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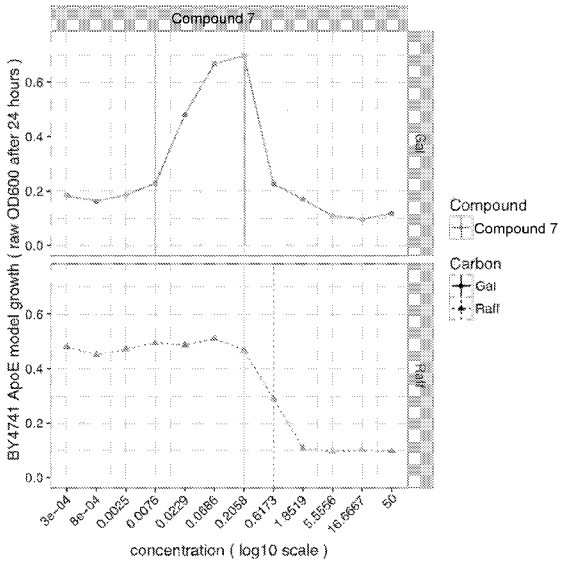
(54) Title: COMPOUNDS AND USES THEREOF

FIG. 1A



(57) Abstract: The present invention features compounds useful in the treatment of neurological disorders. The compounds of the invention, alone or in combination with other pharmaceutically active agents, can be used for treating or preventing neurological disorders.

[Continued on next page]

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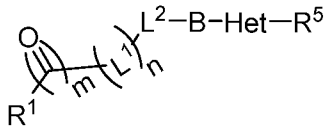
COMPOUNDS AND USES THEREOF

Background

An incomplete understanding of the molecular perturbations that cause disease, as well as a limited arsenal of robust model systems, has contributed to a failure to generate successful disease-modifying therapies against common and progressive neurological disorders, such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). Progress is being made on many fronts to find agents that can arrest the progress of these disorders. However, the present therapies for most, if not all, of these diseases provide very little relief. Accordingly, a need exists to develop therapies that can alter the course of neurodegenerative diseases. More generally, a need exists for better methods and compositions for the treatment of neurodegenerative diseases in order to improve the quality of the lives of those afflicted by such diseases.

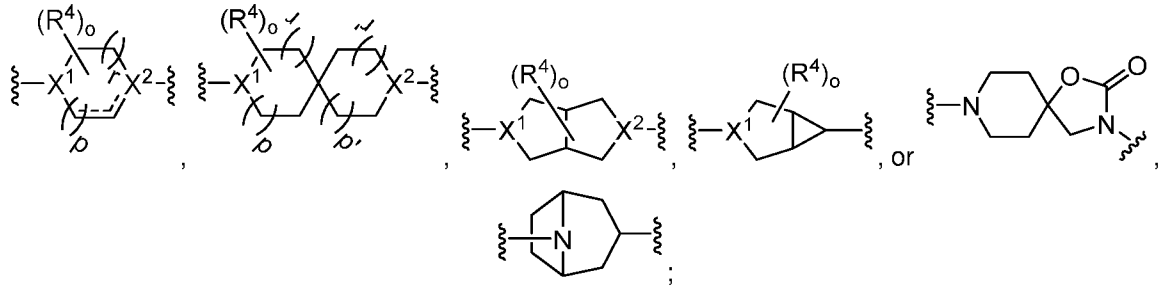
Summary of the Invention

This disclosure provides a compound, or a pharmaceutically acceptable salt thereof, having the structure of Formula I:



Formula Ia

wherein B is absent or has the structure:



Formula Ib **Formula Ic** **Formula Id** **Formula Ie** **Formula If**

the dashed lines represent an optional double bond;

Het is –C(O)NH- or an optionally substituted C_2-C_9 heteroaryl;

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

p, p', r, and r' are, independently, 0 or 1;

X^1 and X^2 are each, independently, N or CR^6;

L^1 is -O-, -SO_2-, NR^2, optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 alkenylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heteroaryl, an optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heterocycle;

L^2 is absent, -O-, -SO_2-, NR^2, or -CR^2R^3-;

R^1 is hydrogen, amino, hydroxy, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_3-C_7 cycloalkyl C_1-C_6 alkyl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle, or optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl;

R^2 and R^3 are each, independently, hydrogen, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or combine with the carbon to which they are attached to form a carbonyl or an optionally substituted C_3-C_7 cycloalkyl;

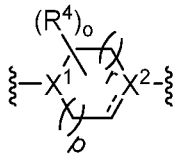
each R^4 is, independently, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or two R^4 combine with the carbon two which they are attached to form a carbonyl or optionally substituted C_3-C_7 cycloalkyl;

R^5 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heterocycle, optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl, or optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl; and

each R^6 is, independently, hydrogen, halogen, hydroxy, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_1-C_6 alkyl.

In some embodiments, B is absent.

In some embodiments, B has the structure of Formula Ib:



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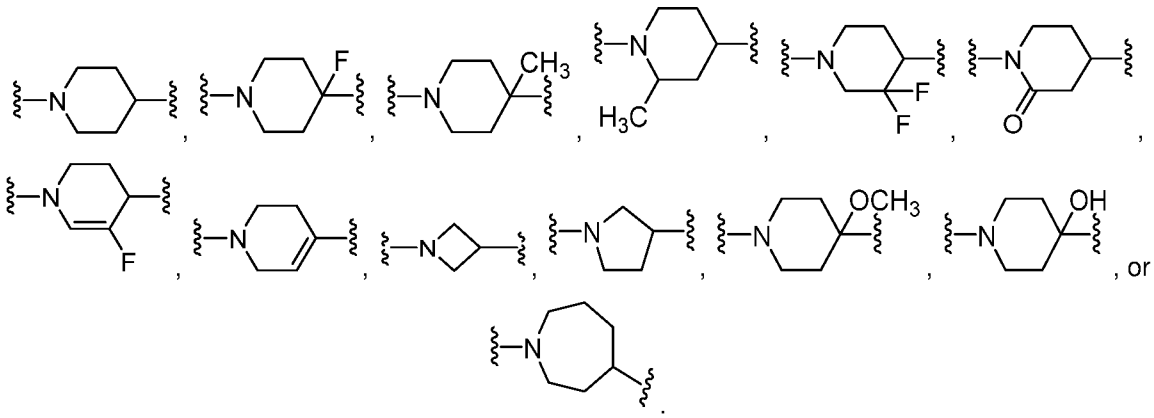
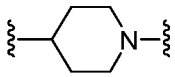
In some embodiments, X^1 is N and X^2 is CR^6. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is halogen (e.g., fluoro). In some embodiments, R^6 is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, the dashed line represents a double bond. In some embodiments, both dashed lines represent a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, B has the structure:

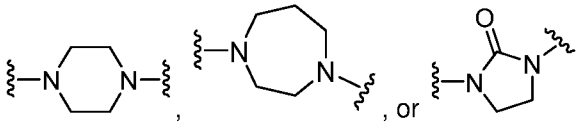


.

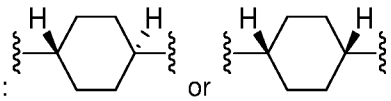
In some embodiments, X^1 is CR^6 and X^2 is N. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is halogen (e.g., fluoro). In some embodiments, R^6 is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, the dashed line represents a double bond. In some embodiments, the dashed line represents a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, B has the structure:



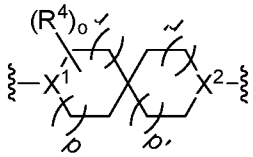
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, the dashed line represents a double bond. In some embodiments, the dashed line represents a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, p is 1 and r is 2. In some embodiments, B has the structure:



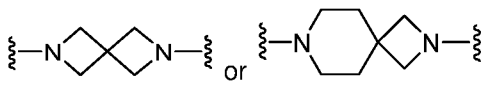
In some embodiments, X^1 is CR^6 and X^2 is CR^6. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, the dashed line represents a double bond. In some embodiments, the dashed line represents a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, B has the structure:



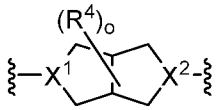
In some embodiments, B has the structure of Formula Ic:



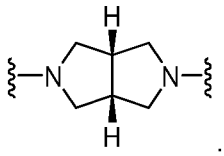
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0. In some embodiments, p, p', r, and r' are 0. In some embodiments, p and r are each 1 and p' and r' are 0. In some embodiments, B has the structure:



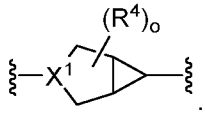
In some embodiments, B has the structure of Formula Id:



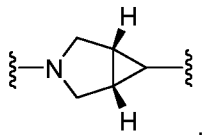
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0. In some embodiments, B has the structure:



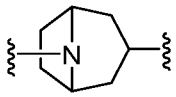
In some embodiments, B has the structure of Formula Ie:



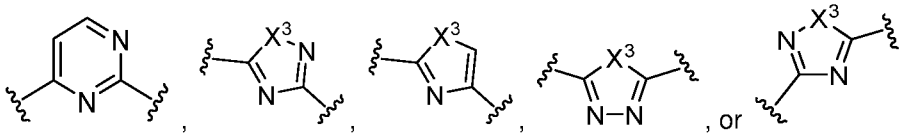
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0. In some embodiments, B has the structure:



In some embodiments, B has the structure of Formula If:

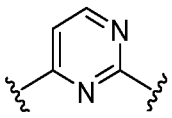


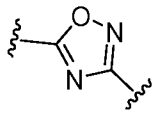
In some embodiments of any of the foregoing compounds, Het is –C(O)NH- or:

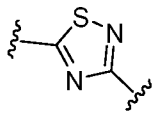


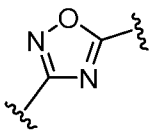
wherein X^3 is O or S.

In some embodiments, Het is –C(O)NH-.

In some embodiments, Het is  .

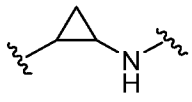
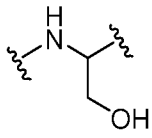
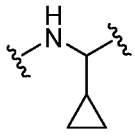
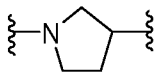
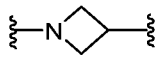
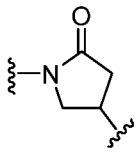
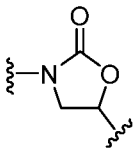
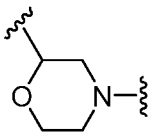
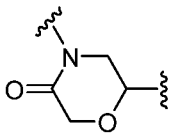
In some embodiments, Het is  .

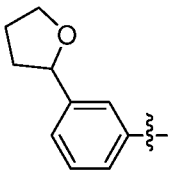
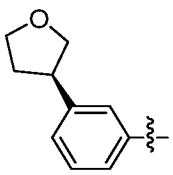
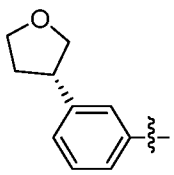
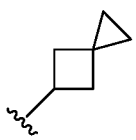
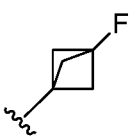
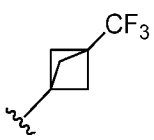
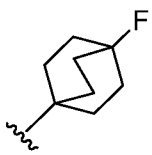
In some embodiments, Het is  .

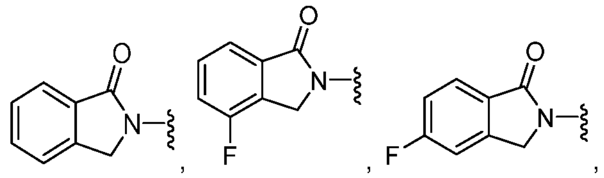
In some embodiments, Het is  .

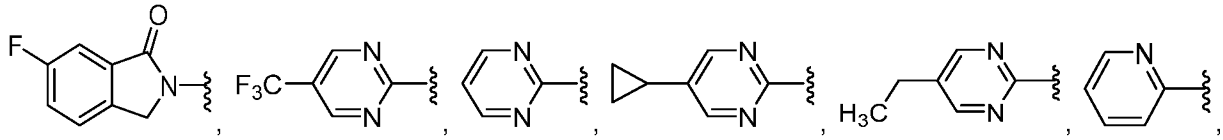
In some embodiments, L^2 is absent. In some embodiments, L^2 is $–NR^2$- (e.g., -NH-). In some embodiments, L^2 is –O-. In some embodiments, L^2 is $–SO_2$-. In some embodiments, L^2 is $–CR^2R^3$-. In some embodiments, R^2 and R^3 combine with the carbon to which they are attached to form a carbonyl. In some embodiments, R^2 and R^3 combine with the carbon to which they are attached to form an optionally

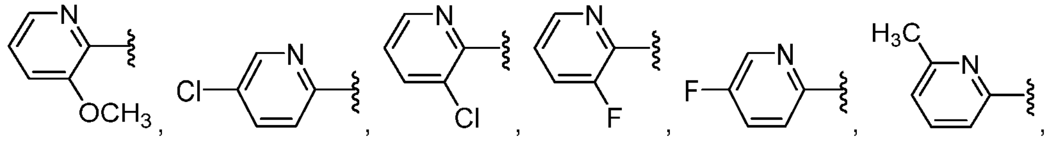
substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl). In some embodiments, R^2 and R^3 are both hydrogen. In some embodiments, R^2 is hydrogen and R^3 is optionally substituted C_1-C_6 alkylene (e.g., methylene).

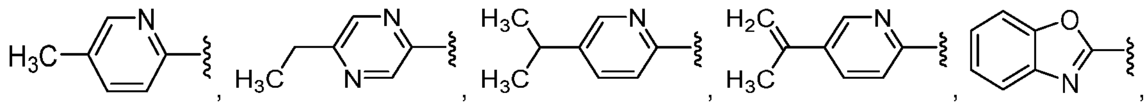
In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, L^1 is $–NR^2$- (e.g., -NH- or –N(Et)-). In some embodiments, L^1 is –O-. In some embodiments, L^1 is $–SO_2$-. In some embodiments, L^1 is optionally substituted C_1-C_6 alkylene (e.g., methylene or hydroxy-methylene). In some embodiments, L^1 is optionally substituted C_1-C_6 heteroalkylene (e.g., -NH-CH_2-, -O-CH_2-, -O-CH_2-CH_2-, -CH_2-O-CH_2-, -CH_2-O-,  ,  , or ). In some embodiments, L^1 is optionally substituted C_2-C_9 heterocycle (e.g.,  ,  ,  ,  ,  , or ).

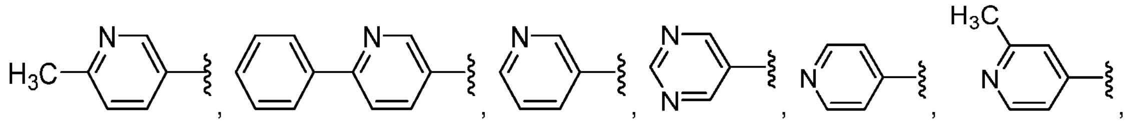
In some embodiments, R^1 is cyano, optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, trifluoroethyl, pentafluoro-ethyl, 2-chloro-ethyl, 1-chloro-3-hydroxy-isopropyl, 2-methoxy-ethyl, or hexafluoro-isopropyl). In some embodiments, R^1 is optionally substituted C_6-C_{10} aryl (e.g., phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4- trifluoromethyl–phenyl, 2-cyano-phenyl, 3-cyano-phenyl, 4-cyano-phenyl, 3-isopropyl-phenyl, 4-isopropyl-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 4-methoxy-phenyl, 4-difluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl, 2-chloro-5-fluoro-phenyl, 2-fluoro-4-chloro-phenyl, 3-fluoro-4-chloro-phenyl, 2-bromo-4-methoxy-phenyl, 2-trifluoromethyl-5-fluoro-phenyl, 2-trifluoromethyl-5-chloro-phenyl, ,  ,  , or ). In some embodiments, R^1 is optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl (e.g., naphthylmethyl). In some embodiments, R^1 is optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl, cyclohexyl, 6-methoxy-cyclohexyl, 1-cyano-cyclopropyl, bicycle[1.1.1]pentane, 1-methyl-cyclopropyl, 1-ethyl-cyclopropyl, 1-fluoro-cyclopropyl, 1-methoxy-cyclopropyl, 1-hydroxy-cyclopropyl, 2,2-dimethyl-cyclopropyl, 2,2-difluoro-cyclopropyl, cyclobutyl,  , ,  ,  , or ). In some embodiments, R^1 is optionally substituted C_3-C_7 cycloalkyl C_1-C_6 alkyl (cyclopropylmethyl). In some embodiments, R^1 is

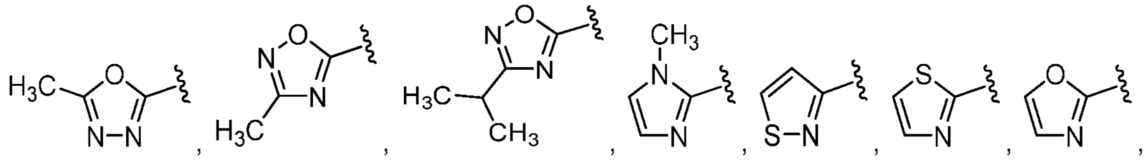
optionally substituted C_2-C_9 heteroaryl (e.g., 

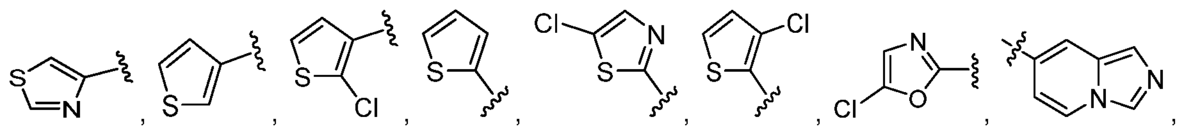


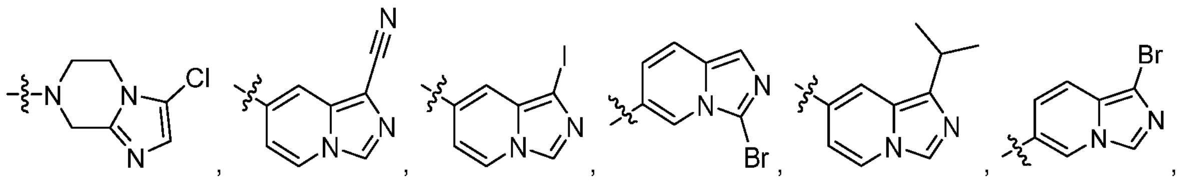


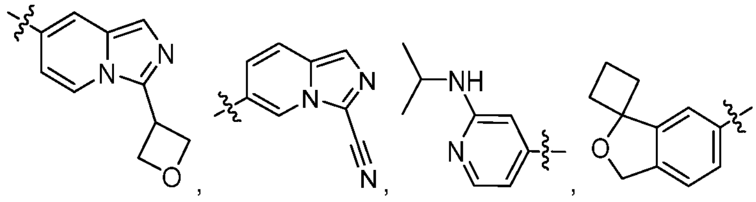
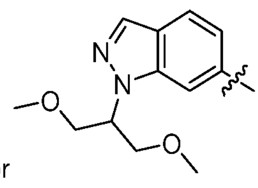
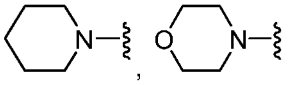


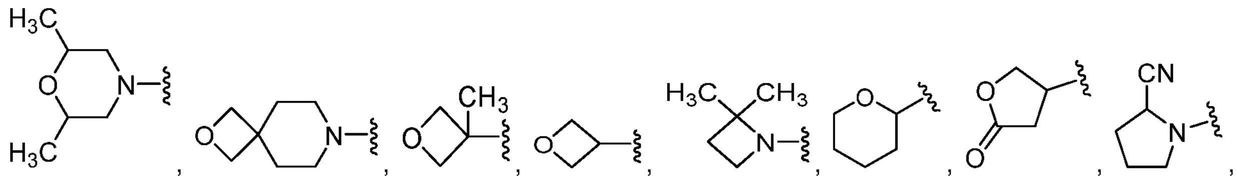


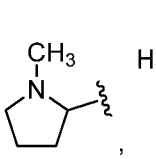
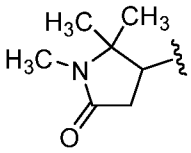
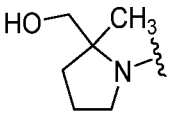
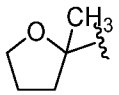
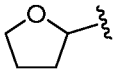
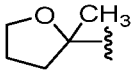
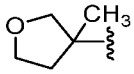
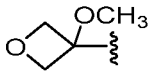
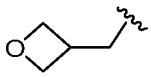


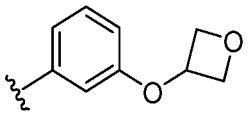
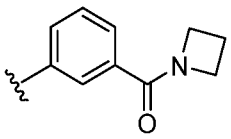
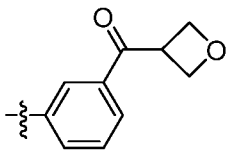
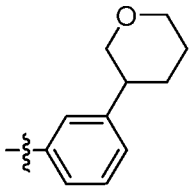
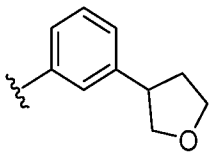
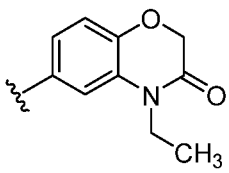
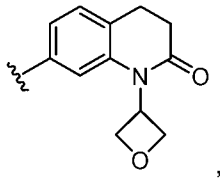
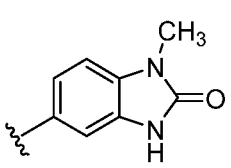
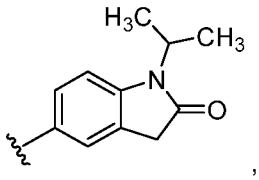
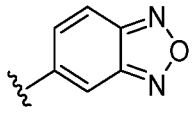
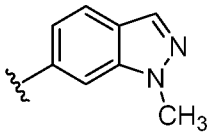
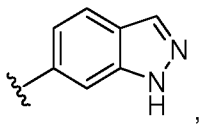
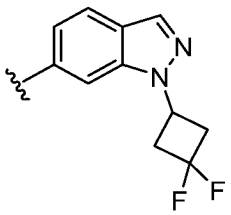
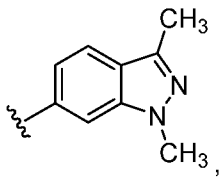
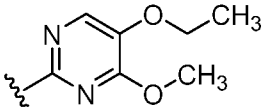
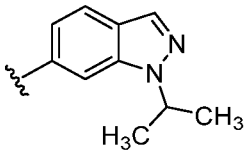
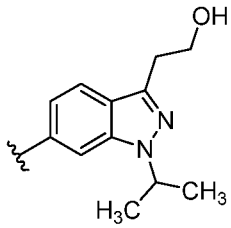
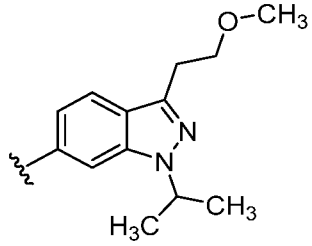
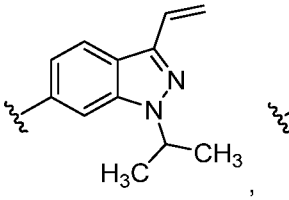
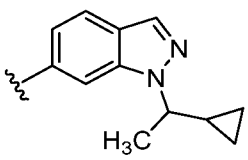
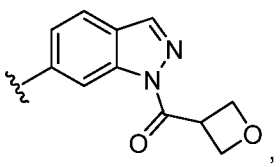
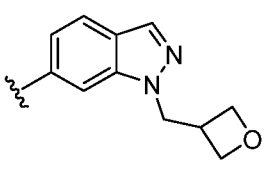
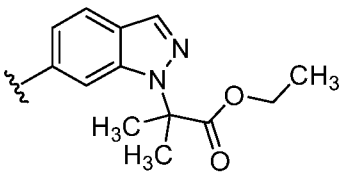
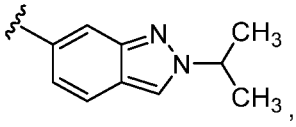
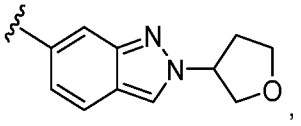


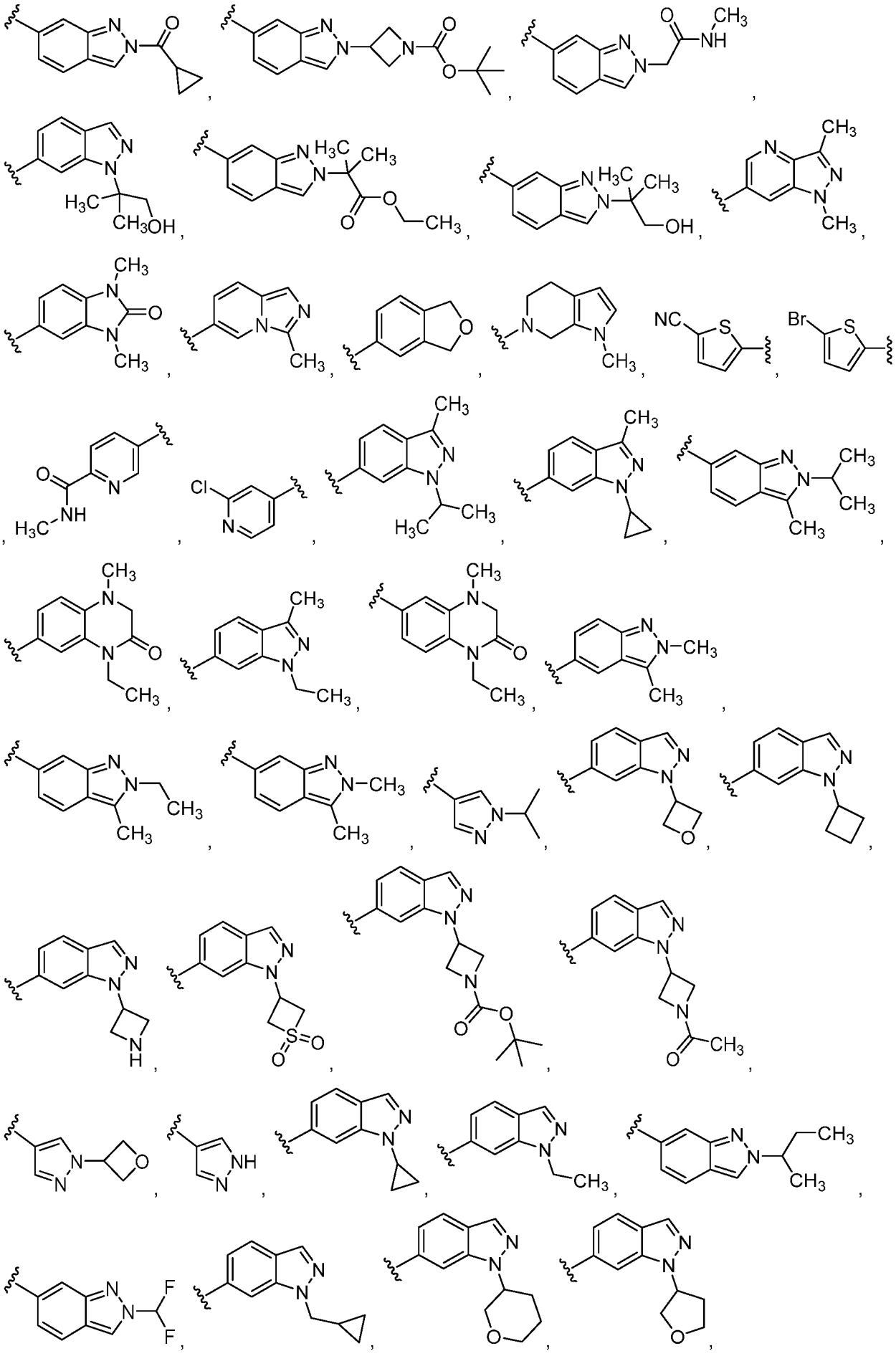


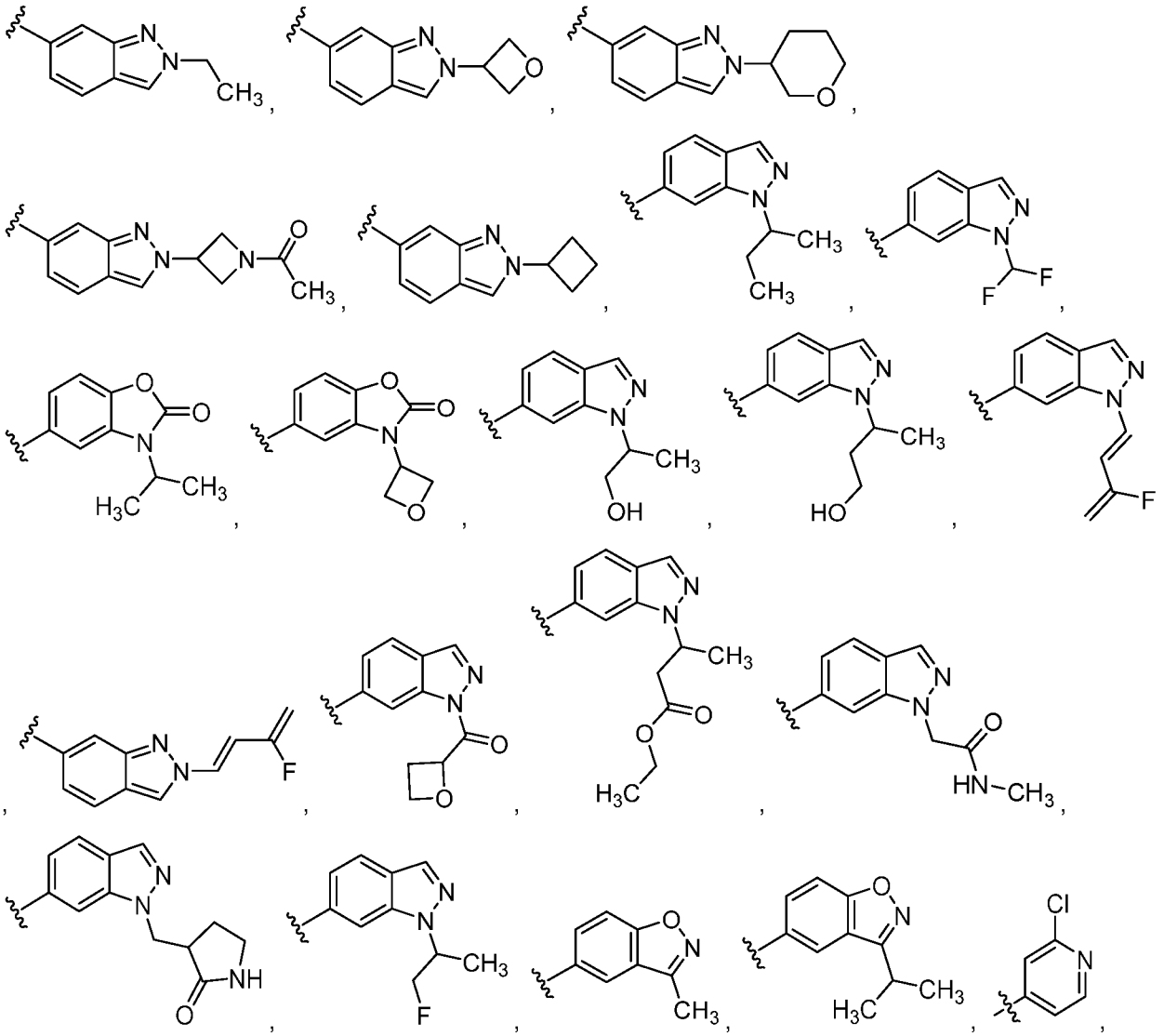
 , or  ,). In some embodiments, R^1 is optionally substituted C_2-C_9 heterocycle (e.g.,  ,

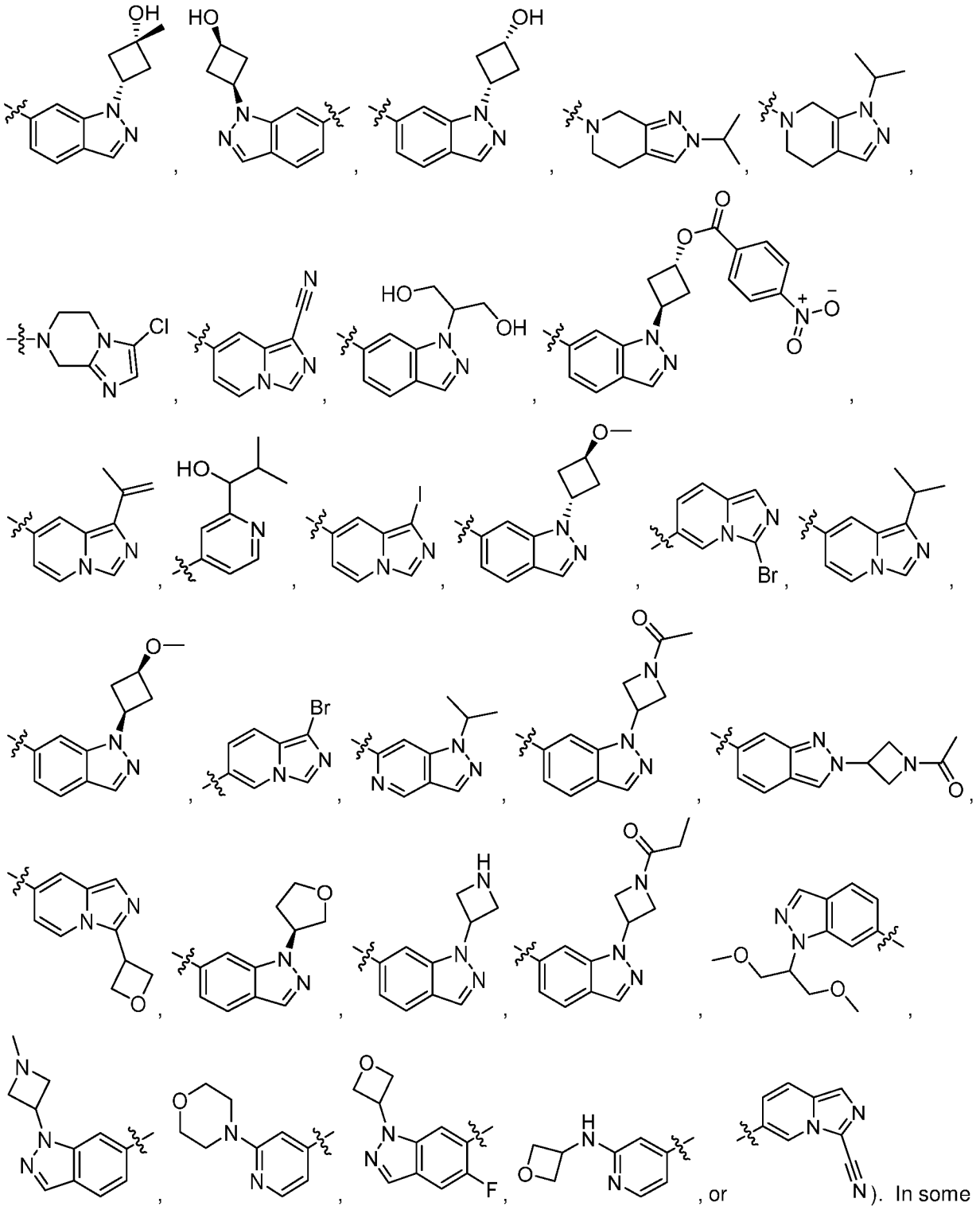


 ,  ,  ,  ,  ,  ,  , or  ,). In some embodiments, R^1 is optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl (e.g., ).

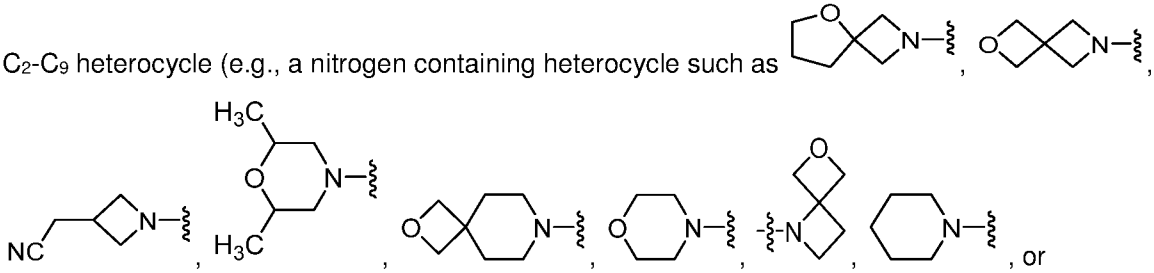
In some embodiments, R^5 is optionally substituted C_6-C_{10} aryl (e.g., phenyl, 3,4-dimethoxy-phenyl, 3-methoxy-4-ethoxy-phenyl, 3,5-dimethoxy-phenyl, 3-methoxy-4-cyclopropoxy-phenyl, 3-methoxy-4-trifluoromethoxy-phenyl, 3-isopropoxy-4-methoxy-phenyl,  ,  ,  ,  , or ). In some embodiments, R^5 is optionally substituted C_2-C_9 heteroaryl (e.g.,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

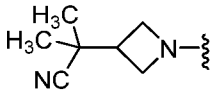


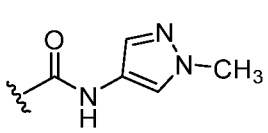
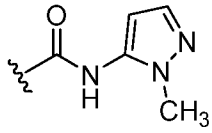




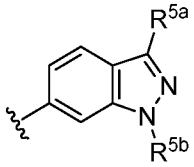
embodiments, R^5 is an optionally substituted indazole. In some embodiments, R^5 is optionally substituted C_2-C_9 heterocycle (e.g., a nitrogen containing heterocycle such as




). In some embodiments, R^5 is optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl (e.g.,

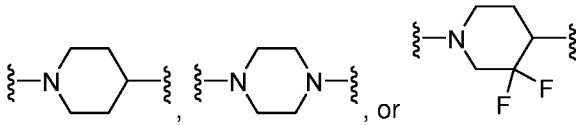

or

).

In some embodiments, R^5 is a bicyclic heterocyle. For example, a bicyclic heterocycle such as an indazole. In some embodiments, R^5 is an indazole having the structure:

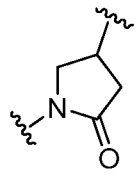
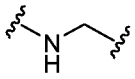


wherein R^{5a} is hydrogen or optionally substituted C_1-C_6 alkyl (e.g., methyl) and R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl).

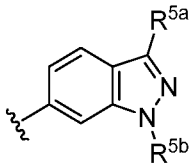
In some embodiments, B has the sturucture:



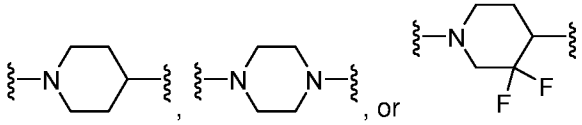
In some embodiments, R^1 is optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, iso-propyl, or tert-butyl), optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

In some embodiments, m is 0, n is 1, L^1 is –O-, and L^2 is –C(O)-. In some embodiments, m is 0, n is 0, and L^2 is –C(O)-. In some embodiments, m is 0, n is 1, L^1 is  , and L^2 is –C(O)-. In some embodiments, m is 1, n is 1, L^1 is  , and L^2 is –C(O)-.

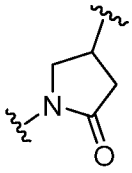
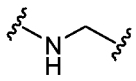
In some embodiments, R^5 is an indazole having the structure:



wherein R^{5a} is hydrogen or optionally substituted C_1-C_6 alkyl (e.g., methyl) and R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl); B has the sturucture:

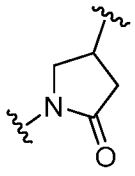


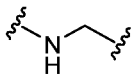
R^1 is optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, iso-propyl, or tert-butyl), optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl; and

m is 0, n is 1, L^1 is –O-, and L^2 is –C(O)-, m is 0, n is 0, and L^2 is –C(O)-, m is 0, n is 1, L^1 is  , and L^2 is –C(O)-, or m is 1, n is 1, L^1 is  , and L^2 is –C(O)-.

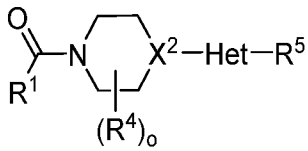
In some embodiments, m is 0, n is 1, L^1 is –O-, L^2 is –C(O)- and R^1 is optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, iso-propyl, or tert-butyl).

In some embodiments, m is 0, n is 0, L^2 is –C(O)-, and R^1 is optionally substituted C_6-C_{10} aryl.

In some embodiments, m is 0, n is 1, L^1 is  , L^2 is –C(O)-, and R^1 is optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

In some embodiments, m is 1, n is 1, L^1 is  , L^2 is –C(O)-, and R^1 is optionally substituted C_6-C_{10} aryl.

In some embodiments, the compound has the structure of Formula Ig:



Formula Ig

wherein Het is an optionally substituted oxadiazole;

o is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

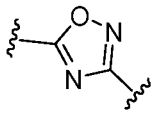
X^2 is N or CR^6;

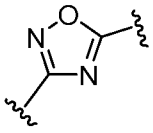
R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_3-C_7 cycloalkyl C_1-C_6 alkyl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle, or optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl;

each R^4 is, independently, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or two R^4 combine with the carbon two which they are attached to form a carbonyl or optionally substituted C_3-C_7 cycloalkyl;

R^5 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heterocycle, optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl, or optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl; and

each R^6 is, independently, hydrogen, halogen, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_1-C_6 alkyl.

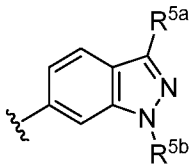
In some embodiments, Het is  .

In some embodiments, Het is  .

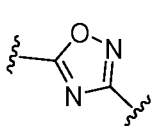
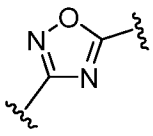
In some embodiments, X^2 is N or CH. In some embodiments, X^2 is N. In some embodiments, X^2 is CH.

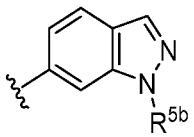
In some embodiments, R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_6-C_{10} aryl.

In some embodiments, R^5 is optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl (e.g., bicyclic heteroaryl such as an indazole). In some embodiments, R^5 has the structure:



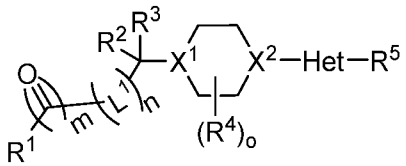
wherein R^{5a} is hydrogen or optionally substituted C_1-C_6 alkyl (e.g., methyl) and R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl). In some embodiments, R^{5a} is hydrogen.

In some embodiments, Het is  or  ; o is 0; X^2 is N or CH; R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl (e.g., C_1-C_6 alkoxy or C_1-C_6 alkylamino), or optionally substituted C_6-C_{10} aryl; and R^5 has the structure:



wherein R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl).

In some embodiments the compound has the structure of Formula I:



Formula I

wherein Het is an optionally substituted optionally substituted C_2-C_9 heteroaryl;

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

X^1 and X^2 are each, independently, N or CR^6;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 alkenylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocycle;

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocycle;

R^2 and R^3 are each, independently, hydrogen, optionally substituted C_1-C_6 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

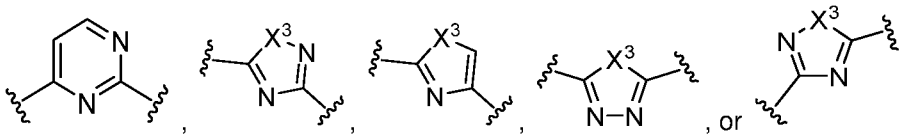
each R^4 is, independently, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or two R^4 combine with the carbon two which they are attached to form a carbonyl;

R^5 is optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl; and

each R^6 is, independently, hydrogen or optionally substituted C_1-C_6 alkyl.

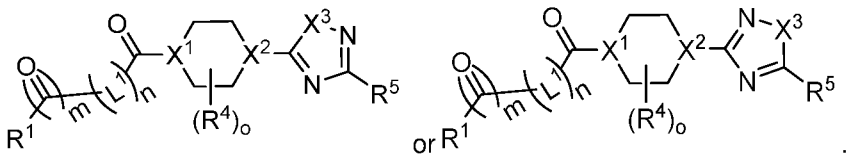
In some embodiments of any of the foregoing compounds, R^2 and R^3 combine with the carbon to which they are attached to form a carbonyl. In some embodiments of any of the foregoing compounds, R^2 and R^3 are both hydrogen.

In some embodiments of any of the foregoing compounds, Het is:



wherein X^3 is O or S.

In some embodiments, the compound has the structure of Formula II or IIa:



Formula II **Formula IIa**

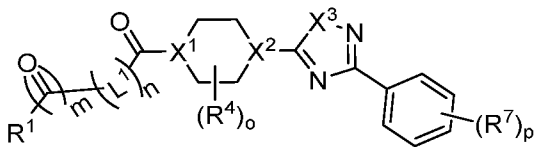
In some embodiments of any of the foregoing compounds, X^3 is O. In some embodiments of any of the foregoing compounds, X^3 is S.

In some embodiments of any of the foregoing compounds, X^1 is N and X^2 is CR^6. In some embodiments of any of the foregoing compounds, X^1 is N and X^2 is N. In some embodiments of any of the foregoing compounds, X^1 is CR^6 and X^2 is N. In some embodiments of any of the foregoing compounds, R^6 is hydrogen.

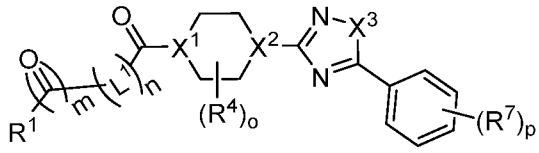
In some embodiments of any of the foregoing compounds, R^5 is optionally substituted C_6-C_{10} aryl. For example, in some embodiments, R^5 is a C_6-C_{10} aryl substituted with 1, 2, 3, or 4 substituents independently selected from C_1-C_6 alkyl (e.g., methyl), halogen (e.g., fluoro, chloro, or bromo), C_1-C_6 alkoxy (e.g., methoxy or ethoxy), nitrile, or two substituents combine to form a 5 or 6-membered heterocycle (e.g., 2,2-difluoro-1,3-benzodioxole). In some embodiments of any of the foregoing compounds, R^5 is phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 3,4-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-fluoro-phenyl, 3- fluoro -

phenyl, 4- fluoro -phenyl, 3,4-di fluoro –phenyl, 3,4-dichloro-phenyl, 3-methoxy-4-ethoxy-phenyl, 3-chloro-4-ethoxy-phenyl, 3-fluoro-4-ethoxy-phenyl, 3-bromo-4-ethoxy-phenyl, 3-cyano-4-ethoxy-phenyl, or 2,2-difluoro-1,3-benzodioxole.

In some embodiments, the compound has the structure of Formula III or IIIa:



Formula III



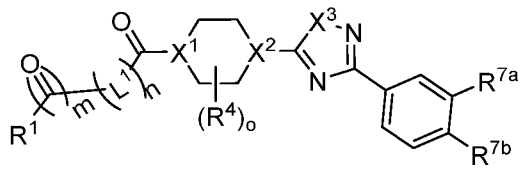
Formula IIIa

wherein p is 1, 2, 3, 4, or 5;

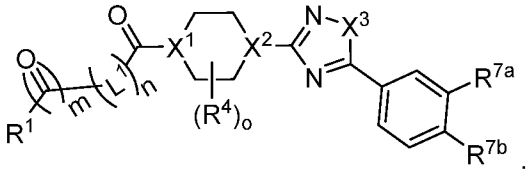
each R^7 is, independently, halogen, nitrile, OR^8, or optionally substituted C_1-C_6 alkyl; and

each R^8 is, independently, hydrogen or optionally substituted C_1-C_6 alkyl.

In some embodiments, the compound has the structure of Formula IV or IVa:



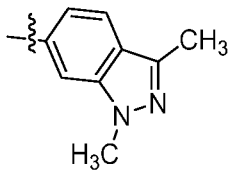
Formula IV



Formula IVa

In some embodiments, each R^7 is OR^8. In some embodiments, each R^8 is optionally substituted C_1-C_6 alkyl (e.g., methyl or ethyl).

In some embodiments of any of the foregoing compounds, R^5 is optionally substituted C_2-C_9 heteroaryl (e.g., bicyclic heteroaryl). In some embodiments of any of the foregoing compounds, R^5 is: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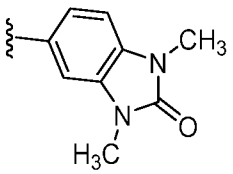
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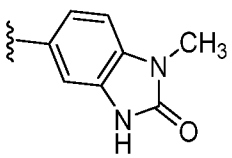
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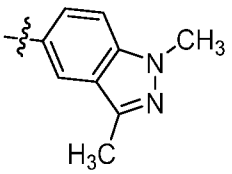
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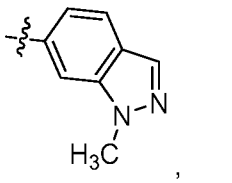
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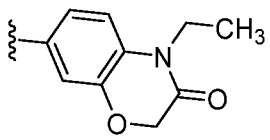
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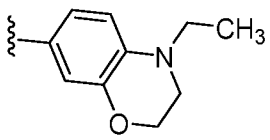
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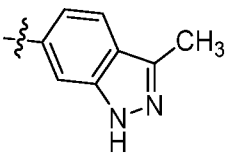
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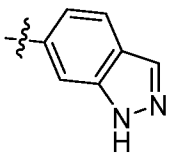
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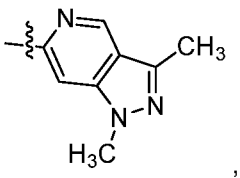
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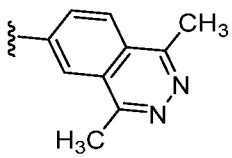
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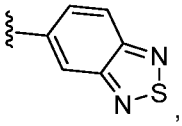
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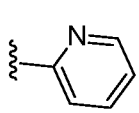
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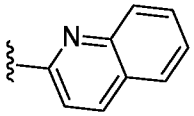
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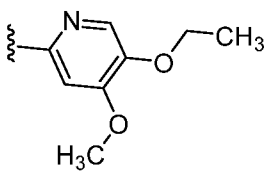
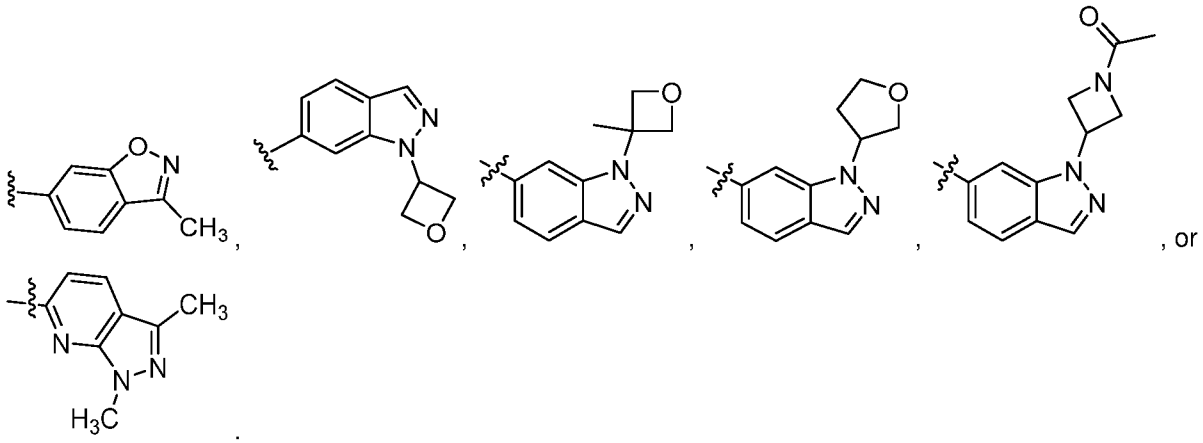
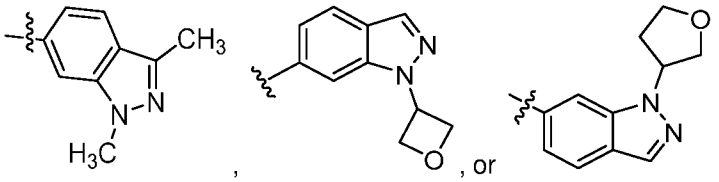
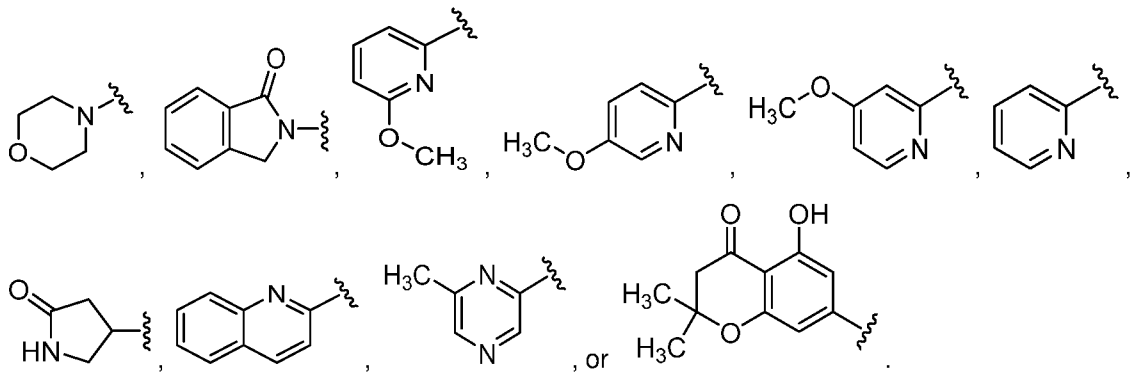

,



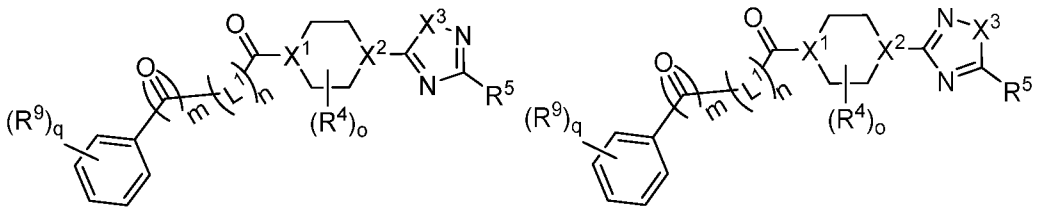
In some embodiments of any of the foregoing compounds, R^5 is:



In some embodiments of any of the foregoing compounds, R^1 is optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl. In some embodiments, R^1 is optionally substituted C_6-C_{10} aryl. For example, phenyl or a C_6-C_{10} aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_1-C_6 alkyl (e.g., methyl or iso-propyl), C_1-C_6 alkoxy (e.g., methoxy), or halogen (e.g., chloro). In some embodiments of any of the foregoing compounds R^1 is 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 3,4-methyl-phenyl, 4-iso-propyl-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, or 4-chloro-phenyl. In some embodiments of any of the foregoing compounds, R^1 is a bicyclic C_6-C_{10} aryl (e.g., naphthalene). In some embodiments of any of the foregoing compounds, R^1 is C_3-C_7 cycloalkyl (e.g., cyclohexyl). In some embodiments of any of the foregoing compounds, R^1 is optionally substituted C_2-C_9 heteroaryl or optionally substituted C_2-C_9 heterocycle. For example, in some embodiments, R^1 is:



In some embodiments of any of the foregoing compounds, the compound has the structure of Formula V or Va:

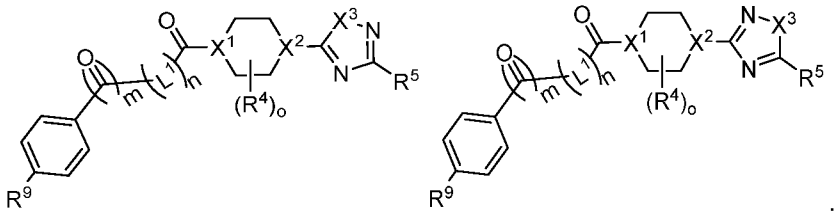


Formula V **Formula Va**

wherein q is 1, 2, 3, 4, or 5; and

R^9 is halogen or optionally substituted C_1-C_6 alkyl.

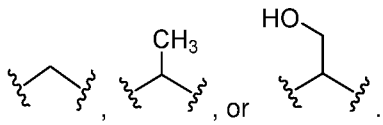
In some embodiments of any of the foregoing compounds, the compound has the structure of Formula VI or VIa:



Formula VI **Formula VIa**

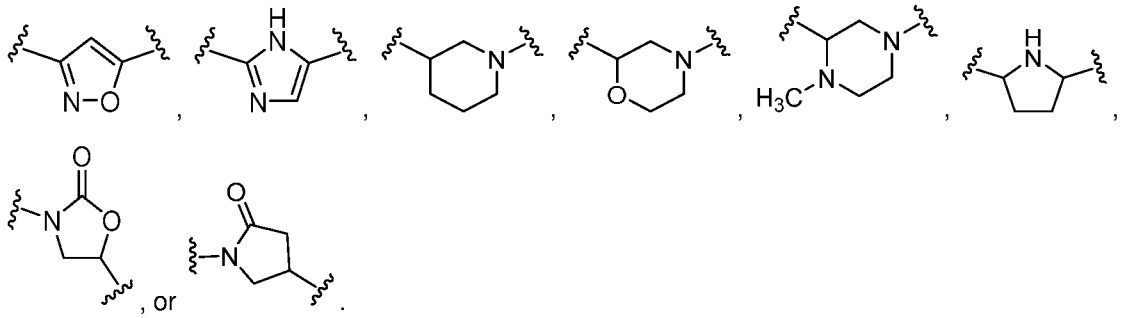
In some embodiments of any of the foregoing compounds, n is 1. In some embodiments of any of the foregoing compounds, n is 0.

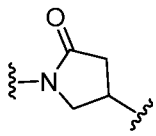
In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_1-C_6 alkyl. For example, L^1 has the structure:



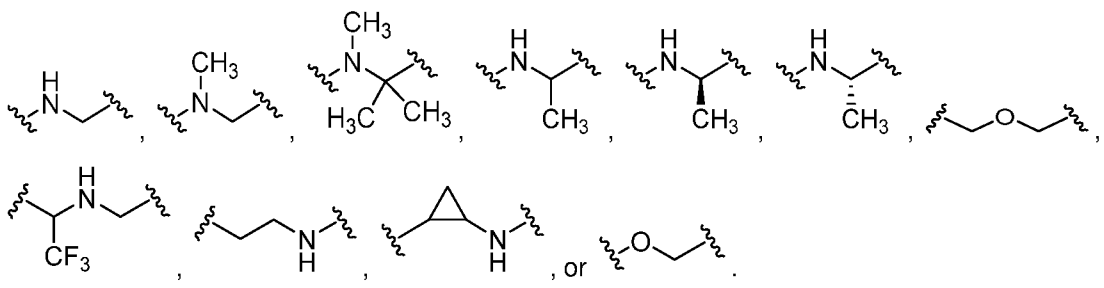
In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_1-C_6 alkenylene (e.g., ethenylene).

In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_2-C_9 heterocyclene or optionally substituted C_2-C_9 heteroarylene. For example,



In some embodiments, L^1 is  .

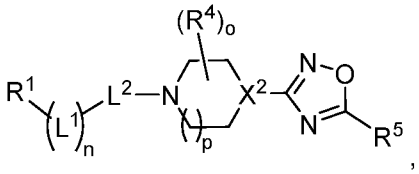
In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_1-C_6 heteroalkylene. For example, in some embodiments, L^1 is:



In some embodiments of any of the foregoing compounds, L^1 is -NH-$(CR^{10}R^{11})_r$-, wherein r is 1, 2, 3, 4, 5, or 6, and each R^{10} and R^{11} is, independently, hydrogen or optionally substituted C_1-C_6 alkyl. For example, in some embodiments, L^1 is -NH-CH_2-, –NH-$CR^{10}R^{11}$-, wherein each of R^{10} and R^{11} is methyl, or –NH-CHR^{11}-, wherein R^{11} is methyl.

In some embodiments of any of the foregoing compounds, m is 1. In some embodiments of any of the foregoing compounds, m is 0.

In some embodiments of any of the foregoing compounds, the compound has the structure of **Formula VII**:



Formula VII

wherein

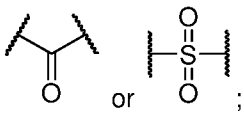
n is 0 or 1;

o is 0, 1, 2, or 3;

p is 1 or 2;

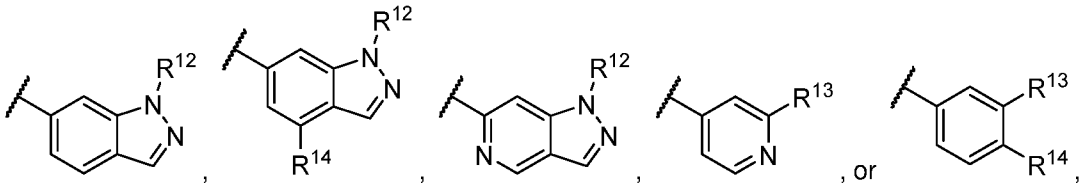
R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heterocycle, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl;

L^1 is –O–;

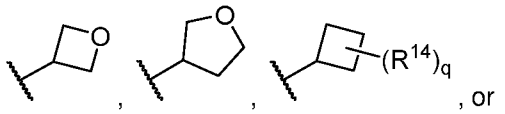
L^2 is  ;

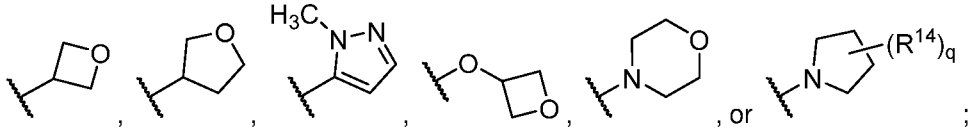
each R^4 is, independently, halogen or optionally substituted C_1-C_6 alkyl;

X^2 is N or CH;

R^5 is  ,

wherein

R^{12} is  ;

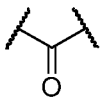
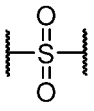
R^{13} is  ;

q is 0, 1, 2, or 3; and

R^{14} is halogen, hydroxyl, or optionally substituted C_1-C_6 alkyl,

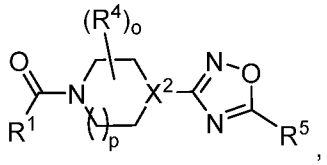
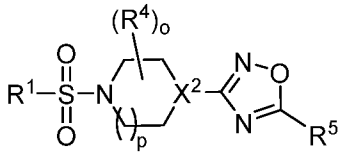
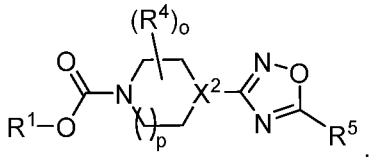
or a pharmaceutically acceptable salt thereof.

In some embodiments, X^2 is CH. In some embodiments, X^2 is N.

In some embodiments, L^1 is  . In some embodiments, L^1 is  .

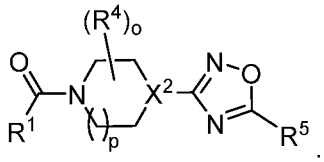
In some embodiments, n is 0. In some embodiments, n is 1.

In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIIa**, **FormulaVIIb**, or **Formula VIIc**:

 ,  , or  .

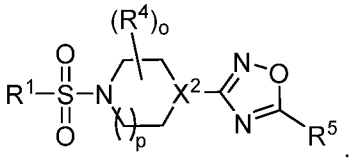
Formula VIIa **Formula VIIb** **Formula VIIc**

In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIIac**:

 .

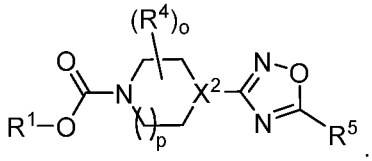
Formula VIIa

In some embodiments any of the foregoing compounds, the compound has the structure of **FormulaVIIb**:

 .

Formula VIIb

In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIIc**:

 .

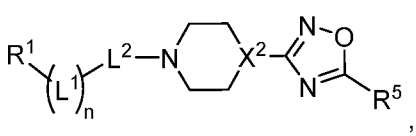
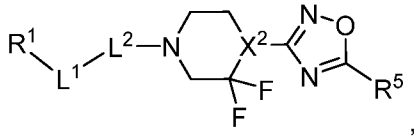
Formula VIIc

In some embodiments, o is 0, 1, or 2.

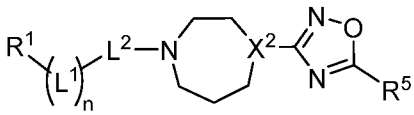
In some embodiments, o is 0. In some embodiments, o is 1. In some embodiments, o is 2.

In some embodiments, p is 1. In some embodiments, p is 2.

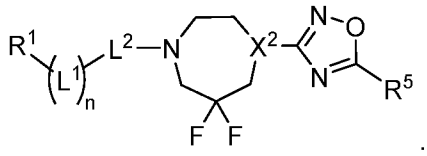
In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIId**, **Formula VIIe**, **Formula VIIf**, or **Formula VIIg**.

 ,  ,

Formula VIId **Formula VIIe**



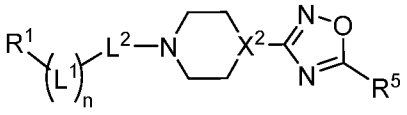
, or



.

Formula VIIf **Formula VIIg**

In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIId**:



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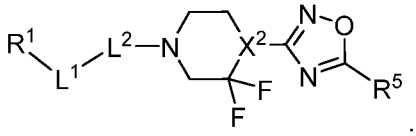
Formula VIId

In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIIe**:



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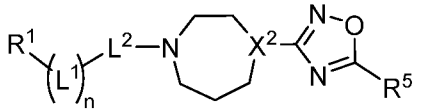
Formula VIIe

In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIIf:**



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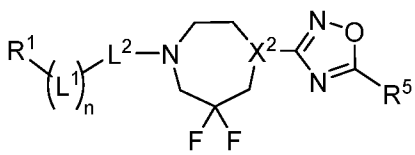
Formula VIIf

In some embodiments any of the foregoing compounds, the compound has the structure of **Formula VIIg**:



.

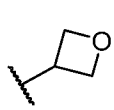
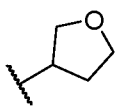
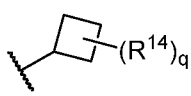
Formula VIIg

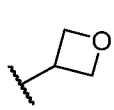
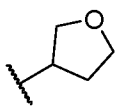
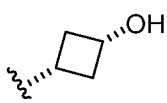
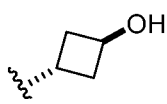
In some embodiments, q is 0 or 1.

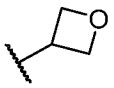
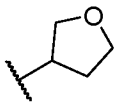
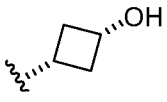
In some embodiments, q is 0. In some embodiments, q is 1.

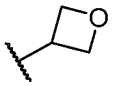
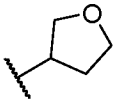
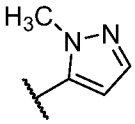
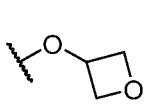
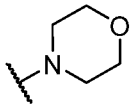
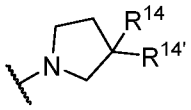
In some embodiments, R^{14} is halogen or hydroxyl.

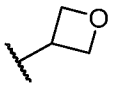
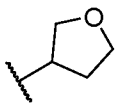
In some embodiments, R^{14} is halogen. In some embodiments, R^{14} is hydroxyl.

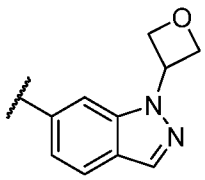
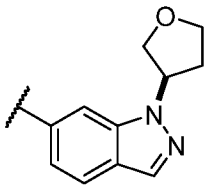
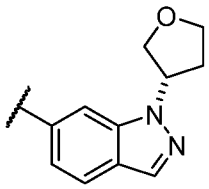
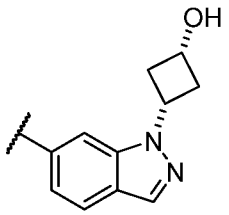
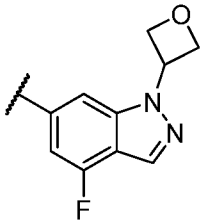
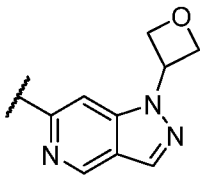
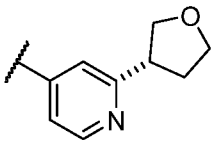
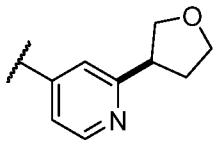
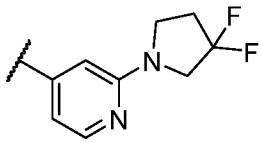
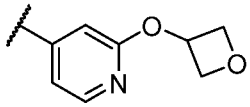
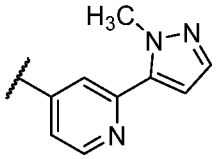
In some embodiments, R^{12} is  ,  , or  .

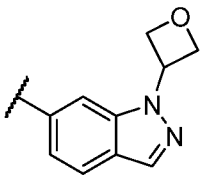
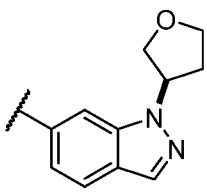
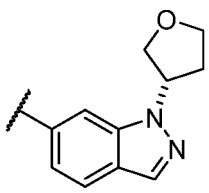
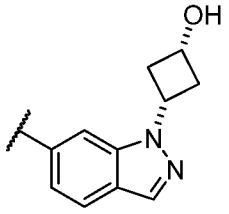
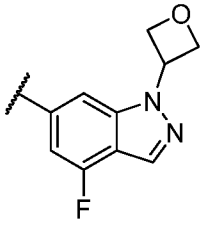
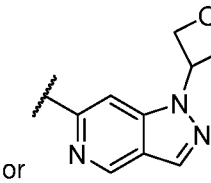
In some embodiments, R^{12} is  ,  ,  , or  .

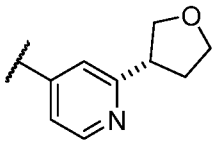
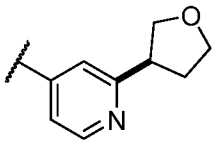
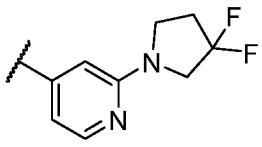
In some embodiments, R^{12} is  . In some embodiments, R^{12} is  . In some embodiments, R^{12} is  .

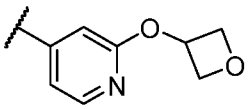
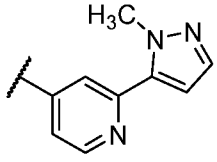
In some embodiments, R^{13} is  ,  ,  ,  ,  , or  .

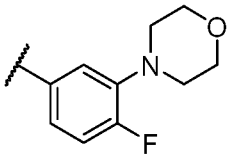
In some embodiments, R^{13} is  or  .

In some embodiments, R^5 is is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or .

In some embodiments, R^5 is  ,  ,  ,  ,  , or  .

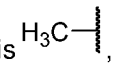
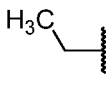
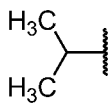
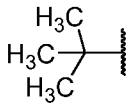
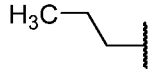
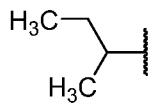
In some embodiments, R^5 is  ,  ,  ,

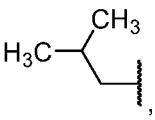
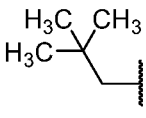
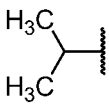
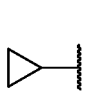
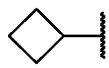
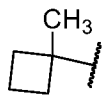
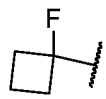
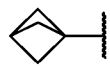
 , or  .

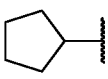
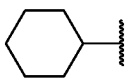
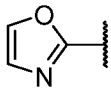
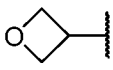
In some embodiments, R^5 is  .

In some embodiments, R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heterocycle, or optionally substituted C_2-C_9 heteroaryl.

In some embodiments, R^1 is optionally substituted C_1-C_6 alkyl or optionally substituted C_3-C_{10} C_3-C_7 cycloalkyl.

In some embodiments, R^1 is  ,  ,  ,  ,  ,  ,

 ,  ,  ,  , , ,  ,  ,  ,  ,

 ,  ,  , or  .

In another aspect, the disclosure provides a compound, or pharmaceutically acceptable salt thereof, having the structure of any one of compounds 1-1195 in Table 1, Table 2A, and Table 2B. In some embodiments, the compound is any one of compounds 1-746 in Table 1. In some embodiments, the compound is any one of compounds 1-155 in Table 1. In some embodiments, the compound is any one of compounds 156-746 in Table 1. In some embodiments, the compound is any one of compounds 747-966. In some embodiments, the compound is any one of compounds 967-1195. In some embodiments, the compound is any one of compounds 527, 615, 617, 676, 713, 735, In some embodiments, the compound is any one of compounds 1-264, 266-271, 274-276, 278-299, 302- 318, 320-329, 331-340, 344-354, 358, 362-364, 367, 369, 371-378, 385, 388-392, 396, 397, 399-401, 403, 406-411, 414, 418-420, 422, 425-432, 434-436, 438, 440-444, 446, 450-454, 456, 458, 460, 461, 464, 466, 470, 472-474, 476, 477, or 481-746 in Table 1. In some embodiments, the compound is any one of compounds 1-347, 349, 350, or 354-746 in Table 1. In some embodiments, the compound is any one of compounds 1-387, 389, 393-405, 407-430, 432-439, 441-449, 452, 454-457, 459-472, 475, 477-480, 482-487, or 489-746 in Table 1, In some embodiments, the compound is any one of compounds 1-483 or 491-746 in Table 1. In some embodiments, the compound is any one of compounds 747-966. In some embodiments, the compound is any one of compounds 27, 40, 96, 128, 140, 168, 184, 204, 226, 244, 265, 268, 269, 284, 286 291, 294, 302, 305, 306, 308, 317, 319, 343, 344, 345, 346, 349, 355-357, or

359-364. In some embodiments, the compound is any one of compounds 244, 265, 269, 319, 345, 349, 355-357, 361, or 364. In some embodiments, the compound is any one of compounds 750, 767, 775-778, 780, 784, 785, 789-792, 795, 799, 812, 813, 817, 828, 838, 839, 842-844, 846, 848, 850, 851, 853, 854, 861, 862, 865, 874-881, 884-888, 890-898, 902, 903, 907, 910, 916, 928, 932, 934, 953, 957, 960, 964, or 965. In some embodiments, the compound is any one of compounds 967-1195. In some embodiments, the compound is any one of compounds 970, 971, 974, 975, 979-982, 986, 988, 990, 992, 997, 999, 1000, 1003-1006, 1010, 1012, 1013, 1015-1026, 1028, 1029, 1031, 1034-1037, 1039-1050, 1052-1062, 1065-1073, 1075-1080, 1082-1087, 1090, 1092, 1093, 1096-1098, 1100, 1104, 1105, 1107, 1109-1114, 1125, 1131, 1134-1141, 1144, 1146, 1149, 1151-1154, 1156, 1161, 1162, 1164, 1170, 1171, 1175-1182, 1190, or 1192. In some embodiments, the compound is any one of compounds 970, 971, 974, 975, 979, 981, 982, 986, 988, 990, 992, 997, 999, 1005, 1012, 1016-1020, 1022, 1024, 1025, 1028, 1029, 1036, 1039, 1041-1043, 1046-1050, 1053-1062, 1065-1073, 1075, 1078, 1082-1084, 1086, 1087, 1092, 1093, 1096-1098, 1104, 1107, 1109-1112, 1114, 1134-1137, 1139, 1140, 1144, 1149, 1152, 1154, 1161, 1162, 1171, 1176, 1180, 1190, or 1192. In some embodiments, the compound is any one of compounds 970, 971, 974, 975, 986, 988, 990, 997, 999, 1005, 1012, 1016-1019, 1022, 1024, 1025, 1028, 1029, 1036, 1039, 1041, 1043, 1046-1050, 1053-1059, 1061, 1062, 1065-1073, 1075, 1078, 1083, 1084, 1086, 1087, 1092, 1093, 1096, 1097, 1104, 1107, 1109, 1110, 1134, 1136, 1137, 1139, 1140, 1144, 1149, 1152, 1154, 1161, 1162, 1171, 1180, 1190, or 1192. In some embodiments, the compound is any one of compounds 970, 1053-1056, 1058, 1059, 1065-1069, 1071-1073, 1093, or 1096.

Table 1. Compounds of the Invention

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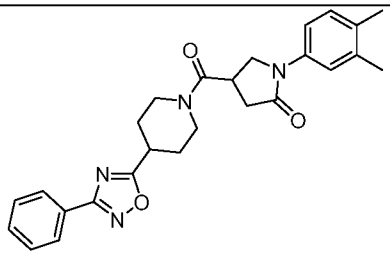
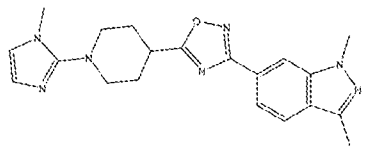
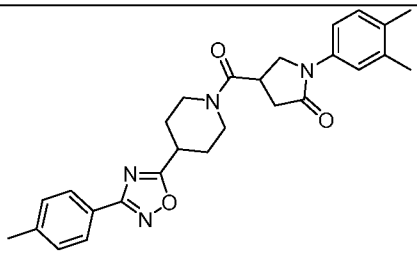
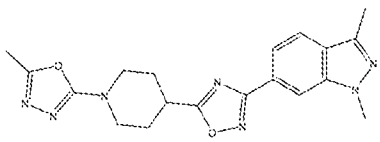
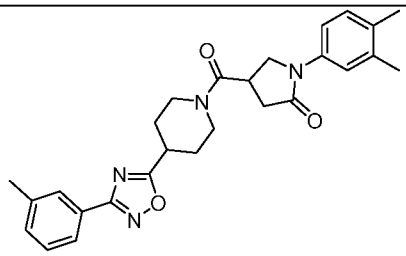
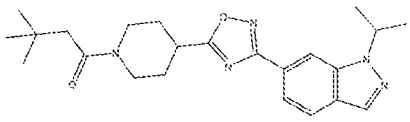
1		374	
2		375	
3		376	

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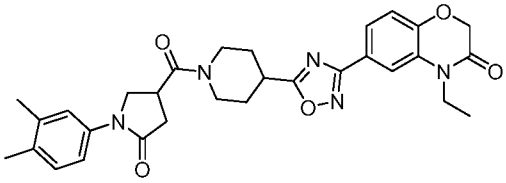
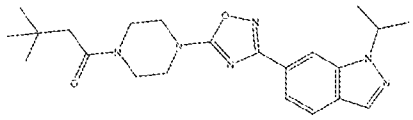
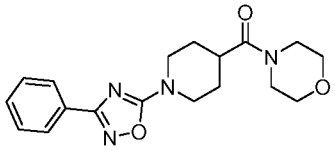
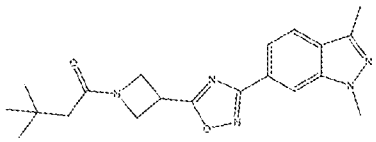
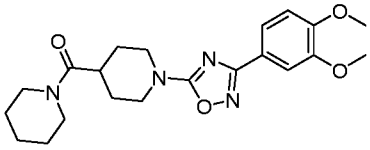
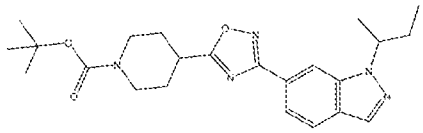
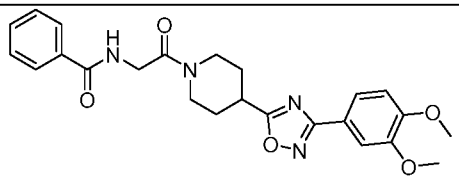
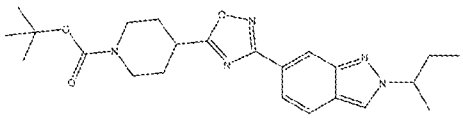
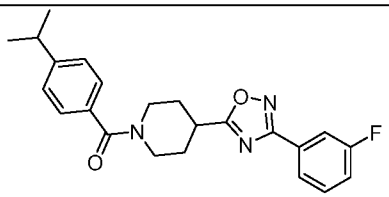
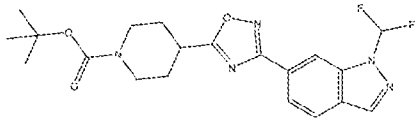
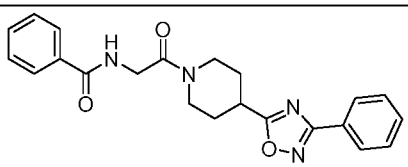
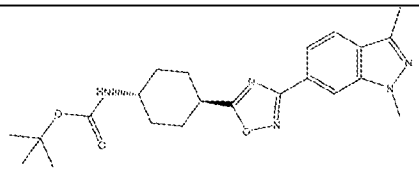
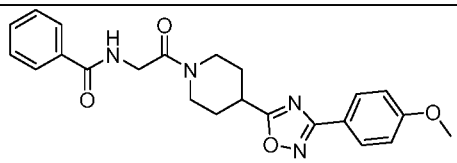
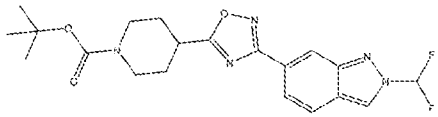
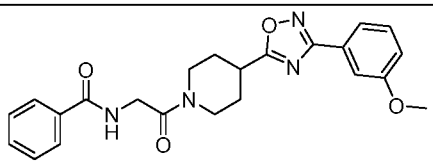
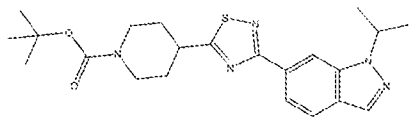
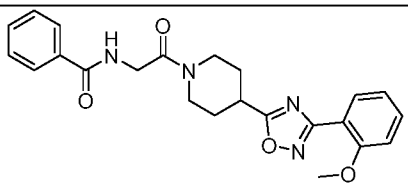
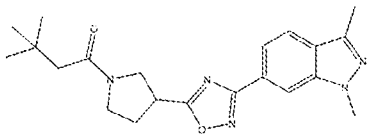
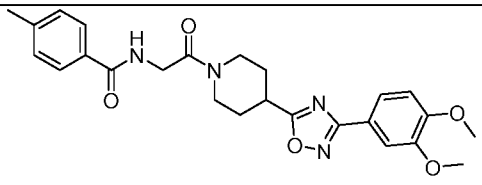
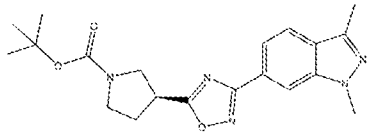
4		377	
5		378	
6		379	
7		380	
8		381	
9		382	
10		383	
11		384	
12		385	
13		386	

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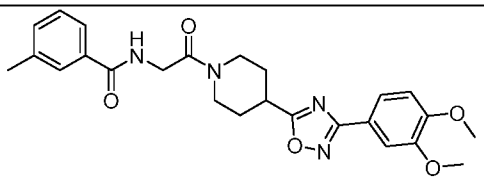
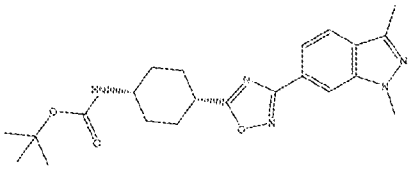
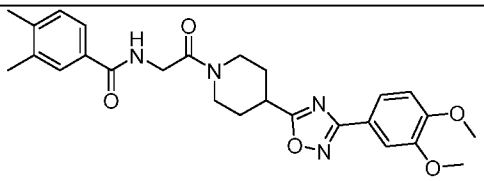
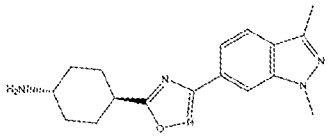
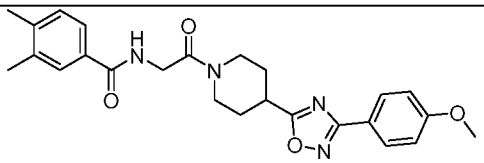
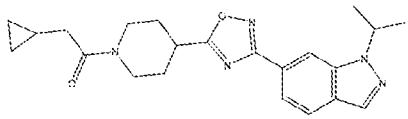
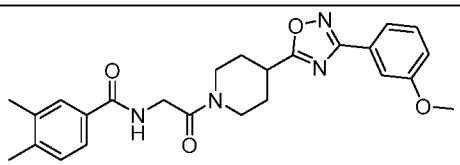
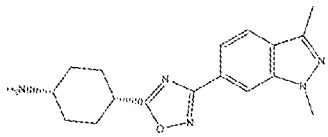
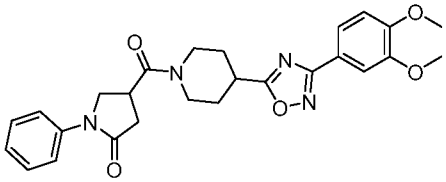
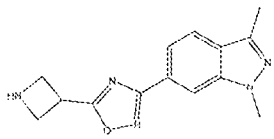
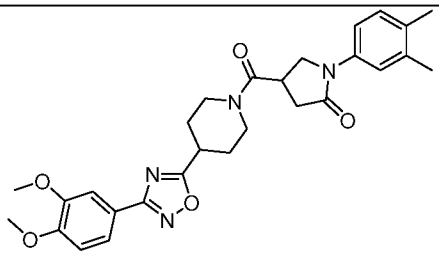
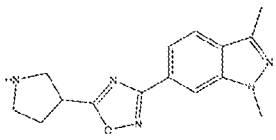
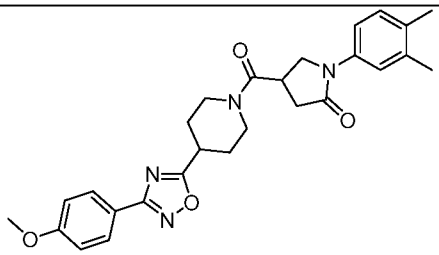
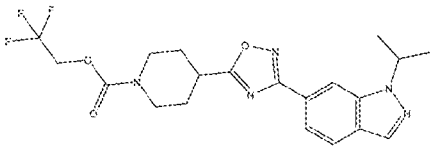
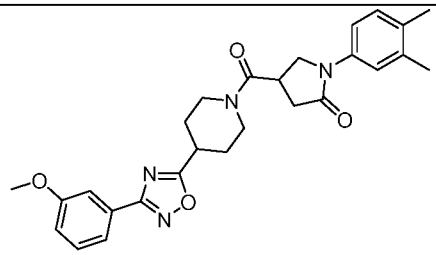
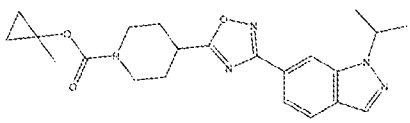
14		387	
15		388	
16		389	
17		390	
18		391	
19		392	
20		393	
21		394	

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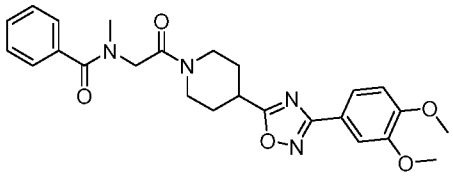
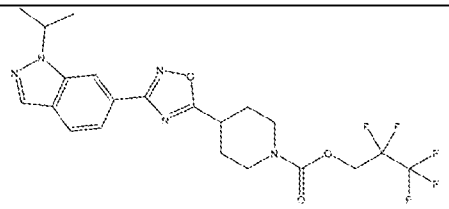
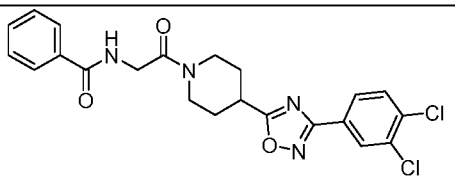
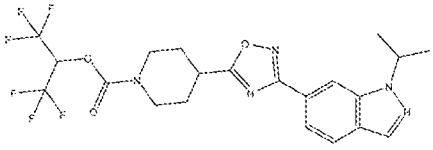
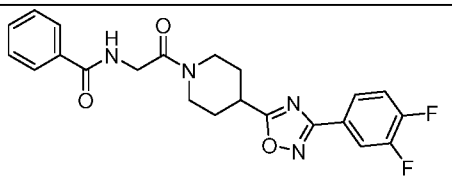
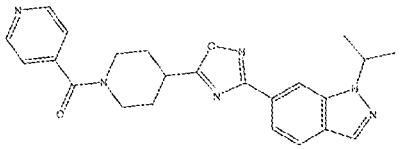
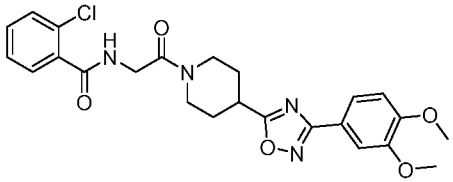
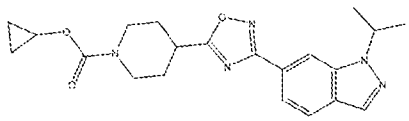
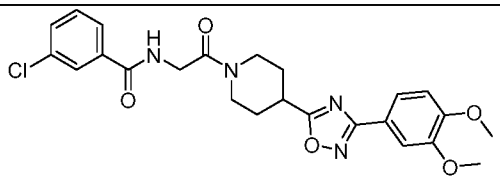
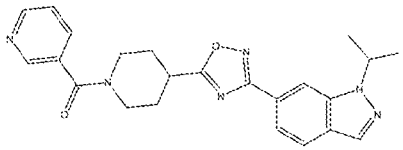
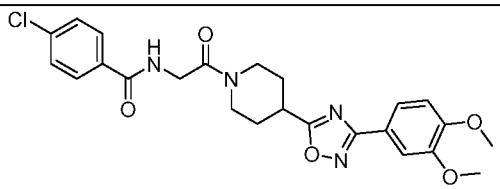
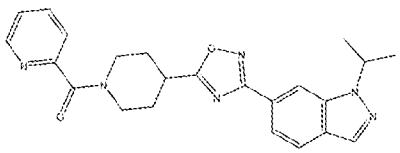
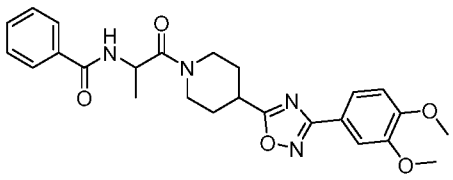
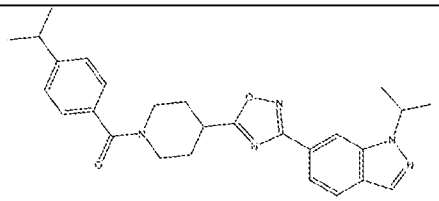
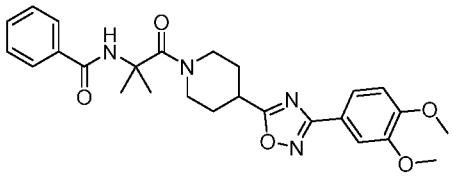
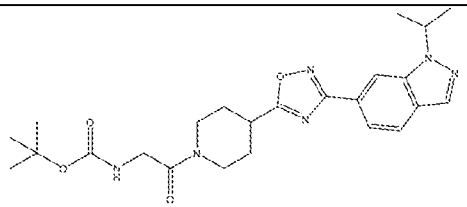
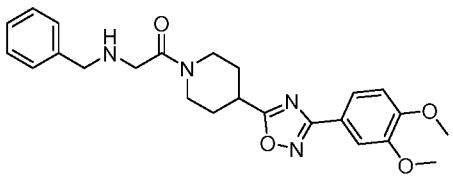
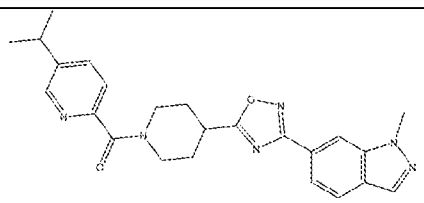
22		395	
23		396	
24		397	
25		398	
26		399	
27		400	
28		401	
29		402	
30		403	

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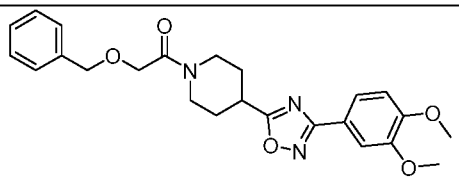
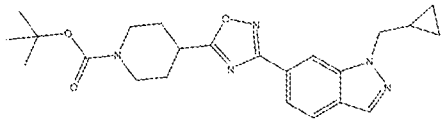
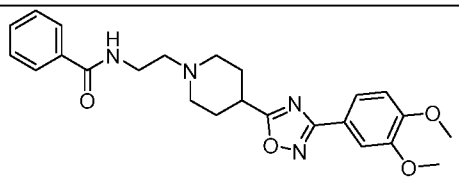
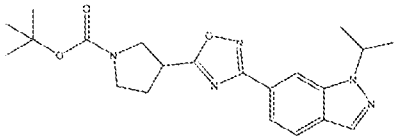
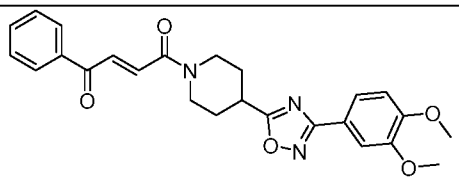
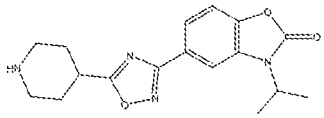
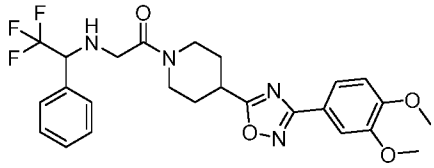
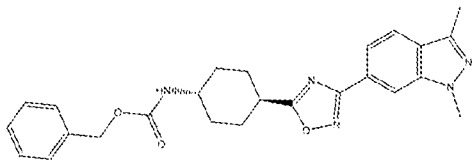
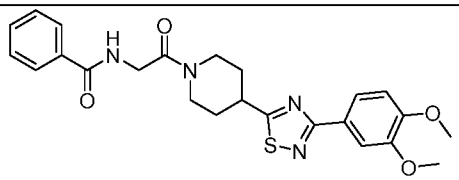
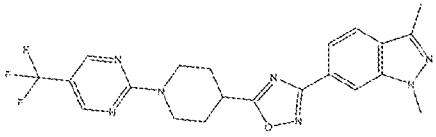
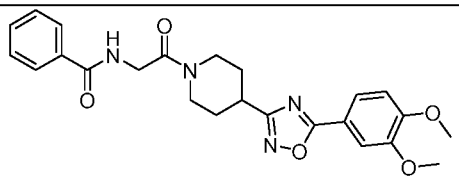
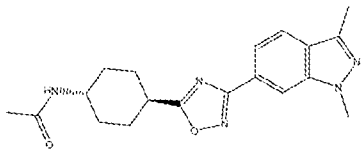
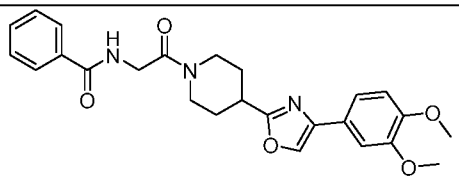
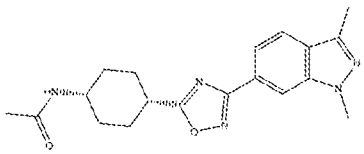
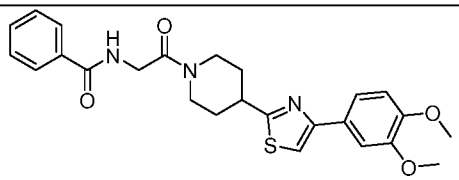
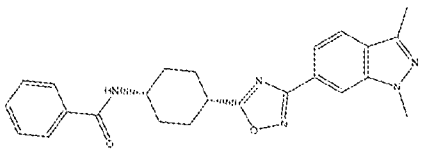
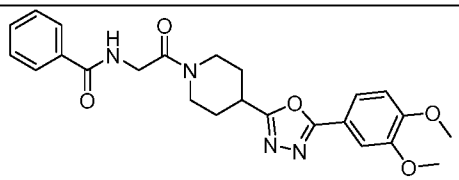
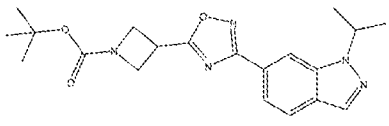
31		404	
32		405	
33		406	
34		407	
35		408	
36		409	
37		410	
38		411	
39		412	

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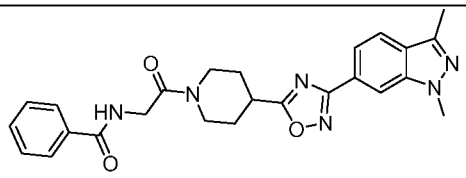
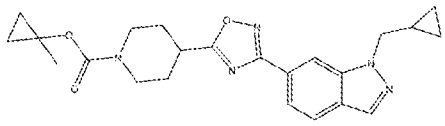
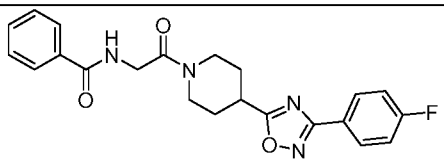
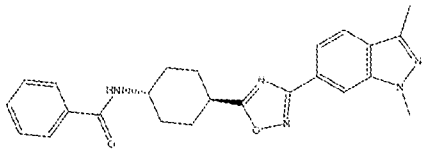
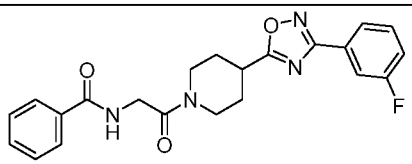
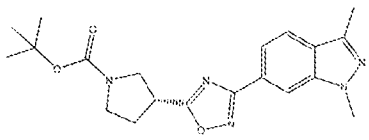
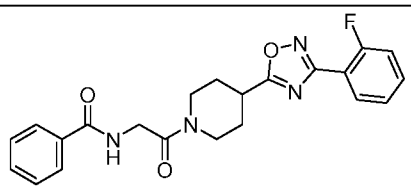
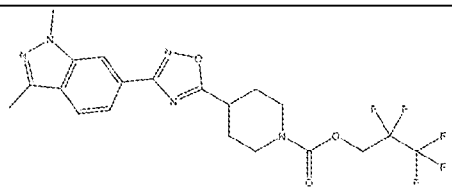
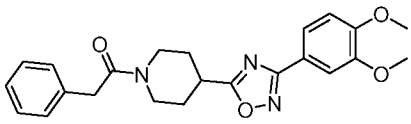
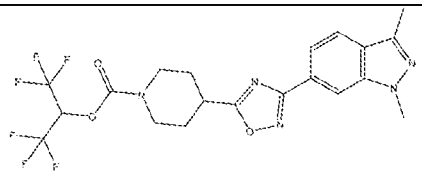
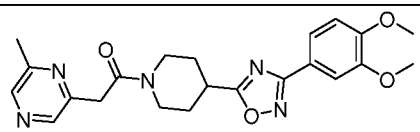
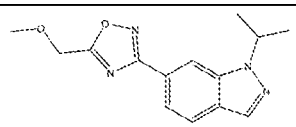
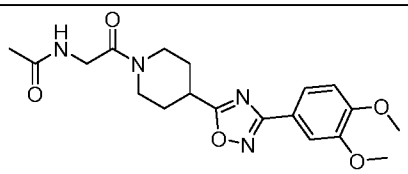
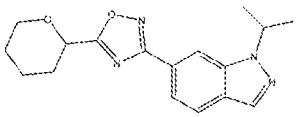
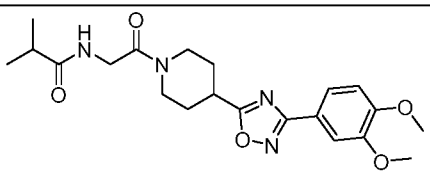
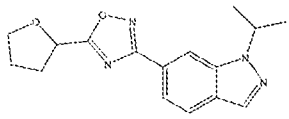
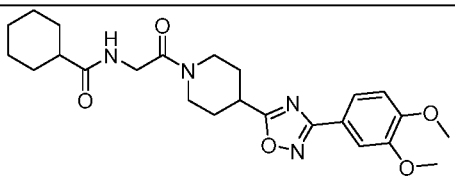
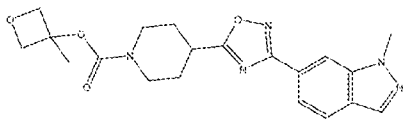
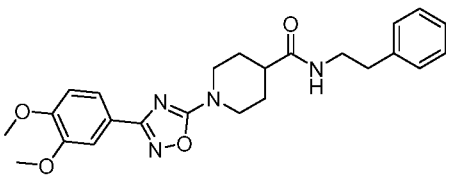
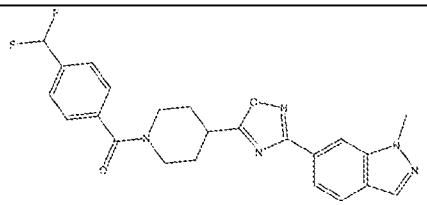
40		413	
41		414	
42		415	
43		416	
44		417	
45		418	
46		419	
47		420	
48		421	
49		422	

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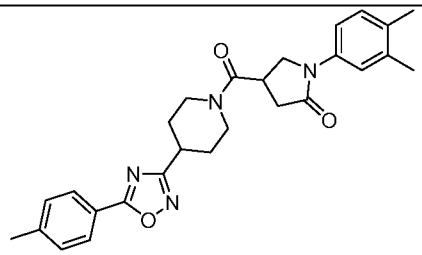
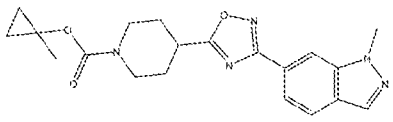
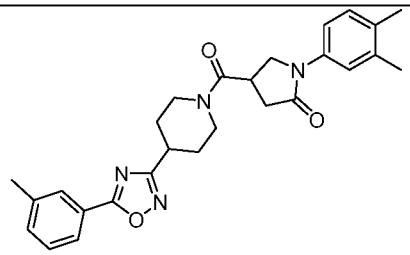
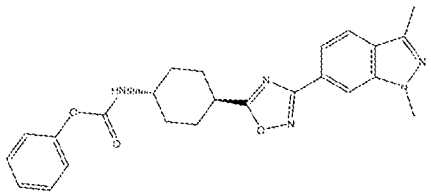
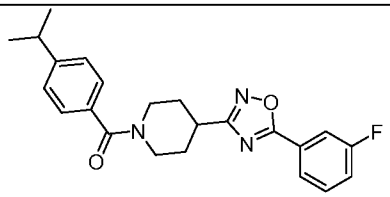
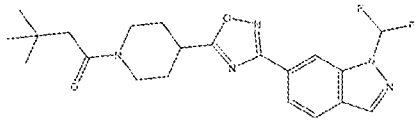
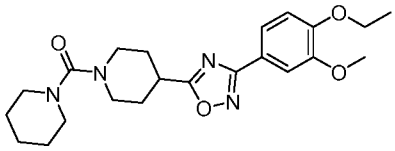
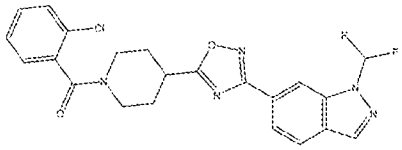
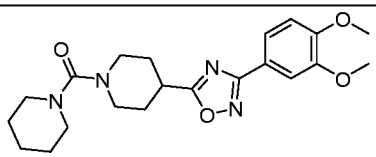
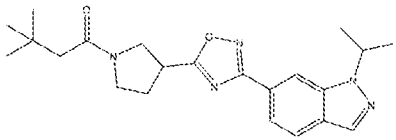
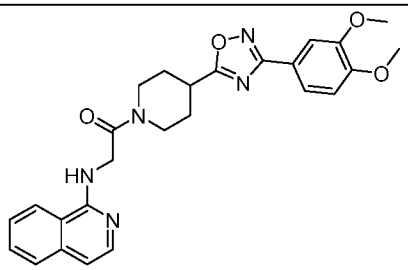
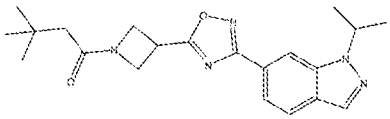
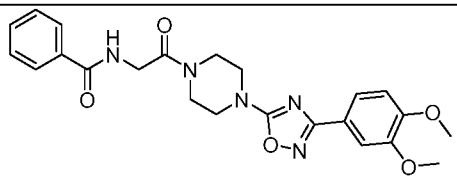
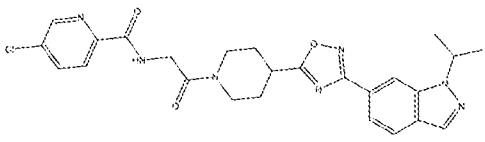
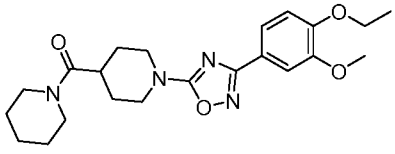
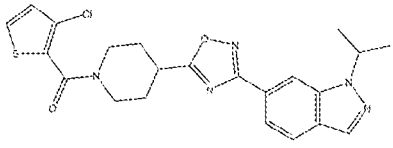
50		423	
51		424	
52		425	
53		426	
54		427	
55		428	
56		429	
57		430	

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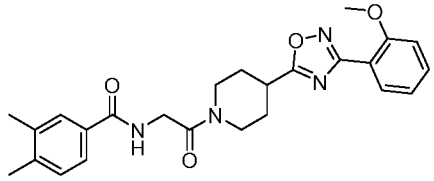
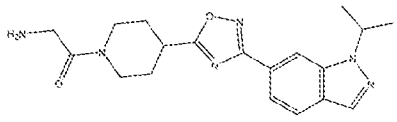
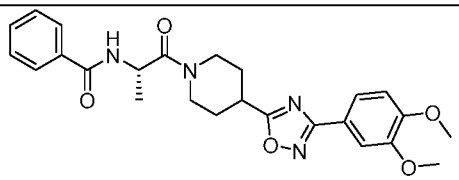
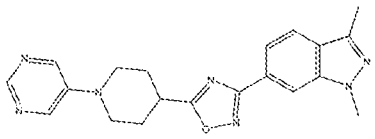
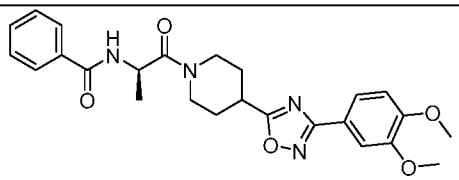
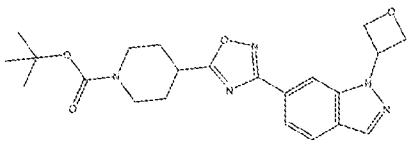
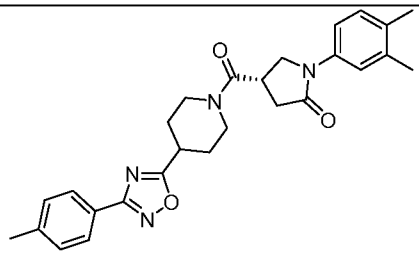
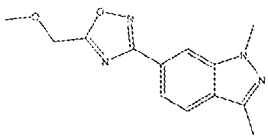
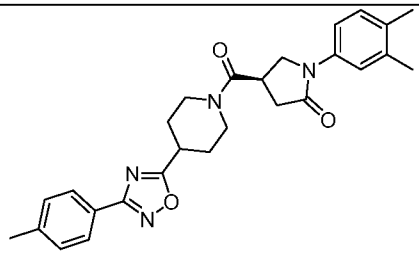
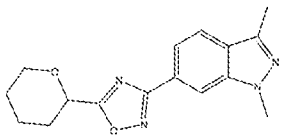
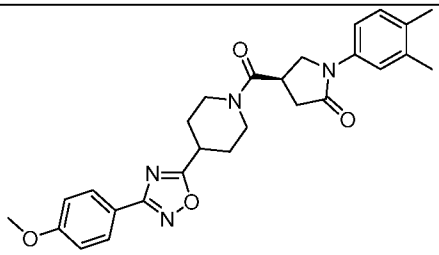
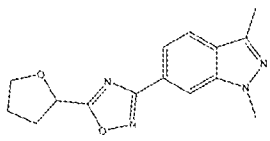
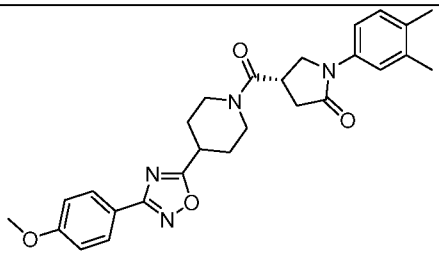
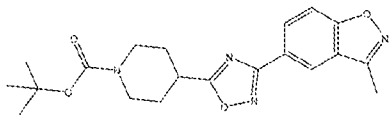
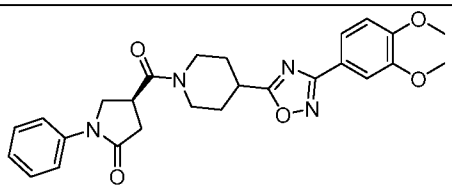
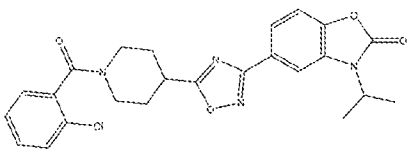
58		431	
59		432	
60		433	
61		434	
62		435	
63		436	
64		437	
65		438	

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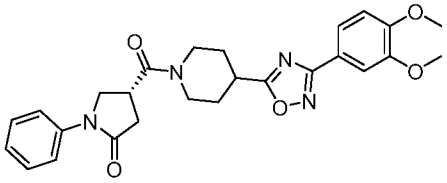
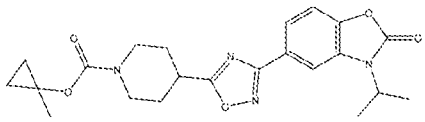
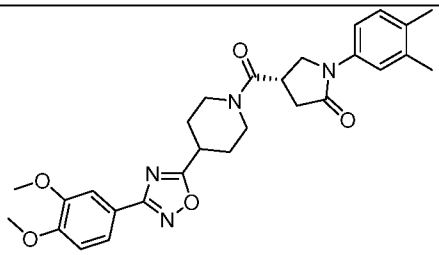
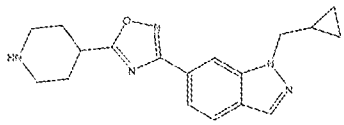
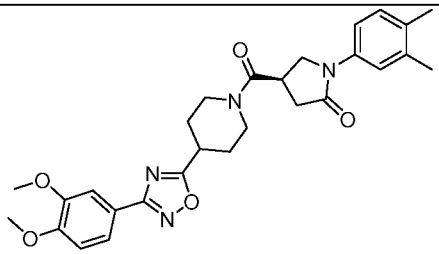
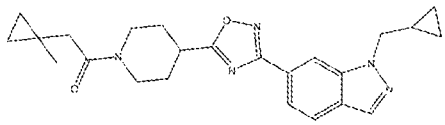
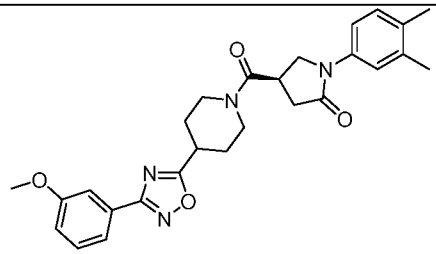
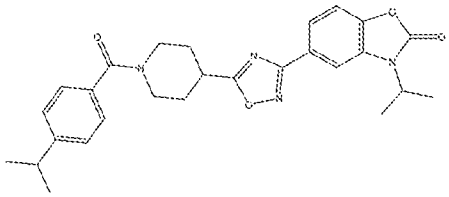
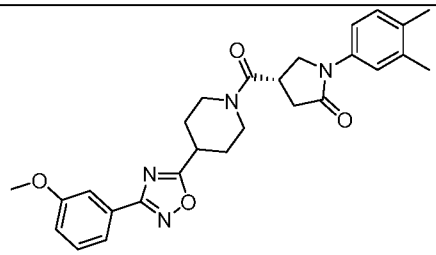
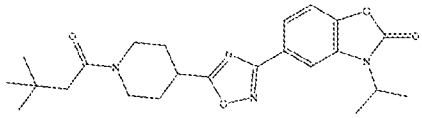
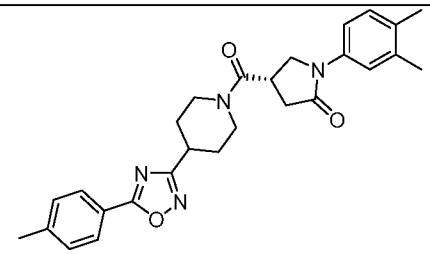
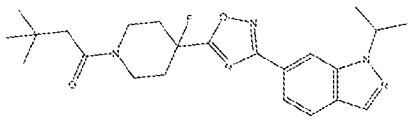
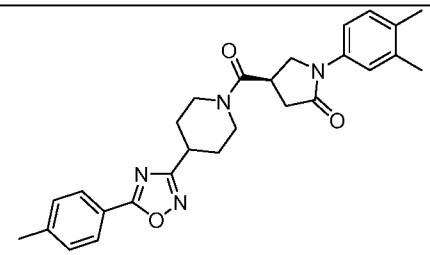
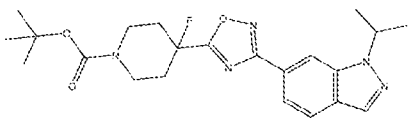
66		439	
67		440	
68		441	
69		442	
70		443	
71		444	
72		445	

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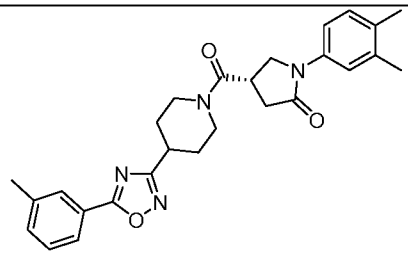
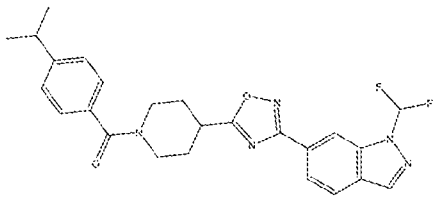
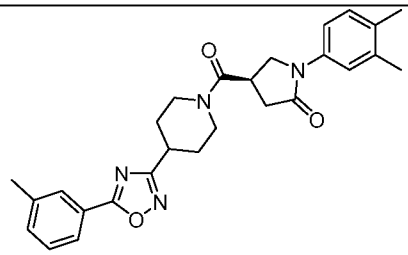
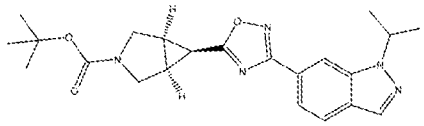
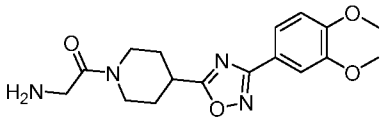
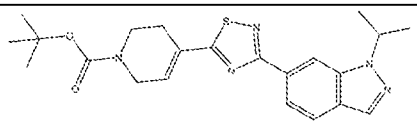
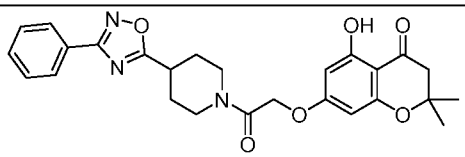
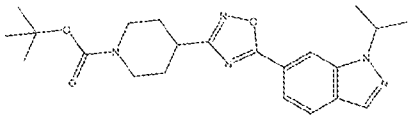
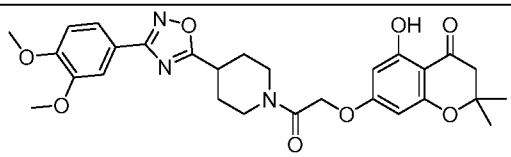
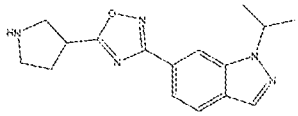
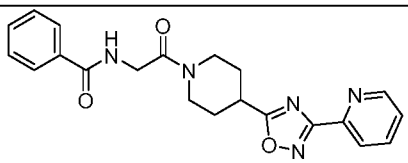
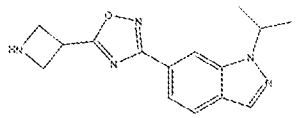
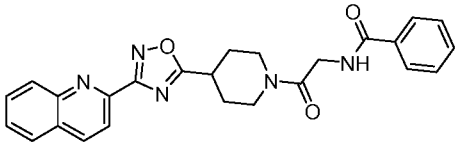
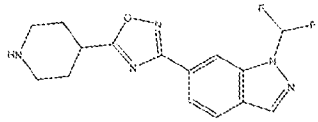
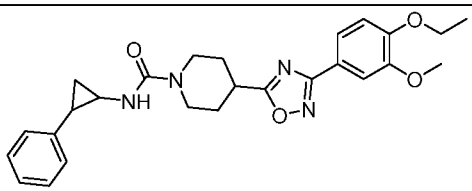
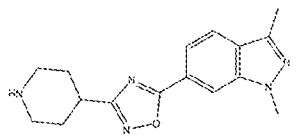
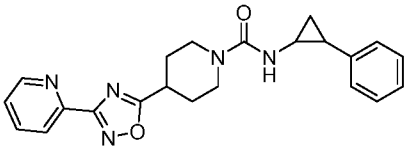
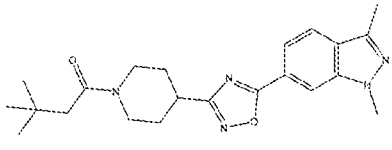
73		446	
74		447	
75		448	
76		449	
77		450	
78		451	
79		452	
80		453	
81		454	

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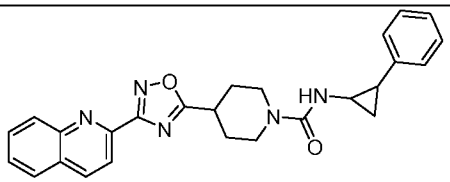
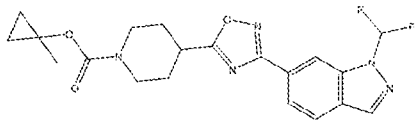
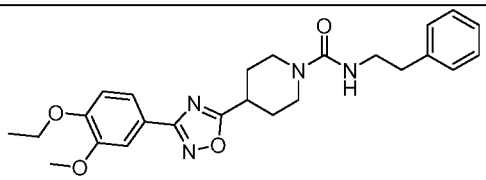
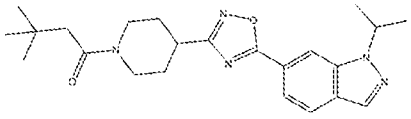
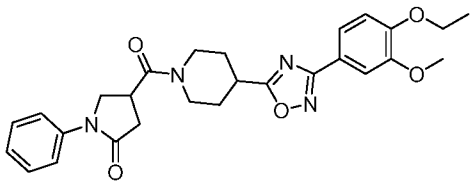
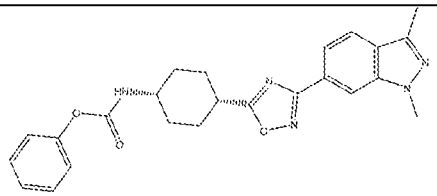
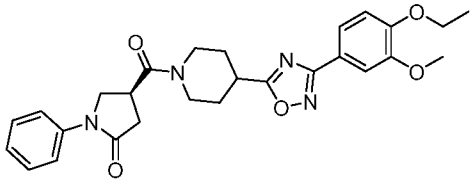
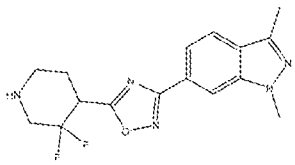
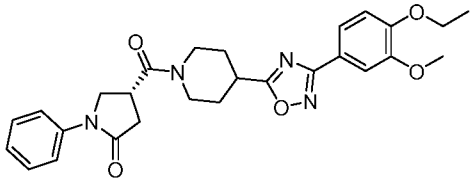
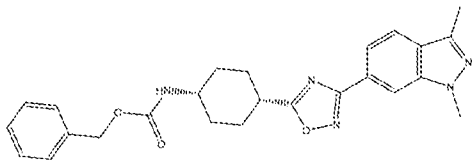
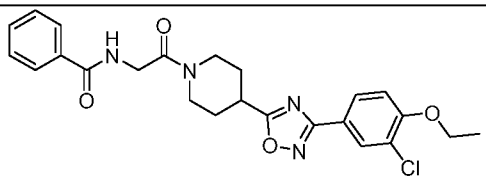
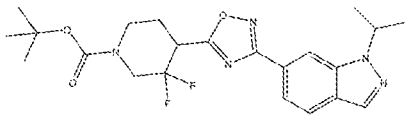
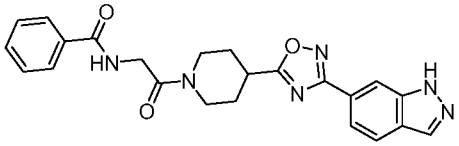
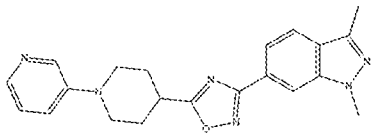
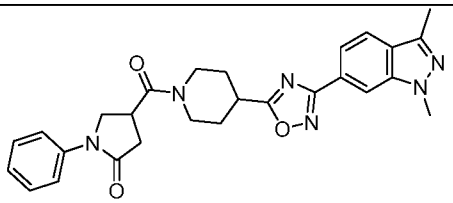
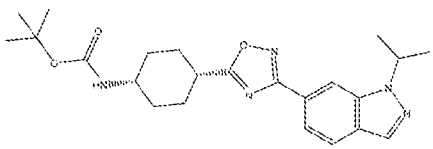
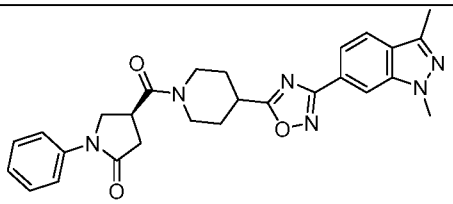
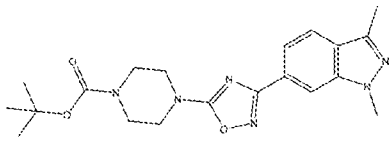
82		455	
83		456	
84		457	
85		458	
86		459	
87		460	
88		461	
89		462	
90		463	

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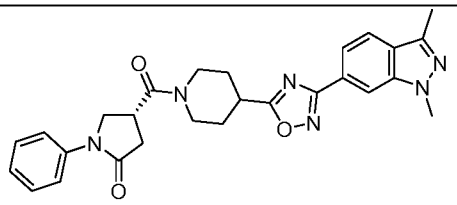
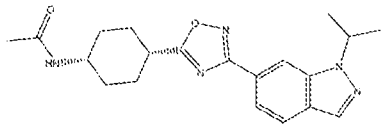
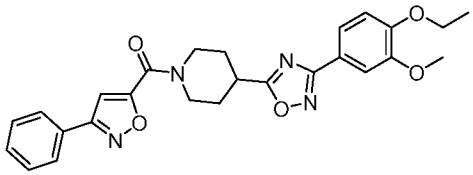
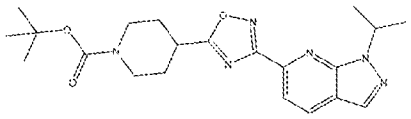
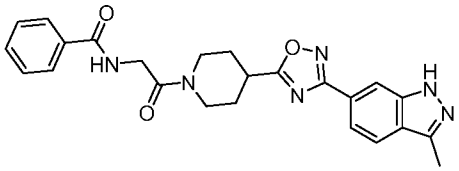
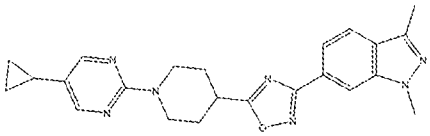
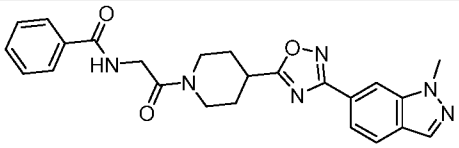
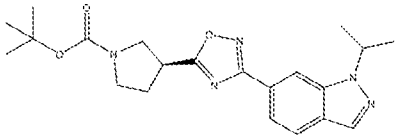
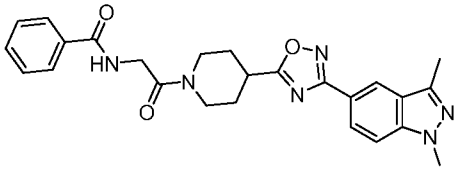
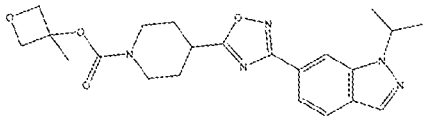
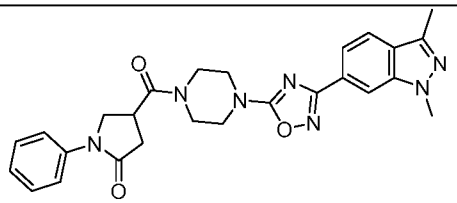
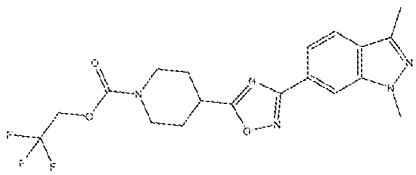
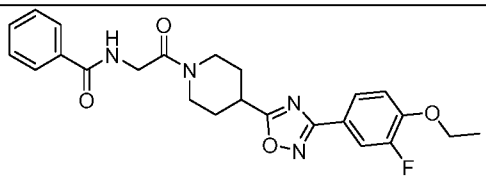
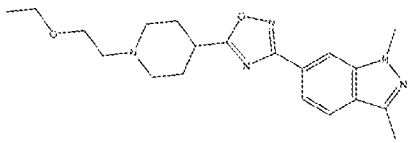
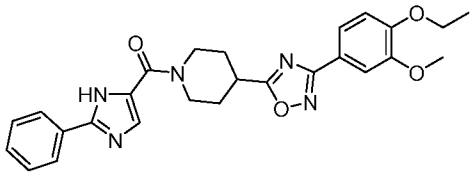
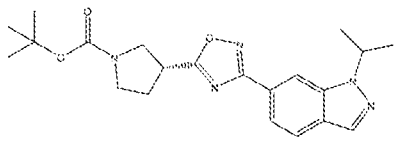
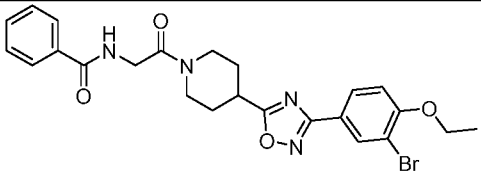
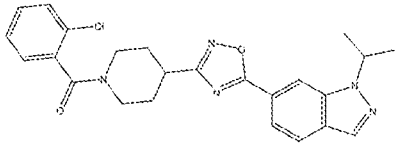
91		464	
92		465	
93		466	
94		467	
95		468	
96		469	
97		470	
98		471	
99		472	

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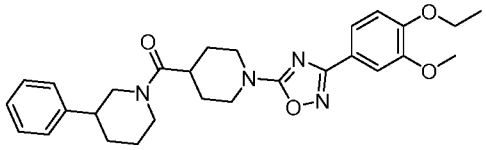
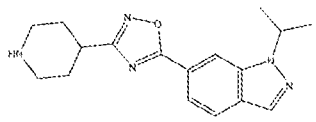
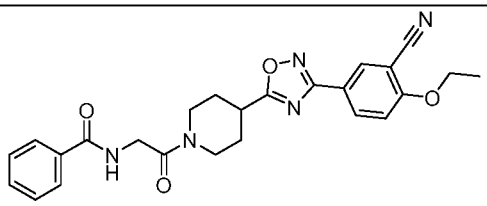
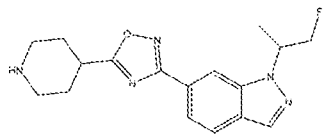
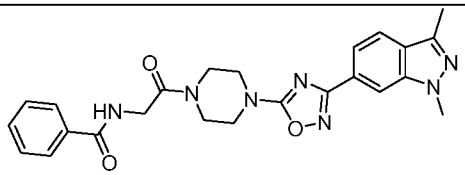
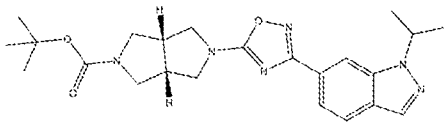
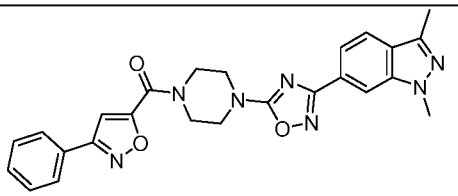
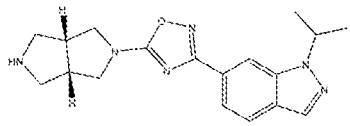
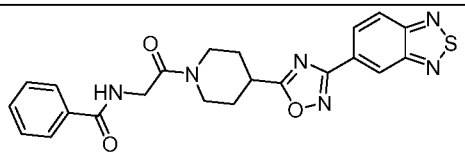
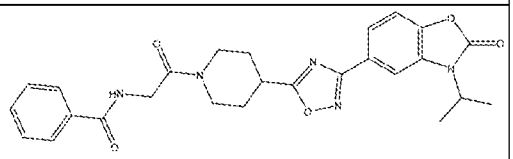
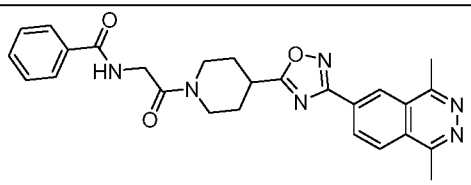
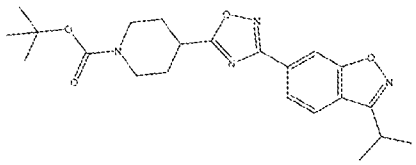
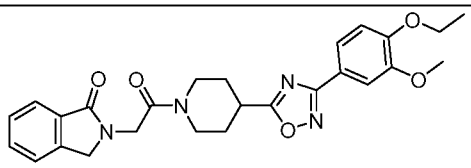
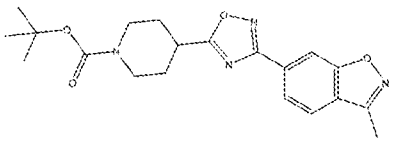
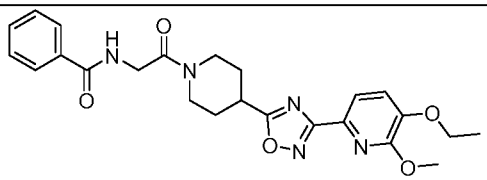
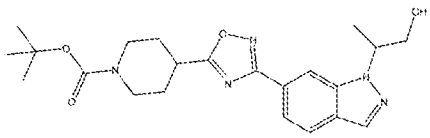
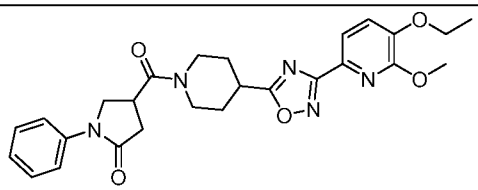
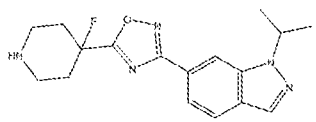
100		473	
101		474	
102		475	
103		476	
104		477	
105		478	
106		479	
107		480	
108		481	

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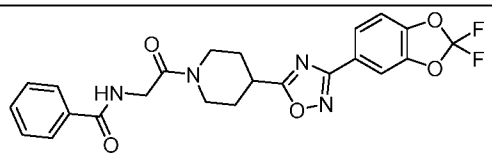
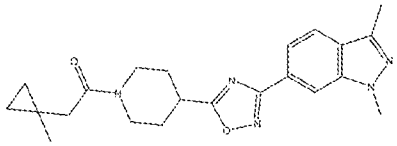
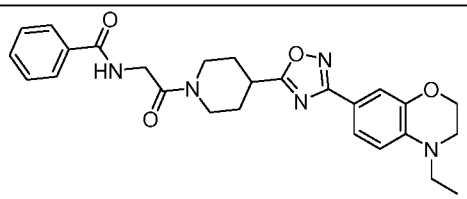
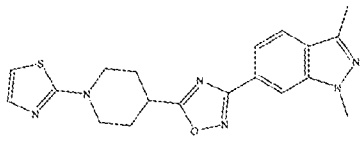
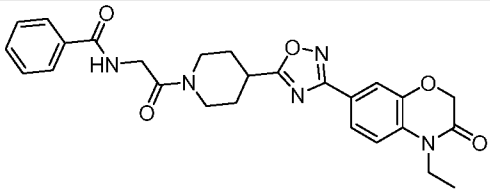
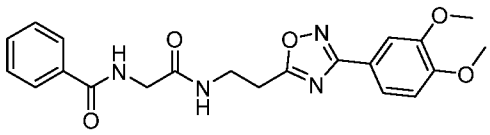
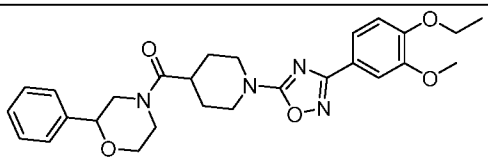
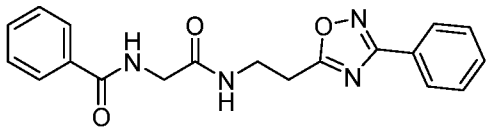
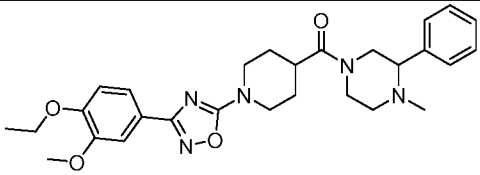
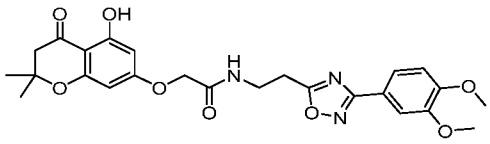
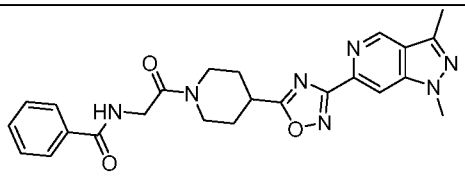
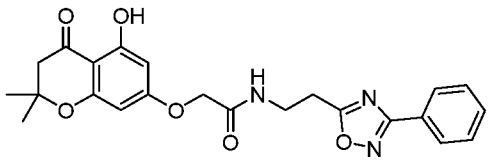
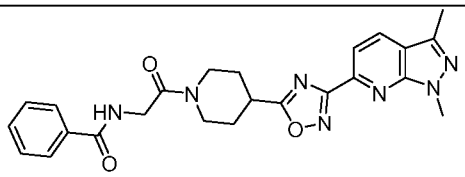
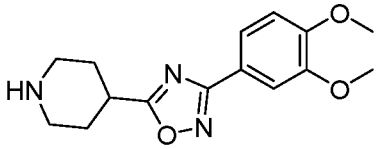
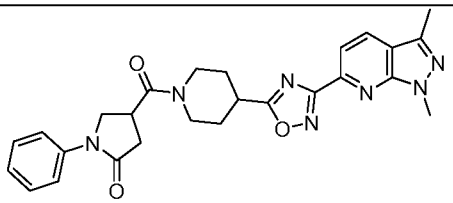
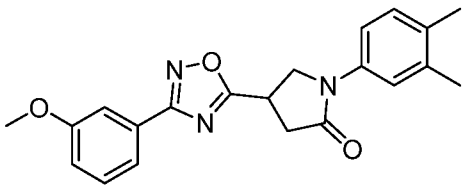
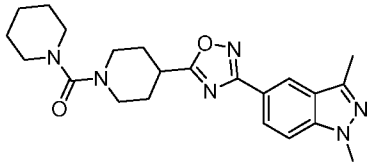
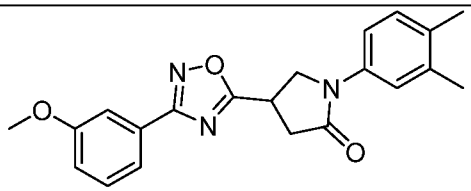
109		482	
110		483	
111		484	
112		485	
113		486	
114		487	
115		488	
116		489	
117		490	

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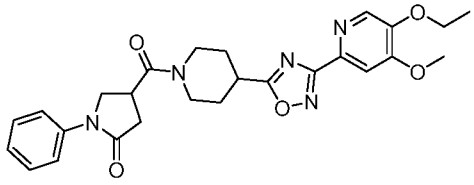
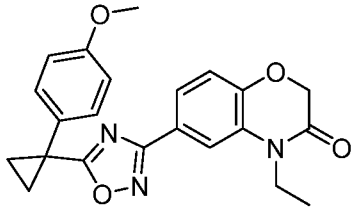
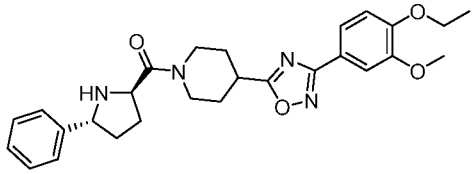
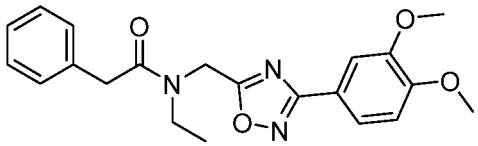
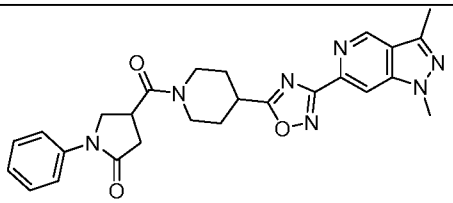
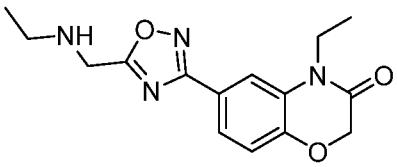
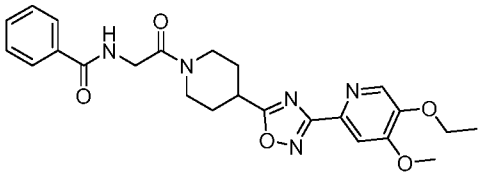
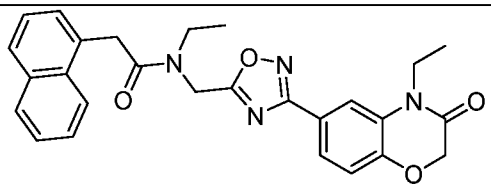
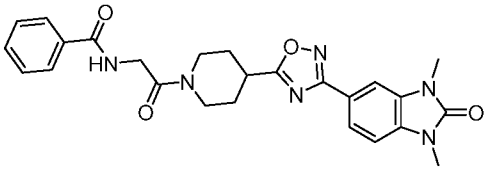
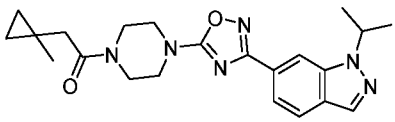
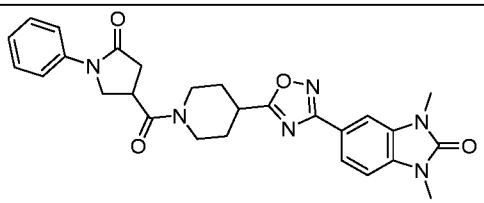
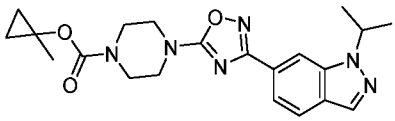
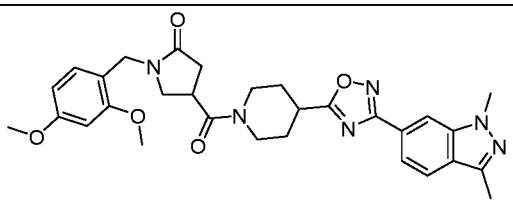
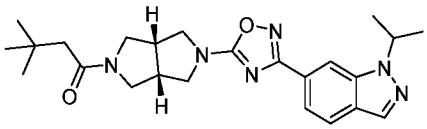
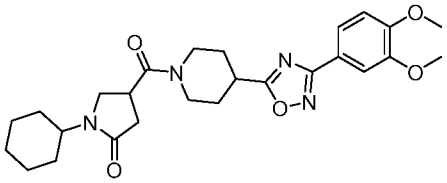
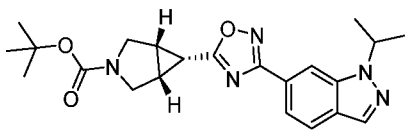
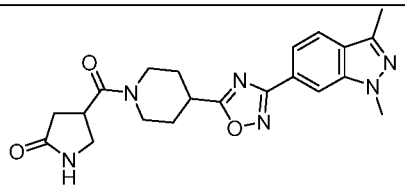
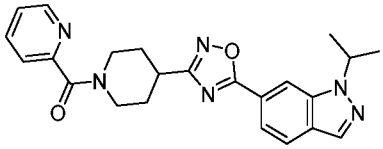
118		491	
119		492	
120		493	
121		494	
122		495	
123		496	
124		497	
125		498	
126		499	

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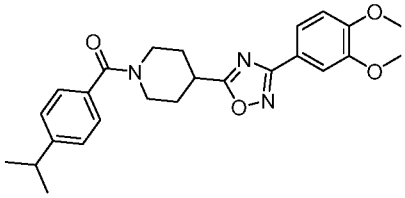
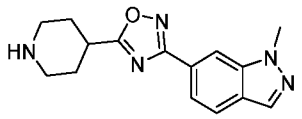
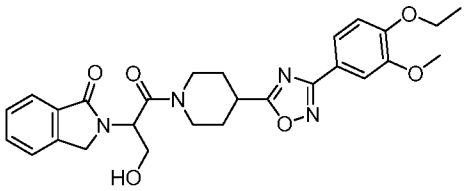
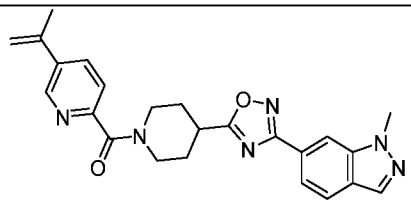
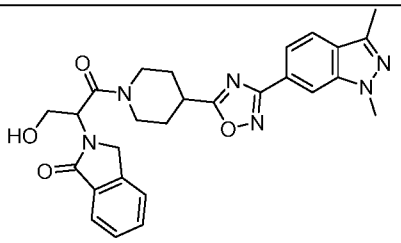
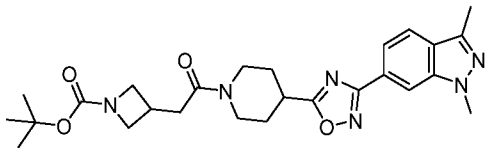
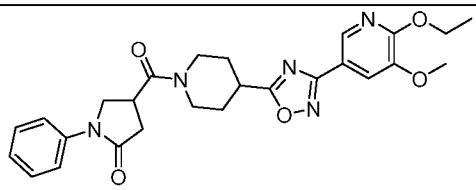
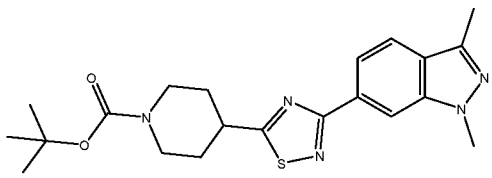
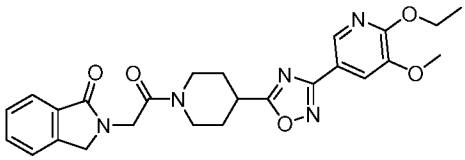
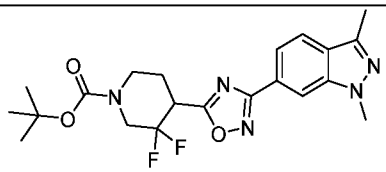
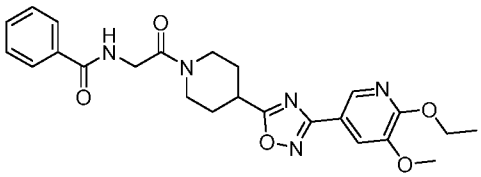
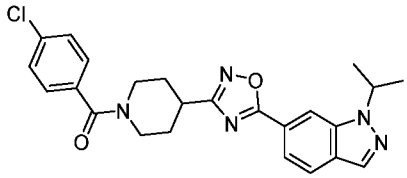
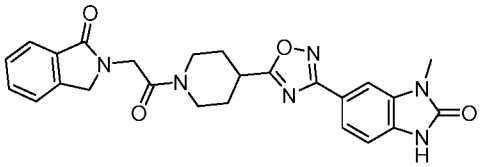
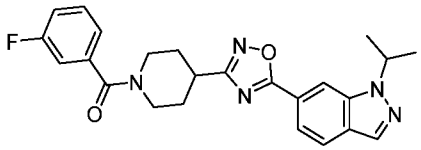
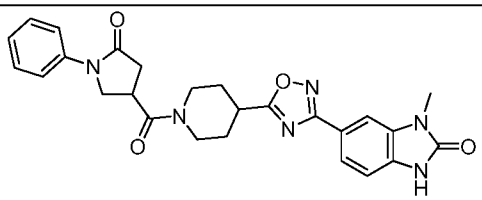
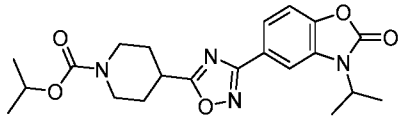
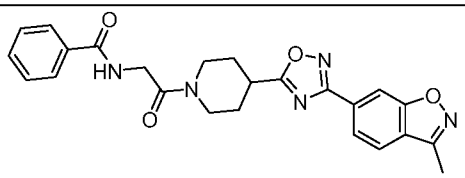
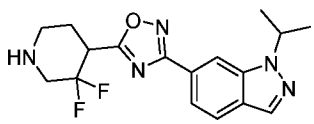
127		500	
128		501	
129		502	
130		503	
131		504	
132		505	
133		506	
134		507	
135		508	

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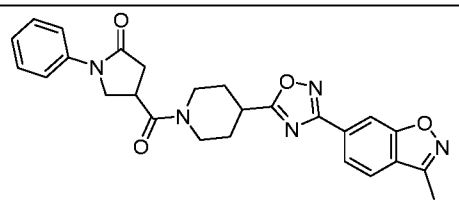
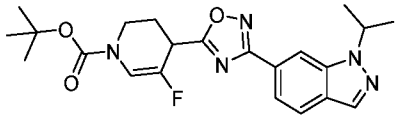
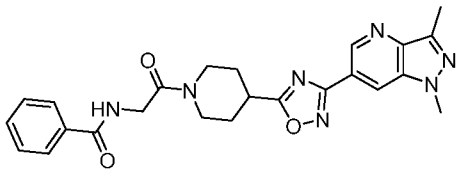
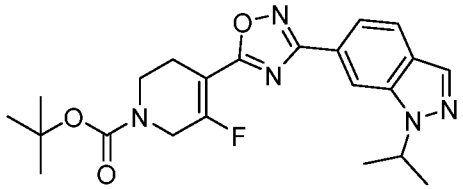
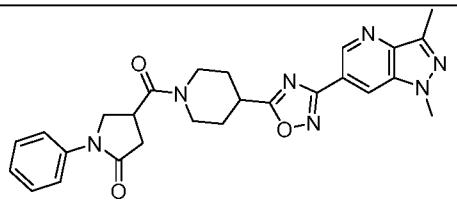
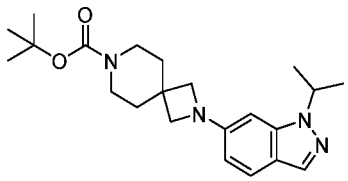
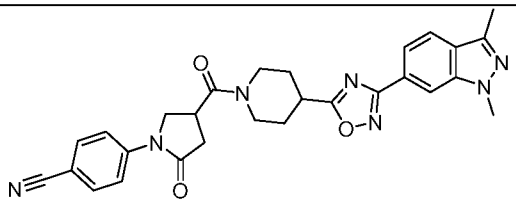
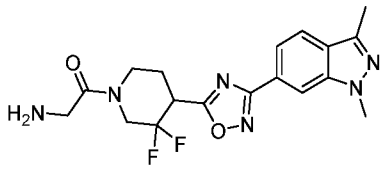
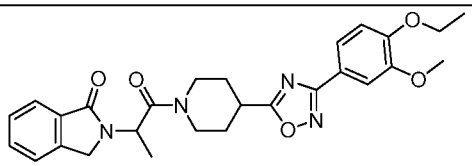
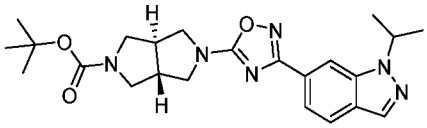
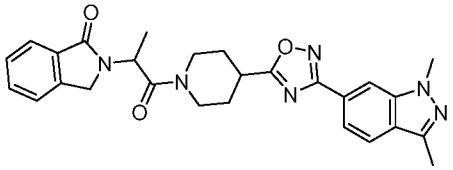
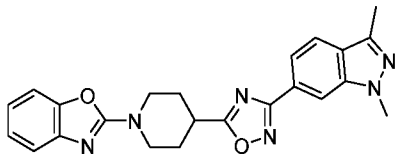
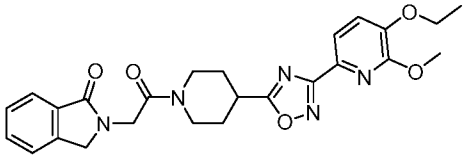
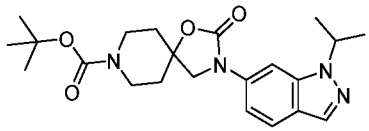
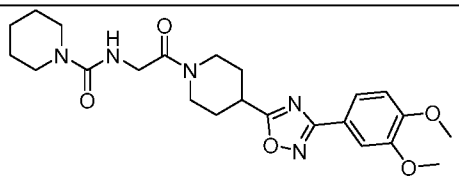
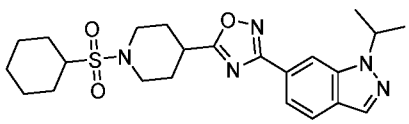
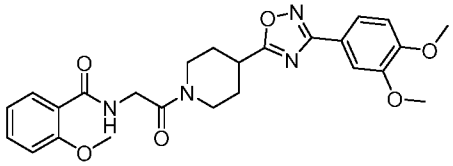
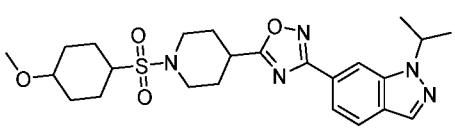
136		509	
137		510	
138		511	
139		512	
140		513	
141		514	
142		515	
143		516	
144		517	

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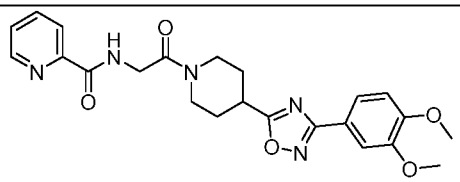
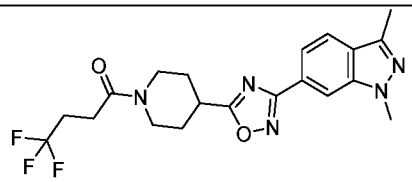
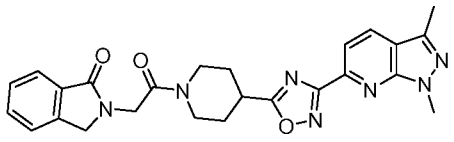
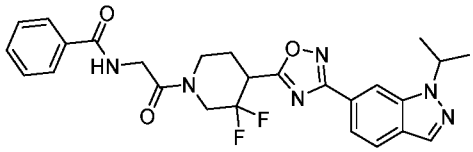
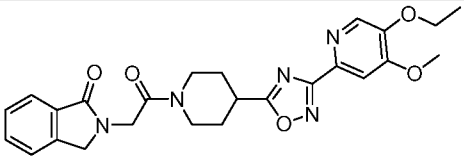
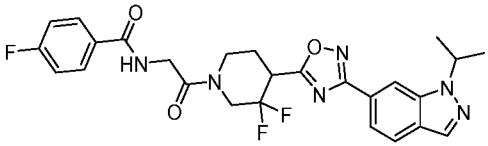
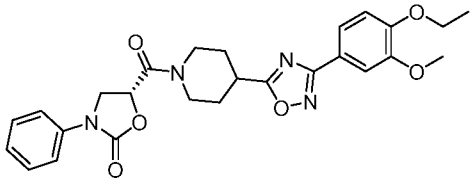
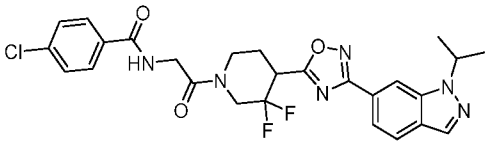
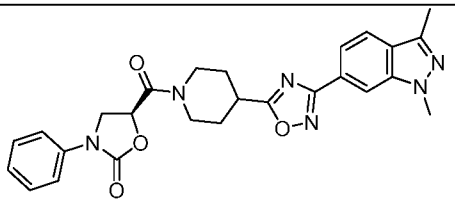
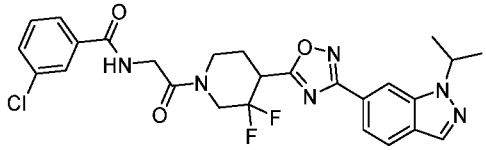
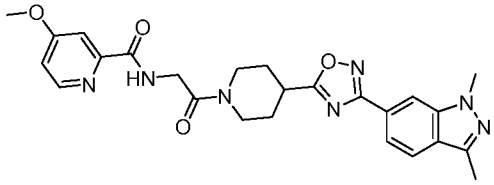
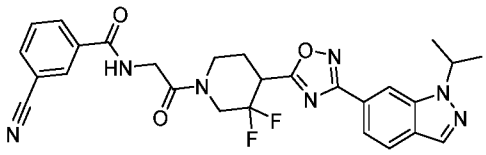
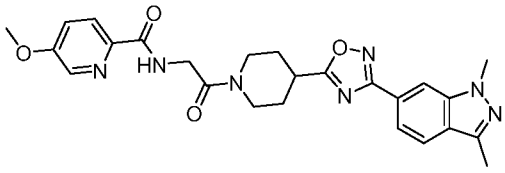
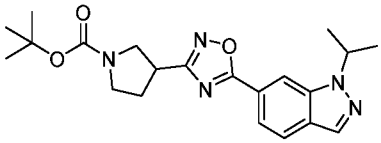
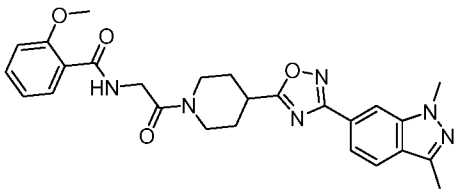
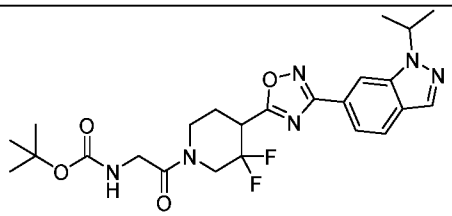
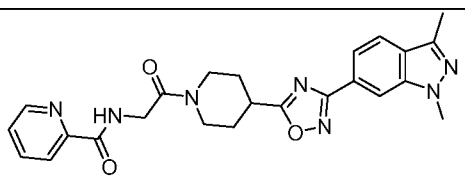
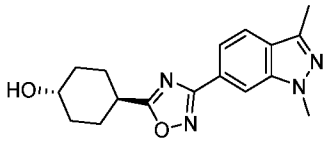
145		518	
146		519	
147		520	
148		521	
149		522	
150		523	
151		524	
152		525	
153		526	

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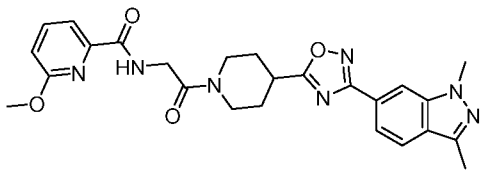
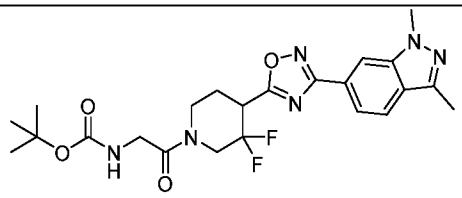
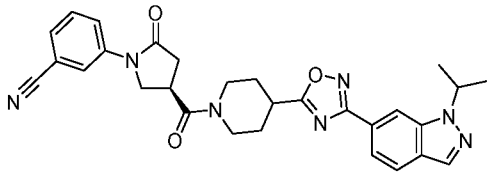
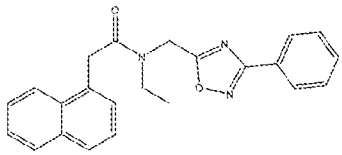
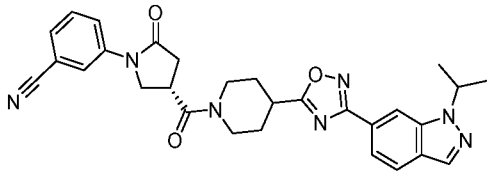
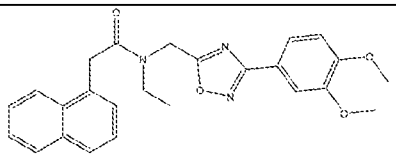
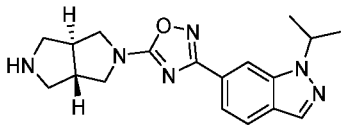
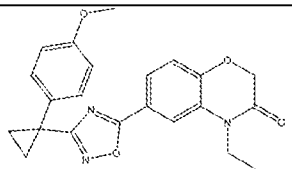
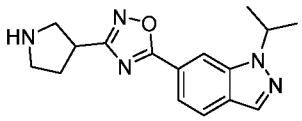
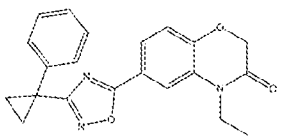
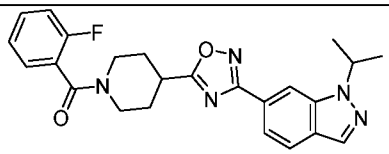
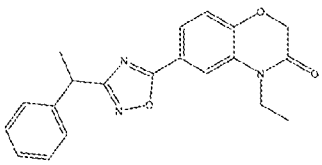
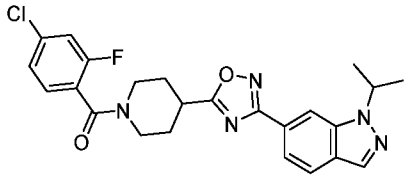
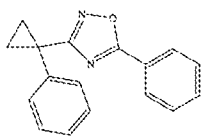
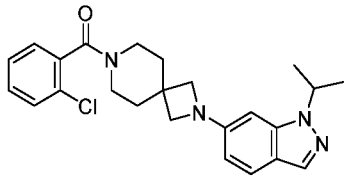
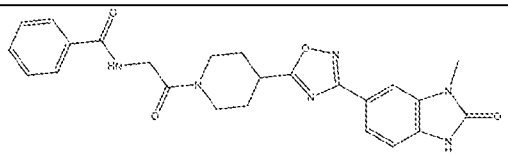
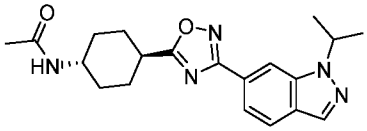
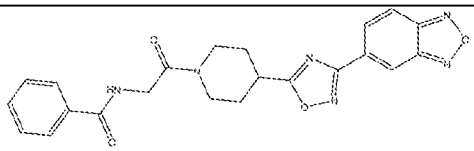
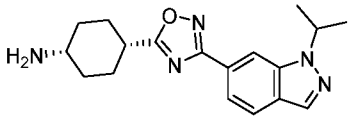
154		527	
155		528	
156		529	
157		530	
158		531	
159		532	
160		533	
161		534	
162		535	
163		536	

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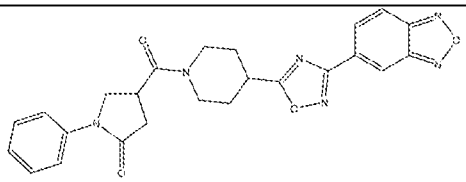
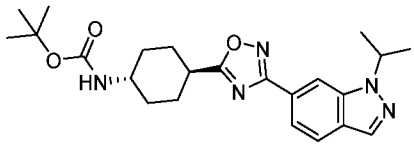
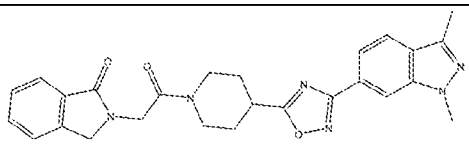
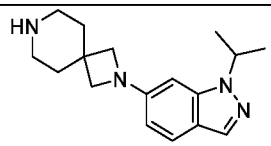
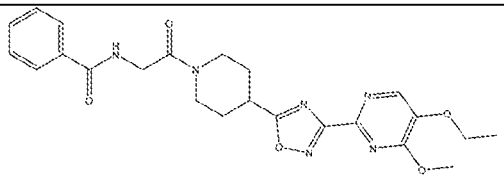
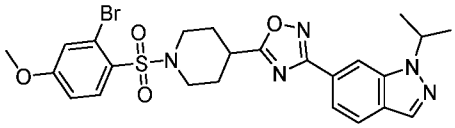
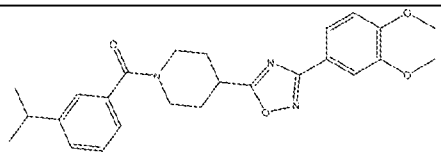
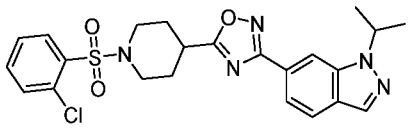
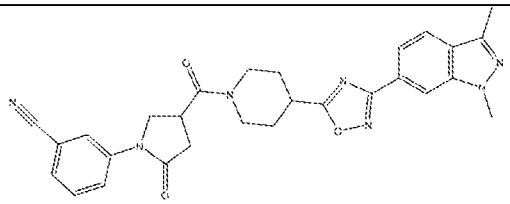
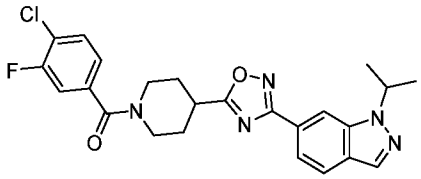
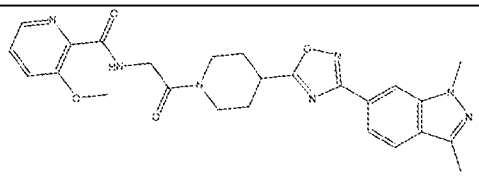
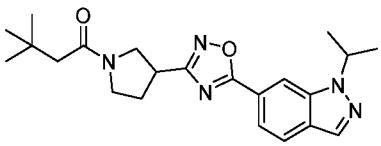
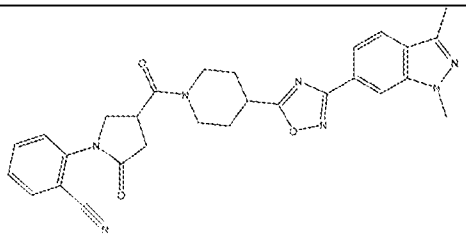
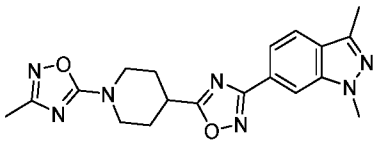
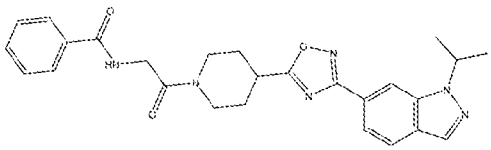
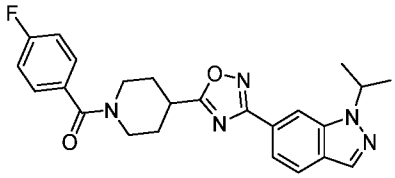
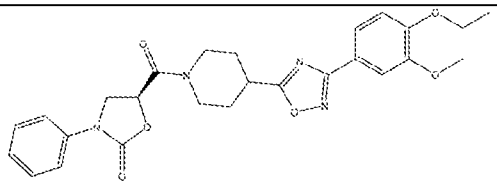
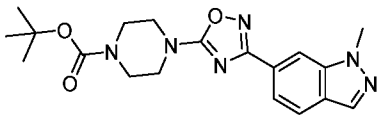
164		537	
165		538	
166		539	
167		540	
168		541	
169		542	
170		543	
171		544	
172		545	

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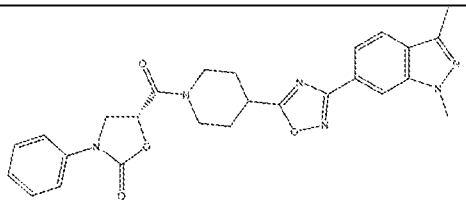
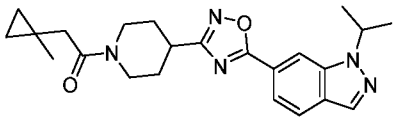
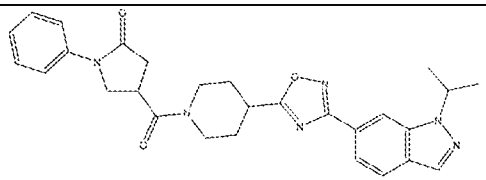
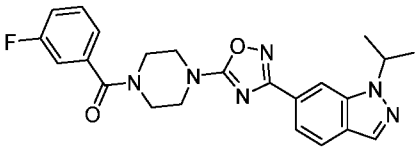
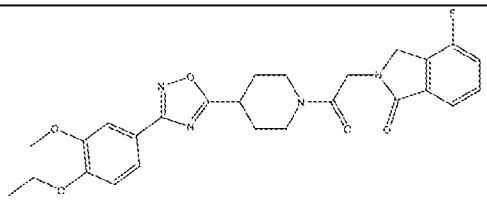
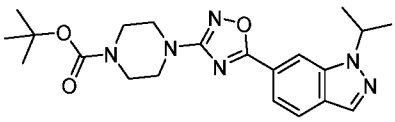
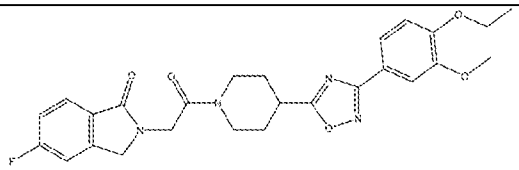
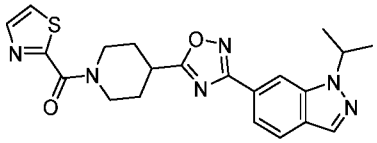
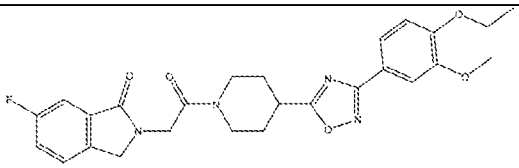
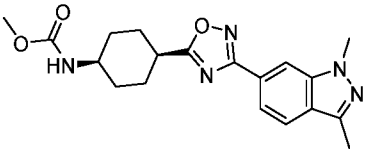
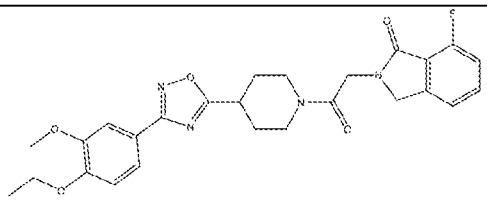
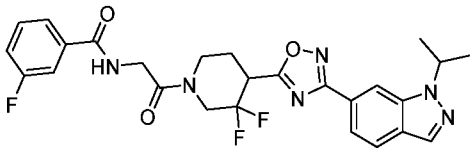
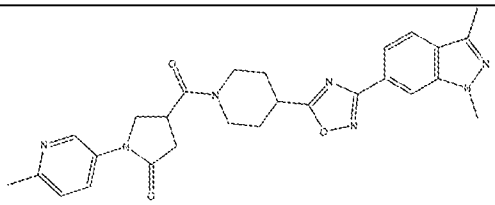
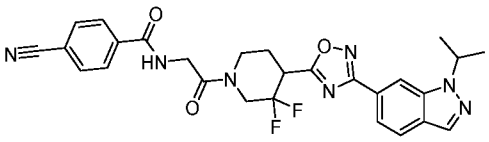
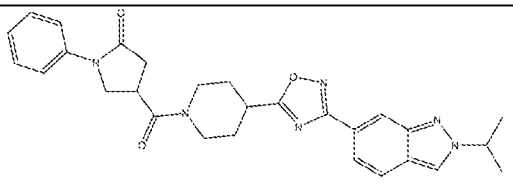
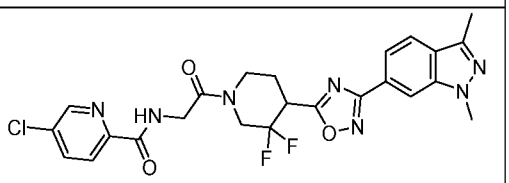
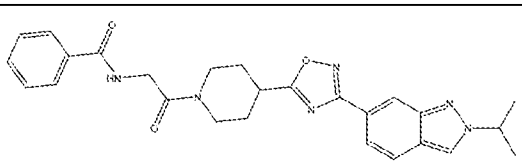
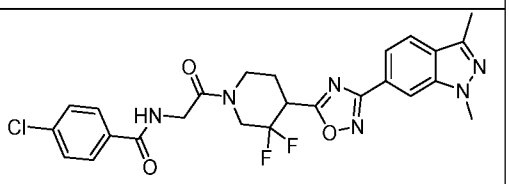
173		546	
174		547	
175		548	
176		549	
177		550	
178		551	
179		552	
180		553	
181		554	

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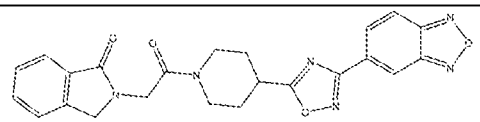
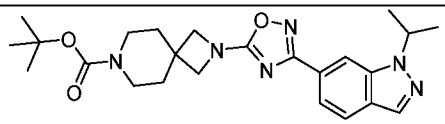
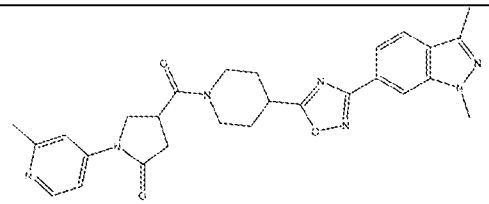
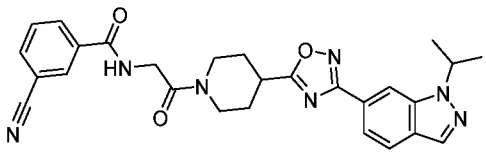
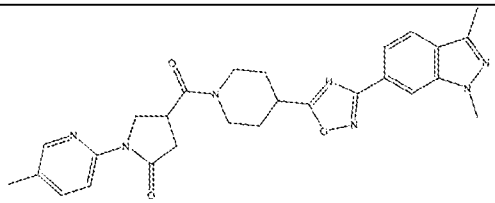
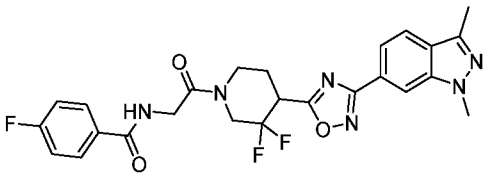
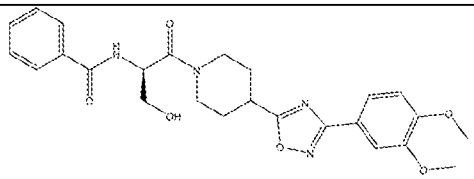
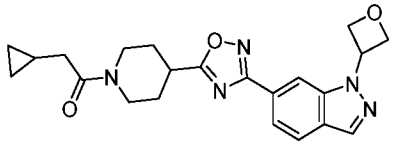
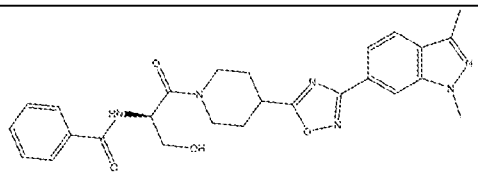
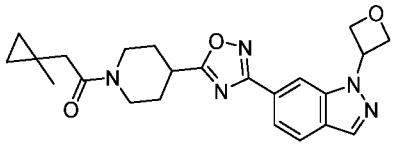
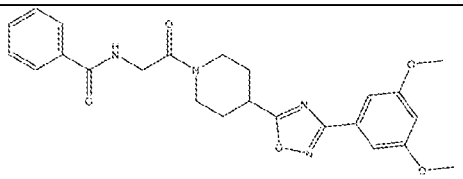
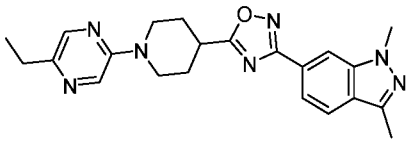
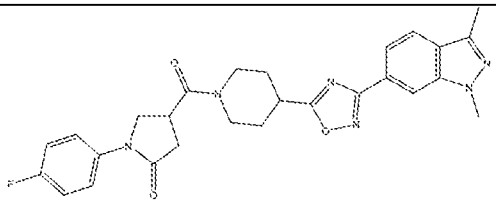
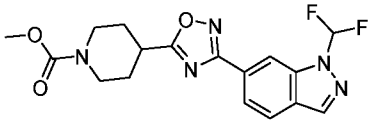
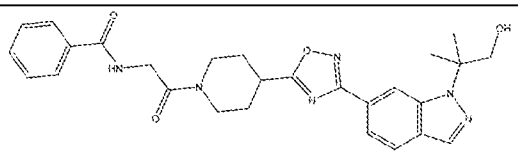
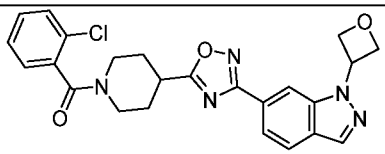
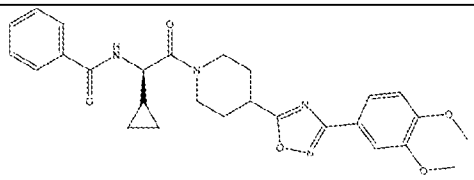
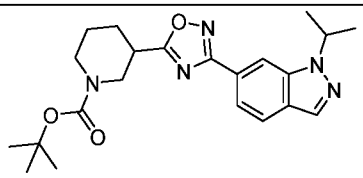
182		555	
183		556	
184		557	
185		558	
186		559	
187		560	
188		561	
189		562	
190		563	

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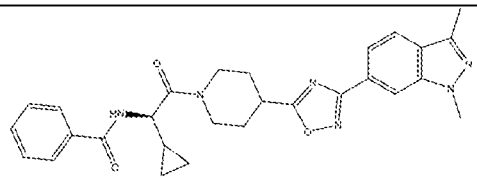
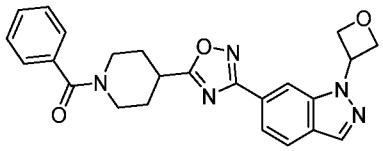
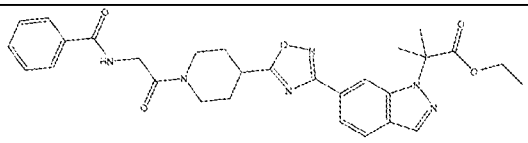
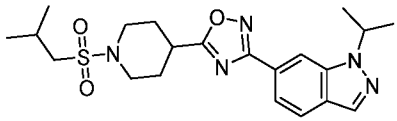
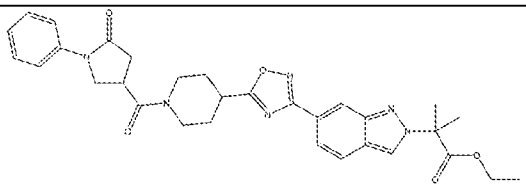
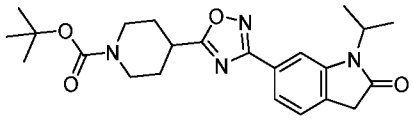
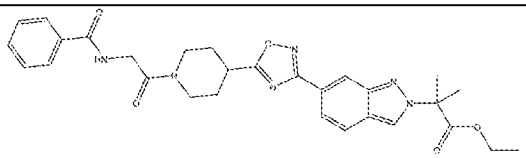
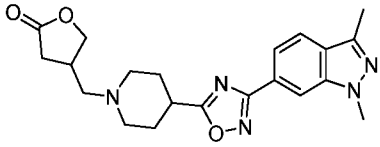
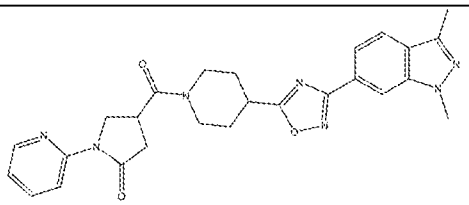
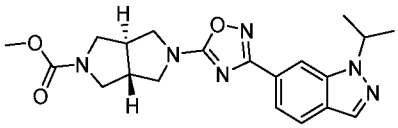
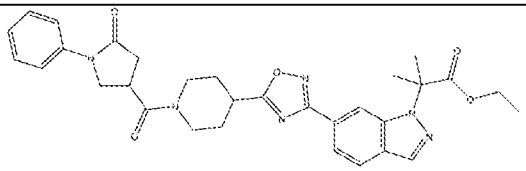
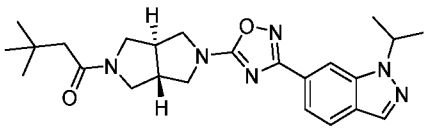
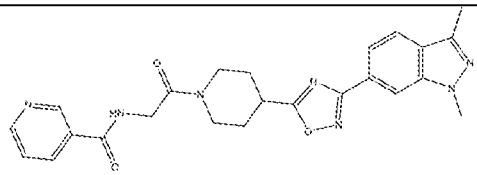
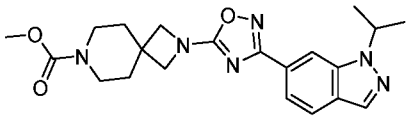
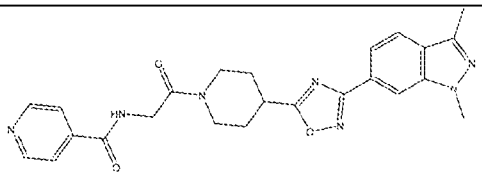
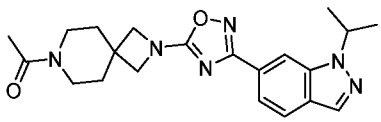
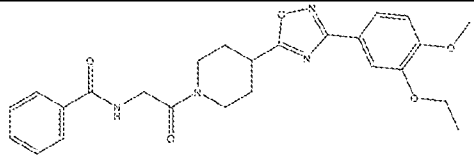
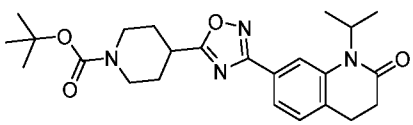
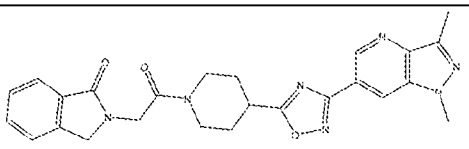
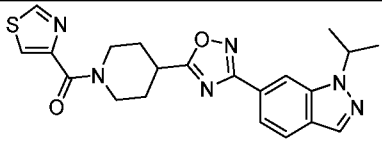
191		564	
192		565	
193		566	
194		567	
195		568	
196		569	
197		570	
198		571	
199		572	
200		573	

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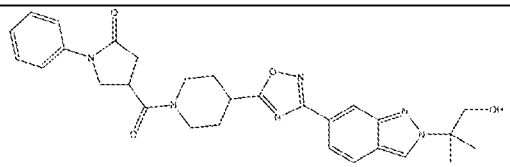
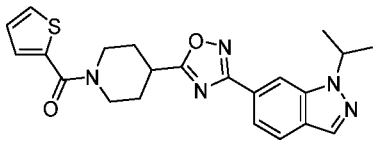
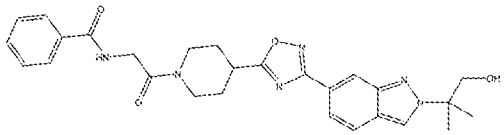
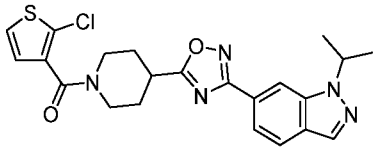
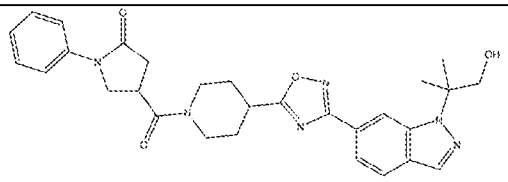
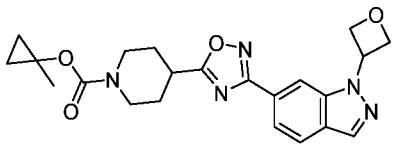
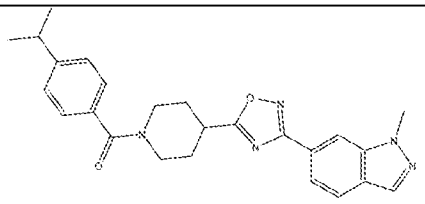
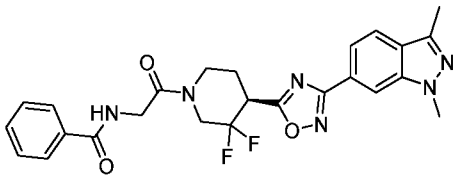
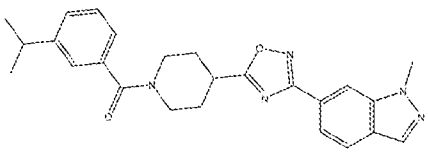
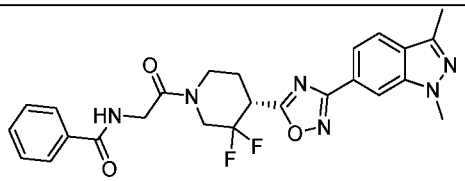
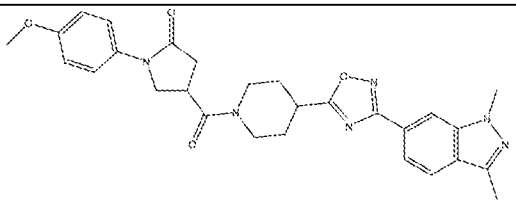
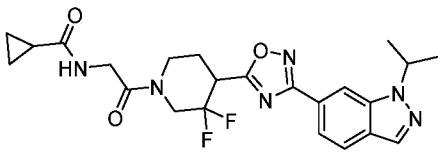
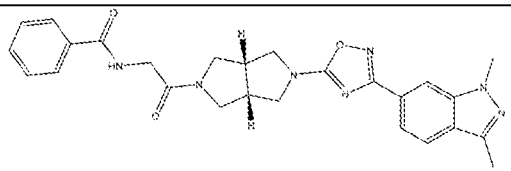
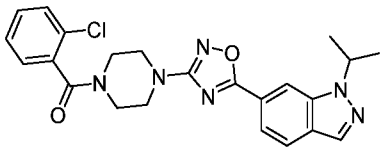
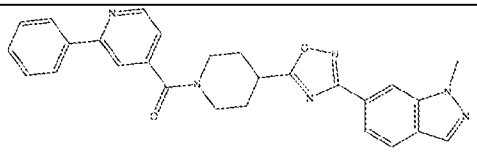
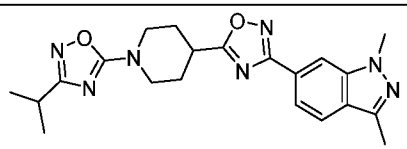
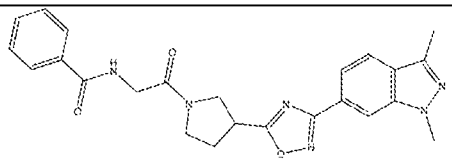
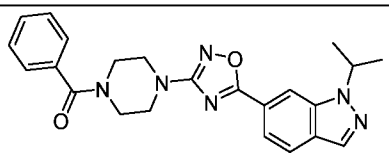
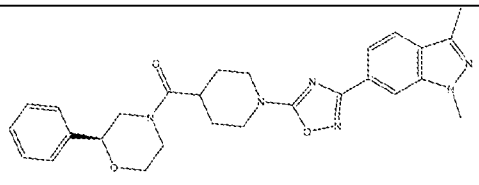
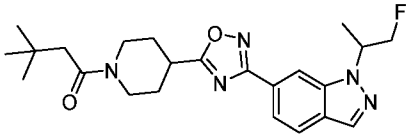
201		574	
202		575	
203		576	
204		577	
205		578	
206		579	
207		580	
208		581	
209		582	
210		583	

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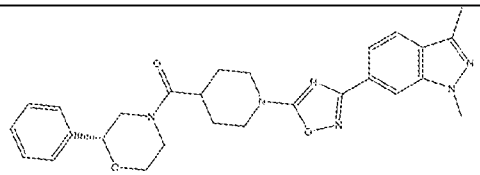
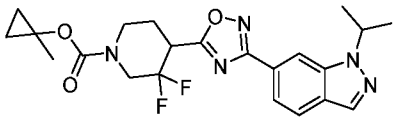
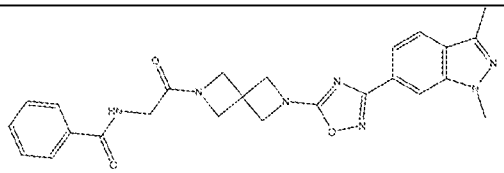
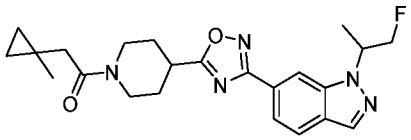
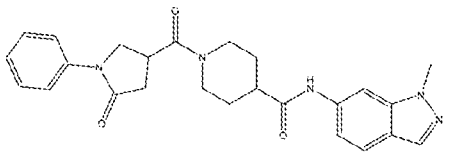
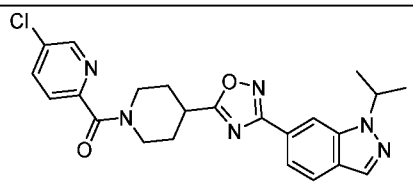
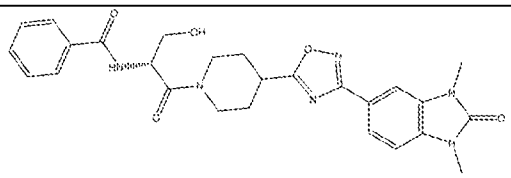
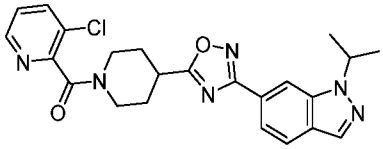
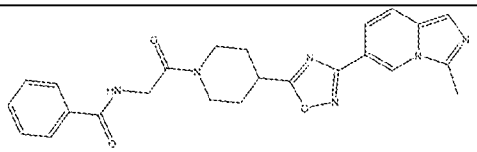
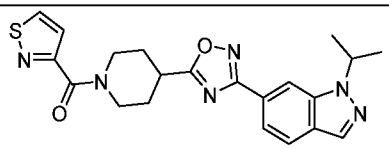
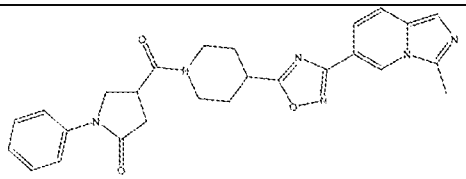
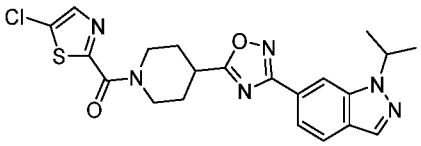
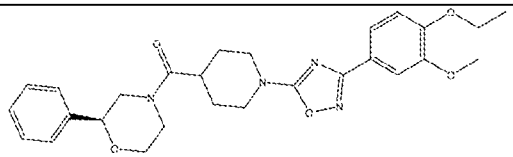
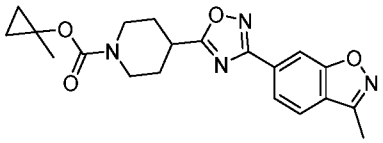
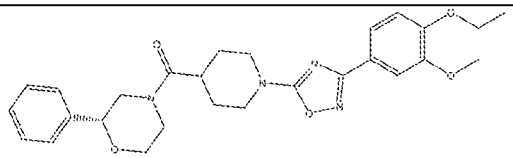
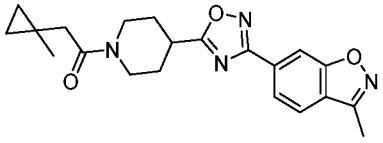
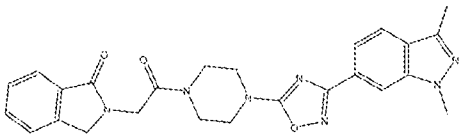
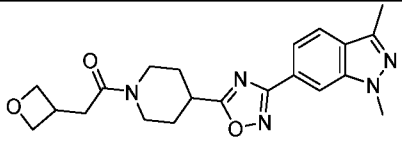
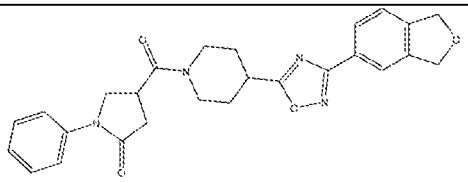
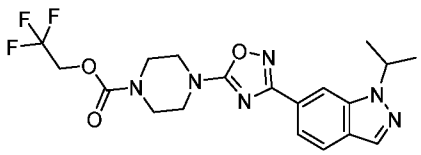
211		584	
212		585	
213		586	
214		587	
215		588	
216		589	
217		590	
218		591	
219		592	
220		593	

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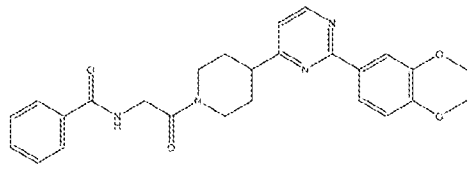
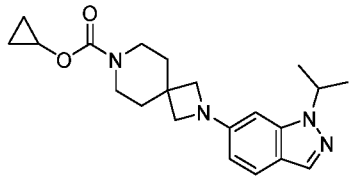
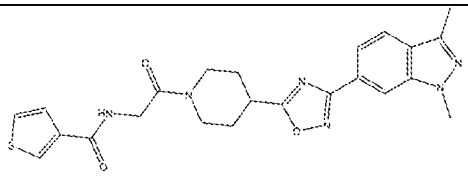
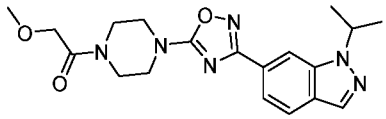
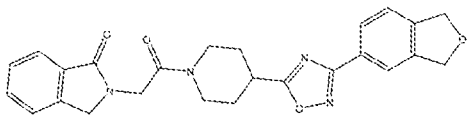
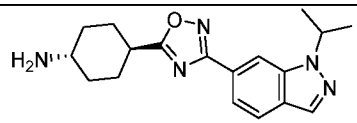
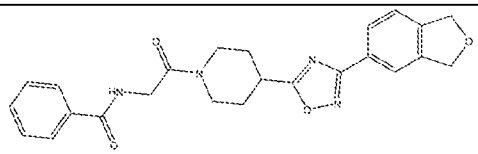
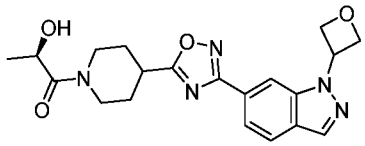
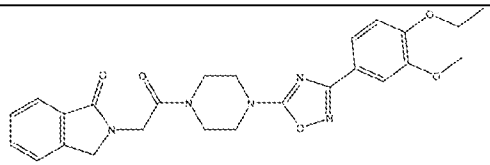
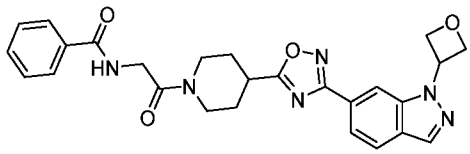
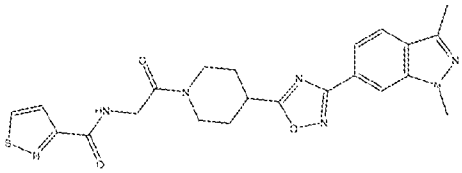
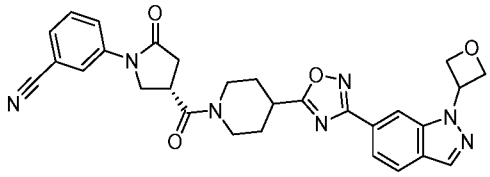
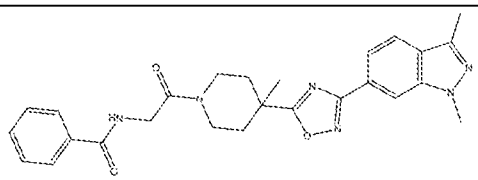
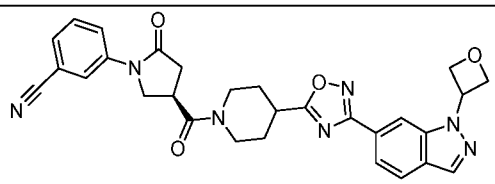
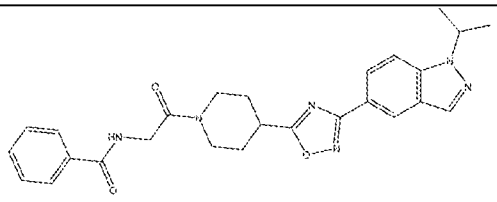
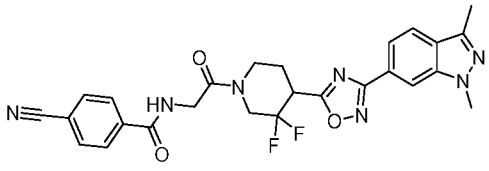
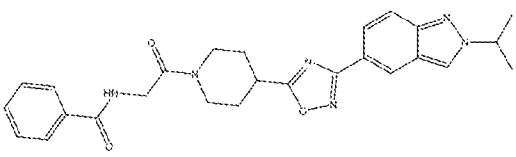
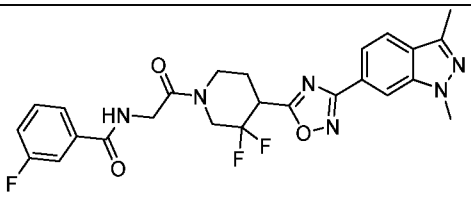
221		594	
222		595	
223		596	
224		597	
225		598	
226		599	
227		600	
228		601	
229		602	

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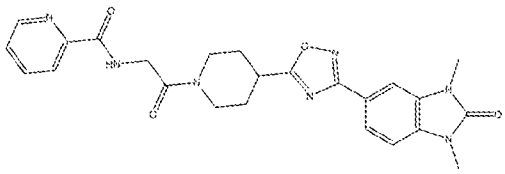
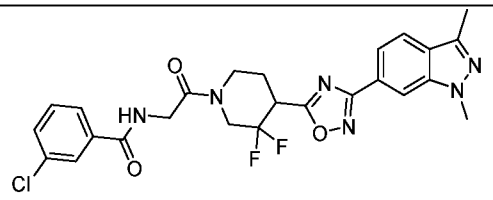
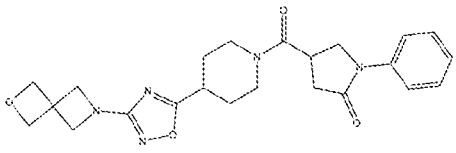
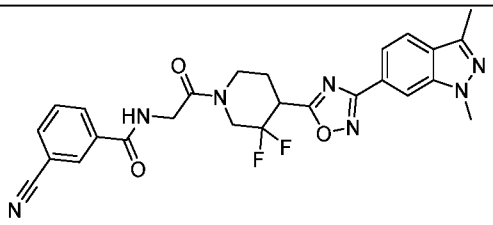
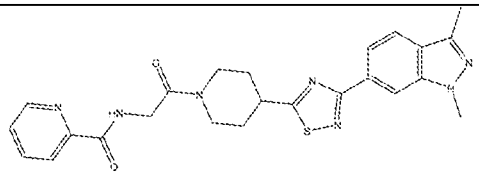
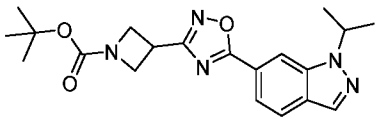
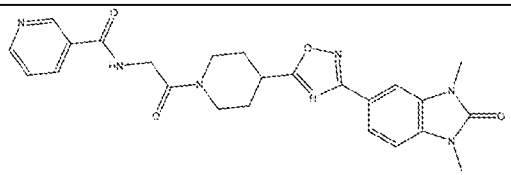
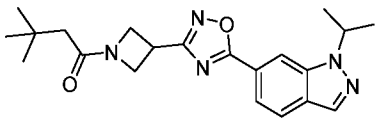
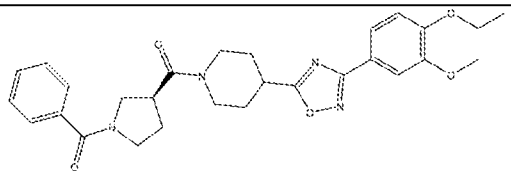
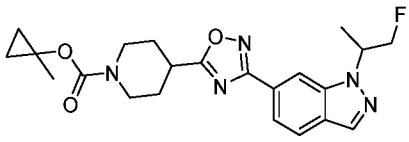
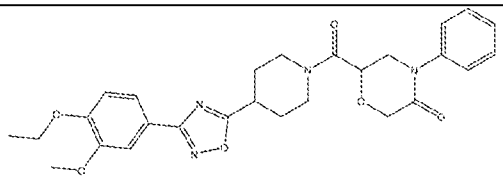
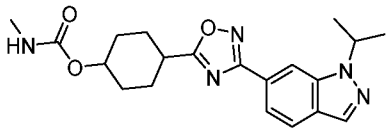
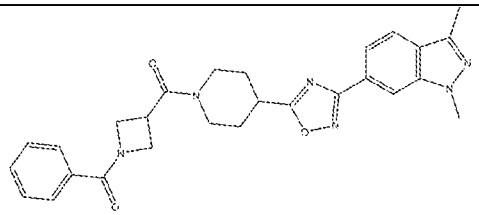
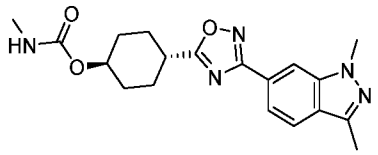
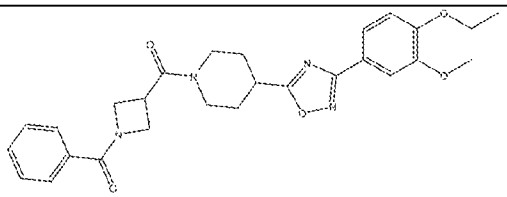
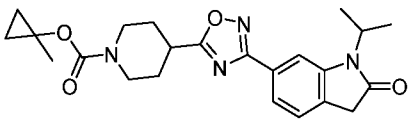
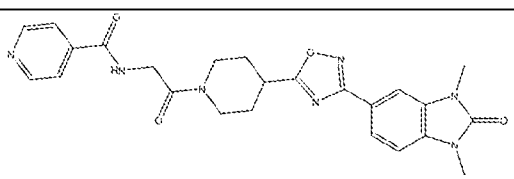
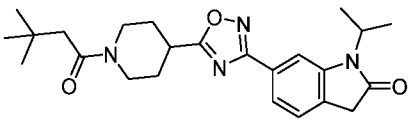
230		603	
231		604	
232		605	
233		606	
234		607	
235		608	
236		609	
237		610	
238		611	

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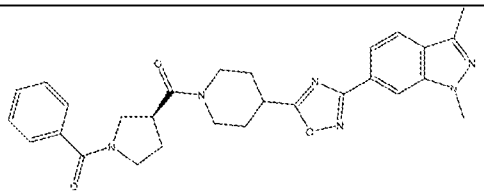
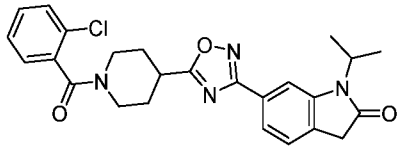
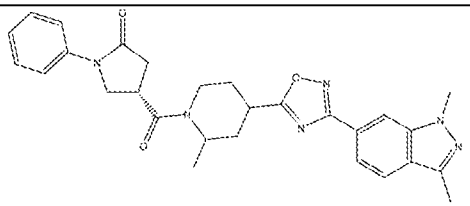
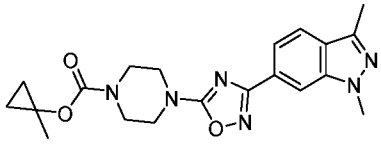
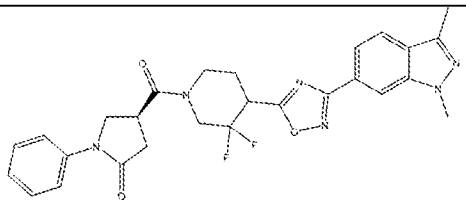
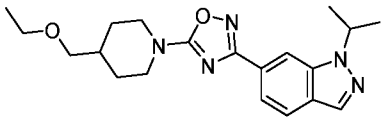
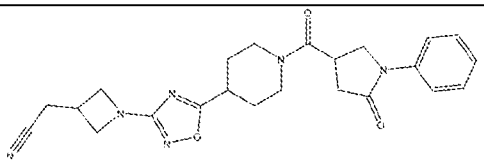
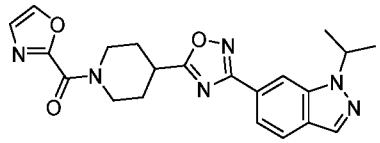
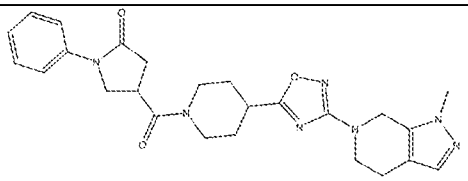
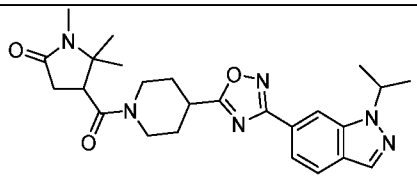
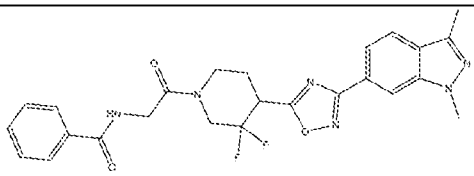
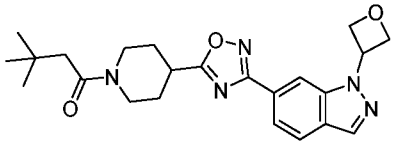
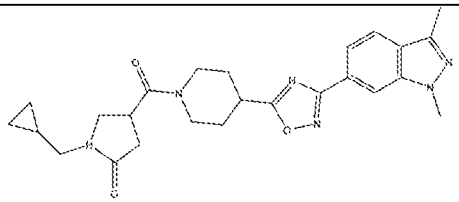
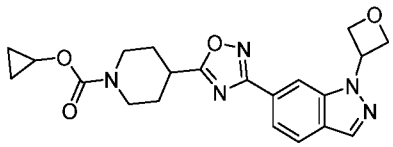
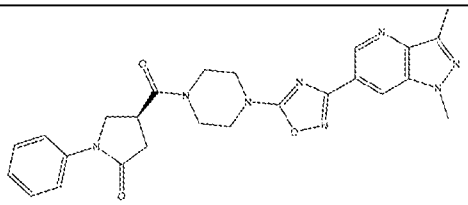
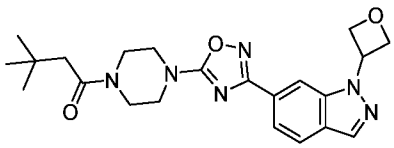
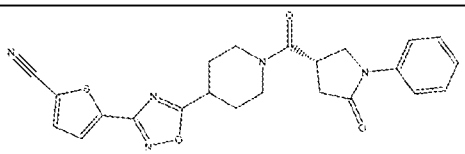
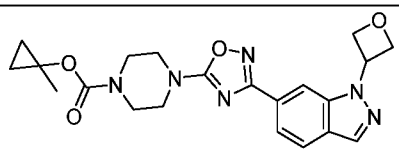
239		612	
240		613	
241		614	
242		615	
243		616	
244		617	
245		618	
246		619	
247		620	

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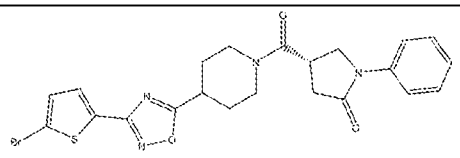
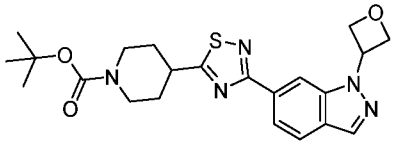
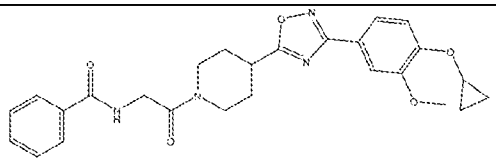
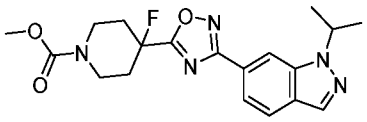
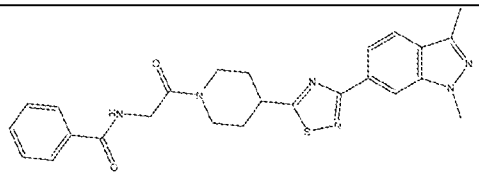
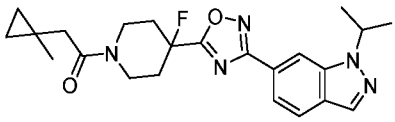
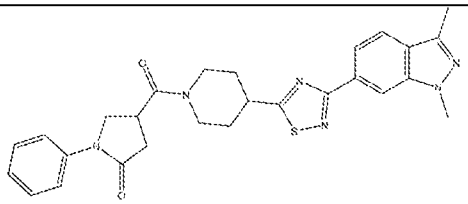
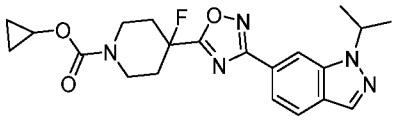
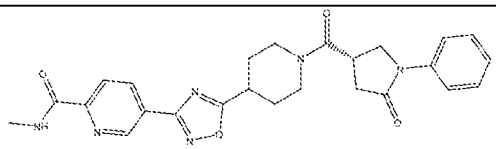
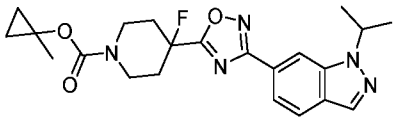
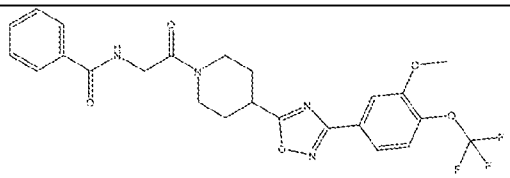
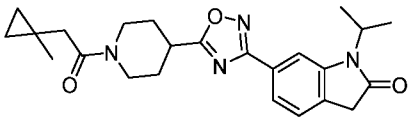
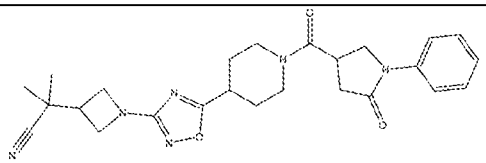
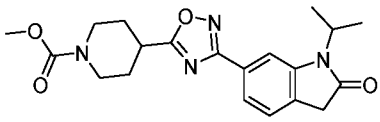
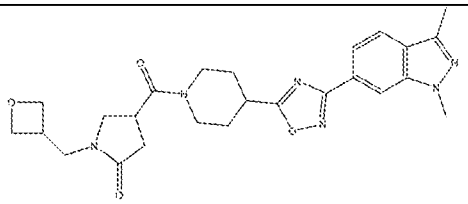
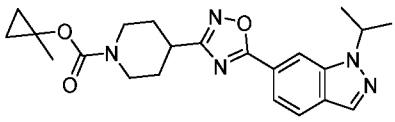
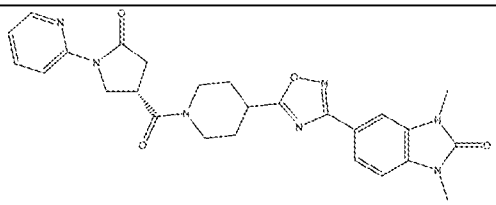
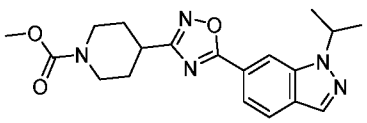
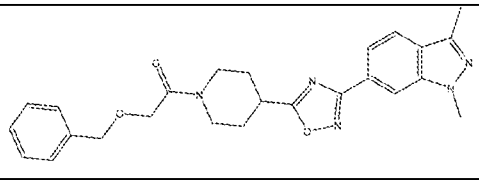
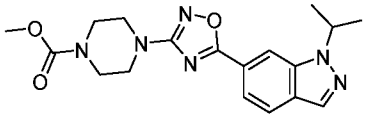
248		621	
249		622	
250		623	
251		624	
252		625	
253		626	
254		627	
255		628	
256		629	
257		630	

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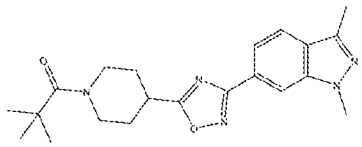
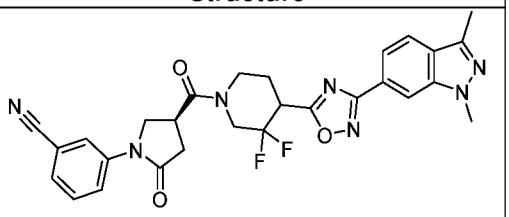
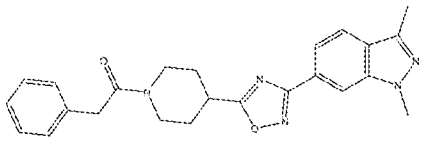
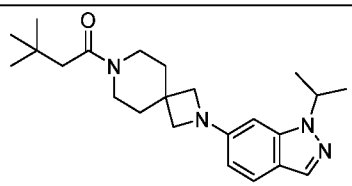
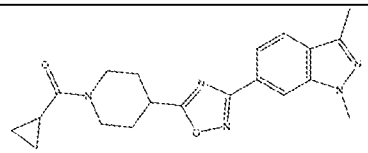
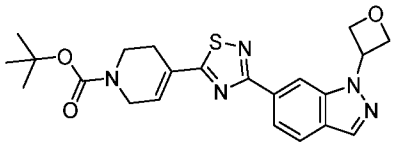
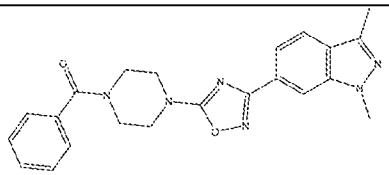
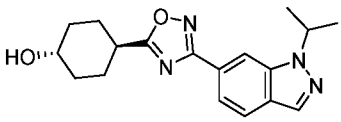
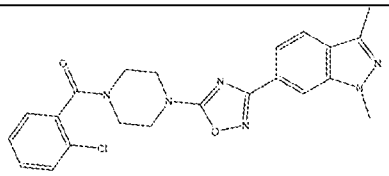
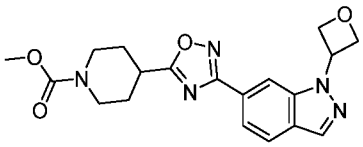
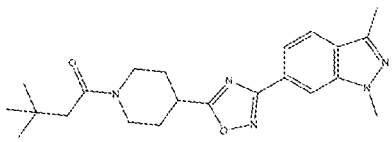
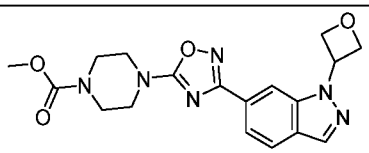
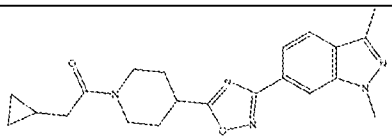
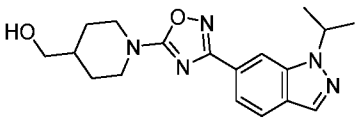
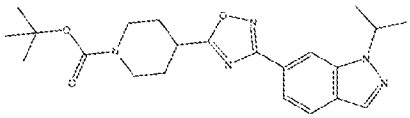
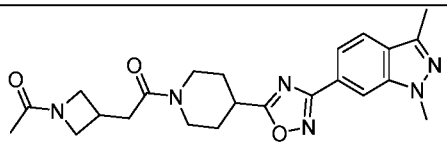
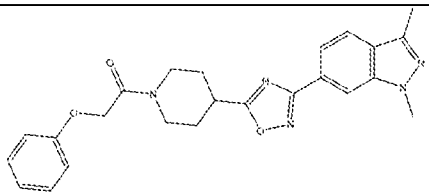
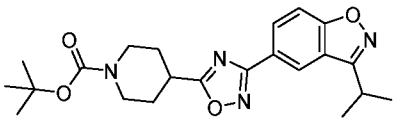
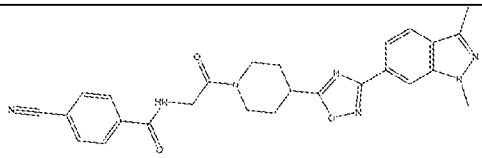
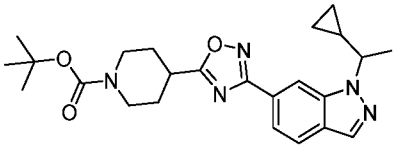
258		631	
259		632	
260		633	
261		634	
262		635	
263		636	
264		637	
265		638	
266		639	
267		640	

