{11}, or independently two geminal R^4 together are oxo;

each R^5 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{2-8} alkoxyalkyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, and -$(CH_2)_n$-(3-10 membered heterocyclyl) optionally substituted with one or more R^{10};

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

R^7 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, (5-10 membered heteroaryl)alkyl optionally substituted with one or more R^{11}, -C(O)R^8, and -C(O)OR^5;

or R^6 and R^7 together with the nitrogen to which they are attached form an 3-10 membered heterocyclyl optionally substituted with one or more R^{10};

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, -N$R^{12}R^{13}$, and -OR^5;

each R^9 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkylthio, optionally substituted C_{2-8}

alkoxyalkyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted C_{6-10} aryl, $-OR^5$, $-NR^{14}R^{15}$, $-C(O)R^8$, $-SO_2R^{16}$, and $-NO_2$;

each R^{10} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, and optionally substituted C_{2-6} alkynyl, or independently two geminal R^{10} together are oxo;

each R^{11} is independently selected from the group consisting of halogen, -CN, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, and optionally substituted C_{1-6} alkoxy;

each R^{12} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

each R^{13} is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, and C_{7-14} aralkyl optionally substituted with one or more R^{11};

R^{14} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

R^{15} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, and $-C(O)R^8$;

each R^{16} is independently selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, C_{6-10} aryl optionally substituted with one or more R^{11}, C_{7-14} aralkyl optionally substituted with one or more R^{11}, $-NR^{12}R^{13}$, and $-OR^5$;

Z is selected from oxygen and sulfur; and

each n is independently an integer from 0 to 4.

274. The compound of Claim 273, wherein R^1 is selected from C_{1-6} alkyl optionally substituted with one or more R^4, C_{6-10} aryl optionally substituted with one or more R^4, or 5-10 membered heteroaryl optionally substituted with one or more R^4.

275. The compound of Claim 274, wherein R^1 is C_{1-6} alkyl optionally substituted with one or more R^4.

276. The compound of Claim 274, wherein R^1 is C_{6-10} aryl optionally substituted with one or more R^4.

277. The compound of Claim 276, wherein R^1 is phenyl optionally substituted with one or more R^4.

278. The compound of Claim 274, wherein R^1 is 5 or 6 membered heteroaryl optionally substituted with one or more R^4.

279. The compound of Claim 278, wherein R^1 is pyrazolyl or 1-methyl pyrazolyl optionally substituted with one or more R^4.

280. The compound of any one of Claims 274 to 279, wherein R^4 is selected from halogen, optionally substituted C_{1-6} alkyl or optionally substituted C_{1-6} alkoxy.

281. The compound of any one of Claims 274 to 279, wherein R^1 is unsubstituted.

282. The compound of any one of Claims 273 to 281, wherein each R^2 is independently selected from hydrogen, halogen or optionally substituted C_{1-6} alkyl.

283. The compound of Claim 282, wherein R^2 is hydrogen.

284. The compound of any one of Claims 273 to 283, wherein R^3 is $-(CH_2)_n-(C_{6-10}$ aryl), optionally substituted with one or more R^9.

285. The compound of Claim 284, wherein R^3 is phenyl optionally substituted with one or more R^9.

286. The compound of Claim 284 or 285, wherein R^9 is selected from halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-8} alkoxyalkyl, $-OR^5$, $-C(O)R^8$ or $-NR^{14}R^{15}$.

287. The compound of Claim 286, wherein R^9 is selected from fluoro, chloro, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-C(O)CH_3$, $-NHCH_3$, $-NH_2$, or $-NHC(O)CH_3$.

288. The compound of Claim 284 or 285, wherein R^3 is unsubstituted.

289. The compound of any one of Claims 273 to 288, wherein Z is oxygen.

290. The compound of Claim 273, wherein the compound is selected from the group consisting of **Compounds 83**, **84**, **520-522** of Table 1, or pharmaceutically acceptable salts thereof.

291. A compound selected from the group consisting of **Compounds 1-20, 217-240, 244, 247, 253, 256, 257, 262, 264-283, 285, 287-339, 341-391, 431, 433, 434, 438-440, 442, 446-512, 546-549, 570, 575, 585, 609, 610, 627, 628, 630, 632, 633, 639, 641, 656, 666-668, 708** and **709** of Table 1, or pharmaceutically acceptable salts thereof.

292. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1 to 291, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

293. A method of treating a fibrotic condition, comprising administering a therapeutically effective amount of a compound of any one of Claims 1 to 291, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 292 to a subject in need thereof.

294. The method of Claim 293, comprising identifying the subject as having or at risk of having said fibrotic condition.

295. The method of Claim 293 or 294, wherein the fibrotic condition is selected from pulmonary fibrosis, dermal fibrosis, pancreatic fibrosis, liver fibrosis, and renal fibrosis.

296. The method of Claim 295, wherein the fibrotic condition is idiopathic pulmonary fibrosis.

297. The method of any one of Claims 293 to 296, wherein the compound, the pharmaceutical acceptable salt thereof, or the pharmaceutical composition is administered by inhalation.

298. The method of any one of Claims 293 to 297, wherein the subject is a human.

299. Use of a therapeutically effective amount of a compound of any one of Claims 1 to 291, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 292 in the preparation of a medicament for treating a fibrotic condition.

300. A therapeutically effective amount of a compound of any one of Claims 1 to 291, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 292 for use in the treatment of a fibrotic condition.