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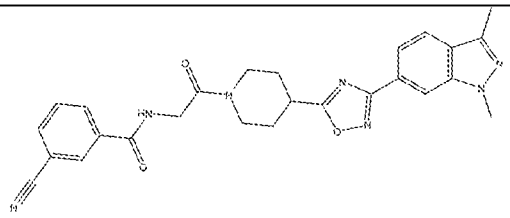
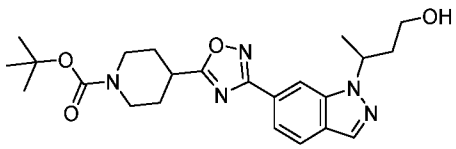
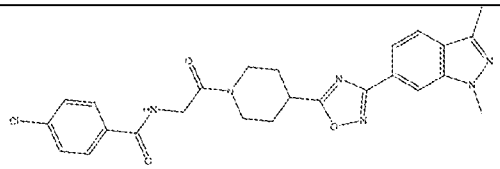
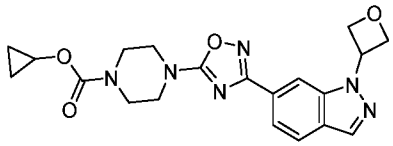
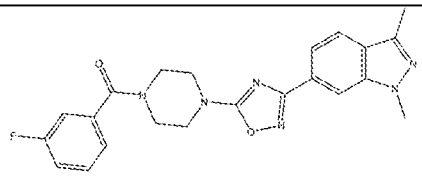
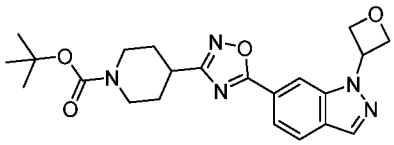
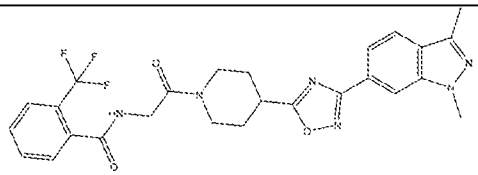
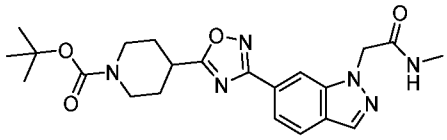
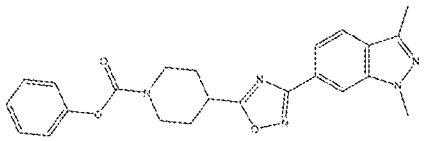
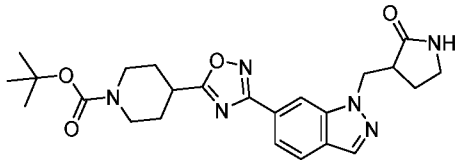
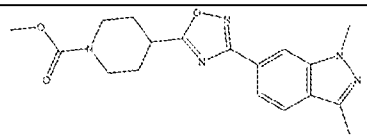
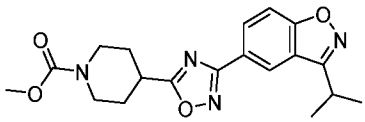
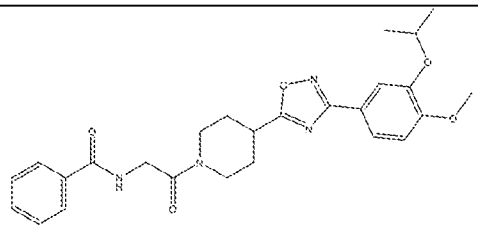
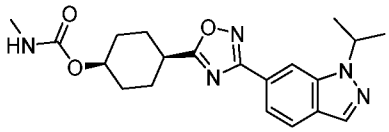
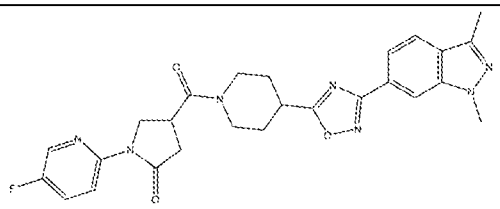
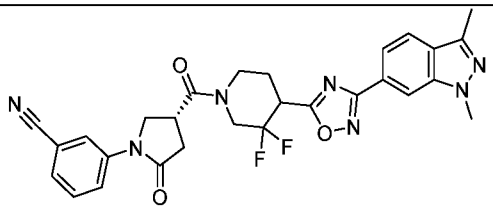
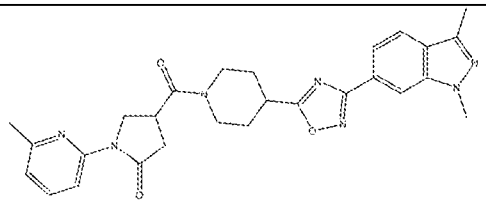
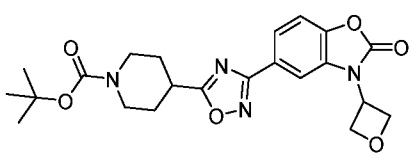
268		641	
269		642	
270		643	
271		644	
272		645	
273		646	
274		647	
275		648	
276		649	

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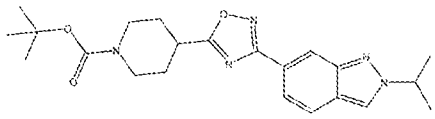
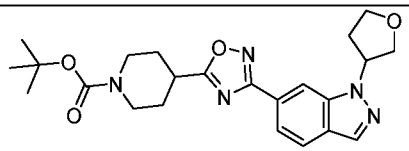
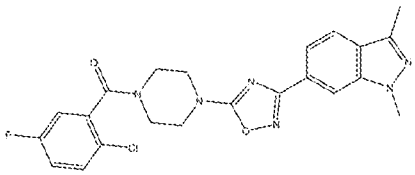
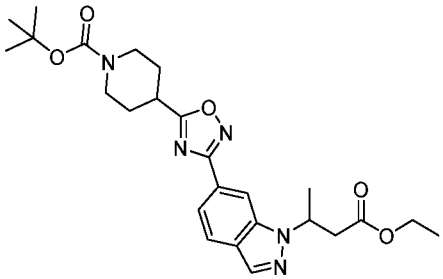
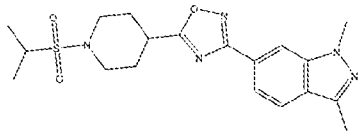
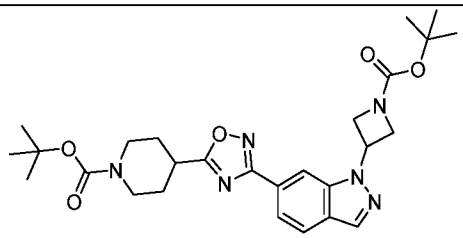
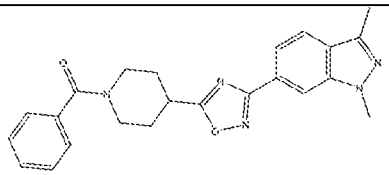
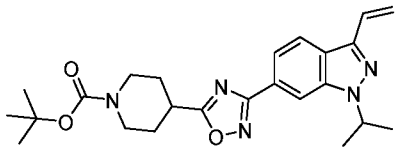
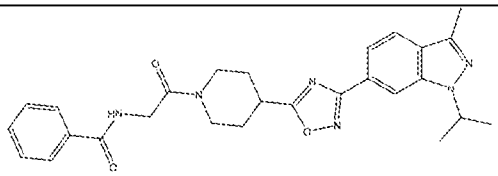
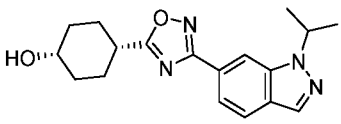
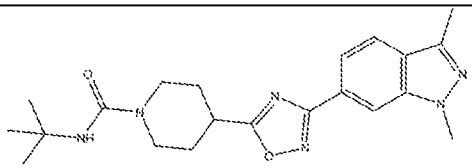
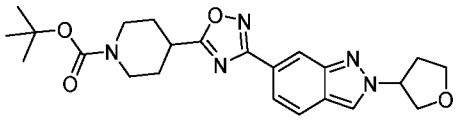
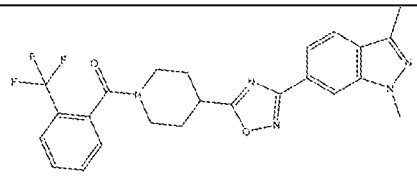
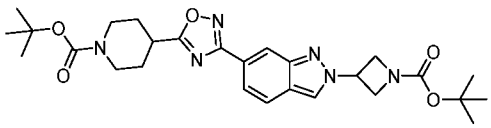
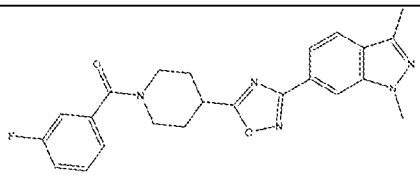
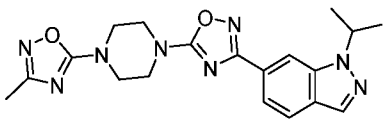
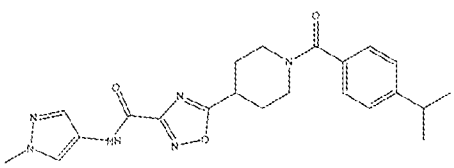
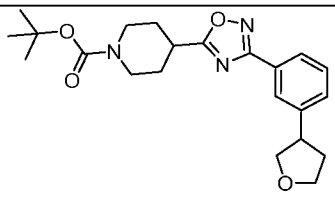
277		650	
278		651	
279		652	
280		653	
281		654	
282		655	
283		656	
284		657	
285		658	

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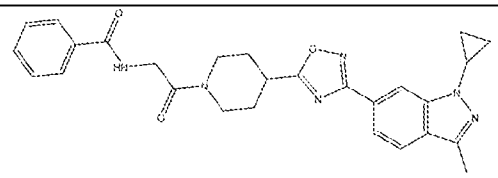
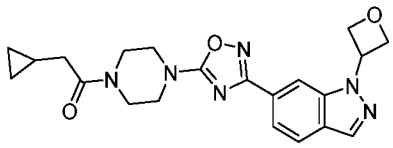
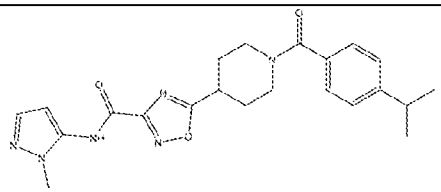
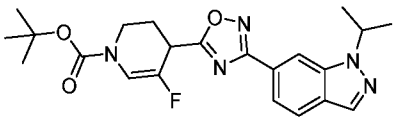
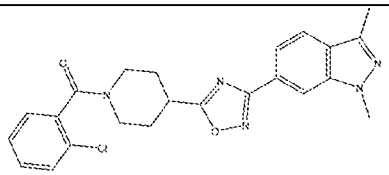
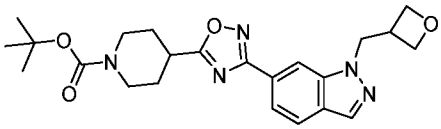
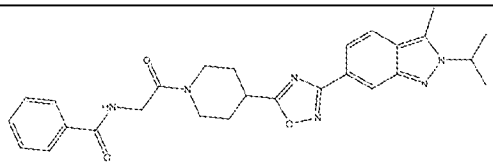
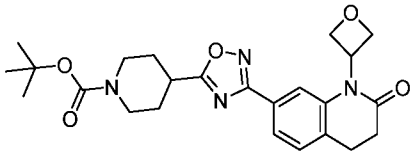
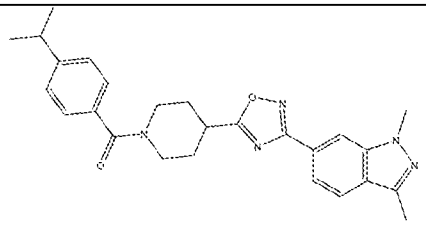
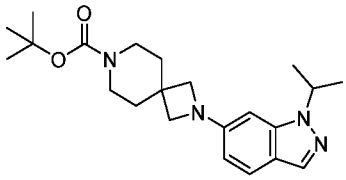
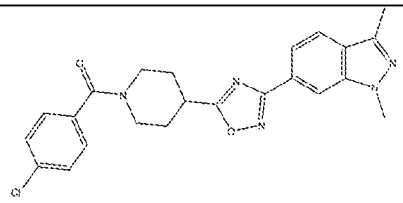
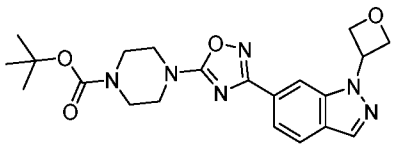
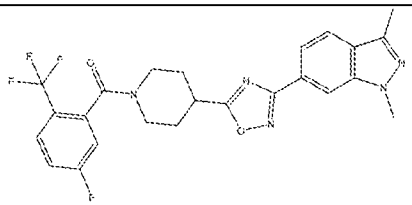
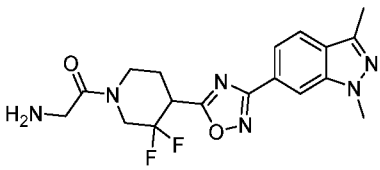
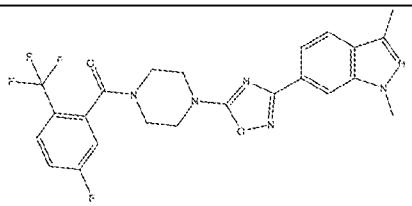
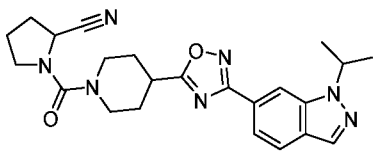
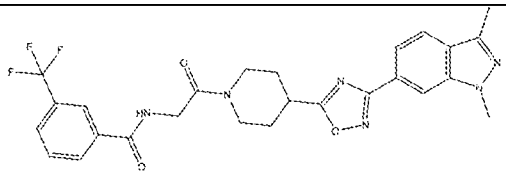
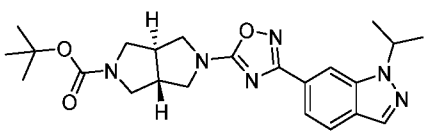
286		659	
287		660	
288		661	
289		662	
290		663	
291		664	
292		665	
293		666	
294		667	

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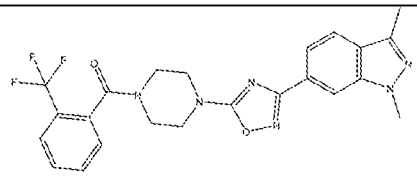
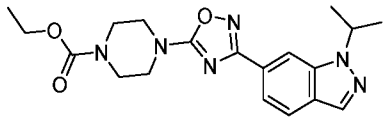
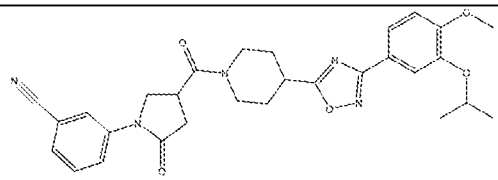
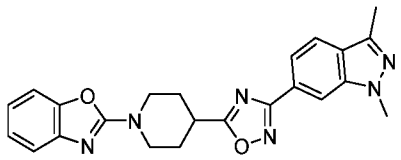
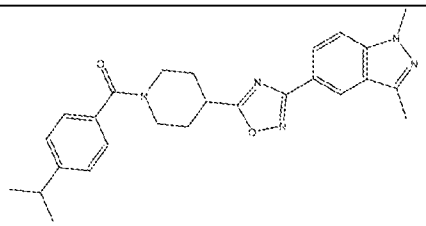
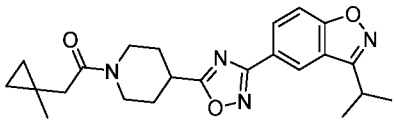
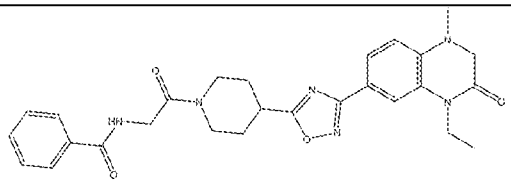
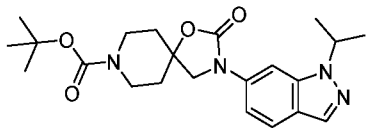
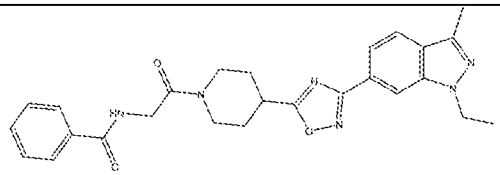
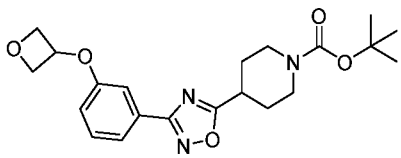
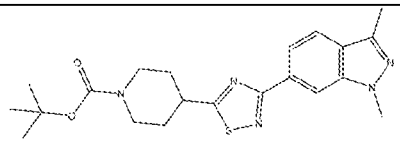
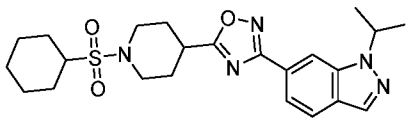
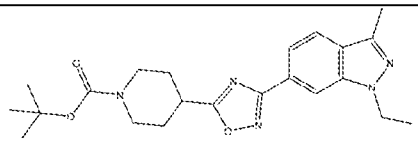
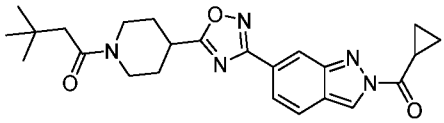
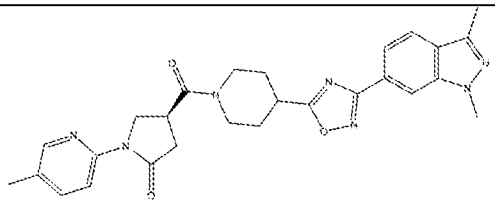
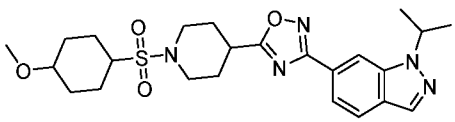
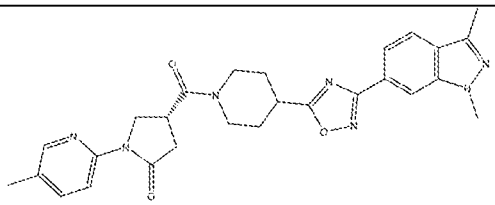
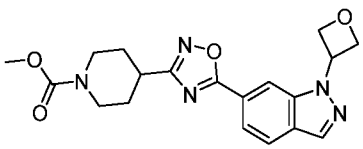
295		668	
296		669	
297		670	
298		671	
299		672	
300		673	
301		674	
302		675	
303		676	

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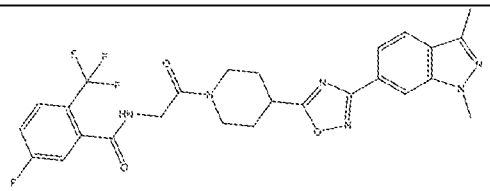
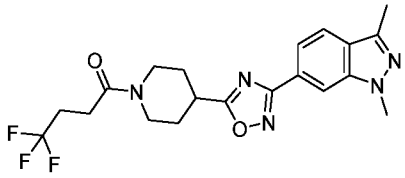
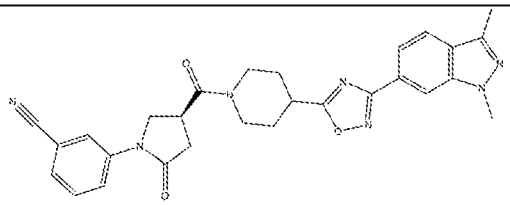
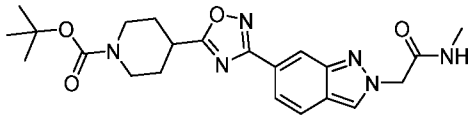
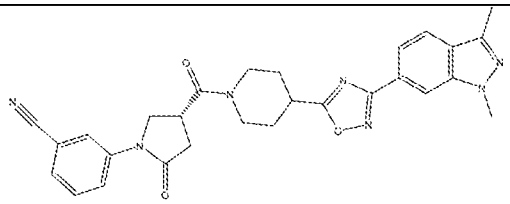
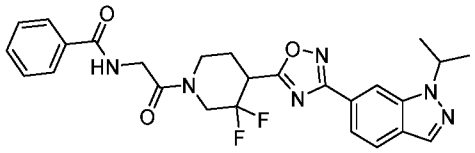
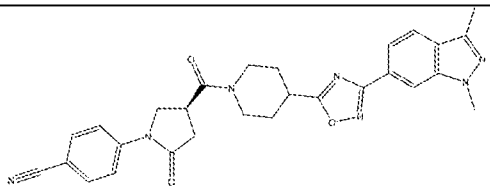
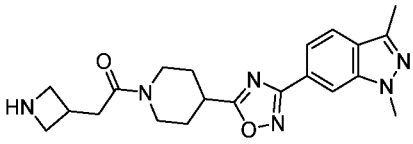
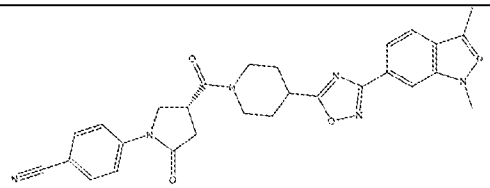
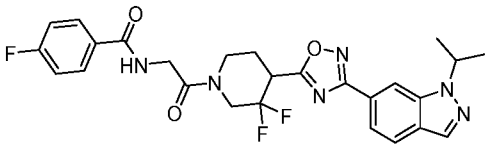
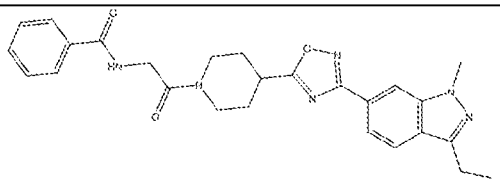
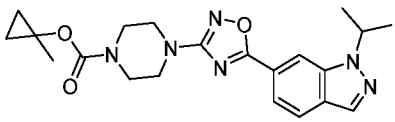
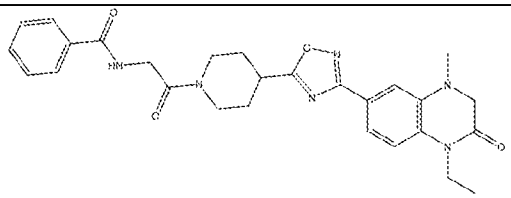
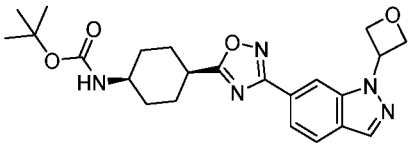
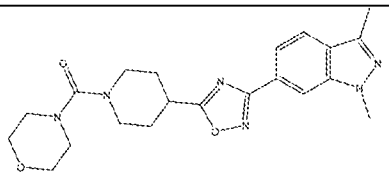
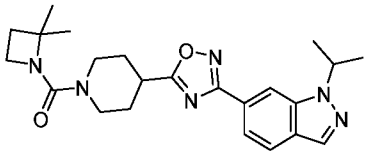
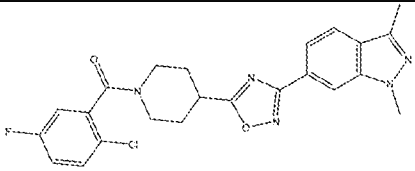
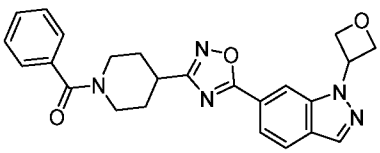
304		677	
305		678	
306		679	
307		680	
308		681	
309		682	
310		683	
311		684	
312		685	

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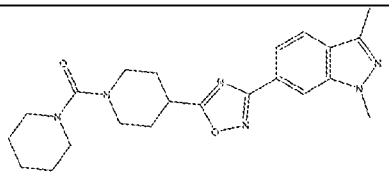
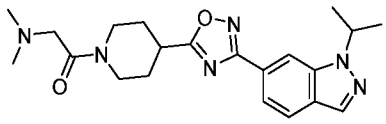
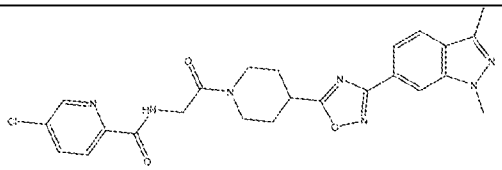
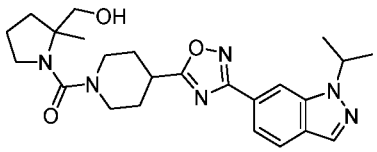
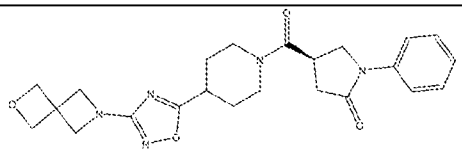
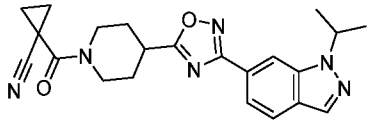
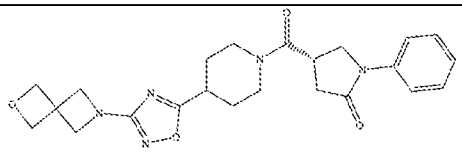
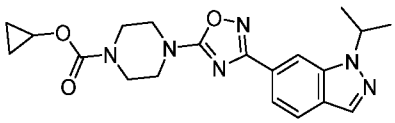
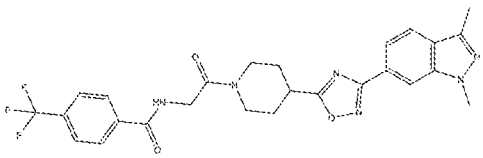
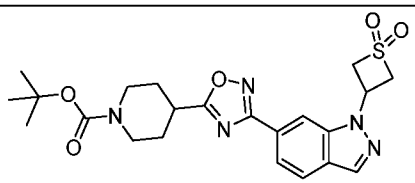
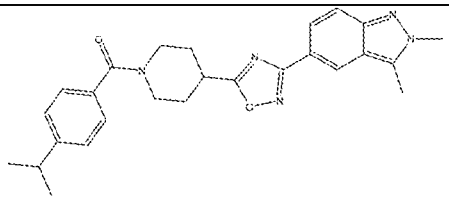
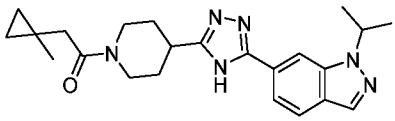
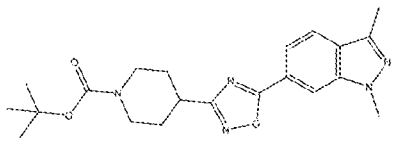
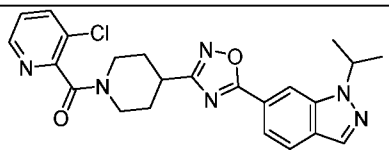
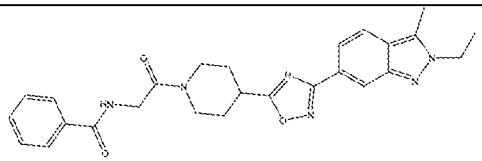
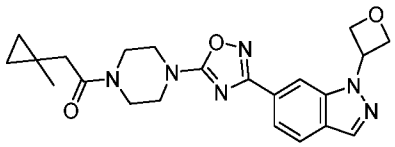
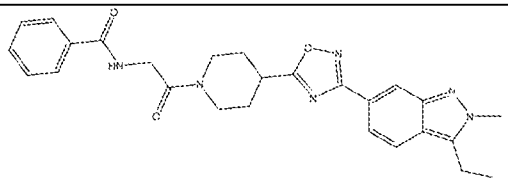
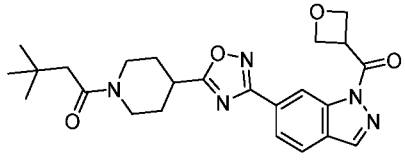
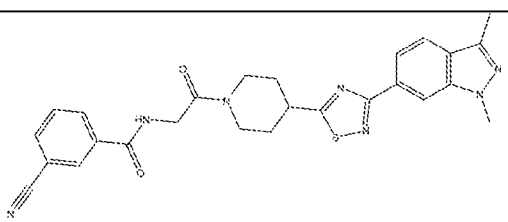
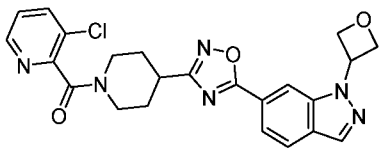
313		686	
314		687	
315		688	
316		689	
317		690	
318		691	
319		692	
320		693	
321		694	
322		695	

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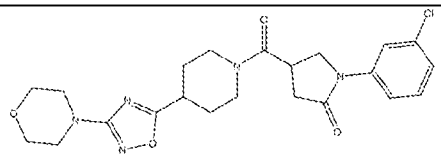
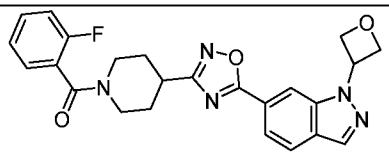
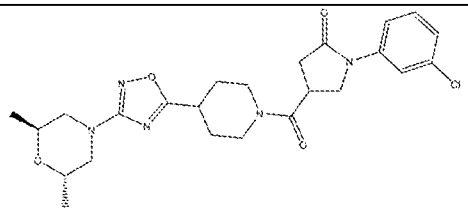
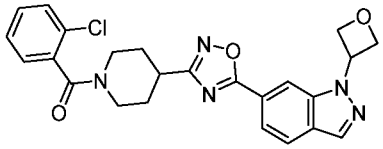
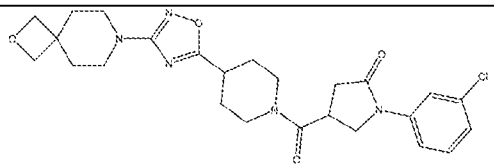
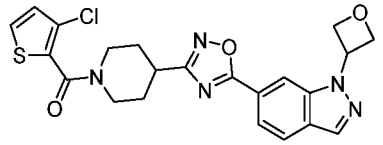
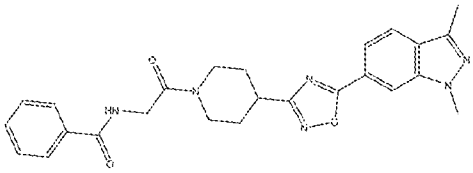
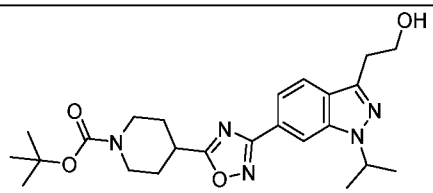
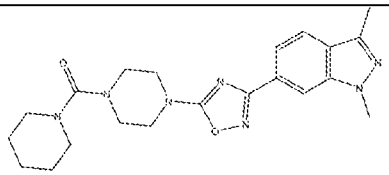
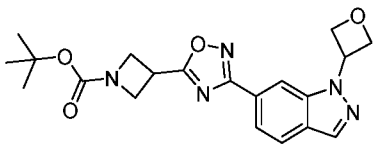
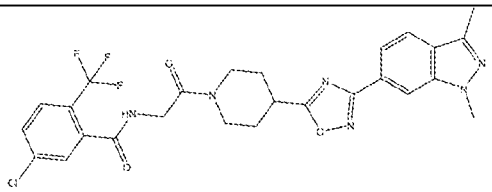
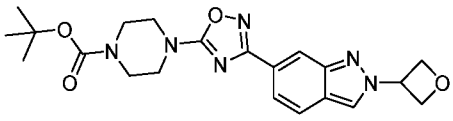
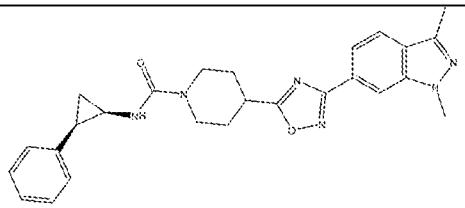
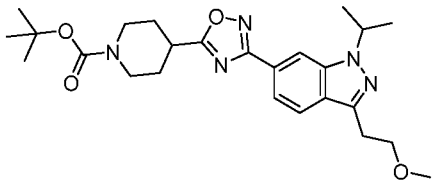
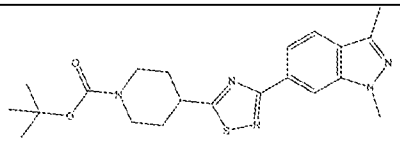
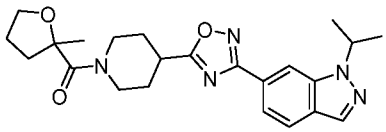
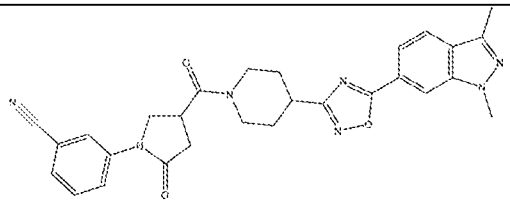
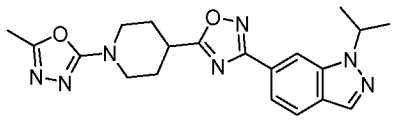
323		696	
324		697	
325		698	
326		699	
327		700	
328		701	
329		702	
330		703	
331		704	

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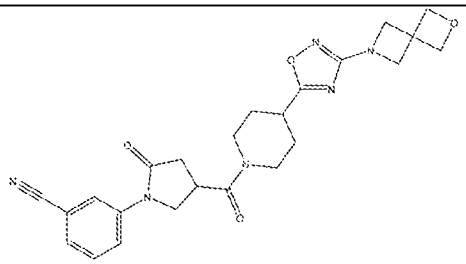
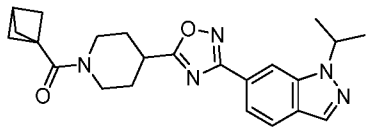
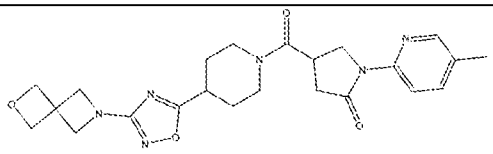
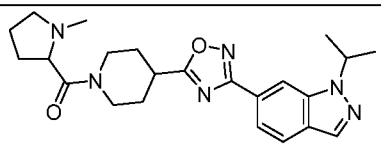
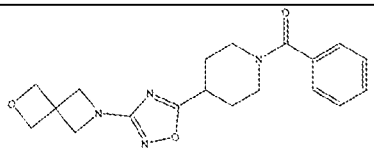
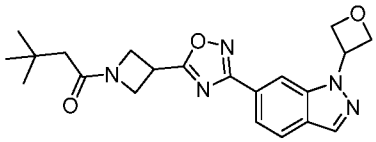
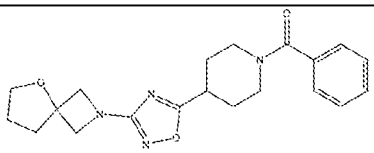
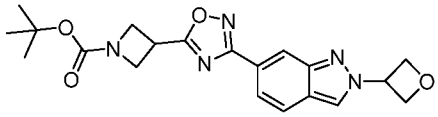
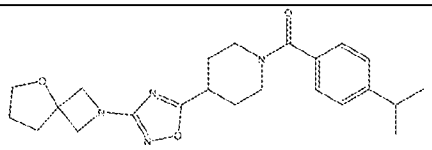
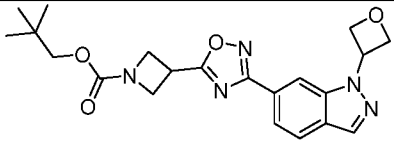
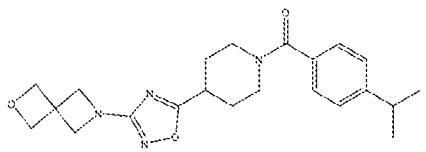
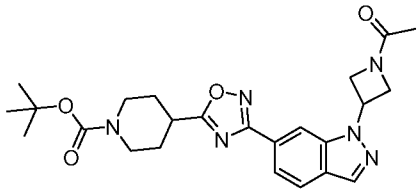
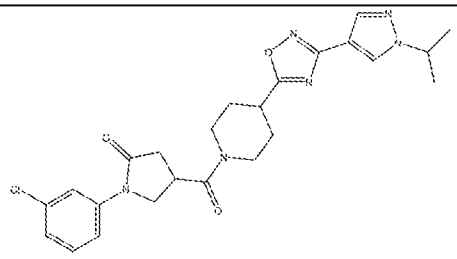
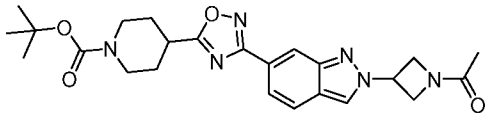
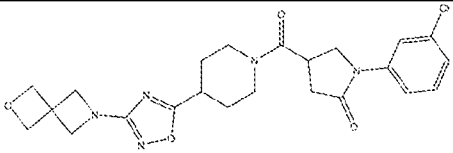
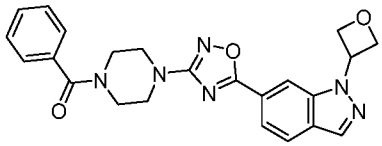
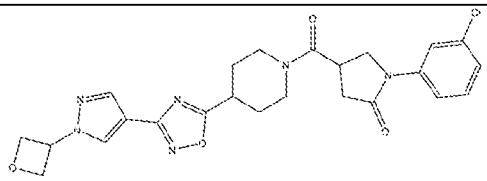
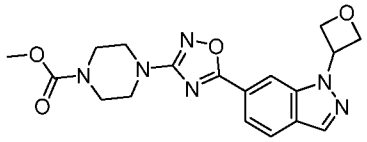
332		705	
333		706	
334		707	
335		708	
336		709	
337		710	
338		711	
339		712	
340		713	

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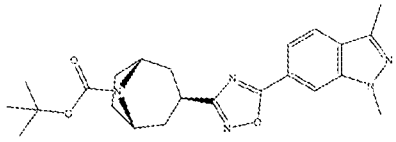
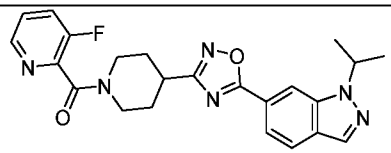
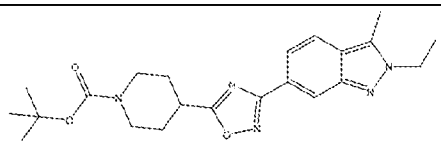
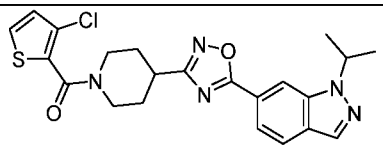
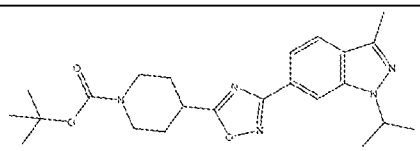
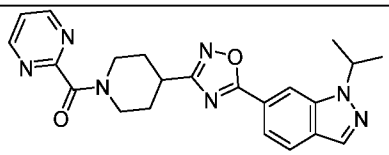
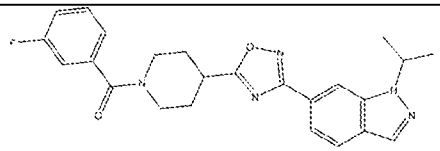
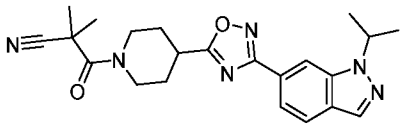
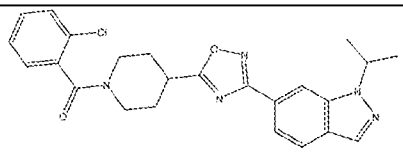
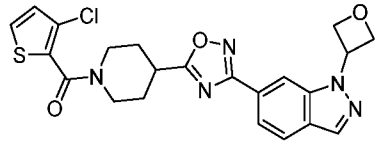
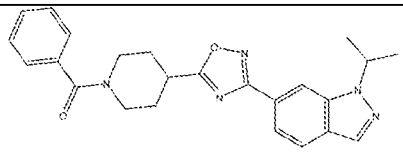
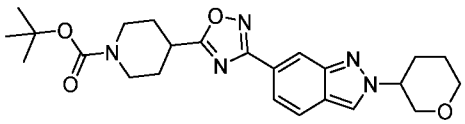
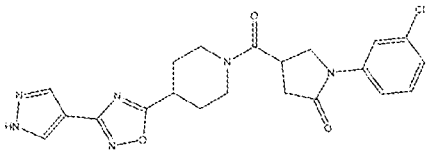
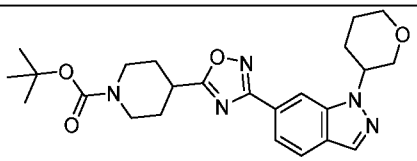
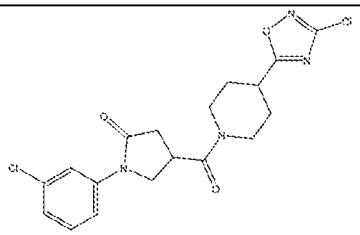
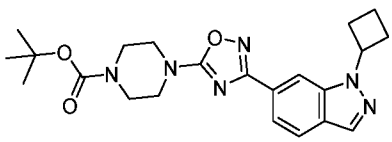
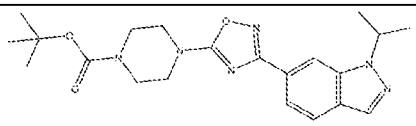
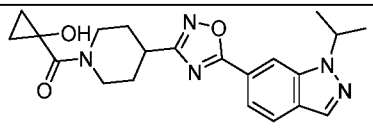
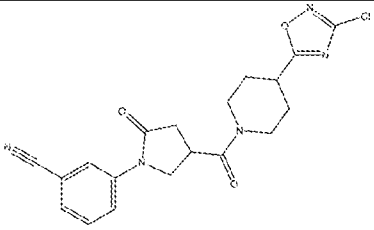
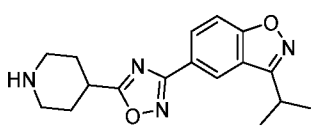
341		714	
342		715	
343		716	
344		717	
345		718	
346		719	
347		720	
348		721	
349		722	
350		723	

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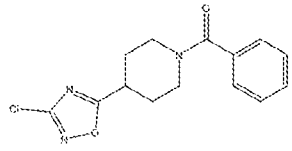
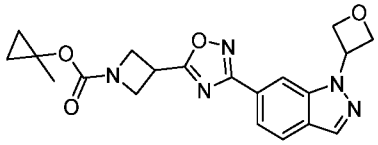
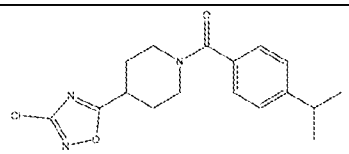
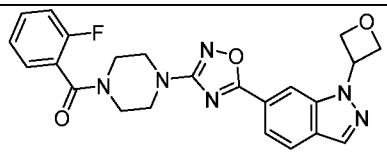
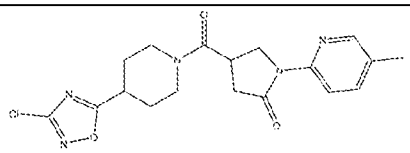
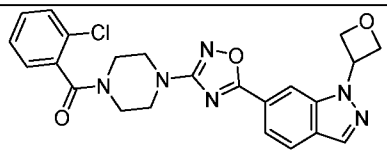
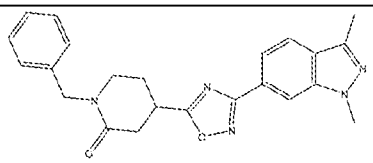
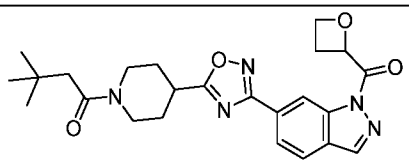
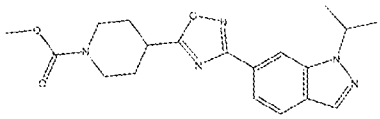
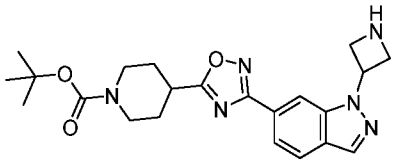
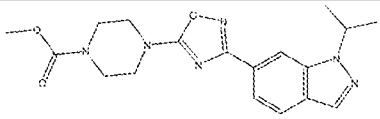
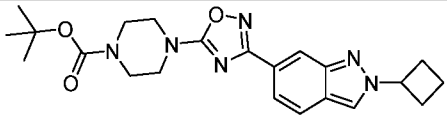
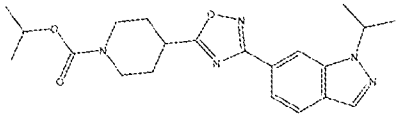
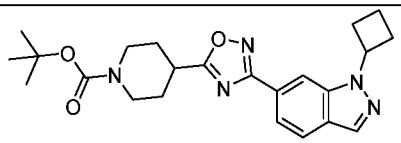
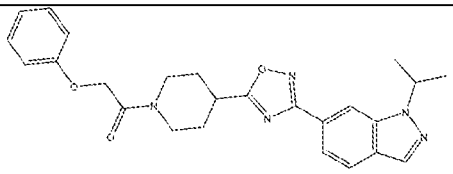
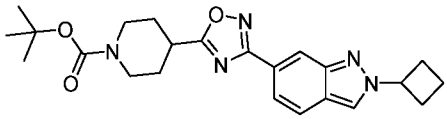
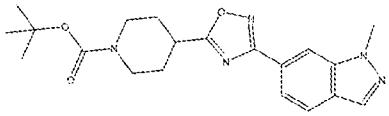
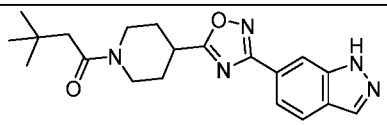
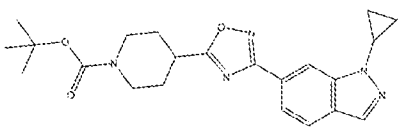
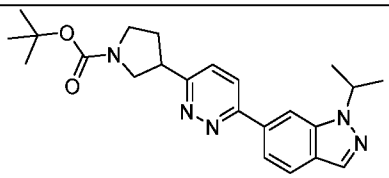
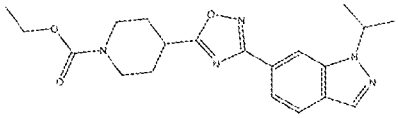
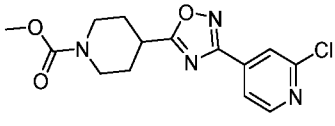
351		724	
352		725	
353		726	
354		727	
355		728	
356		729	
357		730	
358		731	
359		732	
360		733	
361		734	

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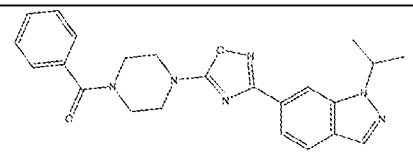
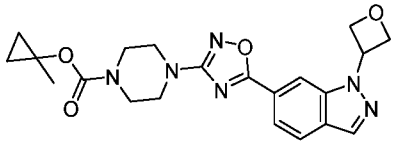
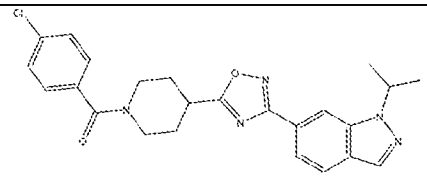
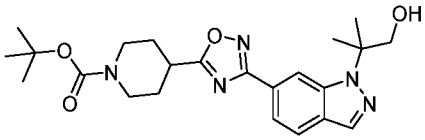
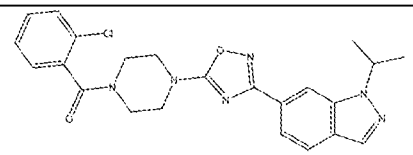
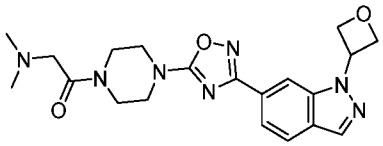
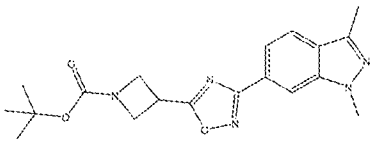
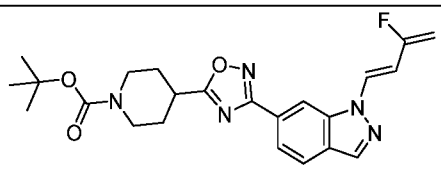
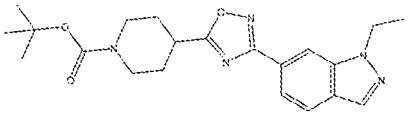
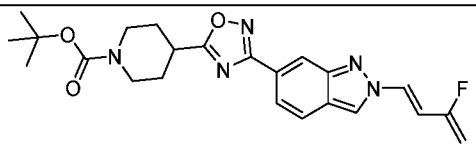
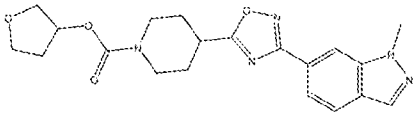
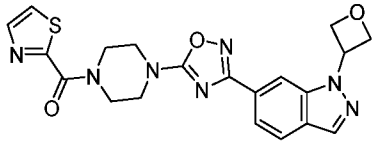
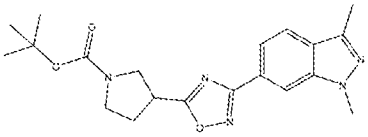
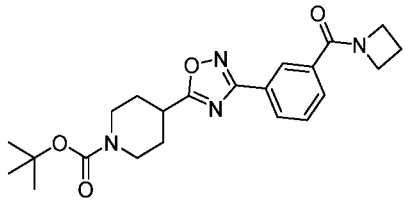
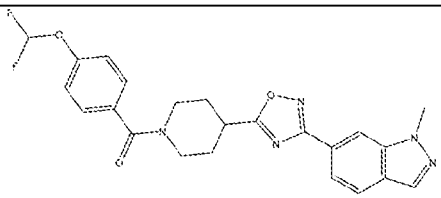
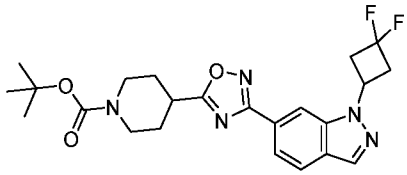
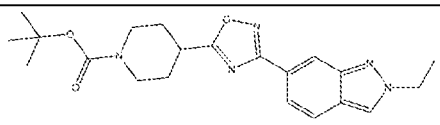
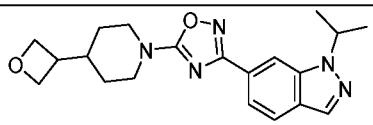
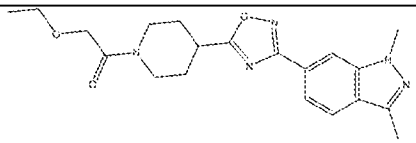
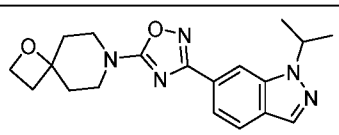
362		735	
363		736	
364		737	
365		738	
366		739	
367		740	
368		741	
369		742	
370		743	
371		744	

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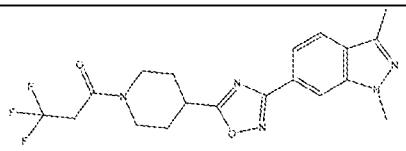
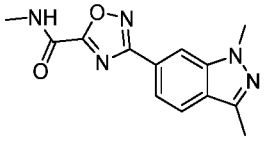
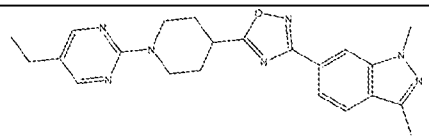
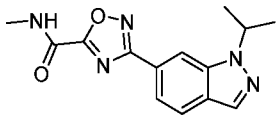
372		745	
373		746	

Table 2A. Compounds of the Invention

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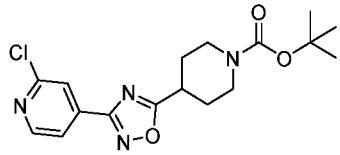
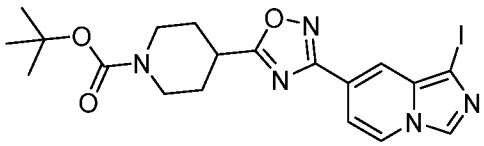
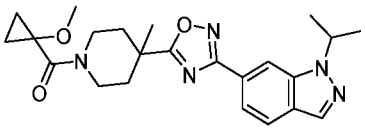
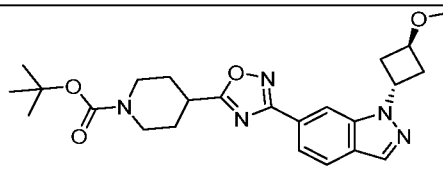
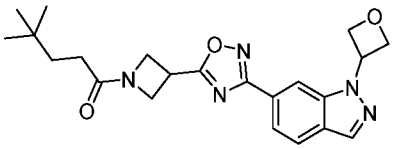
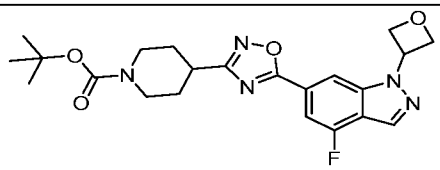
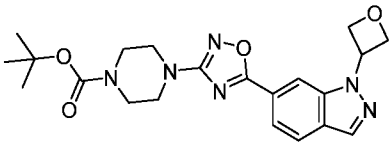
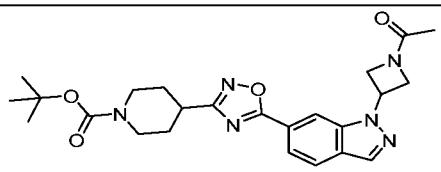
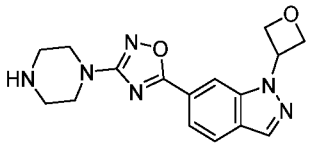
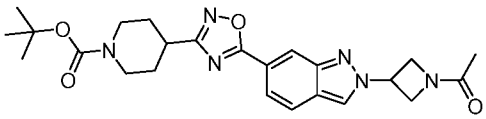
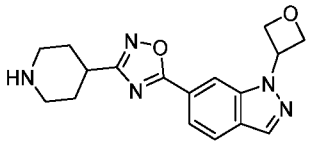
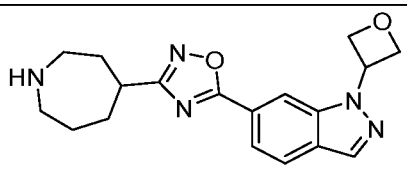
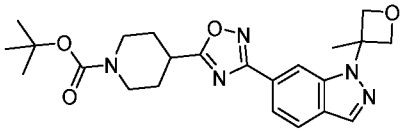
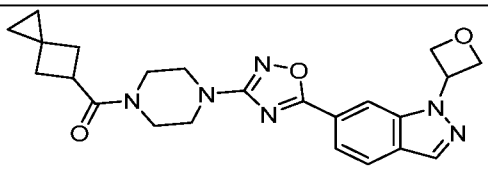
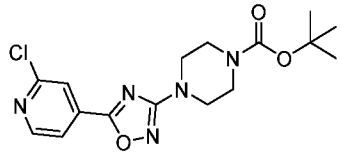
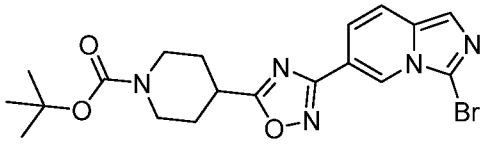
747		858	
748		859	
749		860	
750		861	
751		862	
752		863	
753		864	
754		865	

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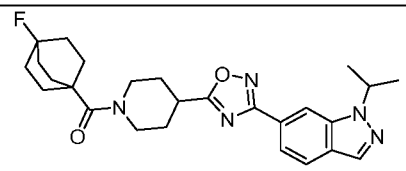
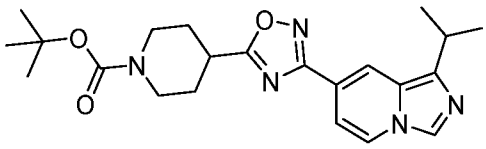
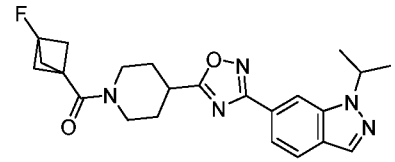
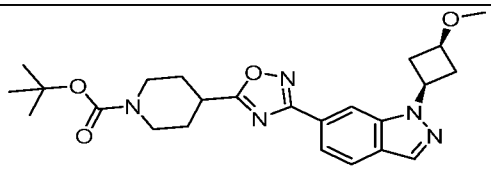
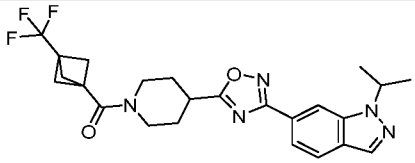
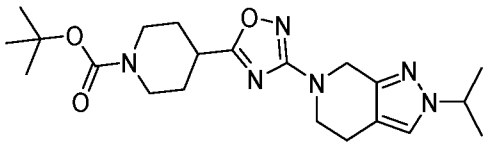
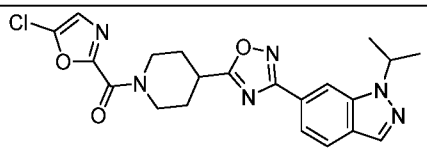
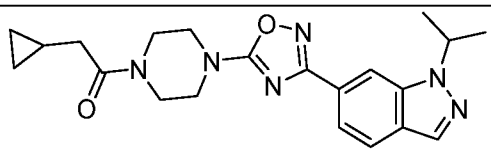
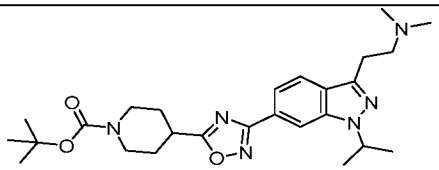
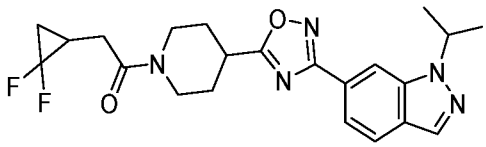
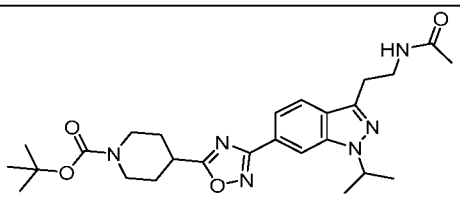
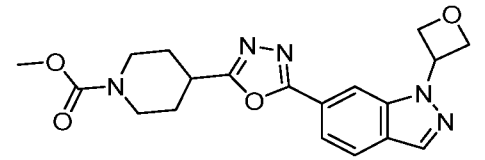
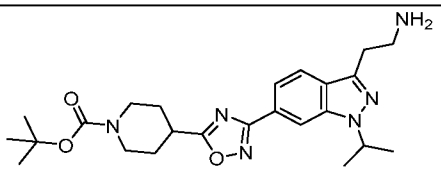
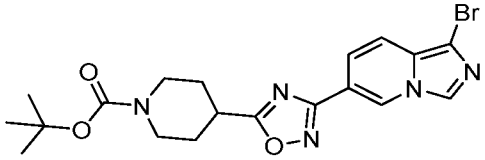
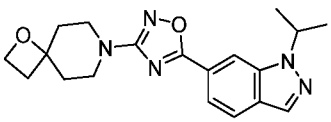
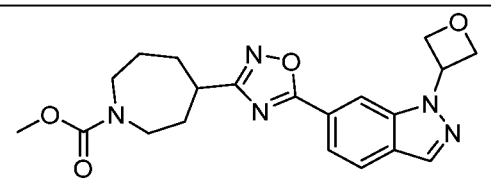
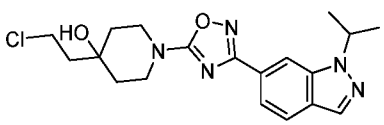
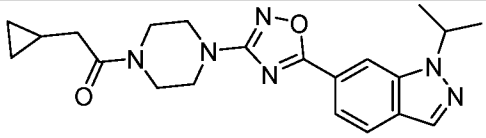
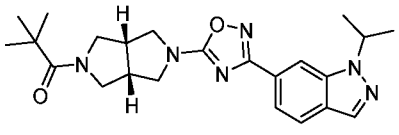
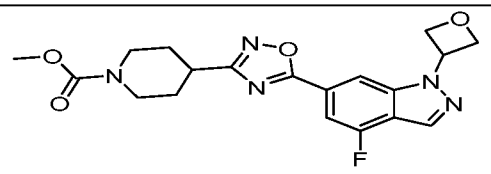
755		866	
756		867	
757		868	
758		869	
759		870	
760		871	
761		872	
762		873	
763		874	
764		875	

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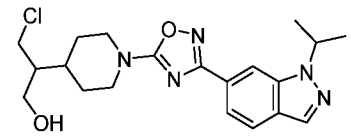
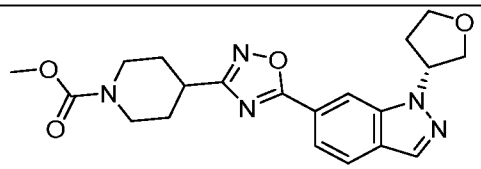
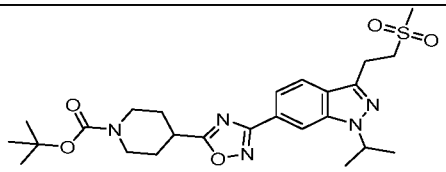
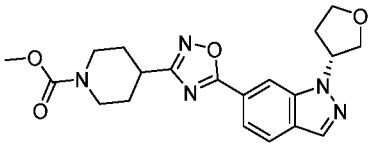
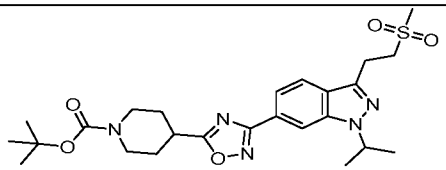
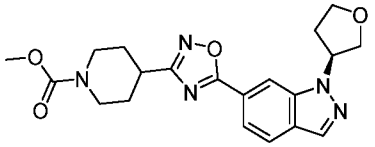
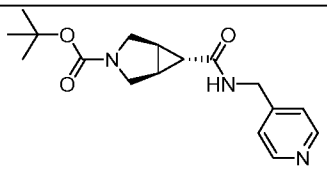
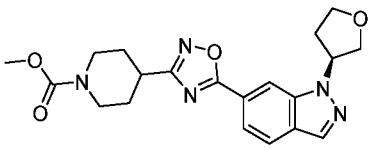
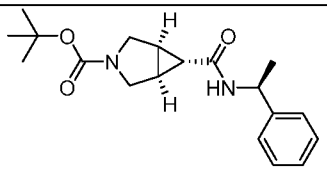
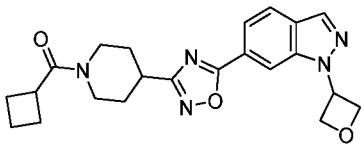
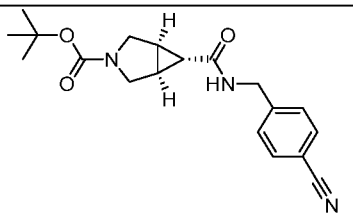
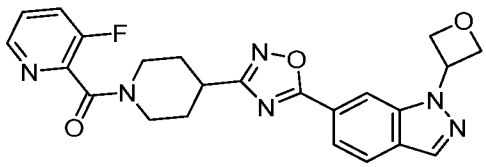
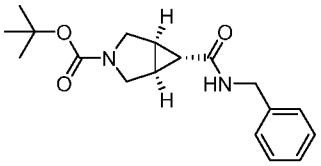
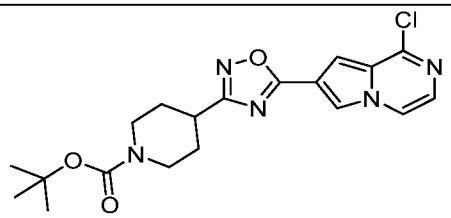
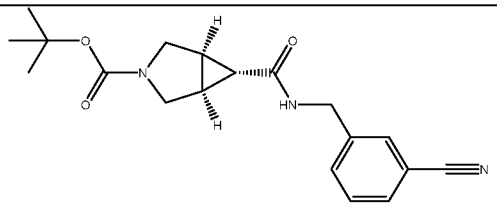
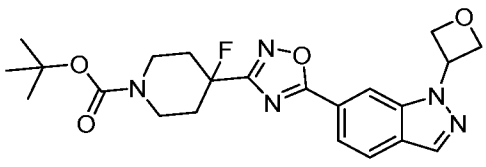
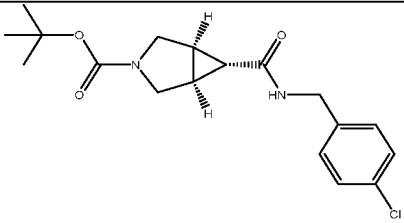
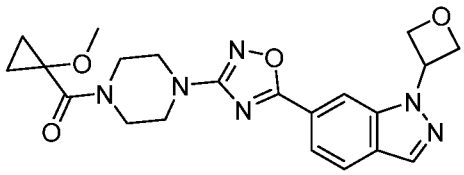
765		876	
766		877	
767		878	
768		879	
769		880	
770		881	
771		882	
772		883	
773		884	

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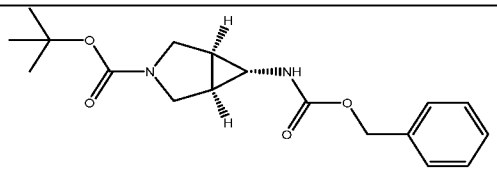
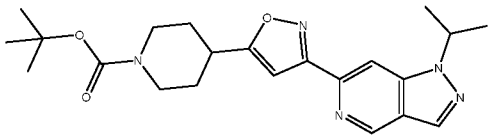
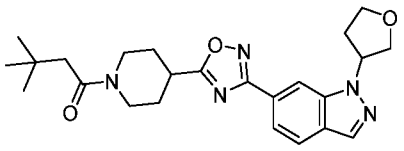
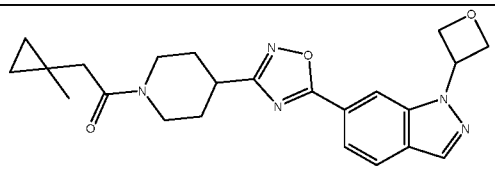
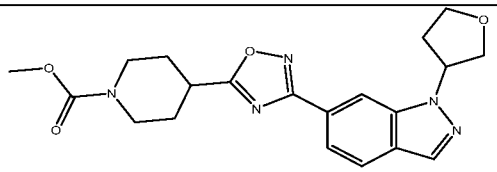
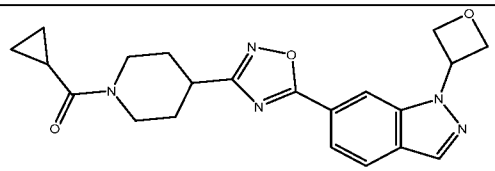
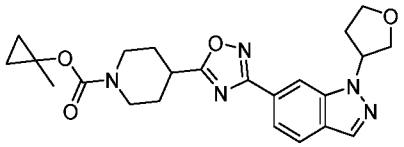
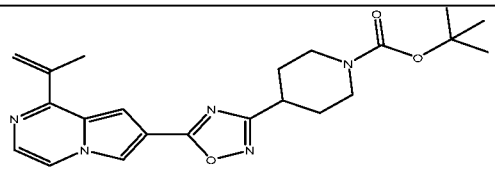
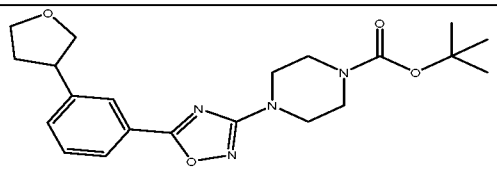
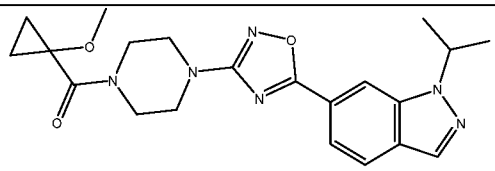
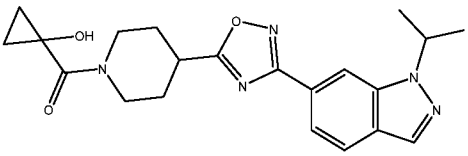
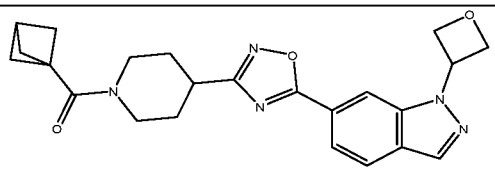
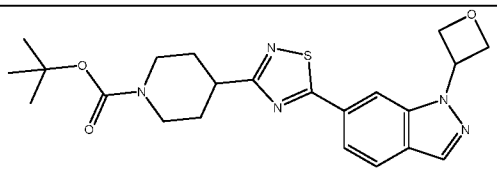
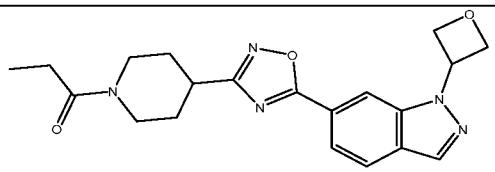
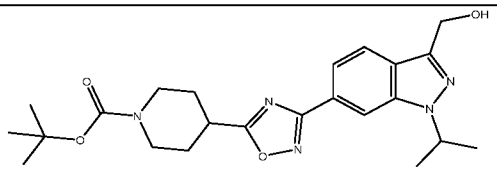
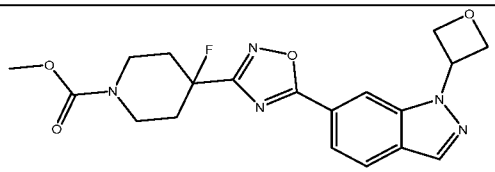
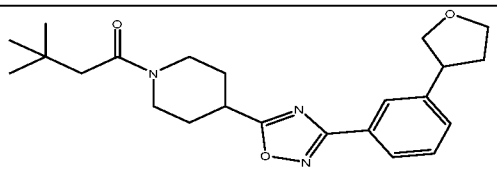
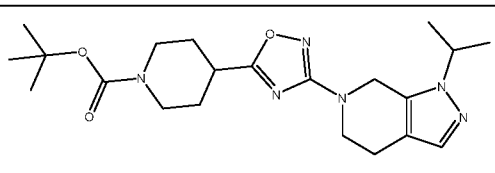
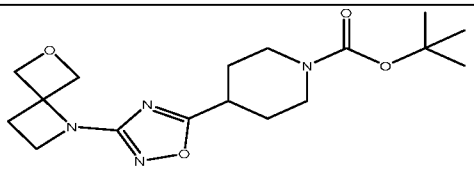
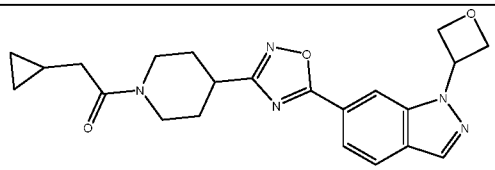
774		885	
775		886	
776		887	
777		888	
778		889	
779		890	
780		891	
781		892	
782		893	
783		894	

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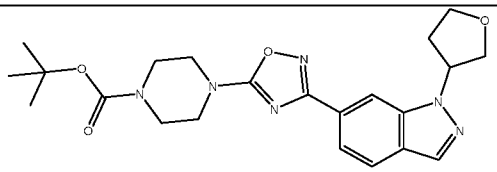
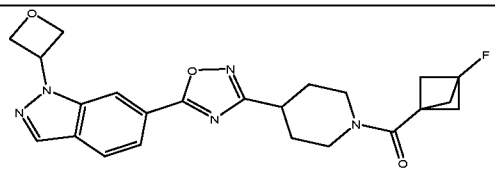
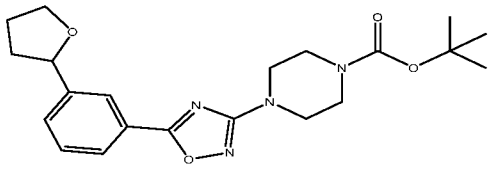
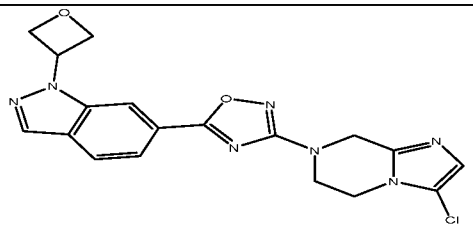
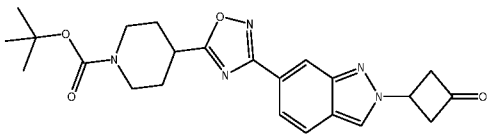
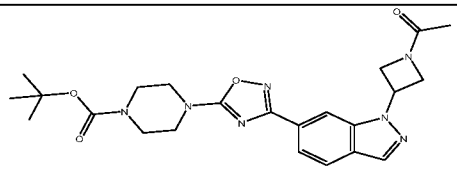
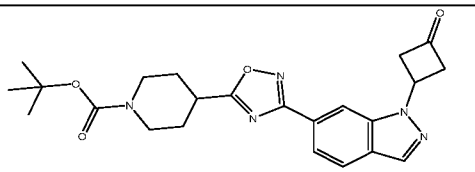
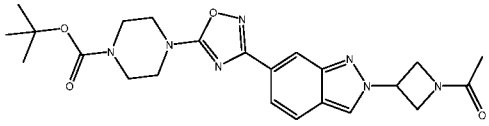
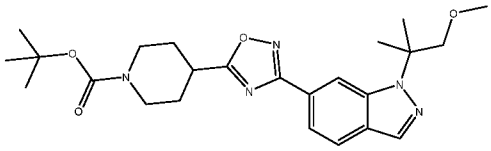
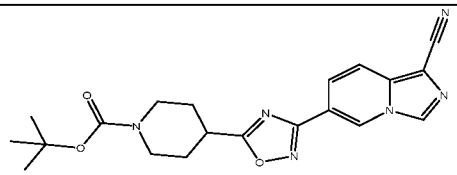
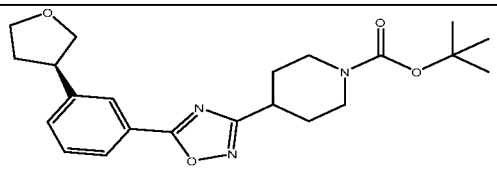
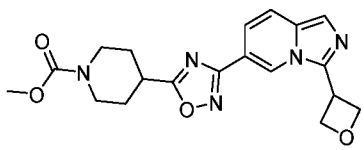
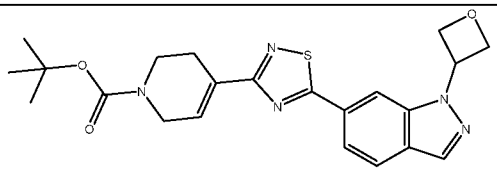
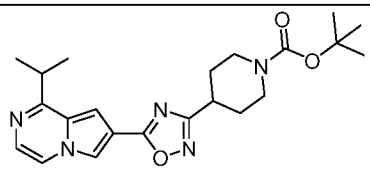
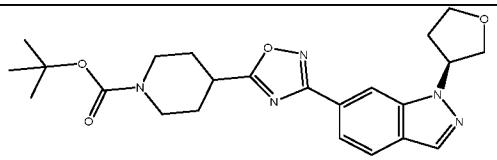
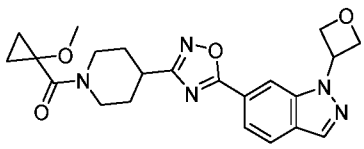
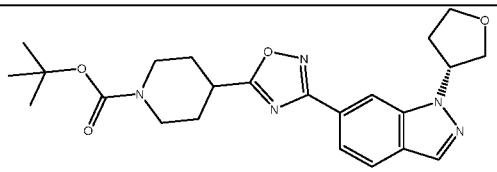
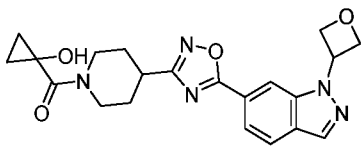
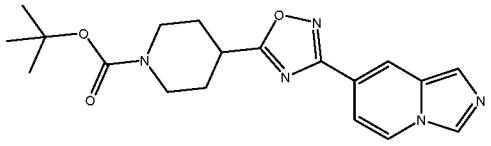
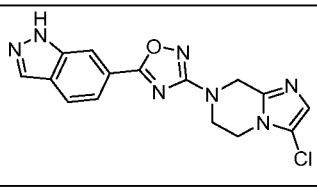
784		895	
785		896	
786		897	
787		898	
788		899	
789		900	
790		901	
791		902	
792		903	
793		904	

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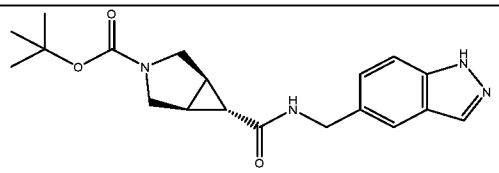
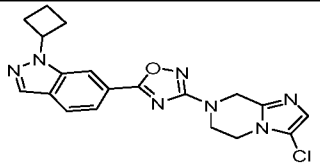
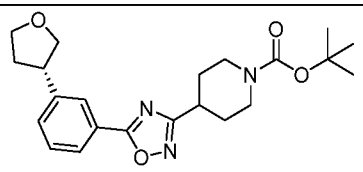
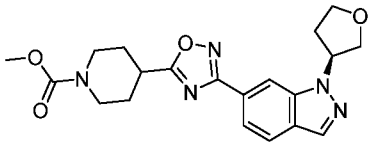
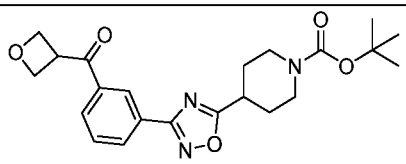
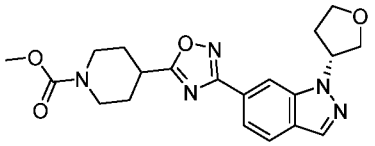
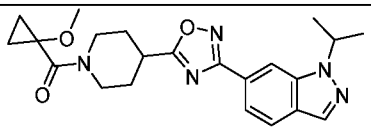
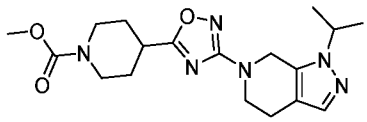
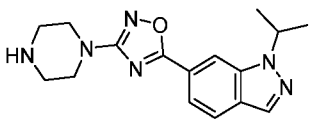
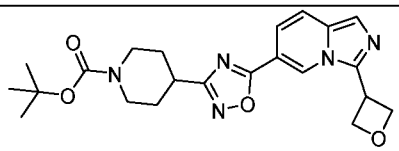
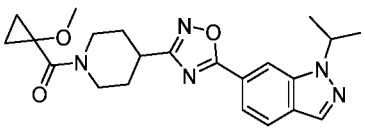
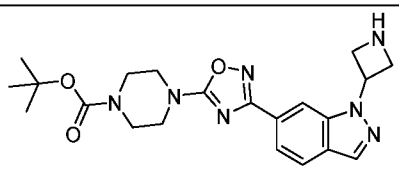
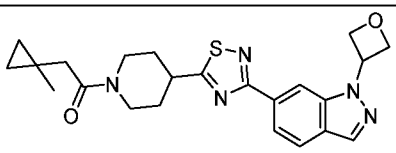
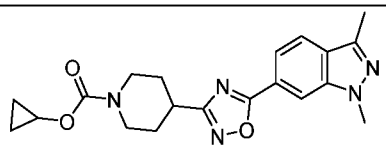
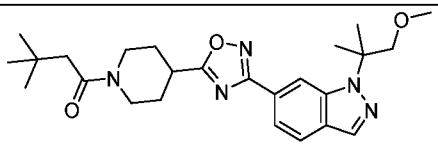
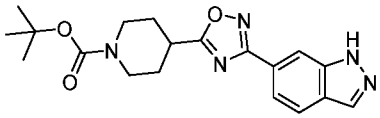
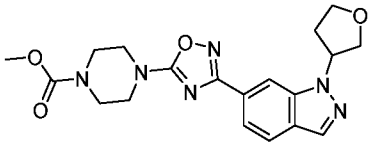
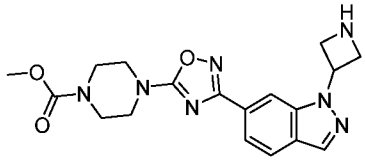
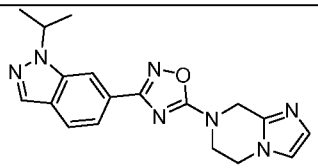
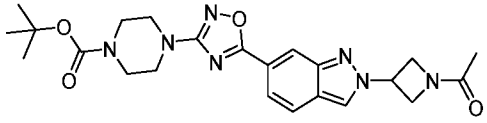
794		905	
795		906	
796		907	
797		908	
798		909	
799		910	
801		911	
802		912	
803		913	
804		914	

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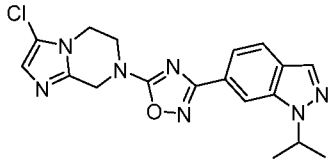
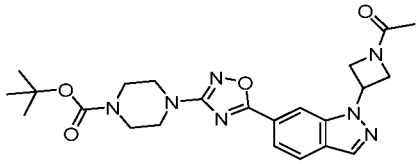
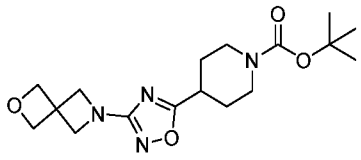
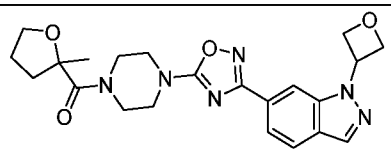
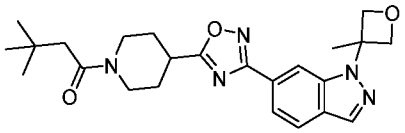
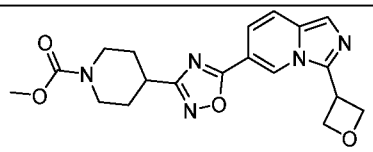
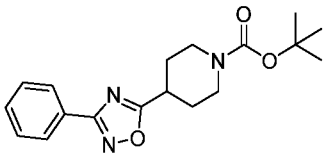
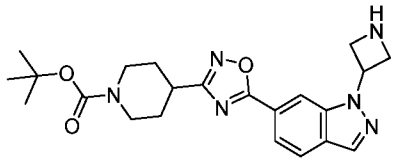
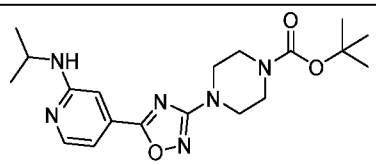
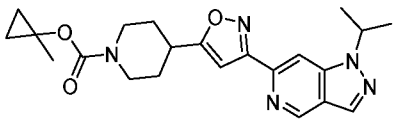
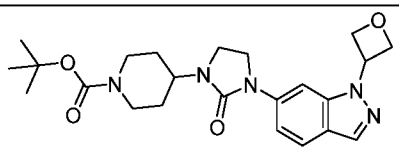
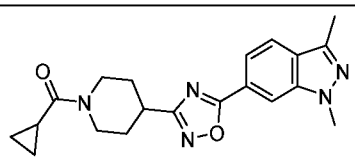
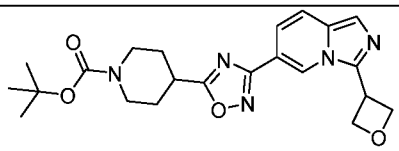
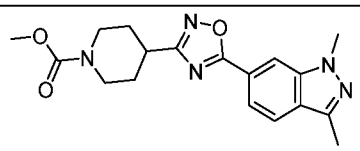
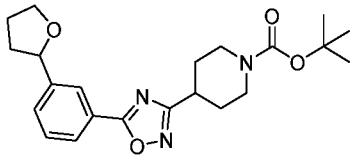
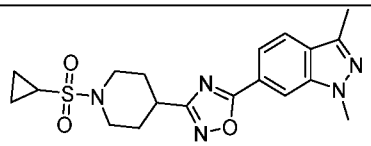
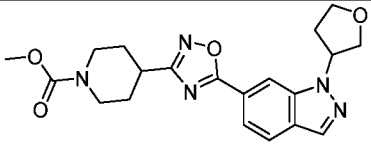
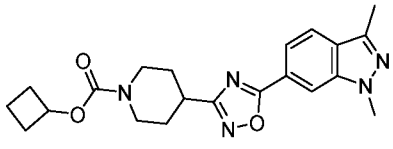
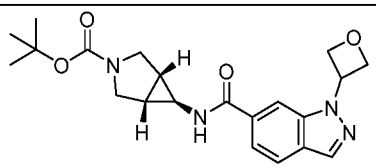
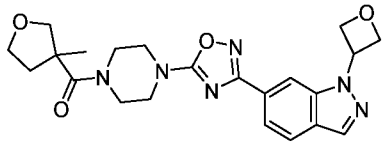
805		915	
806		916	
807		917	
808		918	
809		919	
810		920	
811		921	
812		922	
813		923	
814		924	

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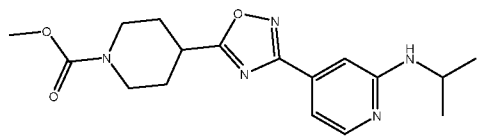
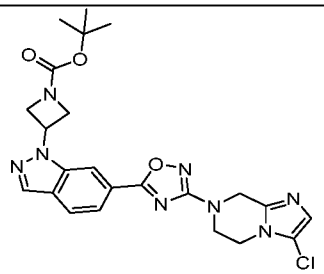
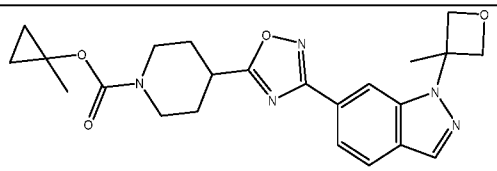
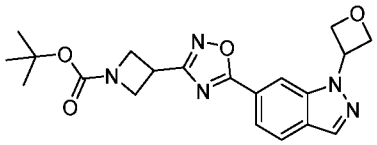
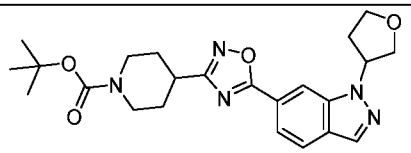
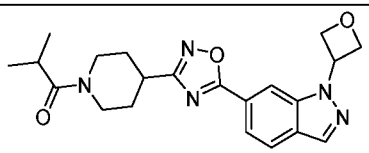
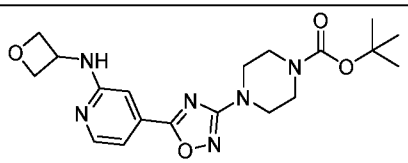
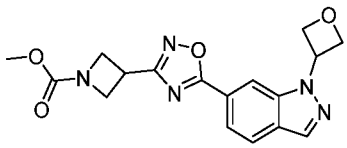
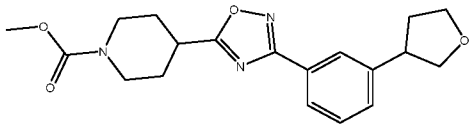
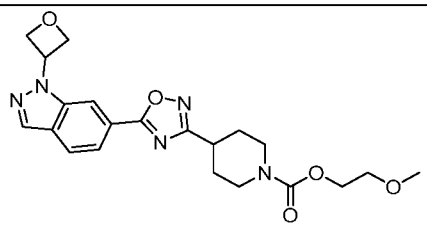
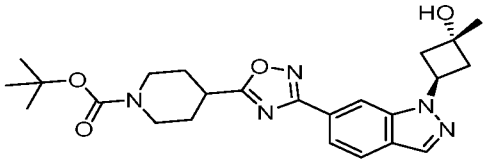
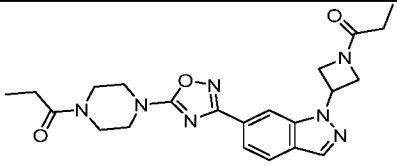
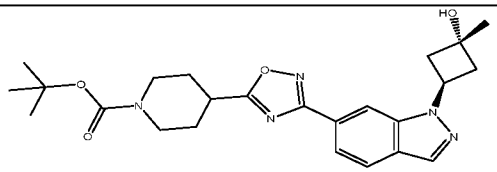
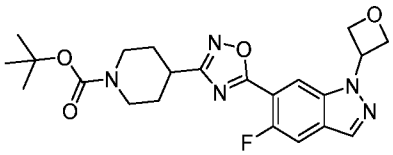
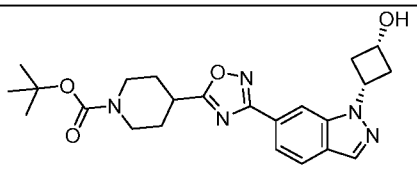
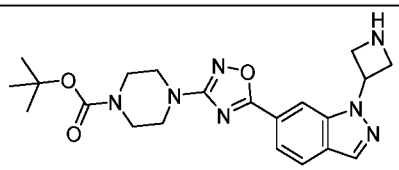
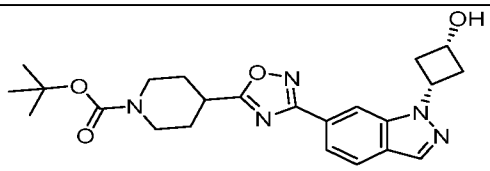
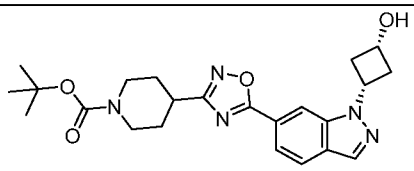
815		925	
816		926	
817		927	
818		928	
819		929	
820		930	
821		931	
822		932	
823		933	

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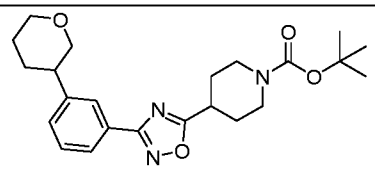
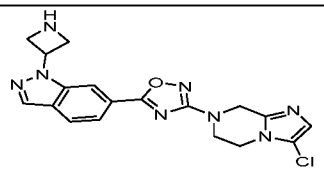
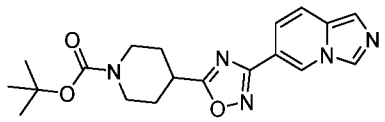
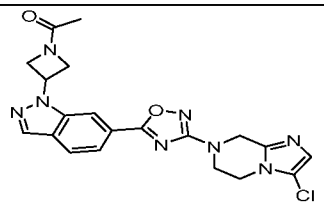
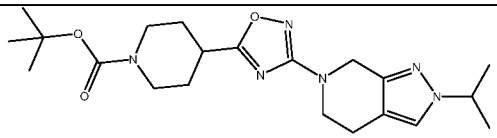
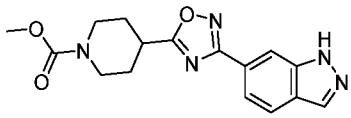
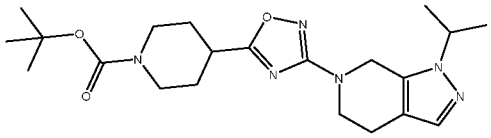
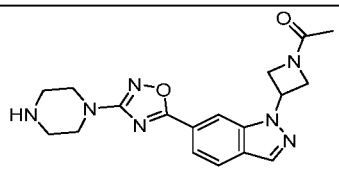
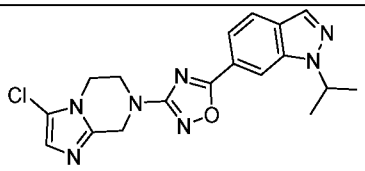
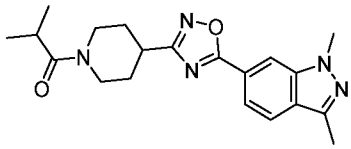
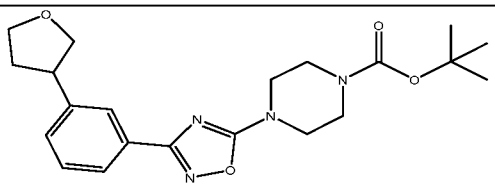
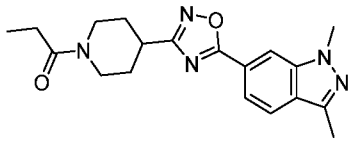
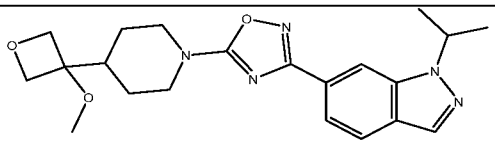
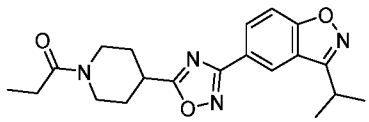
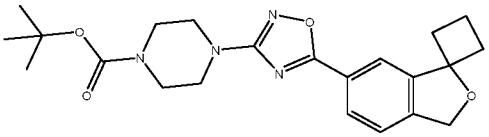
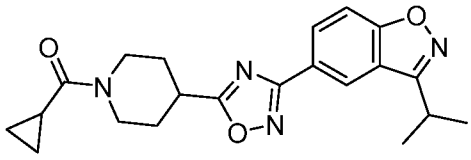
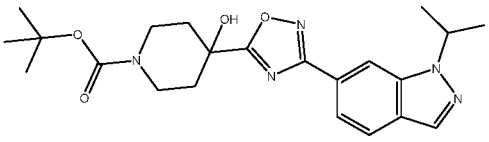
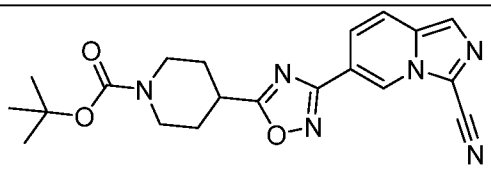
824		934	
825		935	
826		936	
827		937	
828		938	
829		939	
830		940	
831		941	
832		942	

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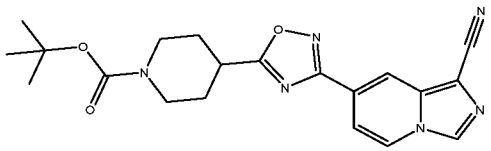
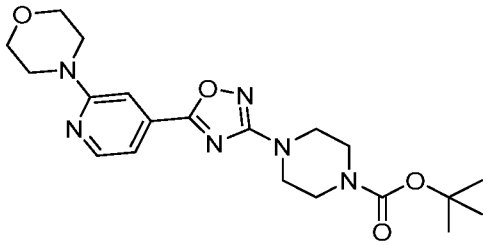
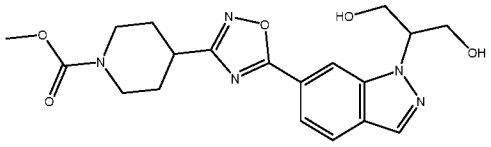
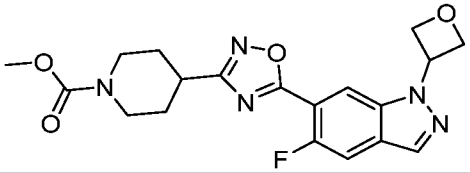
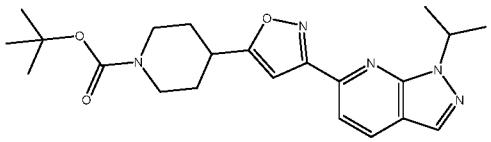
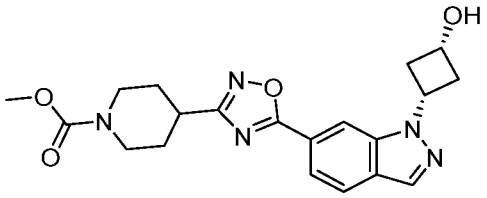
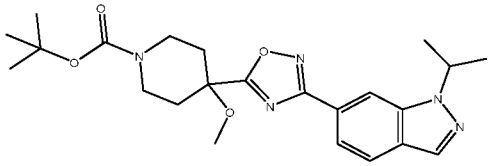
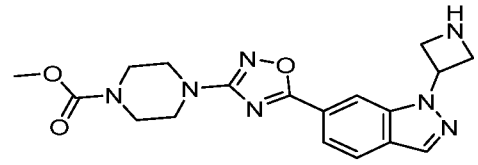
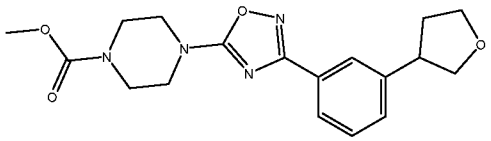
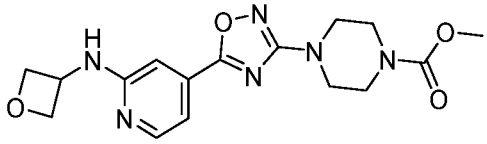
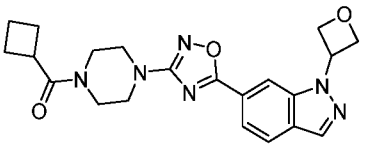
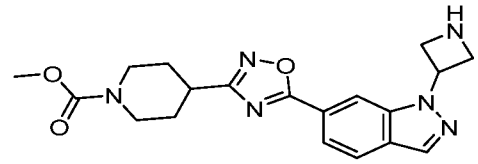
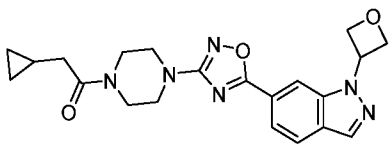
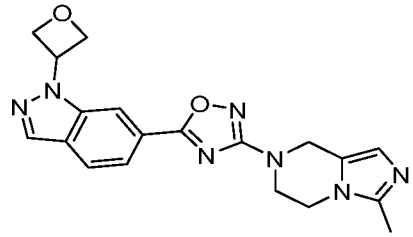
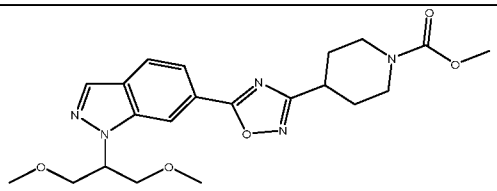
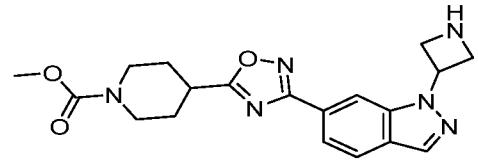
833		943	
834		944	
835		945	
836		946	
837		947	
838		948	
839		949	
840		950	

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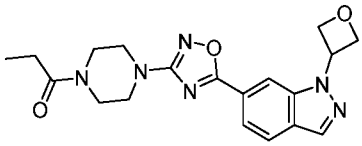
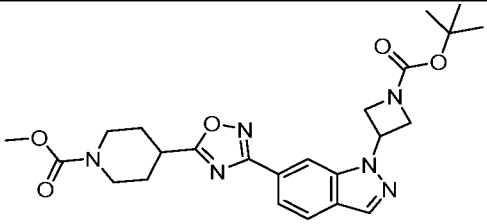
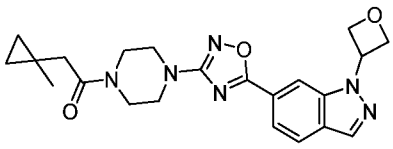
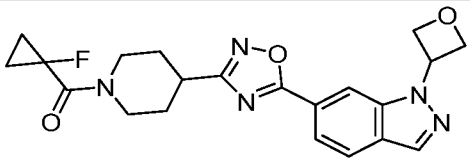
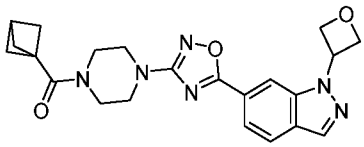
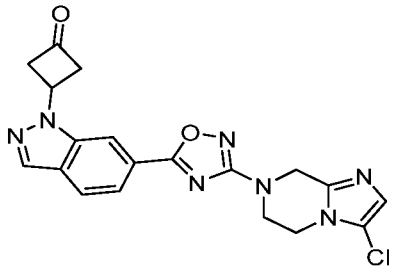
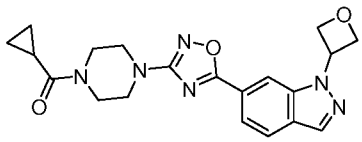
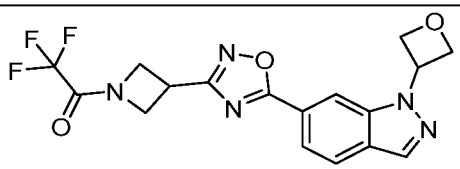
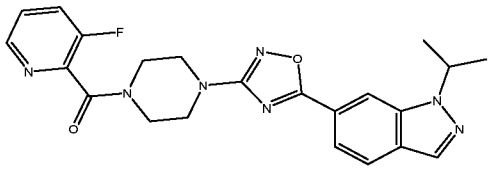
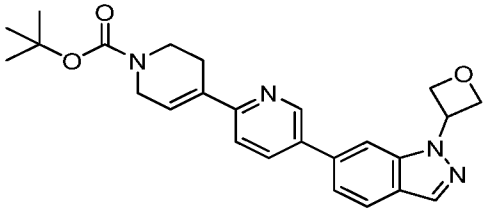
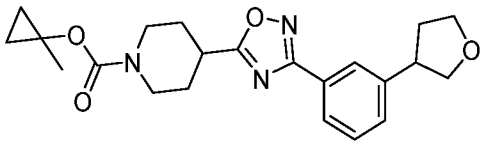
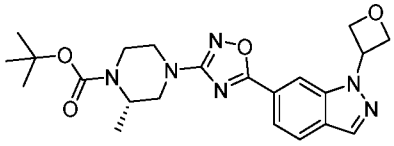
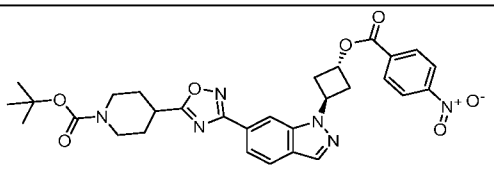
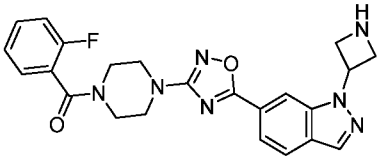
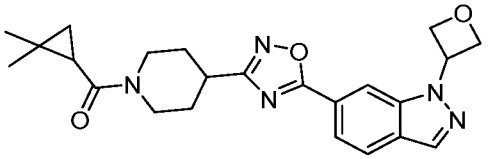
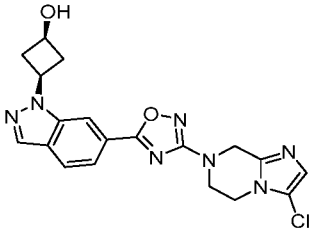
841		951	
842		952	
843		953	
844		954	
845		955	
846		956	
847		957	
848		958	

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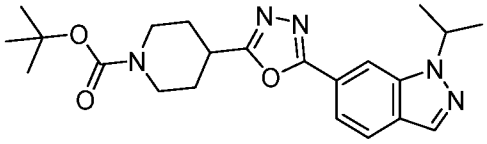
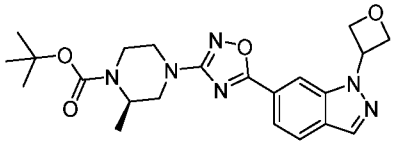
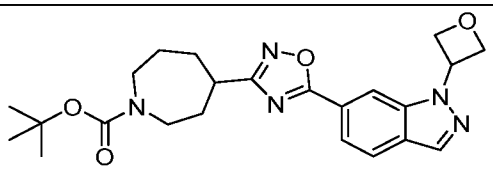
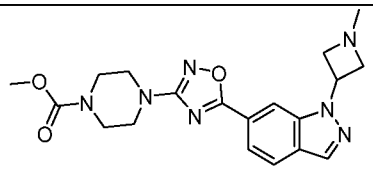
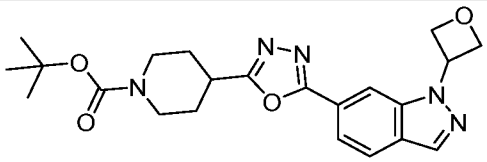
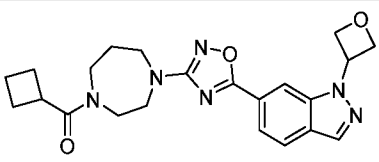
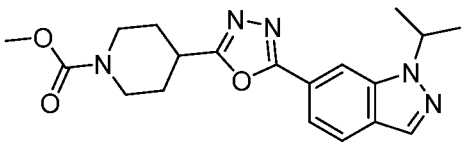
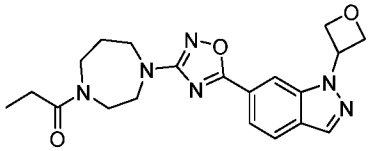
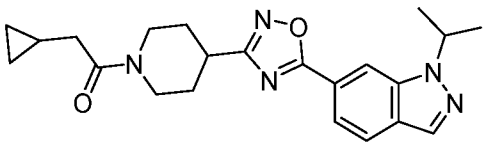
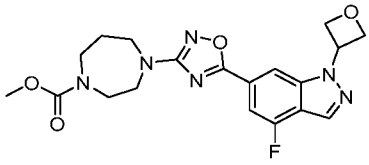
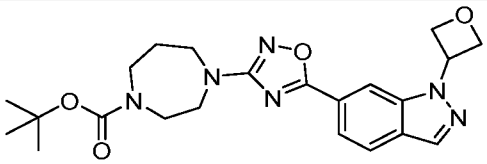
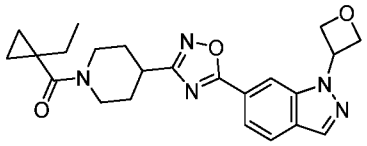
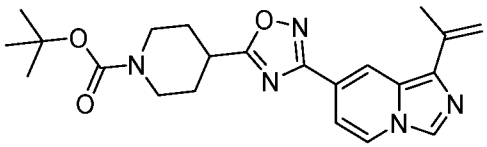
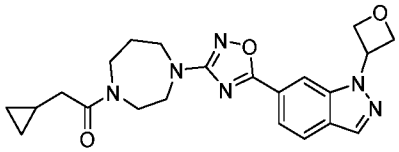
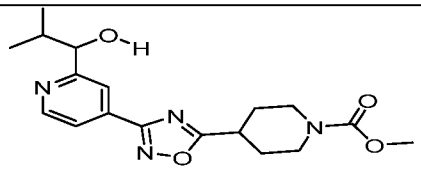
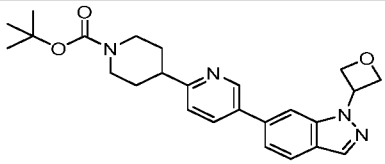
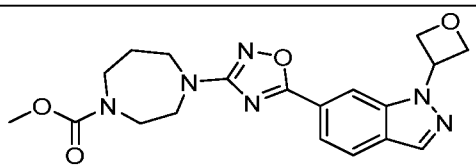
849		959	
850		960	
851		961	
852		962	
853		963	
854		964	
855		965	
856		966	
857			

Table 2B. Compounds of the Invention

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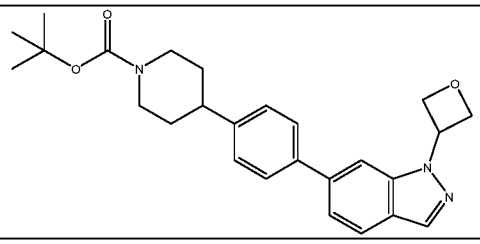
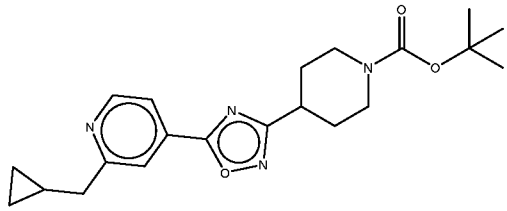
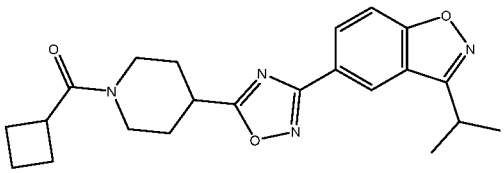
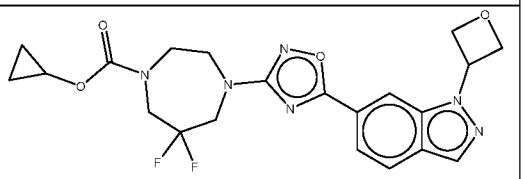
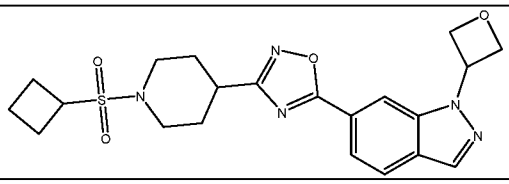
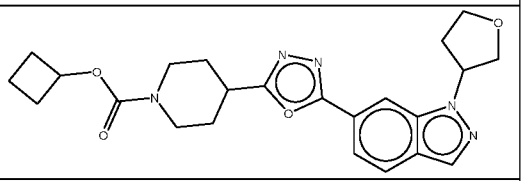
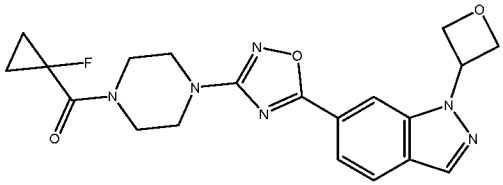
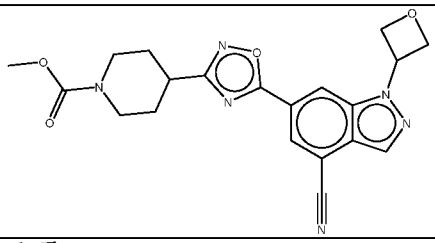
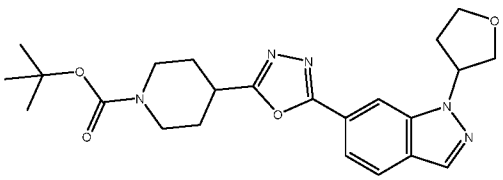
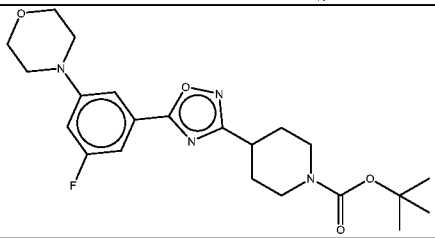
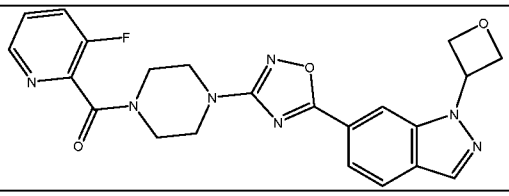
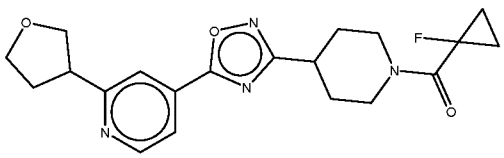
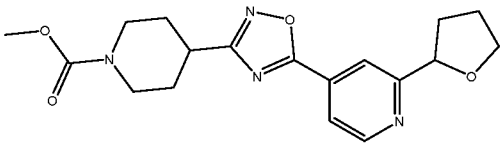
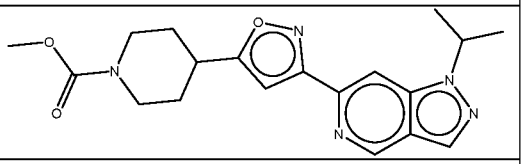
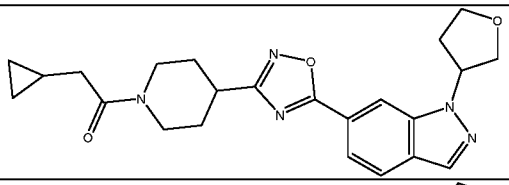
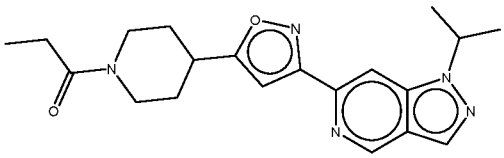
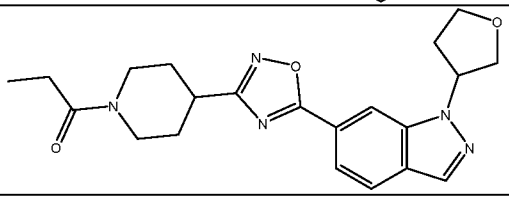
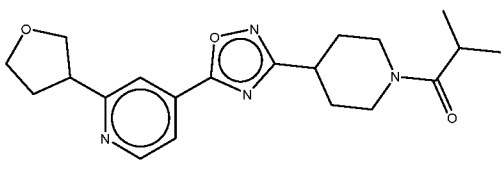
967		1082	
968		1083	
969		1084	
970		1085	
971		1086	
972		1087	
973		1088	
974		1089	
975		1090	

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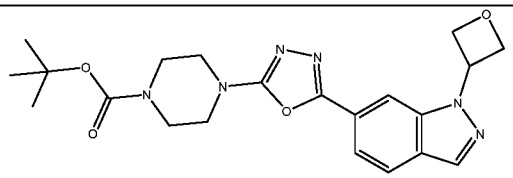
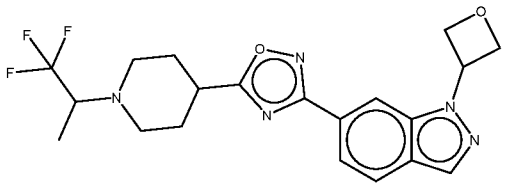
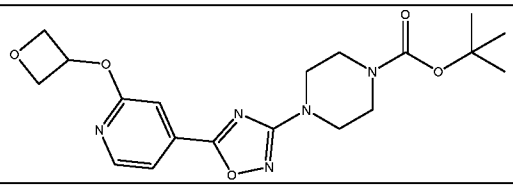
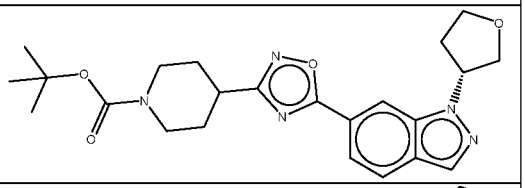
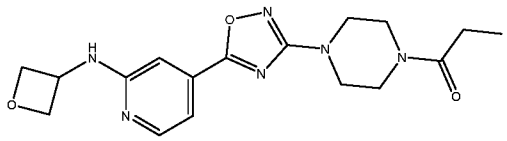
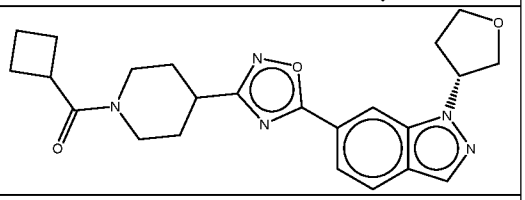
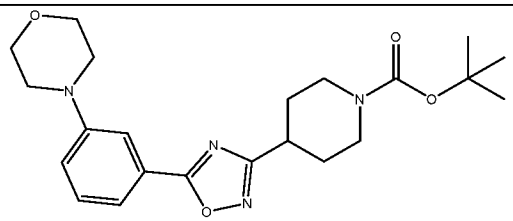
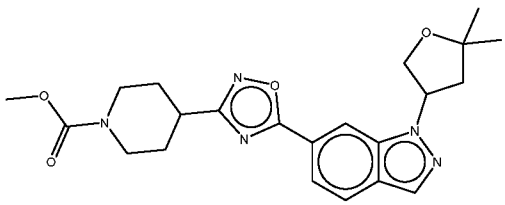
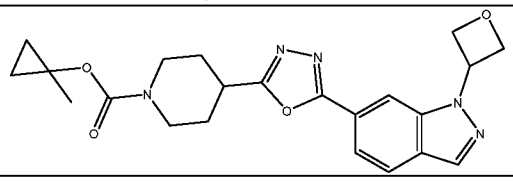
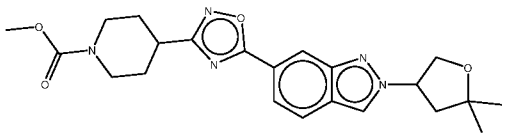
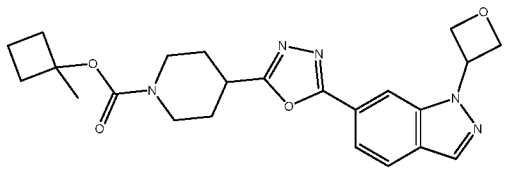
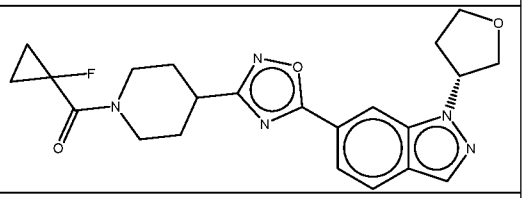
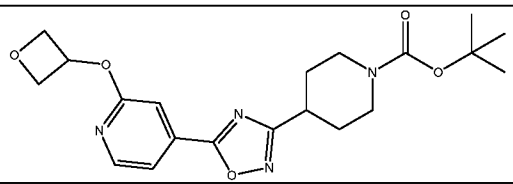
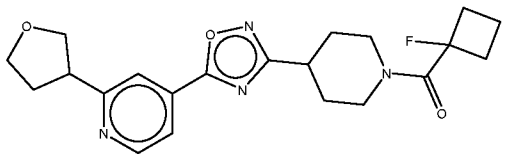
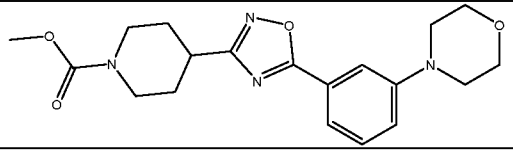
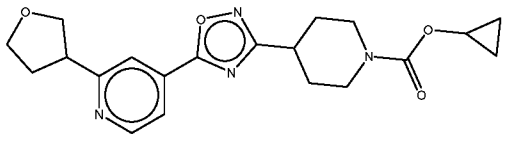
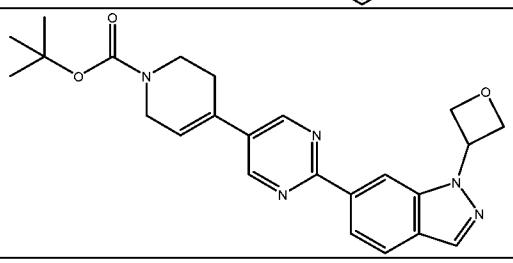
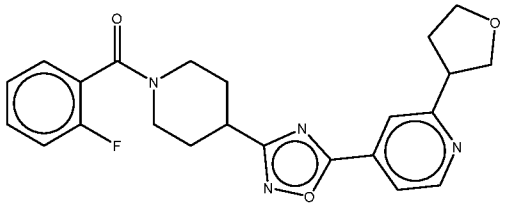
976		1091	
977		1092	
978		1093	
979		1094	
980		1095	
981		1096	
982		1097	
983		1098	
984		1099	

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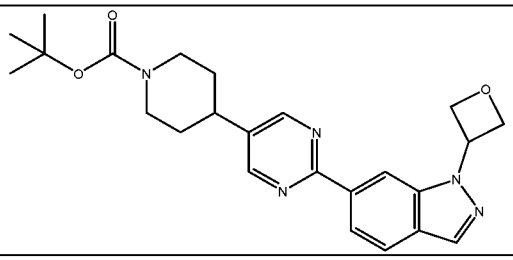
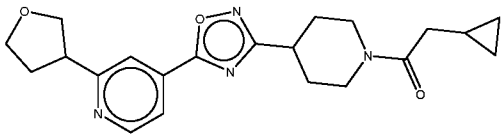
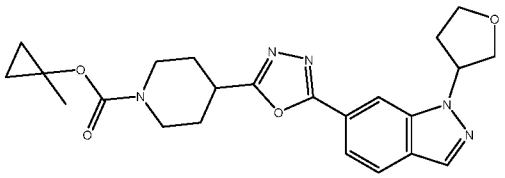
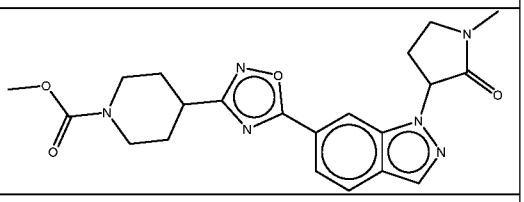
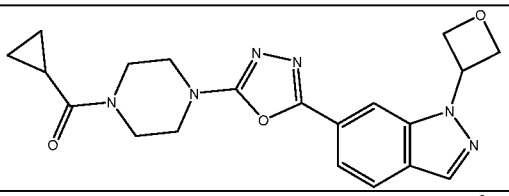
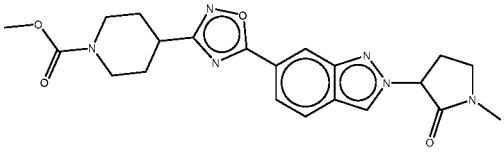
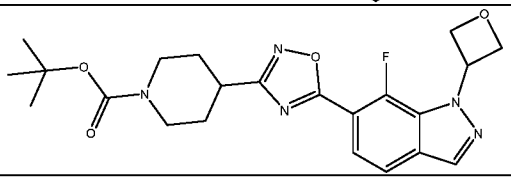
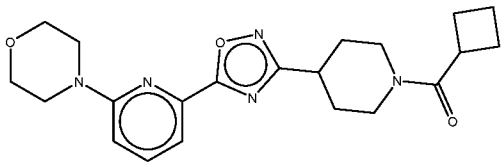
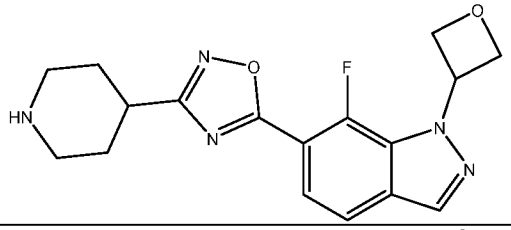
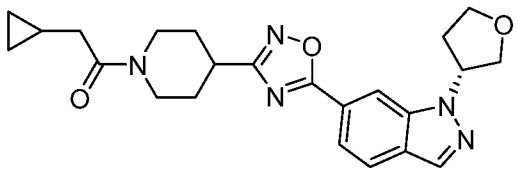
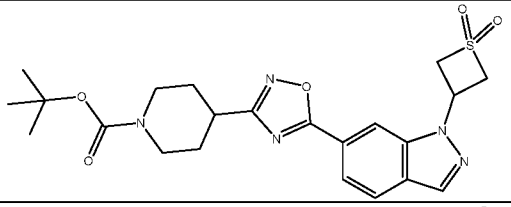
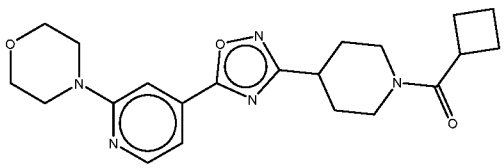
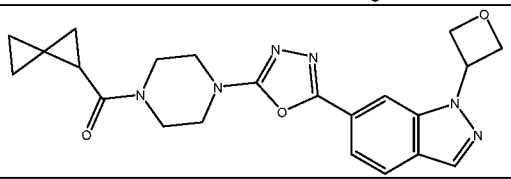
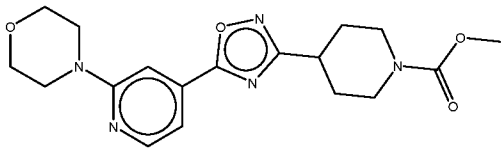
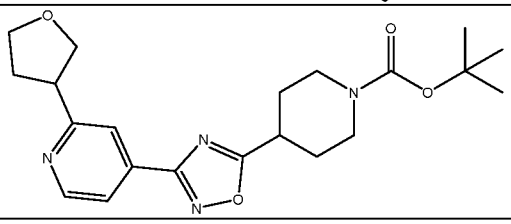
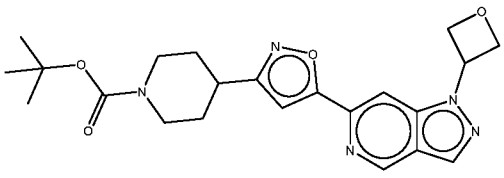
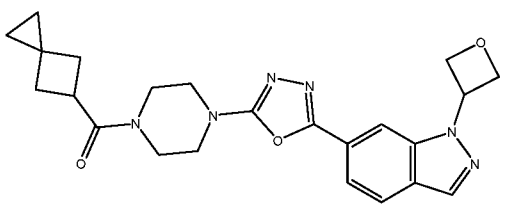
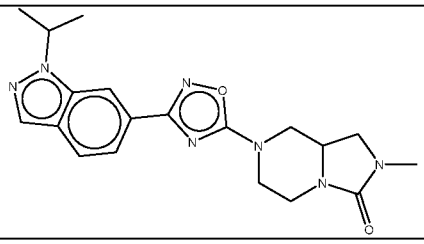
985		1100	
986		1101	
987		1102	
988		1103	
989		1104	
990		1105	
991		1106	
992		1107	
993		1108	

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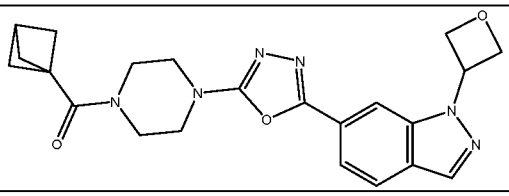
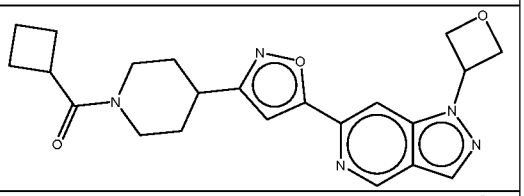
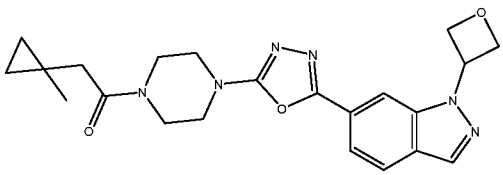
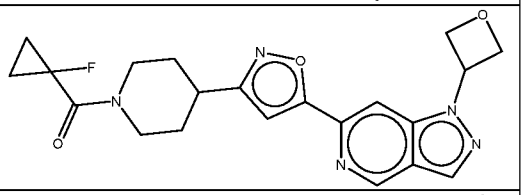
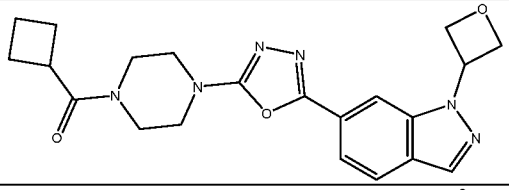
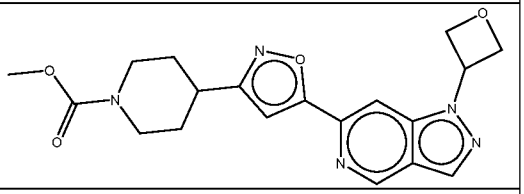
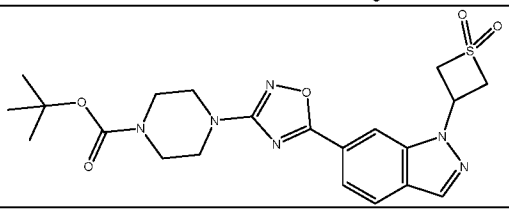
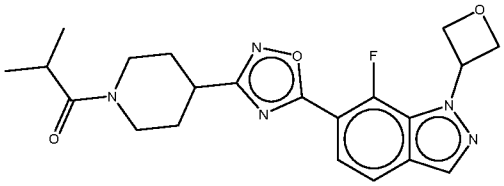
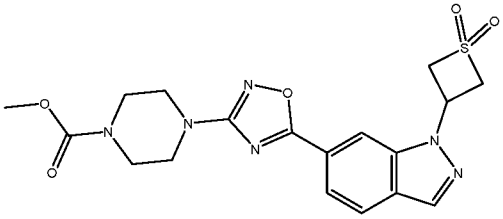
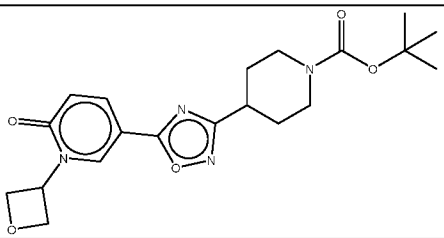
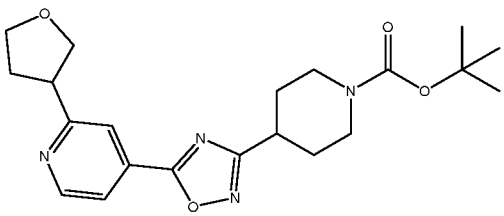
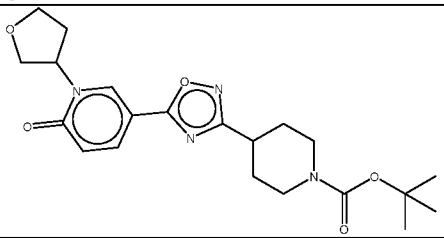
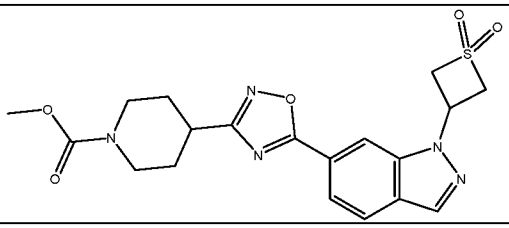
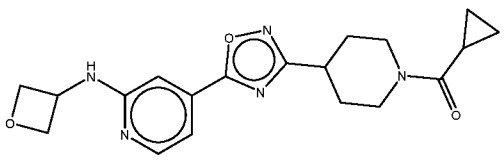
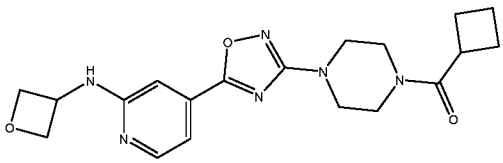
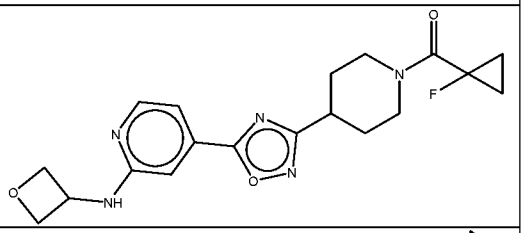
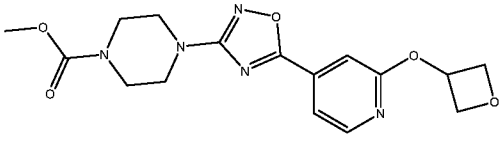
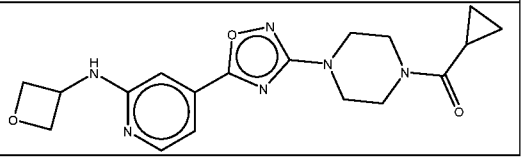
994		1109	
995		1110	
996		1111	
997		1112	
998		1113	
999		1114	
1000		1115	
1001		1116	
1002		1117	

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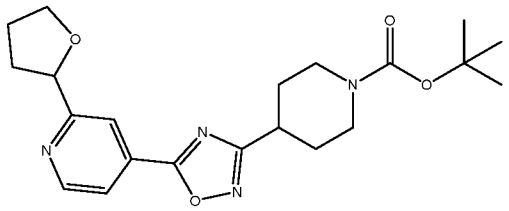
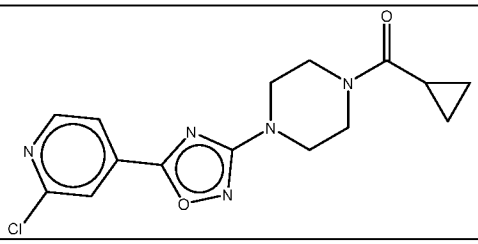
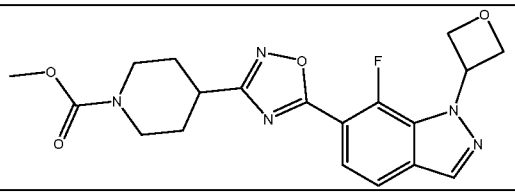
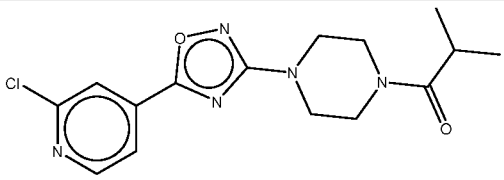
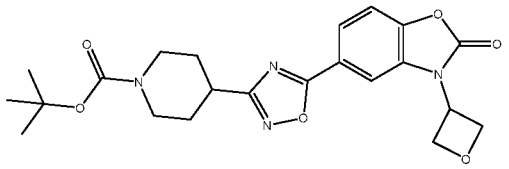
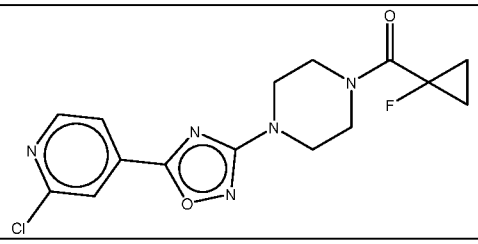
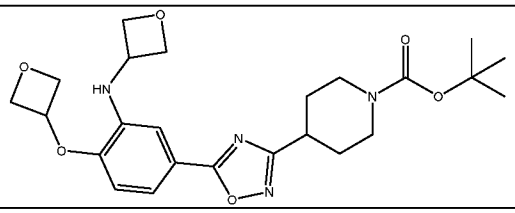
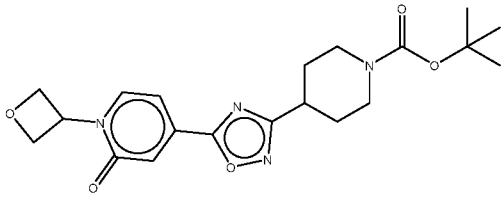
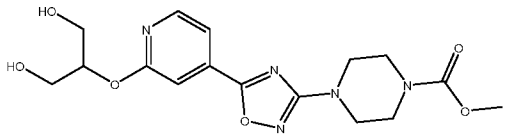
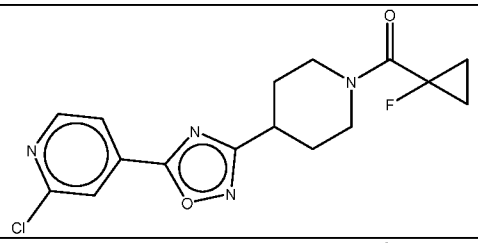
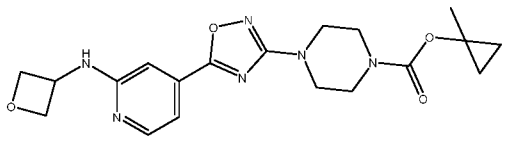
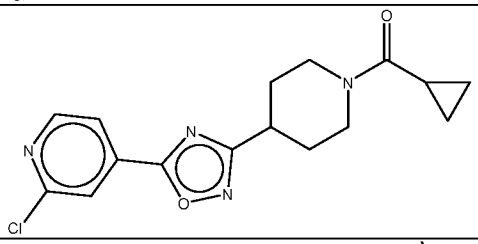
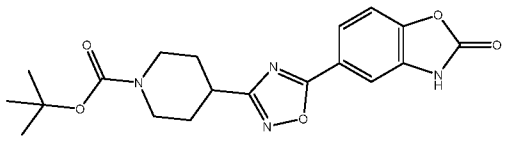
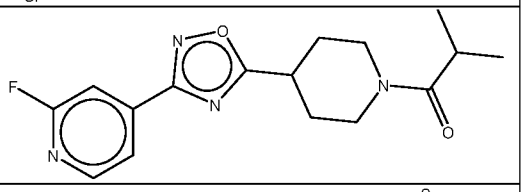
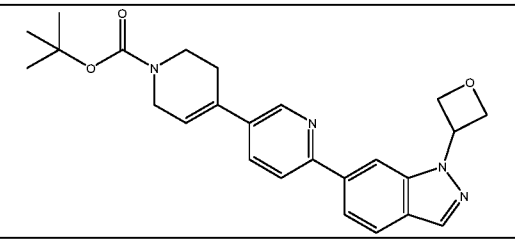
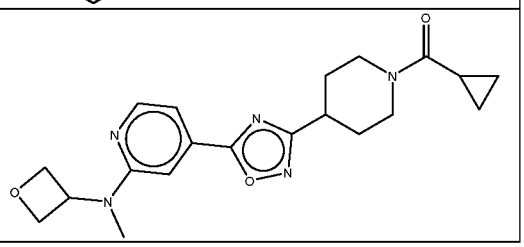
1003		1118	
1004		1119	
1005		1120	
1006		1121	
1007		1122	
1008		1123	
1009		1124	
1010		1125	

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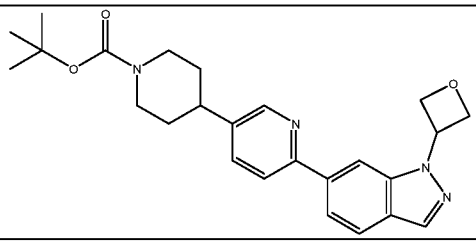
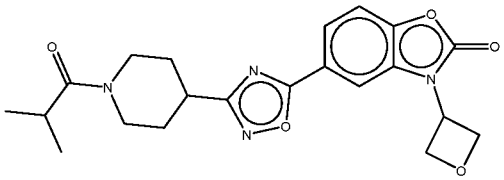
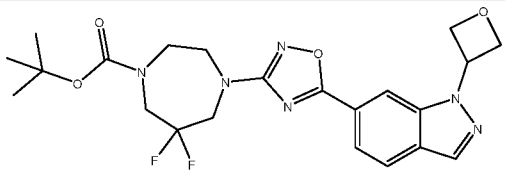
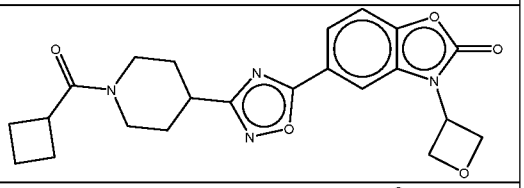
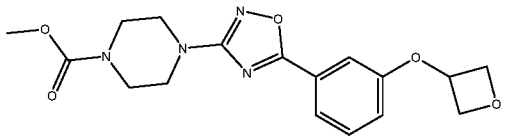
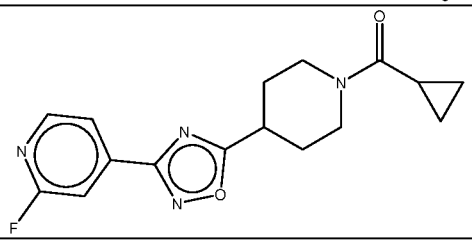
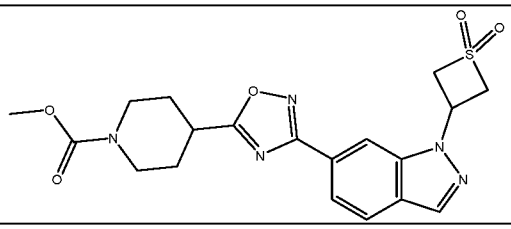
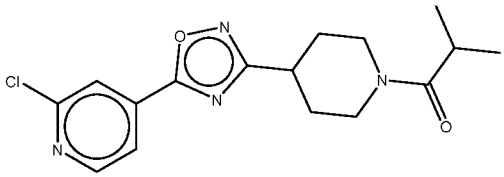
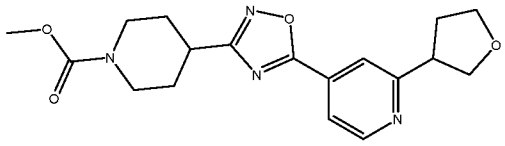
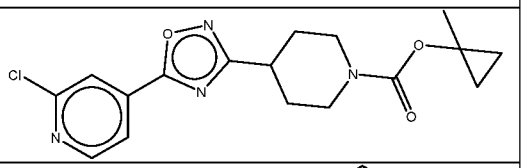
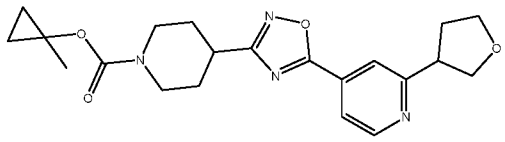
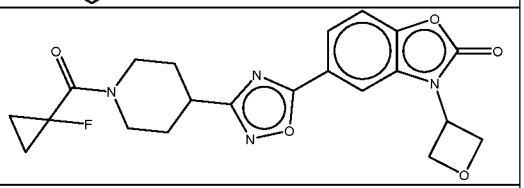
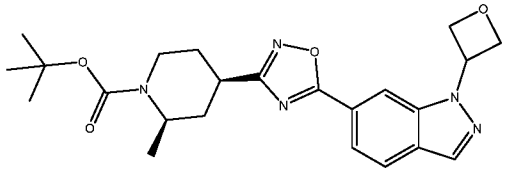
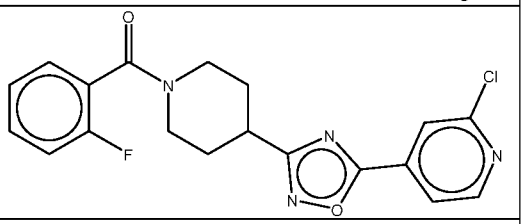
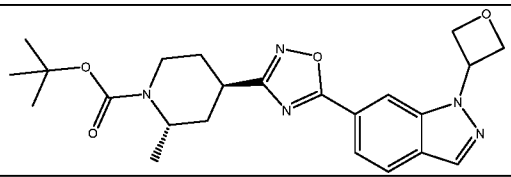
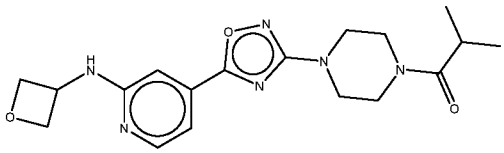
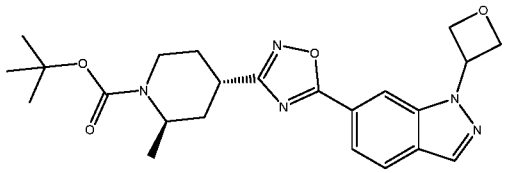
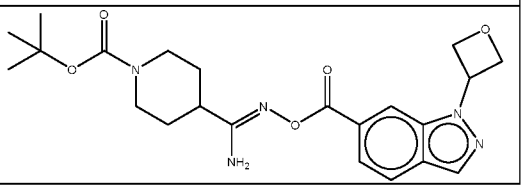
1011		1126	
1012		1127	
1013		1128	
1014		1129	
1015		1130	
1016		1131	
1017		1132	
1018		1133	
1019		1134	

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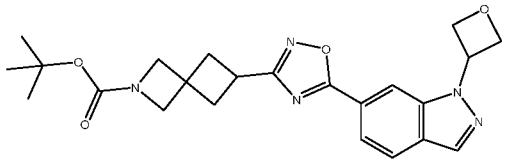
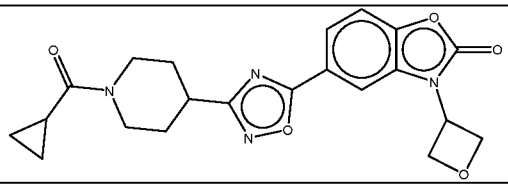
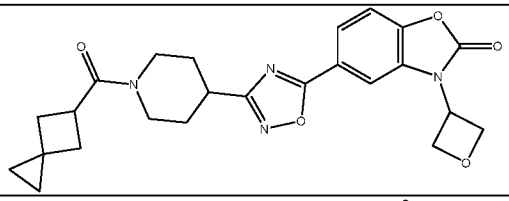
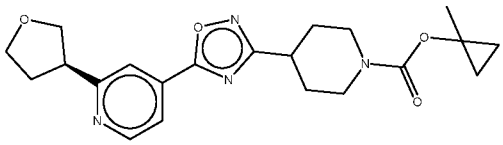
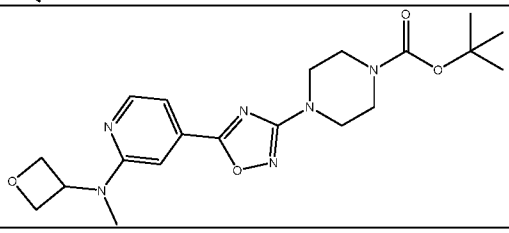
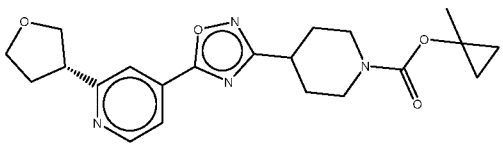
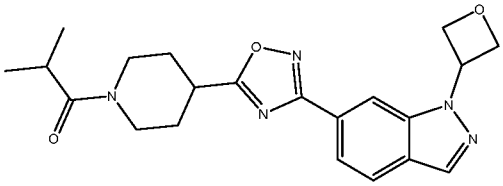
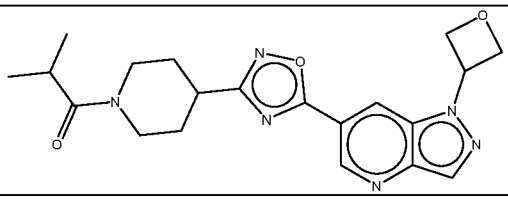
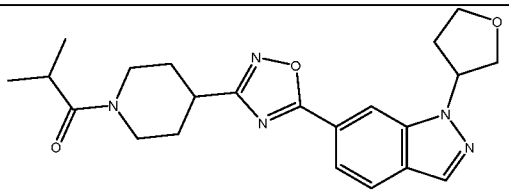
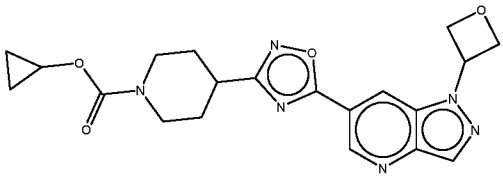
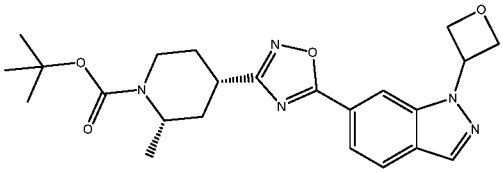
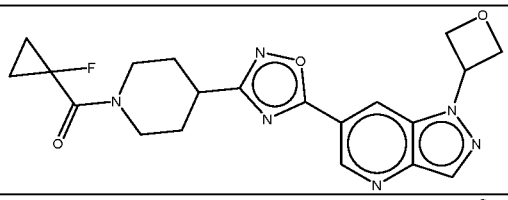
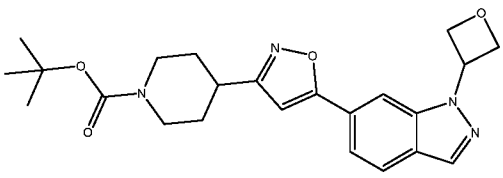
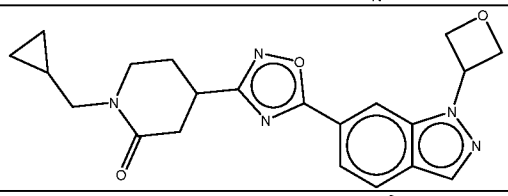
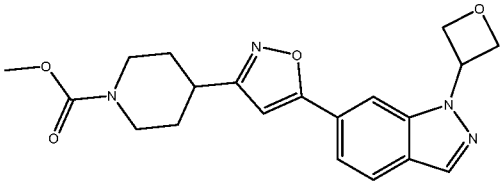
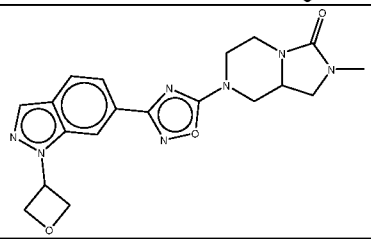
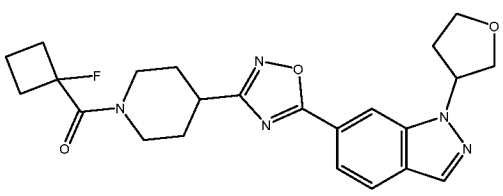
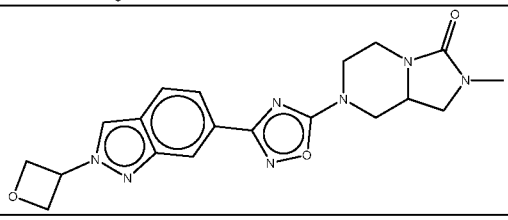
1020		1135	
1021		1136	
1022		1137	
1023		1138	
1024		1139	
1025		1140	
1026		1141	
1027		1142	
1028		1143	

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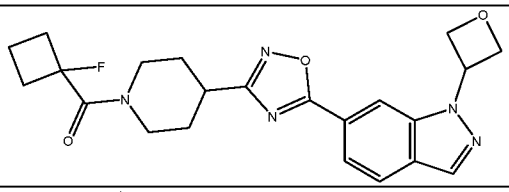
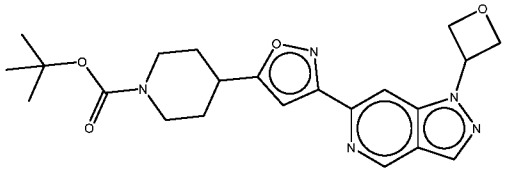
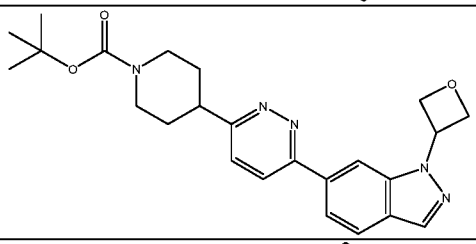
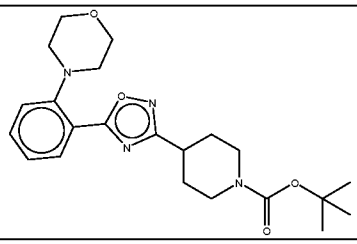
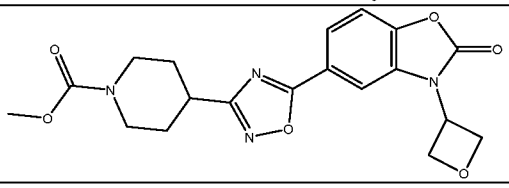
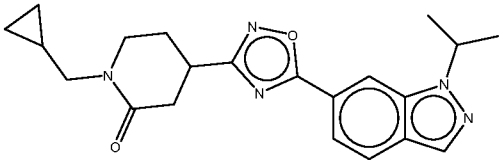
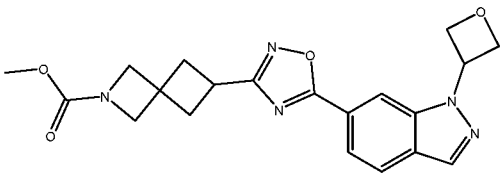
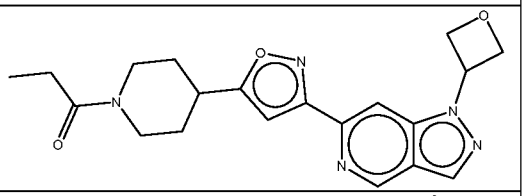
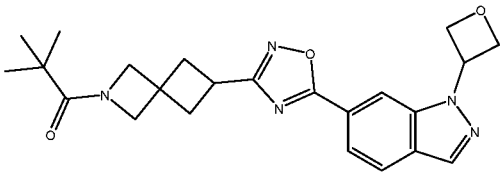
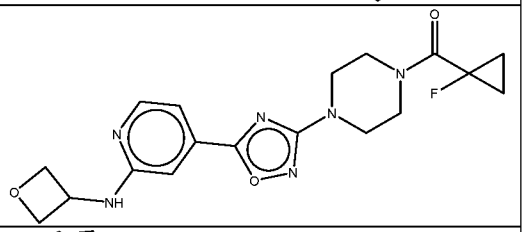
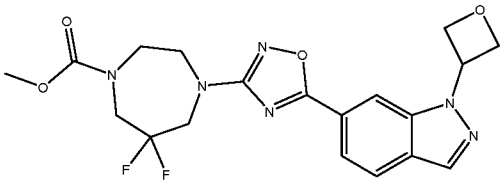
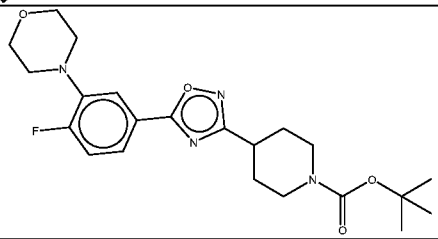
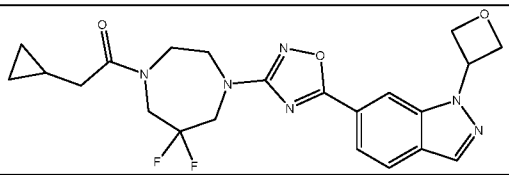
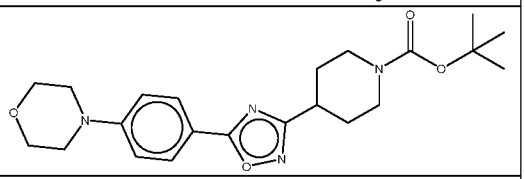
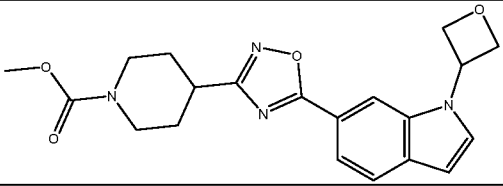
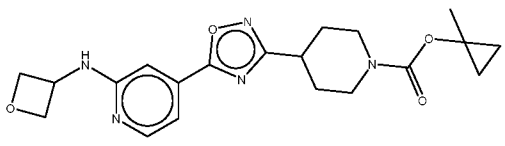
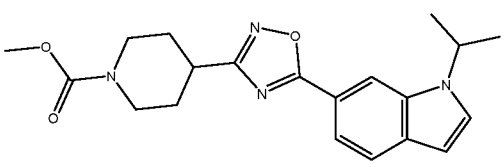
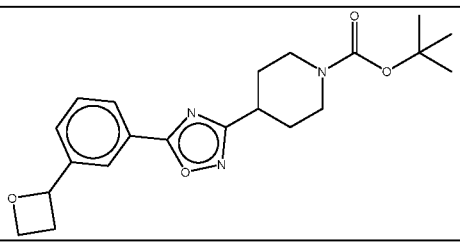
1029		1144	
1030		1145	
1031		1146	
1032		1147	
1033		1148	
1034		1149	
1035		1150	
1036		1151	
1037		1152	

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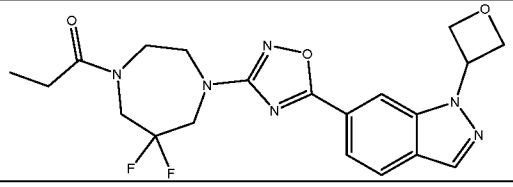
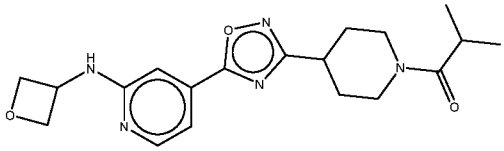
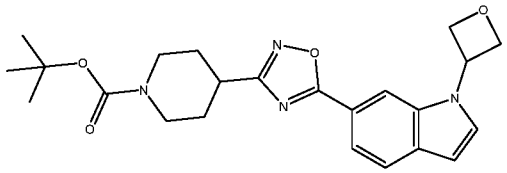
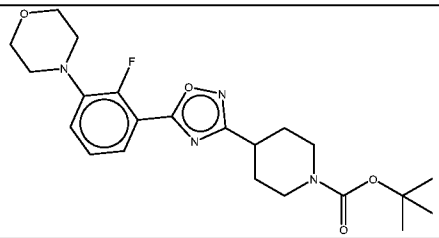
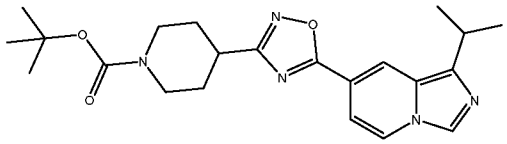
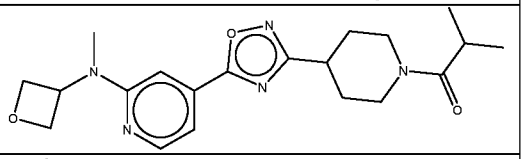
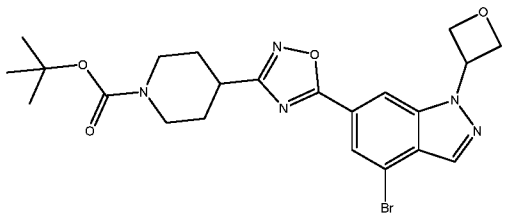
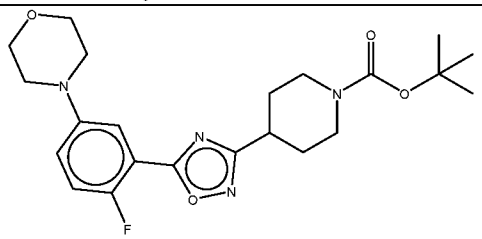
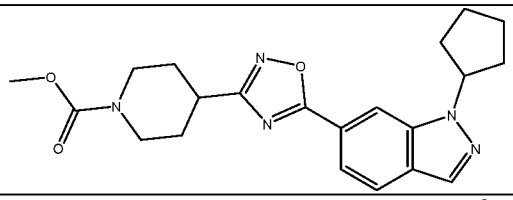
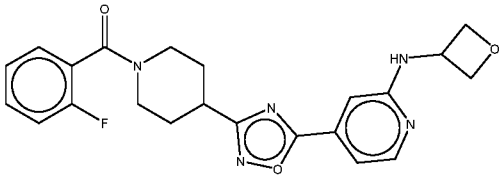
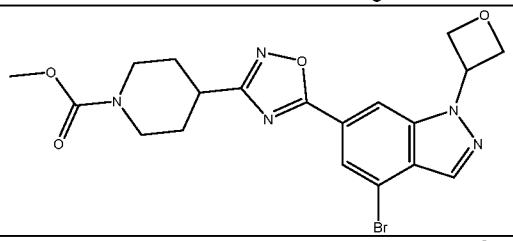
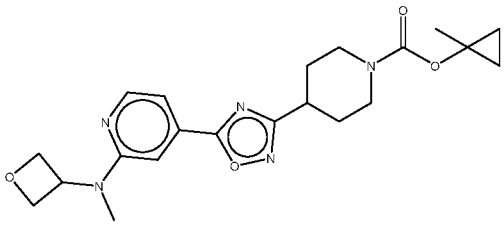
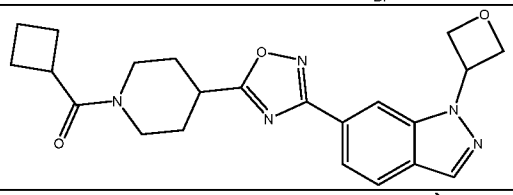
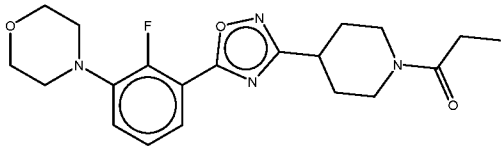
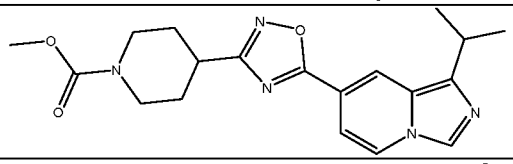
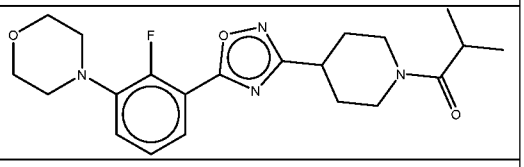
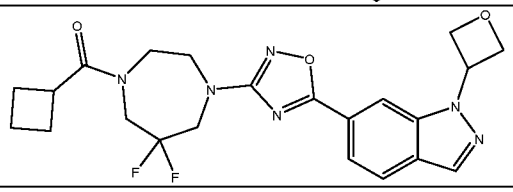
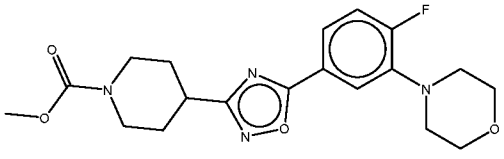
1038		1153	
1039		1154	
1040		1155	
1041		1156	
1042		1157	
1043		1158	
1044		1159	
1045		1160	
1046		1161	

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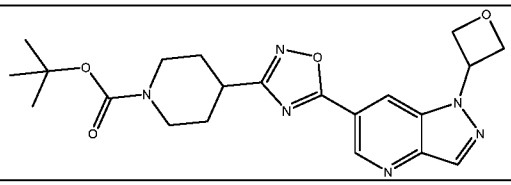
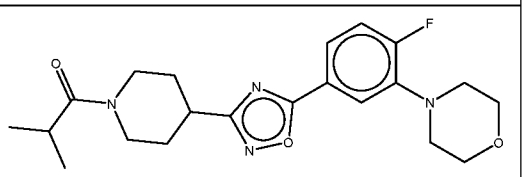
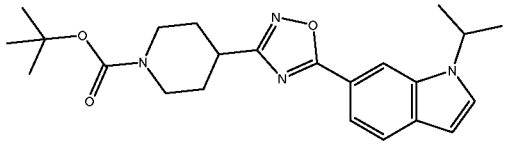
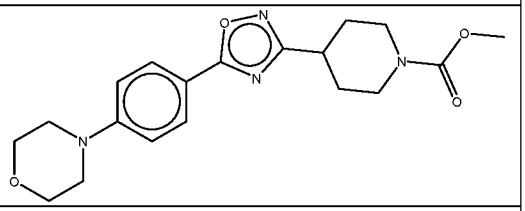
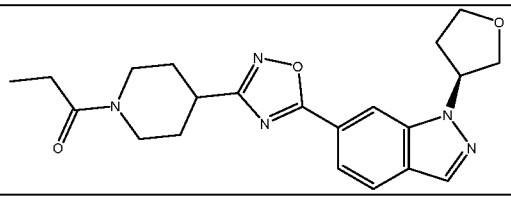
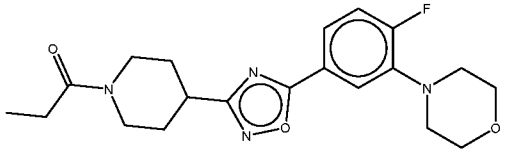
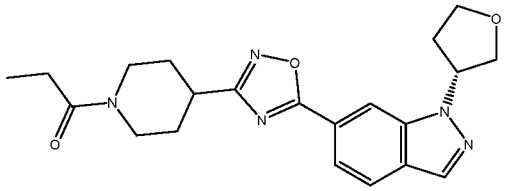
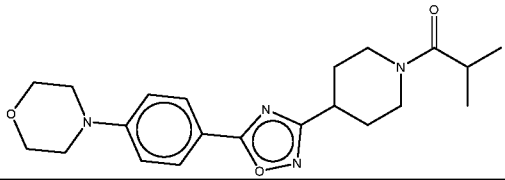
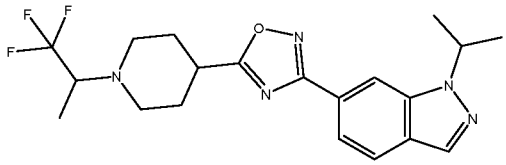
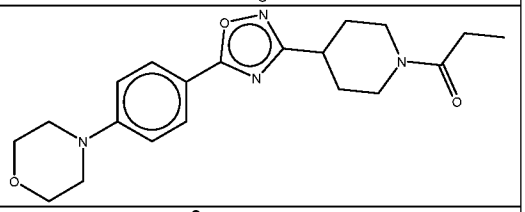
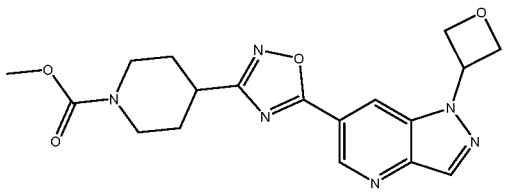
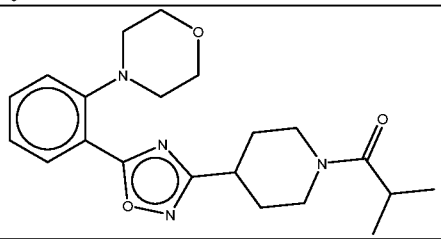
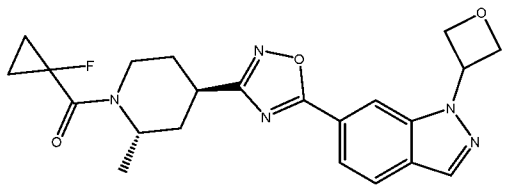
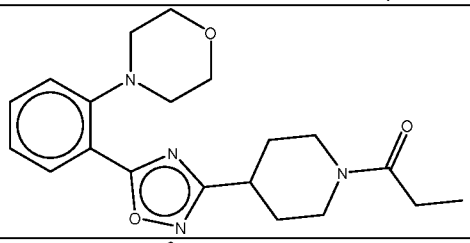
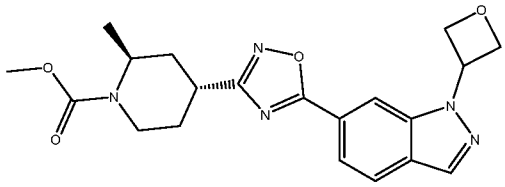
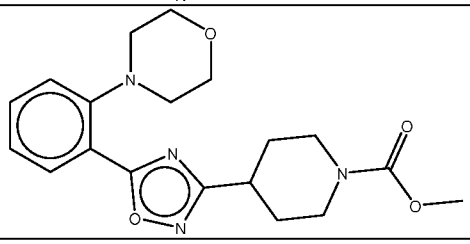
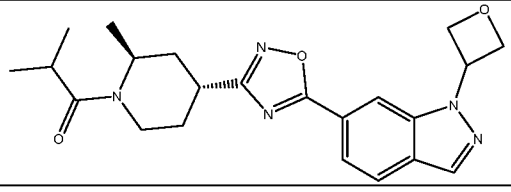
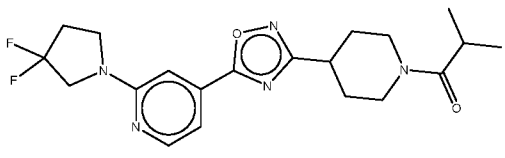
1047		1162	
1048		1163	
1049		1164	
1050		1165	
1051		1166	
1052		1167	
1053		1168	
1054		1169	
1055		1170	

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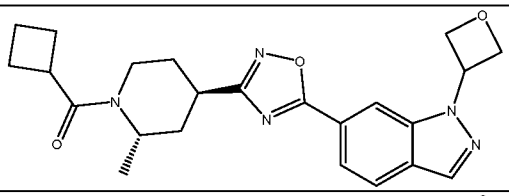
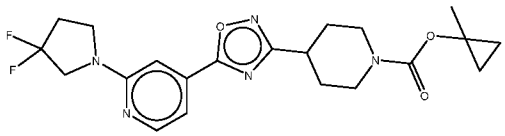
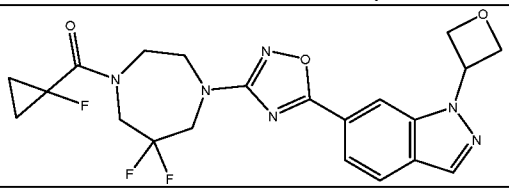
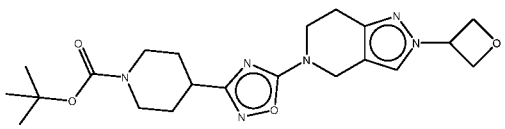
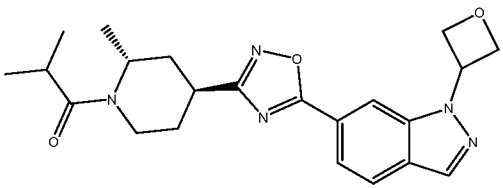
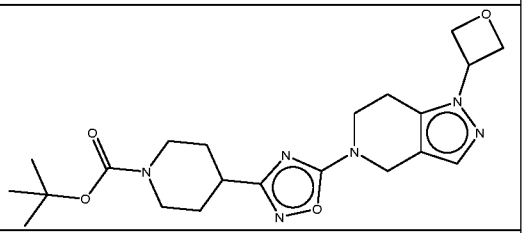
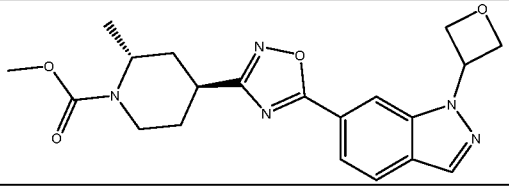
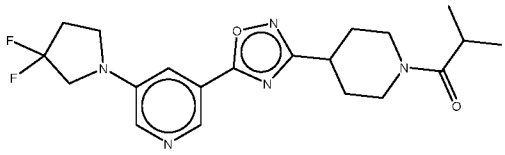
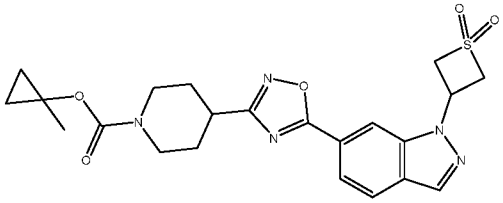
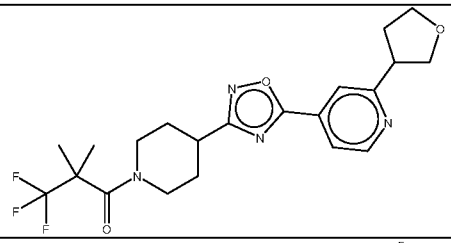
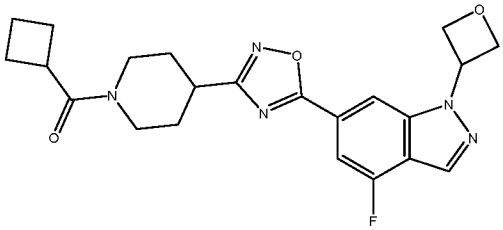
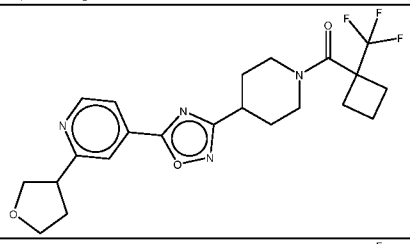
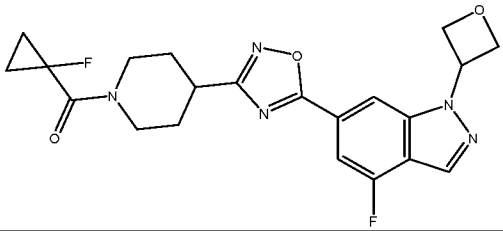
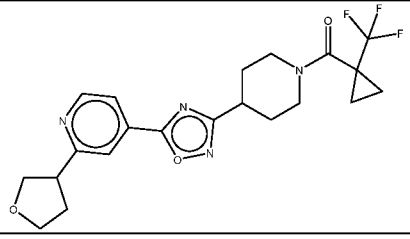
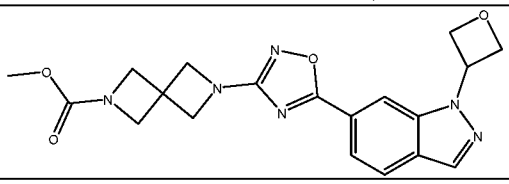
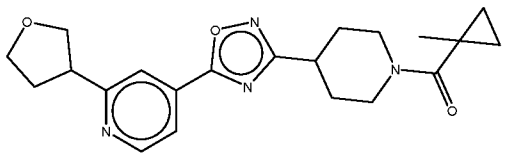
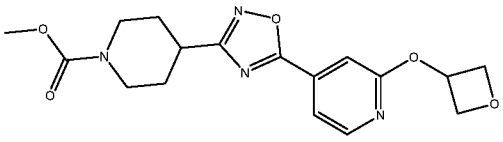
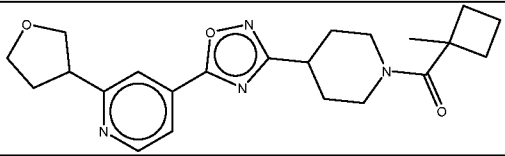
1056		1171	
1057		1172	
1058		1173	
1059		1174	
1060		1175	
1061		1176	
1062		1177	
1063		1178	
1064		1179	

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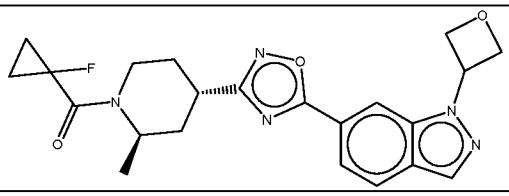
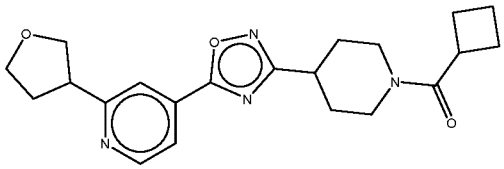
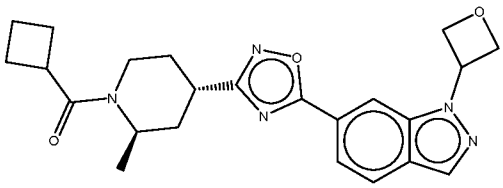
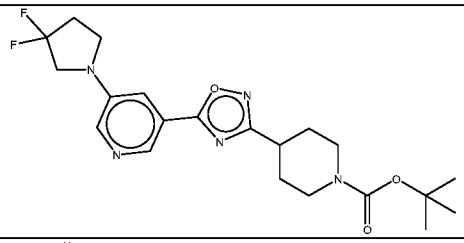
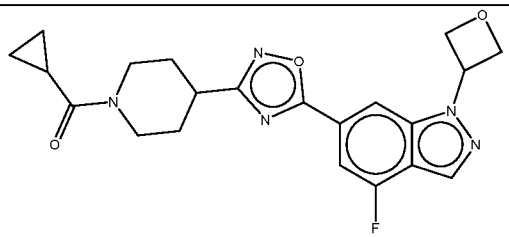
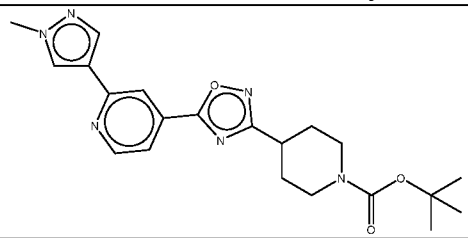
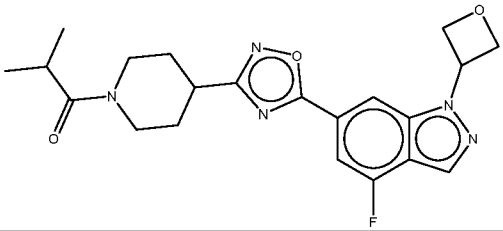
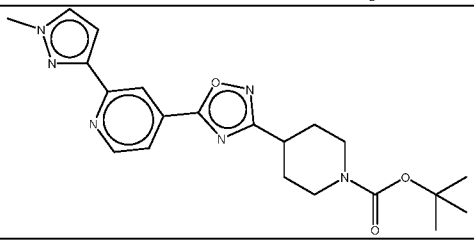
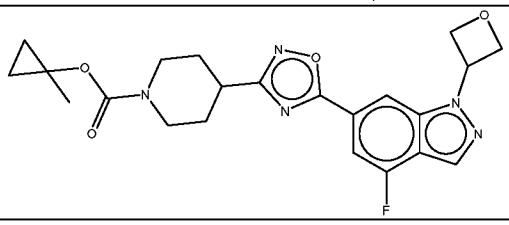
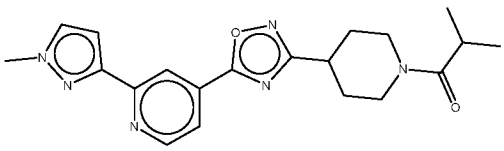
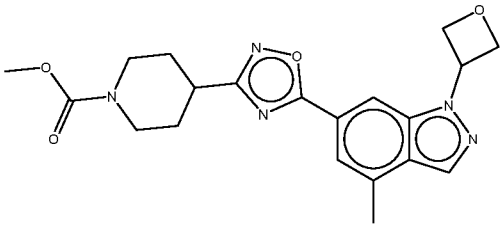
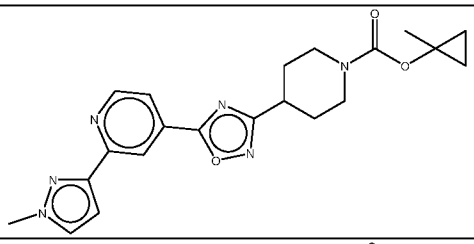
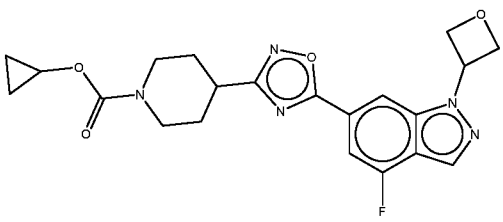
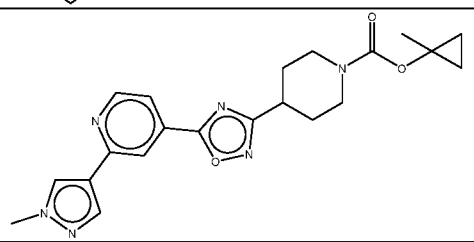
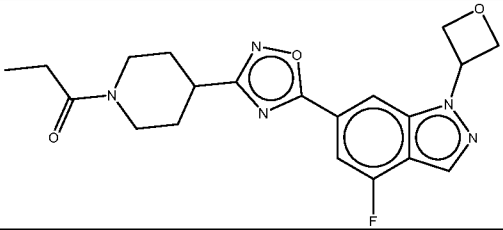
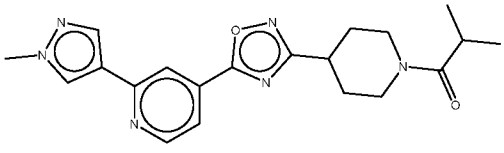
1065		1180	
1066		1181	
1067		1182	
1068		1183	
1069		1184	
1070		1185	
1071		1186	
1072		1187	

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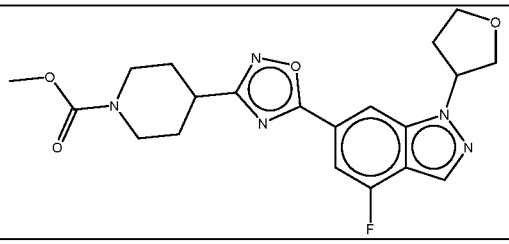
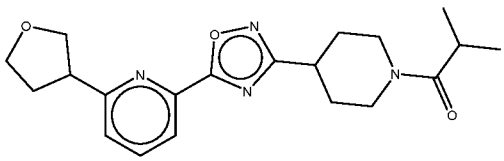
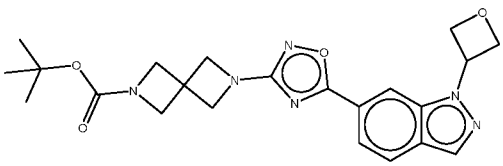
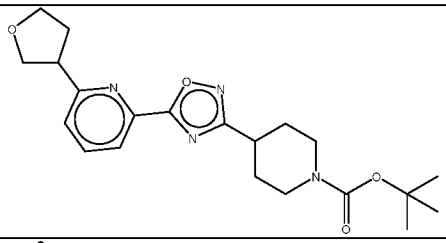
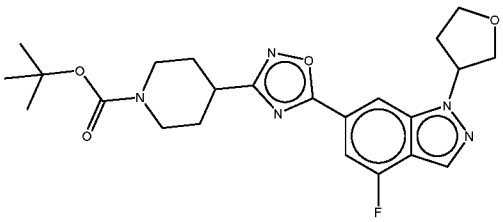
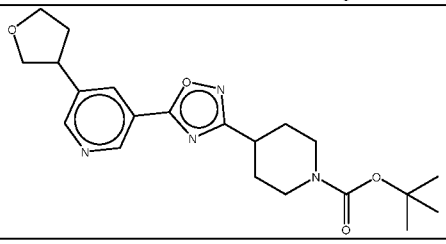
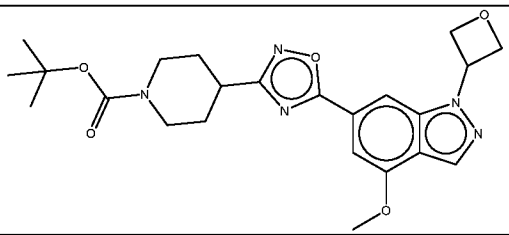
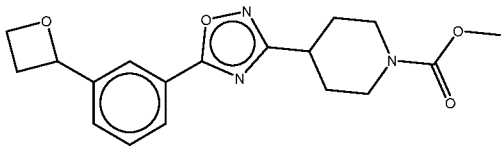
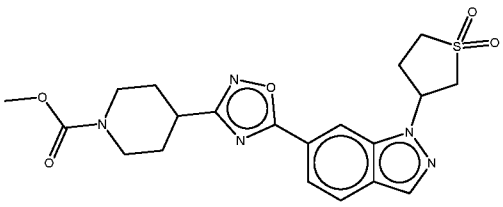
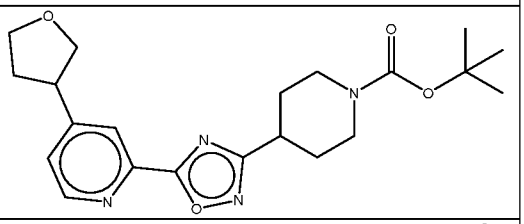
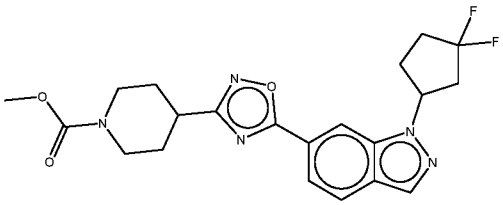
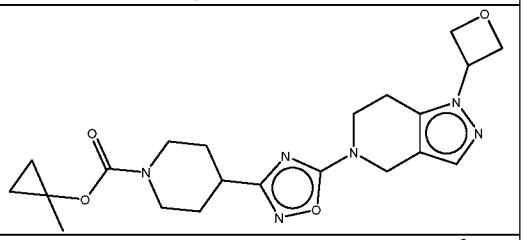
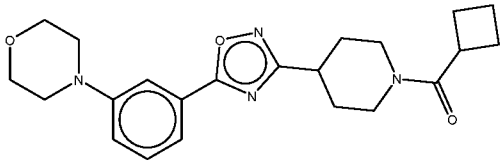
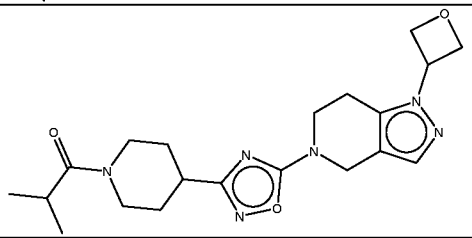
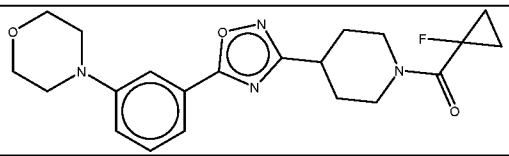
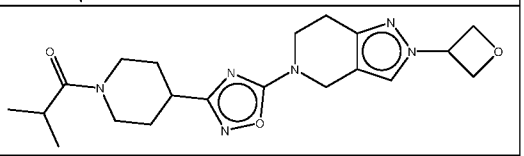
1073		1188	
1074		1189	
1075		1190	
1076		1191	
1077		1192	
1078		1193	
1079		1194	
1080		1195	

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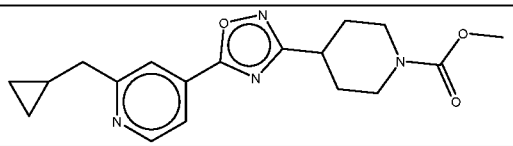
1081			

In another aspect, the disclosure provides pharmaceutical composition comprising any of the foregoing compounds, or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable excipient.

In another aspect, the disclosure provides a method of treating a neurological disorder in a subject in need thereof, the method comprising administering an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions.

In another aspect, the disclosure provides a method of inhibiting toxicity in a cell (e.g., a mammalian neural cell) related to a protein (e.g., toxicity related to protein misfolding and/or aggregation such as protein aggregation related to misfolding of proteins such as α-synuclein or ApoE4), the method comprising administering, or contacting the cell with, an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof. In some embodiments, the toxicity is α-synuclein-related toxicity. In some embodiments, the toxicity is ApoE4-related toxicity.

Non-limiting exemplary neurological disorders include, but are not limited to Alexander disease, Alper' s disease, AD, amyotrophic lateral sclerosis, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, multiple sclerosis, PD, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, Ref sum's disease, Sandhoff disease, Schilder' s disease, Steele-Richardson-Olszewski disease, tabes dorsalis, frontal temporal dementia, vascular dementia, Down's syndrome, and Guillain-Barre Syndrome.

In another aspect, the disclosure provides a method of treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof, the method comprising administering, or contacting the cell with, an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof.

Non-limiting exemplary SCD-associated disorders include, but are not limited to metabolic disorders (e.g., diabetes (e.g., Type I diabetes and Type II diabetes), hyperglycemia, metabolic syndrome, obesity, lipid disorders, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and hypertension), cancer, cardiovascular diseases, cerebrovascular diseases, kidney diseases, liver diseases, skin disorders (e.g., acne (e.g., acne vulgaris)), central nervous system (CNS) disorders, dementia, multiple sclerosis, schizophrenia, mild cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, and dementia associated with Down Syndrome.

In another aspect, the disclosure provides a method of treating cancer in a subject in need thereof, the method including administering, or contacting the cell with, an effective amount of the any of the foregoing compounds, or pharmaceutically acceptable salts thereof.

In some embodiments, the cancer is esophageal cancer, pancreatic cancer, endometrial cancer, kidney cancer, hepatoma, thyroid cancer, gallbladder cancer, prostate cancer, leukemia (e.g., lymphomas

and myelomas), ENT-related cancer, brain cancer, colon cancer, rectal cancer, colorectal cancer, ovarian cancer, uterine cancer, breast cancer, skin cancer, or prostate cancer.

Chemical Terms

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

The term "acyl," as used herein, represents a hydrogen or an alkyl group, as defined herein, that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

The term "alkyl," as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms). An alkylene is a divalent alkyl group.

The term "alkenyl," as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "alkynyl," as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "amino," as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO_2, $N(R^{N2})_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1} groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the invention can be an unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$).

The term "aryl," as used herein, refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

The term "arylalkyl," as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{1-6} alkyl C_{6-10} aryl, C_{1-10} alkyl C_{6-10} aryl, or C_{1-20} alkyl C_{6-10} aryl), such as, benzyl and phenethyl. In some embodiments, the akyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "azido," as used herein, represents a $-N_3$ group.

The term "cyano," as used herein, represents a –CN group.

The terms "carbocyclyl," as used herein, refer to a non-aromatic C_{3-12} monocyclic, bicyclic, or tricyclic structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups and unsaturated carbocyclyl radicals.

The term "cycloalkyl," as used herein, refers to a saturated, non-aromatic, monovalent mono- or polycarbocyclic radical of three to ten, preferably three to six carbon atoms. This term is further

exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

The term "halogen," as used herein, means a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an "alkoxy" which, as used herein, refers alkyl-O- (e.g., methoxy and ethoxy). A heteroalkylene is a divalent heteroalkyl group.

The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an "alkenoxy" which, as used herein, refers alkenyl-O-. A heteroalkenylene is a divalent heteroalkenyl group.

The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups. Examples of heteroalkynyl groups are an "alkynoxy" which, as used herein, refers alkynyl-O-. A heteroalkynylene is a divalent heteroalkynyl group.

The term "heteroaryl," as used herein, refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the remaining ring atoms being C. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxaxolyl, and thiazolyl.

The term "heteroarylalkyl," as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{1-6} alkyl C_{2-9} heteroaryl, C_{1-10} alkyl C_{2-9} heteroaryl, or C_{1-20} alkyl C_{2-9} heteroaryl). In some embodiments, the akyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "heterocyclyl," as used herein, denotes a mono- or polycyclic radical having 3 to 12 atoms having at least one ring containing one, two, three, or four ring heteroatoms selected from N, O or S, wherein no ring is aromatic. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl.

The term "heterocyclylalkyl," as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{1-6} alkyl C_{2-9} heterocyclyl, C_{1-10} alkyl C_{2-9} heterocyclyl, or C_{1-20} alkyl C_{2-9} heterocyclyl). In some embodiments, the akyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "hydroxyl," as used herein, represents an –OH group.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999). *N*-protecting groups include acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred *N*-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "nitro," as used herein, represents an $-NO_2$ group.

The term "thiol," as used herein, represents an –SH group.

The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH_2 or mono- or dialkyl amino), azido, cyano, nitro, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Compounds of the invention can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are

stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. “Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9%) by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by

structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Definitions

In the practice of the methods of the present invention, an "effective amount" of any one of the compounds of the invention or a combination of any of the compounds of the invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination.

The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

A "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). For example pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment,

suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

As used herein, the term "stearoyl-CoA desaturase (SCD)-associated disorder" refers to an undesired physiological condition, disorder, or disease that is associated with and/or mediated at least in part by an SCD protein. In some instances, SCD-associated disorders are associated with excess SCD levels and/or activity. SCDs introduce a double bond in the C9-C10 position of saturated fatty acids such as palmitoyl-CoA and stearoyl-CoA which are converted to palmitoleoyl-CoA and oleoyl-CoA, respectively. One SCD gene, SCD1, has been characterized in humans for which there are two isoforms, SCD1 and SCD5. An SCD-associated disorder may be associated with and/or mediated at least in part by SCD1 and/or SCD5. Exemplary SCD-associated disorders include SCD-associated disorders include, but are not limited to metabolic disorders (e.g., diabetes (e.g., Type I diabetes and Type II diabetes), hyperglycemia, metabolic syndrome, obesity, lipid disorders, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and hypertension), cancer, cardiovascular diseases, cerebrovascular diseases, kidney diseases, liver diseases, skin disorders (e.g., acne (e.g., acne vulgaris)), central nervous system (CNS) disorders, dementia, multiple sclerosis, schizophrenia, mild

cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, and dementia associated with Down Syndrome. Additional SCD-associated disorders are described herein or known in the art.

As used herein, the term "subject" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

As used herein, the terms "treat," "treated," or "treating" mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

Brief Description of the Drawings

FIGS. 1A and **1B** are graphs showing that growth inhibition by 1,2,4-oxadiazoles occurs through same mechanism as the rescue of toxicity in the apolipoprotein E4 (ApoE4) Alzheimer's disease yeast model. (**Fig. 1A**) Compound 7, a representative 1,2,4-oxadiazole, was profiled in ApoE4 (top) and control (bottom) non-inducing conditions at 12-point dose (x-axis). The Y-axis shows raw OD_{600}. Compound 7 exhibited a bell-shaped dose-response curve (DRC) in the ApoE4 model. Rescue decreased at concentrations just above the maximal efficacy (Emax). In the control condition (bottom panel), growth decreased at this same concentration. (**Fig. 1B**) The relationship between Emax (rescue in ApoE4) and growth inhibition (in control condition) correlated across 34 tested 1,2,4-oxadiazoles. The maximal rescue dose (EC100) is shown on the y-axis for ApoE4 and minimal inhibitory dose (IC100) in the control condition is shown on the x-axis. This correlation indicates that growth inhibition is caused by the same on-target activity that rescues ApoE4 toxicity.

FIGS. 2A and **2B** are graphs showing that exogenous oleic acid reverses growth inhibition and model rescue by Ole1/SCD-targeting 1,2,4-oxadiazoles. Growth was measured by reading OD_{600} in a microplate reader and normalized to solvent control DMSO samples. (**Fig. 2A**) Growth inhibition (24 h) of strain GM *yap1 flr1* by Ole1/SCD-targeting 1,2,4-oxadiazoles is reversed by exogenous 0.5 mM oleic/palmitoleic acid, which did not affect growth inhibition by other compounds (black dots indicate other scaffolds tested). Maximal growth inhibition across a dose range from 33 nM to 33 μM is plotted. (**Fig. 2B**) Rescue (40 h) of the yeast alpha-synuclein ("aSyn") model by 1,2,4-oxadiazoles was reversed by exogenous 0.5 mM oleic/palmitoleic acid, which did not affect rescue by other scaffolds. Maximal model rescue across a dose range from 33 nM to 33 μM is plotted.

FIGS. 3A and **3B** are graphs showing that point mutations in yeast *OLE1* confer resistance to growth inhibition and alpha-synuclein model rescue by 1,2,4-oxadiazoles. Growth was measured by reading OD_{600} in a microplate reader. (**Fig. 3A**) Yeast cells deleted for the chromosomal copy of *OLE1* and expressing *OLE1* (wild-type), *ole1P123T*, or *ole1E188Q* mutants from a pRS316-based plasmid were grown in complete synthetic medium (CSM)-glucose media at the indicated doses of 1,2,4-oxadiazole Compound 95 for 24 h. Growth was normalized to samples treated with the solvent control dimethyl sulfoxide (DMSO), set as "1". (**Fig. 3B**) Yeast cells deleted for the chromosomal copy of *OLE1* and expressing *OLE1* (Wild-type), *ole1P123T*, or *ole1E188Q* mutants from a pRS316-based plasmid were grown in CSM-galactose media (inducing expression of alpha-Synuclein) at the indicated doses of the 1,2,4-oxadiazole Compound 95 for 40 h. Growth was normalized to samples treated with the solvent control DMSO, where rescue is set as "1".

FIG. 4 is a graph showing that a *ole1*Δ deletion mutant is resistant to the growth-inhibitory effects of 1,2,4-oxadiazoles, but not other compounds. Twenty-four hour growth (presented as raw OD_{600}) of the *ole1*Δ deletion strain in yeast extract-peptone-dextrose (YPD) media is shown, with drugs added at the indicated concentrations.

FIG. 5 is a graph showing that reducing *OLE1* expression by deleting *MGA2* rescues the growth of the ApoE4 yeast model. Yeast cells expressing ApoE4 were deleted for the *MGA2* gene and their growth was assessed over time (compared to their isogenic, MGA2 wild-type counterpart). Growth was assessed by OD_{600}. Where indicated, 0.08 or 0.32 mM of oleic and palmitoleic acids (each) as added to the growth media in 0.01% tween (final).

FIG. 6 is a series of graphs showing that commercial Scd inhibitors target human SCD1/SCD5 in yeast. Yeast surviving solely on yeast *OLE1*, or human SCD1 or SCD5, were treated with four commercial Scd inhibitors at indicated concentrations. Data are expressed as a percent of the DMSO-treated condition. All four compounds potently reduced growth of both SCD1-expressing yeast and SCD5-expressing yeast, but not the strain expressing Ole1. This growth inhibition was reversed by oleic/palmitoleic acid competition, similar to the results shown in Figs. 2A and 2B.

FIG. 7 is a series of graphs showing that 1,2,4-oxadiazoles target human SCD1 and SCD5. Three "SCD" strains expressing yeast *OLE1* or human SCD1 or SCD5 were treated with five representative 1,2,4-oxadiazoles and a cycloheximide toxicity control at concentrations indicated on the $\log_{10}$ x-axis. The y-axis indicates the percent of the DMSO-treated condition. All of the 1,2,4-oxadiazole compounds potently inhibited Ole1-expressing yeast and showed variable growth inhibition of the SCD1 or SCD5 yeast strains. These data confirm that 1,2,4-oxadiazoles target the human protein and link Scd inhibition to rescue of neurodegenerative disease models. Approximately one half of all (250) 1,2,4-oxadiazoles tested inhibited SCD1 or SCD5 in a manner that was reversed by oleic/palmitoleic acid treatment. Cyclohexamide, a translation inhibitor (top left panel), inhibited growth of all three strains with the same potency, indicating differences in growth inhibition was due to targeting the human protein.

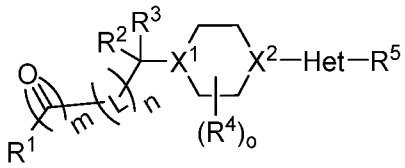
FIGS. 8A-8D are graphs showing that treatment of yeast cells with the 1,2,4-oxadiazole Compound 95 inhibits lipid desaturation. Exponentially-growing wild-type yeast cells were treated with the indicated doses of the 1,2,4-oxadiazole Compound 95 for the indicated times before cellular lysis, lipid extraction, and analysis by global LC-MS/MS profiling. The relative abundance (fraction of total cellular lipid signal) after 1.5 h and 8 h of the most abundant saturated lipid, phosphatidylcholine 26:0, is depicted

in Figs. 8A and 8B, respectively. The relative abundance after 1.5 h and 8 h drug treatment of the most abundant lipid with 2 or more degrees of unsaturation, phosphatidylcholine 16:1; 18:1, is depicted in Figs. 8C and 8D, respectively. The data indicate a >300-fold increase in the abundance of the saturated lipid phosphatidylcholine 26:0 after 8 h treatment with Compound 95, and a >12-fold decrease in the abundance of the unsaturated lipid phosphatidylcholine 16:1, 18:1, indicating that Compound 95 blocks cellular fatty acid desaturase activity (Ole1 is the only fatty acid desaturase in yeast).

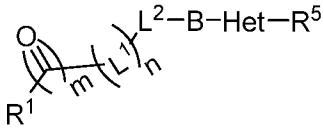
FIG. 9 shows *OLE1* mutations conferring resistance to growth inhibition to 1,2,4-oxadiazoles identified by genome sequencing of resistant mutants. Cells were plated on media containing 10 μM of the 1,2,4-oxadiazole Compound 155 and resistant colonies that emerged were isolated, and genomic DNA was prepared from mutants and the parental, drug-sensitive control strain. Genomic DNA sequence was aligned to the *Saccharomyces cerevisiae* reference and unique mutations in the 1,2,4-oxadiazole-resistant mutants were identified. The position of the mutations, the amino acid changes they encode, and the fold resistance (increase in minimal inhibitory concentration) of Compound 155 are shown.

Detailed Description of the Invention

The invention features compounds useful for the treatment of neurological disorders, e.g., by inhibiting α-synuclein toxicity in a cell such as a neural cell. Exemplary compounds described herein include compounds having a structure according to formula I or formula Ia:



Formula I



Formula Ia

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound has the structure of any one of compounds 1-746 in Table 1. In some embodiments, the compound has the structure of any one of compounds 747-966 in Table 2A. In some emobdiments, the compound has the structure of any one of compounds 967-1195 in Table 2B.

Other embodiments, as well as exemplary methods for the synthesis or production of these compounds, are described herein.

Pharmaceutical Uses

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to inhibit toxicity caused by protein aggregation, e.g., α-synuclein aggregation, in a cell.

Another aspect of the present invention relates to methods of treating and/or preventing a neurological disorder such as neurodegenerative diseases in a subject in need thereof. The pathology of

neurodegenerative disease, may be characterized by the presence of inclusion bodies in brain tissue of affected patients.

In certain embodiments, neurological disorders that may be treated and/or prevented by the inventive methods include, but are not limited to, Alexander disease, Alper' s disease, AD, amyotrophic lateral sclerosis, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, multiple sclerosis, PD, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, Ref sum's disease, Sandhoff disease, Schilder' s disease, Steele-Richardson-Olszewski disease, tabes dorsalis, and Guillain-Barre Syndrome.

The compounds described herein are useful as inhibitors of stearoyl-CoA desaturase (SCD), including SCD1 and/or SCD5. SCD inhibitors are known in the art to be useful in methods of treating and/or preventing SCD-associated disorders. SCD-associated disorders are described, for example, in U.S. Patent No. 8,148,378, and in International Patent Application Publication Nos. WO 2011/047481, WO 2010/112520, WO 2010/045374, WO 2010/028761; WO 2009150196, and WO 2009/106991. Accordingly, another aspect of the present invention relates to methods of treating and/or preventing an SCD-associated disorder in a subject in need thereof.

SCD-associated disorders include metabolic disorders (e.g., insulin resistance, diabetes mellitus (e.g., Type I diabetes, Type II diabetes, non-insulin-dependent diabetes mellitus, gestational diabetes, and diabetic complications (e.g., diabetic peripheral neuropathy, diabetic nephropathy diseases, diabetic retinopathy, diabetic macroangiopathy, vascular complications of diabetes, and diabetic arteriosclerosis)), hyperglycemia, metabolic syndrome, hyperinsulinanemia, glucose intolerance, impaired glucose tolerance, body weight disorders (e.g., obesity (e.g., abdominal obesity), overweight, cachexia, body mass index, and anorexia), lipid disorders (e.g., abnormal lipid levels (e.g., elevated lipid levels, for example, in plasma), dyslipidemia (e.g., diabetic dyslipidemia), mixed dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, atherosclerosis, hypercholesterolemia (e.g., familial hypercholesterolemia), low HDL, high LDL, diseases related to accumulation of lipids in liver, familial histiocytic reticulosis, lipoprotein lipase deficiency, polyunsaturated fatty acid (PUFA) disorder, fatty acid desaturation index (e.g. the ratio of 18:1/18:0 fatty acids, or other fatty acids), and abnormal lipid metabolism disorders), disorders of abnormal plasma lipoprotein, disorders of pancreatic beta cell regeneration, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hypertension, and microalbuminemia, leptin related diseases, hyperleptinaemia, appetite disorder, essential fatty acid deficiency, and adverse weight gain associated with a drug therapy).

Additional SCD-associated disorders include cancer, including solid tumors or hematological malignancies (e.g., esophageal cancer, pancreatic cancer, endometrial cancer, kidney cancer, hepatoma, thyroid cancer, gallbladder cancer, prostate cancer, leukemia (e.g., lymphomas and myelomas), ENT-related cancer, brain cancer, colon cancer, rectal cancer, colorectal cancer, ovarian cancer, uterine cancer, breast cancer, skin cancer, and prostate cancer), neoplasia, malignancy, metastases, tumors (benign or malignant), carcinogenesis, and hepatomas.

Further SCD-associated disorders include cardiovascular disease (e.g., heart disease, atherosclerosis, hypertension, lipidemia, dyslipidemia, elevated blood pressure, microalbuminemia,

hyperuricaemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, arteriosclerosis, coronary artery disease, myocardial infarction, vascular complications of diabetes, and diabetic arteriosclerosis), inflammation, sinusitis, asthma, pancreatitis, osteoarthritis, rheumatoid arthritis, hepatitis (e.g., sexual hepatitis), meibomitis, cystic fibrosis, pre-menstrual syndrome, osteoporosis, thrombosis, cardiovascular risks, weight loss, angina, high blood pressure, ischemia, cardiac ischemia, reperfusion injury, angioplastic restenosis, infertility, liver disease (e.g., fatty liver, cirrhosis, nonalcoholic steatohepatitis, liver fibrosis, and hepatitis C related steatosis), kidney disease (e.g., tubulointerstitial fibrosis, kidney lipid accumulation, glomerular sclerosis, and proteinuria), osteoarthritis (e.g., osteoarthritis of the knee), gastro-esophageal disease, sleep apnea, secondary hyperparathyroidism of renal osteodystrophy, peripheral vascular disease, cerebrovascular disease (e.g., stroke, ischemic stroke and transient ischemic attack (TIA), and ischemic retinopathy), hyperandrogenism, malignant syndrome, extrapyramidal symptoms, hyperuricemia, hypercoagulability, syndrome X, cataract, polycystic ovary syndrome, breathing abnormalities, sleep-disordered breathing, low back pain, gout, gallstone disease, myopathies, lipid myopathies (e.g., carnitine palmitoyltransferase deficiency (CPT I or CPT II)), autoimmune diseases (e.g., lupus, host versus graft rejection, and rejection of organ transplants), asthma, inflammatory bowel diseases, nephropathy, retinopathy, erythrohepatic protoporphyria, iron overload disorders, and hereditary hemochromatosis.

Still further SCD-associated disorders include central nervous system (CNS) disorders, dementia, schizophrenia, mild cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, dementia associated with Down Syndrome, other neurodegenerative diseases, psychiatric disorders, eye diseases, immune disorders, multiple sclerosis, neuropathy, and depression.

Additional SCD-associated disorders include skin disorders (e.g., acne (e.g., acne vulgaris), psoriasis, hirsutism, rosacea, seborrheic skin, oily skin (syn seborrhea), seborrheic dermatitis, hyperseborrhea, eczema, keloid scar, skin ageing, diseases related to production or secretions from mucous membranes, wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, insufficient sebum secretion, oily hair, shiny skin, greasy-looking skin, greasy-looking hair, and other skin conditions caused by lipid imbalance).

An SCD-associated disorder can also include a disease or condition which is, or is related to, viral diseases or infections.

In some embodiments, the SCD-associated disorder is acne (e.g., acne vulgaris). In some embodiments, the SCD-associated disorder is diabetes (e.g., type II diabetes, including diabetes with inadequate glycemic control). In some embodiments, the SCD-associated disorder is nonalcoholic fatty liver disease (NAFLD). In some embodiments, the SCD-associated disorder is nonalcoholic steatohepatitis (NASH). In some embodiments, the SCD- associated disorder is cancer. In some embodiments, the SCD- associated disorder is obesity. In some embodiments, the SCD-associated disorder is metabolic syndrome (e.g., dyslipidemia, obesity, insulin resistance, hypertension, microalbuminemia, hyperuricaemia, and hypercoagulability), syndrome X, diabetes, insulin resistance, decreased glucose tolerance, non-insulin-dependent diabetes mellitus, Type II diabetes, Type I diabetes, diabetic complications, body weight disorders (e.g., obesity, overweight, cachexia, and anorexia), weight loss, body mass index, leptin related diseases, or a skin disorder (e.g., eczema, acne, psoriasis, and keloid scar). In some embodiments, the SCD-associated disorder is diabetes, metabolic syndrome,

insulin resistance, obesity, a cardiovascular disorder, a CNS disorder, schizophrenia, or Alzheimer's disease.

Combination Formulations and Uses Thereof

The compounds of the invention can be combined with one or more therapeutic agents. In particular, the therapeutic agent can be one that treats or prophylactically treats any neurological disorder described herein.

Combination Therapies

A compound of the invention can be used alone or in combination with other agents that treat neurological disorders or symptoms associated therewith, or in combination with other types of treatment to treat, prevent, and/or reduce the risk of any neurological disorders. In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6, 2005). In this case, dosages of the compounds when combined should provide a therapeutic effect.

Pharmaceutical Compositions

The compounds of the invention are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration *in vivo*. Accordingly, in another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention in admixture with a suitable diluent, carrier, or excipient.

The compounds of the invention may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the scope of the invention. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the invention may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound of the invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound of the invention may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers.

A compound of the invention may also be administered parenterally. Solutions of a compound of the invention can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may

contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003, 20th ed.) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19), published in 1999.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter.

The compounds of the invention may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Dosages

The dosage of the compounds of the invention, and/or compositions comprising a compound of the invention, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds of the invention may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds of the invention are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of

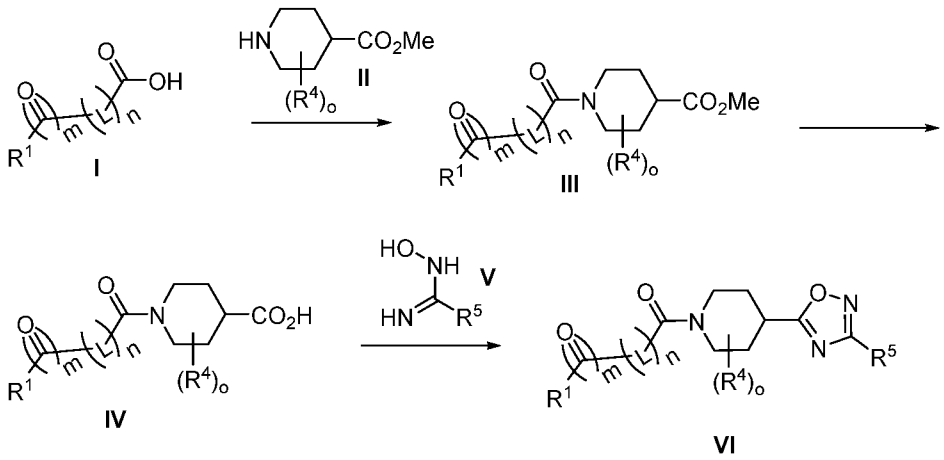
the compound is administered. Preferred dose ranges include, for example, between 0.05-15 mg/kg or between 0.5-15 mg/kg.

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-50 mg/kg (e.g., 0.25-25 mg/kg). In exemplary, non-limiting embodiments, the dose may range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

EXAMPLES

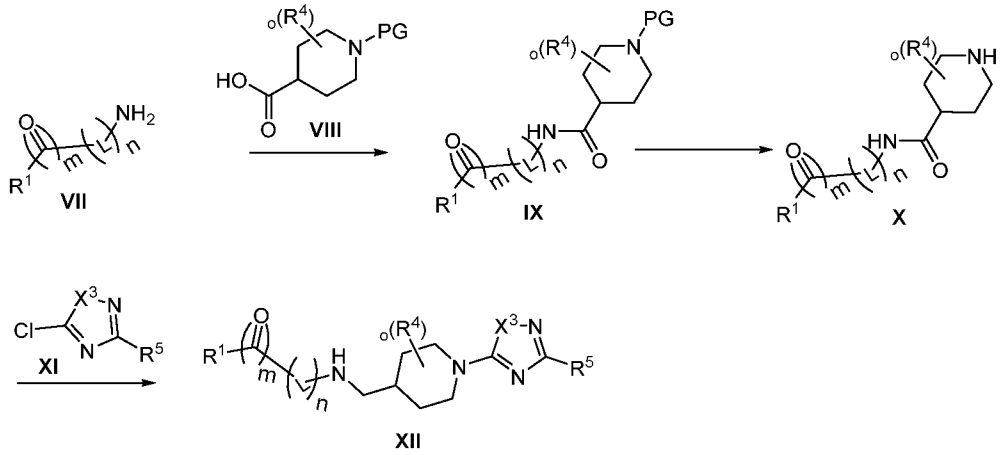
The synthesis of compounds of this invention can be synthesized according to one or more of the general schemes 1-10 shown below. The variables recited in the general schemes below are as defined for Formulae I, II, III, and IV.

General scheme 1



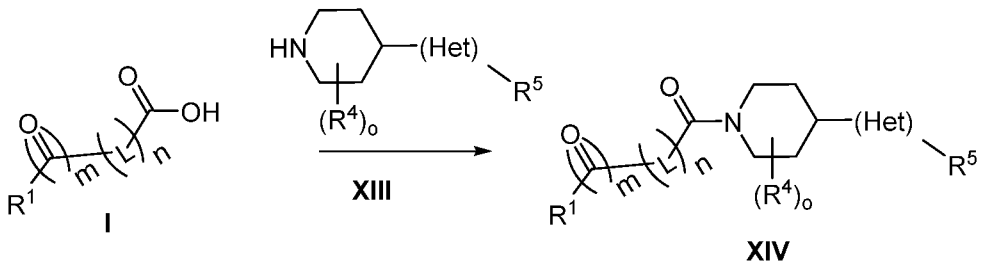
An appropriately substituted carboxylic acid **I** can be coupled with an appropriately substituted piperidine **II** to provide ester **III**. This can be hydrolysed under variety of conditions to provide carboxylic acid intermediate **IV**. This can be condensed with a substituted N-hydroxyimidamide **V** to give the desired 1,2,4-oxadiazole compound **VI**.

General Scheme 2



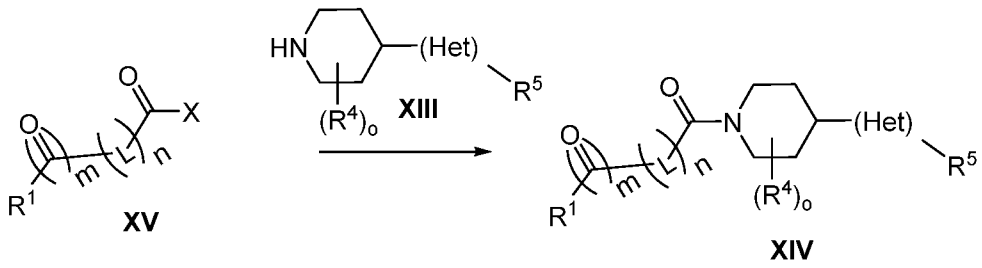
An appropriately substituted carboxylic acid **VII** can be coupled with an appropriately protected (where PG is an *N*-protecting group) and substituted piperidine carboxylic acid **VIII** to provide intermediate **IX**. This can be deprotected using a variety of conditions to provide free amine intermediate **X**. This compound can be coupled using metal catalysis or under thermal conditions with a halogenated heterocycle such as **XI** to give the desired 1,2,4-oxadiazole (X^3 = O) or 1,2,4-thiadiazole (X^3 = S) compound **XII**.

General scheme 3



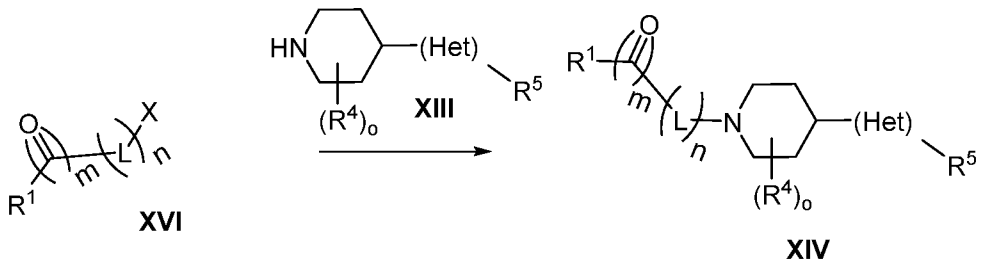
An appropriately substituted carboxylic acid **I** can be coupled with an appropriately substituted piperidine **XIII** to provide the desired heterocyclic compound **XIV**.

General scheme 4



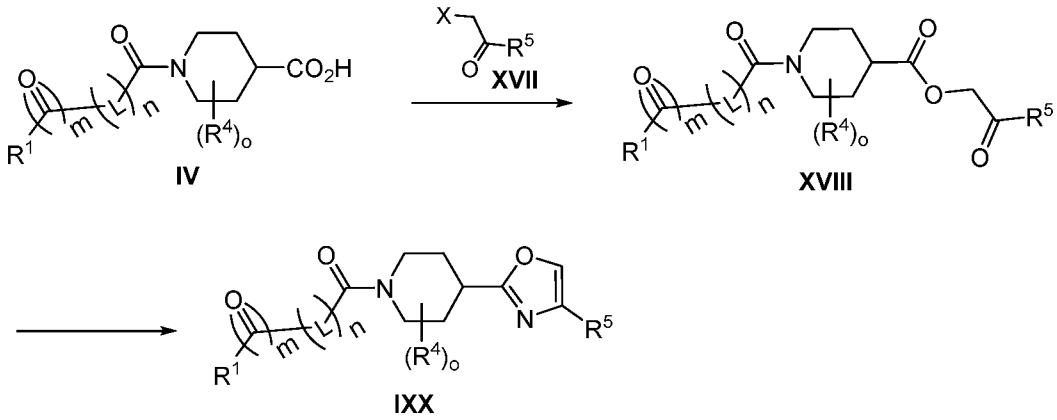
An appropriately substituted acyl halide **XV** (where X is a halogen atom, e.g., chlorine) can be coupled with an appropriately substituted piperidine **XIII** to provide the desired heterocyclic compound **XIV**.

General scheme 5



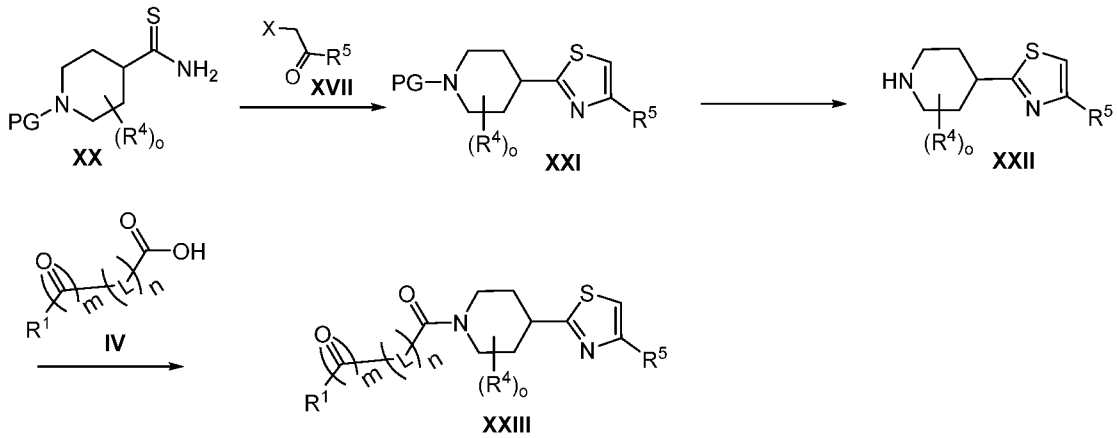
An appropriately substituted alkyl intermediate **XVI** (where X is a good leaving group, e.g., a halogen atom or triflate) can undergo nucleophilic displacement with an appropriately substituted piperidine **XIII** to provide the desired heterocyclic compound **XIV**.

General scheme 6



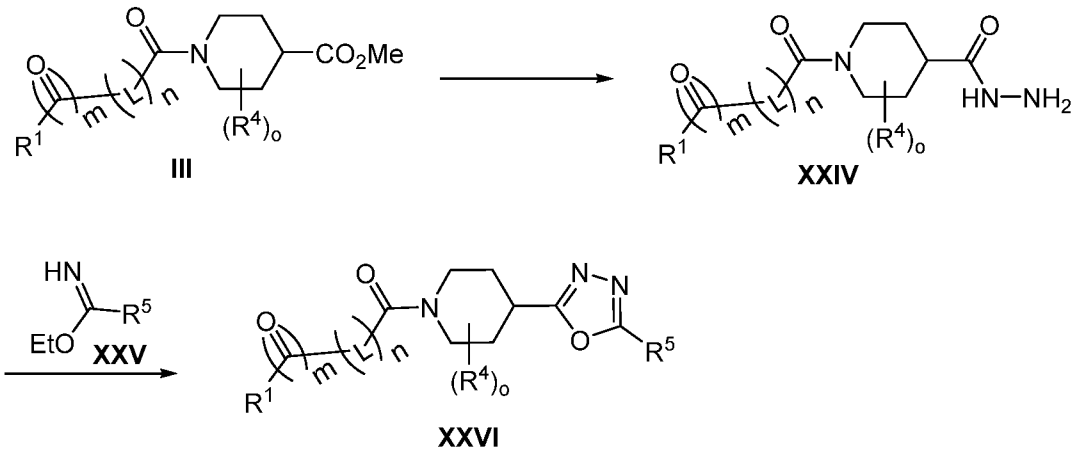
An appropriately substituted carboxylic acid **IV** can be coupled with an appropriately substituted ketone **XVII** (where X is a leaving group, e.g., bromine) to provide the intermediate compound **XVII**. This compound can be condensed with ammonium acetate to provide oxazole **IXX.**

General scheme 7



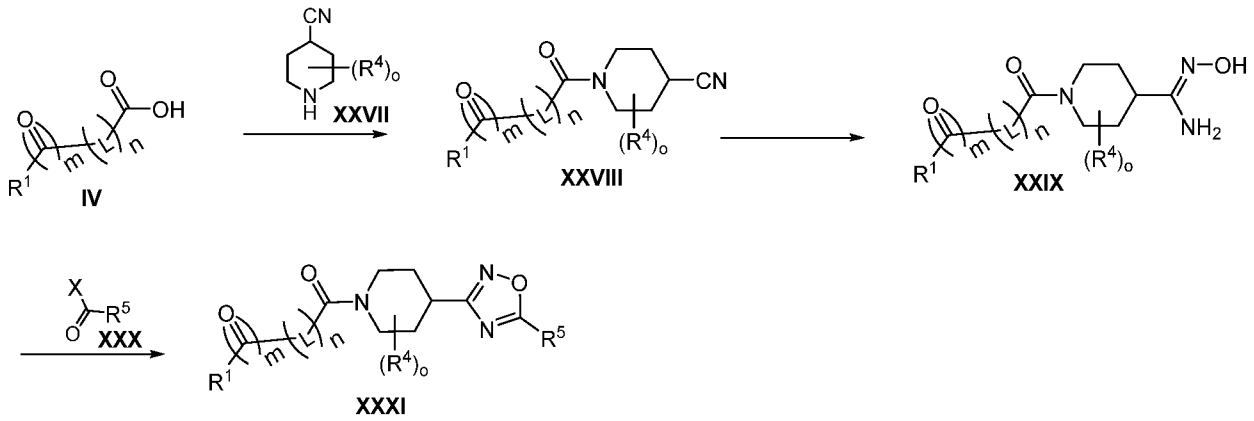
An appropriately protected and substituted thiomide **XX** can be coupled with an appropriately substituted ketone **XVII** (where X is a leaving group, most commonly bromine) to provide the protected (where PG is an amine protecting group, such as tert-butoxycarbonyl) thiazole compound **XXI**. This compound can be deprotected under appropriate conditions to give intermediate piperidine **XXII**. This can be coupled with and appropriately substituted carboxylic acid **IV** to provide thiazole **XXIII**.

General scheme 8



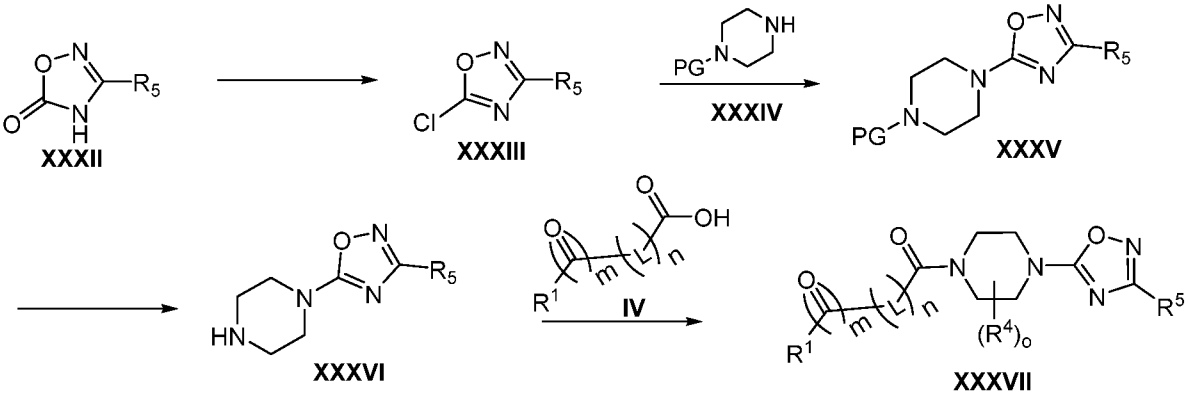
An appropriately protected and substituted ester **III** can be treated with hydrazine to provide the hydrazide compound **XXIV**. This compound can coupled with an appropriately substituted acetimidate **XXV** to provide 1,3,4-oxadiazole **XXVI.**

General scheme 9



An appropriately substituted carboxylic acid **IV** can be couple with and appropriately substituted piperidine compound **XXVII** to give a compound **XXVIII**. This compound can be converted to the corresponding hydroxyimidamide compound **XXIX**. This is can be treated with an appropriately substituted acid halide (most commonly an acid chloride, where X=Cl) **XXX** to provide 1,2,4-oxadiazole **XXXI.**

General scheme 10



An appropriately substituted oxadiazolone **XXXII** can be converted to the appropriately substituted compound **XXXIII**. This compound can be coupled with the appropriate protected piperazine compound **XXXIV** (where PG is an *N*-protecting group, for example, a tert-butyloxycarbonyl group) to give compound **XXXV**. This compound can be deprotected under the appropriate conditions to give piperazine compound **XXXVI**. This can be coupled with a carboxylic acid **IV** to provide 1,2,4-oxadiazole **XXXVII**.

Experimental procedures

The compounds of the invention can be synthesized according to the following procedures.

In the examples below, when purification by preparative HPLC was performed, a Gilson 281 semi-preparative HPLC system was used, using a variety of stationary and mobile phases which are described in the experimental section. For example, (column: Waters X bridge 150x2.5mm 5μm; mobile phase: [water (10 mM NH_4OAc)-acetonitrile]; B%: 36%-66%,12 min) indicates that the following purification conditions were used:

Mobile phase: A: 10mM NH_4OAc in H_2O; B: acetonitrile

Column: Waters Xbridge 150x2.5mm dimensions, 5 μm particle size

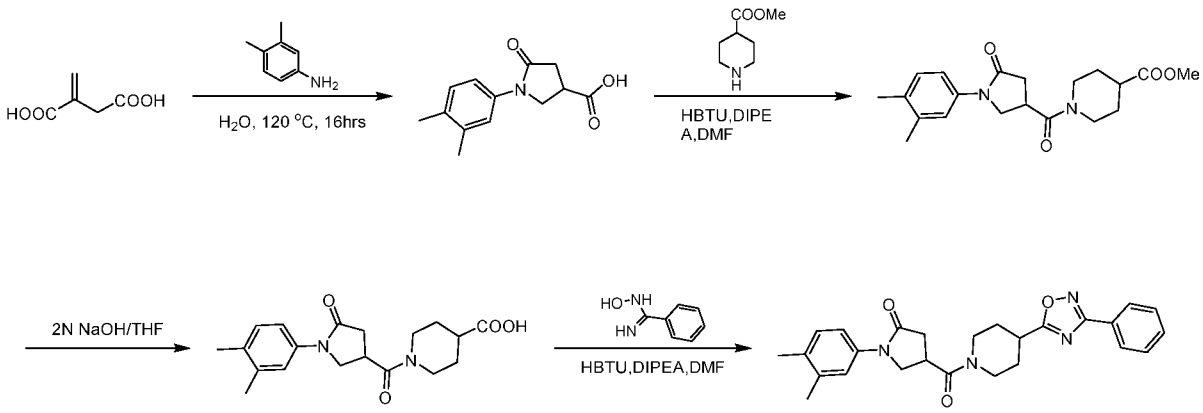
Flow rate: 25mL/min

Monitor wavelength: 220&254nm

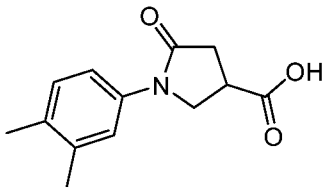
Gradient:

Time / minutes	B %
0.0	36
12.0	66
12.2	100
14.0	100
14.2	36
16.0	36

Example 1. Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one

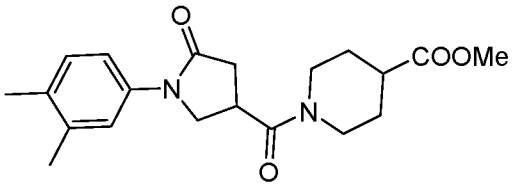


Step 1: Preparation of 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid



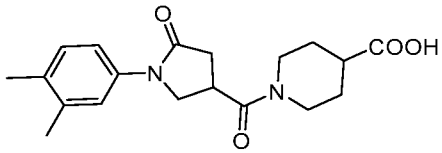
A mixture of 2-methylenesuccinic acid (2.0 g, 1.27 mL, 15.37 mmol) and 3,4-dimethylaniline (1.86 g, 15.37 mmol) in water (20 mL) was stirred at 120 °C (reflux) for 16 h. The mixture was cooled to 25 °C and filtered. The filter cake was washed with cold water (5 mL) to give 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid (3.0 g, 12.9 mmol, 84 %) as a yellow solid. This material was used directly in the next step without further purification. ^{1}H NMR (400MHz, DMSO-d6) δ 7.40-7.35 (m, 2H), 7.13-7.11 (d, 1H), 4.01-3.93 (m, 2H), 3.34-3.30 (m, 1H), 2.75-2.67 (m, 2H), 2.22 (s, 3H) 2.19 (s, 3H); LCMS (ESI) m/z: $[M-H]^-$ = 232.1.

Step 2: Preparation of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate



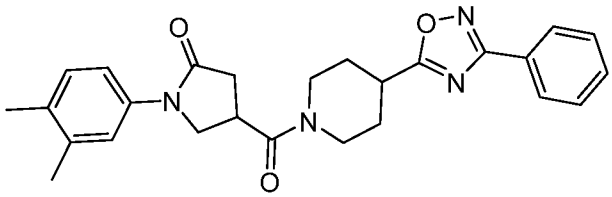
To a stirred solution of 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid (1.0 g, 4.29 mmol) and methyl piperidine-4-carboxylate (737 mg, 5.15 mmol) in N,N-dimethylformamide (10 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.63 g, 4.29 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.11 g, 8.58 mmol, 1.50 mL). After stirring at 15 °C for 16 h, to the mixture was added water (20 mL) and the mixture extracted with ethyl acetate (20 mL x 4). The organic layer was washed with water (10 mL), saturated aqueous sodium chloride solution (10 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give crude product that was purified by chromatography on silica gel eluted with Petroleum ether/ethyl acetate from 1/1 to 0/1 to give methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (1.90 g, 5.30 mmol, quantitative) as a red oil. LCMS (ESI) m/z: $[M+H]^+$ = 359.3.

Step 3: Preparation of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid



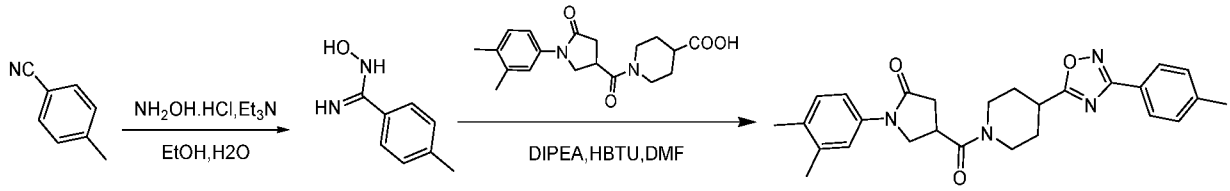
To a stirred solution of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (400 mg, 1.12 mmol) in tetrahydrofuran (4 mL) was added aqueous sodium hydroxide (2 M, 1.68 mL). The mixture was stirred at 40 °C for 2 h, then the mixture was acidified with concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (20 mL x 3), then the organic layer was washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (300 mg, 871 µmol, 78 %) as a white solid that was used directly without further purification.

Step 4: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one

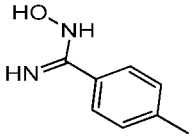


To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (253 mg, 734 µmol) in N,N-dimethylformamide (1 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (279 mg, 734 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (285 mg, 2.20 mmol, 384 µL). The mixture was stirred at 25 °C for 5 min, then N-hydroxybenzimidamide (100 mg, 734 µmol) was added. The mixture was warmed to 25 °C, stirred for 16 h, then the mixture was diluted with water (5 mL) and extracted with ethyl acetate (20 mL x 3). The organic layers were combined and washed with water (5 mL x 2) and saturated aqueous sodium chloride solution (5 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product which was dissolved in N,N-dimethylformamide (2 mL) and then heated at 120 °C for 3 h. Without any additional work-up, the mixture was purified by prep-HPLC (Waters X bridge 150x25 5 µm column; 36-66 % acetonitrile in a 10 mM ammonium acetate solution in water, 12 min gradient) to give 1-(3,4-dimethylphenyl)-4-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (73 mg, 164 µmol, 22 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.10-8.09 (m, 2H), 7.55-7.49 (m, 3H), 7.39 (s, 1H), 7.30 (s, 1H), 7.15-7.13 (d, 1H), 4.54-4.53 (m, 1H), 4.31-4.27 (m, 1H), 3.98-3.90 (m., 2H), 3.60-3.56 (m, 1H), 3.42-3.36 (m, 2H).3.15-2.95 (m, 2H), 2.86-2.79 (m, 1 H), 2.29-2.26(m, 8H), 2.03-1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 445.3.

Example 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one

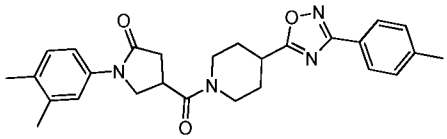


Step 1: Preparation of N-hydroxy-4-methylbenzimidamide



To a stirred solution of 4-methylbenzonitrile (1.0 g, 8.54 mmol, 1.02 mL) in ethanol (10 mL) and water (1 mL) was added hydroxylamine hydrochloride (1.19 g, 17.1 mmol) and triethylamine (1.73 g, 17.1 mmol, 2.37 mL). The mixture was heated at 75 °C for 16 h, then the reaction mixture was concentrated under reduced pressure to give a residue that was diluted with water (5 mL), and then extracted with dichloromethane (8 mL x 10). The combined organic layers were washed with saturated aqueous sodium chloride solution (8 mL x 5), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a N-hydroxy-4-methylbenzimidamide (900 mg, 5.99 mmol, 70 %) as a light green solid. ^{1}H NMR (400MHz, METHANOL-d4) d = 7.49 (d, J=8.2 Hz, 2H), 7.18 (d, J=7.9 Hz, 2H), 2.33 (s, 3H).

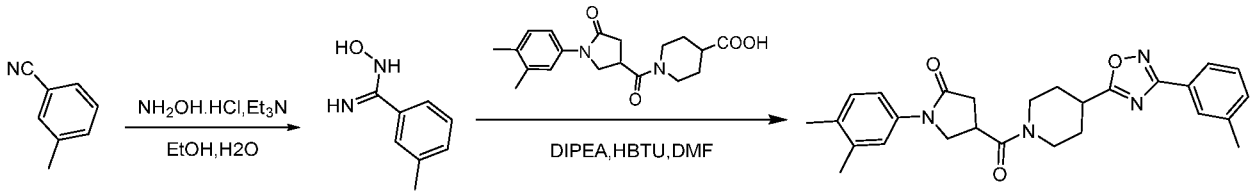
Step 2: Preparation of methyl 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one



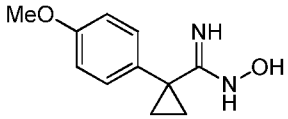
To a stirred solution of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (229 mg, 666 µmol) in N,N-dimethylformamide (1 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (253 mg, 666 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (258 mg, 2.00 mmol, 349 µL). The mixture was stirred at 25 °C for 5 mins, then N-hydroxy-4-methylbenzimidamide (100 mg, 666 µmol) was added. After 16 h, the reaction mixture was extracted with ethyl acetate (5 mL x 3). The organic layers were combined, washed with saturated aqueous sodium chloride solution (5 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue that was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water(10mM NH_4HCO_3)-acetonitrile]; B%: 40%-70%,12min) to give 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (38 mg, 81 µmol, 12%, 98.4% purity) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) d = 7.89 (d, J=7.1 Hz, 2H), 7.29 (s, 1H), 7.22 (t, J=7.9 Hz, 3H), 7.05 (d, J=8.2 Hz, 1H), 4.50 - 4.38 (m, 1H), 4.20 (t, J=8.4 Hz, 1H), 3.95 - 3.79 (m, 2H), 3.49 (td, J=8.5, 16.9 Hz, 1H), 3.36 - 3.20 (m, 2H), 3.12 - 2.97 (m, 1H), 2.89 (td,

J=8.7, 17.1 Hz, 1H), 2.79 - 2.69 (m, 1H), 2.35 (s, 3H), 2.18 (d, J=13.0 Hz, 7H), 2.00 - 1.82 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 3: Preparation of 1-(3,4-dimethylphenyl)-4-[4-[3-(m-tolyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one

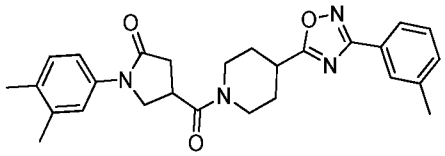


Step 1: Preparation of N-hydroxy-3-methylbenzimidamide.



To a stirred solution of 3-methylbenzonitrile (1.0 g, 8.54 mmol, 1.02 mL) in ethanol (10 mL) and water (1 mL) was added hydroxylamine hydrochloride (1.19 g, 17.1 mmol) and triethylamine (1.73 g, 17.1 mmol, 2.37 mL). The mixture was heated at 75 °C for 16 h and then concentrated under reduced pressure to give a residue that was then diluted with dichloromethane. The organic phase was washed with saturated aqueous sodium chloride solution (5mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give N-hydroxy-3-methyl-benzamidine (1.05 g, solid) as a crude solid that was used directly in the next step without further purification. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.42 - 7.31 (m, 2H), 7.24 - 7.12 (m, 2H), 4.93 - 4.71 (s, 1H), 3.67 - 3.58 (m, 1H), 2.97 (q, J=7.3 Hz, 1H), 2.30 (s, 3H), 1.32 - 1.23 (m, 1H), 1.18 - 1.11 (m, 1H).

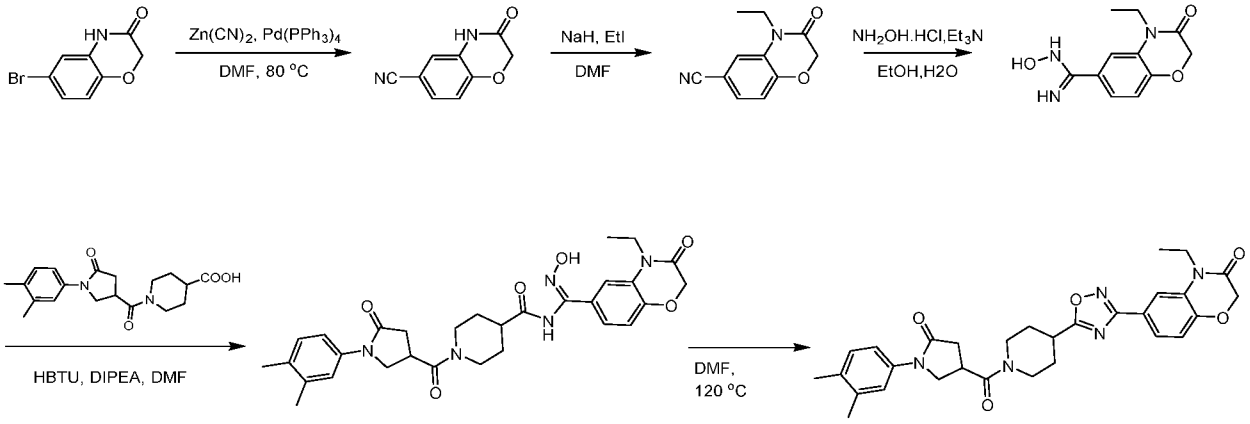
Step 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one



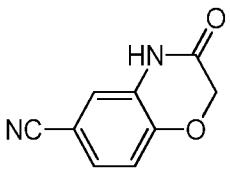
To a stirred solution of 1-[1-(3,4-dimethylphenyl)-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (229 mg, 666 µmol) in N,N-dimethylformamide (1 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (253 mg, 666 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (258 mg, 2.00 mmol, 349 µL). The mixture was stirred at 25 °C for 5 mins then N-hydroxy-3-methyl-benzamidine (100 mg, 666 µmol) was added. After 16 h, the reaction mixture was diluted with water (1 mL) extracted with ethyl acetate (5 mL x 3). The organic layers were combined, washed with saturated aqueous sodium chloride solution (5 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude residue that was purified by prep-HPLC (Waters X bridge 150x25 5µm column, 41%-71% acetonitrile in an a 10 mM ammonium acetate solution in water, 12 min gradient) to give 1-(3,4-dimethylphenyl)-4-[4-[3-(m-tolyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one (118 mg, 266 µmol, 38 %) as a yellow solid. ^{1}H NMR (400MHz,

CHLOROFORM-d) δ = 7.93 - 7.83 (m, 1H), 7.40 – 7.30 (m, 3H), 7.16 - 7.07 (m, 1H), 4.58 - 4.45 (m, 1H), 4.29 – 4.25 (m 1H), 4.00 -3.90 (m, 2H), 3.59 – 3.55 (m, 1H), 3.43 - 3.24 (m, 2H), 3.19 - 3.01 (m, 1H), 3.01 - 2.89 (m, 1H), 2.87 - 2.74 (m, 1H), 2.43 (s, 3H), 2.27 – 2.22 (m, 8H), 2.07 - 1.90 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 4. 6-(5-(1-(1-(3,4-Dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidin-4-yl)-1,2,4-oxadiazol-3-yl)-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one

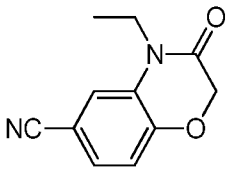


Step 1: Preparation of 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile



To a stirred solution of 6-bromo-2H-benzo[b][1,4]oxazin-3(4H)-one (3.0g, 13.2 mmol) in N,N-dimethylformamide (35 mL) was added zinc cyanide (1.24 g, 10.5 mmol, 668 µL) and tetrakis(triphenylphosphine)palladium(0) (760 mg, 658 µmol) under nitrogen. The mixture was then stirred at 80 °C for 16 h, cooled to room temperature, and extracted with ethyl acetate (60 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and dried over anhydrous sodium sulfate. The combined organic layers were concentrated to dryness to give the crude product. The crude product was further purified by trituration in ethyl acetate and used in the next step without further purification. 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (3.40 g) was obtained as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 175.0.

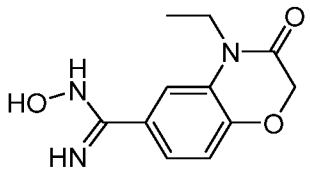
Step 2: Preparation of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile



To a stirred solution of 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (3.30 g, 19.0 mmol) in N,N-dimethylformamide (35 mL) was added sodium hydride (758 mg, 19 mmol, 60% dispersion in mineral oil) and iodoethane (3.84 g, 25 mmol, 1.97 mL) at 0 °C. The mixture was warmed to 20 °C. After 3 h, the mixture was cooled to 0 °C, quenched by addition of water (50 mL), and extracted with ethyl

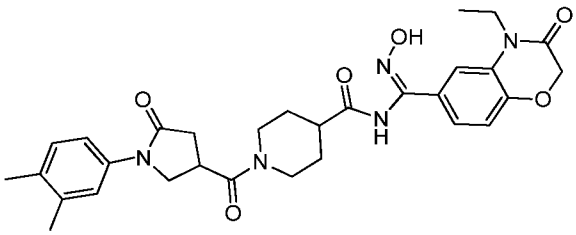
acetate (60 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50:1 to 5:1) to give 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (1.30 g, 6.43 mmol, 34 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 4.62 (s, 2H), 3.93 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); LCMS (ESI) m/z = 203.1 $[M+H]^+$.

Step 3: Preparation of 4-ethyl-N-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboximidamide



To a stirred solution of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (1.20 g, 5.93 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (825 mg, 11.9 mmol), triethylamine (1.20 g, 11.9 mmol, 1.64 mL) and water (2 mL), then the mixture was heated at 75 °C. After 5 h, the mixture was cooled to 20 °C and water (20 mL) added. The mixture was extracted with ethyl acetate (30 mL x 3), then the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give 4-ethyl-N-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboximidamide (1.20 g, 5.10 mmol, 86 %) as a white solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.61 (s, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.87 (s, 2H), 4.66 (s, 2H), 3.96 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

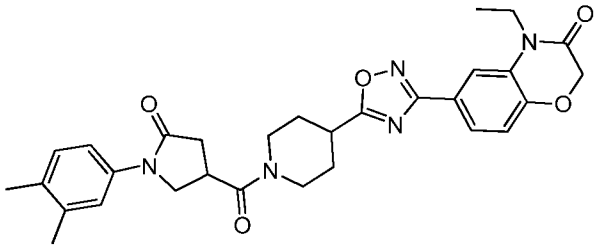
Step 4: Preparation of (E)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N-((4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(hydroxyimino)methyl)piperidine-4-carboxamide



To a stirred solution of 4-ethyl-N-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboximidamide (150 mg, 638 µmol) in N,N-dimethylformamide (5 mL) was added 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (220 mg, 638 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (242 mg, 638 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (247 mg, 1.91 mmol, 334 µL). After 16 h at 20 °C, the reaction mixture was quenched with water (10 mL). The mixture was extracted with ethyl acetate (20 mL x 4), then the combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give (E)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N-((4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-

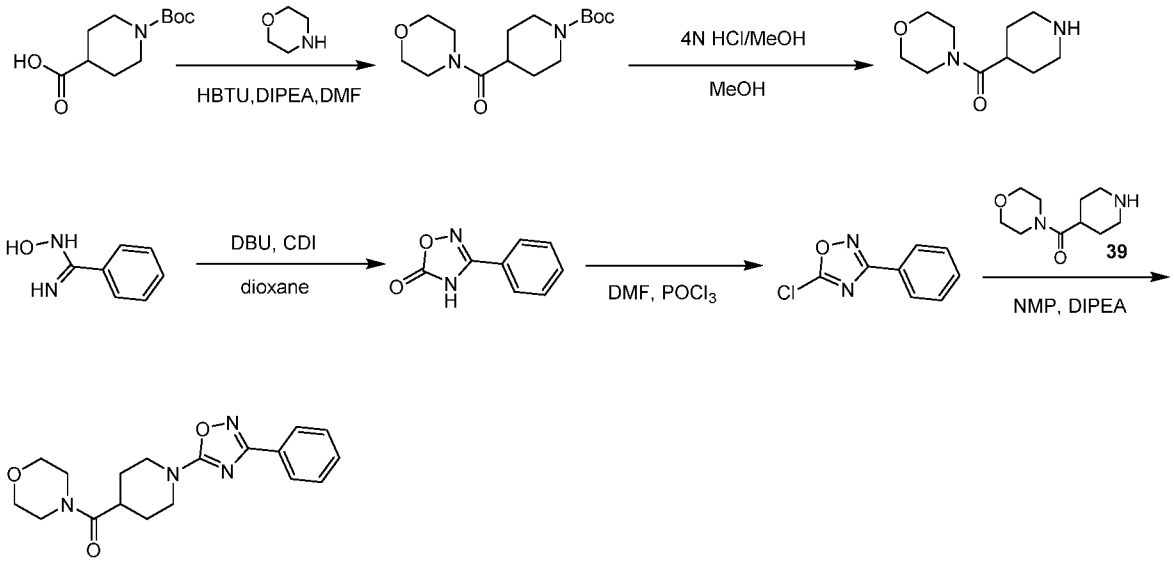
yl)(hydroxyimino)methyl)piperidine-4-carboxamide (450 mg) as a yellow oil. This material was used directly without further purification. LCMS (ESI) m/z = 562.3 $[M+H]^+$.

Step 5: Preparation of 6-(5-(1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidin-4-yl)-1,2,4-oxadiazol-3-yl)-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one

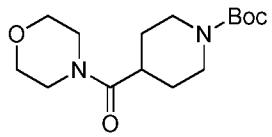


(E)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N-((4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(hydroxyimino)methyl)piperidine-4-carboxamide (450 mg, 801 µmol) was heated in N,N-dimethylformamide (3 mL) at 120 °C for 3 h. The mixture was cooled and purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-65%,12 min) to give 6-(5-(1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidin-4-yl)-1,2,4-oxadiazol-3-yl)-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (142 mg, 255 µmol, 32 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.60 (m, 2H), 7.29 (s, 1H), 7.22-7.19 (m, 1H), 7.03 (dd, *J* = 8.3, 16.9 Hz, 2H), 4.60 (s, 2H), 4.56-4.40 (m, 1H), 4.21 (d, *J* = 7.3 Hz, 1H), 4.00 (d, *J* = 6.5 Hz, 2H), 3.96-3.78 (m, 2H), 3.49 (quin, *J* = 8.3 Hz, 1H), 3.37-3.19 (m, 2H), 3.09-2.82 (m, 2H), 2.81-2.69 (m, 1H), 2.18 (d, *J* = 12.8 Hz, 8H), 1.98-1.82 (m, 2H), 1.26 (t, *J* = 6.8 Hz, 3H); LCMS (ESI) $[M+H]^+$ = 544.2.

Example 5: Morpholino(1-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methanone.

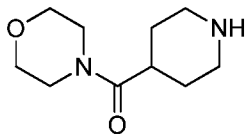


Step 1: Preparation of tert-butyl 4-(morpholine-4-carbonyl)piperidine-1-carboxylate



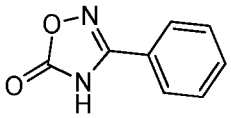
To a stirred solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (300 mg, 1.31 mmol) in N,N-dimethylformamide (10 mL) was added morpholine (136 mg, 1.57 mmol, 138 µL), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (496 mg, 1.31 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (338 mg, 2.62 mmol, 457 µL). The mixture was stirred at 20 °C for 16 h, then quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 4-(morpholine-4-carbonyl)piperidine-1-carboxylate (700 mg) as a yellow oil. This material was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.51 (m, 5H), 3.45 (br. s., 1H), 3.18-3.05 (m, 1H), 2.93-2.86 (m, 3H), 2.81 (s, 3H), 2.75-2.71 (m, 2H), 2.59-2.48 (m, 1H), 1.39 (s, 9H).

Step 2: Preparation of morpholino(piperidin-4-yl)methanone



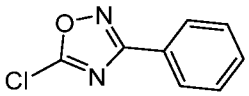
To a stirred solution of tert-butyl 4-(morpholine-4-carbonyl)piperidine-1-carboxylate (700 mg, 2.35 mmol) in methanol (5 mL) was added 4N hydrochloric acid in methanol (15 mL). The mixture was stirred at 20 °C for 16 h then concentrated under reduced pressure to give morpholino(4-piperidyl)methanone (300 mg) as a colorless oil that was used directly without further purification. LCMS (ESI) $[M+H]^+$ = 199.1.

Step 3: Preparation of 3-phenyl-1,2,4-oxadiazol-5(4H)-one



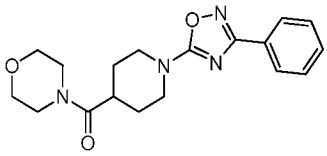
To a stirred solution of N-hydroxybenzamidine (2.0 g, 14.69 mmol) in dioxane (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.46 g, 16 mmol, 2.44 mL) and 1,1'-carbonyldiimidazole (3.57 g, 22 mmol). The mixture was stirred at 110 °C for 16 h, then cooled and quenched with water (10 mL). The mixture was extracted with dichloromethane (50 mL x 4), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:1) to give 3-phenyl-1,2,4-oxadiazol-5(4H)-one (1.30 g, 8.02 mmol, 55 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.83-7.75 (m, 2H), 7.66-7.52 (m, 3H); LCMS (ESI) m/z = 163.2 $[M+H]^+$.

Step 4: Preparation of 5-chloro-3-phenyl-1,2,4-oxadiazole



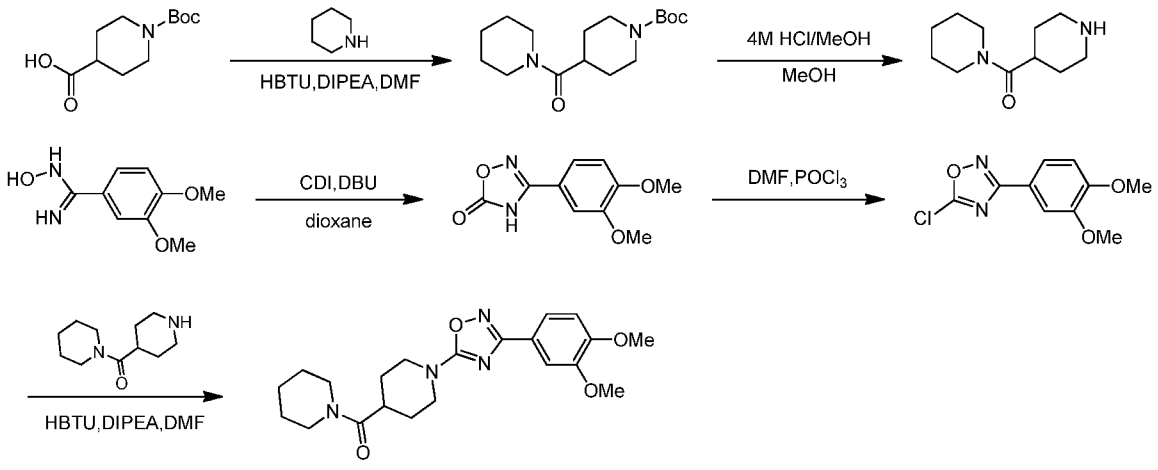
To a stirred solution of 3-phenyl-1,2,4-oxadiazol-5(4H)-one (500 mg, 3.08 mmol) equipped with calcium chloride tube was added N,N-dimethylformamide (1 mL). Phosphoryl chloride (10 mL) was added dropwise, and the resulting mixture was heated at 110 °C for 16 h. The reaction mixture was cooled to 20 °C and poured onto ice water (100 mL), and the resulting mixture was stirred for 30 min. The mixture was extracted with dichloromethane (20 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50:1) to give 5-chloro-3-phenyl-1,2,4-oxadiazole (180 mg, 997 µmol, 32 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-7.98 (m, 2H), 7.57-7.46 (m, 3H).

Step 5: Preparation of morpholino(1-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methanone

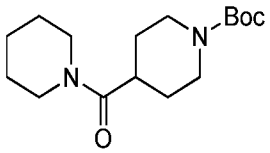


To a stirred solution of morpholino(piperidin-4-yl)methanone (180 mg, 908 µmol) in N-methyl-2-pyrrolidone (5 mL) was added 5-chloro-3-phenyl-1,2,4-oxadiazole (163 mg, 908 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (234 mg, 1.82 mmol, 317 µL). The mixture was stirred at 120 °C for 16 h then cooled and purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10 mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give morpholino(1-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methanone (130 mg, 380 µmol, 42 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.00-7.94 (m, 2H), 7.55-7.45 (m, 3H), 4.26 (d, *J* = 13.3 Hz, 2H), 3.74-3.59 (m, 8H), 3.32-3.26 (m, 2H), 3.08-2.98 (m, 1H), 1.92-1.75 ppm (m, 4H); LCMS (ESI) $[M+H]^+$ = 343.2.

Example 6: (1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone

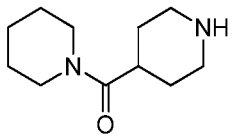


Step 1: Preparation of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate.



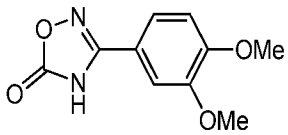
To a mixture of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (300 mg, 1.31 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (496 mg, 1.31 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (338 mg, 2.62 mmol, 457 µL) in N,N-dimethylformamide (1 mL) was added piperidine (133 mg, 1.57 mmol, 155 µL) at 0℃. The mixture was stirred at 25 ℃ for 2 h. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (600 mg) as a yellow oil. This material was used directly without further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 3.73 (dd, *J* = 6.4, 9.9 Hz, 1H), 3.55 (br. s., 2H), 3.44 (br. s., 2H), 3.29-3.15 (m, 2H), 2.68-2.57 (m, 1H), 1.96-1.83 (m, 1H), 1.77-1.62 (m, 8H), 1.56 (br. s., 4H), 1.46 (s, 9H); LCMS (ESI) m/z = 297.3 $[M+H]^+$.

Step 2: Preparation of piperidin-1-yl(piperidin-4-yl)methanone.



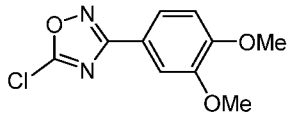
To a mixture of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (500 mg, 1.69 mmol) in methanol (5 mL) was added 4M methanolic hydrochloric acid (10 mL) at 0℃. The mixture was stirred at 25 ℃ for 2 h. The mixture was concentrated in vacuo to give piperidin-1-yl(piperidin-4-yl)methanone (300 mg) as a yellow oil which was used in the next step directly without further purification. LCMS (ESI) $[M+H]^+$ = 197.3.

Step 3: Preparation of 3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5(4H)-one.



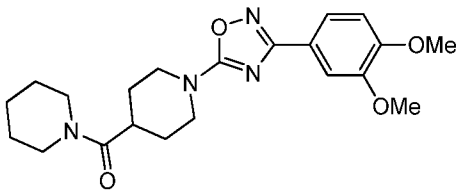
A mixture of N-hydroxy-3,4-dimethoxybenzimidamide (1.0 g, 5.10 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (853 mg, 5.61 mmol, 845 µL) and 1,1'-carbonyldiimidazole (1.24 g, 7.65 mmol) in dioxane (10 mL) was prepared at 15℃. The mixture was warmed to 110℃ for 12 h. The mixture was cooled to 15℃ and then poured into water (5 mL). The aqueous phase was extracted with dichloromethane (10 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (800 mg) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.60-7.52 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 1H), 3.91 (d, *J* = 6.1 Hz, 6H); LCMS (ESI) m/z = 223.2 $[M+H]^+$.

Step 4: Preparation of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole.



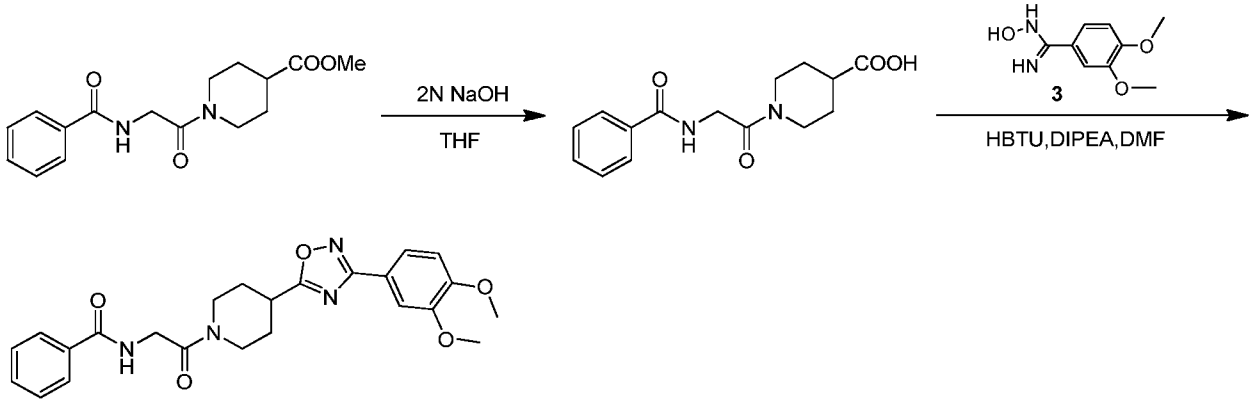
3-(3,4-Dimethoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (500 mg, 2.25 mmol) was added to a mixture of phosphoryl chloride (13.2 g, 86.1 mmol, 8 mL) and N,N-dimethylformamide (1 mL). The mixture was equipped with a calcium chloride tube and heated at 100 °C for 16 h, at which time the mixture was cooled and concentrated in vacuo at 45°C. The residue was poured into ice-water (w/w = 10/1) (11mL) and stirred for 10 min. The mixture was extracted with dichloromethane (10 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography (silica, petroleum ether: ethyl acetate = 5:1 to 1:1 gradient) to afford 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (200 mg, 0.83 mmol, 37 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 3.96 (d, *J* = 2.4 Hz, 6H); LCMS (ESI) m/z =241.1 $[M+H]^+$.

Step 5: Preparation of (1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone.

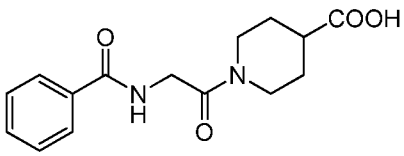


To a stirred solution of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (200 mg, 831 µmol) and triethylamine (252 mg, 2.49 mmol, 345 µL) in dichloromethane (2 mL) was added piperidin-1-yl(piperidin-4-yl)methanone (163 mg, 831 µmol) at 0 °C. The mixture was warmed to 15 °C and stirred for 2h, then concentrated in vacuo to afford crude product. The residue was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10 mM ammonium carbonate)-acetonitrile]; B%: 20%-55%,12 min) to give (1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone (36 mg, 89.7 µmol, 11 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.28 (d, *J* = 13.2 Hz, 2H), 3.95 (d, *J* = 8.8 Hz, 6H), 3.65-3.41 (m, 4H), 3.30-3.15 (m, 2H), 2.85-2.69 (m, 1H), 2.01-1.89 (m, 2H), 1.88-1.79 (m, 2H), 1.68 (d, *J* = 4.9 Hz, 2H), 1.61 (br. s., 1H); LCMS (ESI) m/z = $[M+H]^+$: 401.2.

Example 7: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

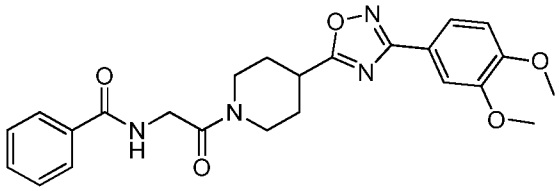


Step 1: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (5.0 g, 16.4 mmol) in tetrahydrofuran (50 mL) was added aqueous sodium hydroxide (2 M, 16.4 mL). The mixture was stirred at 20 °C for 2 h and then acidified by the addition of concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (3.25 g, 11.2 mmol, 68 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.87 (d, *J*=7.5 Hz, 2H), 7.59 - 7.42 (m, 3H), 4.39 - 4.20 (m, 3H), 3.92 (d, *J*=14.1 Hz, 1H), 3.24 (t, *J*=11.5 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.62 (s, 1H), 2.08 - 1.89 (m, 2H), 1.81 - 1.53 (m, 2H).

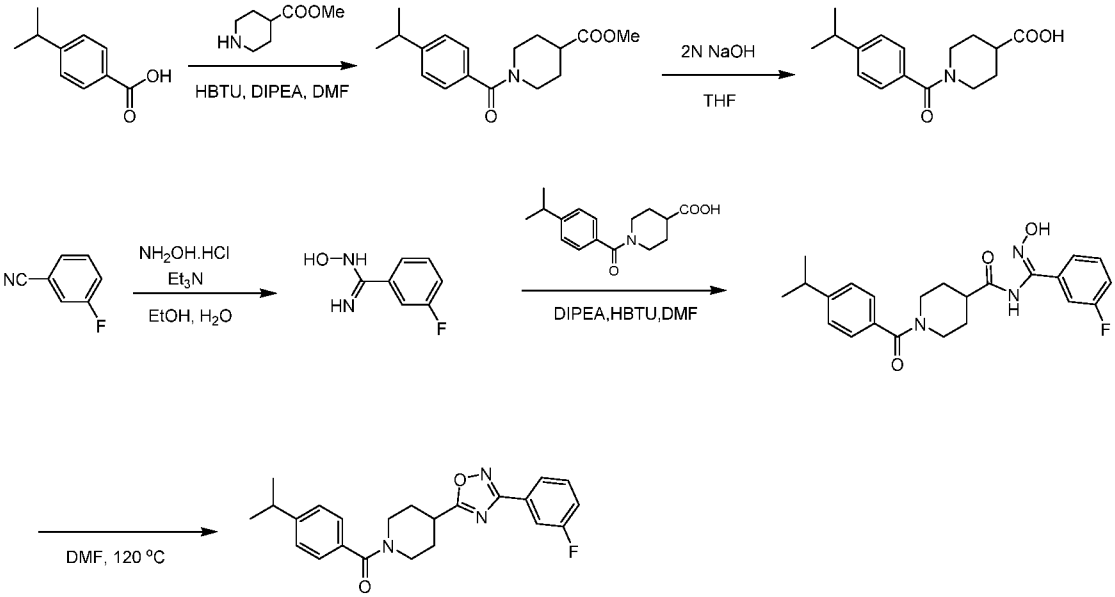
Step 2: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



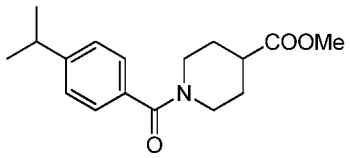
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (2.0 g, 6.89 mmol) in N,N-dimethylformamide (30 mL) was added N-hydroxy-3,4-dimethoxybenzimidamide (1.62 g, 8.27 mmol), N-ethyl-N-(propan-2-yl)propan-2-amine (2.67 g, 20.67 mmol, 3.61 mL) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (2.62 g, 6.89 mmol). The mixture was stirred at 20 °C for 2 h and then warmed at 120 °C for 2 h. The reaction mixture was quenched by addition of water (40 mL), then the mixture was extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was

purified by chromatography (silica, petroleum ether : ethyl acetate = 20 : 1 to 1 : 2) to give a yellow solid. The yellow solid was washed with ethyl acetate (30 mL), then the mixture was filtered, and the filter cake was dried in vacuo to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (1.29 g, 2.86 mmol, 42 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.84 (m, 2H), 7.80 (s, 1H), 7.58 - 7.44 (m, 3H), 7.41 - 7.35 (m, 1H), 7.28 - 7.26 (m, 2H), 6.92 (d, *J*=8.9 Hz, 1H), 4.58 - 4.47 (m, 1H), 4.32 (d, *J*=3.9 Hz, 2H), 3.99 - 3.88 (m, 7H), 3.37 - 3.06 (m, 3H), 2.28 - 2.13 (m, 2H), 2.07 - 1.89 (m, 2H); LCMS (ESI) $[M+H]^+$ = 451.3.

Example 8: (4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.

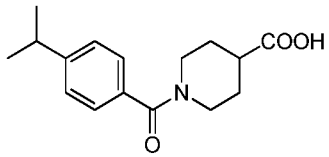


Step 1: Preparation of methyl 1-(4-isopropylbenzoyl)piperidine-4-carboxylate.



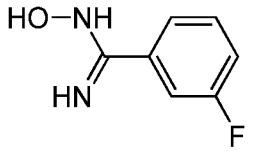
To a stirred solution of 4-isopropylbenzoic acid (250 mg, 1.52 mmol) in N,N-dimethylformamide (10 mL) was added methyl piperidine-4-carboxylate (261 mg, 1.82 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (576 mg, 1.52 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (392 mg, 3.04 mmol, 530 µL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product methyl 1-(4-isopropylbenzoyl)piperidine-4-carboxylate (900 mg) as a yellow oil. LCMS (ESI) m/z: 290.3 $[M+H]^+$.

Step 2: Preparation of 1-(4-isopropylbenzoyl)piperidine-4-carboxylic acid.



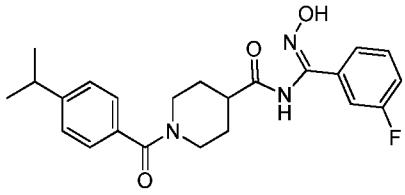
To a stirred solution of methyl 1-(4-isopropylbenzoyl)piperidine-4-carboxylate (900 mg, 3.11 mmol) in tetrahydrofuran (10 mL) was added aqueous sodium hydroxide (2 M, 3.11 mL). The mixture was stirred at 20 °C for 16 h. The mixture was acidified to pH 1 by dropwise addition of concentrated hydrochloric acid. The mixture was extracted with dichloromethane (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product 1-(4-isopropylbenzoyl)piperidine-4-carboxylic acid (400 mg) as a yellow solid. LCMS (ESI) $[M+H]^+$ = 276.2.

Step 3: Preparation of 3-fluoro-N-hydroxybenzimidamide.



To a stirred solution of 3-fluorobenzonitrile (1.0 g, 8.26 mmol, 884 µL) in ethanol (10 mL) were added hydroxylamine hydrochloride (1.15 g, 16.5 mmol), triethylamine (2.09 g, 20.7 mmol, 2.86 mL), and water (1 mL). Then the mixture was heated at 75 °C for 16 h. After cooling to 20 °C, water (10 mL) was added to the solution. The mixture was extracted with ethyl acetate (20 mL x 5). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 3-fluoro-N-hydroxybenzimidamide (2.0 g) as a green solid that was used directly in the next step without further purification. LCMS (ESI) m/z: 155.1 $[M+H]^+$.

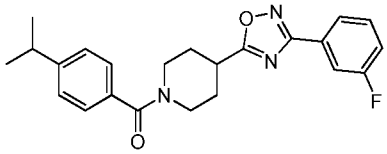
Step 4: Preparation of (E)-N-((3-fluorophenyl)(hydroxyimino)methyl)-1-(4-isopropylbenzoyl)piperidine-4-carboxamide.



To a stirred solution of 1-(4-isopropylbenzoyl)piperidine-4-carboxylic acid (400 mg, 1.45 mmol) in N,N-dimethylformamide (10 mL) were added 3-fluoro-N-hydroxybenzimidamide (223 mg, 1.45 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (550 mg, 1.45 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (563 mg, 4.36 mmol, 761 µL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched with water (10 mL) and then extracted with ethyl acetate (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give (E)-N-((3-

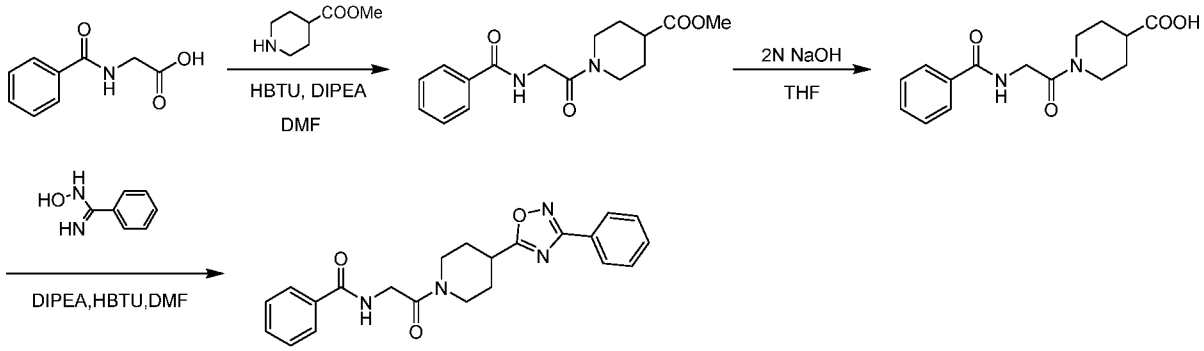
fluorophenyl)(hydroxyimino)methyl)-1-(4-isopropylbenzoyl)piperidine-4-carboxamide (350 mg) as a yellow oil. LCMS (ESI) m/z: 412.3 $[M+H]^+$.

Step 5: Preparation of (4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.

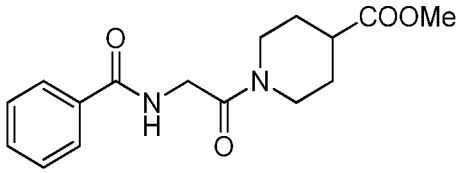


(E)-N-((3-Fluorophenyl)(hydroxyimino)methyl)-1-(4-isopropylbenzoyl)piperidine-4-carboxamide (350 mg, 851 µmol) was added to N,N-dimethylformamide (3 mL), and the mixture was stirred at 120 °C for 16 h. The reaction mixture was cooled and purified by direct injection and prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 50%-80%,12 min) to give (4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(4-isopropylphenyl)methanone (82 mg, 210 µmol, 25 %) as a yellow oil. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 9.7 Hz, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.42-7.28 (m, 5H), 4.69-4.50 (m, 1H), 3.89 (br. s., 1H), 3.53-3.42 (m, 1H), 3.39-3.34 (m, 1H), 3.32-3.28 (m, 1H), 2.99 (td, *J* = 6.9, 13.8 Hz, 1H), 2.43-2.09 (m, 2H), 2.07-1.83 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H); LCMS (ESI) m/z $[M+H]^+$ = 394.2.

Example 9: N-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide.



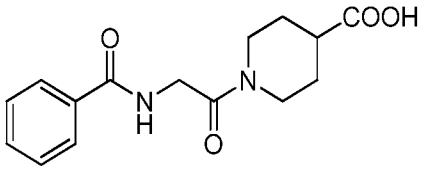
Step 1: Preparation of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



To a stirred solution of 2-benzamidoacetic acid (3.0 g, 16.7 mmol) in N,N-dimethylformamide (30 mL) were added methyl piperidine-4-carboxylate (2.88 g, 20.09 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (6.35 g, 16.7 mmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (6.49 g, 50.2 mmol, 8.77 mL). The mixture was stirred at 20 °C for 3 h and then quenched by addition of water (40 mL). The mixture was extracted with ethyl acetate (80 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by

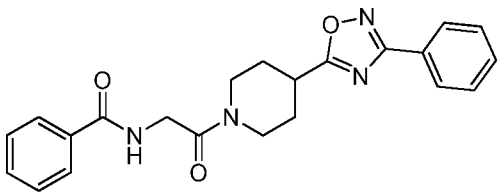
chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) to give methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (7.0 g, 23.0 mmol, quantitative), as a yellow oil. LCMS (ESI) m/z = 305.1 $[M+H]^+$.

Step 2: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



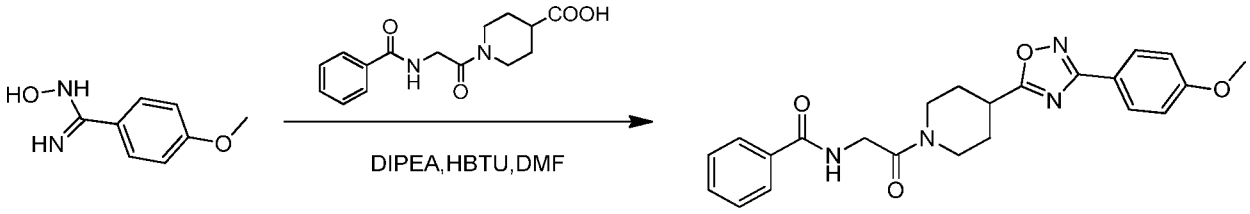
To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (7.0 g, 23.0 mmol) in tetrahydrofuran (50 mL) was added aqueous sodium hydroxide (2 M, 23 mL). The mixture was then stirred at 20 °C for 16 h. The mixture was then acidified to pH 1 using concentrated hydrochloric acid and then extracted with dichloromethane (80 mL x 4). The organic phases were combined, washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (4.20 g, 14.47 mmol, 63 %) as a yellow solid. This was used directly in the next step without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.93-7.85 (m, 2H), 7.59-7.54 (m, 1H), 7.52-7.46 (m, 2H), 4.42-4.33 (m, 1H), 4.29 (s, 2H), 4.01-3.87 (m, 1H), 3.30-3.20 (m, 1H), 2.97-2.88 (m, 1H), 2.63-2.52 (m, 1H), 2.06-1.92 (m, 2H), 1.80-1.55 (m, 2H).

Step 3: Preparation of N-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide.



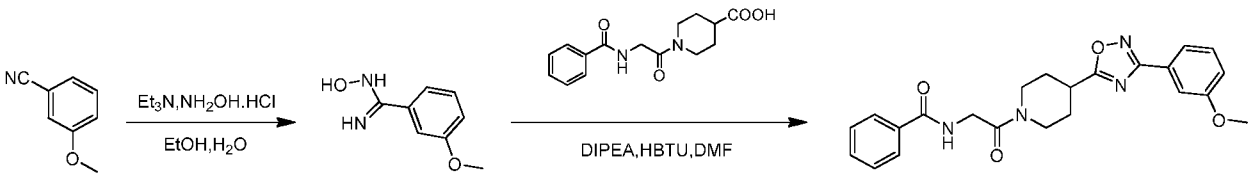
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (200 mg, 689 µmol) in N,N-dimethylformamide (4 mL) were added *N*-hydroxybenzamidine (112 mg, 826 µmol), N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (261 mg, 689 µmol), and N,N-diisopropylethylamine (267 mg, 2.07 mmol, 360.96 µL). The reaction mixture was then stirred at 20 °C for 2 h, quenched by addition of water (5 mL), and extracted with ethyl acetate (20 mL x4). The organic extracts were combined, washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo to provide a crude residue. To the residue was added N,N-dimethylformamide (4 mL), and the resulting mixture was stirred at 120 °C for 2 h, concentrated under vacuum, and purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide (74 mg, 189 µmol, 27 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.08 (m, 2H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.55-7.46 (m, 6H), 7.36 (br. s., 1H), 4.51 (d, *J* = 13.7 Hz, 1H), 4.33 (d, *J* = 3.8 Hz, 2H), 3.94 (d, *J* = 13.3 Hz, 1H), 3.42-3.32 (m, 2H), 3.20 (t, *J* = 10.5 Hz, 1H), 2.28 (br. s., 2H), 2.11-1.96 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 391.1.

Example 10: N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

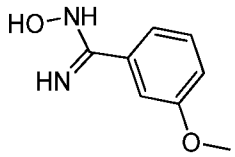


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) and N-hydroxy-4-methoxybenzimidamide (82 mg, 496 µmol) in N,N-dimethylformamide (2 mL) were added N,N-diisopropylamine (106 mg, 827 µmol, 144 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) at 15 °C, then the mixture was stirred for 15h. The mixture was heated to 110 °C and stirred for 5h. After cooling, the mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-65%,12 min) to give N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (87 mg, 205 µmol, 50 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (d, J=8.8 Hz, 2H), 7.88 (d, J=7.5 Hz, 2H), 7.60 - 7.51 (m, 1H), 7.51 - 7.38 (m, 2H), 7.04 (d, J=8.4 Hz, 2H), 4.46 (d, J=13.2 Hz, 1H), 4.38 - 4.21 (m, 2H), 4.04 (d, J=13.7 Hz, 1H), 3.86 (s, 3H), 3.47 - 3.34 (m, 2H), 3.07 (t, J=11.9 Hz, 1H), 2.31 - 2.15 (m, 2H), 2.05 - 1.80 (m, 2H); LCMS (ESI) m/z $[M+H]^+$ = 421.1.

Example 11

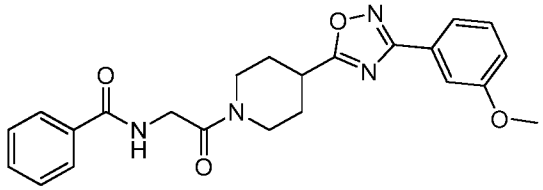


Step 1: Preparation of N-hydroxy-3-methoxybenzimidamide.



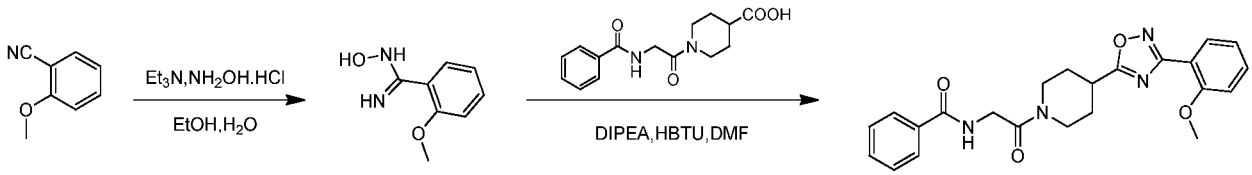
To a stirred solution of 3-methoxybenzonitrile (2.0 g, 15.0 mmol, 1.83 mL) in ethanol (20 mL) was added hydroxylamine hydrochloride (2.09 g, 30.0 mmol), triethylamine (3.04 g, 30.0 mmol, 4.16 mL) and water (2 mL). Then the mixture was heated at 75 °C for 5 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate. The combined organic phases were concentrated in vacuo to give N-hydroxy-3-methoxybenzimidamide (2.60 g) as a white solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.67 (s, 1H), 7.37-7.24 (m, 3H), 7.10-6.88 (m, 1H), 5.84 (br. s., 2H), 3.82 (s, 3H).

Step 2: Preparation of N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

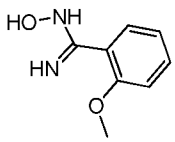


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (3 mL) were added N-hydroxy-3-methoxybenzimidamide (82 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled and purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (83 mg, 198 µmol, 48 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2H), 7.72-7.68 (m, 1H), 7.62 (dd, *J* = 1.5, 2.5 Hz, 1H), 7.57-7.52 (m, 1H), 7.51-7.45 (m, 2H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.38-7.32 (m, 1H), 7.08 (ddd, *J* = 0.9, 2.6, 8.3 Hz, 1H), 4.52 (d, *J* = 13.6 Hz, 1H), 4.33 (d, *J* = 4.0 Hz, 2H), 3.95 (br. s., 1H), 3.91 (s, 3H), 3.42-3.32 (m, 2H), 3.25-3.13 (m, 1H), 2.33-2.22 (m, 2H), 2.11-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 421.2.

Example 12: N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

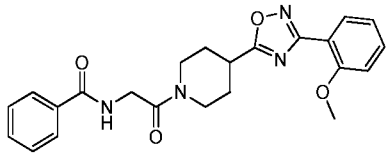


Step 1: Preparation of N-hydroxy-2-methoxybenzimidamide.



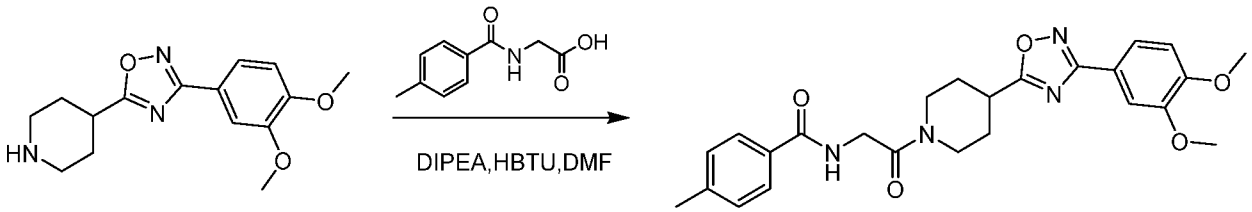
To a stirred solution of 2-methoxybenzonitrile (2.0 g, 15.0 mmol, 1.83 mL) in ethanol (20 mL) were added hydroxylamine hydrochloride (2.09 g, 30.0 mmol), triethylamine (3.04 g, 30.0 mmol, 4.16 mL), and water (2 mL), then the mixture was heated to 70 °C for 15h. The mixture was cooled and quenched with water (20 mL), extracted with dichloromethane (30 mL x 3), and the combined organic phases were washed with water (20 mL), saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give N-hydroxy-2-methoxybenzimidamide (2.80 g) as a light green solid, which was used in next step directly. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.47 - 7.30 (m, 2H), 7.06 (d, J=8.4 Hz, 1H), 6.95 (t, J=7.5 Hz, 1H), 3.86 (s, 3H).

Step 2: Preparation of N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

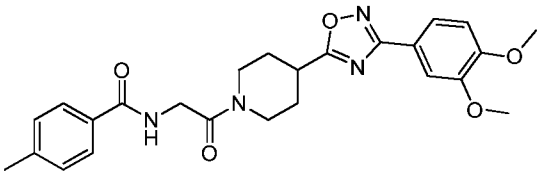


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) and N-hydroxy-2-methoxybenzimidamide (68 mg, 413 µmol) in N,N-dimethylformamide (2 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (106 mg, 826 µmol, 144 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol), and the mixture was stirred for 15 h at 15 °C. The mixture was then heated to 110 °C and stirred for 5h. After cooling, the mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-60%,12 min) to give N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (90 mg, 212 µmol, 51 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.96 (d, J=7.5 Hz, 1H), 7.88 (d, J=7.9 Hz, 2H), 7.61 - 7.41 (m, 4H), 7.18 (d, J=8.8 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 4.47 (d, J=13.2 Hz, 1H), 4.37 - 4.23 (m, 2H), 4.12 - 4.00 (m, 1H), 3.93 (s, 3H), 3.50 - 3.35 (m, 2H), 3.08 (t, J=11.5 Hz, 1H), 2.33 - 2.15 (m, 2H), 2.12 - 1.79 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 421.1.

Example 13: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-4-methyl-benzamide.



Step 1: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-4-methylbenzamide.

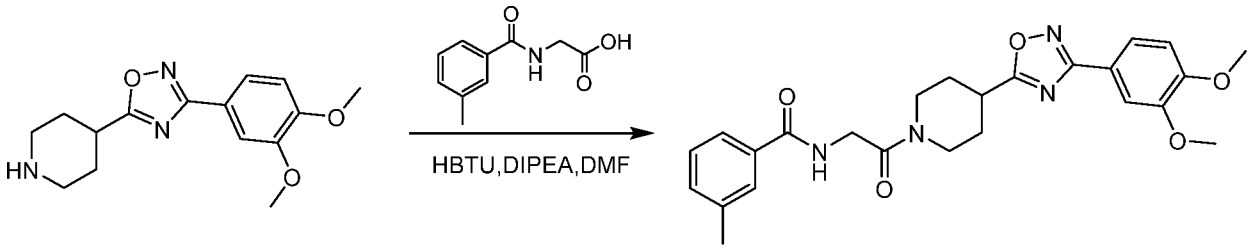


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-[(4-methylbenzoyl)amino]acetic acid (105 mg, 544 µmol). The mixture was stirred at 20 °C for 5 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%:30%-60%,12 min) to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-4-methylbenzamide.

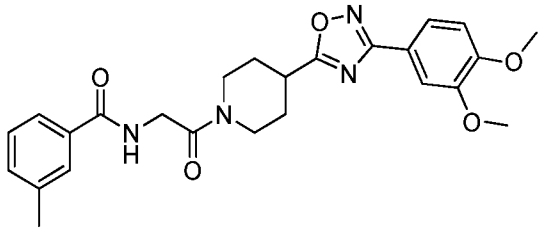
^{1}H NMR (400MHz, METHANOL-d4) δ = 7.77 (d, J=7.5 Hz, 2H), 7.66 (d, J=8.2 Hz, 1H), 7.59 (s, 1H), 7.29 (d, J=7.7 Hz, 2H), 7.08 (d, J=8.4 Hz, 1H), 4.47 (d, J=12.8 Hz, 1H), 4.29 (m, J=6.0 Hz, 2H), 4.05 (d, J=14.1

Hz, 1H), 3.89 (s, 6H), 3.50 - 3.34 (m, 3H), 3.06 (t, J=12.0 Hz, 1H), 2.40 (s, 3H), 2.32 - 2.13 (t, 2H), 2.07 - 1.79 (m, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 14: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3-methylbenzamide.

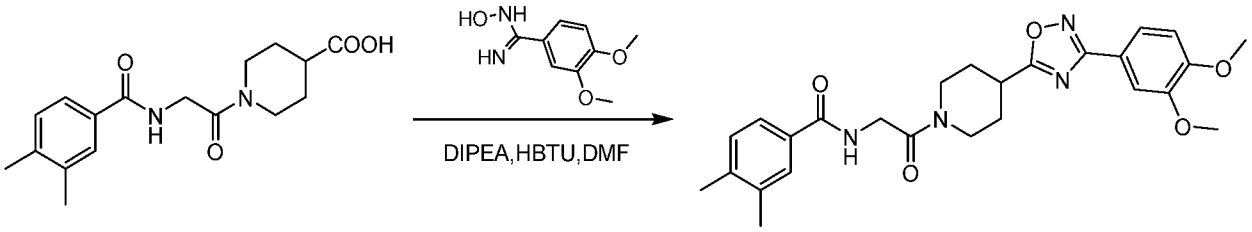


Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3-methylbenzamide

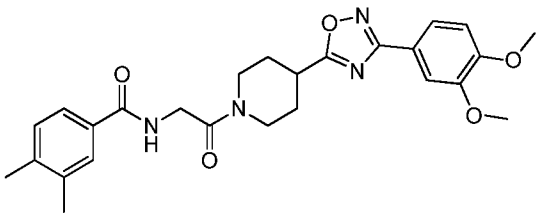


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (200 mg, 691 µmol) in N,N-dimethylformamide (2 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (268 mg, 2.07 mmol, 362 µL), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (262 mg, 691 µmol) and 2-[(3-methylbenzoyl)amino]acetic acid (133 mg, 691 µmol). The mixture was stirred at 20 °C for 16 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-3-methyl-benzamide (157 mg, 338 µmol, 49 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.48 (t, J=5.5 Hz, 1H), 7.72 - 7.63 (m, 2H), 7.58 (dd, J=2.0, 8.4 Hz, 1H), 7.46 (d, J=1.8 Hz, 1H), 7.34 (d, J=4.9 Hz, 2H), 7.11 (d, J=8.4 Hz, 1H), 4.32 (br d, J=13.0 Hz, 1H), 4.15 (dd, J=2.3, 5.4 Hz, 2H), 3.96 (d, J=13.7 Hz, 1H), 3.87 - 3.77 (m, 6H), 3.51 - 3.39 (m, 1H), 3.24 (s, 1H), 2.90 (t, J=11.6 Hz, 1H), 2.35 (s, 3H), 2.20 - 2.04 (m, 2H), 1.89 - 1.75 (m, 1H), 1.72 - 1.54 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 15: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide

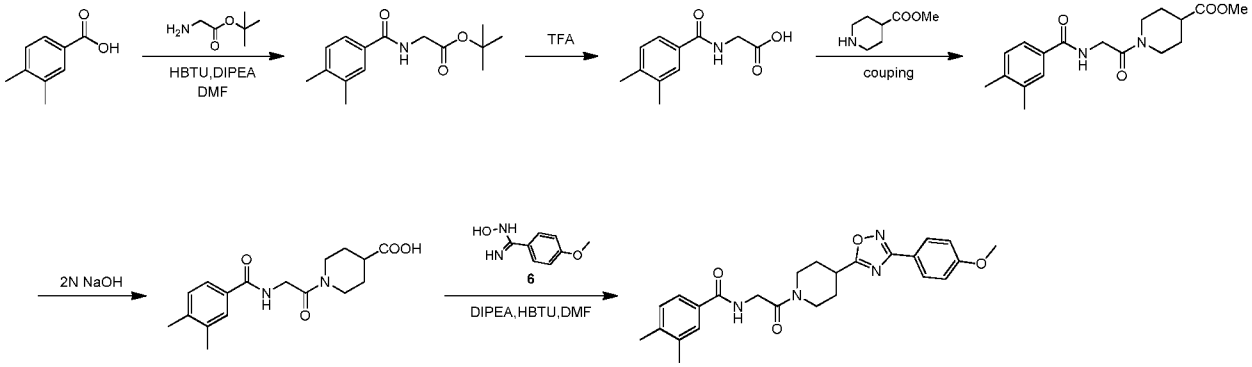


Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide

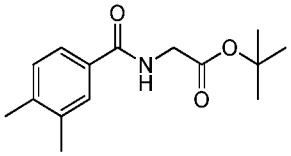


To a stirred solution of 1-[2-[(3,4-dimethylbenzoyl)amino]acetyl]piperidine-4-carboxylic acid (200 mg, 628 µmol) and N-hydroxy-3,4-dimethoxy-benzamidine (184 mg, 942 µmol) in N,N-dimethylformamide (1.50 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (238 mg, 628 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (243 mg, 1.88 mmol, 329 µL). The mixture was stirred at 20 ℃ for 16 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. N,N-Dimethylformamide (2 mL) was added, then the mixture was heated to 120 ℃ and stirred for a further 4 h. The mixture was cooled to 25 ℃, then water (5mL) was added, and the mixture extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. This residue was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-65%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-3,4-dimethyl-benzamide (209 mg, 436 µmol, 69 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.40 (s, 1H), 7.66 (s, 1H), 7.59 (br d, J=7.9 Hz, 2H), 7.46 (s, 1H), 7.21 (br d, J=7.7 Hz, 1H), 7.11 (br d, J=8.4 Hz, 1H), 4.32 (br d, J=12.6 Hz, 1H), 4.14 (br s, 2H), 3.96 (br d, J=13.5 Hz, 1H), 3.89 - 3.72 (m, 6H), 3.43 (br t, J=10.8 Hz, 1H), 3.28 - 3.17 (m, 1H), 2.90 (br t, J=11.5 Hz, 1H), 2.26 (s, 6H), 2.20-2.10 (m, 2H), 1.80 (br d, J=10.4 Hz, 1H), 1.64 (br d, J=10.1 Hz, 1H). (ESI) m/z: $[M+H]^+$ = 479.3.

Example 16: N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide

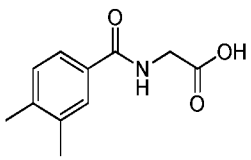


Step 1: Preparation of tert-butyl 2-(3,4-dimethylbenzamido)acetate.



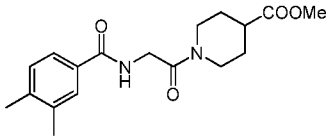
To a stirred solution of 3,4-dimethylbenzoic acid (2.0 g, 13.3 mmol) and tert-butyl 2-aminoacetate (1.92 g, 14.7 mmol) in N,N-dimethylformamide (20 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (3.44 g, 26.6 mmol, 4.65 mL) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (5.06 g, 13.3 mmol). After stirring at 15 °C for 3h, the mixture was treated with water (30 mL), extracted with ethyl acetate (30 mL x 3), and the combined organic phases were washed with water (20 mL), 1N hydrochloric acid (30 mL), saturated aqueous sodium hydrogen carbonate (30 mL), saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give tert-butyl 2-(3,4-dimethylbenzamido)acetate (4.0 g) as light brown oil, which was used in the next step directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J=1.6 Hz, 1H), 7.46 (dd, J=1.9, 7.9 Hz, 1H), 7.11 (d, J=7.8 Hz, 1H), 4.08 - 4.04 (m, 2H), 2.23 (s, 6H), 1.44 (s, 9H).

Step 2: Preparation of 2-(3,4-dimethylbenzamido)acetic acid



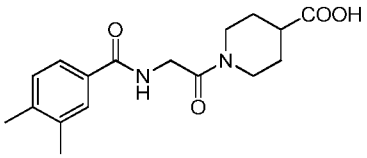
A solution of tert-butyl 2-(3,4-dimethylbenzamido)acetate (4.0 g, 15.2 mmol) in TFA (20 mL) and dichloromethane (20 mL) was stirred for 20 h at 15 °C. The mixture was concentrated, and the residue was treated with water (10 mL) and extracted with dichloromethane/methanol (20/1, 20 mL x 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give 2-(3,4-dimethylbenzamido)acetic acid (3.20 g) as a yellow oil, which was used in next step directly without further purification.

Step 3: Preparation of methyl 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylate.



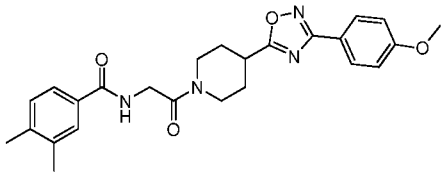
To a stirred solution of 2-(3,4-dimethylbenzamido)acetic acid (3.20 g, 15.4 mmol) and methyl piperidine-4-carboxylate (2.65 g, 18.5 mmol) in N,N-dimethylformamide (20 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (3.99 g, 30.9 mmol, 5.39 mL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (5.86 g, 15.4 mmol) at 0 ℃, then the mixture was warmed slowly to 15 ℃ and stirred for 15h. The mixture was treated with water (30 mL) at 0 ℃, extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with water (20 mL), 1N hydrochloric acid (30 mL), saturated aqueous sodium hydrogen carbonate solution (30 mL), saturated aqueous sodium chloride solution (30 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product. Purification by chromatography (silica, petroleum ether/ethyl acetate from 10:1 to 1:2) gave methyl 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylate (3.50 g, 10.5 mmol, 68 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.28 (m, 1H), 7.19 (d, *J*=7.5 Hz, 1H), 4.39 (d, *J*=13.2 Hz, 1H), 4.24 (d, *J*=3.5 Hz, 2H), 3.78 (d, *J*=13.7 Hz, 1H), 3.71 (s, 3H), 3.17 (t, *J*=11.0 Hz, 1H), 3.02 - 2.91 (m, 1H), 2.67 - 2.54 (m, 1H), 2.30 (s, 6H), 1.98 (m, 2H), 1.80 - 1.64 (m, 2H).

Step 4: Preparation of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid.



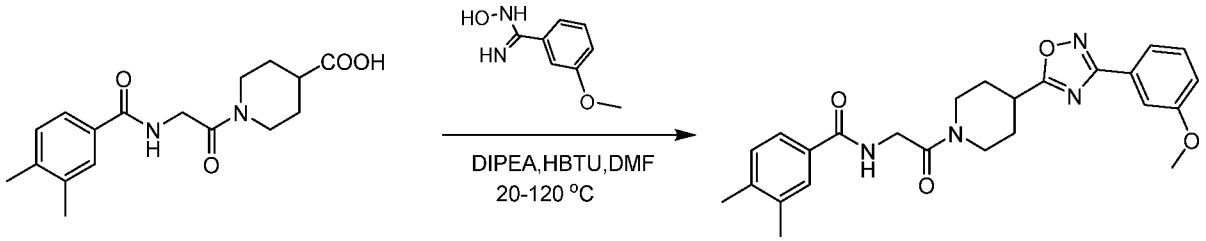
To a stirred solution of methyl 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylate (3.50 g, 10.5 mmol) in tetrahydrofuran (20 mL) and methanol (20 mL) was added aqueous sodium hydroxide (2 M, 7.90 mL), and the mixture was stirred at 15 ℃ for 5h. The mixture was concentrated to remove tetrahydrofuran and methanol, then then residue was acidified by 1N hydrochloric acid to pH = 2-3 at 0 ℃. The mixture was then extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, filtered, concentrated, and purified by prep-HPLC (column: Phenomenex luna C18 250x50mm 10 μm;mobile phase: [water (0.1%TFA)-acetonitrile]; B%: 10%-40%, 20min) to give 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (1.80 g, 5.65 mmol, 54 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ8.39 (s, 1H), 7.67 (s, 1H), 7.61 (d, *J*=7.7 Hz, 1H), 7.24 (d, *J*=7.7 Hz, 1H), 4.21 (d, *J*=12.7 Hz, 1H), 4.12 (d, *J*=4.9 Hz, 2H), 3.85 (d, *J*=13.8 Hz, 1H), 3.14 (t, *J*=11.7 Hz, 1H), 2.79 (t, *J*=11.5 Hz, 1H), 2.28 (s, 6H), 1.86 (m, 2H), 1.63 - 1.32 (m, 2H).

Step 5: Preparation of N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.



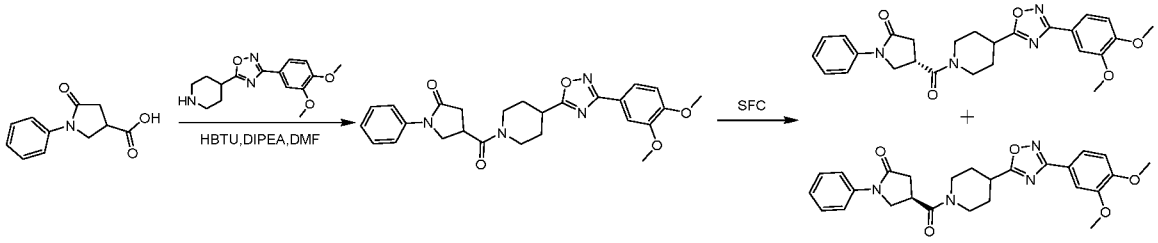
To a stirred solution of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (150 mg, 471 µmol) and N-hydroxy-4-methoxybenzimidamide (93 mg, 565 µmol) in N,N-dimethylformamide (2 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (121 mg, 942 µmol, 164 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (178 mg, 471 µmol) at 15 °C. After 15 h, the mixture was heated to 110 °C and stirred for 5 h. The mixture was cooled and directly purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide (110 mg, 244 µmol, 52 %) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ7.98 (d, J=9.3 Hz, 2H), 7.66 (s, 1H), 7.60 (d, J=7.5 Hz, 1H), 7.23 (d, J=7.9 Hz, 1H), 7.05 (d, J=9.3 Hz, 2H), 4.46 (d, J=13.2 Hz, 1H), 4.34 - 4.23 (m, 2H), 4.04 (d, J=13.7 Hz, 1H), 3.86 (s, 3H), 3.47 - 3.36 (m, 2H), 3.07 (t, J=11.0 Hz, 1H), 2.42 - 2.26 (s, 6H), 2.21 (d, J=17.6 Hz, 2H), 2.04 - 1.82 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 449.2.

Example 17: N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.

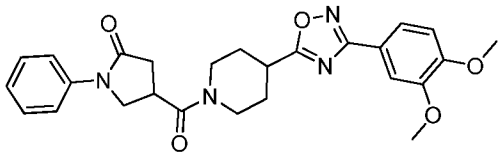


To a stirred solution of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (150 mg, 471 µmol) in N,N-dimethylformamide (3 mL) were added N-hydroxy-3-methoxybenzimidamide (93 mg, 565 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (178 mg, 471 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (182 mg, 1.41 mmol, 246 µL). The mixture was stirred at 20 °C for 2 h and then heated at 120 °C for 2 h. The reaction mixture was cooled and then purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide (119 mg, 263 µmol, 56 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.63-7.47 (m, 4H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.23-7.20 (m, 1H), 7.15-7.10 (m, 1H), 6.98 (dd, *J* = 1.8, 8.3 Hz, 1H), 4.48-4.37 (m, 1H), 4.22 (d, *J* = 3.9 Hz, 2H), 3.88-3.82 (m, 1H), 3.81 (s, 3H), 3.31-3.22 (m, 2H), 3.13-3.04 (m, 1H), 2.24 (s, 6H), 2.22-2.12 (m, 2H), 2.00-1.87 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 449.3.

***Example 18**: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one*

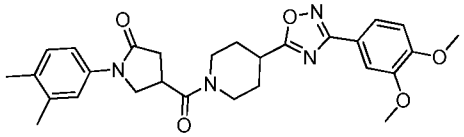


Step 1: Preparation of 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (1.5 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (111 mg, 544 µmol). The mixture was stirred at 20 °C for 16 h. The mixture was filtered, and the filtrate was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (86 mg, 181 µmol, 35 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.69 - 7.56 (m, 4H), 7.38 (br t, J=7.2 Hz, 2H), 7.22 - 7.16 (m, 1H), 7.08 (br d, J=8.4 Hz, 1H), 4.56 - 4.42 (m, 1H), 4.19 - 4.04 (m, 3H), 3.89 (s, 6H), 3.86 - 3.81 (m, 1H), 3.50 - 3.37 (m, 2H), 3.14 - 3.00 (m, 1H), 2.94 - 2.78 (m, 2H), 2.31 - 2.16 (m, 2H), 2.01 - 1.81 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

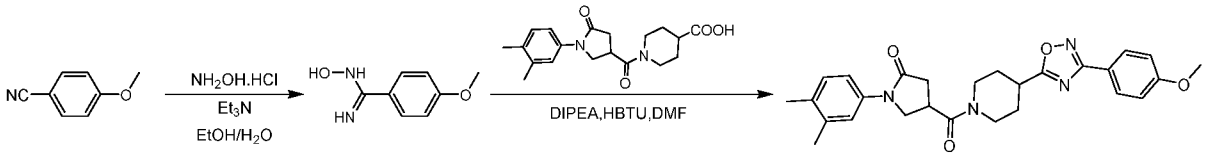
Example 19: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one.



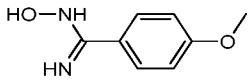
To a stirred solution of 1-[1-(3,4-dimethylphenyl)-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (200 mg, 581 µmol) in N,N-dimethylformamide (1.5 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (220 mg, 581 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (225 mg, 1.74 mmol, 304 µL), and N-hydroxy-3,4-dimethoxy-benzamidine (125 mg, 639 µmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in N,N-dimethylformamide (2 mL) then heated at 120 °C for 5 h. The mixture was cooled to 25 °C then diluted

with water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue that was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min), to give 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-(3,4-dimethylphenyl)pyrrolidin-2-one (7 mg, 15 µmol, 3 %) as a pink solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.66 (br d, J=8.2 Hz, 1H), 7.58 (s, 1H), 7.36 (s, 1H), 7.27 (br d, J=8.2 Hz, 1H), 7.16 - 7.04 (m, 2H), 4.49 (br d, J=8.4 Hz, 1H), 4.18 - 3.98 (m, 3H), 3.93 - 3.77 (m, 7H), 3.48 - 3.36 (m, 2H), 3.12 - 2.97 (m, 1H), 2.92 - 2.78 (m, 2H), 2.32 - 2.14 (m, 8H), 2.01 - 1.79 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.4.

Example 20: 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one.

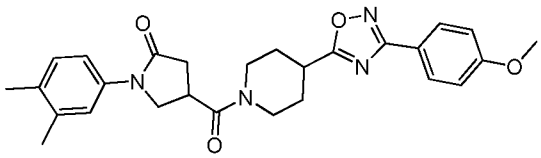


Step 1: Preparation of N-hydroxy-4-methoxybenzimidamide.



To a stirred solution of 4-methoxybenzonitrile (2.0 g, 15.02 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (2.09 g, 30.0mmol) and triethylamine (3.04 g, 30.0mmol, 4.16 mL) and water (2 mL), then the mixture was heated to 70 ℃ for 15h. The mixture was treated with water (20 mL) and extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with water (20 mL), saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude N-hydroxy-4-methoxybenzimidamide (2.50 g) as a white solid, which was used in the next step directly. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.61 - 7.48 (m, 2H), 6.98 - 6.85 (m, 2H), 3.81 (s, 3H).

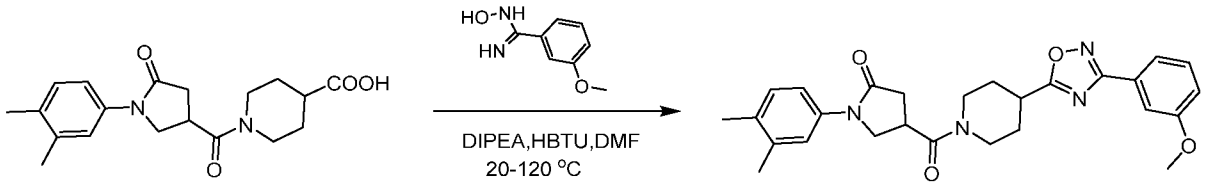
Step 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (250 mg, 726 µmol) and N-hydroxy-4-methoxybenzimidamide (120 mg, 726 µmol) in N,N-dimethylformamide (3 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (187 mg, 1.45 mmol, 253 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (275 mg, 726 µmol), After 15h at 15 ℃, the mixture was heated to 110 ℃ and stirred for 5 h. The reaction mixture was cooled and purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM

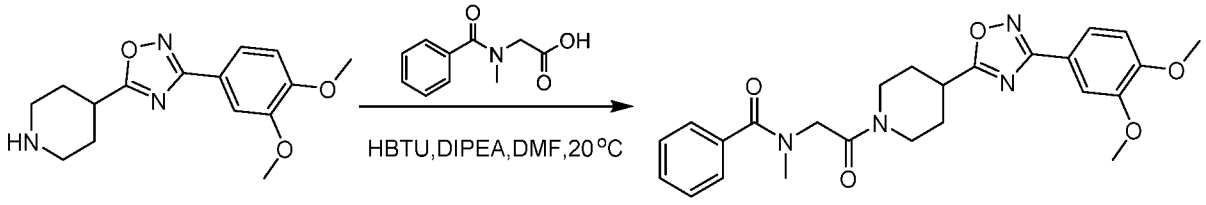
ammonium carbonate)-acetonitrile]; B%: 36%-66%,12 min) to give 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (101 mg, 213 µmol, 29 %) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (d, J=7.5 Hz, 2H), 7.36 (s, 1H), 7.27 (d, J=7.9 Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 7.04 (d, J=8.4 Hz, 2H), 4.47 (m., 1H), 4.19 - 3.96 (m, 3H), 3.86 (s, 3H), 3.84 - 3.78 (m, 1H), 3.42 (m, 2H), 3.16 - 2.98 (m, 1H), 2.93 - 2.74 (m, 2H), 2.37 - 2.10 (m, 8H), 2.02 - 1.78 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3.

Example 21: 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (200 mg, 581 µmol) in N,N-dimethylformamide (3 mL) was added N-hydroxy-3-methoxybenzimidamide (96 mg, 581 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (220 mg, 581 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (225 mg, 1.74 mmol, 304 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-60%,12 min) to give 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (80 mg, 168 µmol, 29 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.72-7.67 (m, 1H), 7.62 (s, 1H), 7.45-7.37 (m, 2H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.11-7.06 (m, 1H), 4.61-4.47 (m, 1H), 4.30 (dd, *J* = 7.3, 9.5 Hz, 1H), 3.91 (s, 5H), 3.64-3.54 (m, 1H), 3.46-3.30 (m, 2H), 3.21-3.05 (m, 1H), 3.03-2.92 (m, 1H), 2.89-2.79 (m, 1H), 2.28 (d, *J* = 13.1 Hz, 8H), 2.10-1.90 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3.

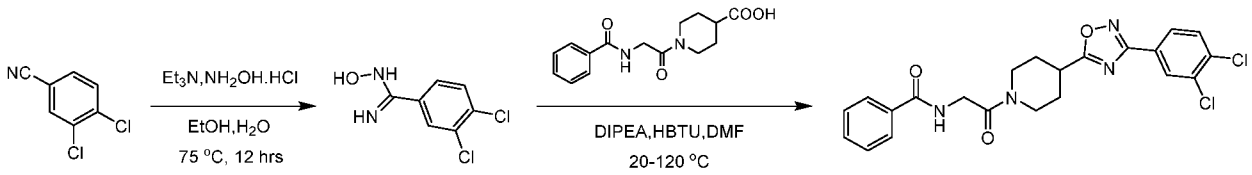
Example 22: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-N-methylbenzamide.



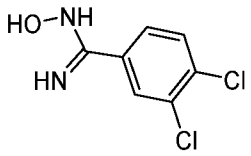
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-[benzoyl(methyl)amino]acetic acid (105 mg, 544 µmol). The mixture was stirred at 20 °C for 5 h, then cooled and purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[3-(3,4-

dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-N-methyl-benzamide (133 mg, 282 µmol, 54 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.59 (dd, *J*=1.8, 8.4 Hz, 1H), 7.49 - 7.32 (m, 5H), 7.27 (br d, *J*=6.8 Hz, 1H), 7.16 - 7.08 (m, 1H), 4.44 - 4.24 (m, 2H), 4.21 - 4.03 (m, 1H), 4.02 - 3.88 (m, 1H), 3.88 - 3.74 (m, 6H), 3.56 (br d, *J*=13.7 Hz, 1H), 3.48 - 3.33 (m, 1H), 3.11 - 2.77 (m, 5H), 2.20 - 1.99 (m, 2H), 1.86 (br t, *J*=12.6 Hz, 1H), 1.74 - 1.48 (m, 2H), 1.43 - 1.26 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 23: N-(2-(4-(3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

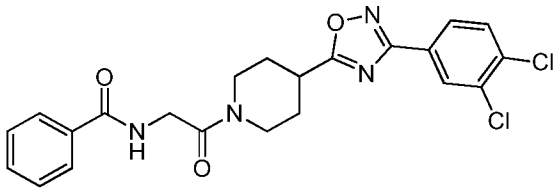


Step 1: Preparation of 3,4-dichloro-N-hydroxybenzimidamide.



To a stirred solution of 3,4-dichlorobenzonitrile (1.0 g, 5.81 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (807 mg, 11.6 mmol), triethylamine (1.18 g, 11.6 mmol, 1.61 mL) and water (2 mL). The mixture was heated at 75 ℃ for 5 h, then cooled to 20 ℃. Water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give 3,4-dichloro-N-hydroxybenzimidamide (1.20 g) as a white solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.69-7.58 (m, 2H), 5.95 (s, 2H).

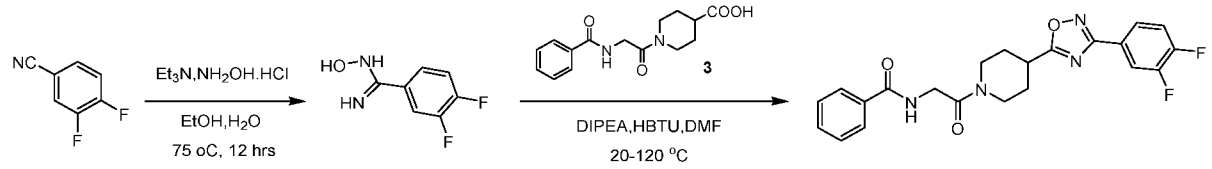
Step 2: Preparation of N-(2-(4-(3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



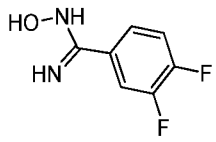
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (200 mg, 688.92 µmol) in N,N-dimethylformamide (4 mL) was added 3,4-dichloro-N-hydroxybenzimidamide (169 mg, 826 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (261 mg, 688.92 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (267 mg, 2.07 mmol, 360 µL). The mixture was stirred at 20 ℃ for 2 h, then heated at 120 ℃ for 2 h. The reaction mixture cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-

1-yl)-2-oxoethyl)benzamide (92 mg, 201 µmol, 29 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.09 (m, 1H), 7.85 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 2H), 7.39 (s, 4H), 7.25 (br. s., 1H), 4.43 (d, *J* = 13.7 Hz, 1H), 4.24 (d, *J* = 3.5 Hz, 2H), 3.84 (d, *J* = 14.1 Hz, 1H), 3.33-3.22 (m, 2H), 3.14-3.03 (m, 1H), 2.23-2.13 (m, 2H), 1.99-1.86 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.1.

Example 24: N-(2-(4-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

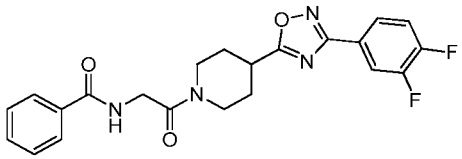


Step 1: Preparation of 3,4-difluoro-N-hydroxybenzimidamide.



To a stirred solution of 3,4-difluorobenzonitrile (1.0 g, 7.19 mmol) in ethanol (20 mL) were added hydroxylamine hydrochloride (999 mg, 14.4 mmol), triethylamine (1.46 g, 14.4 mmol, 1.99 mL), and water (2 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (30 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, then filtered, and concentrated in vacuo to give 3,4-difluoro-N-hydroxybenzimidamide (1.24 g) as a white solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 7.68 (ddd, *J* = 2.0, 8.0, 12.2 Hz, 1H), 7.55 (br. s., 1H), 7.50-7.39 (m, 1H), 5.92 (br. s., 2H).

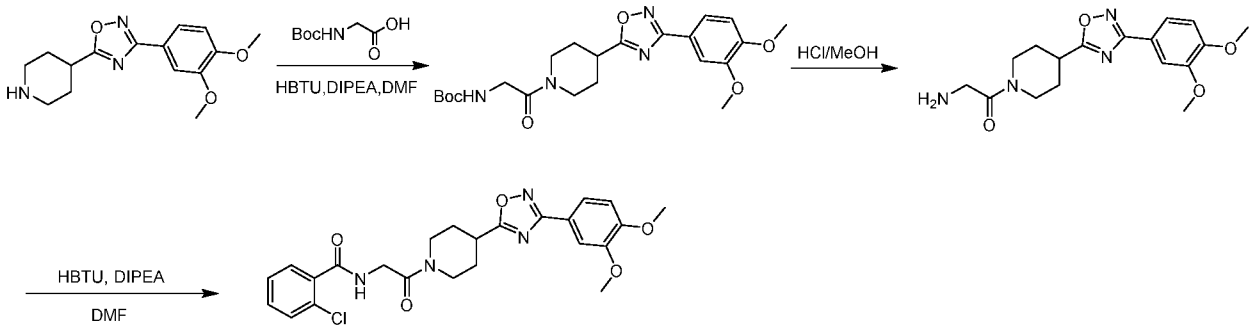
Step 2: Preparation of N-(2-(4-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



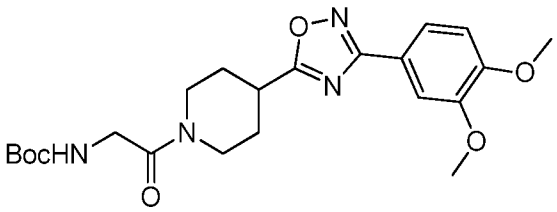
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (4 mL) were added 3,4-difluoro-N-hydroxybenzimidamide (85 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give N-(2-(4-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (50 mg, 118 µmol, 28 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.1 Hz, 4H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.42-7.35 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.43 (d, *J* = 13.7 Hz,

1H), 4.23 (d, *J* = 4.0 Hz, 2H), 3.84 (d, *J* = 13.7 Hz, 1H), 3.32-3.21 (m, 2H), 3.13-3.03 (m, 1H), 2.23-2.12 (m, 2H), 1.99-1.84 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 427.2.

Example 25: 2-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

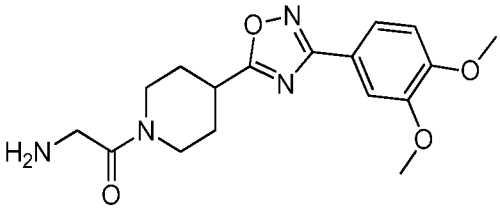


Step 1: Preparation of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (2.0 g, 6.91 mmol) in N,N-dimethylformamide (20 mL) was added 2-(tert-butoxycarbonylamino)acetic acid (1.21 g, 6.91 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (2.62 g, 6.91 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.68 g, 20.7 mmol, 3.62 mL). The mixture was stirred at 15 °C for 2 h. The reaction mixture was quenched by addition of water (20 mL), then the mixture was extracted with ethyl acetate (60 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude residue. Purification by chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) gave tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.60 g, 5.82 mmol, 84 %) as a brown solid that was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 447.2.

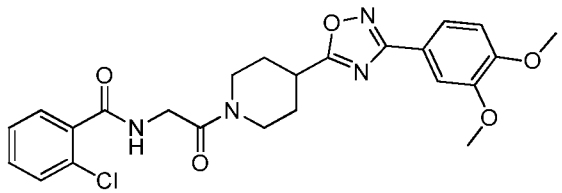
Step 2: Preparation of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone.



To a stirred solution of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.50 g, 5.60 mmol) in methanol (10 mL) was added methanolic hydrogen

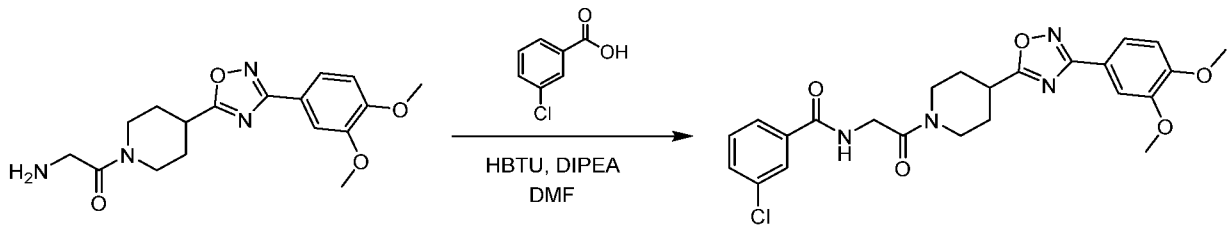
chloride solution (4M, 30 mL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated to give crude product. A part of crude product (0.1 g) was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (32 mg) for analysis. The remaining crude 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (1.90 g, 5.49 mmol, 98 %), obtained as a brown solid, was used directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.67 (m, 1H), 7.58 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 3.98 (d, J = 7.2 Hz, 6H), 3.84 (d, J = 12.0 Hz, 1H), 3.54 (s, 2H), 3.34-3.21 (m, 2H), 3.08 (d, J = 12.3 Hz, 1H), 2.21 (d, J = 13.1 Hz, 2H), 1.98 (d, J = 9.4 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 347.1.

Step 3: Preparation of 2-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (185 mg, 537 µmol) in N,N-dimethylformamide (3 mL) was added 2-chlorobenzoic acid (70 mg, 447 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (169 mg, 447 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (231 mg, 1.79 mmol, 312 µL). The mixture was stirred at 20 °C for 2 h, then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 26%-56%,12 min) to give 2-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (124 mg, 256 µmol, 57 %) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (ddd, *J* = 1.9, 6.3, 7.9 Hz, 2H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.49-7.33 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 13.6 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 2H), 3.99 (d, *J* = 7.8 Hz, 6H), 3.92 (d, *J* = 13.8 Hz, 1H), 3.41-3.30 (m, 2H), 3.16 (t, *J* = 10.9 Hz, 1H), 2.33-2.21 (m, 2H), 2.11-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.2.

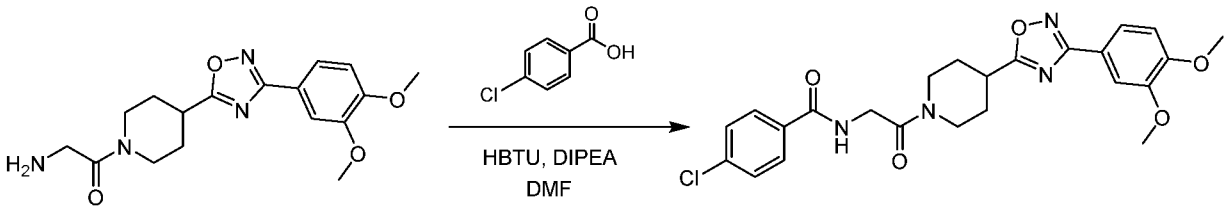
Example 26: 3-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



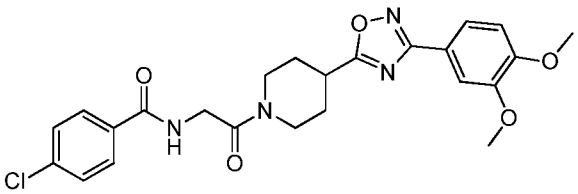
To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (185 mg, 537 µmol) in N,N-dimethylformamide (3 mL) were added 3-chlorobenzoic acid (70 mg, 447 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (169 mg, 447

μmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (231 mg, 1.79 mmol, 312 μL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 26%-56%,12 min) to give 3-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (126 mg, 261 μmol, 58 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.89-7.86 (m, 1H), 7.72 (d, *J* = 2.0 Hz, 2H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.54-7.50 (m, 1H), 7.45-7.39 (m, 1H), 7.34 (br. s., 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 4.53 (d, *J* = 14.3 Hz, 1H), 4.31 (d, *J* = 3.9 Hz, 2H), 3.98 (d, *J* = 7.4 Hz, 6H), 3.96-3.87 (m, 1H), 3.41-3.30 (m, 2H), 3.18 (t, *J* = 10.9 Hz, 1H), 2.33-2.22 (m, 2H), 2.10-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

Example 27: 4-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

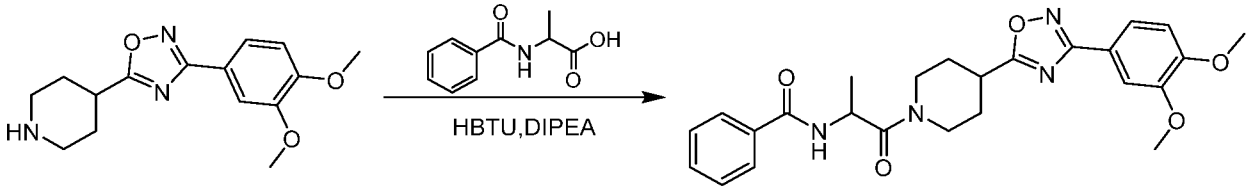


Step 1: Preparation of 4-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



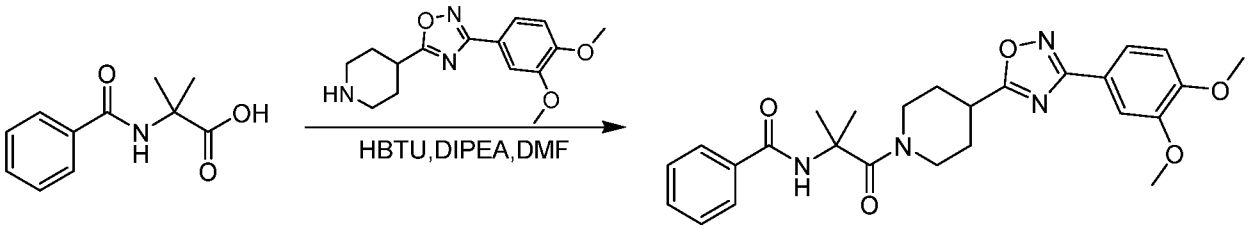
To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (185 mg, 536.5 μmol) in N,N-dimethylformamide (3 mL) were added 4-chlorobenzoic acid (70 mg, 447 μmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (169 mg, 447 μmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (231 mg, 1.79 mmol, 312 μL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 4-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (144 mg, 294 μmol, 66 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.71 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.33 (br. s., 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 14.2 Hz, 1H), 4.31 (d, *J* = 3.9 Hz, 2H), 3.98 (d, *J* = 7.3 Hz, 6H), 3.92 (d, *J* = 13.7 Hz, 1H), 3.41-3.30 (m, 2H), 3.17 (t, *J* = 10.7 Hz, 1H), 2.34-2.21 (m, 2H), 2.10-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.2.

Example 28: N-(1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide.



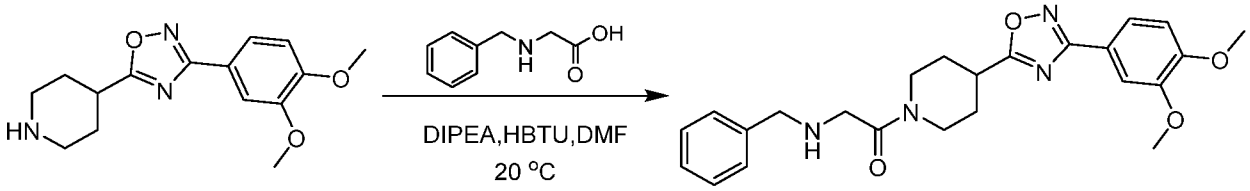
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL), and 2-benzamidopropanoic acid (105 mg, 544 µmol). The mixture was stirred at 20 °C for 7 h, then the crude product was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile; B%: 35%-60%,12 min] to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide (52 mg, 112 µmol, 22 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.63 (br dd, J=7.3, 16.1 Hz, 1H), 7.88 (br d, J=7.3 Hz, 2H), 7.66 - 7.34 (m, 5H), 7.11 (br d, J=7.9 Hz, 1H), 4.97 (br d, J=6.0 Hz, 1H), 4.45 - 4.22 (m, 1H), 4.08 - 3.94 (m, 1H), 3.82 (s, 6H), 3.42 (br t, J=10.7 Hz, 1H), 3.29 - 3.21 (m, 1H), 3.00 - 2.80 (m, 1H), 2.09 (br d, J=11.9 Hz, 2H), 1.87 - 1.56 (m, 1H), 1.29 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 29: N-(1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-methyl-1-oxopropan-2-yl)benzamide.



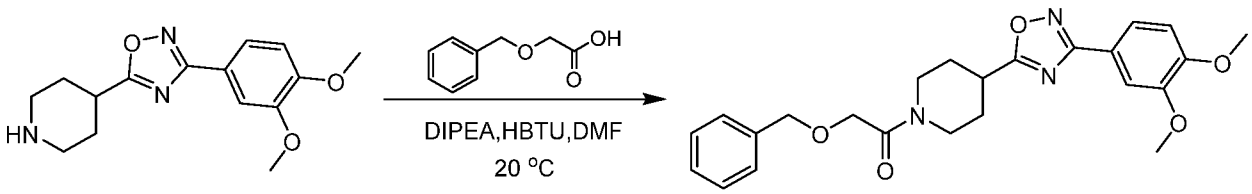
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-benzamido-2-methyl-propanoic acid (112 mg, 544 µmol). The mixture was stirred at 20 °C for 5 h. The crude product was purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 27%-57%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1,1-dimethyl-2-oxo-ethyl]benzamide (47 mg, 99 µmol, 19 %) as a pale yellow solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.88 - 7.81 (m, 2H), 7.62 (dd, J=2.0, 8.4 Hz, 1H), 7.57 - 7.51 (m, 2H), 7.49 - 7.42 (m, 2H), 7.06 (d, J=8.4 Hz, 1H), 4.61 - 4.45 (m, 2H), 3.88 (d, J=5.1 Hz, 6H), 3.13 (s, 3H), 2.08 (br s, 2H), 1.90 - 1.74 (m, 2H), 1.60 (s, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 477.1.

Example 30: 2-(benzylamino)-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone.



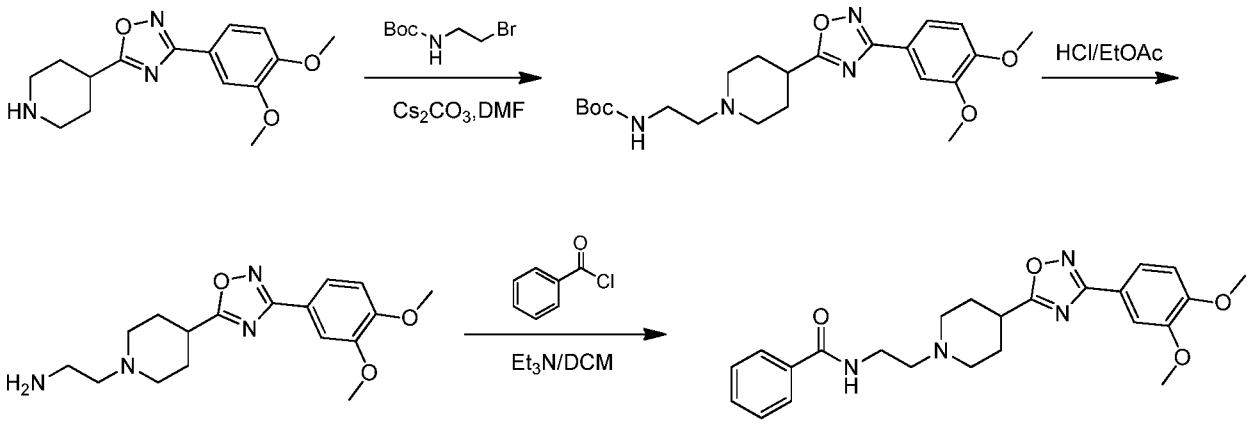
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (1.50 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL), and 2-(benzylamino)acetic acid (89 mg, 544 µmol). The mixture was stirred at 20 °C for 16 h and filtered, and the crude filtrate was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 2-(benzylamino)-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (48 mg, 110 µmol, 21 %) as a yellow solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.65 (dd, J=1.8, 8.2 Hz, 1H), 7.57 (d, J=1.8 Hz, 1H), 7.40 - 7.30 (m, 4H), 7.28 - 7.22 (m, 1H), 7.06 (d, J=8.4 Hz, 1H), 4.45 (br d, J=13.7 Hz, 1H), 3.94 - 3.83 (m, 7H), 3.78 (s, 2H), 3.57 - 3.44 (m, 2H), 3.40 - 3.33 (m, 1H), 3.27 - 3.20 (m, 1H), 3.01 (t, J=11.2 Hz, 1H), 2.17 (dd, J=2.8, 13.3 Hz, 2H), 1.93 - 1.73 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 437.3.

Example 31: 2-(benzyloxy)-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone.

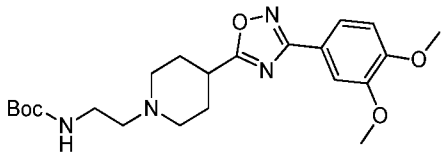


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL), and 2-benzyloxyacetic acid (90 mg, 544 µmol, 77 µL). The mixture was stirred at 20 °C for 5 h. The crude product was purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 32%-62%,12 min) to give 2-benzyloxy-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (68 mg, 157 µmol, 30 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 7.60 (dd, J=1.9, 8.3 Hz, 1H), 7.48 (d, J=1.9 Hz, 1H), 7.40 - 7.35 (m, 4H), 7.34 - 7.26 (m, 1H), 7.14 (d, J=8.4 Hz, 1H), 4.54 (s, 2H), 4.33 (br d, J=13.2 Hz, 1H), 4.25 (br d, J=7.8 Hz, 2H), 3.93 - 3.78 (m, 7H), 3.43 (tt, J=3.9, 11.0 Hz, 1H), 3.22 (br t, J=11.7 Hz, 1H), 2.90 (br t, J=11.7 Hz, 1H), 2.17 - 2.04 (m, 2H), 1.88 - 1.59 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 438.3.

Example 32: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]benzamide

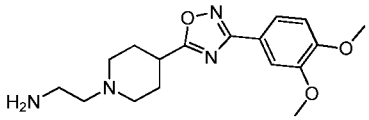


Step 1: Preparation of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)carbamate



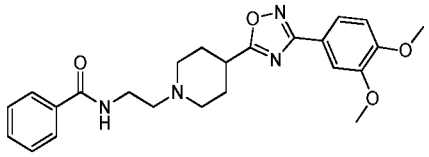
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (750 mg, 2.59 mmol) in N,N-dimethylformamide (1 mL) were added cesium carbonate (844 mg, 2.59 mmol) and tert-butyl N-(2-bromoethyl)carbamate (871 mg, 3.89 mmol). The mixture was stirred at 50 °C for 16 h. The reaction mixture was cooled then extracted with ethyl acetate (5 mL x 2). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]carbamate (1.30 g) which was used directly without further purification. LCMS (ESI) m/z = 433.3 $[M+H]^+$.

Step 2: Preparation of 2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanamine



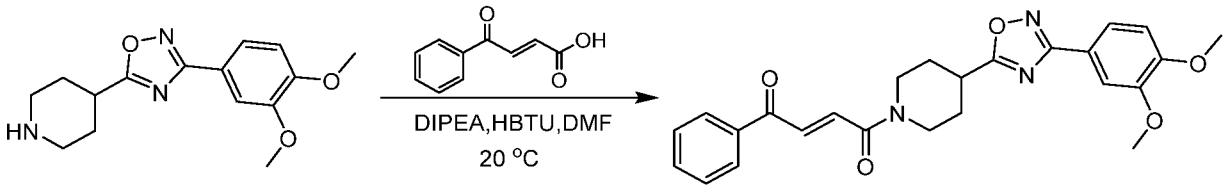
A solution of tert-butyl N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]carbamate (1.0 g, 2.31 mmol) in hydrochloric acid/ethyl acetate (4M, 25 mL) was stirred at 25 °C for 30 mins. The reaction mixture was concentrated under reduced pressure to give 2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanamine (750 mg) which was used directly without further purification. LCMS (ESI) m/z = 333.1 $[M+H]^+$.

Step 3: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide



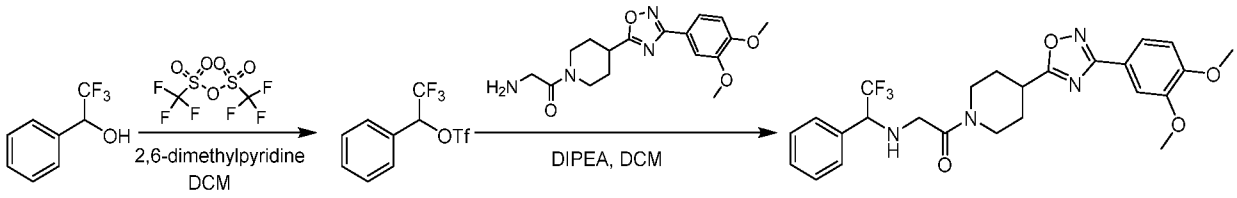
To a mixture of 2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanamine (200 mg, 602 µmol) and benzoyl chloride (109 mg, 782 µmol, 90 µL) in dichloromethane (1 mL) was added triethylamine (182 mg, 1.81 mmol, 250 µL) at 0 ℃. The mixture was stirred at 20 ℃ for 5 h, then purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-50%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]benzamide (25 mg, 56 µmol, 9 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.86 - 7.79 (m, 2H), 7.66 (dd, J=1.8, 8.4 Hz, 1H), 7.58 (d, J=1.8 Hz, 1H), 7.55 - 7.43 (m, 3H), 7.07 (d, J=8.6 Hz, 1H), 3.89 (s, 6H), 3.58 (t, J=6.8 Hz, 2H), 3.16 - 3.09 (m, 2H), 2.67 (t, J=6.8 Hz, 2H), 2.37 - 2.29 (m, 2H), 2.18 (br d, J=11.2 Hz, 2H), 2.07 - 1.91 (m, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 437.3.

Example 33: (E)-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-4-phenylbut-2-ene-1,4-dione

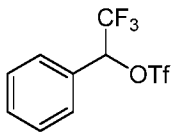


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (250 mg, 864 µmol) in N,N-dimethylformamide (4 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (327 mg, 864 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (335 mg, 2.59 mmol, 452 µL) and (E)-4-oxo-4-phenyl-but-2-enoic acid (152 mg, 864 µmol). The mixture was stirred at 20 ℃ for 5 h, then the crude mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give (E)-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-4-phenyl-but-2-ene-1,4-dione (118 mg, 251 µmol, 29 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.03 (br d, J=7.3 Hz, 2H), 7.75 (d, J=15.4 Hz, 1H), 7.71 - 7.65 (m, 1H), 7.61 - 7.53 (m, 3H), 7.51 - 7.43 (m, 2H), 7.11 (d, J=8.4 Hz, 1H), 4.41 (br d, J=13.2 Hz, 1H), 4.11 - 3.99 (m, 1H), 3.88 - 3.77 (m, 6H), 3.54 - 3.34 (m, 2H), 3.02 (br t, J=11.2 Hz, 1H), 2.15 (br d, J=13.0 Hz, 2H), 1.88 - 1.67 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 448.2.

Example 34: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-((2,2,2-trifluoro-1-phenylethyl)amino)ethanone.

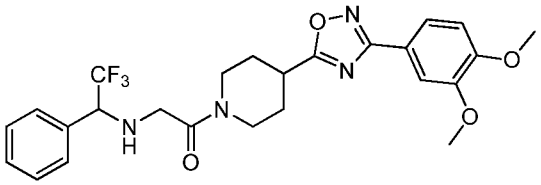


Step 1: Preparation of 2,2,2-trifluoro-1-phenylethyl trifluoromethanesulfonate.



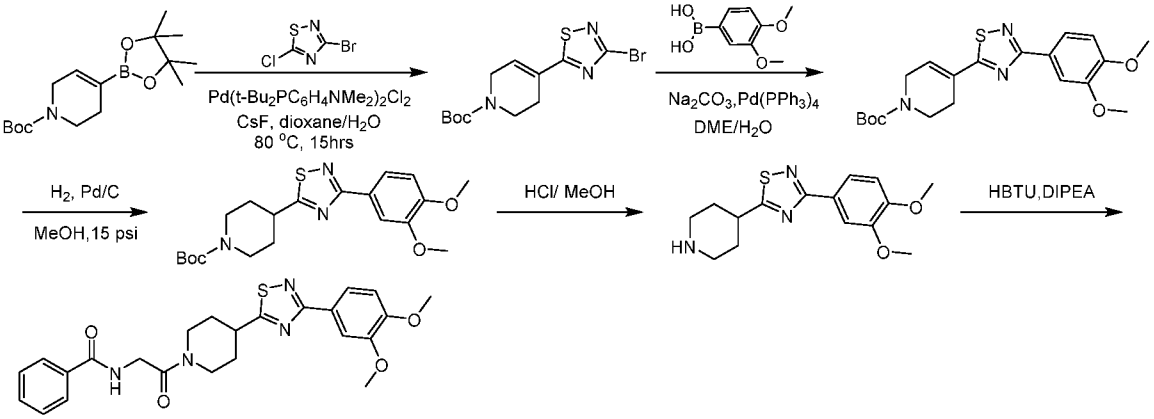
To a stirred solution of 2,2,2-trifluoro-1-phenylethanol (100 mg, 568 µmol, 76 µL) in dichloromethane (2 mL) were added 2,6-dimethylpyridine (121 mg, 1.14 mmol, 132 µL) and trifluoromethanesulfonic anhydride (288 mg, 1.02 mmol, 168 µL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then diluted with dichloromethane (5 mL) and water (5 mL), and the phases separated. The aqueous phase was extracted with dichloromethane (15 mL x 2), then the combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 2,2,2-trifluoro-1-phenylethyl trifluoromethanesulfonate (380 mg) as a brown oil. This material was used directly without further purification.

Step 2: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-((2,2,2-trifluoro-1-phenylethyl)amino)ethanone

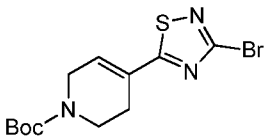


To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (120 mg, 346 µmol) in dichloromethane (2.5 mL) was added 2,2,2-trifluoro-1-phenylethyl trifluoromethanesulfonate (213 mg, 692.88 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (179 mg, 1.39 mmol, 242 µL). The mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-((2,2,2-trifluoro-1-phenylethyl)amino)ethanone (52 mg, 101 µmol, 29 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.63-7.56 (m, 1H), 7.51-7.37 (m, 6H), 7.14 (d, J = 8.4 Hz, 1H), 4.53-4.43 (m, 1H), 4.30 (br. s., 1H), 3.84 (s, 6H), 3.71 (d, J = 10.2 Hz, 1H), 3.44-3.36 (m, 2H), 3.18-3.07 (m, 1H), 2.99 (d, J = 5.5 Hz, 1H), 2.87 (br. s., 1H), 2.08 (d, J = 12.5 Hz, 2H), 1.75-1.56 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.3.

Example 35: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

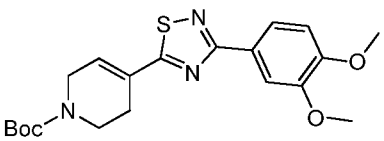


Step 1: Preparation of tert-butyl 4-(3-bromo-1,2,4-thiadiazol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate



A mixture of 3-bromo-5-chloro-1,2,4-thiadiazole (500 mg, 2.51 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (931 mg, 3.01 mmol), cesium fluoride (762 mg, 5.02 mmol, 185 µL) in dioxane (3.5 mL) was degassed and purged with nitrogen 3 times, then 4-ditert-butylphosphanyl-N,N-dimethyl-aniline;dichloropalladium (88 mg, 125.50 µmol, 88 µL, 0.05 eq) was added. The mixture was stirred at 80 °C for 2 h under an atmosphere of nitrogen. The mixture was cooled to 25 °C and concentrated in vacuo at 40 °C. The residue was poured into water (15 mL), the aqueous phase was extracted with dichloromethane (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude product. The crude product was purified by chromatography (silica, petroleum ether/ ethyl acetate (from 20/1 to 2/1) to give tert-butyl 4-(3-bromo-1,2,4-thiadiazol-5-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (260 mg, 750.92 µmol, 30 %) as a yellow oil. LCMS (ESI) m/z: 368.3 $[M+Na]^+$.

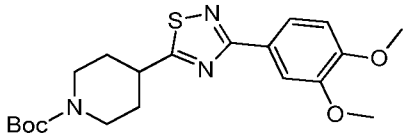
Step 2: Preparation of tert-butyl 4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate



A mixture of tert-butyl 4-(3-bromo-1,2,4-thiadiazol-5-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (260 mg, 751 µmol), (3,4-dimethoxyphenyl)boronic acid (163 mg, 901 µmol), and sodium carbonate (103 mg, 976 µmol) in water (400 µL) and dimethoxyethane(1.2 mL) was degassed and purged with nitrogen 3 times, and then tetrakis(triphenylphosphine)palladium(0) (17 mg, 15 µmol) was added. The mixture was stirred at 100 °C for 6 h under a nitrogen atmosphere. The mixture was cooled to 25 °C and concentrated in vacuo at 40 °C. The residue was poured into water (5 mL), and the aqueous phase was extracted with

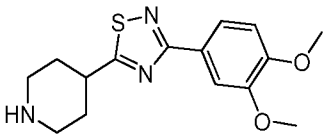
dichloromethane (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude product. The crude residue was purified by prep-TLC (silica, petroleum ether/ ethyl acetate=3:1) to give tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (122 mg, 303 µmol, 40 %) as a yellow oil. LCMS (ESI) m/z: 404.1 $[M+H]^+$.

Step 3: Preparation of tert-butyl 4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)piperidine-1-carboxylate



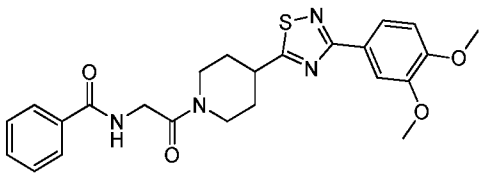
To a stirred solution of tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (100 mg, 248 µmol) in methanol (10 mL) was added palladium(0) on carbon (10%, 150 mg) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen three times. The mixture was stirred under hydrogen (15 psi) at 20 °C for 48 h. The reaction mixture was filtered and concentrated under reduced pressure to give tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]piperidine-1-carboxylate (79 mg) that was used into the next step without further purification. LCMS (ESI) m/z: 406.2 $[M+H]^+$.

Step 4: Preparation of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-thiadiazole



A solution of tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]piperidine-1-carboxylate (79 mg, 195 µmol) in hydrochloric acid/ethyl acetate (4M, 15 mL) was stirred at 20 °C for 3 h. The reaction mixture was concentrated in vacuo to give 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-thiadiazole (65 mg) that was used into the next step without further purification.

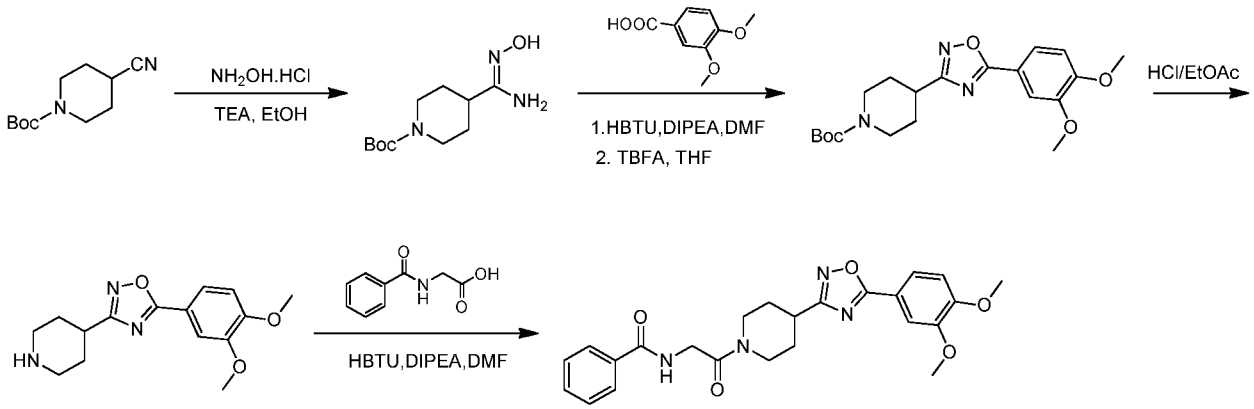
Step 5: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide



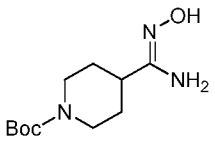
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-thiadiazole (65 mg, 214 µmol) and 2-benzamidoacetic acid (46 mg, 257 µmol) in N,N-dimethylformamide (1 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (81 mg, 214 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (69 mg, 536 µmol, 93 µL). After 2 h, the reaction mixture purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 26%-56%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (10 mg, 22 µmol, 10 %) as a yellow solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.92 - 7.82 (m, 4H), 7.59 - 7.52 (m, 1H), 7.51 - 7.44 (m, 2H), 7.06 (d, J=8.4 Hz, 1H),

4.61 (d, J=12.9 Hz, 1H), 4.41 - 4.24 (m, 2H), 4.11 (br d, J=14.9 Hz, 1H), 3.98 - 3.84 (m, 6H), 3.63 - 3.52 (m, 1H), 3.39 (br t, J=11.7 Hz, 1H), 2.99 (br t, J=11.6 Hz, 1H), 2.35 - 2.20 (m, 2H), 2.03 - 1.74 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 467.2.

Example 36: N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)-2-oxoethyl)benzamide

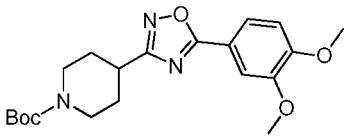


Step 1: Preparation of (Z)-tert-butyl 4-(N'-hydroxycarbamimidoyl)piperidine-1-carboxylate



A mixture of tert-butyl 4-cyanopiperidine-1-carboxylate (2.0 g, 9.51 mmol), hydroxylamine hydrochloride (1.32 g, 19.0 mmol), and triethylamine (1.92 g, 19.0 mmol, 2.64 mL) in ethanol (20 mL) and water (2 mL) was heated at 75 °C for 16 h. The reaction mixture was cooled, diluted with water (10 mL), and extracted with ethyl acetate (15 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl 4-[(Z)-N'-hydroxycarbamimidoyl]piperidine-1-carboxylate (1.90 g) which was used directly without further purification. ^{1}H NMR (400MHz, METHANOL-d4) δ = 4.15 (br d, J=13.3 Hz, 2H), 2.78 (br s, 2H), 2.27 (tt, J=3.6, 12.1 Hz, 1H), 1.84 - 1.70 (m, 2H), 1.62 (dq, J=4.3, 12.6 Hz, 2H), 1.53 - 1.39 (m, 9H).

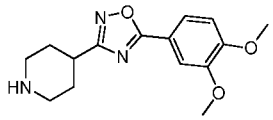
Step 2: Preparation of tert-butyl 4-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carboxylate



To a stirred solution of tert-butyl 4-[(Z)-N'-hydroxycarbamimidoyl]piperidine-1-carboxylate (750 mg, 3.08 mmol) in N,N-dimethylformamide (5 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.17 g, 3.08 mmol), N-ethyl-N-(propan-2-yl)propan-2-amine (1.19 g, 9.24 mmol, 1.61 mL) and 3,4-dimethoxybenzoic acid (561 mg, 3.08 mmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic phases were washed with saturated aqueous sodium

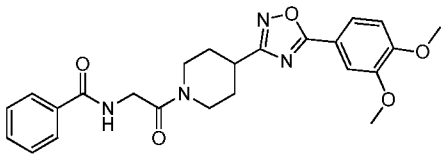
chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. Tetrahydrofuran (500 µL) and tetrabutylammonium fluoride / tetrahydrofuran (1 M, 4.62 mL) were added to the residue, and the resulting mixture was heated at 50 °C for 16 h. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=5:1) to give tert-butyl 4-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylate (970 mg, 2.49 mmol, 81 %) as a white solid. LCMS (ESI) m/z: 412.3 $[M+Na]^+$ = 334.2.

Step 3: Preparation of 5-(3,4-dimethoxyphenyl)-3-(piperidin-4-yl)-1,2,4-oxadiazole



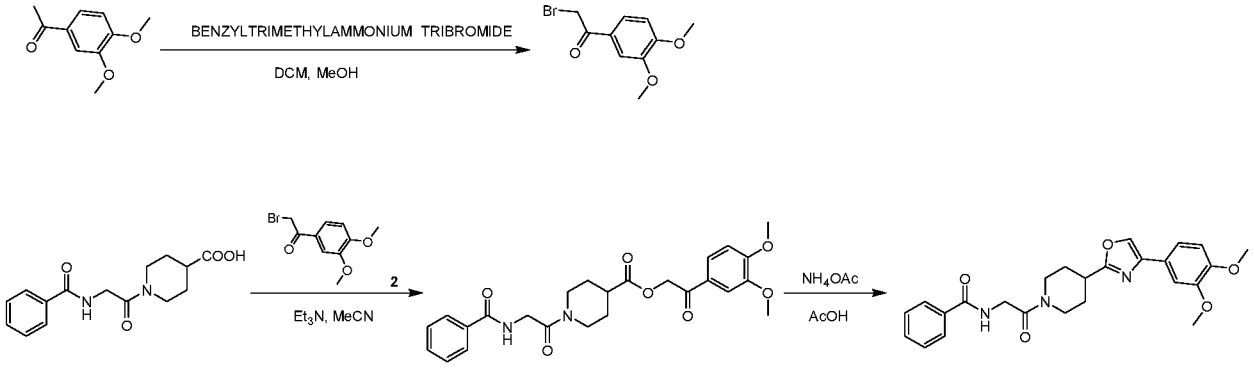
A solution of tert-butyl 4-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylate (750 mg, 1.93 mmol) in hydrochloric acid / ethyl acetate (4M, 30 mL) was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 5-(3,4-dimethoxyphenyl)-3-(4-piperidyl)-1,2,4-oxadiazole (683 mg) that was used directly without further purification.

Step 4: Preparation of N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)-2-oxoethyl)benzamide

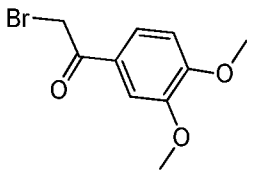


To a stirred solution of 5-(3,4-dimethoxyphenyl)-3-(4-piperidyl)-1,2,4-oxadiazole (180 mg, 622 µmol) in N,N-dimethylformamide (2 mL) were added 2-benzamidoacetic acid (111 mg, 622 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (235 mg, 622 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (241 mg, 1.87 mmol, 325 µL). The mixture was stirred at 20 °C for 16 h. The crude product was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (169 mg, 376 µmol, 60 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.55 (br t, J=5.4 Hz, 1H), 7.87 (br d, J=7.5 Hz, 2H), 7.70 (br d, J=8.4 Hz, 1H), 7.57 - 7.41 (m, 4H), 7.17 (br d, J=8.4 Hz, 1H), 4.34 (br d, J=12.3 Hz, 1H), 4.16 (br d, J=4.2 Hz, 2H), 3.97 (br d, J=13.0 Hz, 1H), 3.90 - 3.74 (m, 6H), 3.27 - 3.09 (m, 2H), 2.88 (br t, J=11.6 Hz, 1H), 2.03 (br t, J=11.8 Hz, 2H), 1.75 (br d, J=10.4 Hz, 1H), 1.59 (br d, J=9.9 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 451.2.

Example 37: N-(2-(4-(4-(3,4-dimethoxyphenyl)oxazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

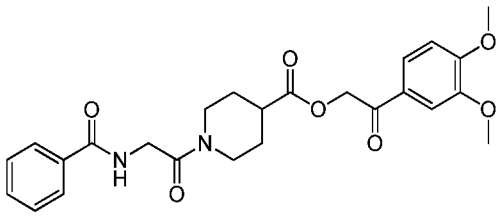


Step 1: Preparation of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone.



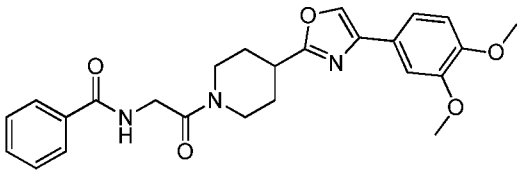
To a stirred solution of 1-(3,4-dimethoxyphenyl)ethanone (1.0 g, 5.55 mmol) in dichloromethane (6 mL) and methanol (3 mL) was added benzyltrimethylammonium tribromide (2.16 g, 5.55 mmol). After 16 h, the mixture was diluted with dichloromethane (80 mL) and water (40 mL), the organic layer was separated, and the water phase was extracted with dichloromethane (80 mL x 2). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (1.20 g, 4.63 mmol, 83 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.57 (d, *J*=2.1 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 4.43 (s, 2H), 3.98 (d, *J*=8.4 Hz, 6H).

Step 2: Preparation of 2-(3,4-dimethoxyphenyl)-2-oxoethyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



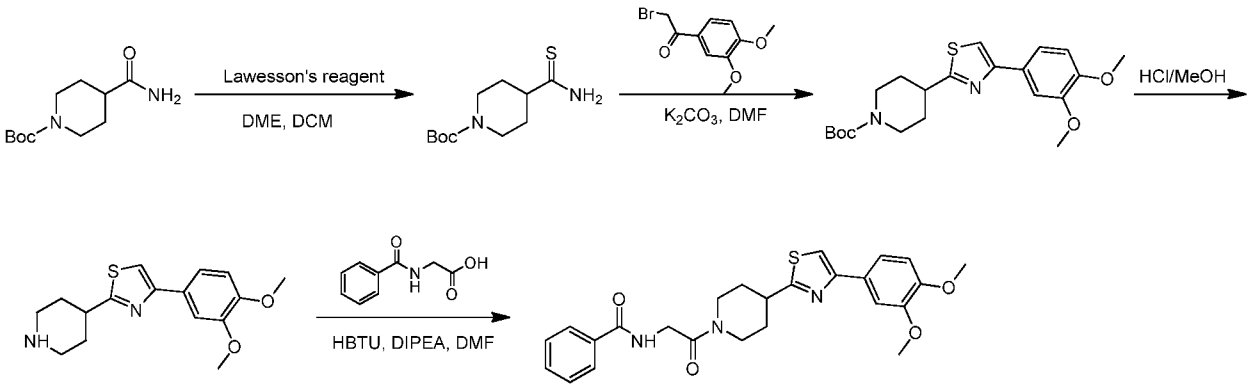
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (200 mg, 689 µmol) in acetonitrile (6 mL) was added 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (214 mg, 826 µmol) and triethylamine (209 mg, 2.07 mmol, 286 µL) under nitrogen. The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated in vacuo to give 2-(3,4-dimethoxyphenyl)-2-oxoethyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (233 mg, 497 µmol, 72 %) as a yellow solid. This was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 469.3.

Step 3: Preparation of N-(2-(4-(4-(3,4-dimethoxyphenyl)oxazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

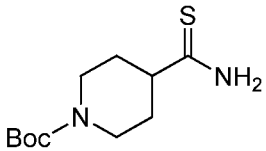


To a stirred solution of 2-(3,4-dimethoxyphenyl)-2-oxoethyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (180 mg, 384 µmol) in acetic acid (8 mL) was added ammonium acetate (148 mg, 1.92 mmol) under nitrogen, then the mixture was heated at 100 °C for 16 h. The reaction mixture was concentrated in vacuo to give crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-55%,12 min) to give N-(2-(4-(4-(3,4-dimethoxyphenyl)oxazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide (55 mg, 120 µmol, 31 %) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.84 (m, 2H), 7.80 (s, 1H), 7.58 - 7.44 (m, 3H), 7.41 - 7.35 (m, 1H), 7.28 - 7.26 (m, 2H), 6.92 (d, *J*=8.9 Hz, 1H), 4.58 - 4.47 (m, 1H), 4.32 (d, *J*=3.9 Hz, 2H), 3.99 - 3.88 (m, 7H), 3.37 - 3.06 (m, 3H), 2.28 - 2.13 (m, 2H), 2.07 - 1.89 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 450.3.

Example 38: N-(2-(4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

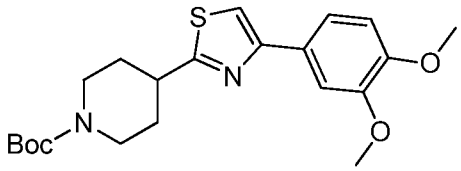


Step 1: Preparation of tert-butyl 4-carbamothioylpiperidine-1-carboxylate.



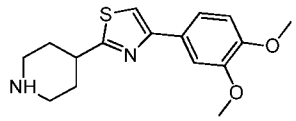
To a stirred solution of tert-butyl 4-carbamoylpiperidine-1-carboxylate (1.0 g, 4.38 mmol) in a mixture of dimethoxyethane (16 mL) and dichloromethane (8 mL) was added 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (885 mg, 2.19 mmol). The mixture was stirred at 20 °C for 16 h, then concentrated in vacuo. The residue dissolved in ethyl acetate and washed with saturated aqueous potassium carbonate (10 mL x 2). The organic layer was separated, dried over sodium sulfate and concentrated in vacuo to give tert-butyl 4-carbamothioylpiperidine-1-carboxylate (1.0 g) as a yellow solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.45 (br. s., 1H), 9.17 (br. s., 1H), 4.14-3.98 (m, 2H), 3.91-3.79 (m, 1H), 2.80-2.66 (m, 2H), 1.74-1.55 (m, 4H), 1.46 (s, 9H).

Step 2: Preparation of tert-butyl 4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidine-1-carboxylate.



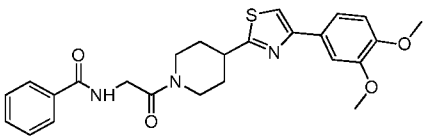
To a stirred solution of tert-butyl 4-carbamothioylpiperidine-1-carboxylate (200 mg, 818.5 µmol) in N,N-dimethylformamide (5 mL) was added 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (212 mg, 818.50 µmol) and potassium carbonate (124 mg, 900 µmol). The mixture was stirred at 110 ℃ for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give tert-butyl 4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidine-1-carboxylate (300 mg, 742 µmol, 91 %) as a yellow solid. This was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 405.3.

Step 3: Preparation of 4-(3,4-dimethoxyphenyl)-2-(piperidin-4-yl)thiazole.



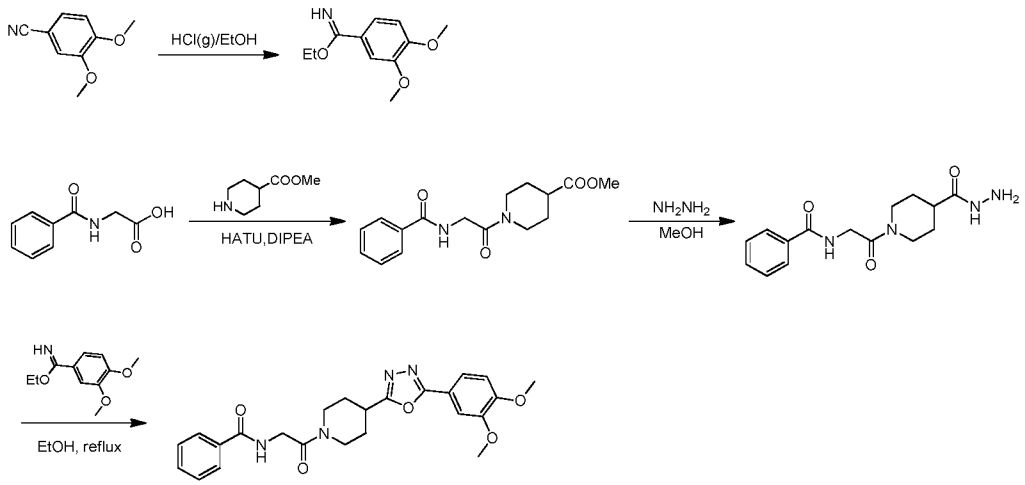
To a stirred solution of tert-butyl 4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidine-1-carboxylate (300 mg, 742 µmol) in methanol (3 mL) was added methanolic hydrogen chloride solution (4M, 10 mL). The mixture was stirred at 20 ℃ for 1 h. The reaction mixture was concentrated under reduced pressure to provide 4-(3,4-dimethoxyphenyl)-2-(piperidin-4-yl)thiazole (260 mg) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 305.1.

Step 4: Preparation of N-(2-(4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

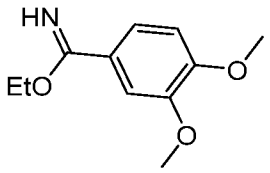


To a stirred solution of 4-(3,4-dimethoxyphenyl)-2-(piperidin-4-yl)thiazole (203 mg, 670 µmol) in N,N-dimethylformamide (4 mL) were added 2-benzamidoacetic acid (100 mg, 558 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (211 mg, 558 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (288 mg, 2.23 mmol, 389 µL). T he mixture was stirred at 20 ℃ for 16 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%, 12 min) to give N-(2-(4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide (111 mg, 239 µmol, 43 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2H), 7.57-7.42 (m, 5H), 7.39 (br. s., 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 4.70 (d, *J* = 13.6 Hz, 1H), 4.40-4.26 (m, 2H), 3.97 (d, *J* = 19.7 Hz, 7H), 3.43-3.26 (m, 2H), 3.05-2.95 (m, 1H), 2.37-2.23 (m, 2H), 1.98-1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 466.3.

Example 39: N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

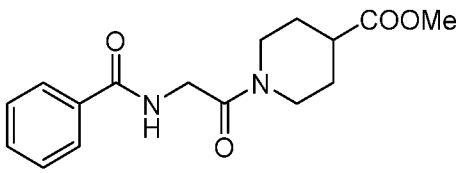


Step 1: Ethyl 3,4-dimethoxybenzimidate.



To a stirred solution of 3,4-dimethoxybenzonitrile (2.0 g, 12.3 mmol) in dry ethanol (50 mL) was added dropwise acetyl chloride (7.70 g, 98.1 mmol, 7.0 mL) at 0 ℃ , after complete addition, the mixture was warmed to 15 ℃ and stirred for 30 h. The reaction was concentrated in vacuo, and then saturated hydrochloric acid in ethanol (50 mL) was added. After 5h, the mixture was concentrated in vacuo to give crude ethyl 3,4-dimethoxybenzenecarboximidate (2.50 g) as a light yellow solid, which was used in next step directly.

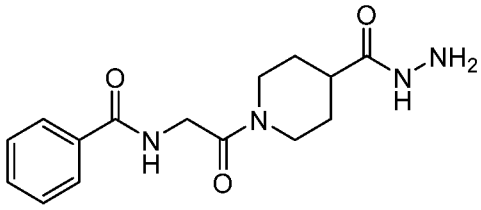
Step 2: Methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



To a stirred solution of 2-benzamidoacetic acid (3.0 g, 16.7 mmol) and methyl piperidine-4-carboxylate (3.60 g, 25.1 mmol) in dry N,N-dimethylformamide (50 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (4.33 g, 33.5 mmol, 5.9 mL) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (7.0 g, 18.4 mmol) at 0 ℃, then the mixture was warmed to 15 ℃ and stirred for 15h. The mixture was poured into ice water (100 mL) then extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with 1N hydrochloric acid (30 mL x 2), saturated aqueous sodium carbonate (30 mL), and saturated aqueous sodium chloride solution (30 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give a crude methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (5.30 g) as a brown oil, which was used in next step directly. ^{1}H

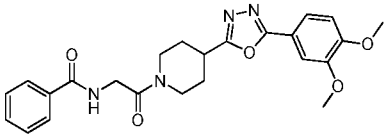
NMR (400 MHz, Methanol-d4) δ 7.87 (d, J=7.1 Hz, 2H), 7.58 - 7.51 (m, 1H), 7.49 - 7.40 (m, 2H), 4.39 - 4.29 (m, 1H), 4.28 - 4.17 (m, 2H), 3.96 - 3.84 (m, 1H), 3.68 (s, 3H), 3.28 - 3.17 (m, 1H), 2.96 - 2.86 (m, 1H), 2.69 – 2.62 (m, 1H), 2.00 - 1.88 (m, 2H), 1.78 - 1.51 (m, 2H).

Step 3: N-(2-(4-(hydrazinecarbonyl)piperidin-1-yl)-2-oxoethyl)benzamide.



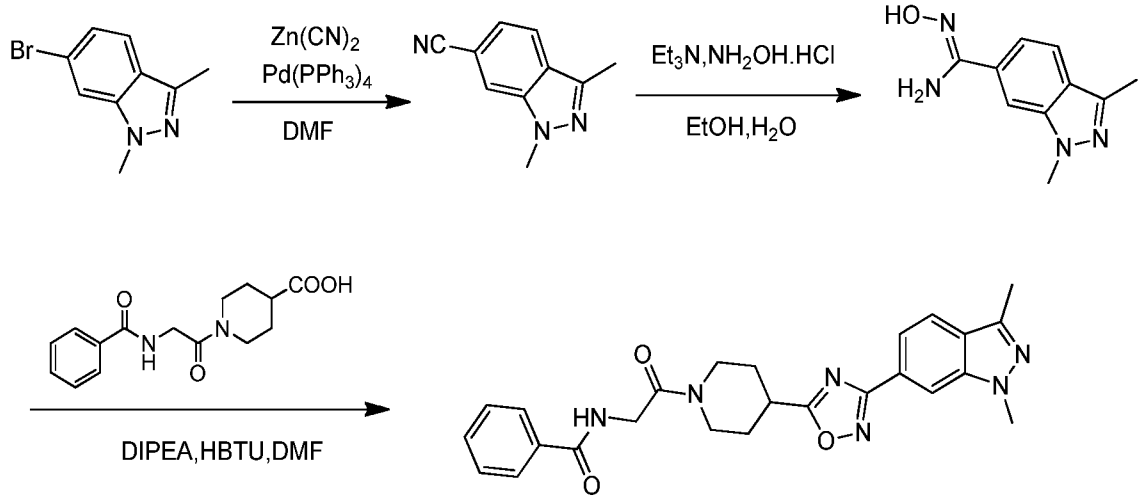
A solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (500 mg, 1.64 mmol) and hydrazine hydrate (328 mg, 6.56 mmol, 318 µL) in methanol (3 mL) was heated to 80 °C for 15 h. The mixture was concentrated in vacuo to give a crude residue that was washed with tert-butyl methyl ether (10 mL) to obtain N-[2-[4-(hydrazinecarbonyl)-1-piperidyl]-2-oxo-ethyl]benzamide (500 mg) as a light yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.54 (t, J=5.6 Hz, 1H), 7.94 - 7.82 (m, 2H), 7.60 - 7.43 (m, 3H), 4.41 - 4.29 (m, 1H), 4.13 (d, J=5.6 Hz, 2H), 3.93 (d, J=12.9 Hz, 1H), 3.05 (t, J=11.9 Hz, 1H), 2.68 - 2.57 (m, 1H), 2.34 (tdd, J=3.9, 7.5, 11.2 Hz, 1H), 1.73 - 1.34 (m, 4H).

Step 4: N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

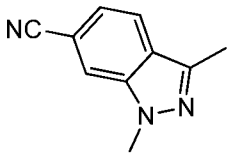


A solution of N-[2-[4-(hydrazinecarbonyl)-1-piperidyl]-2-oxo-ethyl]benzamide (200 mg, 657 µmol) and ethyl 3,4-dimethoxybenzenecarboximidate (151 mg, 723 µmol) in ethanol (4 mL) was heated to 80 °C for 15h. The mixture was concentrated to give a crude product, which was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-35%,12 min) to give N-[2-[4-[5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (23 mg, 48 µmol, 7 %) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.92 - 7.82 (m, 2H), 7.62 (dd, J=1.8, 8.4 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.51 - 7.44 (m, 2H), 7.12 (d, J=8.4 Hz, 1H), 4.49 (d, J=13.2 Hz, 1H), 4.38 - 4.24 (m, 2H), 4.06 (d, J=13.7 Hz, 1H), 3.97 - 3.80 (m, 6H), 3.48 - 3.34 (m, 2H), 3.06 (t, J=11.2 Hz, 1H), 2.33 - 2.15 (m, 2H), 2.06 - 1.94 (m, 1H), 1.92 - 1.75 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 451.2.

Example 40: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

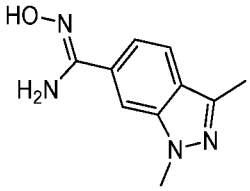


Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (400 mg, 1.78 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (209 mg, 1.78 mmol, 112 µL) and tetrakis(triphenylphosphine)palladium(0) (205 mg, 178 µmol, 0.10 *eq*) under nitrogen. The mixture was heated at 100 °C for 16 h, then cooled to 20 °C, water (10 mL) added, and the resulting mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL) and dried over anhydrous sodium sulfate. The organic phase was filtered and concentrated in vacuo to give crude product. Petroleum ether (40 mL) was added to the crude product, then the mixture was filtered, and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-6-carbonitrile (250 mg, 1.46 mmol, 82 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.71 (m, 2H), 7.34 (dd, *J*=1.3, 8.3 Hz, 1H), 4.07 (s, 3H), 2.61 (s, 3H).

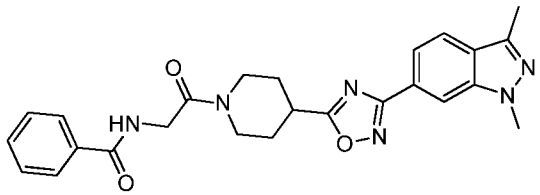
Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (100 mg, 584 µmol) in ethanol (2 mL) was added hydroxylamine hydrochloride (81 mg, 1.17 mmol), triethylamine (118 mg, 1.17 mmol, 161 µL) and water (200 µL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (5 mL) was added to the solution. The mixture was extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL) and dried over

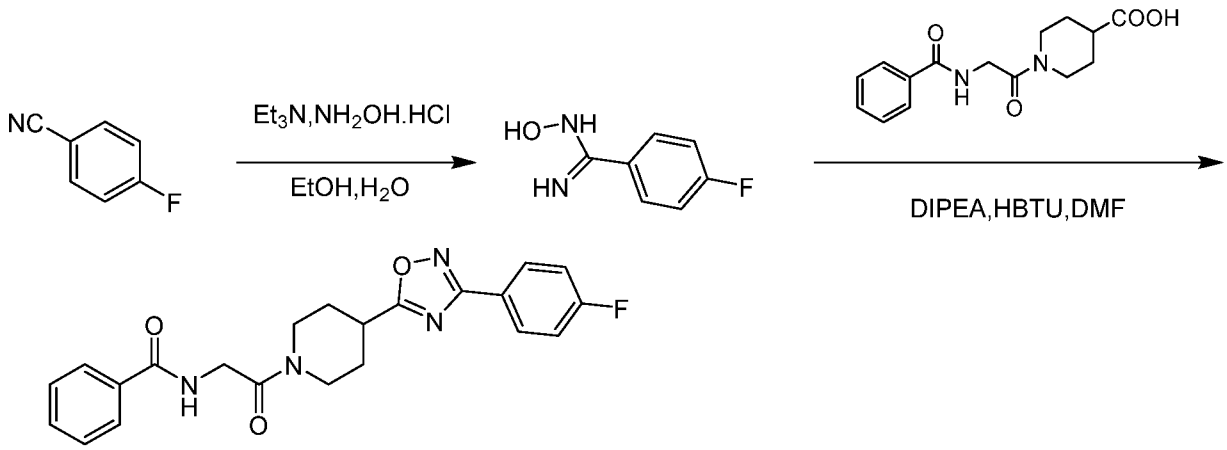
anhydrous sodium sulfate, then filtered and concentrated in vacuo to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (140 mg) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 205.1.

Step 3: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

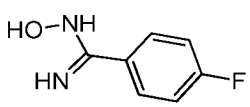


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (101 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-65%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (46 mg, 101 µmol, 25 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.81 - 7.73 (m, 3H), 7.66 (dd, *J*=0.6, 8.4 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.42 - 7.35 (m, 2H), 7.26 (br. s., 1H), 4.46 (d, *J*=14.1 Hz, 1H), 4.24 (d, *J*=3.9 Hz, 2H), 4.01 (s, 3H), 3.86 (d, *J*=13.7 Hz, 1H), 3.29 (ddd, *J*=3.6, 10.5, 14.2 Hz, 2H), 3.13 - 3.04 (m, 1H), 2.53 (s, 3H), 2.26 - 2.15 (m, 2H), 2.04 - 1.89 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 41: N-(2-(4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



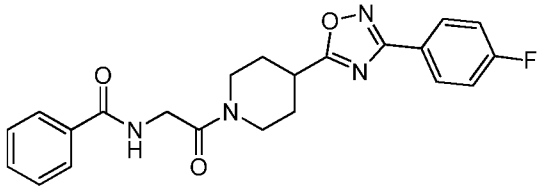
Step 1: Preparation of 4-fluoro-N-hydroxybenzimidamide.



To a stirred solution of 4-fluorobenzonitrile (1.0 g, 8.26 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (1.15 g, 16.5 mmol), triethylamine (1.67 g, 16.52 mmol, 2.29 mL) and water (1 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added to the

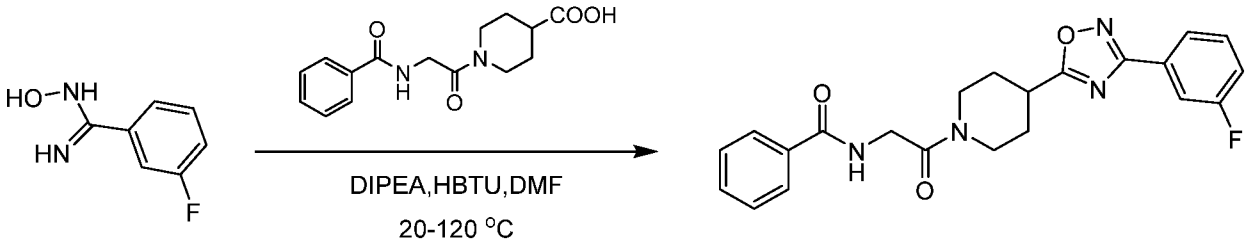
solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give 4-fluoro-N-hydroxybenzimidamide (1.0 g, 6.49 mmol, 79 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.64 (s, 1H), 7.85-7.64 (m, 2H), 7.21 (t, *J* = 8.9 Hz, 2H), 5.84 (br. s., 2H).

Step 2: Preparation of N-(2-(4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

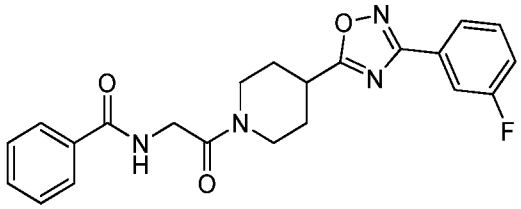


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (3 mL) was added 4-fluoro-N-hydroxybenzimidamide (76 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture cooled then purified directly by prep-HPLC (column: Luna C18 150x2.5mm 5µm; mobile phase: [water (0.225%FA)-acetonitrile]; B%: 35%-65%,12 min) to give N-(2-(4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (56 mg, 135 µmol, 33 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.07 (m, 2H), 7.90-7.86 (m, 2H), 7.58-7.52 (m, 1H), 7.51-7.45 (m, 2H), 7.35 (br. s., 1H), 7.23-7.16 (m, 2H), 4.56-4.47 (m, 1H), 4.33 (d, *J* = 3.9 Hz, 2H), 3.93 (d, *J* = 13.9 Hz, 1H), 3.41-3.31 (m, 2H), 3.23-3.13 (m, 1H), 2.33-2.21 (m, 2H), 2.02 (ddq, *J* = 4.1, 10.5, 14.2 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 409.2.

Example 42: N-(2-(4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



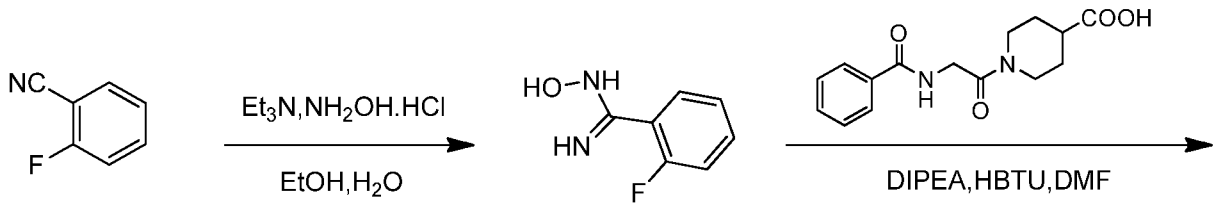
Step 1: Preparation of N-(2-(4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

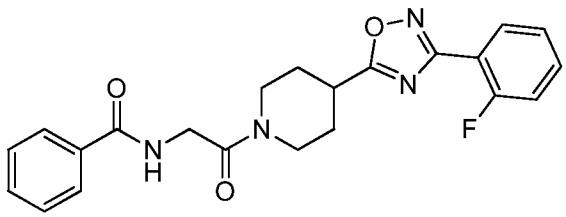


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (4 mL) was added 3-fluoro-N-hydroxybenzimidamide (76 mg, 496 µmol), (2-(1H-

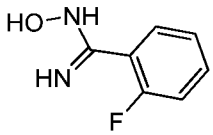
benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give N-(2-(4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (59 mg, 145 µmol, 35 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85-7.76 (m, 3H), 7.71 (d, *J*=9.3 Hz, 1H), 7.49-7.35 (m, 4H), 7.26 (br. s., 1H), 7.15 (s, 1H), 4.43 (d, *J*=13.7 Hz, 1H), 4.24 (d, *J*=3.5 Hz, 2H), 3.84 (d, *J*=14.1 Hz, 1H), 3.33-3.22 (m, 2H), 3.14-3.04 (m, 1H), 2.26-2.13 (m, 2H), 2.00-1.85 ppm (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 409.2.

Example 43: N-(2-(4-(3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



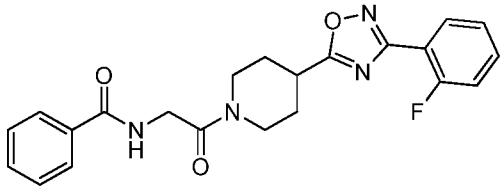


Step 1: Preparation of 2-fluoro-N-hydroxybenzimidamide.



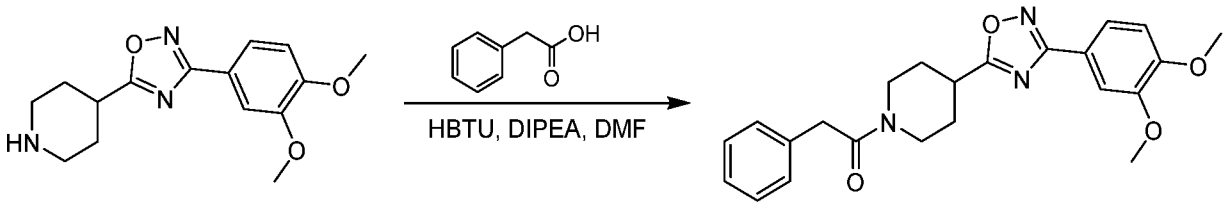
To a stirred solution of 2-fluorobenzonitrile (1.0 g, 8.26 mmol, 877 µL) in ethanol (10 mL) was added hydroxylamine hydrochloride (1.15 g, 16.5 mmol), triethylamine (1.67 g, 16.5 mmol, 2.29 mL) and water (1 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give 2-fluoro-N-hydroxybenzimidamide (1.20 g, 7.79 mmol, 94 %) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 155.1.

Step 2: Preparation of N-(2-(4-(3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

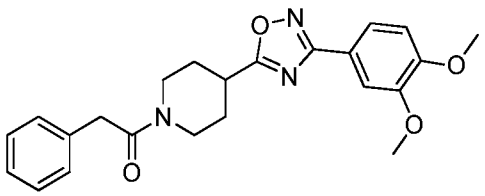


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (150 mg, 516.7 µmol) in N,N-dimethylformamide (4 mL) was added 2-fluoro-N-hydroxybenzimidamide (95 mg, 620 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (195 mg, 516.7 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (200 mg, 1.55 mmol, 270 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-(4-(3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (85 mg, 208.6 µmol, 40 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.81-7.75 (m, 2H), 7.48-7.34 (m, 4H), 7.28-7.20 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 4.42 (d, *J* = 14.1 Hz, 1H), 4.23 (d, *J* = 3.9 Hz, 2H), 3.84 (d, *J* = 13.9 Hz, 1H), 3.29 (dt, *J* = 4.1, 10.4 Hz, 2H), 3.14-3.04 (m, 1H), 2.25-2.13 (m, 2H), 2.02-1.86 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 409.2.

Example 44: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-phenylethanone.



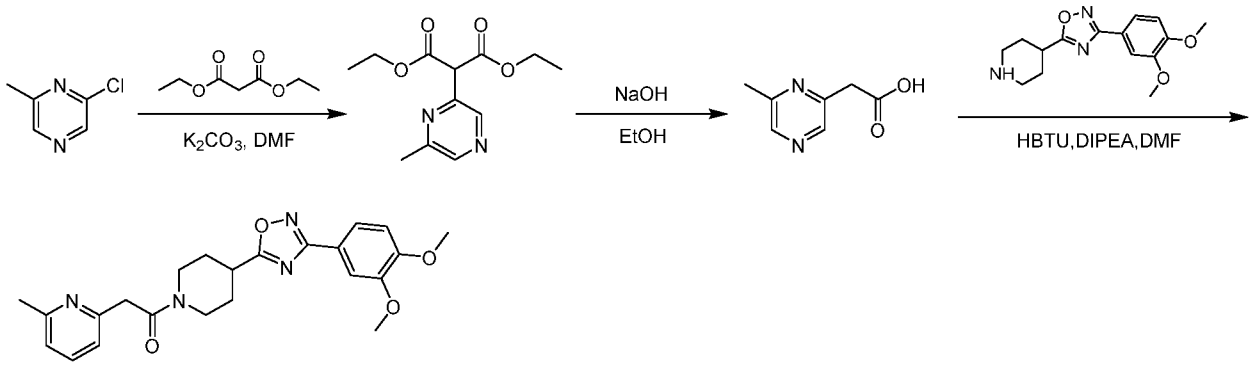
Step 1: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-phenylethanone.



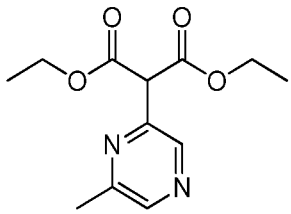
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-phenylacetic acid (74 mg, 544 µmol, 68 µL). The mixture was stirred at 20 °C for 16 h. The crude product was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give 1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-phenyl-ethanone (24 mg, 59 µmol, 11 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.63 (dd, J=2.0, 8.4 Hz, 1H), 7.55 (d, J=1.8 Hz, 1H), 7.39 - 7.20 (m, 5H), 7.05 (d, J=8.4 Hz, 1H), 4.49 (br d, J=13.5 Hz, 1H), 4.04 (br d, J=13.2 Hz, 1H), 3.88

(s, 6H), 3.82 (s, 2H), 3.34 (br d, J=2.6 Hz, 1H), 3.29 - 3.23 (m, 1H), 3.05 - 2.95 (m, 1H), 2.19 - 2.11 (m, 1H), 2.06 - 1.98 (m, 1H), 1.83 - 1.71 (m, 1H), 1.67 - 1.54 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 408.3.

Example 45: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(6-methylpyrazin-2-yl)ethanone.

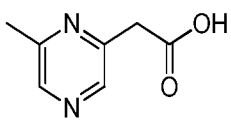


Step 1: Preparation of diethyl 2-(6-methylpyrazin-2-yl)malonate.



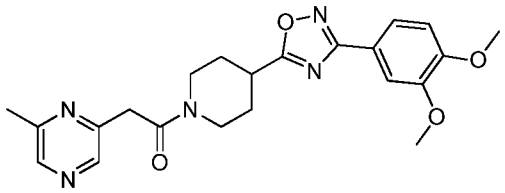
To a stirred solution of 2-chloro-6-methylpyrazine (1.0 g, 7.78 mmol) in N,N-dimethylformamide (20 mL) was added diethyl malonate (3.12 g, 19.5 mmol, 2.94 mL) and potassium carbonate (2.69 g, 19.5 mmol), then the mixture was stirred at 110 °C for 16 h. The reaction mixture was cooled to 20 °C, quenched with water (20 mL), and then extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10 : 1) gave diethyl 2-(6-methylpyrazin-2-yl)malonate (180 mg, 713.5 µmol, 9 %) as a green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.44 (s, 1H), 4.91 (s, 1H), 4.20-4.15 (q, *J* = 7.2 Hz, 4H), 2.58 (s, 3H), 1.25-1.22 (t, *J* = 7.2 Hz, 6H); LCMS (ESI) m/z: 253.1 $[M+H]^+$.

Step 2: Preparation of 2-(6-methylpyrazin-2-yl)acetic acid.



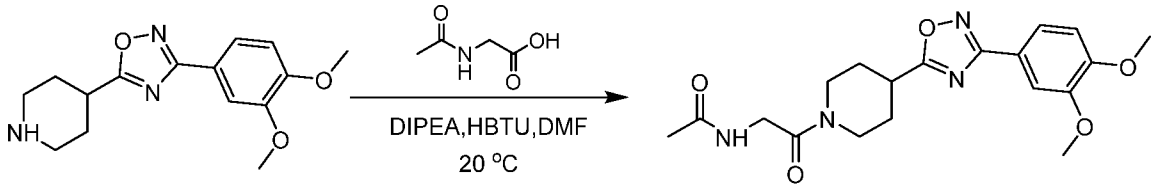
To a stirred solution of diethyl 2-(6-methylpyrazin-2-yl)malonate (180 mg, 713.5 µmol) in ethanol (10 mL) was added sodium hydroxide (2 M, 1.96 mL) and the mixture warmed at 60 °C for 2 h. The reaction was cooled to 20 °C, and acidified with 1 M hydrochloric acid (5 mL). The mixture was concentrated in vacuo to give 2-(6-methylpyrazin-2-yl) acetic acid (1.42 g) as a light yellow solid that was used directly without further purification.

Step 3: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(6-methylpyrazin-2-yl)ethanone.



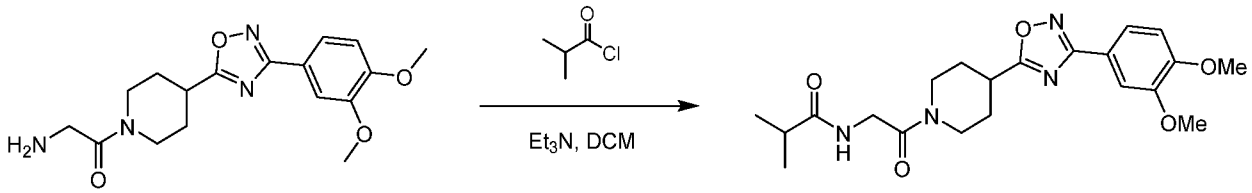
To a stirred solution of 2-(6-methylpyrazin-2-yl)acetic acid (1.05 g, 415 µmol, purity 6 %) in N,N-dimethylformamide (4 mL) was added 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (120 mg, 415 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (157 mg, 415 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (214 mg, 1.66 mmol, 289 µL). The mixture was stirred at 20 °C for 4 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-50%,12 min) to give 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(6-methylpyrazin-2-yl)ethanone (26 mg, 62 µmol, 15 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.41 (s, 2H), 7.68 (dd, *J*=1.9, 8.3 Hz, 1H), 7.61 (d, *J*=1.8 Hz, 1H), 7.10 (d, *J*=8.4 Hz, 1H), 4.51 (d, *J*=13.4 Hz, 1H), 4.22 (d, *J*=13.9 Hz, 1H), 4.12 - 3.93 (m, 2H), 3.92 (s, 6H), 3.52 - 3.38 (m, 2H), 3.12 - 3.02 (m, 1H), 2.57 (s, 3H), 2.28 - 2.17 (m, 2H), 2.04 - 1.80 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 424.2.

Example 46: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)acetamide.



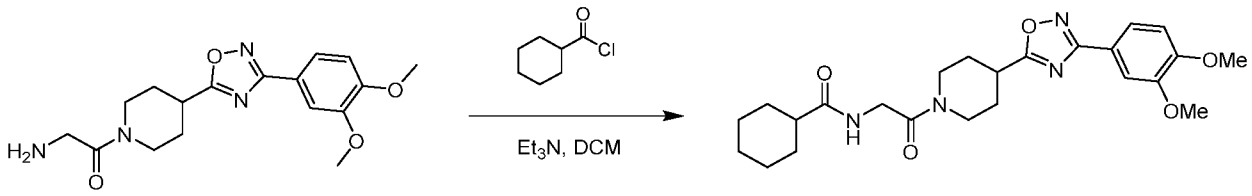
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (250 mg, 864 µmol) in N,N-dimethylformamide (1.5 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (327 mg, 864 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (335 mg, 2.59 mmol, 452 µL) and 2-acetamidoacetic acid (106 mg, 907 µmol). The mixture was stirred at 20 °C for 16 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]acetamide (36 mg, 94 µmol, 11 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.69 (dd, J=1.9, 8.3 Hz, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 4.47 (br d, J=14.2 Hz, 1H), 4.21 - 4.06 (m, 2H), 3.98 (br d, J=13.1 Hz, 1H), 3.92 (s, 6H), 3.47 - 3.38 (m, 2H), 3.13 - 3.00 (m, 1H), 2.31 - 2.16 (m, 2H), 2.05 (s, 3H), 2.00 - 1.79 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 389.2.

Example 47: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isobutyramide.

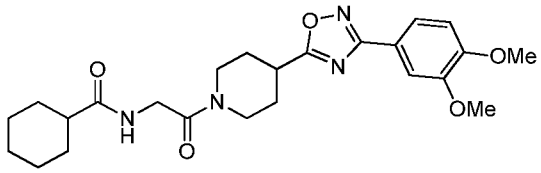


To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (150 mg, 433 µmol) in dichloromethane (3 mL) was added isobutyryl chloride (55 mg, 520 µmol, 54 µL) and triethylamine (131 mg, 1.30 mmol, 180 µL) at 0 °C. The mixture was warmed and stirred at 20 °C for 1 h. The reaction mixture was concentrated in vacuo to give crude product that was purified by HPLC prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 23%-53%,12 min) to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isobutyramide (85 mg, 204 µmol, 47 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74-7.68 (m, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.63 (br. s., 1H), 4.49 (d, *J* = 13.3 Hz, 1H), 4.12 (d, *J* = 4.0 Hz, 2H), 3.98 (d, *J* = 7.3 Hz, 6H), 3.87 (d, *J* = 14.1 Hz, 1H), 3.36-3.26 (m, 2H), 3.13 (t, *J* = 10.9 Hz, 1H), 2.50 (td, *J* = 6.9, 13.8 Hz, 1H), 2.23 (br. s., 2H), 2.06-1.92 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 417.3.

Example 48: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)cyclohexanecarboxamide.

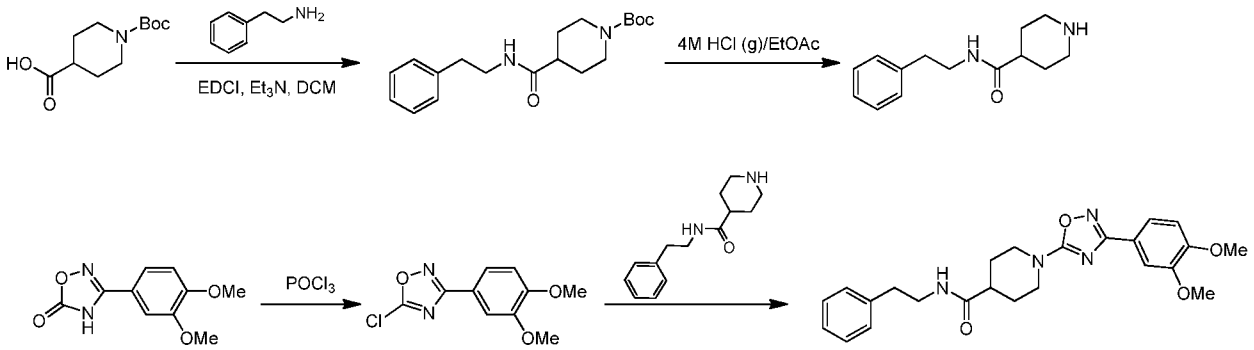


Step 1: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)cyclohexanecarboxamide.

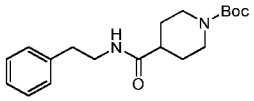


To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (150 mg, 433 µmol) in dichloromethane (3 mL) was added cyclohexanecarbonyl chloride (76 mg, 520 µmol, 69 µL) and triethylamine (131 mg, 1.30 mmol, 180 µL) at 0 °C. The mixture was warmed and stirred at 20 °C for 1 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 23%-53%,12 min) to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)cyclohexanecarboxamide (78 mg, 171 µmol, 39 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.73-7.68 (m, 1H), 7.60-7.57 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.64-6.59 (m, 1H), 4.53-4.45 (m, 1H), 4.11 (d, *J* = 4.0 Hz, 2H), 3.98 (d, *J* = 7.2 Hz, 6H), 3.86 (d, *J* = 13.3 Hz, 1H), 3.36-3.26 (m, 2H), 3.12 (t, *J* = 10.7 Hz, 1H), 2.28-2.18 (m, 3H), 2.05-1.89 (m, 4H), 1.82 (d, *J* = 12.3 Hz, 2H), 1.71 (d, *J* = 10.9 Hz, 1H), 1.54-1.42 (m, 2H), 1.37-1.22 (m, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 457.3.

Example 49: 1-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-N-(2-phenylethyl)piperidine-4-carboxamide.

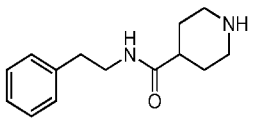


Step 1: Preparation of tert-butyl 4-(phenethylcarbamoyl)piperidine-1-carboxylate.



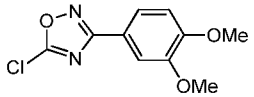
To a stirred solution of 1-tert-butoxycarbonylpiperidine-4-carboxylic acid (1.0 g, 4.36 mmol) in dichloromethane (15 mL) was added 2-phenylethanamine (528 mg, 4.36 mmol, 544 µL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (835 mg, 4.36 mmol) and triethylamine (44 mg, 436 µmol, 60 µL). The mixture was stirred at 20 °C for 5 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by chromatography (silica, petroleum ether / ethyl acetate from 10/1 to 1/1) to give tert-butyl 4-(2-phenylethylcarbamoyl)piperidine-1-carboxylate (800 mg, 2.41 mmol, 55 %) as a white solid. LCMS (ESI) m/z: 355.2 $[M+Na]^+$.

Step 2: Preparation of N-phenethylpiperidine-4-carboxamide.



A solution of tert-butyl 4-(2-phenylethylcarbamoyl)piperidine-1-carboxylate (800 mg, 2.41 mmol) in 4N hydrochloric acid / ethyl acetate (10 mL) was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated in vacuo to give N-(2-phenylethyl)piperidine-4-carboxamide (720 mg) as a hydrochloric acid salt and as a white solid.

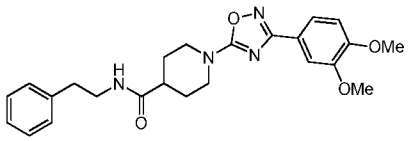
Step 3: Preparation of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole.



3-(3,4-dimethoxyphenyl)-4H-1,2,4-oxadiazol-5-one (900 mg, 4.05 mmol) was added to a mixture of N,N-dimethylformamide (2 mL) and phosphoryl chloride (24.8 g, 161.4 mmol, 15 mL). The mixture was equipped with calcium chloride tube and the mixture was heated at 100 °C for 16 h. The mixture was cooled to 0 °C and concentrated under reduced pressure. The residue was poured into ice-water (20 mL) and stirred for 10 min, then the aqueous phase was extracted with dichloromethane (10 mL x 5). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried

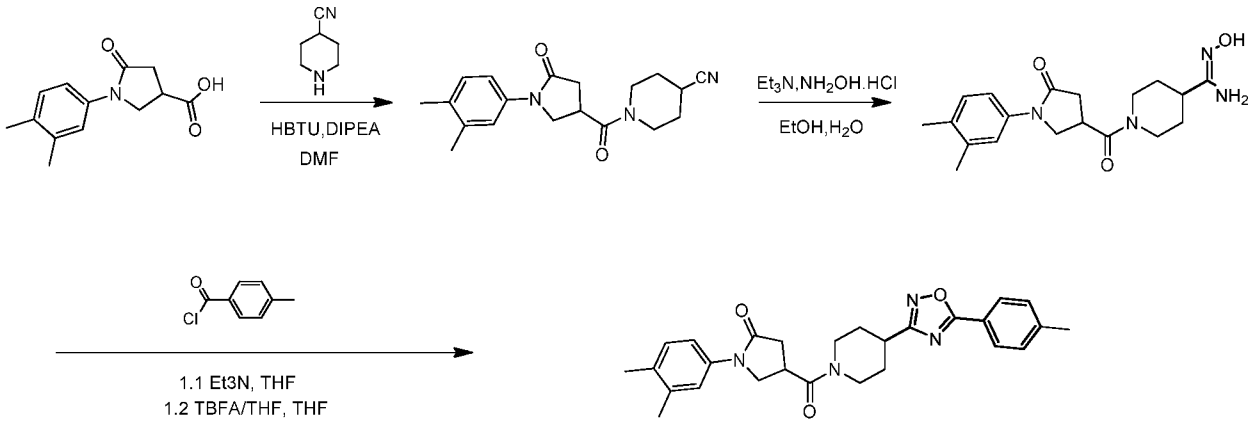
over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=5/1, 1/1) to give 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (104 mg, 432 µmol, 11 %) as a white solid.

Step 4: Preparation of 1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-4-carboxamide.

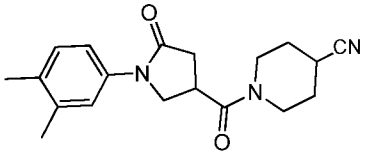


To a stirred solution of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (95 mg, 395 µmol) in N-methyl-2-pyrrolidone (2 mL) was added N-(2-phenylethyl)piperidine-4-carboxamide (110 mg, 474 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (102 mg, 790 µmol, 137 µL) at 20 ℃. Then the mixture was heated to 120 ℃ and stirred for 5 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-65%,12 min), Compound 1-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-N-(2-phenylethyl)piperidine-4-carboxamide (117 mg, 266 µmol, 67 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.57 (dd, J=2.0, 8.4 Hz, 1H), 7.51 (d, J=1.9 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.25 - 7.18 (m, 3H), 7.06 (d, J=8.4 Hz, 1H), 4.22 (br d, J=13.3 Hz, 2H), 3.90 (s, 6H), 3.44 (t, J=7.3 Hz, 2H), 3.27 - 3.17 (m, 2H), 2.82 (t, J=7.2 Hz, 2H), 2.51 - 2.40 (m, 1H), 1.92 - 1.67 (m, 4H); LCMS (ESI) m/z: $[M+H]^+$ = 437.3.

Example 50: 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



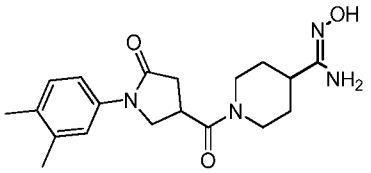
Step 1: Preparation of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carbonitrile.



To a stirred solution of 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid (1.0 g, 4.29 mmol) in N,N-dimethylformamide (10 mL) was added piperidine-4-carbonitrile (567 mg, 5.15 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.63 g, 4.29 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.66 g, 12.87 mmol, 2.25 mL). The mixture was stirred at 20 ℃ for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate

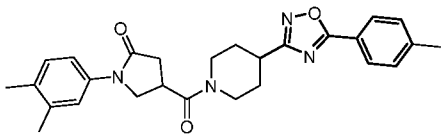
(20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a yellow oil (1.6 g). A portion of the crude product (0.3 g) was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carbonitrile for analysis (144 mg). The remainder of the crude product was used directly without purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.37 (d, *J* = 2.5 Hz, 1H), 7.31-7.25 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 4.08 (d, *J* = 7.0 Hz, 5H), 3.59-3.37 (m, 2H), 3.16-3.03 (m, 1H), 2.91-2.79 (m, 2H), 2.28 (d, *J* = 10.2 Hz, 6H), 2.10-1.72 (m, 4H); LCMS (ESI) m/z: $[M+H]^+$ = 326.2.

Step 2: Preparation of (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide.



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carbonitrile (1.30 g, 4.00 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (555 mg, 8.00 mmol), triethylamine (809 mg, 8.00 mmol, 1.11 mL) and water (1 mL). The mixture was heated at 75 ℃ for 2 h. After cooling to 20 ℃, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a brown solid (1.4 g). A portion of crude product (0.3 g) was purified by prep-HPLC (column: Luna C18 150x2.5mm 5μm; mobile phase: [water (0.225% TFA)-acetonitrile]; B%: 15%-40%,12 min) to give (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide. The remainder was used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.86-8.77 (m, 1H), 8.15 (s, 1H), 7.45-7.33 (m, 2H), 7.12 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.36 (br. s., 2H), 4.47-4.32 (m, 1H), 4.06-3.86 (m, 3H), 3.75-3.60 (m, 1H), 3.07 (br. s., 1H), 2.80-2.57 (m, 3H), 2.36-2.24 (m, 1H), 2.21 (d, *J* = 11.8 Hz, 6H), 1.83-1.67 (m, 2H), 1.56 ppm (br. s., 2H); LCMS (ESI) m/z: $[M+H]^+$ = 359.3.

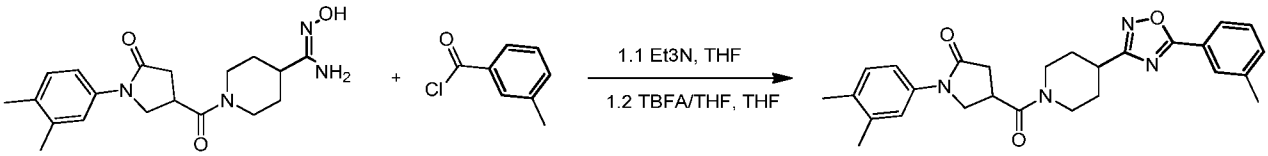
Step 3: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



To a stirred solution of (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide (300 mg, 837 μmol) in tetrahydrofuran (8 mL) was added 4-methylbenzoyl chloride (155 mg, 1.00 mmol, 132 μL) and triethylamine (254 mg, 2.51 mmol, 348 μL) at 0 ℃, then the mixture was warmed at 20 ℃. After 3 h, to the reaction mixture was added ethyl acetate and water and the organic phase was separated. The organic phase was washed with water and saturated aqueous sodium chloride solution and then dried over anhydrous sodium sulfate. The mixture

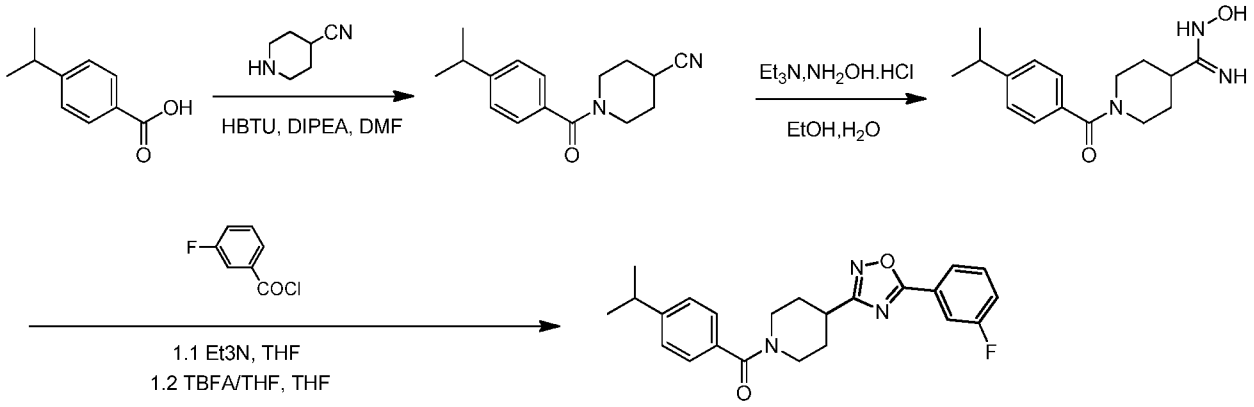
was filtered and concentrated under reduced pressure. To the residue were added tetrahydrofuran (8 mL) and a tetrabutylammonium fluoride in tetrahydrofuran (1 M, 2.51 mL) solution, and the mixture warmed at 50 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Luna C18 100*30 5µm; mobile phase: [water (0.225%TFA)-acetonitrile]; B%: 45%-75%,12 min) to give the racemic of 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (106 mg, 0.23 mmol, 28 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.99 (m, 2H), 7.41-7.33 (m, 3H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 4.60 (t, *J* = 13.2 Hz, 1H), 4.30 (dd, *J* = 7.4, 9.5 Hz, 1H), 4.04-3.88 (m, 2H), 3.60 (quin, *J* = 8.5 Hz, 1H), 3.42-3.31 (m, 1H), 3.25-3.14 (m, 1H), 3.11-2.94 (m, 2H), 2.88-2.78 (m, 1H), 2.47 (s, 3H), 2.32-2.12 (m, 8H), 2.03-1.86 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 51: 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one.

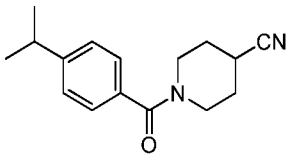


To a stirred solution of (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide (280 mg, 781 µmol) in tetrahydrofuran (8 mL) was added 3-methylbenzoyl chloride (144 mg, 937 µmol, 123 µL) and triethylamine (237 mg, 2.34 mmol, 324 µL) at 0 °C, the mixture was stirred at 20 °C for 3 h. To the reaction mixture was added ethyl acetate and water and the organic phase was separated. The organic phase was washed with water and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. To the residue were addded tetrahydrofuran (8 mL) and a tetrabutylammonium fluoride in tetrahydrofuran solution (1 M, 2.34 mL). The mixture was warmed to 50 °C and stirred for 16 h. The reaction mixture was cooled and concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-75%,12 min) to give the racemic of 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (156 mg, 0.34 mmol, 44 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.91 (m, 2H), 7.43 (d, *J* = 1.0 Hz, 3H), 7.32-7.29 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.60 (t, *J* = 14.1 Hz, 1H), 4.30 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.04-3.88 (m, 2H), 3.65-3.54 (m, 1H), 3.37 (d, *J* = 7.0 Hz, 1H), 3.21 (d, *J* = 3.5 Hz, 1H), 3.11-2.94 (m, 2H), 2.88-2.78 (m, 1H), 2.48 (s, 3H), 2.32-2.13 (m, 8H), 1.93 (d, *J* = 12.2 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 52: (4-(5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.

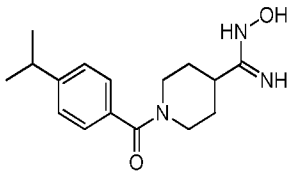


Step 1: Preparation of 1-(4-isopropylbenzoyl)piperidine-4-carbonitrile.



To a stirred solution of 4-isopropylbenzoic acid (1.0 g, 6.09 mmol) in N,N-dimethylformamide (10 mL) was added piperidine-4-carbonitrile (805 mg, 7.31 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (2.31 g, 6.09 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.36 g, 18.27 mmol, 3.19 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give yellow oil (1.8 g). A portion of crude product (0.2 g) was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-55%,12 min) to give 1-(4-isopropylbenzoyl)piperidine-4-carbonitrile (115 mg) as a sample for analysis. The remainder was used directly. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.37 (s, 4H), 4.16-3.40 (m, 4H), 3.15-3.07 (m, 1H), 3.02-2.93 (m, 1H), 2.10-1.76 (m, 4H), 1.31-1.26 (m, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 257.2.

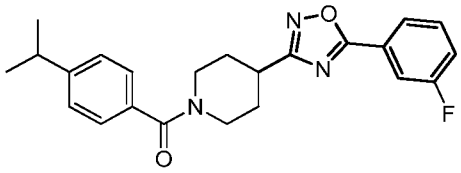
Step 2: Preparation of N-hydroxy-1-(4-isopropylbenzoyl)piperidine-4-carboximidamide.



To a stirred solution of 1-(4-isopropylbenzoyl)piperidine-4-carbonitrile (1.60 g, 6.24 mmol) in ethanol (15 mL) was added hydroxylamine hydrochloride (867 mg, 12.5 mmol), triethylamine (1.26 g, 12.48 mmol, 1.73 mL) and water (1.50 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give N-hydroxy-1-(4-isopropylbenzoyl)piperidine-4-carboximidamide (1.60 g, 5.53 mmol, 89 %) as a white solid that was used directly without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.40-7.33 (m, 4H), 4.78-4.58

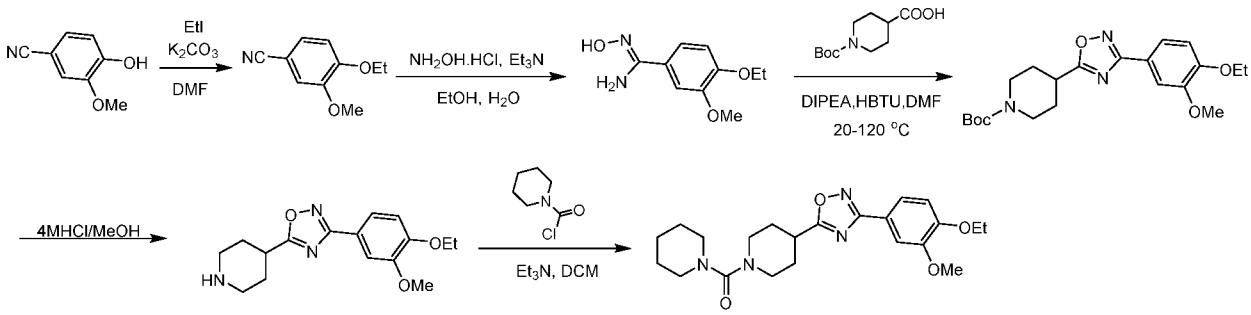
(m, 1H), 3.94-3.73 (m, 1H), 3.22 (d, *J* = 7.3 Hz, 2H), 3.02-2.95 (m, 1H), 2.50-2.35 (m, 1H), 1.96-1.67 (m, 4H), 1.31-1.27 (m, 6H).

Step 3: Preparation of (4-(5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.

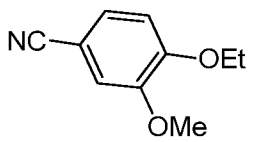


To a stirred solution of N-hydroxy-1-(4-isopropylbenzoyl)piperidine-4-carboximidamide (200 mg, 691 µmol) in tetrahydrofuran (5 mL) was added 3-fluorobenzoyl chloride (131 mg, 829 µmol, 99 µL) and triethylamine (209 mg, 2.07 mmol, 287 µL) at 0 °C. The mixture was warmed and then stirred at 20 °C for 16 h. To the reaction mixture was added ethyl acetate and water and the organic phase was separated. The organic phase was washed with water and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. To the obtained residue were added tetrahydrofuran (5 mL) and a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 2.07 mL), then the mixture was warmed at 50 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 50%-80%,12 min) to give (4-(5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)(4-isopropylphenyl)methanone (76 mg, 193.5 µmol, 28 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.78-7.72 (m, 1H), 7.45 (dt, *J* = 5.6, 8.0 Hz, 1H), 7.32-7.27 (m, 2H), 7.26-7.20 (m, 2H), 7.18 (s, 1H), 4.76-3.64 (m, 2H), 3.20-2.97 (m, 3H), 2.86 (td, *J* = 6.9, 13.8 Hz, 1H), 2.18-1.74 (m, 4H), 1.19 (d, *J* = 6.9 Hz, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 394.2.

Example 53: (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.



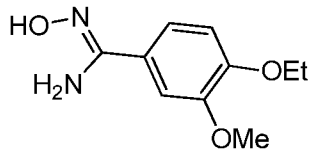
Step 1: Preparation of 4-ethoxy-3-methoxybenzonitrile.



To a stirred solution of 4-hydroxy-3-methoxybenzonitrile (5.0 g, 33.5 mmol) in N,N-dimethylformamide (50 mL) was added iodoethane (6.27 g, 40.2 mmol, 3.22 mL) and potassium carbonate (9.27 g, 67.0 mmol) at 0 °C, then the reaction was warmed and stirred at 40 °C for 16 h. The reaction mixture was quenched by addition of water (50 mL) then the mixture was extracted with ethyl

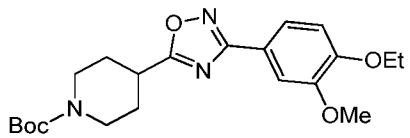
acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 4-ethoxy-3-methoxybenzonitrile (5.80 g, 32.7 mmol, 98 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.16 (m, 1H), 7.00 (d, *J* = 1.9 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.07 (q, *J* = 6.9 Hz, 2H), 3.82 (s, 3H), 1.45-1.39 (m, 3H).

Step 2: Preparation of (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide.



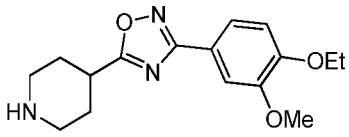
To a stirred solution of 4-ethoxy-3-methoxybenzonitrile (5.80 g, 32.7 mmol) in ethanol (50 mL) was added hydroxylamine hydrochloride (4.55 g, 65.5 mmol), triethylamine (6.62 g, 65.46 mmol, 9.07 mL) and water (5 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, the solvents were evaporated under vacuum, and water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (60 mL x 3). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, and then filtered and concentrated in vacuo to give (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide (5.96 g, 28.4 mmol, 87 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.44 (br. s., 1H), 7.28-7.14 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.73 (s, 2H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.75 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

Step 3: Preparation of tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate.



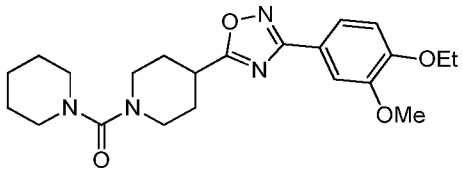
To a stirred solution of (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide (1.0 g, 4.76 mmol) in N,N-dimethylformamide (15 mL) was added 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.09 g, 4.76 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.81 g, 4.76 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.85 g, 14.28 mmol, 2.49 mL). The mixture was stirred at 20 °C for 16 h then heated at 120 °C for 2 h. The reaction mixture was cooled then quenched by addition of water (40 mL), then the mixture was extracted with ethyl acetate (80 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (2.56 g) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 404.3.

Step 4: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole.



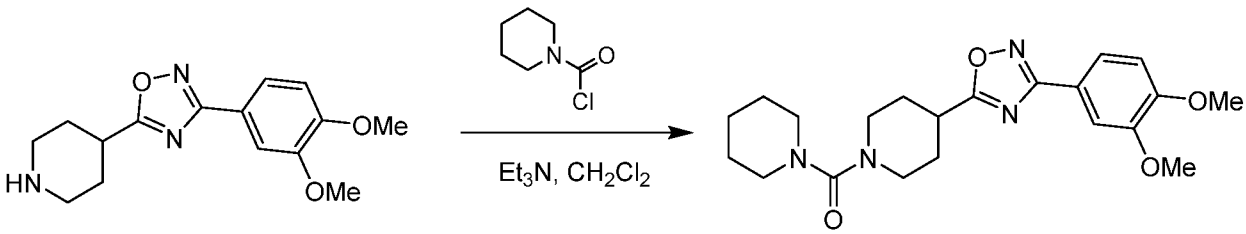
To a stirred solution of tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (1.0 g, 2.48 mmol) in methanol (5 mL) was added 4 M methanolic hydrochloric acid (20 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to provide the crude 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (900 mg) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 304.1

Step 5: Preparation of (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone

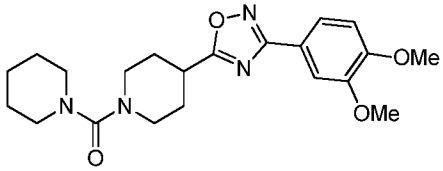


To a stirred solution of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (200 mg, 659 µmol) in dichloromethane (3 mL) was added piperidine-1-carbonyl chloride (116 mg, 791 µmol, 98 µL) and triethylamine (200 mg, 1.98 mmol, 274 µL) at 0 °C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone (65 mg, 158 µmol, 24 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 1H), 7.59 (d, *J* = 1.9 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 3.98 (s, 3H), 3.75 (d, *J* = 13.6 Hz, 2H), 3.29-3.13 (m, 5H), 3.04-2.94 (m, 2H), 2.17 (dd, *J* = 3.1, 13.3 Hz, 2H), 2.05-1.93 (m, 2H), 1.60 (d, *J* = 8.4 Hz, 6H), 1.53 (t, *J* = 7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 415.3.

Example 54: (4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.



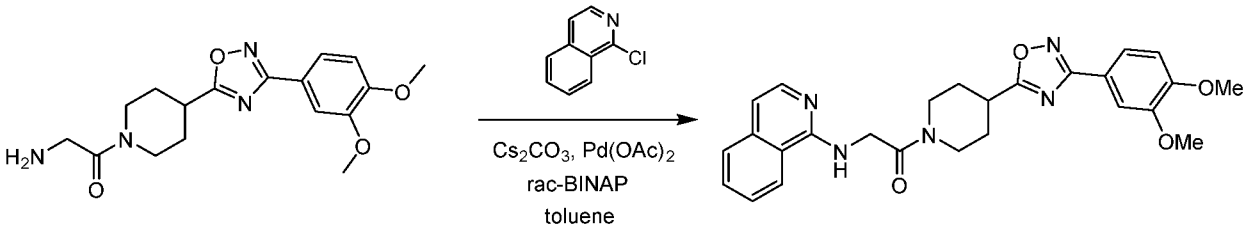
Step 1: Preparation of (4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.



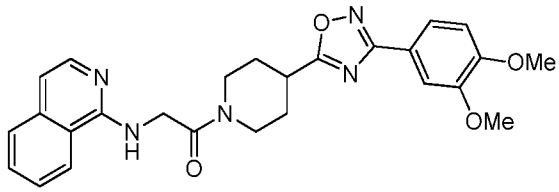
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (100 mg, 346 µmol) in dichloromethane (3 mL) was added piperidine-1-carbonyl chloride (61 mg, 415 µmol, 51 µL) and triethylamine (104 mg, 1.04 mmol, 143 µL) at 0 °C. The mixture was stirred at 20 °C for 1 h. The reaction

mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give (4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone (81 mg, 202 µmol, 58 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74-7.68 (m, 1H), 7.59 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 3.98 (d, *J* = 8.4 Hz, 6H), 3.76 (d, *J* = 13.4 Hz, 2H), 3.29-3.14 (m, 5H), 3.04-2.95 (m, 2H), 2.17 (dd, *J* = 13.3, 3.4 Hz, 2H), 2.05-1.94 (m, 2H), 1.60 ppm (d, *J* = 8.5 Hz, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 401.3.

Example 55: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(isoquinolin-1-ylamino)ethanone.

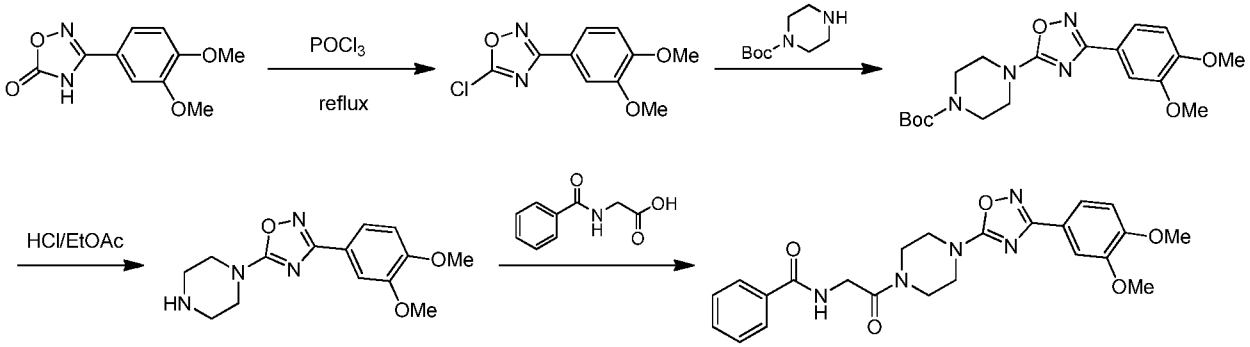


Step 1: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(isoquinolin-1-ylamino)ethanone.

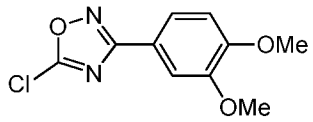


To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (150 mg, 433 µmol) in toluene (2 mL) was added 1-chloroisoquinoline (70 mg, 433 µmol), cesium carbonate (423 mg, 1.30 mmol), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (26 mg, 43 µmol, 0.10 *eq*), and palladium(II) acetate (9 mg, 43 µmol, 0.10 *eq*) under nitrogen. The mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(isoquinolin-1-ylamino)ethanone (57 mg, 119 µmol, 27 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.04-7.96 (m, 2H), 7.75-7.50 (m, 5H), 7.03-6.95 (m, 2H), 6.66 (br. s., 1H), 4.60 (d, *J* = 13.7 Hz, 1H), 4.45 (br. s., 2H), 4.08 (d, *J* = 12.5 Hz, 1H), 3.98 (d, *J* = 7.9 Hz, 6H), 3.46-3.30 (m, 2H), 3.24-3.13 (m, 1H), 2.28 (br. s., 2H), 2.13-1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 474.3.

Example 56: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide.

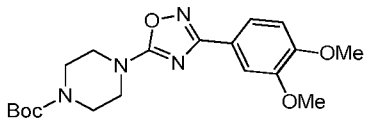


Step 1: Preparation of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole.



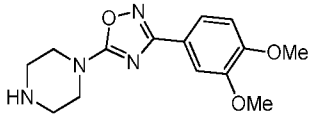
To a mixture of N,N-dimethylformamide (1 mL) and phosphoryl chloride (8.25 g, 53.8 mmol, 5 mL) was added 3-(3,4-dimethoxyphenyl)-4H-1,2,4-oxadiazol-5-one (300 mg, 1.35 mmol) at 25 ℃ under calcium chloride tube. The mixture was heated to 100 ℃ and stirred for 16 h. The mixture was cooled to 25 ℃ and concentrated in vacuo carefully. The residue was poured into ice-water (20 mL) and stirred for 10 min. The aqueous phase was extracted with dichloromethane (10 mL x 5). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography (petroleum ether / ethyl acetate=5/1 to 1/1) to afford 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (99 mg, 414 µmol, 31 %) as a white solid. LCMS (ESI) m/z: 241.1 $[M+H]^+$.

Step 2: Preparation of tert-butyl 4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate.



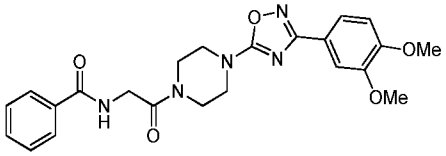
To a stirred solution of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (90 mg, 374 µmol) and tert-butyl piperazine-1-carboxylate (83 mg, 448.80 µmol) in N-methyl-2-pyrrolidone (1.50 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (96 mg, 748 µmol, 130 µL). The mixture was stirred at 120 ℃ for 2 h. The mixture was cooled to 25 ℃ and concentrated in vacuo at 40 ℃. The residue was poured into water (10 mL) then the aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperazine-1-carboxylate (900 mg) that was used directly without further purification.

Step 3: Preparation of 3-(3,4-dimethoxyphenyl)-5-(piperazin-1-yl)-1,2,4-oxadiazole.



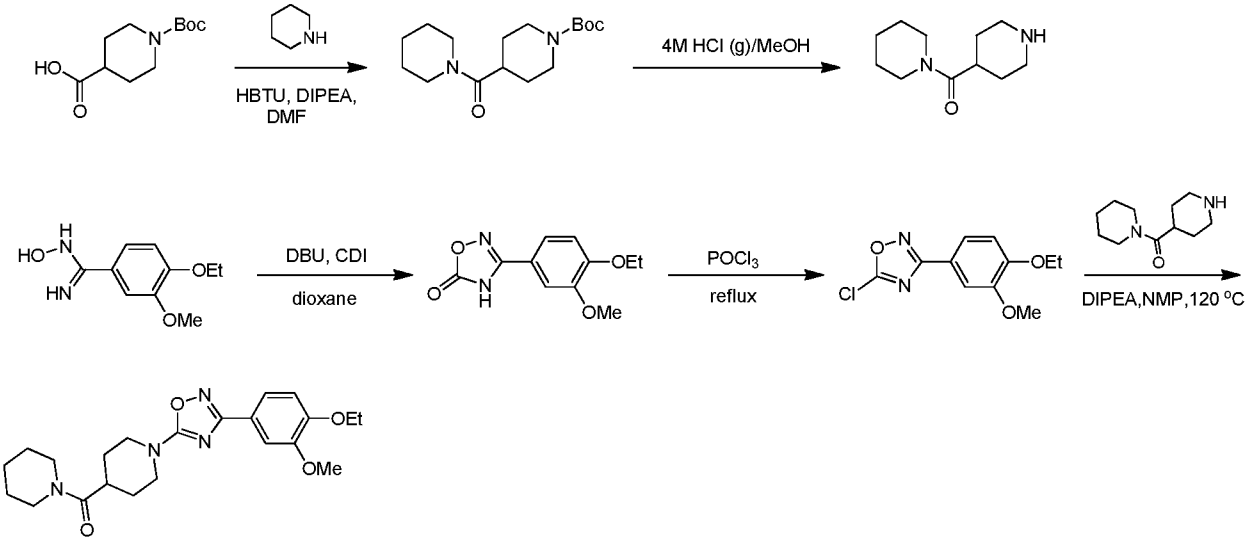
A solution of tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperazine-1-carboxylate (146 mg, 374 µmol) in hydrochloric acid / ethyl acetate (4M, 10 mL) was stirred at 20 °C for 2 h. The reaction mixture was concentrated in vacuo to give 3-(3,4-dimethoxyphenyl)-5-piperazin-1-yl-1,2,4-oxadiazole hydrochloride (900 mg) which was used directly without further purification.

Step 4: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide.

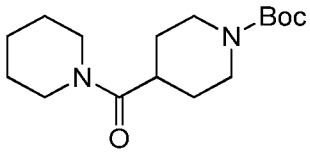


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-piperazin-1-yl-1,2,4-oxadiazole hydrochloride (667 mg, 306 µmol,) and 2-benzamidoacetic acid (137 mg, 765 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (174 mg, 459 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (118 mg, 918.51 µmol, 160 µL) at 20 °C. The mixture was stirred at 20 °C for 5 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-60%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperazin-1-yl]-2-oxo-ethyl]benzamide (55 mg, 121 µmol, 39 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.59 (br t, J=5.6 Hz, 1H), 7.93 - 7.83 (m, 2H), 7.60 - 7.44 (m, 4H), 7.39 (d, J=1.9 Hz, 1H), 7.08 (d, J=8.5 Hz, 1H), 4.20 (d, J=5.6 Hz, 2H), 3.81 (d, J=1.1 Hz, 6H), 3.73 - 3.58 (m, 8H); LCMS (ESI) m/z: $[M+H]^+$ = 452.2.

Example 57: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone.

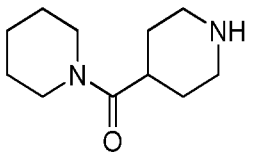


Step 1: Preparation of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate.



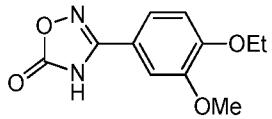
To a stirred solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.0 g, 4.36 mmol) in N,N-dimethylformamide (15 mL) was added piperidine (445 mg, 5.23 mmol, 518 µL), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (1.99 g, 5.23 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.69 g, 13.1 mmol, 2.29 mL). The mixture was stirred at 20 °C for 3 h. The reaction mixture was quenched by addition of water (20 mL) then the mixture was extracted with ethyl acetate (40 mL x 4), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (1.90 g) as a yellow oil. This was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 297.2

Step 2: Preparation of piperidin-1-yl(piperidin-4-yl)methanone.



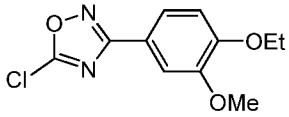
To a stirred solution of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (500 mg, 1.69 mmol) in methanol (5 mL) was added 4N methanolic hydrogen chloride solution (15 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to provide piperidin-1-yl(piperidin-4-yl)methanone (400 mg) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.51-3.36 (m, 4H), 3.28-3.18 (m, 2H), 2.90 (s, 4H), 1.82-1.68 (m, 4H), 1.64-1.37 (m, 6H).

Step 3: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one.



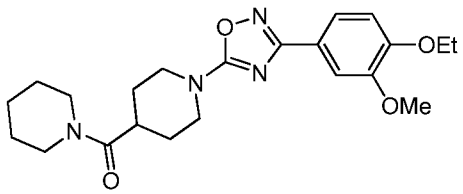
To a stirred solution of 4-ethoxy-N-hydroxy-3-methoxybenzimidamide (800 mg, 3.81 mmol) in dioxane (8 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (638 mg, 4.19 mmol, 631 µL) and 1,1'-carbonyldiimidazole (926 mg, 5.72 mmol). The mixture was stirred at 110 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with dichloromethane (50 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by chromatography (silica, dichloromethane : methanol = 50 :1) gave 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (1.20 g, quant.) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 237.1.

Step 4: Preparation of 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole.



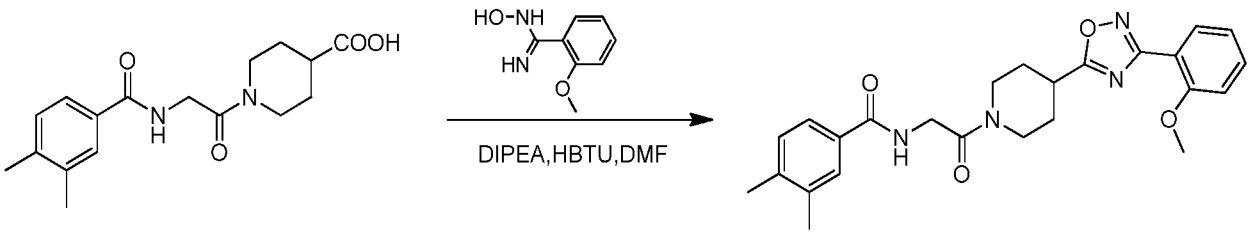
To a stirred mixture of 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (500 mg, 2.12 mmol) and N,N-dimethylformamide (1 mL) was equipped with calcium chloride tube and phosphoryl chloride (10 mL) was added dropwise. The mixture was heated at 110 ℃ for 16 h. The reaction mixture was cooled to 20 ℃, then poured onto ice water (100 mL), and stirred for 30 min. The mixture was extracted with dichloromethane (20 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (360 mg, 1.41 mmol, 67 %) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 255.1

Step 5: Preparation of (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone.

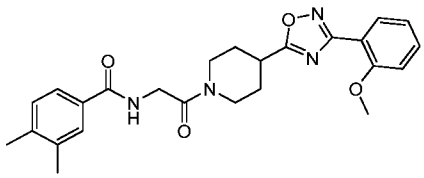


To a stirred solution of piperidin-1-yl(piperidin-4-yl)methanone (100 mg, 509 µmol) in N-methyl-2-pyrrolidone (4 mL) was added 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (194 mg, 764 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (131 mg, 1.02 mmol, 177 µL). The mixture was stirred at 120 ℃ for 16 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone (61 mg, 147.6 µmol, 29 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.47 (m, 1H), 7.42 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.24-4.16 (m, 2H), 4.08 (q, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 3.50 (br. s., 2H), 3.40 (br. s., 2H), 3.19-3.09 (m, 2H), 2.69 (tt, *J* = 3.8, 10.7 Hz, 1H), 1.94-1.71 (m, 4H), 1.63-1.48 (m, 6H), 1.42 (t, *J* = 7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 415.3.

Example 58: N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.

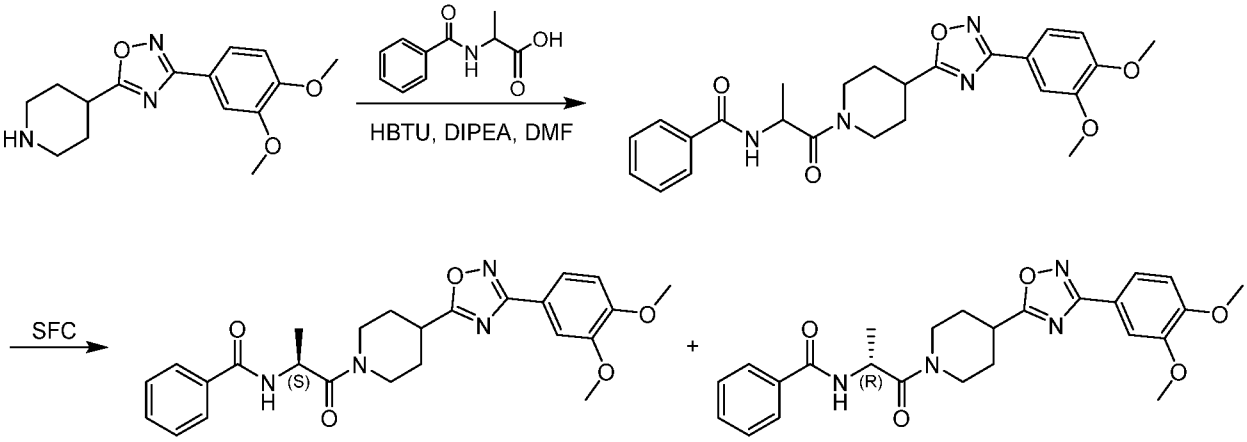


Step 1: N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.

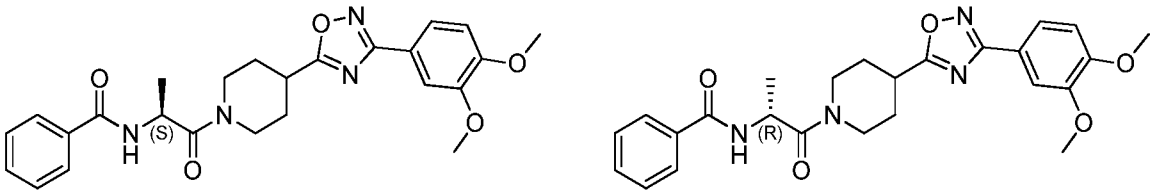


To a stirred solution of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (150 mg, 471 µmol) and N-hydroxy-2-methoxybenzimidamide (78 mg, 471 µmol) in N,N-dimethylformamide (2 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (121 mg, 942 µmol, 164 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (178 mg, 471 µmol) at 15 °C. The mixture was stirred for 15 h, then the mixture was heated to 110 °C and stirred for 5 h. The mixture was cooled and then purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 37%-67%,12 min) to obtain N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide (110 mg, 244 µmol, 52 %) as yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ7.96 (dd, J=1.5, 7.7 Hz, 1H), 7.66 (s, 1H), 7.60 (d, J=7.9 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.23 (d, J=7.5 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 4.47 (d, J=12.8 Hz, 1H), 4.35 - 4.23 (m, 2H), 4.04 (d, J=13.7 Hz, 1H), 3.92 (s, 3H), 3.49 - 3.35 (m, 2H), 3.07 (t, J=11.0 Hz, 1H), 2.32 (s, 6H), 2.27 - 2.10 (m, 2H), 2.06 - 1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 449.3.

Example 59: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1 and Example 60: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2



Step 1: Preparation of N-[(R)-2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide and N-[(S)- 2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) and 2-benzamidopropanoic acid (105 mg, 544 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL). The mixture was stirred at 20 °C for 5

h. The crude product was purified by prep-HPLC (column: Luna C18 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give rac-N-(1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide then the product purified by SFC separation (column: AD(250x30mm, 5µm); mobile phase: [Neu-IPA]; B%: 42%-42%,min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1 (63 mg, 134.93 µmol, 26 %) as a white solid and N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2 (56 mg, 120 µmol, 23% as a white solid.

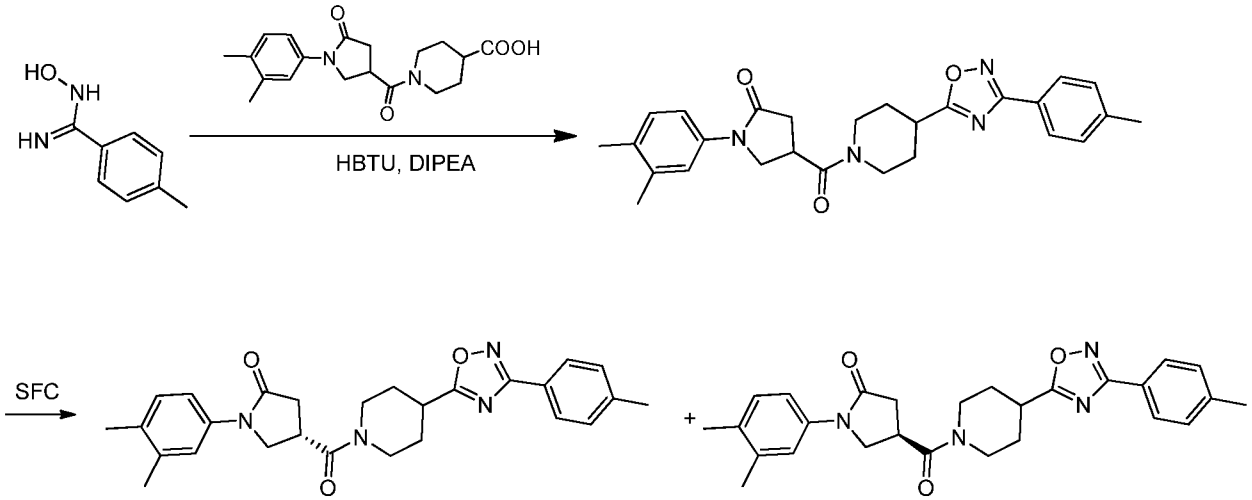
N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1:

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.63 (br dd, *J*=7.3, 16.1 Hz, 1H), 7.88 (br d, *J*=7.5 Hz, 2H), 7.62 - 7.41 (m, 5H), 7.11 (br d, *J*=8.2 Hz, 1H), 4.97 (br d, *J*=6.4 Hz, 1H), 4.43 - 4.24 (m, 1H), 4.10 - 3.95 (m, 1H), 3.82 (s, 6H), 3.42 (br t, *J*=10.8 Hz, 1H), 3.30 - 3.21 (m, 1H), 2.99 - 2.83 (m, 1H), 2.09 (br d, *J*=11.9 Hz, 2H), 1.83 - 1.60 (m, 2H), 1.30 (br s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3. ee = 100%.

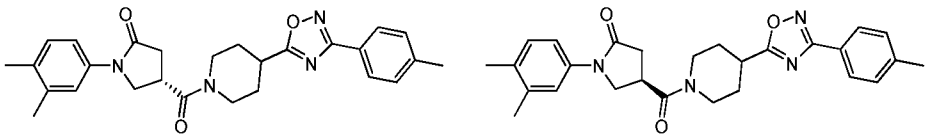
N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2:

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.65 (br dd, *J*=7.6, 16.1 Hz, 1H), 7.98 - 7.86 (m, 2H), 7.70 - 7.41 (m, 5H), 7.13 (br d, *J*=8.2 Hz, 1H), 5.00 (br d, *J*=5.5 Hz, 1H), 4.49 - 4.24 (m, 1H), 4.12 - 3.96 (m, 1H), 3.85 (s, 6H), 3.45 (br t, *J*=10.7 Hz, 1H), 3.27 (br s, 1H), 3.05 - 2.83 (m, 1H), 2.12 (br d, *J*=12.5 Hz, 2H), 1.89 - 1.61 (m, 2H), 1.32 (br s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3. ee = 99.6

Example 61: (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1 and Example 62: (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2



Step 1: Preparation of (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1 and (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2



To a stirred solution of N-hydroxy-4-methylbenzimidamide (300 mg, 2.0 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (834 mg, 2.20 mmol) and 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (688 mg, 2.00 mmol) in N,N-dimethylformamide (10 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (516 mg, 4.00 mmol, 698 µL) at 0 °C. Then the reaction was warmed to 25 °C. After 17 h, the reaction was warmed to 90 °C. After 3 h, the mixture was cooled, diluted with water (10 mL), and extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by prep-HPLC (column: Phenomenex luna(2) C18 250x50 10µm; mobile phase: [water (0.1%TFA)-acetonitrile]; B%: 40%-70%,20min) to give the racemic of 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (600 mg, 1.31 mmol, 65 %). This was purified by SFC (column: AS(250x30mm, 5µm); mobile phase: [CO_2 base-methanol]; B%: 40%-40%) to give (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1 (193 mg, 421 µmol, 21%) as a white solid, and (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2 (199 mg, 433 µmol, 22 %) as a white solid.

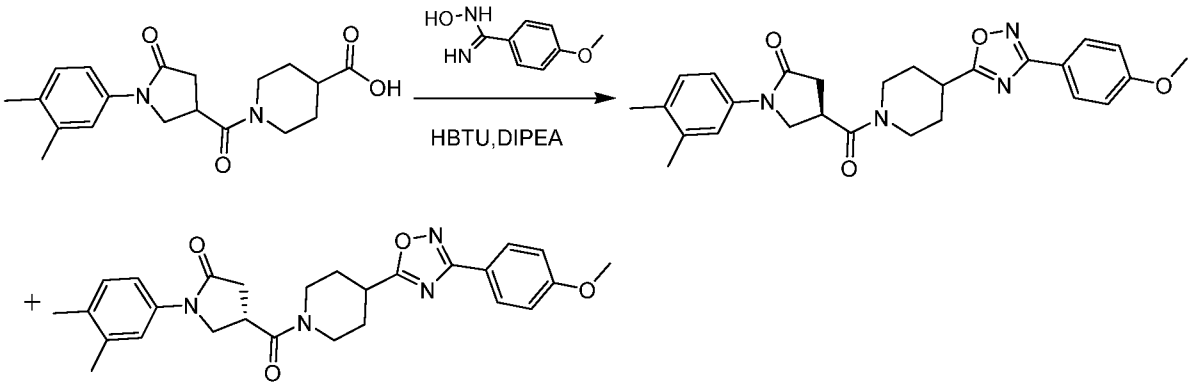
(2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1:

^{1}H NMR (400MHz, DMSO-d6) δ = 7.91 (br d, J=6.9 Hz, 2H), 7.43 (br s, 1H), 7.38 (br d, J=8.0 Hz, 3H), 7.12 (br d, J=6.3 Hz, 1H), 4.35 (br s, 1H), 4.09 - 3.98 (m, 2H), 3.92 (td, J=5.0, 10.0 Hz, 1H), 3.80 - 3.63 (m, 1H), 3.45 (br t, J=10.8 Hz, 1H), 3.36 (br s, 1H), 3.00 - 2.90 (m, 1H), 2.82 - 2.65 (m, 2H), 2.39 (s, 3H), 2.27 - 2.10 (m, 8H), 1.91 - 1.61 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3; ee = 98.6

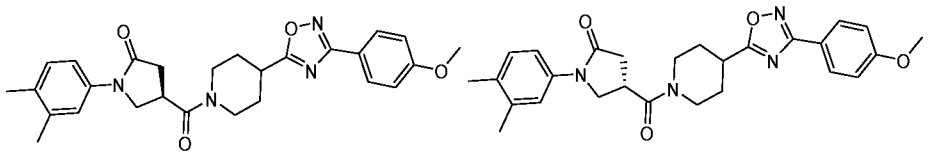
(2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2:

^{1}H NMR (400MHz, DMSO-d6) δ = 7.91 (br d, J=6.9 Hz, 2H), 7.43 (br s, 1H), 7.38 (br d, J=8.0 Hz, 3H), 7.12 (br d, J=6.4 Hz, 1H), 4.35 (br s, 1H), 4.11 - 3.97 (m, 2H), 3.92 (td, J=5.0, 9.9 Hz, 1H), 3.81 - 3.68 (m, 1H), 3.53 - 3.37 (m, 1H), 3.36 (br s, 1H), 3.02 - 2.90 (m, 1H), 2.82 - 2.65 (m, 2H), 2.39 (s, 3H), 2.25 - 2.09 (m, 8H), 1.89 - 1.62 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3; ee = 99%.

Example 63: 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and Example 64: 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2



Step 1: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (350 mg, 1.02 mmol) and N-hydroxy-4-methoxybenzimidamide (168 mg, 1.02 mmol) in N,N-dimethylformamide (3 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (262 mg, 2.03 mmol, 354 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (385 mg, 1.02 mmol), then the mixture was stirred for 15 h at 15 °C. The the mixture was then heated to 110 °C and stirred for 5 h. The mixture was cooled and purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 37%-67%, 12 min) to give racemic 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (0.2 g) as a white solid. This was purified by SFC separation: (column: OJ(250x30mm,10µm); mobile phase: [CO_2 base-ethanol]; B%: 45%-45%) to give ((1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 (84 mg, 177 µmol, 17 %) as a white solid and 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 (96 mg, 198 µmol, 19 %) as a yellow solid

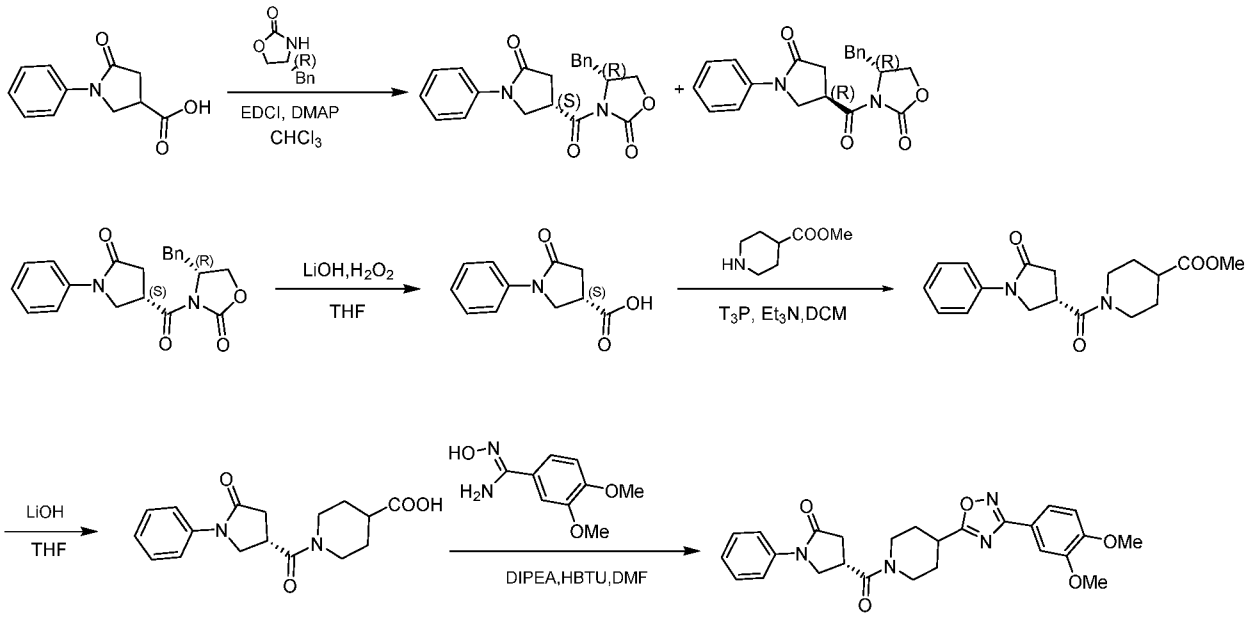
1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1:

^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (dd, J=2.2, 8.8 Hz, 2H), 7.36 (s, 1H), 7.27 (d, J=7.9 Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 7.04 (d, J=7.1 Hz, 2H), 4.53 - 4.43 (m, 1H), 4.18 - 3.99 (m, 3H), 3.95 - 3.73 (m, 4H), 3.49 - 3.36 (m, 2H), 3.14 - 3.01 (m, 1H), 2.93 - 2.77 (m, 2H), 2.47 - 2.04 (m, 8H), 2.01 - 1.80 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3; ee = 100 %.

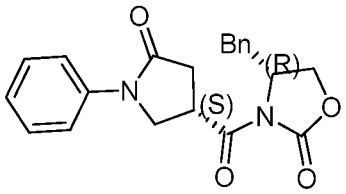
1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2:

^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (dd, J=2.4, 9.0 Hz, 2H), 7.36 (s, 1H), 7.27 (d, J=8.4 Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 7.04 (d, J=7.1 Hz, 2H), 4.48 (d, J=7.5 Hz, 1H), 4.16 - 4.00 (m, 3H), 3.92 - 3.74 (m, 4H), 3.49 - 3.37 (m, 2H), 3.13 - 3.03 (m, 1H), 2.91 - 2.80 (m, 2H), 2.34 - 2.11 (m, 8H), 1.98 - 1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3; ee = 100 %.

Example 65: (4S)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one

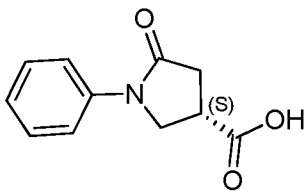


Step 1: (4R)-4-benzyl-3-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]oxazolidin-2-one



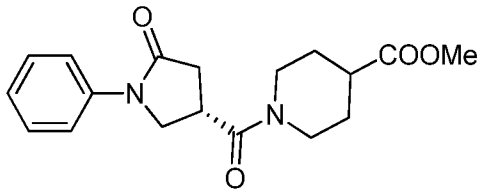
To a stirred solution of 5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (20.0 g, 97.5 mmol) in chloroform (100 mL) was added (4R)-4-benzyloxazolidin-2-one (20.72 g, 117 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (20.74 g, 108.2 mmol) and DMAP (6.43 g, 52.6 mmol) at 0 ℃. After addition, the mixture was stirred for 15 min, then warmed and stirred at 20 ℃ for 18 h. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=1/1 to 1:9) to give (4R)-4-benzyl-3-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]oxazolidin-2-one (10.0 g, 27.4 mmol, 28 %) and (4R)-4-benzyl-3-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]oxazolidin-2-one (10.0 g, 27 mmol, 28 %) each as a white solid. LCMS (ESI) m/z: 365.1 $[M+H]^+$.

Step 2: (3S)-5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid



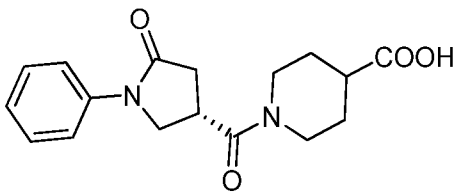
To a stirred solution of lithium hydroxide monohydrate (2.63 g, 62.8 mmol) in water (30 mL) was added dropwise hydrogen peroxide (15.5 g, 456.6 mmol, 13.2 mL) at 0℃. The mixture was stirred for 30 min. To the mixture was then added tetrahydrofuran (80 mL), water (30 mL) followed by a solution of 3-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]-4-phenyl-oxazolidin-2-one (10.0 g, 28.5 mmol) in tetrahydrofuran (80 mL) dropwise. The mixture was stirred at 0 ℃ for 1h, quenched by addition of a sodium sulfate solution in water (10 mL) at 0 ℃, and made basic (pH 11) by addition of an aqueous sodium carbonate solution. The mixture was extracted with ethyl acetate (100 mL), acidified to pH 2 using 1M HCl, and extracted again with ethyl acetate (100 mL). The organic layers were washed with a saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give (3S)-5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (4.80 g, 23.39 mmol, 82 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.57 (dd, J=0.9, 8.6 Hz, 2H), 7.40 - 7.34 (m, 2H), 7.20 - 7.15 (m, 1H), 4.18 - 4.13 (m, 1H), 4.10 - 4.04 (m, 1H), 3.45 - 3.35 (m, 1H), 3.03 - 2.86 (m, 2H).

Step 3: methyl 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylate



A mixture of (3S)-5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (4.50 g, 21.93 mmol), methyl piperidine-4-carboxylate (3.77 g, 26.32 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (27.91 g, 43.86 mmol, 26.08 mL, 50% purity), triethylamine (44.38 g, 438.60 mmol, 60 mL) in dichloromethane (60 mL) was degassed, purged with nitrogen 3 times, and then the mixture was stirred at 20 ℃ for 16 h under a nitrogen atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (50 mL). The organic layers were washed with saturated aqueous sodium chloride solution (50 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by chromatography (silica, petroleum ether / ethyl acetate=1:1) to give methyl 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylate (4.70 g, 14.2 mmol, 65 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.56 (d, J=7.7 Hz, 2H), 7.35 (t, J=7.5 Hz, 2H), 7.16 - 7.11 (m, 1H), 4.47 - 4.34 (m, 1H), 4.24 (dd, J=7.3, 9.5 Hz, 1H), 3.91 - 3.81 (m, 2H), 3.69 (s, 3H), 3.52 (quin, J=8.5 Hz, 1H), 3.24 - 3.12 (m, 1H), 2.98 - 2.87 (m, 2H), 2.80 - 2.73 (m, 1H), 2.64 - 2.52 (m, 1H), 1.97 (br dd, J=4.3, 8.3 Hz, 2H), 1.73 - 1.63 (m, 2H).

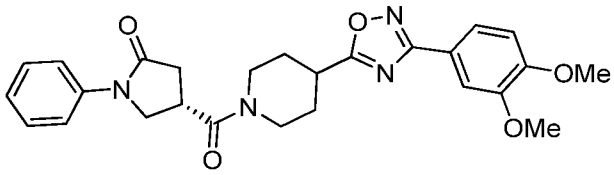
Step 4: 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylate (3.00 g, 9.08 mmol) in tetrahydrofuran (60 mL) was added a solution of lithium hydroxide

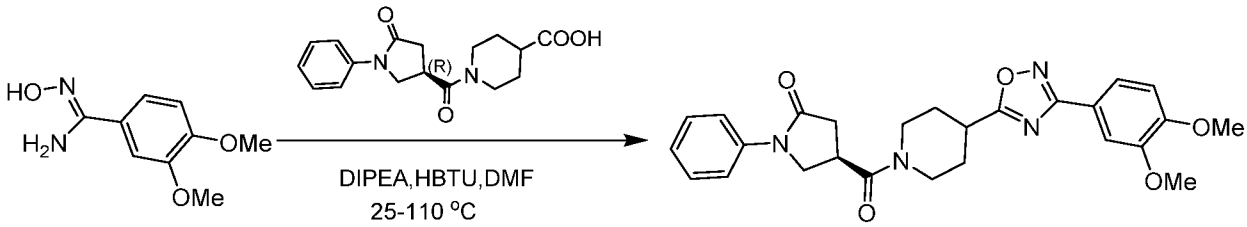
monohydrate (0.5 M, 21.79 mL) in water. The mixture was then stirred at 0 °C for 2 h. The mixture was acidified to pH 4-5 using 1M HCl, and then extracted with dichloromethane (60 mL; 30 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution 40 mL; 20 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (2.70 g, 8.53 mmol, 94 %) as a white solid.

Step 5: (4S)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one



A mixture of N'-hydroxy-3,4-dimethoxy-benzamidine (1.04 g, 5.32 mmol), 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (1.40 g, 4.43 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (2.18 g, 5.76 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.72 g, 13.29 mmol, 2.32 mL) in N,N-dimethylformamide (8.00 mL), was stirred at 20°C for 15h and at 110°C for 1h. The mixture was cooled to room temperature, concentrated under reduced pressure to give a residue purified by prep-HPLC [column: Phenomenex luna C18 250x50mmx10 µm; mobile phase: water / ammonium carbonate (10mM) / acetonitrile]; B%: 30%-60%,30 min. The desired compound (4S)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one was isolated as a light yellow solid (608 mg, 1.28 mmol, 29 %). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.68 (br d, J=8.2 Hz, 1H), 7.61 - 7.53 (m, 3H), 7.40 - 7.33 (m, 2H), 7.18 - 7.12 (m, 1H), 6.95 (d, J=8.4 Hz, 1H), 4.61 - 4.46 (m, 1H), 4.30 (dd, J=7.2, 9.6 Hz, 1H), 4.01 - 3.92 (m, 8H), 3.57 (quin, J=8.4 Hz, 1H), 3.43 - 3.26 (m, 2H), 3.14 - 2.91 (m, 2H), 2.86 - 2.80 (m, 1H), 2.23 (br t, J=13.1 Hz, 2H), 2.02 - 1.93 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

Example 66 [(4R)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one]

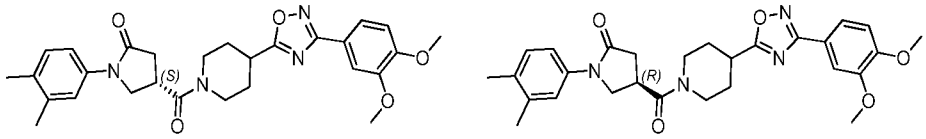


To a stirred solution of 1-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (115 mg, 363.52 µmol) and N'-hydroxy-3,4-dimethoxy-benzamidine (71 mg, 363.52 µmol) in N,N-dimethylformamide (500 µL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (137 mg, 363.52 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (93 mg, 727 µmol, 126 µL) at 25°C. The mixture was then stirred at 25 °C for 2 h, and at 110 °C for 2h. The mixture was concentrated under reduced pressure and the resulting crude product was purified by chromatography (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: water / ammonium carbonate

(10mM) / acetonitrile]; B%: 25%-60%,12 min to give (4R)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (32 mg, 67.45 µmol, 19 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (br d, *J*=8.2 Hz, 1H), 7.61 - 7.55 (t, 3H), 7.37 (t, *J*=7.8 Hz, 2H), 7.19 - 7.14 (t, 1H), 6.95 (d, *J*=8.4 Hz, 1H), 4.60 - 4.46 (m, 1H), 4.31 (dd, *J*=7.2, 9.6 Hz, 1H), 3.98 - 3.94 (m, 7H), 3.98 - 3.92 (m, 1H), 3.58 (quin, *J*=8.5 Hz, 1H), 3.43 - 3.26 (m, 2H), 3.16 - 2.91 (m, 2H), 2.88 - 2.79 (m, 1H), 2.24 (br t, *J*=13.3 Hz, 2H), 2.06 - 1.88 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

Examples 67: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 1 and Example 68: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 2.

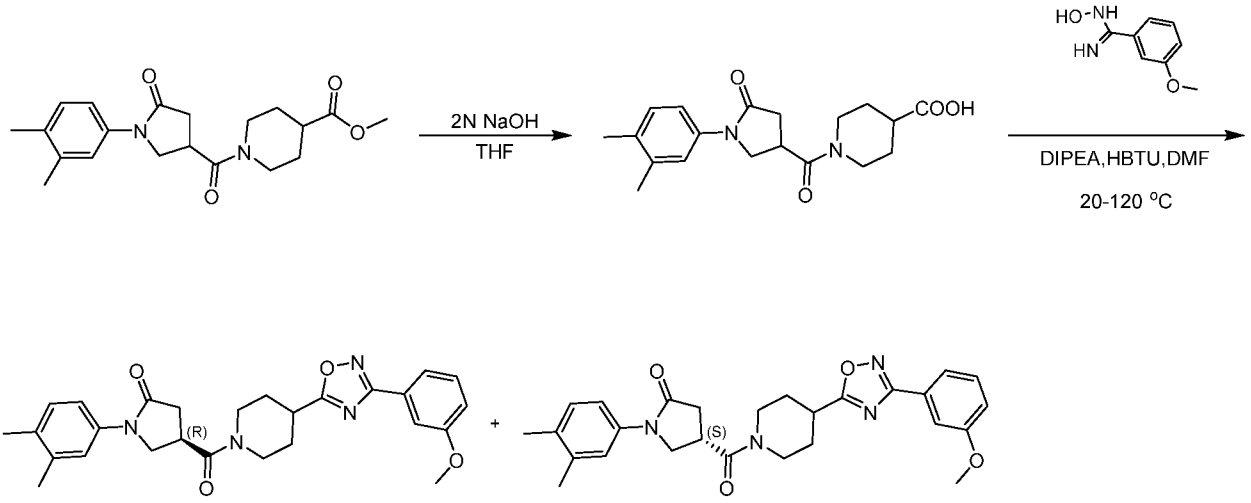
Step 1: Preparation of 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one



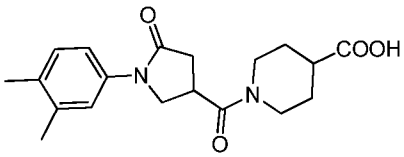
To a stirred solution of 1-[1-(3,4-dimethylphenyl)-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (351 mg, 1.02 mmol) in N,N-dimethylformamide (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (386 mg, 1.02 mmol), N-ethyl-N-(propan-2-yl)propan-2-amine (395 mg, 3.06 mmol, 534 µL) and N-hydroxy-3,4-dimethoxy-benzamidine (200 mg, 1.02 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was then diluted with water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. N,N-dimethylformamide (2 mL) was added to the residue and the resulting mixture was heated at 120 °C for 5 h. The mixture was cooled to 25 °C, diluted by addition of water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue that was purified by prep-HPLC (column: Waters Xbridge 150x25 µm; mobile phase: water / ammonium carbonate (10mM) / acetonitrile]; B%: 33%-63%,12 min) to give racemic 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one. This was separated by chiral-SFC (column: AS(250x30mm, 10µm); mobile phase: [CO_2 base-methanol]; B%: 40%-40%,min) to give firstly 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 1 (51 mg, 102 µmol, 10 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 7.61 (br d, J=8.4 Hz, 1H), 7.48 (s, 1H), 7.43 (br s, 1H), 7.38 (br d, J=7.5 Hz, 1H), 7.16 - 7.10 (m, 2H), 4.37 (br s, 1H), 4.08 - 3.99 (m, 2H), 3.96 - 3.88 (m, 1H), 3.85 (s, 6H), 3.79 - 3.67 (m, 1H), 3.45 (br t, J=10.8 Hz, 1H), 3.32 - 3.28 (m, 1H), 3.02 - 2.87 (m, 1H), 2.82 - 2.70 (m, 2H), 2.24 - 2.18 (m, 6H), 2.18 - 2.10 (m, 2H), 1.91 - 1.61 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.4 and secondly 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 2 (48 mg, 95 µmol, 9 %) also as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 7.61 (br d, J=8.4 Hz, 1H), 7.48 (s, 1H), 7.43 (br s, 1H), 7.41 - 7.35 (m, 1H), 7.17 - 7.10 (m, 2H), 4.37 (br s, 1H), 4.09 - 3.99 (m, 2H), 3.98 - 3.89 (m, 1H), 3.85 (s, 6H), 3.78 - 3.68 (m, 1H), 3.50 - 3.39 (m, 1H), 3.35 (br s, 1H), 3.00 - 2.88 (m, 1H),

2.81 - 2.70 (m, 2H), 2.26 - 2.19 (m, 6H), 2.17 - 2.09 (m, 2H), 1.88 - 1.63 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.4

Example 69 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and Example 70 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2

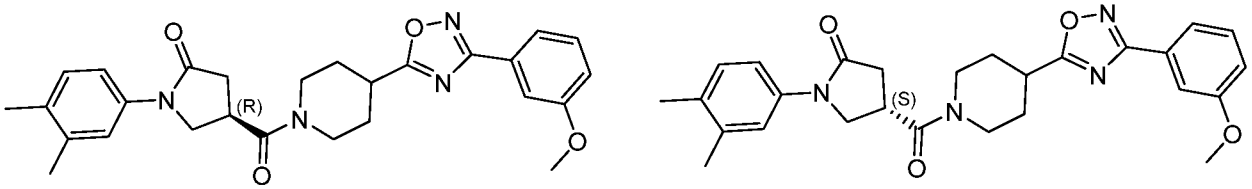


Step 1: Preparation of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid



To a stirred solution of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (470 mg, 1.31 mmol) in tetrahydrofuran (5 mL) was added sodium hydroxide (2 M, 1.31 mL). The mixture was stirred at 20 °C for 16 h. The mixture was acidified with concentrated hydrochloric acid until pH = 1. The mixture was extracted with dichloromethane (20 mL x 4). The organic layers were combined and washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (300 mg) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 345.2.

Step 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (300 mg, 871 µmol) in N,N-dimethylformamide (4 mL) was added N-hydroxy-3-methoxy-benzamidine (173 mg, 1.05 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium

hexafluorophosphate) (330 mg, 871 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (337 mg, 2.61 mmol, 456 µL). The mixture was stirred at 20℃ for 2 h and then at 120 ℃ for 2 h. The reaction mixture was cooled, concentrated under reduced pressure and purified directly by preparative HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-65%,12 min) to give (rac)- 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl) pyrrolidin-2-one that was was purified by chiral-SFC (column: AD(250mm*30mm,5mm); mobile phase: [Base-isopropanol]; B%: 42%-42%,min) to give firstly 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl) yrrolidin-2-one, Enantiomer 1 (75 mg, 158.7 µmol, 18 %, ee 100 %) as a white solid, then 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 (75 mg, 160 µmol, 18 %, ee 99.7 %) as a yellow solid.

1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl) pyrrolidin-2-one, Enantiomer 1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 1H), 7.55-7.50 (m, 1H), 7.31 (d, *J* = 12.3 Hz, 2H), 7.22-7.19 (m, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 4.53-4.37 (m, 1H), 4.21 (dd, *J* = 7.3, 9.6 Hz, 1H), 3.95-3.77 (m, 5H), 3.49 (td, *J* = 8.6, 16.9 Hz, 1H), 3.36-3.20 (m, 2H), 3.12-2.96 (m, 1H), 2.89 (td, *J* = 8.3, 16.9 Hz, 1H), 2.79-2.70 (m, 1H), 2.18 (d, *J* = 13.1 Hz, 8H), 1.99-1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.1.

1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 1H), 7.53 (s, 1H), 7.36-7.27 (m, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 4.53-4.37 (m, 1H), 4.21 (dd, *J* = 7.3, 9.5 Hz, 1H), 3.96-3.77 (m, 5H), 3.55-3.44 (m, 1H), 3.37-3.19 (m, 2H), 3.12-2.82 (m, 2H), 2.76 (d, *J* = 9.4 Hz, 1H), 2.18 (d, *J* = 13.1 Hz, 8H), 1.92 (br. s., 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.1.

Example 71 (1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one), Enantiomer 1 and Example 72 (1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one), Enantiomer 2

Racemic 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (80 mg) was purified by SFC separation (column: AD (250x30mm,5µm); mobile phase: [CO_2 base-isopropanol]; B%: 50%-50%,min) to give firstly 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 (26 mg, 59 µmol, 7 %) as a white solid and secondly 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 as a white solid (23 mg, 52 µmol, 6 %).

1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.00 (m, 2H), 7.41-7.33 (m, 3H), 7.32-7.29 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.66-4.54 (m, 1H), 4.30 (dd, *J* = 7.4, 9.5 Hz, 1H), 4.05-3.88 (m, 2H), 3.65-3.55 (m, 1H), 3.43-3.30 (m, 1H), 3.20 (d, *J* = 3.4 Hz, 1H), 3.12-2.94 (m, 2H), 2.85 (d, *J* = 9.7 Hz, 1H), 2.47 (s, 3H), 2.32-2.14 (m, 8H), 1.94 (br. s., 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.90 (m, 2H), 7.32-7.24 (m, 3H), 7.22-7.19 (m, 1H), 7.05 (d, J=8.2 Hz, 1H), 4.58-4.43 (m, 1H), 4.20 (s, 1H), 3.94-3.79 (m, 2H), 3.50 (quin, J = 8.5 Hz, 1H), 3.28 (br. s., 1H), 3.10 (d, J = 3.9 Hz, 1H), 3.02-2.84 (m, 2H), 2.78-2.68 (m, 1H), 2.38 (s, 3H), 2.23-2.03 (m, 8H), 1.83 (d, J = 10.8 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3

Examples 73 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and Example 74 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2

Racemic 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (120 mg) was purified by SFC separation (column: OJ(250mmX30mm,5mm); mobile phase: [CO_2 base-ethanol]; B%: 30%-30%,min) to give firstly 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 (39 mg, 86.7 µmol, 11 %) as a pink solid and secondly 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 (36 mg, 77.9 µmol, 10 %) as a pink solid.

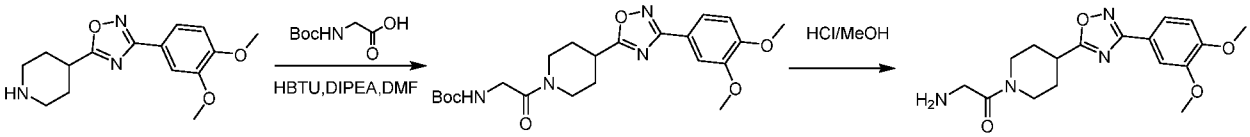
1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br. s., 2H), 7.39 (d, *J* = 15.0 Hz, 3H), 7.29 (br. s., 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 4.58 (t, *J* = 13.9 Hz, 1H), 4.28 (*t*, *J* = 8.6 Hz, 1H), 4.01-3.87 (m, 2H), 3.62-3.53 (m, 1H), 3.35 (br. s., 1H), 3.19 (br. s., 1H), 3.08-2.93 (m, 2H), 2.86-2.76 (m, 1H), 2.45 (s, 3H), 2.32-2.11 (m, 8H), 1.90 (d, *J* = 13.7 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

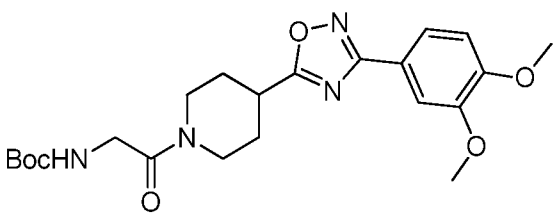
1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2:

^{1}H NMR (400 MHz, Methanol-d4) δ8.00-7.90 (m, 2H), 7.53-7.45 (m, 2H), 7.41-7.37 (m, 1H), 7.32-7.27 (m, 1H), 7.19-7.13 (m, 1H), 4.53 (dd, *J*=3.5, 13.2 Hz, 1H), 4.19-4.03 (m, 3H), 3.90-3.80 (m, 1H), 3.49-3.39 (m, 1H), 3.30-3.20 (m, 1H), 3.12-3.00 (m, 1H), 2.94-2.82 (m, 2H), 2.47 (s, 3H), 2.35-2.11 (m, 8H), 1.99-1.77 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 75: (2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone).

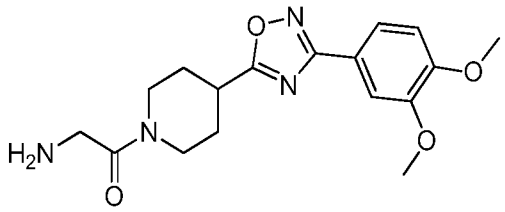


Step 1: Preparation of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate.



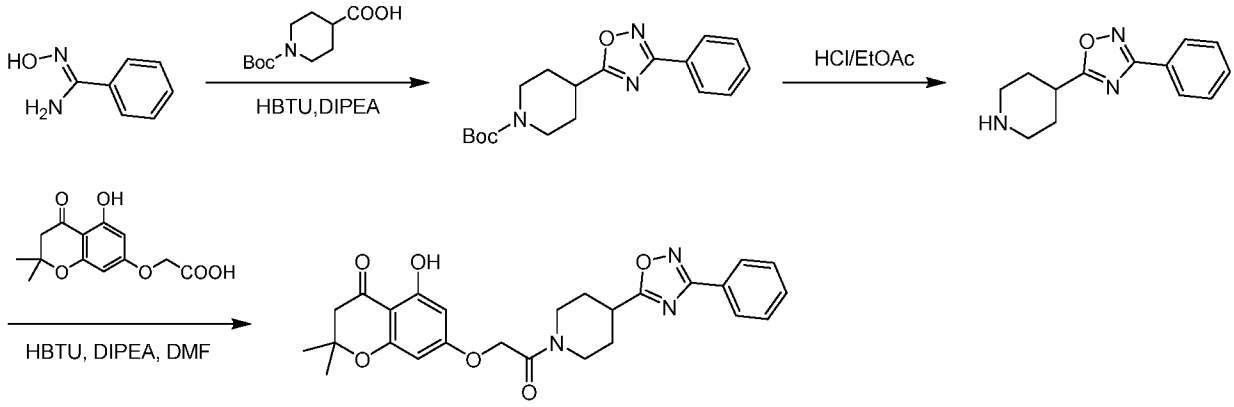
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (2.0 g, 6.91 mmol) in N,N-dimethylformamide (20 mL) was added 2-(tert-butoxycarbonylamino)acetic acid (1.21 g, 6.91 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (2.62 g, 6.91 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.68 g, 20.7 mmol, 3.62 mL). The mixture was stirred at 15 °C for 2 h. The reaction mixture was quenched by addition of water (20 mL) then the mixture was extracted with ethyl acetate (60 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude material that was purified by chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) to give tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.60 g, 5.82 mmol, 84 %) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 447.2.

Step 2: Preparation of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone

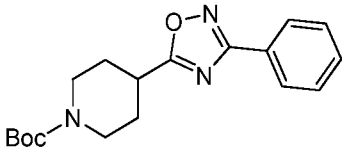


To a stirred solution of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.50 g, 5.60 mmol) in methanol (10 mL) was added methanolic hydrogen chloride solution (30 mL). The mixture was stirred at 20 °C for 1 h and then concentrated to give 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (1.90 g, 5.49 mmol, 97.95 %), isolated as a brown solid and used for the next step without further purification. A small amount (0.1g) of the crude product was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give a pure sample for analysis: 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (32 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.67 (m, 1H), 7.58 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 3.98 (d, J = 7.2 Hz, 6H), 3.84 (d, J = 12.0 Hz, 1H), 3.54 (s, 2H), 3.34-3.21 (m, 2H), 3.08 (d, J = 12.3 Hz, 1H), 2.21 (d, J = 13.1 Hz, 2H), 1.98 (d, J = 9.4 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 347.1.

Example 76: (5-hydroxy-2,2-dimethyl-7-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethoxy)choman-4-one).

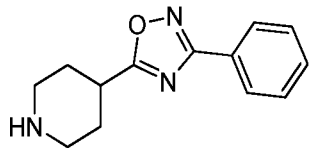


Step 1: Preparation of tert-butyl 4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate



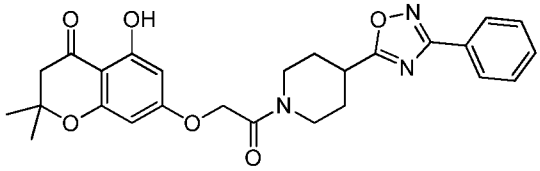
To a stirred solution of (Z)-N'-hydroxybenzimidamide (214 mg, 1.57 mmol) in N,N-dimethylformamide (5 mL) was added 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (300 mg, 1.31 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (496 mg, 1.31 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (507 mg, 3.93 mmol, 686 µL). The mixture was stirred at 20 °C for 2 h, and then heated at 120 °C for 2 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. The crude product was extracted with petroleum ether (30 mL x 2). The combined organic extracts were concentrated under reduced pressure to give tert-butyl 4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (310 mg, 941 µmol, 72 %) as a yellow oil. This product was used in the next step without further purification.

Step 2: Preparation of 3-phenyl-5-(piperidin-4-yl)-1,2,4-oxadiazole



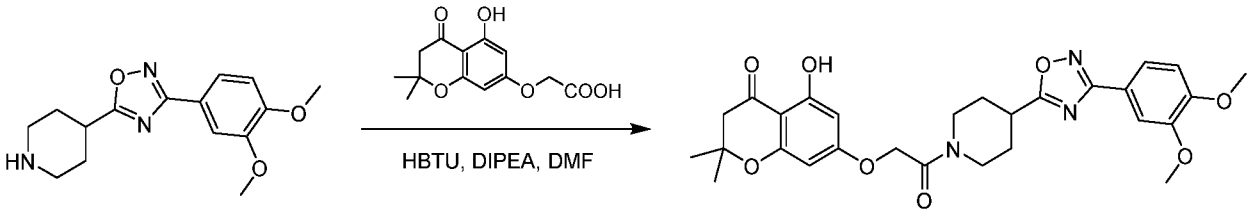
To a stirred solution of tert-butyl 4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (310 mg, 941 µmol) in ethyl acetate (2 mL) was added an anhydrous solution of hydrochloric acid in ethyl acetate (20 mL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to provide the crude 3-phenyl-5-(piperidin-4-yl)-1,2,4-oxadiazole (233 mg) as a yellow solid that was used for the next step without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 230.2.

Step 3: Preparation of 5-hydroxy-2,2-dimethyl-7-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethoxy)choman-4-one



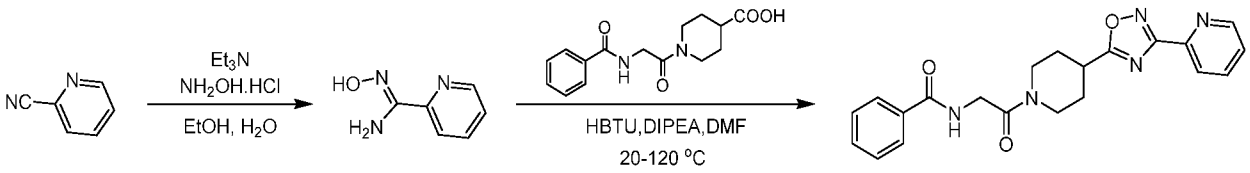
To a stirred solution of 2-((5-hydroxy-2,2-dimethyl-4-oxochoman-7-yl)oxy)acetic acid (150 mg, 563 µmol) in N,N-dimethylformamide (2 mL) was added 3-phenyl-5-(piperidin-4-yl)-1,2,4-oxadiazole (142 mg, 620 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (213 mg, 563 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (291 mg, 2.25 mmol, 393 µL). The mixture was stirred at 20 ℃ for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-75%,12 min) to give 5-hydroxy-2,2-dimethyl-7-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethoxy)choman-4-one (120 mg, 250.6 µmol, 44 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 1H), 8.12 - 8.07 (m, 2H), 7.56 - 7.48 (m, 3H), 6.07 (d, *J*=2.4 Hz, 1H), 6.04 (d, *J*=2.3 Hz, 1H), 4.74 (s, 2H), 4.46 (d, *J*=13.8 Hz, 1H), 3.98 (d, *J*=13.1 Hz, 1H), 3.42 - 3.28 (m, 2H), 3.13 (t, *J*=11.1 Hz, 1H), 2.71 (s, 2H), 2.23 (br. s., 2H), 2.07 - 1.92 (m, 2H), 1.49 - 1.46 (m, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 478.2.

Example 77 (7-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethoxy)-5-hydroxy-2,2-dimethylchoman-4-one).

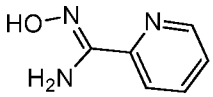


To a stirred solution of 2-((5-hydroxy-2,2-dimethyl-4-oxochoman-7-yl)oxy)acetic acid (150 mg, 563 µmol) in N,N-dimethylformamide (2 mL) was added 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (195 mg, 676 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (213 mg, 563 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (291 mg, 2.25 mmol, 393 µL). The mixture was stirred at 20 ℃ for 2 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give 7-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethoxy)-5-hydroxy-2,2-dimethylchoman-4-one (133 mg, 245.66 µmol, 44 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 12.00 (s, 1H), 7.71 (dd, *J*=1.9, 8.3 Hz, 1H), 7.58 (d, *J*=1.9 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 6.06 (d, *J*=2.4 Hz, 1H), 6.03 (d, *J*=2.4 Hz, 1H), 4.74 (s, 2H), 4.47 (d, *J*=14.2 Hz, 1H), 4.01 - 3.94 (m, 7H), 3.41 - 3.26 (m, 2H), 3.11 (t, *J*=11.0 Hz, 1H), 2.71 (s, 2H), 2.22 (br. s., 2H), 2.06 - 1.93 (m, 2H), 1.47 (s, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 538.3.

Example 78: (N-(2-oxo-2-(4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide.

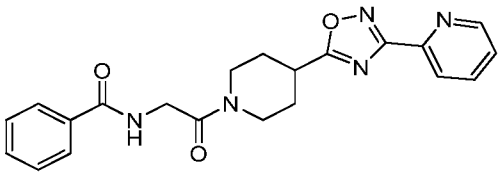


Step 1: Preparation of (Z)-N'-hydroxypicolinimidamide.



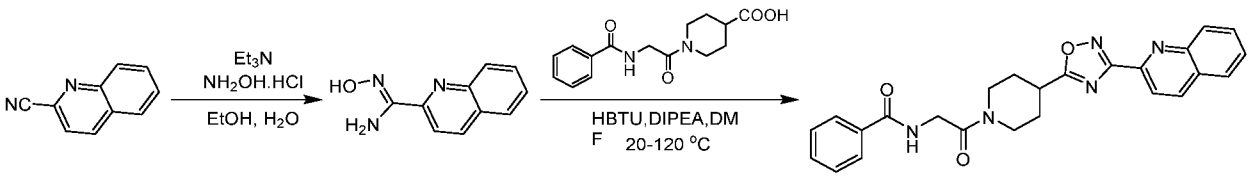
To a stirred solution of picolinonitrile (3.0 g, 28.8 mmol, 2.78 mL) in ethanol (30 mL) was added hydroxylamine hydrochloride (4.01 g, 57.6 mmol), triethylamine (5.83 g, 57.6 mmol, 8.0 mL) and water (5 mL). The mixture was heated at 75 °C for 5 h. The mixture was then concentrated to give a residue. The solid residue was triturated with water (30 mL), filtered, and dried under reduced pressure to give (Z)-N'-hydroxypicolinimidamide (2.0 g, 14.6 mmol, 51 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.57 (d, *J*=4.5 Hz, 1H), 7.92 - 7.75 (m, 2H), 7.47 - 7.35 (m, 1H), 5.85 (br. s., 2H).

Step 2: Preparation of N-(2-oxo-2-(4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide

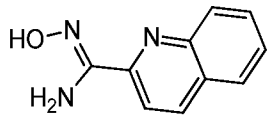


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxypicolinimidamide (56 mg, 413 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled, concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-55%,12 min) to give N-(2-oxo-2-(4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide (75 mg, 192 µmol, 47 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (td, *J*=0.8, 4.0 Hz, 1H), 8.18 - 8.12 (m, 1H), 7.93 - 7.84 (m, 3H), 7.58 - 7.43 (m, 4H), 7.35 (br. s., 1H), 4.53 (d, *J*=13.6 Hz, 1H), 4.32 (t, *J*=3.5 Hz, 2H), 3.93 (d, *J*=14.1 Hz, 1H), 3.45 - 3.31 (m, 2H), 3.21 - 3.10 (m, 1H), 2.37 - 2.24 (m, 2H), 2.15 - 1.98 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 392.2.

Example 79: N-(2-oxo-2-(4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide

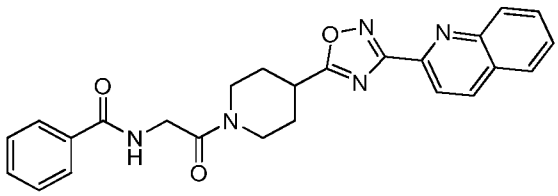


Step 1: Preparation of (Z)-N'-hydroxyquinoline-2-carboximidamide.



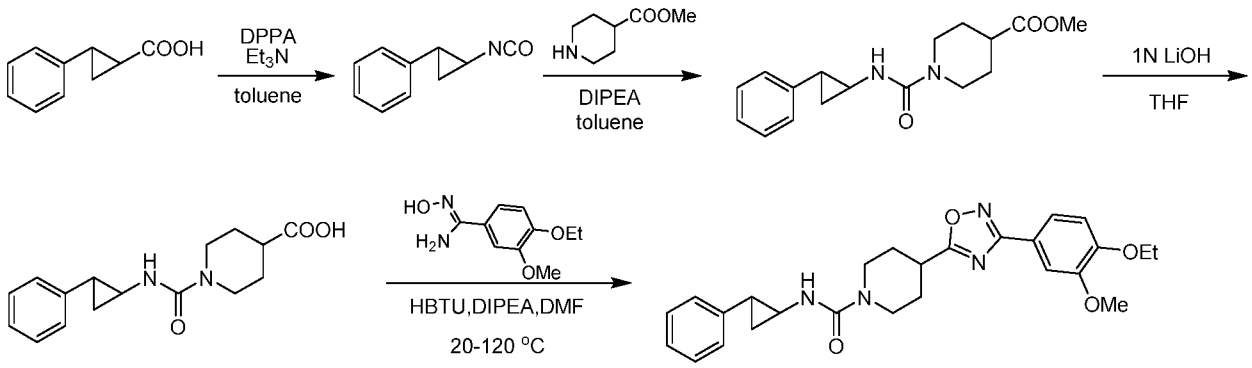
To a stirred solution of quinoline-2-carbonitrile (900 mg, 5.84 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (811 mg, 11.7 mmol), triethylamine (1.18 g, 11.7 mmol, 1.6 mL) and water (1 mL). The mixture was heated at 75 °C for 5 h. The reaction mixture was cooled and filtered, and the filter cake dried in vacuo to give (Z)-N'-hydroxyquinoline-2-carboximidamide (1.0 g, 5.34 mmol, 91 %) as a light yellow solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.34 (d, *J*=8.7 Hz, 1H), 8.10 - 7.93 (m, 3H), 7.80 (s, 1H), 7.67 - 7.59 (m, 1H), 6.02 (br. s., 2H).

Step 2: Preparation of N-(2-oxo-2-(4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide

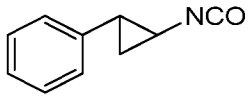


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxyquinoline-2-carboximidamide (77 mg, 413 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol). The mixture was stirred at 20 °C for 2 h firstly, then heated at 120 °C for 2 h. The reaction mixture was cooled and purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%:30%-60%,12 min) to give N-(2-oxo-2-(4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide (66 mg, 150 µmol, 36 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J*=2.1, 8.5 Hz, 2H), 8.14 (d, *J*=8.5 Hz, 1H), 7.86 - 7.77 (m, 3H), 7.72 (dt, *J*=1.3, 7.7 Hz, 1H), 7.61 - 7.53 (m, 1H), 7.49 - 7.34 (m, 3H), 7.27 (br. s., 1H), 4.50 (d, *J*=13.8 Hz, 1H), 4.24 (d, *J*=3.6 Hz, 2H), 3.87 (d, *J*=13.8 Hz, 1H), 3.42 - 3.22 (m, 2H), 3.09 - 2.98 (m, 1H), 2.31 - 2.16 (m, 2H), 2.10 - 1.91 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 442.2.

Example 80: 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-(2-phenylcyclopropyl)piperidine-1-carboxamide

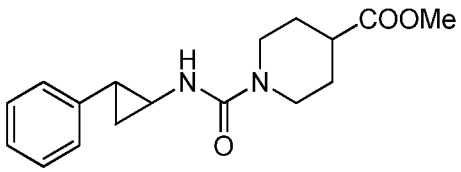


Step 1: (2-isocyanatocyclopropyl)benzene.



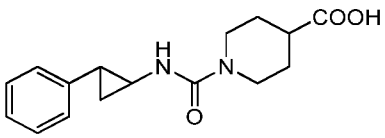
To a stirred solution of 2-phenylcyclopropanecarboxylic acid (1.0 g, 6.17 mmol) in toluene (10 mL) was added diphenylphosphoryl azide (2.04 g, 7.40 mmol, 1.60 mL) and triethylamine (935 mg, 9.25 mmol, 1.28 mL) under nitrogen. The mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled then concentrated in vacuo to give (2-isocyanatocyclopropyl)benzene (2.0 g) as a yellow oil that was used directly without purification.

Step 2: Preparation of methyl 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylate.



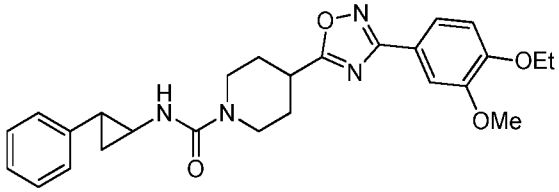
To a stirred solution of methyl piperidine-4-carboxylate (800 mg, 5.59 mmol) in toluene (10 mL) was added (2-isocyanatocyclopropyl)benzene (2.0 g, 12.58 mmol, 2.25 *eq*) and N-ethyl-N-(propan-2-yl)propan-2-amine (722 mg, 5.59 mmol, 975 µL). After 16 h, the reaction mixture was quenched with water (10 mL). The mixture was extracted with ethyl acetate (50 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a residue which was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 2 :1) to give methyl 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylate (820 mg, 2.71 mmol, 48 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 - 7.19 (m, 1H), 7.17 (s, 1H), 7.10 (d, *J*=7.4 Hz, 3H), 4.75 (br. s., 1H), 3.79 (d, *J*=13.3 Hz, 2H), 3.63 (s, 3H), 2.89 - 2.73 (m, 3H), 2.47 - 2.33 (m, 1H), 2.02 - 1.78 (m, 3H), 1.61 (dd, *J*=2.1, 13.1 Hz, 2H), 1.16 - 1.11 (m, 1H), 1.08 - 1.03 (m, 1H).

Step 3: Preparation of 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid.



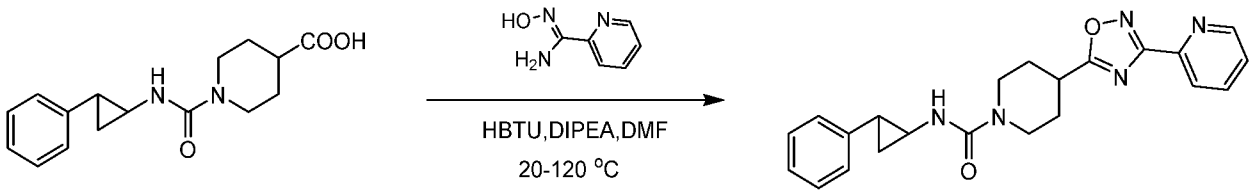
To a stirred solution of methyl 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylate (770 mg, 2.55 mmol) in tetrahydrofuran (10 mL) was added lithium hydroxide (1 M, 5.10 mL). After 2 h, the reaction was acidified with 1 M hydrochloric acid (8 mL). The mixture was extracted with dichloromethane (40 mL x 3). The organic phases were combined and washed with saturated aqueous sodium chloride solution (10 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated to give 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid (660 mg, 2.29 mmol, 90 %) as a yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.22 (s, 1H), 7.33 - 7.01 (m, 5H), 6.78 (d, *J*=2.5 Hz, 1H), 3.85 (d, *J*=13.3 Hz, 2H), 2.81 - 2.66 (m, 3H), 2.40 (br. s., 1H), 1.95 - 1.69 (m, 3H), 1.39 (d, *J*=12.0 Hz, 2H), 1.21 - 1.13 (m, 1H), 1.10 - 1.04 (m, 1H).

Step 4: Preparation of 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-(2-phenylcyclopropyl)piperidine-1-carboxamide.

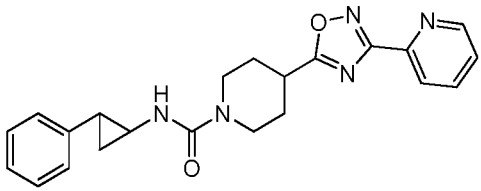


To a stirred solution of 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid (100 mg, 347 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide (72 mg, 347 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (131 mg, 347 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (134 mg, 1.04 mmol, 181 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40 %-75 %,12 min) to give 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-(2-phenylcyclopropyl)piperidine-1-carboxamide (81 mg, 173 µmol, 50 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.66 (m, 1H), 7.58 (d, *J*=1.9 Hz, 1H), 7.31 (s, 1H), 7.27 (s, 1H), 7.23 - 7.17 (m, 3H), 6.97 (d, *J*=8.5 Hz, 1H), 4.91 (s, 1H), 4.19 (q, *J*=7.0 Hz, 2H), 3.98 (s, 5H), 3.25 - 3.16 (m, 1H), 3.13 - 3.03 (m, 2H), 2.91 - 2.85 (m, 1H), 2.18 (dd, *J*=3.5, 13.4 Hz, 2H), 2.07 (ddd, *J*=3.3, 6.2, 9.5 Hz, 1H), 2.03 - 1.91 (m, 2H), 1.53 (t, *J*=7.0 Hz, 3H), 1.28 - 1.22 (m, 1H), 1.17 (td, *J*=5.0, 9.7 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 463.2.

Example 81: N-(2-phenylcyclopropyl)-4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide.



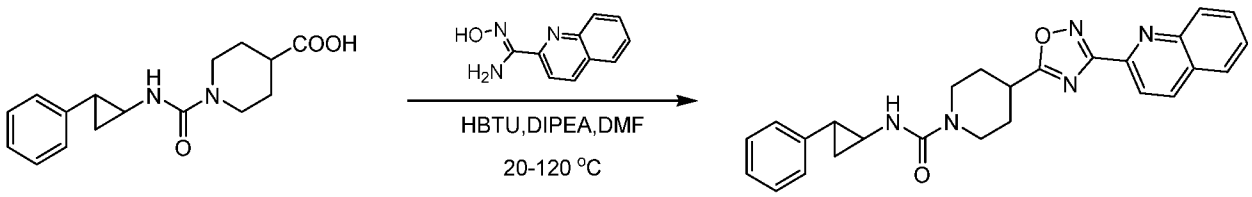
Step 1: Preparation of N-(2-phenylcyclopropyl)-4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide.



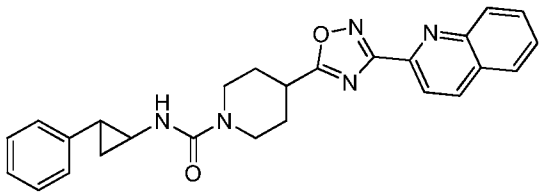
To a stirred solution of 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid (130 mg, 451 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-N'-hydroxypicolinimidamide (74 mg, 541 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (170 mg, 451 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (174 mg, 1.35 mmol, 236 µL). The mixture was stirred at 20 °C for 2 h, then heated at 110 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-phenylcyclopropyl)-4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide (47 mg, 121.6 µmol, 27 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ

8.76 (d, *J*=4.0 Hz, 1H), 8.12 - 7.97 (m, 2H), 7.65 - 7.55 (m, 1H), 7.30 - 7.19 (m, 2H), 7.18 - 7.05 (m, 3H), 6.87 (br. s., 1H), 3.96 (d, *J*=13.2 Hz, 2H), 2.93 (t, *J*=11.7 Hz, 2H), 2.71 (d, *J*=3.1 Hz, 1H), 2.06 (d, *J*=11.5 Hz, 2H), 1.89 (br. s., 1H), 1.68 (d, *J*=11.9 Hz, 3H), 1.20 - 1.04 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 390.1.

Example 82: N-(2-phenylcyclopropyl)-4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide

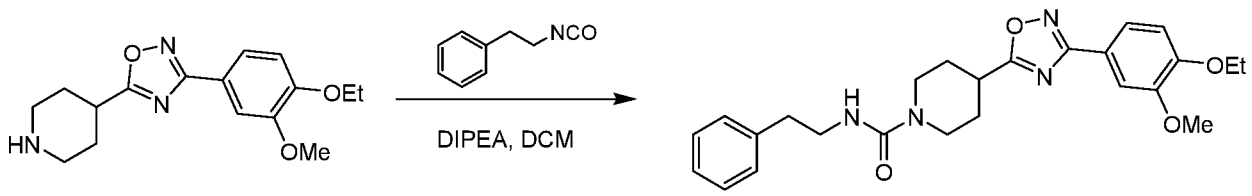


Step 1: Preparation of N-(2-phenylcyclopropyl)-4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide.

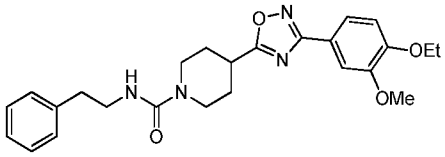


To a stirred solution of 1-[(2-phenylcyclopropyl)carbamoyl]piperidine-4-carboxylic acid (130 mg, 451 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxyquinoline-2-carboximidamide (101 mg, 541 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (170 mg, 451 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (174 mg, 1.35 mmol, 236 µL). The mixture was stirred at 20 ℃ for 2 h, and then heated at 120 ℃ for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-phenylcyclopropyl)-4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide (34 mg, 77 µmol, 17 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ 8.60 (s, 1H), 8.22 - 8.07 (m, 3H), 7.88 (br. s., 1H), 7.74 (d, *J*=7.5 Hz, 1H), 7.30 - 7.20 (m, 2H), 7.18 - 7.06 (m, 3H), 6.89 (br. s., 1H), 3.99 (d, *J*=13.7 Hz, 2H), 3.45 - 3.37 (m, 1H), 2.94 (t, *J*=11.7 Hz, 2H), 2.72 (d, *J*=3.5 Hz, 1H), 2.10 (d, *J*=11.0 Hz, 2H), 1.89 (br. s., 1H), 1.72 (d, *J*=11.5 Hz, 2H), 1.18 (td, *J*=4.6, 9.3 Hz, 1H), 1.11 - 1.05 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 440.1.

Example 83: 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-1-carboxamide.

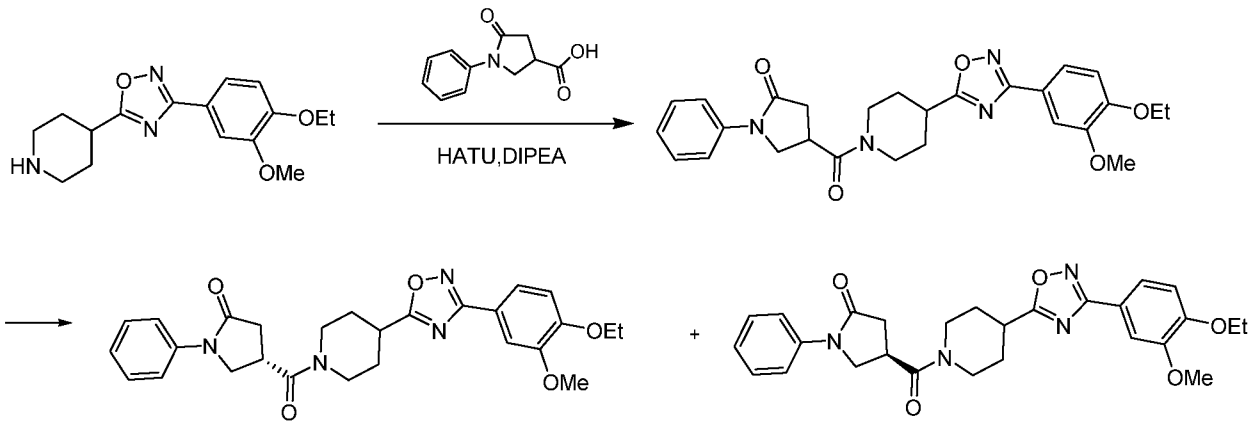


Step 1: Preparation of 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-1-carboxamide.

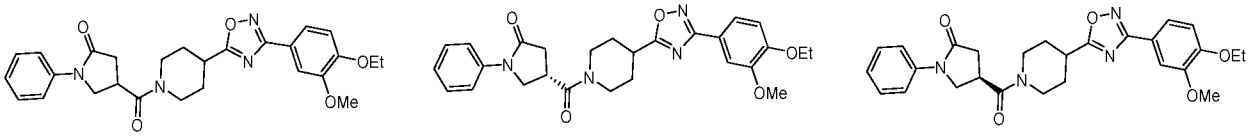


To a stirred solution of (2-isocyanatoethyl)benzene (72 mg, 494 µmol, 68 µL) in toluene (2 mL) was added 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (150 mg, 494 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (63 mg, 494 µmol, 86 µL). Then mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-1-carboxamide (58 mg, 130 µmol, 26 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.59 (dd, *J*=2.0, 8.4 Hz, 1H), 7.49 (d, *J*=1.9 Hz, 1H), 7.28 - 7.22 (m, 2H), 7.18 - 7.12 (m, 3H), 6.87 (d, *J*=8.4 Hz, 1H), 4.40 (br. s., 1H), 4.10 (q, *J*=7.0 Hz, 2H), 3.88 (s, 3H), 3.86 - 3.80 (m, 2H), 3.48 - 3.41 (m, 2H), 3.14 - 3.05 (m, 1H), 2.97 - 2.88 (m, 2H), 2.78 (t, *J*=6.8 Hz, 2H), 2.04 (dd, *J*=3.2, 13.1 Hz, 2H), 1.89 - 1.77 (m, 2H), 1.43 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 451.3.

Example 84: 4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Example 85: (R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, and Example 86: (S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.



Step 1: Preparation of 4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, (S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, and (R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one



To a stirred solution of 5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (200 mg, 975 µmol) in N,N-dimethylformamide (4 mL) was added 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole

(295 mg, 975 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (369 mg, 975 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (377 mg, 2.92 mmol, 510 µL). The mixture was stirred at 20 ℃ for 1 h. The reaction mixture was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give racemic 4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (151 mg, 31 %). A portion of this racemic mixture (140 mg) underwent SFC separation (column: OJ(250x30mm, 5µm);mobile phase: [CO_2 base-isopropanol]; B%: 45%-45%, min]) to give (R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (64 mg, 132 µmol, 14 %, 99.7% purity) as a white solid then (S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (65 mg, 133.9 µmol, 14 %, 99.58% purity) also as a white solid.

4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one:

^{1}H NMR (400 MHz, DMSO-d6) δ 7.68 (d, *J*=8.0 Hz, 2H), 7.62 - 7.56 (m, 1H), 7.48 (s, 1H), 7.39 (t, *J*=6.7 Hz, 2H), 7.19 - 7.09 (m, 2H), 4.38 (d, *J*=13.8 Hz, 1H), 4.14 - 3.93 (m, 5H), 3.85 (s, 3H), 3.80 - 3.71 (m, 1H), 3.51 - 3.40 (m, 1H), 3.30 (br. s., 1H), 3.00 - 2.89 (m, 1H), 2.83 - 2.73 (m, 2H), 2.22 - 2.09 (m, 2H), 1.90 - 1.64 (m, 2H), 1.37 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.2.

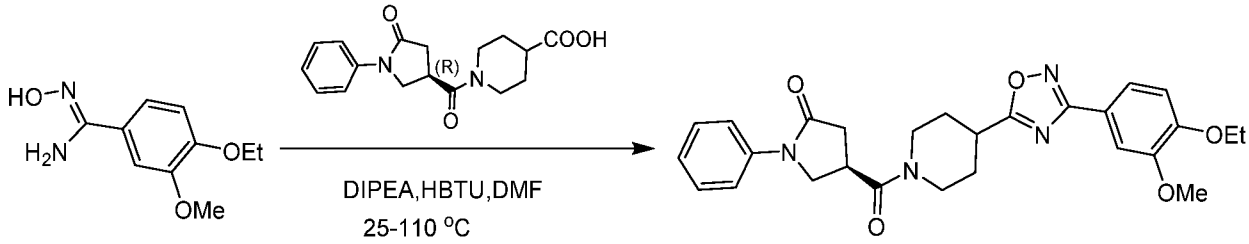
(R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one:

^{1}H NMR (400 MHz, DMSO-d6) δ 7.68 (d, *J*=7.9 Hz, 2H), 7.62 - 7.56 (m, 1H), 7.51 - 7.46 (m, 1H), 7.39 (t, *J*=6.7 Hz, 2H), 7.19 - 7.09 (m, 2H), 4.38 (d, *J*=13.4 Hz, 1H), 4.13 - 3.95 (m, 5H), 3.85 (s, 3H), 3.80 - 3.71 (m, 1H), 3.44 (d, *J*=10.0 Hz, 2H), 2.94 (br. s., 1H), 2.81 - 2.74 (m, 2H), 2.16 (t, *J*=13.6 Hz, 2H), 1.91 - 1.64 (m, 2H), 1.37 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.1.

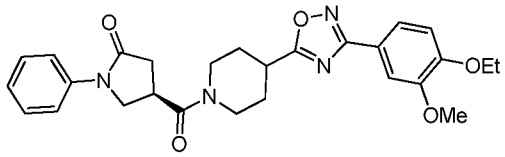
(S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.

^{1}H NMR (400 MHz, DMSO-d6) δ 7.66 (d, *J*=6.6 Hz, 2H), 7.57 (d, *J*=8.4 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.33 (m, 2H), 7.17 - 7.07 (m, 2H), 4.37 (d, *J*=12.8 Hz, 1H), 4.12 - 3.92 (m, 5H), 3.83 (s, 3H), 3.78 - 3.69 (m, 1H), 3.43 (t, *J*=10.6 Hz, 1H), 3.28 (br. s., 1H), 2.92 (t, *J*=13.0 Hz, 1H), 2.81 - 2.70 (m, 2H), 2.14 (t, *J*=13.5 Hz, 2H), 1.88 - 1.78 (m, 1H), 1.74 - 1.64 (m, 1H), 1.35 (t, *J*=7.1 Hz, 3H); LCMS (ESI) m/z: C27H30N4O5 $[M+H]^+$ = 491.1

Alternatively, Example 85: (4R)-4-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one can be prepared in an enantioselective fashion as follows:

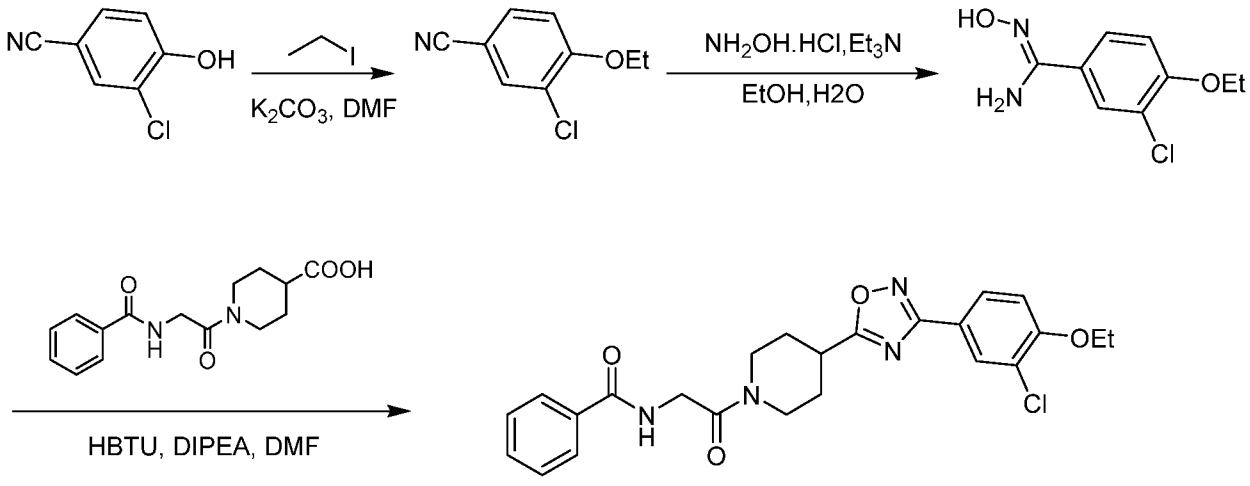


Step 1: Preparation of (4R)-4-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.

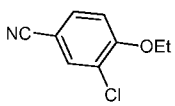


To a stirred solution of 1-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (100 mg, 316 µmol) and 4-ethoxy-N'-hydroxy-3-methoxy-benzamidine (66 mg, 316 µmol) in DMF (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (119 mg, 316 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (81 mg, 632 µmol, 110 µL) at 25℃. After 12h, the mixture was heated and stirred at 110 ℃ for 1 h. The mixture was cooled then purified by prep_HPLC (Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-65%,12 min) to give (4R)-4-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (59 mg,122 µmol, 39 %) as a pink solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.66 (br d, *J*=8.2 Hz, 1H), 7.61 - 7.54 (m, 3H), 7.37 (m, *J*=7.9 Hz, 2H), 7.19 - 7.14 (m, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 4.59 - 4.46 (m, 1H), 4.31 (dd, *J*=7.3, 9.7 Hz, 1H), 4.17 (q, *J*=7.0 Hz, 2H), 3.99 - 3.90 (m, 5H), 3.58 (quin, *J*=8.4 Hz, 1H), 3.43 - 3.26 (m, 2H), 3.16 - 2.92 (m, 2H), 2.88 - 2.79 (m, 1H), 2.24 (br t, *J*=12.9 Hz, 2H), 2.05 - 1.89 (m, 2H), 1.50 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.3.

Example 87: N-(2-(4-(3-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



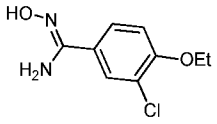
Step 1: Preparation of 3-chloro-4-ethoxybenzonitrile.



To a stirred solution of 3-chloro-4-hydroxybenzonitrile (2.0 g, 13.0 mmol) in N,N-dimethylformamide (20 mL) was added iodoethane (2.44 g, 15.6 mmol, 1.25 mL) and potassium carbonate (3.60 g, 26.1 mmol) at 0 ℃. The reaction was warmed to 40 ℃. After 16 h, the reaction mixture was quenched by addition of water (30 mL) then the mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution

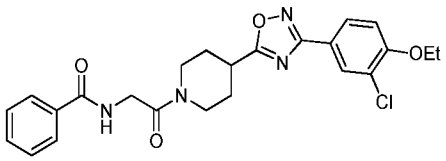
(30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude 3-chloro-4-ethoxybenzonitrile (2.50 g) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J*=1.9 Hz, 1H), 7.45 (dd, *J*=2.0, 8.7 Hz, 1H), 6.88 (d, *J*=8.5 Hz, 1H), 4.10 (q, *J*=7.0 Hz, 2H), 1.43 (t, *J*=7.0 Hz, 3H).

Step 2: Preparation of (Z)-3-chloro-4-ethoxy-N'-hydroxybenzimidamide.



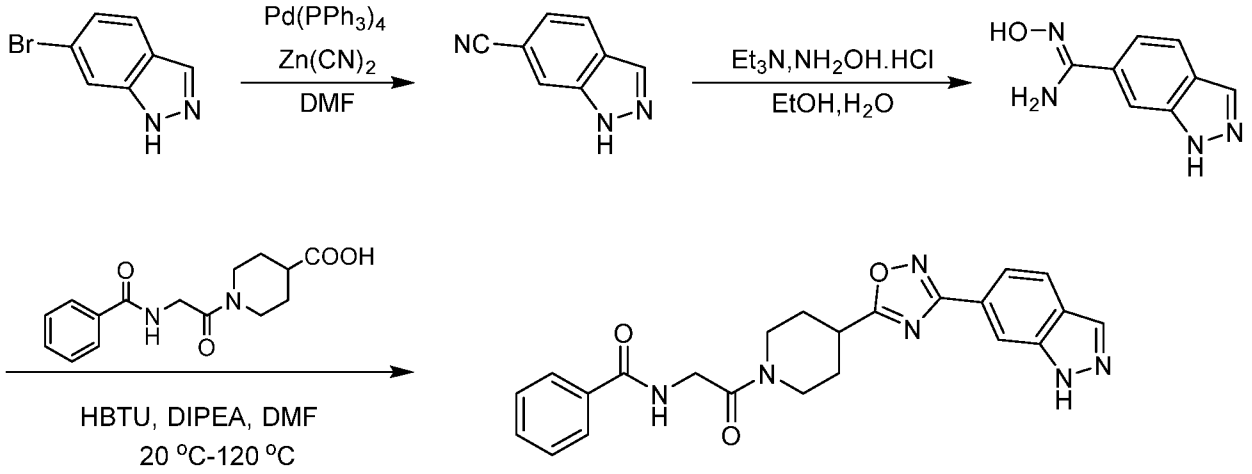
To a stirred solution of 3-chloro-4-ethoxybenzonitrile (2.40 g, 13.2 mmol) in ethanol (30 mL) was added hydroxylamine hydrochloride (1.84 g, 26.4 mmol), triethylamine (2.67 g, 26.4 mmol, 3.66 mL) and water (3 mL). The mixture was heated at 80 °C for 2 h. The reaction mixture was filtered and the filter cake dried in vacuo to give (Z)-3-chloro-4-ethoxy-N'-hydroxybenzimidamide (700 mg, 3.62 mmol, 69 %) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.59 (s, 1H), 7.72 (d, *J*=2.0 Hz, 2H), 7.14 (d, *J*=8.8 Hz, 1H), 5.83 (s, 2H), 4.14 (q, *J*=6.9 Hz, 2H), 1.45 - 1.30 (m, 3H).

Step 3: Preparation of N-(2-(4-(3-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

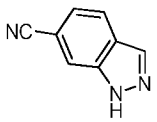


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-3-chloro-4-ethoxy-N'-hydroxybenzimidamide (97 mg, 455 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-80%,12 min) to give N-(2-(4-(3-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (104 mg, 223 µmol, 54 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=2.0 Hz, 1H), 7.95 (dd, *J*=2.1, 8.6 Hz, 1H), 7.91 - 7.86 (m, 2H), 7.58 - 7.44 (m, 3H), 7.35 (br. s., 1H), 7.02 (d, *J*=8.7 Hz, 1H), 4.51 (d, *J*=13.7 Hz, 1H), 4.33 (d, *J*=3.9 Hz, 2H), 4.21 (q, *J*=7.0 Hz, 2H), 3.93 (d, *J*=13.9 Hz, 1H), 3.41 - 3.29 (m, 2H), 3.18 (t, *J*=10.8 Hz, 1H), 2.33 - 2.20 (m, 2H), 2.09 - 1.93 (m, 2H), 1.53 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 469.3.

Example 88: N-(2-(4-(3-(1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

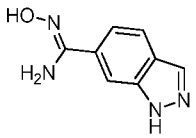


Step 1: Preparation of 1H-indazole-6-carbonitrile



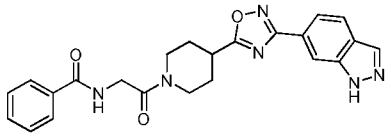
To a stirred solution of 6-bromo-1H-indazole (1.0 g, 5.08 mmol) in N,N-dimethylformamide (12 mL) was added zinc cyanide (595 mg, 5.08 mmol, 322 µL) and tetrakis(triphenylphosphine)palladium(0) (586 mg, 508 µmol), and the mixture was degassed with nitrogen three times. The mixture heated at 100 °C for 4 h under nitrogen. The reaction cooled to 20 °C, water (15 mL) was added, and the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. This was triturated with petroleum ether (30 mL) and dichloromethane (5 mL), and the mixture filtered. The filter cake was dried in vacuo to give 1H-indazole-6-carbonitrile (880 mg) as a yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.65 (br. s., 1H), 8.33 - 8.12 (m, 2H), 7.99 (d, *J*=8.4 Hz, 1H), 7.88 - 7.80 (m, 1H).

Step 2: Preparation of (Z)-N'-hydroxy-1H-indazole-6-carboximidamide.



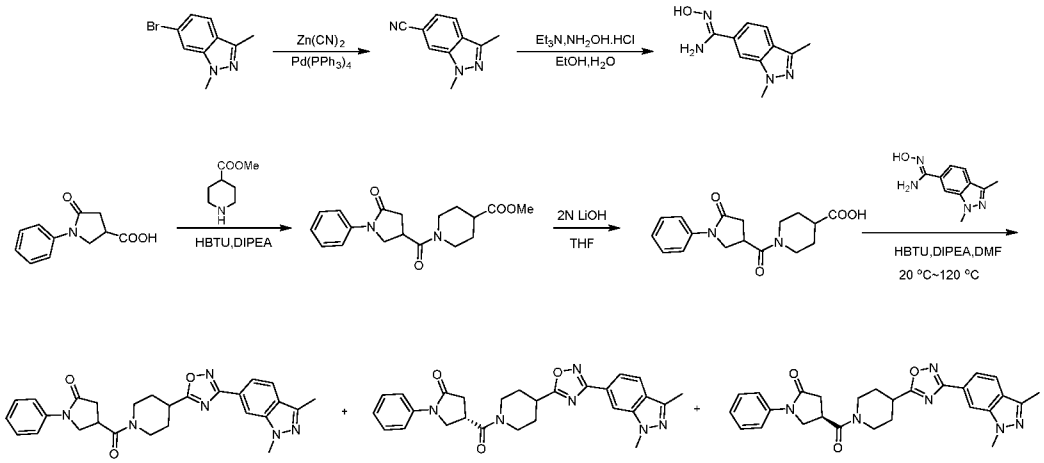
To a stirred solution of 1H-indazole-6-carbonitrile (800 mg, 5.59 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (776 mg, 11.18 mmol), triethylamine (1.13 g, 11.18 mmol, 1.55 mL) and water (100 µL). The mixture was heated at 80 °C for 2 h. The reaction mixture was cooled, concentrated under reduced pressure, and then diluted with water (5 mL). The solid that formed was filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1H-indazole-6-carboximidamide (500 mg, 2.84 mmol, 51 %) as a yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.22 - 13.10 (m, 1H), 9.68 (br. s., 1H), 8.04 (s, 1H), 7.78 (s, 1H), 7.70 - 7.66 (m, 1H), 7.47 - 7.42 (m, 1H), 5.87 (br. s., 2H).

Step 3: Preparation of N-(2-(4-(3-(1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

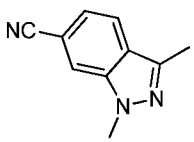


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1H-indazole-6-carboximidamide (94 mg, 537 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C18 100*30 5µm; mobile phase: [water (0.225%TFA)-acetonitrile]; B%: 30%-55%,12 min) to give N-(2-(4-(3-(1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (21 mg, 44 µmol, 11 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.34 (br s, 1H), 8.55 (t, *J*=5.6 Hz, 1H), 8.18 - 8.16 (m, 1H), 7.94 - 7.89 (m, 1H), 7.88 - 7.83 (m, 2H), 7.72 (dd, *J*=1.1, 8.4 Hz, 1H), 7.54 - 7.41 (m, 3H), 4.36 - 4.27 (m, 1H), 4.16 (d, *J*=5.7 Hz, 2H), 3.97 (br d, *J*=14.1 Hz, 1H), 3.59 (br s, 1H), 3.47 (s, 1H), 3.34 - 3.24 (m, 1H), 2.98 - 2.88 (m, 1H), 2.20 - 2.08 (m, 2H), 1.89 - 1.77 (m, 1H), 1.66 (br d, *J*=11.5 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 431.1.

Example 89: 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, example 90: 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 1 and Example 91: (R)-4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2.



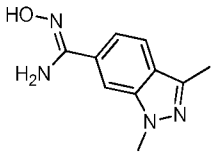
Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (480 mg, 2.13 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (250 mg, 2.13 mmol) and tetrakis(triphenylphosphine)palladium(0) (246 mg, 213 µmol) under nitrogen, then the mixture was heated

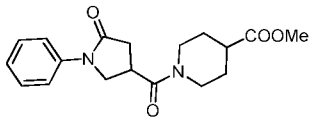
to 100 °C. After 16 h, the reaction was cooled to 20 °C, water (10 mL) was added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo to give crude product. The residue was triturated with petroleum ether (30 mL), then filtered and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-6-carbonitrile (300 mg, 1.75 mmol, 82 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.71 (m, 2H), 7.38 - 7.31 (m, 1H), 4.08 (s, 3H), 2.61 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



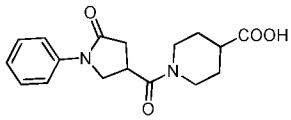
To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (300 mg, 1.75 mmol) in ethanol (5 mL) was added hydroxylamine hydrochloride (243 mg, 3.50 mmol), triethylamine (354 mg, 3.50 mmol, 485 µL) and water (500 µL). The mixture was heated at 80 °C for 5 h, then cooled and filtered, and the filter cake was dried in vacuo to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (290 mg, 1.42 mmol, 81 %) as a white solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.71 (s, 1H), 7.86 (s, 1H), 7.65 (d, *J*=8.5 Hz, 1H), 7.49 (d, *J*=8.5 Hz, 1H), 5.90 (s, 2H), 3.97 (s, 3H), 2.47 (s, 3H).

Step 3: Preparation of methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate.



To a stirred solution of 5-oxo-1-phenylpyrrolidine-3-carboxylic acid (500 mg, 2.44 mmol) in N,N-dimethylformamide (10 mL) was added methyl piperidine-4-carboxylate (349 mg, 2.44 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (925 mg, 2.44 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (946 mg, 7.32 mmol, 1.28 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition of water (20 mL) then extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by chromatography (silica, petroleum ether : ethyl acetate = 20 : 1 to 1 : 1) gave methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate (940 mg) as a yellow oil.

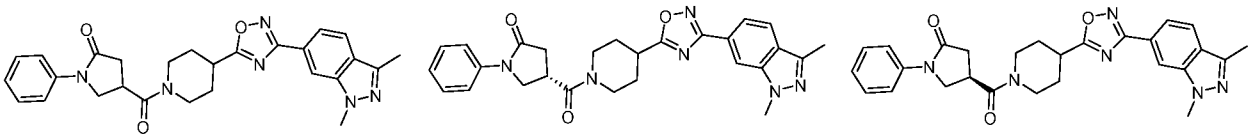
Step 4: Preparation of 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid



To a stirred solution of methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate (900 mg, 2.72 mmol) in tetrahydrofuran (10 mL) was added lithium hydroxide (2 M, 2.72 mL). Afterr 2 h, the reaction mixture was acidified to pH 1 with 1 M hydrochloric acid (6 mL). The mixture was extracted

with ethyl acetate (40 mL x 3). The organic extracts were combined and washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (600 mg, 1.90 mmol, 70 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.37 - 12.17 (m, 1H), 7.66 (dd, *J*=5.8, 7.2 Hz, 2H), 7.38 (t, *J*=7.9 Hz, 2H), 7.19 - 7.09 (m, 1H), 4.28 - 4.19 (m, 1H), 4.04 (s, 1H), 3.93 (br. s., 2H), 3.76 - 3.66 (m, 1H), 3.18 (br. s., 1H), 2.86 - 2.67 (m, 4H), 1.87 (t, *J*=13.2 Hz, 2H), 1.61 - 1.35 (m, 2H).

Step 5: Preparation of 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 1 and 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2.



To a stirred solution of 1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (150 mg, 474 µmol) in N,N-dimethylformamide (2 mL) was added N'-hydroxy-1,3-dimethyl-indazole-6-carboxamidine (96 mg, 474 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (179 mg, 474 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (183 mg, 1.42 mmol, 248 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-55%,12 min) to give the racemic of 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (85 mg) as a white solid. A portion (25 mg, 53 µmol, 11 %, 99.83% purity) was retained for analysis. The remainder (60 mg) was purified by SFC (column: OJ (250x30mm, 5µm); mobile phase: [CO_2 base-methanol]; B%: 45%-45%,min) to give 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enatiomer 1 (27 mg, 56 µmol, 12 %) as a brown solid then 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2 (26 mg, 55 µmol, 12 %) as a white solid.

4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 - 8.07 (m, 1H), 7.83 (s, 1H), 7.78 - 7.72 (m, 1H), 7.61 (d, *J*=8.0 Hz, 2H), 7.39 (t, *J*=7.9 Hz, 2H), 7.18 (s, 1H), 4.65 - 4.50 (m, 1H), 4.34 (t, *J*=7.3 Hz, 1H), 4.09 (d, *J*=3.3 Hz, 3H), 4.05 - 3.92 (m, 2H), 3.60 (quin, *J*=8.4 Hz, 1H), 3.46 - 3.32 (m, 2H), 2.98 (d, *J*=6.7 Hz, 2H), 2.91 - 2.81 (m, 1H), 2.61 (s, 3H), 2.35 - 2.22 (m, 2H), 2.02 (d, *J*=6.1 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.2.

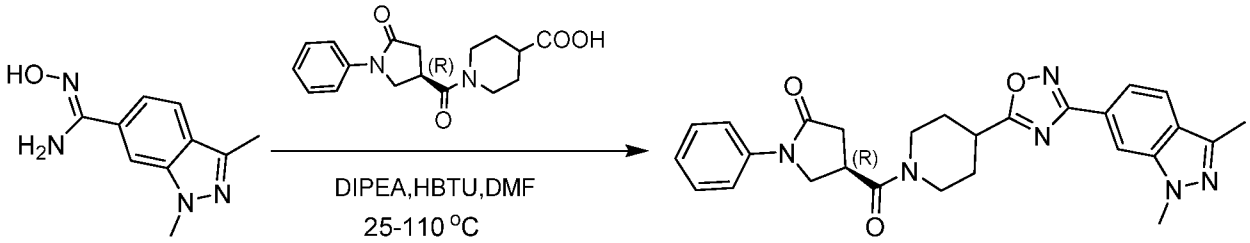
4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=4.1 Hz, 1H), 7.86 (br d, *J*=8.5 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.63 (d, *J*=7.9 Hz, 2H), 7.41 (t, *J*=8.0 Hz, 2H), 7.23 - 7.18 (m, 1H), 4.67 - 4.52 (m, 1H), 4.36 (br t, *J*=7.0 Hz, 1H), 4.11 (d, *J*=3.4 Hz, 3H), 4.07 - 3.94 (m, 2H), 3.62 (quin, *J*=8.5 Hz, 1H), 3.49 - 3.35 (m, 2H), 3.22 - 2.96 (m, 2H), 2.93 - 2.81 (m, 1H), 2.63 (s, 3H), 2.37 - 2.25 (m, 2H), 2.11 - 1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

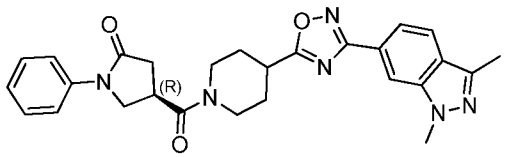
4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=3.9 Hz, 1H), 7.86 (d, *J*=8.4 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.63 (d, *J*=8.3 Hz, 2H), 7.41 (t, *J*=8.0 Hz, 2H), 7.24 - 7.18 (m, 1H), 4.66 - 4.53 (m, 1H), 4.36 (br t, *J*=7.3 Hz, 1H), 4.11 (d, *J*=3.5 Hz, 3H), 4.07 - 3.94 (m, 2H), 3.62 (quin, *J*=8.5 Hz, 1H), 3.48 - 3.36 (m, 2H), 3.21 - 2.96 (m, 2H), 2.93 - 2.81 (m, 1H), 2.63 (s, 3H), 2.36 - 2.26 (m, 2H), 2.06 (br d, *J*=13.4 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

Examples 90 and 91 can be synthesized in an enantiospecific fashion using appropriate enantiopure starting materials, following the representative procedure below:

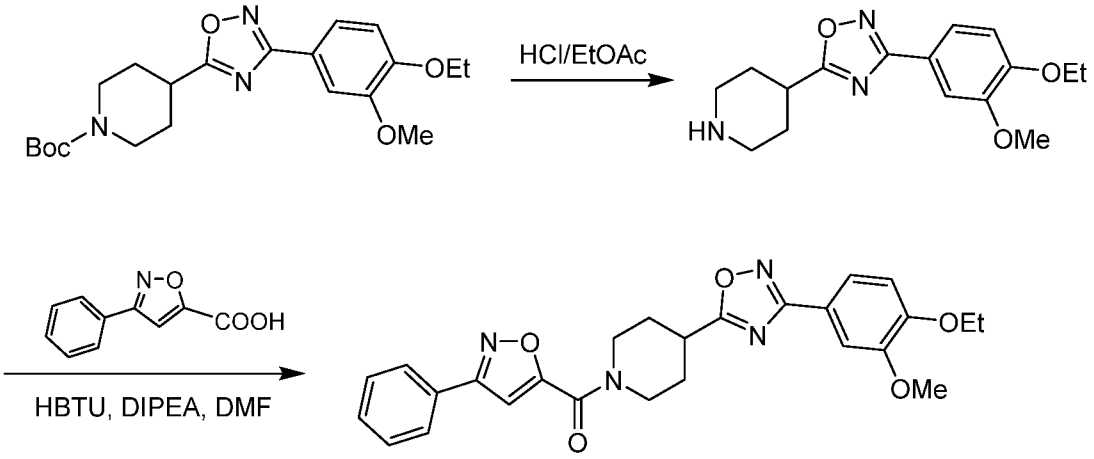


Preparation of (4R)-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.

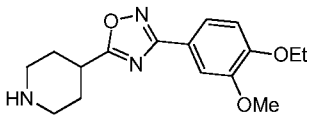


To a stirred solution of 1-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (115 mg, 363.52 µmol) and N'-hydroxy-1,3-dimethyl-indazole-6-carboxamidine (74 mg, 364 µmol) in DMF (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (137 mg, 364 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (93 mg, 727 µmol, 126 µL) at 25 °C. After 3 h, the mixture was warmed to 110 °C. After 1h, the mixture was purified by chromatography (Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-60%,12 min) to give (4R)-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (64 mg,133 µmol, 37 %) as a pink solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.09 (d, *J*=4.0 Hz, 1H), 7.84 - 7.80 (d, 1H), 7.75 - 7.71 (d, 1H), 7.59 (d, *J*=7.9 Hz, 2H), 7.38 (t, *J*=7.9 Hz, 2H), 7.20 - 7.14 (t, 1H), 4.62 - 4.49 (m, 1H), 4.36 - 4.29 (m, 1H), 4.07 (d, *J*=3.3 Hz, 3H), 4.04 - 3.89 (m, 2H), 3.58 (quin, *J*=8.4 Hz, 1H), 3.45 - 3.30 (m, 2H), 3.18 - 2.92 (m, 2H), 2.90 - 2.80 (m, 1H), 2.59 (s, 3H), 2.27 (br t, *J*=13.2 Hz, 2H), 2.09 - 1.91 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

Example 92: (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(3-phenylisoxazol-5-yl)methanone.

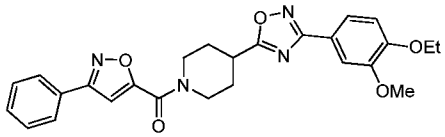


Step 1: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole.



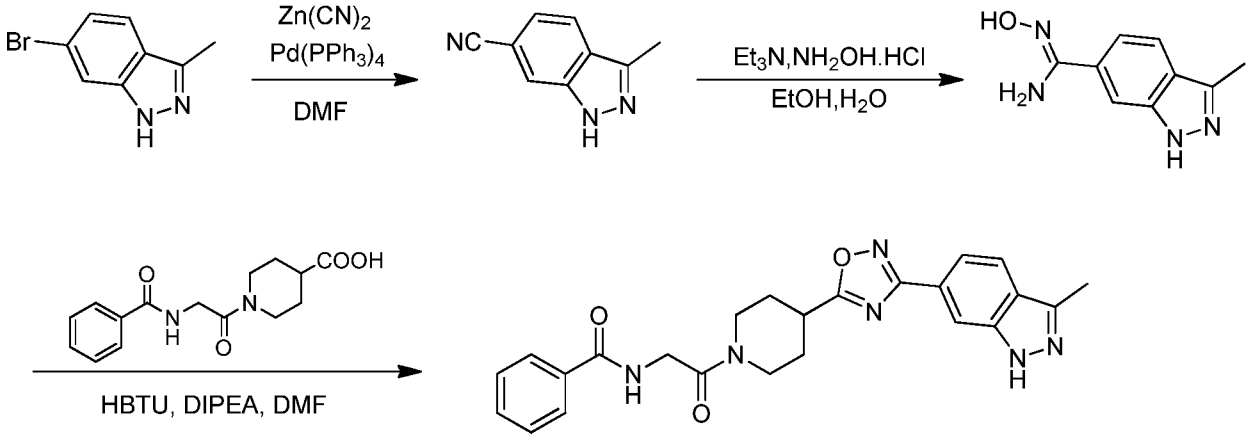
To a stirred solution of tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (800 mg, 1.98 mmol) in ethyl acetate (5 mL) was added 4M hydrochloric acid / ethyl acetate (20 mL). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was filtered and the filter cake was dried in vacuo to give 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (450 mg, 1.48 mmol, 75 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J*=1.6, 8.3 Hz, 1H), 7.60 - 7.54 (m, 1H), 6.97 (d, *J*=8.4 Hz, 1H), 4.24 - 4.13 (m, 2H), 3.98 (s, 3H), 3.56 (br s, 2H), 3.39 (br s, 1H), 3.33 - 3.15 (m, 2H), 2.51 (br s, 2H), 2.48 - 2.33 (m, 2H), 2.19 - 1.83 (m, 1H), 1.53 (t, *J*=7.0 Hz, 3H).

Step 2: Preparation of (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(3-phenylisoxazol-5-yl)methanone.

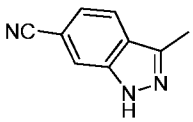


To a stirred solution of 3-phenylisoxazole-5-carboxylic acid (75 mg, 396 µmol) in N,N-dimethylformamide (2 mL) was added 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (120 mg, 396 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (150 mg, 396 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (153 mg, 1.19 mmol, 207 µL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%:40%-70%,12 min) to give (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(3-phenylisoxazol-5-yl)methanone (41 mg, 87 µmol, 22 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 2H), 7.70 (br d, *J*=7.8 Hz, 1H), 7.60 (br s, 1H), 7.53 (br s, 3H), 7.14 (s, 1H), 6.99 (br d, *J*=7.5 Hz, 1H), 4.59 (br s, 1H), 4.36 (br d, *J*=12.5 Hz, 1H), 4.21 (br d, *J*=6.4 Hz, 2H), 4.00 (s, 3H), 3.55 (br s, 1H), 3.46 - 3.25 (m, 2H), 2.32 (br s, 2H), 2.15 (br s, 2H), 1.54 (br t, *J*=6.8 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 475.2.

Example 93: N-(2-(4-(3-(3-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

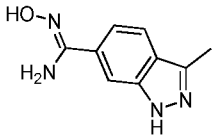


Step 1: Preparation of 3-methyl-1H-indazole-6-carbonitrile.



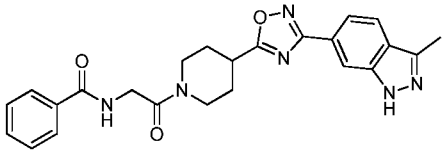
To a stirred solution of 6-bromo-3-methyl-1H-indazole (440 mg, 2.08 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (244 mg, 2.08 mmol) and tetrakis(triphenylphosphine)palladium(0) (240 mg, 208 µmol), then the mixture was degassed with nitrogen three times. The mixture stirred at 100 °C for 4 h under nitrogen, then cooled to 20 °C, water (10 mL) added, and the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give crude product. Petroleum ether (20 mL) was added to the crude product, then the mixture was filtered and the filter cake dried in vacuo to give 3-methyl-1H-indazole-6-carbonitrile (220 mg, 1.40 mmol, 67 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.29 - 13.09 (m, 1H), 8.09 - 8.05 (m, 1H), 7.96 - 7.90 (m, 1H), 7.41 (d, *J*=8.3 Hz, 1H), 2.54 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-3-methyl-1H-indazole-6-carboximidamide.



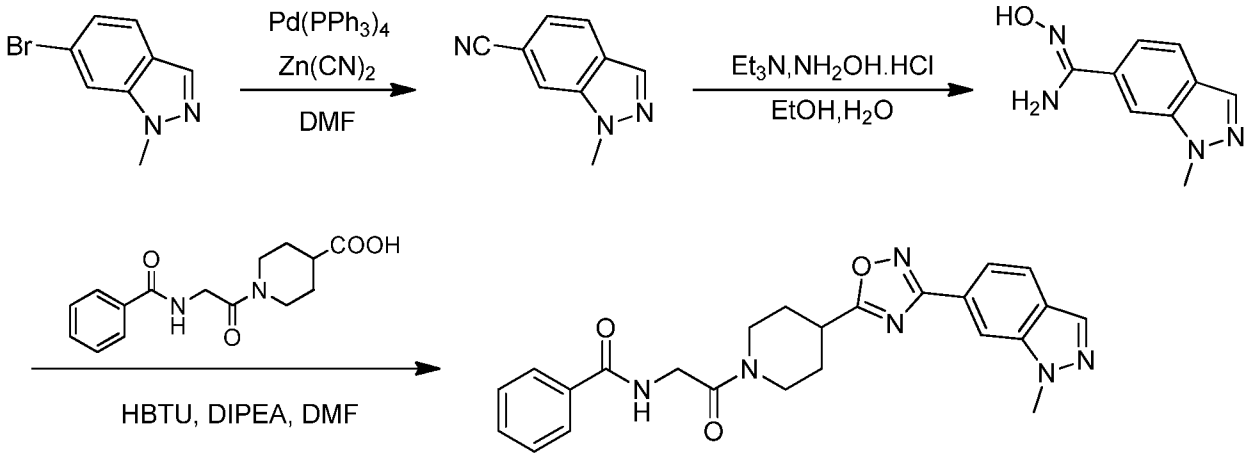
To a stirred solution of 3-methyl-1H-indazole-6-carbonitrile (200 mg, 1.27 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (176 mg, 2.55 mmol), triethylamine (257 mg, 2.55 mmol, 352 µL) and water (100 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled and then concentrated under reduced pressure to remove ethanol. The residue was diluted with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-3-methyl-1H-indazole-6-carboximidamide (150 mg, 789 µmol, 62 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.73 (s, 1H), 9.67 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J*=8.5 Hz, 1H), 7.45 (d, *J*=8.5 Hz, 1H), 5.86 (s, 2H), 2.49 (s, 3H).

Step 3: Preparation of N-(2-(4-(3-(3-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

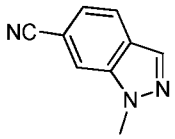


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-3-methyl-1H-indazole-6-carboximidamide (78 mg, 413 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20℃ for 2 h, then heated at 110 ℃ for 1 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-55%,12 min) to give N-(2-(4-(3-(3-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (93 mg, 209 µmol, 51 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 8.59 - 8.53 (m, 1H), 8.08 (s, 1H), 7.86 (d, *J*=8.4 Hz, 3H), 7.71 - 7.65 (m, 1H), 7.55 - 7.42 (m, 3H), 4.30 (d, *J*=13.2 Hz, 1H), 4.16 (d, *J*=5.7 Hz, 2H), 3.97 (d, *J*=14.6 Hz, 1H), 3.49 - 3.43 (m, 1H), 3.29 - 3.24 (m, 1H), 2.92 (t, *J*=11.2 Hz, 1H), 2.50 (s, 3H), 2.14 (t, *J*=13.0 Hz, 2H), 1.88 - 1.78 (m, 1H), 1.66 (d, *J*=9.7 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 445.3.

Example 94: N-(2-(4-(3-(1-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



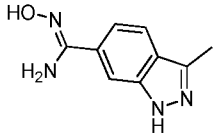
Step 1: Preparation of 1-methyl-1H-indazole-6-carbonitrile.



To a stirred solution of 6-bromo-1-methyl-1H-indazole (500 mg, 2.37 mmol) in N,N-dimethylformamide (8 mL) was added zinc cyanide (278 mg, 2.37 mmol) and tetrakis(triphenylphosphine)palladium(0) (273 mg, 236.90 µmol), the mixture was degassed with nitrogen three times. The mixture was stirred at 100 ℃ for 4 h under nitrogen, then cooled to 20 ℃, water (10 mL) added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases

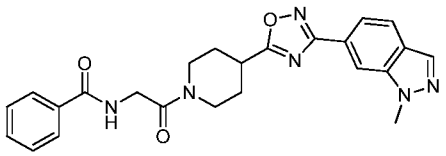
were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. The mixture was triturated with petroleum ether (20 mL) and dichloromethane (3 mL), then filtered and dried in vacuo to give 1-methyl-1H-indazole-6-carbonitrile (300 mg, 1.91 mmol, 81 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.88 - 7.83 (m, 1H), 7.82 (s, 1H), 7.39 (dd, *J*=1.1, 8.3 Hz, 1H), 4.16 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1-methyl-1H-indazole-6-carboximidamide.



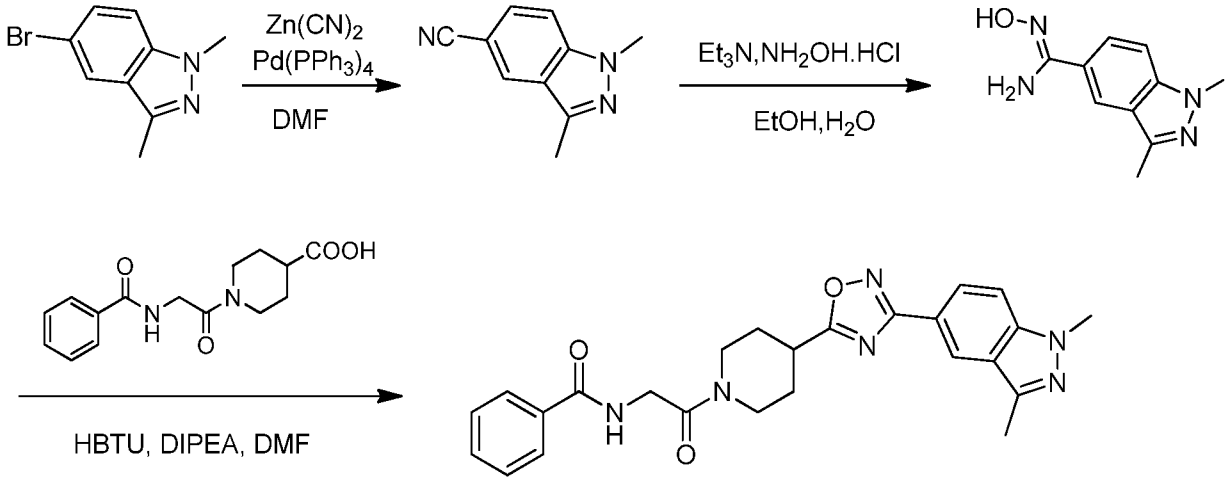
To a stirred solution of 1-methyl-1H-indazole-6-carbonitrile (250 mg, 1.59 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (221 mg, 3.18 mmol), triethylamine (321 mg, 3.18 mmol, 440 µL) and water (100 µL). The mixture was heated at 80 ℃ for 2 h. The reaction mixture was concentrated under reduced pressure and the residue then triturated with water (4 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1-methyl-1H-indazole-6-carboximidamide (500 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.65 (br. s., 2H), 9.65-9.84 (m, 1H), 7.98 (d, *J*=18.1 Hz, 2H), 7.67 (d, *J*=8.8 Hz, 1H), 7.46-7.52 (m, 1H), 4.03 ppm (s, 3H).

Step 3: Preparation of N-(2-(4-(3-(1-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

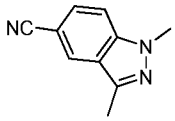


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1-methyl-1H-indazole-6-carboximidamide (125 mg, 661 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 ℃ for 1 h, then heated at 110 ℃ for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 33%-63%,12 min) to give N-(2-(4-(3-(1-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (29 mg, 64 µmol, 15 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.06 (s, 1H), 7.92 - 7.82 (m, 4H), 7.58 - 7.45 (m, 3H), 7.36 (br. s., 1H), 4.56 (d, *J*=14.2 Hz, 1H), 4.34 (d, *J*=3.9 Hz, 2H), 4.19 (s, 3H), 4.00 - 3.92 (m, 1H), 3.44 - 3.34 (m, 2H), 3.19 (t, *J*=10.9 Hz, 1H), 2.36 - 2.26 (m, 2H), 2.14 - 1.98 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 445.2.

Example 95: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

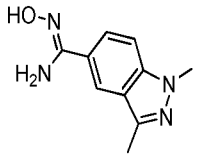


Step 1: Preparation of 1,3-dimethyl-1H-indazole-5-carbonitrile.



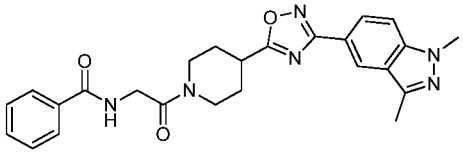
To a stirred solution of 5-bromo-1,3-dimethyl-1H-indazole (600 mg, 2.67 mmol) in N,N-dimethylformamide (10 mL) was added zinc cyanide (313 mg, 2.67 mmol, 169 µL) and tetrakis(triphenylphosphine)palladium(0) (308 mg, 267 µmol) under nitrogen. The mixture was stirred at 100 °C for 16 h, then cooled to 20 °C, and diluted with water (15 mL). The reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. This was triturated with petroleum ether (30 mL) and dichloromethane (5 mL), filtered and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-5-carbonitrile (340 mg, 1.99 mmol, 74 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.54 (d, *J*=8.8 Hz, 1H), 7.37 (d, *J*=8.8 Hz, 1H), 4.02 (s, 3H), 2.57 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-5-carboximidamide.



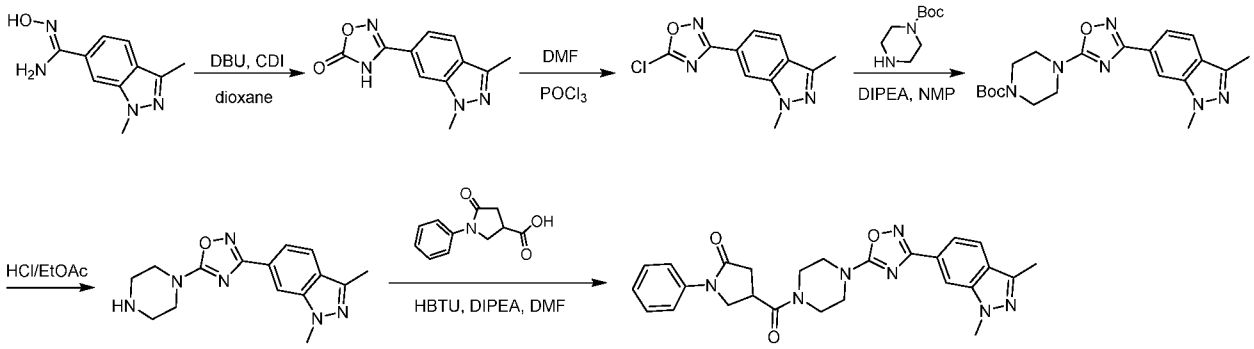
To a stirred solution of 1,3-dimethyl-1H-indazole-5-carbonitrile (340 mg, 1.99 mmol) in ethanol (6 mL) was added hydroxylamine hydrochloride (276 mg, 3.97 mmol), triethylamine (401 mg, 3.97 mmol, 550 µL) and water (600 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was triturated with water (4 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-5-carboximidamide (250 mg, 1.22 mmol, 62 %) as a white solid.^{1}H NMR (400 MHz, DMSO-d6) δ 9.50 (s, 1H), 7.99 (s, 1H), 7.72 (dd, *J*=1.5, 9.0 Hz, 1H), 7.48 (d, *J*=8.8 Hz, 1H), 5.82 (s, 2H), 3.92 (s, 3H), 2.46 (s, 3H).

Step 3: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

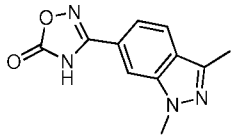


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added N'-hydroxy-1,3-dimethyl-indazole-5-carboxamidine (84 mg, 413 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, and then heated at 110 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-64%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (54 mg, 118 µmol, 29 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (t, *J*=5.5 Hz, 1H), 8.34 (s, 1H), 7.96 (dd, *J*=1.3, 8.8 Hz, 1H), 7.86 (d, *J*=7.1 Hz, 2H), 7.70 (d, *J*=8.8 Hz, 1H), 7.55 - 7.42 (m, 3H), 4.31 (d, *J*=13.2 Hz, 1H), 4.16 (dd, *J*=2.2, 5.3 Hz, 2H), 4.03 - 3.92 (m, 4H), 3.49 - 3.40 (m, 1H), 3.34 - 3.30 (m, 1H), 2.92 (t, *J*=11.5 Hz, 1H), 2.52 (s, 3H), 2.14 (t, *J*=13.0 Hz, 2H), 1.83 (d, *J*=10.1 Hz, 1H), 1.71 - 1.62 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 96: 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carbonyl)-1-phenylpyrrolidin-2-one.

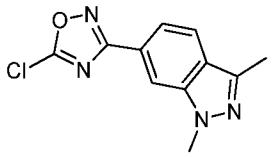


Step 1: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one.



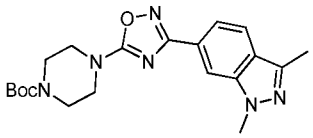
To a stirred solution of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (180 mg, 881 µmol) in dioxane (3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (147 mg, 970 µmol, 146 µL) and 1,1'-carbonyldiimidazole (214 mg, 1.32 mmol). The mixture was stirred at 110 °C for 16 h. The reaction mixture was concentrated in vacuo then purified by chromatography (silica, dichloromethane : methanol = 50 :1) to give 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (220 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.97 - 7.93 (m, 1H), 7.82 - 7.77 (m, 1H), 7.62 (d, *J*=1.1 Hz, 1H), 4.05 (s, 3H), 2.57 (s, 3H).

Step 2: Preparation of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole



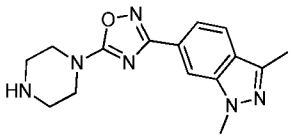
A flask 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (220 mg, 956 µmol) was charged with N,N-dimethylformamide (1 mL) then phosphoryl chloride (10 mL) was added dropwise. The mixture was heated at 110 °C for 16 h, then cooled and concentrated under reduced pressure, poured onto ice water (10 mL), and stirred for 10 min. The mixture was extracted with dichloromethane (20 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (100 mg) as a brown solid.

Step 3: Preparation of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate



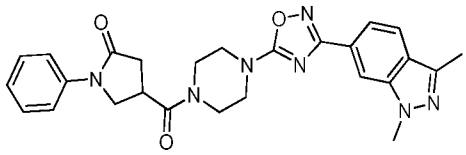
To a stirred solution of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (100 mg, 402.1 µµmol) in N-methyl-2-pyrrolidone (3 mL) was added tert-butyl piperazine-1-carboxylate (74 mg, 402 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (103 mg, 804 µmol, 140 µL). The mixture was stirred at 120 °C for 16 h. The reaction mixture was cooled, quenched by addition of water (5 mL) then the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. Purification by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1) gave tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate (65 mg, 163 µmol, 41 %) as a brown solid.

Step 4: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole



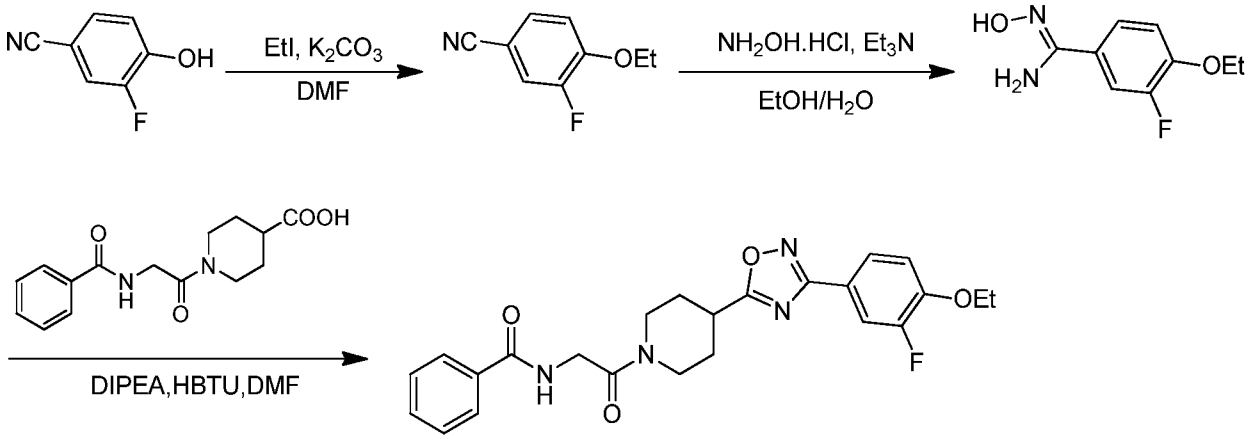
To a stirred solution of tert-butyl 4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperazine-1-carboxylate (65 mg, 163 µmol) in ethyl acetate (1 mL) was added hydrochloric acid / ethyl acetate (4M, 5 mL). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (40 mg, 134 µmol, 82 %) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 299.1.

Step 5: Preparation of 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carbonyl)-1-phenylpyrrolidin-2-one

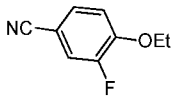


To a stirred solution of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (35 mg, 117 µmol) in N,N-dimethylformamide (1 mL) was added 5-oxo-1-phenylpyrrolidine-3-carboxylic acid (24 mg, 117 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (44 mg, 117 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (45 mg, 352 µmol, 61 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carbonyl)-1-phenylpyrrolidin-2-one (26 mg, 54.58 µmol, 47 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.83 - 7.69 (m, 2H), 7.63 (br d, *J*=7.5 Hz, 2H), 7.42 (br t, *J*=7.5 Hz, 2H), 7.22 (br d, *J*=7.9 Hz, 1H), 4.37 (br t, *J*=8.0 Hz, 1H), 4.09 (s, 3H), 4.03 - 3.96 (m, 1H), 3.93 - 3.72 (m, 8H), 3.63 (br d, *J*=9.7 Hz, 1H), 3.04 - 2.85 (m, 2H), 2.62 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 486.3.

Example 97: N-(2-(4-(3-(4-ethoxy-3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

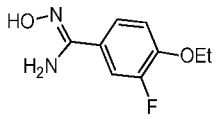


Step 1: Preparation of 4-ethoxy-3-fluorobenzonitrile



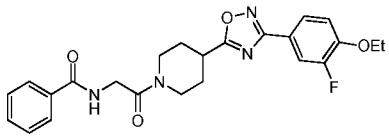
To a stirred solution of 3-fluoro-4-hydroxybenzonitrile (800 mg, 5.83 mmol) in N,N-dimethylformamide (10 mL) was added iodoethane (1.09 g, 7.00 mmol, 559 µL) and potassium carbonate (1.61 g, 11.7 mmol) at 0 °C. The reaction was warmed at 40 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude 4-ethoxy-3-fluorobenzonitrile (750 mg, 4.54 mmol, 78 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.30 (m, 2H), 6.98 (t, *J*=8.3 Hz, 1H), 4.15 (q, *J*=7.0 Hz, 2H), 1.47 (tt, *J*=1.2, 7.0 Hz, 3H).

Step 2: Preparation of (Z)-4-ethoxy-3-fluoro-N'-hydroxybenzimidamide



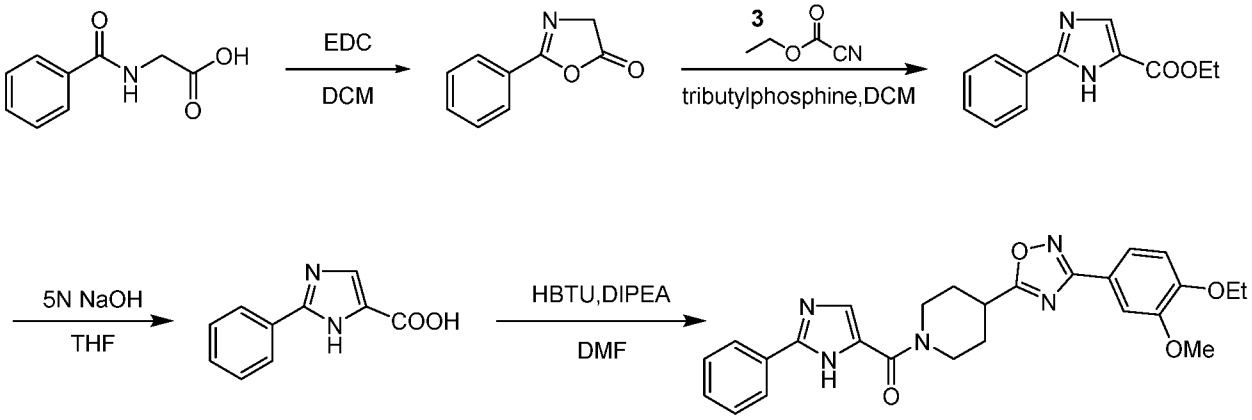
To a stirred solution of 4-ethoxy-3-fluorobenzonitrile (400 mg, 2.42 mmol) in ethanol (6 mL) was added hydroxylamine hydrochloride (336 mg, 4.84 mmol), triethylamine (490 mg, 4.84 mmol, 671 µL) and water (600 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled then concentrated under reduced pressure. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-4-ethoxy-3-fluoro-N'-hydroxybenzimidamide (300 mg, 1.51 mmol, 63 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.57 (s, 1H), 7.47 - 7.39 (m, 2H), 7.12 (t, *J*=8.9 Hz, 1H), 5.80 (s, 2H), 4.13 - 4.06 (m, 2H), 1.34 - 1.29 (m, 3H).

Step 3: Preparation of N-(2-(4-(3-(4-ethoxy-3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

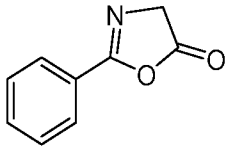


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-4-ethoxy-3-fluoro-N'-hydroxybenzimidamide (68 mg, 344 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (130 mg, 344 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(4-ethoxy-3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (43 mg, 96 µmol, 28 %) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J*=7.0 Hz, 2H), 7.85 - 7.79 (m, 2H), 7.58 - 7.44 (m, 3H), 7.35 (br s, 1H), 7.05 (t, *J*=8.5 Hz, 1H), 4.51 (br d, *J*=13.6 Hz, 1H), 4.33 (d, *J*=3.8 Hz, 2H), 4.20 (q, *J*=7.0 Hz, 2H), 3.93 (br d, *J*=13.7 Hz, 1H), 3.41 - 3.29 (m, 2H), 3.23 - 3.13 (m, 1H), 2.32 - 2.20 (m, 2H), 2.08 - 1.93 (m, 2H), 1.51 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 453.1.

Example 98: [4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(2-phenyl-1H-imidazol-5-yl)methanone

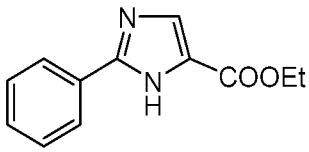


Step 1: Preparation of 2-phenyl-4H-oxazol-5-one



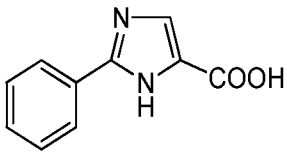
A mixture of 2-benzamidoacetic acid (1.0 g, 5.58 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (953 mg, 6.14 mmol, 1.08 mL) in dichloromethane (25 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 6h under a nitrogen atmosphere. The mixture was concentrated in vacuum to get a crude product. The crude product, 2-phenyl-4H-oxazol-5-one (1.20 g) was used directly without further purification.

Step 2: Ethyl 2-phenyl-1H-imidazole-5-carboxylate



A mixture of 2-phenyl-4H-oxazol-5-one (1.0 g, 6.21 mmol), ethyl cyanoformate (676 mg, 6.83 mmol, 669 µL) and tributylphosphine (753 mg, 3.72 mmol, 918 µL) in dichloromethane (3 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 6h under a nitrogen atmosphere. The reaction mixture was quenched by addition of water (3 mL), then extracted with dichloromethane (10 mL x 2). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue that was purified by chromatography (silica, petroleum ether / ethyl acetate = 2:1) to give ethyl 2-phenyl-1H-imidazole-5-carboxylate (480 mg, 2.22 mmol, 36 %) as a white solid.

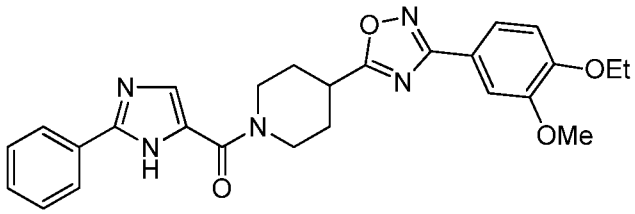
Step 3: 2-phenyl-1H-imidazole-5-carboxylic acid



A mixture of ethyl 2-phenyl-1H-imidazole-5-carboxylate (300 mg, 1.39 mmol) and sodium hydroxide (166 mg, 4.17 mmol) in tetrahydrofuran (3 mL) and water (1.50 mL) was stirred at 20 °C for 2 h. The reaction mixture was extracted with dichloromethane (10 mL x 3). The combined organic phases

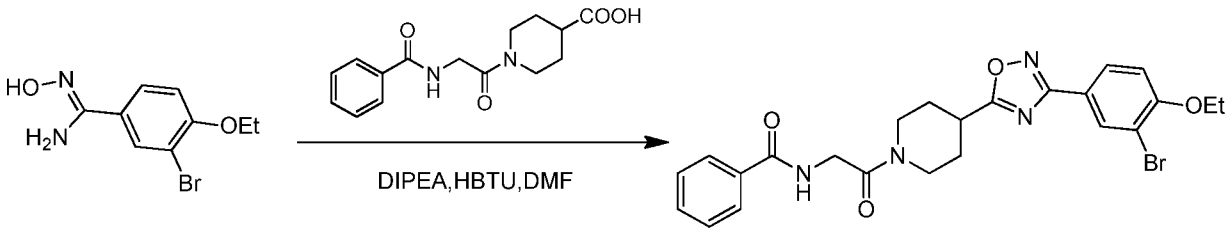
were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-phenyl-1H-imidazole-5-carboxylic acid (200 mg) that was used directly without further purification.

Step 4: [4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(2-phenyl-1H-imidazol-5-yl)methanone

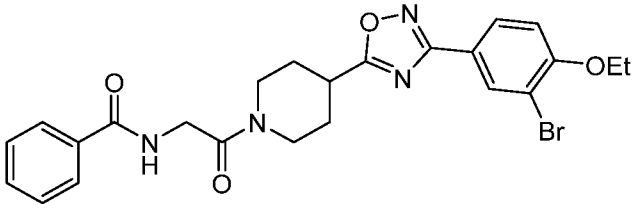


A mixture of 2-phenyl-1H-imidazole-5-carboxylic acid (62 mg, 330 µmol), 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (100 mg, 330 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (125 mg, 330 µmol) and diisopropylethylamine (85 mg, 659 µmol, 115 µL) in N,N-dimethylformamide (3 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 2 h under a nitrogen atmosphere. The mixture was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-65%,12 min) to give [4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(2-phenyl-1H-imidazol-5-yl)methanone (25 mg, 105 µmol, 16 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.95 (br d, J=7.7 Hz, 2H), 7.65 (dd, J=1.8, 8.4 Hz, 1H), 7.54 (s, 2H), 7.47 - 7.32 (m, 3H), 6.92 (d, J=8.4 Hz, 1H), 5.56 - 5.27 (m, 1H), 4.77 - 4.46 (m, 1H), 4.14 (q, J=6.8 Hz, 2H), 3.99 - 3.88 (m, 3H), 3.66 - 3.09 (m, 3H), 2.24 (br d, J=9.7 Hz, 2H), 2.07 (br s, 1H), 1.84 (br s, 1H), 1.47 (t, J=6.8 Hz, 3H); LCMS(ESI) m/z: $[M+H]^+$ = 474.3.

Example 99: N-(2-(4-(3-(3-bromo-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide



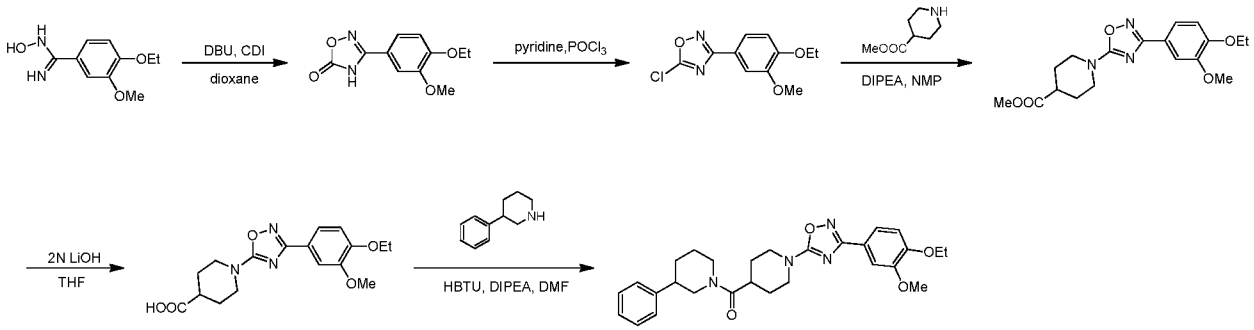
Step 1: Preparation of N-(2-(4-(3-(3-bromo-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide



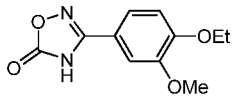
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide (89 mg, 344

μmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (130 mg, 344 μmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 μL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-75%,12 min) to give N-(2-(4-(3-(3-bromo-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (43 mg, 83 μmol, 24 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.30 (d, *J*=2.1 Hz, 1H), 8.00 (dd, *J*=2.1, 8.6 Hz, 1H), 7.91 - 7.85 (m, 2H), 7.58 - 7.44 (m, 3H), 7.35 (br s, 1H), 6.98 (d, *J*=8.7 Hz, 1H), 4.50 (br d, *J*=14.1 Hz, 1H), 4.33 (d, *J*=3.9 Hz, 2H), 4.20 (q, *J*=6.9 Hz, 2H), 3.93 (br d, *J*=13.8 Hz, 1H), 3.41 - 3.29 (m, 2H), 3.18 (br t, *J*=10.6 Hz, 1H), 2.32 - 2.20 (m, 2H), 2.09 - 1.93 (m, 2H), 1.53 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 513.2.

Example 100: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(3-phenylpiperidin-1-yl)methanone.

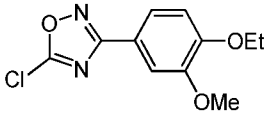


Step 1: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one



To a stirred solution of 4-ethoxy-N-hydroxy-3-methoxybenzimidamide (1.0 g, 4.76 mmol) in dioxane (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (796 mg, 5.24 mmol, 788 μL) and 1,1'-carbonyldiimidazole (1.16 g, 7.14 mmol). The mixture was heated at 110 °C for 16 h. The reaction mixture was cooled, quenched with water (10 mL), and then extracted with dichloromethane (50 mL x 3). The combined organic phases were washed with 1M aqueous hydrochloric acid (5 mL x 2), then with saturated aqueous sodium chloride solution (10 mL), filtered and dried over anhydrous sodium sulfate. The organic layer was concentrated to give 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (1.02 g, 4.32 mmol, 91 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.78 (br s, 1H), 7.38 - 7.28 (m, 2H), 7.08 (d, *J*=8.4 Hz, 1H), 4.05 (q, *J*=7.1 Hz, 2H), 3.77 (s, 3H), 1.30 (t, *J*=6.9 Hz, 3H).

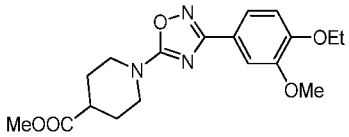
Step 2: Preparation of 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole.



A flask 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (1.02 g, 4.32 mmol) was equipped with calcium chloride tube, then phosphoryl chloride (12 mL) and pyridine (170 mg, 2.16 mmol, 174 μL) were added dropwise and the mixture was heated at 110 °C for 16 h. The reaction mixture was

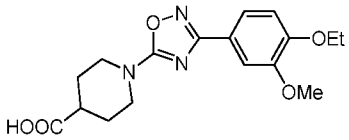
cooled then concentrated under reduced pressure to remove phosphoryl chloride, and the residue added to ice water (20 mL) and stirred for 10 min. The mixture was extracted with dichloromethane (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (910 mg) as a yellow solid.

Step 3: Preparation of methyl 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylate.



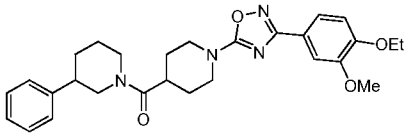
To a stirred solution of 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (600 mg, 2.36 mmol) in N-methyl-2-pyrrolidone (8 mL) was added methyl piperidine-4-carboxylate (337 mg, 2.36 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (610 mg, 4.72 mmol, 824 µL). The mixture was stirred at 120 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10:1) to give methyl 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylate (510 mg, 1.41 mmol, 60 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.47 (dd, *J*=1.9, 8.3 Hz, 1H), 7.38 (d, *J*=2.0 Hz, 1H), 7.06 (d, *J*=8.4 Hz, 1H), 4.08 (q, *J*=7.0 Hz, 2H), 4.00 (td, *J*=3.5, 13.2 Hz, 2H), 3.82 (s, 3H), 3.64 (s, 3H), 3.31 - 3.24 (m, 2H), 2.68 (tt, *J*=3.9, 10.9 Hz, 1H), 1.98 (br dd, *J*=3.2, 13.5 Hz, 2H), 1.70 - 1.58 (m, 2H), 1.36 (t, *J*=7.0 Hz, 3H).

Step 4: Preparation of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid.



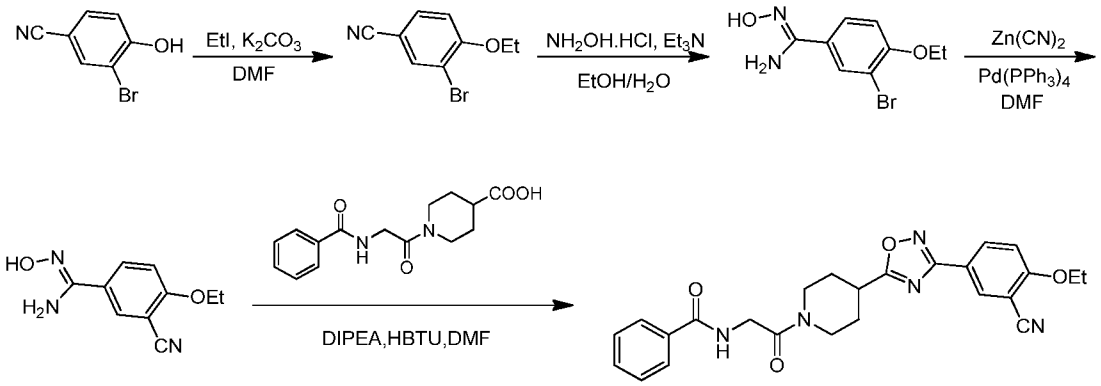
To a stirred solution of methyl 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylate (490 mg, 1.36 mmol) in tetrahydrofuran (10 mL) was added lithium hydroxide (2 M, 2.04 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, then the mixture was acidified with concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (40 mL x 3). The organic layer was washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (400 mg, 1.15 mmol, 85 %) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.52 - 7.45 (m, 2H), 6.99 (d, *J*=8.4 Hz, 1H), 4.15 - 4.05 (m, 4H), 3.86 (s, 3H), 3.32 (br d, *J*=3.1 Hz, 1H), 3.28 - 3.25 (m, 1H), 2.61 (tt, *J*=3.8, 10.8 Hz, 1H), 2.07 - 1.98 (m, 2H), 1.80 - 1.68 (m, 2H), 1.41 (t, *J*=6.9 Hz, 3H).

Step 5: Preparation of (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(3-phenylpiperidin-1-yl)methanone.

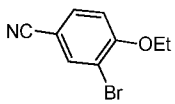


To a stirred solution of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (100 mg, 288 µmol) in N,N-dimethylformamide (500 µL) was added 3-phenylpiperidine (46 mg, 288 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (109 mg, 288 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (111 mg, 863.66 µmol, 150 µL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(3-phenylpiperidin-1-yl)methanone (80 mg, 162 µmol, 56 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.45 - 7.40 (m, 1H), 7.36 - 7.16 (m, 6H), 7.02 (d, *J*=8.4 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.09 - 3.92 (m, 5H), 3.78 (s, 3H), 3.28 - 2.92 (m, 4H), 2.70 - 2.50 (m, 2H), 1.89 (br d, *J*=11.7 Hz, 1H), 1.82 - 1.44 (m, 7H), 1.31 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.3.

Example 101: N-(2-(4-(3-(3-cyano-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

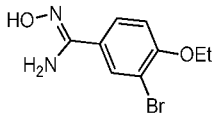


Step 1: Preparation of 3-bromo-4-ethoxybenzonitrile.



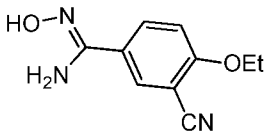
To a stirred solution of 3-bromo-4-hydroxybenzonitrile (1.0 g, 5.05 mmol) in N,N-dimethylformamide (10 mL) was added iodoethane (945 mg, 6.06 mmol, 484 µL) and potassium carbonate (1.40 g, 10.1 mmol) at 0 °C. The reaction was warmed at 40 °C for 16 h. The reaction mixture was quenched by addition of water (15 mL), then the mixture was extracted with ethyl acetate (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 3-bromo-4-ethoxybenzonitrile (1.20 g) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=2.0 Hz, 1H), 7.55 (dd, *J*=2.0, 8.6 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 1H), 4.14 (q, *J*=7.0 Hz, 2H), 1.49 (t, *J*=6.9 Hz, 3H).

Step 2: Preparation of (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide.



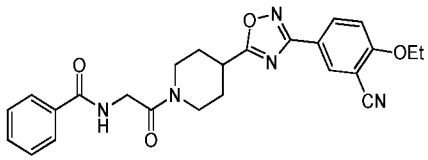
To a stirred solution of 3-bromo-4-ethoxybenzonitrile (1.15 g, 5.09 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (706 mg, 10.2 mmol), triethylamine (1.03 g, 10.2 mmol, 1.41 mL) and water (1 mL). The mixture was heated at 80 °C for 1 h, then cooled and concentrated under reduced pressure to remove ethanol. The residue was triturated with water (5 mL) and filtered, and the filter cake was dried under reduced pressure to give (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide (1.31 g, 5.06 mmol, 99 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.55 (br s, 1H), 7.82 (d, *J*=2.2 Hz, 1H), 7.60 (dd, *J*=2.2, 8.6 Hz, 1H), 7.05 (d, *J*=8.8 Hz, 1H), 5.79 (s, 2H), 4.12 - 4.05 (m, 2H), 1.31 (t, *J*=7.1 Hz, 3H).

Step 3: Preparation of (Z)-3-cyano-4-ethoxy-N'-hydroxybenzimidamide.



To a stirred solution of zinc cyanide (226 mg, 1.93 mmol, 122 µL) in N,N-dimethylformamide (10 mL) was added (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide (500 mg, 1.93 mmol) and tetrakis(triphenylphosphine)palladium(0) (222 mg, 193 µmol), then the mixture was degassed with nitrogen three times. The mixture was heated at 110 °C for 16 h under nitrogen then cooled to 20 °C, water (10 mL) was added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a residue that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 13%-43%,12 min) to give (Z)-3-cyano-4-ethoxy-N'-hydroxybenzimidamide (60 mg, 292 µmol, 15 %) as a white solid.

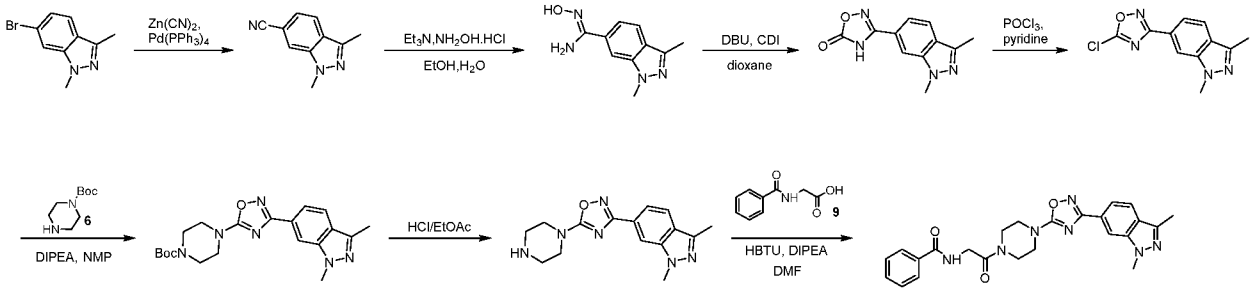
Step 4: Preparation of N-(2-(4-(3-(3-cyano-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



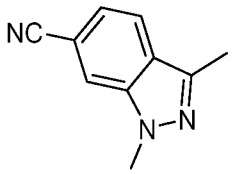
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (70 mg, 241 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-3-cyano-4-ethoxy-N'-hydroxybenzimidamide (49 mg, 241 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (91 mg, 241 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (93 mg, 723 µmol, 126 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-65%,12 min) to give N-(2-(4-(3-(3-cyano-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (20 mg, 43 µmol, 18 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (t,

J=5.5 Hz, 1H), 8.26 - 8.17 (m, 2H), 7.84 (dd, *J*=1.2, 8.3 Hz, 2H), 7.57 - 7.34 (m, 4H), 4.26 (q, *J*=6.9 Hz, 3H), 4.14 (br d, *J*=5.5 Hz, 2H), 3.94 (br d, *J*=14.6 Hz, 1H), 3.48 - 3.40 (m, 1H), 3.29 - 3.22 (m, 1H), 2.90 (br t, *J*=11.4 Hz, 1H), 2.10 (br t, *J*=12.8 Hz, 2H), 1.87 - 1.72 (m, 1H), 1.68 - 1.55 (m, 1H), 1.37 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 460.2.

Example 102: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide

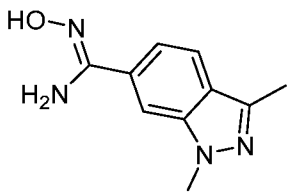


Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (1.0 g, 4.44 mmol) in N,N-dimethylformamide (10 mL) was added zinc cyanide (521 mg, 4.44 mmol, 281 µL) and tetrakis(triphenylphosphine)palladium(0) (513 mg, 444 µmol), then the mixture was degassed with nitrogen three times. The mixture was stirred at 100 °C for 16 h under nitrogen, then cooled to 20 °C, water (10 mL) added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10:1) to give 1,3-dimethyl-1H-indazole-6-carbonitrile (660 mg, 3.86 mmol, 87 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.66 (m, 2H), 7.30 (d, *J*=8.4 Hz, 1H), 4.03 (s, 3H), 2.57 (s, 3H).

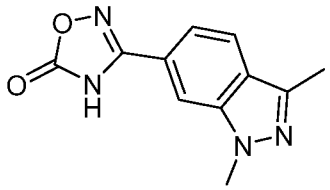
Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (660 mg, 3.86 mmol) in ethanol (8 mL) was added hydroxylamine hydrochloride (536 mg, 7.72 mmol), triethylamine (781 mg, 7.72 mmol, 1.07 mL) and water (800 µL). The mixture was heated at 80 °C for 2 h, then cooled and concentrated under reduced pressure. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (650

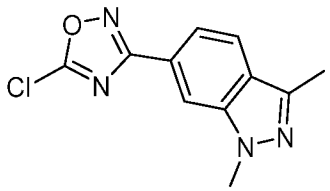
mg, 3.18 mmol, 82 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.72 (br. s., 1H), 7.86 (s, 1H), 7.65 (d, *J*=8.5 Hz, 1H), 7.49 (dd, *J*=1.1, 8.5 Hz, 1H), 5.91 (s, 2H), 3.97 (s, 3H), 2.47 (s, 3H).

Step 3: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one.



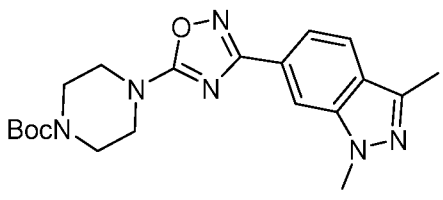
To a stirred solution of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (510 mg, 2.50 mmol) in dioxane (8 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (418 mg, 2.75 mmol, 414 µL) and 1,1'-carbonyldiimidazole (608 mg, 3.75 mmol). The mixture was stirred at 110 °C for 16 h. The reaction mixture was cooled, quenched with water (10 mL), and then extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with 1M hydrochloric acid (5 mL x 2), then washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (430 mg, 1.87 mmol, 75 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.29 - 12.78 (m, 1H), 8.03 (s, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.48 (dd, *J*=1.1, 8.4 Hz, 1H), 3.98 (s, 3H), 2.48 (br s, 3H).

Step 4: Preparation of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole.



A flask 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (180 mg, 781.86 µmol) was equipped with calcium chloride tube then pyridine (123 mg, 1.56 mmol, 126 µL) and phosphoryl chloride (5 mL) were added dropwise. The mixture was heated at 110 °C for 16 h, then cooled and concentrated under reduced pressure to remove phosphoryl chloride, and then added to ice water (20 mL). The mixture was extracted with dichloromethane (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (250 mg) as a brown solid.

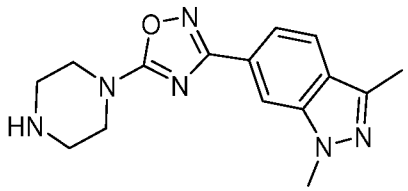
Step 5: Preparation of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate.



To a stirred solution of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (230 mg, 925 µmol) in N-methyl-2-pyrrolidone (3 mL) was added tert-butyl piperazine-1-carboxylate (172 mg, 925 µmol)

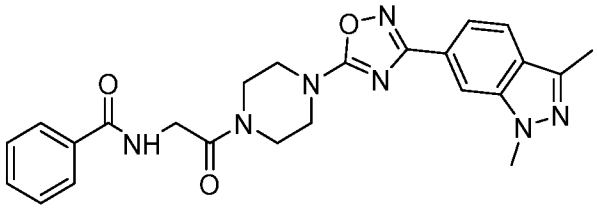
and N-ethyl-N-(propan-2-yl)propan-2-amine (239 mg, 1.85 mmol, 323 µL). The mixture was heated at 120 °C for 2 h. The reaction mixture was cooled, quenched by addition of water (5 mL), then the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1) gave tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate (150 mg, 376 µmol, 41 %) as a pink solid.

Step 6: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole.



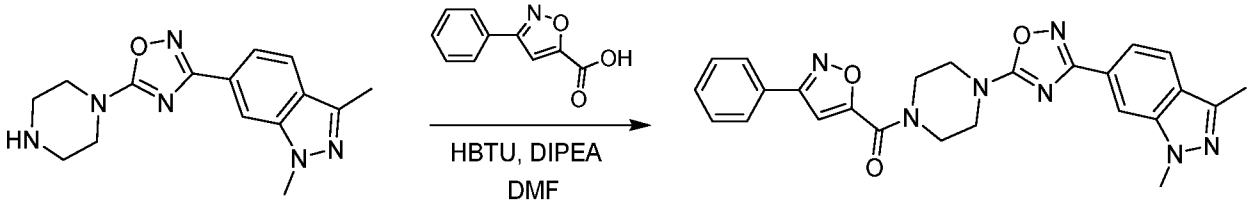
To a stirred solution of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate (150 mg, 376 µmol) in ethyl acetate (1 mL) was added hydrochloric acid / ethyl acetate (4M, 5 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (110 mg, 369 µmol, 98 %) as a pink solid. LCMS (ESI) m/z: $[M+H]^+$ = 299.2.

Step 7: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide.

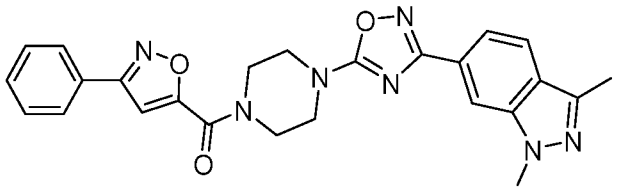


To a stirred solution of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (50 mg, 168 µmol) in N,N-dimethylformamide (1 mL) was added 2-benzamidoacetic acid (30 mg, 168 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (63 mg, 168 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (64 mg, 503 µmol, 87 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide (29 mg, 64 µmol, 38 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.84 (d, *J*=7.7 Hz, 2H), 7.76 - 7.66 (m, 2H), 7.55 - 7.41 (m, 3H), 7.27 - 7.25 (m, 1H), 4.33 (d, *J*=3.7 Hz, 2H), 4.05 (s, 3H), 3.89 - 3.75 (m, 6H), 3.66 (br d, *J*=5.1 Hz, 2H), 2.57 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 460.3.

Example 103: (4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)(3-phenylisoxazol-5-yl)methanone.

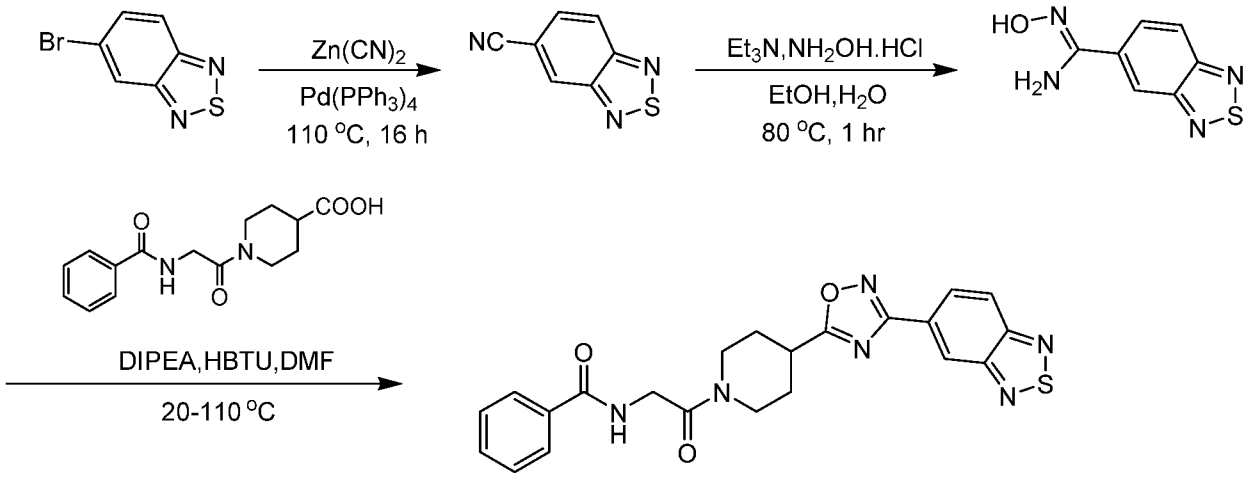


Step 1: Preparation of (4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)(3-phenylisoxazol-5-yl)methanone.

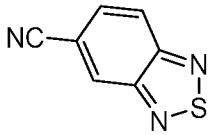


To a stirred solution of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (50 mg, 168 µmol) in N,N-dimethylformamide (1 mL) was added 3-phenylisoxazole-5-carboxylic acid (31 mg, 168 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (63 mg, 168 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (64 mg, 502.8 µmol, 87 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-75%,12 min) to give (4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)(3-phenylisoxazol-5-yl)methanone (26 mg, 56.9 µmol, 34 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.83 (td, *J*=2.8, 4.1 Hz, 2H), 7.76 - 7.73 (m, 1H), 7.71 - 7.67 (m, 1H), 7.51 - 7.47 (m, 3H), 7.18 (s, 1H), 4.05 (s, 3H), 4.03 - 3.93 (m, 4H), 3.89 - 3.84 (m, 4H), 2.57 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 470.3.

Example 104: N-(2-(4-(3-(benzo[c][1,2,5]thiadiazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

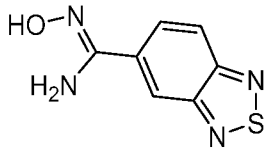


Step 1: Preparation of benzo[c][1,2,5]thiadiazole-5-carbonitrile.



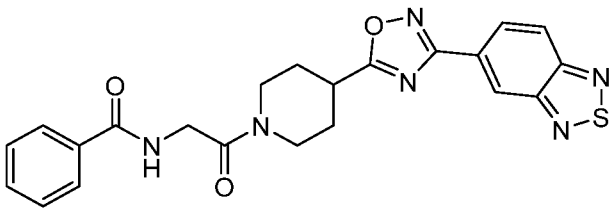
To a stirred solution of 5-bromobenzo[c][1,2,5]thiadiazole (200 mg, 930 µmol) in N,N-dimethylformamide (2 mL) was added zinc cyanide (109 mg, 930 µmol, 59 µL) and tetrakis(triphenylphosphine)palladium(0) (107 mg, 93 µmol), the mixture was degassed with nitrogen three times. The mixture was heated at 110 °C for 16 h under nitrogen. After cooling to 20 °C, water (5 mL) was added to the reaction, and the mixture extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. The mixture was triturated with petroleum ether (20 mL) and dichloromethane (2 mL), then the mixture was filtered, and the filter cake dried in vacuo to give benzo[c][1,2,5]thiadiazole-5-carbonitrile (100 mg, 620 µmol, 67 %) as a red solid. LCMS (ESI) m/z: $[M+H]^+$ = 162.0.

Step 2: Preparation of (Z)-N'-hydroxybenzo[c][1,2,5]thiadiazole-5-carboximidamide.



To a stirred solution of benzo[c][1,2,5]thiadiazole-5-carbonitrile (100 mg, 620 µmol) in ethanol (2 mL) was added hydroxylamine hydrochloride (86 mg, 1.24 mmol), triethylamine (125 mg, 1.24 mmol, 172 µL) and water (200 µL). The mixture was heated at 80 °C for 1 h. The reaction mixture was cooled and then concentrated under reduced pressure to remove ethanol. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxybenzo[c][1,2,5]thiadiazole-5-carboximidamide (70 mg, 360 µmol, 58 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.13 (s, 1H), 8.35 (d, *J*=0.9 Hz, 1H), 8.10 (dd, *J*=1.5, 9.3 Hz, 1H), 8.01 - 7.96 (m, 1H), 6.08 (s, 2H).

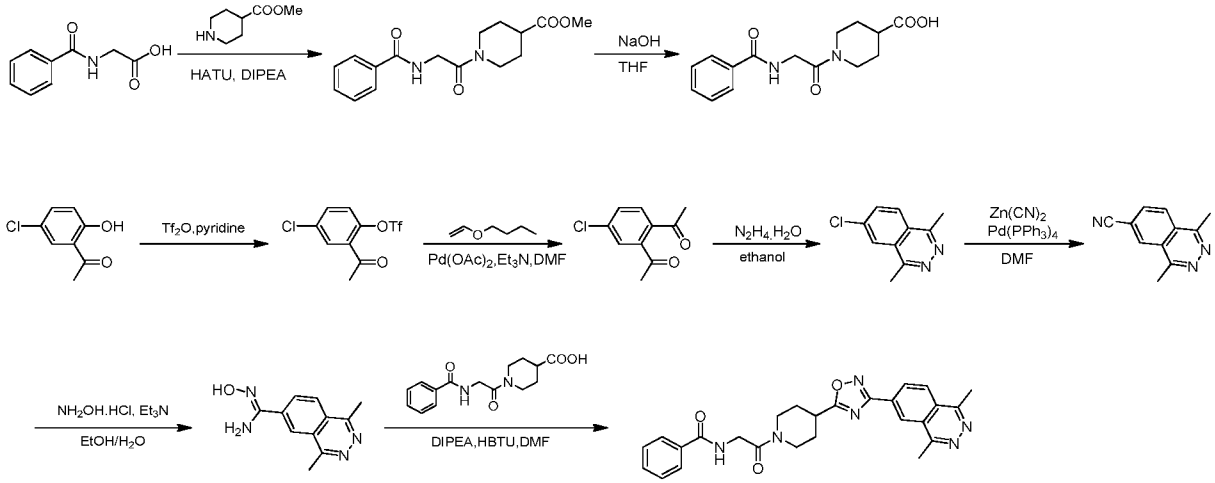
Step 3: Preparation of N-(2-(4-(3-(benzo[c][1,2,5]thiadiazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



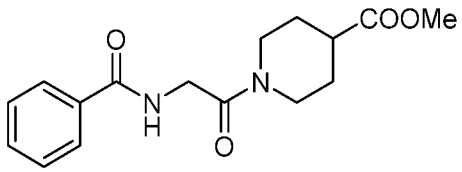
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (80 mg, 276 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxybenzo[c][1,2,5]thiadiazole-5-carboximidamide (53 mg, 276 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (104 mg, 276 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (106 mg, 827 µmol, 144 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-65%,12 min) to give N-(2-(4-(3-(benzo[c][1,2,5]thiadiazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (30 mg, 67 µmol, 24 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (t, *J*=1.2 Hz, 1H), 8.55 (t, *J*=5.7 Hz, 1H), 8.28 - 8.22 (m, 2H), 7.87 - 7.83 (m, 2H), 7.54 - 7.42 (m, 3H), 4.31 (br d, *J*=13.0 Hz, 1H), 4.16 (dd, *J*=1.5, 5.7 Hz, 2H), 3.98 (br d, *J*=13.5 Hz, 1H), 3.54 -

3.51 (m, 1H), 3.29 (br t, *J*=11.5 Hz, 1H), 2.93 (br t, *J*=11.2 Hz, 1H), 2.16 (br t, *J*=13.2 Hz, 2H), 1.90 - 1.78 (m, 1H), 1.73 - 1.62 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 449.2.

Example 105: N-(2-(4-(3-(1,4-dimethylphthalazin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

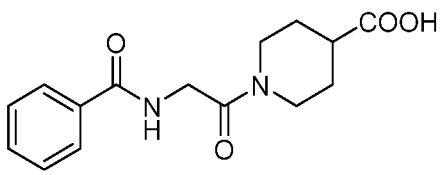


Step 1: Preparation of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



To a stirred solution of 2-benzamidoacetic acid (5.0 g, 27.9 mmol) in N,N-dimethylformamide (50 mL) was added methyl piperidine-4-carboxylate (4.40 g, 30.7 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (10.6 g, 27.9 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (10.8 g, 83.7 mmol, 14.6 mL). The mixture was stirred at 20 °C for 2 h, then quenched by addition of water (50 mL). The mixture was extracted with ethyl acetate (100 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) to give methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (9.17 g) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.88 - 7.83 (m, 2H), 7.55 - 7.49 (m, 1H), 7.48 - 7.41 (m, 2H), 4.35 - 4.28 (m, 1H), 4.24 (d, *J*=5.3 Hz, 2H), 3.88 (d, *J*=14.1 Hz, 1H), 3.66 (s, 3H), 3.20 (d, *J*=2.2 Hz, 1H), 2.92 - 2.84 (m, 1H), 2.65 (tt, *J*=4.0, 10.8 Hz, 1H), 1.99 - 1.87 (m, 2H), 1.74 - 1.64 (m, 1H), 1.62 - 1.51 (m, 1H).

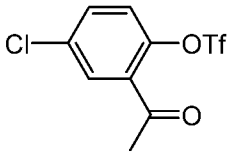
Step 2: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (9.17 g, 30.1 mmol) in tetrahydrofuran (90 mL) was added sodium hydroxide (2 M, 30.1 mL). The mixture was stirred at 20 °C

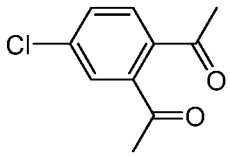
for 2 h. The reaction mixture was concentrated under reduced pressure then acidified with concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (80 mL x 4). The organic phases were combined and then washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue (8.85 g). A portion of crude product (2.5 g) was purified by prep-HPLC (column: Daiso 250*50mm, 10µm; mobile phase: [water (0.1%TFA)-acetonitrile]; B%: 1%-30%, 20 min) to provide 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (0.95 g). The remaining crude product was used directly without purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.87 - 7.83 (m, 2H), 7.55 - 7.50 (m, 1H), 7.48 - 7.42 (m, 2H), 4.36 (td, *J*=3.2, 13.2 Hz, 1H), 4.25 (d, *J*=3.3 Hz, 2H), 3.94 - 3.86 (m, 1H), 3.22 - 3.14 (m, 1H), 2.89 - 2.80 (m, 1H), 2.46 (tt, *J*=3.9, 11.0 Hz, 1H), 2.00 - 1.87 (m, 2H), 1.74 - 1.52 (m, 2H).

Step 3: Preparation of 2-acetyl-4-chlorophenyl trifluoromethanesulfonate.



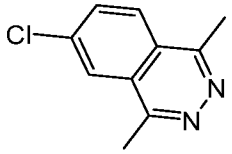
Triflic anhydride (9.92 g, 35.2 mmol, 5.80 mL) was added dropwise at 0 °C to a stirred solution of 1-(5-chloro-2-hydroxy-phenyl)ethanone (5.0 g, 29.3 mmol) in pyridine (50 mL) The reaction was warmed slowly to 15 °C and stirred for 15 h. The reaction solution was diluted with dichloromethane (100 mL), then poured into 1N aqueous hydrochloric acid (100 mL) at 0 °C and the phases separated. The organic phase was washed with 1N hydrochloric acid (50 mL x 2), saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a crude residue. Purification by chromatography (silica, petroleum ether : ethyl acetate from 100/1 to 30/1) gave 2-acetyl-4-chlorophenyl trifluoromethanesulfonate (7.50 g, 24.8 mmol, 85 %) as a yellow liquid.

Step 4: Preparation of 1,1'-(4-chloro-1,2-phenylene)diethanone.



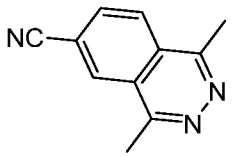
To a stirred solution of 2-acetyl-4-chlorophenyl trifluoromethanesulfonate (3.0 g, 9.91 mmol) in N,N-dimethylformamide (30 mL) was added 1-vinyloxybutane (4.96 g, 49.6 mmol, 6.36 mL), palladium(II) acetate(111 mg, 495.5 µmol), 3-diphenylphosphanylpropyl(diphenyl)phosphane (245 mg, 594.6 µmol) and TEA (1.20 g, 11.9 mmol, 1.65 mL), then the mixture was degassed with nitrogen three times. The mixture was heated at 80 °C for 16 h under nitrogen. After cooling to 20 °C, 2M hydrochloric acid (20 mL) was added and the solution stirred at 20 °C for 2 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10:1) to give 1,1'-(4-chloro-1,2-phenylene)diethanone (800 mg, 4.07 mmol, 41 %) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.54 (m, 1H), 7.51 - 7.47 (m, 1H), 7.43 (t, *J*=1.9 Hz, 1H), 2.52 (d, *J*=2.0 Hz, 3H), 2.50 (d, *J*=2.0 Hz, 3H).

Step 5: Preparation of 6-chloro-1,4-dimethylphthalazine.



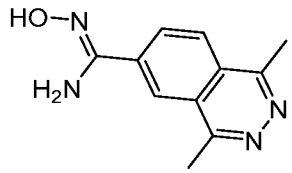
1,1'-(4-chloro-1,2-phenylene)diethanone (800 mg, 4.07 mmol) in ethanol (15 mL) was added to hydrazine hydrate (224 mg, 4.48 mmol, 217 µL) in ethanol (15 mL) at 0 °C over a period of 5 min under argon. The mixture was stirred at 20 °C for 18 h. The reaction mixture was concentrated under reduced pressure to ~15 mL, then extracted with dichloromethane (50 mL x 3). The combined organic phases were washed water (20 mL x 2), then the separated organic layer was washed saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 6-chloro-1,4-dimethylphthalazine (662 mg, 3.44 mmol, 84 %) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 - 7.93 (m, 2H), 7.75 (dd, *J*=2.1, 8.8 Hz, 1H), 2.88 (d, *J*=5.1 Hz, 6H).

Step 6: Preparation of 1,4-dimethylphthalazine-6-carbonitrile.



To a stirred solution of 6-chloro-1,4-dimethylphthalazine (640 mg, 3.32 mmol) in N,N-dimethylformamide (10 mL) was added zinc cyanide (390 mg, 3.32 mmol, 210 µL) and tetrakis(triphenylphosphine)palladium(0) (383 mg, 332 µmol) under nitrogen. The mixture was heated at 110 °C for 16 h, then cooled to 20 °C. Water (15 mL) was added then the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude product. Trituration with petroleum ether (30 mL) and dichloromethane (5 mL) followed by filtration and drying the filter cake in vacuo gave 1,4-dimethylphthalazine-6-carbonitrile (400 mg, 2.18 mmol, 66 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.21 (d, *J*=8.5 Hz, 1H), 8.09 (dd, *J*=1.4, 8.5 Hz, 1H), 3.04 (s, 6H).

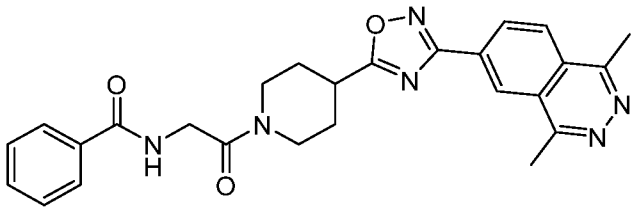
Step 7: Preparation of (Z)-N'-hydroxy-1,4-dimethylphthalazine-6-carboximidamide.



To a stirred solution of 1,4-dimethylphthalazine-6-carbonitrile (380 mg, 2.07 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (288 mg, 4.15 mmol), triethylamine (419 mg, 4.15 mmol, 575 µL) and water (100 µL). The mixture was heated at 80 °C for 1 h. The reaction mixture was cooled then concentrated under reduced pressure. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1,4-dimethylphthalazine-6-carboximidamide (330 mg, 1.53 mmol, 74 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (s,

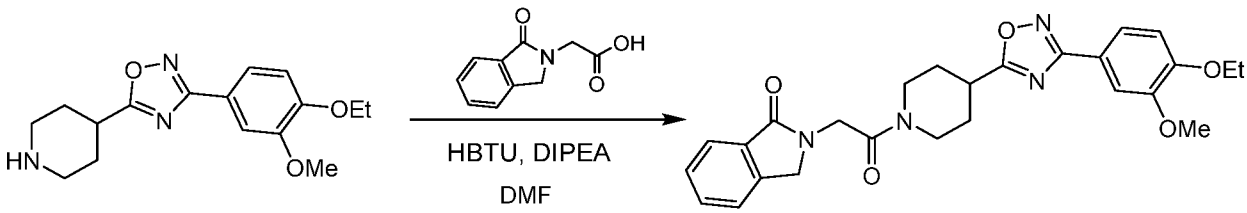
1H), 8.38 (d, *J*=1.3 Hz, 1H), 8.28 (dd, *J*=1.7, 8.7 Hz, 1H), 8.12 (d, *J*=8.8 Hz, 1H), 6.19 (s, 2H), 2.85 (d, *J*=17.0 Hz, 6H).

Step 8: Preparation of N-(2-(4-(3-(1,4-dimethylphthalazin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

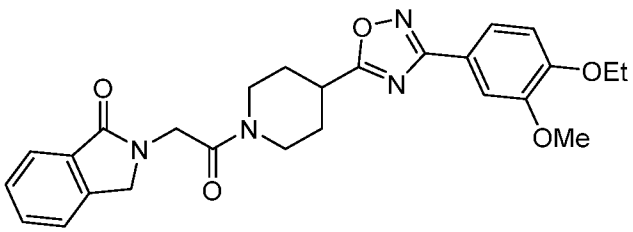


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added N'-hydroxy-1,4-dimethyl-phthalazine-6-carboxamidine (74 mg, 344 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (130 mg, 344 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL). The mixture was stirred at 20 ℃ for 1 h, then heated at 110 ℃ for 1 h. The reaction mixture was cooled, then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-55%,12 min) to give N-(2-(4-(3-(1,4-dimethylphthalazin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (37 mg, 77 µmol, 22 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.71 (d, *J*=1.5 Hz, 1H), 8.59 (t, *J*=5.6 Hz, 1H), 8.54 (dd, *J*=1.5, 8.6 Hz, 1H), 8.39 (d, *J*=8.6 Hz, 1H), 7.90 - 7.86 (m, 2H), 7.57 - 7.45 (m, 3H), 4.37 (br d, *J*=13.2 Hz, 1H), 4.25 - 4.13 (m, 2H), 4.02 (br d, *J*=13.5 Hz, 1H), 3.55 (tt, *J*=3.8, 11.1 Hz, 1H), 3.32 - 3.27 (m, 1H), 2.96 (s, 3H), 2.98 - 2.91 (m, 1H), 2.93 (s, 3H), 2.20 (br t, *J*=13.7 Hz, 2H), 1.95 - 1.82 (m, 1H), 1.77 - 1.65 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 471.3.

Example 106: 2-(2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one.



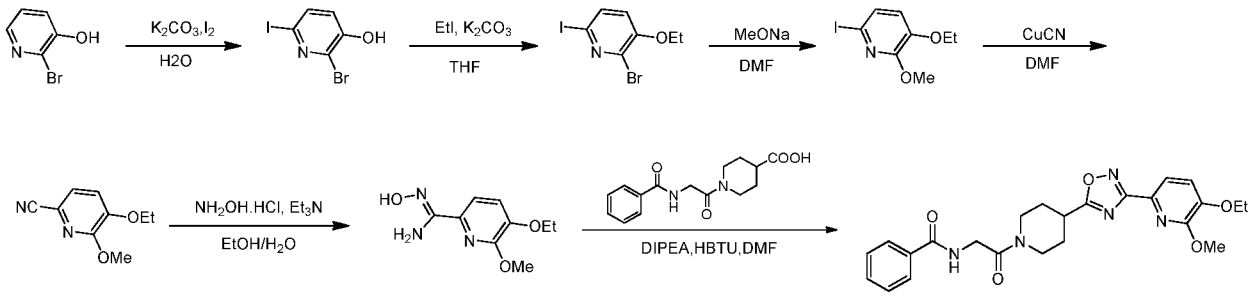
Step 1: Preparation of 2-(2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one.



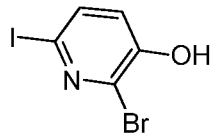
To a stirred solution of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (50 mg, 165 µmol) in N,N-dimethylformamide (1 mL) was added 2-(1-oxoisoindolin-2-yl)acetic acid (31 mg, 165

μmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (62 mg, 165 μmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (63 mg, 494 μmol, 86 μL). The mixture was stirred at 20 °C for 1 h, then the reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 2-(2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one (41 mg, 86 μmol, 52 %) as a gray solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.88 (d, *J*=8.2 Hz, 1H), 7.66 (dd, *J*=1.9, 8.3 Hz, 1H), 7.59 - 7.54 (m, 2H), 7.48 (t, *J*=6.4 Hz, 2H), 6.95 (d, *J*=8.4 Hz, 1H), 4.59 (d, *J*=3.4 Hz, 2H), 4.53 - 4.40 (m, 3H), 4.18 (q, *J*=7.0 Hz, 2H), 4.08 (br d, *J*=13.7 Hz, 1H), 3.96 (s, 3H), 3.43 - 3.24 (m, 2H), 3.11 - 3.02 (m, 1H), 2.28 - 2.15 (m, 2H), 2.05 - 1.90 (m, 2H), 1.51 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

Example 107: N-[2-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.

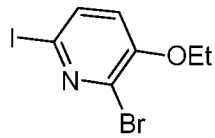


Step 1: 2-bromo-6-iodo-pyridin-3-ol.



A mixture of 2-bromopyridin-3-ol (5.0 g, 28.7 mmol), iodine (8.02 g, 31.6 mmol, 6.37 mL), and potassium carbonate (7.94 g, 57.5 mmol) in water (66 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 16 h under a nitrogen atmosphere. Excess iodine was quenched by addition of solid sodium bisulfite. The pH of the solution was adjusted to 5-6 using glacial acetic acid, and the solid formed was collected by filtration and dried in vacuum to give 2-bromo-6-iodo-pyridin-3-ol (10.0 g) that was used directly without further purification.

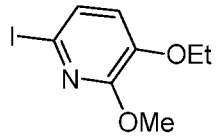
Step 2: 2-bromo-3-ethoxy-6-iodo-pyridine.



To a stirred solution of 2-bromo-6-iodo-pyridin-3-ol (10.0 g, 33.4 mmol) in tetrahydrofuran (200 mL) was added potassium carbonate (6.91 g, 50.0 mmol) and the mixture was stirred for 10 min at 0 °C in an ice bath. Iodoethane (6.24 g, 40.0 mmol, 3.20 mL) was added dropwise, then the reaction mixture was warmed to 40 °C. After 16 h, the reaction mixture was quenched by addition of water (10 mL), and then extracted with ethyl acetate (10 mL x 2). The combined organic phases were washed with saturated

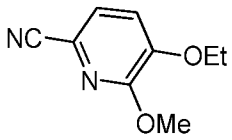
aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-bromo-3-ethoxy-6-iodo-pyridine (7.50 g, 22.9 mmol, 69 %) that was used directly without further purification.

Step 3: 3-ethoxy-6-iodo-2-methoxy-pyridine.



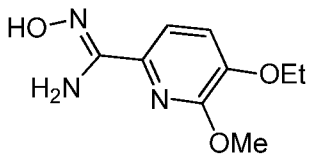
A mixture of 2-bromo-3-ethoxy-6-iodo-pyridine (7.0 g, 21.4 mmol) and sodium methoxide (1.73 g, 32.0 mmol) in N,N-dimethylformamide (3 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 100 °C for 16 h under a nitrogen atmosphere. The reaction mixture was quenched by addition of water (20 mL), then extracted with ethyl acetate (20 mL x 3). The organic layer phases were combined and then washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 3-ethoxy-6-iodo-2-methoxy-pyridine (5.0 g, 17.9 mmol). This was used directly without further purification.

Step 4: 5-ethoxy-6-methoxy-pyridine-2-carbonitrile.



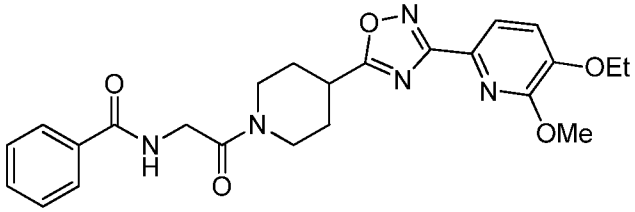
A mixture of 3-ethoxy-6-iodo-2-methoxy-pyridine (2.50 g, 8.96 mmol) and coper(I) cyanide (962 mg, 10.75 mmol, 2.35 mL) in N,N-dimethylformamide (10 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 100 °C for 16 h under a nitrogen atmosphere. The reaction mixture was quenched by addition of water (20 mL), then extracted with ethyl acetate (20 mL x 3). The organic extracts were combined, washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 5-ethoxy-6-methoxy-pyridine-2-carbonitrile (1.40 g). This was used directly without further purification.

Step 5: 5-ethoxy-6-methoxy-pyridine-2-carbonitrile.



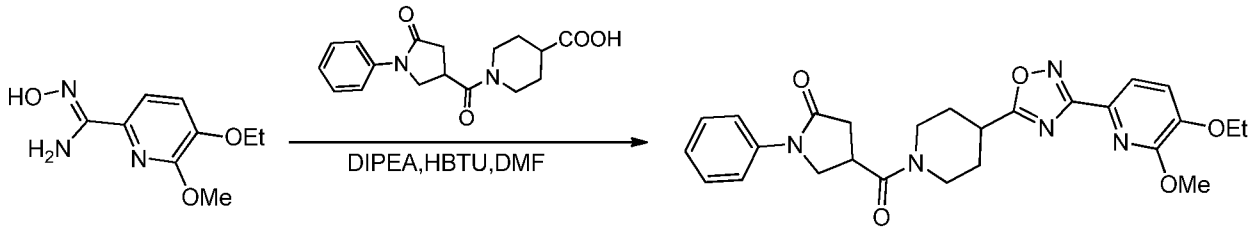
A mixture of 5-ethoxy-6-methoxy-pyridine-2-carbonitrile (1.0 g, 5.61 mmol), hydroxylamine hydrochloride (857 mg, 12.34 mmol) and triethylamine (1.25 g, 12.34 mmol, 1.71 mL) in ethanol (10 mL) was heated at 75 °C for 16 h under a nitrogen atmosphere. The reaction mixture was cooled, diluted with water (10 mL), and filtered. The filter cake was dried in vacuo to give 5-ethoxy-N'-hydroxy-6-methoxy-pyridine-2-carboxamidine (950 mg, 4.50 mmol, 80 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.40 (d, J=8.2 Hz, 1H), 6.99 (d, J=8.2 Hz, 1H), 5.45 (br s, 2H), 4.05 (q, J=6.9 Hz, 2H), 3.98 (s, 3H), 1.41 (t, J=7.0 Hz, 3H).

Step 6: N-[2-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.

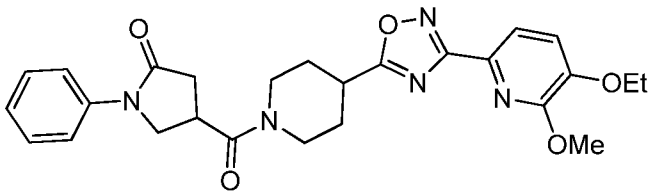


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added 5-ethoxy-N'-hydroxy-6-methoxy-pyridine-2-carboxamidine (72 mg, 344 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL). The mixture was stirred at 20 ℃ for 1 h, then heated at 110 ℃ for 1 h. The crude product was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (37 mg, 79.9 µmol, 23 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.91 - 7.85 (m, 2H), 7.70 (d, J=8.0 Hz, 1H), 7.57 - 7.52 (m, 1H), 7.51 - 7.44 (m, 2H), 7.36 (br s, 1H), 7.13 (d, J=8.2 Hz, 1H), 4.57 - 4.48 (m, 1H), 4.32 (d, J=3.9 Hz, 2H), 4.23 - 4.12 (m, 5H), 4.06 - 3.90 (m, 1H), 3.42 - 3.32 (m, 2H), 3.20 - 3.11 (m, 1H), 2.32 - 2.20 (m, 2H), 2.08 - 1.95 (m, 2H), 1.54 (t, J=7.0 Hz, 3H); LCMS(ESI) m/z: $[M+H]^+$ = 466.3.

Example 108: 4-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.



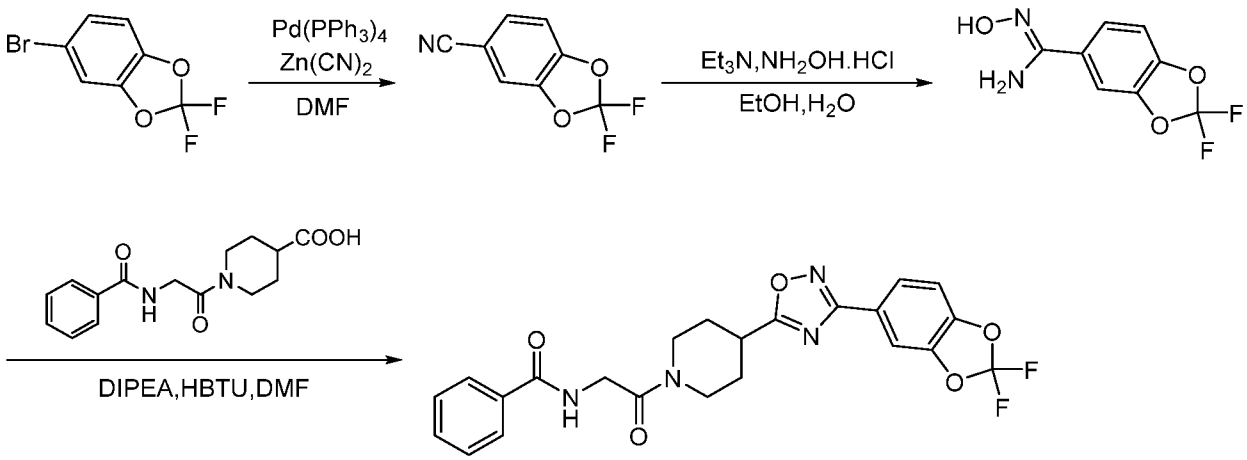
Step 1: 4-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.



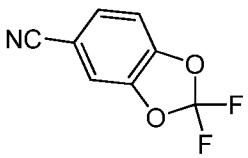
To a stirred solution of 5-ethoxy-N'-hydroxy-6-methoxy-pyridine-2-carboxamidine (66 mg, 316 µmol) in N,N-dimethylformamide (2 mL) was added 1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (100 mg, 316 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (143 mg, 379 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (122 mg, 948 µmol, 165 µL). The mixture was stirred at 20 ℃ for 1 h, then heated at 110 ℃ for 1 h. The mixture was cooled and the crude product was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-70%,12 min) to give 4-[4-[3-(5-

ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (47 mg, 96 µmol, 3 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.71 (dd, J=4.6, 8.0 Hz, 1H), 7.62 (dd, J=1.1, 8.7 Hz, 2H), 7.43 - 7.38 (m, 2H), 7.22 - 7.17 (m, 1H), 7.13 (d, J=7.8 Hz, 1H), 4.63 - 4.48 (m, 1H), 4.34 (t, J=7.9 Hz, 1H), 4.22 - 4.15 (m, 5H), 4.03 - 3.93 (m, 2H), 3.60 (m, 1H), 3.46 - 3.33 (m, 2H), 3.15 - 2.95 (m, 2H), 2.91 - 2.82 (m, 1H), 2.27 (m, 2H), 2.08 - 1.94 (m, 2H), 1.54 (t, J=7.0 Hz, 3H); LCMS(ESI) m/z: $[M+H]^+$ = 492.3.

Example 109: N-[2-[4-[3-(2,2-difluoro-1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide

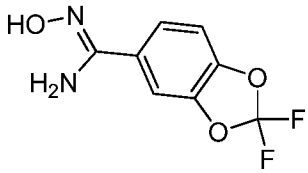


Step 1: 2,2-difluoro-1,3-benzodioxole-5-carbonitrile.



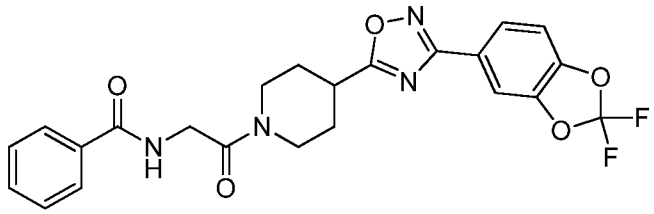
A mixture of 5-bromo-2,2-difluoro-1,3-benzodioxole (500 mg, 2.11 mmol), zinc cyanide (247 mg, 2.11 mmol, 133 µL) and tetrakis(triphenylphosphine)palladium(0) (243 mg, 211 µmol) in N,N-dimethylformamide (4 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 100 ℃ for 16 h under a nitrogen atmosphere. The reaction mixture was cooled, diluted with water (5 mL), and extracted with ethyl acetate (10 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2,2-difluoro-1,3-benzodioxole-5-carbonitrile (300 mg, 1.64 mmol, 78 %) as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.38 (dd, J=1.5, 8.3 Hz, 1H), 7.27 (d, J=1.5 Hz, 1H), 7.08 (d, J=8.3 Hz, 1H).

Step 2: 2,2-difluoro-N'-hydroxy-1,3-benzodioxole-5-carboxamidine.



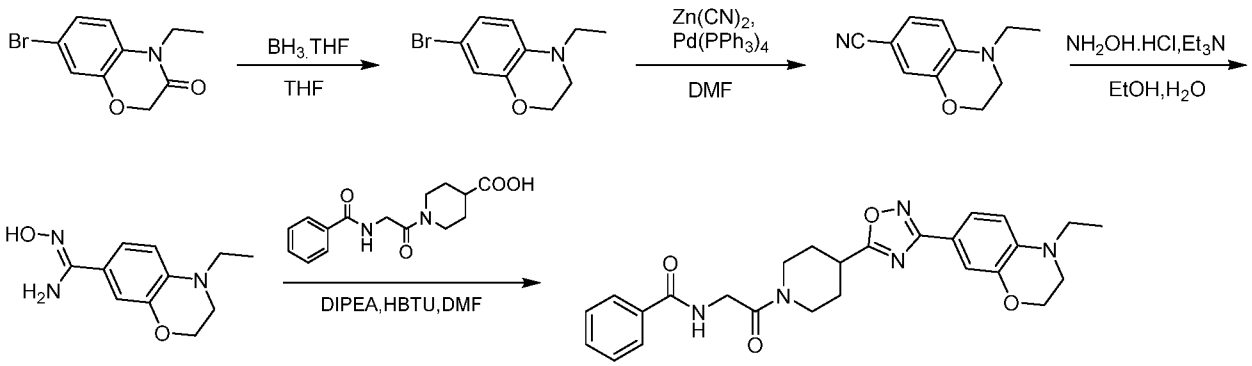
A mixture of 2,2-difluoro-1,3-benzodioxole-5-carbonitrile (300 mg, 1.64 mmol), triethylamine (331 mg, 3.28 mmol, 454 µL) and hydroxylamine hydrochloride (227 mg, 3.28 mmol) in water (500 µL) and ethanol (5 mL) was heated at 70 °C for 16 h. The reaction mixture was cooled, diluted with water (10 mL) and filtered. The collected solid was dried in vacuo to give 2,2-difluoro-N'-hydroxy-1,3-benzodioxole-5-carboxamidine (210 mg) as a solid.

Step 3: N-[2-[4-[3-(2,2-difluoro-1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide,

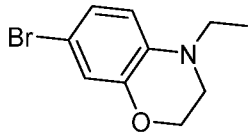


A mixture of 2,2-difluoro-N'-hydroxy-1,3-benzodioxole-5-carboxamidine (74 mg, 344 µmol), 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was stirred at 20 °C for 1 h under a nitrogen atmosphere. The mixture was heated at 120°C for 1 h, then cooled and purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-[2-[4-[3-(2,2-difluoro-1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (58 mg, 124 µmol, 36 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.85 - 7.76 (m, 3H), 7.72 (d, J=1.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.41 - 7.35 (m, 2H), 7.26 (br s, 1H), 7.10 (d, J=8.4 Hz, 1H), 4.53 - 4.37 (m, 1H), 4.23 (d, J=4.0 Hz, 2H), 3.84 (br d, J=13.9 Hz, 1H), 3.35 - 3.21 (m, 2H), 3.12 - 3.02 (m, 1H), 2.26 - 2.10 (m, 2H), 1.98 - 1.85 (m, 2H); LCMS (ESI) m/z: [M+H]$^+$:471.2.

Example 110: N-(2-(4-(3-(4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

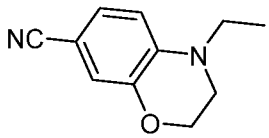


Step 1: Preparation of 7-bromo-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine



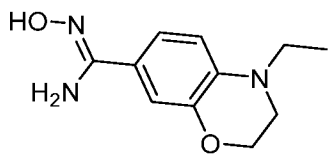
To a stirred solution of 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (900 mg, 3.51 mmol) in tetrahydrofuran (10 mL) was added a solution of borane in tetrahydrofuran (1 M, 12.28 mL), and the mixture was stirred 20 °C for 1 h, then heated at 80 °C for 2 h. The reaction mixture was cooled then quenched by addition of methanol (15 mL). The mixture was concentrated under reduced pressure, then diluted with water (20 mL), extracted with ethyl acetate (60 mL x 2), and the combined organic phases washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 7-bromo-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (750 mg, 3.10 mmol, 88 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 - 6.80 (m, 2H), 6.45 (d, *J*=8.3 Hz, 1H), 4.19 - 4.13 (m, 2H), 3.28 - 3.18 (m, 4H), 1.06 (t, *J*=7.1 Hz, 3H).

Step 2: Preparation of 4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile.



To a stirred solution of 7-bromo-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (80 mg, 330 µmol) in N,N-dimethylformamide (1 mL) was added zinc cyanide (38 mg, 330 µmol) and tetrakis(triphenylphosphine)palladium(0) (38 mg, 33 µmol), then the mixture was degassed with nitrogen three times. The mixture was heated at 110 °C for 16 h under nitrogen, then cooled to 20 °C, and water (3 mL) added. The reaction mixture was extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo to give a crude residue that was purified by prep-TLC (petroleum ether : ethyl acetate=2:1) to give 4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (60 mg, 319 µmol, 96 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (td, *J*=1.4, 8.5 Hz, 1H), 7.00 - 6.92 (m, 1H), 6.59 (d, *J*=8.4 Hz, 1H), 4.20 (dt, *J*=0.9, 4.5 Hz, 2H), 3.42 - 3.33 (m, 4H), 1.16 (dt, *J*=0.9, 7.2 Hz, 3H).

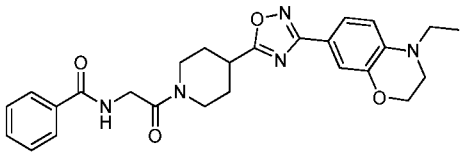
Step 3: Preparation of (Z)-4-ethyl-N'-hydroxy-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide.



To a stirred solution of 4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (60 mg, 319 µmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (44 mg, 638 µmol), triethylamine (64 mg, 638 µmol, 88 µL) and water (100 µL). The mixture was stirred at 80 °C for 5 h. The reaction mixture was cooled, concentrated under reduced pressure, and then diluted with water (5 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and

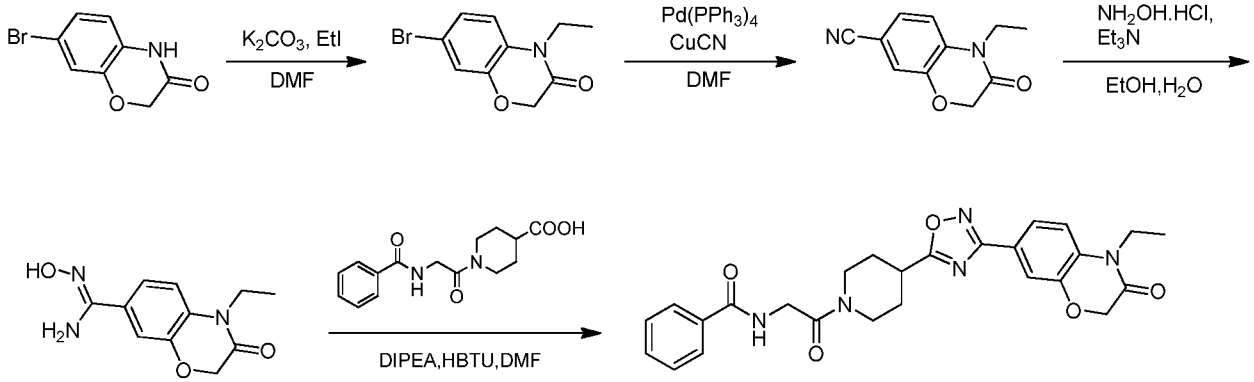
concentrated in vacuo to give crude (Z)-4-ethyl-N'-hydroxy-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (60 mg, 271 µmol, 85 %) as a white solid.

Step 4: Preparation of N-(2-(4-(3-(4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

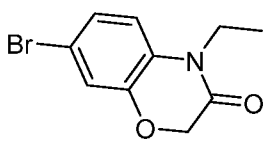


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (60 mg, 207 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-4-ethyl-N'-hydroxy-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (45 mg, 207 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (78 mg, 207 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (80 mg, 620 µmol, 108 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C18 150x2.5mm 5µm; mobile phase: [water (0.225% TFA)-acetonitrile]; B%: 40%-65%,16 min) to give N-(2-(4-(3-(4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (17 mg, 35.8 µmol, 17 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.84 (m, 2H), 7.58 - 7.43 (m, 5H), 7.35 (br s, 1H), 6.72 (d, *J*=8.5 Hz, 1H), 4.45 (br d, *J*=13.8 Hz, 1H), 4.33 - 4.24 (m, 4H), 3.89 (br d, *J*=14.1 Hz, 1H), 3.45 - 3.25 (m, 6H), 3.18 (br t, *J*=10.4 Hz, 1H), 2.28 - 2.18 (m, 2H), 2.07 - 1.92 (m, 2H), 1.20 (t, *J*=7.2 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 476.3.

Example 111: N-(2-(4-(3-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



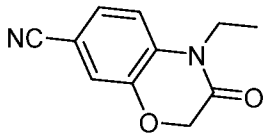
Step 1: Preparation of 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one.



To a stirred solution of 7-bromo-4H-1,4-benzoxazin-3-one (2.0 g, 8.77 mmol) in N,N-dimethylformamide (20 mL) was added iodoethane (1.64 g, 10.52 mmol, 841 µL) and potassium carbonate (3.64 g, 26.3 mmol) at 0 °C. The reaction was warmed at 40 °C for 2 h. The reaction mixture was cooled then quenched by addition of water (30 mL), and then the mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride

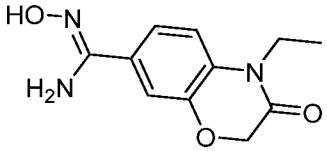
solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (2.06 g, 8.04 mmol, 92 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 - 7.05 (m, 2H), 6.78 (d, *J*=8.9 Hz, 1H), 4.52 (s, 2H), 3.89 (q, *J*=7.2 Hz, 2H), 1.20 (t, *J*=7.2 Hz, 3H).

Step 2: Preparation of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile.



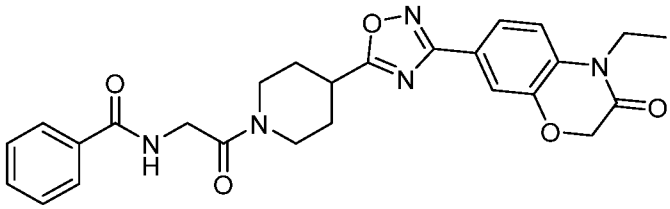
To a stirred solution of 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (800 mg, 3.12 mmol) in N,N-dimethylformamide (10 mL) was added copper(I) cyanide (559 mg, 6.25 mmol, 1.36 mL) and tetrakis(triphenylphosphine)palladium(0) (360 mg, 312 µmol). The mixture was degassed with nitrogen, then heated at 110 °C for 16 h under nitrogen. The reaction mixture was cooled to 20 °C, then water (15 mL) was added and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filetered and concentrated in vacuo to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 5:1) to give 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (70 mg, 346 µmol, 11 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J*=1.9, 8.4 Hz, 1H), 7.30 - 7.29 (m, 1H), 7.08 (d, *J*=8.3 Hz, 1H), 4.68 (s, 2H), 4.04 (q, *J*=7.2 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H).

Step 3: Preparation of (Z)-4-ethyl-N'-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide.



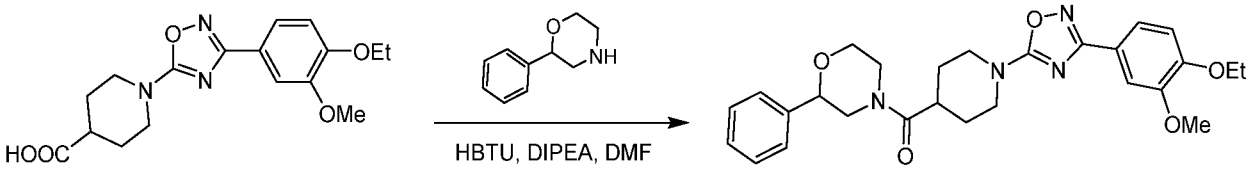
To a stirred solution of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (70 mg, 346 µmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (48 mg, 692 µmol), triethylamine (70 mg, 692 µmol, 95 µL) and water (100 µL). The mixture was heated at 80 °C for 5 h. The reaction mixture was cooled then concentrated under reduced pressure. The residue was diluted with water (5 mL), then the reaction mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give (Z)-4-ethyl-N'-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (60 mg, 255 µmol, 74 %) as a white solid.

Step 4: Preparation of N-(2-(4-(3-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



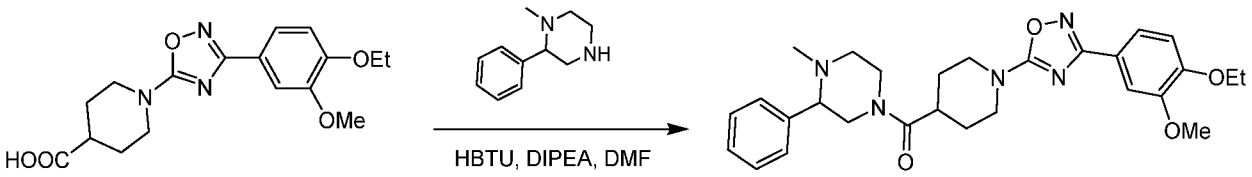
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (60 mg, 206.7 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-4-ethyl-N'-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (48 mg, 206.7 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (78 mg, 206.7 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (80 mg, 620 µmol, 108 µL). The mixture was stirred at 20 ℃ for 1 h, then heated at 110 ℃ for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Luna C18 100x30 5µm; mobile phase: [water (0.1%TFA)-methanol]; B%: 38%-68%,12 min) to give N-(2-(4-(3-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (6 mg, 13 µmol, 6 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J*=7.2 Hz, 2H), 7.77 (dd, *J*=1.8, 8.5 Hz, 1H), 7.71 (d, *J*=1.8 Hz, 1H), 7.56 - 7.43 (m, 3H), 7.34 (br s, 1H), 7.10 (d, *J*=8.4 Hz, 1H), 4.66 (s, 2H), 4.50 (br d, *J*=13.7 Hz, 1H), 4.31 (d, *J*=3.8 Hz, 2H), 4.04 (q, *J*=7.1 Hz, 2H), 3.92 (br d, *J*=14.7 Hz, 1H), 3.40 - 3.29 (m, 2H), 3.17 (br t, *J*=10.7 Hz, 1H), 2.31 - 2.19 (m, 2H), 2.00 (br t, *J*=13.4 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 490.2.

Example 112: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(2-phenylmorpholino)methanone.

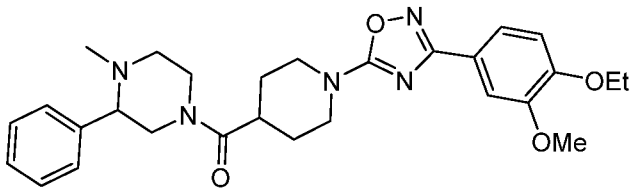


To a stirred solution of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (80 mg, 230 µmol) in N,N-dimethylformamide (1 mL) was added 2-phenylmorpholine (37 mg, 230 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (87 mg, 230 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (89 mg, 690.93 µmol, 120 µL). The mixture was stirred at 20 ℃ for 1 h. The reaction mixture was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-70%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(2-phenylmorpholino)methanone (94 mg, 191.6 µmol, 83 %) as a yellow oil. ^{1}H NMR (400MHz, Methanol-d4) δ 7.55 - 7.41 (m, 3H), 7.40 - 7.26 (m, 4H), 6.99 (d, *J*=8.4 Hz, 1H), 4.51 - 4.36 (m, 2H), 4.26 - 4.13 (m, 2H), 4.12 - 3.98 (m, 4H), 3.86 (s, 3H), 3.75 - 3.58 (m, 1H), 3.46 - 3.30 (m, 1H), 3.28 - 3.17 (m, 2H), 3.04 (br s, 1H), 2.95 - 2.64 (m, 1H), 1.93 - 1.68 (m, 4H), 1.40 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 493.3.

Example 113: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(4-methyl-3-phenylpiperazin-1-yl)methanone.

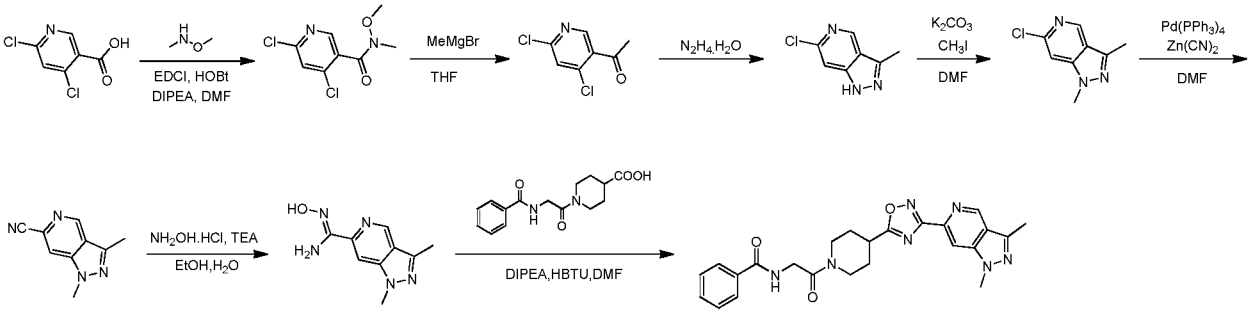


Step 1: Preparation of (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(4-methyl-3-phenylpiperazin-1-yl)methanone.

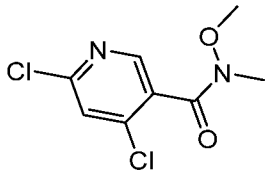


To a stirred solution of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (70 mg, 201.5 µmol) in N,N-dimethylformamide (1 mL) was added 1-methyl-2-phenylpiperazine dihydrochloride (50 mg, 201.5 µmol,), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (76 mg, 201.5 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (78 mg, 604.6 µmol, 105 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 38%-68%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(4-methyl-3-phenylpiperazin-1-yl)methanone (60 mg, 117 µmol, 58 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.57 (br d, *J*=7.9 Hz, 1H), 7.50 (br s, 1H), 7.45 - 7.29 (m, 5H), 6.91 (d, *J*=8.3 Hz, 1H), 4.68 - 4.48 (m, 1H), 4.35 - 4.11 (m, 4H), 3.94 (s, 3H), 3.92 - 3.69 (m, 1H), 3.52 - 3.10 (m, 3H), 3.09 - 2.60 (m, 4H), 2.33 - 2.17 (m, 1H), 2.07 (br d, *J*=4.9 Hz, 3H), 2.04 - 1.73 (m, 4H), 1.49 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 506.4.

Example 114: N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



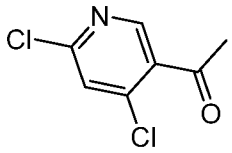
Step 1: Preparation of 4,6-dichloro-N-methoxy-N-methylnicotinamide.



To a stirred solution of 4,6-dichloronicotinic acid (1.0 g, 5.21 mmol) in N,N-dimethylformamide (15 mL) was added N,O-dimethylhydroxylamine (1.02 g, 10.42 mmol), hydroxybenzotriazole (1.41 g, 10.4

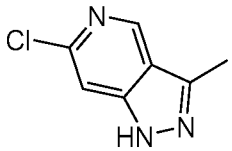
mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.0 g, 10.4 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.02 g, 15.6 mmol, 2.73 mL). The mixture was stirred at 20 °C for 48 h. The reaction mixture was quenched by addition of water (20 mL) then the mixture was extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 5:1 to give 4,6-dichloro-N-methoxy-N-methylnicotinamide (660 mg, 2.81 mmol, 54 %) as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.45 (s, 1H), 3.51 (br s, 3H), 3.40 (br s, 3H).

Step 2: Preparation of 1-(4,6-dichloropyridin-3-yl)ethanone.



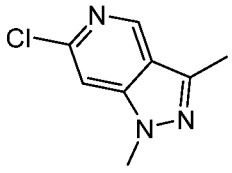
To a stirred solution of 4,6-dichloro-N-methoxy-N-methylnicotinamide (600 mg, 2.55 mmol) in tetrahydrofuran (10 mL) was added methylmagnesium bromide (3 M, 2.16 mL) at 0 °C, then the mixture was stirred at 0 °C for 2 h. After addition of saturated aqueous ammonium chloride (20 mL), the mixture was concentrated to ~20 mL and the residue that remained was extracted with dichloromethane (40 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 1-(4,6-dichloropyridin-3-yl)ethanone (430 mg, 2.26 mmol, 89 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.48 (s, 1H), 2.70 (s, 3H).

Step 3: Preparation of 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine.



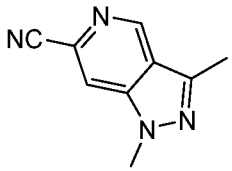
1-(4,6-dichloropyridin-3-yl)ethanone (430 mg, 2.26 mmol) in hydrazine hydrate (10 mL) was stirred at 20 °C for 4 h. The reaction mixture was diluted with water (10 mL), then the mixture was extracted with dichloromethane (40 mL x 3). The combined organic phases were washed with water (10 mL x 2), then saturated aqueous sodium chloride solution (20 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give crude 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine (370 mg, 2.21 mmol, 98 %) as a yellow solid.^{1}H NMR (400 MHz, DMSO-d6) δ 13.23 (br s, 1H), 8.95 (br s, 1H), 7.59 (s, 1H), 2.61 (br s, 3H).

Step 4: Preparation of 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine.



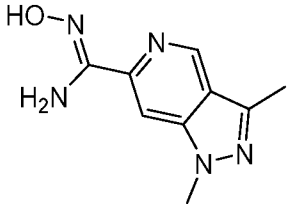
To a stirred solution of 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine (330 mg, 1.97 mmol) in N,N-dimethylformamide (5 mL) was added iodomethane (558 mg, 3.94 mmol, 245 µL) and potassium carbonate (816 mg, 5.91 mmol) at 0 °C. The reaction was heated at 60 °C for 2 h. The reaction mixture was cooled then quenched with water (10 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by prep-TLC (Petroleum ether : ethyl acetate=1:1) to give 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine (120 mg, 661 µmol, 34 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.29 - 7.27 (m, 1H), 3.98 (s, 3H), 2.63 (s, 3H).

Step 5: Preparation of 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile.



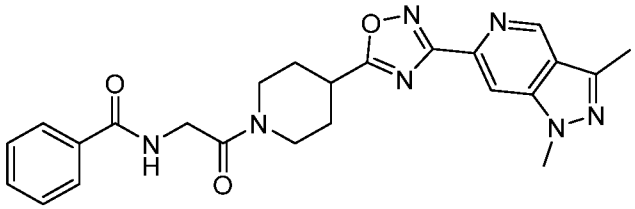
To a stirred solution of 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine (100 mg, 551 µmol) in N,N-dimethylformamide (2 mL) was added zinc cyanide (64 mg, 551 µmol) and tetrakis(triphenylphosphine)palladium(0) (63 mg, 55 µmol), then the mixture was degassed with nitrogen three times. The mixture was stirred at 110 °C for 16 h under nitrogen. The reaction was cooled to 20 °C, then water (3 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue that was purified by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1). 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile (50 mg, 290 µmol, 53 %) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 173.1.

Step 6: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide.



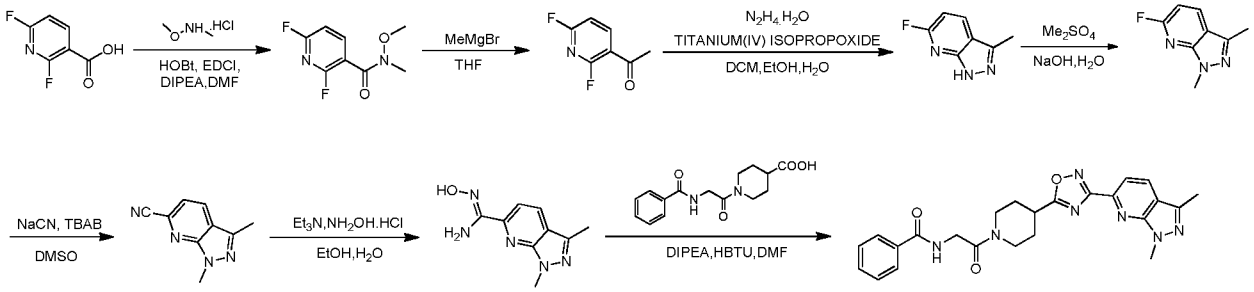
To a stirred solution of 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile (50 mg, 290 µmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (40 mg, 580.76 µmol), triethylamine (58 mg, 580.76 µmol, 80 µL) and water (100 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure then diluted with water (5 mL). The reaction mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide (60 mg) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 206.2.

Step 7: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

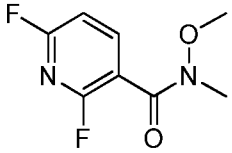


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (35 mg, 120.6 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide (24 mg, 120.6 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (45 mg, 120.6 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (46 mg, 361.7 µmol, 63 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (5 mg, 11 µmol, 9 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J*=1.1 Hz, 1H), 8.12 (d, *J*=1.0 Hz, 1H), 7.89 - 7.84 (m, 2H), 7.56 - 7.43 (m, 3H), 7.34 (br s, 1H), 4.55 (br d, *J*=13.7 Hz, 1H), 4.32 (d, *J*=3.9 Hz, 2H), 4.09 (s, 3H), 3.94 (br d, *J*=13.8 Hz, 1H), 3.44 - 3.32 (m, 2H), 3.14 (br t, *J*=10.9 Hz, 1H), 2.68 (s, 3H), 2.37 - 2.24 (m, 2H), 2.16 - 1.96 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 460.1.

Example 115: N-[2-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.



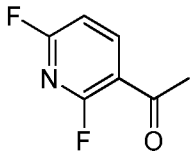
Step 1: 2,6-difluoro-N-methoxy-N-methyl-pyridine-3-carboxamide.



A mixture of 2,6-difluoropyridine-3-carboxylic acid (3.0 g, 18.9 mmol), N-methoxymethanamine hydrochloride (12.9 g, 132.0 mmol) hydroxybenzotriazole (10.2 g, 75.4 mmol), diisopropylethylamine (3.70 g, 28.7 mmol, 5.01 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (7.20 g, 37.5 mmol) in N,N-dimethylformamide (50 mL) was stirred at 20 °C for 16 h under a nitrogen atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL x 3), dried over

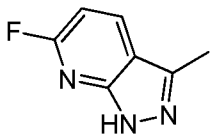
anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2,6-difluoro-N-methoxy-N-methyl-pyridine-3-carboxamide (2.80 g, 13.9 mmol, 73 %) as a solid.

Step 2: 1-(2,6-difluoro-3-pyridyl)ethanone.



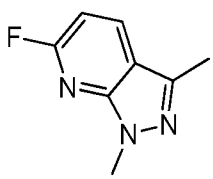
To a stirred solution of 2,6-difluoro-N-methoxy-N-methyl-pyridine-3-carboxamide (3.0 g, 14.8 mmol) in tetrahydrofuran (60 mL) was added dropwise methylmagnesium bromide (1.77 g, 14.84 mmol) at 0℃. The resulting mixture was stirred at 0℃ for 2 h, and then quenched by water at 0 ℃. The mixture was diluted with ethyl acetate (60 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (25 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. Purification by chromatography (silica, petroleum ether / ethyl acetate=2:1) gave 1-(2,6-difluoro-3-pyridyl)ethanone (2.20 g, 14.0 mmol, 94 %) as a white solid.

Step 3: 3-ethoxy-6-iodo-2-methoxy-pyridine.



A solution of 1-(2,6-difluoro-3-pyridyl)ethanone (1.50 g, 9.55 mmol) in dichloromethane (55 mL) was treated with titanium(IV) isopropoxide (10.37 g, 36.48 mmol, 10.80 mL) at room temperature. The resulting mixture was stirred for 15 min, then hydrazine hydrate (2.06 g, 41.16 mmol, 2 mL) was added. Stirring continued for an additional 1.5 h, then water (5 mL) was added, and the resulting thick mixture was stirred vigorously for 20 min. The reaction mixture was filtered, and the solids were washed with dichloromethane (10 mL). The filtrate was concentrated in vacuo to provide the crude hydrazone intermediate as an oil. The crude hydrazine was dissolved in ethanol (15 mL), and the solution was heated at 80 ℃ for 24 h. The reaction mixture was quenched by addition of water (10 mL) at 20℃, and then extracted with dichloromethane (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 6-fluoro-3-methyl-1H-pyrazolo[3,4-b]pyridine (1.20 g) which was used directly without further purification.

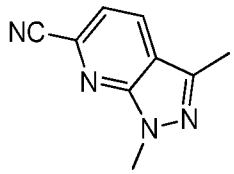
Step 4: 6-fluoro-1,3-dimethyl-pyrazolo[3,4-b]pyridine.



A mixture of 6-fluoro-3-methyl-1H-pyrazolo[3,4-b]pyridine (1.20 g, 7.94 mmol), dimethylsulfate (1.20 g, 9.53 mmol, 903 µL), sodium hydroxide (952 mg, 23.82 mmol) in water (30 mL) was degassed

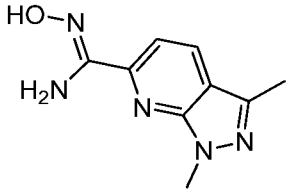
and purged with nitrogen 3 times, and then the mixture was stirred at 70 °C for 2 h under a nitrogen atmosphere. The reaction mixture was cooled, extracted with ethyl acetate (50 mL x 2), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=2:1) to give 6-fluoro-1,3-dimethyl-pyrazolo[3,4-b]pyridine (400 mg, 2.42 mmol, 3 %) as a yellow solid.

Step 5: 1,3-dimethylpyrazolo[3,4-b]pyridine-6-carbonitrile.



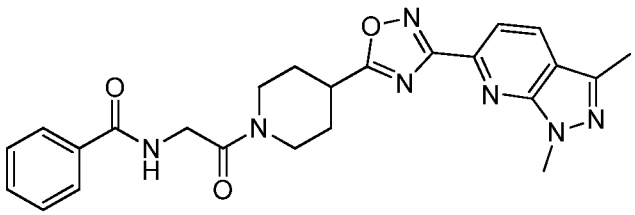
A mixture of 6-fluoro-1,3-dimethyl-pyrazolo[3,4-b]pyridine (350 mg, 2.12 mmol), tetra-n-butylammonium bromide (1.37 g, 4.24 mmol) and sodium cyanide (727 mg, 14.84 mmol) in dimethylsulfoxide (10 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 150 °C for 2 h under a nitrogen atmosphere. The reaction mixture was cooled then extracted with ethyl acetate (5 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, then filtered and concentrated under reduced pressure to give a residue. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=2:1) to give 1,3-dimethylpyrazolo[3,4-b]pyridine-6-carbonitrile (150 mg, 871 µmol, 41 %) as a yellow solid.

Step 6: N'-hydroxy-1,3-dimethyl-pyrazolo[3,4-b]pyridine-6-carboxamidine



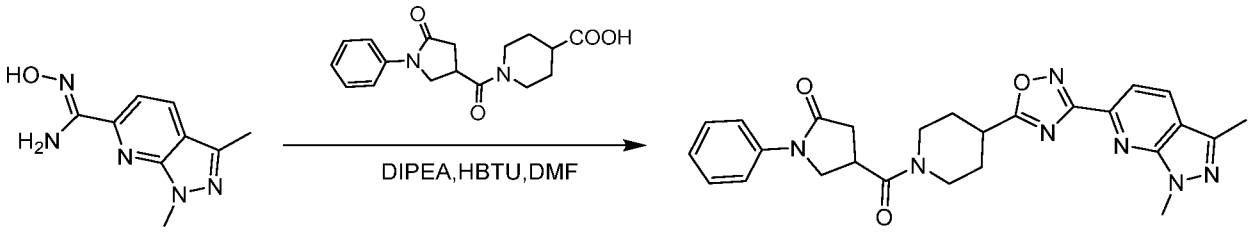
A mixture of 1,3-dimethylpyrazolo[3,4-b]pyridine-6-carbonitrile (150 mg, 871 µmol), hydroxylamine hydrochloride (121 mg, 1.74 mmol) and triethylamine (176 mg, 1.74 mmol, 241 µL) in ethanol (3 mL) and water (300 µL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 70 °C for 5 h under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give N'-hydroxy-1,3-dimethyl-pyrazolo[3,4-b]pyridine-6-carboxamidine (120 mg, 584.7 µmol, 67 %) as a yellow solid.

Step 7: N-[2-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide



A mixture of N'-hydroxy-1,3-dimethyl-pyrazolo[3,4-b]pyridine-6-carboxamidine (50 mg, 243.6 µmol), 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (84 mg, 292 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (110 mg, 292 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (94 mg, 730.92 µmol, 127 µL) in N,N-dimethylformamide (1 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20℃ for 1 h under a nitrogen atmosphere. The mixture was stirred at 120 ℃ for 1h. The mixture was cooled then purified via Prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give N-[2-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (14 mg, 31.71 µmol, 13 %) as a brown solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.17 – 8.15 (d, J=8.3 Hz, 1H), 7.96 – 7.94 (d, J=8.2 Hz, 1H), 7.90 - 7.86 (m, 2H), 7.57 - 7.52 (m, 1H), 7.51 - 7.46 (m, 2H), 7.36 (br s, 1H), 4.60 – 4.56 (br d, J=13.9 Hz, 1H), 4.34 – 4.33 (d, J=4.0 Hz, 2H), 4.20 (s, 3H), 3.98- 3.95 (br d, J=13.3 Hz, 1H), 3.49 - 3.33 (m, 2H), 3.22 - 3.10 (m, 1H), 2.64 (s, 3H), 2.38 - 2.26 (m, 2H), 2.15 - 1.99 (m, 2H); LCMS(ESI) m/z: $[M+H]^+$ = 460.3.

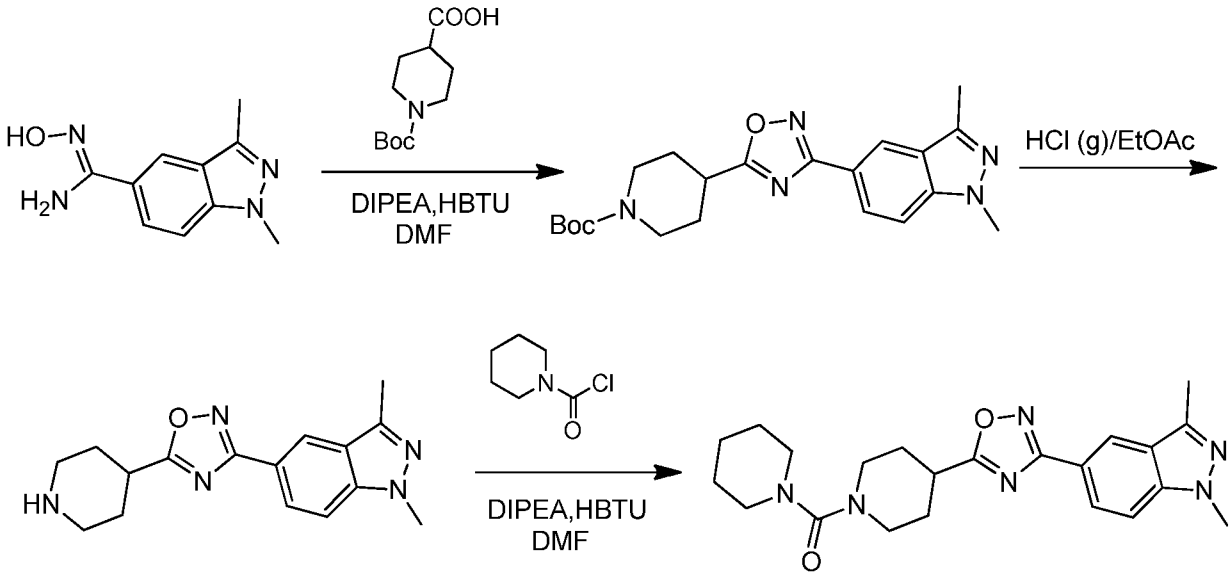
Example 116: 4-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.



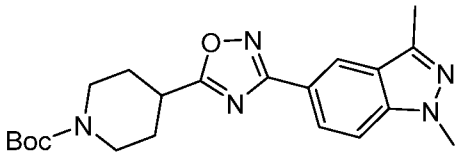
Prepared using a similar experimental procedure as for example 115.

4-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (4.06 mg, 8.36 µmol, 3.43% yield) was obtained as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.15-8.17 (d, J=8.4 Hz, 1H), 7.96-7.93 (dd, J=3.2, 8.2 Hz, 1H), 7.61-7.63 (d, J=7.7 Hz, 2H), 7.42-7.40 (t, J=8.0 Hz, 2H), 7.23 - 7.17 (m, 1H), 4.65-4.62 (br t, J=14.0 Hz, 1H), 4.36-4.32 (dd, J=7.3, 9.6 Hz, 1H), 4.21 (s, 3H), 4.07 - 3.94 (m, 2H), 3.69 - 3.58 (m, 1H), 3.50 - 3.37 (m, 2H), 3.16 - 2.96 (m, 2H), 2.91 - 2.84 (m, 1H), 2.64 (s, 3H), 2.33 (br t, J=13.9 Hz, 2H), 2.13 - 1.97 (m, 2H); LCMS(ESI) m/z: $[M+H]^+$ = 486.3.

Example 117: (4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.

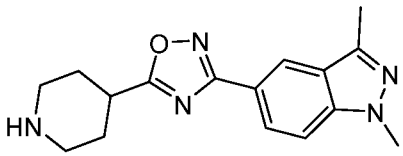


Step 1: Preparation of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate.



To a stirred solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (150 mg, 654 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-5-carboximidamide (133 mg, 654 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (248 mg, 654 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (253 mg, 1.96 mmol, 342 µL). The mixture was stirred at 20 °C for 1 h, then heated at 120 °C for 1 h. The reaction mixture was quenched by addition of water (5 mL) then the mixture was extracted with ethyl acetate (20 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1) to furnish tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (190 mg, 478 µmol, 73 %) as a white solid.

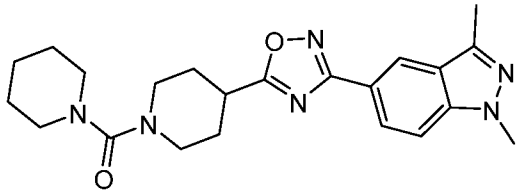
Step 2: Preparation of 3-(1,3-dimethyl-1H-indazol-5-yl)-5-(piperidin-4-yl)-1,2,4-oxadiazole.



To a stirred solution of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (190 mg, 478 µmol) in methanol (3 mL) was added methanolic hydrogen chloride solution (4M, 10 mL). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to provide 3-(1,3-dimethyl-1H-indazol-5-yl)-5-(piperidin-4-yl)-1,2,4-

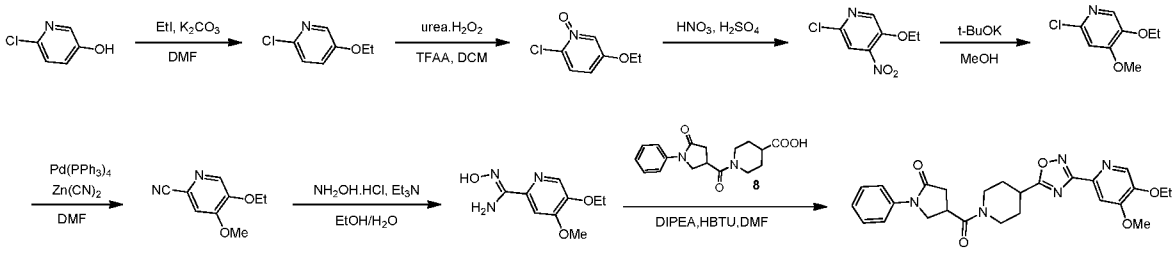
oxadiazole (140 mg, 471 µmol, 98 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.04 (br s, 1H), 8.33 (d, *J*=0.7 Hz, 1H), 7.96 (dd, *J*=1.3, 8.8 Hz, 1H), 7.71 (d, *J*=8.8 Hz, 1H), 3.98 (s, 3H), 3.53 - 3.43 (m, 1H), 3.34 (br d, *J*=12.6 Hz, 2H), 3.11 - 3.00 (m, 2H), 2.52 (s, 3H), 2.26 (br d, *J*=10.8 Hz, 2H), 2.08 - 1.95 (m, 2H).

Step 3: Preparation of (4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.

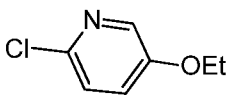


To a stirred solution of 3-(1,3-dimethyl-1H-indazol-5-yl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (130 mg, 437 µmol) in dichloromethane (500 µL) was added piperidine-1-carbonyl chloride (77 mg, 524.6 µmol, 65 µL) and triethylamine (132 mg, 1.31 mmol, 181 µL) at 0 ℃. The mixture was warmed and then stirred at 20 ℃ for 1 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-70%,12 min) to give (4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone (68 mg, 166.6 µmol, 38 %) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.08 (dd, J=1.4, 8.8 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 4.03 (s, 3H), 3.80 - 3.70 (m, 2H), 3.28 - 3.14 (m, 5H), 3.05 - 2.93 (m, 2H), 2.62 (s, 3H), 2.18 (br dd, J=3.3, 13.6 Hz, 2H), 2.07 - 1.93 (m, 2H), 1.60 (br s, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 409.1.

Example 118: 4-(4-(3-(5-ethoxy-4-methoxypyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.



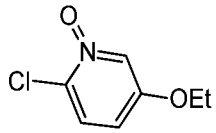
Step 1: Preparation of 2-chloro-5-ethoxypyridine.



To a stirred solution of 6-chloropyridin-3-ol (3.0 g, 23.2 mmol) in N,N-dimethylformamide (30 mL) was added iodoethane (4.33 g, 27.8 mmol, 2.22 mL), and potassium carbonate (9.60 g, 69.6 mmol) at 0 ℃. The reaction was warmed and stirred at 40 ℃ for 2 h. The reaction mixture was quenched by addition of water (30 mL) then the mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 2-chloro-5-ethoxypyridine (3.30 g, 20.9 mmol, 90 %) as a

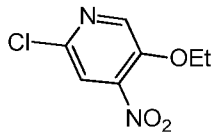
yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J*=2.9 Hz, 1H), 7.17 - 7.07 (m, 2H), 3.99 (q, *J*=7.0 Hz, 2H), 1.36 (t, *J*=7.0 Hz, 3H).

Step 2: Preparation of 2-chloro-5-ethoxypyridine 1-oxide.



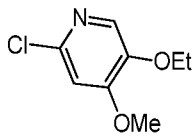
Hydrogen peroxide-urea adduct (3.82 g, 40.61 mmol) was added in one portion to a solution of 2-chloro-5-ethoxypyridine (3.20 g, 20.3 mmol) in dichloromethane (30 mL) at 0 °C, trifluoroacetic anhydride (7.68 g, 36.6 mmol, 5.08 mL) was added dropwise. The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched by addition of saturated aqueous sodium thiosulfate (30 mL). The mixture was extracted with dichloromethane (60 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 2-chloro-5-ethoxypyridine 1-oxide (4.0 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 - 8.28 (m, 1H), 7.44 (dt, *J*=3.0, 6.0 Hz, 1H), 7.13 - 7.04 (m, 1H), 4.13 - 4.00 (m, 2H), 1.50 - 1.40 (m, 3H).

Step 3: Preparation of 2-chloro-5-ethoxy-4-nitropyridine.



To a stirred solution of 2-chloro-5-ethoxypyridine 1-oxide (1.80 g, 10.37 mmol) in concentrated sulfuric acid (12 mL) was added concentrated nitric acid (6.50 mL) at 0 °C, the mixture was stirred at 25 °C for 1 hrs, then heated to 110 °C and stirred for 16 hrs. After cooling to 20 °C, the mixture was poured onto ice, and then aqueous sodium hydroxide solution (40 wt.%) was added carefully to adjust the pH to 14. The mixture was extracted with dichloromethane (80 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 2-chloro-5-ethoxy-4-nitropyridine (810 mg, 4.00 mmol, 39 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.64 (s, 1H), 4.30 (q, *J*=6.9 Hz, 2H), 1.51 (t, *J*=7.0 Hz, 3H).

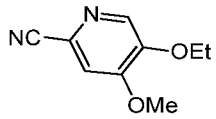
Step 4: Preparation of 2-chloro-5-ethoxy-4-methoxypyridine.



To a stirred solution of 2-chloro-5-ethoxy-4-nitro-pyridine (770 mg, 3.80 mmol) in methanol (8 mL) was added potassium tert-butoxide (644 mg, 4.18 mmol) at 0 °C, then the mixture was warmed and stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure then diluted with water (10 mL) of water. The mixture was extracted with dichloromethane (60 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 2-chloro-5-ethoxy-4-methoxypyridine (660

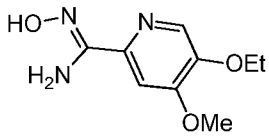
mg, 3.52 mmol, 93 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.80 (s, 1H), 4.13 (q, *J*=7.0 Hz, 2H), 3.95 - 3.88 (m, 3H), 1.47 (t, *J*=7.0 Hz, 3H).

Step 5: Preparation of 5-ethoxy-4-methoxypicolinonitrile.



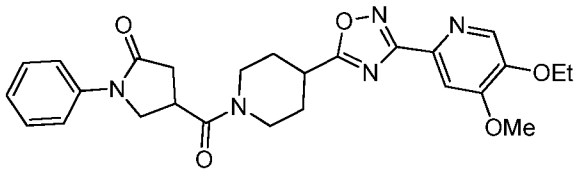
To a stirred solution of zinc cyanide (368 mg, 3.14 mmol) in N,N-dimethylformamide (8 mL) was added 2-chloro-5-ethoxy-4-methoxypyridine (590 mg, 3.14 mmol) and tetrakis(triphenylphosphine)palladium(0) (362 mg, 314 µmol) under nitrogen. The mixture was heated at 120 °C for 16 h. The reaction was cooled to 20 °C, water (20 mL) was added to the reaction, and then the mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 5:1) to give 5-ethoxy-4-methoxypicolinonitrile (320 mg, 1.80 mmol, 57 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.18 (s, 1H), 4.25 (q, *J*=6.9 Hz, 2H), 3.96 (s, 3H), 1.52 (t, *J*=7.0 Hz, 3H).

Step 6: Preparation of (Z)-5-ethoxy-N'-hydroxy-4-methoxypicolinimidamide.



To a stirred solution of 5-ethoxy-4-methoxypicolinonitrile (320 mg, 1.80 mmol) in ethanol (5 mL) was added hydroxylamine hydrochloride (250 mg, 3.60 mmol), triethylamine (364 mg, 3.60 mmol, 499 µL) and water (0.50 mL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure then diluted with water (10 mL). The mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give (Z)-5-ethoxy-N'-hydroxy-4-methoxypicolinimidamide (330 mg, 1.56 mmol, 87 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.71 (s, 1H), 8.10 (s, 1H), 7.39 (s, 1H), 5.75 (br s, 2H), 4.17 - 4.06 (m, 2H), 3.84 (s, 3H), 1.34 (t, *J*=6.9 Hz, 3H).

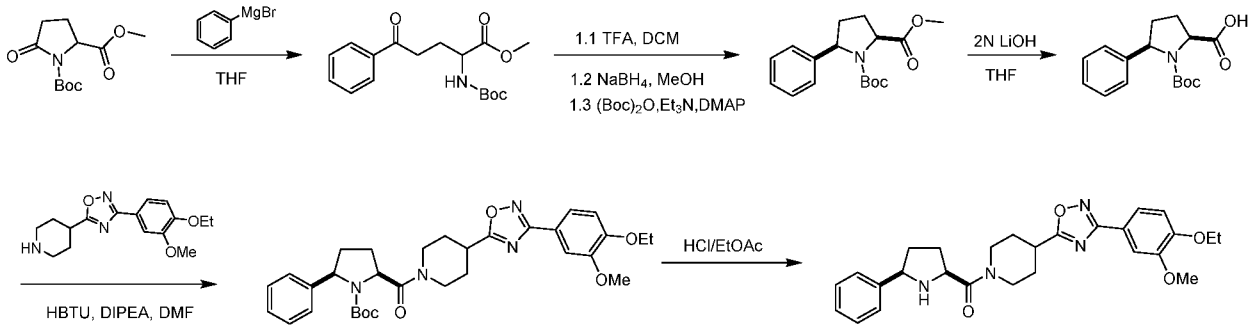
Step 7: Preparation of 4-(4-(3-(5-ethoxy-4-methoxypyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.



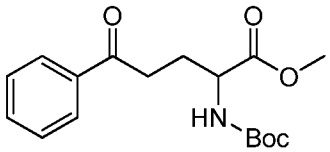
To a stirred solution of 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (90 mg, 285 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-5-ethoxy-N'-hydroxy-4-methoxypicolinimidamide (60 mg, 285 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium

hexafluorophosphate) (107 mg, 285 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (110 mg, 854 µmol, 149 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled and then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-55%,12 min) to give 4-(4-(3-(5-ethoxy-4-methoxypyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (34 mg, 70 µmol, 24 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.68 - 7.57 (m, 3H), 7.44 - 7.33 (m, 2H), 7.22 - 7.13 (m, 1H), 4.63 - 4.50 (m, 1H), 4.36 - 4.22 (m, 3H), 4.04 - 3.90 (m, 5H), 3.59 (td, *J*=8.6, 16.7 Hz, 1H), 3.43 - 3.30 (m, 2H), 3.12 - 2.93 (m, 2H), 2.88 - 2.79 (m, 1H), 2.33 - 2.20 (m, 2H), 2.13 - 1.93 (m, 2H), 1.52 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 492.1.

Example 119: (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)((2S,5R)-5-phenylpyrrolidin-2-yl)methanone.

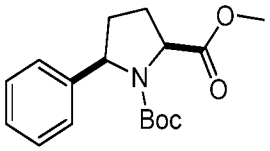


Step 1: Preparation of methyl 2-((tert-butoxycarbonyl)amino)-5-oxo-5-phenylpentanoate.



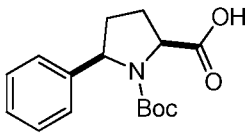
To a stirred solution of O1-tert-butyl O2-methyl 5-oxopyrrolidine-1,2-dicarboxylate (1.0 g, 4.11 mmol) in tetrahydrofuran (10 mL) was added phenylmagnesium bromide (1 M in THF, 4.93 mL) at -30 °C. The reaction mixture was slowly warmed to 20 °C and stirred for 16 h. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (10 mL), and then extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 20:1) to give methyl 2-((tert-butoxycarbonyl)amino)-5-oxo-5-phenylpentanoate (900 mg, 2.80 mmol, 68 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J*=8.0 Hz, 2H), 7.60 - 7.53 (m, 1H), 7.50 - 7.43 (m, 2H), 5.17 (br s, 1H), 4.40 (brs, 1H), 3.75 (s, 3H), 3.19 - 2.99 (m, 2H), 2.37 - 2.26 (m, 1H), 2.15 - 2.02 (m, 1H), 1.42 (s, 9H).

Step 2: Preparation of (2S/R,5R/S)-1-tert-butyl 2-methyl 5-phenylpyrrolidine-1,2-dicarboxylate.



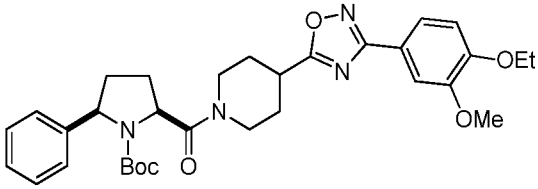
To a stirred solution of methyl 2-((tert-butoxycarbonyl)amino)-5-oxo-5-phenylpentanoate (800 mg, 2.49 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (5.68 g, 49.8 mmol, 3.69 mL) at 20 °C. After 16 h, the solvent was removed under reduced pressure, then the residue was dissolved in methanol (10 mL) and cooled to 0 °C. Sodium borohydride (188 mg, 4.98 mmol) was slowly added, then the mixture was warmed and stirred at 20 °C for 16 h. The mixture was concentrated in vacuo and the resulting orange oil was diluted with methanol (20 mL) and concentrated again a total of four times. The residue was suspended in dichloromethane (10 mL), then di-tert-butyl dicarbonate (815 mg, 3.74 mmol, 858 µL), triethylamine (377 mg, 3.74 mmol, 517 µL), 4-dimethylaminopyridine (3 mg, 24.90 µmol) were added and stirred at 20 °C for 16 h. Sat. aq. ammonium chloride (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (50 mL x 3) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 36%-66%,12min]) to give (2S/R,5R/S)-1-tert-butyl 2-methyl 5-phenylpyrrolidine-1,2-dicarboxylate (230 mg, 753 µmol, 30 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br d, *J*=7.5 Hz, 2H), 7.33 (t, *J*=7.5 Hz, 2H), 7.26 - 7.19 (m, 1H), 5.00 (br d, *J*=3.4 Hz, 0.4H), 4.75 (br t, *J*=7.0 Hz, 0.6H), 4.50 (br dd, *J*=4.7, 8.0 Hz, 0.6H), 4.36 (br t, *J*=7.4 Hz, 0.4H), 3.82 (s, 3H), 2.38 - 2.28 (m, 1H), 2.20 (ddd, *J*=6.5, 7.8, 12.5 Hz, 1H), 2.12 - 1.91 (m, 2H), 1.42 (s, 3.6H), 1.15 (s, 5.4H).

Step 3: Preparation of (2S/R,5R/S)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid.



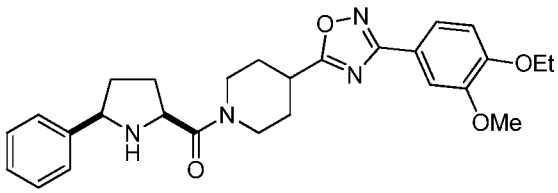
To a stirred solution of (2S/R,5R/S)-1-tert-butyl 2-methyl 5-phenylpyrrolidine-1,2-dicarboxylate (180 mg, 589 µmol) in tetrahydrofuran (2 mL) was added lithium hydroxide (2 M, 589 µL). The mixture was stirred at 20 °C for 16 h. The mixture was acidified to pH 1 by dropwise addition of concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (40 mL x 3). The organic layer was washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give (2S/R,5R/S)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid (300 mg) as a white solid.

Step 4: Preparation of (2S/R,5R/S)-tert-butyl 2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-5-phenylpyrrolidine-1-carboxylate.



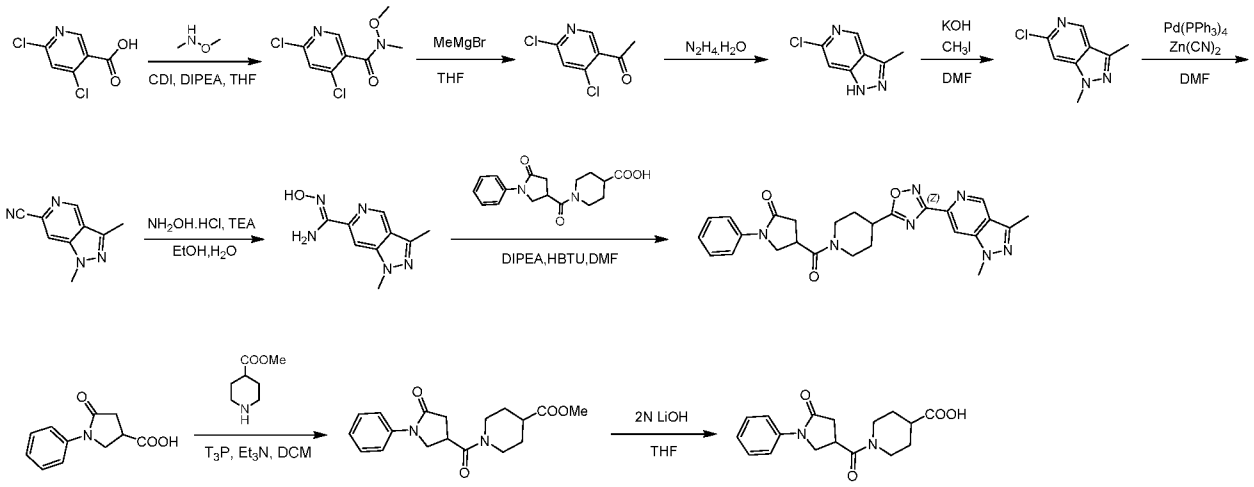
To a stirred solution of (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid (270 mg, 927 µmol) in N,N-dimethylformamide (3 mL) was added 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (281 mg, 927 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (351 mg, 927 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (359 mg, 2.78 mmol, 485 µL). The mixture was stirred at 20 ℃ for 1 h. Water (15 mL) was added to the reaction, then the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give (2S/R,5R/S)-tert-butyl 2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-5-phenylpyrrolidine-1-carboxylate (500 mg) as a yellow oil. This material was used directly without purficication.

Step 5: Preparation of (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)((2S/R,5R/S)-5-phenylpyrrolidin-2-yl)methanone.

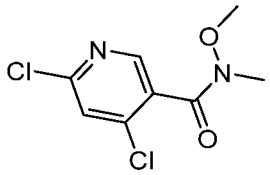


To a stirred solution of (2S/R,5R/S)-tert-butyl 2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-5-phenylpyrrolidine-1-carboxylate (500 mg, 867 µmol) in ethyl acetate (5 mL) was added 4N hydrochloric acid in ethyl acetate (20 mL). The mixture was stirred at 20 ℃ for 0.5 h. The reaction mixture was concentrated under reduced pressure to provide the crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-65%,12 min) to give (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)((2S/R,5R/S)-5-phenylpyrrolidin-2-yl)methanone (78 mg, 161.6 µmol, 19 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.66 (ddd, *J*=2.0, 3.5, 8.3 Hz, 1H), 7.61 (br d, *J*=2.5 Hz, 1H), 7.48 (br d, *J*=7.8 Hz, 2H), 7.39 (t, *J*=7.4 Hz, 2H), 7.35 - 7.28 (m, 1H), 7.11 - 7.04 (m, 1H), 4.53 (br t, *J*=12.5 Hz, 1H), 4.24 - 4.05 (m, 5H), 3.92 (d, *J*=1.8 Hz, 3H), 3.49 - 3.38 (m, 2H), 3.18 - 3.06 (m, 1H), 2.45 - 2.20 (m, 4H), 2.04 - 1.66 (m, 4H), 1.45 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 477.1.

Example 120: 4-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.

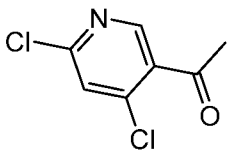


Step 1: Preparation of 4,6-dichloro-N-methoxy-N-methylnicotinamide.



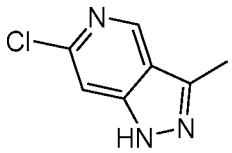
A solution of 4,6-dichloropyridine-3-carboxylic acid (13.5 g, 70.3 mmol) and 1,1'-carbonyldiimidazole (17.10 g, 105.5 mmol) in tetrahydrofuran (200 mL) was stirred for 0.5 h at 25 °C. N-ethyl-N-(propan-2-yl)propan-2-amine (18.17 g, 140.62 mmol, 24.55 mL) and N,O-dimethylhydroxylamine hydrochloride (8.23 g, 84.4 mmol) were added and the resulting solution was stirred at 25 °C for 16 h. The reaction mixture was diluted with water (200 mL), then the mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layer was washed with water (50 mL x 3) then saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 4,6-dichloro-N-methoxy-N-methylnicotinamide (19.0 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.44 (d, *J*=0.6 Hz, 1H), 3.49 (br s, 3H), 3.38 (br s, 3H).

Step 2: Preparation of 1-(4,6-dichloropyridin-3-yl)ethanone.



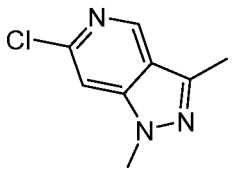
To a stirred solution of 4,6-dichloro-N-methoxy-N-methylnicotinamide (16.0 g, 68.1 mmol) in tetrahydrofuran (200 mL) was added a solution of methylmagnesium bromide in tetrahydrofuran (3 M, 57.6 mL) at 0 °C, the mixture was stirred at 0 °C for 2 h. After addition of saturated aqueous ammonium chloride (100 mL), the mixture was concentrated to ~ 200 mL and the residue was extracted with dichloromethane (200 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 1-(4,6-dichloropyridin-3-yl)ethanone (8.95 g, 47.1 mmol, 69 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.46 (s, 1H), 2.68 (s, 3H).

Step 3: Preparation of 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine.



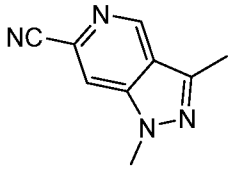
1-(4,6-dichloropyridin-3-yl)ethanone (8.40 g, 44.2 mmol) in hydrazine hydrate (60 mL) was stirred at 20 °C for 1 h. The reaction mixture was diluted with water (100 mL), then the mixture was extracted with dichloromethane (150 mL x 3). The separated organic layer was washed water (40 mL x 3) and saturated aqueous sodium chloride solution (50 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine (6.10 g, 36.4 mmol, 82 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.17 (br s, 1H), 8.88 (s, 1H), 7.53 (s, 1H), 2.55 (s, 3H).

Step 4: Preparation of 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine.



To a stirred solution of 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine (5.90 g, 35.2 mmol) in N,N-dimethylformamide (80 mL) was added iodomethane (9.99 g, 70.4 mmol, 4.38 mL), and potassium hydroxide (7.90 g, 140.8 mmol) at 0 °C. The reaction was stirred at 60 °C for 2 h. The reaction mixture was cooled then quenched by addition of water (100 mL). The mixture was extracted with ethyl acetate (150 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 5:1)to give 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine (2.73 g, 15.0 mmol, 43 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.22 (s, 1H), 3.93 (s, 3H), 2.58 (s, 3H).

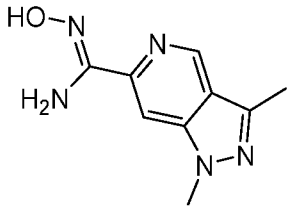
Step 5: Preparation of 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile.



To a stirred solution of 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine (1.70 g, 9.36 mmol) in N,N-dimethylformamide (20 mL) was added zinc cyanide (1.10 g, 9.36 mmol, 594 µL) and tetrakis(triphenylphosphine)palladium(0) (1.08 g, 936 µmol) under nitrogen. The mixture was stirred at 110 °C for 16 h. The reaction was cooled to 20 °C, water (30 mL) was added to the reaction, and then the reaction mixture was extracted with ethyl acetate (80 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50:1 to 1:1) to give 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile

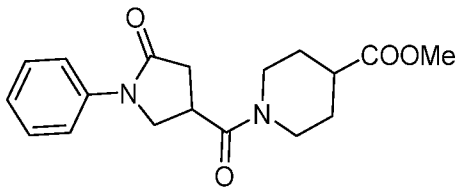
(1.06 g, 6.16 mmol, 66 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J*=1.0 Hz, 1H), 7.73 (d, *J*=1.0 Hz, 1H), 4.07 (s, 3H), 2.67 (s, 3H).

Step 6: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide.



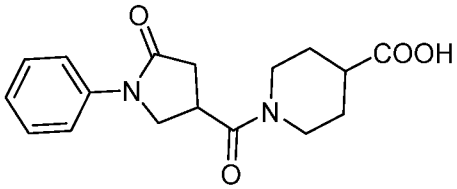
To a stirred solution of 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile (1.06 g, 6.16 mmol) in ethanol (15 mL) was added hydroxylamine hydrochloride (855 mg, 12.3 mmol), triethylamine (1.25 g, 12.3 mmol, 1.71 mL) and water (1.50 mL). The mixture was heated at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure then the residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide (1.0 g, 4.87 mmol, 79 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.73 (s, 1H), 9.02 (s, 1H), 7.91 (s, 1H), 5.91 (br s, 2H), 3.98 (s, 3H), 2.56 (s, 3H).

Step 7: Preparation of methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate.



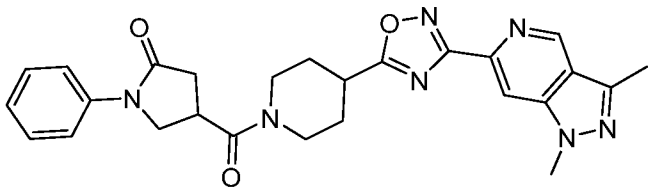
To a stirred solution of 5-oxo-1-phenylpyrrolidine-3-carboxylic acid (3.0 g, 14.6 mmol) in dichloromethane (30 mL) was added methyl piperidine-4-carboxylate (2.09 g, 14.6 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (9.30 g, 14.6 mmol, 8.69 mL, 50% purity in ethyl acetate) and triethylamine (1.48 g, 14.6 mmol, 2.03 mL). The mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted by addition of water (20 mL) then extracted with dichloromethane (60 mL x 3). The combined organic layer was washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate (4.02 g, 12.2 mmol, 83 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J*=7.7 Hz, 2H), 7.38 (t, *J*=7.3 Hz, 2H), 7.21 - 7.12 (m, 1H), 4.43 (m, 1H), 4.29 (dd, *J*=7.3, 9.6 Hz, 1H), 3.97 - 3.81 (m, 2H), 3.72 (s, 3H), 3.55 (m, 1H), 3.28 - 3.17 (m, 1H), 3.01 - 2.75 (m, 3H), 2.62 (dt, *J*=6.3, 10.4 Hz, 1H), 2.08 - 1.94 (m, 2H), 1.80 - 1.64 (m, 2H).

Step 8: Preparation of 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid.



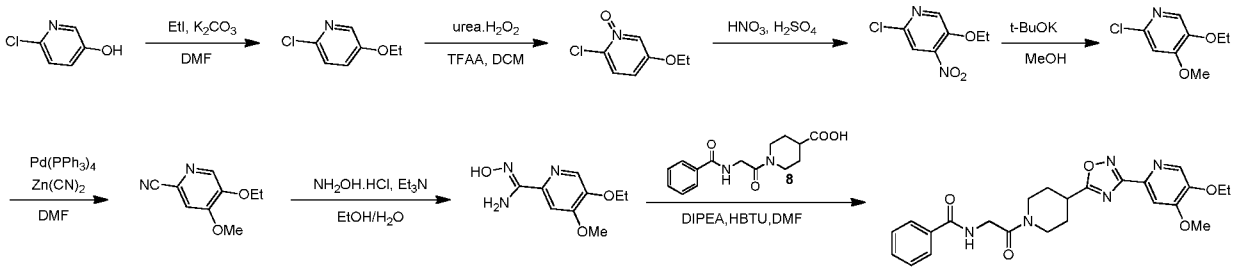
To a stirred solution of methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate (4.0 g, 12.11 mmol) in tetrahydrofuran (30 mL) was added aqueous lithium hydroxide (2 M, 12.11 mL). After 1 h, the reaction mixture was cooled to 0 °C then acidified with 2 M hydrochloric acid (6 mL). The mixture was extracted with ethyl acetate (80 mL x 3). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (3.60 g, 11.38 mmol, 94 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.59 (dd, *J*=4.0, 7.7 Hz, 2H), 7.38 (t, *J*=7.6 Hz, 2H), 7.23 - 7.15 (m, 1H), 4.41 - 4.30 (m, 1H), 4.15 - 3.96 (m, 3H), 3.85 - 3.75 (m, 1H), 3.30 - 3.22 (m, 1H), 2.99 - 2.77 (m, 3H), 2.63 (m, 1H), 2.06 - 1.93 (m, 2H), 1.74 - 1.53 (m, 2H).

Step 9: Preparation of 4-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.

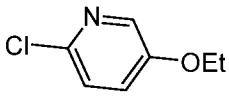


To a stirred solution of (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide (84 mg, 410.9 µmol) in N,N-dimethylformamide (2 mL) was added 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (130 mg, 410.9 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (155 mg, 410.9 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (159 mg, 1.23 mmol, 215 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-40%,12 min) to give 4-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (78 mg, 155 µmol, 38 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J*=1.0 Hz, 1H), 8.12 (br d, *J*=3.9 Hz, 1H), 7.60 (br d, *J*=7.8 Hz, 2H), 7.39 (br t, *J*=8.0 Hz, 2H), 7.18 (br t, *J*=7.4 Hz, 1H), 4.59 (br t, *J*=13.8 Hz, 1H), 4.36 - 4.27 (m, 1H), 4.09 (d, *J*=3.8 Hz, 3H), 4.03 - 3.92 (m, 2H), 3.60 (m, 1H), 3.39 (br s, 2H), 3.14 - 2.94 (m, 2H), 2.90 - 2.80 (m, 1H), 2.68 (s, 3H), 2.37 - 2.23 (m, 2H), 2.12 - 1.96 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 486.1.

Example 121: N-(2-(4-(3-(5-ethoxy-4-methoxypyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

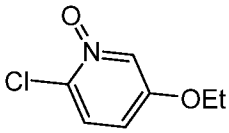


Step 1: Preparation of 2-chloro-5-ethoxypyridine.



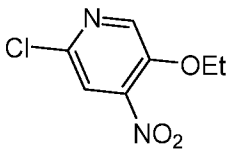
To a stirred solution of 6-chloropyridin-3-ol (21.0 g, 162.1 mmol) in N,N-dimethylformamide (200 mL) was added iodoethane (30.34 g, 194.5 mmol, 15.6 mL) and potassium carbonate (67.2 g, 486.3 mmol) at 0 ℃, then the reaction was warmed and stirred at 40 ℃ for 2 h. The reaction mixture was quenched by addition of water (200 mL), then the mixture was extracted with ethyl acetate (300 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 2-chloro-5-ethoxypyridine (26.0 g) as a yellow oil. This was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J*=2.9 Hz, 1H), 7.15 - 7.06 (m, 2H), 3.98 (q, *J*=7.0 Hz, 2H), 1.35 (t, *J*=7.0 Hz, 3H).

Step 2: Preparation of 2-chloro-5-ethoxypyridine 1-oxide.



Hydrogen peroxide-urea complex (31.04 g, 330 mmol) was added in one portion to a solution of 2-chloro-5-ethoxypyridine (26.0 g, 165 mmol) in dichloromethane (250 mL) at 0 ℃, then trifluoroacetic anhydride (62.4 g, 297 mmol, 41.3 0 mL) was added dropwise. The mixture was stirred at 20 ℃ for 16 h. The reaction mixture was quenched by addition of saturated aqueous sodium thiosulfate (150 mL). The mixture was extracted with dichloromethane (200 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 1:2) to give 2-chloro-5-ethoxypyridine 1-oxide (22.0 g, 126.7 mmol, 77 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J*=2.6 Hz, 1H), 7.29 (d, *J*=9.0 Hz, 1H), 6.81 (dd, *J*=2.6, 9.1 Hz, 1H), 3.97 (q, *J*=6.9 Hz, 2H), 1.37 (t, *J*=7.0 Hz, 3H).

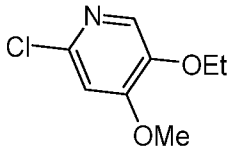
Step 3: Preparation of 2-chloro-5-ethoxy-4-nitropyridine.



To a stirred solution of 2-chloro-5-ethoxypyridine 1-oxide (5.0 g, 28.8 mmol) in concentrated sulfuric acid (30 mL) was added dropwise concentrated nitric acid (15 mL) at 0 ℃, then the mixture was

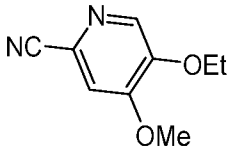
warmed, stirred at 25 °C for 1 h, and then heated to 110 °C for 16 h. After cooling to 20 °C, the mixture was poured onto ice, and then aqueous sodium hydroxide solution (40 wt.%) was added carefully to adjust the pH to 14. The mixture was extracted with dichloromethane (100 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 2-chloro-5-ethoxy-4-nitropyridine (3.10 g, 15.3 mmol, 53 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.64 (s, 1H), 4.30 (q, *J*=7.0 Hz, 2H), 1.50 (t, *J*=7.0 Hz, 3H).

Step 4: Preparation of 2-chloro-5-ethoxy-4-methoxypyridine.



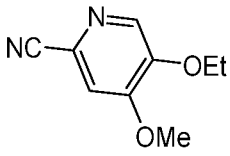
To a stirred solution of 2-chloro-5-ethoxy-4-nitro-pyridine (3.10 g, 15.3 mmol) in methanol (32 mL) was added potassium tert-butoxide (2.60 g, 16.8 mmol) at 0 °C, the mixture was warmed and stirred at 20 °C for 2 h. The reaction was concentrated under reduced pressure then diluted with water (20 mL). The mixture was extracted with dichloromethane (60 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 2-chloro-5-ethoxy-4-methoxypyridine (2.68 g, 14.28 mmol, 93 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.81 (m, 1H), 6.83 - 6.76 (m, 1H), 4.18 - 4.07 (m, 2H), 3.91 (dd, *J*=2.1, 2.8 Hz, 3H), 1.46 (m, 3H).

Step 5: Preparation of 5-ethoxy-4-methoxypicolinonitrile.



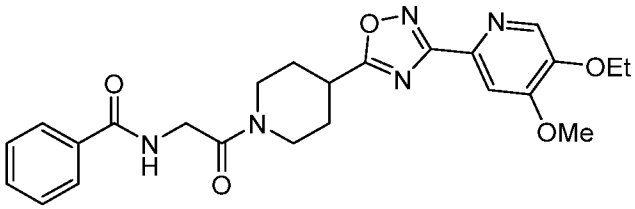
To a stirred solution of zinc cyanide (1.31 g, 11.2 mmol) in N,N-dimethylformamide (25 mL) was added 2-chloro-5-ethoxy-4-methoxypyridine (2.10 g, 11.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.29 g, 1.12 mmol) under nitrogen. The mixture was heated at 110 °C for 16 h. The reaction was cooled to 20 °C, then water (40 mL) was added and the reaction mixture extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 5:1) to give 5-ethoxy-4-methoxypicolinonitrile (1.20 g, 6.73 mmol, 60 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.18 (s, 1H), 4.24 (q, *J*=7.0 Hz, 2H), 3.96 (s, 3H), 1.51 (t, *J*=7.0 Hz, 3H).

Step 6: Preparation of (Z)-5-ethoxy-N'-hydroxy-4-methoxypicolinimidamide.



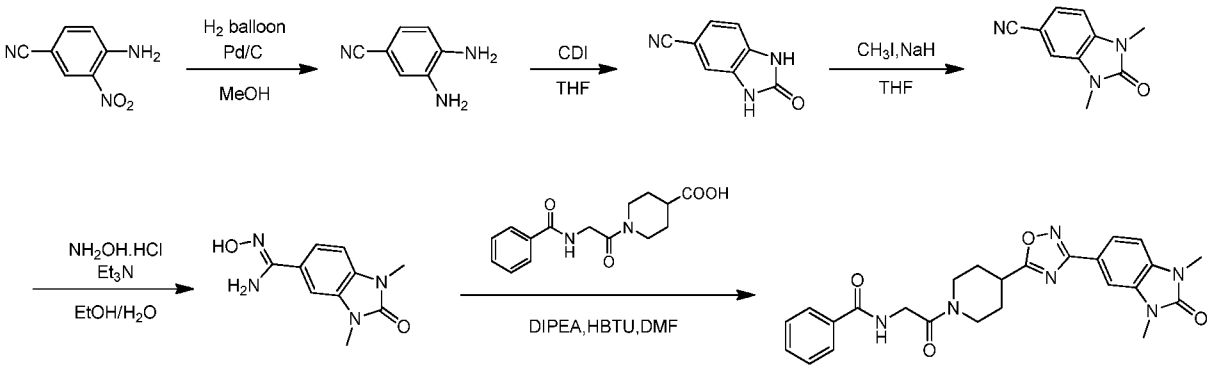
To a stirred solution of 5-ethoxy-4-methoxypicolinonitrile (1.20 g, 6.73 mmol) in ethanol (15 mL) was added hydroxylamine hydrochloride (935 mg, 13.5 mmol), triethylamine (1.36 g, 13.5 mmol, 1.87 mL) and water (1.50 mL). The mixture was heated at 80 °C for 2 h. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-5-ethoxy-N'-hydroxy-4-methoxypicolinimidamide (1.30 g, 6.15 mmol, 91 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.70 (s, 1H), 8.10 (s, 1H), 7.38 (s, 1H), 5.72 (s, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 3.84 (s, 3H), 1.34 (t, *J*=6.9 Hz, 3H).

Step 7: Preparation of N-(2-(4-(3-(5-ethoxy-4-methoxypyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

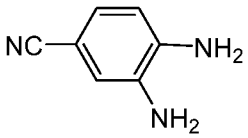


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (150 mg, 516.7 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-5-ethoxy-N'-hydroxy-4-methoxypicolinimidamide (109 mg, 516.7 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (195 mg, 516.7 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (200 mg, 1.55 mmol, 270 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled and then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-40%,12 min) to give N-(2-(4-(3-(5-ethoxy-4-methoxypyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (32 mg, 67 µmol, 13 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.90 - 7.82 (m, 2H), 7.64 (s, 1H), 7.56 - 7.42 (m, 3H), 7.34 (br s, 1H), 4.52 (br d, *J*=13.6 Hz, 1H), 4.34 - 4.21 (m, 4H), 4.02 (s, 3H), 3.91 (br d, *J*=14.1 Hz, 1H), 3.41 - 3.28 (m, 2H), 3.12 (br t, *J*=11.0 Hz, 1H), 2.33 - 2.21 (m, 2H), 2.13 - 1.95 (m, 2H), 1.52 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 466.3.

Example 122: N-[2-[4-[3-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide:

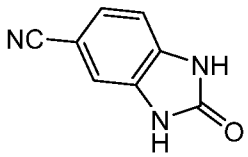


Step 1: Preparation of 3,4-diaminobenzonitrile.



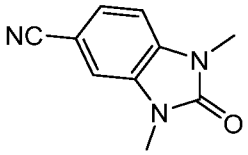
To a stirred solution of 4-amino-3-nitro-benzonitrile (2.00 g, 12.3 mmol) in methanol (20 mL) was added Pd/C (500 mg, 10% purity), then the flask was degassed and filled with hydrogen three times, and the reaction mixture stirred vigorously under hydrogen (balloon) for 18 h at 25 °C. The mixture was evacuated and backfilled with nitrogen three times, then filtered through a pad of celite, and the filtrate concentrated in vacuo to give 3,4-diaminobenzonitrile (1.47 g, 11.04 mmol, 90 %) as a green oil that was used in next step directly.

Step 2: Preparation of 2-oxo-1,3-dihydrobenzimidazole-5-carbonitrile



To a stirred solution of 3,4-diaminobenzonitrile (1.40 g, 10.5 mmol) in tetrahydrofuran (70 mL) at 0 °C was added 1,1'-carbonyldiimidazole (2.22 g, 13.7 mmol), then the mixture was warmed to 25 °C and stirred for 18 h. The mixture was treated with ethyl acetate (100 mL), washed with 1N HCl (20 mL x 2) and saturated aqueous sodium chloride solution (30 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give 2-oxo-1,3-dihydrobenzimidazole-5-carbonitrile (1.50 g) as a pale yellow solid, which was used in next step directly.

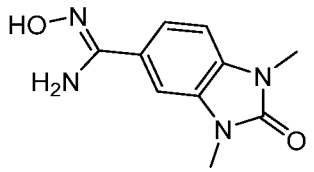
Step 3: Preparation of 1,3-dimethyl-2-oxo-benzimidazole-5-carbonitrile.



To a stirred suspension of sodium hydride (1.13 g, 28.29 mmol, 47.15 mL, 60% dispersion in mineral oil) in N,N-dimethylformamide (5 mL) was added 2-oxo-1,3-dihydrobenzimidazole-5-carbonitrile (1.50 g, 9.43 mmol) in N,N-dimethylformamide (5 mL) at 25 °C. After 15 min, the mixture was cooled to 5 °C then methyl iodide (4.70 g, 33.1 mmol, 2.06 mL) was added dropwise. The reaction mixture was

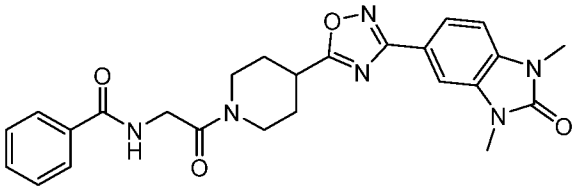
warmed to 25℃ and stirred for 1 h. The mixture was poured into ice-water (100 mL), filtered and the residue dissolved in dichloromethane (10 mL). The phases were separated and the organic phase was washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 1,3-dimethyl-2-oxo-benzimidazole-5-carbonitrile (1.26 g, 6.73 mmol, 71 %) as pale yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.37 (dd, *J*=1.4, 8.2 Hz, 1H), 7.15 (s, 1H), 6.95 (d, *J*=8.2 Hz, 1H), 3.38 (d, *J*=3.3 Hz, 6H).

Step 4: Preparation of N'-hydroxy-1,3-dimethyl-2-oxo-benzimidazole-5-carboxamidine.



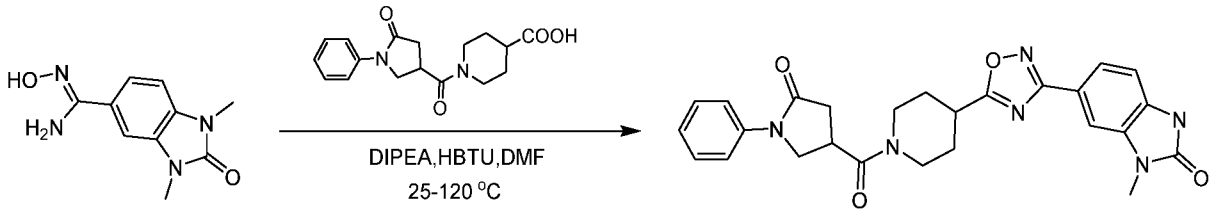
A mixture of 1,3-dimethyl-2-oxo-benzimidazole-5-carbonitrile (1.25 g, 6.68 mmol), hydroxylamine hydrochloride (928 mg, 13.4 mmol) and triethylamine (1.35 g, 13.4 mmol, 1.85 mL) in ethanol (15 mL) and water (1.50 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 70 ℃ for 5 h under a nitrogen atmosphere. The resulting suspension was filtered then the filter cake was dissolved in ethyl acetate (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuo to give N'-hydroxy-1,3-dimethyl-2-oxo-benzimidazole-5-carboxamidine (1.25 g, 5.68 mmol, 85 %) as a white solid.

Step 5: Preparation of N-[2-[4-[3-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.

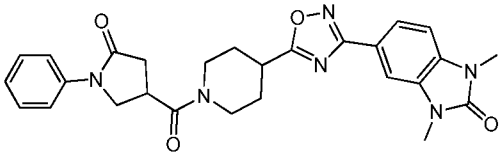


To a stirred solution of N'-hydroxy-1,3-dimethyl-2-oxo-benzimidazole-5-carboxamidine (80 mg, 363 µmol) and 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (105 mg, 363 µmol) in N,N-dimethylformamide (1 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (137 mg, 363 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (93 mg, 726.5 µmol, 126 µL) at 25 ℃. After stirring at 25 ℃ for 1h, the mixture was warmed to 110 ℃ and stirred for 1 h. The mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-40%,12 min) to give N-[2-[4-[3-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (38 mg, 78.7 µmol, 22 %) as pale yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.55 (t, J=5.7 Hz, 1H), 7.89 - 7.83 (m, 2H), 7.75 (dd, J=1.5, 8.2 Hz, 1H), 7.67 (d, J=1.3 Hz, 1H), 7.55 - 7.42 (m, 3H), 7.29 (d, J=8.2 Hz, 1H), 4.31 (br d, J=13.0 Hz, 1H), 4.16 (dd, J=3.6, 5.4 Hz, 2H), 3.97 (br d, J=13.9 Hz, 1H), 3.48 - 3.40 (m, 1H), 3.37 (d, J=10.4 Hz, 6H), 3.29 - 3.22 (m, 1H), 2.91 (br t, J=11.2 Hz, 1H), 2.13 (br t, J=12.9 Hz, 2H), 1.89 - 1.58 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3.

Example 123: 1,3-dimethyl-5-[5-[1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)-4-piperidyl]-1,2,4-oxadiazol-3-yl]benzimidazol-2-one.

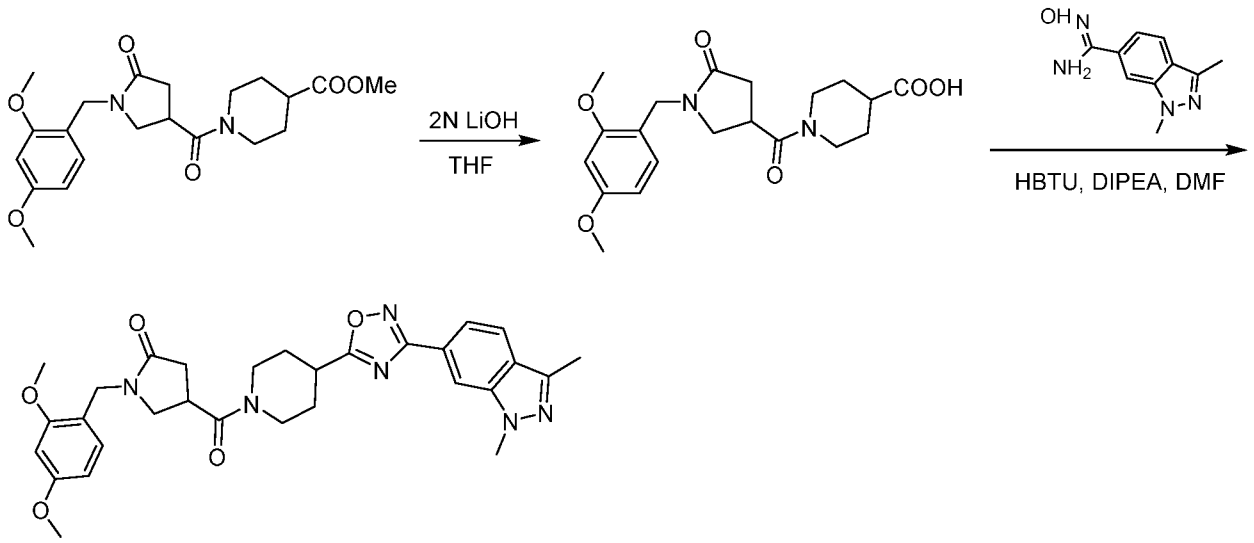


Step 1: Preparation of 1,3-dimethyl-5-[5-[1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)-4-piperidyl]-1,2,4-oxadiazol-3-yl]benzimidazol-2-one.

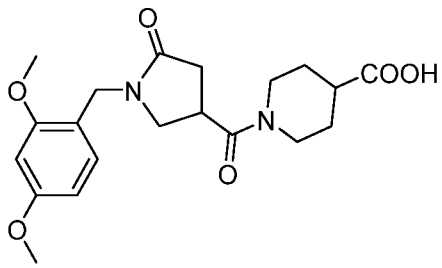


To a stirred solution of N'-hydroxy-1,3-dimethyl-2-oxo-benzimidazole-5-carboxamidine (120 mg, 544.9 µmol) and 1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (206 mg, 653.9 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (206 mg, 544.9 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (140 mg, 1.09 mmol, 190 µL) at 25℃. After stirring at 25 ℃ for 2h, the mixture was heated at 120 ℃ for 1 h. The mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-55%,12 min) to give 1,3-dimethyl-5-[5-[1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)-4-piperidyl]-1,2,4-oxadiazol-3-yl]benzimidazol-2-one (57 mg, 110.5 µmol, 20 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.75 (td, *J*=1.5, 8.2 Hz, 1H), 7.69 - 7.62 (m, 3H), 7.38 - 7.32 (m, 2H), 7.29 (d, *J*=8.4 Hz, 1H), 7.15 - 7.08 (m, 1H), 4.35 (br d, *J*=12.8 Hz, 1H), 4.07 - 3.91 (m, 3H), 3.77 - 3.68 (m, 1H), 3.47 - 3.39 (m, 1H), 3.39 - 3.34 (m, 6H), 3.34 - 3.32 (m, 1H), 3.28 (s, 1H), 2.98 - 2.88 (m, 1H), 2.82 - 2.67 (m, 2H), 2.14 (br t, *J*=13.8 Hz, 2H), 1.90 - 1.63 (m, 2H).LCMS (ESI) m/z: $[M+H]^+$ = 501.3.

Example 124: 1-[(2,4-dimethoxyphenyl)methyl]-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one

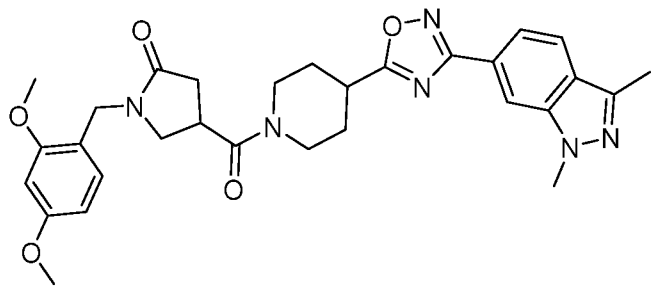


Step 1: Preparation of 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid



To a stirred solution of methyl 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylate (200 mg, 494 µmol) in tetrahydrofuran (2 mL) was added aqueous lithium hydroxide (2 M, 494 µL). The mixture was stirred at 20 °C for 2 h, then the mixture was acidified with 2N hydrochloric acid to pH 1. The mixture was extracted with ethyl acetate (20 mL x 3), then the organic extracts were combined and washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (160 mg, 409.8 µmol, 83 %) as a yellow solid.

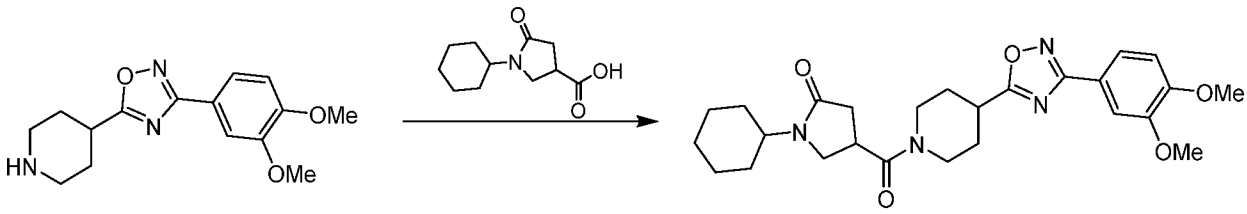
Step 2: Preparation of 1-[(2,4-dimethoxyphenyl)methyl]-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one.



To a stirred solution of N'-hydroxy-1,3-dimethyl-indazole-6-carboxamidine (78 mg, 384 µmol) in N,N-dimethylformamide (2 mL) was added 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-

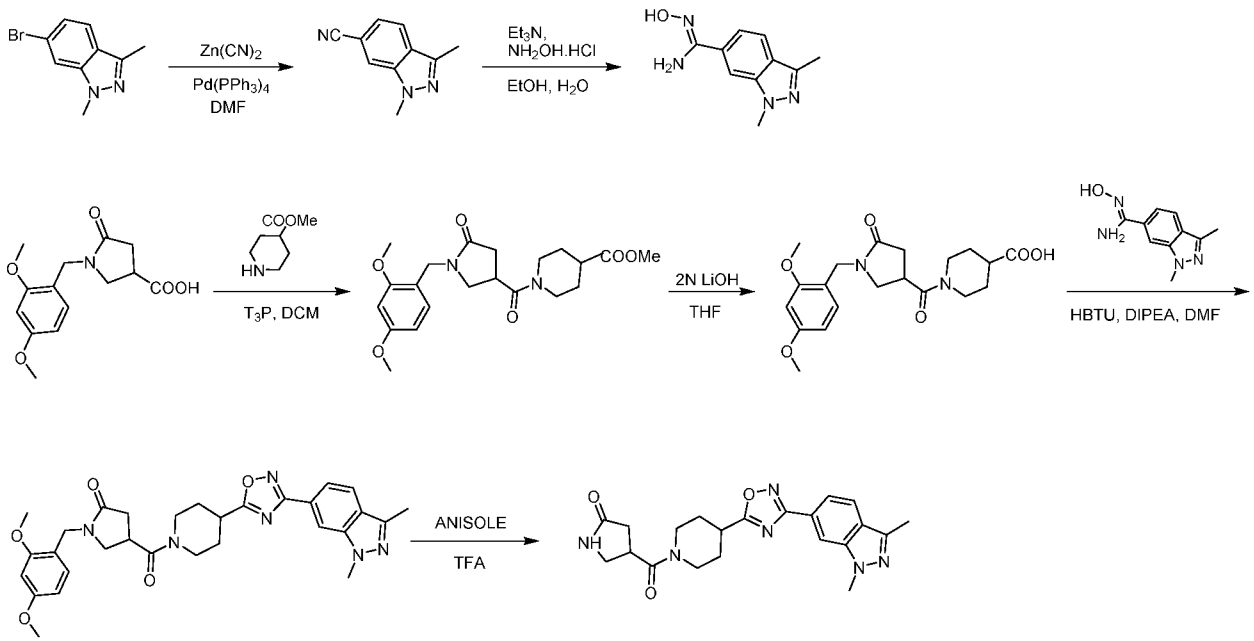
carbonyl]piperidine-4-carboxylic acid (150 mg, 384 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (145 mg, 384 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (148 mg, 1.15 mmol, 201 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-50%,12 min) to give 1-[(2,4-dimethoxyphenyl)methyl]-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one (35 mg, 64 µmol, 17 %) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J*=4.1 Hz, 1H), 7.85 - 7.80 (m, 1H), 7.77 - 7.71 (m, 1H), 7.17 (d, *J*=8.7 Hz, 1H), 6.49 - 6.43 (m, 2H), 4.59 - 4.38 (m, 3H), 4.08 (d, *J*=1.8 Hz, 3H), 3.98 - 3.86 (m, 1H), 3.84 - 3.77 (m, 6H), 3.71 - 3.62 (m, 1H), 3.46 - 3.24 (m, 4H), 3.13 - 2.96 (m, 1H), 2.85 - 2.75 (m, 1H), 2.67 (m, 1H), 2.60 (s, 3H), 2.21 (br s, 2H), 2.04 - 1.87 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 559.3.

Example 125: 1-cyclohexyl-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one

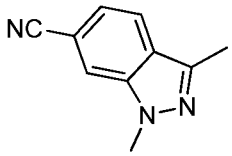


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (100 mg, 345.6 µmol) and 1-cyclohexyl-5-oxo-pyrrolidine-3-carboxylic acid (73 mg, 345.6 µmol) in N,N-dimethylformamide (1.00 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (131 mg, 345.63 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (89 mg, 691 µmol, 120 µL) at 25 °C. The mixture was then stirred for an additional 2h at 25 °C. The reaction mixture was concentrated under reduced pressure to give a residue further purified by chromatography [Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-50%,12 min]. The title product, 1-cyclohexyl-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one, was isolated as a white solid (97 mg, 201.6 µmol, 58 %). ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (dd, *J*=1.7, 8.3 Hz, 1H), 7.57 (d, *J*=1.8 Hz, 1H), 6.97 (d, *J*=8.4 Hz, 1H), 4.60 - 4.44 (dd, 1H), 3.97 (d, *J*=7.9 Hz, 6H), 3.77 (br t, *J*=7.0 Hz, 1H), 3.51 - 3.21 (m, 4H), 3.14 - 2.97 (m, 1H), 2.77 - 2.61 (m, 2H), 2.28 - 2.17 (m, 2H), 2.03 - 1.89 (m, 2H), 1.88 - 1.64 (m, 7H), 1.48 - 1.32 (m, 4H), 1.23 - 1.04 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 483.3.

Example 126: 4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one.

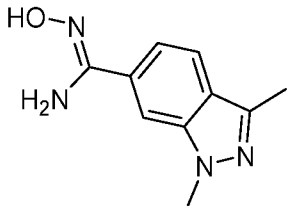


Step 1: Preparation of 1,3-dimethylindazole-6-carbonitrile.



To a stirred solution of 6-bromo-1,3-dimethyl-indazole (3.0 g, 13.33 mmol) in N,N-dimethylformamide (30 mL) was added, under a nitrogen atmosphere, zinc cyanide (1.57 g, 13.33 mmol, 846 µL) and tetrakis(triphenylphosphine)palladium(0) (1.54 g, 1.33 mmol). The mixture was then stirred at 110 °C for 16 h and then cooled to 20 °C. Water (50 mL) was added to the reaction mixture which was extracted with ethyl acetate (80 mL x 3). The organic extracts were combined, washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product further purified by chromatography (silica, petroleum ether: ethyl acetate = 50 : 1 to 10:1. The title compound, 1,3-dimethylindazole-6-carbonitrile was isolated as a white solid (1.92 g, 11.21 mmol, 84 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.67 (m, 2H), 7.33 (dd, *J*=1.0, 8.3 Hz, 1H), 4.05 (s, 3H), 2.59 (s, 3H)

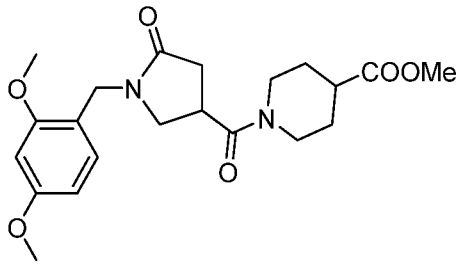
Step 2: Preparation of N'-hydroxy-1,3-dimethyl-indazole-6-carboxamidine.



To a stirred solution of 1,3-dimethylindazole-6-carbonitrile (2.50 g, 14.60 mmol) in ethanol (30 mL) was added hydroxylamine hydrochloride (2.03 g, 29.20 mmol), triethylamine (2.95 g, 29.20 mmol, 4.05 mL) and water (3 mL). The mixture was stirred at 80 °C for 2 h, and then concentrated under reduced pressure. Water (5mL) was added to the residue, the resulting solid was collected by filtration and used for the next step without further purification. The title compound, N'-hydroxy-1,3-dimethyl-

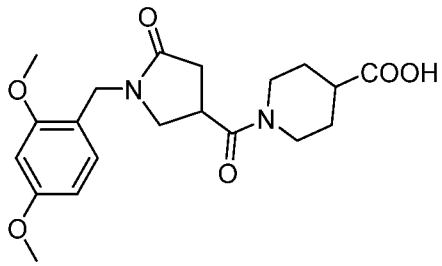
indazole-6-carboxamidine, was isolated as a white solid (2.86 g, 14.00 mmol, 96 %); ^{1}H NMR (400 MHz, DMSO-d6) δ 9.70 (s, 1H), 7.85 (s, 1H), 7.63 (d, *J*=8.4 Hz, 1H), 7.47 (dd, *J*=1.2, 8.5 Hz, 1H), 5.89 (s, 2H), 3.96 (s, 3H), 2.46 (s, 3H).

Step 3: Preparation of methyl 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylate.



To a stirred solution of 1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carboxylic acid (1.0 g, 3.58 mmol) in dichloromethane (15 mL) was added methyl piperidine-4-carboxylate (512 mg, 3.58 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (2.51 g, 3.94 mmol, 2.34 mL, 50% purity), triethylamine (724 mg, 7.16 mmol, 992 µL), and the reaction mixture was stirred at 20 °C for 2 h. Water (30 mL) was added to the mixture which was extracted with dichloromethane (50 mL x 3)). The organic extracts were combined, washed with saturated aqueous sodium chloride (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylate isolated as a yellow oil (1.37 g, 3.39 mmol, 95 %) and used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (br d, *J*=8.5 Hz, 1H), 6.51 - 6.39 (m, 2H), 4.50 - 4.33 (m, 3H), 3.80 (s, 6H), 3.75 (br d, *J*=5.0 Hz, 1H), 3.70 (s, 3H), 3.65 - 3.55 (m, 1H), 3.42 - 3.29 (m, 2H), 3.19 - 3.05 (m, 1H), 2.94 - 2.71 (m, 2H), 2.64 - 2.49 (m, 2H), 1.94 (br dd, *J*=3.3, 13.3 Hz, 2H), 1.62 (br s, 2H).

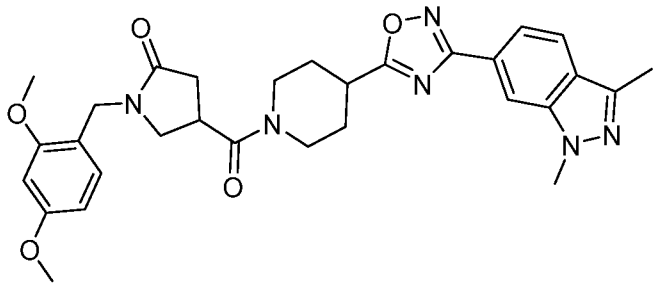
Step 4: Preparation of 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylate (1.17 g, 2.89 mmol) in tetrahydrofuran (15 mL) was added lithium hydroxide (2 M solution in tetrahydrofuran, 2.89 mL). The reaction mixture was stirred at 20 °C for 1 h, and then acidified until pH 1 using a 2M aqueous solution of hydrochloric acid. The resulting mixture was extracted with ethyl acetate (80 mL x 3). The organic extracts were combined, washed with saturated aqueous sodium chloride (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid isolated as a white solid (1.0 g, 2.56 mmol, 89 %) and used for the next step without further purification.^{1}H NMR (400

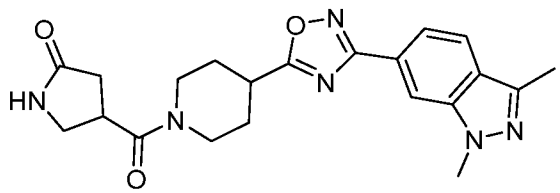
MHz, Methanol-d4) δ 7.09 (dd, *J*=2.9, 8.4 Hz, 1H), 6.52 (d, *J*=2.2 Hz, 1H), 6.47 (dd, *J*=2.3, 8.3 Hz, 1H), 4.46 - 4.25 (m, 3H), 3.92 - 3.83 (m, 1H), 3.80 (d, *J*=1.3 Hz, 3H), 3.78 - 3.75 (m, 3H), 3.65 - 3.36 (m, 3H), 3.25 - 3.11 (m, 1H), 2.92 - 2.80 (m, 1H), 2.71 - 2.52 (m, 3H), 1.97 - 1.87 (m, 2H), 1.68 - 1.42 (m, 2H).

Step 5: Preparation of 1-[(2,4-dimethoxyphenyl)methyl]-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one.



To a stirred solution of N'-hydroxy-1,3-dimethyl-indazole-6-carboxamidine (261 mg, 1.28 mmol) in N,N-dimethylformamide (6 mL) was added 1-[1-[(2,4-dimethoxyphenyl)methyl]-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (500 mg, 1.28 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (485 mg, 1.28 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (496 mg, 3.84 mmol, 670 µL). The reaction mixture was stirred at 20 °C for 1 h, at 110 °C for 1 h. and then cooled to 20 °C. Water (10 mL) was added to the mixture, which was extracted with ethyl acetate (40 mL x 3). The organic extracts were combined, washed with saturated aqueous sodium chloride (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide the crude product further purified by chromatography (Dichloromethane : Methanol = 1:0 to 10:1). The title compound, 1-[(2,4-dimethoxyphenyl)methyl]-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one was isolated as a yellow solid (500 mg, 895 µmol, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J*=5.0 Hz, 1H), 7.84 (d, *J*=8.5 Hz, 1H), 7.79 - 7.73 (m, 1H), 7.17 (d, *J*=8.9 Hz, 1H), 6.50 - 6.44 (m, 2H), 4.58 - 4.41 (m, 3H), 4.10 (s, 3H), 3.97 - 3.88 (m, 1H), 3.84 - 3.79 (m, 6H), 3.69 (br d, *J*=6.7 Hz, 1H), 3.47 - 3.27 (m, 4H), 3.16 (q, *J*=7.5 Hz, 1H), 2.83 - 2.76 (m, 1H), 2.71 - 2.64 (m, 1H), 2.62 (s, 3H), 2.25 (br s, 2H), 2.03 - 1.88 (m, 2H)

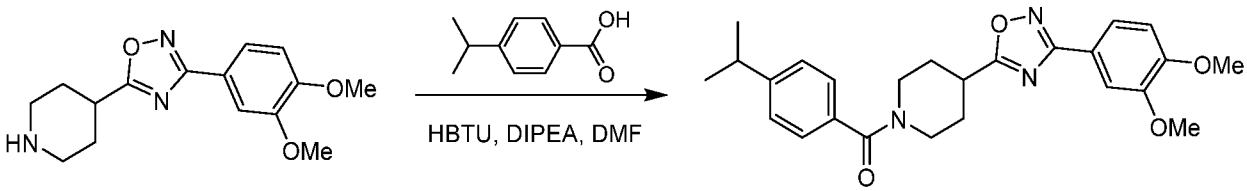
Step 6: Preparation of 4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one.



A mixture of 1-[(2,4-dimethoxyphenyl)methyl]-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one (150 mg, 268.51 µmol), anisole (58 mg, 537 µmol, 58 µL) in trifluoro acetic acid (2 mL) was degassed, purged with nitrogen three times, and then stirred at 80 °C for 2 h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give the crude product further purified by chromatography (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 15%-35%,12min). The title compound, 4-

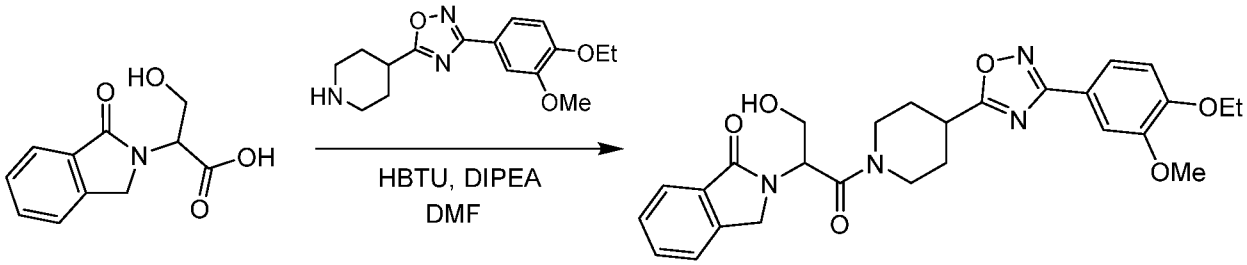
[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one, was isolated as a white solid (50 mg, 122.8 µmol, 46 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.86 - 7.80 (m, 1H), 7.77 - 7.72 (m, 1H), 5.74 (br s, 1H), 4.55 (br t, *J*=14.1 Hz, 1H), 4.08 (s, 3H), 3.95 (br d, *J*=9.0 Hz, 1H), 3.82 - 3.75 (m, 1H), 3.66 - 3.53 (m, 2H), 3.43 - 3.29 (m, 2H), 3.15 - 3.02 (m, 1H), 2.77 - 2.67 (m, 1H), 2.60 (s, 3H), 2.59 - 2.52 (m, 1H), 2.33 - 2.18 (m, 2H), 2.08 - 1.92 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 409.3.

Example 127: [4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(4-isopropylphenyl)methanone.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (80 mg, 276.50 µmol) and 4-isopropylbenzoic acid (54 mg, 331.80 µmol) in N,N-dimethylformamide (1.00 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (125 mg, 331.80 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (71 mg, 553 µmol, 96 µL) at 25 ℃. The mixture was stirred at 25 ℃ for 2h and then concentrated under reduced pressure to provide a residue purified by chromatography (Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12min. The title compound, [4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(4-isopropylphenyl)methanone was isolated as a yellow solid (83 mg, 191.6 µmol, 69 %) ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.71 (dd, *J*=1.9, 8.3 Hz, 1H), 7.59 (d, *J*=1.9 Hz, 1H), 7.40 - 7.36 (dd, 2H), 7.31 - 7.26 (t, 2H), 6.97 (d, *J*=8.4 Hz, 1H), 4.65 (br s, 1H), 3.97 (d, *J*=8.5 Hz, 6H), 3.36 - 3.15 (m, 3H), 2.95 (spt, *J*=6.9 Hz, 1H), 2.33 - 1.62 (m, 4H), 2.36 - 1.62 (m, 1H), 1.28 (d, *J*=6.9 Hz, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 436.3.

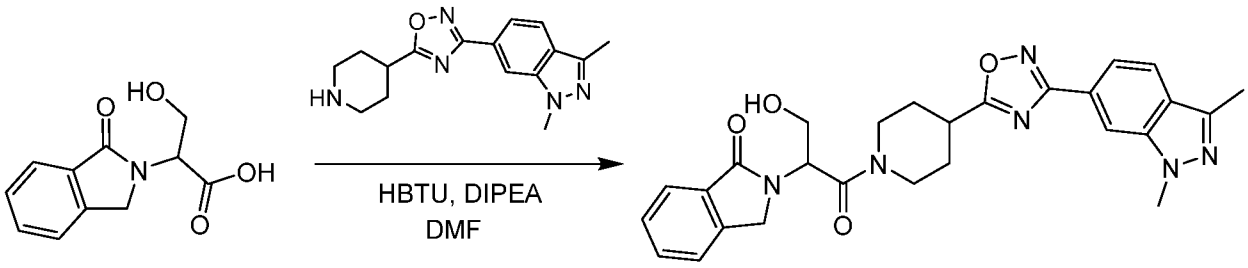
Example 128: 2-[2-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-(hydroxymethyl)-2-oxo-ethyl]isoindolin-1-one.



To a stirred solution of 3-hydroxy-2-(1-oxoisoindolin-2-yl)propanoic acid (120 mg, 542 µmol) in N,N-dimethylformamide (2 mL) was added 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (153 mg, 452 µmol, 1.00 *eq*, hydrochloric acid), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (205 mg, 542 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (175 mg, 1.36 mmol, 236 µL). The mixture was stirred at 20 ℃ for 1 h, and then purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium

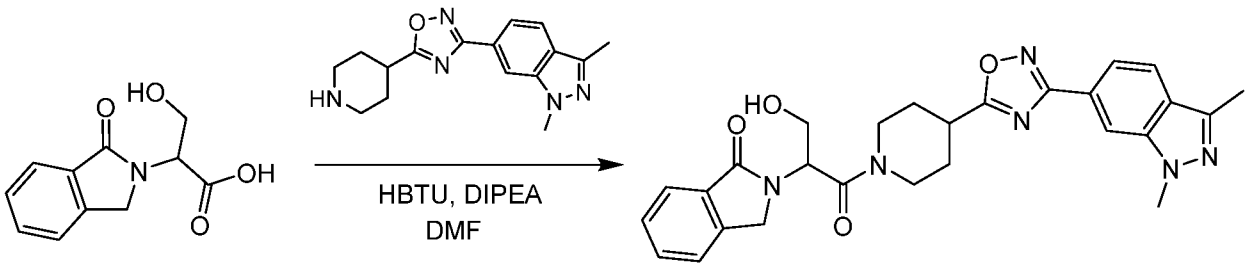
carbonate)-acetonitrile]; B%: 30%-60%,12min). The title compound, 2-[2-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-(hydroxymethyl)-2-oxo-ethyl]isoindolin-1-one was isolated as a white solid (139 mg, 274.8 µmol, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J*=6.8 Hz, 1H), 7.68 - 7.44 (m, 5H), 6.92 (dd, *J*=8.4, 17.7 Hz, 1H), 5.38 (t, *J*=4.6 Hz, 1H), 4.84 (br d, *J*=17.2 Hz, 1H), 4.48 - 4.35 (m, 2H), 4.21 - 3.98 (m, 5H), 3.94 (d, *J*=17.1 Hz, 3H), 3.77 - 3.41 (m, 1H), 3.39 - 3.04 (m, 3H), 2.26 - 1.78 (m, 4H), 1.50 (q, *J*=6.8 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 507.3.

Example 129: 2-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-(hydroxymethyl)-2-oxo-ethyl]isoindolin-1-one.



To a stirred solution of 3-hydroxy-2-(1-oxoisoindolin-2-yl)propanoic acid (120 mg, 542 µmol) in N,N-dimethylformamide (2 mL) was added 3-(1,3-dimethylindazol-6-yl)-5-(4-piperidyl)-1,2,4-oxadiazole, hydrochloride (150 mg, 452 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (205 mg, 542 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (175 mg, 1.36 mmol, 236 µL). The reaction mixture was stirred at 20 °C for 1 h and then purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-55%,12min). The title compound, 2-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-(hydroxymethyl)-2-oxo-ethyl]isoindolin-1-one was isolated as a white solid (68 mg, 137 µmol, 30 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 - 7.97 (m, 1H), 7.91 - 7.65 (m, 3H), 7.62 - 7.44 (m, 3H), 5.40 (t, *J*=4.9 Hz, 1H), 4.82 (dd, *J*=3.0, 17.3 Hz, 1H), 4.51 - 4.37 (m, 2H), 4.16 - 3.99 (m, 6H), 3.65 (br s, 1H), 3.43 - 3.04 (m, 3H), 2.58 (d, *J*=6.7 Hz, 3H), 2.27 - 1.93 (m, 3.6H), 1.62 - 1.50 (m, 0.4H); LCMS (ESI) m/z: $[M+H]^+$ = 501.3.

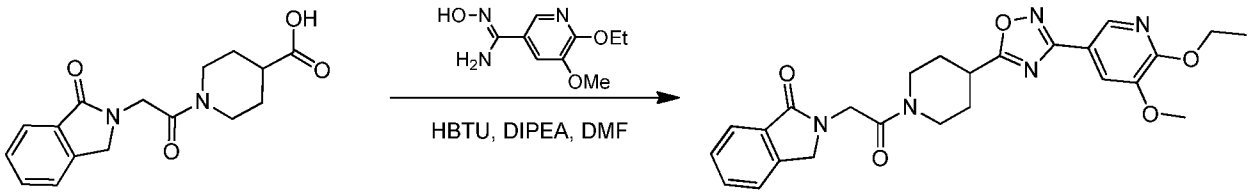
Example 130: 4-[4-[3-(6-ethoxy-5-methoxy-3-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.



A solution of (Z)-6-ethoxy-N'-hydroxy-5-methoxynicotinimidamide (100 mg, 474 µmol) in N,N-dimethylformamide (2.00 mL) was added 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (150 mg, 474 µmol) N-ethyl-N-(propan-2-yl)propan-2-amine (183 mg, 1.42 mmol, 248 µL), and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (197 mg, 521.58 µmol). The

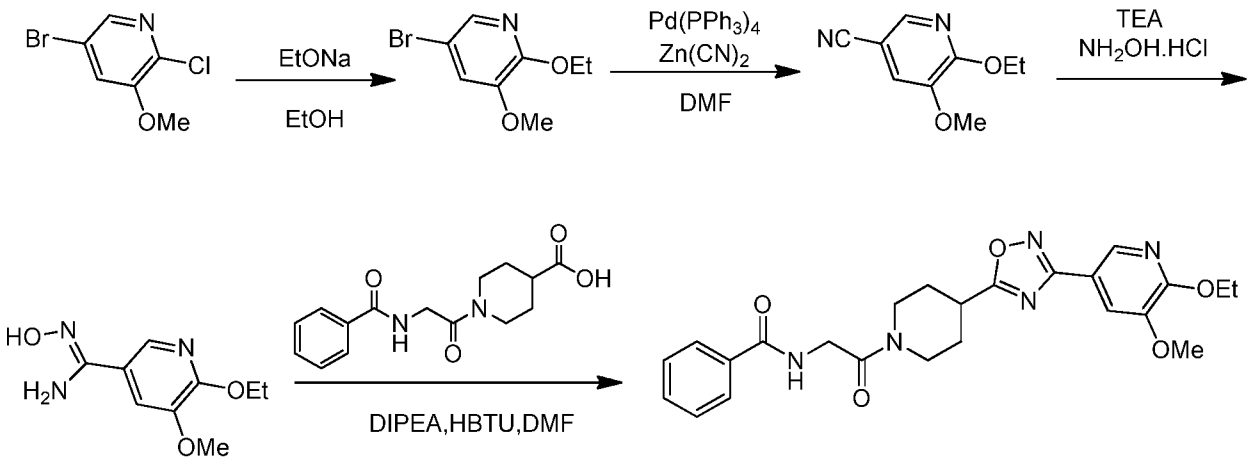
mixture was stirred at 25 °C for 12 h, and then at 110 °C for 1 h. The residue was purified directly by pre-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-50%,12min) to give 4-[4-[3-(6-ethoxy-5-methoxy-3-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (96 mg, 194.7 μmol, 41 %), isolated as as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.44 (s, 1H), 7.64 - 7.57 (m, 3H), 7.41 - 7.34 (m, 2H), 7.21 - 7.14 (m, 1H), 4.61 - 4.46 (m, 3H), 4.37 - 4.28 (m, 1H), 4.02 - 3.90 (m, 5H), 3.58 (td, J=8.4, 16.6 Hz, 1H), 3.44 - 3.26 (m, 2H), 3.17 - 2.91 (m, 2H), 2.89 - 2.78 (m, 1H), 2.31 - 2.17 (m, 2H), 2.06 - 1.87 (m, 2H), 1.47 (t, J=7.2 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 492.1.

Example 131: 2-(2-(4-(3-(6-ethoxy-5-methoxypyridin-3-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one.

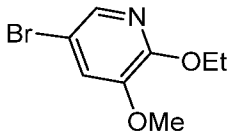


A solution of 6-ethoxy-N'-hydroxy-5-methoxy-pyridine-3-carboxamidine (104 mg, 496 μmol) in N,N-dimethylformamide (2 mL) was added 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylic acid (150 mg, 496 μmol), N-ethyl-N-(propan-2-yl)propan-2-amine (192 mg, 1.49 mmol, 259 μL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (206 mg, 545.77 μmol). The mixture was stirred at 25 °C for 12 h, and then at 110 °C for 1 h. The mixture was purified by pre-HPLC (column: Waters Xbridge 150x25 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-50%,12min) to give 2-[2-[4-[3-(6-ethoxy-5-methoxy-3-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]isoindolin-1-one (82 mg, 171 μmol, 34 %), isolated as a pink solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.46 (d, J=1.8 Hz, 1H), 7.89 (d, J=7.8 Hz, 1H), 7.65 (d, J=1.5 Hz, 1H), 7.62 - 7.56 (m, 1H), 7.50 (t, J=6.7 Hz, 2H), 4.64 - 4.44 (m, 7H), 4.11 (br d, J=13.7 Hz, 1H), 3.98 (s, 3H), 3.46 - 3.26 (m, 2H), 3.08 (br t, J=10.9 Hz, 1H), 2.24 (br t, J=14.0 Hz, 2H), 2.09 - 1.89 (m, 2H), 1.50 (t, J=7.1 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 478.1.

Example 132: N-(2-(4-(3-(6-ethoxy-5-methoxypyridin-3-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

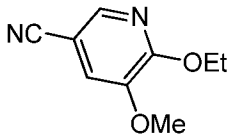


Step 1: Preparation of 5-bromo-2-ethoxy-3-methoxypyridine.



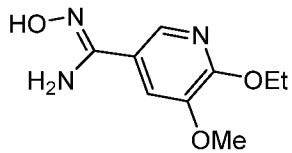
A solution of sodium (465 mg, 20.23 mmol, 479 µL) in ethanol (5 mL) was stirred at 20 °C for 2 h. 5-Bromo-2-chloro-3-methoxypyridine (1.50 g, 6.74 mmol) was then added to the mixture which was stirred at 100 °C for 12 h. The reaction mixture was concentrated under reduced pressure. Water (50 mL) was then added to the residue. The mixture was extracted with dichloromethane (60 mL x 3). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide 5-bromo-2-ethoxy-3-methoxypyridinee, isolated as a white solid (1.70 g, crude), and used for the next step without further purification. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.70 (d, J=2.0 Hz, 1H), 7.34 (d, J=2.2 Hz, 1H), 4.34 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 1.36 (t, J=7.1 Hz, 3H).

Step 2: Preparation of 6-ethoxy-5-methoxynicotinonitrile.



To a stirred solution of 5-bromo-2-ethoxy-3-methoxy-pyridine (1.70 g, 7.33 mmol) in N,N-dimethylformamide (10 mL) was added zinc cyanide (860 mg, 7.33 mmol, 464 µL), and tetrakis(triphenylphosphine)palladium(0) (847 mg, 733 µmol, 0.10 eq), the mixture was degassed with nitrogen for three times. The resulting mixture was stirred at 110 °C for 12 h under nitrogen atmosphere and then poured into water (30 mL). The mixture was then extracted with dichloromethane (50 mL x 3). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide the crude product purified by chromatography (silica, petroleum ether : ethyl acetate = 50:1 R_f= 0.6). The title compound, 6-ethoxy-5-methoxy-pyridine-3-carbonitrile was isolated as a white solid (820 mg, 4.60 mmol, 63 %) ^{1}H NMR (400MHz, METHANOL-d4) δ = 8.08 (d, J=1.8 Hz, 1H), 7.49 (d, J=1.8 Hz, 1H), 4.48 (q, J=7.1 Hz, 2H), 3.92 - 3.88 (m, 3H), 1.42 (t, J=7.1 Hz, 3H) .

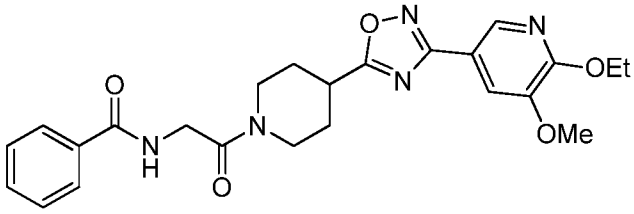
Step 3: Preparation of (Z)-6-ethoxy-N'-hydroxy-5-methoxynicotinimidamide.



To a stirred solution of 6-ethoxy-5-methoxynicotinonitrile (820 mg, 4.60 mmol) in ethanol (20 mL) and water (2 mL) was added hydroxylamine hydrochloride (639 mg, 9.20 mmol) and triethylamine (931 mg, 9.20 mmol, 1.28 mL). The mixture was stirred at 80 °C for 2 h, cooled to room temperature, concentrated under reduced pressure and poured into water (5 mL). The resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to give (Z)-6-ethoxy-N'-hydroxy-5-methoxynicotinimidamide

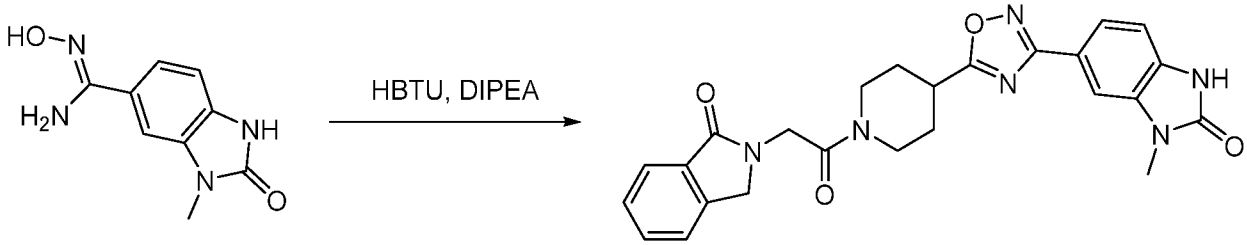
(1.0 g, crude) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.94 (d, J=2.0 Hz, 1H), 7.44 (d, J=2.0 Hz, 1H), 4.43 - 4.36 (m, 2H), 3.86 (s, 3H), 1.38 (t, J=7.1 Hz, 3H).

Step 4: Preparation of N-(2-(4-(3-(6-ethoxy-5-methoxypyridin-3-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



To a stirred solution of (Z)-6-ethoxy-N'-hydroxy-5-methoxynicotinimidamide (109 mg, 516.69 µmol) in N,N-dimethylformamide (2 mL) was added 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (150 mg, 516.69 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (200 mg, 1.55 mmol, 270 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (215 mg, 568 µmol). The mixture was stirred at 25 ℃ for 12 h, and at 110 ℃ for 1 h. The residue was purified directly by chromatography (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-50%,12min) to give N-(2-(4-(3-(6-ethoxy-5-methoxypyridin-3-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (83 mg, 177.7 µmol, 34 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.44 (d, J=1.8 Hz, 1H), 7.88 - 7.82 (m, 2H), 7.62 (d, J=2.0 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.48 - 7.42 (m, 2H), 7.32 (br s, 1H), 4.58 - 4.47 (m, 3H), 4.30 (d, J=4.0 Hz, 2H), 3.95 (s, 3H), 3.39 - 3.28 (m, 2H), 3.18 - 3.09 (m, 1H), 2.30 - 2.19 (m, 2H), 2.07 - 1.91 (m, 2H), 1.47 (t, J=7.1 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 466.1.

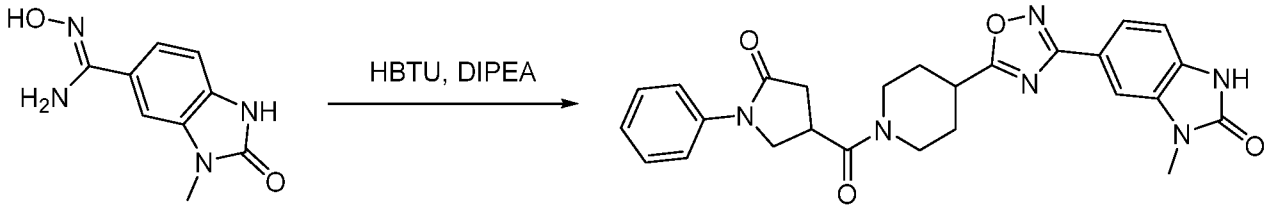
Example 133: 3-methyl-5-[5-[1-[2-(1-oxoisoindolin-2-yl)acetyl]-4-piperidyl]-1,2,4-oxadiazol-3-yl]-1H-benzimidazol-2-one.



A mixture of N'-hydroxy-3-methyl-2-oxo-1H-benzimidazole-5-carboxamidine (81.85 mg, 396.94 µmol, 1.20 eq), 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylic acid (100.00 mg, 330.78 µmol, 1.00 eq), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (188.16 mg, 496.16 µmol, 1.50 eq), N-ethyl-N-(propan-2-yl)propan-2-amine (128.25 mg, 992.33 µmol, 173.31 µL, 3.00 eq) in N,N-dimethylformamide (2.00 mL) then the mixture was stirred at 20 ℃ for 15h then the mixture was stirred at 110 ℃ for 1 h. The product was purified by column: Waters Xbridge 150x25 5µm; mobile phase: [water (10 mM NH_4HCO_3)-acetonitrile]; B%: 20%-45%,12min to obtain compound 3-methyl-5-[5-[1-[2-(1-oxoisoindolin-2-yl)acetyl]-4-piperidyl]-1,2,4-oxadiazol-3-yl]-1H-benzimidazol-2-one (53.58 mg, 113.40 µmol, 34.28 %) as a pink solid. 1H NMR (400MHz, CHLOROFORM-d) δ = 9.60 (br s, 1H), 7.79 (t, J=9.0 Hz, 2H), 7.61 (s, 1H), 7.51 - 7.46 (m, 1H), 7.42 - 7.37 (m, 2H), 7.10 (d, J=8.2 Hz, 1H), 4.52 (s, 2H), 4.45 -

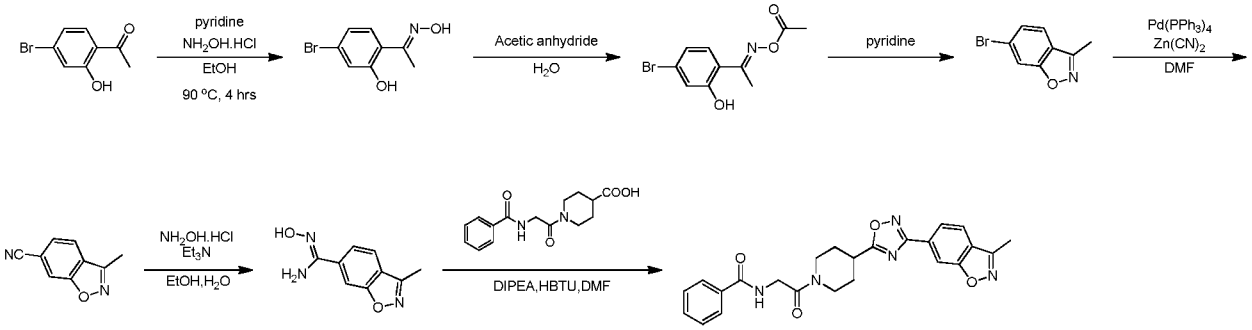
4.37 (m, 3H), 4.02 (br d, J=13.6 Hz, 1H), 3.42 (s, 3H), 3.37 - 3.19 (m, 2H), 3.00 (br t, J=11.0 Hz, 1H), 2.21 - 2.10 (m, 2H), 1.99 - 1.85 (m, 2H); LCMS (ESI) m/z $[M+H]^+$ = 473.3.

Example 134: 3-methyl-5-[5-[1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)-4-piperidyl]-1,2,4-oxadiazol-3-yl]-1H-benzimidazol-2-one.

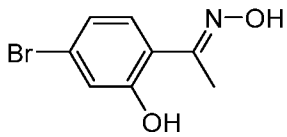


Example 134 was synthesized according to the synthetic procedure reported for the preparation of Example 133. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.82 (br s, 1H), 7.79 (br d, J=8.2 Hz, 1H), 7.62 (br s, 1H), 7.52 (d, J=8.2 Hz, 2H), 7.34 - 7.29 (m, 2H), 7.14 - 7.08 (m, 2H), 4.57 - 4.40 (m, 1H), 4.26 (br t, J=7.3 Hz, 1H), 3.97 - 3.84 (m, 2H), 3.52 (quin, J=8.4 Hz, 1H), 3.42 (d, J=1.6 Hz, 3H), 3.37 - 3.23 (m, 2H), 3.13 - 2.86 (m, 2H), 2.83 - 2.76 (m, 1H), 2.19 (br t, J=12.5 Hz, 2H), 2.00 - 1.82 (m, 2H). LCMS (ESI) m/z: $[M+H]^+$ = 487.3.

Example 135: N-[2-[4-[3-(3-methyl-1,2-benzoxazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide

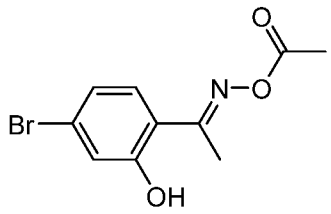


Step 1: Preparation of 1-(4-bromo-2-hydroxy-phenyl)ethanone oxime



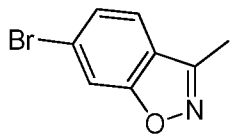
To a stirred solution of 1-(4-bromo-2-hydroxy-phenyl)ethanone (10.00 g, 46.50 mmol) and pyridine (49.66 g, 627.75 mmol, 50.67 mL) in ethanol (100 mL) was added hydroxylamine hydrochloride (16.16 g, 232.50 mmol) at 25 ℃. The mixture was heated to 90℃ for 4 h and was poured into a 2M aqueous solution of hydrochloric acid (250 mL). The mixture was then extracted with ethyl acetate (100 mL x 4), washed with saturated aqueous sodium chloride solution (25 mL x 1), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 1-(4-bromo-2-hydroxy-phenyl)ethanone oxime (12.49 g, crude), isolated as pale yellow solid, and used for the next step without further purification. (^{1}H NMR (400MHz, CHLOROFORM-d) δ = 11.47 (br s, 1H), 8.65 (br d, *J*=4.3 Hz, 1H), 7.94 (br s, 1H), 7.31 - 7.28 (d, 1H), 7.17 (d, *J*=1.9 Hz, 1H), 7.06 (dd, *J*=2.0, 8.5 Hz, 1H), 2.37 (s, 3H)

Step 2: Preparation of [(E)-1-(4-bromo-2-hydroxy-phenyl)ethylideneamino] acetate.



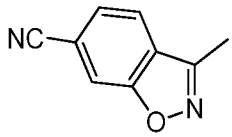
Acetic anhydride (25.50 mL) was added to 1-(4-bromo-2-hydroxy-phenyl)ethanone oxime (12.49 g, 54.29 mmol, 1.00 eq) one portion at 25 °C, then the mixture was stirred at 25 °C for 30 mins. Water (100 mL) was then added to the suspension (a solid precipitated from the reaction mixture after 30 min stirring at room temperature), further stirred for 30 min at 25 °C. The suspension was filtered and the resulting solid was washed with water (10 mL x 3) and dissolved in ethyl acetate (20 mL). The organic solution was then dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to give [(E)-1-(4-bromo-2-hydroxy-phenyl)ethylideneamino] acetate (12.18 g, 44.8 mmol, 82 %) as pale white solid. ^1H NMR (400MHz, CHLOROFORM-d) δ = 11.48 (s, 1H), 7.34 (d, *J*=8.7 Hz, 1H), 7.24 (d, *J*=1.9 Hz, 1H), 7.07 (dd, *J*=1.9, 8.6 Hz, 1H), 2.45 (s, 3H), 2.28 (s, 3H).

Step 3: Preparation of 6-bromo-3-methyl-1,2-benzoxazole



[(E)-1-(4-bromo-2-hydroxy-phenyl)ethylideneamino] acetate (11.00 g, 40.4 mmol) was added in one portion to pyridine (100 mL) and the resulting solution was refluxed at 130 °C for 15 h. The mixture was cooled to room temperature and poured into a 2M aqueous solution of hydrochloric acid (500 mL). The resulting mixture was extracted with methyl tert-butyl ether (200 mL x 3). The organic extracts were washed with saturated aqueous sodium chloride solution (20 mL x 1), dried with anhydrous Na_2SO_4, filtered and concentrated under vaccum to give the crude product further purified by chromatography (silica, petroleum ether / ethyl acetate=200/1 to 100/1). The desired compound (6-bromo-3-methyl-1,2-benzoxazole) was obtained as a yellow solid (7.50 g). ^1H NMR (400MHz, DMSO-d_6) δ = 8.05 (s, 1H), 8.08 - 8.03 (d, 1H), 8.08 - 8.03 (, 1H), 7.82 (d, *J*=8.4 Hz, 1H), 7.56 (dd, *J*=1.1, 8.3 Hz, 1H), 2.56 (s, 3H).

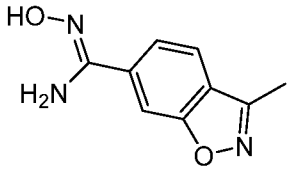
Step 4: Preparation of 3-methyl-1,2-benzoxazole-6-carbonitrile.



To a stirred solution of 6-bromo-3-methyl-1,2-benzoxazole (2.50 g, 11.8 mmol) and zinc cyanide (1.38 g, 11.8 mmol, 748 µL) in N,N-dimethylformamide (12 mL) was added tetrakis(triphenylphosphine)palladium(0) (1.36 g, 1.18 mmol) at 25 °C ,the mixture was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 110 °C for 24 hrs under a nitrogen atmosphere. The suspension was filtered through a pad of Celite. The filtrate was then poured into water (50 mL), extracted with ethyl acetate (50 mL x 3) and the organic layer was washed with saturated aqueous sodium chloride solution (20 mL x 1), dried with anhydrous Na_2SO_4, and concentrated in vacuo.

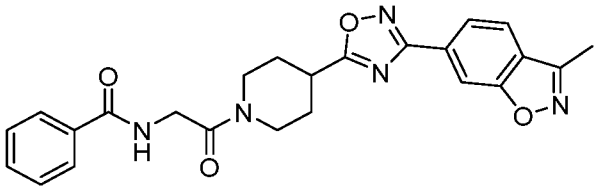
The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=100/1 to 50:1) to give 3-methyl-1,2-benzoxazole-6-carbonitrile (240 mg, 1.52 mmol, 13 %), isolated as awhite solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.89 (t, *J*=1.0 Hz, 1H), 7.76 (dd, *J*=0.7, 8.2 Hz, 1H), 7.60 - 7.57 (m, 1H), 2.63 (s, 3H).

Step 5: Preparation of N'-hydroxy-3-methyl-1,2-benzoxazole-6-carboxamidine



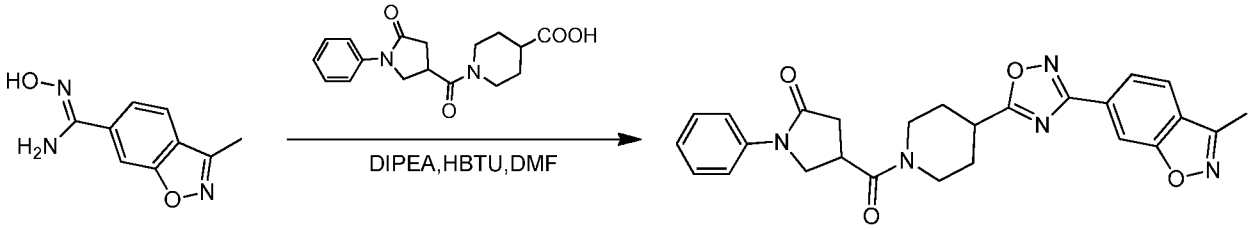
To a stirred solution of 3-methyl-1,2-benzoxazole-6-carbonitrile (240 mg, 1.52 mmol) in ethanol (4.00 mL) and water (400 µL) was added hydroxylamine hydrochloride (210 mg, 3.03 mmol) and triethylamine (307 mg, 3.03 mmol, 420 µL) at 25 ℃. The mixture was then stirred at 70 ℃ for 5 h and concentrated in vacuo to give N'-hydroxy-3-methyl-1,2-benzoxazole-6-carboxamidine (265 mg, 1.39 mmol, 91.60 %) isolated as a white solid, and used for the next step without further purification.

Step 6: Preparation of N-[2-[4-[3-(3-methyl-1,2-benzoxazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.



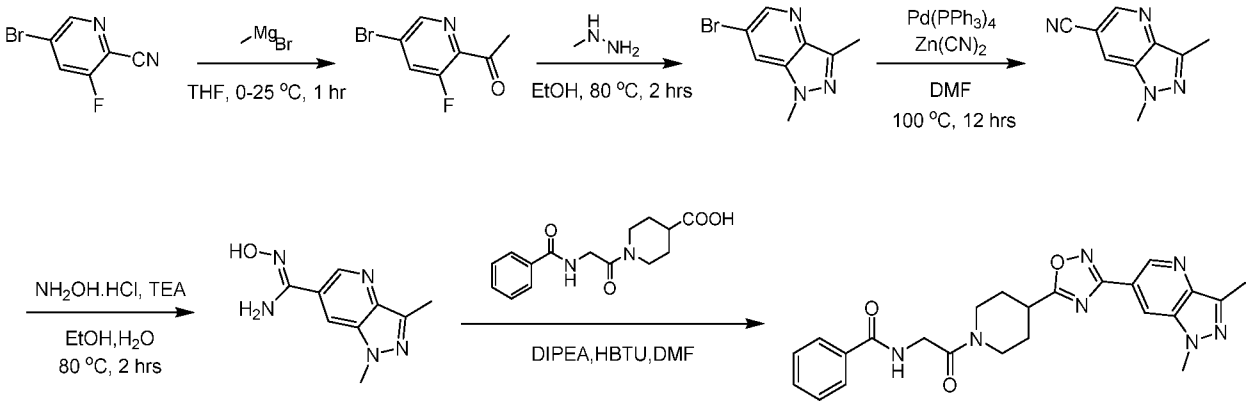
To a stirred solution of N'-hydroxy-3-methyl-1,2-benzoxazole-6-carboxamidine (85 mg, 447.80 µmol) and 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (130 mg, 447.80 µmol) in N,N-dimethylformamide (2.00 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (169 mg, 447.80 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (115 mg, 895.60 µmol, 156 µL) at 25 ℃. The mixture was then stirred at 25 ℃ for 4 h and warmed to 110 ℃ for 1 h. The mixture was concentrated in vacuo and the resulting residue was purified by chromatography (Boston Green ODS 150x30mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 26%-56%,11.5 min) to give N-[2-[4-[3-(3-methyl-1,2-benzoxazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (48 mg, 107.82 µmol,24%, 99% purity), isolated as a pale yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.28 (s, 1H), 8.05 (d, *J*=8.3 Hz, 1H), 7.85 (d, *J*=7.5 Hz, 2H), 7.74 (d, *J*=7.9 Hz, 1H), 7.55 - 7.42 (m, 3H), 7.34 (br s, 1H), 4.51 (br d, *J*=13.6 Hz, 1H), 4.31 (d, *J*=3.9 Hz, 2H), 3.93 (br d, *J*=14.0 Hz, 1H), 3.41 - 3.32 (m, 2H), 3.16 (br t, *J*=10.7 Hz, 1H), 2.63 (s, 3H), 2.33 - 2.22 (m, 2H), 2.09 - 1.93 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$:446.2.

Example 136: 4-[4-[3-(3-methyl-1,2-benzoxazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.



To a stirred solution of N'-hydroxy-3-methyl-1,2-benzoxazole-6-carboxamidine (78 mg, 410.94 µmol) and 1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (130 mg, 410.94 µmol) in N,N-dimethylformamide (2.00 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (155 mg, 410.94 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (106 mg, 821.88 µmol, 143 µL) at 25 °C. The mixture was then stirred at 25 °C for 4 h and warmed to 110 °C for 1 h. The mixture was concentrated in vacuo and the resulting residue was purified by chromatography (Boston Green ODS 150x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,11.5 min) to give 4-[4-[3-(3-methyl-1,2-benzoxazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (42 mg, 89.8 µmol, 22 %) isolated as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.28 (s, 1H), 8.06 (d, *J*=8.3 Hz, 1H), 7.74 (d, *J*=8.3 Hz, 1H), 7.60 (d, *J*=7.9 Hz, 2H), 7.38 (t, *J*=7.9 Hz, 2H), 7.20 - 7.14 (t, 1H), 4.61 - 4.48 (t, 1H), 4.35 - 4.29 (t, 1H), 4.04 - 3.92 (dd, 2H), 3.59 (quin, *J*=8.4 Hz, 1H), 3.46 - 3.31 (m, 2H), 3.20 - 3.05 (m, 1H), 3.03 - 2.92 (m, 1H), 2.89 - 2.80 (m, 1H), 2.63 (s, 3H), 2.28 (br t, *J*=12.3 Hz, 2H), 2.08 - 1.91 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 472.2.

Example 137: N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

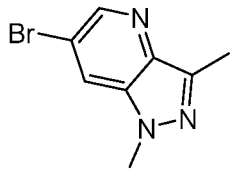


Step 1: Preparation of 1-(5-bromo-3-fluoropyridin-2-yl)ethanone.

A 3M solution of ethylmagnesium bromide in tetrahydrofuran (4.97 mL) was added at 0 °C to a stirred solution of 5-bromo-3-fluoropicolinonitrile (2.0 g, 9.95 mmol) in tetrahydrofuran (20 mL). The

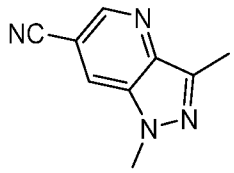
mixture was then stirred at 25 °C for 1 h, and quenched by addition of an aqueous solution of ammonium hydroxide ammonium chloride solution (20 mL). The resulting mixture was extracted with ethyl acetate (2 X 20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give the crude product further purified by chromatography (silica, petroleum ether : ethyl acetate = 20:1 to 1:1). The desired compound (1-(5-bromo-3-fluoropyridin-2-yl)ethanone) was isolated as a yellow solid (580 mg, 1.49 mmol, 15 %). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.56 (s, 1H), 7.74 (dd, *J*=1.8, 9.8 Hz, 1H), 2.68 (s, 3H).

Step 2 preparation of 6-bromo-1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine



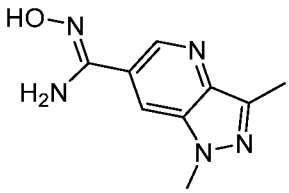
To a stirred solution of 1-(5-bromo-3-fluoropyridin-2-yl)ethanone (570 mg, 1.46 mmol) in ethanol (5 mL), was added methylhydrazine (1.68 g, 14.60 mmol, 1.91 mL), and the resulting mixture was heated at 80 °C for 2 h. The reaction mixture was then quenched with water (5 mL) and extracted with ethyl acetate (2X5 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give the crude product further purified by prep-TLC (silica, petroleum ether : ethyl acetate = 3:1). The title compound (6-bromo-1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine) was isolated as a yellow solid (280 mg, 1.23 mmol, 84 %) ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.54 (d, *J*=1.9 Hz, 1H), 7.86 (d, *J*=1.9 Hz, 1H), 3.99 (s, 3H), 2.64 (s, 3H).

Step 3 preparation of 1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine-6-carbonitrile.



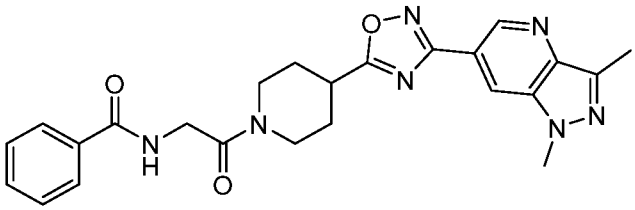
A solution of 6-bromo-1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine (280 mg, 1.24 mmol), tetrakis(triphenylphosphine)palladium(0) (214 mg, 186 µmol), and zinc cyanide (87 mg, 744 µmol, 47 µL) in N,N-dimethylformamide (2 mL) under nitrogen was heated to 100 °C and stirred for 12 h at 100 °C. The reaction mixture was cooled to room temperature, filtered and the filtrate was concentrated to give a residue poured into water (3 mL). The aqueous phase was extracted with ethyl acetate (3 mL x 3). The combined organic extracts were then washed with saturated aqueous sodium chloride solution (5 mL x 1), dried over anhydrous anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1) to give 1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine-6-carbonitrile (190 mg, 805.5 µmol, 65 %) as a light yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.72 (d, *J*=1.5 Hz, 1H), 8.04 (d, *J*=1.5 Hz, 1H), 4.09 (s, 3H), 2.69 (s, 3H).

Step 4: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine-6-carboximidamide.



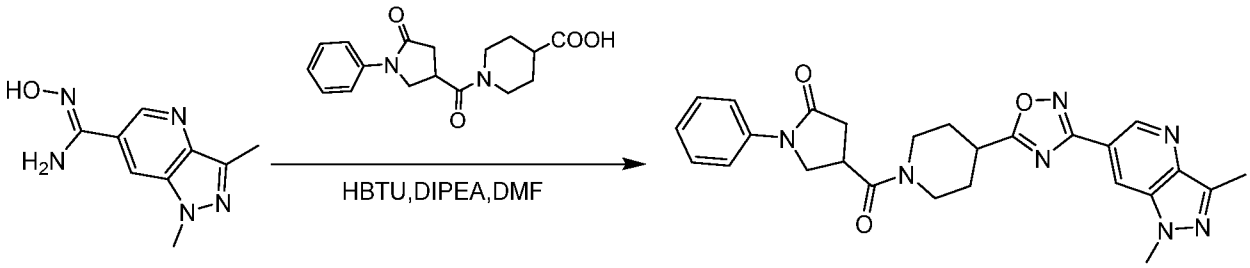
To a stirred solution of 1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine-6-carbonitrile (170 mg, 987 µmol) in ethanol (2 mL) was added hydroxylamine hydrochloride (137 mg, 1.97 mmol), triethylamine (199 mg, 1.97 mmol, 273 µL) and water (200 µL). The reaction mixture was then stirred at 80 °C for 2 h. and concentrated under reduced pressure. The residue was diluted with water (5 mL). The resulting solid was filtered to give (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine-6-carboximidamide (160 mg, 779.7 µmol, 79 %) isolated as a light yellow solid, and used for the next step without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.82 (d, *J*=1.8 Hz, 1H), 8.29 (d, *J*=2.0 Hz, 1H), 6.07 (br s, 2H), 4.00 (s, 3H), 2.51 (s, 3H).

Step 5: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



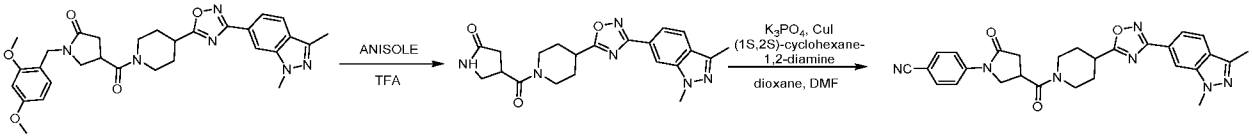
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (150 mg, 516.69 µmol) in N,N-dimethylformamide (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (215 mg, 568 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (200 mg, 1.55 mmol, 270 µL) and (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine-6-carboximidamide (106 mg, 516.69 µmol). The reaction mixture was stirred at 25 °C for 1 h, and then warmed to 110 °C for 1 h. The reaction mixture was concentrated under vacuum and the resulting residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-45%,12min) to give N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (116 mg, 252.7 µmol, 49 %) isolated as a brown solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.05 (d, *J*=1.8 Hz, 1H), 8.64 (d, *J*=1.8 Hz, 1H), 8.61 - 8.54 (m, 1H), 7.88 (br d, *J*=7.1 Hz, 2H), 7.57 - 7.45 (m, 3H), 4.35 (br d, *J*=13.0 Hz, 1H), 4.19 (br t, *J*=5.6 Hz, 2H), 4.10 (s, 3H), 4.01 (br d, *J*=13.2 Hz, 1H), 3.53 (br t, *J*=10.9 Hz, 1H), 3.58 - 3.48 (m, 1H), 3.32 - 3.24 (m, 1H), 2.96 (br t, *J*=11.8 Hz, 1H), 2.56 (s, 3H), 2.18 (br t, *J*=13.7 Hz, 2H), 1.88 (br d, *J*=10.1 Hz, 1H), 1.81 - 1.57 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 460.3.

Example 138: 4-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.

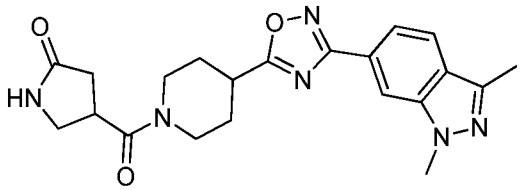


To a stirred solution of 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (150 mg, 474 µmol) in N,N-dimethylformamide (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (197 mg, 521.58 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (183 mg, 1.42 mmol, 248 µL) and (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-b]pyridine-6-carboximidamide (97 mg, 474 µmol). The reaction mixture was stirred at 25 °C for 1 h and then warmed to 110 °C for 1 h. The reaction mixture was concentrated under vacuum and the resulting residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12min) to give 4-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (121 mg, 249 µmol, 52 %) isolated as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.64 (br s, 1H), 7.66 (br d, *J*=8.2 Hz, 2H), 7.41 - 7.34 (m, 2H), 7.17 - 7.11 (m, 1H), 4.39 (br d, *J*=13.5 Hz, 1H), 4.10 (s, 3H), 4.06 (br d, *J*=9.0 Hz, 2H), 4.00 - 3.93 (m, 1H), 3.80 - 3.71 (m, 1H), 3.52 (br t, *J*=10.9 Hz, 1H), 3.40 - 3.34 (m, 1H), 3.03 - 2.92 (m, 1H), 2.85 - 2.71 (m, 2H), 2.56 (s, 3H), 2.19 (t, *J*=14.3 Hz, 2H), 1.95 - 1.82 (m, 1H), 1.80-1.70 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 486.3.

Example 139: 4-[4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-2-oxo-pyrrolidin-1-yl]benzonitrile.

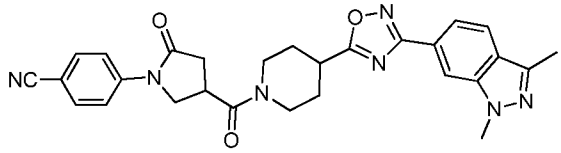


Step 1: Preparation of 4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one.



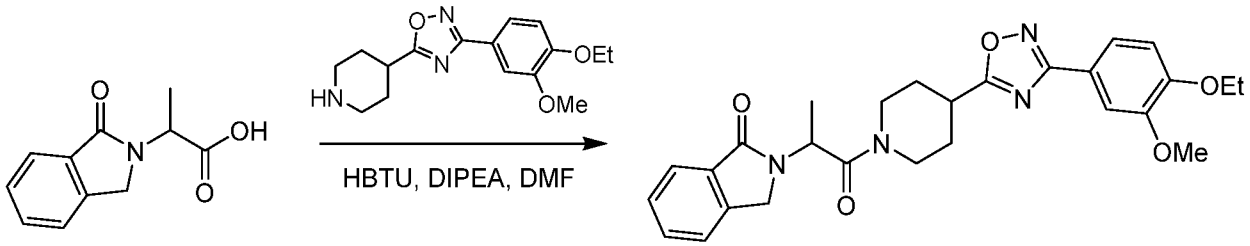
A mixture of 1-[(2,4-dimethoxyphenyl)methyl]-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one (350 mg, 626.53 µmol), anisole (135 mg, 1.25 mmol, 135 µL) in trifluoroacetic acid (5 mL) was degassed and purged with nitrogen three times. The reaction mixture was stirred at 80 °C for 2 h under a nitrogen atmosphere and then concentrated under reduced pressure to to provide the crude product (500 mg) isolated as a yellow oil and used for the next step without further purification.

Step 2: Preparation of 4-[4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-2-oxo-pyrrolidin-1-yl]benzonitrile.

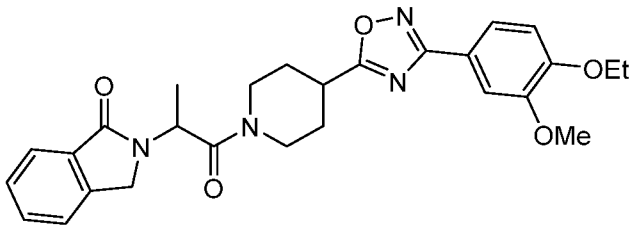


A mixture of 4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one (200 mg, 489.66 µmol), 4-iodobenzonitrile (112 mg, 489.66 µmol), potassium phosphate tribasic (187 mg, 881 µmol), copper iodide (18 mg, 97.93 µmol) and (1S,2S)-cyclohexane-1,2-diamine (55 mg, 489.66 µmol, 60 µL) in dioxane (1 mL) and N,N-dimethylformamide (1 mL) was degassed and purged with nitrogen three times. The mixture was stirred at 110 °C for 16 h under a nitrogen atmosphere. After the reaction cooled to 20 °C, water (10 mL) was added to the mixture which was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give the crude product further purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 15%-40%,12min). The title compound (4-[4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-2-oxo-pyrrolidin-1-yl]benzonitrile) was isolated as a pale yellow solid (17 mg, 34 µmol, 7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.87 - 7.72 (m, 4H), 7.67 (d, *J*=8.8 Hz, 2H), 4.63 - 4.47 (m, 1H), 4.36 (dd, *J*=7.1, 9.5 Hz, 1H), 4.09 (s, 3H), 4.03 - 3.93 (m, 2H), 3.62 (m, 1H), 3.48 - 3.32 (m, 2H), 3.20 - 3.04 (m, 1H), 3.02 - 2.88 (m, 2H), 2.61 (s, 3H), 2.30 (br t, *J*=14.4 Hz, 2H), 2.10 - 1.96 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 510.3.

Example 140: 2-[2-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]isoindolin-1-one.



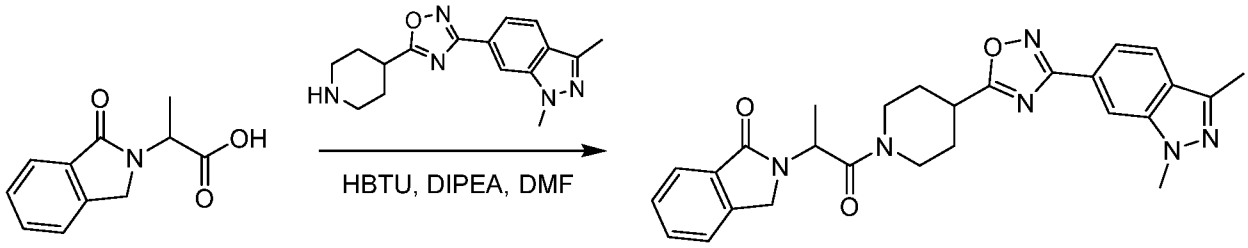
Step 1: Preparation of 2-[2-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]isoindolin-1-one.



To a stirred solution of 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (130 mg, 382.56 µmol, 1.00 eq, hydrochloric acid) in N,N-dimethylformamide (2 mL) was added 2-(1-oxoisoindolin-2-yl)propanoic acid (78 mg, 382.56 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium

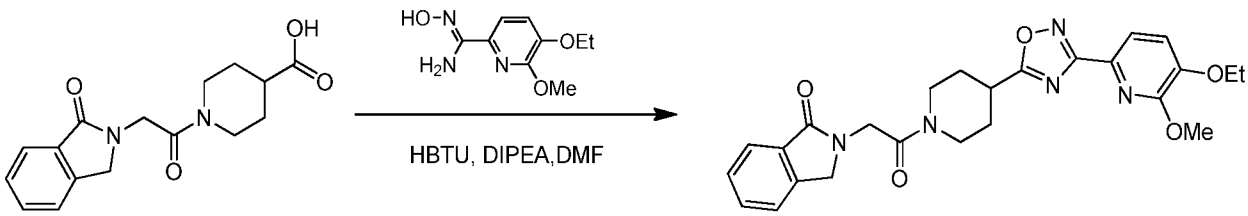
hexafluorophosphate) (174 mg, 459 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (148 mg, 1.15 mmol, 200 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under vacuum and the residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12min) to give 2-[2-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]isoindolin-1-one (132 mg, 266 µmol, 70 %), isolated as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (br t, *J*=6.2 Hz, 1H), 7.69 - 7.43 (m, 5H), 6.93 (dd, *J*=8.4, 15.4 Hz, 1H), 5.55 (q, *J*=6.8 Hz, 1H), 4.57 - 4.36 (m, 3H), 4.29 - 4.11 (m, 3H), 3.95 (d, *J*=13.5 Hz, 3H), 3.42 - 3.19 (m, 2H), 3.14 - 3.00 (m, 1H), 2.16 (br dd, *J*=4.4, 8.8 Hz, 2H), 2.06 - 1.67 (m, 2H), 1.54 - 1.47 (m, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 491.1.

Example 141: 2-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]isoindolin-1-one



To a stirred solution of 2-(1-oxoisoindolin-2-yl)propanoic acid (79 mg, 389 µmol) in N,N-dimethylformamide (2 mL) was added 3-(1,3-dimethylindazol-6-yl)-5-(4-piperidyl)-1,2,4-oxadiazole (130 mg, 389 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (177 mg, 467 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (150 mg, 1.17 mmol, 204 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under vacuum and the residue was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12min) to give 2-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]isoindolin-1-one (118 mg, 243.5 µmol, 63 %) isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 - 8.01 (m, 1H), 7.90 - 7.67 (m, 3H), 7.60 - 7.44 (m, 3H), 5.56 (q, *J*=6.6 Hz, 1H), 4.58 - 4.40 (m, 3H), 4.27 (br t, *J*=13.7 Hz, 1H), 4.07 (d, *J*=9.9 Hz, 3H), 3.45 - 3.24 (m, 2H), 3.14 - 3.03 (m, 1H), 2.59 (d, *J*=6.6 Hz, 3H), 2.21 (br d, *J*=12.8 Hz, 2H), 2.10 - 1.70 (m, 2H), 1.52 (br dd, *J*=4.3, 6.3 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 485.1.

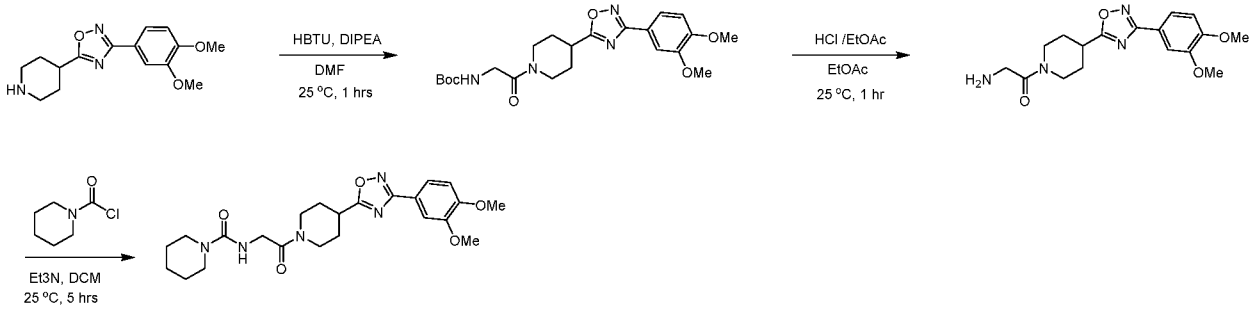
Example 142: 2-(2-(4-(3-(5-ethoxy-6-methoxypyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one



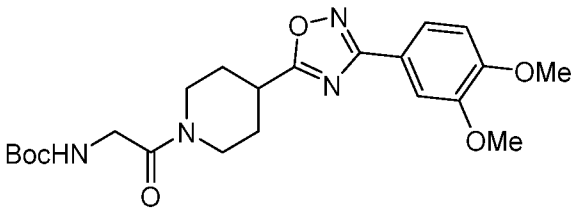
Example 142 was synthesized according to the synthetic procedure reported for the preparation of Example 147. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.87 (d, J=7.5 Hz, 1H), 7.67 (d, J=8.3 Hz, 1H), 7.58 - 7.53 (m, 1H), 7.47 (t, J=6.8 Hz, 2H), 7.10 (d, J=7.9 Hz, 1H), 4.58 (d, J=5.7 Hz, 2H), 4.52 (s,

1H), 4.48 - 4.41 (m, 2H), 4.19 - 4.12 (m, 5H), 4.04 (s, 1H), 3.44 - 3.26 (m, 2H), 3.05 (br t, J=11.0 Hz, 1H), 2.26 - 2.13 (m, 2H), 1.96 (br dd, J=10.1, 19.7 Hz, 2H), 1.52 (t, J=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$:478.1.

Example 143: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]piperidine-1-carboxamide

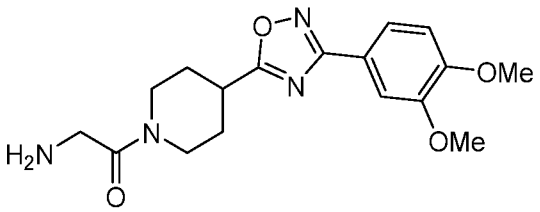


Step 1: Preparation of tert-butyl N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]carbamate.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole hydrochloride (1.00 g, 3.07 mmol, 1.00 *eq*) and 2-(tert-butoxycarbonylamino) acetic acid (537 mg, 3.07 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.16 g, 3.07 mmol) in N,N-dimethylformamide (10.00 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (793 mg, 6.14 mmol, 1.07 mL) at 25 ℃. The mixture was then stirred at 25 ℃ for 1h. The mixture was poured into water (20 mL) and extracted with ethyl acetate (20 mL x 3). The organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to provide the crude product further purified by chromatography (silica, petroleum ether / ethyl acetate=100/1 to 50:1to 1:1). The title compound (tert-butyl N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]carbamate)was isolated as a pale yellow oil (1.70 g, crude) (contained some residual ethyl acetate and dimethylformamide, and was used without further purification).

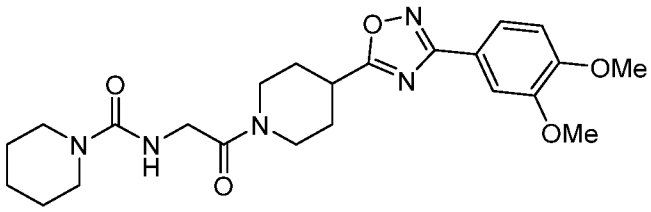
Step 2: 2-amino-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone.



To a stirred solution of tert-butyl N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]carbamate (800 mg, 1.79 mmol) in ethyl acetate (5.00 mL) was added a 4M

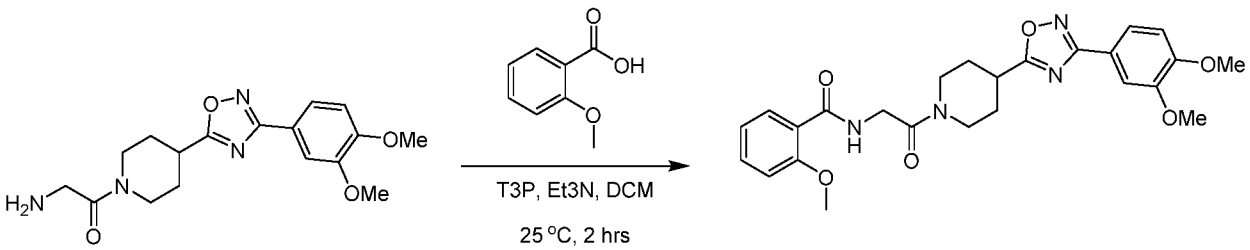
hydrochloric acid in ethyl acetate (15.00 mL). The mixture was then stirred at 25 °C for1 h, and then concentrated under vacuum to give 2-amino-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone hydrochloride (660 mg, crude), isolated as a white solid and used for the next step without further purification.

Step 3: Preparation of N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]piperidine-1-carboxamide.



To a stirred solution of 2-amino-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (200 mg, 522 µmol) and piperidine-1-carbonyl chloride (77 mg, 522 µmol, 65 µL) in dichloromethane (3.00 mL) was added triethylamine (158 mg, 1.57 mmol, 217 µL) at 25 °C. The mixture was then stirred at 25 °C for 5 h. The reaction mixture was poured into 5mL water and extracted with dichloromethane (5 mL x 3). The combined organic extracts were concentrated under vacuum, dissolved in N,N-dimethylformamide (3 mL)and purified by chromatography (Boston Green ODS 150x30 5µm;mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-70%,11.5min to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]piperidine-1-carboxamide (113 mg, 248 µmol, 48 %) isolated as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (dd, *J*=1.8, 8.3 Hz, 1H), 7.56 (d, *J*=1.8 Hz, 1H), 6.95 (d, *J*=8.8 Hz, 1H), 5.57 (br s, 1H), 4.46 (br d, *J*=13.6 Hz, 1H), 4.10 (d, *J*=3.5 Hz, 2H), 3.95 (d, *J*=7.5 Hz, 6H), 3.86 (br d, *J*=14.0 Hz, 1H), 3.40 - 3.35 (m, 4H), 3.32 - 3.23 (m, 2H), 3.08 (br t, *J*=11.0 Hz, 1H), 2.25 - 2.15 (m, 2H), 2.03 - 1.88 (m, 2H), 1.62 - 1.51 (m, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 458.1.

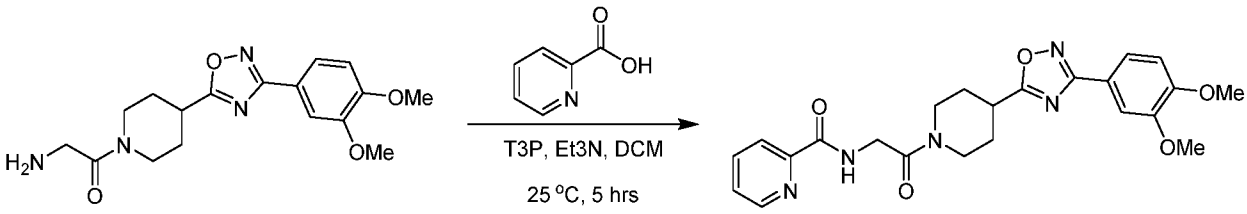
Example 144: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-2-methoxy-benzamide.



To a stirred solution of 2-amino-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone hydrochloride (200 mg, 522 µmol) and 2-methoxybenzoic acid (79 mg, 522 µmol) in dichloromethane (3.00 mL) was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (661.8 mg,1.04 mmol, 681.51 µL, 50% purity) and triethylamine (158 mg, 1.57 mmol, 217 µL) at 25 °C. The mixture was then stirred at 25 °C for 5 h. The reaction mixture was poured into water (5mL) and extracted with dichloromethane (5 mL x 3). The combined organic extracts were concentrated under vacuum. The resulting residue, dissolved in dimethylsulphoxide (3mL), was purified by

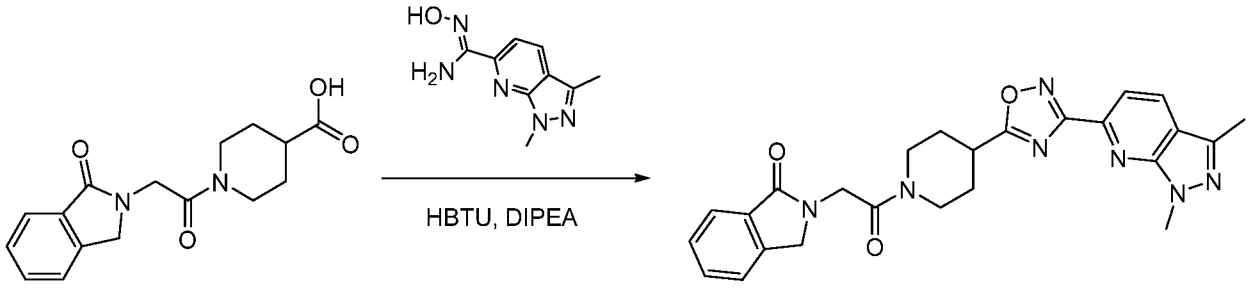
chromatography (Boston Green ODS 150*30mm 5μm;mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 42%-72%,11.5 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-2-methoxy-benzamide (83 mg, 169.3 μmol, 32 %) isolated as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.01 (br s, 1H), 8.21 (dd, *J*=1.8, 7.9 Hz, 1H), 7.68 (dd, *J*=2.2, 8.3 Hz, 1H), 7.56 (d, *J*=1.8 Hz, 1H), 7.49 - 7.43 (m, 1H), 7.11 - 6.93 (m, 3H), 4.51 (br d, *J*=13.6 Hz, 1H), 4.36 (d, *J*=3.9 Hz, 2H), 4.04 (s, 3H), 3.95 (t, *J*=7.9 Hz, 7H), 3.38 - 3.26 (m, 2H), 3.13 (br t, *J*=11.0 Hz, 1H), 2.28 - 2.17 (d, 2H), 2.07 - 1.91 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 481.1.

Example 145: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]pyridine-2-carboxamide.



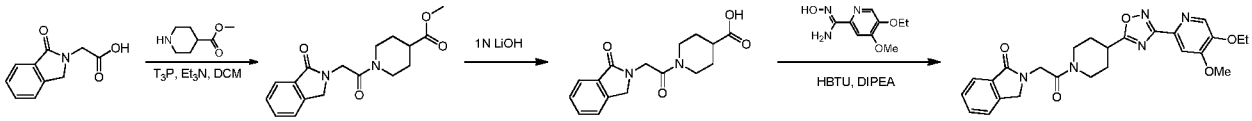
To a stirred solution of 2-amino-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (200 mg, 522 μmol,1.00 *eq*, HCl) and pyridine-2-carboxylic acid (64 mg, 522 μmol) in dichloromethane (3.00 mL) was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (661.81 mg,1.04 mmol, 681.51 μL, 50% purity, 2eq) and triethylamine (158 mg, 1.57 mmol, 217 μL) at 25 ℃, then the mixture was stirred at 25 ℃ for 5 h. The reaction mixture was poured into water (5mL) and extracted with dichloromethane (5 mL x 3). The combined organic extracts were concentrated under vacuum. The resulting residue, dissolved in dimethylsulphoxide (3mL), was purified by prep-HPLC (Boston Green ODS 150x30mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,11.5 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]pyridine-2-carboxamide (85 mg, 182.18 μmol, 35 %) isolated as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.91 (br s, 1H), 8.61 (d, *J*=3.9 Hz, 1H), 8.17 (d, *J*=7.9 Hz, 1H), 7.84 (dt, *J*=1.8, 7.7 Hz, 1H), 7.68 (dd, *J*=1.8, 8.3 Hz, 1H), 7.56 (d, *J*=1.8 Hz, 1H), 7.46 - 7.40 (dd, 1H), 6.95 (d, *J*=8.3 Hz, 1H), 4.53 (br d, *J*=13.6 Hz, 1H), 4.33 (d, *J*=4.4 Hz, 2H), 3.95 (d, *J*=7.9 Hz, 6H), 3.91 (br s, 1H), 3.39 - 3.26 (m, 2H), 3.12 (br t, *J*=11.0 Hz, 1H), 2.29 - 2.18 (t, 2H), 2.07 - 1.91 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 452.1.

Example 146: 2-[2-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]isoindolin-1-one.

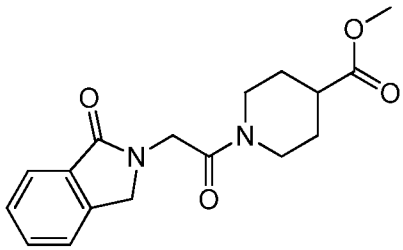


Example 146 was synthesized according to the synthetic procedure reported for the preparation of Example 147. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.11 (d, J=8.4 Hz, 1H), 7.89 (d, J=8.2 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.47 - 7.41 (m, 2H), 4.60 - 4.41 (m, 5H), 4.16 (s, 3H), 4.12 - 4.05 (m, 1H), 3.41 - 3.31 (m, 2H), 3.06 - 2.98 (m, 1H), 2.62 - 2.57 (m, 3H), 2.25 (br t, J=14.6 Hz, 2H), 2.05 - 1.94 (m, 2H); LCMS(ESI) m/z: $[M+H]^+$:472.3.

Example 147: 2-[2-[4-[3-(5-ethoxy-4-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]isoindolin-1-one.

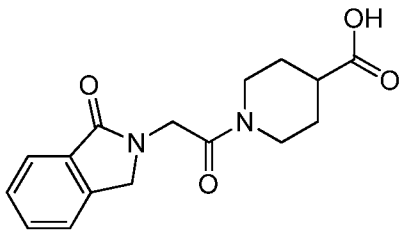


Step 1: methyl 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylate.



A mixture of 2-(1-oxoisoindolin-2-yl)acetic acid (3.0 g, 15.69 mmol), methyl piperidine-4-carboxylate (2.47 g, 17.26 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (12.98 g, 20.40 mmol, 12.13 mL, 50% purity) and triethylamine (31.76 g, 313.80 mmol, 43.51 mL) in dichloromethane (60 mL), was stirred at 20 ℃ for 16 h. The reaction mixture was then diluted with water (20 mL) and extracted with dichloromethane (60 mL). The organic layers were combined, washed with saturated aqueous sodium chloride solution (30 mL x 2), dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure to give the crude product further purified by chromatography (silica, petroleum ether / ethyl acetate=1:2). The title compound methyl 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylate was isolated as a yellow solid (4.30 g, 13.6 mmol, 87 %).

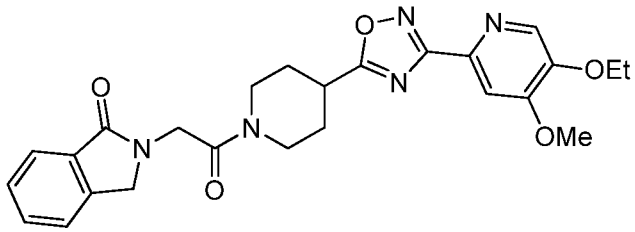
Step 2: Preparation of 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylic acid.



A mixture of methyl 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylate (4.30 g, 13.59 mmol), Lithium hydroxide monohydrate (1 M, 13.59 mL) in tetrahydrofuran (50 mL) was stirred at 20 ℃ for 1 h, and then acidified to pH 3 by addition of a 1M aqueous hydrochloric acid solution. The mixture was extracted with dichloromethane 20 mL. The organic layers were combined, washed with saturated aqueous sodium chloride solution (25 mL x 2), dried over anhydrous sodium sulfate, filtered and

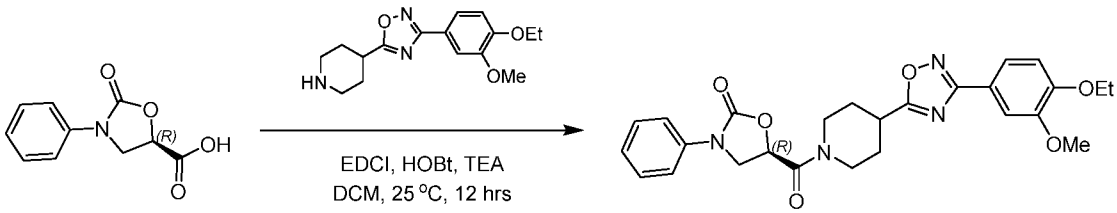
concentrated under reduced pressure to give 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylic acid (2.50 g, 8.27 mmol, 60.85 %) isolated as a white solid, and used for the next step without further purification.

Step 3: 2-[2-[4-[3-(5-ethoxy-4-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]isoindolin-1-one.



A mixture of 1-[2-(1-oxoisoindolin-2-yl)acetyl]piperidine-4-carboxylic acid (150 mg, 496 µmol), 5-ethoxy-N'-hydroxy-4-methoxy-pyridine-2-carboxamidine (125 mg, 595 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (282 mg, 744 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (192 mg, 1.49 mmol, 259 µL) in N,N-dimethylformamide (2 mL) was stirred at 20 °C for 5 h, and at 110°C for 1h. The mixture was then cooled to room temperature and concentrated under vacuum to give a residue purified by chromatography (Boston Green ODS 150x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-45%,11.5min). The title compound 2-[2-[4-[3-(5-ethoxy-4-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]isoindolin-1-one was isolated as a white solid (76 mg, 160 µmol, 32 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.26 (s, 1H), 7.88 - 7.82 (m, 1H), 7.62 (s, 1H), 7.56 - 7.52 (m, 1H), 7.48 - 7.43 (m, 2H), 4.56 (d, J=9.3 Hz, 2H), 4.52 - 4.40 (m, 3H), 4.24 (q, J=7.1 Hz, 2H), 4.07 (br d, J=13.7 Hz, 1H), 4.00 (s, 3H), 3.40 - 3.26 (m, 2H), 3.05 - 2.97 (m, 1H), 2.27 - 2.16 (m, 2H), 2.07 - 1.93 (m, 2H), 1.50 (t, J=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 478.3.

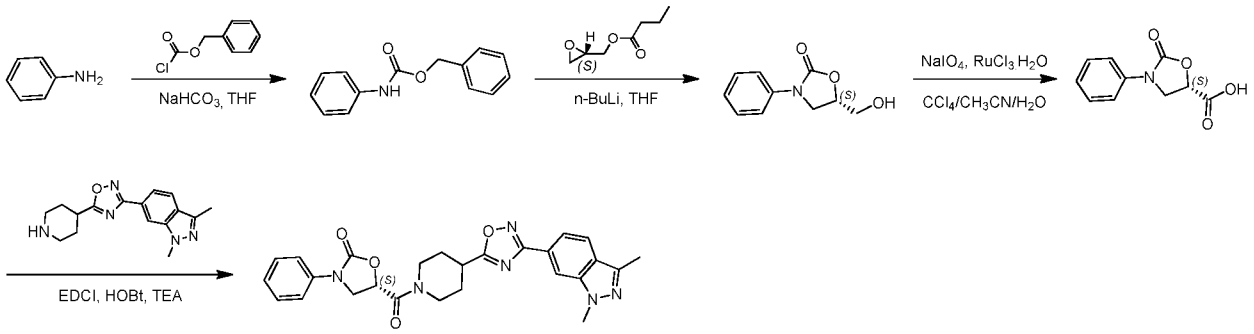
Example 148: (R)-5-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-3-phenyloxazolidin-2-one.



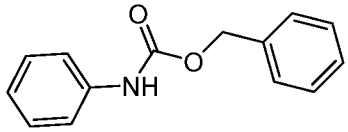
To a stirred solution of (R)-2-oxo-3-phenyloxazolidine-5-carboxylic acid (100 mg, 482.67 µmol) in dichloromethane (2 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (111 mg, 579 µmol), HOBt (78 mg, 579 µmol), triethylamine (146 mg, 1.45 mmol, 200 µL) and 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole hydrochloride (164 mg, 482.67 µmol). The reaction mixture was stirred at 25 °C for 12 h and then concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Boston Green ODS 150x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-75%,11.5min) to give (R)-5-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-3-phenyloxazolidin-2-one (139 mg, 280 µmol, 58 %) as a pale yellow solid. ^{1}H

NMR (400MHz, CHLOROFORM-d) δ 7.67 (d, *J*=8.3 Hz, 1H), 7.59 - 7.55 (m, 3H), 7.40 (t, *J*=7.7 Hz, 2H), 7.17 (t, *J*=6.9 Hz, 1H), 6.95 (dd, *J*=1.1, 8.6 Hz, 1H), 5.25 (ddd, *J*=3.1, 6.2, 9.1 Hz, 1H), 4.81 (dd, *J*=6.8, 8.6 Hz, 1H), 4.58 (br d, *J*=14.0 Hz, 0.5H), 4.37 - 4.21 (m, 1H), 4.17 (q, *J*=7.0 Hz, 2H), 4.07 (dt, *J*=2.6, 9.0 Hz, 1.5H), 3.96 (d, *J*=2.2 Hz, 3H), 3.59 (ddd, *J*=3.3, 10.3, 14.0 Hz, 0.5H), 3.41 - 3.17 (m, 2H), 3.09 - 3.00 (m, 0.5H), 2.34 - 1.95 (m, 4H), 1.54 - 1.47 (m, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 493.3.

Example 149: (S)-5-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-3-phenyloxazolidin-2-one.

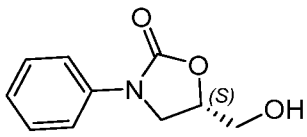


Step 1: Preparation of benzyl phenylcarbamate.



To a stirred solution of aniline (5.0 g, 53.69 mmol, 4.90 mL) in tetrahydrofuran (100 mL) at 0 °C was added saturated aqueous sodium hydrogen carbonate (4.96 g, 59.06 mmol, 2.30 mL) followed by benzyl chloroformate (10.07 g, 59.06 mmol, 8.39 mL). The reaction mixture was stirred for 0.25h at 0 °C, warmed to 25 °C and stirring was continued for 0.75 h at 25 °C. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were dried over anhydrous anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide benzyl phenylcarbamate (12.98 g, 53.7 mmol, 100 %) isolated as a white solid, and used for the next step without further purification ^{1}H NMR (400MHz, DMSO-d_6) δ 9.76 (s, 1H), 7.53 - 7.23 (m, 9H), 6.99 (t, *J*=7.1 Hz, 1H), 5.15 (s, 2H).

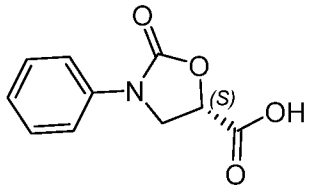
Step 2: Preparation of (S)-5-(hydroxymethyl)-3-phenyloxazolidin-2-one.



A solution of benzyl phenylcarbamate (3.0 g, 13.20 mmol) in dry tetrahydrofuran (30 mL) was cooled to -78 °C under dry nitrogen atmosphere. A solution of n-butyl lithium in tetrahydrofuran (2.5 M, 7.92 mL) was slowly added to the reaction mixture which was stirred for 0.75h at -78 °C. A solution of (S)-oxiran-2-ylmethyl butyrate (2.28 g, 15.84 mmol) in dry tetrahydrofuran (10 mL) was slowly added to the mixture which was stirred at -78 °C for 2 h and then slowly warmed to 25 °C. Stirring was continued for 12h at room temperature and the reaction mixture was quenched by the addition of saturated aqueous

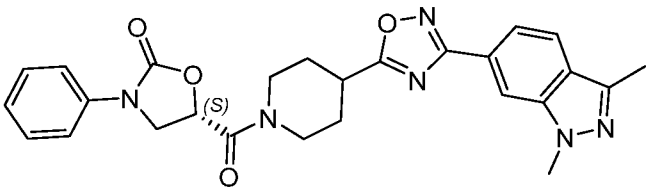
ammonium chloride (30 mL). Ethyl acetate (30 mL) and water (30 mL) were added to the mixture and the layers were separated. The aqueous layer was further extracted with ethyl acetate (3 X30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give the crude product purified by chromatography (silica, petroleum ether : ethyl acetate = 1:1). The title compound (S)-5-(hydroxymethyl)-3-phenyloxazolidin-2-one was isolated as a white solid (1.70 g, 8.80 mmol, 67 %). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.57 (d, *J*=7.8 Hz, 2H), 7.43 - 7.31 (m, 2H), 7.14 (t, *J*=7.2 Hz, 1H), 4.78 - 4.71 (m, 1H), 4.13 (t, *J*=9.0 Hz, 1H), 3.94 (dd, *J*=6.6, 8.8 Hz, 1H), 3.85 (dd, *J*=3.4, 12.5 Hz, 1H), 3.70 (dd, *J*=4.2, 12.6 Hz, 1H).

Step 3: Preparation of (S)-2-oxo-3-phenyloxazolidine-5-carboxylic acid.



To an ice-cooled solution of $NaIO_4$ (3.88 g, 18.13 mmol, 1.01 mL) in water (30 mL) was added a solution of (S)-5-(hydroxymethyl)-3-phenyloxazolidin-2-one (1.0 g, 5.18 mmol) in a mixture of acetonitrile (20 mL) and carbon tetrachloride (20 mL). Solid $RuCl_3.H_2O$ (58 mg, 259 µmol) was added to the reaction mixture which was stirred at 0 °C for 0.5 h, warmed to 25 °C and then stirred at 25 °C for an additional 12 h. The suspension was then filtered and the filtered solid was washed thoroughly with dichloromethane (50 mL). The filtrate was concentrated under reduced pressure to provide a residue further dissolved in ethyl acetate (50mL). The organic solution was washed with saturated aqueous sodium carbonate (2 X 20 mL). The organic layer was discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 X 30 mL). The combined organic phases were dried over anhydrous anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product (850 mg) crude. 500 mg of this crude product was purified by prep-HPLC (column: Luna C18 150x25mm 5µm; mobile phase: [water (0.225%FA)-acetonitrile]; B%: 30%-50%,12min) to give 150 mg of (S)-2-oxo-3-phenyloxazolidine-5-carboxylic acid as an off-white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.57 - 7.45 (m, 2H), 7.44 - 7.34 (m, 2H), 7.24 - 7.10 (m, 1H), 5.12 (dd, *J*=5.3, 9.8 Hz, 1H), 4.37 (t, *J*=9.6 Hz, 1H), 4.19 (dd, *J*=5.3, 9.4 Hz, 1H).

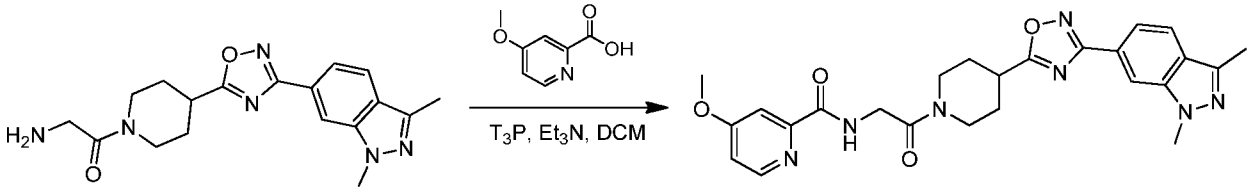
Step 4: Preparation of (S)-5-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-3-phenyloxazolidin-2-one.



To a stirred solution of (S)-2-oxo-3-phenyloxazolidine-5-carboxylic acid (80 mg, 386 µmol) in hydroxybenzotriazole (62 mg, 463 µmol), triethylamine (117 mg, 1.16 mmol, 160 µL) and 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperidin-4-yl)-1,2,4-oxadiazole, hydrochloride (128 mg, 386 µmol, hydrochloric acid).

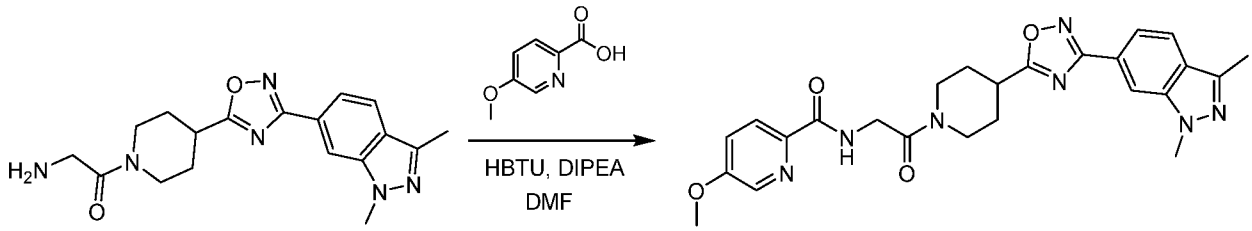
The reaction mixture was stirred at 25 °C for 12 h and was then concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Boston Green ODS 150x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 43%-73%,11.5min) to give (S)-5-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-3-phenyloxazolidin-2-one (82 mg, 168.7 µmol, 44 %) isolated as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.11 (d, *J*=7.9 Hz, 1H), 7.84 (d, *J*=8.8 Hz, 1H), 7.74 (dd, *J*=3.5, 8.3 Hz, 1H), 7.58 (d, *J*=8.3 Hz, 2H), 7.41 (t, *J*=7.7 Hz, 2H), 7.20 - 7.16 (m, 1H), 5.26 (dd, *J*=7.5, 8.3 Hz, 1H), 4.83 (dd, *J*=6.4, 9.0 Hz, 1H), 4.66 - 4.57 (m, 0.5H), 4.38 - 4.27 (m, 1H), 4.09 (d, *J*=3.1 Hz, 4.5H), 3.66 - 3.59 (m, 0.5H), 3.45 - 3.32 (m, 2H), 3.08 (br t, *J*=11.2 Hz, 0.5H), 2.60 (s, 3H), 2.39 - 2.25 (m, 2H), 2.24 - 1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 487.3.

Example 150: N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-4-methoxy-pyridine-2-carboxamide.



To a stirred solution of 2-amino-1-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (130 mg, 366.81 µmol) in dichloromethane (3 mL) was added 4-methoxypyridine-2-carboxylic acid (56 mg, 366.81 µmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (256 mg, 403 µmol, 239 µL, 50% purity) and triethylamine (111 mg, 1.10 mmol, 152 µL). The mixture was stirred at 20 °C for 1 h and then concentrated under reduced pressure. The resulting residue was purified by chromatography (column: Luna C18 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-60%,10min) to give N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-4-methoxy-pyridine-2-carboxamide (18 mg, 35 µmol, 10 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 8.41 (d, *J*=5.5 Hz, 1H), 8.10 (s, 1H), 7.86 - 7.80 (m, 1H), 7.77 - 7.69 (m, 2H), 6.93 (dd, *J*=2.4, 5.5 Hz, 1H), 4.56 (br d, *J*=14.1 Hz, 1H), 4.34 (d, *J*=4.4 Hz, 2H), 4.08 (s, 3H), 3.96 (br d, *J*=13.9 Hz, 1H), 3.92 (s, 3H), 3.41 - 3.31 (m, 2H), 3.14 (br t, *J*=11.6 Hz, 1H), 2.60 (s, 3H), 2.33 - 2.22 (m, 2H), 2.11 - 1.95 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 490.2.

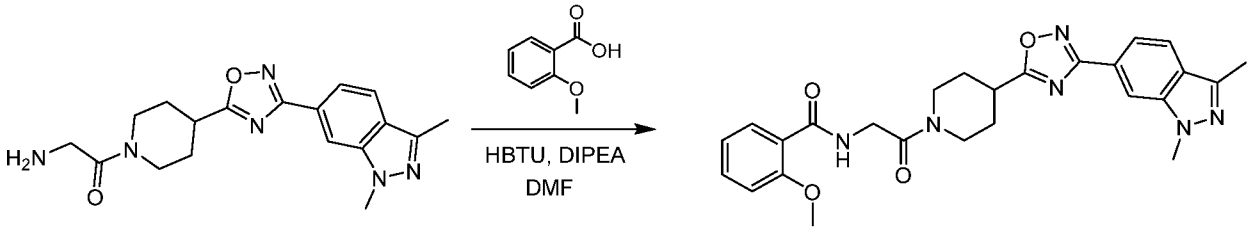
Example 151: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-5-methoxypicolinamide.



Example 151 was synthesized according to a procedure similar to the one described in Example 154. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 8.27 (d, *J*=2.6 Hz, 1H), 8.13 (d, *J*=8.6 Hz, 1H), 8.09 (s, 1H), 7.85 - 7.79 (m, 1H), 7.77 - 7.68 (m, 1H), 7.29 (d, *J*=2.6 Hz, 1H), 4.55 (br d, *J*=13.7 Hz, 1H), 4.33 (d, *J*=4.2 Hz, 2H), 4.08 (s, 3H), 3.96 (br d, *J*=13.9 Hz, 1H), 3.91 (s, 3H), 3.40 - 3.30 (m, 2H), 3.13 (br t,

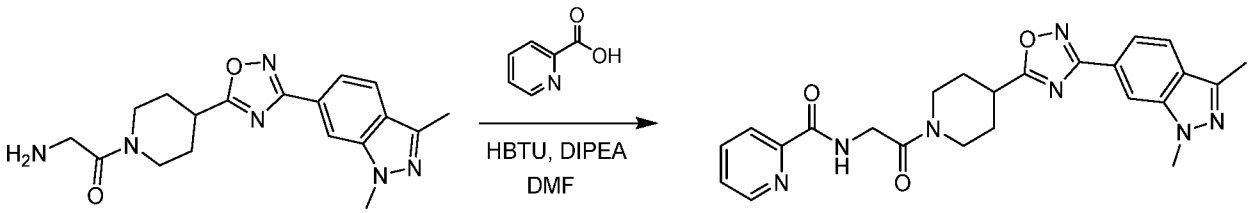
J=10.9 Hz, 1H), 2.60 (s, 3H), 2.27 (br t, *J*=11.8 Hz, 2H), 2.09 - 1.95 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 490.2.

Example 152: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-2-methoxybenzamide.



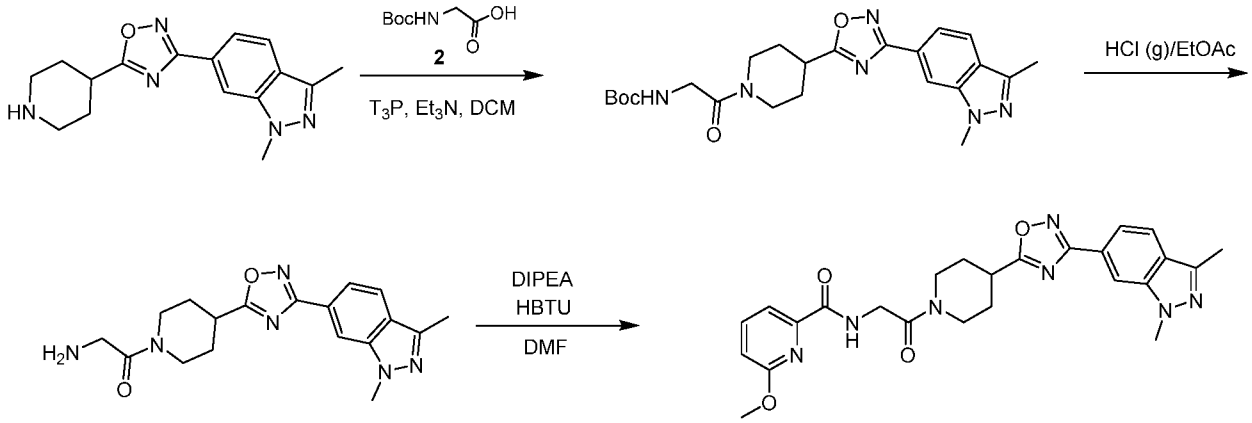
Example 152 was synthesized according to a procedure similar to the one described in Example 154. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (br s, 1H), 8.22 (dd, *J*=1.4, 7.8 Hz, 1H), 8.10 (s, 1H), 7.87 - 7.80 (m, 1H), 7.77 - 7.71 (m, 1H), 7.51 - 7.43 (m, 1H), 7.09 (t, *J*=7.6 Hz, 1H), 7.01 (d, *J*=8.2 Hz, 1H), 4.55 (br d, *J*=13.9 Hz, 1H), 4.38 (d, *J*=4.0 Hz, 2H), 4.08 (s, 3H), 4.05 (s, 3H), 3.96 (br d, *J*=14.1 Hz, 1H), 3.41 - 3.31 (m, 2H), 3.15 (br t, *J*=11.4 Hz, 1H), 2.60 (s, 3H), 2.28 (br t, *J*=10.6 Hz, 2H), 2.10 - 1.96 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 489.3.

Example 153: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)picolinamide.

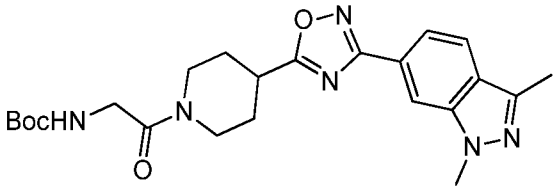


Example 153 was synthesized according to a procedure similar to the one described in Example 154. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 8.63 (d, *J*=4.0 Hz, 1H), 8.19 (d, *J*=7.7 Hz, 1H), 8.10 (s, 1H), 7.89 - 7.80 (m, 2H), 7.76 - 7.71 (m, 1H), 7.47 - 7.41 (m, 1H), 4.56 (br d, *J*=13.7 Hz, 1H), 4.35 (d, *J*=4.4 Hz, 2H), 4.09 (s, 3H), 3.96 (br d, *J*=13.9 Hz, 1H), 3.44 - 3.31 (m, 2H), 3.15 (br t, *J*=10.7 Hz, 1H), 2.60 (s, 3H), 2.34 - 2.23 (m, 2H), 2.11 - 1.95 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 460.2.

Example 154: N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-6-methoxy-pyridine-2-carboxamide.

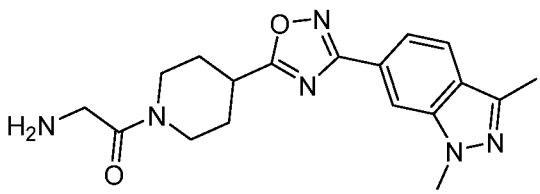


Step 1: Preparation of tert-butyl N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]carbamate.



To a stirred solution of 3-(1,3-dimethylindazol-6-yl)-5-(4-piperidyl)-1,2,4-oxadiazole (1.0 g, 3.00 mmol, 1.00 *eq*, hydrochloric acid salt) in dichloromethane (20 mL) was added 2-(tert-butoxycarbonylamino)acetic acid (525 mg, 3.00 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (2.86 g, 4.50 mmol, 2.68 mL, 50% purity) and triethylamine (1.82 g, 18.00 mmol, 2.49 mL, 6.00 *eq*). The mixture was stirred at 20 °C for 16 h. Water (30 mL) was then added to the reaction mixture which was extracted with dichloromethane (60 mL x 3). The combined organic extracts were washed with saturated aqueous sodium chloride (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide the crude product further purified by chromatography (silica, petroleum ether : ethyl acetate = 20:1 to 1:4). The title compound (tert-butyl N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]carbamate) was isolated as a white solid (1.0 g, 2.20 mmol, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.86 - 7.80 (m, 1H), 7.77 - 7.72 (m, 1H), 5.53 (br s, 1H), 4.50 (br d, *J*=12.3 Hz, 1H), 4.09 (s, 3H), 4.02 (br d, *J*=3.5 Hz, 2H), 3.83 (br d, *J*=12.7 Hz, 1H), 3.38 - 3.23 (m, 2H), 3.10 (br t, *J*=11.6 Hz, 1H), 2.60 (s, 3H), 2.23 (br s, 2H), 2.06 - 1.94 (m, 2H), 1.47 (s, 9H).

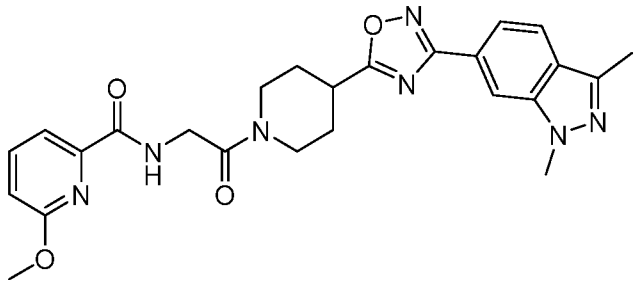
Step 2: Preparation of 2-amino-1-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone.



To a stirred solution of tert-butyl N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]carbamate (980 mg, 2.16 mmol) in ethyl acetate (5 mL) was added a 4M solution of

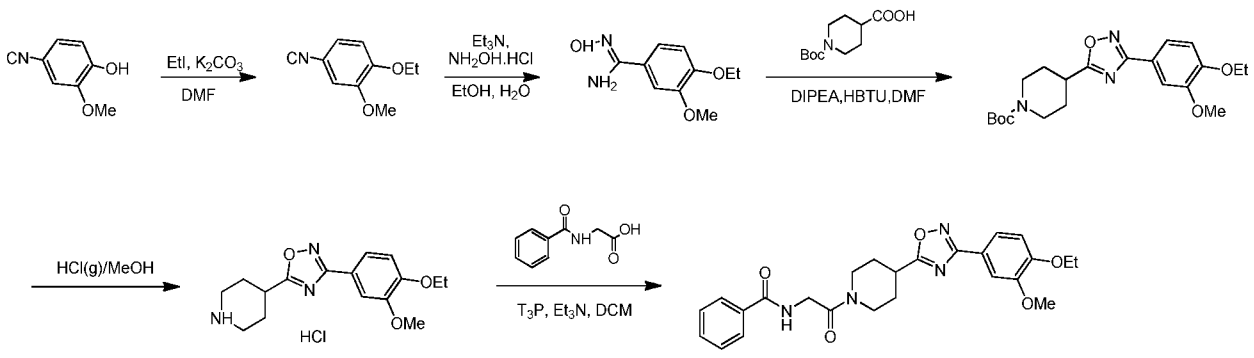
hydrochloric acid in ethyl acetate (50 mL). The mixture was stirred at 20 °C for 0.5 h and then concentrated under reduced pressure to give 2-amino-1-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone, hydrochloride (940 mg, crude)) isolated as a white solid and used for the next step without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.19 (s, 1H), 7.83 (d, *J*=0.9 Hz, 2H), 4.48 (br d, *J*=13.9 Hz, 1H), 4.06 (s, 3H), 4.04 - 3.95 (m, 2H), 3.86 (br d, *J*=13.9 Hz, 1H), 3.53 - 3.43 (m, 1H), 3.38 (br t, *J*=11.5 Hz, 1H), 3.13 (br t, *J*=11.2 Hz, 1H), 2.58 (s, 3H), 2.28 (br t, *J*=9.3 Hz, 2H), 2.01 - 1.84 (m, 2H).

Step 3: Preparation of N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-6-methoxy-pyridine-2-carboxamide.

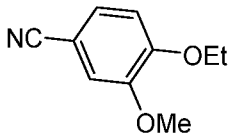


To a stirred solution of 2-amino-1-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (130 mg, 366.81 µmol) in N,N-dimethylformamide (2 mL) was added 6-methoxypyridine-2-carboxylic acid (56 mg, 366.81 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (166 mg, 440 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (142 mg, 1.10 mmol, 192 µL). The mixture was stirred at 20 °C for 1 h and concentrated under reduced pressure. The resulting residue was purified by chromatography (column: Luna C18 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-65%,10min) to give N-[2-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-6-methoxy-pyridine-2-carboxamide (92 mg, 187.6 µmol, 51 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.10 (s, 1H), 7.86 - 7.69 (m, 4H), 6.92 (d, *J*=8.2 Hz, 1H), 4.55 (br d, *J*=13.9 Hz, 1H), 4.34 (d, *J*=4.2 Hz, 2H), 4.08 (s, 3H), 4.05 (s, 3H), 4.01 - 3.92 (m, 1H), 3.43 - 3.32 (m, 2H), 3.17 (br t, *J*=11.1 Hz, 1H), 2.60 (s, 3H), 2.34 - 2.23 (m, 2H), 2.12 - 1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 490.3.

Example 155: N-(2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

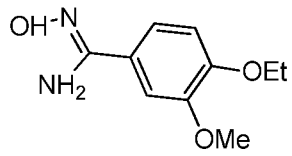


Step 1: Preparation of 4-ethoxy-3-methoxy-benzonitrile.



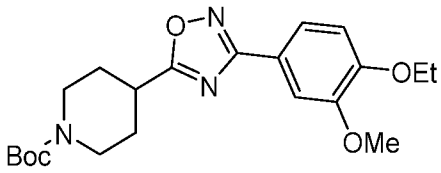
To a 0 °C stirred solution of 4-hydroxy-3-methoxy-benzonitrile (20g, 134.09 mmol) in N,N-dimethylformamide (200 mL) was added iodoethane (25.10 g, 160.91 mmol, 12.87 mL), potassium carbonate (37.07 g, 268.18 mmol). The reaction mixture was stirred at 40 °C for 16 h and then quenched by addition of water (300 mL). The mixture was extracted with ethyl acetate (200mL x 3) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 4-ethoxy-3-methoxy-benzonitrile (25.0 g, crude), isolated as a yellow solid and used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.20 (m, 1H), 7.07 (d, *J*=1.8 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 1H), 4.14 (q, *J*=7.0 Hz, 2H), 3.88 (s, 3H), 1.49 (t, *J*=7.0 Hz, 3H).

Step 2: Preparation of 4-ethoxy-N'-hydroxy-3-methoxy-benzamidine.



To a stirred solution of 4-ethoxy-3-methoxy-benzonitrile (25.0 g, 141.08 mmol) in ethanol (200 mL) was added hydroxylamine hydrochloride (19.61 g, 282.17 mmol), triethylamine (28.55 g, 282.17 mmol, 39.11 mL) and water (20 mL). The mixture was stirred at 80 °C for 2 h and then concentrated under reduced pressure. The resulting residue was diluted with water (30 mL) and filtered to provide 4-ethoxy-N'-hydroxy-3-methoxy-benzamidine isolated as a white solid (24.0 g, 114.2 mmol, 81 %) and used for the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.47 (br s, 1H), 7.25 (d, *J*=2.0 Hz, 1H), 7.20 (dd, *J*=2.0, 8.4 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 1H), 5.75 (br s, 2H), 4.01 (q, *J*=7.0 Hz, 2H), 3.76 (s, 3H), 1.32 (t, *J*=7.0 Hz, 3H).

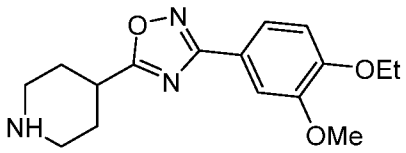
Step 3: Preparation of tert-butyl 4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate.



To a stirred solution of 4-ethoxy-N'-hydroxy-3-methoxy-benzamidine (10.0 g, 47.57 mmol) in N,N-dimethylformamide (100 mL) was added 1-tert-butoxycarbonylpiperidine-4-carboxylic acid (10.91 g, 47.57 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (18.04 g, 47.57 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (18.44 g, 142.71 mmol, 24.92 mL). The mixture was stirred at 20 °C for 16 h and at 110 °C for 1 h. The reaction mixture was then cooled to room temperature, quenched by addition of water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product further was purified by

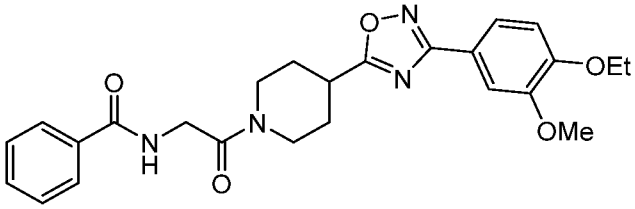
chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 10:1). The title compound, tert-butyl 4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate, was isolated as a yellow solid (13.30 g, 33.0 mmol, 69 %).

Step 4: Preparation of 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole.



To a stirred solution of tert-butyl 4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate (13.30 g, 32.96 mmol) in ethyl acetate (300 mL) was added a 4M solution of hydrochloric acid in methanol (30 mL). The mixture was stirred at 20 °C for 2 h and filtered to give 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole hydrochloride (10.0 g, 29.4 mmol, 89 %), isolated as a white solid and used for the next step without further purification.

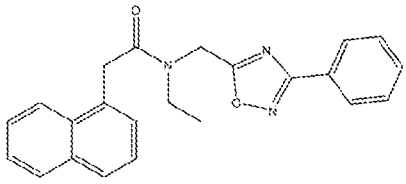
Step 5: Preparation of N-[2-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.



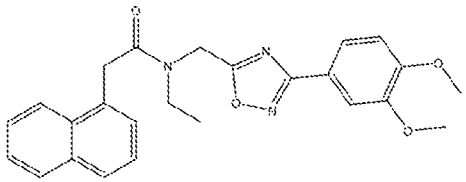
To a stirred solution of 2-benzamidoacetic acid (1.16 g, 6.48 mmol) in dichloromethane (20 mL) was added 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole hydrochloride (2.0 g, 5.89 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (4.87 g, 7.65 mmol, 4.55 mL, 50% in ethyl acetate) and triethylamine (2.38 g, 23.5 mmol, 3.26 mL). The mixture was stirred at 20 °C for 16 h. Water (20 mL) was then added to the mixture which was extracted with dichloromethane (80 mL x 2). The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to give a residue dissolved in with ethyl acetate (40 mL). The organic solution was washed with 1N aqueous hydrochloric acid solution (15 mL x 2), saturated sodium carbonate (15 mL x 2), saturated aqueous sodium chloride solution (15 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. To a solution of the crude product in methyl tert-butyl ether (20 mL) was added petroleum ether (2 mL). The precipitate, formed after 2 h stirring at room temperature, was collected by filtration, washed with methyl tert-butyl ether (5 mL x 2) and dried under reduced pressure to give N-[2-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (1.68 g, 3.60 mmol, 61 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.83 (m, 2H), 7.66 (dd, *J*=1.9, 8.3 Hz, 1H), 7.58 - 7.42 (m, 4H), 7.35 (br s, 1H), 6.95 (d, *J*=8.4 Hz, 1H), 4.50 (td, *J*=3.8, 13.6 Hz, 1H), 4.30 (d, *J*=4.0 Hz, 2H), 4.17 (q, *J*=7.0 Hz, 2H), 3.96 (s, 3H), 3.94 - 3.87 (m, 1H), 3.38 - 3.27 (m, 2H), 3.19 - 3.08 (m, 1H), 2.24 (m, 2H), 2.07 - 1.91 (m, 2H), 1.50 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.2.

Example 156. Characterization Data of Compounds of the Invention

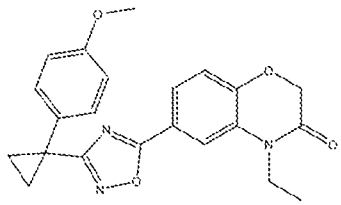
The following compounds were synthesized by methods similar to those described above.



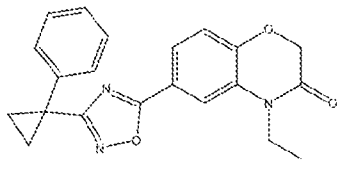
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10-7.71 (m, 5H), 7.65-7.30 (m, 7H), 4.87 (br s, 2H), 4.26 (s, 2H), 3.69 (br s, 2H), 1.23 (br s, 3H); LCMS (ESI) [M+H]+: 372.1.



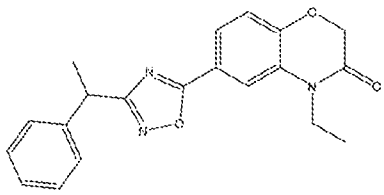
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07-8.00 (m, 1H), 7.99-7.91 (m, 1H), 7.86 (d, J = 6.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.58-7.52 (m, 3H), 7.49 (br s, 2H), 7.20 (d, J = 8.4 Hz, 1H), 4.92 (br s, 2H), 4.32 (s, 2H), 3.91 (d, J = 6.2 Hz, 6H), 3.74 (br s, 2H), 1.28 (br s, 3H); LCMS (ESI) [M+H]+: 432.1.



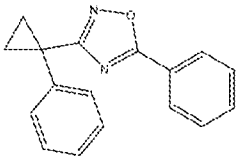
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71-7.59 (m, 1H), 7.33 (br d, J = 8.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.89 (br d, J = 8.6 Hz, 2H), 4.76 (s, 2H), 4.06-3.91 (m, 2H), 3.74 (s, 3H), 1.60-1.49 (m, 2H), 1.34 (br d, J = 2.2 Hz, 2H), 1.16 (br t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 392.2.



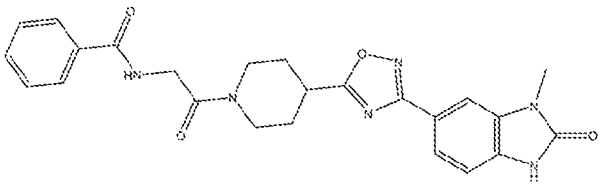
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73-7.63 (m, 2H), 7.44-7.39 (m, 2H), 7.37-7.25 (m, 3H), 7.21-7.15 (m, 1H), 4.84-4.69 (s, 2H), 4.05-3.91 (m, 2H), 1.62-1.54 (m, 2H), 1.43-1.36 (m, 2H), 1.16 (s, 3H); LCMS (ESI) [M+H]+: 362.2.



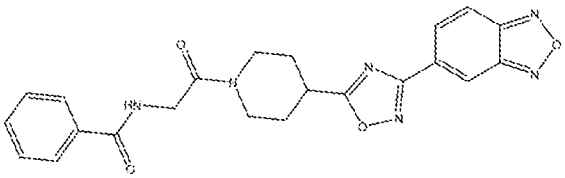
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.71 (dd, J = 1.8, 8.3 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.37-7.31 (m, 2H), 7.27 (t, J = 7.5 Hz, 2H), 7.22-7.16 (m, 2H), 7.00 (d, J = 8.3 Hz, 1H), 4.60 (s, 2H), 4.28 (q, J = 7.2 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 1.69 (d, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); LCMS (ESI) [M+H]+: 350.2.



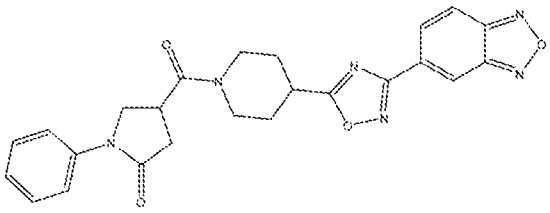
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09-8.11 (m, 2H), 7.51-7.53 (m, 5H), 7.25-7.40 (m, 3H), 1.72-1.74 (t, 2H), 1.43-1.46 (t, 2H); LCMS (ESI) [M+H]+: 263.1.



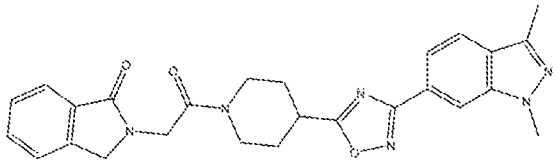
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.06 (br s, 1H), 7.88-7.80 (m, 3H), 7.69 (s, 1H), 7.53-7.44 (m, 3H), 7.40-7.30 (m, 1H), 7.18-7.16 (d, J = 8.4 Hz, 1H), 4.54-4.50 (m, 1H), 4.33-4.32 (d, J = 4.0 Hz, 2H), 3.95-3.91 (m, 1H), 3.49 (s, 3H), 3.39-3.13 (m, 1H), 2.30-2.23 (m, 2H), 2.05-1.98 (m, 2H); LCMS (ESI) [M+H]+: 461.1.



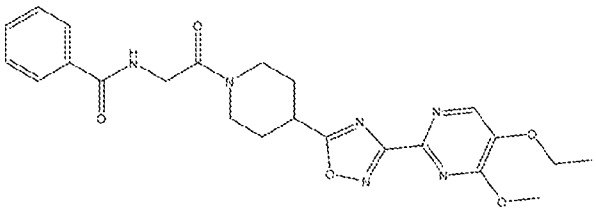
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.64 (t, J = 1.1 Hz, 1H), 8.11 (dd, J = 1.2, 9.4 Hz, 1H), 7.96 (dd, J = 1.0, 9.4 Hz, 1H), 7.87-7.81 (m, 2H), 7.54-7.48 (m, 1H), 7.47-7.41 (m, 2H), 7.31 (br s, 1H), 4.57-4.48 (m, 1H), 4.30 (d, J = 3.7 Hz, 2H), 3.92 (br d, J = 14.1 Hz, 1H), 3.41-3.31 (m, 2H), 3.20-3.09 (m, 1H), 2.27 (dt, J = 3.7, 13.2 Hz, 2H), 2.00 (ddq, J = 4.1, 10.6, 14.4 Hz, 2H); LCMS (ESI) [M+H]+: 433.1.



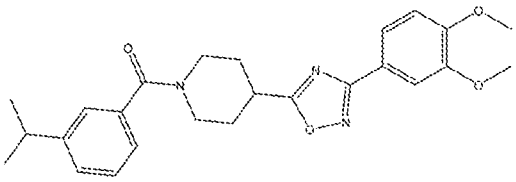
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.63 (s, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.95 (d, J = 9.3 Hz, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.18-7.12 (m, 1H), 4.63-4.43 (m, 1H), 4.30 (br t, J = 7.9 Hz, 1H), 4.06-3.87 (m, 2H), 3.57 (quin, J = 8.6 Hz, 1H), 3.45-3.28 (m, 2H), 3.17-2.75 (m, 3H), 2.36-2.20 (m, 2H), 2.07-1.89 (m, 2H); LCMS (ESI) [M+H]+: 459.2.



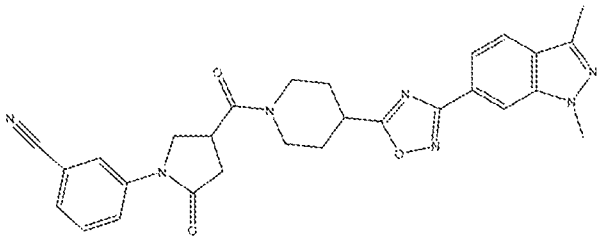
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.14 (s, 1H), 7.77-7.70 (m, 3H), 7.62-7.47 (m, 2H), 7.51-7.46 (m, 1H), 4.64-4.42 (m, 5H), 4.09-4.01 (m, 1H), 4.01 (s, 3H), 3.48-3.37 (m, 2H), 3.06 (br t, J = 11.0 Hz, 1H), 2.53 (s, 3H), 2.32-2.18 (m, 2H), 2.07-1.84 (m, 2H); LCMS (ESI) [M+H]+: 471.3.



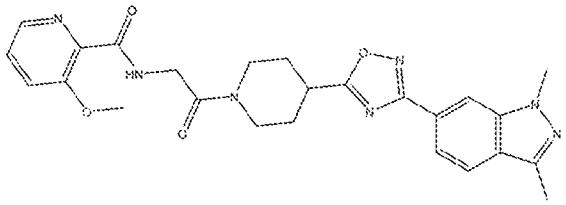
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 7.85 (d, J = 7.0 Hz, 2H), 7.54-7.42 (m, 3H), 7.32 (br s, 1H), 4.51 (br d, J = 13.6 Hz, 1H), 4.29 (t, J = 4.8 Hz, 2H), 4.26-4.17 (m, 5H), 3.90 (br d, J = 14.0 Hz, 1H), 3.42-3.28 (m, 2H), 3.10 (br t, J = 11.0 Hz, 1H), 2.33-2.22 (m, 2H), 2.13-1.95 (m, 2H), 1.52 (t, J = 7.0 Hz, 3H); LCMS (ESI) [M+H]+: 467.3.



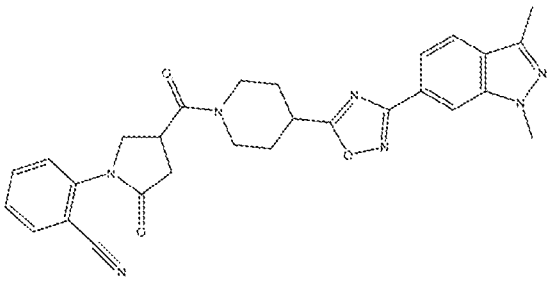
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.68 (dd, J = 1.8, 8.3 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.36-7.27 (m, 3H), 7.24-7.20 (m, 1H), 6.95 (d, J = 8.3 Hz, 1H), 4.76-4.53 (m, 1H), 3.86-3.93 (m, 1H), 3.94-3.96 (d, J = 8.3 Hz, 6H), 3.34-3.14 (m, 2H), 3.34-3.11 (m, 1H), 2.93 (quin, J = 7.0 Hz, 1H), 2.97-2.89 (m, 1H), 2.34-1.88 (m, 4H), 1.26 (d, J = 7.0 Hz, 6H); LCMS (ESI) [M+H]+: 436.2.



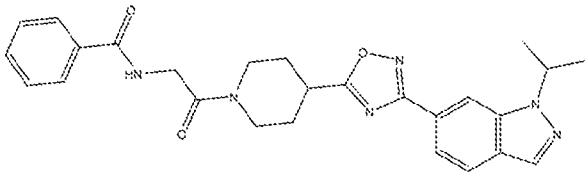
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (d, J = 3.1 Hz, 1H), 8.01-7.88 (m, 2H), 7.87-7.80 (m, 1H), 7.78-7.71 (m, 1H), 7.53-7.42 (m, 2H), 4.63-4.49 (m, 1H), 4.34 (dd, J = 7.1, 8.8 Hz, 1H), 4.09 (d, J = 2.6 Hz, 3H), 4.04-3.92 (m, 2H), 3.63 (quin, J = 8.2 Hz, 1H), 3.48-3.34 (m, 2H), 3.21-2.85 (m, 3H), 2.61 (s, 3H), 2.30 (br t, J = 14.3 Hz, 2H), 2.11-1.94 (m, 2H); LCMS (ESI) [M+H]+: 510.0.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.69 (br s, 1H), 8.32 (dd, J = 1.5, 4.2 Hz, 1H), 8.10 (s, 1H), 7.86-7.80 (m, 1H), 7.77-7.71 (m, 1H), 7.45-7.36 (m, 2H), 4.54 (br d, J = 13.9 Hz, 1H), 4.37 (br d, J = 3.5 Hz, 2H), 4.09 (s, 3H), 4.00 (s, 3H), 3.96 (br s, 1H), 3.41-3.31 (m, 2H), 3.14 (br t, J = 11.1 Hz, 1H), 2.60 (s, 3H), 2.33-2.22 (m, 2H), 2.11-1.94 (m, 2H); LCMS (ESI) [M+H]+: 490.2.

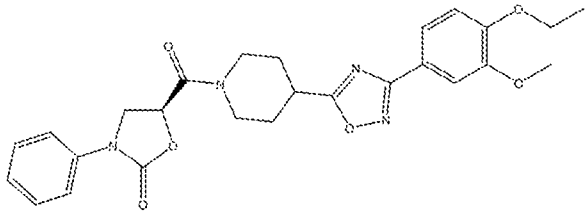


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (br d, J = 7.1 Hz, 1H), 7.87-7.79 (m, 1H), 7.78-7.63 (m, 3H), 7.56-7.48 (m, 1H), 7.46-7.38 (m, 1H), 4.56 (br t, J = 13.6 Hz, 1H), 4.32-4.22 (m, 1H), 4.17-3.96 (m, 5H), 3.74 (quin, J = 8.2 Hz, 1H), 3.48-3.31 (m, 2H), 3.20-3.04 (m, 1H), 3.01-2.84 (m, 2H), 2.60 (s, 3H), 2.36- 2.21 (m, 2H), 2.10- 1.93 (m, 2H); LCMS (ESI) [M+H]+: 510.3.



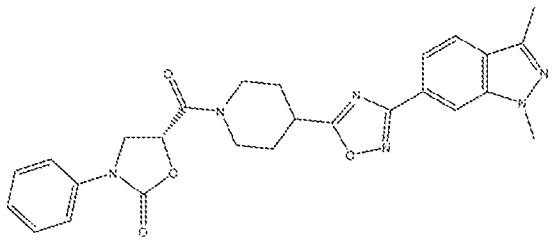
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.05 (s, 1H), 7.87-7.78 (m, 4H), 7.54-7.42 (m, 2H), 7.35 (br s, 1H), 5.00-4.91 (spt, J = 6.8 Hz, 1H), 4.52-4.50 (br d, J = 13.7 Hz, 1H), 4.35-4.27 (d, J = 3.7 Hz,

2H), 3.94-3.91 (br d, J = 13.9 Hz, 1H), 3.38-3.32 (m, 2H), 3.18-3.12 (br t, J = 11.0 Hz, 1H), 2.35-2.21 (m, 2H), 2.09-1.96 (m, 2H), 1.63-1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 473.2.

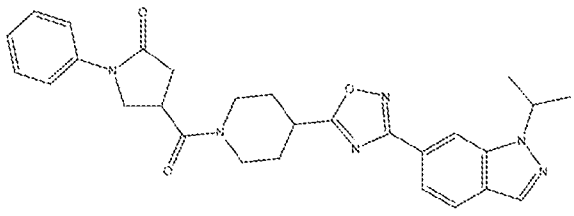


5

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.67 (br d, J = 8.2 Hz, 1H), 7.60-7.55 (m, 3H), 7.40 (t, J = 7.7 Hz, 2H), 7.18 (t, J = 6.9 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 5.28-5.22 (m, 1H), 4.84-4.79 (m, 1H), 4.59 (br d, J = 13.5 Hz, 0.5H), 4.36-4.22 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.13-4.03 (m, 1.5H), 3.97 (d, J = 2.2 Hz, 3H), 3.64-3.54 (m, 0.5H), 3.41-3.27 (m, 2H), 3.09-3.01 (m, 0.5H), 2.35-2.15 (m, 2.5H), 2.11-1.93 (m,
10 1.5H), 1.51 (t, J = 6.8 Hz, 3H); LCMS (ESI) [M+H]+: 492.8.

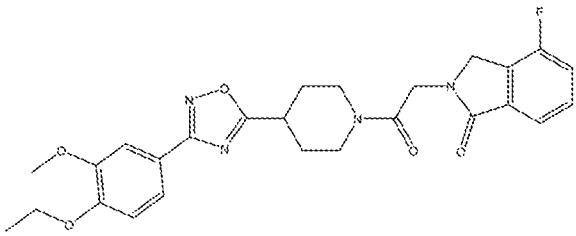


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (d, J = 7.5 Hz, 1H), 7.84 (dd, J = 1.3, 8.3 Hz, 1H), 7.74 (dd,
15 J = 3.9, 8.3 Hz, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 5.26 (t, J = 7.7 Hz, 1H), 4.83 (dd, J = 6.6, 8.8 Hz, 1H), 4.62 (d, J = 13.6 Hz, 0.5H), 4.38-4.26 (m, 1H), 4.13-4.05 (m, 4.5H), 3.66-3.58 (m, 0.5H), 3.45-3.31 (m, 2H), 3.11-3.04 (m, 0.5H), 2.60 (s, 3H), 2.40-2.25 (m, 2H), 2.24-1.96 (m, 2H); LCMS (ESI) [M+H]+: 487.3.

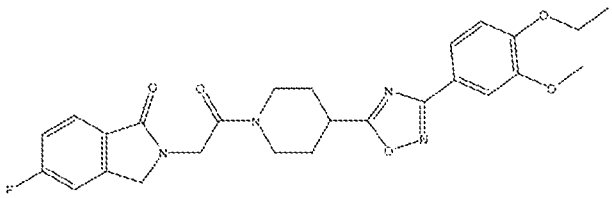


20

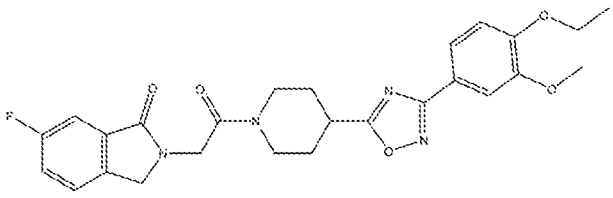
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.17 (s, 1H), 7.92-7.90 (d, J = 8.4 Hz, 1H), 7.75-7.73 (d, J = 8.4 Hz, 1H), 7.66-7.64 (br d, J = 8.2 Hz, 2H), 7.38-7.33 (dt, J = 3.7, 7.8 Hz, 2H), 7.13-7.11 (m, 1H), 5.15-5.11 (dt, J = 3.5, 6.5 Hz, 1H), 4.39-4.35 (br d, J = 13.2 Hz, 1H), 4.06-3.93 (m, 3H), 3.78-3.70 (m, 1H),
25 3.50-3.45 (br t, J = 10.7 Hz, 1H), 3.36-3.33 (m, 1H), 2.98-2.93 (m, 1H), 2.81-2.71 (m, 2H), 2.20-2.13 (br t, J = 14.0 Hz, 2H), 1.89-1.65 (m, 2H), 1.49-1.48 (d, J = 6.4 Hz, 6H); LCMS (ESI) [M+H]+: 499.2.



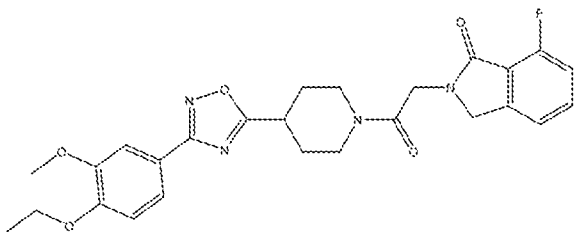
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.69-7.62 (m, 2H), 7.55 (d, J = 1.8 Hz, 1H), 7.45 (dt, J = 4.6, 7.7 Hz, 1H), 7.27-7.24 (m, 1H), 7.27-7.19 (m, 1H), 6.94 (d, J = 8.6 Hz, 1H), 4.63 (d, J = 2.9 Hz, 2H), 4.55-4.39 (m, 3H), 4.16 (q, J = 6.9 Hz, 2H), 4.02 (br d, J = 13.7 Hz, 1H), 3.95 (s, 3H), 3.43-3.23 (m, 2H), 3.06 (br t, J = 10.9 Hz, 1H), 2.29-2.15 (m, 2H), 2.08-1.88 (m, 2H), 1.50 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 495.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.85 (dd, J = 5.3, 8.4 Hz, 1H), 7.65 (dd, J = 1.8, 8.4 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.20-7.13 (m, 2H), 6.95 (d, J = 8.4 Hz, 1H), 4.57 (d, J = 3.7 Hz, 2H), 4.51-4.41 (m, 3H), 4.18 (q, J = 7.0 Hz, 2H), 4.05 (br d, J = 13.9 Hz, 1H), 3.96 (s, 3H), 3.42-3.24 (m, 2H), 3.07 (br t, J = 10.9 Hz, 1H), 2.29-2.15 (m, 2H), 2.07-1.89 (m, 2H), 1.51 (t, J = 6.9 Hz, 3H); LCMS (ESI) [M+H]+: 495.1.

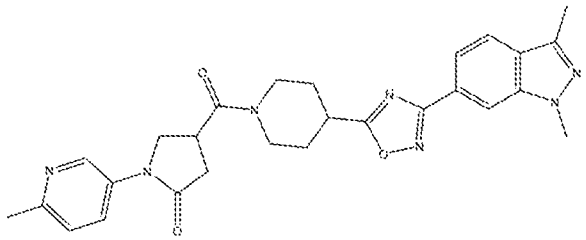


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.53 (dd, J = 2.0, 8.4 Hz, 1H), 7.46-7.39 (m, 2H), 7.30 (dd, J = 4.4, 8.2 Hz, 1H), 7.18-7.10 (m, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.52-4.27 (m, 5H), 4.05 (q, J = 7.0 Hz, 2H), 3.92 (br d, J = 13.7 Hz, 1H), 3.84 (s, 3H), 3.32-3.10 (m, 2H), 2.94 (br t, J = 10.8 Hz, 1H), 2.10 (br t, J = 15.0 Hz, 2H), 1.95-1.76 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 495.1.

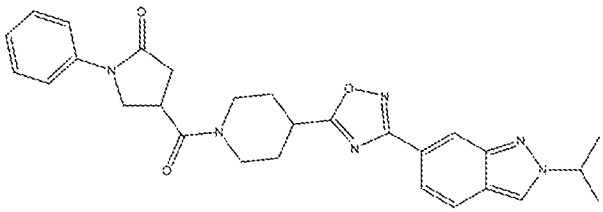


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.66 (dd, J = 2.0, 8.4 Hz, 1H), 7.58-7.49 (m, 2H), 7.24 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 8.8 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.59 (d, J = 5.1 Hz, 2H), 4.53-4.38 (m, 3H),

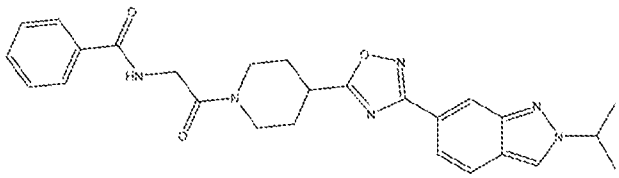
4.17 (q, J = 6.9 Hz, 2H), 4.07 (br d, J = 13.9 Hz, 1H), 3.96 (s, 3H), 3.45-3.22 (m, 2H), 3.12-3.02 (m, 1H), 2.22 (br dd, J = 14.2, 18.2 Hz, 2H), 2.09-1.88 (m, 2H), 1.51 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 495.3.



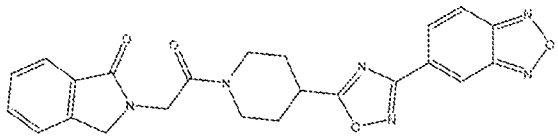
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.56 (dd, J = 2.3, 7.2 Hz, 1H), 8.13-8.02 (m, 2H), 7.86-7.79 (m, 1H), 7.77-7.71 (m, 1H), 7.17 (d, J = 8.6 Hz, 1H), 4.64-4.47 (m, 1H), 4.32 (ddd, J = 3.3, 6.6, 9.5 Hz, 1H), 4.08 (d, J = 2.2 Hz, 3H), 4.04-3.91 (m, 2H), 3.63 (quin, J = 8.3 Hz, 1H), 3.46-3.32 (m, 2H), 3.19-3.04 (m, 1H), 3.01-2.81 (m, 2H), 2.60 (s, 3H), 2.54 (s, 3H), 2.28 (br t, J = 13.3 Hz, 2H), 2.11-1.95 (m, 2H); LCMS (ESI) [M+H]+: 500.3.



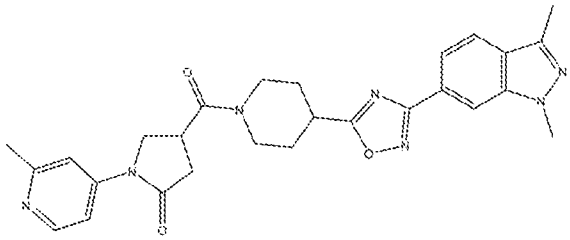
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (s, 1H), 7.98 (s, 1H), 7.73 (s, 2H), 7.59-7.57 (br d, J = 8.2 Hz, 2H), 7.38-7.34 (t, J = 7.9 Hz, 2H), 7.17-7.13 (m, 1H), 4.85-4.77 (m, 1H), 4.50-4.42 (br t, J = 14.9 Hz, 1H), 4.33-4.23 (m, 1H), 4.01-3.89 (m, 2H), 3.62-3.54 (quin, J = 8.5 Hz, 1H), 3.45-3.27 (m, 2H), 3.22-2.90 (m, 2H), 2.87-2.75 (m, 1H), 2.31-2.17 (m, 2H), 2.07-1.91 (m, 2H), 1.67-1.66 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 499.3.



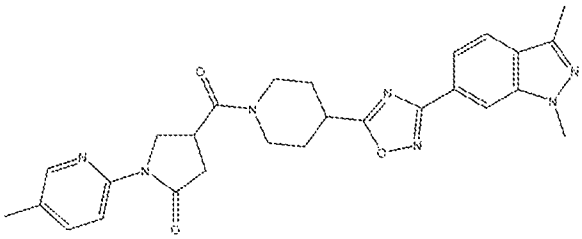
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57-8.52 (m, 2H), 8.27 (s, 1H), 7.88-7.84 (t, J = 7.6 Hz, 3H), 7.62-7.60 (dd, J = 1.2, 8.7 Hz, 1H), 7.55-7.43 (m, 3H), 4.92-4.82 (spt, J = 6.7 Hz, 1H), 4.34-4.31 (br d, J = 13.5 Hz, 1H), 4.18-4.16 (d, J = 5.5 Hz, 2H), 4.00-3.96 (br d, J = 13.9 Hz, 1H), 3.50-3.43 (m, 1H), 3.29-3.25 (m, 1H), 2.95-2.90 (br t, J = 11.2 Hz, 1H), 2.18-2.12 (br t, J = 12.3 Hz, 2H), 1.88-1.80 (q, J = 10.6 Hz, 1H), 1.73-1.63 (m, 1H), 1.60-1.55 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 473.3.



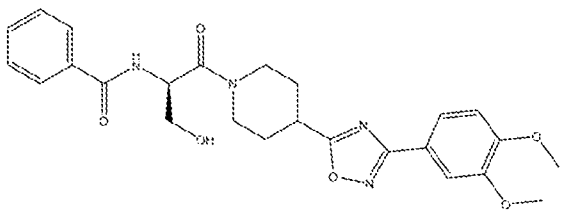
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.63 (t, J = 1.1 Hz, 1H), 8.11 (dd, J = 1.3, 9.3 Hz, 1H), 7.96 (dd, J = 1.0, 9.4 Hz, 1H), 7.88-7.83 (m, 1H), 7.59-7.53 (m, 1H), 7.50-7.43 (m, 2H), 4.58 (s, 2H), 4.53-4.43 (m, 3H), 4.11 (br d, J = 14.1 Hz, 1H), 3.45-3.28 (m, 2H), 3.12-3.01 (m, 1H), 2.25 (br t, J = 14.1 Hz, 2H), 2.07-1.87 (m, 2H); LCMS (ESI) [M+H]+: 445.2.



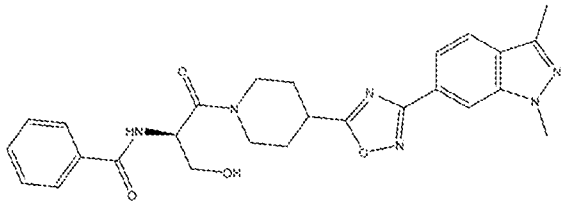
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.44 (br d, J = 5.5 Hz, 1H), 8.09 (s, 1H), 7.87-7.80 (m, 1H), 7.78-7.71 (m, 1H), 7.50 (br s, 1H), 7.40 (br d, J = 5.3 Hz, 1H), 4.64-4.48 (m, 1H), 4.29 (dd, J = 6.9, 9.6 Hz, 1H), 4.08 (s, 3H), 4.04-3.90 (m, 2H), 3.61 (quin, J = 8.4 Hz, 1H), 3.40 (br d, J = 10.8 Hz, 2H), 3.21-3.04 (m, 1H), 3.02-2.82 (m, 2H), 2.60 (s, 3H), 2.56 (s, 3H), 2.29 (br t, J = 14.7 Hz, 2H), 2.11-1.96 (m, 2H); LCMS (ESI) [M+H]+: 500.2.



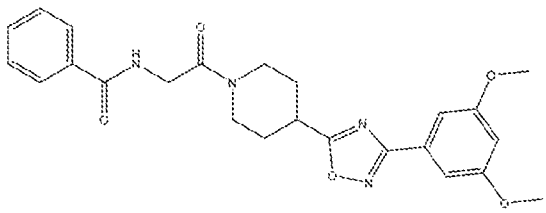
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.27 (br dd, J = 4.7, 8.3 Hz, 1H), 8.15 (br s, 1H), 8.10 (br s, 1H), 7.86-7.79 (m, 1H), 7.78-7.71 (m, 1H), 7.52 (br d, J = 8.4 Hz, 1H), 4.57 (br t, J = 12.7 Hz, 1H), 4.41 (dd, J = 9.0, 10.8 Hz, 1H), 4.22-4.14 (m, 1H), 4.09 (s, 3H), 4.04 (br d, J = 14.1 Hz, 1H), 3.57 (quin, J = 8.2 Hz, 1H), 3.47-3.32 (m, 2H), 3.25 (br dd, J = 7.7, 17.2 Hz, 1H), 3.16-3.04 (m, 1H), 2.86-2.76 (m, 1H), 2.60 (s, 3H), 2.36-2.21 (m, 5H), 2.12-1.93 (m, 2H); LCMS (ESI) [M+H]+: 500.3.



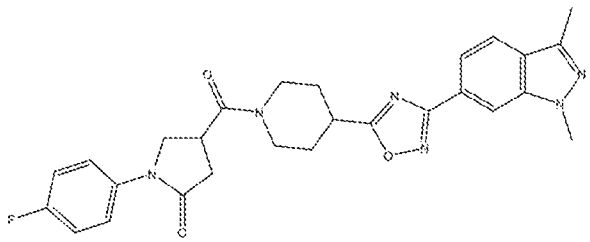
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.85-7.80 (m, 2H), 7.66 (br t, J = 8.8 Hz, 1H), 7.58-7.49 (m, 3H), 7.47-7.41 (m, 2H), 6.94 (t, J = 7.9 Hz, 1H), 5.18 (br d, J = 2.6 Hz, 1H), 4.54-4.38 (m, 1H), 4.18 (br t, J = 14.0 Hz, 1H), 3.97-3.92 (m, 7H), 3.89-3.83 (m, 1H), 3.46-3.36 (m, 1H), 3.34-3.23 (m, 1H), 3.19-3.03 (m, 1H), 2.23 (br s, 2H), 2.11-1.92 (m, 2H); LCMS (ESI) [M+H]+: 481.3.



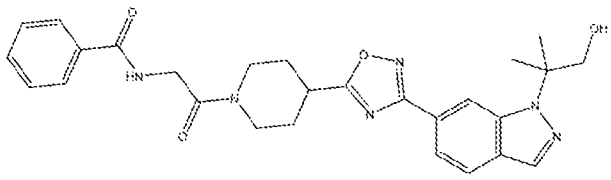
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.14 (br d, J = 11.0 Hz, 1H), 7.89-7.84 (m, 2H), 7.77 (br d, J = 7.0 Hz, 2H), 7.55-7.43 (m, 3H), 5.23 (t, J = 6.1 Hz, 1H), 4.58-4.45 (m, 1H), 4.28 (br t, J = 14.9 Hz, 1H), 4.02 (br d, J = 5.3 Hz, 3H), 3.93-3.82 (m, 2H), 3.54-3.40 (m, 2H), 3.16-3.03 (m, 1H), 2.54 (s, 3H), 2.34-2.18 (m, 2H), 2.08-1.86 (m, 2H); LCMS (ESI) [M+H]+: 489.3.



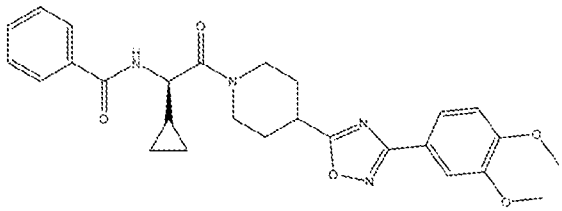
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.86 (d, J = 7.1 Hz, 2H), 7.58-7.42 (m, 3H), 7.35 (br s, 1H), 7.23 (d, J = 2.2 Hz, 2H), 6.61 (t, J = 2.2 Hz, 1H), 4.50 (br d, J = 13.7 Hz, 1H), 4.31 (d, J = 4.0 Hz, 2H), 3.91 (br d, J = 14.3 Hz, 1H), 3.86 (s, 6H), 3.39-3.29 (m, 2H), 3.15 (br t, J = 10.7 Hz, 1H), 2.30-2.20 (m, 2H), 2.08-1.93 (m, 2H); LCMS (ESI) [M+H]+: 451.3.



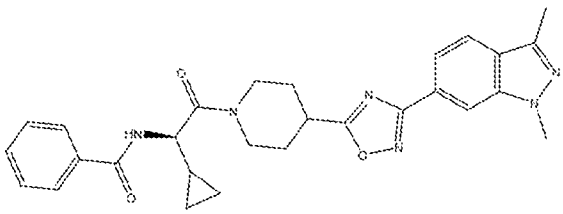
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (d, J = 4.9 Hz, 1H), 7.87-7.80 (m, 1H), 7.79-7.72 (m, 1H), 7.57 (br dd, J = 4.6, 8.6 Hz, 2H), 7.08 (t, J = 8.6 Hz, 2H), 4.65-4.48 (m, 1H), 4.36-4.29 (m, 1H), 4.09 (d, J = 3.3 Hz, 3H), 4.05-3.87 (m, 2H), 3.60 (quin, J = 8.3 Hz, 1H), 3.48-3.32 (m, 2H), 3.20-3.03 (m, 1H), 3.01-2.82 (m, 2H), 2.61 (s, 3H), 2.29 (br t, J = 13.7 Hz, 2H), 2.10-1.94 (m, 2H); LCMS (ESI) [M+H]+: 503.3.



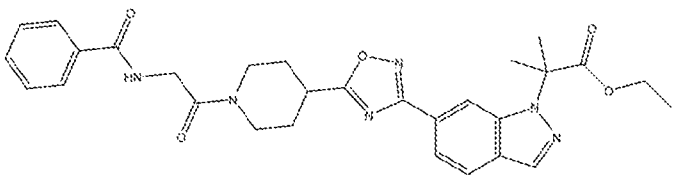
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.34 (d, J = 0.9 Hz, 1H), 7.93 (d, J = 1.1 Hz, 1H), 7.83-7.75 (m, 4H), 7.49-7.35 (m, 3H), 7.27 (br s, 1H), 4.52-4.43 (m, 1H), 4.25 (dd, J = 2.4, 3.7 Hz, 2H), 4.02 (br d, J = 6.4 Hz, 2H), 3.91-3.81 (m, 2H), 3.34-3.24 (m, 2H), 3.11-3.02 (m, 1H), 2.21 (dt, J = 3.4, 13.2 Hz, 2H), 2.05-1.87 (m, 2H), 1.69 (s, 6H); LCMS (ESI) [M+H]+: 503.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.83-7.78 (m, 2H), 7.67 (br t, J = 8.6 Hz, 1H), 7.58-7.47 (m, 2H), 7.46-7.40 (m, 2H), 7.16 (br d, J = 6.6 Hz, 1H), 6.97-6.90 (m, 1H), 5.09-4.96 (m, 1H), 4.59-4.38 (m, 1H), 4.23-4.06 (m, 1H), 3.99-3.91 (m, 6H), 3.49-3.25 (m, 2H), 3.21-3.04 (m, 1H), 2.34-2.13 (m, 2H), 2.10-1.90 (m, 2H), 1.25 (br d, J = 5.7 Hz, 1H), 0.74-0.43 (m, 4H); LCMS (ESI) [M+H]+: 491.0.

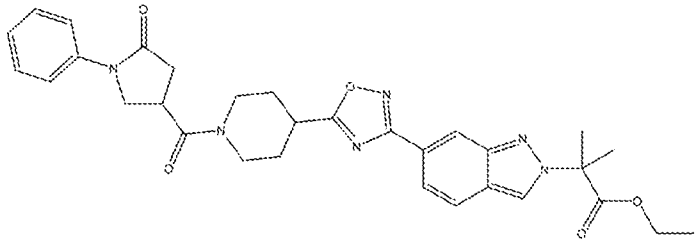


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.08 (br d, J = 6.6 Hz, 1H), 7.85-7.77 (m, 3H), 7.75-7.67 (m, 1H), 7.53-7.46 (m, 1H), 7.45-7.40 (m, 2H), 7.18 (br s, 1H), 5.09-4.96 (m, 1H), 4.59-4.43 (m, 1H), 4.23-4.10 (m, 1H), 4.06 (br d, J = 5.3 Hz, 3H), 3.52-3.30 (m, 2H), 3.21-3.05 (m, 1H), 2.58 (d, J = 2.2 Hz, 3H), 2.37-2.19 (m, 2H), 2.13-1.97 (m, 1H), 2.13-1.97 (m, 1H), 1.27 (br s, 1H), 0.63-0.43 (m, 4H); LCMS (ESI) [M+H]+: 499.3.

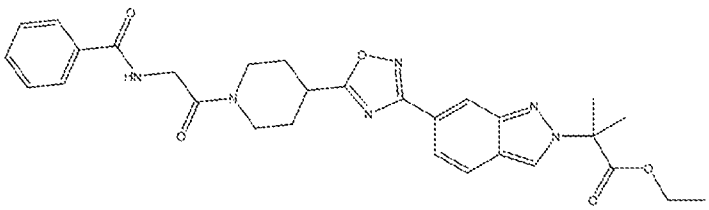


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.04 (d, J = 5.7 Hz, 2H), 7.88-7.78 (m, 4H), 7.55-7.40 (m, 3H), 7.33 (br s, 1H), 4.51 (br d, J = 13.7 Hz, 1H), 4.30 (d, J = 3.7 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.90 (br d, J

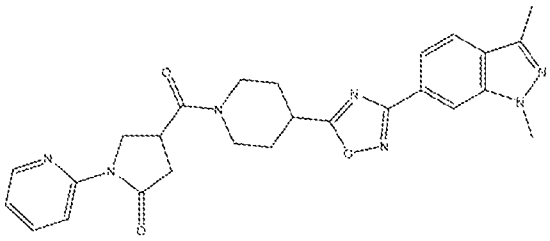
= 14.1 Hz, 1H), 3.39-3.28 (m, 2H), 3.12 (br t, J = 11.1 Hz, 1H), 2.32-2.17 (m, 2H), 1.99 (s, 8H), 1.15 (t, J = 7.2 Hz, 3H); LCMS (ESI) [M+H]+: 545.2.



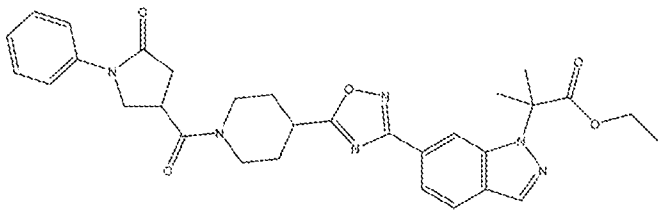
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.53 (s, 1H), 8.12 (s, 1H), 7.76-7.71 (m, 2H), 7.58 (br d, J = 7.9 Hz, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 4.51-4.37 (m, 1H), 4.28 (q, J = 8.3 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.01-3.89 (m, 2H), 3.57 (quin, J = 8.4 Hz, 1H), 3.45-3.28 (m, 2H), 3.23-3.09 (m, 1H), 3.02-2.91 (m, 1H), 2.86-2.76 (m, 1H), 2.31-2.16 (m, 2H), 2.00 (s, 8H), 1.17 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 571.2.



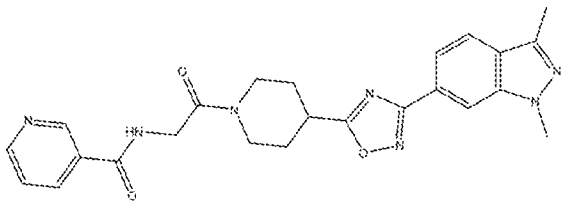
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.55 (s, 1H), 8.15 (s, 1H), 7.86 (d, J = 7.1 Hz, 2H), 7.76 (s, 2H), 7.56-7.42 (m, 3H), 7.36 (br s, 1H), 4.45 (br d, J = 13.7 Hz, 1H), 4.32 (br s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.91 (br d, J = 14.1 Hz, 1H), 3.42-3.29 (m, 2H), 3.22 (br t, J = 10.6 Hz, 1H), 2.26 (br t, J = 10.8 Hz, 2H), 2.10-1.94 (m, 8H),1.20 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 545.2.



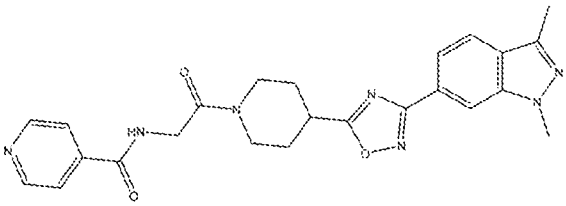
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.44-8.31 (m, 2H), 8.11 (s, 1H), 7.87-7.81 (m, 1H), 7.78-7.66 (m, 2H), 7.06 (br s, 1H), 4.64-4.52 (m, 1H), 4.44 (dd, J = 9.0, 11.0 Hz, 1H), 4.25-4.17 (m, 1H), 4.09 (s, 3H), 4.04 (br d, J = 13.0 Hz, 1H), 3.58 (quin, J = 8.2 Hz, 1H), 3.48-3.32 (m, 2H), 3.27 (dd, J = 7.7, 17.4 Hz, 1H), 3.17-3.05 (m, 1H), 2.88-2.78 (m, 1H), 2.61 (s, 3H), 2.36-2.22 (m, 2H), 2.14-1.94 (m, 2H); LCMS (ESI) [M+H]+: 486.3.



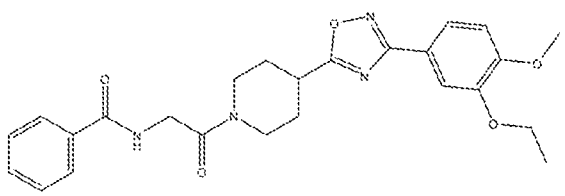
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.08-8.02 (m, 2H), 7.88-7.79 (m, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.19-7.12 (m, 1H), 4.60-4.47 (m, 1H), 4.36-4.26 (m, 1H), 4.20 (br dd, J = 3.4, 6.9 Hz, 2H), 3.94 (q, J = 9.3 Hz, 2H), 3.58 (quin, J = 8.4 Hz, 1H), 3.43-3.27 (m, 2H), 3.16-2.89 (m, 2H), 2.88-2.79 (m, 1H), 2.25 (br t, J = 12.8 Hz, 2H), 1.99 (s, 8H), 1.18-1.10 (m, 3H); LCMS (ESI) [M+H]+: 571.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.09 (d, J = 1.6 Hz, 1H), 8.76 (dd, J = 1.6, 4.9 Hz, 1H), 8.16 (td, J = 2.0, 8.0 Hz, 1H), 8.10 (s, 1H), 7.87-7.80 (m, 1H), 7.78-7.71 (m, 1H), 7.46-7.37 (m, 2H), 4.58-4.48 (m, 1H), 4.33 (d, J = 3.9 Hz, 2H), 4.08 (s, 3H), 3.93 (br d, J = 13.8 Hz, 1H), 3.44-3.33 (m, 2H), 3.23-3.13 (m, 1H), 2.60 (s, 3H), 2.36-2.24 (m, 2H), 2.13-1.97 (m, 2H); LCMS (ESI) [M+H]+: 460.2.

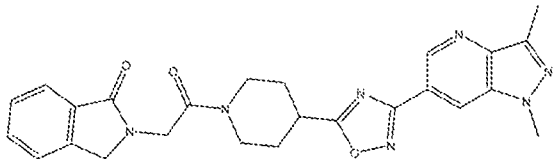


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.81-8.76 (m, 2H), 8.09 (s, 1H), 7.86-7.80 (m, 1H), 7.77-7.67 (m, 3H), 7.48 (br s, 1H), 4.58-4.48 (m, 1H), 4.31 (d, J = 3.9 Hz, 2H), 4.08 (s, 3H), 3.92 (br d, J = 14.1 Hz, 1H), 3.38 (ddd, J = 3.4, 10.6, 14.0 Hz, 2H), 3.23-3.13 (m, 1H), 2.60 (s, 3H), 2.36-2.24 (m, 2H), 2.12-1.96 (m, 2H); LCMS (ESI) [M+H]+: 460.3.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.89-7.83 (m, 2H), 7.67 (dd, J = 1.9, 8.3 Hz, 1H), 7.60-7.42 (m, 4H), 7.35 (br s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.55-4.46 (m, 1H), 4.31 (d, J = 3.9 Hz, 2H), 4.20 (q, J = 7.0

Hz, 2H), 3.94 (s, 3H), 3.93-3.87 (m, 1H), 3.40-3.27 (m, 2H), 3.20-3.09 (m, 1H), 2.25 (dt, J = 3.9, 12.8 Hz, 2H), 2.08-1.92 (m, 2H), 1.51 (t, J = 7.0 Hz, 3H); LCMS (ESI) [M+H]+: 465.3.



5

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.16 (br d, J = 1.8 Hz, 1H), 8.33 (d, J = 1.5 Hz, 1H), 7.82 (br d, J = 7.5 Hz, 1H), 7.55-7.48 (m, 1H), 7.45-7.39 (m, 2H), 4.54 (s, 2H), 4.49-4.41 (m, 3H), 4.05 (s, 4H), 3.41-3.24 (m, 2H), 3.03 (br t, J = 11.8 Hz, 1H), 2.65 (s, 3H), 2.22 (br t, J = 15.8 Hz, 2H), 2.07-1.86 (m, 4H); LCMS (ESI) [M+H]+: 472.1.

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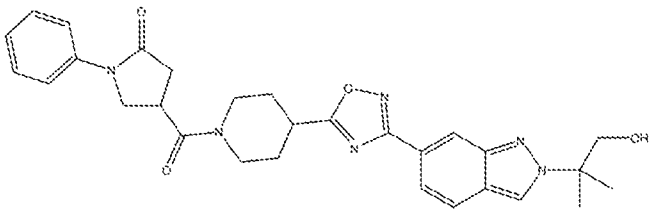
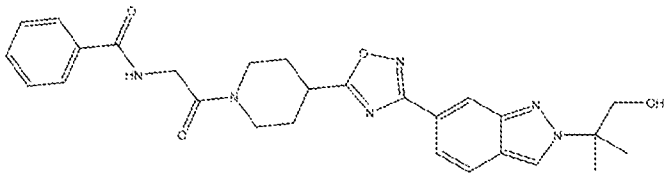
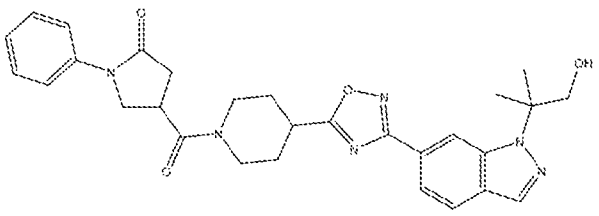


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.48 (s, 1H), 8.08 (s, 1H), 7.74 (s, 2H), 7.58 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.18-7.11 (m, 1H), 4.53-4.40 (m, 1H), 4.33-4.24 (m, 1H), 4.00-3.89 (m, 4H), 3.57
15 (quin, J = 8.4 Hz, 1H), 3.44-3.28 (m, 2H), 3.20-3.06 (m, 1H), 3.03-2.90 (m, 1H), 2.86-2.77 (m, 1H), 2.30-2.18 (m, 2H), 2.07-1.88 (m, 3H), 1.71 (s, 6H); LCMS (ESI) [M+H]+: 529.3.



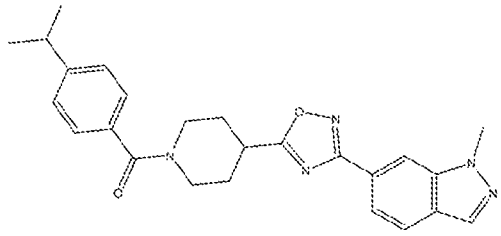
20 ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.50 (d, J = 0.9 Hz, 1H), 8.10 (d, J = 0.7 Hz, 1H), 7.86 (d, J = 7.3 Hz, 2H), 7.77 (s, 2H), 7.56-7.50 (m, 1H), 7.49-7.43 (m, 2H), 7.36 (br s, 1H), 4.47 (br d, J = 13.5 Hz, 1H), 4.31 (d, J = 2.6 Hz, 2H), 4.06 (br s, 1H), 3.99-3.87 (m, 3H), 3.43-3.31 (m, 2H), 3.21 (br t, J = 10.7 Hz, 1H), 2.33-2.21 (m, 2H), 2.11-1.94 (m, 2H), 1.73 (s, 6H); LCMS (ESI) [M+H]+: 503.3.



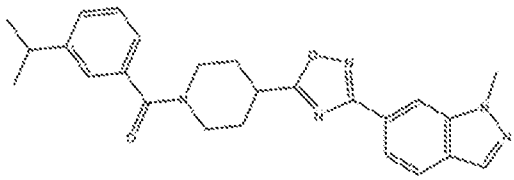
25

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.39 (s, 1H), 7.99 (s, 1H), 7.88-7.79 (m, 1H), 7.88-7.79 (m, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.19-7.12 (m, 1H), 4.64-4.49 (m, 1H), 4.36-4.27 (m, 1H),

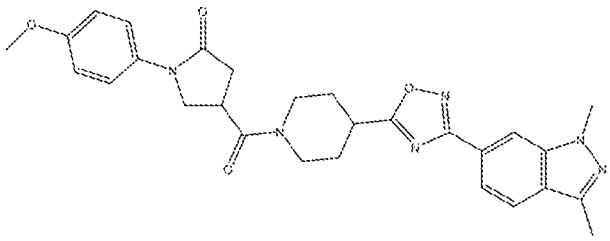
4.07 (br s, 2H), 4.02-3.85 (m, 3H), 3.57 (quin, J = 8.5 Hz, 1H), 3.43-3.29 (m, 2H), 3.16-2.89 (m, 2H), 2.88-2.78 (m, 1H), 2.34-2.19 (m, 2H), 2.05-1.96 (m, 2H), 1.74 (d, J = 2.0 Hz, 6H); LCMS (ESI) [M+H]+: 529.3.



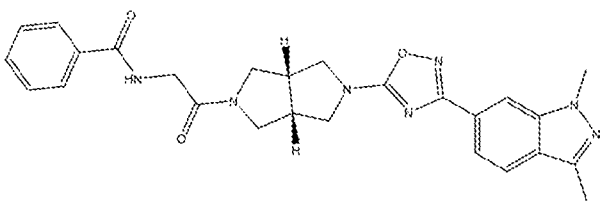
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.01 (s, 1H), 7.87-7.78 (m, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.24 (s, 1H), 4.64 (br s, 1H), 4.14 (s, 3H), 4.09-3.71 (m, 1H), 3.37-3.27 (m, 1H), 3.20 (br s, 2H), 2.97-2.87 (m, 1H), 2.28-1.96 (m, 4H), 1.24 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 430.0.



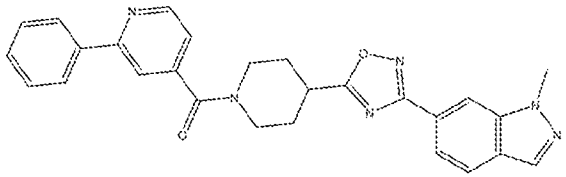
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.01 (d, J = 0.7 Hz, 1H), 7.87-7.78 (m, 2H), 7.34-7.26 (m, 3H), 7.21 (br d, J = 7.3 Hz, 1H), 4.66 (br s, 1H), 4.14 (s, 3H), 3.97-3.78 (m, 1H), 3.36-3.12 (m, 3H), 2.96-2.87 (m, 1H), 2.32-1.90 (m, 4H), 1.25 (d, J = 7.1 Hz, 6H); LCMS (ESI) [M+H]+: 430.0.



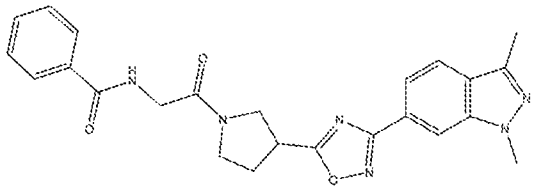
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (br d, J = 4.9 Hz, 1H), 7.86-7.81 (m, 1H), 7.77-7.72 (m, 1H), 7.49 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.64-4.51 (m, 1H), 4.30 (br s, 1H), 4.09 (d, J = 3.5 Hz, 3H), 3.99 (br s, 1H), 3.91 (br t, J = 8.8 Hz, 1H), 3.81 (s, 3H), 3.59 (quin, J = 8.2 Hz, 1H), 3.47-3.31 (m, 2H), 3.19-3.03 (m, 1H), 3.00-2.79 (m, 2H), 2.61 (s, 3H), 2.34-2.23 (m, 2H), 2.01 (br d, J = 10.8 Hz, 2H); LCMS (ESI) [M+H]+: 515.3.



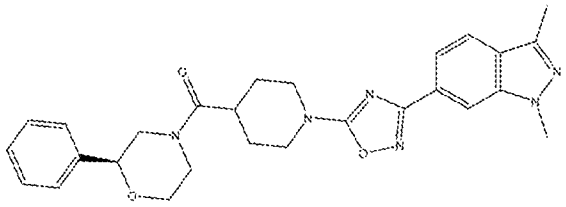
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.84 (d, J = 7.1 Hz, 2H), 7.79-7.66 (m, 2H), 7.55-7.41 (m, 3H), 7.22 (br s, 1H), 4.29-4.13 (m, 2H), 4.06 (s, 3H), 4.04-3.96 (m, 2H), 3.96-3.84 (m, 2H), 3.69-3.56 (m, 3H), 3.50 (dd, J = 5.1, 10.8 Hz, 1H), 3.31-3.22 (m, 1H), 3.20-3.11 (m, 1H), 2.59 (s, 3H); LCMS (ESI) [M+H]+: 486.3.



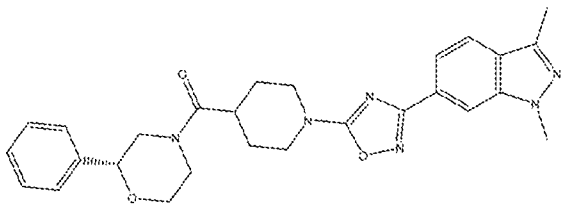
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.79 (d, J = 4.8 Hz, 1H), 8.16 (s, 1H), 8.05-7.99 (m, 3H), 7.87-7.80 (m, 2H), 7.75 (s, 1H), 7.52-7.44 (m, 3H), 7.25 (d, J = 4.8 Hz, 1H), 4.67 (br d, J = 11.4 Hz, 1H), 4.16 (s, 3H), 3.83 (br d, J = 14.0 Hz, 1H), 3.41-3.21 (m, 3H), 2.34 (br s, 1H), 2.22-1.97 (m, 3H); LCMS (ESI) [M+H]+: 465.0.



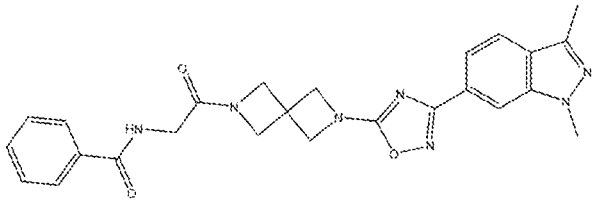
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12-8.08 (m, 1H), 7.89-7.80 (m, 3H), 7.77-7.72 (m, 1H), 7.56-7.42 (m, 3H), 7.25 (br d, J = 3.1 Hz, 1H), 4.33-4.24 (m, 2H), 4.17-3.99 (m, 5H), 3.97-3.68 (m, 3H), 2.68-2.38 (m, 5H); LCMS (ESI) [M+H]+: 445.2.



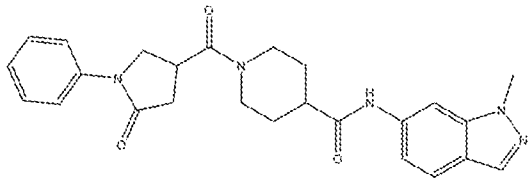
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.79-7.74 (m, 1H), 7.73-7.67 (m, 1H), 7.46-7.30 (m, 5H), 4.71-4.51 (m, 1H), 4.44 (br d, J = 10.4 Hz, 1H), 4.39-4.25 (m, 2H), 4.15 (br d, J = 11.7 Hz, 1H), 4.07 (s, 3H), 3.90-3.65 (m, 2H), 3.51-3.17 (m, 3H), 2.98-2.70 (m, 2H), 2.59 (s, 3H), 2.11-1.79 (m, 4H); LCMS (ESI) [M+H]+: 487.3.



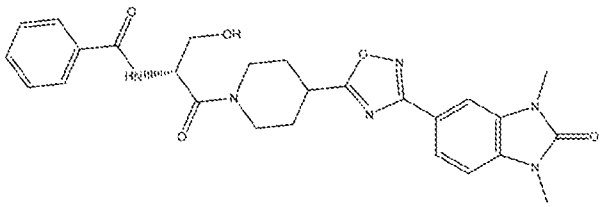
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.79-7.73 (m, 1H), 7.72-7.65 (m, 1H), 7.47-7.30 (m, 5H), 4.71-4.51 (m, 1H), 4.44 (br d, J = 10.4 Hz, 1H), 4.39-4.25 (m, 2H), 4.15 (br d, J = 11.7 Hz, 1H), 4.06 (s, 3H), 3.90-3.66 (m, 2H), 3.51-3.17 (m, 3H), 2.98-2.71 (m, 2H), 2.59 (s, 3H), 2.11-1.79 (m, 4H); LCMS (ESI) [M+H]+: 487.3.



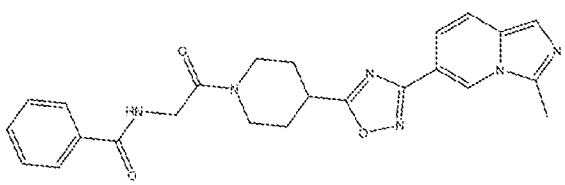
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.01 (t, J = 1.0 Hz, 1H), 7.89-7.80 (m, 2H), 7.72 (dq, J = 1.0, 8.6 Hz, 2H), 7.60-7.50 (m, 1H), 7.50-7.43 (m, 2H), 6.98 (br s, 1H), 4.52 (s, 4H), 4.49 (s, 2H), 4.34 (s, 2H), 4.08 (d, J = 4.6 Hz, 2H), 4.07 (s, 3H), 2.59 (s, 3H); LCMS (ESI) [M+H]+: 472.3.



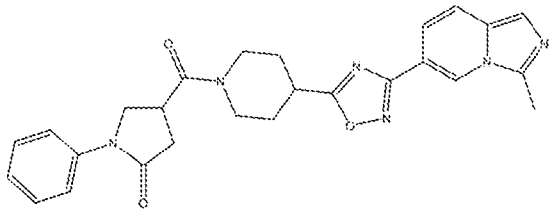
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.00 (s, 1H), 7.91 (d, J = 0.9 Hz, 1H), 7.59 (dd, J = 8.5, 12.0 Hz, 3H), 7.43-7.32 (m, 2H), 7.22-7.13 (m, 1H), 6.85 (td, J = 1.5, 8.6 Hz, 1H), 4.71-4.53 (m, 1H), 4.27 (ddd, J = 6.8, 9.6, 18.8 Hz, 1H), 4.03 (s, 3H), 4.00-3.91 (m, 2H), 3.57 (quin, J = 8.3 Hz, 1H), 3.25-3.11 (m, 1H), 3.04-2.90 (m, 1H), 2.87-2.76 (m, 2H), 2.57 (dt, J = 4.1, 10.9 Hz, 1H), 2.08-1.94 (m, 2H), 1.89-1.80 (m, 1H), 1.89-1.79 (m, 1H); LCMS (ESI) [M+H]+: 446.1.



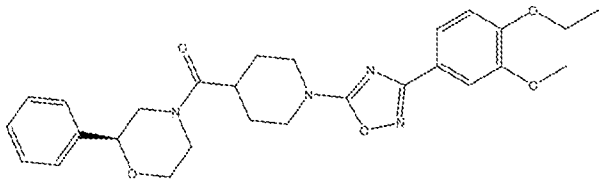
^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.93-7.70 (m, 4H), 7.55-7.35 (m, 3H), 7.25-7.10 (m, 1H), 5.23-5.19 (t, J = 6.0 Hz, 1H), 4.60-4.40 (m, 1H), 4.30-4.15 (m, 1H), 3.90-3.75 (m, 2H), 3.55-3.35 (m, 8H), 3.20-2.95 (m, 1H), 2.30-2.10 (m, 2H), 2.10-1.95 (m, 1H), 1.95-1.75 (m, 1H); LCMS (ESI) [M+H]+: 505.2.



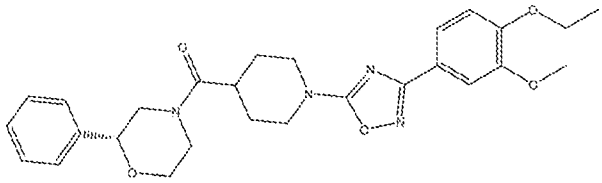
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.47 (s, 1H), 7.84 (d, J = 7.3 Hz, 2H), 7.54-7.41 (m, 4H), 7.38 (s, 1H), 7.26-7.22 (t, 2H), 4.53 (br d, J = 13.9 Hz, 1H), 4.30 (t, J = 3.7 Hz, 2H), 3.91 (br d, J = 13.7 Hz, 1H), 3.38-3.27 (m, 2H), 3.11 (br t, J = 11.1 Hz, 1H), 2.73 (s, 3H), 2.31-2.19 (t, 2H), 2.07-1.90 (m, 2H); LCMS (ESI) [M+H]+: 445.2.



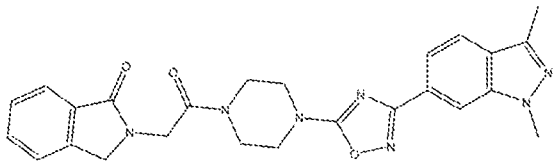
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.42 (br d, J = 4.4 Hz, 1H), 7.53 (br d, J = 8.2 Hz, 2H), 7.43 (d, J = 9.5 Hz, 1H), 7.36-7.28 (dd, 3H), 7.20 (m, 1H), 7.14-7.07 (t, 1H), 4.59-4.43 (dd, 1H), 4.31-4.23 (m, 1H), 3.98-3.82 (m, 2H), 3.52 (quin, J = 8.4 Hz, 1H), 3.39-3.21 (m, 2H), 3.15-2.73 (m, 3H), 2.68 (d, J = 5.7 Hz, 3H), 2.27-2.13 (t, 2H), 1.99-1.81 (m, 2H); LCMS (ESI) [M+H]+: 471.3.



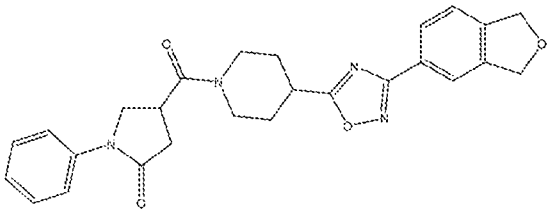
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.57 (br d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 7.43-7.31 (m, 5H), 6.90 (d, J = 8.3 Hz, 1H), 4.65 (br d, J = 13.6 Hz, 1H), 4.53 (br d, J = 12.7 Hz, 1H), 4.42 (br d, J = 10.5 Hz, 1H), 4.34-4.21 (m, 2H), 4.14 (q, J = 7.0 Hz, 3H), 3.93 (s, 3H), 3.86-3.64 (m, 2H), 3.43 (br t, J = 11.4 Hz, 1H), 3.27-3.16 (m, 2H), 2.91 (br t, J = 11.4 Hz, 1H), 2.81-2.67 (m, 2H), 2.07-1.77 (m, 4H), 1.48 (t, J = 7.0 Hz, 3H); LCMS (ESI) [M+H]+: 493.0.



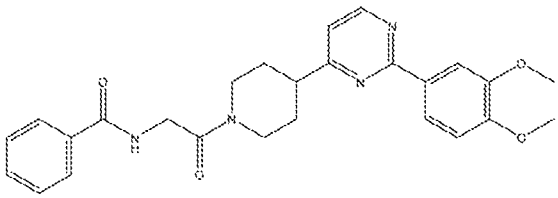
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.57 (br d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 7.43-7.32 (m, 5H), 6.90 (d, J = 8.3 Hz, 1H), 4.66 (br d, J = 13.6 Hz, 0.5H), 4.54 (br d, J = 13.6 Hz, 0.5H), 4.42 (br d, J = 10.1 Hz, 1H), 4.34-4.22 (m, 2H), 4.15 (q, J = 7.0 Hz, 3H), 3.93 (s, 3H), 3.87-3.65 (m, 2H), 3.44 (br t, J = 11.6 Hz, 0.5H), 3.27-3.17 (m, 2H), 2.91 (br t, J = 11.8 Hz, 0.5H), 2.81-2.69 (m, 2H), 2.06-1.78 (m, 4H), 1.48 (t, J = 7.0 Hz, 3H); LCMS (ESI) [M+H]+: 493.0.



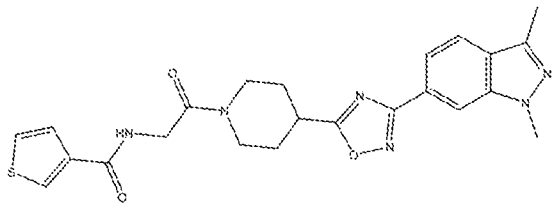
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.01 (s, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.78-7.67 (m, 2H), 7.61-7.55 (m, 1H), 7.52-7.46 (m, 2H), 4.59 (s, 2H), 4.52 (s, 2H), 4.06 (s, 3H), 3.83-3.73 (m, 8H), 2.59 (s, 3H); LCMS (ESI) [M+H]+: 472.0.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.00 (br d, J = 7.5 Hz, 1H), 7.95 (br s, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.41-7.33 (m, 3H), 7.19-7.14 (m, 1H), 5.16 (s, 4H), 4.58-4.47 (m, 1H), 4.31 (dd, J = 7.2, 9.4 Hz, 1H), 4.00-3.89 (m, 2H), 3.62-3.55 (m, 1H), 3.44-3.28 (m, 2H), 3.18-2.92 (m, 2H), 2.87-2.80 (m, 1H), 2.32-2.18 (m, 2H), 2.06-1.90 (m, 2H); LCMS (ESI) [M+H]+: 459.2.

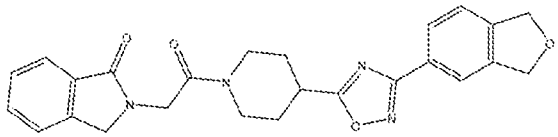


^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 5.3 Hz, 1H), 8.57 (br t, J = 5.7 Hz, 1H), 8.06-8.00 (m, 1H), 7.96 (s, 1H), 7.89 (d, J = 7.0 Hz, 2H), 7.58-7.52 (m, 1H), 7.52-7.44 (m, 2H), 7.29 (d, J = 5.3 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 4.51 (br d, J = 12.3 Hz, 1H), 4.27-4.12 (m, 2H), 4.06 (br d, J = 13.6 Hz, 1H), 3.84 (d, J = 4.4 Hz, 6H), 3.23 (br t, J = 12.1 Hz, 1H), 3.04 (br t, J = 11.8 Hz, 1H), 2.79 (br t, J = 12.1 Hz, 1H), 2.00 (br t, J = 12.1 Hz, 2H), 1.86-1.73 (m, 1H), 1.70-1.56 (m, 1H); LCMS (ESI) [M+H]+: 461.3.

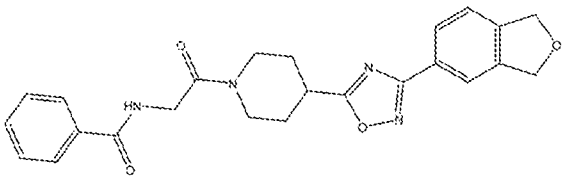


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.95 (dd, J = 1.2, 2.8 Hz, 1H), 7.86-7.80 (m, 1H), 7.78-7.72 (m, 1H), 7.46 (dd, J = 1.1, 5.1 Hz, 1H), 7.36 (dd, J = 3.1, 5.1 Hz, 1H), 7.15 (br s, 1H), 4.53 (br d, J = 13.7 Hz, 1H), 4.29 (d, J = 4.0 Hz, 2H), 4.09 (s, 3H), 3.93 (br d, J = 14.3 Hz, 1H), 3.42-3.32 (m, 2H),

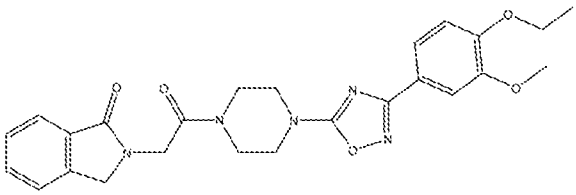
3.16 (br t, J = 10.8 Hz, 1H), 2.60 (s, 3H), 2.29 (br t, J = 10.9 Hz, 2H), 2.11-1.95 (m, 2H); LCMS (ESI) [M+H]+: 465.2.



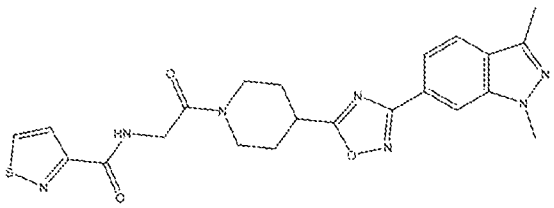
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.99 (d, J = 7.9 Hz, 1H), 7.94 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.57-7.52 (m, 1H), 7.49-7.43 (m, 2H), 7.34 (d, J = 7.9 Hz, 1H), 5.16 (s, 4H), 4.60-4.39 (m, 5H), 4.07 (br d, J = 14.0 Hz, 1H), 3.43-3.24 (m, 2H), 3.07 (br t, J = 11.2 Hz, 1H), 2.21 (br t, J = 13.8 Hz, 2H), 2.03-1.88 (m, 2H); LCMS (ESI) [M+H]+: 445.2.



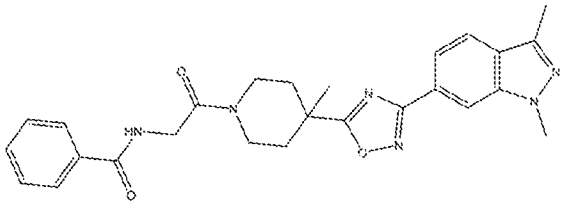
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.99 (d, J = 7.9 Hz, 1H), 7.94 (s, 1H), 7.85 (d, J = 7.0 Hz, 2H), 7.54-7.48 (m, 1H), 7.48-7.42 (m, 2H), 7.35 (br d, J = 7.9 Hz, 2H), 5.16 (s, 4H), 4.49 (br d, J = 14.0 Hz, 1H), 4.30 (d, J = 3.9 Hz, 2H), 3.90 (br d, J = 14.0 Hz, 1H), 3.40-3.26 (m, 2H), 3.21-3.13 (m, 1H), 2.32-2.18 (m, 2H), 2.07-1.91 (m, 2H); LCMS (ESI) [M+H]+: 433.2.



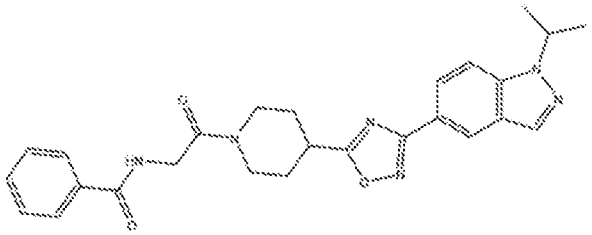
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.87 (d, J = 7.5 Hz, 1H), 7.59-7.54 (m, 2H), 7.51-7.45 (m, 3H), 6.91 (d, J = 8.4 Hz, 1H), 4.58 (s, 2H), 4.51 (s, 2H), 4.15 (q, J = 6.9 Hz, 2H), 3.94 (s, 3H), 3.79-3.68 (m, 8H), 1.49 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 478.2.



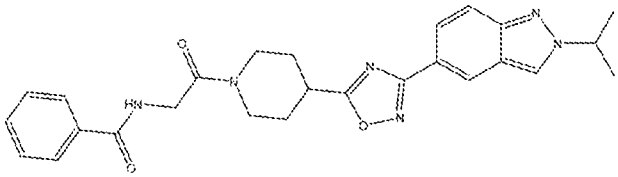
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.70 (d, J = 4.6 Hz, 1H), 8.23 (br s, 1H), 8.10 (s, 1H), 7.89-7.80 (m, 2H), 7.77-7.70 (m, 1H), 4.55 (br d, J = 14.1 Hz, 1H), 4.32 (d, J = 4.4 Hz, 2H), 4.09 (s, 3H), 3.93 (br d, J = 13.5 Hz, 1H), 3.41-3.32 (m, 2H), 3.15 (br t, J = 11.4 Hz, 1H), 2.60 (s, 3H), 2.34-2.22 (m, 2H), 2.12-1.95 (m, 2H); LCMS (ESI) [M+H]+: 466.2.



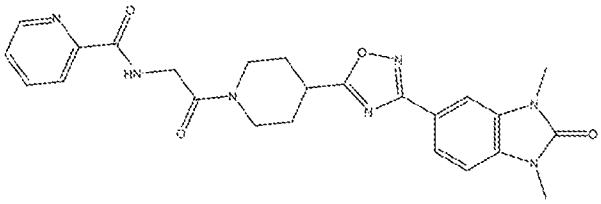
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.88-7.81 (m, 3H), 7.78-7.72 (m, 1H), 7.55-7.50 (m, 1H), 7.49-7.43 (m, 2H), 7.35 (br s, 1H), 4.42-4.31 (m, 2H), 4.28-4.19 (m, 1H), 4.10 (s, 3H), 3.76 (br d, J = 14.3 Hz, 1H), 3.46-3.36 (m, 1H), 3.21-3.11 (m, 1H), 2.61 (s, 3H), 2.58-2.45 (m, 2H), 1.84-1.74 (m, 2H), 1.61 (s, 3H); LCMS (ESI) [M+H]+: 473.3.



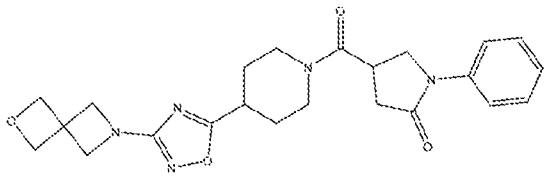
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.49 (s, 1H), 8.11-8.04 (m, 2H), 7.87-7.83 (m, 2H), 7.54-7.49 (m, 2H), 7.47-7.42 (m, 2H), 7.35 (br s, 1H), 4.88 (td, J = 6.7, 13.3 Hz, 1H), 4.53-4.46 (m, 1H), 4.31 (d, J = 3.7 Hz, 2H), 3.96-3.88 (m, 1H), 3.40-3.28 (m, 2H), 3.22-3.12 (m, 1H), 2.26 (dt, J = 3.6, 13.0 Hz, 2H), 2.09-1.93 (m, 2H), 1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 473.3.



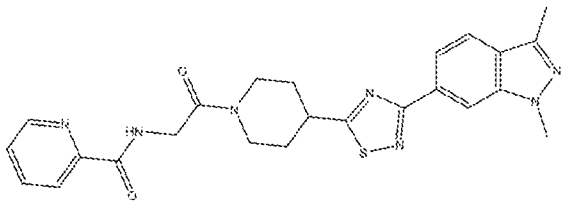
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.45 (s, 1H), 8.06 (s, 1H), 7.95 (dd, J = 1.3, 9.0 Hz, 1H), 7.85 (d, J = 7.3 Hz, 2H), 7.79 (d, J = 9.0 Hz, 1H), 7.54-7.49 (m, 1H), 7.47-7.42 (m, 2H), 7.35 (br s, 1H), 4.82 (quin, J = 6.7 Hz, 1H), 4.49 (td, J = 4.0, 13.7 Hz, 1H), 4.30 (d, J = 4.0 Hz, 2H), 3.95-3.87 (m, 1H), 3.38-3.27 (m, 2H), 3.21-3.13 (m, 1H), 2.25 (dt, J = 3.7, 12.9 Hz, 2H), 2.07-1.95 (m, 2H), 1.68 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 473.2.



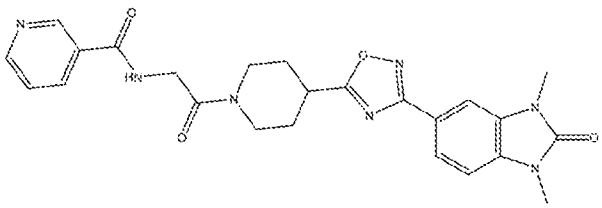
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.93 (br s, 1H), 8.64 (br d, J = 4.3 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 7.94-7.84 (m, 2H), 7.70 (s, 1H), 7.49-7.41 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H), 4.56 (br d, J = 13.6 Hz, 1H), 4.36 (br d, J = 4.4 Hz, 2H), 3.97 (br d, J = 14.3 Hz, 1H), 3.50 (d, J = 8.3 Hz, 6H), 3.43-3.32 (m, 2H), 3.16 (br t, J = 11.2 Hz, 1H), 2.27 (br t, J = 12.1 Hz, 2H), 2.11-1.91 (m, 2H); LCMS (ESI) [M+H]+: 476.3.



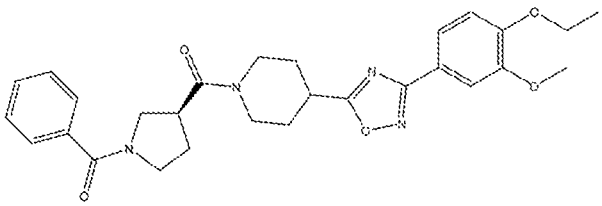
^{1}HNMR (400 MHz, CHLOROFORM-d) δ 7.60-7.54 (m, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.19-7.10 (m, 1H), 4.81 (s, 4H), 4.52-4.39 (m, 1H), 4.27 (dd, J = 7.3, 9.7 Hz, 1H), 4.20 (s, 4H), 3.95-3.84 (m, 2H), 3.53 (quin, J = 8.4 Hz, 1H), 3.34-3.23 (m, 1H), 3.15-2.87 (m, 3H), 2.84-2.75 (m, 1H), 2.16-2.04 (m, 2H), 1.90-1.75 (m, 2H); LCMS (ESI) [M+H]+: 438.2.



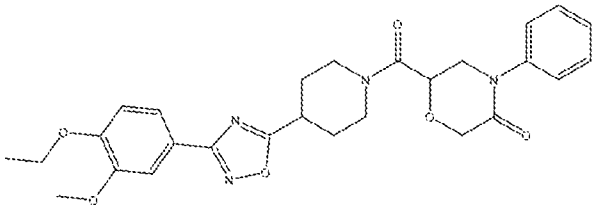
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.94 (br s, 1H), 8.63 (br s, 1H), 8.36-8.27 (m, 1H), 8.19 (br d, J = 7.3 Hz, 1H), 8.08 (br d, J = 7.9 Hz, 1H), 7.90-7.81 (m, 1H), 7.73 (br d, J = 7.7 Hz, 1H), 7.52-7.40 (m, 1H), 4.75 (br d, J = 12.1 Hz, 1H), 4.36 (br s, 2H), 4.10 (br s, 3H), 4.02 (br d, J = 12.6 Hz, 1H), 3.51 (br s, 1H), 3.36 (br t, J = 11.2 Hz, 1H), 3.08-2.94 (m, 1H), 2.61 (br s, 3H), 2.32 (br d, J = 14.8 Hz, 2H), 1.96 (br d, J = 10.8 Hz, 2H); LCMS (ESI) [M+H]+: 476.2.



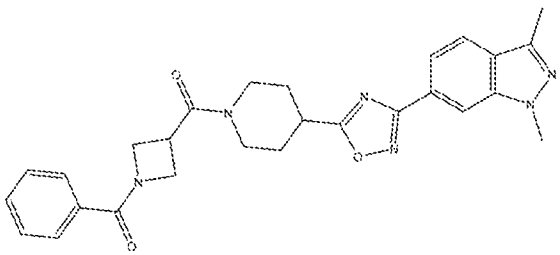
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.10 (dd, J = 0.7, 2.3 Hz, 1H), 8.77 (dd, J = 1.7, 4.9 Hz, 1H), 8.17 (td, J = 2.0, 7.9 Hz, 1H), 7.89 (dd, J = 1.5, 8.2 Hz, 1H), 7.69 (d, J = 1.3 Hz, 1H), 7.42 (ddd, J = 0.8, 4.9, 7.9 Hz, 2H), 7.07 (d, J = 8.2 Hz, 1H), 4.53 (td, J = 3.8, 13.8 Hz, 1H), 4.33 (d, J = 3.9 Hz, 2H), 3.96-3.89 (m, 1H), 3.49 (d, J = 7.6 Hz, 6H), 3.42-3.32 (m, 2H), 3.18 (ddd, J = 3.1, 10.9, 13.6 Hz, 1H), 2.29 (dt, J = 3.8, 13.8 Hz, 2H), 2.12-1.95 (m, 2H); LCMS (ESI) [M+H]+: 476.2.



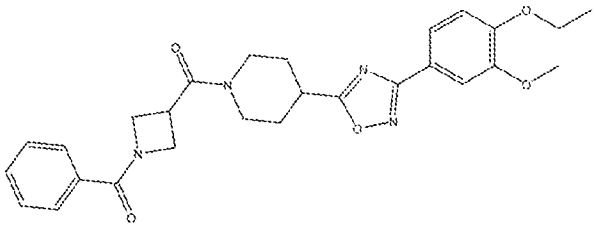
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.67-7.58 (m, 1H), 7.55-7.46 (m, 3H), 7.42-7.32 (m, 3H), 6.91 (br d, J = 8.4 Hz, 1H), 4.57-4.39 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.05-3.97 (m, 1H), 3.96-3.91 (m, 3H), 3.90-3.61 (m, 3H), 3.58-3.42 (m, 1H), 3.39-3.18 (m, 3H), 3.08-2.91 (m, 1H), 2.34-1.82 (m, 6H), 1.47 (t, J = 6.9 Hz, 3H); LCMS (ESI) [M+H]+: 505.3.



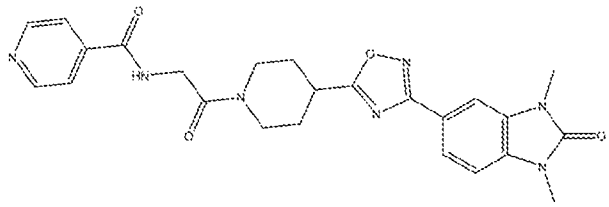
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.63 (br s, 1H), 7.54 (br s, 1H), 7.45-7.39 (m, 2H), 7.38-7.34 (m, 2H), 7.32-7.27 (m, 1H), 6.93 (br d, J = 8.4 Hz, 1H), 4.67 (br s, 1H), 4.45-4.39 (m, 1H), 4.26 (br dd, J = 8.5, 12.7 Hz, 1H), 4.15 (q, J = 6.6 Hz, 2H), 3.94 (br s, 3H), 3.77 (br d, J = 12.8 Hz, 1H), 3.47 (br t, J = 11.5 Hz, 0.5H), 3.35-3.15 (m, 2H), 2.97 (br t, J = 12.1 Hz, 0.5H), 2.23 (br s, 2H), 2.12-1.87 (m, 2H), 1.49 (br t, J = 6.9 Hz, 3H); LCMS (ESI) [M+H]+: 507.3.



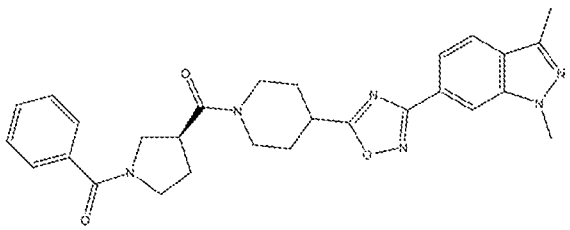
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (br d, J = 8.6 Hz, 1H), 7.82 (br s, 1H), 7.77-7.70 (m, 1H), 7.65 (d, J = 7.1 Hz, 2H), 7.51-7.38 (m, 3H), 4.75 (br s, 1H), 4.63-4.27 (m, 4H), 4.08 (br d, J = 4.6 Hz, 3H), 3.70-3.59 (m, 2H), 3.39-2.99 (m, 3H), 2.60 (s, 3H), 2.24 (br d, J = 11.0 Hz, 2H), 2.05-1.91 (m, 2H); LCMS (ESI) [M+H]+: 485.3.



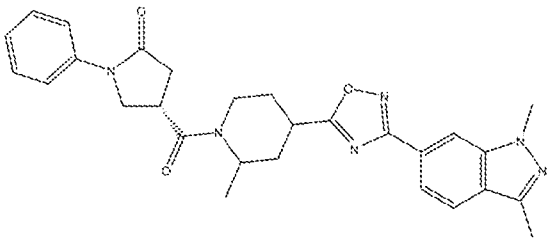
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.65 (br d, J = 7.1 Hz, 3H), 7.56 (br s, 1H), 7.51-7.39 (m, 3H), 6.95 (br d, J = 8.2 Hz, 1H), 4.74 (br t, J = 7.1 Hz, 1H), 4.59-4.25 (m, 4H), 4.17 (q, J = 7.1 Hz, 2H), 3.97 (br s, 3H), 3.68-3.57 (m, 2H), 3.35-2.97 (m, 3H), 2.20 (br d, J = 12.1 Hz, 2H), 2.03-1.87 (m, 2H), 1.51 (t, J = 6.9 Hz, 3H); LCMS (ESI) [M+H]+: 491.3.



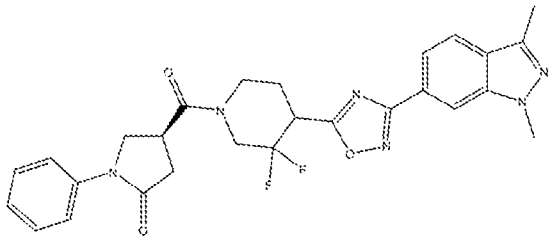
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.80-8.74 (m, 2H), 7.87 (dd, J = 1.5, 8.2 Hz, 1H), 7.70-7.66 (m, 3H), 7.46 (br s, 1H), 7.07-7.02 (m, 1H), 7.05 (d, J = 8.2 Hz, 1H), 4.51 (td, J = 3.7, 13.7 Hz, 1H), 4.30 (d, J = 3.7 Hz, 2H), 3.93-3.86 (m, 1H), 3.47 (d, J = 7.1 Hz, 6H), 3.40-3.29 (m, 2H), 3.21-3.13 (m, 1H), 2.27 (dt, J = 3.5, 13.3 Hz, 2H), 2.09-1.94 (m, 2H); LCMS (ESI) [M+H]+: 476.2.



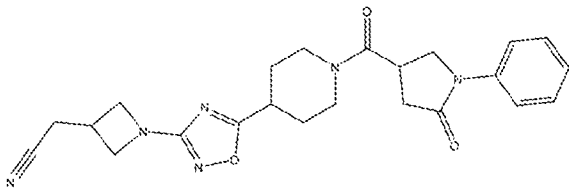
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11-8.04 (m, 1H), 7.84-7.76 (m, 1H), 7.74-7.70 (m, 1H), 7.56-7.48 (m, 2H), 7.43-7.35 (m, 3H), 4.62-4.46 (m, 1H), 4.10-4.02 (m, 4H), 4.00-3.67 (m, 3H), 3.62-3.45 (m, 1H), 3.41-3.20 (m, 3H), 3.12-2.94 (m, 1H), 2.58 (s, 3H), 2.38-1.86 (m, 6H); LCMS (ESI) [M+H]+: 499.3.



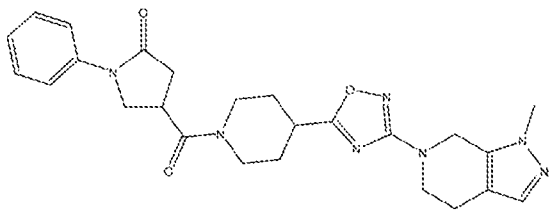
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22-8.17 (m, 1H), 7.91-7.86 (m, 1H), 7.76-7.64 (m, 3H), 7.41-7.34 (m, 2H), 7.18-7.11 (m, 1H), 4.99-4.34 (m, 1H), 4.13-3.86 (m, 6H), 3.77-3.64 (m, 1H), 3.49 (br s, 1H), 2.90-2.62 (m, 3H), 2.52-2.52 (m, 3H), 2.38-2.03 (m, 4H), 1.42-0.87 (m, 3H); LCMS (ESI) [M+H]+: 499.3.



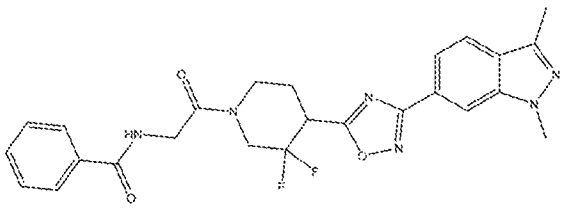
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (br s, 1H), 7.85 (br d, J = 8.4 Hz, 1H), 7.80-7.71 (m, 1H), 7.60 (br d, J = 7.0 Hz, 2H), 7.47-7.33 (m, 2H), 7.19 (br d, J = 5.1 Hz, 1H), 4.76-4.16 (m, 3H), 4.09 (br s, 3H), 4.03-3.39 (m, 5H), 3.08-2.80 (m, 2H), 2.61 (s, 3H), 2.52-2.23 (m, 2H); LCMS (ESI) [M+H]+: 521.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.59 (d, J = 8.2 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.21-7.14 (m, 1H), 4.56-4.42 (m, 1H), 4.33-4.23 (m, 3H), 3.97-3.83 (m, 4H), 3.56 (quin, J = 8.5 Hz, 1H), 3.37-3.27 (m, 1H), 3.19-2.90 (m, 4H), 2.87-2.78 (m, 1H), 2.75 (d, J = 7.1 Hz, 2H), 2.14 (br t, J = 12.5 Hz, 2H), 1.93-1.78 (m, 2H); LCMS (ESI) [M+H]+: 435.1.

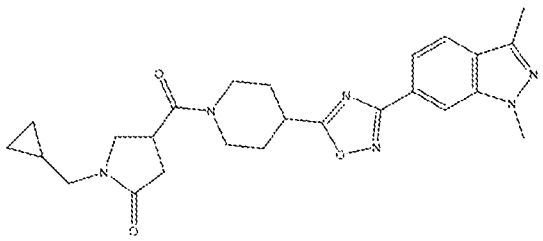


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.59 (d, J = 8.2 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.32 (s, 1H), 7.22-7.13 (m, 1H), 4.55-4.41 (m, 3H), 4.31 (br t, J = 8.3 Hz, 1H), 3.96-3.79 (m, 4H), 3.76 (s, 3H), 3.56 (quin, J = 8.5 Hz, 1H), 3.38-3.27 (m, 1H), 3.18-2.90 (m, 3H), 2.89-2.74 (m, 3H), 2.14 (br t, J = 13.0 Hz, 2H), 1.94-1.79 (m, 2H); LCMS (ESI) [M+H]+: 476.2.

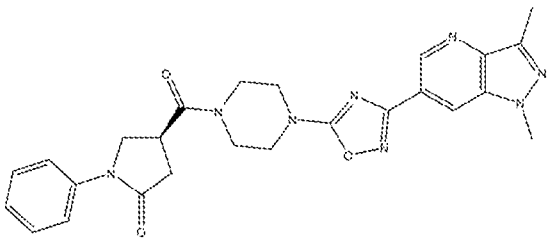


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.85 (t, J = 7.3 Hz, 3H), 7.78-7.73 (m, 1H), 7.58-7.51 (m, 1H), 7.50-7.43 (m, 2H), 7.22 (br s, 1H), 4.65-4.49 (m, 0.5H), 4.44-4.18 (m, 3H), 4.09 (s, 3H),

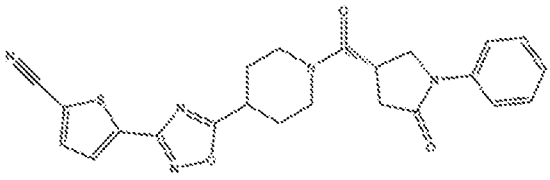
4.07-4.01 (m, 0.5H), 3.94-3.70 (m, 2H), 3.67-3.50 (m, 1H), 2.61 (s, 3H), 2.47-2.31 (m, 2H); LCMS (ESI) [M+H]+: 495.3.



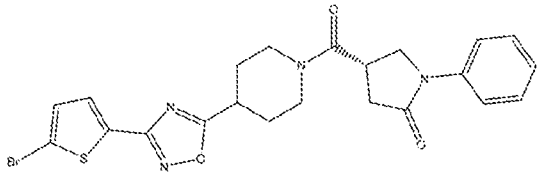
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.88-7.80 (d, J = 2, 1H), 7.60 (dd, J = 1.1, 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 4.40-4.26 (m, 1H), 3.88-3.84 (s, 3H), 3.80-3.64 (m, 2H), 3.40 (t, J = 9.2 Hz, 1H), 3.25 (td, J = 8.4, 16.6 Hz, 1H), 3.18-3.08 (m, 2H), 3.03-2.78 (m, 3H), 2.57-2.41 (m, 2H), 2.38 (s, 3H), 2.11-1.96 (m, 2H), 1.85-1.67 (m, 2H), 0.76-0.66 (m, 1H), 0.36-0.29 (m, 2H), 0.02 (q, J = 4.8 Hz, 2H); LCMS (ESI) [M+H]+: 463.2.



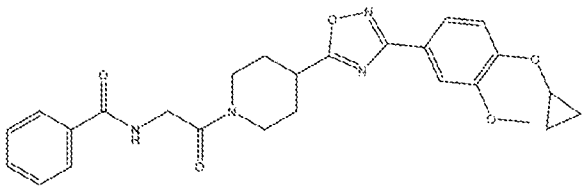
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.13 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 1.8 Hz, 1H), 7.61-7.55 (m, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.19-7.14 (m, 1H), 4.32 (dd, J = 7.2, 9.4 Hz, 1H), 4.07 (s, 3H), 3.95 (t, J = 9.2 Hz, 1H), 3.86-3.67 (m, 8H), 3.63-3.54 (m, 1H), 2.97-2.81 (m, 2H), 2.68 (s, 3H); LCMS (ESI) [M+H]+: 487.2.



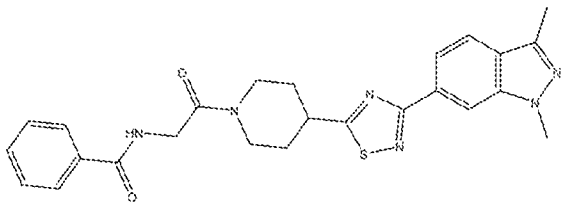
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.75 (br s, 1H), 7.64 (d, J = 3.7 Hz, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.20-7.13 (m, 1H), 4.61-4.46 (m, 1H), 4.30 (br t, J = 8.4 Hz, 1H), 4.01-3.88 (m, 2H), 3.56 (quin, J = 8.4 Hz, 1H), 3.43-3.25 (m, 2H), 3.12-2.88 (m, 2H), 2.87-2.79 (m, 1H), 2.23 (br t, J = 12.8 Hz, 2H), 2.01-1.86 (m, 2H); LCMS (ESI) [M+H]+: 448.1.



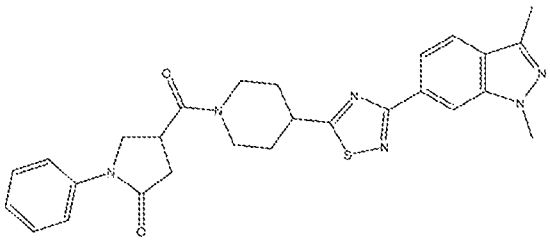
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.54-7.43 (m, 3H), 7.34-7.26 (m, 2H), 7.12-7.03 (m, 2H), 4.44 (br t, J = 15.5 Hz, 1H), 4.22 (br d, J = 2.3 Hz, 1H), 3.94-3.83 (m, 2H), 3.55-3.45 (m, 1H), 3.35-3.15 (m, 2H), 3.05-2.83 (m, 2H), 2.81-2.71 (m, 1H), 2.15 (br t, J = 13.6 Hz, 2H), 1.95-1.78 (m, 2H); LCMS (ESI) [M+H]+: 501.1.



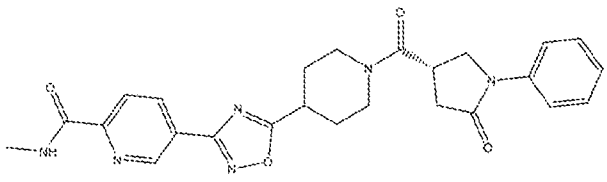
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.93-7.82 (m, 2H), 7.69 (dd, J = 1.9, 8.4 Hz, 1H), 7.61-7.42 (m, 4H), 7.38-7.31 (m, 2H), 4.57-4.45 (m, 1H), 4.31 (d, J = 3.8 Hz, 2H), 3.94 (s, 3H), 3.93-3.86 (m, 1H), 3.85-3.78 (m, 1H), 3.41-3.26 (m, 2H), 3.22-3.09 (m, 1H), 2.34-2.18 (m, 2H), 2.10-1.92 (m, 2H), 0.95-0.81 (m, 4H); LCMS (ESI) [M+H]+: 477.2.



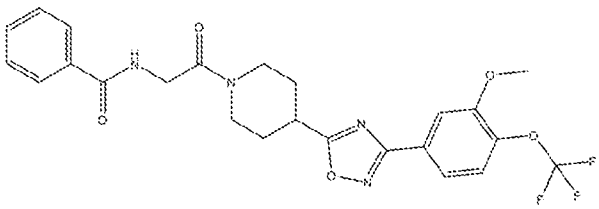
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.3 Hz, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.56-7.50 (m, 1H), 7.49-7.44 (m, 2H), 7.36 (br s, 1H), 4.72 (br d, J = 13.4 Hz, 1H), 4.40-4.27 (m, 2H), 4.10 (s, 3H), 4.00 (br d, J = 13.9 Hz, 1H), 3.52 (tt, J = 3.7, 11.0 Hz, 1H), 3.41-3.31 (m, 1H), 3.04 (br t, J = 11.3 Hz, 1H), 2.61 (s, 3H), 2.35 (br t, J = 15.7 Hz, 2H), 1.95 (dquin, J = 3.9, 12.1 Hz, 2H); LCMS (ESI) [M+H]+: 475.2.



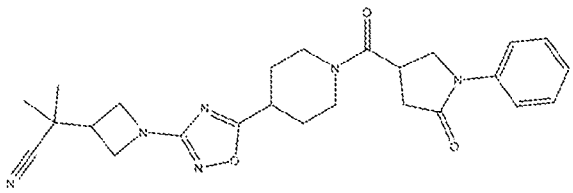
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.22-7.15 (m, 1H), 4.75 (br t, J = 14.6 Hz, 1H), 4.35 (q, J = 8.1 Hz, 1H), 4.10 (d, J = 2.2 Hz, 3H), 4.04 (br s, 1H), 3.96 (dt, J = 3.1, 9.0 Hz, 1H), 3.60 (quin, J = 8.5 Hz, 1H), 3.51 (dt, J = 4.0, 11.0 Hz, 1H), 3.46-3.33 (m, 1H), 3.07-2.92 (m, 2H), 2.91-2.82 (m, 1H), 2.61 (s, 3H), 2.43-2.28 (m, 2H), 2.01-1.87 (m, 2H); LCMS (ESI) [M+H]+: 501.2.



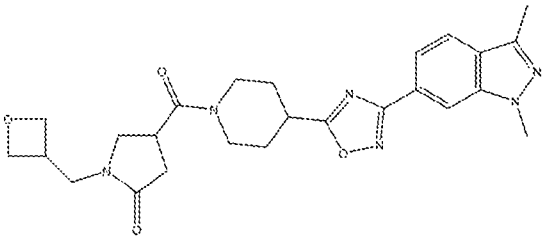
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.24 (s, 1H), 8.53 (br d, J = 8.1 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 8.07 (br s, 1H), 7.62 (d, J = 8.1 Hz, 2H), 7.40 (t, J = 7.9 Hz, 2H), 7.22-7.17 (m, 1H), 4.64-4.50 (m, 1H), 4.37-4.30 (m, 1H), 4.05-3.94 (m, 2H), 3.61 (quin, J = 8.4 Hz, 1H), 3.47-3.33 (m, 2H), 3.09 (d, J = 5.1 Hz, 4H), 3.04-2.94 (m, 1H), 2.91-2.82 (m, 1H), 2.35-2.22 (m, 2H), 2.07-1.92 (m, 2H); LCMS (ESI) [M+H]+: 475.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.89-7.83 (m, 2H), 7.73-7.67 (m, 2H), 7.57-7.50 (m, 1H), 7.50-7.43 (m, 2H), 7.38-7.31 (m, 2H), 4.53 (br d, J = 14.6 Hz, 1H), 4.32 (d, J = 3.3 Hz, 2H), 3.98 (s, 3H), 3.92 (br d, J = 13.5 Hz, 1H), 3.40-3.30 (m, 2H), 3.19-3.09 (m, 1H), 2.32-2.20 (m, 2H), 2.08-1.93 (m, 2H); LCMS (ESI) [M+H]+: 505.1.

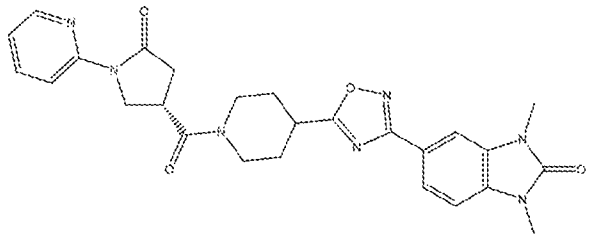


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.60 (d, J = 8.2 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.21-7.14 (m, 1H), 4.49 (br t, J = 14.6 Hz, 1H), 4.30 (dd, J = 7.3, 9.7 Hz, 1H), 4.21-4.13 (m, 2H), 4.05-3.98 (m, 2H), 3.93 (br t, J = 8.7 Hz, 2H), 3.57 (quin, J = 8.5 Hz, 1H), 3.39-3.27 (m, 1H), 3.18-2.92 (m, 3H), 2.88-2.79 (m, 2H), 2.20-2.08 (m, 2H), 1.88 (br d, J = 12.1 Hz, 2H), 1.35 (s, 6H); LCMS (ESI) [M+H]+: 463.2.



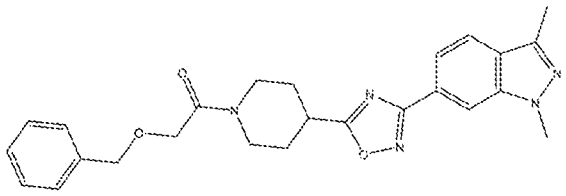
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (d, J = 4.4 Hz, 1H), 7.86-7.79 (m, 1H), 7.77-7.71 (m, 1H), 4.87-4.78 (m, 2H), 4.61-4.45 (m, 3H), 4.09 (d, J = 2.6 Hz, 3H), 3.92 (br d, J = 8.4 Hz, 1H), 3.87-3.79 (m,

1H), 3.77-3.69 (m, 1H), 3.63-3.56 (m, 1H), 3.50-3.42 (m, 2H), 3.41-3.23 (m, 3H), 3.15-3.00 (m, 1H), 2.79-2.63 (m, 2H), 2.61 (s, 3H), 2.26 (br s, 2H), 2.06-1.90 (m, 2H); LCMS (ESI) [M+H]+: 479.2.

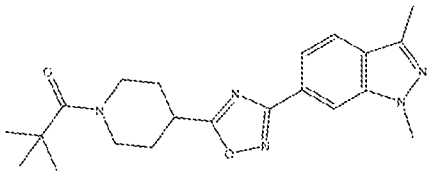


5

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.35-8.25 (m, 2H), 7.82 (br d, J = 8.2 Hz, 1H), 7.66-7.59 (m, 2H), 7.02-6.95 (m, 2H), 4.52-4.42 (m, 1H), 4.35 (dd, J = 8.9, 11.0 Hz, 1H), 4.18-4.08 (m, 1H), 3.95 (br d, J = 13.6 Hz, 1H), 3.54-3.47 (m, 1H), 3.41 (d, J = 8.8 Hz, 6H), 3.36-3.23 (m, 2H), 3.18 (dd, J = 7.8, 17.2 Hz, 1H), 3.10-2.97 (m, 1H), 2.81-2.69 (m, 1H), 2.22-2.15 (m, 2H), 2.07-1.84 (m, 2H); LCMS (ESI) [M+H]+:
10 502.3.

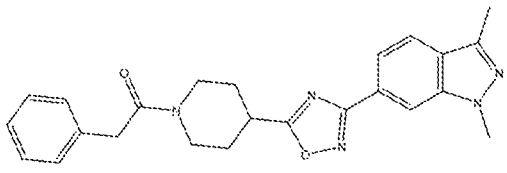


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.87-7.80 (m, 1H), 7.78-7.71 (m, 1H), 7.43-7.29
15 (m, 5H), 4.63 (s, 2H), 4.51 (br d, J = 13.0 Hz, 1H), 4.23 (d, J = 2.8 Hz, 2H), 4.08 (s, 3H), 4.02 (br d, J = 13.6 Hz, 1H), 3.36-3.23 (m, 2H), 3.04 (br t, J = 11.8 Hz, 1H), 2.61 (s, 3H), 2.21 (br s, 2H), 2.04-1.92 (m, 2H); LCMS (ESI) [M+H]+: 446.2.



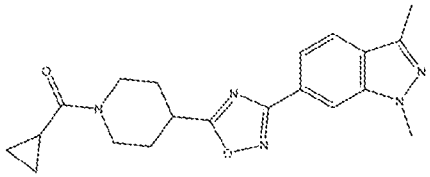
20

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.87-7.80 (m, 1H), 7.78-7.66 (m, 1H), 4.43 (br d, J = 13.8 Hz, 2H), 4.08 (s, 3H), 3.36-3.26 (m, 1H), 3.16 (br t, J = 11.8 Hz, 2H), 2.60 (s, 3H), 2.26-2.18 (m, 2H), 2.03-1.92 (m, 2H), 1.33 (s, 9H); LCMS (ESI) [M+H]+: 382.2.

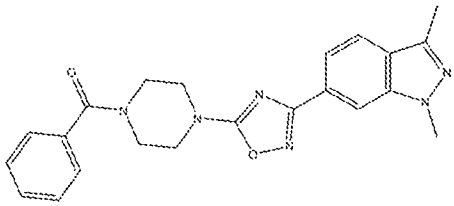


25

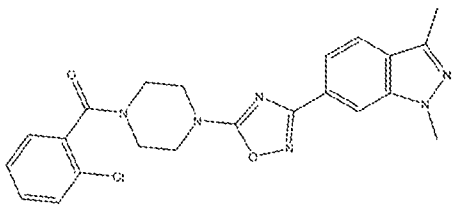
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.00 (s, 1H), 7.77-7.70 (m, 1H), 7.67-7.62 (m, 1H), 7.30-7.23 (m, 2H), 7.23-7.16 (m, 3H), 4.48 (br d, J = 13.4 Hz, 1H), 4.00 (s, 3H), 3.87 (br d, J = 13.7 Hz, 1H), 3.72 (s, 2H), 3.22-3.12 (m, 2H), 2.97 (br t, J = 11.1 Hz, 1H), 2.52 (s, 3H), 2.12 (br d, J = 10.8 Hz, 1H), 1.97 (br d, J = 10.8 Hz, 1H), 1.91-1.80 (m, 1H), 1.71-1.60 (m, 1H); LCMS (ESI) [M+H]+: 416.2.



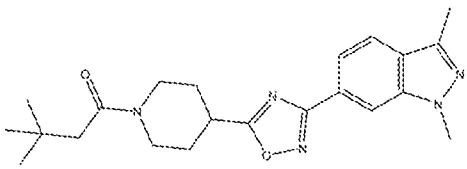
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.87-7.80 (m, 1H), 7.77-7.70 (m, 1H), 4.55 (br s, 1H), 4.31 (br s, 1H), 4.08 (s, 3H), 3.49-3.27 (m, 2H), 3.01 (br s, 1H), 2.60 (s, 3H), 2.24 (br s, 2H), 2.01 (br s, 2H), 1.85-1.75 (m, 1H), 1.02 (br s, 2H), 0.80 (br dd, J = 2.8, 7.6 Hz, 2H); LCMS (ESI) [M+H]+: 366.1.



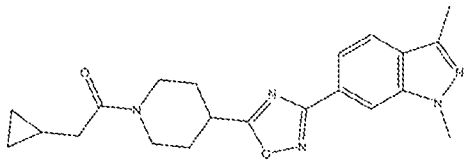
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.04 (s, 1H), 7.80-7.70 (m, 2H), 7.53-7.45 (m, 5H), 4.08 (s, 3H), 3.96-3.65 (m, 8H), 2.61 (s, 3H); LCMS (ESI) [M+H]+: 403.1.



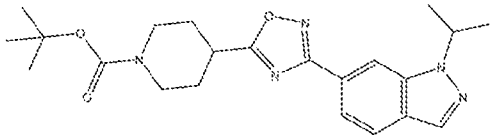
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.03 (s, 1H), 7.81-7.67 (m, 2H), 7.52-7.32 (m, 4H), 4.19-4.06 (m, 4H), 3.94-3.70 (m, 5H), 3.55-3.35 (m, 2H), 2.61 (s, 3H); LCMS (ESI) [M+H]+: 437.0.



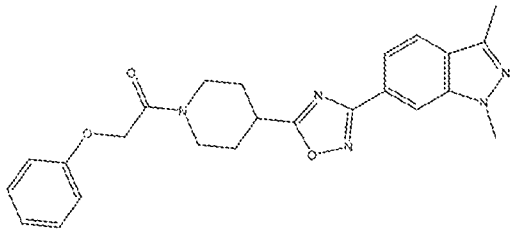
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.78-7.70 (m, 1H), 4.62 (br d, J = 13.1 Hz, 1H), 4.08 (s, 3H), 4.05 (br d, J = 15.3 Hz, 1H), 3.36-3.25 (m, 2H), 2.97 (br t, J = 11.7 Hz, 1H), 2.60 (s, 3H), 2.32 (s, 2H), 2.22 (br d, J = 12.2 Hz, 2H), 2.05-1.88 (m, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 396.2.



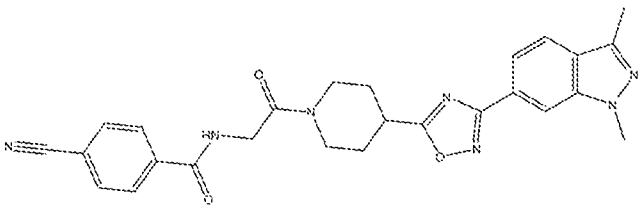
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.87-7.79 (m, 1H), 7.77-7.69 (m, 1H), 4.59 (br d, J = 13.1 Hz, 1H), 4.08 (s, 3H), 4.02-3.90 (m, 1H), 3.38-3.23 (m, 2H), 3.00 (br t, J = 11.5 Hz, 1H), 2.60 (s, 3H), 2.34 (d, J = 6.8 Hz, 2H), 2.23 (br d, J = 13.1 Hz, 2H), 2.06-1.89 (m, 2H), 1.15-1.02 (m, 1H), 0.66-0.53 (m, 2H), 0.25-0.18 (m, 2H); LCMS (ESI) [M+H]+: 380.2.



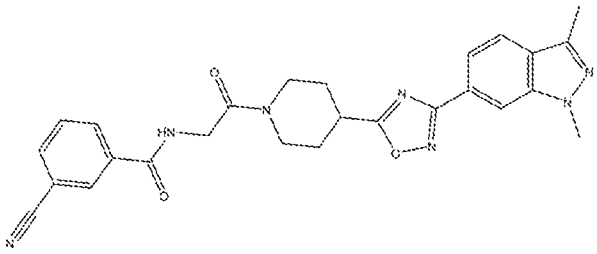
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.06 (s, 1H), 7.90-7.77 (m, 2H), 5.10-4.88 (m, 1H), 4.30-4.01 (m, 2H), 3.32-3.15 (m, 1H), 3.02 (t, J = 12.0 Hz, 2H), 2.29-2.06 (m, 2H), 2.04 -1.87 (m, 2H), 1.63 (d, J = 6.8 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 412.1.



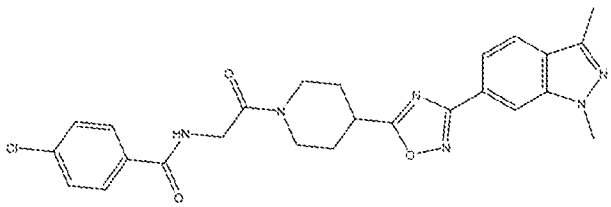
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.87-7.80 (m, 1H), 7.78-7.69 (m, 1H), 7.32 (t, J = 7.7 Hz, 2H), 7.05-6.94 (m, 3H), 4.74 (s, 2H), 4.49 (br d, J = 13.3 Hz, 1H), 4.14 (br s, 1H), 4.08 (s, 3H), 3.46-3.25 (m, 2H), 3.10 (br t, J = 11.4 Hz, 1H), 2.60 (s, 3H), 2.22 (br s, 2H), 2.10-1.91 (m, 2H); LCMS (ESI) [M+H]+: 432.2.



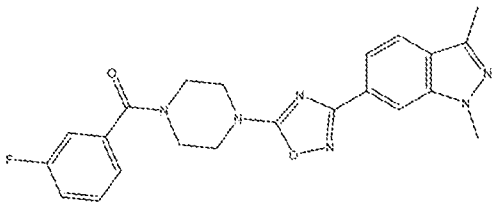
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.87-7.83 (m, 1H), 7.81-7.74 (m, 3H), 7.42 (br s, 1H), 4.54 (br d, J = 13.6 Hz, 1H), 4.33 (d, J = 3.7 Hz, 2H), 4.10 (s, 3H), 3.93 (br d, J = 14.1 Hz, 1H), 3.40 (br t, J = 10.7 Hz, 2H), 3.27-3.16 (m, 1H), 2.62 (s, 3H), 2.37-2.25 (m, 2H), 2.14-2.00 (m, 2H); LCMS (ESI) [M+H]+: 484.2.



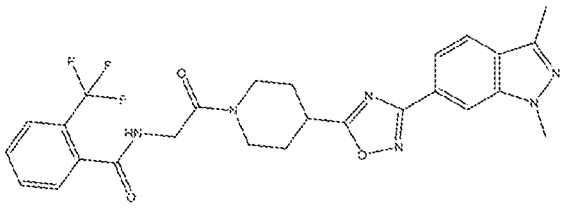
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 8.12-8.06 (m, 2H), 7.86-7.81 (m, 2H), 7.74 (s, 1H), 7.64-7.58 (m, 1H), 7.43 (br s, 1H), 4.58-4.50 (m, 1H), 4.33 (d, J = 3.8 Hz, 2H), 4.10 (s, 3H), 3.98-3.89 (m, 1H), 3.46-3.33 (m, 2H), 3.28-3.15 (m, 1H), 2.62 (s, 3H), 2.31 (dt, J = 3.3, 13.3 Hz, 2H), 2.14-1.98 (m, 2H); LCMS (ESI) [M+H]+: 484.2.



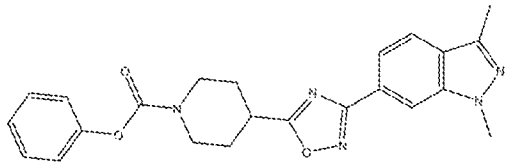
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.88-7.79 (m, 3H), 7.78-7.74 (m, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.33 (br s, 1H), 4.54 (br d, J = 13.4 Hz, 1H), 4.32 (d, J = 3.5 Hz, 2H), 4.10 (s, 3H), 3.94 (br d, J = 14.1 Hz, 1H), 3.39 (br t, J = 10.6 Hz, 2H), 3.19 (br t, J = 10.8 Hz, 1H), 2.62 (s, 3H), 2.35-2.23 (m, 2H), 2.13-1.99 (m, 2H); LCMS (ESI) [M+H]+: 493.1.



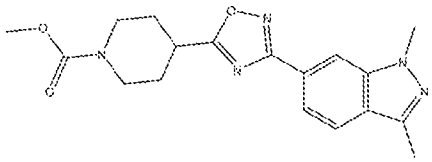
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.94 (s, 1H), 7.70-7.60 (m, 2H), 7.41-7.32 (m, 1H), 7.17-7.07 (m, 3H), 3.98 (s, 3H), 3.89-3.55 (m, 8H), 2.51 (s, 3H); LCMS (ESI) [M+H]+: 421.2.



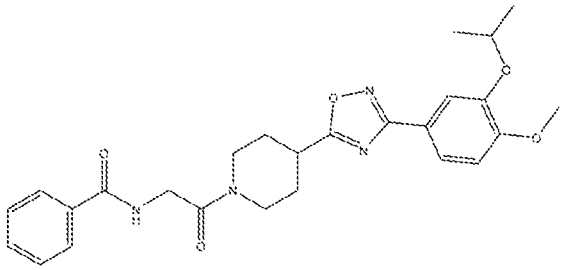
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.81-7.72 (m, 2H), 7.66-7.55 (m, 3H), 7.03 (br s, 1H), 4.52 (br d, J = 13.4 Hz, 1H), 4.34 (d, J = 3.9 Hz, 2H), 4.13 (s, 3H), 3.92 (br d, J = 13.7 Hz, 1H), 3.38 (br t, J = 10.6 Hz, 2H), 3.17 (br t, J = 11.0 Hz, 1H), 2.65 (s, 3H), 2.30 (br t, J = 13.9 Hz, 2H), 2.14-1.99 (m, 2H); LCMS (ESI) [M+H]+: 527.1.



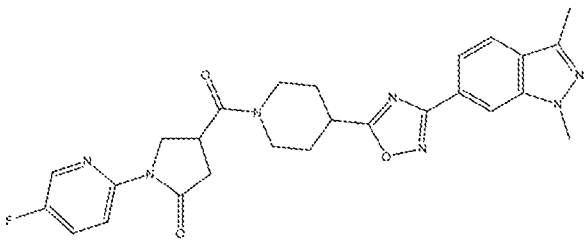
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 7.85 (dd, J = 1.0, 8.4 Hz, 1H), 7.78-7.71 (m, 1H), 7.43-7.34 (m, 2H), 7.25-7.19 (m, 1H), 7.14 (d, J = 7.7 Hz, 2H), 4.43-4.25 (m, 2H), 4.09 (s, 3H), 3.32 (tt, J = 3.9, 10.7 Hz, 2H), 3.20 (br s, 1H), 2.61 (s, 3H), 2.28 (br dd, J = 3.3, 13.4 Hz, 2H), 2.09 (br d, J = 10.8 Hz, 2H); LCMS (ESI) [M+H]+: 418.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.78-7.69 (m, 1H), 4.20 (br s, 2H), 4.08 (s, 3H), 3.74 (s, 3H), 3.29-3.19 (m, 1H), 3.10 (br t, J = 11.6 Hz, 2H), 2.60 (s, 3H), 2.18 (br d, J = 11.0 Hz, 2H), 2.03-1.90 (m, 2H); LCMS (ESI) [M+H]+: 356.2.

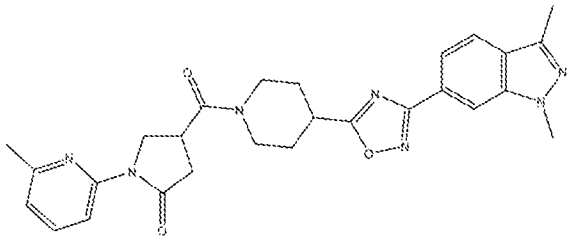


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.86 (d, J = 7.2 Hz, 2H), 7.67 (dd, J = 1.8, 8.3 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.56-7.50 (m, 1H), 7.49-7.43 (m, 2H), 7.34 (br s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.66 (spt, J = 6.1 Hz, 1H), 4.55-4.45 (m, 1H), 4.31 (d, J = 3.9 Hz, 2H), 3.92 (s, 3H), 3.90 (br d, J = 3.7 Hz, 1H), 3.39-3.27 (m, 2H), 3.21-3.10 (m, 1H), 2.24 (dt, J = 3.5, 12.9 Hz, 2H), 2.08-1.92 (m, 2H), 1.41 (d, J = 6.0 Hz, 6H); LCMS (ESI) [M+H]+: 479.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.45-8.39 (m, 1H), 8.18 (br s, 1H), 8.09 (s, 1H), 7.86-7.80 (m, 1H), 7.76-7.72 (m, 1H), 7.44 (br t, J = 8.3 Hz, 1H), 4.61-4.51 (m, 1H), 4.41-4.34 (m, 1H), 4.20 (td, J = 5.9,

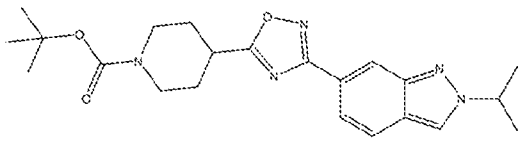
11.3 Hz, 1H), 4.08 (s, 3H), 4.02 (br d, J = 14.3 Hz, 1H), 3.57 (quin, J = 8.0 Hz, 1H), 3.47-3.31 (m, 2H), 3.22 (dd, J = 7.6, 17.3 Hz, 1H), 3.16-3.04 (m, 1H), 2.88-2.78 (m, 1H), 2.60 (s, 3H), 2.37-2.21 (m, 2H), 2.12-1.92 (m, 2H); LCMS (ESI) [M+H]+: 504.2.



5

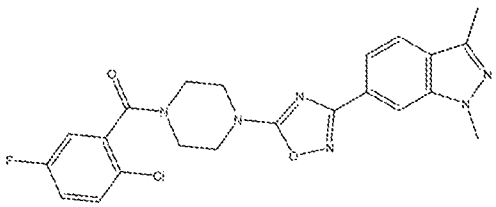
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (dd, J = 4.9, 7.9 Hz, 1H), 8.10 (s, 1H), 7.85-7.80 (m, 1H), 7.76-7.72 (m, 1H), 7.57 (t, J = 7.9 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 4.64-4.49 (m, 1H), 4.47-4.39 (m, 1H), 4.20 (dd, J = 7.1, 11.2 Hz, 1H), 4.08 (s, 3H), 4.03 (br s, 1H), 3.55 (quin, J = 8.3 Hz, 1H), 3.47-3.31 (m, 2H), 3.26-3.01 (m, 2H), 2.85-2.76 (m, 1H), 2.60 (s, 3H), 2.46 (d, J = 2.2 Hz, 3H), 2.26 (br d, J = 14.1 Hz, 2H), 2.12-1.91 (m, 2H); LCMS (ESI) [M+H]+: 500.2.

10



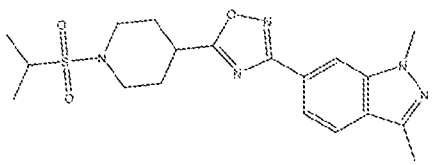
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.53 (s, 1H), 8.00 (s, 1H), 7.79-7.70 (m, 2H), 4.91-4.77 (m, 1H), 4.22-4.05 (m, 2H), 3.26-3.14 (m, 1H), 3.03 (br t, J = 11.2 Hz, 2H), 2.22-2.08 (m, 2H), 1.98-1.85 (m, 2H), 1.69 (d, J = 6.8 Hz, 6H), 1.94 (s, 9H); LCMS (ESI) [M+H]+: 412.2.

15



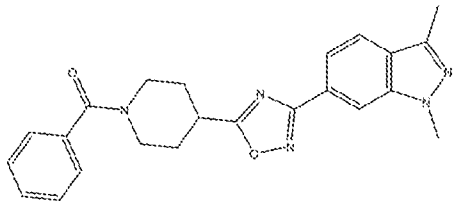
20

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.94 (s, 1H), 7.70-7.60 (m, 2H), 7.35 (dd, J = 4.8, 8.8 Hz, 1H), 7.06-6.96 (m, 2H), 4.07-3.96 (m, 4H), 3.88-3.60 (m, 5H), 3.45-3.28 (m, 2H), 2.51 (s, 3H); LCMS (ESI) [M+H]+: 455.1.

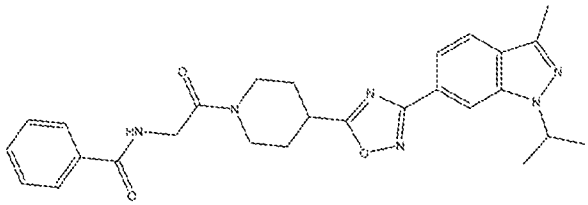


25

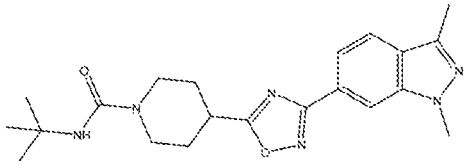
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.78-7.69 (m, 1H), 4.09 (s, 3H), 3.89 (br d, J = 13.1 Hz, 2H), 3.28-3.14 (m, 4H), 2.60 (s, 3H), 2.26 (br dd, J = 2.9, 13.4 Hz, 2H), 2.17-2.05 (m, 2H), 1.38 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 404.1.



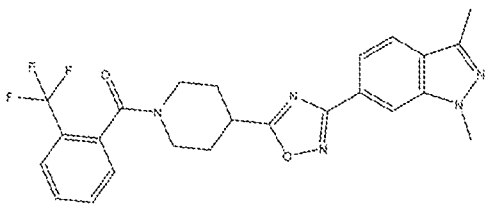
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.90-7.81 (m, 1H), 7.78-7.70 (m, 1H), 7.44 (s, 5H), 4.82-4.37 (m, 1H), 4.09 (s, 3H), 3.91 (br s, 1H), 3.40-3.30 (m, 1H), 3.30-3.17 (m, 2H), 2.61 (s, 3H), 2.37-1.96 (m, 4H); LCMS (ESI) [M+H]+: 402.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 7.89-7.84 (m, 2H), 7.83-7.78 (m, 1H), 7.75-7.70 (m, 1H), 7.55-7.49 (m, 1H), 7.49-7.42 (m, 2H), 7.33 (br s, 1H), 4.88 (m, 1H), 4.53 (m, J = 3.7, 13.5 Hz, 1H), 4.32 (d, J = 3.9 Hz, 2H), 3.99-3.87 (m, 1H), 3.43-3.29 (m, 2H), 3.23-3.09 (m, 1H), 2.61 (s, 3H), 2.28 (m, 2H), 2.13-1.92 (m, 2H), 1.60 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 487.2.

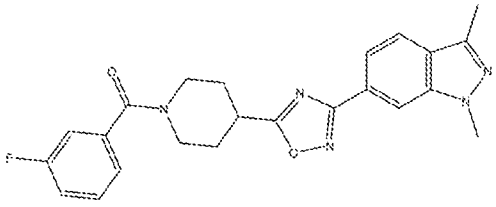


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.77-7.70 (m, 1H), 4.35 (br s, 1H), 4.08 (s, 3H), 3.96 (br d, J = 13.4 Hz, 2H), 3.26-3.16 (m, 1H), 3.08-2.99 (m, 2H), 2.60 (s, 3H), 2.19 (br d, J = 10.3 Hz, 2H), 2.04-1.92 (m, 2H), 1.38 (s, 9H); LCMS (ESI) [M+H]+: 397.2.

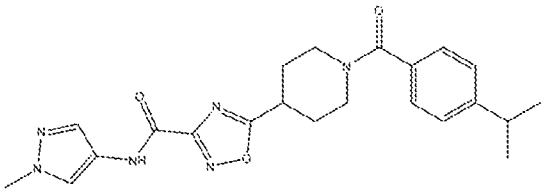


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.88-7.80 (m, 1H), 7.74 (br d, J = 7.9 Hz, 2H), 7.68-7.60 (m, 1H), 7.59-7.52 (m, 1H), 7.38 (dd, J = 7.5, 17.2 Hz, 1H), 4.78-4.63 (m, 1H), 4.09 (s, 3H),

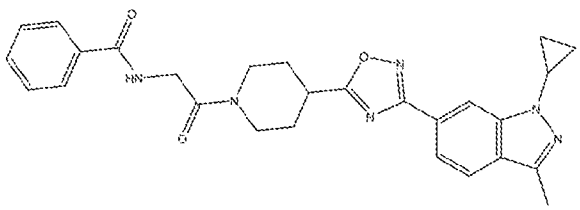
3.58-3.46 (m, 1H), 3.39-3.14 (m, 3H), 2.61 (s, 3H), 2.38-2.30 (m, 1H), 2.16-1.86 (m, 3H); LCMS (ESI) [M+H]+: 470.1.



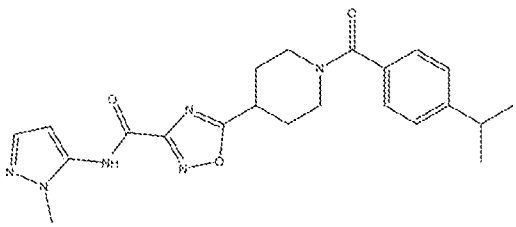
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.84 (dd, J = 1.0, 8.4 Hz, 1H), 7.79-7.70 (m, 1H), 7.48-7.37 (m, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.19-7.10 (m, 2H), 4.65 (br s, 1H), 4.09 (s, 3H), 3.91 (br s, 1H), 3.45-3.16 (m, 3H), 2.61 (s, 3H), 2.42-1.91 (m, 4H); LCMS (ESI) [M+H]+: 420.1.



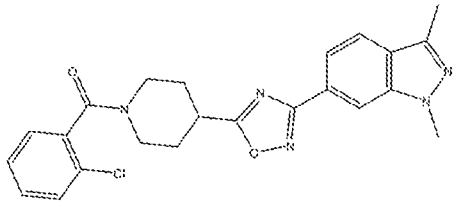
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.67 (s, 1H), 8.10 (s, 1H), 7.54 (s, 1H), 7.38-7.33 (m, 2H), 7.29-7.26 (m, 2H), 4.62 (br s, 1H), 4.10 (s, 1H), 3.93 (s, 3H), 3.34 (tt, J = 4.0, 10.8 Hz, 1H), 3.19 (br s, 2H), 2.94 (spt, J = 6.9 Hz, 1H), 2.18 (br d, J = 4.6 Hz, 2H), 1.98 (br d, J = 9.5 Hz, 2H), 1.27 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 423.2.



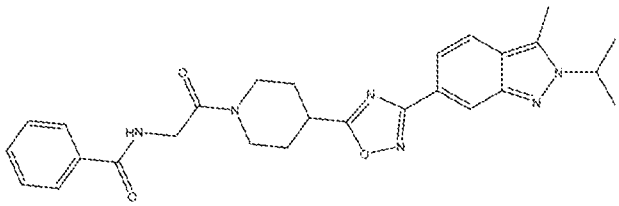
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 7.89-7.82 (m, 3H), 7.72 (d, J = 8.6 Hz, 1H), 7.56-7.50 (m, 1H), 7.49-7.43 (m, 2H), 7.35 (br s, 1H), 4.59-4.49 (m, 1H), 4.32 (d, J = 3.7 Hz, 2H), 3.94 (br d, J = 13.9 Hz, 1H), 3.58 (tt, J = 3.6, 6.9 Hz, 1H), 3.44-3.30 (m, 2H), 3.23-3.10 (m, 1H), 2.58 (s, 3H), 2.29 (dt, J = 3.2, 13.1 Hz, 2H), 2.15-1.95 (m, 2H), 1.28-1.17 (m, 4H); LCMS (ESI) [M+H]+: 485.2.



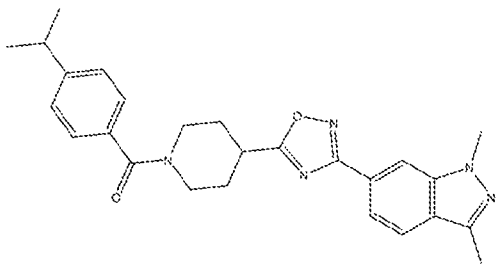
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.52 (s, 1H), 7.49 (d, J = 1.8 Hz, 1H), 7.38-7.34 (m, 2H), 7.28 (d, J = 7.7 Hz, 2H), 6.43 (d, J = 1.8 Hz, 1H), 4.84-4.39 (m, 1H), 4.35-3.91 (m, 1H), 3.85 (s, 3H), 3.37 (tt, J = 4.0, 10.9 Hz, 1H), 3.28-3.10 (m, 2H), 2.95 (spt, J = 6.9 Hz, 1H), 2.19 (br d, J = 9.9 Hz, 2H), 2.08-1.87 (m, 2H), 1.27 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 423.2.



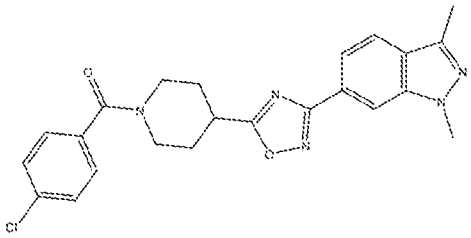
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (d, J = 2.6 Hz, 1H), 7.87-7.80 (m, 1H), 7.78-7.70 (m, 1H), 7.43 (br d, J = 5.4 Hz, 1H), 7.40-7.28 (m, 3H), 4.80-4.63 (m, 1H), 4.08 (s, 3H), 3.67-3.53 (m, 1H), 3.41-3.12 (m, 3H), 2.60 (s, 3H), 2.34 (br d, J = 13.1 Hz, 1H), 2.20-1.87 (m, 3H); LCMS (ESI) [M+H]+: 436.1.



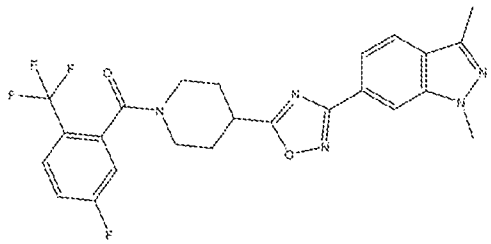
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.50 (s, 1H), 7.85 (br d, J = 7.3 Hz, 2H), 7.66 (m, 2H), 7.55-7.41 (m, 3H), 7.35 (br s, 1H), 4.78 (td, J = 6.7, 13.3 Hz, 1H), 4.44 (br d, J = 13.2 Hz, 1H), 4.30 (m, 2H), 3.90 (br d, J = 13.5 Hz, 1H), 3.43-3.28 (m, 2H), 3.22 (br t, J = 11.4 Hz, 1H), 2.72-2.56 (s, 3H), 2.33-2.17 (m, 2H), 2.13-1.91 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 487.2.



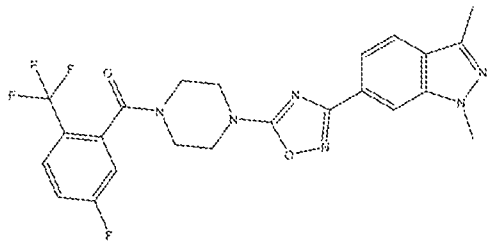
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.79-7.67 (m, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 4.63 (br s, 1H), 4.10 (s, 3H), 3.92 (br s, 1H), 3.45-3.13 (m, 3H), 2.96 (quind, J = 6.8, 13.8 Hz, 1H), 2.62 (s, 3H), 2.38-1.94 (m, 4H), 1.28 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 444.2.



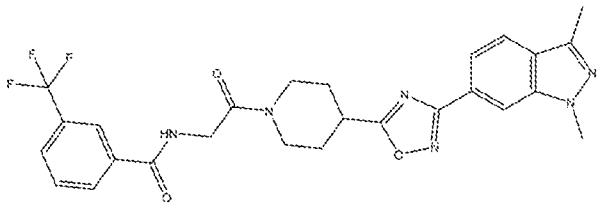
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.88-7.81 (m, 1H), 7.78-7.71 (m, 1H), 7.46-7.37 (m, 4H), 4.60 (br s, 1H), 4.09 (s, 3H), 3.91 (br s, 1H), 3.44-3.13 (m, 3H), 2.61 (s, 3H), 2.40-1.88 (m, 4H); LCMS (ESI) [M+H]+: 436.1.



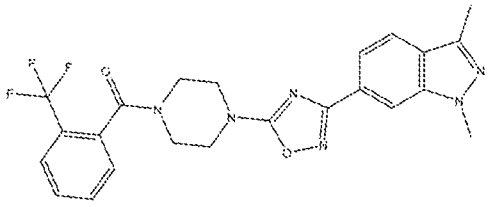
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.88-7.80 (m, 1H), 7.78-7.69 (m, 2H), 7.27-7.20 (m, 1H), 7.09 (br dd, J = 7.9, 16.6 Hz, 1H), 4.78-4.55 (m, 1H), 4.09 (s, 3H), 3.58-3.46 (m, 1H), 3.41-3.16 (m, 3H), 2.61 (s, 3H), 2.43-2.26 (m, 1H), 2.19-1.90 (m, 3H); LCMS (ESI) [M+H]+: 488.1.



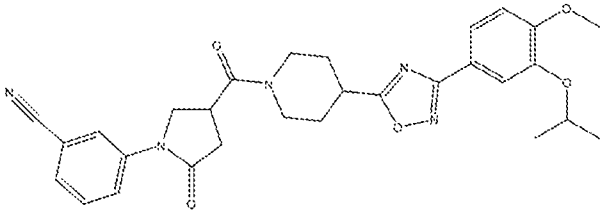
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.93 (s, 1H), 7.72-7.60 (m, 3H), 7.21 (br d, J = 2.3 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.02 (dd, J = 2.4, 7.9 Hz, 1H), 4.05-3.96 (m, 4H), 3.86-3.69 (m, 3H), 3.65-3.55 (m, 2H), 3.30 (t, J = 5.2 Hz, 2H), 2.51 (s, 3H); LCMS (ESI) [M+H]+: 489.1.



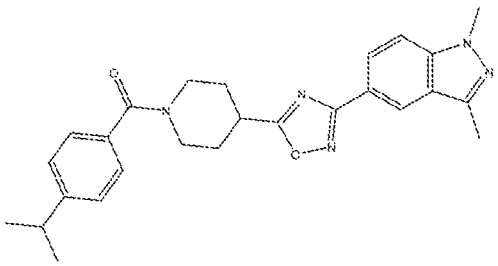
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09-8.00 (m, 2H), 7.95 (d, J = 7.8 Hz, 1H), 7.78-7.65 (m, 3H), 7.56-7.50 (m, 1H), 7.32 (br s, 1H), 4.49-4.41 (m, 1H), 4.25 (d, J = 3.9 Hz, 2H), 4.01 (s, 3H), 3.89-3.81 (m, 1H), 3.34-3.26 (m, 2H), 3.16-3.07 (m, 1H), 2.52 (s, 3H), 2.22 (dt, J = 3.5, 13.5 Hz, 2H), 2.04-1.90 (m, 2H); LCMS (ESI) [M+H]+: 527.1.



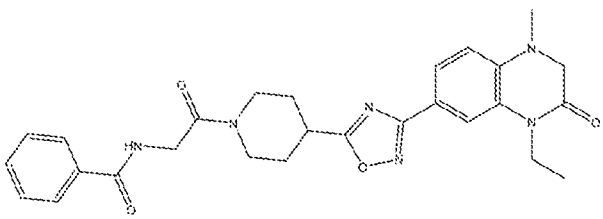
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.82-7.69 (m, 3H), 7.69-7.57 (m, 2H), 7.39 (d, J = 7.5 Hz, 1H), 4.15-4.06 (m, 4H), 3.96-3.79 (m, 3H), 3.71-3.61 (m, 2H), 3.40-3.33 (m, 2H), 2.60 (s, 3H); LCMS (ESI) [M+H]+: 471.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) 8.02-7.83 (m, 2H), 7.66 (br d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.51-7.40 (m, 2H), 6.95 (d, J = 8.6 Hz, 1H), 4.67-4.62 (m, 1H), 4.58-4.44 (m, 1H), 4.37-4.27 (m, 1H), 4.01-3.93 (m, 2H), 3.91 (s, 3H), 3.64-3.56 (m, 1H), 3.45-3.24 (m, 2H), 3.19-3.02 (m, 1H), 3.01-2.83 (m, 2H), 2.24 (br t, J = 14.4 Hz, 2H), 2.09-1.88 (m, 2H), 1.40 (br d, J = 5.7 Hz, 6H); LCMS (ESI) [M+H]+: 530.2.

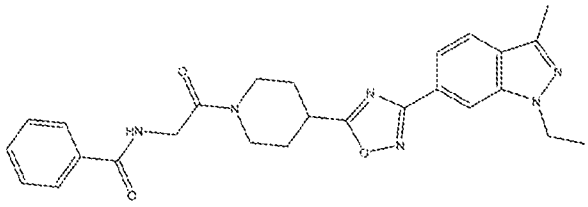


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.41 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.44-7.33 (m, 3H), 7.27 (d, J = 7.9 Hz, 2H), 4.63 (br s, 1H), 4.03 (s, 4H), 3.32 (br t, J = 10.7 Hz, 1H), 3.21 (br s, 2H), 2.97-2.90 (m, 1H), 2.62 (s, 3H), 2.36-1.87 (m, 4H), 1.26 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 444.1.

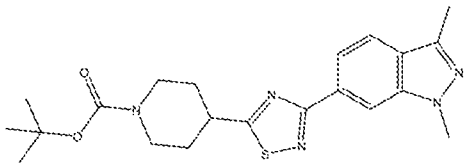


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.86 (d, J = 7.1 Hz, 2H), 7.75 (dd, J = 1.5, 8.4 Hz, 1H), 7.65 (d, J = 1.3 Hz, 1H), 7.57-7.50 (m, 1H), 7.49-7.43 (m, 2H), 7.35 (br s, 1H), 6.76 (d, J = 8.4 Hz, 1H), 4.52 (br d, J = 13.7 Hz, 1H), 4.31 (d, J = 3.7 Hz, 2H), 4.17-4.05 (m, 2H), 3.92 (br d, J = 14.1 Hz, 1H), 3.85 (s, 2H),

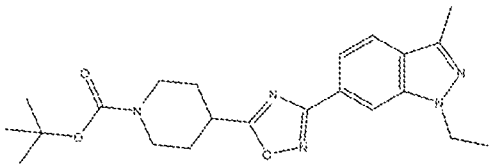
3.42-3.28 (m, 2H), 3.19-3.07 (m, 1H), 2.92 (s, 3H), 2.33-2.19 (m, 2H), 2.10-1.91 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 503.2.



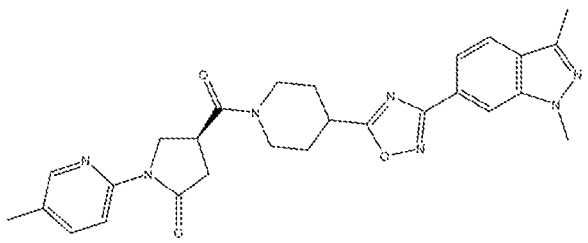
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.42 (s, 1H), 8.07 (dd, J = 0.9, 8.8 Hz, 1H), 7.87 (d, J = 7.3 Hz, 2H), 7.56-7.51 (m, 1H), 7.45 (dd, J = 8.4, 17.2 Hz, 3H), 7.35 (br s, 1H), 4.53 (br d, J = 13.7 Hz, 1H), 4.43-4.37 (m, 2H), 4.32 (d, J = 3.7 Hz, 2H), 3.94 (br d, J = 13.9 Hz, 1H), 3.41-3.32 (m, 1H), 3.36 (dt, J = 4.1, 10.3 Hz, 1H), 3.17 (br t, J = 10.9 Hz, 1H), 2.63 (s, 3H), 2.35-2.22 (m, 2H), 2.12-1.96 (m, 2H), 1.52 (t, J = 7.3 Hz, 3H; LCMS (ESI) [M+H]+: 473.2.



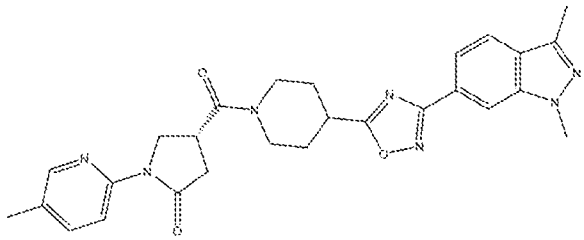
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 4.26 (br s, 2H), 4.09 (s, 3H), 3.41-3.31 (m, 1H), 2.98 (br t, J = 12.0 Hz, 2H), 2.60 (s, 3H), 2.23 (br d, J = 12.0 Hz, 2H), 1.85 (dq, J = 4.0, 12.0 Hz, 2H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 414.1.



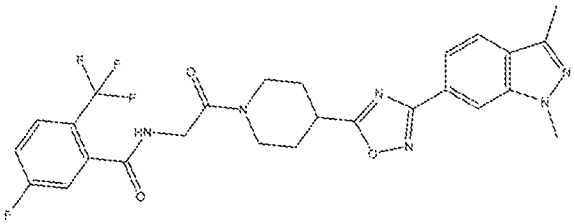
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.34 (s, 1H), 7.99 (dd, J = 1.2, 8.7 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 4.31 (q, J = 7.3 Hz, 2H), 4.08 (br d, J = 10.1 Hz, 2H), 3.15-3.08 (m, 1H), 2.94 (br t, J = 11.7 Hz, 2H), 2.55 (s, 3H), 2.07 (br dd, J = 2.9, 13.2 Hz, 2H), 1.93-1.82 (m, 2H), 1.46-1.43 (m, 3H), 1.41 (s, 9H); LCMS (ESI) [M+H]+: 412.2.



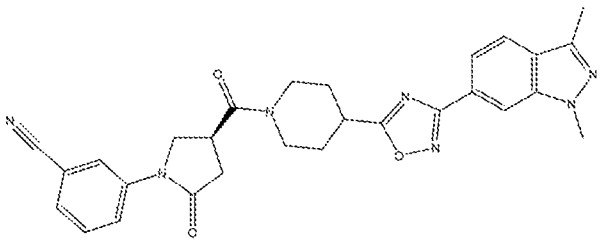
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28-8.24 (m, 1H), 8.14 (br s, 1H), 8.09 (d, J = 3.5 Hz, 1H), 7.85-7.80 (m, 1H), 7.74-7.72 (m, 1H), 7.51 (br d, J = 8.8 Hz, 1H), 4.56 (br t, J = 13.4 Hz, 1H), 4.40 (dd, J = 9.2, 11.0 Hz, 1H), 4.21-4.12 (m, 1H), 4.08 (s, 3H), 4.03 (br d, J = 13.6 Hz, 1H), 3.62-3.51 (m, 1H), 3.46-3.30 (m, 2H), 3.25 (dd, J = 7.9, 17.1 Hz, 1H), 3.15-3.01 (m, 1H), 2.86-2.74 (m, 1H), 2.59 (s, 3H), 2.35-2.20 (m, 5H), 2.12-1.91 (m, 2H); LCMS (ESI) [M+H]+: 500.2.



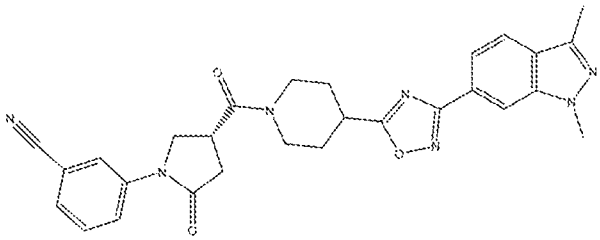
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28-8.24 (m, 1H), 8.14 (br s, 1H), 8.09 (d, J = 3.5 Hz, 1H), 7.85-7.80 (m, 1H), 7.76-7.71 (m, 1H), 7.51 (br d, J = 8.3 Hz, 1H), 4.56 (br t, J = 12.7 Hz, 1H), 4.40-4.37 (m, 1H), 4.21-4.13 (m, 1H), 4.08 (s, 3H), 4.03 (br d, J = 13.2 Hz, 1H), 3.62-3.51 (m, 1H), 3.46-3.30 (m, 2H), 3.25 (dd, J = 7.7, 17.3 Hz, 1H), 3.15-3.01 (m, 1H), 2.86-2.75 (m, 1H), 2.59 (s, 3H), 2.35-2.20 (m, 5H), 2.11-1.91 (m, 2H); LCMS (ESI) [M+H]+: 500.2.



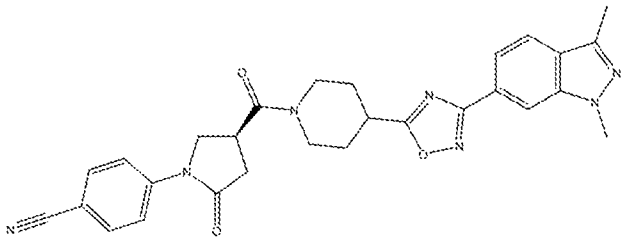
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.75 (dd, J = 0.9, 8.4 Hz, 1H), 7.69-7.62 (m, 2H), 7.22 (dd, J = 2.4, 8.1 Hz, 1H), 7.19-7.14 (m, 1H), 6.97 (br s, 1H), 4.46-4.36 (m, 1H), 4.23 (d, J = 4.0 Hz, 2H), 4.01 (s, 3H), 3.81 (br d, J = 13.9 Hz, 1H), 3.34-3.24 (m, 2H), 3.13-3.04 (m, 1H), 2.53 (s, 3H), 2.27-2.15 (m, 2H), 2.05-1.91 (m, 2H); LCMS (ESI) [M+H]+: 545.1.



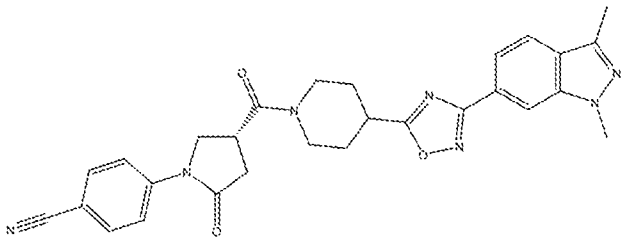
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (d, J = 2.3 Hz, 1H), 8.02-7.89 (m, 2H), 7.87-7.82 (m, 1H), 7.79-7.73 (m, 1H), 7.54-7.43 (m, 2H), 4.66-4.48 (m, 1H), 4.35 (dd, J = 6.6, 9.4 Hz, 1H), 4.10 (d, J = 2.1 Hz, 3H), 4.06-3.92 (m, 2H), 3.64 (m, 1H), 3.52-3.33 (m, 2H), 3.25-3.07 (m, 1H), 3.06-2.86 (m, 2H), 2.62 (s, 3H), 2.39-2.23 (m, 2H), 2.15-1.95 (m, 2H); LCMS (ESI) [M+H]+: 510.2.



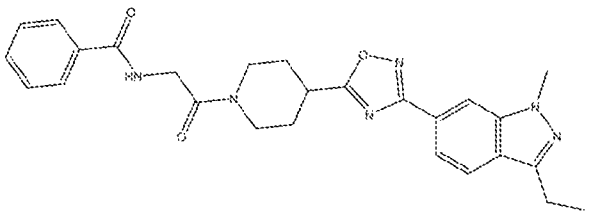
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (d, J = 2.3 Hz, 1H), 8.00-7.87 (m, 2H), 7.86-7.80 (m, 1H), 7.77-7.70 (m, 1H), 7.53-7.40 (m, 2H), 4.62-4.47 (m, 1H), 4.33 (dd, J = 6.7, 9.4 Hz, 1H), 4.08 (d, J = 2.3 Hz, 3H), 4.03-3.90 (m, 2H), 3.61 (td, J = 8.3, 16.1 Hz, 1H), 3.51-3.31 (m, 2H), 3.13 (m, 1H), 3.02-2.83 (m, 2H), 2.60 (s, 3H), 2.38-2.20 (m, 2H), 2.12-1.92 (m, 2H); LCMS (ESI) [M+H]+: 510.2.



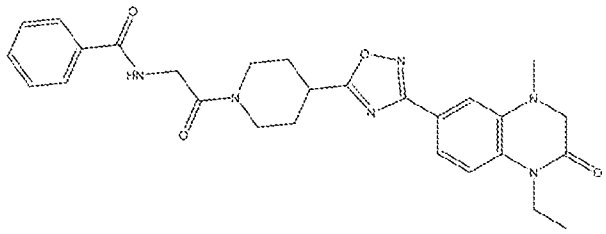
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.85-7.71 (m, 4H), 7.66 (d, J = 8.8 Hz, 2H), 4.62-4.47 (m, 1H), 4.35 (dd, J = 6.8, 9.6 Hz, 1H), 4.08 (s, 3H), 4.03-3.91 (m, 2H), 3.61 (m, 1H), 3.48-3.30 (m, 2H), 3.22-3.05 (m, 1H), 3.03-2.84 (m, 2H), 2.60 (s, 3H), 2.29 (br t, J = 13.2 Hz, 2H), 2.12-1.92 (m, 2H); LCMS (ESI) [M+H]+: 510.2.



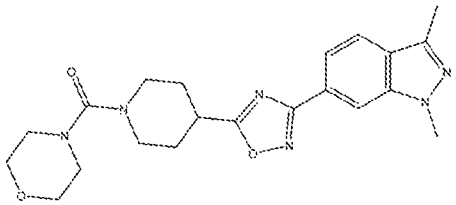
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.85-7.72 (m, 4H), 7.66 (d, J = 8.8 Hz, 2H), 4.65-4.47 (m, 1H), 4.35 (dd, J = 6.8, 9.6 Hz, 1H), 4.08 (s, 3H), 4.03-3.89 (m, 2H), 3.61 (m, 1H), 3.48-3.31 (m, 2H), 3.22-3.05 (m, 1H), 3.03-2.85 (m, 2H), 2.60 (s, 3H), 2.29 (br t, J = 13.3 Hz, 2H), 2.14-1.92 (m, 2H); LCMS (ESI) [M+H]+: 510.2.



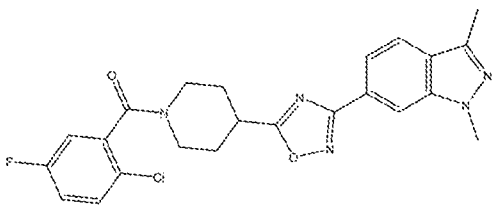
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.90-7.77 (m, 4H), 7.57-7.45 (m, 3H), 7.36 (br s, 1H), 4.59-4.50 (m, 1H), 4.33 (d, J = 3.8 Hz, 2H), 4.10 (s, 3H), 3.95 (br d, J = 14.1 Hz, 1H), 3.38 (ddd, J = 3.3, 10.6, 14.0 Hz, 2H), 3.22-3.12 (m, 1H), 3.07-3.00 (m, 1H), 3.04 (q, J = 7.6 Hz, 1H), 2.30 (dt, J = 3.3, 13.0 Hz, 2H), 2.11-1.97 (m, 2H), 1.44 (t, J = 7.6 Hz, 3H); LCMS (ESI) [M+H]+: 473.2.



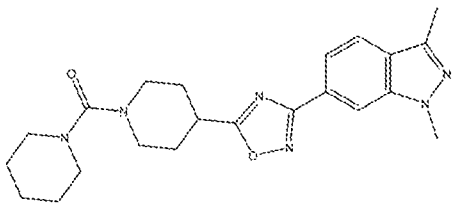
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.86 (br d, J = 6.8 Hz, 2H), 7.60 (dd, J = 1.6, 8.4 Hz, 1H), 7.53 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 1.2 Hz, 1H), 7.37-7.31 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 4.52 (td, J = 3.6, 13.6 Hz, 1H), 4.31 (d, J = 8.0 Hz, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.92 (d, J = 13.6 Hz, 1H), 3.42-3.27 (m, 2H), 3.20-3.07 (m, 1H), 2.93 (s, 3H), 2.34-2.17 (m, 2H), 2.08-1.90 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); LCMS (ESI) [M+H]+: 503.3.



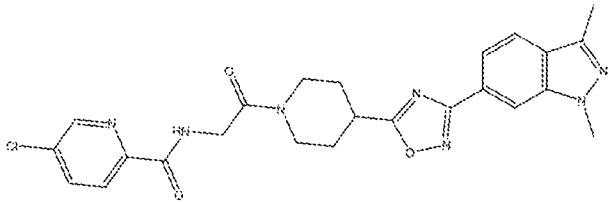
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.87-7.79 (m, 1H), 7.78-7.66 (m, 1H), 4.08 (s, 3H), 3.79 (br d, J = 13.4 Hz, 2H), 3.74-3.64 (m, 4H), 3.37-3.28 (m, 4H), 3.28-3.18 (m, 1H), 3.04 (br t, J = 11.6 Hz, 2H), 2.60 (s, 3H), 2.20 (br d, J = 10.9 Hz, 2H), 2.09-1.95 (m, 2H); LCMS (ESI) [M+H]+: 411.2.



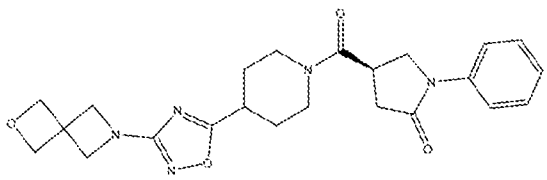
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.87-7.80 (m, 1H), 7.78-7.70 (m, 1H), 7.45-7.32 (m, 1H), 7.16-6.98 (m, 2H), 4.76-4.60 (m, 1H), 4.09 (s, 3H), 3.59 (br t, J = 12.8 Hz, 1H), 3.41-3.16 (m, 3H), 2.60 (s, 3H), 2.34 (br d, J = 11.1 Hz, 1H), 2.24-1.87 (m, 3H); LCMS (ESI) [M+H]+: 454.1.



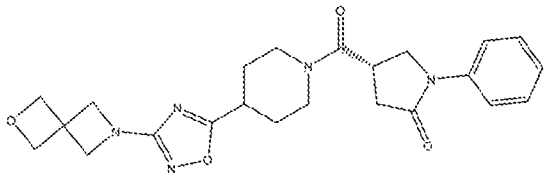
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.77-7.68 (m, 1H), 4.08 (s, 3H), 3.75 (br d, J = 13.4 Hz, 2H), 3.30-3.15 (m, 5H), 2.99 (br t, J = 11.8 Hz, 2H), 2.60 (s, 3H), 2.18 (br d, J = 10.9 Hz, 2H), 2.08-1.95 (m, 2H), 1.60 (br s, 6H); LCMS (ESI) [M+H]+: 409.2.



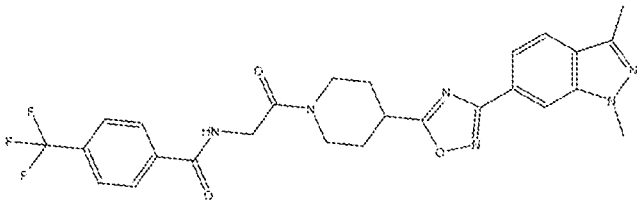
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.79 (br s, 1H), 8.55 (s, 1H), 8.14-8.07 (m, 2H), 7.81 (br d, J = 8.4 Hz, 2H), 7.75-7.70 (m, 1H), 4.54 (br d, J = 13.7 Hz, 1H), 4.32 (br d, J = 4.2 Hz, 2H), 4.07 (s, 3H), 3.93 (br d, J = 13.7 Hz, 1H), 3.41-3.30 (m, 2H), 3.13 (br t, J = 11.6 Hz, 1H), 2.59 (s, 3H), 2.32-2.19 (m, 2H), 2.10-1.93 (m, 2H); LCMS (ESI) [M+H]+: 494.1.



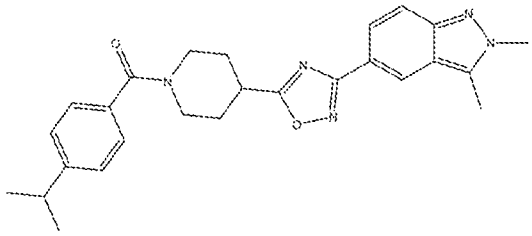
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.59 (br d, J = 7.7 Hz, 2H), 7.38 (br t, J = 7.4 Hz, 2H), 7.22-7.13 (m, 1H), 4.83 (s, 4H), 4.49 (br t, J = 15.0 Hz, 1H), 4.33-4.27 (m, 1H), 4.22 (s, 4H), 3.97-3.87 (m, 2H), 3.61-3.50 (m, 1H), 3.31 (br d, J = 8.2 Hz, 1H), 3.16-2.90 (m, 3H), 2.87-2.77 (m, 1H), 2.19-2.07 (m, 2H), 1.86 (br d, J = 10.4 Hz, 2H); LCMS (ESI) [M+H]+: 438.2.



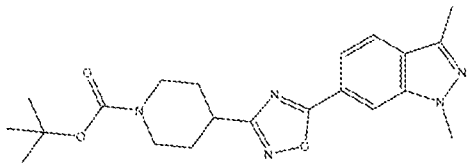
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.59 (br d, J = 7.5 Hz, 2H), 7.38 (br t, J = 7.2 Hz, 2H), 7.22-7.13 (m, 1H), 4.83 (br s, 4H), 4.49 (br t, J = 15.0 Hz, 1H), 4.30 (br t, J = 8.2 Hz, 1H), 4.22 (br s, 4H), 3.97-3.87 (m, 2H), 3.61-3.51 (m, 1H), 3.31 (br d, J = 6.8 Hz, 1H), 3.17-2.90 (m, 3H), 2.87-2.77 (m, 1H), 2.19-2.07 (m, 2H), 1.86 (br d, J = 10.6 Hz, 2H); LCMS (ESI) [M+H]+: 438.2.



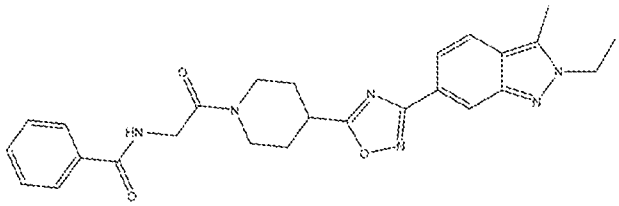
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.99 (d, J = 8.1 Hz, 2H), 7.84 (dd, J = 0.9, 8.4 Hz, 1H), 7.75 (dd, J = 5.0, 8.1 Hz, 3H), 7.43 (br s, 1H), 4.60-4.50 (m, 1H), 4.34 (d, J = 3.8 Hz, 2H), 4.10 (s, 3H), 3.94 (br d, J = 14.1 Hz, 1H), 3.45-3.33 (m, 2H), 3.25-3.14 (m, 1H), 2.62 (s, 3H), 2.37-2.25 (m, 2H), 2.14-1.99 (m, 2H); LCMS (ESI) [M+H]+: 527.1.



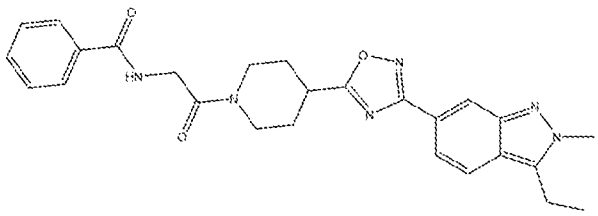
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.29 (s, 1H), 7.86 (dd, J = 1.5, 9.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 8.0, 2H), 7.20 (d, J = 7.6 Hz, 2H), 4.54 (br s, 1H), 4.05 (s, 4H), 4.26-3.24 (m, 1H), 3.15 (br t, J = 11.4 Hz, 2H), 2.90-2.81 (m, 1H), 2.60 (s, 3H), 2.22-1.86 (m, 4H), 1.19 (d, J = 7.0 Hz, 6H); LCMS (ESI) [M+H]+: 444.2.



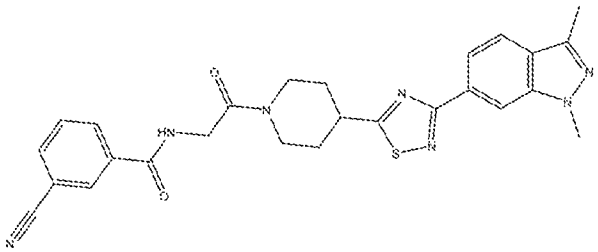
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 7.86-7.83 (m, 1H), 7.79-7.76 (m, 1H), 4.16 (br s, 2H), 4.09 (s, 3H), 3.10-2.91 (m, 3H), 2.61 (s, 3H), 2.08 (br d, J = 10.6 Hz, 2H), 1.94-1.82 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 398.2.



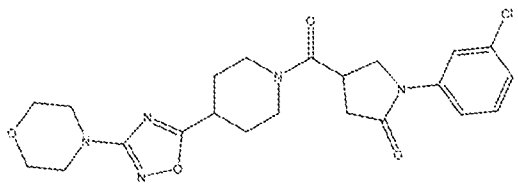
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.38 (s, 1H), 7.95 (br d, J = 9.2 Hz, 1H), 7.88 (br d, J = 7.6 Hz, 2H), 7.72 (d, J = 8.9 Hz, 1H), 7.57-7.44 (m, 3H), 7.36 (br s, 1H), 4.58-4.40 (m, 3H), 4.33 (br d, J = 3.5 Hz, 2H), 3.94 (br d, J = 13.6 Hz, 1H), 3.43-3.32 (m, 2H), 3.19 (br t, J = 11.1 Hz, 1H), 2.70 (s, 3H), 2.33-2.23 (m, 2H), 2.13-1.99 (m, 2H), 1.60 (t, J = 7.2 Hz, 3H); LCMS (ESI) [M+H]+: 473.2.



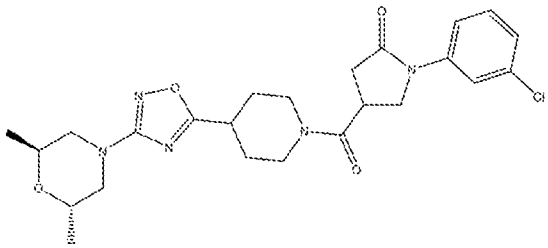
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.43 (s, 1H), 7.88 (br d, J = 7.7 Hz, 2H), 7.71 (s, 2H), 7.57-7.51 (m, 1H), 7.51-7.45 (m, 2H), 7.36 (br s, 1H), 4.51 (br d, J = 13.8 Hz, 1H), 4.33 (br d, J = 2.3 Hz, 2H), 4.18 (s, 3H), 3.94 (br d, J = 13.9 Hz, 1H), 3.42-3.33 (m, 2H), 3.21 (br t, J = 10.7 Hz, 1H), 3.13-3.07 (m, 2H), 2.34-2.24 (m, 2H), 2.12-2.00 (m, 2H), 1.40 (t, J = 7.6 Hz, 3H); LCMS (ESI) [M+H]+: 473.2.



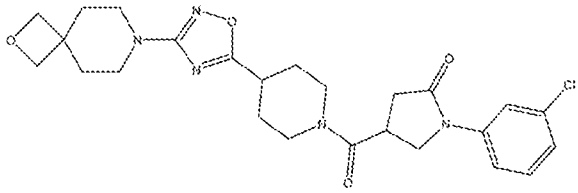
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.18 (s, 1H), 8.11-8.00 (m, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.42 (br s, 1H), 4.90 (br d, J = 13.2 Hz, 1H), 4.43-4.22 (m, 2H), 4.10 (s, 3H), 3.97 (d, J = 14.0 Hz, 1H), 3.60-3.46 (m, 1H), 3.37 (t, J = 12.0 Hz, 1H), 3.06 (t, J = 11.6 Hz, 1H), 2.61 (s, 3H), 2.37 (t, J = 11.6 Hz, 2H), 2.05-1.86 (m, 2H); LCMS (ESI) [M+H]+: 500.2.



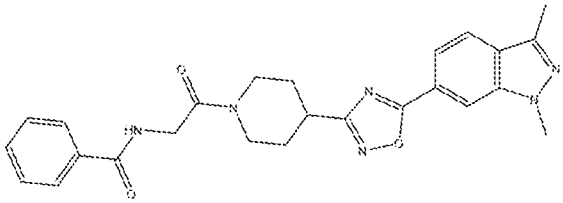
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.67 (br s, 1H), 7.53 (br t, J = 6.0 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.15 (br d, J = 7.9 Hz, 1H), 4.56-4.38 (m, 1H), 4.28 (dd, J = 7.1, 9.5 Hz, 1H), 4.01-3.86 (m, 2H), 3.84-3.76 (m, 4H), 3.60-3.52 (m, 1H), 3.44 (br t, J = 4.3 Hz, 4H), 3.39-3.28 (m, 1H), 3.20-2.90 (m, 3H), 2.89-2.78 (m, 1H), 2.23-2.08 (m, 2H), 1.96-1.77 (m, 2H); LCMS (ESI) [M+H]+: 460.2.



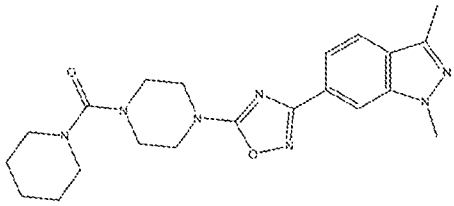
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.67 (s, 1H), 7.56-7.49 (m, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 4.56-4.41 (m, 1H), 4.28 (dd, J = 7.1, 9.5 Hz, 1H), 4.19-4.03 (m, 2H), 3.91 (br t, J = 7.9 Hz, 2H), 3.63-3.46 (m, 3H), 3.40-3.27 (m, 1H), 3.21-2.90 (m, 5H), 2.89-2.76 (m, 1H), 2.15 (br t, J = 13.2 Hz, 2H), 1.96-1.77 (m, 2H), 1.27 (d, J = 6.4 Hz, 6H); LCMS (ESI) [M+H]+: 488.1.



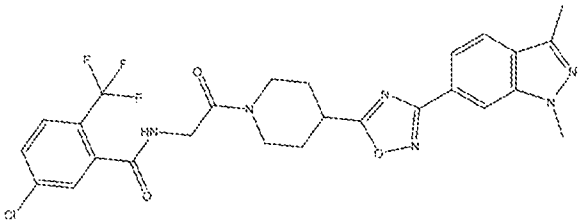
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.67 (br s, 1H), 7.53 (br d, J = 6.0 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.15 (br d, J = 7.1 Hz, 1H), 4.48 (s, 5H), 4.28 (dd, J = 7.1, 9.5 Hz, 1H), 3.91 (br t, J = 7.9 Hz, 2H), 3.56 (quin, J = 8.3 Hz, 1H), 3.43-3.28 (m, 5H), 3.18-2.89 (m, 3H), 2.87-2.77 (m, 1H), 2.20-2.07 (m, 2H), 1.98-1.92 (m, 4H), 1.91-1.76 (m, 2H); LCMS (ESI) [M+H]+: 500.2.



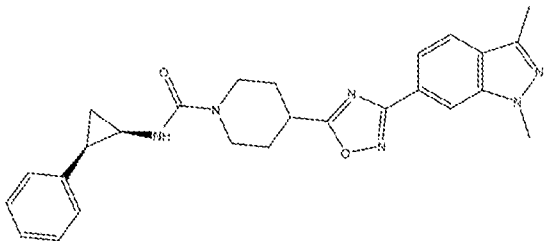
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 7.89-7.82 (m, 3H), 7.80-7.75 (m, 1H), 7.55-7.49 (m, 1H), 7.48-7.42 (m, 2H), 7.36 (br s, 1H), 4.57 (br d, J = 13.8 Hz, 1H), 4.31 (d, J = 3.8 Hz, 2H), 4.09 (s, 3H), 3.92 (br d, J = 13.9 Hz, 1H), 3.37-3.28 (m, 1H), 3.26-3.17 (m, 1H), 3.13-3.04 (m, 1H), 2.60 (s, 3H), 2.26-2.15 (m, 2H), 2.05-1.90 (m, 2H); LCMS (ESI) [M+H]+: 459.1.



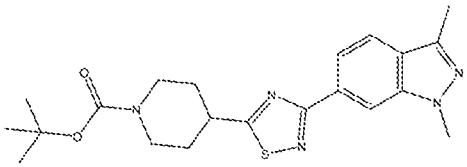
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.89-7.84 (m, 1H), 7.79-7.75 (m, 1H), 4.20 (s, 3H), 3.81-3.73 (m, 4H), 3.44-3.36 (m, 4H), 3.27 (br s, 4H), 2.71 (s, 3H); LCMS (ESI) [M+H]+: 410.2.



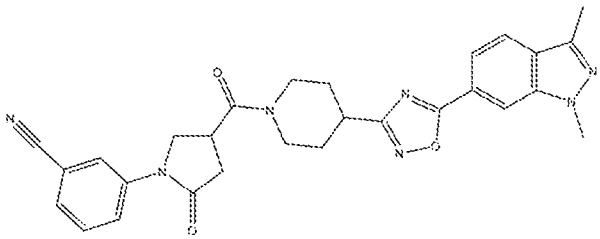
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.70-7.65 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.54-7.42 (m, 2H), 6.97 (br s, 1H), 4.42 (br d, J = 13.6 Hz, 1H), 4.23 (d, J = 3.9 Hz, 2H), 4.01 (s, 3H), 3.81 (br d, J = 14.2 Hz, 1H), 3.34-3.23 (m, 2H), 3.09 (br t, J = 11.1 Hz, 1H), 2.53 (s, 3H), 2.21 (br t, J = 13.4 Hz, 2H), 2.05-1.91 (m, 2H); LCMS (ESI) [M+H]+: 561.1.



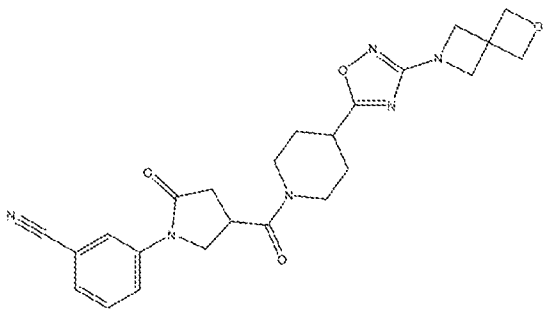
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17-7.97 (m, 1H), 7.87-7.77 (m, 1H), 7.75-7.66 (m, 1H), 7.24 (br d, J = 6.6 Hz, 2H), 7.20-7.12 (m, 3H), 4.89 (s, 1H), 4.06 (s, 3H), 3.99 (br d, J = 13.5 Hz, 2H), 3.21 (br t, J = 10.8 Hz, 1H), 3.06 (br t, J = 11.5 Hz, 2H), 2.85 (br s, 1H), 2.58 (s, 3H), 2.18 (br d, J = 11.5 Hz, 2H), 2.09-1.87 (m, 3H), 1.25-1.20 (m, 1H), 1.17-1.10 (m, 1H); LCMS (ESI) [M+H]+: 457.2.



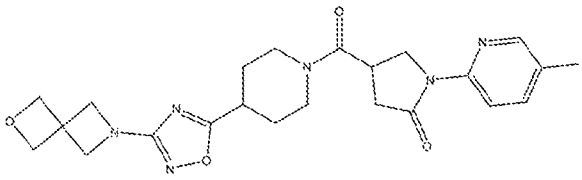
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 4.26 (br s, 2H), 4.09 (s, 3H), 3.41-3.31 (m, 1H), 2.98 (br t, J = 12.0 Hz, 2H), 2.60 (s, 3H), 2.23 (br d, J = 12.0 Hz, 2H), 1.85 (dq, J = 4.0, 12.0 Hz, 2H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 414.1.



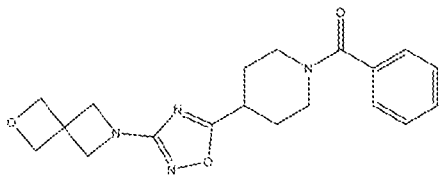
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (d, J = 4.3 Hz, 1H), 8.00 (br d, J = 4.6 Hz, 1H), 7.94 (br t, J = 7.6 Hz, 1H), 7.89-7.84 (d, 1H), 7.83-7.77 (d, 1H), 7.54-7.43 (m, 2H), 4.61 (m, 1H), 4.35 (m, 1H), 4.12 (d, J = 1.7 Hz, 3H), 4.05-3.92 (m, 2H), 3.65 (m, 1H), 3.47-3.34 (m, 1H), 3.31-3.19 (m, 1H), 3.16-2.86 (m, 3H), 2.63 (s, 3H), 2.31-2.16 (m, 2H), 2.09-1.89 (m, 2H); LCMS (ESI) [M+H]+: 510.2.



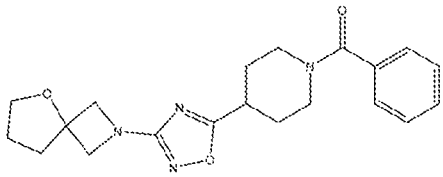
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.96 (br d, J = 10.6 Hz, 1H), 7.90 (br t, J = 9.0 Hz, 1H), 7.52-7.41 (m, 2H), 4.83 (s, 4H), 4.47 (br t, J = 14.4 Hz, 1H), 4.35-4.27 (m, 1H), 4.22 (s, 4H), 3.99-3.84 (m, 2H), 3.58 (quin, J = 8.2 Hz, 1H), 3.40-3.26 (m, 1H), 3.19-2.82 (m, 4H), 2.14 (br t, J = 14.0 Hz, 2H), 1.96-1.72 (m, 2H); LCMS (ESI) [M+H]+: 463.2.



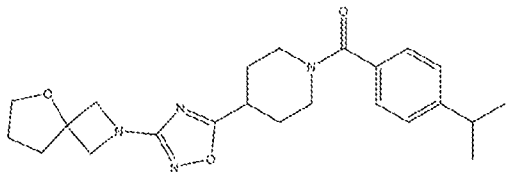
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (dd, J = 3.9, 8.3 Hz, 1H), 8.13 (s, 1H), 7.50 (dd, J = 1.8, 8.3 Hz, 1H), 4.82 (s, 4H), 4.52-4.41 (m, 1H), 4.36 (t, J = 9.9 Hz, 1H), 4.21 (s, 4H), 4.13 (br t, J = 7.7 Hz, 1H), 3.93 (br d, J = 13.2 Hz, 1H), 3.51 (quin, J = 8.1 Hz, 1H), 3.32 (br t, J = 11.2 Hz, 1H), 3.21 (br dd, J = 7.5, 17.1 Hz, 1H), 3.14-2.93 (m, 2H), 2.77 (br dd, J = 9.2, 18.9 Hz, 1H), 2.29 (s, 3H), 2.18-2.05 (m, 2H), 1.94-1.74 (m, 2H); LCMS (ESI) [M+H]+: 453.2.



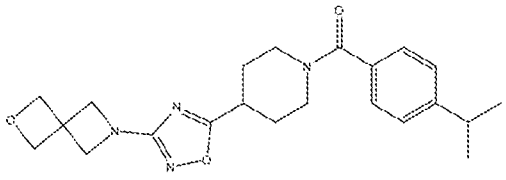
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.48-7.36 (m, 5H), 4.83 (s, 4H), 4.74-4.45 (m, 1H), 4.22 (s, 4H), 3.81 (br d, J = 15.4 Hz, 1H), 3.27-3.00 (m, 3H), 2.30-1.94 (m, 2H), 1.87 (br s, 2H); LCMS (ESI) [M+H]+: 355.2.



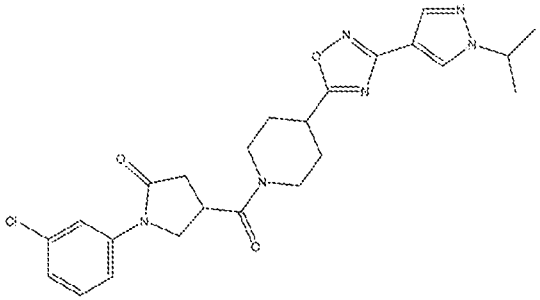
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.49-7.35 (m, 5H), 4.59 (br s, 1H), 4.13 (d, J = 8.6 Hz, 2H), 4.01 (d, J = 8.6 Hz, 2H), 3.87 (t, J = 6.8 Hz, 2H), 3.84-3.67 (m, 1H), 3.26-3.02 (m, 3H), 2.25-2.11 (m, 3H), 2.02-1.73 (m, 5H); LCMS (ESI) [M+H]+: 369.2.



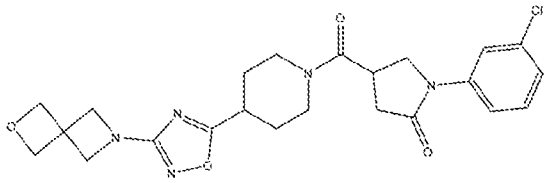
^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.39-7.29 (m, 4H), 4.52 (br s, 1H), 4.08-3.97 (m, 4H), 3.86 (t, J = 6.8 Hz, 3H), 3.23 (tt, J = 4.0, 10.8 Hz, 3H), 2.96 (td, J = 6.9, 13.8 Hz, 1H), 2.25-2.02 (m, 4H), 1.95 (quin, J = 7.1 Hz, 2H), 1.81 (br s, 2H), 1.27 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 411.2.



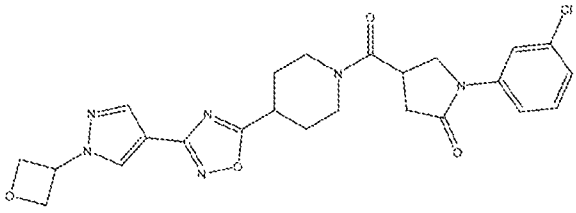
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.38-7.31 (m, 2H), 7.27-7.24 (m, 2H), 4.83 (s, 4H), 4.71-4.40 (m, 1H), 4.22 (s, 4H), 4.09-3.68 (m, 1H), 3.31-3.03 (m, 3H), 2.94 (spt, J = 6.9 Hz, 1H), 2.06 (br d, J = 7.1 Hz, 2H), 1.88 (br s, 2H), 1.26 (d, J = 7.1 Hz, 6H); LCMS (ESI) [M+H]+: 397.2.



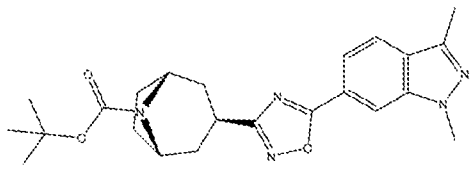
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.05-7.92 (m, 2H), 7.71-7.60 (m, 1H), 7.50 (br t, J = 7.4 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 7.13 (dd, J = 1.0, 8.0 Hz, 1H), 4.64-4.40 (m, 2H), 4.26 (dd, J = 7.1, 9.3 Hz, 1H), 4.00-3.85 (m, 2H), 3.60-3.51 (m, 1H), 3.41-3.20 (m, 2H), 3.15-2.99 (m, 1H), 2.99-2.77 (m, 2H), 2.21 (br t, J = 13.6 Hz, 2H), 2.02-1.84 (m, 2H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 483.1.



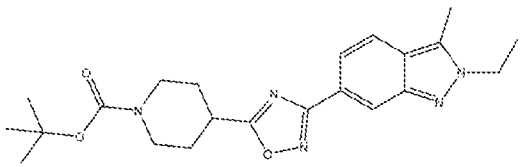
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.68-7.64 (m, 1H), 7.52 (br t, J = 6.2 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 4.84 (s, 4H), 4.56-4.39 (m, 1H), 4.30-4.24 (m, 1H), 4.22 (s, 4H), 3.90 (dt, J = 3.5, 8.9 Hz, 2H), 3.60-3.51 (m, 1H), 3.40-3.25 (m, 1H), 3.18-2.97 (m, 2H), 2.97-2.88 (m, 1H), 2.87-2.78 (m, 1H), 2.13 (t, J = 12 Hz, 2H), 1.96-1.72 (m, 2H); LCMS (ESI) [M+H]+: 472.2.



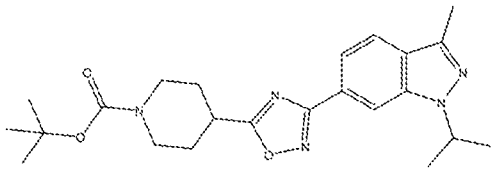
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.0 Hz, 1H), 8.06 (s, 1H), 7.86-7.80 (m, 1H), 7.55 (br d, J = 8.2 Hz, 1H), 7.37 (dt, J = 2.3, 8.1 Hz, 1H), 7.17 (br d, J = 8.2 Hz, 1H), 5.68-5.61 (m, 1H), 4.96-4.83 (m, 4H), 4.31 (br d, J = 12.6 Hz, 1H), 4.08-4.01 (m, 1H), 3.97 (br d, J = 13.9 Hz, 1H), 3.91 (dd, J = 5.7, 9.7 Hz, 1H), 3.76-3.65 (m, 1H), 3.44-3.34 (m, 1H), 3.29-3.21 (m, 1H), 2.90 (br t, J = 13.8 Hz, 1H), 2.79-2.68 (m, 2H), 2.09 (br t, J = 14.0 Hz, 2H), 1.87-1.56 (m, 2H); LCMS (ESI) [M+H]+: 497.1.



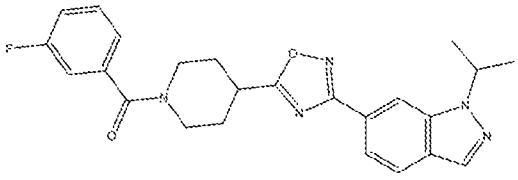
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (t, 1H), 7.79 (m, 2H), 4.38 (m, 2H), 4.09 (s, 3H), 3.59 (m, 1H), 2.61 (s, 3H), 2.06 (m, 5H), 1.81 (d, J = 8Hz, 2H), 1.51 (s, 9H); LCMS (ESI) [M+H]+: 424.



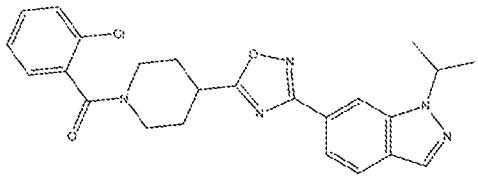
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.29 (s, 1H), 7.86 (dd, J = 1.5, 9.0 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 4.35 (q, J = 7.3 Hz, 2H), 4.06 (br s, 2H), 3.11 (tt, J = 3.6, 10.8 Hz, 1H), 2.93 (br t, J = 11.7 Hz, 2H), 2.60 (s, 3H), 2.06 (br dd, J = 2.7, 13.1 Hz, 2H), 1.90-1.81 (m, 2H), 1.50 (t, J = 7.3 Hz, 3H), 1.41 (s, 9H); LCMS (ESI) [M+H]+: 412.2.



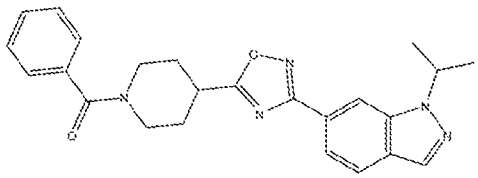
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 7.84-7.78 (m, 1H), 7.75-7.69 (m, 1H), 4.88 (m, 1H), 4.16 (br s, 2H), 3.25-3.15 (m, 1H), 3.07-2.94 (m, 2H), 2.60 (s, 3H), 2.20-2.10 (m, 2H), 2.00-1.87 (m, 2H), 1.59 (d, J = 6.6 Hz, 6H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 426.2.



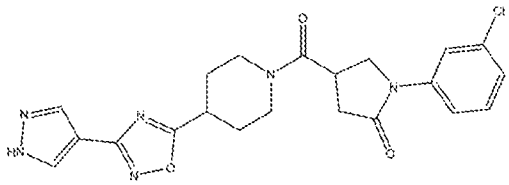
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.07 (s, 1H), 7.95-7.78 (m, 2H), 7.49-7.36 (m, 1H), 7.25-7.20 (m, 1H), 7.19-7.10 (m, 2H), 5.06-4.89 (m, 1H), 4.86-4.50 (m, 1H), 4.05-3.72 (m, 1H), 3.46-3.32 (m, 1H), 3.30-3.15 (m, 2H), 2.46-1.92 (m, 4H), 1.64 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 434.2.



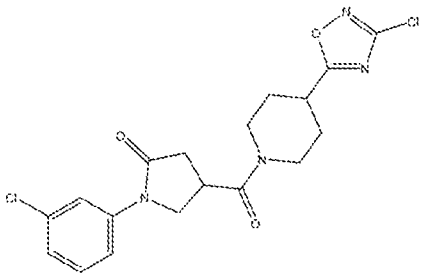
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.90-7.74 (m, 2H), 7.49-7.27 (m, 4H), 5.09-4.98 (m, 1H), 4.82-4.68 (m, 1H), 3.70-3.52 (m, 1H), 3.44-3.10 (m, 3H), 2.43-2.27 (m, 1H), 2.22-1.81 (m, 3H), 1.64 (d, J = 6.4 Hz, 6H); LCMS (ESI) [M+H]+: 450.2.



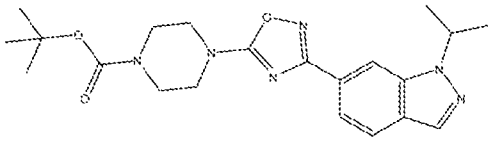
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.84 (q, J = 8.4 Hz, 2H), 7.45 (s, 5H), 5.06-4.90 (m, 1H), 4.77-4.54 (m, 1H), 4.10-3.77 (m, 1H), 3.45-3.30 (m, 1H), 3.30-3.07 (m, 2H), 2.45-1.93 (m, 4H), 1.64 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 416.2.



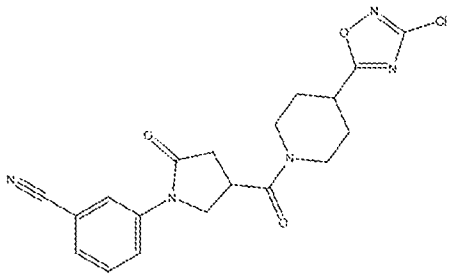
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 11.23-10.26 (m, 1H), 8.16 (s, 2H), 7.72-7.63 (m, 1H), 7.53 (br t, J = 7.3 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 4.66-4.44 (m, 1H), 4.35-4.23 (m, 1H), 4.02-3.89 (m, 2H), 3.63-3.54 (m, 1H), 3.44-3.26 (m, 2H), 3.21-2.77 (m, 3H), 2.24 (br t, J = 13.5 Hz, 2H), 2.06-1.87 (m, 2H); LCMS (ESI) [M+H]+: 441.1.



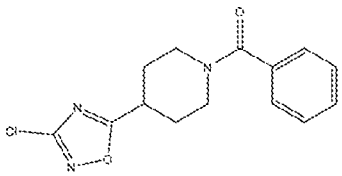
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.67 (br d, J = 10.1 Hz, 1H), 7.52 (br t, J = 8.7 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.15 (br d, J = 7.9 Hz, 1H), 4.50 (br dd, J = 14.2, 18.4 Hz, 1H), 4.34-4.18 (m, 1H), 4.04-3.85 (m, 2H), 3.60-3.52 (m, 1H), 3.44-3.22 (m, 2H), 3.16-3.00 (m, 1H), 3.00-2.77 (m, 2H), 2.31-2.13 (m, 2H), 2.03-1.79 (m, 2H); LCMS (ESI) [M+H]+: 409.0.



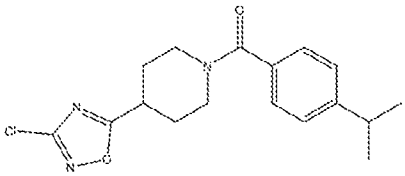
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 8.03 (s, 1H), 7.77 (s, 2H), 4.94 (spt, J = 6.6 Hz, 1H), 3.70 (br d, J = 5.1 Hz, 4H), , 3.62-3.55 (m, 4H), 1.61 (d, J = 6.8 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 413.2.



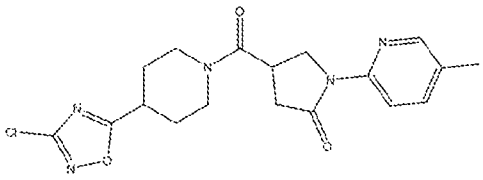
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.03-7.94 (m, 1H), 7.89 (br dd, J = 8.2, 19.2 Hz, 1H), 7.54-7.41 (m, 2H), 4.50 (br t, J = 14.3 Hz, 1H), 4.36-4.24 (m, 1H), 4.02-3.87 (m, 2H), 3.60 (s, J = 8.2 Hz, 1H), 3.46-3.24 (m, 2H), 3.18-3.01 (m, 1H), 3.00-2.82 (m, 2H), 2.22 (br t, J = 14.0 Hz, 2H), 2.03-1.79 (m, 2H); LCMS (ESI) [M+H]+: 400.1.



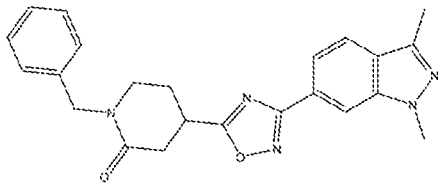
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.49-7.34 (m, 5H), 4.61 (br s, 1H), 3.86 (br s, 1H), 3.31-3.10 (m, 3H), 2.27 -1.92 (m, 4H); LCMS (ESI) [M+H]+: 292.1.



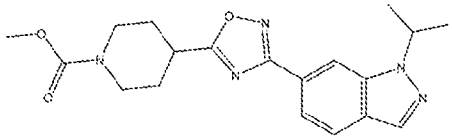
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.38-7.32 (m, 2H), 7.29-7.25 (m, 2H), 4.60 (br s, 1H), 3.94 (br s, 1H), 3.35-3.08 (m, 3H), 2.94 (spt, J = 6.8 Hz, 1H), 2.15 (br s, 2H), 1.93 (br s, 2H), 1.26 (d, J = 7.1 Hz, 6H); LCMS (ESI) [M+H]+: 334.2.



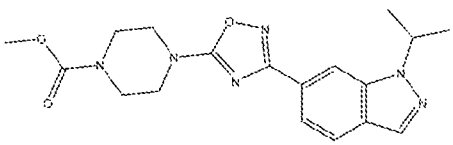
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.26 (t, J = 8.6 Hz, 1H), 8.14 (br s, 1H), 7.51 (br d, J = 7.9 Hz, 1H), 4.50 (br s, 1H), 4.38 (br t, J = 10.1 Hz, 1H), 4.13 (dd, J = 7.2, 11.2 Hz, 1H), 3.98 (br d, J = 13.6 Hz, 1H), 3.57-3.48 (m, 1H), 3.37 (br t, J = 11.8 Hz, 1H), 3.31-3.17 (m, 2H), 3.09-2.98 (m, 1H), 2.78 (dd, J = 9.2, 17.1 Hz, 1H), 2.30 (s, 3H), 2.18 (br d, J = 14.0 Hz, 2H), 1.99-1.83 (m, 2H); LCMS (ESI) [M+H]+: 390.3.



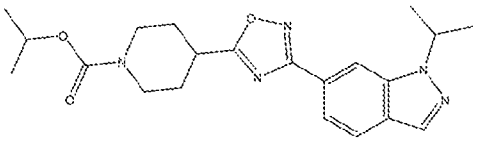
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 7.86-7.82 (d, J = 1.2 Hz, 1H), 7.78-7.74 (d, J = 8.4 Hz, 1H), 7.34-7.27 (m, 5H), 4.86 (d, J = 14.7 Hz, 1H), 4.52 (d, J = 14.7 Hz, 1H), 4.10 (s, 3H), 3.63 (tdd, J = 3.6, 7.3, 13.5 Hz, 1H), 3.40-3.34 (m, 2H), 3.05 (d, J = 7.5 Hz, 2H), 2.62 (s, 3H), 2.45-2.36 (m, 1H), 2.29-2.19 (m, 1H); LCMS (ESI) [M+H]+: 402.2.



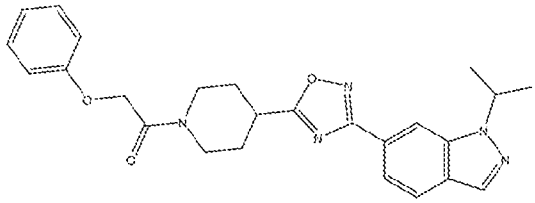
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.05 (s, 1H), 7.90-7.75 (m, 2H), 4.95 (spt, J = 6.6 Hz, 1H), 4.18 (br s, 2H), 3.72 (s, 3H), 3.22 (tt, J = 3.9, 10.7 Hz, 1H), 3.08 (br t, J = 11.7 Hz, 2H), 2.16 (br d, J = 11.0 Hz, 2H), 2.03-1.86 (m, 2H), 1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 370.2.



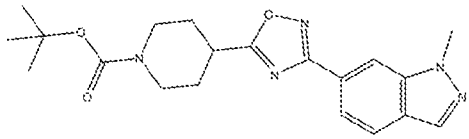
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 8.03 (s, 1H), 7.77 (s, 2H), 4.94 (spt, J = 6.6 Hz, 1H), 3.76 (s, 3H), 3.72 (br s, 4H), 3.65 (br s, 4H), 1.61 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 371.2.



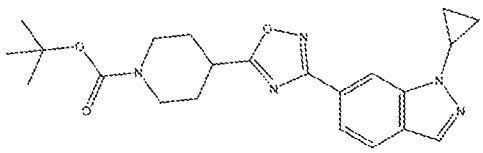
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.06 (s, 1H), 7.83 (q, J = 8.4 Hz, 2H), 5.07-4.87 (m, 2H), 4.20 (br s, 2H), 3.23 (tt, J = 4.0, 10.8 Hz, 1H), 3.06 (br t, J = 11.6 Hz, 2H), 2.25-2.09 (m, 2H), 2.05-1.87 (m, 2H), 1.64 (d, J = 6.8 Hz, 6H), 1.28 (d, J = 6.0 Hz, 6H); LCMS (ESI) [M+H]+: 398.2.



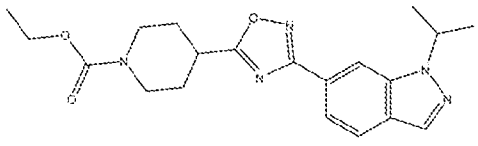
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.93-7.77 (m, 2H), 7.32 (br t, J = 7.2 Hz, 2H), 7.09-6.92 (m, 3H), 5.09-4.90 (m, 1H), 4.74 (s, 2H), 4.49 (br d, J = 13.6 Hz, 1H), 4.13 (br d, J = 13.6 Hz, 1H), 3.57-3.25 (m, 2H), 3.10 (br t, J = 11.6 Hz, 1H), 2.35-2.17 (m, 2H), 2.12-1.87 (m, 2H), 1.64 (d, J = 5.6 Hz, J = 6H); LCMS (ESI) [M+H]+: 446.2.



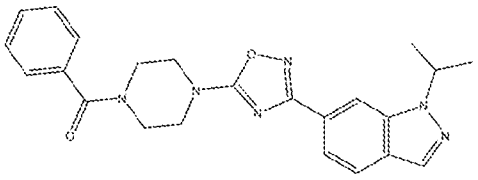
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 8.04 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 4.26-4.08 (m, 5H), 3.27-3.16 (m, 1H), 3.03 (br t, J = 11.6 Hz, 2H), 2.16 (br d, J = 10.0 Hz, 2H), 2.03-1.87 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 384.2.



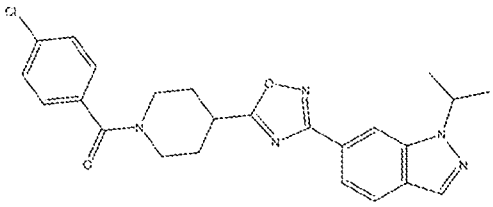
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.34 (s, 1H), 7.98 (s, 1H), 7.92-7.84 (m, 1H), 7.83-7.75 (m, 1H), 4.24-4.07 (m, 2H), 3.72-3.62 (m, 1H), 3.27-3.15 (m, 1H), 3.09-2.93 (m, 2H), 2.16 (br d, J = 11.0 Hz, 2H), 2.01-1.87 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 410.2.



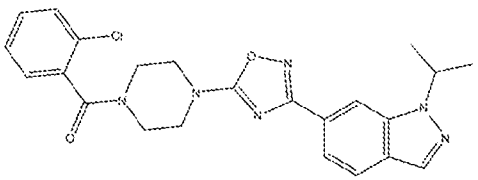
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.05 (s, 1H), 7.82 (q, J = 8.5 Hz, 2H), 4.96 (spt, J = 6.7 Hz, 1H), 4.16 (q, J = 7.2 Hz, 4H), 3.22 (tt, J = 3.9, 10.8 Hz, 1H), 3.07 (br t, J = 11.7 Hz, 2H), 2.22-2.11 (m, 2H), 2.02-1.89 (m, 2H), 1.62 (d, J = 6.6 Hz, 6H), 1.28 (t, J = 7.2 Hz, 3H); LCMS (ESI) [M+H]+: 384.2.



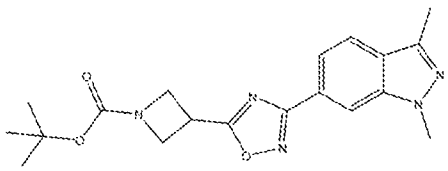
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 8.12 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 1.0, 8.5 Hz, 1H), 7.53-7.41 (m, 4H), 5.06 (quin, J = 6.5 Hz, 1H), 3.78-3.62 (m, 8H), 1.53 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 417.1.



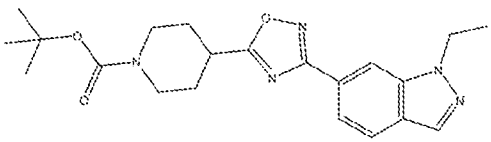
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.09 (s, 1H), 7.91-7.81 (m, 2H), 7.47-7.39 (m, 4H), 5.07-4.92 (m, 1H), 4.65 (br s, 1H), 3.89 (br s, 1H), 3.44-3.15 (m, 3H), 2.40-1.94 (m, 4H), 1.65 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 450.2.



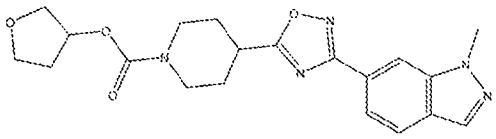
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 8.04 (s, 1H), 7.77 (s, 2H), 7.47-7.30 (m, 4H), 5.01-4.86 (m, 1H), 4.16-4.07 (m, 1H), 3.95-3.64 (m, 5H), 3.52-3.31 (m, 2H), 1.61 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 451.0.



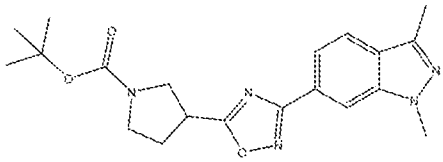
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 7.89-7.81 (d, J = 8.4 Hz, 1H), 7.78-7.69 (d, J = 8.4 Hz, 1H), 4.48-4.33 (m, 4H), 4.15-4.02 (m, 4H), 2.61 (s, 3H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 370.1.



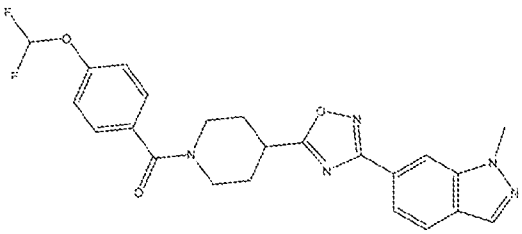
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 8.05 (s, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 4.52 (q, J = 7.2 Hz, 2H), 4.30-4.12 (m, 2H), 3.24-3.18 (m, 1H), 3.01 (t, J = 5.6 Hz, 2H), 2.18-2.14 (m, 2H), 1.98-1.92 (m, 2H), 1.57 (t, J = 7.2 Hz, 3H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 398.1.



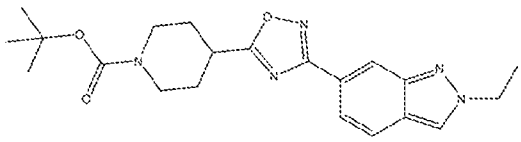
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17 (s, 1H), 8.04 (s, 1H), 7.92-7.85 (d, J = 8.4 Hz, 1H), 7.84-7.78 (d, J = 8.4 Hz, 1H), 5.36-5.26 (m, 1H), 4.36-4.06 (m, 5H), 4.00-3.82 (m, 4H), 3.29-3.18 (m, 1H), 3.16-3.00 (m, 2H), 2.30-2.17 (m, 3H), 2.11-1.88 (m, 3H); LCMS (ESI) [M+H]+: 398.1.



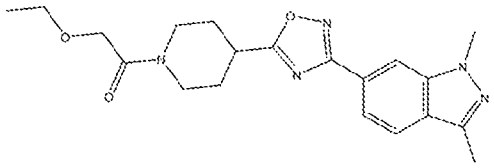
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.86-7.80 (d, J = 8.4 Hz, 1H), 7.78-7.72 (d, J = 8.4 Hz, 1H), 4.08 (s, 3H), 3.98-3.46 (m, 5H), 2.60 (s, 3H), 2.50-2.35 (m, 2H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 384.2.



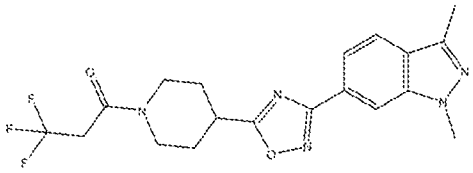
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.11 (s, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.39 (s, 0.2H), 7.25-7.22 (d, J = 8.4 Hz, 2H), 7.22-7.20 (s, 0.6H), 7.03 (s, 0.2H), 4.14-3.93 (m, 5H), 3.54-3.43 (m, 1H), 3.23 (br t, J = 11.2 Hz, 2H), 2.17 (br dd, J = 2.5, 13.1 Hz, 2H), 1.93-1.82 (m, 2H); LCMS (ESI) [M+H]+: 454.2.



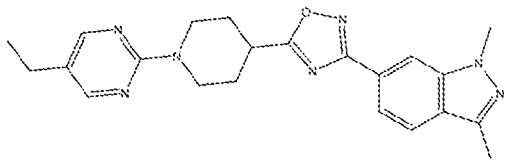
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.50 (s, 1H), 7.97 (s, 1H), 7.79-7.71 (m, 2H), 4.51 (q, J = 7.6 Hz, 2H), 4.13 (br d, J = 8.8 Hz, 2H), 3.19 (tt, J = 4.0, 10.8 Hz, 1H), 3.01 (br t, J = 11.6 Hz, 2H), 2.14 (br dd, J = 2.8, 13.2 Hz, 2H), 2.00-1.86 (m, 2H), 1.66 (t, J = 7.6 Hz, 3H), 1.48 (s, 9H); LCMS (ESI) [M+H-56]+: 342.2, LCMS (ESI) [M+23]+: 420.2.



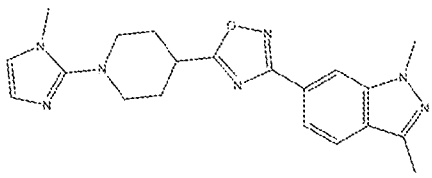
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.85-7.80 (d, J = 8.4 Hz, 1H), 7.76-7.71 (d, J = 8.4 Hz, 1H), 4.51 (br d, J = 13.0 Hz, 1H), 4.19 (d, J = 6.8 Hz, 2H), 4.08 (s, 4H), 3.64-3.56 (m, 2H), 3.37-3.25 (m, 2H), 3.03 (br t, J = 11.5 Hz, 1H), 2.60 (s, 3H), 2.24 (br d, J = 12.3 Hz, 2H), 2.07-1.91 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 384.2.



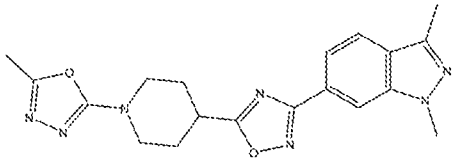
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.85-7.81 (d, J = 8.4 Hz, 1H), 7.77-7.72 (d, J = 8.4 Hz, 1H), 4.55 (br d, J = 13.5 Hz, 1H), 4.09 (s, 3H), 3.91 (br d, J = 14.3 Hz, 1H), 3.46-3.25 (m, 4H), 3.20-3.07 (m, 1H), 2.61 (s, 3H), 2.33-2.21 (m, 2H), 2.11-1.95 (m, 2H); LCMS (ESI) [M+H]+: 408.2.



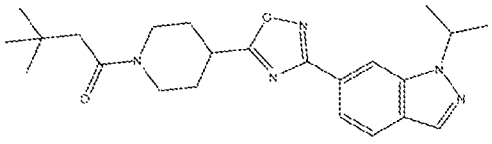
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 2H), 8.10 (s, 1H), 7.83 (dd, J = 1.1, 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 4.76 (td, J = 3.5, 13.5 Hz, 2H), 4.07 (s, 3H), 3.32 (tt, J = 4.0, 11.0 Hz, 1H), 3.25-3.15 (m, 2H), 2.59 (s, 3H), 2.49 (q, J = 7.5 Hz, 2H), 2.25 (br dd, J = 3.0, 13.6 Hz, 2H), 2.07-1.95 (m, 2H), 1.21 (t, J = 7.6 Hz, 3H); LCMS (ESI) [M+H]+: 404.2.



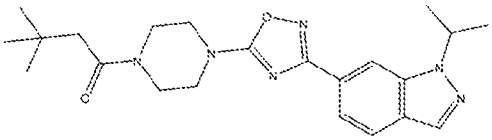
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 1.3 Hz, 1H), 6.59 (d, J = 1.3 Hz, 1H), 4.04 (s, 3H), 3.45 (s, 3H), 3.38-3.32 (m, 1H), 3.27-3.24 (m, 2H), 2.92 (br t, J = 10.7 Hz, 2H), 2.21-2.12 (m, 2H), 2.08-1.96 (m, 2H); LCMS (ESI) [M+H]+: 378.3.



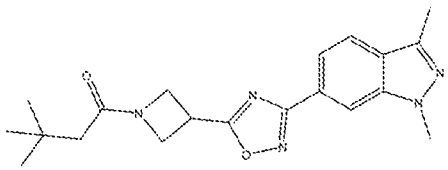
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.88-7.86 (d, J = 8 Hz, 1H), 4.71- 4.73 (d, J = 8 Hz, 1H), 4.05 (s, 3H), 3.95-9.32 (m, 2H), 3.49-3.53 (m, 1H), 3.32-3.48 (m, 1H), 2.25-2.22 (m, 2H), 1.99-1.96 (m, 2H); LCMS (ESI) [M+H]+: 380.2.



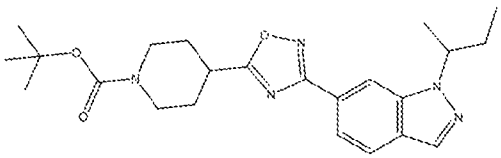
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.05 (s, 1H), 7.82 (q, J = 8.5 Hz, 2H), 5.05-4.90 (m, 1H), 4.62 (br d, J = 13.7 Hz, 1H), 4.03 (br d, J = 13.2 Hz, 1H), 3.36-3.22 (m, 2H), 2.95 (br t, J = 11.1 Hz, 1H), 2.31 (s, 2H), 2.21 (br d, J = 10.8 Hz, 2H), 2.07-1.86 (m, 2H), 1.62 (d, J = 6.6 Hz, 6H), 1.08 (s, 9H); LCMS (ESI) [M+H]+: 410.1.



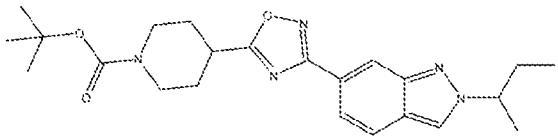
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.06 (s, 1H), 7.98 (s, 1H), 7.70 (s, 2H), 4.88 (spt, J = 6.6 Hz, 1H), 3.75 (br d, J = 4.8 Hz, 2H), 3.67 (br d, J = 4.9 Hz, 4H), 3.62 (br d, J = 5.3 Hz, 2H), 2.26 (s, 2H), 1.55 (d, J = 6.7 Hz, 6H), 1.02 (s, 9H); LCMS (ESI) [M+H]+: 411.2.



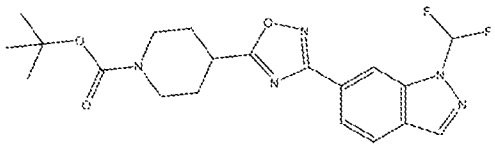
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 7.87-7.81 (d, J = 8.4 Hz, 1H), 7.78-7.72 (d, J = 8.4 Hz, 1H), 4.65-4.40 (m, 4H), 4.17-4.11 (m, 1H), 4.09 (s, 3H), 2.61 (s, 3H), 2.06 (s, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 368.2.



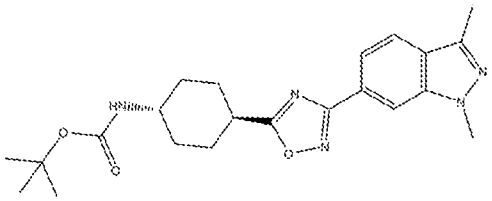
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 8.07 (s, 1H), 7.83 (q, J = 8.4 Hz, 2H), 4.72-4.62 (m, 1H), 4.16 (br s, 2H), 3.25-3.16 (m, 1H), 3.01 (br t, J = 11.7 Hz, 2H), 2.20-2.08 (m, 3H), 2.00-1.87 (m, 3H), 1.60 (d, J = 6.6 Hz, 3H), 1.48 (s, 9H), 0.80 (t, J = 7.4 Hz, 3H); LCMS (ESI) [M+H]+: 426.2.



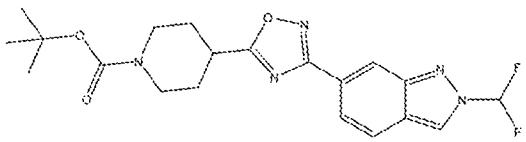
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.53 (s, 1H), 7.96 (s, 1H), 7.77-7.70 (m, 2H), 4.54 (qd, J = 6.9, 14.0 Hz, 1H), 4.10 (br s, 2H), 3.22-3.13 (m, 1H), 3.02 (br t, J = 11.4 Hz, 2H), 2.17-2.04 (m, 3H), 2.00-1.85 (m, 3H), 1.66 (d, J = 6.8 Hz, 3H), 1.48 (s, 9H), 0.84 (t, J = 7.4 Hz, 3H); LCMS (ESI) [M+H]+: 426.2, LCMS (ESI) [M-55]+: 370.1.



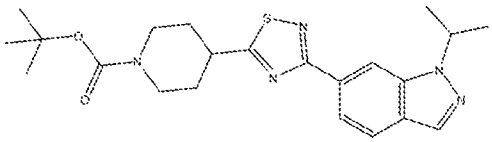
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (s, 1H), 8.15 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.66 (s, 0.2H), 7.51 (s, 0.5H), 7.36 (s, 0.3H), 4.15 (br s, 2H), 3.26-3.16 (m, 1H), 3.01 (br t, J = 12.8 Hz, 2H), 2.15 (br d, J = 10.4 Hz, 2H), 1.99-1.87 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 420.2, LCMS (ESI) [M+23]+: 442.1, LCMS (ESI) [M-100+23]+: 342.0.



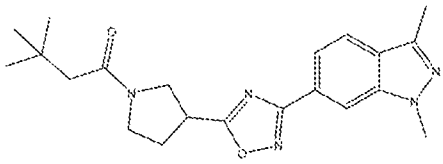
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.08 (s, 1H), 7.82-7.80 (d, J = 8.4 Hz, 1H), 7.76-7.69 (d, J = 8.4 Hz, 1H), 4.57-4.37 (m, 1H), 4.07 (s, 3H), 3.65-3.47 (m, 1H), 3.04-2.87 (m, 1H), 2.59 (s, 3H), 2.36-2.14 (m, 4H), 1.82 (dq, J = 2.9, 12.9 Hz, 2H), 1.46 (s, 9H), 1.29 (dq, J = 3.0, 12.5 Hz, 2H); LCMS (ESI) [M+H]+: 412.2.



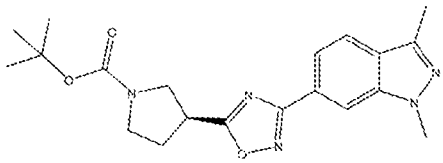
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.53 (s, 1H), 8.39 (s, 1H), 7.87-7.78 (m, 2H), 7.65 (s, 0.2H), 7.49 (s, 0.5H), 7.34 (s, 0.3H), 4.13 (br s, 2H), 3.24-3.15 (m, 1H), 3.07-2.96 (m, 2H), 2.15 (br d, J = 10.8 Hz, 2H), 1.98-1.86 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+23]+: 442.1, LCMS (ESI) [M-100]+: 320.0, LCMS (ESI) [M-55]+: 364.0.



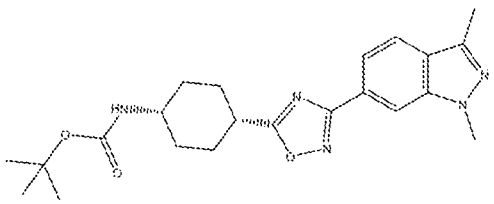
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.42 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 4.99 (td, J = 6.7, 13.3 Hz, 1H), 4.35-4.14 (m, 2H), 3.43-3.29 (m, 1H), 2.97 (br t, J = 12.0 Hz, 2H), 2.22 (br d, J = 11.7 Hz, 2H), 1.85 (m, 2H), 1.63 (d, J = 6.6 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 428.2.



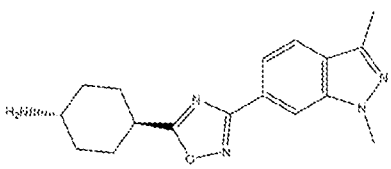
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.85-7.79 (m, 1H), 7.77-7.70 (m, 1H), 4.08 (d, J = 1.8 Hz, 3H), 4.06-3.92 (m, 2H), 3.88-3.73 (m, 2H), 3.71-3.62 (m, 1H), 2.60 (s, 3H), 2.56-2.35 (m, 2H), 2.30-2.20 (m, 2H), 1.10 (d, J = 1.8 Hz, 9H); LCMS (ESI) [M+H]+: 382.2.



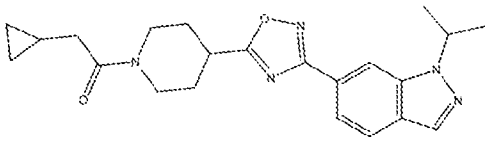
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12-8.08 (m, 1H), 7.83 (dd, J = 1.1, 8.6 Hz, 1H), 7.76-7.72 (m, 1H), 4.09 (s, 3H), 3.99-3.49 (m, 5H), 2.60 (s, 3H), 2.50-2.34 (m, 2H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 384.1.



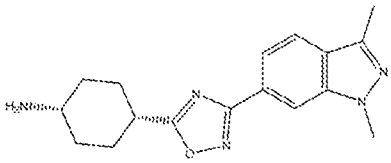
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.87-7.81 (m, 1H), 7.74 (d, J = 8.3 Hz, 1H), 4.64-4.62 (m, 1H), 4.09 (s, 3H), 3.77-3.74 (m, 1H), 3.23-3.20 (m, 1H), 2.61 (s, 3H), 2.15 (br s, 2H), 2.01 (dt, J = 4.2, 8.9 Hz, 2H), 1.85 (br d, J = 4.4 Hz, 2H), 1.73 (br s, 2H), 1.46 (s, 9H); LCMS (ESI) [M+H]+: 412.2.



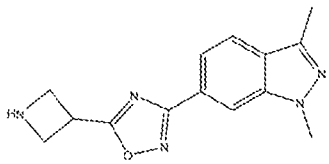
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.16 (s, 1H), 7.85-7.74 (m, 2H), 4.04 (s, 3H), 3.27-3.06 (m, 2H), 2.56 (s, 3H), 2.44-2.30 (m, 2H), 2.21 (br d, J = 10.6 Hz, 2H), 1.83 (m, 2H), 1.70-1.51 (m, 2H); LCMS (ESI) [M+H]+: 312.2.



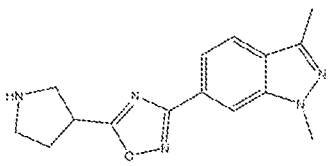
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.06 (s, 1H), 7.94-7.78 (m, 2H), 4.97 (td, J = 6.7, 13.3 Hz, 1H), 4.59 (br d, J = 13.7 Hz, 1H), 3.95 (br d, J = 13.9 Hz, 1H), 3.39-3.21 (m, 2H), 3.00 (br t, J = 11.4 Hz, 1H), 2.34 (d, J = 6.8 Hz, 2H), 2.28-2.13 (m, 2H), 2.07-1.88 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H), 1.14-1.00 (m, 1H), 0.67-0.52 (m, 2H), 0.21 (q, J = 4.9 Hz, 2H); LCMS (ESI) [M+H]+: 394.3.



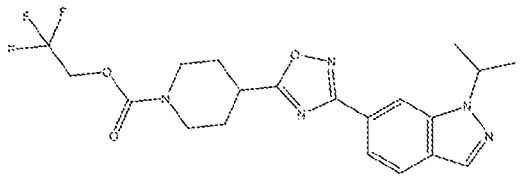
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.24 (s, 1H), 7.86 (s, 2H), 4.08 (s, 3H), 3.47 (br t, J = 4.3 Hz, 1H), 3.36-3.32 (m, 1H), 2.60 (s, 3H), 2.49-2.39 (m, 2H), 2.12-1.98 (m, 4H), 1.84-1.68 (m, 2H); LCMS (ESI) [M+H]+: 312.2.



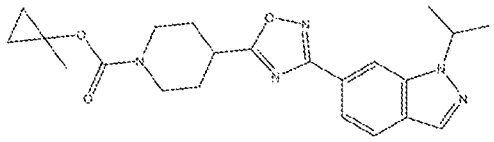
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.40 (br s, 1H), 8.22 (s, 1H), 7.83 (s, 2H), 4.63-4.45 (m, 5H), 4.05 (s, 3H), 2.57 (s, 3H); LCMS (ESI) [M+H]+: 270.1.



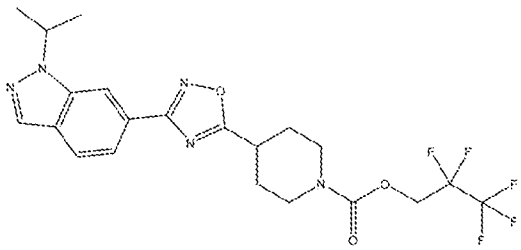
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.25 (s, 1H), 7.87 (s, 2H), 4.15 (quin, J = 7.2 Hz, 1H), 4.09 (s, 3H), 3.91-3.80 (m, 2H), 3.63-3.50 (m, 2H), 2.72-2.62 (m, 1H), 2.61 (s, 3H), 2.50 (qd, J = 6.9, 13.8 Hz, 1H); LCMS (ESI) [M+H]+: 284.2.



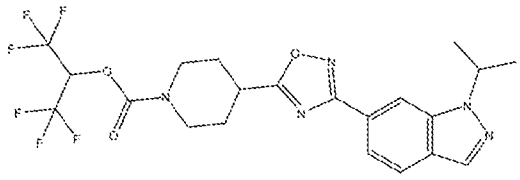
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.06 (s, 1H), 7.87-7.79 (m, 2H), 4.96 (quind, J = 6.7, 13.3 Hz, 1H), 4.52 (dq, J = 2.0, 8.5 Hz, 2H), 4.19 (br t, J = 17.3 Hz, 2H), 3.33-3.08 (m, 3H), 2.21 (br d, J = 11.5 Hz, 2H), 2.07-1.92 (m, 2H), 1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 438.1.



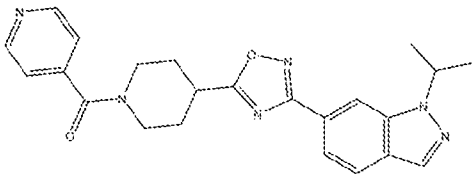
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.05 (s, 1H), 7.90-7.75 (m, 2H), 4.95 (spt, J = 6.6 Hz, 1H), 4.18 (br s, 2H), 3.72 (s, 3H), 3.22 (tt, J = 3.9, 10.7 Hz, 1H), 3.08 (br t, J = 11.7 Hz, 2H), 2.16 (br d, J = 11.0 Hz, 2H), 2.03-1.86 (m, 2H), 1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 370.2.



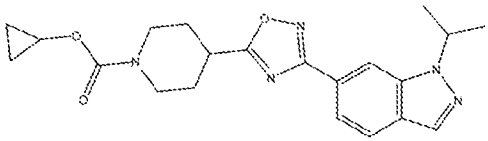
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.08 (s, 1H), 7.91-7.79 (m, 2H), 4.99 (td, J = 6.7, 13.3 Hz, 1H), 4.62 (br t, J = 12.5 Hz, 2H), 4.31-4.08 (m, 2H), 3.36-3.09 (m, 4H), 2.23 (br s, 2H), 2.02 (br s, 2H), 1.65 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 488.0.



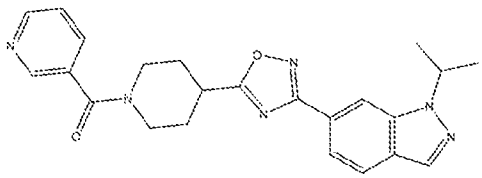
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.08 (s, 1H), 7.91-7.80 (m, 2H), 5.81 (spt, J = 6.1 Hz, 1H), 4.99 (spt, J = 6.6 Hz, 1H), 4.34-4.07 (m, 2H), 3.42-3.14 (m, 3H), 2.26 (br d, J = 3.5 Hz, 2H), 2.13-1.94 (m, 2H), 1.65 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 506.0.



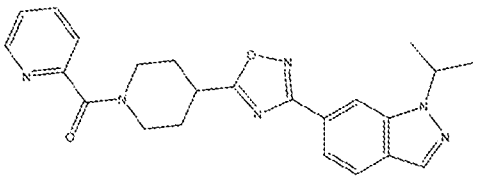
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.72 (d, J = 6.0 Hz, 2H), 8.20 (s, 1H), 8.06 (s, 1H), 7.91-7.77 (m, 2H), 7.32 (d, J = 6.0 Hz, 2H), 4.96 (spt, J = 6.6 Hz, 1H), 4.64 (br d, J = 11.2 Hz, 1H), 3.76 (br d, J = 11.9 Hz, 1H), 3.44-3.32 (m, 1H), 3.26 (br d, J = 10.8 Hz, 2H), 2.32 (br s, 1H), 2.23-1.88 (m, 3H), 1.63 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 417.1.



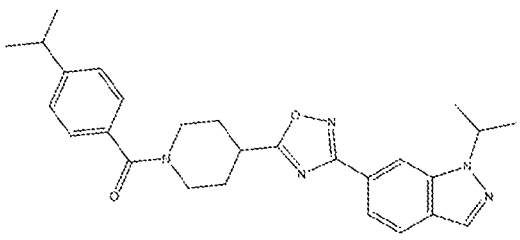
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.15 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 5.11 (spt, J = 6.7 Hz, 1H), 4.14-4.00 (m, 1H), 3.94 (br d, J = 13.5 Hz, 2H), 3.49-3.36 (m, 1H), 3.49-3.36 (m, 1H), 3.13-3.08 (m, 2H), 2.13 (br dd, J = 3.3, 13.2 Hz, 2H), 1.86-1.70 (m, 2H), 1.53 (d, J = 6.4 Hz, 6H), 0.72-0.60 (m, 4H); LCMS (ESI) [M+H]+: 396.2.



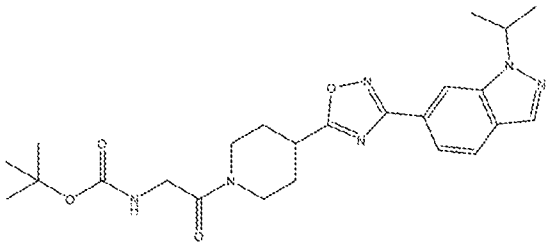
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68-8.63 (m, 2H), 8.28 (s, 1H), 8.16 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 4.9, 7.7 Hz, 1H), 5.11 (spt, J = 6.6 Hz, 1H), 4.06 (br s, 2H), 3.59-3.46 (m, 1H), 3.29 (br t, J = 11.2 Hz, 2H), 2.25-2.15 (m, 2H), 1.98-1.83 (m, 2H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 417.1.



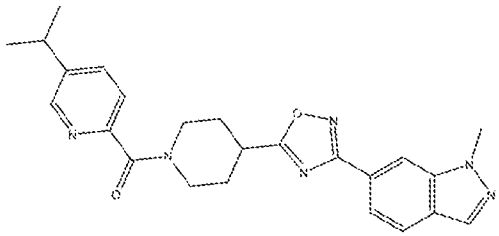
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.60 (br d, J = 4.4 Hz, 1H), 8.21 (s, 1H), 8.05 (s, 1H), 7.88-7.78 (m, 3H), 7.67 (br d, J = 7.7 Hz, 1H), 7.40-7.33 (m, 1H), 4.96 (td, J = 6.6, 13.2 Hz, 1H), 4.68 (br d, J = 13.2 Hz, 1H), 4.11 (br d, J = 13.2 Hz, 1H), 3.36 (br t, J = 10.5 Hz, 2H), 3.24 (br t, J = 11.5 Hz, 1H), 2.32 (br d, J = 11.7 Hz, 1H), 2.24-2.01 (m, 3H), 1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 417.1.



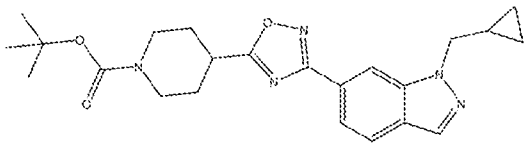
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.13 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.32 (q, J = 8.2 Hz, 4H), 5.09 (spt, J = 6.5 Hz, 1H), 4.06 (br s, 2H), 3.58-3.42 (m, 1H), 3.27-3.11 (m, 2H), 2.94 (spt, J = 6.8 Hz, 1H), 2.16 (br dd, J = 2.9, 13.0 Hz, 2H), 1.93-1.77 (m, 2H), 1.52 (d, J = 6.6 Hz, 6H), 1.23 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 458.3.



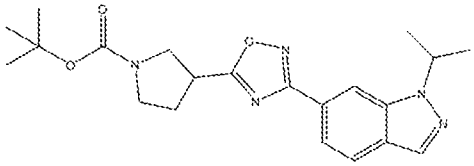
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.09-8.06 (m, 1H), 7.90-7.76 (m, 2H), 5.52 (br s, 1H), 4.96 (dq, J = 4.2, 6.5 Hz, 1H), 4.49 (br d, J = 13.2 Hz, 1H), 4.01 (br s, 2H), 3.82 (br d, J = 13.5 Hz, 1H), 3.39-3.22 (m, 2H), 3.08 (br t, J = 12.0 Hz, 1H), 2.21 (br s, 2H), 2.06-1.89 (m, 2H), 1.63 (dd, J = 2.6, 6.6 Hz, 6H), 1.46 (d, J = 2.0 Hz, 9H); LCMS (ESI) [M+H]+: 349.2.



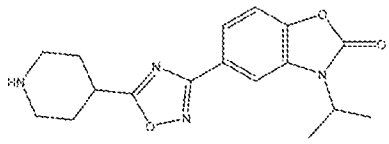
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.49 (d, J = 1.7 Hz, 1H), 8.20 (s, 1H), 8.05 (s, 1H), 7.91-7.82 (m, 2H), 7.70-7.62 (m, 2H), 4.71 (br d, J = 13.4 Hz, 1H), 4.18 (s, 4H), 3.45-3.33 (m, 2H), 3.25 (br t, J = 11.1 Hz, 1H), 3.02 (spt, J = 6.9 Hz, 1H), 2.34 (br d, J = 10.9 Hz, 1H), 2.23-2.11 (m, 3H), 1.33 (d, J = 7.0 Hz, 6H); LCMS (ESI) [M+H]+: 431.1.



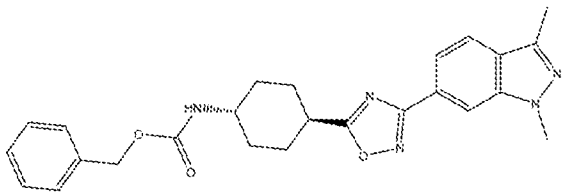
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.06 (s, 1H), 7.89-7.81 (m, 2H), 4.35 (d, J = 6.8 Hz, 2H), 4.25-4.11 (m, 2H), 3.25-3.18 (m, 1H), 3.09-2.97 (m, 2H), 2.21-2.12 (m, 2H), 2.01-1.89 (m, 2H), 1.50 (s, 9H), 1.41 (br d, J = 4.9 Hz, 1H), 0.65-0.59 (m, 2H), 0.49-0.44 (m, 2H); LCMS (ESI) [M+H]+: 424.1.



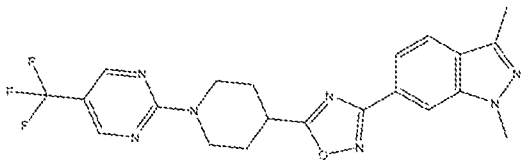
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.19 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 1.1, 8.4 Hz, 1H), 5.14 (quin, J = 6.6 Hz, 1H), 3.93 (br d, J = 7.3 Hz, 1H), 3.78 (br d, J = 8.2 Hz, 1H), 3.68-3.60 (m, 1H), 3.52-3.44 (m, 1H), 3.40 (br d, J = 7.5 Hz, 1H), 2.40 (br s, 1H), 2.24 (br d, J = 6.8 Hz, 1H), 1.50 (d, J = 6.4 Hz, 6H), 1.42 (s, 9H); LCMS (ESI) [M+H]+: 398.2.



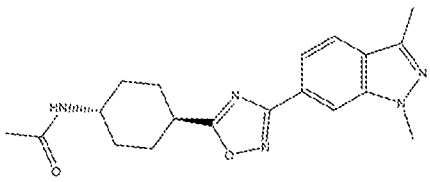
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (br s, 2H), 7.85 (d, J = 1.3 Hz, 1H), 7.80 (dd, J = 1.5, 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 4.58 (spt, J = 6.9 Hz, 1H), 3.52 (tt, J = 3.8, 10.9 Hz, 1H), 3.38-3.33 (m, 2H), 3.07 (br t, J = 11.2 Hz, 2H), 2.27 (br dd, J = 2.9, 14.1 Hz, 2H), 2.10-1.98 (m, 2H), 1.49 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 329.1.



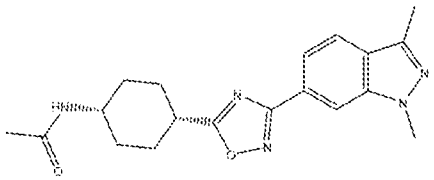
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.08 (s, 1H), 7.85-7.79 (d, J = 8.4 Hz 1H), 7.75-7.68 (d, J = 8.4 Hz 1H), 7.42-7.29 (m, 5H), 5.11 (s, 2H), 4.68 (br d, J = 5.5 Hz, 1H), 4.07 (s, 3H), 3.73-3.55 (m, 1H), 3.05-2.90 (m, 1H), 2.59 (s, 3H), 2.36-2.16 (m, 4H), 1.94-1.75 (m, 2H), 1.43-1.24 (m, 2H); LCMS (ESI) [M+H]+: 446.2.



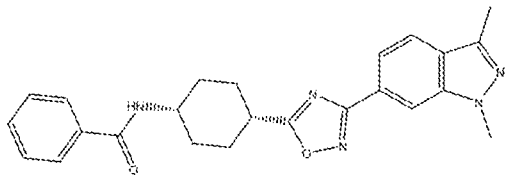
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.52 (s, 2H), 8.10 (s, 1H), 7.86-7.81 (d, J = 8.4 Hz, 1H), 7.76-7.72 (d, J = 8.4 Hz, 1H), 4.85 (td, J = 3.7, 13.6 Hz, 2H), 4.08 (s, 3H), 3.45-3.25 (m, 3H), 2.60 (s, 3H), 2.29 (br dd, J = 3.3, 13.6 Hz, 2H), 2.11-1.94 (m, 2H); LCMS (ESI) [M+H]+: 444.2.



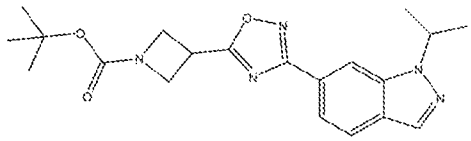
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.08 (s, 1H), 7.82-7.80 (d,J = 8.0 Hz, 1H) 7.73- 7.70 (d,J = 8.0 Hz, 1H), 5.40-5.30 (m, 1H), 4.07 (s, 3H), 3.89 (m, 1H), 2.97 (tt, J = 3.5, 12.2 Hz, 1H), 2.59 (s, 3H), 2.34-2.15 (m, 4H), 1.99 (s, 3H), 1.86 (m, 2H), 1.39-1.20 (m, 2H); LCMS (ESI) [M+H]+: 354.2.



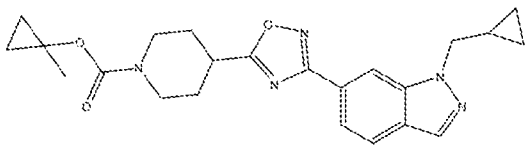
1H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.78-7.70 (m, 1H), 5.50-5.47 (br s, 1H), 4.09 (s, 3H), 4.08-3.99 (m, 1H), 3.31-3.23 (m, 1H), 2.61 (s, 3H), 2.27-2.16 (m, 2H), 2.08-2.00 (m, 2H), 1.99 (s, 3H), 1.95-1.84 (m, 2H), 1.73-1.64 (m, 2H); LCMS (ESI) [M+H]+: 354.2.



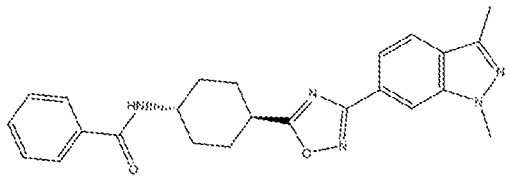
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.79-7.71 (m, 3H), 7.54-7.40 (m, 3H), 6.10 (br d, J = 7.1 Hz, 1H), 4.26 (tt, J = 4.1, 7.9 Hz, 1H), 4.09 (s, 3H), 3.32 (quin, J = 5.2 Hz, 1H), 2.61 (s, 3H), 2.35-2.23 (m, 2H), 2.15-1.98 (m, 4H), 1.86-1.73 (m, 2H); LCMS (ESI) [M+H]+: 416.3.



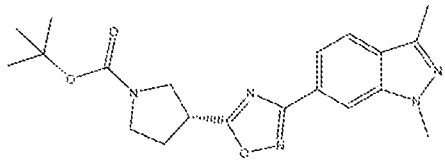
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.07 (s, 1H), 7.85 (q, J = 8.4 Hz, 2H), 4.98 (quin, J = 6.7 Hz, 1H), 4.48-4.32 (m, 4H), 4.16-4.02 (m, 1H), 1.64 (d, J = 6.8 Hz, 6H), 1.50-1.45 (m, 9H); LCMS (ESI) [M+H]+: 384.2.



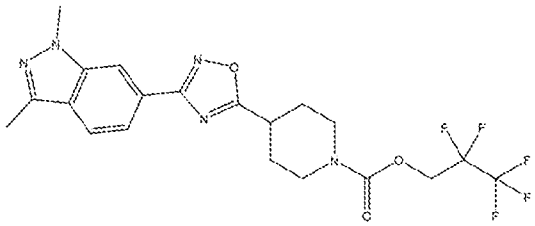
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.14 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 4.41 (d, J = 6.8 Hz, 2H), 3.93 (br d, J = 13.5 Hz, 2H), 3.45-3.32 (m, 1H), 3.04-2.95 (m, 2H), 2.11 (br dd, J = 3.2, 13.8 Hz, 2H), 1.84-1.67 (m, 2H), 1.51 (s, 3H), 1.39-1.26 (m, 1H), 0.89-0.77 (m, 2H), 0.64-0.59 (m, 2H), 0.56-0.50 (m, 2H), 0.44-0.38 (m, 2H); LCMS (ESI) [M+H]+: 422.2.



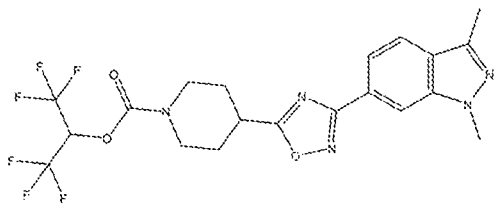
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.86-7.82 (m, 1H), 7.80-7.71 (m, 3H), 7.55-7.42 (m, 3H), 5.99 (br d, J = 7.8 Hz, 1H), 4.20-4.03 (m, 4H), 3.03 (tt, J = 3.2, 12.2 Hz, 1H), 2.60 (s, 3H), 2.41-2.28 (m, 4H), 2.03-1.84 (m, 2H), 1.52-1.36 (m, 2H); LCMS (ESI) [M+H]+: 416.3.



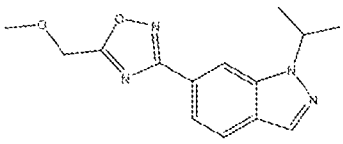
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.86-7.81 (m, 1H), 7.77-7.70 (m, 1H), 4.08 (s, 3H), 3.96-3.49 (m, 5H), 2.60 (s, 3H), 2.51-2.32 (m, 2H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 384.2.



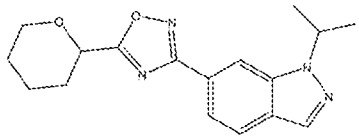
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.83 (dd, J = 1.0, 8.4 Hz, 1H), 7.76-7.72 (d,J = 8.4 Hz, 1H), 4.61 (t, J = 12.7 Hz, 2H), 4.27-4.10 (m, 2H), 4.08 (s, 3H), 3.32-3.10 (m, 3H), 2.60 (s, 3H), 2.24-2.15 (m, 2H), 2.00 (br d, J = 4.9 Hz, 2H); LCMS (ESI) [M+H]+: 474.1.



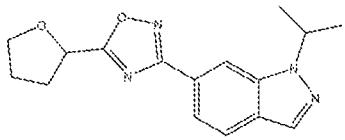
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.86-7.81 (m, 1H), 7.77-7.71 (m, 1H), 5.79 (spt, J = 6.2 Hz, 1H), 4.25-4.15 (m, 2H), 4.09 (s, 3H), 3.37-3.20 (m, 3H), 2.61 (s, 3H), 2.32-2.21 (m, 2H), 2.12-1.97 (m, 2H); LCMS (ESI) [M+H]+: 492.1.



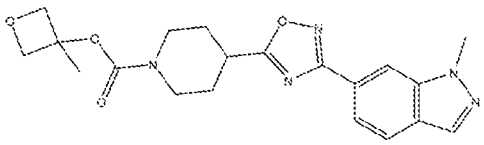
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.07 (s, 1H), 7.92-7.86 (m, 1H), 7.85-7.80 (m, 1H), 5.01-4.91 (m, 1H), 4.80 (s, 2H), 3.60 (s, 3H), 1.63 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 273.1.



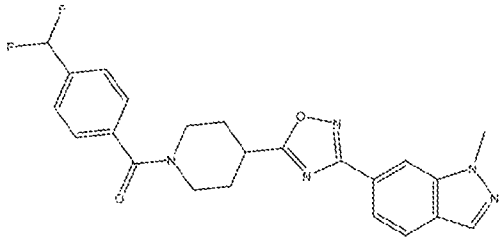
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.29 (s, 1H), 8.06 (s, 1H), 7.93-7.86 (m, 1H), 7.83-7.77 (m, 1H), 4.96 (spt, J = 6.8 Hz, 1H), 4.83 (dd, J = 2.8, 10.7 Hz, 1H), 4.24 (br d, J = 11.7 Hz, 1H), 3.84-3.62 (m, 1H), 2.22-2.11 (m, 1H), 2.09-1.91 (m, 2H), 1.86-1.74 (m, 2H), 1.73-1.65 (m, 1H), 1.62 (dd, J = 1.1, 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 313.1.



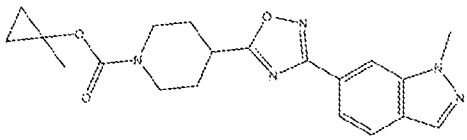
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.06 (s, 1H), 7.91-7.85 (m, 1H), 7.84-7.78 (m, 1H), 5.29 (dd, J = 5.4, 7.8 Hz, 1H), 4.97 (spt, J = 6.7 Hz, 1H), 4.27-4.14 (m, 1H), 4.11-3.99 (m, 1H), 2.55-2.42 (m, 1H), 2.40-2.31 (m, 1H), 2.28-2.04 (m, 2H), 1.63 (dd, J = 1.1, 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 299.1.



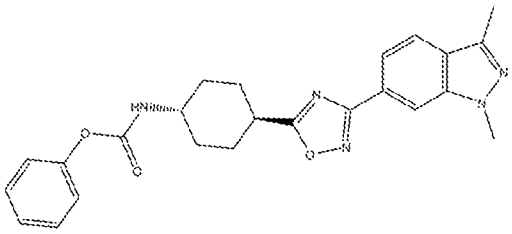
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.16 (s, 1H), 8.02 (s, 1H), 7.88-7.79 (m, 2H), 4.80 (d, J = 7.0 Hz, 2H), 4.50 (d, J = 7.0 Hz, 2H),4.21-4.08 (m, 5H), 3.29-3.20 (m, 1H), 3.21-3.09 (m, 2H), 2.18 (br d, J = 13.6 Hz, 2H), 2.02-1.92 (m, 2H), 1.75 (s, 3H); LCMS (ESI) [M+H]+: 398.1.



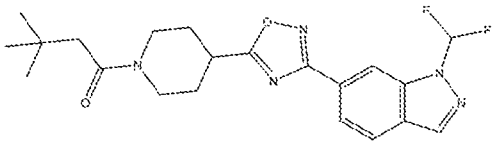
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 0.9 Hz, 1H), 8.17 (d, J = 0.9 Hz, 1H), 7.94 (dd, J = 0.6, 8.4 Hz, 1H), 7.77 (dd, J = 1.2, 8.4 Hz, 1H), 7.69-7.64 (m, 2H), 7.60-7.56 (m, 2H), 7.24-6.96 (t, J = 55.6 Hz, 1H), 4.55-4.45 (m, 1H), 4.15 (s, 3H), 3.67-3.48 (m, 2H), 3.29-3.08 (m, 2H), 2.33-2.00 (m, 2H), 1.91-1.75 (m, 2H); LCMS (ESI) [M+H]+: 438.2.



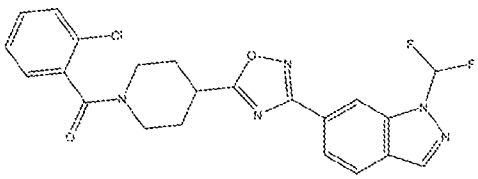
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.16 (s, 1H), 8.02 (s, 1H), 7.87-7.78 (m, 2H), 4.31-3.96 (m, 5H), 3.26-3.16 (m, 1H), 3.03 (br t, J = 11.1 Hz, 2H), 2.15 (br d, J = 11.5 Hz, 2H), 1.92 (br d, J = 9.3 Hz, 2H), 1.56 (s, 3H), 0.91-0.84 (m, 2H), 0.67-0.55 (m, 2H); LCMS (ESI) [M+H]+: 382.1.



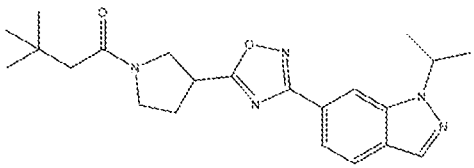
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.76-7.69 (d, J = 8.4 Hz, 1H), 7.42-7.32 (m, 2H), 7.25-7.08 (m, 3H), 4.96 (br d, J = 7.6 Hz, 1H), 4.07 (s, 3H), 3.70 (br dd, J = 4.1, 7.4 Hz, 1H), 3.01 (br t, J = 12.2 Hz, 1H), 2.59 (s, 3H), 2.40-2.25 (m, 4H), 1.95-1.81 (m, 2H), 1.49-1.36 (m, 2H); LCMS (ESI) [M+H]+: 432.2.



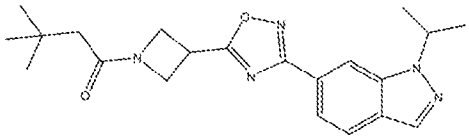
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (s, 1H), 8.15 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.66- 7.36 (t,J = 59.2 Hz, 1H), 4.62 (br d, J = 13.6 Hz, 1H), 4.04 (br d, J = 13.9 Hz, 1H), 3.35-3.24 (m, 2H), 3.01-2.90 (m, 1H), 2.31 (s, 2H), 2.22 (br d, J = 12.7 Hz, 2H), 2.04-1.86 (m, 2H), 1.08 (s, 9H); LCMS (ESI) [M+H]+: 418.



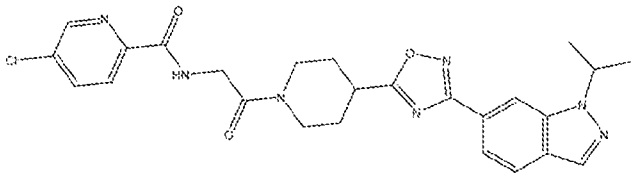
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (s, 1H), 8.15 (s, 1H), 8.07-8.01 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.67-7.37(t, J = 59.6 Hz,1H), 7.45-7.40 (m, 1H), 7.36-7.27(m, 3H), 4.78-4.63 (m, 1H), 3.64-3.53 (m, 1H), 3.40-3.13 (m, 3H), 2.34 (br dd, J = 3.3, 13.6 Hz, 1H), 2.20-1.85 (m, 3H); LCMS (ESI) [M+H]+: 458.0.



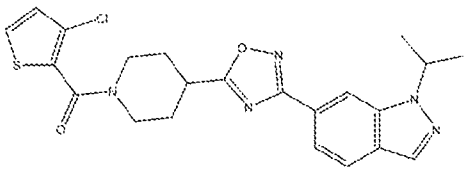
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.97 (br s, 1H), 7.82 (br d, J = 6.4 Hz, 1H), 7.66-7.50 (m, 2H), 4.78-4.64 (m, 1H), 3.87-3.34 (m, 5H), 2.35-2.09 (m, 2H), 2.06-1.93 (m, 2H), 1.45-1.31 (m, 6H), 0.95-0.75 (m, 9H); LCMS (ESI) [M+H]+: 396.2.



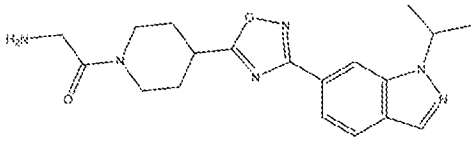
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31-8.21 (m, 1H), 8.15-8.04 (m, 1H), 7.91-7.77 (m, 2H), 4.99 (quind, J = 6.6, 13.3 Hz, 1H), 4.69-4.39 (m, 4H), 4.14 (tt, J = 6.0, 8.9 Hz, 1H), 2.14-2.00 (m, 2H), 1.65 (d, J = 6.6 Hz, 6H), 1.15-1.03 (m, 9H); LCMS (ESI) [M+H]+: 382.1.



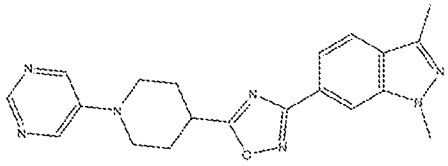
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.80 (br s, 1H), 8.57 (s, 1H), 8.21 (s, 1H), 8.14 (br d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.90-7.76 (m, 3H), 4.97 (td, J = 6.6, 13.1 Hz, 1H), 4.56 (br d, J = 13.0 Hz, 1H), 4.33 (br s, 2H), 3.94 (br d, J = 14.1 Hz, 1H), 3.44-3.26 (m, 2H), 3.15 (br t, J = 11.5 Hz, 1H), 2.28 (br t, J = 12.5 Hz, 2H), 2.14-1.94 (m, 2H), 1.63 (br d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 508.2.



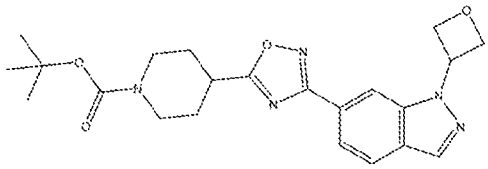
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.14 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.79-7.71 (m, 1H), 7.08 (d, J = 5.1 Hz, 1H), 5.09 (spt, J = 6.7 Hz, 1H), 4.03 (br d, J = 10.8 Hz, 2H), 3.56-3.45 (m, 1H), 3.36-3.22 (m, 2H), 2.21 (br dd, J = 3.1, 13.2 Hz, 2H), 1.96-1.78 (m, 2H), 1.52 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 456.1.



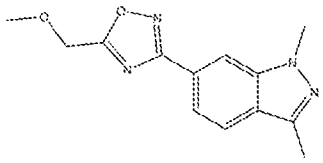
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.20 (br s, 2H), 8.14-8.08 (m, 1H), 7.94 (br d, J = 8.3 Hz, 1H), 7.75 (br d, J = 8.3 Hz, 1H), 5.14 (td, J = 6.3, 12.8 Hz, 1H), 4.36 (br d, J = 12.8 Hz, 1H), 4.02-3.74 (m, 3H), 3.63-3.47 (m, 1H), 3.30-3.21 (m, 1H), 3.01 (br t, J = 11.7 Hz, 1H), 2.18 (br d, J = 12.1 Hz, 2H), 2.00-1.83 (m, 1H), 1.78-1.61 (m, 1H), 1.51 (br d, J = 6.4 Hz, 6H); LCMS (ESI) [M+H]+: 369.1.



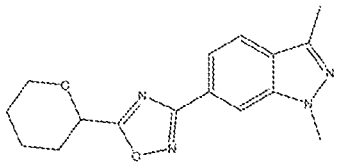
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.74 (s, 1H), 8.46 (s, 2H), 8.12 (s, 1H), 7.91-7.80 (m, 1H), 7.76 (d, J = 8.5 Hz, 1H), 4.10 (s, 3H), 3.83 (d, J = 12.8 Hz, 2H), 3.12 (t, J = 10.3 Hz, 2H), 2.61 (s, 3H), 2.37 (d, J = 12.7 Hz, 2H), 2.29-2.16 (m, 2H); LCMS (ESI) [M+H]+: 376.1.



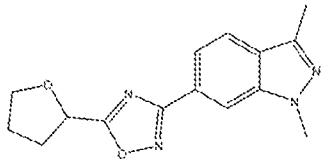
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.21 (d, J = 14.0 Hz, 2H), 7.96-7.82 (m, 2H), 5.91 (t, J = 7.1 Hz, 1H), 5.35 (t, J = 6.5 Hz, 2H), 5.17 (t, J = 7.2 Hz, 2H), 4.16 (s,2H), 3.02 (t, J = 12.0 Hz, 2H), 2.17 (d, J = 13.4 Hz, 2H), 2.07-1.77 (m, 2H), 1.50 (s, 8H); LCMS (ESI) [M+H]+: 426.



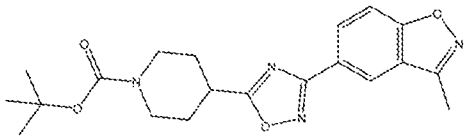
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.16 (s, 1H), 7.86 (dd, J = 1.3, 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 4.80 (s, 2H), 4.08 (s, 3H), 3.60 (s, 3H), 2.60 (s, 3H); LCMS (ESI) [M+H]+: 259.1.



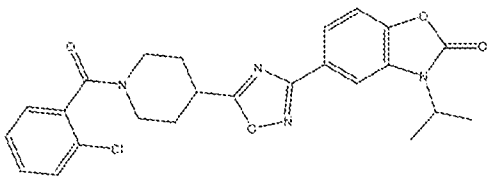
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 7.87 (dd, J = 1.1, 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 4.83 (dd, J = 2.6, 10.5 Hz, 1H), 4.24 (br d, J = 11.8 Hz, 1H), 4.07 (s, 3H), 3.75-3.67 (m, 1H), 2.60 (s, 3H), 2.16 (br d, J = 15.8 Hz, 1H), 2.08-1.91 (m, 2H), 1.84-1.64 (m, 3H); LCMS (ESI) [M+H]+: 299.1.



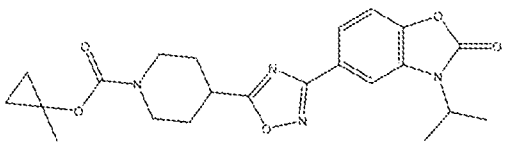
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 7.85 (dd, J = 1.3, 8.3 Hz, 1H), 7.76-7.70 (m, 1H), 5.29 (dd, J = 5.3, 7.9 Hz, 1H), 4.24-4.15 (m, 1H), 4.08 (s, 3H), 4.07-4.02 (m, 1H), 2.60 (s, 3H), 2.54-2.43 (m, 1H), 2.41-2.32 (m, 1H), 2.26-2.06 (m, 2H); LCMS (ESI) [M+H]+: 285.1.



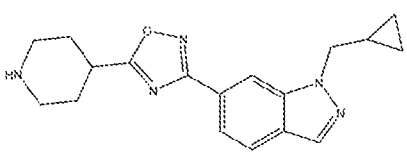
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.40 (s, 1H), 8.30 (dd, J = 1.5, 8.8 Hz, 1H), 7.69-7.61 (m, 1H), 4.20-4.05 (m, 2H), 3.20 (tt, J = 3.9, 10.9 Hz, 1H), 3.02 (br t, J = 11.3 Hz, 2H), 2.66 (s, 3H), 2.15 (br d, J = 10.8 Hz, 2H), 1.98-1.88 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 385.1.



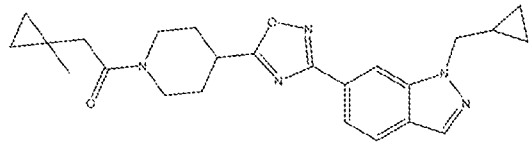
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.86-7.78 (m, 1H), 7.71 (s, 1H), 7.44-7.28 (m, 3H), 7.25-7.19 (m, 2H), 4.70-4.57 (m, 1H), 4.52 (td, J = 7.0, 13.9 Hz, 1H), 3.51 (br t, J = 13.9 Hz, 1H), 3.28-3.19 (m, 2H), 3.16-3.05 (m, 1H), 2.25 (br d, J = 13.4 Hz, 1H), 2.08-1.99 (m, 2H), 1.90-1.74 (m, 1H), 1.53 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 467.0.



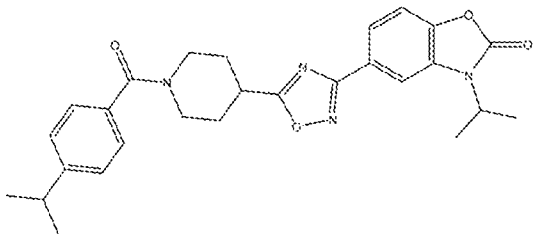
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.88 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 4.59 (spt, J = 6.9 Hz, 1H), 4.32-3.96 (m, 2H), 3.25-3.13 (m, 1H), 3.05-3.00 (m, 2H), 2.18-2.10 (m, 2H), 1.95-1.89 (m, 2H), 1.64-1.56 (m, 9H), 0.92-0.86 (m, 2H), 0.69-0.61 (m, 2H); LCMS (ESI) [M+H]+: 427.1.



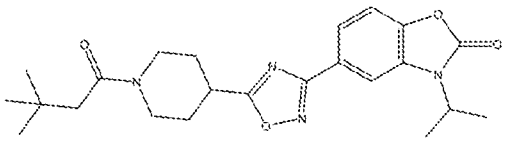
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.32 (s, 1H), 8.10 (s, 1H), 7.96-7.78 (m, 2H), 4.39 (d, J = 6.8 Hz, 2H), 3.60-3.50 (m, 3H), 3.29-3.21 (m, 2H), 2.47 (br dd, J = 3.3, 14.5 Hz, 2H), 2.29-2.10 (m, 2H), 1.44-1.28 (m, 1H), 0.64-0.53 (m, 2H), 0.46 (m, 2H); LCMS (ESI) [M+H]+: 324.1.



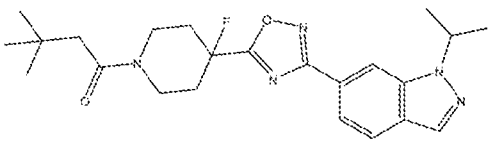
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.06 (s, 1H), 7.92-7.78 (m, 2H), 4.61 (br d, J = 14.1 Hz, 1H), 4.36 (d, J = 6.8 Hz, 2H), 3.98 (br d, J = 13.4 Hz, 1H), 3.37-3.22 (m, 2H), 3.05-2.90 (m, 1H), 2.40 (d, J = 4.0 Hz, 2H), 2.23 (br d, J = 13.3 Hz, 2H), 2.06-1.86 (m, 2H), 1.40 (br d, J = 7.2 Hz, 1H), 1.18 (s, 3H), 0.67-0.55 (m, 2H), 0.49-0.40 (m, 6H); LCMS (ESI) [M+H]+: 420.2.



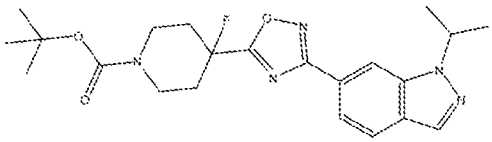
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.85 (dd, J = 1.2, 8.4 Hz, 1H), 7.75 (s, 1H), 7.36-7.30 (m, 2H), 7.24 (m, 3H), 4.60-4.50 (m, 2H), 3.98-3.94 (m, 1H), 3.33-3.08 (m, 3H), 2.91 (td, J = 6.9, 13.8 Hz, 1H), 2.30-1.90 (m, 4H), 1.56 (d, J = 7.0 Hz, 6H), 1.23 (d, J = 7.0 Hz, 6H); LCMS (ESI) [M+H]+: 475.1.



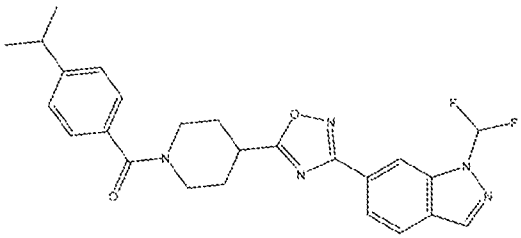
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.81 (dd, J = 1.1, 8.3 Hz, 1H), 7.71 (s, 1H), 7.22 (d, J = 8.3 Hz, 1H), 4.59-4.48 (m, 2H), 3.96 (br d, J = 13.8 Hz, 1H), 3.28-3.15 (m, 2H), 2.87 (br t, J = 11.2 Hz, 1H), 2.24 (d, J = 1.7 Hz, 2H), 2.12 (br d, J = 13.2 Hz, 2H), 1.94-1.79 (m, 2H), 1.52 (d, J = 7.0 Hz, 6H), 1.00 (s, 9H); LCMS (ESI) [M+H]+: 427.1.



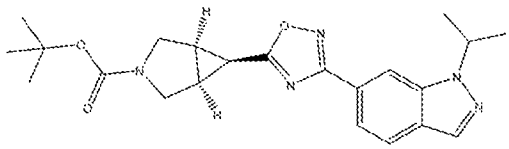
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.06 (s, 1H), 7.87-7.80 (m, 2H), 4.96 (spt, J = 6.7 Hz, 1H), 4.57 (br d, J = 13.6 Hz, 1H), 3.93 (br d, J = 14.5 Hz, 1H), 3.66-3.51 (m, 1H), 3.30-3.22 (m, 1H), 2.43-2.21 (m, 6H), 1.62 (d, J = 7.0 Hz, 6H), 1.08 (s, 9H); LCMS (ESI) [M+H]+: 428.2.



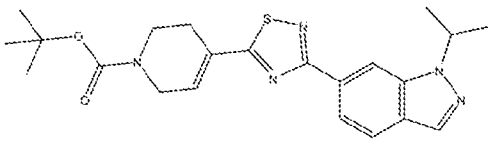
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.08 (s, 1H), 7.90-7.82 (m, 2H), 5.02-4.95 (m, 1H), 4.08-4.00 (m, 2H), 3.40 (br d, J = 9.8 Hz, 2H), 2.40-2.24 (m, 4H), 1.65 (d, J = 6.7 Hz, 6H), 1.51 (s, 9H); LCMS (ESI) [M+H]+: 430.2.



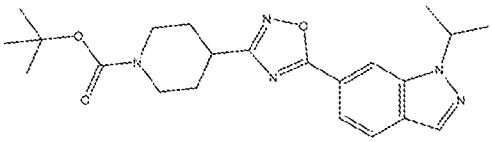
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.45 (s, 1H), 8.36-8.07 (t, J = 58.8, 1H), 8.09-8.05 (m, 1H), 7.99-7.95 (m, 1H), 7.36-7.28 (m, 4H), 4.05 (br d, J = 4.6 Hz, 2H), 3.54-3.41 (m, 1H), 3.26-3.17 (m, 2H), 2.98-2.88 (m, 1H), 2.17 (br dd, J = 3.2, 13.3 Hz, 2H), 1.91-1.80 (m, 2H), 1.23 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 466.0.



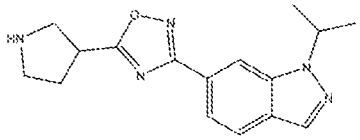
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.16 (s, 1H), 8.05 (s, 1H), 7.84-7.77 (m, 2H), 4.94 (m, 1H), 3.92-3.72 (m, 2H), 3.61-3.48 (m, 2H), 2.40 (m, 2H), 2.17 (t, J = 3.1 Hz, 1H), 1.62 (d, J = 7.0 Hz, 6H), 1.47 (s, 9H); LCMS (ESI) [M+H]+: 410.2.



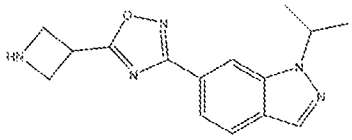
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.44 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 6.89 (br s, 1H), 4.99 (td, J = 6.7, 13.3 Hz, 1H), 4.21 (m, 2H), 3.71 (br t, J = 5.5 Hz, 2H), 2.77 (br s, J = 1.6 Hz, 2H), 1.64 (d, J = 6.6 Hz, 6H), 1.51 (s, 9H); LCMS (ESI) [M+H]+: 426.2.



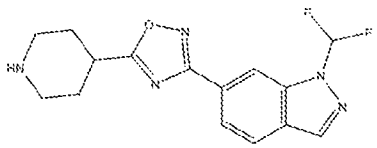
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.08 (s, 1H), 7.86 (m, 2H), 4.97 (td, J = 6.6, 13.2 Hz, 1H), 4.20-4.12 (m, 2H), 3.12-2.87 (m, 3H), 2.08 (br d, J = 11.2 Hz, 2H), 1.95-1.79 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 412.2.



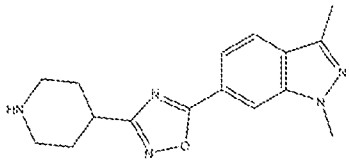
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.36 (s, 1H), 8.13 (s, 1H), 7.97-7.82 (m, 2H), 5.08 (td, J = 6.6, 13.2 Hz, 1H), 4.25-4.12 (m, 1H), 3.92-3.80 (m, 2H), 3.70-3.49 (m, 2H), 2.79-2.64 (m, 1H), 2.52 (qd, J = 6.9, 13.6 Hz, 1H), 1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 298.1.



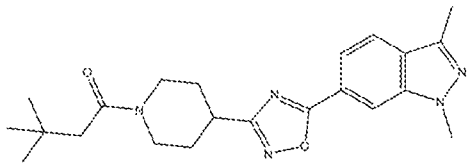
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (br s, 2H), 8.34 (s, 1H), 8.21 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 5.14 (td, J = 6.6, 13.0 Hz, 1H), 4.64-4.45 (m, 1H), 4.41-4.28 (m, 4H), 1.51 (d, J = 6.5 Hz, 6H); LCMS (ESI) [M+H]+: 284.1.



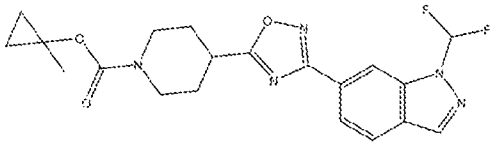
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (br s, 2H), 8.56 (s, 1H), 8.50-8.21 (t, J = 58 Hz, 1H), 8.47 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 3.60-3.51 (m, 1H), 3.36 (br d, J = 12.8 Hz, 2H), 3.09 (br t, J = 11.0 Hz, 2H), 2.30 (br d, J = 14.3 Hz, 2H), 2.14-2.01 (m, 2H); LCMS (ESI) [M+H]+: 320.1.



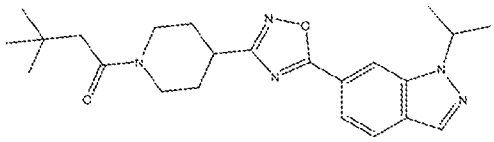
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31-8.98 (m, 2H), 8.36 (s, 1H), 7.94 (br d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 4.08 (s, 3H), 3.62-3.58 (m, 1H), 3.39-3.24 (m, 3H), 3.15-3.01 (m, 2H), 2.52 (s, 3H), 2.25-2.15 (m, 2H), 2.09-1.95 (m, 2H); LCMS (ESI) [M+H]+: 298.1.



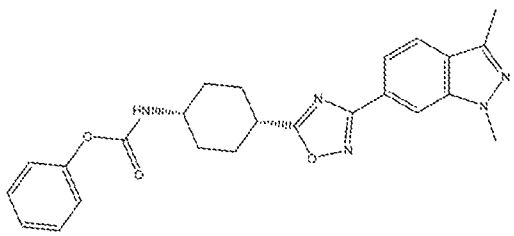
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 7.86-7.82 (m, 1H), 7.79-7.75 (m, 1H), 4.66 (br d, J = 13.8 Hz, 1H), 4.09 (s, 3H), 4.04 (br d, J = 15.0 Hz, 1H), 3.26 (br t, J = 11.7 Hz, 1H), 3.18-3.08 (m, 1H), 2.89 (br t, J = 11.8 Hz, 1H), 2.60 (s, 3H), 2.31 (s, 2H), 2.14 (br dd, J = 3.1, 13.6 Hz, 2H), 1.99-1.80 (m, 2H), 1.08 (s, 9H); LCMS (ESI) [M+H]+: 396.2.



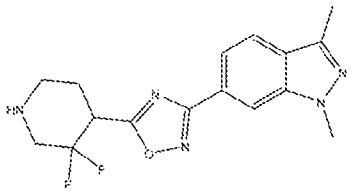
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.49-8.21 (t, J = 58 Hz, 1H), 8.48 (s, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.99 (dd, J = 1.2, 8.4 Hz, 1H), 4.05-3.80 (m, 2H), 3.41 (tt, J = 3.9, 11.0 Hz, 1H), 3.02 (br t, J = 10.8 Hz, 2H), 2.16-2.07 (m, 2H), 1.79-1.66 (m, 2H), 1.49 (s, 3H), 0.83-0.78 (m, 2H), 0.67-0.57 (m, 2H); LCMS (ESI) [M+H]+: 418.1.



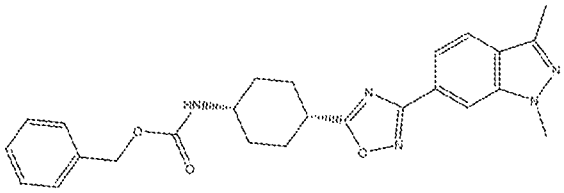
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.10 (s, 1H), 7.87 (m, 2H), 4.98 (td, J = 6.7, 13.3 Hz, 1H), 4.67 (br d, J = 13.5 Hz, 1H), 4.06-4.00 (m, 1H), 3.27 (br t, J = 11.6 Hz, 1H), 3.18-3.07 (m, 1H), 2.90 (br t, J = 11.4 Hz, 1H), 2.33 (d, J = 1.1 Hz, 2H), 2.16 (br dd, J = 3.1, 13.2 Hz, 2H), 2.02-1.78 (m, 2H), 1.65 (d, J = 6.8 Hz, 6H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 410.2.



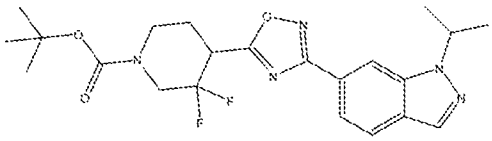
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 7.85 (dd, J = 1.2 ,8.4 Hz, 1H), 7.78-7.72 (d,J = 8.4 Hz,1H), 7.41-7.32 (m, 2H), 7.24-7.17 (m, 1H), 7.14 (d, J = 7.7 Hz, 2H), 5.11 (br d, J = 6.5 Hz, 1H), 4.09 (s, 3H), 3.95-3.83 (m, 1H), 3.31-3.21 (m, 1H), 2.61 (s, 3H), 2.29-2.18 (m, 2H), 2.11-1.92 (m, 4H), 1.89-1.78 (m, 2H); LCMS (ESI) [M+H]+: 432.2.



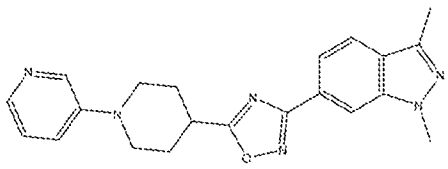
^{1}H NMR (400 MHz, MATHANOL-d_4) δ 8.27 (s, 1H), 7.98-7.83 (m, 2H), 4.42-4.25 (m, 1H), 4.11 (s, 3H), 3.99 (td, J = 8.6, 13.6 Hz, 1H), 3.88-3.74 (m, 1H), 3.69 (br d, J = 13.6 Hz, 1H), 3.46-3.35 (m, 1H), 2.72-2.56 (m, 5H); LCMS (ESI) [M+H]+: 334.1.



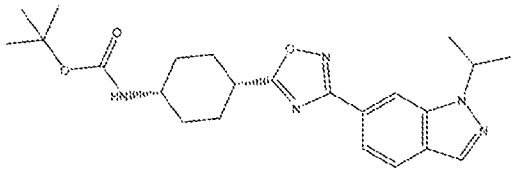
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.84 (dd, J = 1.2, 8.4 Hz, 1H), 7.73 (dd, J = 0.6, 8.4 Hz, 1H), 7.42-7.30 (m, 5H), 5.11 (s, 2H), 4.86-4.82 (m, 1H), 4.08 (s, 3H), 3.86-3.82 (m, 1H), 3.27-3.18 (m, 1H), 2.60 (s, 3H), 2.22-2.10 (m, 2H), 2.07-1.97 (m, 2H), 1.91-1.87 (m, 2H), 1.81-1.69 (m, 2H); LCMS (ESI) [M+H]+: 446.2.



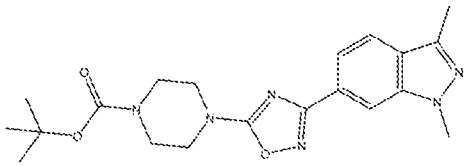
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (d, J = 0.7 Hz, 1H), 7.99 (s, 1H), 7.82-7.77 (m, 1H), 7.76-7.72 (m, 1H), 4.89 (spt, J = 6.7 Hz, 1H), 4.40-3.98 (m, 2H), 3.75-3.58 (m, 1H), 3.51-3.36 (m, 1H), 3.31-3.13 (m, 1H), 2.39-2.12 (m, 2H), 1.56 (d, J = 6.6 Hz, 6H), 1.48-1.32 (m, 9H); LCMS (ESI) [M+H]+: 448.2.



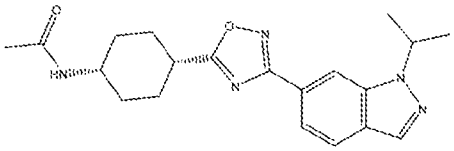
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.39 (s, 1H), 8.12 (s, 2H), 7.85 (dd, J = 8.4, 1.3 Hz, 1H), 7.75 (dd, J = 8.4, 0.9 Hz, 1H), 7.26-7.14 (m, 1H), 4.09 (s, 3H), 3.80 (d, J = 12.7 Hz, 2H), 3.25 (m, 1H), 3.07 (d, J = 14.2 Hz, 2H), 2.61 (s, 3H), 2.32 (s, 2H), 2.26-2.16 (m, 1H); LCMS (ESI) [M+H]+: 375.1.



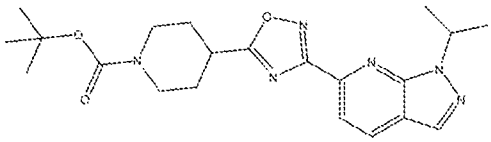
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.88-7.80 (m, 2H), 4.98 (td, J = 6.6, 13.4 Hz, 1H), 4.65-4.50 (m, 1H), 3.80-3.70 (m, 1H), 3.21 (br d, J = 4.0 Hz, 1H), 2.16 (br d, J = 7.9 Hz, 2H), 2.05-1.97 (m, 2H), 1.85 (br d, J = 4.4 Hz, 2H), 1.75-1.70 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H), 1.46 (s, 9H); LCMS (ESI) [M+H]+: 426.2.



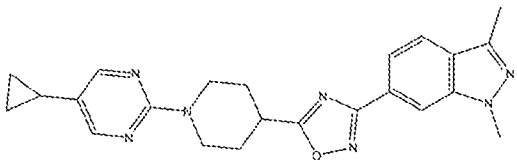
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.04 (s, 1H), 7.79-7.76 (m, 1H), 7.73-7.70 (m, 1H), 4.08 (s, 3H), 3.76-3.70 (m, 4H), 3.65-3.59 (m, 4H), 2.61 (s, 3H), 1.52 (s, 9H); LCMS (ESI) [M+H]+: 399.1.



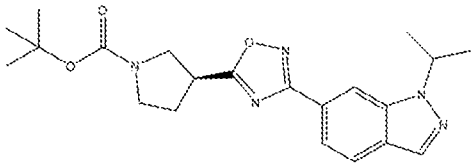
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.06 (s, 1H), 7.88-7.78 (m, 2H), 5.50-5.35 (m, 1H), 4.96 (spt, J = 6.7 Hz, 1H), 4.04 (td, J = 3.9, 8.2 Hz, 1H), 3.30-3.22 (m, 1H), 2.25-2.16 (m, 2H), 2.03 (qd, J = 4.6, 9.2 Hz, 2H), 1.98 (s, 3H), 1.93-1.84 (m, 2H), 1.70-1.60 (m, 8H); LCMS (ESI) [M+H]+: 368.2.



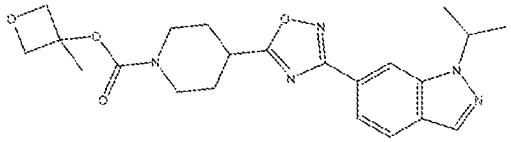
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.95 (d, J = 8.2 Hz, 1H), 5.52 (spt, J = 6.7 Hz, 1H), 4.20-4.10 (m, 2H), 3.26 (tt, J = 3.8, 11.1 Hz, 1H), 2.99 (br t, J = 12.0 Hz, 2H), 2.16 (br d, J = 10.4 Hz, 2H), 2.00-1.89 (m, 2H), 1.59 (d, J = 6.6 Hz, 6H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 413.2.



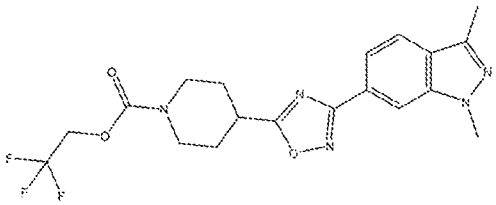
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 2H), 8.10 (s, 1H), 7.83 (dd, J = 1.2, 8.4 Hz, 1H), 7.73 (dd, J = 0.6, 8.4 Hz, 1H), 4.74 (td, J = 3.5, 13.6 Hz, 2H), 4.07 (s, 3H), 3.32 (tt, J = 4.0, 11.0 Hz, 1H), 3.20 (ddd, J = 2.8, 11.3, 13.7 Hz, 2H), 2.60 (s, 3H), 2.24 (br dd, J = 3.2, 13.5 Hz, 2H), 2.07-1.92 (m, 2H), 1.73 (tt, J = 5.1, 8.5 Hz, 1H), 0.97-0.86 (m, 2H), 0.63-0.57 (m, 2H); LCMS (ESI) [M+H]+: 416.1.



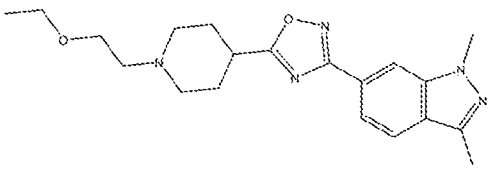
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.19 (s, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.75 (dd, J = 1.0, 8.4 Hz, 1H), 5.14 (spt, J = 6.5 Hz, 1H), 3.93 (br d, J = 6.7 Hz, 1H), 3.78 (br d, J = 7.2 Hz, 1H), 3.68-3.61 (m, 1H), 3.51-3.44 (m, 1H), 3.40 (br d, J = 6.6 Hz, 1H), 2.46-2.33 (m, 1H), 2.24 (br d, J = 7.1 Hz, 1H), 1.50 (d, J = 6.6 Hz, 6H), 1.42 (s, 9H); LCMS (ESI) [M+H]+: 398.2.



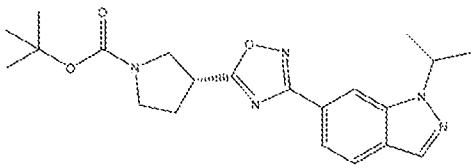
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.08 (s, 1H), 7.92-7.81 (m, 2H), 4.98 (quind, J = 6.7, 13.3 Hz, 1H), 4.83 (d, J = 7.1 Hz, 2H), 4.53 (d, J = 7.5 Hz, 2H), 4.17 (br s, 2H), 3.35-3.20 (m, 1H), 3.13 (br s, 2H), 2.22 (br d, J = 11.1 Hz, 2H), 2.06-1.92 (m, 2H), 1.78 (s, 3H), 1.65 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 426.1.



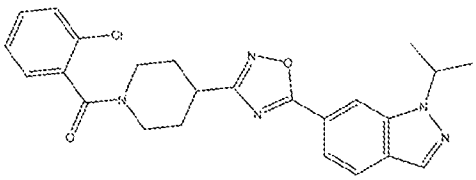
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.86-7.81 (m, 1H), 7.77-7.72 (m, 1H), 4.53 (dq, J = 2.2, 8.4 Hz, 2H), 4.20 (br t, J = 16.1 Hz, 2H), 4.08 (s, 3H), 3.32-3.23 (m, 1H), 3.22-3.10 (m, 2H), 2.60 (s, 3H), 2.22 (br d, J = 11.9 Hz, 2H), 2.07-1.94 (m, 2H); LCMS (ESI) [M+H]+: 424.1.



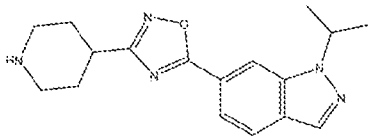
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.84 (dd, J = 1.2, 8.4 Hz, 1H), 7.73 (dd, J = 0.7, 8.4 Hz, 1H), 4.08 (s, 3H), 3.60 (t, J = 5.9 Hz, 2H), 3.54 (q, J = 7.0 Hz, 2H), 3.10-2.99 (m, 3H), 2.65 (t, J = 6.0 Hz, 2H), 2.60 (s, 3H), 2.27 (dt, J = 2.3, 11.3 Hz, 2H), 2.21-2.03 (m, 4H), 1.23 (t, J = 7.0 Hz, 3H); LCMS (ESI) [M+H]+: 370.2.



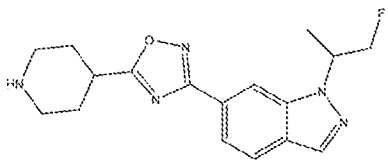
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.06 (s, 1H), 7.89-7.78 (m, 2H), 4.97 (td, J = 6.6, 13.4 Hz, 1H), 4.02-3.43 (m, 5H), 2.52-2.32 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 398.2.



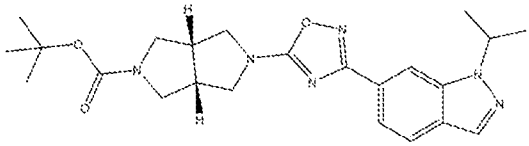
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.10 (s, 1H), 7.91-7.81 (m, 2H), 7.47-7.40 (m, 1H), 7.39-7.28 (m, 3H), 4.98 (td, J = 6.6, 13.5 Hz, 1H), 4.76 (br t, J = 12.5 Hz, 1H), 3.65-3.52 (m, 1H), 3.36-3.10 (m, 3H), 2.28 (br dd, J = 3.5, 13.6 Hz, 1H), 2.15-1.95 (m, 2.5H), 1.94-1.79 (m, 0.5H), 1.65 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 450.1.



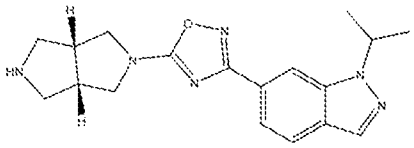
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 2H), 8.49 (s, 1H), 8.25 (s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.80 (dd, J = 1.1, 8.6 Hz, 1H), 5.22 (spt, J = 6.4 Hz, 1H), 3.39-3.35 (m, 1H), 3.33-3.24 (m, 2H), 3.14-3.00 (m, 2H), 2.20 (br d, J = 11.8 Hz, 2H), 2.08-1.92 (m, 2H), 1.50 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 312.1.



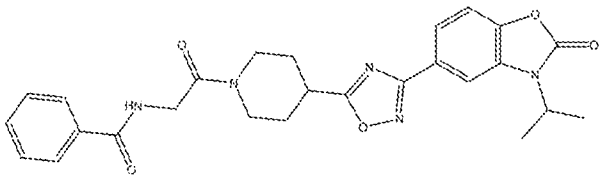
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.16 (s, 1H), 8.12 (s, 1H), 7.94-7.89 (m, 1H), 7.87-7.82 (m, 1H), 5.46 (q, J = 7.2 Hz, 1H), 4.20-4.05 (m 2H), 3.72 (s, 3H), 3.21 (tt, J = 3.9, 10.8 Hz, 1H), 3.02 (br t, J = 11.9 Hz, 2H), 2.15 (br d, J = 10.5 Hz, 2H), 1.98 (d, J = 7.2 Hz, 3H), 1.97-1.87 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 456.2.



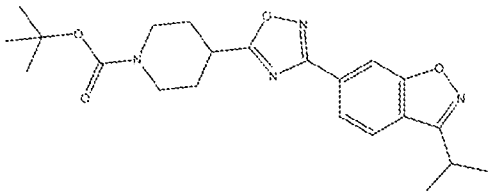
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.04 (s, 1H), 7.77 (m, 2H), 4.95 (m, 1H), 3.99-3.87 (m, 2H), 3.74-3.56 (m, 4H), 3.47-3.24 (m, 2H), 3.07 (br s, 2H), 1.61 (d, J = 7.0 Hz, 6H), 1.47 (s, 9H) LCMS (ESI) [M+H]+: 439.2.



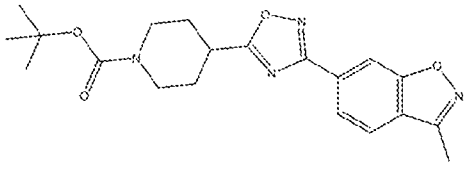
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.22 (s, 1H), 8.09 (s, 1H), 7.84 (dd, J = 1.2, 8.4 Hz, 1H), 7.73 (dd, J = 0.7, 8.4 Hz, 1H), 5.03 (m, 1H), 3.93 (br dd, J = 7.4, 11.2 Hz, 2H), 3.75 (dd, J = 3.1, 11.2 Hz, 2H), 3.65 (br dd, J = 6.8, 11.6 Hz, 2H), 3.41-3.32 (m, 3H), 3.29 (m, 1H), 1.59 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 339.1.



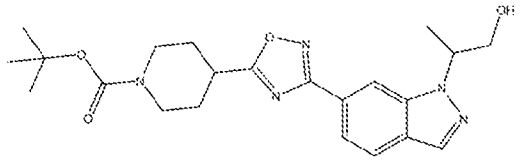
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.92-7.84 (m, 3H), 7.79 (d, J = 1.1 Hz, 1H), 7.56-7.51 (m, 1H), 7.49-7.43 (m, 2H), 7.36-7.28 (m, 2H), 4.64-4.49 (m, 2H), 4.32 (t, J = 3.2 Hz, 2H), 3.93 (br d, J = 13.7 Hz, 1H), 3.40-3.30 (m, 2H), 3.14 (br t, J = 11.0 Hz, 1H), 2.33-2.21 (m, 2H), 2.09-1.94 (m, 2H), 1.60 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 490.2.



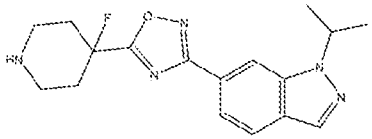
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.29 (s, 1H), 8.04 (dd, J = 1.2, 8.3 Hz, 1H), 7.81 (dd, J = 0.6, 8.2 Hz, 1H), 4.20-4.05 (m, 2H), 3.46 (spt, J = 7.0 Hz, 1H), 3.21 (tt, J = 3.9, 10.9 Hz, 1H), 3.02 (br t, J = 11.6 Hz, 2H), 2.15 (br dd, J = 3.0, 13.3 Hz, 2H), 1.92 (dtd, J = 4.2, 11.1, 13.5 Hz, 2H), 1.53 (d, J = 7.0 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 413.2.



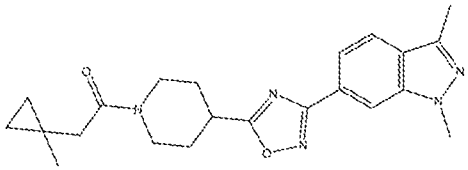
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.05 (dd, J = 1.1, 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 4.20-4.05 (m, 2H), 3.20 (tt, J = 3.9, 10.9 Hz, 1H), 3.01 (br t, J = 11.9 Hz, 2H), 2.63 (s, 3H), 2.14 (br dd, J = 3.0, 13.3 Hz, 2H), 1.97-1.85 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-55]+: 329.1.



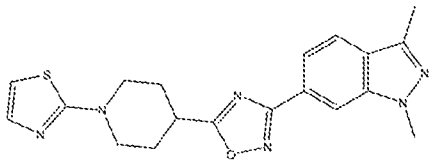
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.08 (s, 1H), 7.91-7.87 (m, 1H), 7.86-7.81 (m, 1H), 4.95-4.83 (m, 1H), 4.27-4.02 (m, 4H), 3.21 (tt, J = 3.9, 10.9 Hz, 1H), 3.02 (br t, J = 11.6 Hz, 2H), 2.82-2.78 (m, 1H), 2.16 (br dd, J = 2.6, 13.3 Hz, 2H), 2.00-1.87 (m, 2H), 1.60 (d, J = 6.7 Hz, 3H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 428.2.



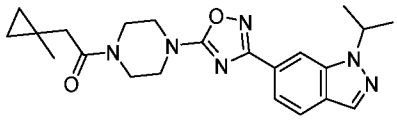
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.06 (s, 1H), 7.88-7.78 (m, 2H), 5.01-4.93 (m, 1H), 3.19-2.99 (m, 4H), 2.37-2.24 (m, 4H), 1.63 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 330.1.



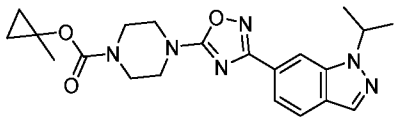
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.69 (s, 1H), 7.45-7.41 (m, 1H), 7.36-7.32 (m, 1H), 4.20 (br d, J = 13.5 Hz, 1H), 3.68 (s, 3H), 3.57 (br d, J = 14.1 Hz, 1H), 2.92-2.84 (m, 2H), 2.58 (br t, J = 11.8 Hz, 1H), 2.20 (s, 3H), 2.00 (d, J = 3.1 Hz, 2H), 1.83 (br d, J = 13.2 Hz, 2H), 1.62-1.50 (m, 2H), 0.78 (s, 3H), 0.08--0.03 (m, 4H); LCMS (ESI) [M+H]+: 394.2.



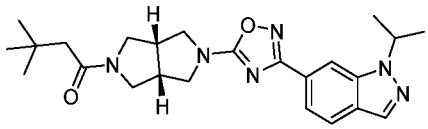
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.11 (s, J = 1.0 Hz, 1H), 7.85 (dd, J = 8.4, 1.3 Hz, 1H), 7.75 (dd, J = 8.4, 0.8 Hz, 1H), 7.22 (d, J = 3.6 Hz, 1H), 6.62 (d, J = 3.6 Hz, 1H), 4.14 (m, 2H), 4.09 (s, 3H), 3.32 (td, J = 12.9, 11.9, 3.1 Hz, 2H), 2.61 (s, 3H), 2.38-2.25 (m, 2H), 2.25-2.10 (m, 2H); LCMS (ESI) [M+H]+: 381.1.



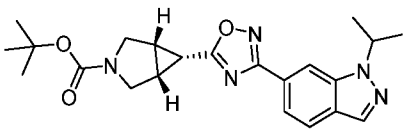
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.05 (s, 1H), 7.78 (s, 2H), 4.95 (td, J = 6.6, 13.3 Hz, 1H), 3.93-3.57 (m, 8H), 2.41 (s, 2H), 1.63 (d, J = 6.7 Hz, 6H), 1.18 (s, 3H), 0.58-0.37 (m, 4H); LCMS (ESI) [M+H]+: 409.2.



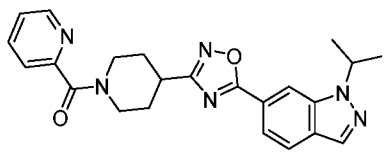
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.05 (s, 1H), 7.78 (d, J = 0.9 Hz, 2H), 5.03-4.86 (m, 1H), 3.84-3.49 (m, 8H), 1.62 (d, J = 6.7 Hz, 6H), 1.59 (s, 3H), 0.95-0.88 (m, 2H), 0.72-0.64 (m, 2H); LCMS (ESI) [M+H]+: 411.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.04 (s, 1H), 7.79-7.75 (m, 2H), 5.01-4.90 (m, 1H), 3.96 (td, J = 7.9, 10.8 Hz, 2H), 3.88-3.77 (m, 2H), 3.68-3.50 (m, 3H), 3.45 (dd, J = 5.3, 10.7 Hz, 1H), 3.23-3.03 (m, 2H), 2.19 (s, 2H), 1.61 (d, J = 6.6 Hz, 6H), 1.06 (s, 9H); LCMS (ESI) [M+H]+: 437.2.

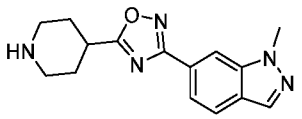


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.04 (s, 1H), 7.86-7.74 (m, 2H), 5.02-4.89 (m, 1H), 4.02 (d, J = 11.5 Hz, 1H), 3.81 (d, J = 11.5 Hz, 1H), 3.50 (dt, J = 2.8, 11.9 Hz, 2H), 2.32-2.16 (m, 3H), 1.61 (dd, J = 6.7, 11.7 Hz, 6H), 1.19 (s, 9H); LCMS (ESI) [M+H]+: 410.2.

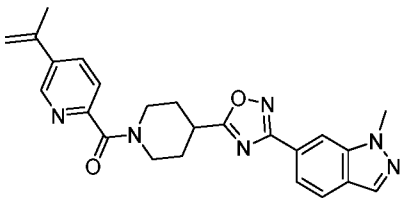


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.62 (d, J = 4.2 Hz, 1H), 8.29 (d, J = 0.9 Hz, 1H), 8.10 (s, 1H), 7.87 (s, 2H), 7.82 (dt, J = 1.8, 7.7 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.36 (ddd, J = 1.1, 4.9, 7.7 Hz, 1H), 4.99 (td, J = 6.6, 13.4 Hz, 1H), 4.74 (br d, J = 13.9 Hz, 1H), 4.08 (br d, J = 12.6 Hz, 1H), 3.40-3.27 (m,

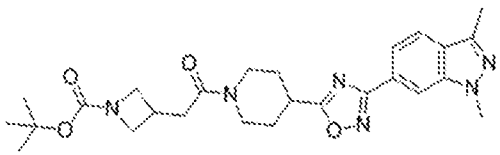
1H), 3.26-3.10 (m, 2H), 2.26 (br d, J = 10.6 Hz, 1H), 2.16-1.95 (m, 3H), 1.65 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 417.1.



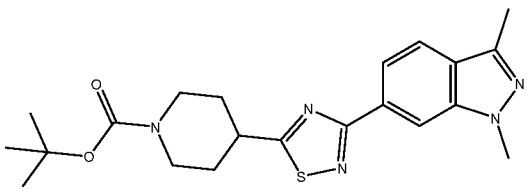
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.27 (s, 1H), 8.08 (s, 1H), 7.90-7.83 (m, 2H), 4.14 (s, 3H), 3.59-3.50 (m, 3H), 3.28-3.21 (m, 2H), 2.46 (br dd, J = 3.6, 14.9 Hz, 2H), 2.24-2.13 (m, 2H); LCMS (ESI) [M+H]+: 284.1.



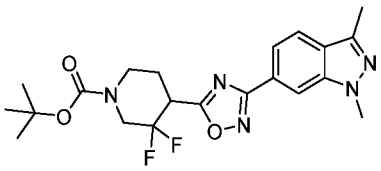
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.63 (d, J = 1.8 Hz, 1H), 8.10 (d, J = 0.6 Hz, 1H), 7.96 (d, J = 0.7 Hz, 1H), 7.81-7.73 (m, 3H), 7.59 (d, J = 8.2 Hz, 1H), 5.42 (s, 1H), 5.19 (s, 1H), 4.62 (br d, J = 13.4 Hz, 1H), 4.09 (s, 4H), 3.36-3.27 (m, 2H), 3.22-3.11 (m, 1H), 2.30-2.20 (m, 1H), 2.14-2.03 (m, 6H); LCMS (ESI) [M+H]+: 429.2.



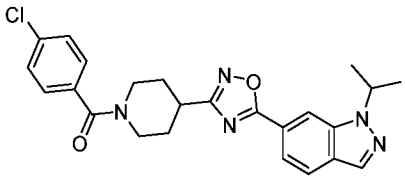
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.25-8.12 (m, 1H), 7.83 (br s, 2H), 4.47 (br d, J = 13.4 Hz, 1H), 4.14-4.01 (m, 6H), 3.63 (br s, 2H), 3.47-3.35 (m, 2H), 3.07-2.90 (m, 2H), 2.83 (br d, J = 5.7 Hz, 2H), 2.59 (s, 3H), 2.34-2.18 (m, 2H), 2.03-1.83 (m, 2H), 1.45 (s, 9H); LCMS (ESI) [M+H]+: 495.3.



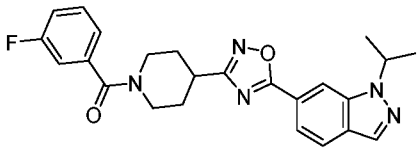
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.11 (s, 1H), 7.92-7.86 (m, 1H), 7.86-7.79 (m, 1H), 5.17-5.02 (m, 1H), 4.91 (dd, J = 8.0, 9.2 Hz, 0.5H), 4.84-4.74 (m, 1H), 4.67 (dd, J = 4.9, 9.3 Hz, 0.5H), 4.16 (br s, 2H), 3.21 (tt, J = 3.9, 10.9 Hz, 1H), 3.02 (br t, J = 11.7 Hz, 2H), 2.22-2.09 (m, 2H), 2.02-1.87 (m, 2H), 1.66 (dd, J = 1.6, 6.8 Hz, 3H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 430.1.



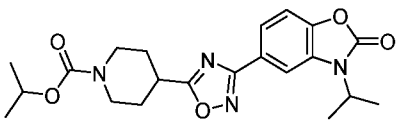
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 7.89 (dd, J = 0.9, 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 4.31 (br s, 1H), 4.22-4.14 (m, 1H), 4.13 (s, 3H), 3.79-3.66 (m, 1H), 3.48 (br d, J = 14.5 Hz, 1H), 3.27 (br t, J = 10.6 Hz, 1H), 2.65 (s, 3H), 2.42-2.30 (m, 1H), 2.30-2.20 (m, 1H), 1.51 (s, 9H); LCMS (ESI) [M+H]+: 434.2.



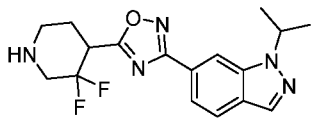
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.21 (s, 1H), 7.98 (m, J = 8.4 Hz, 1H), 7.80 (dd, J = 0.9, 8.4 Hz, 1H), 7.53-7.48 (m, 2H), 7.47-7.42 (m, 2H), 5.18 (spt, J = 6.7 Hz, 1H), 4.00-4.2 (m, 2H), 3.35-3.16 (m, 3H), 2.10 (br d, J = 10.8 Hz, 2H), 1.90-1.71 (m, 2H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 450.1.



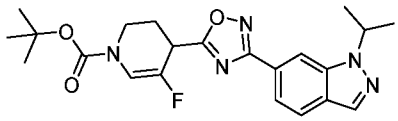
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.21 (s, 1H), 7.98 (m, J = 8.6 Hz, 1H), 7.81 (dd, J = 1.0, 8.5 Hz, 1H), 7.51 (dt, J = 5.7, 7.9 Hz, 1H), 7.32-7.20 (m, 3H), 5.18 (spt, J = 6.6 Hz, 1H), 4.00-4.20 (m, 2H), 3.36-3.16 (m, 3H), 2.11 (br d, J = 10.6 Hz, 2H), 1.89-1.75 (m, 2H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 434.1.



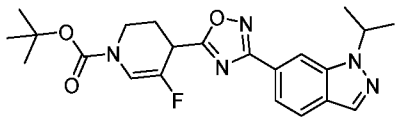
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.89 (dd, J = 1.5, 8.4 Hz, 1H), 7.79 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 4.96 (spt, J = 6.2 Hz, 1H), 4.64-4.53 (m, 1H), 4.19 (br d, J = 11.9 Hz, 2H), 3.20 (tt, J = 3.9, 10.9 Hz, 1H), 3.11-2.99 (m, 2H), 2.15 (br dd, J = 3.1, 13.2 Hz, 2H), 1.99-1.87 (m, 2H), 1.60 (d, J = 6.8 Hz, 6H), 1.27 (d, J = 6.2 Hz, 6H); LCMS (ESI) [M+H]+: 415.2.



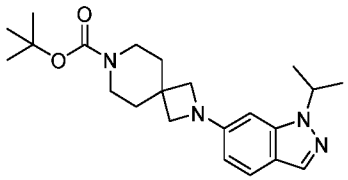
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.35 (s, 1H), 8.12 (s, 1H), 7.93-7.84 (m, 2H), 5.13-5.02 (m, 1H), 4.36-4.21 (m, 1H), 3.99 (td, J = 8.5, 13.4 Hz, 1H), 3.86-3.63 (m, 2H), 3.43-3.34 (m, 1H), 2.68-2.56 (m, 2H), 1.60 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 348.1.



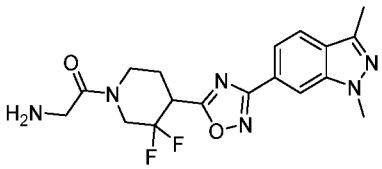
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 7.99 (s, 1H), 7.80-7.72 (m, 2H), 7.03 (br d, J = 10.3 Hz, 1H), 4.95-4.84 (m, 1H), 4.11 (q, J = 5.0 Hz, 1H), 3.98-3.78 (m, 1H), 3.52-3.35 (m, 1H), 2.35-2.14 (m, 2H), 1.56 (d, J = 6.6 Hz, 6H), 1.45 (s, 9H); LCMS (ESI) [M+H]+: 428.2.



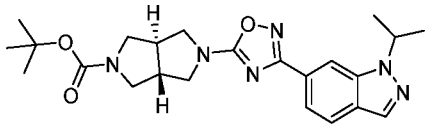
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31-8.23 (m, 1H), 8.09 (s, 1H), 7.94-7.89 (m, 1H), 7.86-7.80 (m, 1H), 5.08-4.93 (m, 1H), 4.28 (br s, 2H), 3.69 (br d, J = 5.0 Hz, 2H), 2.85 (br s, 2H), 1.65 (dd, J = 1.3, 6.7 Hz, 6H), 1.53 (d, J = 1.3 Hz, 9H); LCMS (ESI) [M+H]+: 428.2.



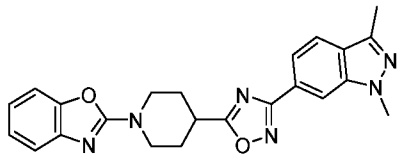
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.84 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 6.40 (dd, J = 8.8, 2.0 Hz, 1H), 6.22 (s, 1H), 4.79-4.61 (m, 1H), 3.71 (s, 4H), 3.43 (t, J = 5.6 Hz, 4H), 1.81 (br t, J = 5.2 Hz, 4H), 1.56 (d, J = 6.8 Hz, 6H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 385.2.



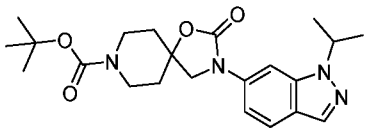
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.29 (s, 1H), 7.97-7.85 (m, 2H), 4.80 (td, J = 9.1, 13.6 Hz, 0.7H), 4.63 (br d, J = 14.2 Hz, 0.4H), 4.34-4.16 (m, 2.4H), 4.13 (s, 3H), 4.10-3.98 (m, 1.5H), 3.96-3.79 (m, 0.6H), 3.66-3.48 (m, 1H), 3.33-3.25 (m, 0.4H), 2.64 (s, 3H), 2.56-2.26 (m, 2H); LCMS (ESI) [M+H]+: 391.1.



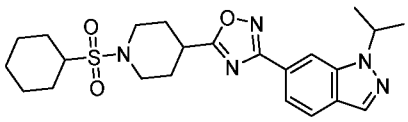
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (d, J = 0.9 Hz, 1H), 8.03 (s, 1H), 7.81-7.74 (m, 2H), 5.03-4.87 (m, 1H), 4.03-3.90 (m, 2H), 3.84-3.67 (m, 2H), 3.43-3.32 (m, 2H), 3.13 (t, J = 10.3 Hz, 2H), 2.41 (m, 2H), 1.61 (d, J = 6.7 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 439.2.



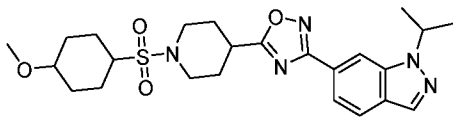
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.85 (dd, J = 8.4, 1.3 Hz, 1H), 7.75 (dd, J = 8.5, 0.8 Hz, 1H), 7.39 (s, 1H), 7.21 (d, J = 1.2 Hz, 1H), 7.15-7.04 (m, 1H), 4.45-4.32 (m, 2H), 4.09 (s, 3H), 3.53-3.30 (m, 3H), 2.61 (s, 3H), 2.43-2.28 (m, 2H), 2.28-2.12 (m, 2H); LCMS (ESI) [M+H]+: 415.3.



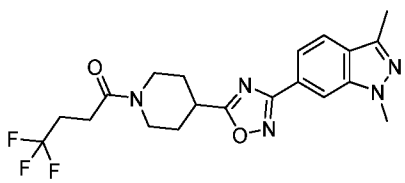
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.98 (t, J = 0.7 Hz, 1H), 7.88-7.77 (m, 1H), 7.72 (d, J = 8.8 Hz 1H), 7.20 (d, J = 8.8, 1H), 4.90-4.76 (m, 1H), 3.95 (ms, 2H), 3.88 (s, 2H), 3.38 (t, J = 12.4 Hz, 2H), 2.02 (m, 2H), 1.84 (m, 2H), 1.60 (d, J = 6.7 Hz, 6H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 415.3.



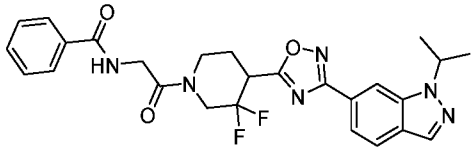
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.19 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 8.4, 1.2 Hz, 1H), 5.16 (p, J = 6.5 Hz, 1H), 3.71 (dt, J = 13.2, 3.8 Hz, 2H), 3.39 (tt, J = 10.9, 3.8 Hz, 1H), 3.13 (td, J = 12.4, 12.0, 2.7 Hz, 3H), 2.19 (dd, J = 13.7, 3.6 Hz, 2H), 2.01 (t, J = 11.9 Hz, 2H), 1.92-1.72 (m, 4H), 1.62 (d, J = 12.6 Hz, 1H), 1.50 (d, J = 6.5 Hz, 6H), 1.45-1.21 (m, 5H); LCMS (ESI) [M+H]+: 458.4.



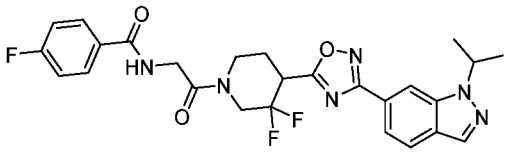
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 7.93 (dd, J = 8.4, 0.8 Hz, 1H), 7.75 (dd, J = 8.5, 1.3 Hz, 1H), 5.15 (p, J = 6.5 Hz, 1H), 3.71 (d, J = 12.7 Hz, 3H), 3.47-3.35 (m, 2H), 3.21 (s, 2H), 3.13 (t, J = 11.4 Hz, 2H), 2.19 (dd, J = 13.9, 2.4 Hz, 3H), 1.95 (d, J = 13.7 Hz, 2H), 1.88-1.60 (m, 7H), 1.50 (d, J = 6.5 Hz, 6H), 1.44 (d, J = 2.9 Hz, 1H); LCMS (ESI) [M+H]+: 488.4..



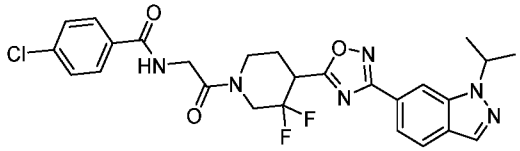
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.85-7.81 (m, 1H), 7.76-7.72 (m, 1H), 4.54 (br d, J = 13.9 Hz, 1H), 4.08 (s, 3H), 3.99-3.89 (m, 1H), 3.39-3.28 (m, 2H), 3.10-2.99 (m, 1H), 2.66-2.61 (m, 2H), 2.60 (s, 3H), 2.59-2.50 (m, 2H), 2.31-2.17 (m, 2H), 2.09-1.90 (m, 2H); LCMS (ESI) [M+H]+: 422.1.



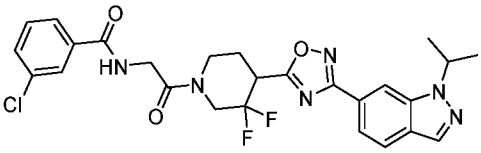
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 8.00 (s, 1H), 7.83-7.72 (m, 4H), 7.50-7.43 (m, 1H), 7.42-7.34 (m, 2H), 7.14 (br s, 1H), 4.90 (td, J = 6.6, 13.3 Hz, 1H), 4.51 (dt, J = 6.7, 14.7 Hz, 0.5H), 4.38-4.08 (m, 3H), 3.96 (br s, 0.5H), 3.86-3.63 (m, 2H), 3.61-3.41 (m, 1H), 2.40-2.18 (m, 2H), 1.56 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 509.2.



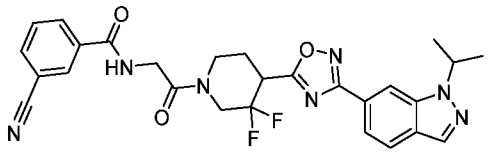
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.10 (s, 1H), 7.94-7.83 (m, 4H), 7.31-7.23 (m, 1H), 7.15 (br t, J = 8.6 Hz, 2H), 5.07-4.93 (m, 1H), 4.70-4.50 (m, 0.5H), 4.45-4.16 (m, 3H), 4.06 (br d, J = 13.4 Hz, 0.5H), 3.95-3.69 (m, 2H), 3.67-3.49 (m, 1H), 2.51-2.26 (m, 2H), 1.66 (br d, J = 6.5 Hz, 6H); LCMS (ESI) [M+H]+: 527.2.



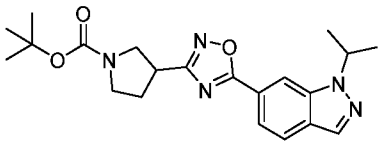
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28-8.22 (m, 1H), 8.13 (br s, 1H), 7.95-7.79 (m, 4H), 7.49 (br d, J = 8.2 Hz, 2H), 7.35-7.18 (m, 1H), 5.02 (br d, J = 6.7 Hz, 1H), 4.62 (br s, 0.5H), 4.46-4.18 (m, 3H), 4.07 (br s, 0.5H), 3.99-3.50 (m, 3H), 2.56-2.28 (m, 2H), 1.69 (br d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 543.2.



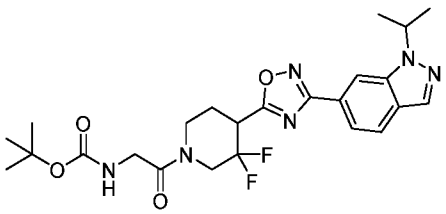
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 8.00 (s, 1H), 7.86-7.71 (m, 3H), 7.64 (br d, J = 7.6 Hz, 1H), 7.43 (br d, J = 7.7 Hz, 1H), 7.37-7.28 (m, 1H), 4.98-4.80 (m, 1H), 4.50 (dt, J = 6.2, 14.5 Hz, 0.5H), 4.37-4.22 (m, 2.5H), 4.22-4.08 (m, 0.5H), 3.96 (br d, J = 13.6 Hz, 0.5H), 3.87-3.62 (m, 2H), 3.60-3.38 (m, 1H), 2.42-2.18 (m, 2H); LCMS (ESI) [M+H]+: 543.2.



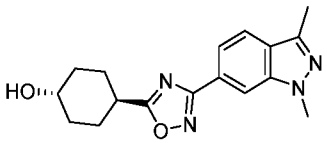
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 8.09 (br d, J = 4.6 Hz, 1H), 8.02-7.95 (m, 2H), 7.83-7.68 (m, 3H), 7.52 (br t, J = 7.7 Hz, 1H), 7.38-7.21 (m, 1H), 4.90 (td, J = 6.6, 13.2 Hz, 1H), 4.60-4.41 (m, 0.5H), 4.37-4.21 (m, 2.5H), 4.20-4.08 (m, 0.5H), 3.97 (br d, J = 13.4 Hz, 0.5H), 3.89-3.62 (m, 2H), 3.61-3.42 (m, 1H), 2.42-2.22 (m, 2H), 1.56 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 534.2.



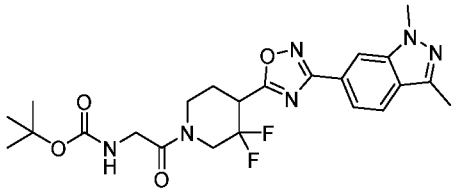
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.25 (s, 1H), 7.99 (m, J = 8.4 Hz, 1H), 7.81 (dd, J = 1.2, 8.5 Hz, 1H), 5.23 (spt, J = 6.6 Hz, 1H), 3.78-3.66 (m, 2H), 3.60-3.52 (m, 1H), 3.52-3.43 (m, 1H), 3.38 (br t, J = 8.4 Hz, 1H), 2.33 (br s, 1H), 2.25-2.07 (m, 1H), 1.50 (d, J = 6.6 Hz, 6H), 1.42 (s, 9H); LCMS (ESI) [M+H]+: 398.2.



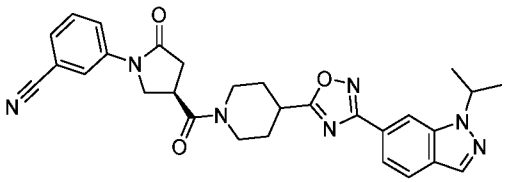
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.06 (s, 1H), 7.88-7.79 (m, 2H), 5.51-5.37 (m, 1H), 4.97 (td, J = 6.6, 13.2 Hz, 1H), 4.60-4.48 (m, 0.5H), 4.30 (m, 0.5H), 4.20-4.01 (m, 2.5H), 3.93 (m, 0.5H), 3.89-3.59 (m, 2H), 3.56-3.37 (m, 1H), 2.46-2.21 (m, 2H), 1.63 (d, J = 6.6 Hz, 6H), 1.46 (s, 9H); LCMS (ESI) [M-55]+: 449.1.



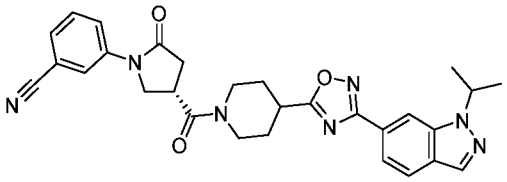
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.68-7.63 (m, 1H), 4.00 (s, 3H), 3.69 (br t, J = 10.3 Hz, 1H), 2.93 (tt, J = 3.7, 11.8 Hz, 1H), 2.52 (s, 3H), 2.26-2.18 (m, 2H), 2.10 (br dd, J = 3.3, 13.0 Hz, 2H), 1.79-1.69 (m, 2H), 1.45-1.34 (m, 2H); LCMS (ESI) [M+H]+: 313.1.



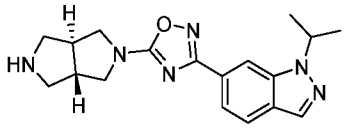
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.86-7.81 (m, 1H), 7.77-7.70 (m, 1H), 5.55-5.39 (m, 1H), 4.55 (dt, J = 6.6, 14.4 Hz, 0.5H), 4.35-4.26 (m, 0.5H), 4.22-4.10 (m, 1H), 4.08 (s, 3H), 4.07-3.90 (m, 2H), 3.89-3.60 (m, 2H), 3.58-3.39 (m, 1H), 2.60 (s, 3H), 2.43-2.25 (m, 2H), 1.47 (s, 9H); LCMS (ESI) [M+H]+: 435.1.



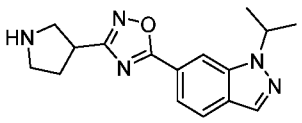
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (br s, 1H), 8.09 (s, 1H), 8.02-7.82 (m, 4H), 7.54-7.44 (m, 2H), 5.05-4.92 (m, 1H), 4.66-4.51 (m, 1H), 4.36 (dd, J = 6.6, 9.5 Hz, 1H), 4.06-3.93 (m, 2H), 3.69-3.60 (m, 1H), 3.49-3.35 (m, 2H), 3.23-3.07 (m, 1H), 3.02-2.90 (m, 2H), 2.31 (br t, J = 14.1 Hz, 2H), 2.13-1.96 (m, 2H), 1.65 (dd, J = 1.2, 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 524.2.



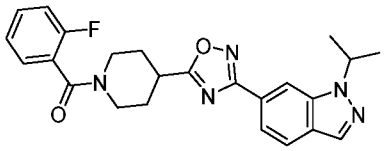
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (br s, 1H), 7.99 (s, 1H), 7.93-7.73 (m, 4H), 7.43-7.34 (m, 2H), 4.89 (qd, J = 6.6, 13.3 Hz, 1H), 4.55-4.41 (m, 1H), 4.26 (dd, J = 7.0, 8.9 Hz, 1H), 3.96-3.84 (m, 2H), 3.55 (td, J = 8.3, 16.0 Hz, 1H), 3.40-3.26 (m, 2H), 3.13-2.97 (m, 1H), 2.94-2.81 (m, 2H), 2.22 (br t, J = 14.3 Hz, 2H), 2.03-1.89 (m, 2H), 1.56 (br d, J = 5.9 Hz, 6H); LCMS (ESI) [M+H]+: 524.2.



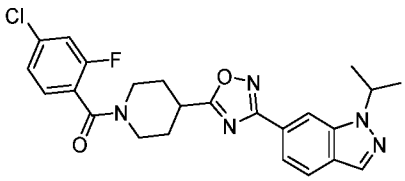
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.23 (s, 1H), 8.11 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 5.12-4.98 (m, 1H), 4.07-3.96 (m, 2H), 3.63 (br dd, J = 5.9, 10.5 Hz, 2H), 3.51 (br t, J = 9.7 Hz, 2H), 3.17 (br t, J = 10.8 Hz, 2H), 2.81-2.65 (m, 2H), 1.61 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 339.1.



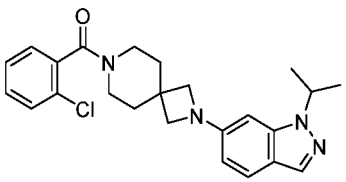
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.25 (s, 1H), 8.01 (m, J = 8.4 Hz, 1H), 7.82 (dd, J = 1.1, 8.6 Hz, 1H), 5.20 (spt, J = 6.5 Hz, 1H), 3.86 (quin, J = 7.6 Hz, 1H), 3.68 (dd, J = 8.2, 11.7 Hz, 1H), 3.46 (dd, J = 7.5, 11.7 Hz, 1H), 3.41-3.26 (m, 2H), 2.47-2.37 (m, 1H), 2.29-2.15 (m, 1H), 1.50 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 298.1.



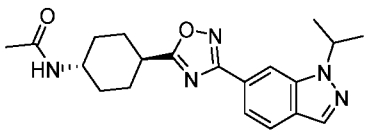
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.88-7.79 (m, 2H), 7.47-7.39 (m, 2H), 7.26-7.22 (m, 1H), 7.16-7.10 (m, 1H), 4.98 (td, J = 6.7, 13.3 Hz, 1H), 4.71 (br d, J = 12.8 Hz, 1H), 3.72 (br d, J = 13.6 Hz, 1H), 3.42-3.17 (m, 3H), 2.33 (br dd, J = 3.3, 13.6 Hz, 1H), 2.23-2.03 (m, 3H), 1.64 (d, J = 6.7 Hz, 5H), 1.66-1.62 (m, 1H).; LCMS (ESI) [M+H]+: 434.2.



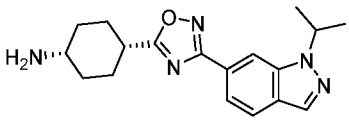
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.88-7.80 (m, 2H), 7.41-7.36 (m, 1H), 7.25 (dd, J = 1.8, 8.3 Hz, 1H), 7.18 (dd, J = 1.9, 9.2 Hz, 1H), 4.97 (spt, J = 6.7 Hz, 1H), 4.67 (br d, J = 13.4 Hz, 1H), 3.70 (br d, J = 13.8 Hz, 1H), 3.42-3.18 (m, 3H), 2.33 (br dd, J = 3.4, 13.6 Hz, 1H), 2.24-1.95 (m, 3H), 1.66-1.62 (m, 1H), 1.64 (d, J = 6.7 Hz, 5H); LCMS (ESI) [M+H]+: 468.1.



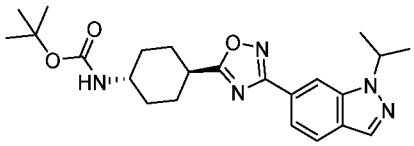
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.85 (s, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.46-7.40 (m, 1H), 7.38-7.28 (m, 3H), 6.40 (dd, J = 1.6, 8.7 Hz, 1H), 6.23 (s, 1H), 4.70 (spt, J = 6.6 Hz, 1H), 3.92-3.70 (m, 6H), 3.38-3.17 (m, 2H), 2.06-1.87 (m, 3H), 1.82-1.73 (m, 1H), 1.56 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 423.2.



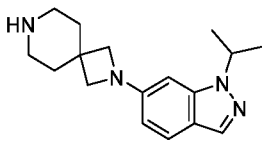
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 7.98 (s, 1H), 7.80-7.71 (m, 2H), 5.27 (br d, J = 7.9 Hz, 1H), 4.94-4.84 (m, 1H), 3.90-3.78 (m, 1H), 2.91 (tt, J = 3.5, 12.2 Hz, 1H), 2.25-2.11 (m, 4H), 1.93 (s, 3H), 1.79 (dq, J = 3.2, 13.0 Hz, 2H), 1.56 (d, J = 6.7 Hz, 6H), 1.24 (dq, J = 3.3, 12.5 Hz, 2H); LCMS (ESI) [M+H]+: 368.1.



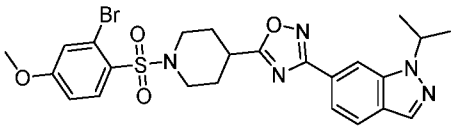
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.19 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 1.1, 8.4 Hz, 1H), 5.17-5.07 (m, 1H), 3.43 (br t, J = 4.5 Hz, 1H), 3.25-3.16 (m, 1H), 2.25 (br dd, J = 4.6, 9.2 Hz, 2H), 1.97-1.88 (m, 4H), 1.66-1.57 (m, 2H), 1.50 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 326.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.89-7.81 (m, 2H), 4.99 (td, J = 6.7, 13.3 Hz, 1H), 4.48 (br s, 1H), 3.57 (br s, 1H), 2.99 (tt, J = 3.4, 12.2 Hz, 1H), 2.33-2.20 (m, 4H), 1.85 (dq, J = 3.0, 13.0 Hz, 2H), 1.64 (d, J = 6.6 Hz, 6H), 1.48 (s, 9H), 1.38-1.26 (m, 2H); LCMS (ESI) [M+H]+: 426.2.

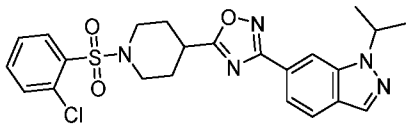


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.84 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.40 (dd, J = 8.8, 2.0 Hz, 1H), 6.22 (s, 1H), 4.79-4.61 (m, 1H), 3.69 (s, 4H), 3.10-2.66 (m, 5H), 1.83 (br t, J = 5.2 Hz, 4H), 1.56 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 285.1.

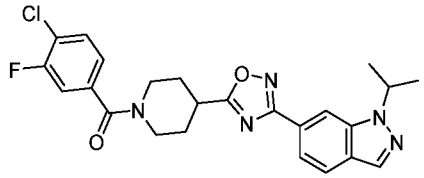


^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (d, J = 1.2 Hz, 1H), 8.19 (s, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.79 (dd, J = 8.7, 2.3 Hz, 1H), 7.72 (dd, J = 8.5, 1.3 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 5.14

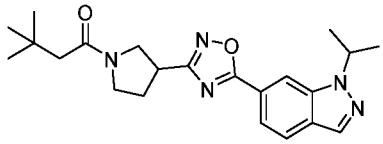
(p, J = 6.6 Hz, 1H), 3.96 (s, 3H), 3.69 (d, J = 11.9 Hz, 3H), 2.22 (d, J = 12.9 Hz, 3H), 1.87 (q, J = 10.5, 9.9 Hz, 2H), 1.50 (d, J = 6.5 Hz, 6H); LCMS (ESI) [M+H]+: 560.2, 562.1.



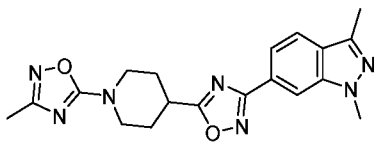
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29 (d, J = 1.1 Hz, 1H), 8.19 (s, 1H), 8.02 (dd, J = 7.7, 1.6 Hz, 1H), 7.92 (dd, J = 8.5, 0.8 Hz, 1H), 7.76-7.66 (m, 3H), 7.59 (ddd, J = 7.9, 6.8, 1.9 Hz, 1H), 5.15 (p, J = 6.5 Hz, 1H), 3.78 (d, J = 12.8 Hz, 2H), 3.39 (d, J = 15.0 Hz, 1H), 3.09-2.93 (m, 2H), 2.21 (dd, J = 13.4, 3.5 Hz, 2H), 1.93-1.74 (m, 1H), 1.50 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 486.3, 488.2.



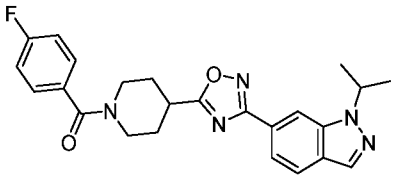
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.15 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.48 (dd, J = 1.9, 9.6 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 5.10 (td, J = 6.6, 13.2 Hz, 1H), 4.03 (br s, 1H), 4.20-3.86 (m, 1H), 3.58-3.43 (m, 1H), 3.25 (br t, J = 11.2 Hz, 2H), 2.19 (br d, J = 9.9 Hz, 2H), 1.99-1.81 (m, 2H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 468.1.



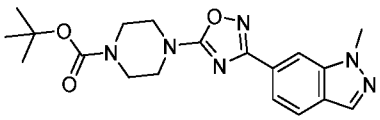
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.29 (s, 1H), 8.11 (d, J = 3.4 Hz, 1H), 7.88 (d, J = 5.4 Hz, 2H), 5.07-4.90 (m, 1H), 4.09-3.95 (m, 1H), 3.94-3.77 (m, 2H), 3.76-3.57 (m, 2H), 2.55-2.31 (m, 2H), 2.29-2.24 (m, 2H), 1.66 (d, J = 6.6 Hz, 6H), 1.11 (d, J = 1.8 Hz, 9H); LCMS (ESI) [M+H]+: 396.2.



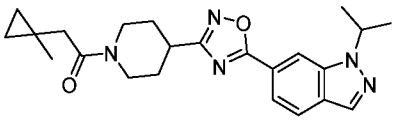
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.08 (d, J = 2.9 Hz, 1H), 7.82 (br dd, J = 2.6, 8.4 Hz, 1H), 7.72 (dd, J = 3.4, 8.3 Hz, 1H), 4.24-4.13 (m, 2H), 4.07 (d, J = 3.7 Hz, 3H), 3.44-3.25 (m, 3H), 2.59-2.57 (m, 3H), 2.29-2.27 (m, 2H), 2.23 (d, J = 4.0 Hz, 3H), 2.16-2.04 (m, 2H); LCMS (ESI) [M+H]+: 380.2.



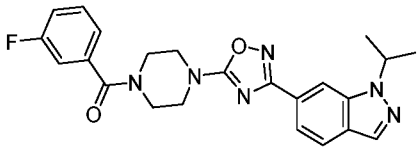
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 1.0, 8.5 Hz, 1H), 7.55-7.47 (m, 2H), 7.30-7.22 (m, 2H), 5.11 (quin, J = 6.6 Hz, 1H), 4.06 (br s, 2H), 3.57-3.45 (m, 1H), 3.32-3.18 (m, 2H), 2.19 (br dd, J = 3.4, 13.1 Hz, 2H), 1.97-1.81 (m, 2H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 434.2.



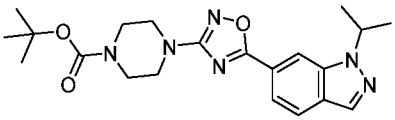
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (d, J = 0.9 Hz, 1H), 8.01 (d, J = 0.9 Hz, 1H), 7.79-7.77 (m, 2H), 4.14 (s, 3H), 3.74-3.68 (m, 4H), 3.62-3.56 (m, 4H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 385.2.



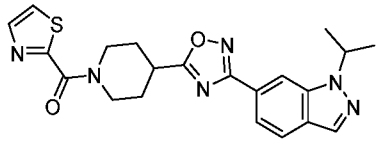
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, J = 0.7 Hz, 1H), 8.10 (s, 1H), 7.91-7.82 (m, 2H), 4.98 (spt, J = 6.6 Hz, 1H), 4.64 (br d, J = 13.6 Hz, 1H), 3.98 (br d, J = 13.6 Hz, 1H), 3.32-3.20 (m, 1H), 3.15 (tt, J = 3.9, 10.9 Hz, 1H), 2.91 (br t, J = 11.2 Hz, 1H), 2.40 (d, J = 4.2 Hz, 2H), 2.16 (br d, J = 11.1 Hz, 2H), 1.99-1.80 (m, 2H), 1.65 (d, J = 6.7 Hz, 6H), 1.18 (s, 3H), 0.55-0.31 (m, 4H); LCMS (ESI) [M+H]+: 408.2.



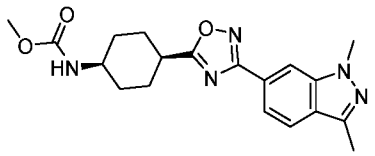
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 10.8 Hz, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 1.1, 8.4 Hz, 1H), 7.61-7.49 (m, 1H), 7.41-7.24 (m, 3H), 5.10 (td, J = 6.6, 13.1 Hz, 1H), 3.94-3.43 (m, 8H), 1.50 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 435.2.



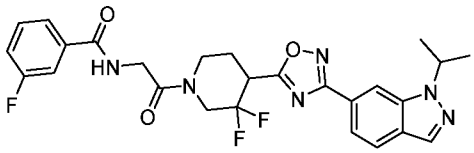
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.09 (s, 1H), 7.84 (d, J = 0.7 Hz, 2H), 4.97 (quin, J = 6.7 Hz, 1H), 3.57 (br d, J = 5.5 Hz, 8H), 1.65 (d, J = 6.6 Hz, 6H), 1.51 (s, 9H); LCMS (ESI) [M+H]+: 413.2.



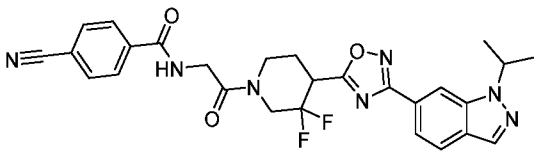
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.06 (s, 1H), 7.92 (d, J = 3.1 Hz, 1H), 7.88-7.77 (m, 2H), 7.57 (d, J = 3.3 Hz, 1H), 5.43 (br d, J = 13.7 Hz, 1H), 4.97 (spt, J = 6.7 Hz, 1H), 4.67 (br d, J = 12.6 Hz, 1H), 3.80-3.60 (m, 1H), 3.48-3.36 (m, 1H), 3.34-3.18 (m, 1H), 2.31 (br s, 2H), 2.15 (br s, 2H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 423.1.



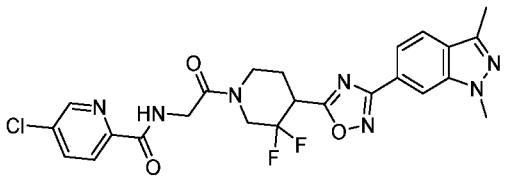
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.84 (dd, J = 1.2, 8.4 Hz, 1H), 7.77-7.71 (m, 1H), 4.76 (br s, 1H), 4.09 (s, 3H), 3.81 (br s, 1H), 3.68 (s, 3H), 3.28-3.16 (m, 1H), 2.61 (s, 3H), 2.25-2.12 (m, 2H), 2.07-1.97 (m, 2H), 1.88 (dt, J = 4.0, 8.7 Hz, 2H), 1.79-1.69 (m, 2H); LCMS (ESI) [M+H]+: 370.1.



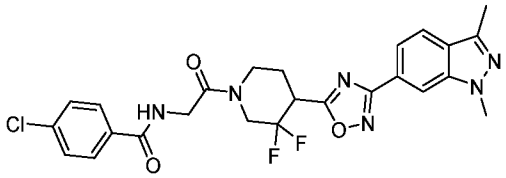
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (br s, 1H), 8.06 (br s, 1H), 7.91-7.77 (m, 2H), 7.65-7.55 (m, 2H), 7.43 (br d, J = 5.7 Hz, 1H), 7.33-7.15 (m, 2H), 5.04-4.91 (m, 0.8H), 4.57 (br s, 0.4H), 4.44-4.31 (m, 2H), 4.28-4.14 (m, 0.5H), 4.02 (br s, 0.5H), 3.93-3.68 (m, 2H), 3.68-3.46 (m, 1H), 2.50-2.25 (m, 2H), 1.63 (br d, J = 6.4 Hz, 6H); LCMS (ESI) [M+H]+: 527.2.



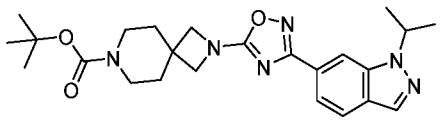
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.96-7.94 (d, J = 8.0 Hz, 2H), 7.87-7.81 (m, 2H), 7.80-7.60 (d, J = 8.0 Hz, 2H), 7.33-7.25 (m, 1H), 5.00-4.93 (m, 1H), 4.65-4.50 (m, 0.5H), 4.45-4.25 (m, 2.6H, 4.25-4.15 (m, 0.5 h), 4.08-3.98 (m, 0.5H), 3.95-3.80 (m, 1.5H), 3.80 -3.05 (m, 0.5H), 3.65-3.50 (m, 1H), 2.50-2.33 (m, 2H), 1.64-1.62 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 534.2.



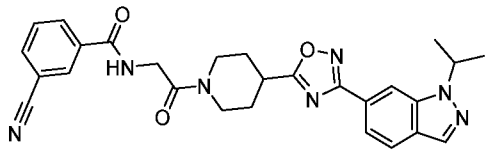
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.73 (br d, J = 15.2 Hz, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.20-8.11 (m, 2H), 7.92 (d, J = 8.6 Hz, 1H), 7.87-7.78 (m, 2H), 4.64 (dt, J = 6.8, 14.3 Hz, 0.5H), 4.39 (br t, J = 5.4 Hz, 2.4H), 4.30-4.22 (m, 0.6H), 4.18 (s, 3H), 4.06 (br d, J = 14.4 Hz, 0.6H), 3.93-3.70 (m, 2H), 3.62-3.49 (m, 1H), 2.69 (s, 3H), 2.50-2.29 (m, 2H); LCMS (ESI) [M+H]+: 530.1.



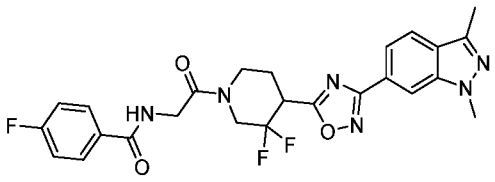
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.48-7.39 (m, 2H), 7.28-7.19 (m, 1H), 4.64 (dt, J = 7.3, 14.2 Hz, 0.5H), 4.48-4.32 (m, 2.3H), 4.26 (br s, 0.6H), 4.22 (s, 3H), 4.06 (br d, J = 8.8 Hz, 0.7H), 3.95-3.69 (m, 2H), 3.61-3.47 (m, 1H), 2.73 (s, 3H), 2.50-2.30 (m, 2H); LCMS (ESI) [M+H]+: 529.1.



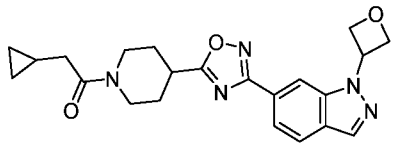
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (d, J = 0.8 Hz, 1H), 8.04 (s, 1H), 7.77 (d, J = 0.8 Hz, 2H), 5.05-4.85 (m, 1H), 4.06 (s, 4H), 3.42 (t, J = 5.6 Hz, 4H), 1.85 (t, J = 5.6 Hz, 4H), 1.61 (d, J = 6.4 Hz, 6H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 453.2.



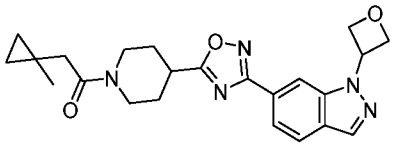
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.19 (s, 1H),8.16 (s, 1H), 8.08-8.04 (m, 2H), 7.87-7.78 (m, 3H), 7.59 (t, J = 7.8 Hz, 1H), 7.41-7.35 (m, 1H), 4.96 (quin, J = 6.7 Hz, 1H), 4.52 (br d, J = 13.7 Hz, 1H), 4.31 (d, J = 3.7 Hz, 2H), 3.91 (br d, J = 13.9 Hz, 1H), 3.37 (ddd, J = 3.3, 10.5, 13.9 Hz, 2H), 3.25-3.11 (m, 1H), 2.37-2.21 (m, 2H), 2.13-1.94 (m, 2H), 1.63 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 498.2.



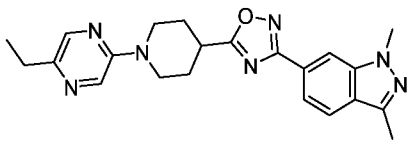
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.93-7.81 (m, 3H), 7.79-7.72 (m, 1H), 7.25-7.10 (m, 3H), 4.59 (dt, J = 6.7, 14.9 Hz, 0.5H), 4.43-4.30 (m, 2.5H), 4.24 (dt, J = 6.3, 14.6 Hz, 0.5H), 4.10 (s, 3H), 4.05 (br d, J = 13.9 Hz, 0.5H), 3.95-3.70 (m, 2H), 3.68-3.50 (m, 1H), 2.61 (s, 3H), 2.49-2.31 (m, 2H); LCMS (ESI) [M+H]+: 513.1.



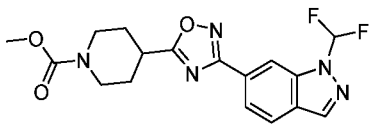
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.06-7.90 (m, 2H), 7.75-7.57 (m, 2H), 5.76-5.60 (m, 1H), 5.12 (t, J = 6.5 Hz, 2H), 4.95 (t, J = 7.3 Hz, 2H), 4.38 (m, 1H), 3.74 (m, 1H), 3.17-2.98 (m, 2H), 2.86-2.69 (m, 1H), 2.12 (d, J = 6.8 Hz, 2H), 2.07-1.95 (m, 2H), 1.84-1.66 (m, 2H), 0.93-0.80 (m, 1H), 0.44-0.33 (m, 2H), 0.05--0.05 (m, 2H); LCMS (ESI) [M+H]+: 408.2.



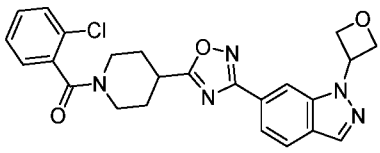
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (d, J = 0.7 Hz, 1H), 8.17 (s, 1H), 7.93-7.81 (m, 2H), 5.96-5.83 (m, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.16 (t, J = 7.3 Hz, 2H), 4.60 (br d, J = 13.4 Hz, 1H), 3.97 (br d, J = 13.9 Hz, 1H), 3.36-3.20 (m, 2H), 2.96 (br t, J = 11.2 Hz, 1H), 2.39 (m, 2H), 2.22 (br d, J = 13.4 Hz, 2H), 2.05-1.85 (m, 2H), 1.17 (s, 3H), 0.55-0.32 (m, 4H); LCMS (ESI) [M+H]+: 422.2.



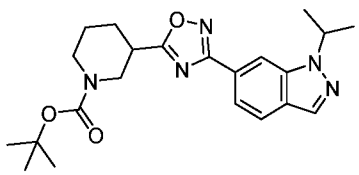
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.10 (s, 1H), 7.99 (s, 1H), 7.85-7.80 (m, 1H), 7.73 (d, J = 8.3 Hz, 1H), 4.32 (br d, J = 13.2 Hz, 2H), 4.08 (s, 3H), 3.36-3.27 (m, 1H), 3.23-3.11 (m, 2H), 2.72 (q, J = 7.7 Hz, 2H), 2.60 (s, 3H), 2.34-2.25 (m, 2H), 2.15-2.03 (m, 2H), 1.28 (t, J = 7.7 Hz, 3H); LCMS (ESI) [M+H]+: 404.1.



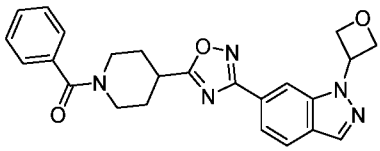
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (s, 1H), 8.15 (d, J = 0.7 Hz, 1H), 8.04 (dd, J = 1.1, 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.68-7.35 (t, J = 59.2 Hz, 1H), 4.19 (br s, 2H), 3.73 (s, 3H), 3.23 (tt, J = 3.9, 10.9 Hz, 1H), 3.08 (br t, J = 11.6 Hz, 2H), 2.17 (br d, J = 10.9 Hz, 2H), 2.01-1.89 (m, 2H); LCMS (ESI) [M+H]+: 378.1.



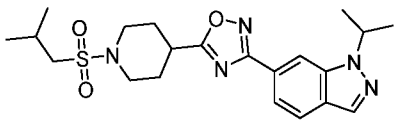
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.10 (s, 1H), 7.85-7.82 (m, 1H), 7.80-7.75 (m, 1H), 7.40-7.33 (m, 1H), 7.32-7.20 (m, 3H), 5.92-5.74 (m, 1H), 5.26 (t, J = 6.6 Hz, 2H), 5.09 (t, J = 7.0 Hz, 2H), 4.76-4.55 (m, 1H), 3.61-3.44 (m, 1H), 3.36-3.01 (m, 3H), 2.27 (m, 1H), 2.15-1.93 (m, 2H), 1.93-1.77 (m, 1H); LCMS (ESI) [M+H]+: 464.1.



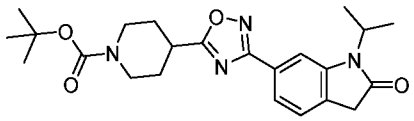
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.14 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 5.11-5.05 (m, 1H), 4.07-3.99 (m, 1H), 3.66-3.56 (m, 1H), 3.49 (br dd, J = 9.2, 13.3 Hz, 1H), 3.32-3.15 (m, 2H), 2.22-2.13 (m, 1H), 1.98-1.93 (m, 1H), 1.84-1.75 (m, 1H), 1.60-1.45 (m, 7H), 1.38 (s, 9H); LCMS (ESI) [M+H]+: 412.2.



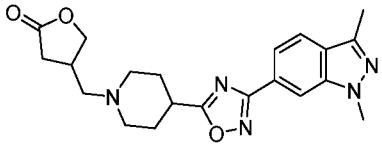
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.29-8.16 (m, 2H), 7.97-7.84 (m, 2H), 7.46 (m, 5H), 5.99-5.85 (m, 1H), 5.36 (t, J = 6.7 Hz, 2H), 5.18 (t, J = 7.3 Hz, 2H), 4.86-4.54 (m, 1H), 3.94 (m, 1H), 3.46-3.31 (m, 1H), 3.25 (br s, 2H), 2.39-1.82 (m, 4H); LCMS (ESI) [M+H]+: 430.1.



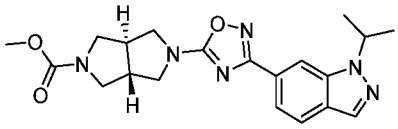
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (d, J = 1.1 Hz, 1H), 8.19 (s, 0H), 7.93 (dd, J = 8.4, 0.8 Hz, 1H), 7.75 (dd, J = 8.5, 1.3 Hz, 1H), 5.16 (h, J = 6.6 Hz, 1H), 3.65 (dt, J = 11.7, 3.3 Hz, 3H), 3.43-3.27 (m, 1H), 3.02 (td, J = 12.6, 2.7 Hz, 3H), 2.95 (d, J = 6.6 Hz, 2H), 2.23 (dd, J = 13.6, 3.7 Hz, 2H), 2.12 (dq, J = 13.3, 6.7 Hz, 1H), 1.97-1.78 (m, 2H), 1.50 (d, J = 6.6 Hz, 6H), 1.05 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 432.3.



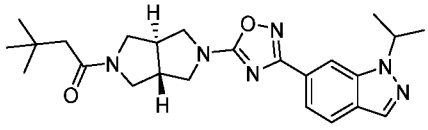
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.77 (dd, J = 1.1, 7.7 Hz, 1H), 7.67 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 4.68 (spt, J = 7.0 Hz, 1H), 4.14 (m, 2H), 3.56 (s, 2H), 3.19 (tt, J = 4.0, 10.9 Hz, 1H), 3.01 (br t, J = 11.6 Hz, 2H), 2.14 (br dd, J = 2.8, 13.3 Hz, 2H), 1.98-1.84 (m, 2H), 1.54 (d, J = 7.1 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 427.2.



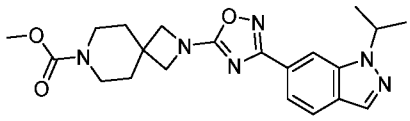
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.86-7.81 (m, 1H), 7.74 (d, J = 8.4 Hz, 1H), 4.42 (dd, J = 7.2, 9.2 Hz, 1H), 4.16 (dd, J = 5.3, 9.3 Hz, 1H), 4.08 (s, 3H), 3.09-2.89 (m, 3H), 2.87-2.76 (m, 1H), 2.68-2.61 (m, 1H), 2.60 (s, 3H), 2.45 (d, J = 7.9 Hz, 2H), 2.37 (dd, J = 5.7, 17.6 Hz, 1H), 2.31-2.13 (m, 4H), 2.11-1.98 (m, 2H)



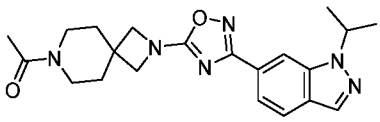
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (d, J = 0.7 Hz, 1H), 8.04 (s, 1H), 7.77 (m, 2H), 4.95 (m, 1H), 3.99 (m, 2H), 3.84 (dd, J = 6.3, 9.8 Hz, 1H), 3.80-3.71 (m, 4H), 3.39 (m, 2H), 3.17 (q, J = 10.4 Hz, 2H), 2.53-2.34 (m, 2H), 1.61 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 397.1.



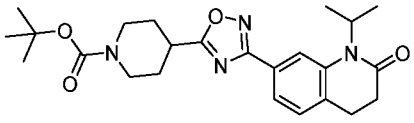
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (d, J = 0.9 Hz, 1H), 8.04 (s, 1H), 7.81-7.73 (m, 2H), 4.95 (m, 1H), 4.07-3.93 (m, 3H), 3.84 (dd, J = 6.6, 8.9 Hz, 1H), 3.45-3.36 (m, 2H), 3.30 (dd, J = 9.2, 10.8 Hz, 1H), 3.16 (t, J = 11.0 Hz, 1H), 2.57-2.32 (m, 2H), 2.26-2.15 (m, 2H), 1.61 (d, J = 6.6 Hz, 6H), 1.12-1.04 (m, 9H); LCMS (ESI) [M+H]+: 437.2.



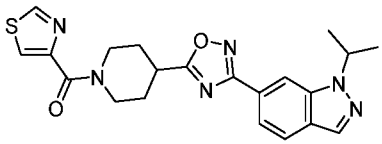
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 8.04 (s, 1H), 7.77 (s, 2H), 5.00-4.88 (m, 1H), 4.07 (s, 4H), 3.71 (s, 3H), 3.47 (t, J = 4.8 Hz, 4H), 1.86 (t, J = 5.6 Hz, 4H), 1.61 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 411.1.



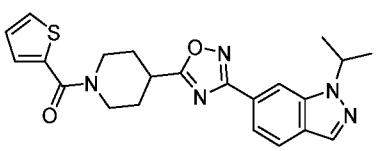
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s. 1H), 8.05 (s, 1H), 7.76 (s, 2H), 5.01-4.90 (m, 1H), 4.15-4.04 (m, 4H), 3.61 (t, J = 5.2 Hz, 2H), 3.45 (t, J = 5.6 Hz, 2H), 2.13 (s, 3H), 1.89 (dt, J = 16.6, 4.4 Hz, 4H), 1.61 (d, J = 6.4 Hz, 6H); LCMS (ESI) [M+H]+: 395.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.83 (s, 1H), 7.71 (dd, J = 1.2, 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 4.73 (spt, J = 6.9 Hz, 1H), 4.25-4.00 (m, 2H), 3.18 (tt, J = 3.9, 10.9 Hz, 1H), 3.00 (br t, J = 11.7 Hz, 2H), 2.91-2.85 (m, 2H), 2.60 (dd, J = 5.8, 8.3 Hz, 2H), 2.13 (br dd, J = 2.8, 13.1 Hz, 2H), 1.96-1.85 (m, 2H), 1.58 (d, J = 7.1 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M-55]+: 385.1.

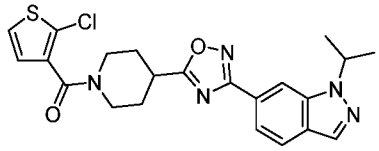


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.82 (d, J = 2.2 Hz, 1H), 8.22 (s, 1H), 8.06 (s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.92-7.77 (m, 2H), 4.97 (spt, J = 6.7 Hz, 1H), 4.63 (br d, J = 7.3 Hz, 2H), 3.47 (br s, 1H), 3.38 (tt, J = 4.2, 10.5 Hz, 1H), 3.24 (br s, 1H), 2.29 (br s, 2H), 2.19-2.07 (m, 2H), 1.63 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 423.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.90-7.79 (m, 2H), 7.48 (dd, J = 1.0, 5.0 Hz, 1H), 7.34 (dd, J = 1.0, 3.6 Hz, 1H), 7.08 (dd, J = 3.7, 4.9 Hz, 1H), 4.98 (td, J = 6.6, 13.2 Hz, 1H),

4.47 (br d, J = 12.8 Hz, 2H), 3.45-3.27 (m, 3H), 2.28 (br dd, J = 3.4, 13.6 Hz, 2H), 2.15-2.01 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 422.1.



5

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.89-7.79 (m, 2H), 7.18 (d, J = 5.7 Hz, 1H), 6.99 (d, J = 5.7 Hz, 1H), 4.97 (td, J = 6.6, 13.4 Hz, 1H), 4.66 (br d, J = 12.8 Hz, 1H), 3.80 (br d, J = 13.5 Hz, 1H), 3.43-3.16 (m, 3H), 2.40-2.17 (m, 2H), 2.17-1.93 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 456.1.

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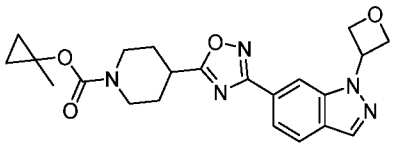
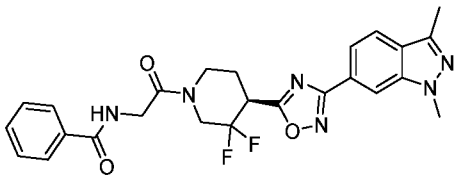
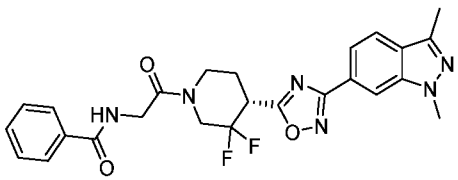


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (d, J = 0.6 Hz, 1H), 8.16 (s, 1H), 7.93-7.87 (m, 1H), 7.86-7.81 (m, 1H), 5.89 (quin, J = 7.0 Hz, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.15 (t, J = 7.3 Hz, 2H), 4.32-3.96 (m,
15 2H), 3.20 (m, 1H), 3.08-2.96 (m, 2H), 2.15 (br d, J = 12.5 Hz, 2H), 1.99-1.83 (m, 2H), 1.59 (br s, 1H), 1.57 (s, 3H), 0.93-0.83 (m, 2H), 0.72-0.59 (m, 2H); LCMS (ESI) [M+H]+: 424.2.



20 ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.92-7.81 (m, 3H), 7.79-7.72 (m, 1H), 7.57-7.52 (m, 1H), 7.51-7.43 (m, 2H), 7.26-7.17 (m, 1H), 4.65-4.50 (m, 0.5H), 4.44-4.32 (m, 2.5H), 4.25 (dt, J = 5.7, 14.8 Hz, 0.5H), 4.09 (s, 3H), 4.04 (br d, J = 4.9 Hz, 0.5H), 3.96-3.69 (m, 2H), 3.68-3.50 (m, 1H), 2.61 (s, 3H), 2.50-2.23 (m, 2H); LCMS (ESI) [M+H]+: 495.1.



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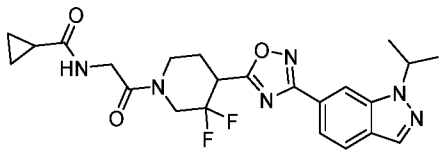
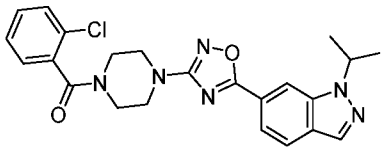
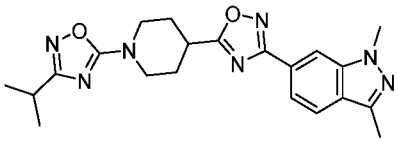
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.90-7.81 (m, 3H), 7.78-7.73 (m, 1H), 7.58-7.51 (m, 1H), 7.50-7.43 (m, 2H), 7.30-7.19 (m, 1H), 4.65-4.49 (m, 0.5H), 4.45-4.31 (m, 2.5H), 4.25 (dt, J = 5.6, 14.8 Hz, 0.5H), 4.09 (s, 3H), 4.08-4.00 (m, 0.5H), 3.98-3.70 (m, 2H), 3.66-3.51 (m, 1H), 2.61 (s, 3H),
30 2.50-2.31 (m, 2H); LCMS (ESI) [M+H]+: 495.1.



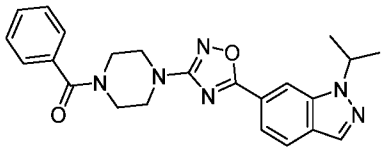
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.10 (s, 1H), 7.91-7.83 (m, 2H), 6.77-6.62 (m, 1H), 5.00 (td, J = 6.6, 13.2 Hz, 1H), 4.58 (dt, J = 6.8, 14.5 Hz, 0.5H), 4.34 (br d, J = 13.9 Hz, 0.5H), 4.28-4.14 (m, 2.5H), 4.00 (br d, J = 13.6 Hz, 0.5H), 3.94-3.45 (m, 3H), 2.36 (br d, J = 16.4 Hz, 2H), 1.66 (d, J = 6.7 Hz, 6H), 1.57-1.49 (m, 1H), 1.06-0.99 (m, 2H), 0.82 (td, J = 3.6, 7.4 Hz, 2H); LCMS (ESI) [M+H]+: 473.2.



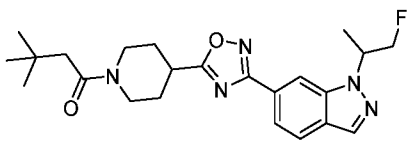
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.09 (s, 1H), 7.87-7.79 (m, 2H), 7.48-7.43 (m, 1H), 7.42-7.30 (m, 3H), 4.97 (td, J = 6.8, 13.2 Hz, 1H), 4.13-4.00 (m, 1H), 3.97-3.84 (m, 1H), 3.72 (br s, 2H), 3.66-3.57 (m, 1H), 3.56-3.41 (m, 2H), 3.38 (br d, J = 7.1 Hz, 1H), 1.64 (br d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 451.1.



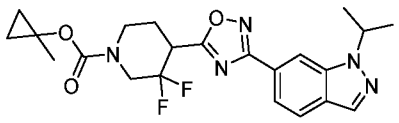
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.07 (s, 1H), 7.83-7.78 (m, 1H), 7.74-7.69 (m, 1H), 4.19 (td, J = 3.8, 13.6 Hz, 2H), 4.06 (s, 3H), 3.40-3.23 (m, 3H), 2.94-2.84 (m, 1H), 2.58 (s, 3H), 2.27 (br dd, J = 3.3, 13.7 Hz, 2H), 2.15-2.02 (m, 2H), 1.28 (d, J = 6.8 Hz, 6H); LCMS (ESI) [M+H]+: 408.2.



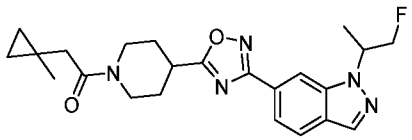
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.19 (s, 1H), 7.95 (m, J = 8.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.54-7.37 (m, 5H), 5.15 (spt, J = 6.6 Hz, 1H), 3.66 (br s, 4H), 3.58-3.50 (m, 4H), 1.53 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 417.2.



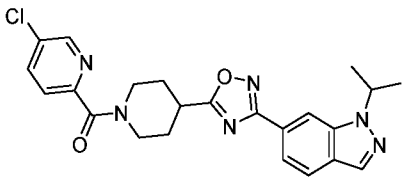
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.11 (s, 1H), 7.91-7.86 (m, 1H), 7.85-7.81 (m, 1H), 5.16-5.03 (m, 1H), 4.91 (dd, J = 7.9, 9.3 Hz, 0.5H), 4.82-4.76 (m, 1H), 4.67 (dd, J = 4.9, 9.4 Hz, 0.5H), 4.61 (br s, 1H), 4.04 (br d, J = 13.7 Hz, 1H), 3.36-3.24 (m, 2H), 2.97 (br t, J = 12.1 Hz, 1H), 2.32 (s, 2H), 2.27-2.17 (m, 2H), 2.05-1.89 (m, 2H), 1.66 (dd, J = 1.6, 6.8 Hz, 3H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 428.2.



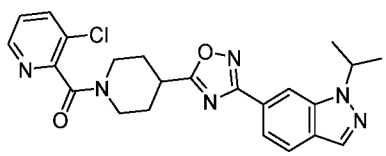
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.07 (s, 1H), 7.90-7.81 (m, 2H), 4.98 (spt, J = 6.6 Hz, 1H), 4.48-3.98 (m, 2H), 3.81-3.68 (m, 1H), 3.61-3.47 (m, 1H), 3.32 (br t, J = 10.1 Hz, 1H), 2.42-2.20 (m, 2H), 1.64 (d, J = 6.7 Hz, 6H), 1.59 (s, 3H), 0.96-0.90 (m, 2H), 0.72-0.65 (m, 2H); LCMS (ESI) [M+H]+: 446.1.



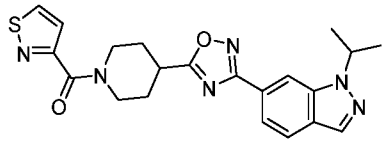
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.11 (s, 1H), 7.92-7.86 (m, 1H), 7.85-7.79 (m, 1H), 5.16-5.03 (m, 1H), 4.90 (dd, J = 8.0, 9.4 Hz, 0.5H), 4.82-4.76 (m, 1H), 4.67 (dd, J = 4.9, 9.4 Hz, 0.5H), 4.60 (br d, J = 13.6 Hz, 1H), 3.97 (br d, J = 13.4 Hz, 1H), 3.34-3.24 (m, 2H), 2.98 (br t, J = 11.9 Hz, 1H), 2.40 (d, J = 3.2 Hz, 2H), 2.22 (br d, J = 13.1 Hz, 2H), 1.96 (quin, J = 11.9 Hz, 2H), 1.66 (dd, J = 1.5, 6.8 Hz, 3H), 1.18 (s, 3H), 0.50-0.44 (m, 2H), 0.44-0.38 (m, 2H); LCMS (ESI) [M+H]+: 426.2.



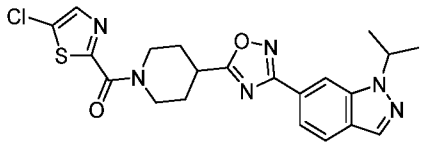
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.57 (d, J = 2.0 Hz, 1H), 8.22 (s, 1H), 8.07 (s, 1H), 7.89-7.78 (m, 3H), 7.69 (d, J = 8.3 Hz, 1H), 4.98 (td, J = 6.7, 13.4 Hz, 1H), 4.67 (br d, J = 13.1 Hz, 1H), 4.16 (br d, J = 13.4 Hz, 1H), 3.45-3.33 (m, 2H), 3.26 (br t, J = 10.8 Hz, 1H), 2.33 (br d, J = 10.9 Hz, 1H), 2.24-2.07 (m, 3H), 1.64 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 451.2.



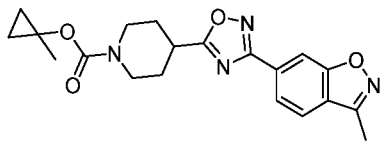
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.56 (dd, J = 1.2, 4.6 Hz, 1H), 8.22 (s, 1H), 8.07 (s, 1H), 7.91-7.75 (m, 3H), 7.33 (dd, J = 4.6, 8.2 Hz, 1H), 4.98 (td, J = 6.6, 13.3 Hz, 1H), 4.78-4.63 (m, 1H), 3.53 (td, J = 3.8, 13.6 Hz, 1H), 3.42-3.19 (m, 3H), 2.35 (br dd, J = 3.9, 13.6 Hz, 1H), 2.25-2.03 (m, 2H), 2.25-2.03 (m, 1H), 1.64 (d, J = 6.6 Hz, 6H); M+H]+: 451.1.



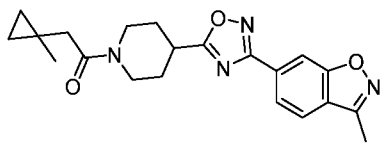
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.71 (d, J = 4.6 Hz, 1H), 8.22 (s, 1H), 8.07 (s, 1H), 7.89-7.79 (m, 2H), 7.68 (d, J = 4.9 Hz, 1H), 4.98 (td, J = 6.6, 13.4 Hz, 1H), 4.68 (br d, J = 13.5 Hz, 1H), 4.57 (br d, J = 13.9 Hz, 1H), 3.53-3.44 (m, 1H), 3.44-3.35 (m, 1H), 3.32-3.17 (m, 1H), 2.38-2.21 (m, 2H), 2.21-2.07 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 423.2.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.89-7.80 (m, 2H), 7.68 (s, 1H), 5.41 (br d, J = 12.3 Hz, 1H), 4.97 (td, J = 6.6, 13.4 Hz, 1H), 4.60 (br d, J = 11.5 Hz, 1H), 3.75-3.62 (m, 1H), 3.49-3.35 (m, 1H), 3.33-3.19 (m, 1H), 2.30 (br s, 2H), 2.14 (br s, 2H), 1.64 (d, J = 6.6 Hz, 5H), 1.66-1.61 (m, 1H); LCMS (ESI) [M+H]+: 457.1.

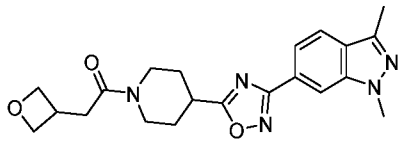


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.05 (dd, J = 1.1, 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 4.16 (br s, 2H), 3.20 (tt, J = 3.9, 10.8 Hz, 1H), 3.09-2.97 (m, 2H), 2.62 (s, 3H), 2.14 (br d, J = 11.4 Hz, 2H), 1.98-1.84 (m, 2H), 1.56 (s, 3H), 0.91-0.85 (m, 2H), 0.67-0.61 (m, 2H); LCMS (ESI) [M+H]+: 383.1.

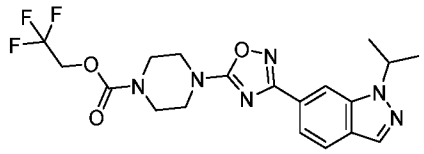


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.05 (dd, J = 1.1, 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 4.58 (br d, J = 13.7 Hz, 1H), 3.96 (br d, J = 13.5 Hz, 1H), 3.34-3.22 (m, 2H), 2.97 (br t, J = 11.2 Hz,

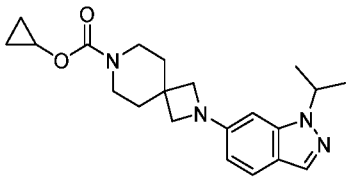
1H), 2.63 (s, 3H), 2.39 (s, 2H), 2.21 (br d, J = 13.2 Hz, 2H), 2.03-1.85 (m, 2H), 1.16 (s, 3H), 0.48-0.38 (m, 4H); LCMS (ESI) [M+H]+: 381.1.



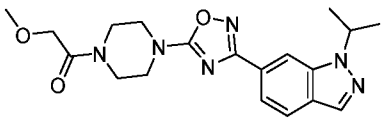
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.88-7.81 (m, 1H), 7.79-7.70 (m, 1H), 4.94 (t, J = 7.0 Hz, 2H), 4.52 (br d, J = 13.7 Hz, 1H), 4.43 (t, J = 5.6 Hz, 2H), 4.09 (s, 3H), 3.98 (br d, J = 13.6 Hz, 1H), 3.50-3.39 (m, 1H), 3.33 (br s, 2H), 3.00 (br s, 1H), 2.83 (d, J = 7.7 Hz, 2H), 2.61 (s, 3H), 2.25 (br t, J = 14.4 Hz, 2H), 2.09-1.89 (m, 2H); LCMS (ESI) [M+H]+: 396.2.



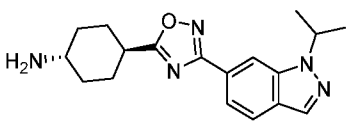
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (d, J = 0.7 Hz, 1H), 8.05 (s, 1H), 7.78 (d, J = 0.9 Hz, 2H), 4.95 (spt, J = 6.6 Hz, 1H), 4.56 (q, J = 8.4 Hz, 2H), 3.78 (br s, 4H), 3.74-3.68 (m, 4H), 1.63 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 439.2.



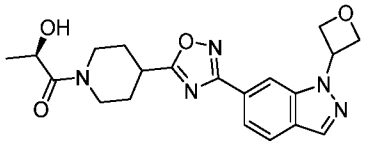
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.84 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 8.39 (dd, J = 8.4, 1.6 Hz, 1H), 6.22 (s, 1H), 4.75-4.64 (m, 1H), 4.13-4.05 (m, 1H), 3.71 (s, 4H), 3.55-3.30 (m, 4H), 1.93-1.72 (m, 4H), 1.56 (d, J = 6.8 Hz, 6H), 0.75-0.62 (m, 4H); LCMS (ESI) [M+H]+: 369.2.



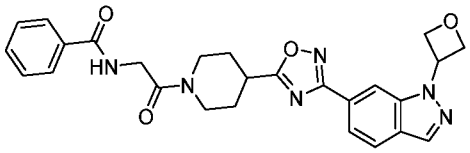
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (d, J = 0.9 Hz, 1H), 8.05 (s, 1H), 7.78 (d, J = 1.0 Hz, 2H), 4.95 (td, J = 6.7, 13.3 Hz, 1H), 4.17 (s, 2H), 3.84-3.68 (m, 8H), 3.51-3.42 (m, 1H), 3.46 (s, 2H), 1.63 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 485.1.



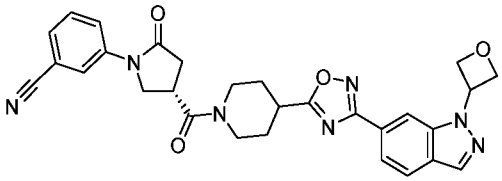
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.18 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 1.1, 8.4 Hz, 1H), 5.09 (spt, J = 6.6 Hz, 1H), 3.16-3.05 (m, 2H), 2.24 (br d, J = 11.4 Hz, 2H), 2.10 (br d, J = 10.0 Hz, 2H), 1.76-1.65 (m, 2H), 1.54 (br dd, J = 2.8, 12.6 Hz, 2H), 1.49 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 326.1.



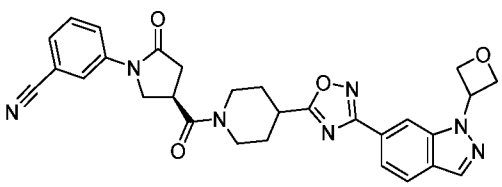
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.19 (dd, J = 14.6, 1.0 Hz, 2H), 7.95-7.80 (m, 2H), 5.89 (p, J = 7.1 Hz, 1H), 5.33 (t, J = 6.9, 6.2 Hz, 2H), 5.16 (t, J = 7.2 Hz, 2H), 4.51 (q, J = 6.7 Hz, 2H), 3.83 (s, 1H), 3.37 (d, J = 10.6 Hz, 1H), 3.32 (s, 1H), 3.19-3.05 (m, 1H), 2.80 (s, 1H), 2.25 (s, 1H), 1.64 (d, J = 7.0 Hz, 1H), 1.57-1.42 (m, 1H), 1.38 (dd, J = 8.8, 6.1 Hz, 3H), 1.25 (s, 1H), 1.06 (s, 1H); LCMS (ESI) [M+H]+: 398.3.



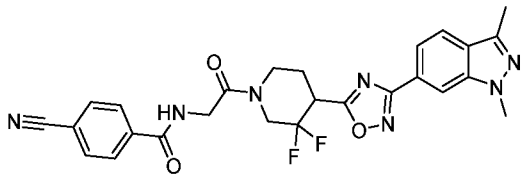
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.26-8.14 (m, 2H), 7.96-7.80 (m, 4H), 7.59-7.40 (m, 3H), 7.33 (s, 1H), 5.88 (q, J = 6.8 Hz, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.3 Hz, 2H), 4.54 (d, J = 14.0 Hz, 1H), 4.32 (d, J = 4.0 Hz, 2H), 3.93 (d, J = 13.8 Hz, 1H), 3.43-3.28 (m, 2H), 3.15 (t, J = 12.1 Hz, 1H), 2.02 (dd, J = 14.6, 10.7 Hz, 2H), 1.47 (s, 1H), 1.25 (s, 2H); LCMS (ESI) [M+H]+: 487.3.



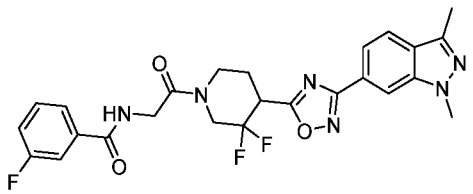
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.27-8.14 (m, 2H), 8.01-7.81 (m, 4H), 7.55-7.40 (m, 2H), 5.90 (s, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.2 Hz, 2H), 4.57 (t, J = 15.7 Hz, 1H), 4.34 (dd, J = 9.5, 6.6 Hz, 1H), 3.95 (t, J = 8.1 Hz, 2H), 3.62 (p, J = 8.2 Hz, 1H), 3.40 (d, J = 8.2 Hz, 1H), 3.37 (s, 1H), 3.21-2.87 (m, 3H), 2.28 (d, J = 13.1 Hz, 2H), 2.06 (s, 1H), 1.25 (s, 1H); LCMS (ESI) [M+H]+: 538.3.



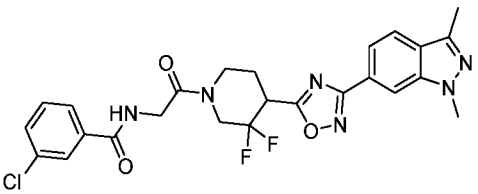
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.27-8.14 (m, 2H), 8.01-7.81 (m, 4H), 7.55-7.40 (m, 2H), 5.89 (s, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.17 (t, J = 7.1 Hz, 2H), 4.57 (s, 1H), 4.34 (dd, J = 9.5, 6.6 Hz, 1H), 3.96 (t, J = 8.5 Hz, 2H), 3.68-3.56 (m, 1H), 3.39 (s, 1H), 3.12 (s, 1H), 3.06-2.89 (m, 2H), 2.29 (s, 1H), 2.06 (s, 1H), 1.25 (s, 1H); LCMS (ESI) [M+H]+: 538.3.



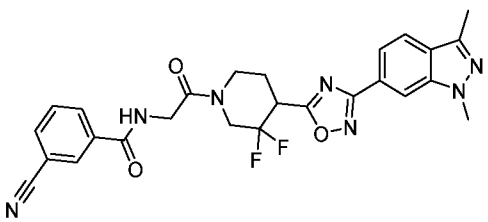
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (s, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.83 (dd, J = 0.7, 8.4 Hz, 1H), 7.79-7.71 (m, 3H), 7.42-7.29 (m, 1H), 4.58 (dt, J = 6.5, 14.7 Hz, 0.5H), 4.44-4.30 (m, 2.5H), 4.29-4.16 (m, 0.5H), 4.08 (s, 3H), 4.06-3.99 (m, 0.5H), 3.96-3.69 (m, 2H), 3.67-3.50 (m, 1H), 2.60 (s, 3H), 2.49-2.29 (m, 2H); LCMS (ESI) [M+H]+: 520.1.



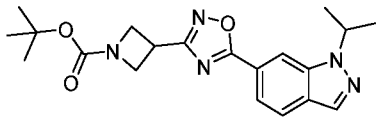
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.03 (s, 1H), 7.76 (dd, J = 1.1, 8.4 Hz, 1H), 7.70-7.64 (m, 1H), 7.57-7.46 (m, 2H), 7.36 (dt, J = 5.6, 7.9 Hz, 1H), 7.21-7.11 (m, 2H), 4.57-4.42 (m, 0.5H), 4.34-4.22 (m, 2.6H), 4.21-4.10 (m, 0.6H), 4.01 (s, 3H), 3.99-3.90 (m, 0.5H), 3.87-3.62 (m, 2H), 3.60-3.42 (m, 1H), 2.53 (s, 3H), 2.41-2.22 (m, 2H); LCMS (ESI) [M+H]+: 513.2.



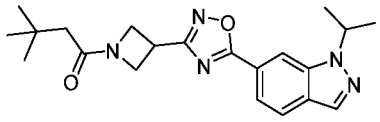
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 7.91-7.85 (m, 2H), 7.81-7.76 (m, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.46-7.40 (m, 1H), 7.23 (br d, J = 19.8 Hz, 1H), 4.60 (dt, J = 6.4, 14.7 Hz, 0.5H), 4.44-4.32 (m, 2.5H), 4.25 (dt, J = 5.3, 14.7 Hz, 0.5H), 4.13 (s, 3H), 4.06 (br d, J = 13.4 Hz, 0.5H), 3.97-3.71 (m, 2H), 3.69-3.52 (m, 1H), 2.65 (s, 3H), 2.48-2.33 (m, 2H); LCMS (ESI) [M+H]+: 529.1.



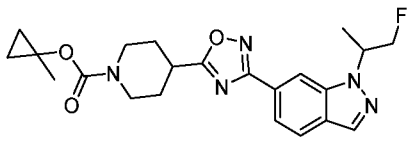
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17 (br d, J = 5.3 Hz, 1H), 8.11 (s, 1H), 8.07 (br d, J = 7.9 Hz, 1H), 7.87-7.80 (m, 2H), 7.76 (dd, J = 0.7, 8.4 Hz, 1H), 7.64-7.59 (m, 1H), 7.35-7.26 (m, 1H), 4.58 (dt, J = 6.3, 14.9 Hz, 0.5H), 4.44-4.30 (m, 2.5H), 4.24 (dt, J = 5.6, 15.1 Hz, 0.5H), 4.09 (s, 3H), 4.04 (br d, J = 14.5 Hz, 0.5H), 3.96-3.84 (m, 1.5H), 3.82-3.70 (m, 0.5H), 3.70-3.49 (m, 1H), 2.61 (s, 3H), 2.47-2.31 (m, 2H); LCMS (ESI) [M+H]+: 520.2.



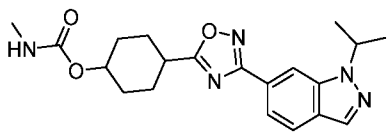
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.32 (s, 1H), 8.11 (s, 1H), 7.95-7.79 (m, 2H), 5.00 (spt, J = 6.6 Hz, 1H), 4.42-4.24 (m, 4H), 4.01 (tt, J = 6.1, 8.8 Hz, 1H), 1.66 (d, J = 6.6 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M-55]+: 328.1.



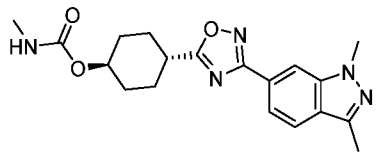
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.11 (s, 1H), 7.88 (m, 2H), 4.99 (spt, J = 6.7 Hz, 1H), 4.59-4.49 (m, 2H), 4.48-4.41 (m, 1H), 4.39-4.32 (m, 1H), 4.04 (tt, J = 6.0, 8.8 Hz, 1H), 2.14-2.02 (m, 2H), 1.66 (d, J = 6.6 Hz, 6H), 1.10 (s, 9H); LCMS (ESI) [M+H]+: 382.2.



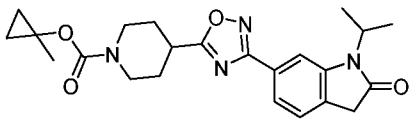
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.11 (s, 1H), 7.91-7.86 (m, 1H), 7.85-7.80 (m, 1H), 5.16-5.03 (m, 1H), 4.90 (t, J = 8.6 Hz, 0.5H), 4.82-4.74 (m, 1H), 4.67 (dd, J = 5.0, 9.4 Hz, 0.5H), 4.34-3.93 (br s, 2H), 3.21 (tt, J = 3.9, 10.8 Hz, 1H), 3.11-2.97 (m, 2H), 2.16 (br d, J = 12.0 Hz, 2H), 1.94 (br d, J = 9.7 Hz, 2H), 1.66 (dd, J = 1.5, 6.9 Hz, 3H), 1.58 (s, 3H), 0.95-0.84 (m, 2H), 0.69-0.60 (m, 2H); LCMS (ESI) [M+H]+: 428.1.



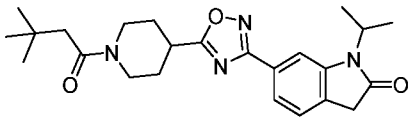
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.19 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 6.95 (br d, J = 4.5 Hz, 1H), 5.14 (spt, J = 6.5 Hz, 1H), 4.65-4.43 (m, 1H), 3.20-3.12 (m, 1H), 2.58 (d, J = 4.5 Hz, 3H), 2.21 (br d, J = 11.4 Hz, 2H), 2.04 (br dd, J = 3.1, 12.5 Hz, 2H), 1.82-1.71 (m, 2H), 1.57-1.44 (m, 8H); LCMS (ESI) [M+H]+: 384.2.



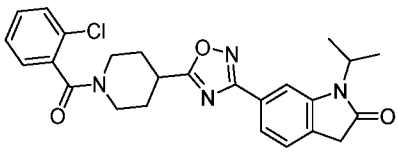
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.83 (dd, J = 1.0, 8.4 Hz, 1H), 7.76-7.70 (m, 1H), 4.80-4.54 (m, 2H), 4.08 (s, 3H), 3.06-2.96 (m, 1H), 2.82 (d, J = 4.8 Hz, 3H), 2.60 (s, 3H), 2.34-2.16 (m, 4H), 1.94-1.82 (m, 2H), 1.60-1.46 (m, 2H); LCMS (ESI) [M+H]+: 370.1.



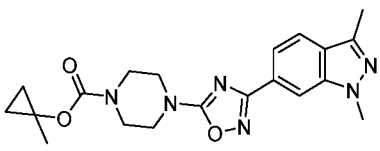
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.77 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 4.72-4.65 (m, 1H), 4.25-4.00 (m, 2H), 3.56 (s, 2H), 3.24-3.15 (m, 1H), 3.03 (br t, J = 11.1 Hz, 2H), 2.14 (br d, J = 11.9 Hz, 2H), 1.92 (br d, J = 9.5 Hz, 2H), 1.57 (s, 3H), 1.54 (d, J = 7.0 Hz, 6H), 0.92-0.87 (m, 2H), 0.68-0.63 (m, 2H); LCMS (ESI) [M+H]+: 425.2.



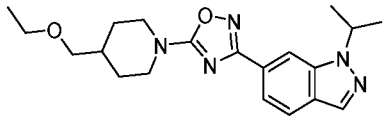
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.77 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 4.72-4.65 (m, 1H), 4.62 (br d, J = 14.1 Hz, 1H),4.03 (br d, J = 14.1 Hz, 1H), 3.56 (s, 2H), 3.34-3.22 (m, 2H), 2.95 (br t, J = 11.5 Hz, 1H), 2.32 (s, 2H), 2.20 (br d, J = 11.5 Hz, 2H), 2.03-1.84 (m, 2H), 1.54 (d, J = 6.8 Hz, 6H), 1.08 (s, 9H); LCMS (ESI) [M+H]+: 425.2.



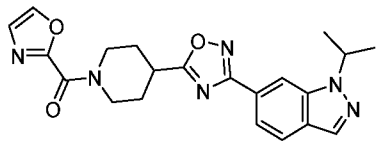
^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.80 (d, J = 7.7 Hz, 1H), 7.75 (s, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.49-7.35 (m, 4H), 4.70-4.63 (m, 2H), 3.60-3.53 (m, 1H), 3.44-3.39 (m, 1H), 3.52-3.37 (m, 1H), 3.32-3.22 (m, 2H), 2.35 (br d, J = 11.9 Hz, 1H), 2.17 (br d, J = 13.0 Hz, 1H), 2.10-1.96 (m, 2H), 1.95-1.81 (m, 1H), 1.55 (d, J = 7.1 Hz, 6H). LCMS (ESI) [M+H]+: 465.1.



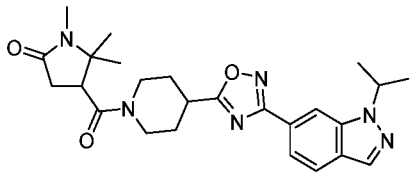
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.94 (s, 1H), 7.70-7.61 (m, 2H), 3.99 (s, 3H), 3.67-3.49 (m, 8H), 2.51 (s, 3H), 1.51 (s, 3H), 0.88-0.79 (m, 2H), 0.64-0.56 (m, 2H); LCMS (ESI) [M+H]+: 397.1.



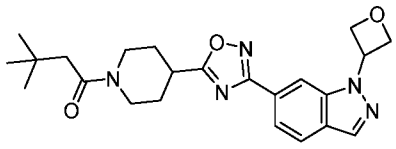
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 8.03 (s, 1H), 7.81-7.73 (m, 2H), 4.95 (m, 1H), 4.30 (m, 2H), 3.49 (q, J = 7.1 Hz, 2H), 3.32 (d, J = 6.0 Hz, 2H), 3.15 (dt, J = 2.3, 12.8 Hz, 2H), 1.96-1.80 (m, 3H), 1.61 (d, J = 6.6 Hz, 6H), 1.46-1.29 (m, 2H), 1.21 (t, J = 6.9 Hz, 3H); LCMS (ESI) [M+H]+: 370.2.



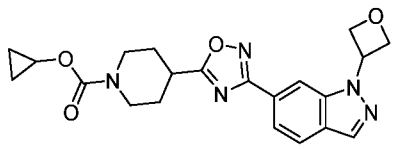
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.90-7.78 (m, 3H), 7.28 (s, 1H), 5.09-4.91 (m, 2H), 4.65 (br d, J = 13.2 Hz, 1H), 3.70-3.58 (m, 1H), 3.47-3.36 (m, 1H), 3.34-3.23 (m, 1H), 2.30 (br d, J = 3.5 Hz, 2H), 2.23-2.05 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 407.1.



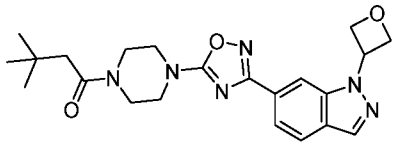
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.08 (s, 1H), 7.91-7.79 (m, 2H), 4.98 (td, J = 6.6, 13.3 Hz, 1H), 4.74-4.49 (m, 1H), 4.25-4.03 (m, 1H), 3.53-3.29 (m, 3H), 3.23-2.97 (m, 2H), 2.77 (s, 3H), 2.48 (br dd, J = 7.6, 17.0 Hz, 1H), 2.38-2.21 (m, 2H), 2.11-1.92 (m, 2H), 1.65 (d, J = 6.6 Hz, 6H), 1.43 (s, 3H), 1.17 (d, J = 5.0 Hz, 3H); LCMS (ESI) [M+H]+: 465.2.



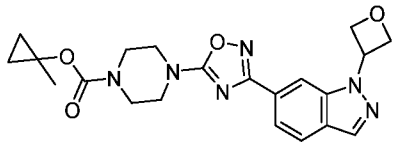
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.17 (s, 1H), 7.94-7.89 (m, 1H), 7.88-7.83 (m, 1H), 5.90 (quin, J = 7.0 Hz, 1H), 5.34 (t, J = 6.6 Hz, 2H), 5.16 (t, J = 7.3 Hz, 2H), 4.63 (br d, J = 13.4 Hz, 1H), 4.05 (br d, J = 13.4 Hz, 1H), 3.37-3.23 (m, 2H), 2.96 (br t, J = 11.2 Hz, 1H), 2.32 (s, 2H), 2.22 (br d, J = 12.8 Hz, 2H), 2.03-1.88 (m, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 424.2.



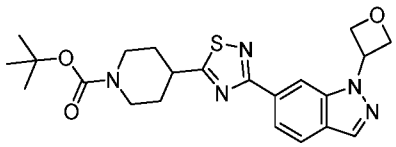
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.17 (s, 1H), 7.94-7.88 (m, 1H), 7.88-7.82 (m, 1H), 5.90 (quin, J = 7.0 Hz, 1H), 5.34 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.3 Hz, 2H), 4.39-3.91 (m, 3H), 3.23 (tt, J = 3.9, 10.9 Hz, 1H), 3.07 (ddd, J = 2.9, 11.2, 13.8 Hz, 2H), 2.25-2.08 (m, 2H), 2.03-1.85 (m, 2H), 0.76-0.66 (m, 4H); LCMS (ESI) [M+H]+: 410.1.



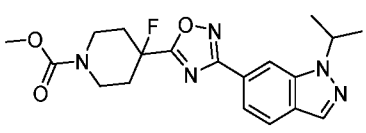
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (br d, J = 2.9 Hz, 2H), 7.86-7.78 (m, 2H), 5.93-5.84 (m, 1H), 5.33 (m, 2H), 5.19-5.11 (m, 2H), 3.85-3.67 (m, 8H), 2.33 (d, J = 2.4 Hz, 2H), 1.09 (d, J = 2.4 Hz, 9H); LCMS (ESI) [M+H]+: 425.2.



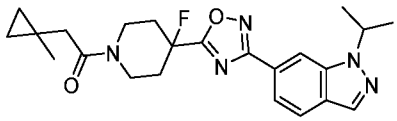
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (d, J = 7.1 Hz, 2H), 7.84-7.78 (m, 2H), 5.88 (quin, J = 7.1 Hz, 1H), 5.32 (t, J = 6.6 Hz, 2H), 5.14 (t, J = 7.3 Hz, 2H), 3.74-3.56 (m, 8H), 1.58 (s, 3H), 0.93-0.88 (t, J = 6.4 Hz, 2H), 0.70-0.65 (t, J = 6.4 Hz, 2H); LCMS (ESI) [M+H]+: 425.2.



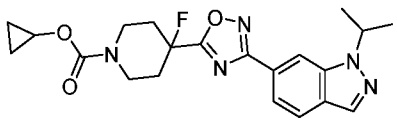
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.46 (s, 1H), 8.21-8.14 (m, 2H), 7.85 (d, J = 8.4 Hz, 1H), 5.94 (m, 1H), 5.37 (t, J = 6.6 Hz, 2H), 5.18 (t, J = 7.3 Hz, 2H), 4.26 (m, 2H), 3.38 (m, 1H), 3.00 (m, 2H), 2.25 (m, 2H), 1.87 (m, 2H), 1.52 (s, 9H); LCMS (ESI) [M+H]+: 442.1.



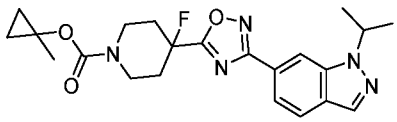
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.07 (s, 1H), 7.89-7.80 (m, 2H), 5.02-4.93 (m, 1H), 4.10 (br s, 2H), 3.75 (s, 3H), 3.42 (br t, J = 10.6 Hz, 2H), 2.41-2.23 (m, 4H), 1.63 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 388.1.



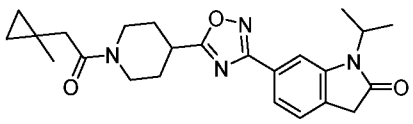
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.09 (s, 1H), 7.90-7.83 (m, 2H), 5.03-4.96 (m, 1H), 4.56 (br d, J = 13.4 Hz, 1H), 3.89 (br d, J = 13.9 Hz, 1H), 3.62 (br t, J = 11.4 Hz, 1H), 3.29 (br t, J = 11.2 Hz, 1H), 2.48-2.24 (m, 6H), 1.65 (d, J = 6.6 Hz, 6H), 1.20 (s, 3H), 0.52-0.40 (m, 4H); LCMS (ESI) [M+H]+: 426.2.



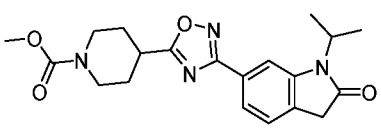
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 7.99 (s, 1H), 7.80-7.73 (m, 2H), 4.95-4.84 (m, 1H), 4.19-3.78 (m, 3H), 3.39-3.24 (m, 2H), 2.34-2.11 (m, 4H), 1.55 (d, J = 6.7 Hz, 6H), 0.67-0.61 (m, 4H); LCMS (ESI) [M+H]+: 414.1.



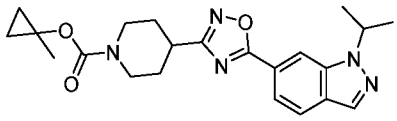
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.08 (s, 1H), 7.89-7.82 (m, 2H), 4.98 (spt, J = 6.6 Hz, 1H), 4.22-3.89 (m, 2H), 3.46-3.32 (m, 2H), 2.40-2.23 (m, 4H), 1.65 (d, J = 6.6 Hz, 6H), 1.59 (s, 3H), 1.05-0.86 (m, 2H), 0.71-0.65 (m, 2H); LCMS (ESI) [M+H]+: 428.1.



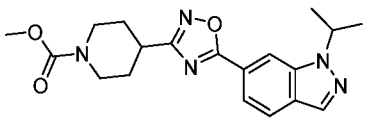
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.77 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.35 (d, J = 7.5 Hz, 1H), 4.72-4.65 (m, 1H), 4.59 (br d, J = 13.5 Hz, 1H), 3.96 (br d, J = 13.7 Hz, 1H), 3.56 (s, 2H), 3.33-3.23 (m, 2H), 2.97 (br t, J = 11.4 Hz, 1H), 2.39 (d, J = 4.4 Hz, 2H), 2.21 (br d, J = 13.2 Hz, 2H), 2.01-1.87 (m, 2H), 1.54 (d, J = 7.1 Hz, 6H), 1.17 (s, 3H), 0.48-0.38 (m, 4H); LCMS (ESI) [M+H]+: 423.2.



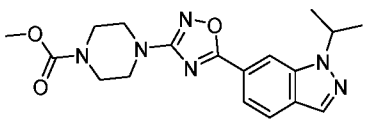
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.77 (dd, J = 1.0, 7.6 Hz, 1H), 7.66 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 4.68 (spt, J = 7.0 Hz, 1H), 4.30-4.00 (m, 2H), 3.73 (s, 3H), 3.55 (s, 2H), 3.22 (tt, J = 4.0, 10.8 Hz, 1H), 3.08 (br t, J = 11.7 Hz, 2H), 2.16 (br d, J = 10.8 Hz, 2H), 2.03-1.84 (m, 2H), 1.54 (d, J = 7.1 Hz, 6H); LCMS (ESI) [M+H]+: 385.2.



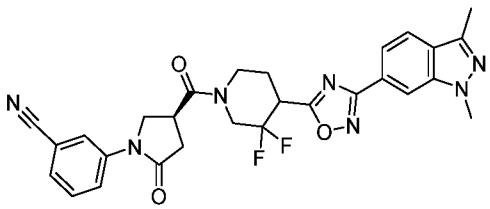
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.87 (m, 2H), 5.06-4.92 (m, 1H), 4.37-3.97 (m, 2H), 3.14-2.90 (m, 3H), 2.09 (br d, J = 10.8 Hz, 2H), 1.88 (br d, J = 9.9 Hz, 2H), 1.65 (d, J = 6.6 Hz, 6H), 1.58 (s, 3H), 0.97-0.83 (m, 2H), 0.70-0.59 (m, 2H); LCMS (ESI) [M+H]+: 410.2.



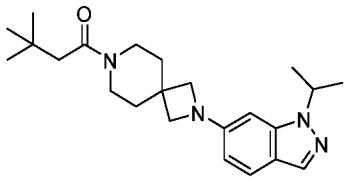
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, J = 0.6 Hz, 1H), 8.10 (s, 1H), 7.92-7.82 (m, 2H), 4.98 (spt, J = 6.7 Hz, 1H), 4.22 (br s, 2H), 3.74 (s, 3H), 3.16-2.97 (m, 3H), 2.11 (m, J = 11.7 Hz, 2H), 1.99-1.82 (m, 2H), 1.65 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 370.1.



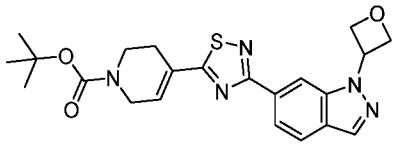
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.09 (s, 1H), 7.84 (m, 2H), 4.97 (spt, J = 6.6 Hz, 1H), 3.76 (s, 3H), 3.69-3.44 (m, 8H), 1.64 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 371.1.



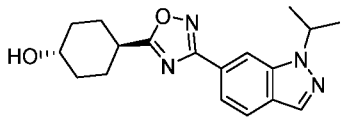
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 8.03-7.82 (m, 3H), 7.78-7.73 (m, 1H), 7.53-7.43 (m, 2H), 4.65 (m 0.4H), 4.48 (m, 0.5H), 4.41-4.24 (m, 2H), 4.10 (br d, J = 2.4 Hz, 3H), 4.00 (t, J = 9.0 Hz, 1H), 3.95-3.75 (m, 2H), 3.73-3.45 (m, 2H), 3.07-2.89 (m, 2H), 2.62 (s, 3H), 2.49-2.32 (m, 2H); LCMS (ESI) [M+H]+: 546.2.



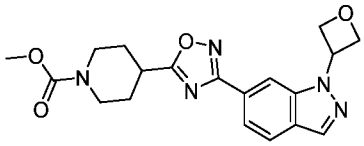
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.85 (s, 1H), 7.54 (d, J = 8.7 Hz, 1H), 6.40 (dd, J = 1.6, 8.7 Hz, 1H), 6.23 (s, 1H), 4.83-4.60 (m, 1H), 3.73 (s, 4H), 3.69-3.44 (m, 4H), 2.30 (s, 2H), 1.85 (br dd, J = 5.4, 8.8 Hz, 4H), 1.57 (d, J = 6.6 Hz, 6H), 1.08 (s, 9H); LCMS (ESI) [M+H]+: 383.2.



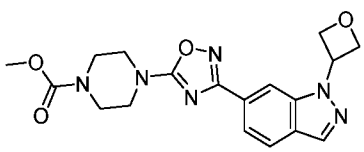
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.38 (s, 1H), 8.14-8.04 (m, 2H), 7.76 (d, J = 8.4 Hz, 1H), 6.83 (br s, 1H), 5.85 (t, J = 6.9 Hz, 1H), 5.28 (t, J = 6.5 Hz, 2H), 5.09 (t, J = 7.3 Hz, 2H), 4.15 (d, J = 2.4 Hz, 2H), 3.64 (t, J = 5.4 Hz, 2H), 2.70 (m, 2H), 1.44 (s, 9H) LCMS (ESI) [M+H]+: 440.1.



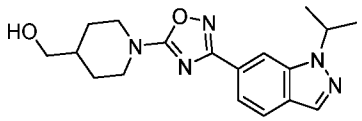
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.08 (s, 1H), 7.89-7.81 (m, 2H), 5.04-4.93 (m, 1H), 3.84-3.73 (m, 1H), 3.03 (tt, J = 3.7, 11.9 Hz, 1H), 2.33-2.26 (m, 2H), 2.24-2.15 (m, 2H), 1.88-1.77 (m, 2H), 1.64 (d, J = 6.7 Hz, 6H), 1.55-1.44 (m, 2H); LCMS (ESI) [M+H]+: 327.1.



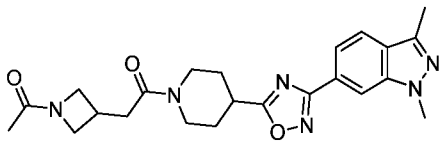
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.17 (s, 1H), 7.94-7.88 (m, 1H), 7.87-7.81 (m, 1H), 5.90 (quin, J = 7.0 Hz, 1H), 5.34 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.3 Hz, 2H), 4.31-4.08 (m, 2H), 3.74 (s, 3H), 3.23 (tt, J = 3.9, 10.9 Hz, 1H), 3.09 (br t, J = 11.5 Hz, 2H), 2.18 (br dd, J = 2.8, 13.3 Hz, 2H), 2.02-1.89 (m, 2H); LCMS (ESI) [M+H]+: 384.1.



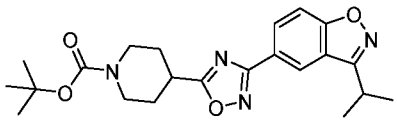
^{1}HNMR (400 MHz, CHLOROFORM-d) δ 8.14 (d, J = 4.5 Hz, 2H), 7.81 -7.81 (m, 2H), 5.87 (quin, J = 7.0 Hz, 1H), 5.32 (t, J = 6.5 Hz, 2H), 5.14 (t, J = 7.3 Hz, 2H), 3.76 (s, 3H), 3.72 (m, 4H), 3.65 (m, 4H); LCMS (ESI) [M+H]+: 385.1.



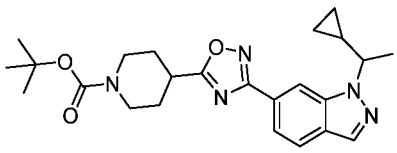
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1H), 8.03 (s, 1H), 7.81-7.73 (m, 2H), 4.95 (m, 1H), 4.33 (m, 2H), 3.57 (d, J = 6.2 Hz, 2H), 3.16 (dt, J = 2.8, 13.0 Hz, 2H), 1.90 (br d, J = 12.6 Hz, 2H), 1.84-1.73 (m, 1H), 1.61 (d, J = 6.6 Hz, 6H), 1.45-1.33 (m, 2H); LCMS (ESI) [M+H]+: 342.1.



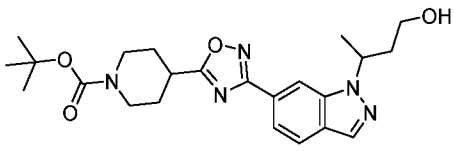
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.08 (s, 1H), 7.84-7.79 (m, 1H), 7.75-7.71 (m, 1H), 4.50 (br dd, J = 10.0, 13.3 Hz, 1H), 4.37 (t, J = 8.5 Hz, 1H), 4.19 (t, J = 9.3 Hz, 1H), 4.07 (s, 3H), 3.92 (br d, J = 13.5 Hz, 1H), 3.79 (dd, J = 5.6, 8.5 Hz, 1H), 3.67 (br dd, J = 5.7, 9.5 Hz, 1H), 3.31 (br t, J = 10.9 Hz, 2H), 3.06-2.96 (m, 2H), 2.80-2.62 (m, 2H), 2.59 (s, 3H), 2.29-2.18 (m, 2H), 2.05-1.91 (m, 2H), 1.85 (s, 3H); LCMS (ESI) [M+H]+: 437.5.



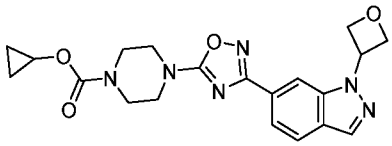
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.45 (s, 1H), 8.28 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 4.16 (br s, 2H), 3.48 (td, J = 7.0, 14.0 Hz, 1H), 3.28-3.13 (m, 1H), 3.02 (br t, J = 11.6 Hz, 2H), 2.15 (br d, J = 10.4 Hz, 2H), 2.03-1.86 (m, 2H), 1.54 (d, J = 7.0 Hz, 6H), 1.49 (s, 9H).; LCMS (ESI) [M+H]+: 413.1.



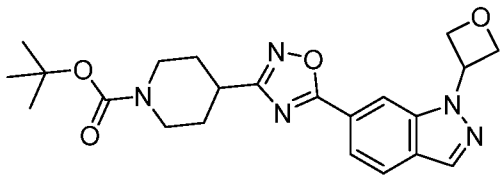
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.20 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 1.2, 8.5 Hz, 1H), 4.46-4.29 (m, 1H), 3.98 (br d, J = 13.2 Hz, 2H), 3.48-3.35 (m, 1H), 2.99 (br s, 2H), 2.10 (br dd, J = 3.1, 13.2 Hz, 2H), 1.80-1.64 (m, 2H), 1.59 (d, J = 6.6 Hz, 3H), 1.47-1.36 (m, 10H), 0.64-0.55 (m, 1H), 0.44 (qd, J = 4.8, 9.5 Hz, 1H), 0.38-0.30 (m, 1H), 0.25 (qd, J = 4.9, 9.6 Hz, 1H); LCMS (ESI) [M+H]+: 438.2.



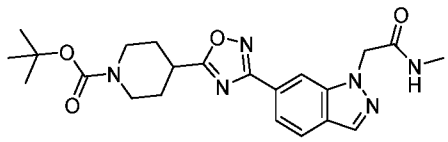
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.07 (s, 1H), 7.88-7.84 (d, J = 12 Hz, 1H), 7.83-7.79 (d, J = 12 Hz, 1H), 5.15-5.01 (m, 1H), 4.16 -4.13 (m, 2H), 3.64-3.62 (m, 1H), 3.45-3.34 (m, 1H), 3.21 -3. 18 (m, 1H), 2.98-3.02 (m, 2H), 2.39- 2.36 (m, 1H), 2.24-2.09 (m, 3H), 1.99-1.86 (m, 3H), 1.63 (d, J = 6.6 Hz, 3H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 442.2.



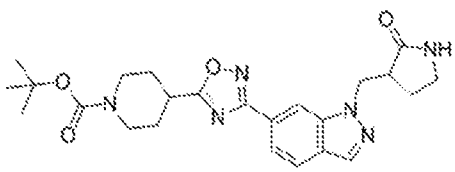
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (d, J = 6.1 Hz, 2H), 7.84-7.78 (m, 2H), 5.88 (quin, J = 7.1 Hz, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.14 (t, J = 7.3 Hz, 2H), 4.16-4.10 (m, 1H), 3.79-3.56 (m, 8H), 0.78-0.67 (m, 4H); LCMS (ESI) [M+H]+: 411.1.



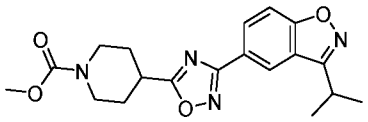
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.98-7.83 (m, 2H), 5.91 (m, J = 7.0 Hz, 1H), 5.40-5.30 (m, 2H), 5.24-5.11 (m, 2H), 4.29-4.06 (m, 2H), 3.06 (tt, J = 3.7, 11.2 Hz, 1H), 2.97 (br t, J = 11.9 Hz, 2H), 2.16-2.01 (m, 2H), 1.97-1.79 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-55]+: 370.1.



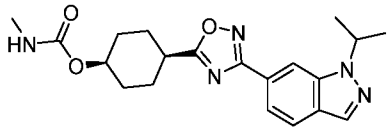
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (d, J = 8.4 Hz, 2H), 8.00-7.94 (m, 1H), 7.92-7.83 (m, 1H), 5.90-5.75 (m, 1H), 5.16 (s, 2H), 4.25-4.10 (m, 2H), 3.29-2.96 (m, 3H), 2.80 (d, J = 4.8 Hz, 3H), 2.18 (br d, J = 11.1 Hz, 2H), 2.05-1.85 (m, 2H), 1.51 (s, 9H); LCMS (ESI) [M-100+H]+: 341.1.



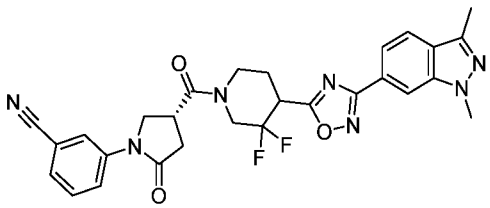
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.32 (s, 1H), 8.08 (s, 1H), 7.91-7.88 (m, 1H), 7.85-7.81 (m, 1H), 5.61 (br s, 1H), 4.92 (dd, J = 4.3, 14.4 Hz, 1H), 4.63 (dd, J = 8.5, 14.4 Hz, 1H), 4.17 (m, 2H), 3.39-3.16 (m, 3H), 3.14-2.95 (m, 3H), 2.31-2.07 (m, 4H), 2.02-1.89 (m, 2H); LCMS (ESI) [M+H]+: 367.1.



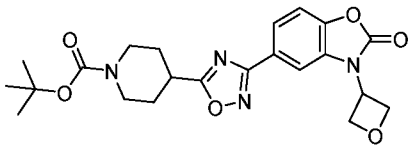
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.45 (s, 1H), 8.28 (dd, J = 1.6, 8.8 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 4.19 (br s, 2H), 3.74 (s, 3H), 3.48 (td, J = 6.9, 14.0 Hz, 1H), 3.29-3.18 (m, 1H), 3.09 (br t, J = 12.5 Hz, 2H), 2.17 (br d, J = 13.6 Hz, 2H), 2.02-1.88 (m, 2H), 1.55 (s, 3H), 1.54 (s, 3H); LCMS (ESI) [M+H]+: 371.1.



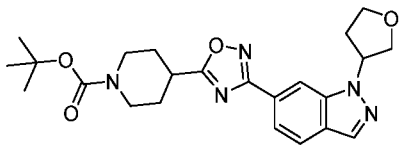
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.06 (s, 1H), 7.89-7.80 (m, 2H), 5.04-4.93 (m, 2H), 4.65 (br s, 1H), 3.18-3.09 (m, 1H), 2.82 (d, J = 4.9 Hz, 3H), 2.23-1.97 (m, 6H), 1.77 (br d, J = 11.1 Hz, 2H), 1.63 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 384.1.



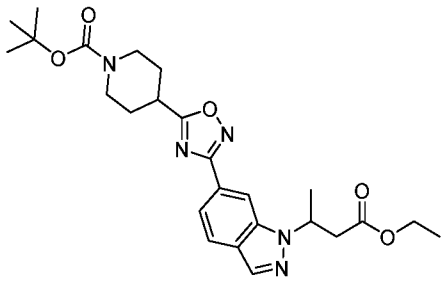
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 8.01-7.83 (m, 3H), 7.79-7.73 (m, 1H), 7.52-7.43 (m, 2H), 4.64 (dt, J = 6.5, 14.2 Hz, 1H), 4.47 (br d, J = 13.3 Hz, 1H), 4.41-4.25 (m, 2H), 4.10 (br d, J = 2.8 Hz, 3H), 3.99 (t, J = 9.0 Hz, 1H), 3.94-3.75 (m, 2H), 3.71-3.43 (m, 2H), 3.05-2.87 (m, 2H), 2.61 (s, 3H), 2.48-2.30 (m, 2H); LCMS (ESI) [M+H]+: 546.2.



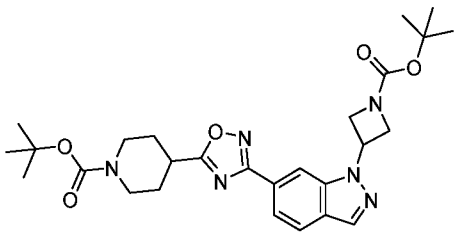
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 5.55-5.48 (m, 1H), 5.24-5.21 (m, 2H), 5.15-5.11 (m, 2H), 4.22-4.05 (m, 2H), 3.19 (tt, J = 3.8, 11.0 Hz, 1H), 3.00 (br t, J = 11.8 Hz, 2H), 2.14 (br d, J = 10.6 Hz, 2H), 1.98-1.85 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-55]+: 387.1.



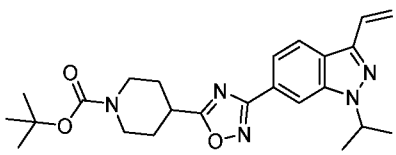
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.08 (s, 1H), 7.93-7.87 (m, 1H), 7.86-7.79 (m, 1H), 5.43-5.33 (m, 1H), 4.34-4.12 (m, 5H), 4.05 (q, J = 7.3 Hz, 1H), 3.21 (br t, J = 10.9 Hz, 1H), 3.02 (br t, J = 11.7 Hz, 2H), 2.55 (q, J = 6.7 Hz, 2H), 2.16 (br d, J = 13.0 Hz, 2H), 2.01-1.86 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 440.5.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.07 (s, 1H), 7.88-7.84 (d, J = 8.4 Hz, 1H), 7.82-7.77 (d, J = 8.4 Hz, 1H), 5.35-5.23 (m, 1H), 4.18 -4.16 (m, 2H), 4.05-3.96 (m, 2H), 3.25-3.14 (m, 2H), 3.03 (br t, J = 11.9 Hz, 2H), 2.93 (dd, J = 6.1, 16.0 Hz, 1H), 2.16 (br d, J = 10.8 Hz, 2H), 2.01-1.89 (m, 2H), 1.64 (d, J = 6.6 Hz, 3H), 1.50 (s, 9H), 1.10 (t, J = 7.2 Hz, 3H); LCMS (ESI) [M+H]+: 484.2.

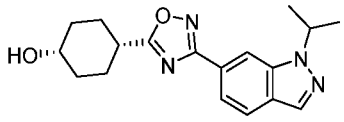


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17 (s, 1H), 8.14 (s, 1H), 7.93-7.87 (m, 1H), 7.86-7.80 (m, 1H), 5.54-5.42 (m, 1H), 4.60-4.52 (m, 2H), 4.51-4.43 (m, 2H), 4.22-4.07 (m, 2H), 3.20 (tt, J = 3.9, 10.9 Hz, 1H), 3.01 (br t, J = 12.0 Hz, 2H), 2.15 (br dd, J = 2.6, 13.2 Hz, 2H), 2.00-1.83 (m, 2H), 1.49 (d, J = 2.6 Hz, 18H); LCMS (ESI) [M-100+H]+: 425.2.



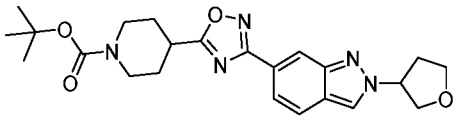
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.93-7.85 (m, 1H), 7.07 (dd, J = 11.5, 18.0 Hz, 1H), 6.09 (d, J = 18.1 Hz, 1H), 5.63-5.46 (m, 1H), 5.05-4.85 (m, 1H), 4.16 (br s,

2H), 3.21 (ddd, J = 4.2, 6.9, 10.8 Hz, 1H), 3.02 (br t, J = 11.6 Hz, 2H), 2.16 (br d, J = 11.1 Hz, 2H), 2.00-1.88 (m, 2H), 1.63 (d, J = 6.7 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 438.5.



5

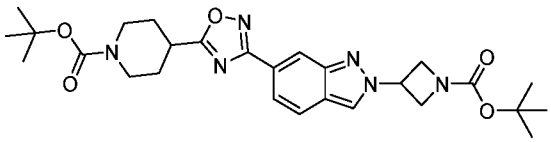
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.06 (s, 1H), 7.90-7.80 (m, 2H), 4.98 (spt, J = 6.6 Hz, 1H), 4.05 (br d, J = 2.9 Hz, 1H), 3.19-3.03 (m, 1H), 2.32-2.21 (m, 2H), 1.98 (qd, J = 4.5, 13.7 Hz, 2H), 1.91-1.77 (m, 4H), 1.64 (d, J = 6.6 Hz, 6H), 1.43 (d, J = 3.4 Hz, 1H); LCMS (ESI) [M+H]+: 327.1



10

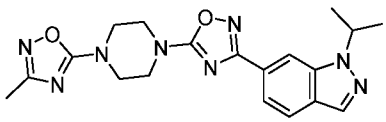
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (s, 1H), 8.07 (s, 1H), 7.80-7.76 (m, 1H), 7.75-7.72 (m, 1H), 5.36-5.26 (m, 1H), 4.32-4.08 (m, 5H), 4.06-3.99 (m, 1H), 3.24-3.14 (m, 1H), 3.03 (br t, J = 11.8 Hz, 2H), 2.69-2.58 (m, 1H), 2.54-2.44 (m, 1H), 2.15 (br d, J = 11.4 Hz, 2H), 1.99-1.87 (m, 2H), 1.49 (s, 9H); LCMS

15 (ESI) [M+H]+: 440.5.

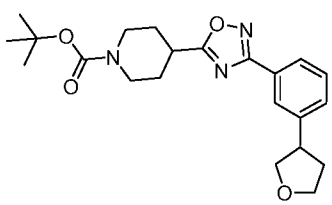


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.53 (d, J = 0.7 Hz, 1H), 8.10 (s, 1H), 7.82-7.77 (m, 1H), 7.76-7.71 (m, 1H), 5.35 (m, 1H), 4.55-4.45 (m, 4H), 4.21-4.04 (m, 2H), 3.25-3.12 (m, 1H), 3.02 (br t, J = 11.7

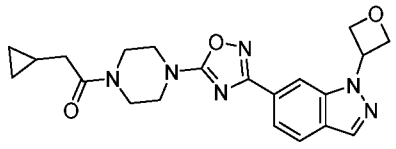
20 Hz, 2H), 2.14 (br dd, J = 2.9, 13.2 Hz, 2H), 2.00-1.83 (m, 2H), 1.48 (d, J = 1.5 Hz, 18H); LCMS (ESI) [M+23]+: 547.2,LCMS (ESI) [M-100+H]+: 425.2, LCMS (ESI) [M-100-55+H]+: 369.1.



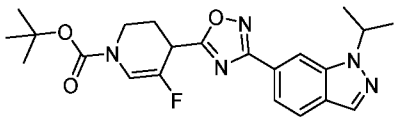
25 ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.07 (s, 1H), 7.79 (m, 2H), 5.04-4.88 (m, 1H), 3.85 (m, 8H), 2.28 (s, 3H), 1.64 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 395.1.



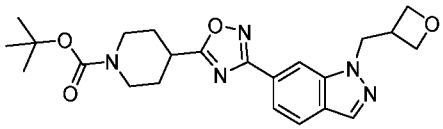
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.98-7.90 (m, 2H), 7.46-7.36 (m, 2H), 4.22-4.05 (m, 4H), 3.94 (q, J = 7.9 Hz, 1H), 3.80-3.73 (m, 1H), 3.48 (quin, J = 7.8 Hz, 1H), 3.17 (m, 1H), 2.99 (br t, J = 11.4 Hz, 2H), 2.41 (m, 1H), 2.18-1.99 (m, 3H), 1.97-1.83 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-100+H]+: 300.1.



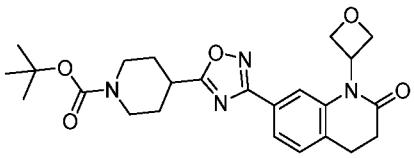
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (d, J = 3.4 Hz, 2H), 7.85-7.78 (m, 2H), 5.88 (quin, J = 7.1 Hz, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.14 (t, J = 7.3 Hz, 2H), 3.83-3.62 (m, 8H), 2.35 (d, J = 6.7 Hz, 2H), 1.12-1.02 (m, 1H), 0.65-0.58 (m, 2H),0.25-0.18 (m, 2H); LCMS (ESI) [M+H]+: 409.2.



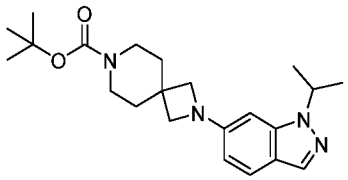
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.43 (s, 1H), 8.13 (s, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.68-7.34 (t,J = 59.6 Hz, 1H), 3.70 (m, 4H), 3.62-3.57 (m, 4H),1.50 (s, 9H); LCMS (ESI) [M-55]+: 365.1.



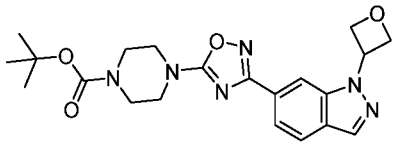
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.04 (d, J = 0.7 Hz, 1H), 7.91-7.86 (m, 1H), 7.84-7.80 (m, 1H), 4.85 (dd, J = 6.5, 7.5 Hz, 2H), 4.76 (d, J = 7.5 Hz, 2H), 4.62 (t, J = 6.1 Hz, 2H), 4.26-4.05 (m, 2H), 3.72-3.60 (m, 1H), 3.21 (tt, J = 3.9, 11.0 Hz, 1H), 3.02 (br t, J = 11.6 Hz, 1H), 3.08-2.96 (m, 1H), 2.16 (br dd, J = 2.4, 13.6 Hz, 2H), 2.01-1.87 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 440.2.



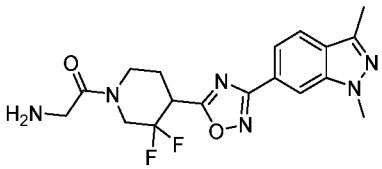
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.76 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.05 (s, 1H), 5.22-5.09 (m, 1H), 5.02 (t, J = 7.1 Hz, 2H), 4.70 (t, J = 7.3 Hz, 2H), 4.21-4.08 (m, 2H), 3.17 (tt, J = 3.8, 10.9 Hz, 1H), 3.06-2.94 (m, 4H), 2.62 (t, J = 7.2 Hz, 2H), 2.12 (br d, J = 11.0 Hz, 2H), 1.97-1.83 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 455.2.



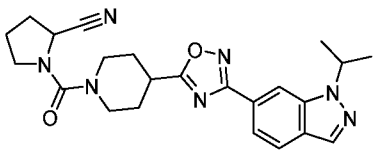
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.34 (s, 1H), 8.24 (s, 1H), 8.00-7.89 (m, 2H), 5.93 (quin, J = 6.9 Hz, 1H), 5.35 (t, J = 6.5 Hz, 2H), 5.20 (t, J = 7.2 Hz, 2H), 4.53-4.04 (m, 2H), 3.69-3.38 (m, 2H), 3.35-3.22 (m, 1H), 2.41-2.14 (m, 2H), 1.53 (s, 9H); LCMS (ESI) [M+H]+: 462.1.



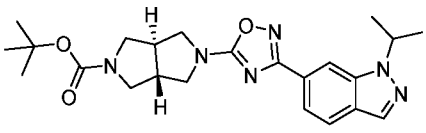
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (d, J = 4.4 Hz, 2H), 7.85-7.78 (m, 2H), 5.88(quin, J = 7.1 Hz, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.14 (t, J = 7.3 Hz, 2H), 3.75-3.67 (m, 4H), 3.63-3.57(m, 4H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 427.1.



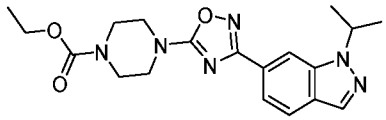
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.64 (br d, J = 8.1 Hz, 1H), 7.40-7.33 (m, 1H), 4.14 (br s, 2H), 3.18 (tt, J = 3.8, 10.9 Hz, 1H), 3.01 (br t, J = 11.6 Hz, 2H), 2.13 (br d, J = 10.9 Hz, 2H), 1.98-1.82 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-55]+: 352.0.



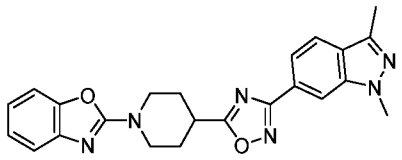
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.84 (q, J = 8.4 Hz, 1H), 7.90-7.80 (m, 1H), 4.98 (td, J = 6.7, 13.4 Hz, 1H), 4.86 (t, J = 6.8 Hz, 1H), 3.93 (br t, J = 12.8 Hz, 2H), 3.59-3.41 (m, 2H), 3.34-3.22 (m, 1H), 3.20-3.03 (m, 2H), 2.38-2.28 (m, 1H), 2.36-1.92 (m, 7H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 434.2.



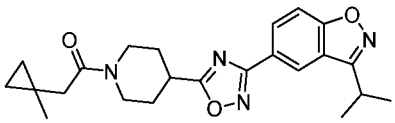
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.07 (s, 1H), 7.90-7.79 (m, 2H), 4.98 (td, J = 6.7, 13.3 Hz, 1H), 3.68 (br d, J = 13.4 Hz, 2H), 3.50 (t, J = 6.6 Hz, 2H), 3.19 (tt, J = 4.0, 11.1 Hz, 1H), 2.99-2.82 (m, 2H), 2.26-2.13 (m, 2H), 2.06-1.94 (m, 2H), 1.91-1.82 (m, 2H), 1.80-1.74 (m, 2H), 1.64 (d, J = 6.7 Hz, 6H), 1.46 (s, 6H); LCMS (ESI) [M+H]+: 437.2.



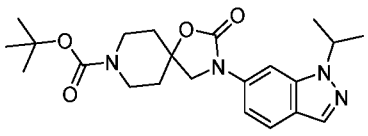
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.05 (s, 1H), 7.78 (s, 2H), 4.96 (td, J = 6.6, 13.3 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.79-3.61 (m, 8H), 1.63 (d, J = 6.7 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H); LCMS (ESI) [M+H]+: 385.1.



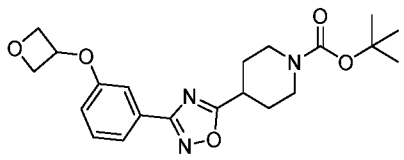
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.05 (s, 1H), 7.78 (s, 2H), 4.95 (td, J = 6.6, 13.3 Hz, 1H), 3.92-3.68 (m, 8H), 3.18 (s, 2H), 2.31 (s, 6H), 1.63 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 398.2.



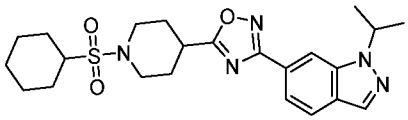
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.45 (s, 1H), 8.28 (dd, J = 1.4, 8.7 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 4.60 (br d, J = 13.3 Hz, 1H), 3.97 (br d, J = 13.6 Hz, 1H), 3.48 (td, J = 6.9, 14.0 Hz, 1H), 3.37-3.22 (m, 2H), 2.97 (br t, J = 11.1 Hz, 1H), 2.40 (d, J = 4.0 Hz, 2H), 2.22 (br d, J = 12.6 Hz, 2H), 2.04-1.86 (m, 2H), 1.55 (s, 6H), 1.18 (s, 3H), 0.49-0.40 (m, 4H); LCMS (ESI) [M+H]+: 409.2.



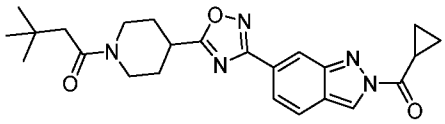
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.20 (s, 1H), 8.24 (s, 1H), 8.09 (m, J = 8.2 Hz, 1H), 7.85 (br d, J = 8.2 Hz, 1H), 4.58 (br d, J = 14.1 Hz, 1H), 4.03 (br d, J = 13.7 Hz, 1H), 3.28 (br d, J = 11.7 Hz, 3H), 2.98 (br t, J = 11.8 Hz, 1H), 2.32 (s, 2H), 2.21 (br d, J = 12.6 Hz, 2H), 2.05-1.80 (m, 2H), 1.37 (m, 2H), 1.18 (m, J = 4.0 Hz, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 436.20.



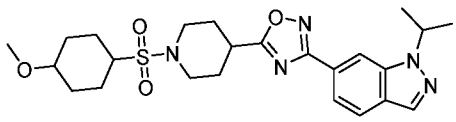
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.71 (d, J = 7.7 Hz, 1H), 7.43-7.35 (m, 2H), 6.89 (dd, J = 2.5, 8.3 Hz, 1H), 5.32-5.26 (m, 1H), 5.02 (t, J = 6.8 Hz, 2H), 4.79 (dd, J = 5.3, 7.2 Hz, 2H), 4.13 (br d, J = 9.9 Hz, 2H), 3.17 (tt, J = 3.9, 10.9 Hz, 1H), 3.00 (br t, J = 11.8 Hz, 2H), 2.12 (br dd, J = 2.8, 13.3 Hz, 2H), 1.94-1.83 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-55]+: 346.1.



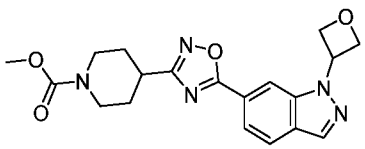
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 8.04 (s, 1H), 7.79 (s, 2H), 5.01-4.90 (m, 1H), 4.24 (br s, 2H),3.12-3.04 (m, 1H), 2.99-2.88 (m, 2H), 2.15-2.06 (m, 2H), 1.89-1.80 (m, 2H), 1.61 (d, J = 6.6 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 411.2.



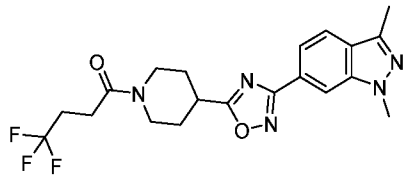
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.79 (s, 1H), 8.54 (s, 1H), 7.79 (m, 2H), 4.60 (m, J = 13.0 Hz, 1H), 4.04 (m, J = 13.5 Hz, 1H), 3.47 (s, 1H), 3.39-3.22 (m, 2H), 3.00 (t, J = 11.7 Hz, 1H), 2.33 (m, 2H), 2.22 (m, J = 13.5 Hz, 2H), 2.07-1.82 (m, 2H), 1.44 (m, 2H), 1.32 (m, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 436.2.



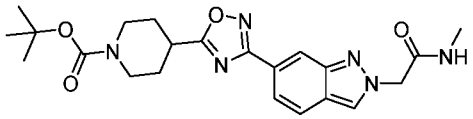
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 8.01-7.82 (m, 2H), 5.91 (quin, J = 7.0 Hz, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.19 (t, J = 7.2 Hz, 2H), 4.27 (m, 1H), 4.16-3.98 (m, 2H), 3.18-2.93 (m, 3H), 2.08 (m, 2H), 1.90 (m, 2H), 0.78-0.65 (m, 4H); LCMS (ESI) [M+H]+: 410.1.



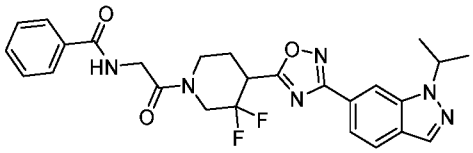
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.98-7.86 (m, 2H), 5.97-5.81 (m, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.18 (t, J = 7.2 Hz, 2H), 4.21 (m, 2H), 3.74 (s, 3H), 3.20-2.92 (m, 3H), 2.11 (m, J = 11.8 Hz, 2H), 1.96-1.79 (m, 2H); LCMS (ESI) [M+H]+: 384.1.



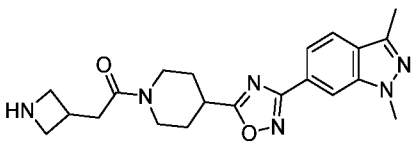
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.97 (s, 1H), 7.73-7.66 (m, 2H), 4.94-4.78 (m, 1H), 4.19 (br s, 2H), 3.66 (s, 3H), 3.09-2.86 (m, 3H), 2.06 (br d, J = 10.9 Hz, 2H), 1.87-1.71 (m, 2H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 369.1.



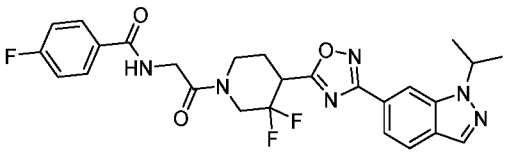
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.54 (s, 1H), 8.08 (s, 1H), 7.91-7.71 (m, 2H), 6.65 (br s, 1H), 5.15 (s, 2H), 4.25-4.07 (m, 2H), 3.22 (br t, J = 10.8 Hz, 1H), 3.12-2.97 (m, 2H), 2.83 (d, J = 4.9 Hz, 3H), 2.17 (br d, J = 11.1 Hz, 2H), 2.04-1.87 (m, 2H), 1.51 (s, 9H); LCMS (ESI) [M+H]+: 441.2.



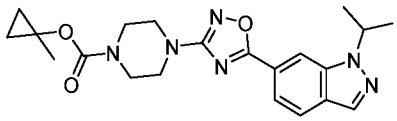
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 7.94 (s, 1H), 7.73-7.62 (m, 2H), 7.37-7.25 (m, 5H), 4.84-4.64 (m, 2H), 3.87-3.67 (m, 1H), 3.16-2.88 (m, 3H), 2.12-1.74 (m, 4H), 1.47 (br d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 415.2.



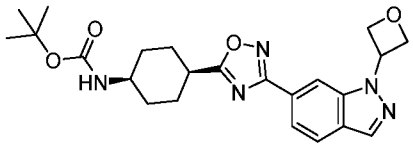
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.56 (br s, 1H), 8.02 (s, 1H), 7.77-7.72 (m, 1H), 7.68-7.63 (m, 1H), 4.38 (br d, J = 13.4 Hz, 1H), 4.20-4.07 (m, 2H), 4.01 (s, 3H), 3.85 (br d, J = 14.4 Hz, 1H), 3.66 (br s, 2H), 3.30-3.10 (m, 3H), 2.93 (br t, J = 10.5 Hz, 1H), 2.84-2.73 (m, 2H), 2.52 (s, 3H), 2.21-2.08 (m, 2H), 1.96-1.81 (m, 2H); LCMS (ESI) [M+H]+: 395.2.



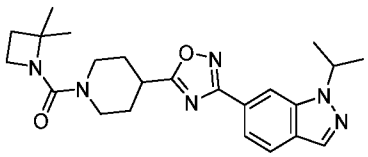
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.35 (s, 1H), 8.21 (s, 1H), 7.98-7.90 (m, 1H), 7.89-7.81 (m, 1H), 5.99-5.86 (m, 1H), 5.35 (t, J = 6.6 Hz, 2H), 5.24-5.12 (m, 2H); LCMS (ESI) [M+H]+: 219.0.



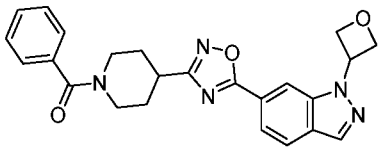
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.08 (s, 1H), 7.82 (m, 2H), 5.08-4.88 (m, 1H), 3.55 (m, 8H), 1.63 (d, J = 6.6 Hz, 6H), 1.57 (s, 3H), 0.96-0.85 (m, 2H), 0.68-0.60 (m, 2H); LCMS (ESI) [M+H]+: 411.1.



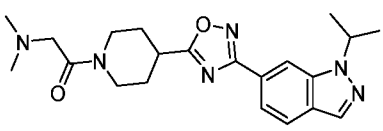
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (d, J = 0.9 Hz, 1H), 8.18 (s, 1H), 7.94-7.90 (m, 1H), 7.87-7.84 (m, 1H), 5.92 (quin, J = 7.1 Hz, 1H), 5.35 (t, J = 6.7 Hz, 2H), 5.17 (t, J = 7.4 Hz, 2H), 4.61 (br s, 1H), 3.76 (br s, 1H), 3.26-3.16 (m, 1H), 2.21-2.10 (m, 2H), 2.06-1.96 (m, 2H), 1.92-1.81 (m, 2H), 1.77-1.66 (m, 2H), 1.46 (s, 9H); LCMS (ESI) [M+H]+: 440.2.



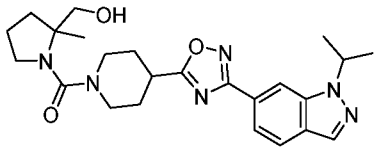
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.06 (s, 1H), 7.88-7.80 (m, 2H), 4.97 (quin, J = 6.6 Hz, 1H), 3.99-3.90 (m, 4H), 3.22 (tt, J = 3.9, 10.9 Hz, 1H), 3.01-2.92 (m, 2H), 2.16 (br dd, J = 3.2, 13.4 Hz, 2H), 2.05-1.95 (m, 4H), 1.64 (d, J = 6.6 Hz, 6H), 1.53 (s, 6H); LCMS (ESI) [M+H]+: 423.2.



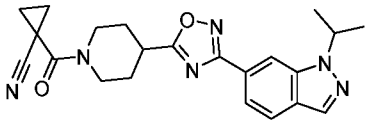
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.37 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.50-7.39 (m, 5H), 6.28-6.15 (m, 1H), 5.08 (d, J = 6.8 Hz, 4H), 4.07 (br s, 2H), 3.32-3.15 (m, 3H), 2.11 (br d, J = 11.5 Hz, 2H), 1.89-1.74 (m, 2H); LCMS (ESI) [M+H]+: 430.1.



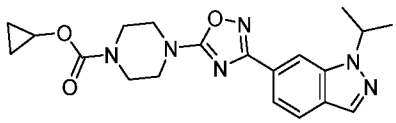
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.84 (q, J = 8.4 Hz, 2H), 4.97 (td, J = 6.5, 13.4 Hz, 1H), 4.54 (br d, J = 12.7 Hz, 1H), 4.22 (br d, J = 13.8 Hz, 1H), 3.31 (br t, J = 10.5 Hz, 2H), 3.25-3.10 (m, 2H), 3.01 (br t, J = 11.0 Hz, 1H), 2.33 (s, 6H), 2.23 (br d, J = 13.6 Hz, 2H), 2.07-1.89 (m, 2H), 1.64 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 397.1.



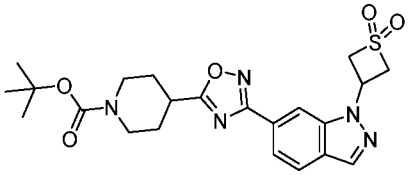
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.06 (s, 1H), 7.89-7.78 (m, 2H), 5.66 (dd, J = 1.7, 9.5 Hz, 1H), 4.97 (td, J = 6.6, 13.3 Hz, 1H), 3.80-3.67 (m, 3H), 3.63-3.45 (m, 3H), 3.23 (tt, J = 4.1, 10.9 Hz, 1H), 3.07-2.90 (m, 2H), 2.22 (br t, J = 10.7 Hz, 2H), 2.13-1.91 (m, 2H), 1.90-1.73 (m, 4H), 1.63 (d, J = 6.6 Hz, 6H), 1.43 (s, 3H); LCMS (ESI) [M+H]+: 453.2.



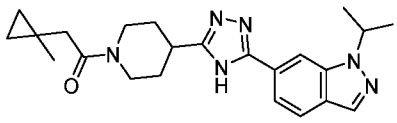
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.15 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 5.11 (td, J = 6.7, 13.1 Hz, 1H), 4.26 (br d, J = 13.9 Hz, 2H), 3.62-3.47 (m, 1H), 3.39-3.26 (m, 2H), 2.29-2.20 (m, 2H), 1.89 (q, J = 10.4 Hz, 2H), 1.62-1.56 (m, 2H), 1.53 (m, 8H); LCMS (ESI) [M+H]+: 405.1.



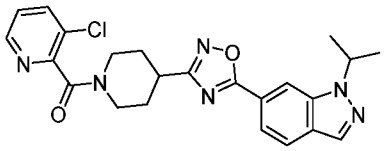
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.05 (s, 1H), 7.78 (d, J = 0.7 Hz, 2H), 4.95 (td, J = 6.7, 13.3 Hz, 1H), 4.21-4.05 (m, 1H), 3.80-3.52 (m, 8H), 1.62 (d, J = 6.6 Hz, 6H), 0.79-0.67 (m, 4H); LCMS (ESI) [M+H]+: 397.1.



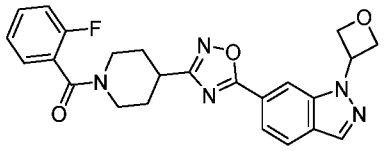
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (d, J = 4.5 Hz, 2H), 7.91-7.85 (m, 1H), 7.81-7.77 (m, 1H), 5.53-5.42 (m, 1H), 4.93-4.83 (m, 2H), 4.66-4.56 (m, 2H), 4.08 (br s, 2H), 3.14 (tt, J = 3.8, 10.9 Hz, 1H), 2.95 (br t, J = 11.6 Hz, 2H), 2.14-2.03 (m, 2H), 1.93-1.80 (m, 2H), 1.42 (s, 9H); LCMS (ESI) [M+H]+: 418.1.



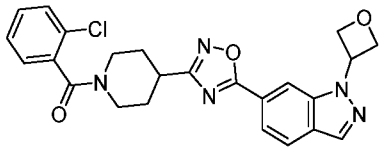
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.05 (s, 1H), 7.87-7.76 (m, 2H), 4.96 (td, J = 6.6, 13.2 Hz, 1H), 4.76 (br d, J = 13.3 Hz, 1H), 4.03 (br d, J = 13.6 Hz, 1H), 3.30-3.13 (m, 2H), 2.85 (br t, J = 11.7 Hz, 1H), 2.51-2.35 (m, 2H), 2.28-2.10 (m, 2H), 2.02-1.84 (m, 2H), 1.61 (d, J = 6.6 Hz, 6H), 1.19 (s, 2H), 1.20-1.17 (m, 1H), 0.50-0.38 (m, 4H); LCMS (ESI) [M+H]+: 407.2.



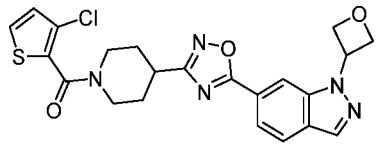
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.55 (dd, J = 1.0, 4.7 Hz, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 7.86 (s, 2H), 7.78 (dd, J = 1.0, 8.2 Hz, 1H), 7.32 (dd, J = 4.6, 8.2 Hz, 1H), 4.99 (td, J = 6.7, 13.3 Hz, 1H), 4.78-4.71 (m, 1H), 3.55-3.46 (m, 1H), 3.30-3.14 (m, 3H), 2.28 (br dd, J = 3.5, 13.6 Hz, 1H), 2.14-2.02 (m, 3H), 1.65 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 451.1.



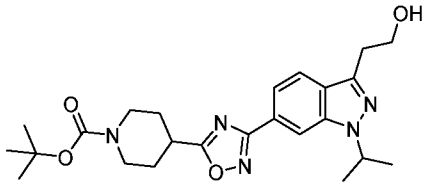
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.41 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.84 (dd, J = 1.2, 8.5 Hz, 1H), 7.55-7.47 (m, 1H), 7.44 (br t, J = 6.7 Hz, 1H), 7.35-7.27 (m, 2H), 6.29 (quin, J = 6.9 Hz, 1H), 5.04 (d, J = 7.1 Hz, 4H), 4.53 (br d, J = 13.2 Hz, 1H), 3.49 (br d, J = 13.7 Hz, 1H), 3.31-3.23 (m, 2H), 3.15-3.06 (m, 1H), 2.16 (br d, J = 11.5 Hz, 1H), 2.02 (br d, J = 12.1 Hz, 1H), 1.82-1.65 (m, 2H); LCMS (ESI) [M+H]+: 448.1.



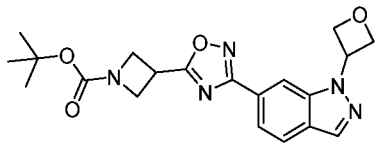
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.42 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.55 (br d, J = 6.8 Hz, 1H), 7.49-7.36 (m, 3H), 6.34-6.23 (m, 1H), 5.04 (d, J = 6.8 Hz, 4H), 4.54 (br d, J = 12.1 Hz, 1H), 3.37 (br d, J = 2.4 Hz, 1H), 3.32-3.16 (m, 2H), 3.16-3.05 (m, 1H), 2.20-2.09 (m, 1H), 2.07-1.95 (m, 1H), 1.85-1.72 (m, 2H), 1.72-1.61 (m, 1H); LCMS (ESI) [M+H]+: 464.1.



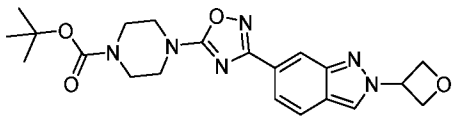
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.37 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 5.3 Hz, 1H), 7.10 (d, J = 5.3 Hz, 1H), 6.21 (m, 1H), 5.08 (d, J = 6.8 Hz, 4H), 4.15-3.95 (m, 2H), 3.35-3.23 (m, 3H), 2.14 (br dd, J = 3.2, 13.3 Hz, 2H), 1.89-1.75 (m, 2H); LCMS (ESI) [M+H]+: 470.0.



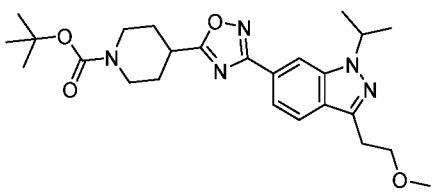
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17 (s, 1H), 7.90-7.81 (m, 1H), 7.79-7.67 (m, 1H), 4.91 (td, J = 6.6, 13.3 Hz, 1H), 4.16 (br s, 2H), 4.09 (q, J = 5.9 Hz, 2H), 3.28-3.18 (m, 3H), 3.11 (t, J = 6.3 Hz, 1H), 3.02 (br t, J = 11.7 Hz, 2H), 2.16 (br d, J = 11.5 Hz, 2H), 2.02-1.87 (m, 2H), 1.60 (d, J = 6.6 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 456.2.



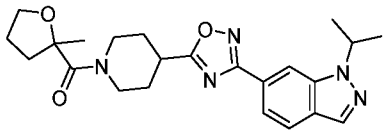
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.17 (s, 1H), 7.94-7.89 (m, 1H), 7.88-7.82 (m, 1H), 5.96-5.85 (m, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.17 (t, J = 7.3 Hz, 2H), 4.47-4.32 (m, 4H), 4.14-4.04 (m, 1H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 398.1.



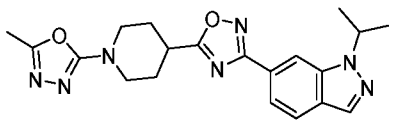
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.46 (d, J = 0.9 Hz, 1H), 8.18-8.11 (m, 1H), 7.72 (m, 2H), 5.79-5.71 (m, 1H), 5.25-5.16 (m, 4H), 3.72-3.67 (m, 4H), 3.62-3.56 (m, 4H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 427.1.



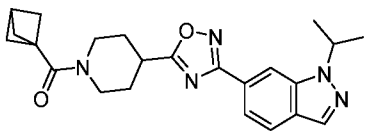
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 7.81 (s, 2H), 4.90 (quin, J = 6.7 Hz, 1H), 4.15 (br s, 2H), 3.88-3.75 (m, 2H), 3.40 (s, 3H), 3.29 (t, J = 7.1 Hz, 2H), 3.24-3.14 (m, 1H), 3.02 (br t, J = 11.1 Hz, 2H), 2.15 (br d, J = 13.3 Hz, 2H), 2.01-1.88 (m, 2H), 1.63-1.57 (m, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 470.2.



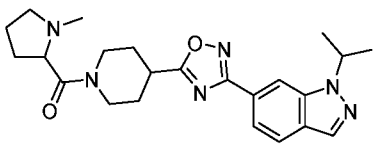
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.15 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 5.11 (td, J = 6.6, 13.2 Hz, 1H), 4.56-4.37 (m, 2H), 3.97-3.85 (m, 1H), 3.75 (q, J = 7.4 Hz, 1H), 3.53-3.41 (m, 1H), 3.24-3.11 (m, 2H), 2.72-2.63 (m, 1H), 2.16 (br s, 2H), 1.91-1.71 (m, 4H), 1.64-1.56 (m, 1H), 1.53 (d, J = 6.6 Hz, 6H), 1.42 (s, 3H); LCMS (ESI) [M+H]+: 424.2.



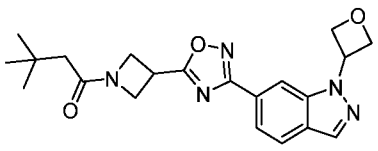
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.06 (s, 1H), 7.90-7.78 (m, 2H), 4.97 (td, J = 6.7, 13.3 Hz, 1H), 4.06 (td, J = 3.8, 13.4 Hz, 2H), 3.36-3.22 (m, 3H), 2.42 (s, 3H), 2.29 (br dd, J = 3.4, 13.7 Hz, 2H), 2.20-2.05 (m, 2H), 1.65-1.62 (m, 6H); LCMS (ESI) [M+H]+: 394.1.



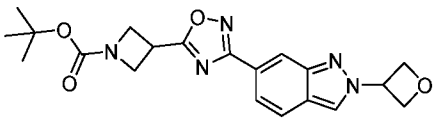
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.89-7.78 (m, 2H), 5.03-4.90 (m, 1H), 4.51 (br d, J = 13.2 Hz, 1H), 4.27 (br d, J = 13.4 Hz, 1H), 3.40-3.24 (m, 2H), 3.03-2.90 (m, 1H), 2.53 (s, 1H), 2.27-2.15 (m, 8H), 2.03-1.89 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 406.1.



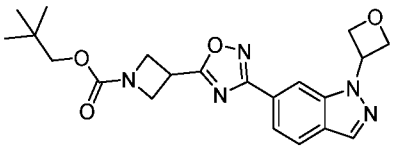
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.92-7.77 (m, 2H), 4.97 (td, J = 6.6, 13.2 Hz, 1H), 4.74-4.49 (m, 1H), 4.40-4.16 (m, 1H), 3.31 (br s, 2H), 3.23-2.91 (m, 3H), 2.38 (s, 3H), 2.30-2.13 (m, 4H), 2.04-1.76 (m, 5H), 1.64 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 423.2.



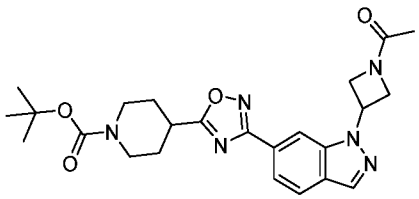
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (d, J = 0.7 Hz, 1H), 8.17 (s, 1H), 7.94-7.82 (m, 2H), 5.95-5.83 (m, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.17 (t, J = 7.3 Hz, 2H), 4.66-4.36 (m, 4H), 4.18-4.07 (m, 1H), 2.05 (s, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 369.2.



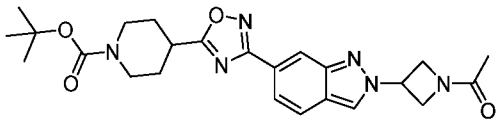
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.56 (s, 1H), 8.17 (s, 1H), 7.84-7.73 (m, 2H), 5.76 (m, 1H), 5.28-5.14 (m, 4H), 4.45-4.30 (m, 4H), 4.14-4.03 (m, 1H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 398.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (d, J = 0.7 Hz, 1H), 8.17 (s, 1H), 7.94-7.90 (m, 1H), 7.88-7.83 (m, 1H), 5.96-5.85 (m, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.21-5.11 (t, J = 7.3 Hz, 2H), 4.53-4.40 (m, 4H), 4.15 (m, 1H), 3.80 (s, 2H), 0.96 (s, 9H); LCMS (ESI) [M+H]+: 412.2.

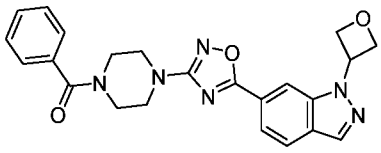


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.53 (s, 1H), 8.07 (s, 1H), 7.82-7.77 (m, 1H), 7.77-7.71 (m, 1H), 5.40 (m, 1H), 4.79 (dd, J = 5.3, 8.8 Hz, 1H), 4.73-4.65 (m, 1H), 4.63-4.55 (m, 2H), 4.13 (br d, J = 8.2 Hz, 2H), 3.25-3.13 (m, 1H), 3.02 (br t, J = 11.5 Hz, 2H), 2.14 (br d, J = 11.2 Hz, 2H), 1.99 (s, 3H), 1.97-1.85 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-100+H]+: 367.1.



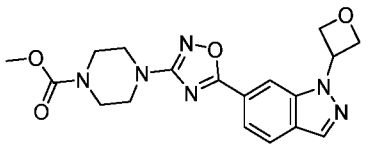
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.16 (s, 2H), 7.95-7.89 (m, 1H), 7.87-7.82 (m, 1H), 5.54 (m, 1H), 4.80 (dd, J = 5.4, 8.7 Hz, 1H), 4.72-4.63 (m, 1H), 4.62-4.51 (m, 2H), 4.23-4.07 (m, 2H), 3.26-3.14 (m, 1H),

3.02 (br t, J = 11.5 Hz, 2H), 2.15 (m, 2H), 1.99 (s, 3H), 1.98-1.86 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-100+H]+: 367.1.



5

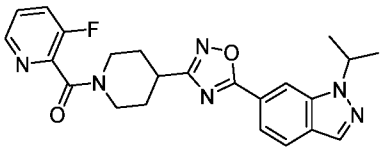
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.20 (s, 1H), 7.88 (m, 2H), 7.46 (s, 5H), 5.90 (quin, J = 6.9 Hz, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.18 (t, J = 7.3 Hz, 2H), 3.61 (m, 8H); LCMS (ESI) [M+H]+: 431.1.



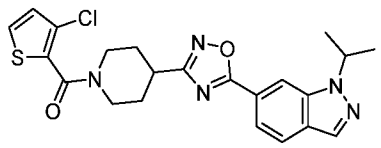
10

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.19 (s, 1H), 7.94-7.82 (m, 2H), 5.90 (quin, J = 7.0 Hz, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.18 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.69-3.41 (m, 8H); LCMS (ESI) [M+H]+: 385.1.

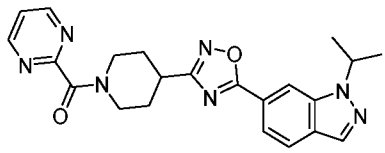
15



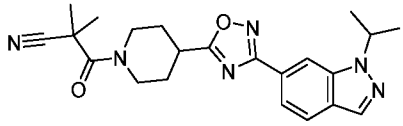
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.49 (d, J = 4.6 Hz, 1H), 8.29 (s, 1H), 8.10 (s, 1H), 7.87 (s, 2H), 7.55-7.49 (m, 1H), 7.40 (td, J = 4.4, 8.6 Hz, 1H), 4.99 (spt, J = 6.7 Hz, 1H), 4.78-4.68 (m, 1H), 3.67 (br d,
20 J = 13.8 Hz, 1H), 3.32-3.17 (m, 3H), 2.27 (br dd, J = 3.5, 13.6 Hz, 1H), 2.15-2.01 (m, 3H), 1.65 (d, J = 6.7 Hz, 6H); LCMS (ESI) [M+H]+: 435.2.



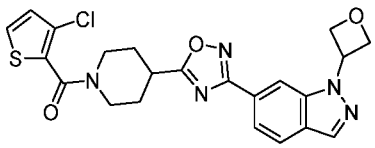
25 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.19 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.81-7.75 (m, 2H), 7.08 (d, J = 5.3 Hz, 1H), 5.22-5.10 (m, 1H), 4.02 (br s, 2H), 3.33-3.20 (m, 3H), 2.13 (m, 2H), 1.86-1.75 (m, 2H), 1.52 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 456.1.



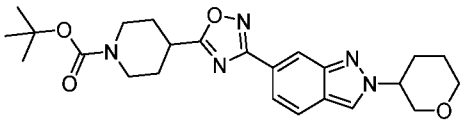
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.85 (d, J = 5.0 Hz, 2H), 8.30 (s, 1H), 8.09 (s, 1H), 7.86 (d, J = 0.9 Hz, 2H), 7.37 (t, J = 5.0 Hz, 1H), 4.99 (spt, J = 6.6 Hz, 1H), 4.78-4.68 (m, 1H), 3.73-3.65 (m, 1H), 3.33-3.17 (m, 3H), 2.29-2.21 (m, 1H), 2.16-2.04 (m, 3H), 1.65 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 418.2.



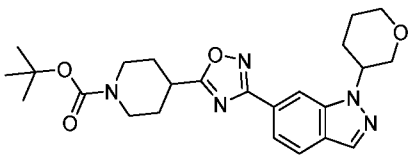
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 5.12 (quin, J = 6.6 Hz, 1H), 4.31 (br d, J = 14.1 Hz, 2H), 3.62-3.49 (m, 1H), 3.33 (br t, J = 12.1 Hz, 2H), 2.25 (br d, J = 10.4 Hz, 2H), 1.98-1.82 (m, 2H), 1.59 (s, 6H), 1.54 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 407.1.



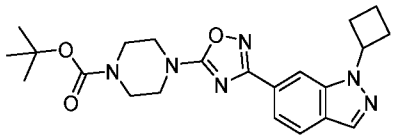
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.18 (s, 1H), 7.94-7.89 (m, 1H), 7.88-7.83 (m, 1H), 7.41 (d, J = 5.3 Hz, 1H), 6.95 (d, J = 5.3 Hz, 1H), 5.90 (quin, J = 7.1 Hz, 1H), 5.34 (t, J = 6.5 Hz, 2H), 5.20-5.14 (m, 2H), 4.77-3.73 (m, 2H), 3.50-3.16 (m, 3H), 2.28 (br d, J = 11.6 Hz, 2H), 2.18-2.03 (m, 2H); LCMS (ESI) [M+H]+: 470.1.



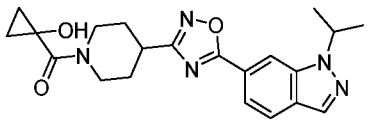
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (s, 1H), 8.14 (s, 1H), 7.79-7.73 (m, 2H), 4.69-4.61 (m, 1H), 4.23 (dd, J = 4.0, 11.4 Hz, 1H), 4.14 (br d, J = 6.2 Hz, 2H), 4.03-3.91 (m, 2H), 3.72-3.63 (m, 1H), 3.19 (tt, J = 3.9, 10.8 Hz, 1H), 3.03 (br t, J = 11.4 Hz, 2H), 2.41-2.32 (m, 2H), 2.15 (br d, J = 10.3 Hz, 2H), 1.98-1.79 (m, 4H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 454.2.



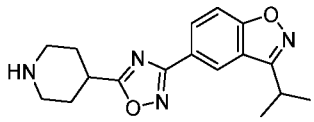
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.06 (s, 1H), 7.91-7.86 (m, 1H), 7.84-7.79 (m, 1H), 4.79-4.68 (m, 1H), 4.24-4.02 (m, 4H), 3.85 (t, J = 10.7 Hz, 1H), 3.60-3.50 (m, 1H), 3.22 (tt, J = 3.9, 10.9 Hz, 1H), 3.03 (br t, J = 11.6 Hz, 2H), 2.48-2.35 (m, 1H), 2.27 (br d, J = 12.5 Hz, 1H), 2.17 (br d, J = 10.6 Hz, 2H), 2.02-1.89 (m, 4H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 454.2.



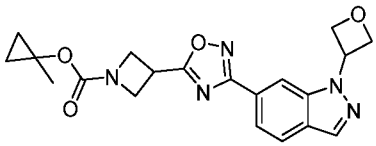
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11 (d, J = 0.9 Hz, 1H), 8.06 (s, 1H), 7.79-7.74 (m, 2H), 5.16 (quin, J = 8.3 Hz, 1H), 3.77-3.65 (m, 4H), 3.63-3.53 (m, 4H), 2.89-2.75 (m, 2H), 2.61-2.50 (m, 2H), 2.06-1.86 (m, 2H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 425.2.



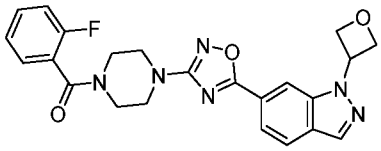
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (br d, J = 2.6 Hz, 1H), 8.10 (br d, J = 3.4 Hz, 1H), 7.86 (br d, J = 4.2 Hz, 2H), 5.06-4.91 (m, 1H), 4.60 (br d, J = 12.2 Hz, 2H), 3.36-3.03 (m, 3H), 2.27-2.13 (m, 2H), 2.05-1.90 (m, 2H), 1.70-1.62 (m, 6H), 1.17-1.08 (m, 2H), 0.99 (br s, 2H); LCMS (ESI) [M+H]+: 396.2.



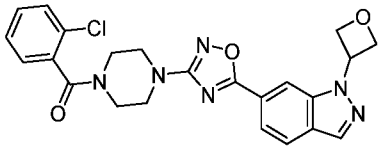
^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.53 (s, 1H), 8.35-8.27 (m, 1H), 7.75 (d, J = 8.8 Hz, 1H), 3.60-3.45 (m, 4H), 3.30-3.21 (m, 2H), 2.47 (br dd, J = 3.2, 14.4 Hz, 2H), 2.25-2.11 (m, 2H), 1.51 (d, J = 7.1 Hz, 6H; LCMS (ESI) [M+H]+: 313.1.



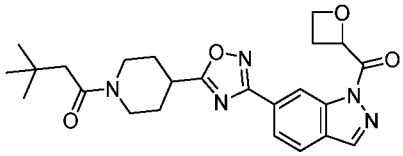
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.17 (s, 1H), 7.94-7.89 (m, 1H), 7.88-7.83 (m, 1H), 5.90 (quin, J = 7.0 Hz, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.17 (t, J = 7.3 Hz, 2H), 4.50-4.31 (m, 4H), 4.18-4.03 (m, 1H), 1.57 (s, 3H), 0.96-0.85 (m, 2H), 0.68-0.61 (m, 2H); LCMS (ESI) [M+H]+: 396.1.



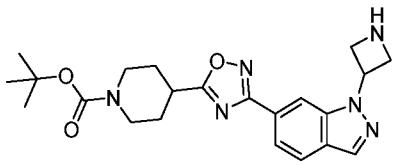
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, J = 0.9 Hz, 1H), 8.20 (s, 1H), 7.88 (m, J = 0.9 Hz, 2H), 7.50-7.40 (m, 2H), 7.28 (d, J = 0.9 Hz, 0.3H), 7.26-7.22 (m, 0.7H), 7.14 (t, J = 9.2 Hz, 1H), 5.96-5.81 (m, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.18 (t, J = 7.5 Hz, 2H), 3.98 (br s, 2H), 3.71 (br t, J = 4.8 Hz, 2H), 3.62-3.41 (m, 4H); LCMS (ESI) [M+H]+: 449.1.



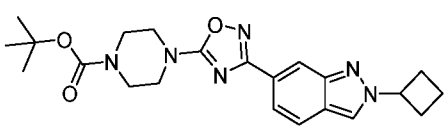
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.20 (s, 1H), 7.88 (m, 2H), 7.48-7.42 (m, 1H), 7.41-7.31 (m, 3H), 5.89 (quin, J = 7.0 Hz, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.23-5.14 (m, 2H), 4.13-4.02 (m, 1H), 3.98-3.85 (m, 1H), 3.78-3.69 (m, 2H), 3.68-3.57 (m, 1H), 3.57-3.41 (m, 2H), 3.40-3.32 (m, 1H); LCMS (ESI) [M+H]+: 465.1.



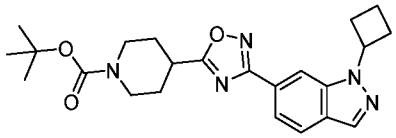
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.23 (s, 1H), 8.19 (d, J = 0.9 Hz, 1H), 8.13 (dd, J = 1.3, 8.3 Hz, 1H), 7.86 (dd, J = 0.7, 8.3 Hz, 1H), 6.22 (dd, J = 6.8, 9.0 Hz, 1H), 4.93-4.76 (m, 2H), 4.57 (br d, J = 13.2 Hz, 1H), 4.05 (br d, J = 12.2 Hz, 1H), 3.41-3.19 (m, 3H), 3.10-2.87 (m, 2H), 2.35 (s, 2H), 2.24 (br dd, J = 3.5, 13.4 Hz, 2H), 2.03 (m, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 452.2.



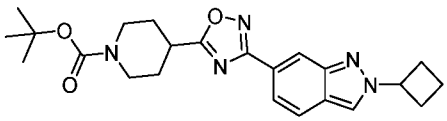
^{1}H NMR (400 MHz, METHANOL-d$_4$) δ 8.54 (br d, J = 4.3 Hz, 1H), 8.36 (s, 1H), 8.33 (s, 1H), 7.97-7.89 (m, 2H), 5.98 (quin, J = 7.2 Hz, 1H), 4.72-4.57 (m, 4H), 4.14 (m, 2H), 3.42-3.34 (m, 1H), 3.20-3.01 (m, 2H), 2.19 (m, 2H), 1.94-1.79 (m, 2H), 1.56-1.46 (s, 9H); LCMS (ESI) [M+H]+: 425.2.



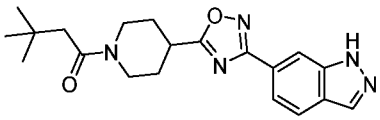
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.43 (d, J = 1.0 Hz, 1H), 7.98 (s, 1H), 7.68 (d, J = 0.9 Hz, 2H), 5.07 (quin, J = 8.4 Hz, 1H), 3.71-3.64 (m, 4H), 3.62-3.54 (m, 4H), 2.83-2.67 (m, 2H), 2.66-2.51 (m, 2H), 2.06-1.89 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 425.2.



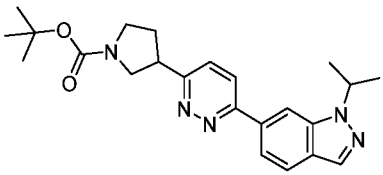
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 8.07 (s, 1H), 7.88-7.74 (m, 2H), 5.17 (quin, J = 8.3 Hz, 1H), 4.15 (br s, 2H), 3.20 (tt, J = 3.9, 11.0 Hz, 1H), 3.01 (br t, J = 12.0 Hz, 2H), 2.91-2.76 (m, 2H), 2.63-2.50 (m, 2H), 2.15 (br d, J = 10.8 Hz, 2H), 2.06-1.84 (m, 4H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 424.2.



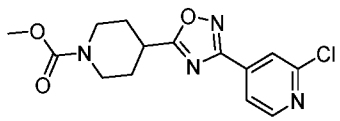
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.52 (d, J = 1.1 Hz, 1H), 8.00 (s, 1H), 7.77-7.70 (m, 2H), 5.08 (quin, J = 8.3 Hz, 1H), 4.20-4.07 (m, 2H), 3.21-3.12 (m, 1H), 3.02 (br t, J = 11.5 Hz, 2H), 2.82-2.58 (m, 4H), 2.14 (br d, J = 9.9 Hz, 2H), 2.06-1.85 (m, 4H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 424.2.



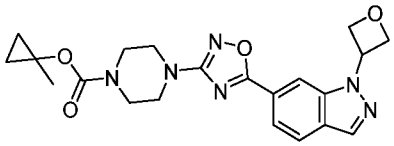
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 10.59 (br s, 1H), 8.29 (s, J = 0.9 Hz, 1H), 8.15 (s, J = 0.9 Hz, 1H), 7.89 (m, J = 1.0, 8.5 Hz, 2H), 4.62 (br d, J = 13.7 Hz, 1H), 4.04 (br d, J = 13.9 Hz, 1H), 3.45-3.20 (m, 2H), 2.99 (br t, J = 11.0 Hz, 1H), 2.33 (m, 2H), 2.22 (m, J = 13.5 Hz, 2H), 2.00-1.85 (m, 2H), 1.09 (s, 9H); LCMS (ESI) [M+H]+: 368.1.



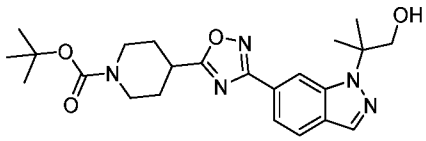
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.41 (br s, 1H), 8.07 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.71 (dd, J = 1.1, 8.6 Hz, 1H), 7.47 (br d, J = 8.8 Hz, 1H), 4.99 (spt, J = 6.7 Hz, 1H), 4.05-3.90 (m, 1H), 3.86-3.60 (m, 3H), 3.58-3.45 (m, 1H), 2.51-2.22 (m, 2H), 1.64 (d, J = 6.6 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 408.2.



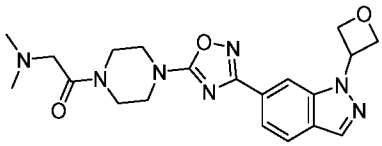
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.55 (d, J = 5.1 Hz, 1H), 8.00 (s, 1H), 7.88 (dd, J = 1.3, 5.1 Hz, 1H), 4.18 (br s, 2H), 3.73 (s, 3H), 3.23 (tt, J = 3.9, 10.9 Hz, 1H), 3.08 (br t, J = 11.7 Hz, 2H), 2.20-2.12 (m, 2H), 1.99-1.86 (m, 2H); LCMS (ESI) [M+H]+: 323.0.



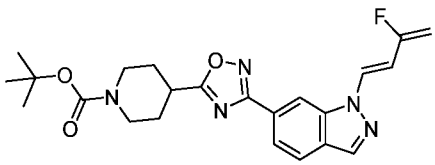
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, J = 0.7 Hz, 1H), 8.20 (s, 1H), 7.88 (m, 2H), 5.90 (quin, J = 7.0 Hz, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.22-5.11 (m, 2H), 3.56 (br s, 8H), 1.58 (s, 3H), 0.95-0.85 (m, 2H), 0.72-0.61 (m, 2H); LCMS (ESI) [M+H]+: 425.1.



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 0.9 Hz, 1H), 8.15 (d, J = 0.9 Hz, 1H), 7.97-7.88 (m, 1H), 7.73 (dd, J = 1.2, 8.4 Hz, 1H), 5.07 (t, J = 5.7 Hz, 1H), 3.98 (br d, J = 13.0 Hz, 2H), 3.81 (d, J = 5.7 Hz, 2H), 3.43-3.36 (m, 1H), 2.98 (br s, 2H), 2.11 (br dd, J = 2.9, 13.3 Hz, 2H), 1.79-1.63 (m, 8H), 1.42 (s, 9H); LCMS (ESI) [M+H]+: 442.1.

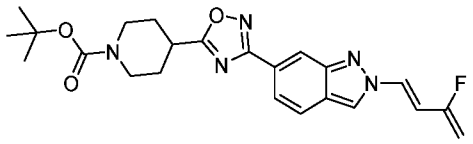


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.16-8.12 (m, 2H), 7.85-7.78 (m, 2H), 5.92-5.84 (m, 1H), 5.33 (t, J = 6.7 Hz, 2H), 5.14 (t, J = 7.3 Hz, 2H), 3.84-3.71 (m, 8H), 3.17 (s, 2H), 2.30 (s, 6H); LCMS (ESI) [M+H]+: 412.2.

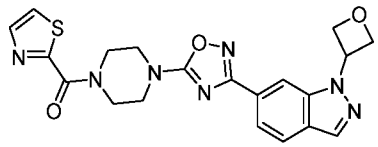


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.20 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 13.7 Hz, 1H), 6.85-6.73 (m, 1H), 4.78 (dd, J = 2.9, 17.0 Hz, 1H), 4.67-4.52 (m,

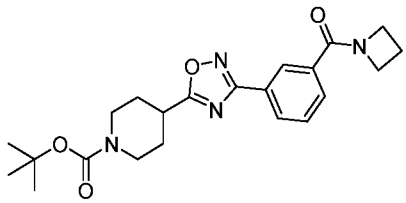
1H), 4.16 (br s, 2H), 3.21 (tt, J = 3.8, 10.9 Hz, 1H), 3.01 (br t, J = 11.4 Hz, 2H), 2.16 (br d, J = 11.2 Hz, 2H), 2.00-1.86 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 440.2.



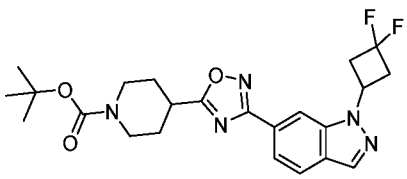
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.48 (s, 1H), 8.07 (s, 1H), 7.79-7.70 (m, 2H), 7.51 (d, J = 13.7 Hz, 1H), 7.14-7.02 (m, 1H), 4.92 (dd, J = 2.9, 16.3 Hz, 1H), 4.81-4.66 (d, J = 48 Hz, 1H), 4.13 (br s, 2H), 3.25-3.14 (m, 1H), 3.02 (br t, J = 11.7 Hz, 2H), 2.14 (br d, J = 11.0 Hz, 2H), 1.98-1.85 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-55]+: 384.1.



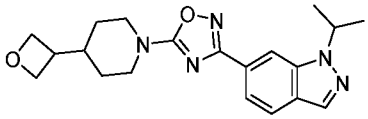
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (s, 2H), 7.93 (d, J = 3.2 Hz, 1H), 7.86-7.79 (m, 2H), 7.60 (d, J = 3.2 Hz, 1H), 5.93-5.84 (m, 1H), 5.33 (t, J = 6.6 Hz, 2H), 5.15 (t, J = 7.3 Hz, 2H), 4.66 (m, 2H), 3.98 (m, 2H), 3.87 (br t, J = 4.9 Hz, 4H); LCMS (ESI) [M+H]+: 438.1.



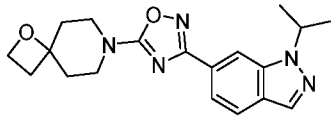
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (t, J = 1.5 Hz, 1H), 8.09 (td, J = 1.4, 7.8 Hz, 1H), 7.73 (td, J = 1.4, 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 4.34-4.14 (m, 4H), 4.05 (br d, J = 9.0 Hz, 2H), 3.14-3.06 (m, 1H), 2.94 (br t, J = 11.7 Hz, 2H), 2.35-2.23 (m, 2H), 2.05 (br dd, J = 3.2, 13.3 Hz, 2H), 1.88-1.74 (m, 2H), 1.41 (s, 9H); LCMS (ESI) [M-100+1]+: 313.1, LCMS (ESI) [M+23]+: 435.1.



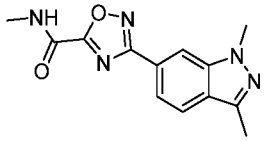
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17 (s, 1H), 8.11 (s, 1H), 7.92-7.88 (dd, J = 8.8, 1H), 7.85-7.81 (d, J = 8.8, 1H), 5.19-5.05 (m, 1H), 4.14 (m, 2H), 3.51-3.35 (m, 2H), 3.28-3.15 (m, 3H), 3.02 (br t, J = 11.6 Hz, 2H), 2.15 (br dd, J = 2.6, 13.4 Hz, 2H), 2.00-1.87 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-55]+: 404.1.



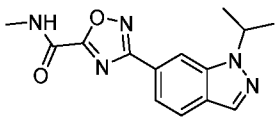
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.04 (s, 1H), 7.81-7.74 (m, 2H), 4.95 (td, J = 6.6, 13.4 Hz, 1H), 4.81 (dd, J = 6.2, 7.7 Hz, 2H), 4.51 (t, J = 6.3 Hz, 2H), 4.33 (br d, J = 13.2 Hz, 2H), 3.17 (dt, J = 2.6, 12.9 Hz, 2H), 2.86-2.74 (m, 1H), 2.03-1.91 (m, 1H), 1.77 (br d, J = 11.9 Hz, 2H), 1.62 (d, J = 6.6 Hz, 6H), 1.25 (dq, J = 4.4, 12.5 Hz, 2H); LCMS (ESI) [M+H]+: 368.2.



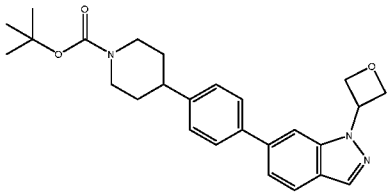
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 8.04 (s, 1H), 7.80-7.75 (m, 2H), 4.95 (quin, J = 6.7 Hz, 1H), 4.60 (t, J = 7.7 Hz, 2H), 3.85 (td, J = 4.9, 13.6 Hz, 2H), 3.68 (ddd, J = 3.3, 9.8, 13.3 Hz, 2H), 2.47 (t, J = 7.8 Hz, 2H), 2.13 (td, J = 4.2, 13.3 Hz, 2H), 1.92 (ddd, J = 4.4, 9.6, 13.6 Hz, 2H), 1.62 (d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 354.2.



^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (br s, 1H), 8.25 (s, 1H), 7.92 (br d, J = 8.3 Hz, 1H), 7.76 (br d, J = 8.3 Hz, 1H), 4.05 (s, 3H), 2.85 (br d, J = 3.5 Hz, 3H), 2.52 (br s, 3H); LCMS (ESI) [M+H]+: 272.1.

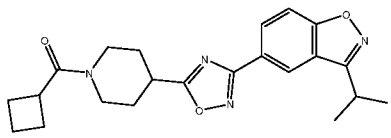


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.06 (s, 1H), 7.90-7.78 (m, 2H), 7.19 (br s, 1H), 5.03-4.87 (m, 1H), 3.21-3.06 (m, 3H), 1.63 (br d, J = 6.6 Hz, 6H); LCMS (ESI) [M+H]+: 286.1.

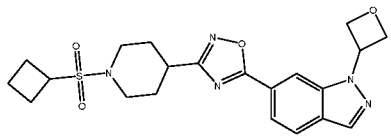


^{1}H NMR (300 MHz, Chloroform-d) δ 8.10 (d, J = 0.9 Hz, 1H), 7.80 (dd, J = 8.4, 0.8 Hz, 1H), 7.70 – 7.56 (m, 3H), 7.43 (dd, J = 8.4, 1.4 Hz, 1H), 7.38 – 7.28 (m, 2H), 5.93 – 5.77 (m, 1H), 5.35 (dd, J = 6.9, 6.2 Hz,

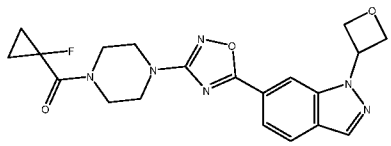
2H), 5.15 (t, J = 7.4 Hz, 2H), 4.27 (s, 2H), 2.91 – 2.66 (m, 3H), 1.88 (d, J = 13.0 Hz, 2H), 1.70 (td, J = 12.5, 4.3 Hz, 2H), 1.52 – 1.42 (m, 9H); LCMS (ESI) [M+H]+: 433.4.



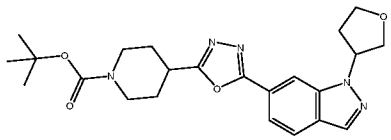
^{1}H NMR (300 MHz, Chloroform-d) δ 8.43 (dd, J = 1.6, 0.8 Hz, 1H), 8.26 (dd, J = 8.8, 1.6 Hz, 1H), 7.64 (dd, J = 8.8, 0.8 Hz, 1H), 4.55 (d, J = 13.9 Hz, 1H), 3.81 (d, J = 14.1 Hz, 1H), 3.47 (hept, J = 7.0 Hz, 1H), 3.38 – 3.10 (m, 3H), 3.03 – 2.87 (m, 1H), 2.48 – 2.29 (m, 2H), 2.19 (dd, J = 10.7, 7.2 Hz, 4H), 2.09 – 1.80 (m, 4H), 1.53 (d, J = 7.0 Hz, 6H); LCMS (ESI) [M+H]+: 395.6.



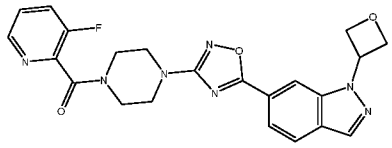
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.31 (d, J=0.9 Hz, 1H), 8.21 (s, 1H), 7.95 - 7.87 (m, 2H), 5.96 - 5.86 (m, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.23 - 5.15 (m, 2H), 3.90 - 3.77 (m, 3H), 3.09 - 2.97 (m, 3H), 2.66 - 2.53 (m, 2H), 2.37 - 2.26 (m, 2H), 2.19 (br dd, J=3.6, 13.5 Hz, 2H), 2.10 - 1.96 (m, 4H); LCMS (ESI) [M+H]+: 444.1.



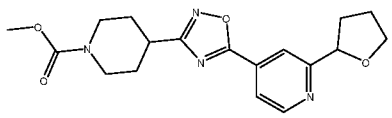
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 (d, J=0.8 Hz, 1H), 8.19 (br s, 1H), 7.91 - 7.85 (m, 2H), 5.92 -5.84 (m, 1H), 5.32 (t, J=6.4 Hz, 2H), 5.17 (t, J=7.2 Hz, 2H), 3.85 (br s, 4H), 3.67 - 3.60 (m, 4H), 1.40 - 1.22 (m, 4H); LCMS (ESI) [M+H]+: 413.2.



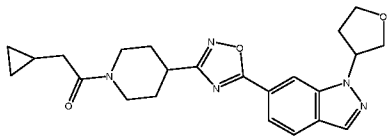
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 8.09 (s, 1H), 7.89 - 7.79 (m, 2H), 5.37 (quin, J=5.9 Hz, 1H), 4.33 - 4.10 (m, 5H), 4.09 - 4.00 (m, 1H), 3.20 (tt, J=3.8, 11.0 Hz, 1H), 3.01 (br t, J=11.6 Hz, 2H), 2.61 - 2.48 (m, 2H), 2.15 (br dd, J=2.8, 13.2 Hz, 2H), 2.00 - 1.86 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-56+H]+: 384.1.



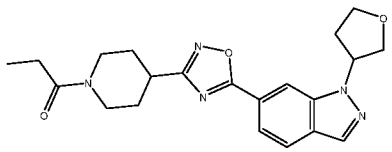
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.48 (td, J=1.2, 4.8 Hz, 1H), 8.24 (d, J=0.8 Hz, 1H), 8.18 (s, 1H), 7.87 (d, J=0.8 Hz, 2H), 7.54 (dt, J=1.2, 8.8 Hz, 1H), 7.75 -7.40 (m, 1H), 5.92 -5.84 (m, 1H), 5.31 (t, J=6.4 Hz, 2H), 5.20 - 5.13 (t, J=6.8 Hz, 2H), 4.00 -3.98 (m, 2H), 3.77 - 3.70 (m, 2H), 3.63 - 3.57 (m, 2H), 3.52 - 3.46 (m, 2H); LCMS (ESI) [M+H]+: 450.2.



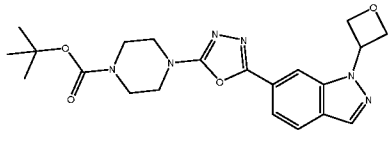
^{1}H NMR (400MHz, METHANOL-d4) δ 8.74 (d, J=5.1 Hz, 1H), 8.13 (s, 1H), 7.93 (d, J=5.0 Hz, 1H), 5.05 (t, J=6.9 Hz, 1H), 4.20 - 4.09 (m, 3H), 4.00 (q, J=7.4 Hz, 1H), 3.70 (s, 3H), 3.21 - 3.01 (m, 3H), 2.54 - 2.43 (m, 1H), 2.13 - 1.89 (m, 5H), 1.86 - 1.73 (m, 2H); LCMS (ESI) [M+H]+: 359.2.



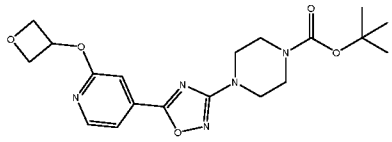
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.11 (s, 1H), 7.95 - 7.83 (m, 2H), 5.40 (quin, J=5.8 Hz, 1H), 4.63 (br d, J=13.5 Hz, 1H), 4.34 - 4.18 (m, 3H), 4.09 - 4.01 (m, 1H), 3.96 (br d, J=13.2 Hz, 1H), 3.26 (br t, J=11.5 Hz, 1H), 3.20 - 3.11 (m, 1H), 2.92 (br t, J=11.7 Hz, 1H), 2.62 - 2.50 (m, 2H), 2.33 (d, J=6.8 Hz, 2H), 2.15 (br d, J=13.0 Hz, 2H), 1.99 - 1.83 (m, 2H), 1.14 - 1.02 (m, 1H), 0.63 - 0.55 (m, 2H), 0.24 - 0.18 (m, 2H); LCMS (ESI) [M+H]+: 422.2.



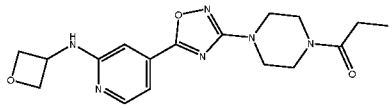
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.32 (s, 1H), 8.12 (s, 1H), 7.94 - 7.85 (m, 2H), 5.45 - 5.35 (m, 1H), 4.63 (br d, J=13.7 Hz, 1H), 4.35 - 4.18 (m, 3H), 4.09 - 4.02 (m, 1H), 3.98 (br d, J=13.2 Hz, 1H), 3.25 (br t, J=11.6 Hz, 1H), 3.21 - 3.11 (m, 1H), 2.91 (br t, J=11.1 Hz, 1H), 2.63 - 2.51 (m, 2H), 2.41 (q, J=7.5 Hz, 2H), 2.15 (br s, 2H), 2.00 - 1.81 (m, 2H), 1.19 (t, J=7.4 Hz, 3H); LCMS (ESI) [M+H]+: 396.1.



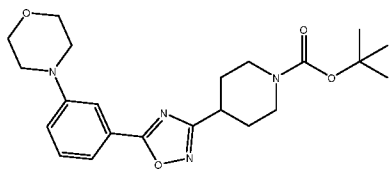
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.15 (s, 1H), 8.03 (s, 1H), 7.86 - 7.81 (m, 1H), 7.78 - 7.72 (m, 1H), 5.86 (m, 1H), 5.32 (t, J=6.5 Hz, 2H), 5.16 (t, J=7.3 Hz, 2H), 3.61 (s, 8H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 427.1.



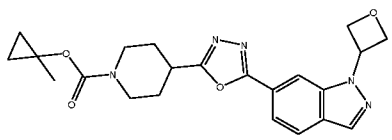
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (dd, J=0.8, 4.8 Hz, 1H), 7.49 (dd, J=1.2, 4.0 Hz, 1H), 7.44 -7.40 (m, 1H), 5.69 - 5.62 (m, 1H), 5.00 (t, J=6.4 Hz, 2H), 4.75 (t, J=7.2 Hz, 2H), 3.58 - 3.48 (m, 8H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 404.1.



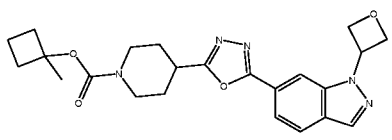
^{1}H NMR (400MHz, CHLOROFORM-d-d) δ 8.25 (d, J=5.1 Hz, 1H), 7.22 (br d, J=5.1 Hz, 1H), 6.98 (s, 1H), 5.18 (br s, 1H), 5.05 (br s, 3H), 4.58 (br s, 2H), 3.77 (br s, 2H), 3.65 - 3.44 (m, 6H), 2.41 (q, J=7.4 Hz, 2H), 1.19 (t, J=7.3 Hz, 3H); LCMS (ESI) [M+H]+: 359.1.



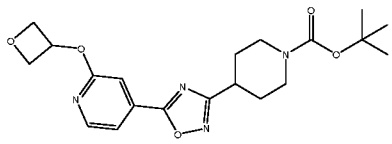
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.65 – 7.59 (m, 2H), 7.41 (t, J=8.0 Hz, 1H), 7.12 (br d, J=8.0 Hz, 1H), 4.28 – 4.05 (m, 2H), 3.93 – 3.86 (m, 4 H), 3.29 – 3.22 (m, 4H), 3.07 – 2.89 (m, 3H), 2.06 (br d, J=12.4 Hz, 2H), 1.92 – 1.78 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H-Boc]+: 315.2.



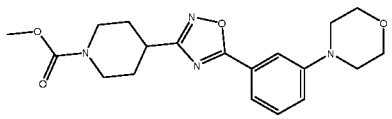
^{1}H NMR (400MHz, METHANOL-d4) δ = 8.33 (s, 1H), 8.27 (s, 1H), 7.96 (d, J=7.8 Hz, 1H), 7.85 (dd, J=1.2, 8.3 Hz, 1H), 6.14 (quin, J=6.8 Hz, 1H), 5.28 - 5.15 (m, 4H), 4.10 (br s, 2H), 3.38 - 3.33 (m, 1H), 3.10 (br s, 2H), 2.18 (br s, 2H), 1.93 - 1.77 (m, 2H), 1.55 (s, 3H), 0.92 - 0.84 (m, 2H), 0.70 - 0.63 (m, 2H); LCMS (ESI) [M+H]+: 424.2.



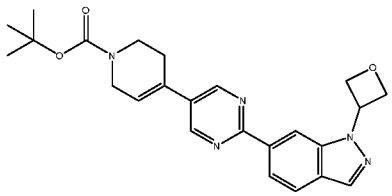
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.19 (s, 2H), 7.92 - 7.83 (m, 2H), 5.89 (br t, J=6.8 Hz, 1H), 5.33 (t, J=6.4 Hz, 2H), 5.23 - 5.15 (m, 2H), 4.17 (br s, 2H), 3.21 (br t, J=10.8 Hz, 1H), 3.03 (br s, 2H), 2.41 - 2.28 (m, 2H), 2.23 - 2.10 (m, 4H), 1.94 (q, J=10.6 Hz, 2H), 1.82 (br d, J=10.8 Hz, 1H), 1.76 - 1.62 (m, 1H), 1.59 (br s, 3H); LCMS (ESI) [M+H]+: 438.2.



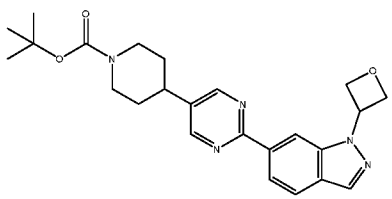
^{1}H NMR (400 MHz, DMSO-d6) δ 8.39 (d, J=4.8 Hz, 1H), 7.62 (dd, J=5.6, 1.2 Hz, 1H), 7.47 (s, 1H) 5.67 – 5.59 (m, 1H), 4.91 (t, J=7.2 Hz, 2H), 4.59 (dd, J=7.6, 5.4 Hz, 2H), 3.96 (br d, J=12.0 Hz, 2H), 3.14 (tt, J=11.2, 3.6 Hz, 1H), 3.05 – 2.85 (m, 2H), 2.00 (br dd, J=13.2, 2.4 Hz, 2H), 1.68 – 1.54 (m, 2H), 1.41 (s, 9H); LCMS (ESI) [M+H]+: 403.1.



^{1}H NMR (400 MHz, DMSO-d6) δ 7.54 – 7.42 (m, 3H), 7.27 (dd, J=8.0, 1.2 Hz, 1H), 3.99 (br d, J=10.8 Hz, 2H), 3.79 – 3.72 (m, 4H), 3.60 (s, 3H), 3.24 – 3.16 (m, 4H), 3.15 – 2.94 (m, 3H), 2.04 – 1.94 (m, 2H), 1.69 – 1.56 (m, 2H); LCMS (ESI) [M+H]+: 373.1.

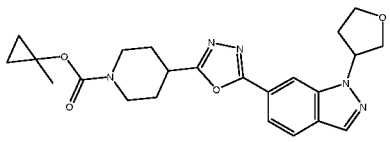


^{1}H NMR (300 MHz, Chloroform-d) δ 8.84 (d, J = 0.9 Hz, 2H), 8.61 (q, J = 1.1 Hz, 1H), 8.30 (dd, J = 8.6, 1.2 Hz, 1H), 8.15 (d, J = 1.0 Hz, 1H), 7.84 (dd, J = 8.5, 0.9 Hz, 1H), 6.25 (s, 1H), 5.95 (p, J = 7.1 Hz, 1H), 5.36 (t, J = 6.5 Hz, 2H), 5.22 – 5.05 (m, 2H), 4.16 (d, J = 3.2 Hz, 2H), 3.71 (t, J = 5.6 Hz, 2H), 2.58 (s, 2H), 1.44 (s, 9H); LCMS (ESI) [M+H]+: 434.6.

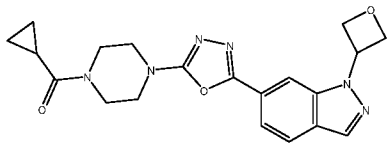


^{1}H NMR (300 MHz, Chloroform-d) δ 8.70 (s, 2H), 8.59 (s, 1H), 8.28 (dd, J = 8.5, 1.3 Hz, 1H), 7.84 (dd, J = 8.6, 0.8 Hz, 1H), 5.95 (p, J = 7.0 Hz, 1H), 5.36 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.2 Hz, 2H), 4.31 (s, 2H),

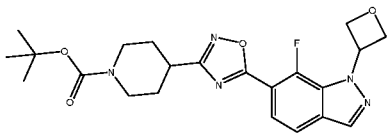
2.83 (dd, J = 29.2, 14.6 Hz, 3H), 1.91 (d, J = 13.2 Hz, 2H), 1.80 – 1.62 (m, 2H), 1.50 (s, 9H); LCMS (ESI) [M+H]+: 436.6.



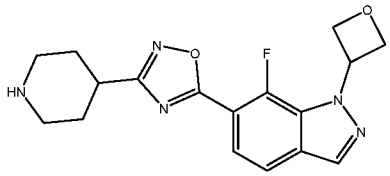
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.10 (s, 1H), 7.89 - 7.80 (m, 2H), 5.38 (quin, J=5.8 Hz, 1H), 4.38 - 3.97 (m, 6H), 3.21 (tt, J=3.6, 10.9 Hz, 1H), 3.03 (br t, J=11.0 Hz, 2H), 2.59 - 2.52 (m, 2H), 2.16 (br d, J=12.3 Hz, 2H), 1.98 - 1.86 (m, 2H), 1.58 (s, 3H), 0.93 - 0.87 (m, 2H), 0.69 - 0.63 (m, 2H); LCMS (ESI) [M+H]+: 438.2.



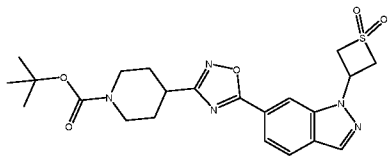
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.05 (d, J=0.9 Hz, 1H), 7.87 - 7.81 (m, 1H), 7.79 - 7.72 (m, 1H), 5.94 - 5.79 (m, 1H), 5.32 (t, J=6.7 Hz, 2H), 5.16 (t, J=7.4 Hz, 2H), 3.85 (m, 4H), 3.76 - 3.58 (m, 4H), 1.78 (m, 1H), 1.08 - 1.00 (m, 2H), 0.88 - 0.81 (m, 2H); LCMS (ESI) [M+H]+: 395.1.



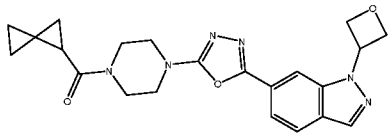
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.21 (d, J=2.2 Hz, 1H), 7.82 (dd, J=5.6, 8.4 Hz, 1H), 7.64 (d, J=8.6 Hz, 1H), 6.17 - 6.07 (m, 1H), 5.33 (t, J=6.4 Hz, 2H), 5.15 (t, J=7.0 Hz, 2H), 4.18 (br s, 2H), 3.09 (tt, J=3.8, 11.2 Hz, 1H), 2.97 (br t, J=11.8 Hz, 2H), 2.10 (br d, J=10.8 Hz, 2H), 1.95 - 1.81 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H-56]+: 388.1.



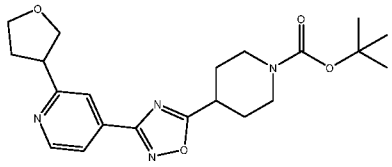
^{1}H NMR (400MHz, METHANOL-d4) δ = 8.32 (d, J=2.2 Hz, 1H), 7.86 - 7.78 (m, 1H), 7.77 - 7.73 (m, 1H), 6.23 - 6.13 (m, 1H), 5.30 - 5.23 (m, 2H), 5.19 - 5.11 (m, 2H), 3.51 (td, J=3.8, 13.2 Hz, 2H), 3.40 - 3.32 (m, 1H), 3.28 - 3.19 (m, 2H), 2.38 (br dd, J=3.4, 14.8 Hz, 2H), 2.19 - 2.06 (m, 2H); LCMS (ESI) [M+H]+: 344.1.



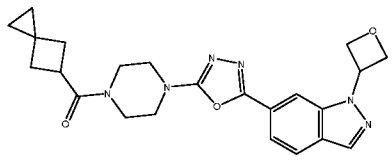
^{1}H NMR (400MHz, CHLOROFORM-d) 8.24 (d, J=3.3 Hz, 2H), 8.00 - 7.96 (m, 1H), 7.94 - 7.90 (m, 1H), 5.62 - 5.53 (m, 1H), 5.03 - 4.95 (m, 2H), 4.77 - 4.68 (m, 2H), 4.18 (br s, 2H), 3.11 - 2.91 (m, 3H), 2.09 (br d, J=11.2 Hz, 2H), 1.94 - 1.82 (m, 2H), 1.50 (s, 9H); LCMS (ESI) [M-56+H]+: 418.1.



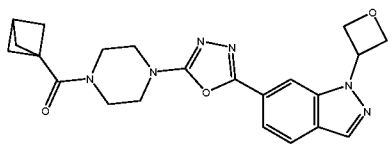
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 8.07 (s, 1H), 7.88 - 7.83 (m, 1H), 7.80 - 7.75 (m, 1H), 5.95 - 5.82 (m, 1H), 5.34 (m, 2H), 5.24 - 5.13 (m, 2H), 3.90 - 3.58 (m, 8H), 2.18 (dd, J=4.3, 7.4 Hz, 1H), 1.67 (m, 1H), 1.36 (dd, J=3.7, 7.4 Hz, 1H), 1.04 - 0.90 (m, 3H), 0.89 - 0.82 (m, 1H); LCMS (ESI) [M+H]+: 421.2.



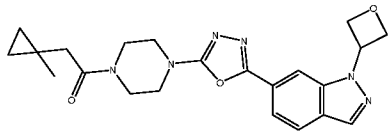
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.71 (d, J=5.1 Hz, 1H), 7.85 (s, 1H), 7.78 (dd, J=1.5, 5.0 Hz, 1H), 4.27 - 4.08 (m, 4H), 4.02 - 3.92 (m, 2H), 3.68 (quin, J=7.7 Hz, 1H), 3.20 (tt, J=3.8, 11.0 Hz, 1H), 3.07 - 2.92 (m, 2H), 2.50 - 2.36 (m, 1H), 2.28 (qd, J=7.8, 12.3 Hz, 1H), 2.13 (br dd, J=2.5, 13.1 Hz, 2H), 1.96 - 1.83 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 401.1.



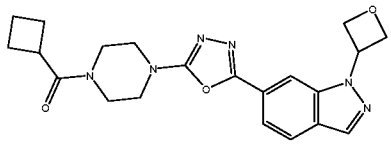
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.04 (s, 1H), 7.87 - 7.80 (m, 1H), 7.78 - 7.71 (m, 1H), 5.86 (m, 1H), 5.31 (m, 2H), 5.22 - 5.10 (m, 2H), 3.91 - 3.77 (m, 2H), 3.67 - 3.52 (m, 6H), 3.51 - 3.40 (m, 1H), 2.70 - 2.54 (m, 2H), 2.27 - 2.17 (m, 2H), 0.56 - 0.37 (m, 4H); LCMS (ESI) [M+H]+: 435.2.



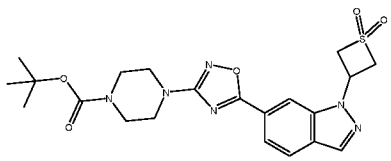
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.04 (s, 1H), 7.86 - 7.81 (m, 1H), 7.78 - 7.72 (m, 1H), 5.86 (m, 1H), 5.32 (m, 2H), 5.20 - 5.12 (m, 2H), 3.88 - 3.73 (m, 4H), 3.70 - 3.57 (m, 4H), 2.55 (s, 1H), 2.21 (s, 6H); LCMS (ESI) [M+H]+: 421.1.



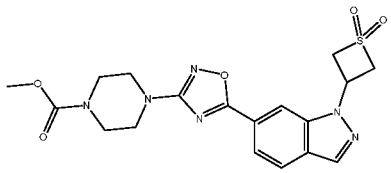
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.05 (s, 1H), 7.86 - 7.81 (m, 1H), 7.78 - 7.72 (m, 1H), 5.86 (m, 1H), 5.32 (t, J=6.5 Hz, 2H), 5.16 (t, J=7.3 Hz, 2H), 3.82 (m, 2H), 3.66 (br s, 6H), 2.40 (s, 2H), 1.17 (s, 3H), 0.51 - 0.37 (m, 4H); LCMS (ESI) [M+H]+: 423.2.



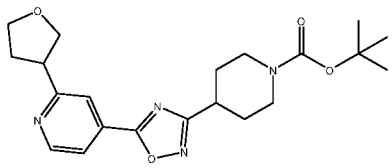
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.04 (s, 1H), 7.86 - 7.80 (m, 1H), 7.78 - 7.72 (m, 1H), 5.92 - 5.79 (m, 1H), 5.32 (m, 2H), 5.22 - 5.10 (m, 2H), 3.86 - 3.75 (m, 2H), 3.67 - 3.49 (m, 6H), 3.31 (m, 1H), 2.46 - 2.32 (m, 2H), 2.26 - 2.14 (m, 2H), 2.09 - 1.84 (m, 2H); LCMS (ESI) [M+H]+: 409.1.



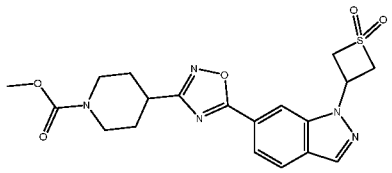
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.18 (s, 1H), 7.96 - 7.87 (m, 2H), 5.62 - 5.52 (m, 1H), 5.02 - 4.94 (m, 2H), 4.76 - 4.68 (m, 2H), 3.60 - 3.54 (m, 8H), 1.51 (s, 9H); LCMS (ESI) [M+H]+: 419.0.



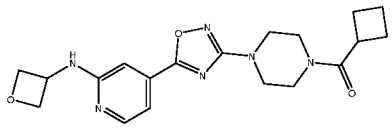
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.18 (s, 1H), 7.95 - 7.86 (m, 2H), 5.61 - 5.52 (m, 1H), 5.02 - 4.94 (m, 2H), 4.74 - 4.68 (m, 2H), 3.75 (s, 3H), 3.63 -3.62 (m, 4H), 3.59 -3.53 (m, 4H); LCMS (ESI) [M+H]+: 433.1.



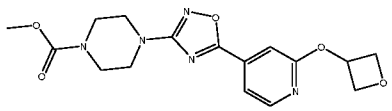
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.83 - 7.78 (m, 1H), 4.27 - 4.08 (m, 4H), 4.03 - 3.91 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.11 - 3.01 (m, 1H), 2.96 (br t, J=11.4 Hz, 2H), 2.49 - 2.38 (m, 1H), 2.34 - 2.22 (m, 1H), 2.06 (br d, J=12.1 Hz, 2H), 1.91 - 1.78 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+: 401.2.



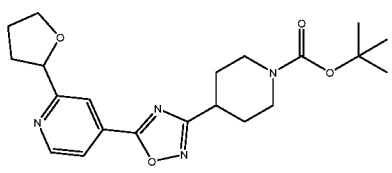
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.24 (d, J=4.2 Hz, 2H), 8.00 - 7.95 (m, 1H), 7.94 - 7.90 (m, 1H), 5.62 - 5.53 (m, 1H), 4.99 (br dd, J=6.6, 14.6 Hz, 2H), 4.73 (br dd, J=9.0, 14.6 Hz, 2H), 4.21 (br s, 2H), 3.74 (s, 3H), 3.14 - 2.99 (m, 3H), 2.11 (br d, J=12.6 Hz, 2H), 1.97 - 1.83 (m, 2H); LCMS (ESI) [M+H]+: 432.1.



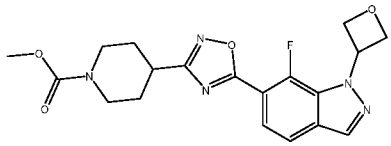
^{1}H NMR (400MHz, CHLOROFORM-d-d) δ 8.26 (d, J=5.1 Hz, 1H), 7.22 (dd, J=1.3, 5.3 Hz, 1H), 6.97 (s, 1H), 5.15 (br d, J=5.3 Hz, 1H), 5.10 - 4.98 (m, 3H), 4.65 - 4.50 (m, 2H), 3.84 - 3.70 (m, 2H), 3.58 - 3.44 (m, 6H), 3.31 (quin, J=8.7 Hz, 1H), 2.48 - 2.30 (m, 2H), 2.30 - 2.10 (m, 2H), 2.08 - 1.80 (m, 2H); LCMS (ESI) [M+H]+: 385.1.



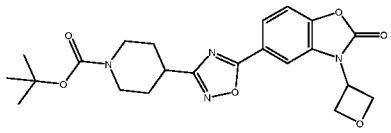
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.24 (d, J=5.2 Hz, 1H), 7.49 (dd, J=1.2, 5.2 Hz, 1H), 7.42 (br s, 1H), 5.66 (quin, J=5.6 Hz, 1H), 5.00 (t, J=7.2 Hz, 2H), 4.75 (t, J=5.6 Hz, 2H), 3.75 (s, 3H), 3.65 - 3.58 (m, 4H), 3.53 -3.52 (m, 4H); LCMS (ESI) [M+H]+: 362.1.



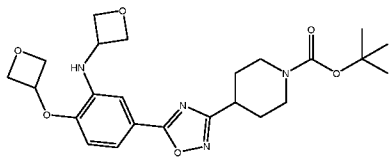
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.76 (d, J=5.0 Hz, 1H), 8.12 (s, 1H), 7.82 (d, J=5.0 Hz, 1H), 5.15 - 5.07 (m, 1H), 4.26 - 4.11 (m, 3H), 4.07 - 3.97 (m, 1H), 3.12 - 3.01 (m, 1H), 3.01 - 2.88 (m, 2H), 2.55 - 2.42 (m, 1H), 2.10 - 1.96 (m, 5H), 1.92 - 1.78 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+: 401.1.



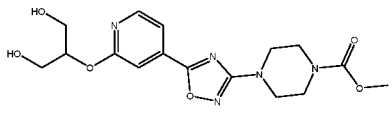
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.21 (d, J=2.4 Hz, 1H), 7.81 (dd, J=5.6, 8.3 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 6.11 (q, J=7.0 Hz, 1H), 5.33 (t, J=6.4 Hz, 2H), 5.15 (t, J=7.6 Hz, 2H), 4.22 (br d, 2H), 3.73 (s, 3H), 3.18 - 3.09 (m, 1H), 3.09 - 2.96 (m, 2H), 2.11 (br d, J=12.8 Hz, 2H), 1.97 - 1.82 (m, 2H); LCMS (ESI) [M+H]+: 402.1.



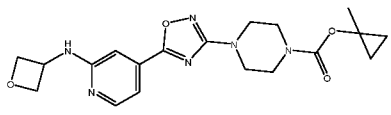
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.29 (d, J=1.2 Hz, 1H), 8.03 (dd, J=2.0, 8.4 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H), 5.59 - 5.45 (m, 1H), 5.25 - 5.10 (m, 4H), 4.27 - 4.04 (m, 2H), 3.17 - 2.83 (m, 3H), 2.07 (br d, J=11.2 Hz, 2H), 1.94 - 1.76 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H-56]+: 387.1.



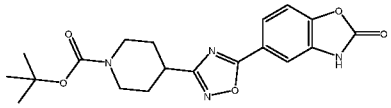
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.46 (dd, J=2.0, 8.4 Hz, 1H), 7.02 (d, J=2.0 Hz, 1H), 6.41 (d, J=8.4 Hz, 1H), 5.33 (quin, J=5.6 Hz, 1H), 5.08 (td, J=6.8, 18.0 Hz, 4H), 4.89 - 4.81 (m, 3H), 4.80 - 4.70 (m, 1H), 4.61 (t, J=6.0 Hz, 2H), 4.14 (br s, 2H), 3.06 - 2.87 (m, 3H), 2.05 (br d, J=10.8 Hz, 2H), 1.90 - 1.78 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H-56]+: 417.2.



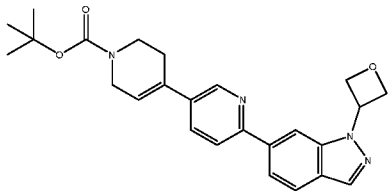
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.52 (d, J=6.8 Hz, 1H), 7.30 (br s, 1H), 6.82 (br d, J=6.8 Hz, 1H), 4.19 (br d, J=5.2 Hz, 2H), 4.06 (br t, J=4.4 Hz, 1H), 3.74 (s, 3H), 3.64 - 3.55 (m, 6H), 3.51 (br s, 4H), 3.30 -3.10 (m, 1H); LCMS (ESI) [M+H]+: 380.1.



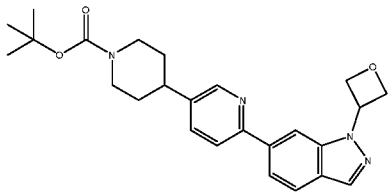
^{1}H NMR (400MHz, DMSO-d6) δ 8.18 (d, J=5.3 Hz, 1H), 7.77 (d, J=6.0 Hz, 1H), 7.10 (s, 1H), 7.03 (dd, J=1.3, 5.3 Hz, 1H), 4.98 - 4.88 (m, 1H), 4.82 (t, J=6.6 Hz, 2H), 4.44 (t, J=6.3 Hz, 2H), 3.42 (br d, J=13.5 Hz, 8H), 1.49 (s, 3H), 0.86 - 0.76 (m, 2H), 0.67 - 0.56 (m, 2H); LCMS (ESI) [M+H]+: 401.1.



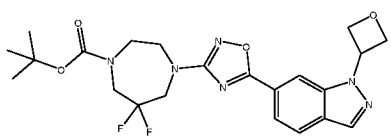
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.48 (br s, 1H), 7.96 (dd, J=1.6, 8.4 Hz, 1H), 7.86 (d, J=1.2 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 4.30 - 4.06 (m, 2H), 3.10 - 2.90 (m, 3H), 2.13 - 1.99 (m, 2H), 1.92 - 1.80 (m, 1H), 1.92 - 1.80 (m, 2H), 1.60 - 1.40 (m, 9H); LCMS (ESI) [M+H-56]+: 331.0.



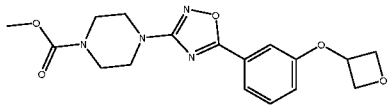
^{1}H NMR (300 MHz, Chloroform-d) δ 8.76 (dd, J = 2.3, 1.0 Hz, 1H), 8.21 (q, J = 1.0 Hz, 1H), 8.14 (d, J = 0.9 Hz, 1H), 7.88 – 7.71 (m, 4H), 6.19 (s, 1H), 6.00 – 5.84 (m, 1H), 5.35 (dd, J = 6.9, 6.2 Hz, 2H), 5.21 – 5.09 (m, 2H), 4.14 (d, J = 3.2 Hz, 2H), 3.69 (t, J = 5.7 Hz, 2H), 2.58 (s, 2H), 1.51 (d, J = 39.9 Hz, 9H), 1.27 (d, J = 13.0 Hz, 1H); LCMS (ESI) [M+H]+: 433.6.



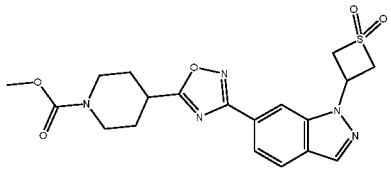
^{1}H NMR (300 MHz, Chloroform-d) δ 8.59 (d, J = 2.3 Hz, 1H), 8.21 – 8.09 (m, 2H), 7.89 – 7.67 (m, 3H), 7.62 (dd, J = 8.2, 2.4 Hz, 1H), 5.91 (ddd, J = 14.2, 7.7, 6.3 Hz, 1H), 5.34 (dd, J = 6.9, 6.1 Hz, 2H), 5.14 (dd, J = 7.7, 6.8 Hz, 2H), 4.30 (d, J = 13.0 Hz, 2H), 2.93 – 2.68 (m, 3H), 1.89 (d, J = 13.0 Hz, 2H), 1.69 (tt, J = 13.2, 6.6 Hz, 2H), 1.46 (d, J = 17.7 Hz, 9H); LCMS (ESI) [M+H]+: 435.6.



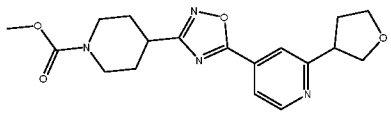
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.20 (s, 1H), 7.92 - 7.83 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.18 (t, J=7.3 Hz, 2H), 4.08 (br t, J=11.9 Hz, 2H), 3.96 - 3.68 (m, 6H), 1.50 (s, 9H); LCMS (ESI) [M-56+H]+: 421.1.



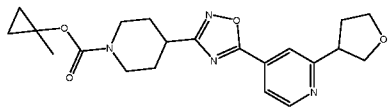
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.70 (br d, J=7.6 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.34 -7.31 (m, 1H), 6.94 -6.92(m, 1H), 5.29 (quin, J=5.6 Hz, 1H), 5.01 (t J = 8.0, 2H), 4.77 (t J = 8.0, 12.0, 2H), 3.74 (s, 3H), 3.65 -3.60 (m, 4H), 3.55 3.50 (m, 4H); LCMS (ESI) [M+H]+:361.1.



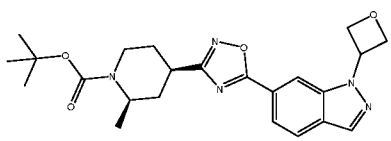
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.18 (d, J=5.7 Hz, 2H), 7.99 - 7.94 (m, 1H), 7.89 - 7.85 (m, 1H), 5.61 - 5.52 (m, 1H), 5.02 - 4.95 (m, 2H), 4.74 - 4.66 (m, 2H), 4.19 (br s, 2H), 3.74 (s, 3H), 3.29 - 3.19 (m, 1H), 3.10 (br t, J=12.1 Hz, 2H), 2.19 (br d, J=11.0 Hz, 2H), 2.03 - 1.89 (m, 2H); LCMS (ESI) [M+H]+: 432.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.1, 5.0 Hz, 1H), 4.31 - 4.08 (m, 4H), 4.03 - 3.93 (m, 2H), 3.76 - 3.66 (m, 4H), 3.14 - 2.97 (m, 3H), 2.49 - 2.38 (m, 1H), 2.33 - 2.22 (m, 1H), 2.08 (br d, J=12.2 Hz, 2H), 1.94 - 1.81 (m, 2H); LCMS (ESI) [M+H]+: 359.0.

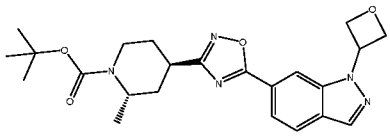


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.78 (d, J=5.0 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.0 Hz, 1H), 4.29 - 4.03 (m, 4H), 4.02 - 3.92 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.12 - 2.90 (m, 3H), 2.49 - 2.38 (m, 1H), 2.28 (qd, J=7.6, 12.4 Hz, 1H), 2.06 (br d, J=11.0 Hz, 2H), 1.91 - 1.77 (m, 2H), 1.57 (s, 3H), 0.93 - 0.86 (m, 2H), 0.69 - 0.61 (m, 2H); LCMS (ESI) [M+H]+: 399.1.



^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.99 - 7.85 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.34 (dt, J=3.1, 6.5 Hz, 2H), 5.18 (t, J=7.3 Hz, 2H), 4.22 (sxt, J=6.6 Hz, 1H), 4.01 - 3.91 (m, 1H),

3.31 (ddd, J=5.5, 10.7, 14.0 Hz, 1H), 3.22 - 3.12 (m, 1H), 2.23 - 2.00 (m, 4H), 1.49 (s, 9H), 1.09 (d, J=6.6 Hz, 3H); LCMS (ESI) [M-56+H]+: 384.1.



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^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.97 - 7.85 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.5 Hz, 2H), 5.18 (t, J=7.3 Hz, 2H), 4.61 (br s, 1H), 4.16 (br s, 1H), 3.26 (tt, J=3.6, 12.4 Hz, 1H), 3.03 (br t, J=13.2 Hz, 1H), 2.16 - 1.91 (m, 3H), 1.80 (dq, J=4.7, 12.9 Hz, 1H), 1.49 (s, 9H), 1.27 (d, J=7.1 Hz, 3H); LCMS (ESI) [M-56+H]+: 384.2.

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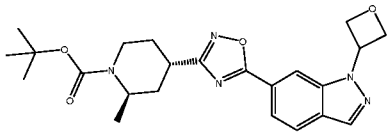
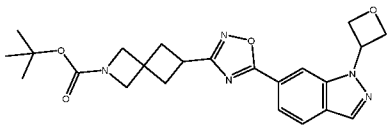
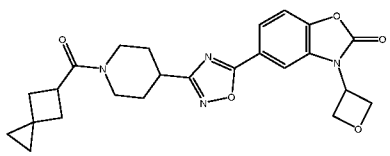


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.96 - 7.85 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.24 - 5.14 (m, 2H), 4.60 (br s, 1H), 4.15 (br s, 1H), 3.26 (tt, J=3.6, 12.3
15 Hz, 1H), 3.03 (br t, J=12.8 Hz, 1H), 2.15 - 1.93 (m, 3H), 1.80 (dq, J=4.7, 12.9 Hz, 1H), 1.49 (s, 9H), 1.27 (d, J=6.8 Hz, 3H); LCMS (ESI) [M-56+H]+: 384.1.

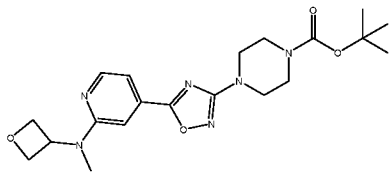


20 ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.13 (s, 1H), 7.84 (q, J=8.4 Hz, 2H), 5.83 (quin, J=7.0 Hz, 1H), 5.26 (t, J=6.5 Hz, 2H), 5.10 (t, J=7.2 Hz, 2H), 3.98 (s, 2H), 3.93 (s, 2H), 3.54 (quin, J=8.2 Hz, 1H), 2.65 - 2.51 (m, 4H), 1.38 (s, 9H); LCMS (ESI) [M+H]+: 438.2.

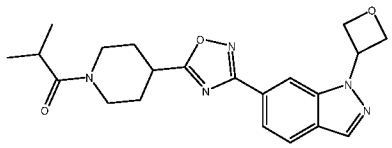


25

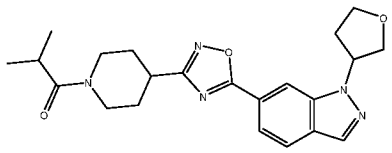
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.28 (d, J=1.2 Hz, 1H), 8.03 (dd, J=1.6, 8.4 Hz, 1H), 7.40 (d, J=8.4 Hz, 1H), 5.60 - 5.44 (m, 1H), 5.25 - 5.09 (m, 4H), 4.61 (br d, J=13.2 Hz, 1H), 3.83 (br d, J=13.6 Hz, 1H), 3.45 (quin, J=8.4 Hz, 1H), 3.22 - 3.06 (m, 2H), 2.99 - 2.83 (m, 1H), 2.62 (td, J=7.6, 11.6 Hz, 2H), 2.25 - 2.16 (m, 2H), 2.16 - 2.04 (m, 2H), 1.93 - 1.78 (m, 2H), 0.52 - 0.45 (m, 2H), 0.45 - 0.37 (m, 2H);
30 LCMS (ESI) [M+H]+: 451.9.



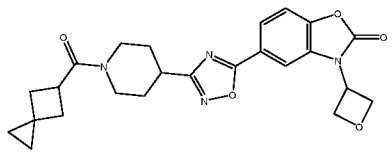
^{1}H NMR (400MHz, CHLOROFORM-d-d) δ 8.28 (d, J=4.8 Hz, 1H), 7.20 (dd, J=0.9, 5.3 Hz, 1H), 7.12 (s, 1H), 5.51 (quin, J=7.1 Hz, 1H), 4.94 (t, J=7.2 Hz, 2H), 4.80 (t, J=6.8 Hz, 2H), 3.64 - 3.41 (m, 8H), 3.16 (s, 3H), 1.50 (s, 9H); LCMS (ESI) [M+H]+:417.1.



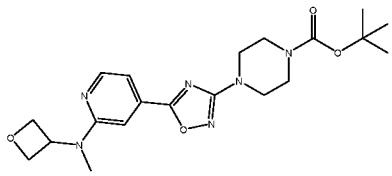
^{1}H NMR (300 MHz, Chloroform-d) δ 8.28 – 8.12 (m, 2H), 7.96 – 7.79 (m, 2H), 5.89 (tt, J = 7.6, 6.3 Hz, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.2 Hz, 2H), 4.60 (d, J = 13.6 Hz, 1H), 4.04 (d, J = 14.0 Hz, 1H), 3.30 (tt, J = 10.6, 3.6 Hz, 2H), 2.96 (t, J = 12.7 Hz, 1H), 2.84 (h, J = 6.7 Hz, 1H), 2.22 (s, 2H), 1.97 (d, J = 14.9 Hz, 2H), 1.27 – 1.05 (m, 7H); LCMS (ESI) [M+H]+ 396.6.



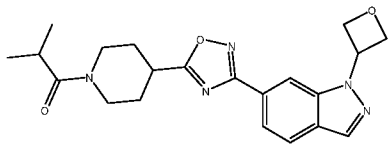
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.31 (d, J=1.0 Hz, 1H), 8.10 (s, 1H), 7.93 - 7.84 (m, 2H), 5.44 - 5.35 (m, 1H), 4.63 (br d, J=11.1 Hz, 1H), 4.34 - 4.25 (m, 1H), 4.25 - 4.17 (m, 2H), 4.10 - 4.00 (m, 2H), 3.36 - 3.08 (m, 2H), 2.98 - 2.78 (m, 2H), 2.62 - 2.49 (m, 2H), 2.14 (m, 2H), 2.01 - 1.79 (m, 2H), 1.16 (br d, J=6.7 Hz, 6H); LCMS (ESI) [M+H]+: 410.2.



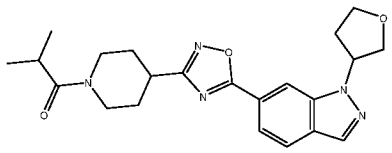
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.28 (d, J=1.2 Hz, 1H), 8.03 (dd, J=1.6, 8.4 Hz, 1H), 7.40 (d, J=8.4 Hz, 1H), 5.60 - 5.44 (m, 1H), 5.25 - 5.09 (m, 4H), 4.61 (br d, J=13.2 Hz, 1H), 3.83 (br d, J=13.6 Hz, 1H), 3.45 (quin, J=8.4 Hz, 1H), 3.22 - 3.06 (m, 2H), 2.99 - 2.83 (m, 1H), 2.62 (td, J=7.6, 11.6 Hz, 2H), 2.25 - 2.16 (m, 2H), 2.16 - 2.04 (m, 2H), 1.93 - 1.78 (m, 2H), 0.52 - 0.45 (m, 2H), 0.45 - 0.37 (m, 2H); LCMS (ESI) [M+H]+: 451.9.



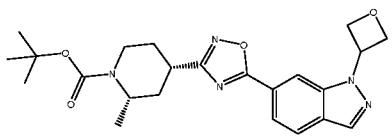
^{1}H NMR (400MHz, CHLOROFORM-d-d) δ 8.28 (d, J=4.8 Hz, 1H), 7.20 (dd, J=0.9, 5.3 Hz, 1H), 7.12 (s, 1H), 5.51 (quin, J=7.1 Hz, 1H), 4.94 (t, J=7.2 Hz, 2H), 4.80 (t, J=6.8 Hz, 2H), 3.64 - 3.41 (m, 8H), 3.16 (s, 3H), 1.50 (s, 9H); LCMS (ESI) [M+H]+:417.1.



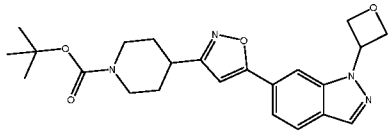
^{1}H NMR (300 MHz, Chloroform-d) δ 8.28 – 8.12 (m, 2H), 7.96 – 7.79 (m, 2H), 5.89 (tt, J = 7.6, 6.3 Hz, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.2 Hz, 2H), 4.60 (d, J = 13.6 Hz, 1H), 4.04 (d, J = 14.0 Hz, 1H), 3.30 (tt, J = 10.6, 3.6 Hz, 2H), 2.96 (t, J = 12.7 Hz, 1H), 2.84 (h, J = 6.7 Hz, 1H), 2.22 (s, 2H), 1.97 (d, J = 14.9 Hz, 2H), 1.27 – 1.05 (m, 7H); LCMS (ESI) [M+H]+ 396.6.



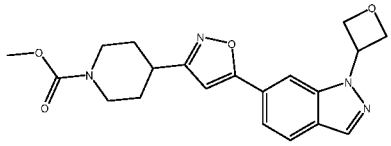
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.31 (d, J=1.0 Hz, 1H), 8.10 (s, 1H), 7.93 - 7.84 (m, 2H), 5.44 - 5.35 (m, 1H), 4.63 (br d, J=11.1 Hz, 1H), 4.34 - 4.25 (m, 1H), 4.25 - 4.17 (m, 2H), 4.10 - 4.00 (m, 2H), 3.36 - 3.08 (m, 2H), 2.98 - 2.78 (m, 2H), 2.62 - 2.49 (m, 2H), 2.14 (m, 2H), 2.01 - 1.79 (m, 2H), 1.16 (br d, J=6.7 Hz, 6H); LCMS (ESI) [M+H]+: 410.2.



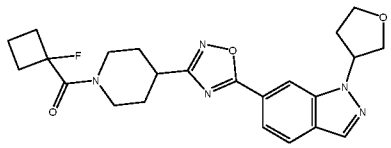
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.21 (s, 1H), 7.97 - 7.87 (m, 2H), 5.91 (quin, J=6.9 Hz, 1H), 5.34 (dt, J=3.0, 6.4 Hz, 2H), 5.23 - 5.14 (m, 2H), 4.22 (sxt, J=6.7 Hz, 1H), 4.01 - 3.90 (m, 1H), 3.31 (ddd, J=5.6, 10.6, 14.0 Hz, 1H), 3.23 - 3.13 (m, 1H), 2.24 - 2.00 (m, 4H), 1.49 (s, 9H), 1.09 (d, J=6.6 Hz, 3H); LCMS (ESI) [M-100+H]+: 340.2.



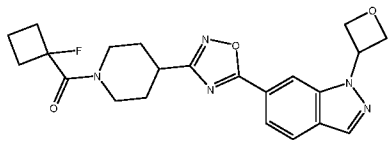
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.06 (s, 1H), 7.88 (s, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.46 (d, J=8.4 Hz, 1H), 6.42 (s, 1H), 5.78 (quin, J=7.0 Hz, 1H), 5.25 (t, J=6.5 Hz, 2H), 5.10 (t, J=7.2 Hz, 2H), 4.12 (br s, 2H), 2.97 - 2.89 (m, 1H), 2.89 - 2.77 (m, 2H), 1.97 - 1.90 (m, 2H), 1.65 (dq, J=4.3, 12.3 Hz, 2H), 1.42 (s, 9H); LCMS (ESI) [M-56+H]+: 369.1.



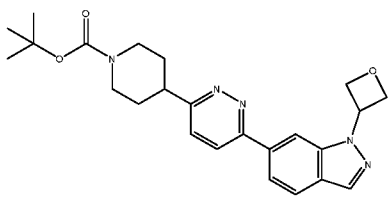
H NMR (400MHz, CHLOROFORM-d) δ 8.07 (s, 1H), 7.88 (s, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.46 (d, J=8.4 Hz, 1H), 6.42 (s, 1H), 5.78 (quin, J=7.0 Hz, 1H), 5.25 (t, J=6.5 Hz, 2H), 5.14 - 5.06 (m, 2H), 4.16 (br s, 2H), 3.66 (s, 3H), 3.00 - 2.86 (m, 3H), 1.96 (br d, J=10.9 Hz, 2H), 1.68 (dq, J=4.2, 12.4 Hz, 2H); LCMS (ESI) [M+H]+: 383.1.



^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.31 (d, J=0.7 Hz, 1H), 8.10 (s, 1H), 7.94 - 7.82 (m, 2H), 5.46 - 5.32 (m, 1H), 4.54 (br d, J=13.2 Hz, 1H), 4.36 - 4.14 (m, 3H), 4.11 - 3.95 (m, 2H), 3.32 - 3.11 (m, 2H), 3.01 (br t, J=12.2 Hz, 1H), 2.90 - 2.65 (m, 2H), 2.61 - 2.32 (m, 4H), 2.24 - 2.06 (m, 2H), 2.03 - 1.85 (m, 3H), 1.79 - 1.61 (m, 1H); LCMS (ESI) [M+H]+: 440.3.

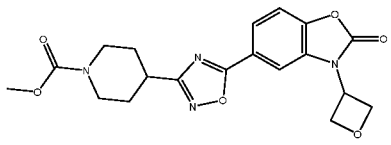


^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.29 (s, 1H), 8.20 (s, 1H), 7.95 - 7.85 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.4 Hz, 2H), 5.22 - 5.14 (m, 2H), 4.55 (br d, J=13.5 Hz, 1H), 4.02 (br d, J=13.7 Hz, 1H), 3.33 - 3.12 (m, 2H), 3.01 (br t, J=12.2 Hz, 1H), 2.87 - 2.67 (m, 2H), 2.54 - 2.35 (m, 2H), 2.22 - 2.09 (m, 2H), 2.03 - 1.87 (m, 3H), 1.76 - 1.62 (m, 1H); LCMS (ESI) [M+H]+: 426.2.



^{1}H NMR (300 MHz, Chloroform-d) δ 8.38 (t, J = 1.1 Hz, 1H), 8.16 (d, J = 0.9 Hz, 1H), 7.96 – 7.82 (m, 2H), 7.77 (dd, J = 8.5, 1.4 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 5.90 (ddd, J = 14.1, 7.7, 6.3 Hz, 1H), 5.34 (t, J =

6.5 Hz, 2H), 5.16 (t, J = 7.2 Hz, 2H), 4.30 (s, 2H), 3.18 (tt, J = 11.9, 3.7 Hz, 1H), 2.93 (t, J = 12.7 Hz, 2H), 2.04 (d, J = 12.1 Hz, 2H), 1.85 (qd, J = 12.5, 4.3 Hz, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+ 436.6.



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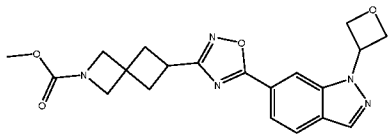
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.29 (d, J=1.2 Hz, 1H), 8.03 (dd, J=1.2, 8.4 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H), 5.60 - 5.44 (m, 1H), 5.25 - 5.10 (m, 4H), 4.36 – 4.05 (m, 2H), 3.73 (s, 3H), 3.15 - 2.92 (m, 3H), 2.08 (br d, J=12.3 Hz, 2H), 1.96 - 1.80 (m, 2H); LCMS (ESI) [M+H]+: 401.1.



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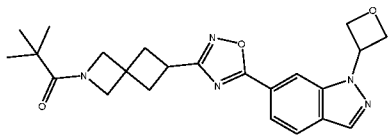
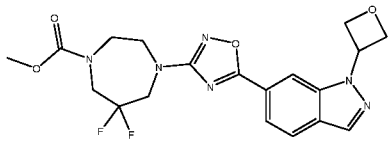
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.13 (s, 1H), 7.88 - 7.77 (m, 2H), 5.83 (quin, J 7.0 Hz, 1H), 5.25 (t, J 6.5 Hz, 2H), 5.10 (t, J 7.2 Hz, 2H), 4.04 (s, 2H), 3.99 (s, 2H), 3.61 (s, 3H), 3.58 - 3.50 (m, 1H), 2.66 - 2.53 (m, 4H); LCMS (ESI) [M+H]+: 396.1.

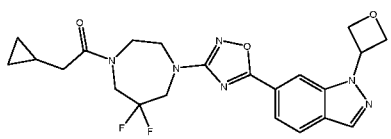
15



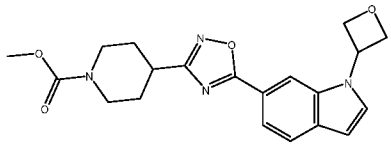
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.32 (s, 1H), 8.22 (s, 1H), 8.00 - 7.89 (m, 2H), 5.92 (quin, J 7.0 Hz, 1H), 5.35 (t, J 6.5 Hz, 2H), 5.20 (t, J 7.3 Hz, 2H), 4.42 (br s, 2H), 4.14 (br s, 2H), 3.66 (br t, J 7.9 Hz,
20 1H), 2.76 - 2.65 (m, 4H), 1.23 (s, 9H); LCMS (ESI) [M+H]+:422.2.



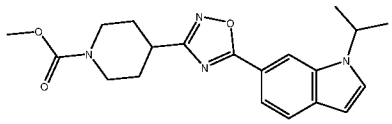
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.20 (s, 1H), 7.91 - 7.83 (m, 2H), 5.91 (quin, J=7.1
25 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.19 (t, J=7.3 Hz, 2H), 4.12 (q, J=11.2 Hz, 2H), 4.01 - 3.79 (m, 6H), 3.78 (s, 3H); LCMS (ESI) [M+H]+: 435.2.



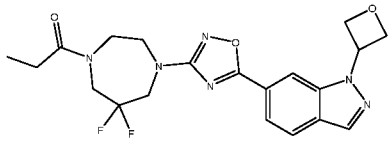
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.21 (s, 1H), 7.91 - 7.83 (m, 2H), 5.91 (quin, J=7.1 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.22 - 5.16 (m, 2H), 4.15 - 4.08 (m, 2H), 3.95 - 3.76 (m, 6H), 2.46 - 2.34 (m, 2H), 1.20 - 1.04 (m, 1H), 0.68 - 0.53 (m, 2H), 0.22 - 0.16 (m, 2H); LCMS (ESI) [M+H]+: 459.3.



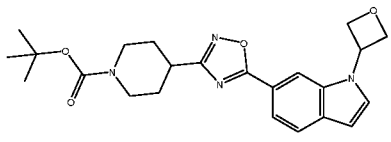
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 7.89 (dd, J=1.3, 8.4 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.72 (d, J=3.3 Hz, 1H), 6.72 (d, J=3.1 Hz, 1H), 5.73 (quin, J=6.8 Hz, 1H), 5.25 (t, J=7.4 Hz, 2H), 5.06 (t, J=6.6 Hz, 2H), 4.20 (br s, 2H), 3.73 (s, 3H), 3.12 - 2.97 (m, 3H), 2.11 (br d, J=12.1 Hz, 2H), 1.97 - 1.84 (m, 2H); LCMS (ESI) [M+H]+: 383.1.



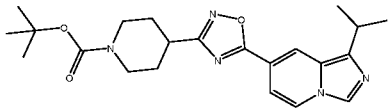
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 7.84 (dd, J=1.3, 8.2 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.42 (d, J=3.1 Hz, 1H), 6.60 (d, J=3.1 Hz, 1H), 4.82 (td, J=6.6, 13.4 Hz, 1H), 4.23 (br s, 2H), 3.73 (s, 3H), 3.11 - 2.97 (m, 3H), 2.11 (br d, J=12.3 Hz, 2H), 1.97 - 1.84 (m, 2H), 1.58 (d, J=6.6 Hz, 6H); LCMS (ESI) [M+H]+: 369.2.



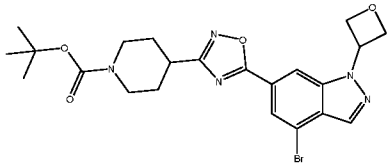
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.20 (s, 1H), 7.91 - 7.84 (m, 2H), 5.91 (quin, J=6.9 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.22 - 5.15 (m, 2H), 4.15 - 4.05 (m, 2H), 3.96 - 3.75 (m, 6H), 2.53 - 2.40 (m, 2H), 1.23 - 1.14 (m, 3H); LCMS (ESI) [M+H]+: 433.1.



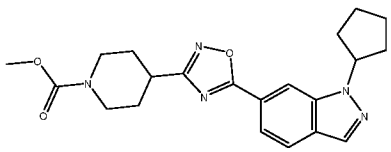
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 7.89 (dd, J=1.2, 8.3 Hz, 1H), 7.78 - 7.69 (m, 2H), 6.72 (d, J=3.3 Hz, 1H), 5.73 (quin, J=6.8 Hz, 1H), 5.24 (t, J=7.4 Hz, 2H), 5.06 (t, J=6.6 Hz, 2H), 4.18 (br d, J=6.2 Hz, 2H), 3.09 - 2.90 (m, 3H), 2.14 - 2.02 (m, 2H), 1.94 - 1.82 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-56+H]+: 369.1.



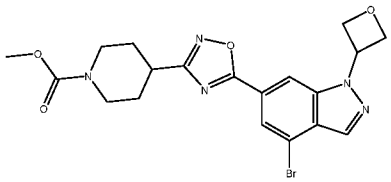
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.07 (s, 1H), 7.83 (dd, J=0.7, 7.5 Hz, 1H), 7.05 (dd, J=1.5, 7.4 Hz, 1H), 4.09 (m, 2H), 3.34 (td, J=6.9, 13.8 Hz, 1H), 3.03 - 2.78 (m, 3H), 1.99 (br d, J=11.0 Hz, 2H), 1.86 - 1.69 (m, 2H), 1.41 (s, 9H), 1.36 (d, J=7.0 Hz, 6H); LCMS (ESI) [M+H]+: 412.2.



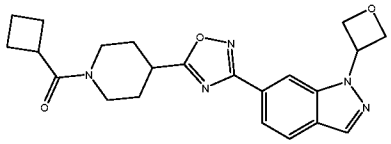
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.22 (s, 1H), 8.20 (s, 1H), 8.09 (d, J=0.8 Hz, 1H), 5.92 - 5.82 (m, 1H), 5.30 (t, J=6.4 Hz, 2H), 5.17 (t, J=7.2 Hz, 2H), 4.17 (br s, 2H), 3.10 - 3.00 (m, 1H), 2.98 -2.93 (m, 2H), 2.08 -2.05 (m, 2H), 1.93 - 1.79 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-56+H]+: 448.0.



^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.28 (d, J=0.8 Hz, 1H), 8.06 (br s, 1H), 7.86 -7.82 (m, 2H), 5.10 -5.06 (m, 1H), 4.30 - 4.14 (m, 2H), 3.72 (s, 3H), 3.16 - 2.94 (m, 3H), 2.26 - 2.16 (m, 4H), 2.14 - 2.06 (m, 2H), 2.04 - 1.97 (m, 2H), 1.96 - 1.84 (m, 2H), 1.83 - 1.72 (m, 2H); LCMS (ESI) [M+H]+: 396.2.

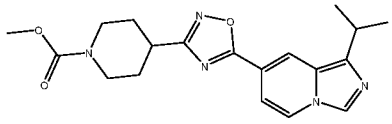


^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.22 (m, 1H), 8.10 - 8.09 (m, 1H), 8.08 (m, 1H), 5.59 -5.82 (m, 1H), 5.30 (t, J=6.8 Hz, 2H), 5.30 (t, J=7.6 Hz, 2H), 4.20 (br s, 2H), 3.72 (s, 3H), 3.10 – 3.00 (m, 3H), 2.10 - 2.03 (m, 2H), 1.92 – 1.86 (m, 2H); LCMS (ESI) [M+H]+: 462.0.



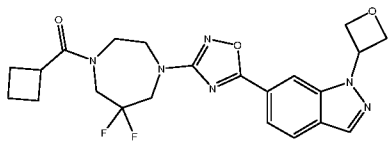
^{1}H NMR (300 MHz, Chloroform-d) δ 8.19 (d, J = 12.9 Hz, 2H), 7.87 (qd, J = 8.5, 1.1 Hz, 2H), 5.97 – 5.81 (m, 1H), 5.33 (t, J = 6.5 Hz, 2H), 5.16 (t, J = 7.2 Hz, 2H), 4.56 (d, J = 13.5 Hz, 1H), 3.82 (d, J = 14.0 Hz,

1H), 3.39 – 3.12 (m, 3H), 3.04 – 2.89 (m, 1H), 2.39 (p, J = 9.2 Hz, 2H), 2.26 – 2.14 (m, 4H), 2.09 – 1.82 (m, 4H); LCMS (ESI) [M+H] 408.5+.



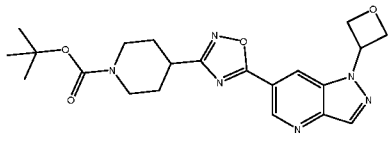
5

^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.25 (s, 1H), 8.07 (s, 1H), 7.83 (dd, J=0.7, 7.3 Hz, 1H), 7.05 (dd, J=1.5, 7.3 Hz, 1H), 4.24 - 4.00 (m, 2H), 3.65 (s, 3H), 3.34 (td, J=6.9, 13.8 Hz, 1H), 3.05 - 2.88 (m, 3H), 2.00 (br d, J=11.4 Hz, 2H), 1.88 - 1.72 (m, 2H), 1.36 (d, J=7.0 Hz, 6H); LCMS (ESI) [M+H]+: 370.1.

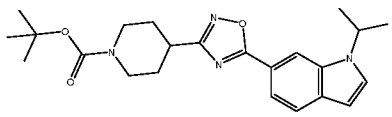


10

^{1}H NMR (400 MHz, DMSO) δ 8.45 (s, 1H), 8.41 (s, 1H), 8.00 (dd, J=1.4, 8.5 Hz, 1H), 7.79 (d, J=8.4 Hz, 1H), 6.33 - 6.22 (m, 1H), 5.03 (d, J=6.8 Hz, 4H), 4.22 - 3.87 (m, 4H), 3.83 - 3.73 (m, 2H), 3.68 (q, J=5.1 Hz, 2H), 3.46 - 3.40 (m, 1H), 2.20 - 2.04 (m, 4H), 1.96 - 1.82 (m, 1H), 1.79 - 1.65 (m, 1H); LCMS (ESI)
15 [M+H]+: 459.1.



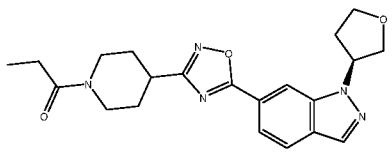
^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.34 (d, J=1.5 Hz, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 5.88 (quin,
20 J=6.9 Hz, 1H), 5.35 - 5.28 (m, 2H), 5.24 - 5.15 (m, 2H), 4.20 (br d, J=9.7 Hz, 2H), 3.08 (tt, J=3.7, 11.2 Hz, 1H), 2.97 (br s, 2H), 2.09 (br d, J=11.0 Hz, 2H), 1.95 - 1.81 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-56+H]+: 371.1.



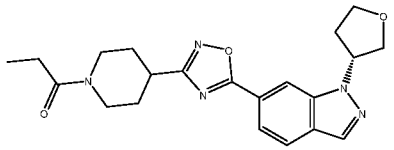
25

^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 7.85 (dd, J=1.3, 8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.42 (d, J=3.1 Hz, 1H), 6.60 (d, J=3.1 Hz, 1H), 4.87 - 4.76 (m, 1H), 4.18 (br d, J=5.7 Hz, 2H), 3.09 - 2.88 (m, 3H), 2.15 - 2.04 (m, 2H), 1.95 - 1.82 (m, 2H), 1.58 (d, J=6.6 Hz, 6H), 1.49 (s, 9H); LCMS (ESI) [M-56+H]+: 355.1.

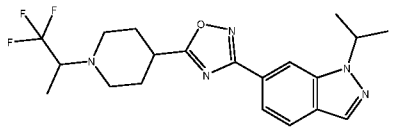
30



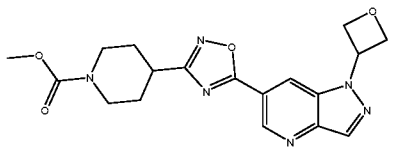
^{1}H NMR (400MHz, CHLOROFORM-d-d) δ 8.31 (d, J=0.9 Hz, 1H), 8.11 (s, 1H), 7.96 - 7.84 (m, 2H), 5.50 - 5.33 (m, 1H), 4.63 (br d, J=13.4 Hz, 1H), 4.36 - 4.17 (m, 3H), 4.09 - 4.02 (m, 1H), 3.97 (br d, J=13.6 Hz, 1H), 3.31 - 3.21 (m, 1H), 3.16 (tt, J=3.9, 10.9 Hz, 1H), 2.97 - 2.84 (m, 1H), 2.60 - 2.51 (m, 2H), 2.41 (q, J=7.5 Hz, 2H), 2.21 - 2.09 (m, 2H), 1.98 - 1.79 (m, 2H), 1.19 (t, J=7.5 Hz, 3H); LCMS (ESI) [M+H]+:396.2.



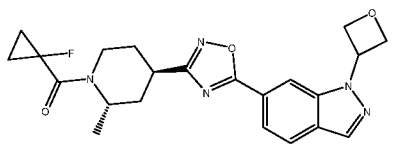
^{1}H NMR (400MHz, CHLOROFORM-d -d) δ 8.32 (d, J=0.7 Hz, 1H), 8.11 (s, 1H), 7.94 - 7.84 (m, 2H), 5.44 - 5.34 (m, 1H), 4.63 (br d, J=13.7 Hz, 1H), 4.35 - 4.17 (m, 3H), 4.10 - 4.02 (m, 1H), 3.97 (br d, J=13.2 Hz, 1H), 3.32 - 3.21 (m, 1H), 3.16 (tt, J=3.9, 10.9 Hz, 1H), 2.91 (br t, J=11.4 Hz, 1H), 2.62 - 2.50 (m, 2H), 2.41 (q, J=7.5 Hz, 2H), 2.23 - 2.08 (m, 2H), 2.01 - 1.78 (m, 2H), 1.19 (t, J=7.5 Hz, 3H); LCMS (ESI) [M+H]+:396.2.



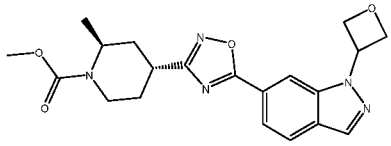
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.08 (s, 1H), 7.91 - 7.79 (m, 2H), 4.99 (td, J=6.6, 13.3 Hz, 1H), 3.32 - 3.17 (m, 1H), 3.15 - 2.99 (m, 3H), 2.80 (br t, J=11.1 Hz, 1H), 2.62 (br t, J=11.0 Hz, 1H), 2.24 - 2.12 (m, 2H), 2.09 - 1.94 (m, 2H), 1.65 (d, J=6.7 Hz, 6H), 1.30 (d, J=7.1 Hz, 3H); LCMS (ESI) [M+H]+:408.2.



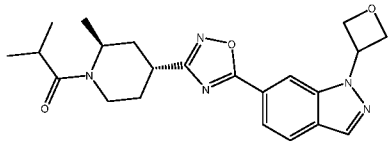
^{1}H NMR (400MHz,CHLOROFORM-d) δ 9.33 (d, J=1.5 Hz, 1H), 8.63 (s, 1H), 8.45 (s, 1H), 5.92 - 5.84 (m, 1H), 5.31 (t, J=6.5 Hz, 2H), 5.24 - 5.17 (m, 2H), 4.21 (br s, 2H), 3.74 (s, 3H), 3.17 - 2.99 (m, 3H), 2.11 (br d, J=11.2 Hz, 2H), 1.97 - 1.84 (m, 2H); LCMS (ESI) [M+H]+: 385.1.



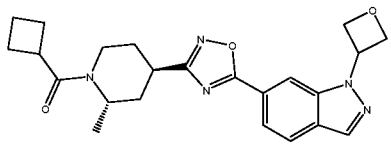
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.96 - 7.86 (m, 2H), 5.91 (quin, J=6.9 Hz, 1H), 5.33 (t, J=6.5 Hz, 2H), 5.18 (t, J=7.4 Hz, 2H), 5.06 - 4.78 (m, 1H), 4.63 - 4.30 (m, 1H), 3.42 (br s, 1.5H), 3.04 (br s, 0.5H), 2.25 - 1.78 (m, 4H), 1.50 - 1.18 (m, 7H); LCMS (ESI) [M+H]+: 426.1.



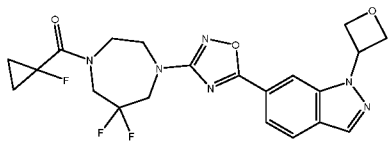
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.97 - 7.85 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.23 - 5.13 (m, 2H), 4.66 (br s, 1H), 4.20 (br s, 1H), 3.74 (s, 3H), 3.28 (tt, J=3.9, 12.2 Hz, 1H), 3.10 (br t, J=12.9 Hz, 1H), 2.17 - 1.95 (m, 3H), 1.81 (dq, J=4.6, 12.9 Hz, 1H), 1.30 (d, J=7.1 Hz, 3H); LCMS (ESI) [M+H]+: 398.1.



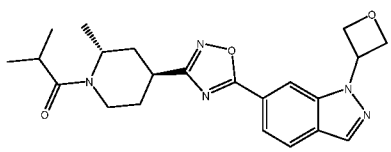
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.96 - 7.87 (m, 2H), 5.91 (quin, J=6.9 Hz, 1H), 5.33 (t, J=6.5 Hz, 2H), 5.22 – 5.12 (m, 2.6H), 4.76 (br d, J=12.6 Hz, 0.4H), 4.45 (br s, 0.4H), 3.94 (br d, J=13.2 Hz, 0.6H), 3.44 - 3.28 (m, 1.6H), 2.92 - 2.76 (m, 1.4H), 2.23 - 1.69 (m, 4H), 1.44 - 1.24 (m, 3H), 1.22 - 1.08 (m, 6H); LCMS (ESI) [M+H]+: 410.2.



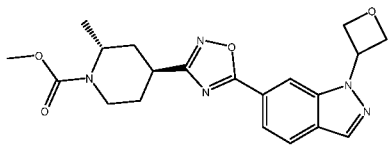
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.19 (s, 1H), 7.94 - 7.84 (m, 2H), 5.89 (quin, J=6.9 Hz, 1H), 5.32 (t, J=6.5 Hz, 2H), 5.17 (t, J=7.3 Hz, 2H), 5.13 - 5.06 (m, 0.5H), 4.69 (br d, J=14.3 Hz, 0.5H), 4.19 (br s, 0.5H), 3.67 (br d, J=13.9 Hz, 0.5H), 3.41 - 3.15 (m, 2.5H), 2.93 - 2.78 (m, 0.5H), 2.50 - 2.28 (m, 2H), 2.26 - 2.07 (m, 3H), 2.05 - 1.68 (m, 5H), 1.37 - 1.23 (m, 3H); LCMS (ESI) [M+H]+: 422.2.



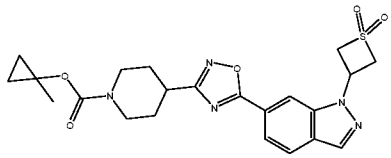
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.24 (s, 1H), 8.21 (s, 1H), 7.92 - 7.86 (m, 2H), 5.91 (quin, J=6.9 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.19 (t, J=7.3 Hz, 2H), 4.30 - 3.86 (m, 8H), 1.44 - 1.25 (m, 4H); LCMS (ESI) [M+H]+: 463.1.



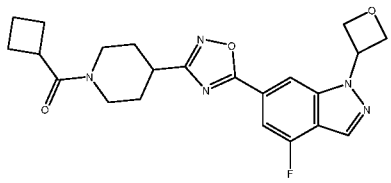
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.96 - 7.86 (m, 2H), 5.95 - 5.87 (m, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.23 – 5.12 (m, 2.6H), 4.76 (br d, J=15.4 Hz, 0.4H), 4.45 (br s, 0.4H), 3.94 (br d, J=13.7 Hz, 0.6H), 3.43 - 3.28 (m, 1.6H), 2.93 - 2.77 (m, 1.4H), 2.22 - 1.69 (m, 4H), 1.43 - 1.25 (m, 3H), 1.22 - 1.10 (m, 6H); LCMS (ESI) [M+H]+: 410.2.



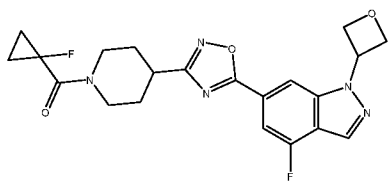
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.97 - 7.87 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.5 Hz, 2H), 5.25 - 5.12 (m, 2H), 4.67 (br s, 1H), 4.19 (br s, 1H), 3.74 (s, 3H), 3.28 (tt, J=3.9, 12.1 Hz, 1H), 3.15 - 3.02 (m, 1H), 2.19 - 1.94 (m, 3H), 1.82 (dq, J=4.6, 12.9 Hz, 1H), 1.30 (d, J=7.1 Hz, 3H); LCMS (ESI) [M+H]+: 398.1.



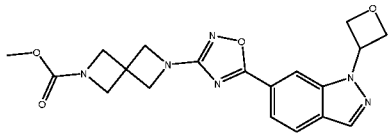
^{1}H NMR (400MHz, DMSO-d6) δ 8.62 (s, 1H), 8.43 (s, 1H), 8.04 (d, J=8.4 Hz, 1H), 7.87 (dd, J=1.1, 8.4 Hz, 1H), 6.16 - 6.01 (m, 1H), 4.93 - 4.84 (m, 2H), 4.81 - 4.73 (m, 2H), 4.11 - 3.83 (m, 2H), 3.20 - 3.10 (m, 1H), 3.00 (br s, 2H), 2.02 (br d, J=11.5 Hz, 2H), 1.72 - 1.58 (m, 2H), 1.49 (s, 3H), 0.83 - 0.75 (m, 2H), 0.65 - 0.58 (m, 2H); LCMS (ESI) [M+H]+: 472.1.



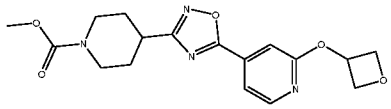
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.57 (d, J=9.9 Hz, 1H), 5.89 (quin, J=7.0 Hz, 1H), 5.31 (t, J=6.5 Hz, 2H), 5.24 - 5.10 (m, 2H), 4.60 (br d, J=13.7 Hz, 1H), 3.82 (br d, J=13.5 Hz, 1H), 3.31 (quin, J=8.6 Hz, 1H), 3.22 - 3.04 (m, 2H), 2.96 - 2.83 (m, 1H), 2.46 - 2.31 (m, 2H), 2.24 - 1.78 (m, 8H); LCMS (ESI) [M+H]+: 426.1.



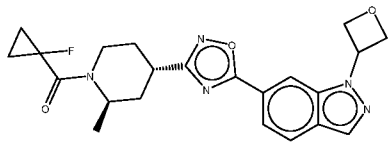
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.11 (s, 1H), 7.58 (dd, J=0.7, 9.9 Hz, 1H), 5.94 - 5.84 (m, 1H), 5.32 (t, J=6.6 Hz, 2H), 5.23 - 5.14 (m, 2H), 4.45 (br s, 2H), 3.43 - 3.00 (m, 3H), 2.18 (br dd, J=3.1, 13.5 Hz, 2H), 2.08 - 1.89 (m, 2H), 1.37 - 1.19 (m, 4H); LCMS (ESI) [M+H]+: 430.1.



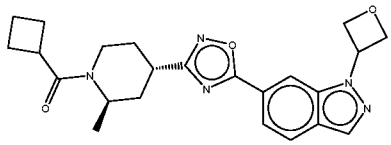
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.23 (d, J=1.0 Hz, 1H), 8.20 (s, 1H), 7.87 (d, J=1.0 Hz, 2H), 5.94 - 5.86 (m, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.17 (t, J=7.4 Hz, 2H), 4.29 (s, 4H), 4.21 (s, 4H), 3.70 (s, 3H); LCMS (ESI) [M+H]+: 397.1.



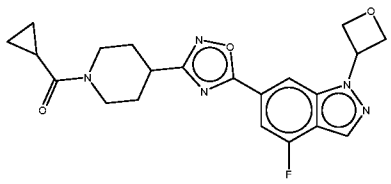
^{1}H NMR (400MHz, DMSO-d6) δ 8.43 - 8.36 (m, 1H), 7.62 (dd, J=1.2, 5.3 Hz, 1H), 7.47 (s, 1H), 5.64 (q, J=5.6 Hz, 1H), 4.92 (t, J=7.2 Hz, 2H), 4.60 (dd, J=5.2, 7.6 Hz, 2H), 3.99 (br d, J=12.2 Hz, 2H), 3.61 (s, 3H), 3.17 (tt, J=3.6, 11.2 Hz, 1H), 3.12 - 2.93 (m, 2H), 2.02 (br d, J=10.8 Hz, 2H), 1.73 - 1.57 (m, 2H); LCMS (ESI) [M+H]+: 361.2.



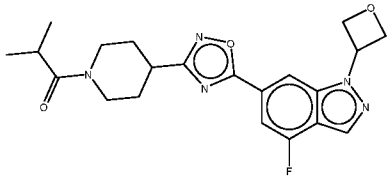
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (d, J=0.7 Hz, 1H), 8.21 (s, 1H), 7.98 - 7.86 (m, 2H), 5.95 - 5.87 (m, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.23 - 5.14 (m, 2H), 5.08 - 4.80 (m, 1H), 4.64 - 4.31 (m, 1H), 3.41 (br s, 1.5H), 3.04 (br s, 0.5H), 2.25 - 1.76 (m, 4H), 1.50 - 1.19 (m, 7H); LCMS (ESI) [M+H]+: 426.1.



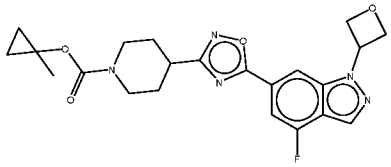
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.95 - 7.82 (m, 2H), 5.91 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.5 Hz, 2H), 5.18 (t, J=7.3 Hz, 2H), 5.15 - 5.07 (m, 0.5H), 4.76 - 4.66 (m, 0.5H), 4.27 - 4.13 (m, 0.5H), 3.68 (br d, J=12.3 Hz, 0.5H), 3.41 - 3.20 (m, 2.5H), 2.88 (dt, J=2.9, 13.6 Hz, 0.5H), 2.51 - 2.31 (m, 2H), 2.26 - 2.09 (m, 3H), 2.06 - 1.69 (m, 5H), 1.37 - 1.25 (m, 3H); LCMS (ESI) [M+H]+: 422.2.



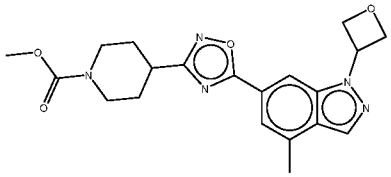
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 8.11 (s, 1H), 7.58 (d, J=9.9 Hz, 1H), 5.89 (quin, J=7.0 Hz, 1H), 5.32 (t, J=6.6 Hz, 2H), 5.22 - 5.15 (m, 2H), 4.59 (br s, 1H), 4.33 (br s, 1H), 3.36 (br s, 1H), 3.18 (tt, J=3.9, 10.9 Hz, 1H), 2.94 (br s, 1H), 2.16 (br s, 2H), 2.06 - 1.84 (m, 2H), 1.84 - 1.76 (m, 1H), 1.02 (br s, 2H), 0.80 (dd, J=3.0, 8.0 Hz, 2H); LCMS (ESI) [M+H]+: 412.1.



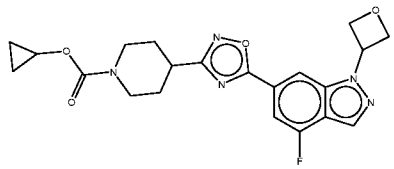
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.58 (d, J=9.8 Hz, 1H), 5.89 (quin, J=7.0 Hz, 1H), 5.32 (t, J=6.5 Hz, 2H), 5.22 - 5.16 (m, 2H), 4.64 (br d, J=13.2 Hz, 1H), 4.05 (br d, J=13.0 Hz, 1H), 3.28 (br t, J=12.0 Hz, 1H), 3.16 (tt, J=3.9, 11.0 Hz, 1H), 2.95 - 2.80 (m, 2H), 2.16 (br s, 2H), 1.99 - 1.79 (m, 2H), 1.17 (br s, 6H); LCMS (ESI) [M+H]+: 414.2.



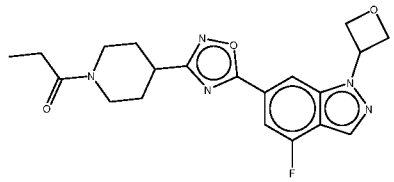
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.62 - 7.54 (m, 1H), 5.94 - 5.83 (m, 1H), 5.32 (t, J=6.6 Hz, 2H), 5.22 - 5.14 (m, 2H), 4.35 - 3.99 (m, 2H), 3.12 - 2.91 (m, 3H), 2.08 (br d, J=11.5 Hz, 2H), 1.94 - 1.79 (m, 2H), 1.58 (s, 3H), 0.93 - 0.86 (m, 2H), 0.69 - 0.62 (m, 2H); LCMS (ESI) [M+H]+: 442.1.



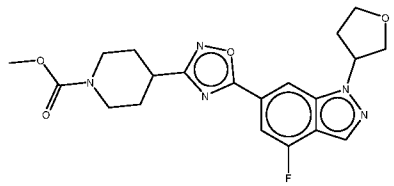
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 8.10 (s, 1H), 7.70 (s, 1H), 5.87 (quin, J=6.8 Hz, 1H), 5.32 (t, J=6.4 Hz, 2H), 5.16 (t, J=7.2 Hz, 2H), 4.21 (br s, 2H), 3.73 (s, 3H), 3.13 - 2.93 (m, 3H), 2.69 (s, 3H), 2.09 (br d, J=12.8 Hz, 2H), 1.98 - 1.79 (m, 2H); LCMS (ESI) [M+H]+: 398.1.



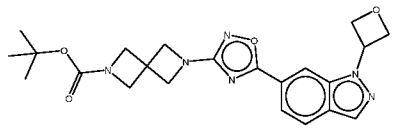
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.57 (d, J=9.9 Hz, 1H), 5.88 (quin, J=6.9 Hz, 1H), 5.32 (t, J=6.6 Hz, 2H), 5.22 - 5.15 (m, 2H), 4.34 - 4.04 (m, 3H), 3.13 - 2.96 (m, 3H), 2.15 - 2.01 (m, 2H), 1.88 (br d, J=9.5 Hz, 2H), 0.76 - 0.65 (m, 4H); LCMS (ESI) [M+H]+: 428.2.



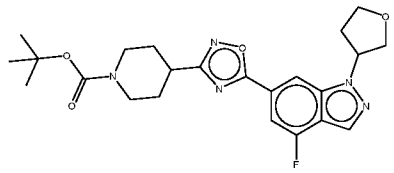
^{1}H NMR (400MHz, CHLOROFORM-d-d) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.58 (dd, J=0.8, 9.8 Hz, 1H), 6.01 - 5.80 (m, 1H), 5.32 (t, J=6.6 Hz, 2H), 5.23 - 5.13 (m, 2H), 4.63 (br d, J=13.3 Hz, 1H), 3.97 (br d, J=13.8 Hz, 1H), 3.36 - 3.09 (m, 2H), 2.98 - 2.81 (m, 1H), 2.41 (q, J=7.5 Hz, 2H), 2.23 - 2.05 (m, 2H), 1.98 - 1.76 (m, 2H), 1.19 (t, J=7.5 Hz, 3H); LCMS (ESI) [M+H]+:400.1.



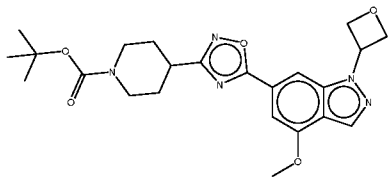
^{1}H NMR (400MHz, DMSO-d6) δ 8.09 (s, 1H), 8.04 (s, 1H), 7.47 (d, J=9.9 Hz, 1H), 5.33 - 5.26 (m, 1H), 4.25 - 4.16 (m, 2H), 4.14 (d, J=5.1 Hz, 2H), 4.12 - 3.94 (m, 2H), 3.66 (s, 3H), 3.05 - 2.99 (m, 1H), 2.99 - 2.89 (m, 2H), 2.55 - 2.42 (m, 2H), 2.02 (br d, J=11.4 Hz, 2H), 1.88 - 1.76 (m, 2H); LCMS (ESI) [M+H]+: 416.2.



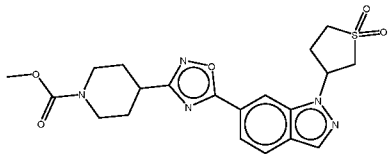
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.15 (s, 1H), 8.12 (s, 1H), 7.79 (d, J=0.9 Hz, 2H), 5.82 (quin, J=7.0 Hz, 1H), 5.25 (t, J=6.6 Hz, 2H), 5.09 (t, J=7.3 Hz, 2H), 4.20 (s, 4H), 4.06 (s, 4H), 1.38 (s, 9H); LCMS (ESI) [M+H]+: 439.1.



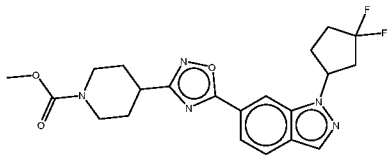
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 8.04 (s, 1H), 7.48 (d, J=9.9 Hz, 1H), 5.34 - 5.26 (m, 1H), 4.26 - 4.16 (m, 2H), 4.15 - 4.12 (m, 2H), 3.98 (dt, J=6.1, 8.2 Hz, 2H), 3.03 - 2.95 (m, 1H), 2.89 (br s, 2H), 2.55 - 2.41 (m, 2H), 2.01 (br d, J=11.7 Hz, 2H), 1.85 - 1.74 (m, 2H), 1.42 (s, 9H); LCMS (ESI) [M+23]+: 480.2, [M-56+H]: 402.1.



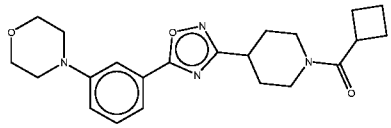
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.16 (s, 1H), 7.80 (s, 1H), 7.14 (s, 1H), 5.77 (quin, J=7.0 Hz, 1H), 5.24 (t, J=6.5 Hz, 2H), 5.08 (t, J=7.2 Hz, 2H), 4.20 - 4.04 (m, 2H), 4.00 (s, 3H), 3.02 - 2.94 (m, 1H), 2.89 (br t, J=11.9 Hz, 2H), 2.01 (br d, J=11.2 Hz, 2H), 1.87 - 1.73 (m, 2H), 1.42 (s, 9H); LCMS (ESI) [M-56+H]+: 400.1.



^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.26 (s, 1H), 8.12 (s, 1H), 7.94 - 7.85 (m, 2H), 5.27 (quin, J=7.6 Hz, 1H), 4.21 (br s, 2H), 3.73 (s, 3H), 3.10 – 3.00 (m, 3H), 2.97 - 2.69 (m, 2H), 2.66 - 2.51 (m, 1H), 2.44 (q, J=7.5 Hz, 2H), 2.37 - 2.20 (m, 1H), 2.10 -2.04 (m, 2H), 1.97 - 1.83 (m, 2H); LCMS (ESI) [M+H]+: 446.1.

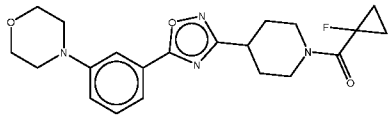


^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.26 (s, 1H), 8.16 (s, 1H), 7.97 - 7.74 (m, 2H), 5.56 (quin, J=7.2 Hz, 1H), 4.20 (br s, 2H), 3.72 - 3.60 (m, 6H),3.30 - 3.11 (m, 1H), 3.08 - 3.00 (m, 3H), 2.95 - 2.7(m, 2H), 2.20 - 1.99 (m, 2H), 1.97 - 1.84 (m, 2H); LCMS (ESI) [M+H]+: 432.1.

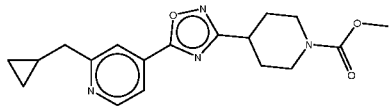


^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.67 - 7.57 (m, 2H), 7.42 (t, J=7.9 Hz, 1H), 7.13 (dd, J=2.1, 8.3 Hz, 1H), 4.58 (br d, J=13.3 Hz, 1H), 3.97 - 3.86 (m, 4H), 3.81 (br d, J=13.7 Hz, 1H), 3.36 - 3.24 (m, 5H),

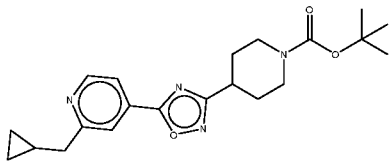
3.20 - 3.07 (m, 2H), 2.94 - 2.83 (m, 1H), 2.40 (quin, J=9.0 Hz, 2H), 2.25 - 2.15 (m, 2H), 2.15 - 2.07 (m, 2H), 2.05 - 1.89 (m, 2H), 1.89 - 1.80 (m, 2H); LCMS (ESI) [M+H]+: 397.2.



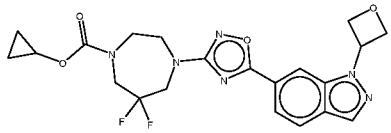
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.69 - 7.58 (m, 2H), 7.43 (t, J=7.9 Hz, 1H), 7.14 (dd, J=2.0, 8.3 Hz, 1H), 4.45 (br d, J=9.5 Hz, 2H), 3.96 - 3.87 (m, 4H), 3.39 - 3.04 (m, 7H), 2.18 (br d, J=10.8 Hz, 2H), 2.09 - 1.89 (m, 2H), 1.37 - 1.21 (m, 4H); LCMS (ESI) [M+H]+: 401.2.



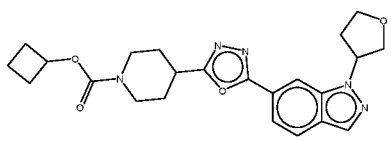
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.77 (d, J=5.0 Hz, 1H), 7.96 (s, 1H), 7.80 (d, J=4.9 Hz, 1H), 4.22 (br s, 2H), 3.75 (s, 3H), 3.17 - 2.97 (m, 3H), 2.86 (d, J=7.0 Hz, 2H), 2.10 (br d, J=12.8 Hz, 2H), 1.99 - 1.81 (m, 2H), 1.26 - 1.13 (m, 1H), 0.71 - 0.58 (m, 2H), 0.38 - 0.27 (m, 2H); LCMS (ESI) [M+H]+:343.1.



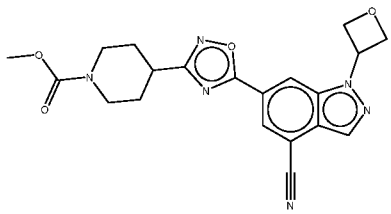
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.77 (d, J=5.1 Hz, 1H), 7.96 (s, 1H), 7.81 (d, J=4.8 Hz, 1H), 4.20 (br s, 2H), 3.16 - 2.92 (m, 3H), 2.86 (d, J=7.1 Hz, 2H), 2.08 (br d, J=11.2 Hz, 2H), 1.97 - 1.78 (m, 2H), 1.50 (s, 9H), 1.25 - 1.13 (m, 1H), 0.67 - 0.58 (m, 2H), 0.32 (q, J=4.8 Hz, 2H); LCMS (ESI) [M+H]+:385.2.



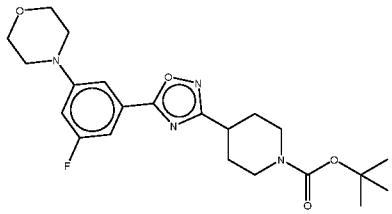
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.23 (s, 1H), 8.20 (s, 1H), 7.91 - 7.85 (m, 2H), 5.91 (quin, J=6.9 Hz, 1H), 5.33 (t, J=6.6 Hz, 2H), 5.23 - 5.15 (m, 2H), 4.21 - 4.04 (m, 3H), 4.02 - 3.66 (m, 6H), 0.74 (d, J=3.5 Hz, 4H); LCMS (ESI) [M+H]+: 461.1.



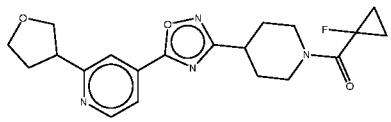
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.21 (s, 1H), 8.10 (s, 1H), 7.90 - 7.80 (m, 2H), 5.43 - 5.34 (m, 1H), 4.97 (q, J=7.4 Hz, 1H), 4.34 - 4.26 (m, 1H), 4.25 - 4.15 (m, 4H), 4.11 - 4.00 (m, 1H), 3.23 (tt, J=3.8, 11.0 Hz, 1H), 3.06 (br s, 2H), 2.59 - 2.51 (m, 2H), 2.42 - 2.31 (m, 2H), 2.17 (br dd, J=2.8, 13.4 Hz, 2H), 2.13 - 2.02 (m, 2H), 2.01 - 1.88 (m, 2H), 1.79 (q, J=10.4 Hz, 1H), 1.69 - 1.56 (m, 1H); LCMS (ESI) [M+H]+: 438.2.



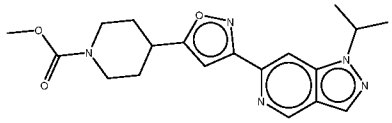
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.53 (s, 1H), 8.40 (s, 1H), 8.30 (s, 1H), 5.96 -5.89 (m, 1H), 5.30 (t, J=7.2 Hz, 2H), 5.20 (t, J=7.2 Hz, 2H), 4.21 (br s, 2H), 3.73 (s, 3H), 3.10 – 3.00 (m, 3H), 2.10 -1.93 (m, 2H), 1.92 – 1.84 (m, 2H); LCMS (ESI) [M+H]+: 409.1.



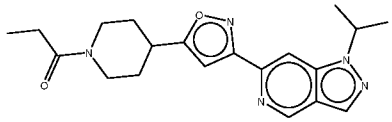
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.34 (s, 1H), 7.20 (s, 1H), 6.69 (br d, J=11.6 Hz, 1H), 4.09 (br s, 2H), 3.84 - 3.78 (m, 4H), 3.20 - 3.15 (m, 4H), 2.99 - 2.93 (m, 1H), 2.89 (br d, J=15.3 Hz, 2H), 1.98 (br d, J=12.2 Hz, 2H), 1.82 - 1.74 (m, 2H), 1.41 (s, 9H); LCMS (ESI) [M-100+H]+: 333.1.



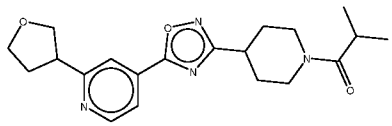
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.89 (s, 1H), 7.81 (dd, J=1.3, 5.1 Hz, 1H), 4.45 (br s, 2H), 4.23 (t, J=8.2 Hz, 1H), 4.13 (dt, J=5.2, 8.3 Hz, 1H), 4.04 - 3.93 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.50 - 2.86 (m, 3H), 2.50 - 2.39 (m, 1H), 2.28 (qd, J=7.6, 12.3 Hz, 1H), 2.21 - 2.14 (m, 2H), 1.96 (br d, J=10.8 Hz, 2H), 1.39 - 1.12 (m, 4H); LCMS (ESI) [M+H]+:387.1.



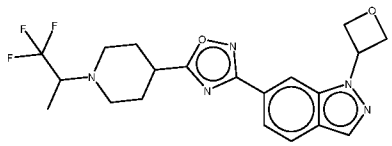
^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.12 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 6.74 (s, 1H), 4.92 (quin, J=6.7 Hz, 1H), 4.22 (br s, 2H), 3.73 (s, 3H), 3.11 - 2.94 (m, 3H), 2.13 (br d, J=11.2 Hz, 2H), 1.81 - 1.66 (m, 2H), 1.63 (d, J=6.6 Hz, 6H); LCMS (ESI) [M+H]+:370.1.



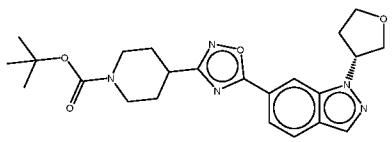
^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.12 (d, J=0.9 Hz, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 6.74 (s, 1H), 4.92 (td, J=6.6, 13.4 Hz, 1H), 4.67 (br d, J=13.9 Hz, 1H), 3.96 (br d, J=14.1 Hz, 1H), 3.23 (br t, J=11.7 Hz, 1H), 3.18 - 3.08 (m, 1H), 2.85 (br t, J=11.7 Hz, 1H), 2.40 (q, J=7.4 Hz, 2H), 2.18 (br t, J=13.7 Hz, 2H), 1.82 - 1.69 (m, 2H), 1.63 (d, J=6.6 Hz, 6H), 1.18 (t, J=7.5 Hz, 3H); LCMS (ESI) [M+H]+:368.2.



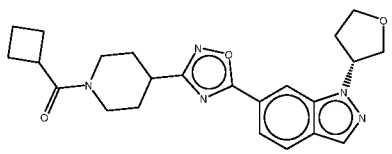
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz, 1H), 4.64 (br d, J=13.7 Hz, 1H), 4.23 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.2, 8.4 Hz, 1H), 4.09 - 3.94 (m, 3H), 3.71 (quin, J=7.6 Hz, 1H), 3.32 - 3.12 (m, 2H), 2.93 - 2.80 (m, 2H), 2.49 - 2.39 (m, 1H), 2.33 - 2.23 (m, 1H), 2.19 - 2.09 (m, 2H), 1.97 - 1.77 (m, 2H), 1.16 (br d, J=5.1 Hz, 6H); LCMS (ESI) [M+H]+:371.2.



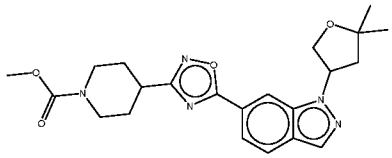
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.14 (s, 1H), 8.09 (s, 1H), 7.85 - 7.81 (d,J=8.4 1H), 7.79 - 7.74 (d,J=8.4 1H), 5.87 - 5.76 (m, 1H), 5.26 (t, J=6.7 Hz, 2H), 5.08 (t, J=7.3 Hz, 2H), 3.21 - 3.08 (m, 1H), 3.05 - 2.91 (m, 3H), 2.71 (br t, J=10.8 Hz, 1H), 2.53 (br t, J=11.1 Hz, 1H), 2.15 - 2.01 (m, 2H), 1.99 - 1.83 (m, 2H), 1.21 (d, J=7.1 Hz, 3H); LCMS (ESI) [M+H]+:422.2.



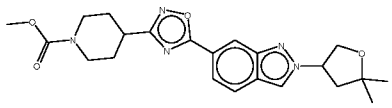
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.31 (s, 1H), 8.11 (s, 1H), 7.95 - 7.85 (m, 2H), 5.46 - 5.36 (m, 1H), 4.38 - 4.11 (m, 5H), 4.09 - 3.98 (m, 1H), 3.15 - 2.89 (m, 3H), 2.63 - 2.49 (m, 2H), 2.09 (br d, J=11.9 Hz, 2H), 1.98 - 1.81 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-56+H]+:384.1.



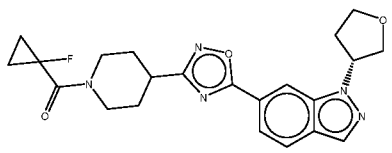
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.31 (s, 1H), 8.11 (s, 1H), 7.94 - 7.83 (m, 2H), 5.45 - 5.34 (m, 1H), 4.60 (br d, J=13.2 Hz, 1H), 4.36 - 4.25 (m, 1H), 4.25 - 4.17 (m, 2H), 4.10 - 4.01 (m, 1H), 3.82 (br d, J=13.7 Hz, 1H), 3.31 (quin, J=8.6 Hz, 1H), 3.21 - 3.08 (m, 2H), 2.95 - 2.84 (m, 1H), 2.59 - 2.51 (m, 2H), 2.46 - 2.32 (m, 2H), 2.24 - 2.08 (m, 4H), 2.05 - 1.94 (m, 1H), 1.93 - 1.80 (m, 3H); LCMS (ESI) [M+H]+:422.2.



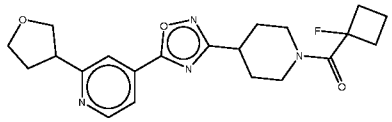
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.31 (s, 1H), 8.10 (s, 1H), 7.93 - 7.83 (m, 2H), 5.43 (quin, J=7.2 Hz, 1H), 4.40 - 4.09 (m, 4H), 3.73 (s, 3H), 3.19 - 2.91 (m, 3H), 2.54 - 2.35 (m, 2H), 2.10 (br d, J=11.2 Hz, 2H),1.96 - 1.84 (m, 2H), 1.52 (s, 3H), 1.40 (s, 3H); LCMS (ESI) [M+H]+:426.2.



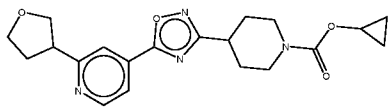
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.55 (s, 1H), 8.15 (s, 1H), 7.77 (s, 2H), 5.37 - 5.26 (m, 1H), 4.41 - 4.29 (m, 2H), 4.18 (br s, 2H), 3.72 (s, 3H), 3.13 - 2.94 (m, 3H), 2.59 - 2.46 (m, 1H), 2.39 (br dd, J=5.2, 13.2 Hz, 1H), 2.09 (br d, J=12.0 Hz, 2H), 1.97 - 1.77 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H); LCMS (ESI) [M+H]+:426.2.



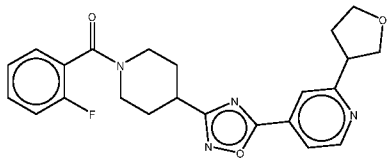
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.32 (d, J=0.6 Hz, 1H), 8.11 (s, 1H), 7.94 - 7.84 (m, 2H), 5.45 - 5.35 (m, 1H), 4.46 (br d, J=8.8 Hz, 2H), 4.34 - 4.17 (m, 3H), 4.11 - 4.00 (m, 1H), 3.51 - 2.91 (m, 3H), 2.63 - 2.49 (m, 2H), 2.19 (br dd, J=3.0, 13.5 Hz, 2H), 2.00 (br d, J=10.1 Hz, 2H), 1.39 - 1.17 (m, 4H); LCMS (ESI) [M+H]+:426.2.



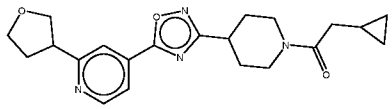
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.4, 5.0 Hz, 1H), 4.54 (br d, J=12.6 Hz, 1H), 4.23 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.1, 8.3 Hz, 1H), 4.06 - 3.94 (m, 3H), 3.71 (quin, J=7.6 Hz, 1H), 3.29 - 3.13 (m, 2H), 3.00 (br t, J=12.5 Hz, 1H), 2.87 - 2.66 (m, 2H), 2.55 - 2.36 (m, 3H), 2.28 (qd, J=7.6, 12.4 Hz, 1H), 2.20 - 2.06 (m, 2H), 2.00 - 1.84 (m, 3H), 1.69 (qd, J=8.9, 17.9 Hz, 1H); LCMS (ESI) [M+H]+:401.1.



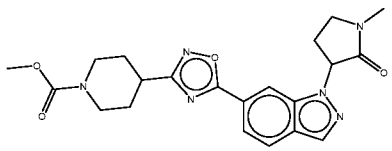
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz, 1H), 4.23 (t, J=8.0 Hz, 2H), 4.17 - 4.03 (m, 3H), 4.02 - 3.94 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.16 - 2.93 (m, 3H), 2.50 - 2.38 (m, 1H), 2.34 - 2.22 (m, 1H), 2.07 (br d, J=11.2 Hz, 2H), 1.86 (br d, J=11.5 Hz, 2H), 0.75 - 0.67 (m, 4H); LCMS (ESI) [M+H]+:385.1.



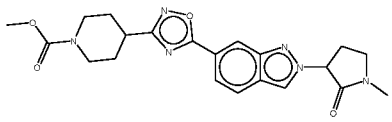
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.81 (dd, J=1.2, 5.0 Hz, 1H), 7.47 - 7.36 (m, 2H), 7.26 - 7.19 (m, 1H), 7.12 (t, J=9.0 Hz, 1H), 4.74 (br d, J=13.2 Hz, 1H), 4.23 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.1, 8.3 Hz, 1H), 4.03 - 3.93 (m, 2H), 3.78 - 3.64 (m, 2H), 3.38 - 3.05 (m, 3H), 2.51 - 2.38 (m, 1H), 2.35 - 2.18 (m, 2H), 2.12 - 1.80 (m, 3H); LCMS (ESI) [M+H]+:423.1.



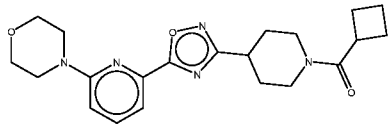
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=4.9 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.2, 5.2 Hz, 1H), 4.63 (br d, J=13.2 Hz, 1H), 4.23 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.1, 8.3 Hz, 1H), 3.97 (quin, J=7.6 Hz, 3H), 3.71 (quin, J=7.6 Hz, 1H), 3.31 - 3.10 (m, 2H), 2.91 (br t, J=12.1 Hz, 1H), 2.50 - 2.39 (m, 1H), 2.33 (d, J=6.6 Hz, 2H), 2.31 - 2.22 (m, 1H), 2.20 - 2.07 (m, 2H), 1.97 - 1.79 (m, 2H), 1.14 - 1.02 (m, 1H), 0.63 - 0.55 (m, 2H), 0.25 - 0.18 (m, 2H); LCMS (ESI) [M+H]+:383.1.



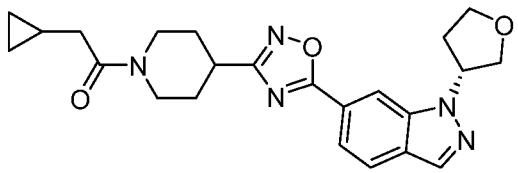
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.30 (s, 1H), 8.13 (s, 1H), 7.92 - 7.83 (m, 2H), 5.41 (t, J=8.4 Hz, 1H), 4.20 (br s, 2H), 3.78 - 3.66 (m, 4H), 3.59 -3.53 (m, 1H), 3.12 - 2.97 (m, 6H), 2.82 - 2.63 (m, 2H), 2.09 (br d, J=11.2 Hz, 2H), 1.96 - 1.82 (m, 2H); LCMS (ESI) [M+H]+:425.2.



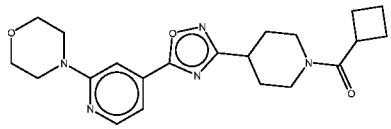
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.54 (d, J=0.9 Hz, 1H), 8.22 (br s, 1H), 7.82 - 7.73 (m, 2H), 5.27 - 5.18 (m, 1H), 4.18 (br s, 2H), 3.78 - 3.73 (m, 1H), 3.72 (s, 3H), 3.61 - 3.49 (m, 1H), 3.11 - 3.01 (m, 3H), 3.00 (s, 3H), 2.97 - 2.85 (m, 1H), 2.85 - 2.71 (m, 1H), 2.09 (br d, J=11.2 Hz, 2H), 1.96 - 1.81 (m, 2H); LCMS (ESI) [M+H]+:425.2.



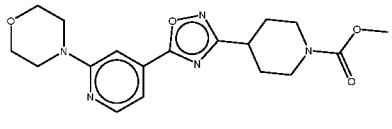
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.70 - 7.65 (m, 1H), 7.55 (d, J=7.3 Hz, 1H), 6.84 (d, J=8.6 Hz, 1H), 4.57 (br d, J=13.0 Hz, 1H), 3.89 - 3.85 (m, 4H), 3.81 (br d, J=13.3 Hz, 1H), 3.68 - 3.63 (m, 4H), 3.31 (quin, J=8.6 Hz, 1H), 3.19 - 3.09 (m, 2H), 2.96 - 2.86 (m, 1H), 2.45 - 2.33 (m, 2H), 2.24 - 2.07 (m, 4H), 2.04 - 1.94 (m, 1H), 1.93 - 1.80 (m, 3H); LCMS (ESI) [M+H]+:398.2.



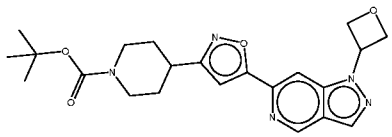
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.31 (s, 1H), 8.11 (s, 1H), 7.94 - 7.84 (m, 2H), 5.45 - 5.35 (m, 1H), 4.64 (br d, J=13.2 Hz, 1H), 4.36 - 4.26 (m, 1H), 4.25 - 4.17 (m, 2H), 4.11 - 4.01 (m, 1H), 3.96 (br d, J=13.8Hz, 1H), 3.26 (br t, J=11.4 Hz, 1H), 3.16 (tt, J=4.0, 10.9 Hz, 1H), 2.92 (br t, J=11.2 Hz, 1H), 2.60 - 2.51 (m, 2H), 2.34 (d, J=6.8 Hz, 2H), 2.16 (br d, J=14.6 Hz, 2H), 2.00 - 1.85 (m, 2H), 1.14 - 1.02 (m, 1H), 0.65 - 0.55 (m, 2H), 0.26 - 0.17 (m, 2H); LCMS (ESI) [M+H]+:422.2.



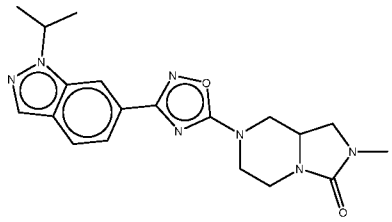
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.37 (d, J=5.1 Hz, 1H), 7.29 (s, 1H), 7.26 (br s, 1H), 4.59 (br d, J=13.0 Hz, 1H), 3.89 - 3.75 (m, 5H), 3.65 - 3.57 (m, 4H), 3.30 (quin, J=8.7 Hz, 1H), 3.20 - 3.06 (m, 2H), 2.92 - 2.80 (m, 1H), 2.46 - 2.30 (m, 2H), 2.22 - 1.77 (m, 8H); LCMS (ESI) [M+H]+: 398.2.



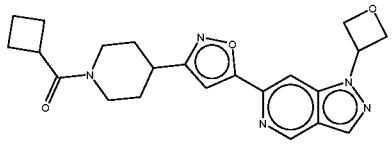
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.37 (d, J=5.1 Hz, 1H), 7.29 (s, 1H), 7.27 - 7.25 (m, 1H), 4.20 (br s, 2H), 3.89 - 3.82 (m, 4H), 3.73 (s, 3H), 3.65 - 3.58 (m, 4H), 3.12 - 2.97 (m, 3H), 2.07 (br d, J=12.3 Hz, 2H), 1.92 - 1.81 (m, 2H); LCMS (ESI) [M+H]+: 374.1.



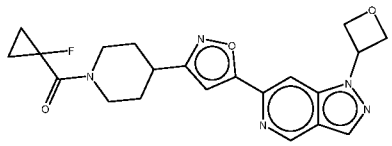
^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.06 (s, 1H), 8.22 (s, 1H), 7.92 (s, 1H), 6.80 (s, 1H), 5.80 - 5.72 (m, 1H), 5.23 (t, J=6.5 Hz, 2H), 5.15 - 5.04 (m, 2H), 4.15-4.01 (m, 2H), 2.97 - 2.71 (m, 3H), 1.94 (br d, J=12.3 Hz, 2H), 1.75 - 1.57 (m, 2H), 1.41 (s, 9H); LCMS (ESI) [M+H]+:426.2.



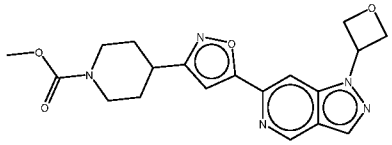
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.11 (s, 1H), 8.04 (s, 1H), 7.80 - 7.73 (m, 2H), 5.01 - 4.86 (m, 1H), 4.35 - 4.17 (m, 2H), 4.00 (dd, J=2.8, 13.2 Hz, 1H), 3.86 - 3.74 (m, 1H), 3.51 (t, J=8.8 Hz, 1H), 3.26 - 3.16 (m, 1H), 3.15 - 3.03 (m, 3H), 2.85 (s, 3H), 1.62 (d, J=6.8 Hz, 6H); LCMS (ESI) [M+H]+:382.1.



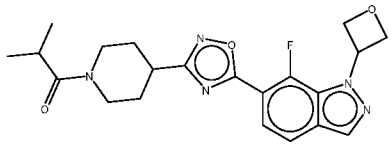
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.06 (d, J=1.0 Hz, 1H), 8.23 (s, 1H), 7.92 (s, 1H), 6.79 (s, 1H), 5.79 (quin, J=6.9 Hz, 1H), 5.27 - 5.17 (m, 2H), 5.11 (t, J=7.3 Hz, 2H), 4.57 (br d, J=13.3 Hz, 1H), 3.75 (br d, J=13.4 Hz, 1H), 3.29 - 3.16 (m, 1H), 3.12 - 2.95 (m, 2H), 2.79 - 2.68 (m, 1H), 2.39 - 2.25 (m, 2H), 2.16 - 2.05 (m, 2H), 1.99 (br d, J=13.1 Hz, 2H), 1.95 - 1.76 (m, 2H), 1.70 - 1.58 (m, 3H); LCMS (ESI) [M+H]+:408.2.



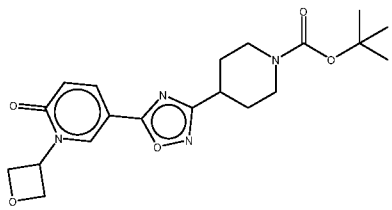
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.06 (d, J=1.1 Hz, 1H), 8.23 (s, 1H), 7.93 (s, 1H), 6.82 (s, 1H), 5.86 - 5.72 (m, 1H), 5.24 (t, J=6.6 Hz, 2H), 5.15 - 5.09 (m, 2H), 4.42 (br s, 2H), 3.36 - 2.75 (m, 3H), 2.06 (br d, J=11.1 Hz, 2H), 1.77 (br d, J=8.8 Hz, 2H), 1.36 - 1.06 (m, 4H); LCMS (ESI) [M+H]+:412.1.



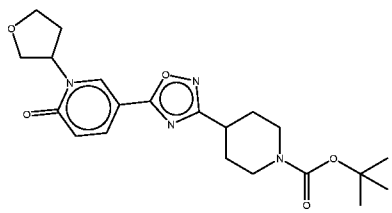
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.13 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 6.86 (s, 1H), 5.85 (quin, J=6.9 Hz, 1H), 5.30 (t, J=6.6 Hz, 2H), 5.21 - 5.14 (m, 2H), 4.22 (m, 2H), 3.72 (s, 3H), 3.10 - 2.86 (m, 3H), 2.03 (br d, J=12.6 Hz, 2H), 1.75 (dq, J=4.2, 12.3 Hz, 2H); LCMS (ESI) [M+H]+:384.1.



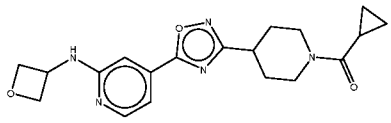
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.21 (d, J=2.2 Hz, 1H), 7.82 (dd, J=5.6, 8.5 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 6.12 (quin, J=7.0 Hz, 1H), 5.33 (t, J=6.4 Hz, 2H), 5.15 (t, J=7.1 Hz, 2H), 4.64 (br d, J=13.7 Hz, 1H), 4.05 (br d, J=12.8 Hz, 1H), 3.36 - 3.13 (m, 2H), 2.98 - 2.78 (m, 2H), 2.17 (br s, 2H), 2.03 - 1.78 (m, 2H), 1.17 (br s, 6H); LCMS (ESI) [M+H]+:414.1.



^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.52 (d, J=2.4 Hz, 1H), 8.00 - 7.95 (m, 1H), 6.71 - 6.64 (m, 1H), 5.86 - 5.76 (m, 1H), 5.16 (t, J=7.6 Hz, 2H), 4.88 - 4.79 (m, 2H), 4.16 (br s, 2H), 3.08 - 2.85 (m, 3H), 2.11 - 1.94 (m, 2H), 1.90 - 1.74 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-55+H]+:347.1.

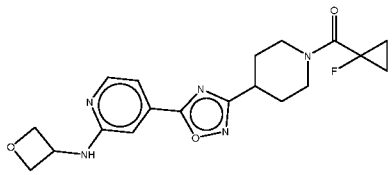


^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.40 (d, J=2.4 Hz, 1H), 7.92 (dd, J=2.4, 9.5 Hz, 1H), 6.65 (d, J=9.6 Hz, 1H), 5.71 - 5.62 (m, 1H), 4.25 (dt, J=5.6, 8.7 Hz, 1H), 4.20 - 4.03 (m, 3H), 3.99 - 3.84 (m, 2H), 3.04 - 2.86 (m, 3H), 2.65 (dtd, J=5.6, 8.4, 14.2 Hz, 1H), 2.11 - 1.95 (m, 3H), 1.88 - 1.74 (m, 2H), 1.53 - 1.42 (m, 1H), 1.48 (s, 9H); LCMS (ESI) [M+H]+:417.2.

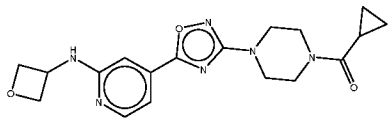


^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.28 (d, J=5.3 Hz, 1H), 7.26 (d, J=1.3 Hz, 1H), 7.03 (s, 1H), 5.21 (br d, J=4.4 Hz, 1H), 5.10 - 5.02 (m, 3H), 4.63 - 4.55 (m, 3H), 4.30 (br d, J=12.8 Hz, 1H), 3.35 (br s, 1H), 3.17 (tt, J=3.9, 10.9 Hz, 1H), 2.92 (br s, 1H), 2.14 (br s, 2H), 2.01 - 1.75 (m, 3H), 1.01 (br s, 2H), 0.79 (dd,

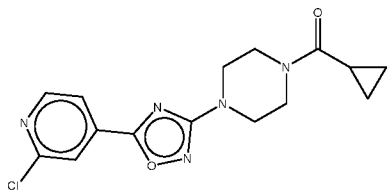
J=3.0, 8.0 Hz, 2H); ^{1}H NMR (400MHz, METHANOL-d4) δ 8.17 (dd, J=0.6, 5.4 Hz, 1H), 7.22 (s, 1H), 7.19 (dd, J=1.5, 5.4 Hz, 1H), 5.08 - 5.01 (m, 1H), 5.01 - 4.96 (m, 2H), 4.60 (t, J=6.0 Hz, 2H), 4.52 - 4.34 (m, 2H), 3.50 - 3.38 (m, 1H), 3.28 - 3.21 (m, 1H), 2.99 (br t, J=12.5 Hz, 1H), 2.23 - 2.05 (m, 2H), 2.05 - 1.97 (m, 1H), 1.88 (br d, J=10.1 Hz, 1H), 1.76 (br d, J=10.5 Hz, 1H), 0.93 - 0.87 (m, 2H), 0.86 - 0.79 (m, 2H); LCMS (ESI) [M+H]+:370.1.



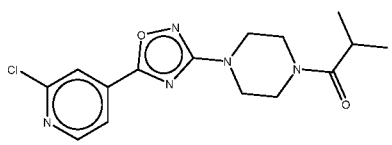
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.28 (d, J=5.1 Hz, 1H), 7.26 (br s, 1H), 7.03 (s, 1H), 5.19 (br d, J=5.1 Hz, 1H), 5.10 - 5.02 (m, 3H), 4.62 - 4.55 (m, 2H), 4.46 (br s, 2H), 3.33 (br s, 1H), 3.24 - 3.15 (m, 1H), 3.05 (br s, 1H), 2.20 - 2.12 (m, 2H), 1.95 (br d, J=9.7 Hz, 2H), 1.35 - 1.21 (m, 4H); LCMS (ESI) [M+H]+: 388.1.



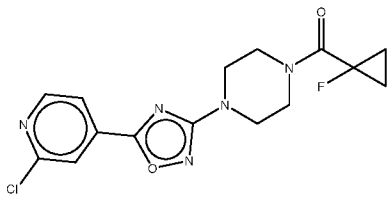
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.30 - 8.21 (m, 1H), 7.22 (dd, J=1.1, 5.3 Hz, 1H), 6.98 (s, 1H), 5.17 (br d, J=4.0 Hz, 1H), 5.09 - 5.00 (m, 3H), 4.61 - 4.55 (m, 2H), 3.80 (br s, 4H), 3.57 (br s, 4H), 1.83 - 1.73 (m, 1H), 1.07 - 1.01 (m, 2H), 0.86 - 0.78 (m, 2H); LCMS (ESI) [M+H]+: 371.1.



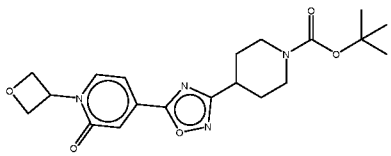
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.61 (d, J=5.1 Hz, 1H), 7.98 (s, 1H), 7.85 (dd, J=1.3, 5.1 Hz, 1H), 3.81 (br s, 4H), 3.59 (br d, J=10.8 Hz, 4H), 1.83 - 1.73 (m, 1H), 1.08 - 1.02 (m, 2H), 0.87 - 0.79 (m, 2H); LCMS (ESI) [M+H]+: 334.1.



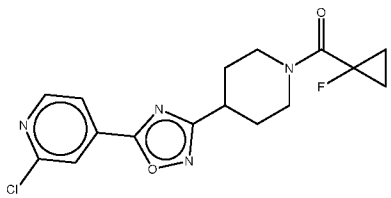
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.61 (d, J=5.1 Hz, 1H), 7.97 (s, 1H), 7.84 (dd, J=1.2, 5.2 Hz, 1H), 3.85 - 3.62 (m, 4H), 3.57 (br s, 4H), 2.84 (td, J=6.7, 13.5 Hz, 1H), 1.18 (d, J=6.8 Hz, 6H); [M+H]+: 336.1.



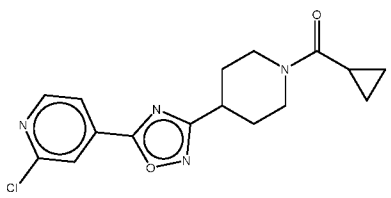
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.61 (d, J=5.1 Hz, 1H), 7.98 (s, 1H), 7.85 (dd, J=1.3, 5.1 Hz, 1H), 3.85 (br s, 4H), 3.66 - 3.58 (m, 4H), 1.38 - 1.23 (m, 4H); LCMS (ESI) [M+H]+: 352.1.



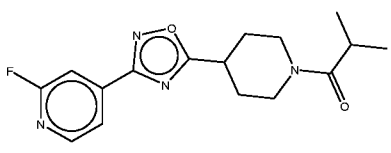
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.80 (d, J=7.3 Hz, 1H), 7.31 (d, J=1.1 Hz, 1H), 6.95 (dd, J=1.8, 7.3 Hz, 1H), 5.86 (quin, J=6.8 Hz, 1H), 5.16 (t, J=7.5 Hz, 2H), 4.78 (t, J=6.7 Hz, 2H), 4.27 - 4.03 (m, 2H), 3.10 - 2.86 (m, 3H), 2.11 - 2.00 (m, 2H), 1.89 - 1.76 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-Boc+H]+:303.1.



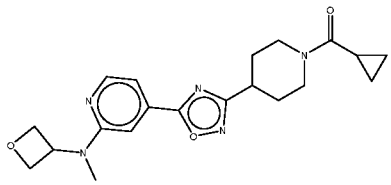
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.64 (d, J=5.0 Hz, 1H), 8.03 (s, 1H), 7.90 (dd, J=1.3, 5.0 Hz, 1H), 4.45 (br d, J=11.5 Hz, 2H), 3.45 - 2.92 (m, 3H), 2.17 (br dd, J=3.3, 13.3 Hz, 2H), 1.95 (br d, J=11.0 Hz, 2H), 1.37 - 1.26 (m, 3H), 1.24 (br d, J=3.1 Hz, 1H); LCMS (ESI) [M+H]+:351.0.



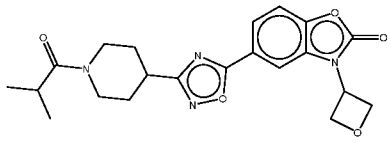
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.63 (d, J=5.0 Hz, 1H), 8.03 (s, 1H), 7.90 (dd, J=1.3, 5.1 Hz, 1H), 4.58 (br s, 1H), 4.31 (br d, J=7.3 Hz, 1H), 3.35 (br s, 1H), 3.19 (tt, J=4.0, 11.0 Hz, 1H), 2.93 (br s, 1H), 2.14 (br s, 2H), 2.02 - 1.84 (m, 2H), 1.83 - 1.74 (m, 1H), 1.07 - 0.94 (m, 2H), 0.79 (dd, J=3.0, 8.0 Hz, 2H); LCMS (ESI) [M+H]+:333.0.



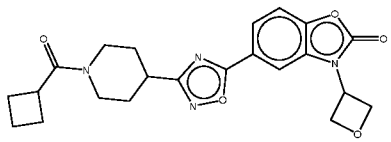
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.40 (d, J=5.3 Hz, 1H), 7.86 (d, J=5.1 Hz, 1H), 7.61 (s, 1H), 4.59 (br d, J=12.5 Hz, 1H), 4.05 (br d, J=13.0 Hz, 1H), 3.41 - 3.23 (m, 2H), 2.97 (br t, J=11.9 Hz, 1H), 2.85 (td, J=6.7, 13.5 Hz, 1H), 2.23 (br s, 2H), 2.03 - 1.82 (m, 2H), 1.17 (d, J=6.7 Hz, 6H); LCMS (ESI) [M+H]+:319.1.



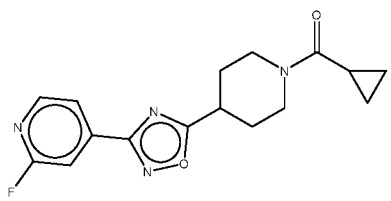
^{1}H NMR (400MHz, CHLOROFORM-d-d) δ 8.32 (d, J=5.1 Hz, 1H), 7.26 (dd, J=1.3, 5.1 Hz, 1H), 7.20 (s, 1H), 5.53 (quin, J=7.2 Hz, 1H), 4.96 (t, J=7.2 Hz, 2H), 4.84 (t, J=6.8 Hz, 2H), 4.69 - 4.51 (m, 1H), 4.31 (br s, 1H), 3.36 (br s, 1H), 3.19 (s, 4H), 2.94 (br s, 1H), 2.16 (br s, 2H), 2.05 - 1.84 (m, 2H), 1.83 - 1.74 (m, 1H), 1.03 (br s, 2H), 0.80 (dd, J=3.1, 7.9 Hz, 2H); LCMS (ESI) [MS+H]+:384.2.



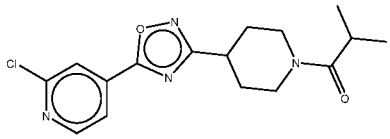
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.28 (d, J=1.5 Hz, 1H), 8.03 (dd, J=1.6, 8.4 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H), 5.58 - 5.48 (m, 1H), 5.23 - 5.12 (m, 4H), 4.63 (br d, J=12.7 Hz, 1H), 4.04 (br d, J=13.3 Hz, 1H), 3.26 (br t, J=11.9 Hz, 1H), 3.14 (tt, J=3.9, 11.0 Hz, 1H), 2.96 - 2.79 (m, 2H), 2.16 (br d, J=13.1 Hz, 2H), 2.00 - 1.76 (m, 2H), 1.16 (br s, 6H); LCMS (ESI) [M+H]+:413.1.



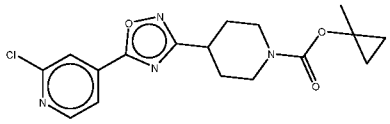
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.29 (d, J=1.3 Hz, 1H), 8.04 (dd, J=1.6, 8.4 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H), 5.58 - 5.48 (m, 1H), 5.23 - 5.12 (m, 4H), 4.63 (br d, J=13.0 Hz, 1H), 4.04 (br d, J=13.2 Hz, 1H), 3.26 (br t, J=12.0 Hz, 1H), 3.14 (tt, J=3.8, 11.0 Hz, 2H), 2.95 - 2.79 (m, 1H), 2.50 - 2.31 (m, 1H), 2.22 - 2.07 (m, 4H), 2.05 - 1.93 (m, 1H), 1.92 - 1.76 (m, 3H); LCMS (ESI) [M+H]+:425.1.



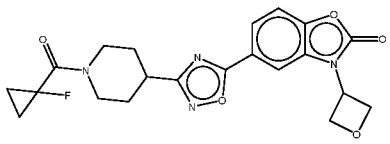
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.31 (d, J=5.1 Hz, 1H), 7.78 (d, J=5.1 Hz, 1H), 7.53 (s, 1H), 4.54 - 4.13 (m, 2H), 3.39 - 3.17 (m, 2H), 2.93 (br s, 1H), 2.15 (br s, 2H), 1.98 - 1.77 (m, 2H), 1.75 - 1.66 (m, 1H), 0.99 - 0.89 (m, 2H), 0.76 - 0.66 (m, 2H); LCMS (ESI) [M+H]+:317.1.



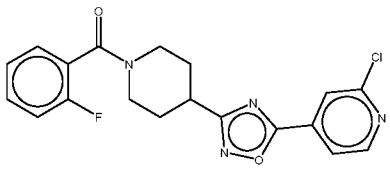
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.63 (d, J=5.0 Hz, 1H), 8.03 (s, 1H), 7.90 (d, J=4.8 Hz, 1H), 4.64 (br d, J=12.8 Hz, 1H), 4.04 (br d, J=13.8 Hz, 1H), 3.26 (br t, J=11.9 Hz, 1H), 3.17 (tt, J=3.9, 11.0 Hz, 1H), 2.94 - 2.80 (m, 2H), 2.14 (br s, 2H), 1.96 - 1.76 (m, 2H), 1.16 (br d, J=4.2 Hz, 6H); LCMS (ESI) [M+H]+:335.1.



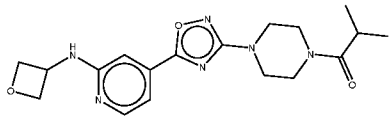
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.63 (d, J=5.1 Hz, 1H), 8.03 (s, 1H), 7.89 (dd, J=1.2, 5.2 Hz, 1H), 4.31 - 3.99 (m, 2H), 3.07 (tt, J=3.8, 11.2 Hz, 1H), 2.97 (br t, J=12.1 Hz, 2H), 2.06 (br d, J=11.0 Hz, 2H), 1.83 (br d, J=10.4 Hz, 2H), 1.57 (s, 3H), 0.92 - 0.86 (m, 2H), 0.68 - 0.62 (m, 2H); LCMS (ESI) [M+H]+:363.0.



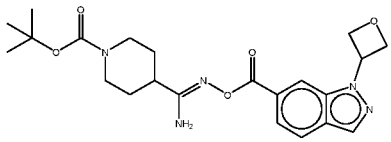
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.29 (d, J=1.5 Hz, 1H), 8.04 (dd, J=1.6, 8.4 Hz, 1H), 7.41 (d, J=8.3 Hz, 1H), 5.57 - 5.48 (m, 1H), 5.23 - 5.13 (m, 4H), 4.45 (br d, J=11.1 Hz, 2H), 3.48 - 2.95 (m, 3H), 2.23 - 2.10 (m, 2H), 1.97 (br d, J=10.9 Hz, 2H), 1.40 - 1.16 (m, 4H); LCMS (ESI) [M+H]+:429.1.



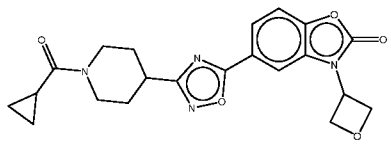
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.64 (d, J=4.9 Hz, 1H), 8.05 - 8.02 (m, 1H), 7.90 (d, J=4.9 Hz, 1H), 7.46 - 7.38 (m, 2H), 7.27 - 7.21 (m, 1H), 7.17 - 7.08 (m, 1H), 4.74 (br d, J=13.2 Hz, 1H), 3.70 (br d, J=13.3 Hz, 1H), 3.33 - 3.08 (m, 3H), 2.23 (br d, J=13.3 Hz, 1H), 2.11 - 1.83 (m, 3H); LCMS (ESI) [M+H]+:387.1.



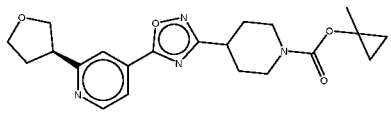
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.29 - 8.22 (m, 1H), 7.22 (dd, J=1.3, 5.3 Hz, 1H), 6.98 (s, 1H), 5.17 (br d, J=4.0 Hz, 1H), 5.12 - 4.98 (m, 3H), 4.64 - 4.52 (m, 2H), 3.82 - 3.61 (m, 4H), 3.55 (br s, 4H), 2.89 - 2.77 (m, 1H), 1.17 (d, J=6.8 Hz, 6H); LCMS (ESI) [M+H]+:373.2.



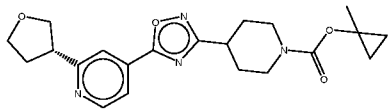
^{1}H NMR (400MHz, DMSO-d6) δ 8.50 (s, 1H), 8.37 (s, 1H), 7.94 - 7.79 (m, 2H), 6.58 (br s, 2H), 6.29 (quin, J=7.1 Hz, 1H), 5.15 - 4.95 (m, 4H), 4.13 - 3.95 (m, 2H), 2.95 - 2.70 (m, 2H), 2.43 - 2.29 (m, 1H), 1.85 - 1.55 (m, 4H), 1.42 (s, 9H); LCMS (ESI) [M-56+H]+:388.2.



^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.29 (d, J=1.5 Hz, 1H), 8.04 (dd, J=1.6, 8.3 Hz, 1H), 7.41 (d, J=8.3 Hz, 1H), 5.59 - 5.46 (m, 1H), 5.25 - 5.10 (m, 4H), 4.58 (br s, 1H), 4.30 (br s, 1H), 3.35 (br s, 1H), 3.16 (tt, J=3.9, 11.0 Hz, 1H), 2.93 (br s, 1H), 2.15 (br s, 2H), 2.04 - 1.86 (m, 2H), 1.83 - 1.76 (m, 1H), 1.02 (br s, 2H), 0.79 (dd, J=2.9, 7.9 Hz, 2H); LCMS (ESI) [M+H]+:411.1.

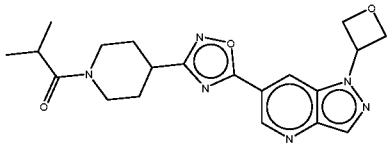


^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.78 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz, 1H), 4.29 - 4.02 (m, 4H), 4.01 - 3.93 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.11 - 2.91 (m, 3H), 2.49 - 2.39 (m, 1H), 2.28 (qd, J=7.6, 12.3 Hz, 1H), 2.11 - 2.01 (m, 2H), 1.84 (br d, J=10.4 Hz, 2H), 1.57 (s, 3H), 0.94 - 0.86 (m, 2H), 0.69 - 0.61 (m, 2H); LCMS (ESI) [M+H]+:399.2.



^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.78 (d, J=4.9 Hz, 1H), 7.87 (s, 1H), 7.80 (dd, J=1.5, 5.1 Hz, 1H), 4.32 - 4.02 (m, 4H), 4.02 - 3.91 (m, 2H), 3.70 (quin, J=7.6 Hz, 1H), 3.10 - 2.88 (m, 3H), 2.50 - 2.38

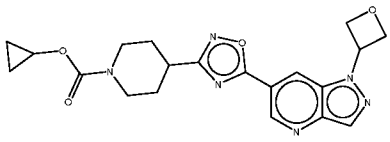
(m, 1H), 2.28 (qd, J=7.6, 12.3 Hz, 1H), 2.10 - 2.01 (m, 2H), 1.84 (br d, J=10.1 Hz, 2H), 1.57 (s, 3H), 0.94 - 0.81 (m, 2H), 0.67 - 0.62 (m, 2H); LCMS (ESI) [M+H]+:399.2.



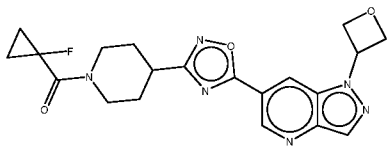
5

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.34 (d, J=1.6 Hz, 1H), 8.64 (s, 1H), 8.46 (s, 1H), 5.88 (quin, J=6.9 Hz, 1H), 5.35 - 5.28 (m, 2H), 5.25 - 5.16 (m, 2H), 4.66 (br d, J=13.2 Hz, 1H), 4.06 (br d, J=13.2 Hz, 1H), 3.28 (br t, J=12.7 Hz, 1H), 3.19 (tt, J=4.0, 11.0 Hz, 1H), 2.96 - 2.78 (m, 2H), 2.25 - 2.09 (m, 2H), 2.02 - 1.79 (m, 2H), 1.17 (br t, J=5.9 Hz, 6H); LCMS (ESI) [M+H]+:397.2.

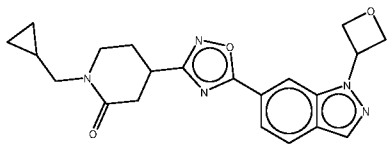
10



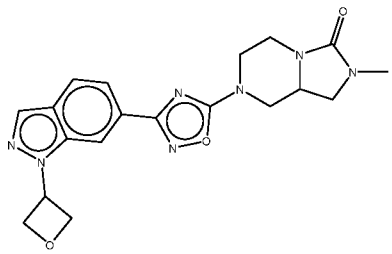
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.35 (d, J=1.6 Hz, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 5.90 (quin, J=6.9 Hz, 1H), 5.38 - 5.29 (m, 2H), 5.27 - 5.18 (m, 2H), 4.43 - 3.98 (m, 3H), 3.18 - 3.08 (m, 1H), 3.08 -
15 2.98 (m, 2H), 2.11 (br s, 2H), 1.91 (br d, J=9.9 Hz, 2H), 0.78 - 0.69 (m, 4H); LCMS (ESI) [M+H]+:411.1.



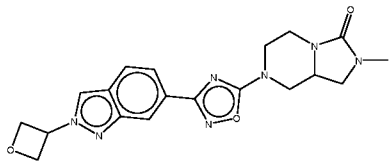
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.34 (d, J=1.7 Hz, 1H), 8.64 (s, 1H), 8.46 (s, 1H), 5.96 - 5.82
20 (m, 1H), 5.31 (t, J=6.6 Hz, 2H), 5.26 - 5.17 (m, 2H), 4.49 (br s, 2H), 3.57 - 2.87 (m, 3H), 2.20 (br dd, J=2.8, 13.4 Hz, 2H), 2.10 - 1.89 (m, 2H), 1.42 - 1.18 (m, 4H); LCMS (ESI) [M+H]+:413.1.



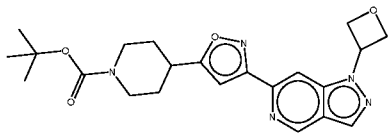
25 ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.30 (d, J=0.9 Hz, 1H), 8.20 (s, 1H), 7.95 - 7.87 (m, 2H), 5.97 - 5.84 (m, 1H), 5.33 (t, J=6.5 Hz, 2H), 5.23 - 5.11 (m, 2H), 3.60 - 3.53 (m, 2H), 3.51 - 3.36 (m, 2H), 3.34 - 3.27 (m, 1H), 2.94 - 2.80 (m, 2H), 2.42 - 2.31 (m, 1H), 2.29 - 2.15 (m, 1H), 1.09 - 0.96 (m, 1H), 0.58 - 0.48 (m, 2H), 0.28 (q, J=5.0 Hz, 2H); LCMS (ESI) [M+H]+:394.1.



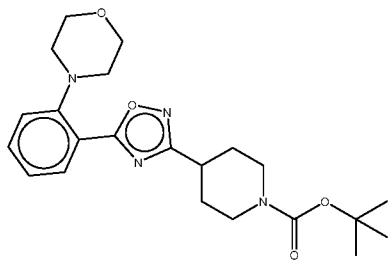
^{1}H NMR (400MHz, METHANOL-d4) δ 8.25 (s, 1H), 8.21 (s, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.79 - 7.75 (m, 1H), 6.13 - 6.01 (m, 1H), 5.26 - 5.21 (m, 2H), 5.19 - 5.14 (m, 2H), 4.29 (dd, J=3.2, 12.8 Hz, 1H), 4.19 (br d, J=13.2 Hz, 1H), 3.92 - 3.81 (m, 2H), 3.55 (t, J=8.8 Hz, 1H), 3.25 - 3.10 (m, 4H), 2.82 (s, 3H); LCMS (ESI) [M+H]+:396.1.



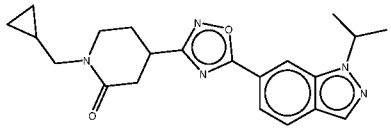
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.45 (s, 1H), 8.14 (s, 1H), 7.72 (s, 2H), 5.75 (quin, J=6.8 Hz, 1H), 5.26 - 5.15 (m, 4H), 4.31 - 4.24 (m, 1H), 4.18 (br d, J=13.2 Hz, 1H), 4.03 - 3.95 (m, 1H), 3.84 - 3.74 (m, 1H), 3.51 (t, J=8.6 Hz, 1H), 3.25 - 3.15 (m, 1H), 3.14 - 3.11 (m, 1H), 3.10 - 3.03 (m, 2H), 2.85 (s, 3H); LCMS (ESI) [M+H]+:396.1.



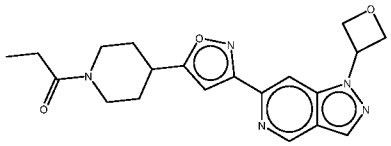
^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.16 (d, J=1.1 Hz, 1H), 8.30 (s, 1H), 8.16 (s, 1H), 6.73 (s, 1H), 5.85 (quin, J=6.9 Hz, 1H), 5.31 (t, J=6.6 Hz, 2H), 5.20 - 5.13 (m, 2H), 4.19 (br s, 2H), 3.09 - 3.00 (m, 1H), 2.99 - 2.87 (m, 2H), 2.11 (br d, J=11.0 Hz, 2H), 1.80 - 1.67 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+:426.2.



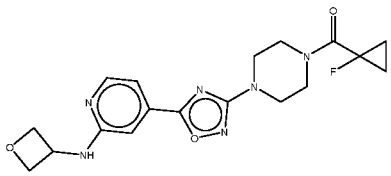
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.02 (dd, J=1.2, 7.7 Hz, 1H), 7.58 - 7.45 (m, 1H), 7.20 - 7.12 (m, 2H), 4.26 - 4.07 (m, 2H), 3.93 - 3.84 (m, 4H), 3.07 - 2.90 (m, 7H), 2.09 (br d, J=11.2 Hz, 2H), 1.92 - 1.80 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+:415.2.



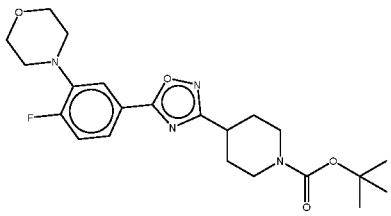
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.27 (s, 1H), 8.09 (s, 1H), 7.89 - 7.83 (m, 2H), 4.97 (td, J=6.7, 13.3 Hz, 1H), 3.59 - 3.52 (m, 2H), 3.50 - 3.26 (m, 3H), 2.97 - 2.79 (m, 2H), 2.36 (td, J=4.4, 9.0 Hz, 1H), 2.29 - 2.14 (m, 1H), 1.64 (d, J=6.7 Hz, 6H), 1.09 - 0.96 (m, 1H), 0.59 - 0.45 (m, 2H), 0.27 (q, J=4.9 Hz, 2H); LCMS (ESI) [M+H]+:380.2.



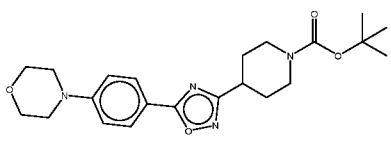
^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.17 (d, J=0.7 Hz, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 6.75 (s, 1H), 5.86 (quin, J=7.0 Hz, 1H), 5.32 (t, J=6.6 Hz, 2H), 5.23 - 5.12 (m, 2H), 4.68 (br d, J=13.3 Hz, 1H), 3.97 (br d, J=13.3 Hz, 1H), 3.30 -3.19 (t, 1H), 3.19- 3.09 (m, 1H), 2.86 (br t, J=11.4 Hz, 1H), 2.41 (q, J=7.5 Hz, 2H), 2.19 (br t, J=14.2 Hz, 2H), 1.76 (q, J=12.0 Hz, 2H), 1.21 - 1.17 (t,3 H); LCMS (ESI) [M+H]+:382.2.



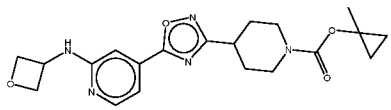
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.26 (d, J=5.3 Hz, 1H), 7.22 (dd, J=1.1, 5.3 Hz, 1H), 6.98 (s, 1H), 5.18 (br d, J=4.4 Hz, 1H), 5.11 - 4.98 (m, 3H), 4.64 - 4.53 (m, 2H), 3.98 - 3.69 (m, 4H), 3.65 - 3.50 (m, 4H), 1.39 - 1.21 (m, 4H); LCMS (ESI) [M+H]+:389.1.



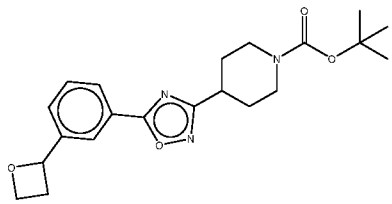
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.74 (ddd, J=2.1, 4.4, 8.3 Hz, 1H), 7.68 (dd, J=2.1, 8.3 Hz, 1H), 7.17 (dd, J=8.4, 12.1 Hz, 1H), 4.15 (br s, 2H), 3.93 - 3.88 (m, 4H), 3.20 - 3.15 (m, 4H), 3.06 - 2.89 (m, 3H), 2.05 (br d, J=12.1 Hz, 2H), 1.91 - 1.78 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M-100+H]+:333.1.



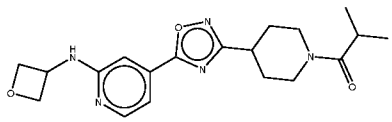
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.00 (d, J=9.0 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 4.15 (br d, J=6.8 Hz, 2H), 3.91 - 3.86 (m, 4H), 3.35 - 3.30 (m, 4H), 3.04 - 2.89 (m, 3H), 2.09 - 2.01 (m, 2H), 1.90 - 1.78 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-56+H]+:359.1.



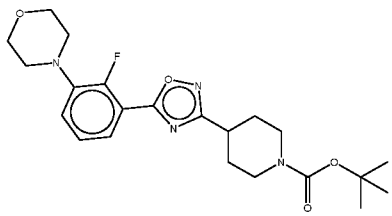
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.27 (d, J=5.3 Hz, 1H), 7.25 (br d, J=1.2 Hz, 1H), 7.03 (s, 1H), 5.19 (br d, J=4.9 Hz, 1H), 5.09 - 5.02 (m, 3H), 4.62 - 4.55 (m, 2H), 4.33 - 3.98 (m, 2H), 3.11 - 2.91 (m, 3H), 2.05 (br d, J=11.7 Hz, 2H), 1.83 (br d, J=10.6 Hz, 2H), 1.57 (s, 3H), 0.92 - 0.86 (m, 2H), 0.68 - 0.62 (m, 2H); LCMS (ESI) [M+H]+:400.2.



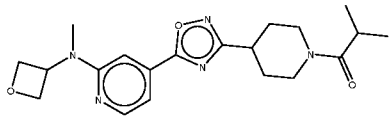
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 8.07 (d, J=7.8 Hz, 1H), 7.70 (d, J=7.7 Hz, 1H), 7.62 - 7.54 (m, 1H), 5.91 (t, J=7.5 Hz, 1H), 4.95 - 4.85 (m, 1H), 4.73 (td, J=5.8, 9.2 Hz, 1H), 4.17-4.07 (m, 2H), 3.17 - 2.92 (m, 4H), 2.77 - 2.62 (m, 1H), 2.08 (br d, J=11.0 Hz, 2H), 1.96 - 1.83 (m, 2H), 1.50 (s, 9H); LCMS (ESI) [M+Na]+:408.1.



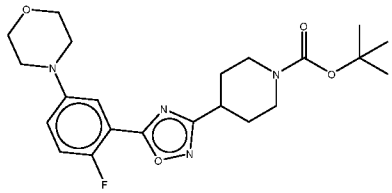
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.28 (d, J=5.3 Hz, 1H), 7.26 (s, 1H), 7.03 (s, 1H), 5.20 (br s, 1H), 5.10 - 5.02 (m, 3H), 4.67 - 4.55 (m, 3H), 4.04 (br d, J=13.7 Hz, 1H), 3.26 (br t, J=11.7 Hz, 1H), 3.20 - 3.10 (m, 1H), 2.93 - 2.79 (m, 2H), 2.20 - 2.07 (m, 2H), 1.96 - 1.76 (m, 2H), 1.17 (br s, 6H); LCMS (ESI) [M-Boc+H]+:333.1.



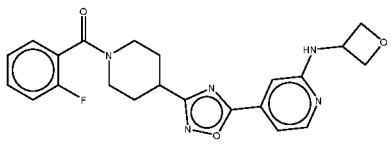
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.71 - 7.65 (m, 1H), 7.25 - 7.20 (m, 1H), 7.19 - 7.11 (m, 1H), 4.16 (br s, 2H), 3.93 - 3.87 (m, 4H), 3.18 - 3.12 (m, 4H), 3.06 (tt, J=3.8, 11.2 Hz, 1H), 2.95 (br t, J=11.5 Hz, 2H), 2.07 (br d, J=12.1 Hz, 2H), 1.94 - 1.77 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M-Boc+H]+:333.1.



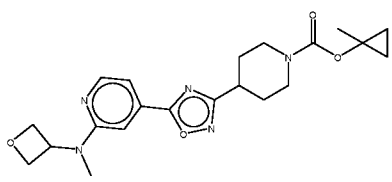
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.31 (dd, J=0.7, 5.1 Hz, 1H), 7.25 (dd, J=1.2, 5.1 Hz, 1H), 7.18 (s, 1H), 5.52 (quin, J=7.1 Hz, 1H), 4.95 (t, J=7.3 Hz, 2H), 4.81 (t, J=6.9 Hz, 2H), 4.63 (br d, J=12.3 Hz, 1H), 4.04 (br d, J=13.1 Hz, 1H), 3.26 (br t, J=13.0 Hz, 1H), 3.18 (s, 3H), 3.16 - 3.10 (m, 1H), 2.94 - 2.80 (m, 2H), 2.22 - 2.07 (m, 2H), 1.97 - 1.73 (m, 2H), 1.19 - 1.15 (m, 6H); LCMS (ESI) [M+H]+:386.2.



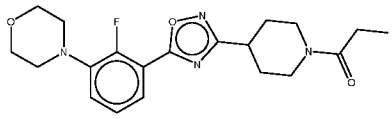
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.54 (dd, J=3.2, 5.6 Hz, 1H), 7.20 - 7.14 (m, 1H), 7.13 - 7.07 (m, 1H), 4.15 (br s, 2H), 3.90 - 3.86 (m, 4H), 3.20 - 3.15 (m, 4H), 3.05 - 3.01(m, 1H), 2.97- 2.91 (m, 2H), 2.06 (br d, J=10.8 Hz, 2H), 1.91 - 1.79 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+23]+:455.1, [M+H-100]+:333.1.



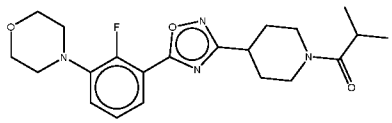
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.28 (d, J=5.3 Hz, 1H), 7.45 - 7.38 (m, 2H), 7.26 - 7.20 (m, 2H), 7.15 - 7.08 (m, 1H), 7.04 (s, 1H), 5.22 (br d, J=5.1 Hz, 1H), 5.08 - 5.02 (m, 3H), 4.73 (br d, J=13.2 Hz, 1H), 4.63 - 4.53 (m, 2H), 3.70 (br d, J=13.7 Hz, 1H), 3.30 - 3.08 (m, 3H), 2.28 - 2.16 (m, 1H), 2.11 - 1.85 (m, 3H); LCMS (ESI) [M+H]+:424.2.



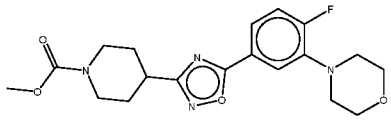
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.30 (dd, J=0.7, 5.1 Hz, 1H), 7.24 (dd, J=1.3, 5.1 Hz, 1H), 7.17 (t, J=1.0 Hz, 1H), 5.52 (quin, J=7.2 Hz, 1H), 4.94 (t, J=7.3 Hz, 2H), 4.80 (t, J=6.9 Hz, 2H), 4.37 - 3.90 (m, 2H), 3.17 (s, 3H), 3.10 - 2.87 (m, 3H), 2.13 - 1.99 (m, 2H), 1.84 (br d, J=9.9 Hz, 2H), 1.57 (s, 3H), 0.92 - 0.85 (m, 2H), 0.68 - 0.61 (m, 2H); LCMS (ESI) [M+H]+:414.2.



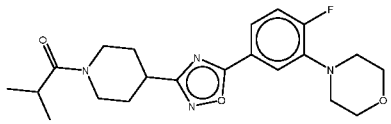
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (t, J=6.3 Hz, 1H), 7.25 - 7.19 (m, 1H), 7.18 - 7.11 (m, 1H), 4.59 (br d, J=13.0 Hz, 1H), 4.00 - 3.84 (m, 5H), 3.27 - 3.09 (m, 6H), 2.88 (br t, J=11.2 Hz, 1H), 2.38 (q, J=7.5 Hz, 2H), 2.19 - 2.06 (m, 2H), 1.96 - 1.76 (m, 2H), 1.17 (t, J=7.4 Hz, 3H); LCMS (ESI) [M+H]+:389.2.



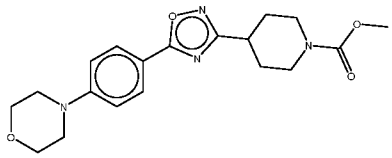
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.72 - 7.66 (m, 1H), 7.26 - 7.20 (m, 1H), 7.19 - 7.13 (m, 1H), 4.62 (br d, J=13.0 Hz, 1H), 4.03 (br d, J=13.5 Hz, 1H), 3.94 - 3.85 (m, 4H), 3.32 - 3.12 (m, 6H), 2.96 - 2.79 (m, 2H), 2.22 - 2.07 (m, 2H), 1.99 - 1.78 (m, 2H), 1.19 - 1.12 (m, 6H); LCMS (ESI) [M+H]+:403.2.



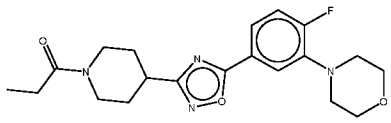
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.73 (ddd, J=2.1, 4.3, 8.4 Hz, 1H), 7.68 (dd, J=2.0, 8.1 Hz, 1H), 7.17 (dd, J=8.4, 12.1 Hz, 1H), 4.20 (br s, 2H), 3.94 - 3.87 (m, 4H), 3.73 (s, 3H), 3.20 - 3.16 (m, 4H), 3.09 - 2.97 (m, 3H), 2.07 (br d, J=12.7 Hz, 2H), 1.93 - 1.81 (m, 2H); LCMS (ESI) [M+H]+:391.1.



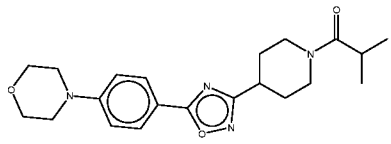
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.74 (ddd, J=2.1, 4.4, 8.4 Hz, 1H), 7.68 (dd, J=2.1, 8.2 Hz, 1H), 7.18 (dd, J=8.4, 12.2 Hz, 1H), 4.63 (br d, J=13.6 Hz, 1H), 4.03 (br d, J=13.6 Hz, 1H), 3.94 - 3.88 (m, 4H), 3.25 (br t, J=11.6 Hz, 1H), 3.21 - 3.16 (m, 4H), 3.15 - 3.08 (m, 1H), 2.92 - 2.80 (m, 2H), 2.18 - 2.07 (m, 2H), 1.97 - 1.77 (m, 2H), 1.16 (br t, J=5.7 Hz, 6H); LCMS (ESI) [M+H]+:403.2.



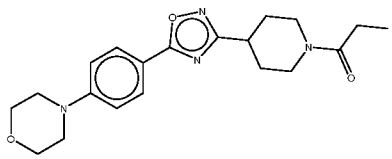
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.00 (d, J=9.0 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 4.18 (br s, 2H), 3.92 - 3.85 (m, 4H), 3.72 (s, 3H), 3.35 - 3.29 (m, 4H), 3.01 (tdd, J=3.7, 7.4, 11.0 Hz, 3H), 2.07 (br d, J=11.9 Hz, 2H), 1.93 - 1.80 (m, 2H); LCMS (ESI) [M+H]+:373.2.



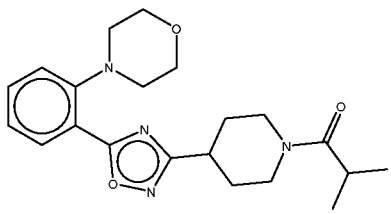
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.73 (ddd, J=2.1, 4.3, 8.4 Hz, 1H), 7.68 (dd, J=2.1, 8.2 Hz, 1H), 7.17 (dd, J=8.4, 12.2 Hz, 1H), 4.61 (br d, J=13.2 Hz, 1H), 3.95 (br d, J=14.4 Hz, 1H), 3.93 - 3.89 (m, 4H), 3.27 - 3.22 (m, 1H), 3.21 - 3.16 (m, 4H), 3.11 (tt, J=4.0, 11.0 Hz, 1H), 2.93 - 2.83 (m, 1H), 2.40 (q, J=7.5 Hz, 2H), 2.16 - 2.06 (m, 2H), 1.95 - 1.79 (m, 2H), 1.18 (t, J=7.5 Hz, 3H); LCMS (ESI) [M+H]+:389.2.



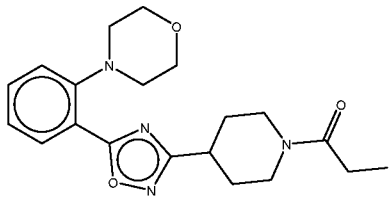
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.03 - 7.97 (m, 2H), 6.98 - 6.92 (m, 2H), 4.61 (br d, J=13.1 Hz, 1H), 4.02 (br d, J=14.2 Hz, 1H), 3.91 - 3.85 (m, 4H), 3.35 - 3.30 (m, 4H), 3.24 (br t, J=11.6 Hz, 1H), 3.10 (tt, J=3.9, 11.0 Hz, 1H), 2.92 - 2.80 (m, 2H), 2.12 (br t, J=10.3 Hz, 2H), 1.96 - 1.77 (m, 2H), 1.16 (br t, J=5.7 Hz, 6H); LCMS (ESI) [M+H]+:385.2.



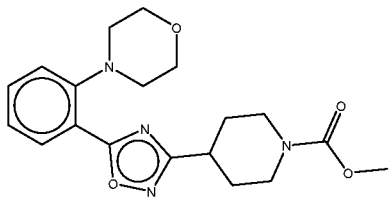
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.00 (d, J=9.0 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 4.60 (br d, J=12.8 Hz, 1H), 3.95 (br d, J=13.0 Hz, 1H), 3.91 - 3.86 (m, 4H), 3.35 - 3.30 (m, 4H), 3.27 - 3.18 (m, 1H), 3.09 (tt, J=3.9, 11.0 Hz, 1H), 2.93 - 2.84 (m, 1H), 2.40 (q, J=7.4 Hz, 2H), 2.10 (br d, J=3.9 Hz, 2H), 1.95 - 1.78 (m, 2H), 1.18 (t, J=7.5 Hz, 3H); LCMS (ESI) [M+H]+:371.2.



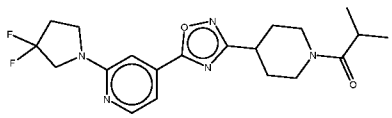
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.94 (dd, J=1.4, 7.8 Hz, 1H), 7.50 - 7.40 (m, 1H), 7.12 - 7.03 (m, 2H), 4.56 (br d, J=13.4 Hz, 1H), 3.96 (br d, J=13.4 Hz, 1H), 3.85 - 3.74 (m, 4H), 3.19 (br t, J=11.8 Hz, 1H), 3.07 (tt, J=3.9, 11.0 Hz, 1H), 2.98 - 2.89 (m, 4H), 2.86 - 2.73 (m, 2H), 2.08 (br t, J=11.0 Hz, 2H), 1.90 - 1.70 (m, 2H), 1.08 (br d, J=5.4 Hz, 6H); LCMS (ESI) [M+H]+:385.1.



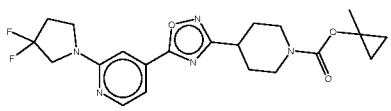
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.94 (dd, J=1.4, 7.9 Hz, 1H), 7.50 - 7.40 (m, 1H), 7.12 - 7.04 (m, 2H), 4.54 (br d, J=13.2 Hz, 1H), 3.88 (br d, J=13.6 Hz, 1H), 3.84 - 3.77 (m, 4H), 3.21 - 3.13 (m, 1H), 3.11 - 3.03 (m, 1H), 2.99 - 2.91 (m, 4H), 2.88 - 2.77 (m, 1H), 2.33 (q, J=7.5 Hz, 2H), 2.13 - 2.01 (m, 2H), 1.88 - 1.71 (m, 2H), 1.11 (t, J=7.5 Hz, 3H); LCMS (ESI) [M+H]+:371.1.



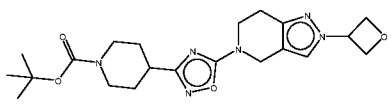
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.94 (dd, J=1.4, 7.9 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.11 - 7.05 (m, 2H), 4.27 - 3.95 (m, 2H), 3.86 - 3.77 (m, 4H), 3.65 (s, 3H), 3.02 - 2.91 (m, 7H), 2.03 (br d, J=11.2 Hz, 2H), 1.86 - 1.74 (m, 2H); LCMS (ESI) [M+H]+:373.1.



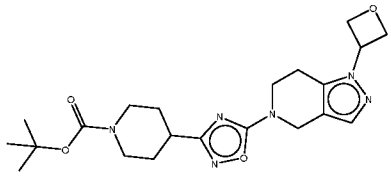
^{1}H NMR (400MHz, METHANOL-d4) δ = 8.32 (d, J=5.3 Hz, 1H), 7.31 (d, J=5.3 Hz, 1H), 7.19 (s, 1H), 4.54 (br d, J=13.4 Hz, 1H), 4.16 (br d, J=13.8 Hz, 1H), 3.93 (t, J=13.0 Hz, 2H), 3.78 (t, J=7.3 Hz, 2H), 3.43 - 3.35 (m, 1H), 3.30 - 3.20 (m, 1H), 3.07 - 2.90 (m, 2H), 2.59 (tt, J=7.1, 13.9 Hz, 2H), 2.24 - 2.08 (m, 2H), 1.92 - 1.70 (m, 2H), 1.14 (t, J=6.5 Hz, 6H); LCMS (ESI) [M+H]+:406.1.



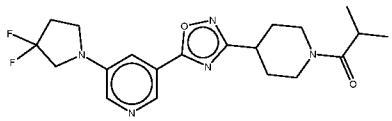
^{1}H NMR (400MHz, METHANOL-d4) δ = 8.31 (dd, J=0.7, 5.3 Hz, 1H), 7.28 (dd, J=1.3, 5.3 Hz, 1H), 7.16 (s, 1H), 4.09 (br s, 2H), 3.91 (t, J=13.0 Hz, 2H), 3.76 (t, J=7.3 Hz, 2H), 3.20 - 2.97 (m, 3H), 2.64 - 2.51 (m, 2H), 2.12 - 2.00 (m, 2H), 1.84 - 1.69 (m, 2H), 1.54 (s, 3H), 0.91 - 0.84 (m, 2H), 0.69 - 0.61 (m, 2H); LCMS (ESI) [M+H]+:434.2.



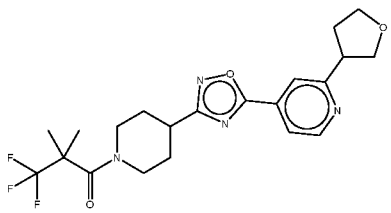
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.40 (s, 1H), 5.39 (quin, J=6.8 Hz, 1H), 5.03 (d, J=7.2 Hz, 4H), 4.67 (s, 2H), 4.11 (br s, 2H), 3.92 (t, J=6.0 Hz, 2H), 2.93 (t, J=6.0 Hz, 2H), 2.89 - 2.82 (m, 2H), 2.79 - 2.72 (m, 1H), 1.93 (br d, J=11.2 Hz, 2H), 1.78 - 1.67 (m, 2H), 1.46 (s, 9H); LCMS (ESI) [M+H]+:431.2.



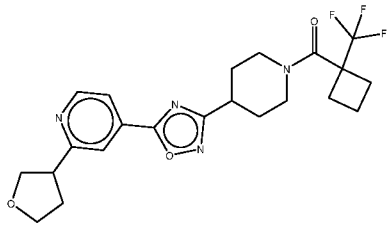
^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.48 (s, 1H), 5.41 - 5.28 (m, 1H), 5.23 - 5.14 (m, 2H), 5.04 - 4.95 (m, 2H), 4.63 (br s, 2H), 4.12 (br s, 2H), 4.01 - 3.86 (m, 2H), 2.86 (br s, 1H), 2.85 - 2.78 (m, 3H), 2.77 - 2.71 (m, 1H), 1.92 (br d, J=10.2 Hz, 2H), 1.77 - 1.60 (m, 2H), 1.48 - 1.41 (m, 9H); LCMS (ESI) [M+1]+:431.2, [M+H-100]+:331.1.



^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.75 (br s, 1H), 8.18 (br s, 1H), 7.96 (br s, 1H), 4.36 (br s, 2H), 4.02 - 3.71 (m, 4H), 3.30 - 2.92 (m, 3H), 2.86 (td, J=6.7, 13.5 Hz, 1H), 2.70 (br s, 2H), 2.14 (br d, J=10.8 Hz, 2H), 1.85 (br d, J=12.8 Hz, 2H), 1.17 (d, J=6.8 Hz, 6H); LCMS (ESI) [M+H]+:406.2.

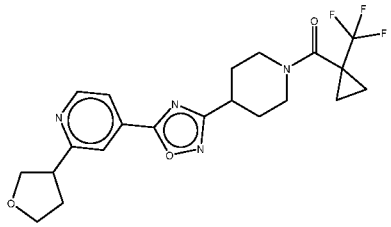


^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.82 - 8.76 (m, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz, 1H), 4.41 (br d, J=13.7 Hz, 2H), 4.23 (t, J=8.2 Hz, 1H), 4.13 (dt, J=5.1, 8.3 Hz, 1H), 4.04 - 3.93 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.24 - 3.10 (m, 3H), 2.50 - 2.37 (m, 1H), 2.28 (qd, J=7.6, 12.4 Hz, 1H), 2.15 (br dd, J=3.3, 13.7 Hz, 2H), 1.98 - 1.86 (m, 2H), 1.57 (s, 6H); LCMS (ESI) [M+H]+:439.2.



^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz, 1H), 4.59 (br d, J=12.6 Hz, 1H), 4.23 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.2, 8.2 Hz, 1H), 4.02 - 3.92 (m, 2H),

3.80 - 3.65 (m, 2H), 3.24 - 3.11 (m, 2H), 2.99 (br t, J=11.9 Hz, 1H), 2.79 - 2.66 (m, 2H), 2.56 (br s, 2H), 2.50 - 2.38 (m, 1H), 2.28 (qd, J=7.6, 12.3 Hz, 1H), 2.20 - 2.06 (m, 3H), 1.97 - 1.81 (m, 3H); LCMS (ESI) [M+H]+:451.2.



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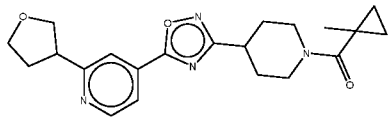
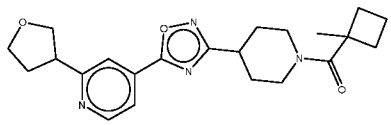
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz, 1H), 4.44 (br s, 2H), 4.22 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.3, 8.3 Hz, 1H), 4.05 - 3.92 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.41 - 2.92 (m, 3H), 2.49 - 2.38 (m, 1H), 2.28 (qd, J=7.6, 12.3 Hz, 1H), 2.16 (br dd, J=3.0,
10 13.6 Hz, 2H), 1.98 - 1.82 (m, 2H), 1.40 - 1.33 (m, 2H), 1.24 - 1.15 (m, 2H); LCMS (ESI) [M+H]+:437.2.

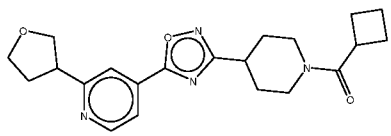


^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz,
15 1H), 4.48 (br d, J=13.5 Hz, 2H), 4.23 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.2, 8.3 Hz, 1H), 4.03 - 3.93 (m, 2H), 3.71 (quin, J=7.6 Hz, 1H), 3.25 - 2.95 (m, 3H), 2.51 - 2.38 (m, 1H), 2.28 (qd, J=7.6, 12.4 Hz, 1H), 2.14 (br dd, J=2.6, 13.5 Hz, 2H), 1.95 - 1.80 (m, 2H), 1.35 (s, 3H), 1.01 - 0.93 (m, 2H), 0.66 - 0.57 (m, 2H); LCMS (ESI) [M+H]+:383.2.



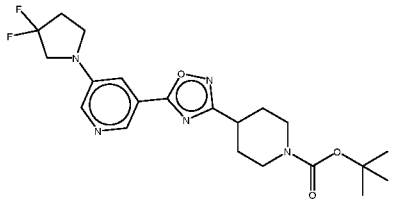
20

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.3, 5.1 Hz, 1H), 4.58 (br d, J=11.0 Hz, 1H), 4.22 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.1, 8.3 Hz, 1H), 4.03 - 3.92 (m, 2H), 3.81 - 3.65 (m, 2H), 3.14 (tdd, J=3.9, 7.3, 14.7 Hz, 2H), 2.87 (br t, J=11.1 Hz, 1H), 2.63 - 2.51 (m, 2H),
25 2.49 - 2.38 (m, 1H), 2.28 (qd, J=7.6, 12.4 Hz, 1H), 2.17 - 2.05 (m, 2H), 2.04 - 1.81 (m, 5H), 1.80 - 1.70 (m, 1H), 1.47 (s, 3H); LCMS (ESI) [M+H]+:397.2.

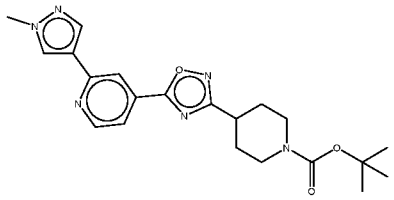


30 ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.79 (d, J=5.1 Hz, 1H), 7.88 (s, 1H), 7.80 (dd, J=1.5, 5.1 Hz, 1H), 4.59 (br d, J=13.0 Hz, 1H), 4.23 (t, J=8.0 Hz, 1H), 4.13 (dt, J=5.1, 8.3 Hz, 1H), 4.03 - 3.93 (m, 2H),

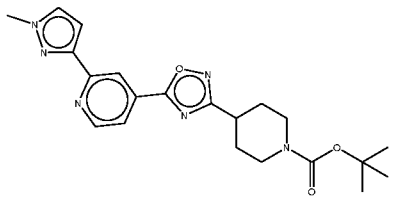
3.81 (br d, J=13.5 Hz, 1H), 3.71 (quin, J=7.6 Hz, 1H), 3.30 (quin, J=8.6 Hz, 1H), 3.20 - 3.09 (m, 2H), 2.94 - 2.82 (m, 1H), 2.49 - 2.33 (m, 3H), 2.33 - 2.24 (m, 1H), 2.24 - 2.06 (m, 4H), 2.05 - 1.76 (m, 4H); ^{1}H NMR (400MHz, METHANOL-d4) δ = 8.97 (d, J=6.4 Hz, 1H), 8.58 (s, 1H), 8.54 (dd, J=1.5, 6.2 Hz, 1H), 4.49 (br d, J=13.0 Hz, 1H), 4.21 (dt, J=4.9, 8.5 Hz, 1H), 4.17 - 4.08 (m, 2H), 4.03 - 3.87 (m, 3H), 3.47 (quin, J=8.5 Hz, 1H), 3.36 - 3.33 (m, 1H), 3.29 - 3.22 (m, 1H), 2.96 (br t, J=11.5 Hz, 1H), 2.73 - 2.61 (m, 1H), 2.37 - 2.11 (m, 7H), 2.09 - 1.98 (m, 1H), 1.90 - 1.71 (m, 3H); LCMS (ESI) [M+H]+:383.2.



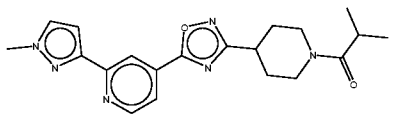
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.76 (d, J=1.6 Hz, 1H), 8.17 (d, J=2.9 Hz, 1H), 7.46 (dd, J=1.8, 2.8 Hz, 1H), 4.17 (br s, 2H), 3.80 (t, J=12.8 Hz, 2H), 3.67 (t, J=7.2 Hz, 2H), 3.13 - 2.87 (m, 3H), 2.58 (tt, J=7.0, 13.7 Hz, 2H), 2.07 (br d, J=11.7 Hz, 2H), 1.92 - 1.78 (m, 2H), 1.49 (s, 9H); LCMS (ESI) [M+H]+:436.1.



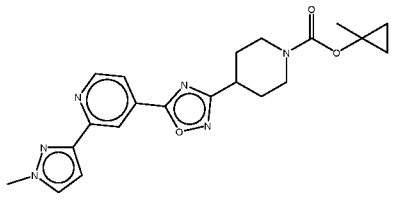
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.74 (dd, J=0.8, 5.2 Hz, 1H), 8.08 (s, 1H), 8.06 (s, 1H), 8.01 (s, 1H), 7.75 - 7.70 (m, 1H), 4.25 -4.10 (br s, 2H), 3.99 (s, 3H), 3.06 -3.02 (m, 1H), 2.96 -2.90 (m, 2H), 2.08 - 2.05 (m, 2H), 1.92 - 1.80 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+:411.2.



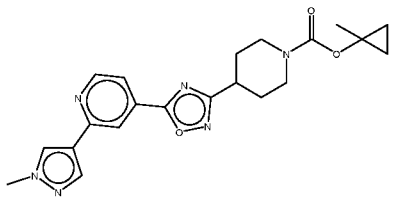
^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.82 (d, J=5.2 Hz, 1H), 8.57 (s, 1H), 7.83 (dd, J=1.6, 5.2 Hz, 1H), 7.46 (d, J=2.4 Hz, 1H), 6.93 (d, J=2.0 Hz, 1H), 4.18 (br d, J=8.4 Hz, 2H), 4.02 (s, 3H), 3.06 -3.02 (m, 1H), 3.00 - 2.87 (m, 2H), 2.11 - 2.01 (m, 2H), 1.91 - 1.79 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+:411.2.



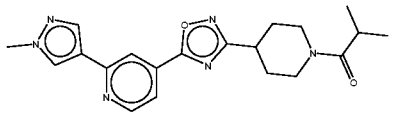
^{1}H NMR (400MHz, METHANOL-d4) δ 9.00 (d, J=0.9 Hz, 1H), 8.90 (d, J=6.4 Hz, 1H), 8.48 (dd, J=1.6, 6.4 Hz, 1H), 7.93 (d, J=2.2 Hz, 1H), 7.32 (d, J=2.4 Hz, 1H), 4.55 (br d, J=13.5 Hz, 1H), 4.17 (br d, J=13.7 Hz, 1H), 4.11 (s, 3H), 3.44 - 3.32 (m, 2H), 3.06 - 2.92 (m, 2H), 2.29 - 2.11 (m, 2H), 1.97 - 1.72 (m, 2H), 1.13 (t, J=6.0 Hz, 6H); LCMS (ESI) [M+H]+:381.2.



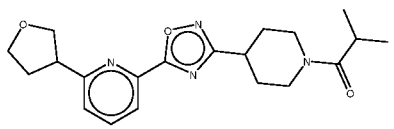
^{1}H NMR (400MHz, METHANOL-d4) δ 8.78 (d, J=5.2 Hz, 1H), 8.60 (s, 1H), 7.94 (dd, J=1.2, 5.2 Hz, 1H), 7.69 (d, J=2.0 Hz, 1H), 6.95 (d, J=2.4 Hz, 1H), 4.21 - 4.04 (m, 2H), 4.01 (s, 3H), 3.18 -3.14 (m, 1H), 3.06 (br s, 2H), 2.17 - 2.00 (m, 2H), 1.79 (br d, J=11.0 Hz, 2H), 1.54 (s, 3H), 0.92 - 0.85 (m, 2H), 0.69 - 0.62 (m, 2H); LCMS (ESI) [M+H]+:409.2.



^{1}H NMR (400MHz, METHANOL-d4) δ 8.71 (d, J=5.2 Hz, 1H), 8.27 (s, 1H), 8.23 (s, 1H), 8.10 (s, 1H), 7.81 (dd, J=1.6, 5.2 Hz, 1H), 4.12 (br d, J=14.8 Hz, 2H), 3.97 (s, 3H), 3.17 (tt, J=3.6, 11.2 Hz, 1H), 3.05 (br s, 2H), 2.13 - 2.03 (m, 2H), 1.88 - 1.71 (m, 2H), 1.54 (s, 3H), 0.91 - 0.85 (m, 2H), 0.68 - 0.63 (m, 2H); LCMS (ESI) [M+H]+:409.1.

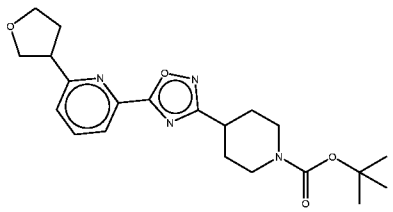


^{1}H NMR (400MHz, METHANOL-d4) δ 8.72 (d, J=5.2 Hz, 1H), 8.28 (s, 1H), 8.26 (s, 1H), 8.11 (s, 1H), 7.83 (dd, J=1.6, 5.2 Hz, 1H), 4.53 (br d, J=13.2 Hz, 1H), 4.15 (br d, J=13.6 Hz, 1H), 3.97 (s, 3H), 3.41 - 3.33 (m, 1H), 3.29 - 3.23 (m, 1H), 3.10 - 2.88 (m, 2H), 2.29 - 2.04 (m, 2H), 1.95 - 1.69 (m, 2H), 1.13 (t, J=6.8 Hz, 6H); LCMS (ESI) [M+H]+:381.2.



^{1}H NMR (400MHz, DMSO-d6) δ = 8.10 - 7.99 (m, 2H), 7.65 (dd, J=1.0, 7.7 Hz, 1H), 4.39 (br d, J=12.8 Hz, 1H), 4.11 (t, J=7.9 Hz, 1H), 4.06 - 3.92 (m, 2H), 3.87 - 3.74 (m, 2H), 3.74 - 3.65 (m, 1H), 3.27 - 3.18 (m,

2H), 2.96 - 2.79 (m, 2H), 2.40 - 2.29 (m, 1H), 2.18 (qd, J=7.7, 12.1 Hz, 1H), 2.12 - 1.96 (m, 2H), 1.78 - 1.50 (m, 2H), 1.02 (br d, J=6.4 Hz, 6H); LCMS (ESI) [M+H]+:371.1.



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^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.98 (dd, J=0.7, 7.7 Hz, 1H), 7.77 (t, J=7.8 Hz, 1H), 7.39 (dd, J=0.6, 7.8 Hz, 1H), 4.18 - 4.01 (m, 4H), 3.93 - 3.85 (m, 1H), 3.93 - 3.85 (m, 1H), 3.70 (quin, J=7.3 Hz, 1H), 3.00 (tt, J=3.8, 11.2 Hz, 1H), 2.88 (br t, J=11.6 Hz, 2H), 2.44 - 2.31 (m, 1H), 2.18 (qd, J=7.4, 12.5 Hz, 1H), 2.00 (br d, J=10.9 Hz, 2H), 1.85 - 1.72 (m, 2H), 1.41 (s, 9H); LCMS (ESI) [M+H]+:401.1.

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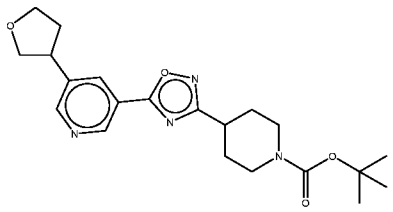
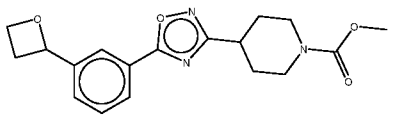
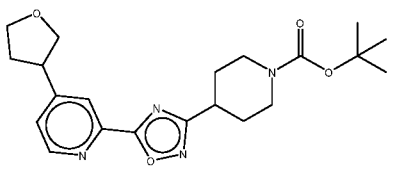


^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.20 (d, J=2.0 Hz, 1H), 8.71 (d, J=2.2 Hz, 1H), 8.26 (t, J=2.0 Hz, 1H), 4.22 - 4.10 (m, 4H), 4.01 - 3.92 (m, 1H), 3.82 (dd, J=6.5, 8.7 Hz, 1H), 3.58 - 3.48 (m, 1H), 3.12 -
15 2.87 (m, 3H), 2.54 - 2.44 (m, 1H), 2.12 - 1.98 (m, 3H), 1.92 - 1.78 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+:401.1.



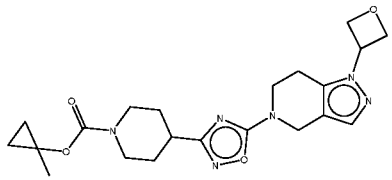
20 ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.19 (s, 1H), 8.10 - 8.05 (m, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.61 - 7.54 (m, 1H), 5.91 (t, J=7.5 Hz, 1H), 4.90 (dt, J=6.0, 7.9 Hz, 1H), 4.74 (td, J=5.8, 9.2 Hz, 1H), 4.32-4.10 (m, 2H), 3.75 (s, 3H), 3.19 - 3.00 (m, 4H), 2.70 (tdd, J=7.5, 9.1, 11.0 Hz, 1H), 2.10 (br d, J=11.2 Hz, 2H), 1.98 - 1.82 (m, 2H); LCMS (ESI) [M+Na]+:366.1.



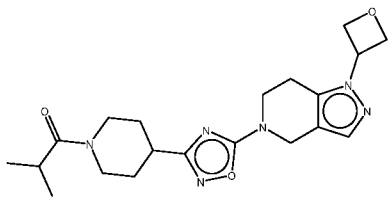
25

^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.74 (d, J=5.1 Hz, 1H), 8.08 (s, 1H), 7.41 - 7.38 (m, 1H), 4.25 - 4.09 (m, 4H), 3.99 - 3.92 (m, 1H), 3.85 (dd, J=6.2, 8.8 Hz, 1H), 3.52 (quin, J=7.1 Hz, 1H), 3.13 - 3.03 (m,

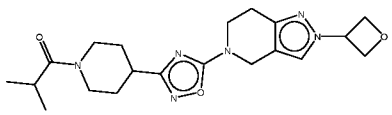
1H), 3.01 - 2.88 (m, 2H), 2.54 - 2.44 (m, 1H), 2.11 - 2.00 (m, 3H), 1.96 - 1.83 (m, 2H), 1.48 (s, 9H); LCMS (ESI) [M+H]+:401.2.



^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.46 (s, 1H), 5.37 - 5.26 (m, 1H), 5.16 (t, J=6.4 Hz, 2H), 4.96 (t, J=7.2 Hz, 2H), 4.61 (s, 2H), 4.23 - 3.95 (m, 2H), 3.90 (t, J=5.6 Hz, 2H), 2.87 (br t, J=11.2 Hz, 2H), 2.79 (br t, J=5.6 Hz, 2H), 2.76 - 2.70 (m, 1H), 1.91 (br d, J=11.2 Hz, 2H), 1.80 - 1.61 (m, 2H), 1.53 (s, 3H), 0.94 - 0.80 (m, 2H), 0.65 - 0.55 (m, 2H); LCMS (ESI) [M+H]+:429.1.



^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.48 (s, 1H), 5.33 (quin, J=7.2 Hz, 1H), 5.17 (t, J=6.4 Hz, 2H), 4.97 (t, J=7.2 Hz, 2H), 4.63 (s, 2H), 4.55 (br d, J=12.8 Hz, 1H), 4.05 - 3.81 (m, 3H), 3.17 (br t, J=11.6 Hz, 1H), 2.95 - 2.69 (m, 5H), 1.99 (br s, 2H), 1.84 - 1.68 (m, 2H), 1.17 - 1.08 (m, 6H); LCMS (ESI) [M+H]+:401.1.



^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.39 (s, 1H), 5.38 (quin, J=6.8 Hz, 1H), 5.04 -4.99 (m, 4H), 4.67 (s, 2H), 4.61 - 4.45 (m, 1H), 4.01 - 3.83 (m, 3H), 3.17 (br t, J=12.0 Hz, 1H), 2.92 (t, J=6.0 Hz, 2H), 2.89 - 2.75 (m, 3H), 2.01 -1.96 (m, 2H), 1.80 - 1.67 (m, 2H), 1.16 -1.07 (m, 6H); LCMS (ESI) [M+H]+:401.1.

Example 157. Description of yeast models

α-synuclein and ApoE4 yeast strains were previously engineered to express the human α-synuclein or ApoE4 genes under control of the yeast galactose-regulated promoter, *GAL1*, as described in International Patent Publication No. WO2016/040794 and U.S. Patent Nos. 7,452,670 and 7,045,290, the procedures for the production of such strains of which are herein incorporated by reference. The induced expression of α-synuclein and ApoE4 confers cytotoxicity, thus enabling the identification of compounds that can restore cell viability. This instantaneous/synchronous induction of α-synuclein and ApoE4 can be achieved due to the following expression control. In glucose-containing media, gene expression from the *GAL1* promoter is 'off' and actively repressed by additional epigenetic factors. In

raffinose, expression is 'off', but the promoter not actively repressed. Upon transition to galactose-containing media, the promoter is instantaneously turned 'on' to achieve robust and synchronous induction of α-synuclein or ApoE4 expression. This highly regulated induction provides a robust window for the determination of both efficacy (amplitude of protective effect) and potency (concentration of protective effect) of cytoprotective compounds.

Compound Profiling

Fresh powders (~5 mg) of newly synthesized compounds were dissolved to 10 mM in 100% DMSO using a Janus (Perkin Elmer) robotic workstation. Re-suspended compound stocks were subsequently arrayed into 384 well compound plates using automated pipetting. All other wells not receiving stock compound were filled with 10 µL of 100% DMSO using an automated plate filler (Multidrop Combi). An 11 point, 2-fold serial dilution was then performed using the robotic platform. Compound assay plates were covered with foil and stored at -20°C until use.

Each strain was handled according to standard protocols and cultured in media composed of CSM (complete synthetic media), YNB (yeast nitrogenous base), and a 2% (w/v) carbon source (either glucose, raffinose, or galactose). Single use frozen aliquots of each strain were generated by growing cells in CSM/glucose media to an OD_{600} of 0.6-0.8, concentrating the yeast to 12.5 OD_{600} units per 30 µL of CSM/glucose media supplemented with 20% glycerol, and freezing 30 µL aliquots at -80°C.

In a standard yeast assay, a single-use aliquot of cells was thawed on ice and diluted into CSM/glucose (5 mL). Cultures were grown for 8 hours at 30°C. This pre-growth enables the yeast to exit the thaw and begin to grow without expressing aSyn or ApoE4. After 8 hours, cell density (OD_{600}) was determined and cultures diluted to an OD_{600} of 0.01 in CSM/raffinose for an overnight culture phase at 30°C. During this period, the active glucose repression of the *GAL1* promoter was relieved; however, expression of the α-Syn/ApoE4 genes were not yet induced. After ~16 hours of growth, cultures attain an OD_{600} of 0.4-0.8 and were ready to apply to assay plates containing compound.

Compound profiling assays were executed in clear-bottom 384 well plates. First, compound plates were thawed at room temperature for 45', centrifuged at 1,000xg for 1 minute, and the foil removed. Clear 384 well assay plates were then filled with 15 µL of CSM/galactose. Both compound and media-containing plates were arranged on the Janus workstation and a compound pin tool (384 x 100 nL slotted pins) used to deliver 100 nL of compounds to each well according to the well map of the compound plate. Based on the previous serial dilution, the final concentration of compound ranged from 33.3 µL to 12.5 nM. The pin tool was washed iteratively with both 50% DMSO and 100% ethanol between each assay plate. After delivering compound to each assay plate, the overnight CSM/raffinose aSyn or ApoE4 cultures were added at a 2X cell density (0.04 for aSyn and 0.08 for ApoE4) in CSM/galactose to achieve a final assay OD_{600} of 0.02 and 0.04 for aSyn and ApoE, respectively. The cultures (15 µL per well) were then dispensed to the compound-containing 384 well assay plates using an automated plate filler. Plates were incubated in a humidified 30°C incubator for 40 or 24 hours for aSyn and ApoE4, respectively. The OD_{600} of each assay plate was then read with a microplate reader (e.g., Perkin Elmer Envision).

The efficacy and potency of compounds were calculated according to the following. Raw data (OD_{600} values) were first background corrected to account for OD_{600} contributed by the plate and media

itself. The efficacy (percent above DMSO, herein referred to as “Emax”) was calculated according to the equation: (Experimental well – DMSO control well)/(DMSO control well)*100. For each individual compound with positive activity (>30% above DMSO – or 3 standard deviations from the DMSO negative control wells), the dose-response data were normalized to a scale of 0 – 100% to enable potency (herein referred to as “EC50”) determination. Normalized dose-response data was fit with a logistic regression curve using Spotfire (TIBCO), or similar curve-fitting software package. EC50 values were then reported along with EMax to provide both efficacy and potency measures for each analog and enable further compound design. As shown in Table 3, compounds of the invention are able to reduce the toxicity of the expressed alpha-synuclein and/or ApoE4 proteins.

Table 3: Yeast rescue data for examples 1-155 showing that compounds of the invention were able to reduce toxicity in yeast strains expressing the human proteins α-synuclein and/or ApoE4.

Compound #	α-Syn EC50 (nM)	α-Syn Emax (%)	ApoE4 EC50 (nM)	ApoE4 Emax (%)
1	n/a	155	n/a	320
2	8569	80		
3	17843	307	n/a	200
4	8428	59	11756	76
6	10194	460	15110	815
7	40	594	176	782
8	13764	188	n/a	111
9	12113	167	n/a	301
10	4870	392	4614	736
11	5892	309	n/a	600
12	16197	43		
13	58	712	368	837
14	1164	463	1830	771
15	1711	628	3627	866
16	17823	249	21200	418
17	17395	330	n/a	246
18	266	452	1512	826
19	2425	574	5627	891
20	15131	181	16216	529
21	n/a	276	n/a	447
22	8423	334	n/a	372
23	7680	182	6513	466
24	5126	76	13342	301
25	751	619	1855	889
26	42	608	377	811
27	59	589	390	761

Compound #	α-Syn EC50 (nM)	α-Syn Emax (%)	ApoE4 EC50 (nM)	ApoE4 Emax (%)
28	66	576	1594	836
29	13928	38		
31	7506	438	9813	721
32	9883	41		
33	111	260	717	281
34	11112	562	n/a	596
35	52	626	1122	911
36	1757	629	2154	908
37	2205	608	6530	849
38	3296	336	6014	750
39	18143	216		
40	86	443		
41	10899	211	n/a	400
42	12462	255	n/a	399
43	14607	222	17730	517
44	10870	579	13312	676
45	26019	121	29268	19
46	10930	35		
47	16513	88		
48	1471	615	2944	874
49	1469	636	4336	942
50	7857	85	n/a	133
51	10924	137	n/a	286
52	9059	82	14485	154
53	6603	81	16643	296
54	9095	95	17308	240
55	23816	47	7902	29
56	1665	549	8325	793
57	9005	503	12060	797
58	7943	23		
59	15667	82	n/a	47
60	32	605	119	795
61	19706	229	19380	465
62	21699	204	21427	430
63	17170	68	13385	250
64	13746	228	15275	330
65	36	643	987	779
66	11067	350	21212	790

Compound #	α-Syn EC50 (nM)	α-Syn Emax (%)	ApoE4 EC50 (nM)	ApoE4 Emax (%)
67	7377	255	17364	420
68	1864	652	3123	775
69	n/a	294	n/a	387
70	n/a	605	n/a	580
71	8093	151	8969	235
72	12665	35		
73	15760	151	n/a	303
74	17866	155	n/a	411
76	9921	76	14827	162
77	n/a	345	n/a	436
78	14604	38		
79	9907	627	18845	631
80	3322	188	6014	262
82			16773	40
83	9309	151	n/a	567
84	60	463	956	866
85	12610	486	17049	602
86	18	772	64	633
87	1929	579		
88	9037	130		
89	165	580		
90	1646	281		
91	107	452		
92	2499	187		
93	1800	626		
94	40	1083		
95	91	827		
96	26	343	228	840
97	707	132	3884	704
98	8009	386	9747	650
99	1032	209	2749	663
100	1191	385	2106	651
101	1175	122		
102	284	411		
103	2023	75		
104	1872	253		
105	3180	391		
106	100	415		

Compound #	α-Syn EC50 (nM)	α-Syn Emax (%)	ApoE4 EC50 (nM)	ApoE4 Emax (%)
107	2899	312		
108	11149	316		
109	3041	35		
110	4493	374		
111	339	289		
112	320	258		
113	15628	55		
114	17316	373		
115	887	326		
116	9038	345		
117	7502	124		
118	15667	65		
119	20897	61		
120	19502	139		
121	15527	388		
122	139	414		
123	69	343		
124	17661	395		
125	16712	200		
127	7416	349		
128	252	306		
129	47	360		
130	1443	328		
131	167	352		
132	1006	253		
133	6381	281		
134	13976	357		
135	593	144		
136	4080	67		
137	1052	376		
138	1280	353		
139	21	437		
140	49	322		
141	19	259		
142	7644	319		
143	16891	73		
144	521	537		
145	100	432		

Compound #	α-Syn EC50 (nM)	α-Syn Emax (%)	ApoE4 EC50 (nM)	ApoE4 Emax (%)
146	1941	516		
147	17902	453		
148	13652	258		
149	60	458		
150	99	473		
151	45	405		
152	134	474		
153	20	271		
154	57	410		
155	11	556	2159	865

Example 158: U2OS transient overexpression induced cytotoxicity assay

U2OS (Sigma-Aldrich), a human bone osteosarcoma epithelial cell line, is regularly maintained in McCoy's 5A medium (ATCC) supplemented with 10% FBS (ThermoFisher) between passage 11-21 and sub-cultured twice a week for the assay.

On the day of experiment, cells are about 80% confluence and trypsinized using 0.25% trypsin-EDTA (ThermoFisher Inc.) for 5 minutes at 37c. Based on a ratio of 2ug DNA/2e5 cells, required cells are spun down at 800 rpm for 5 minutes at room temperature. Cells are then re-suspended in SE solution (Lonza Inc.) at a density of 2e4 cells/µl. Nucleofection is performed using 4D-Nucleofector™ System (Lonza Inc.) under program code CM130. Cells are allowed to recover in the cuvette at room temperature for 10-15 minutes before further handling. Pre-warmed medium is added and cells suspension is thoroughly but gently mixed before plating. Cells are seeded at 2e4 cells/100µl/well into 96 well PLD-coated white plate (Corning) using customized Viaflow program (Integra Biosciences). Serial dilution of drugs is carried out in DMSO. Drug solution is prepared at 6x fold, 20ul of which is added to cells 4 hours after transfection. The final DMSO concentration is 0.3%. Microclimate lid (Labcyte) is strongly recommended to reduce evaporation and variation. Seventy-two hours post transfection, cells are lysed using CellTiter-Glow (Promega) and ATP content is determined using a luminescence plate reader (Perkin Elmer).

%Maximum fold rescue at each concentration is calculated as follows:

$$\%\ \text{Fold} = \frac{(RLU^{ASYN}drug)*100}{RLU^{ASYN}DMSO}$$

FK506 (tacrolimus), a macrolide calcineurin inhibitor, is used as reference compound in the assay. FK506 has been shown to rescue αSyn toxicity in yeast models, and this activity has translated to rodent in vivo models of neurodegeneration.

% Rescue (normalized by max fold rescue of FK506) =(%Fold $^{\alpha Syn}$ drug-100)*100/(%Max fold$^{\alpha Syn}$ FK506-100).

As shown in Table 4, the compounds of the invention were able to rescue human bone osteosarcoma epithelial U2OS cells that were transiently overexpressing the toxic alpha-synuclein protein, reducing the level of induced cytotoxicity:

Table 4.

% Rescue (normalized by FK506 max rescue)

Example #	1 (μM)	0.3 (μM)	0.1 (μM)	0.01 (μM)
40	77	105	137	107
155	10	44	83	-23

Example 159: Stearoyl-CoA desaturase (SCD) is the target of 1,2,4-oxadiazoles

A. Materials and Methods

Strain Construction and OLE1 Replacement with SCD1 or SCD5

Strain GMYF was constructed from the ABC16/Green monster strain described in Suzuki et al. *Nat. Methods* 8(2):159-164, 2011. In this strain, *YAP1* was deleted using a HIS3-MX6 cassette, and *FLR1* was deleted using a NAT-MX6 cassette using standard methods. The knockout cassettes were PCR-amplified from plasmid templates (see, e.g., Bahler et al. *Yeast* 14(10):943-951, 1998; Longtine et al. *Yeast* 14(10):953-961, 1998) and transformed into yeast using lithium acetate-based transformation (Gietz et al. *Methods Mol. Biol.* 1205:1-12, 2014). The *yap1::his3* deletion strain was selected on media lacking histidine and *flr1::NAT* on plates containing 100 μg/mL nourseothricin. All strains were confirmed by diagnostic PCR. Strain W303 *pdr1Δ pdr3Δ* was constructed from W303-1A (American Type Culture Collection (ATCC) 208352) by deleting *PDR1* and *PDR3* with kan-MX6 cassettes separately in MATa and MATα W303a isolates, mating, sporulating, and identifying double deletion haploids by tetrad dissection and identification of non-parental ditype tetrads. Strain W-erg3 was derived from W303 *pdr1Δ pdr3Δ* by deleting *SNQ2* with NAT-MX6, *YAP1* with HIS3-MX6, and *ERG3* with BleMX.

Strain ApoE-*mga2Δ* was generated by amplifying 1000 base pairs (bp) upstream and downstream of the *MGA2* ORF in a strain in which *MGA2* was deleted using a G418 (GENETICIN®) resistance cassette (kanMX) (Piotrowski et al. *Proc. Natl. Acad. Sci. USA* 112(12):E1490-1497, 2015) and transforming the resulting deletion cassette into the ApoE4 strain in the BY4741 (ATCC 201388) genetic background. The ApoE strain is described, for example, in International Patent Application Publication No. WO 2016/040794, which is incorporated herein by reference in its entirety.

The alpha-synuclein expression strain was made in the same manner as described in Su et al. *Dis. Model Mech.* 3(3-4):194-208, 2010, except that the alpha-synuclein construct lacked the green fluorescent protein (GFP) tag.

Strain *ole1Δ* (yeast *ole1* deletion mutant) was constructed by deleting *OLE1* with NAT-MX6 in BY4741, amplifying the deletion cassette from the genomic DNA of the resulting strain with primers flanking the ORF by 1000 bp upstream and downstream, transforming the resulting deletion cassette into W303 *pdr1Δ pdr3Δ*, and plating transformants on YPD media containing G418 (200 μg/mL) and nourseothricin (100 μg/mL) with 0.01% TWEEN®-20 and 0.5 mM oleic and palmitoleic acids.

To generate yeast strains expressing SCD1 or SCD5 as the sole desaturase, the human SCD1 and SCD5 genes were cloned from cDNAs (Harvard PlasmID database Clone ID HsCD00340237 for SCD1 and HsCD00342695 for SCD5) into yeast plasmid pRS316 (ATCC 77145) between the yeast *TDH3* promoter and the *CYC1* terminator. The coding sequence of yeast *OLE1* was also cloned into this

plasmid). These clones were then transformed into the *ole1Δ* strain and plated on CSM-Ura media (CSM lacking uracil) with 2% glucose (w/v) and independent colonies were isolated and amplified.

Compound Profiling Methods

All compound profiling experiments were performed using the same basic protocol. Different genetic backgrounds (e.g., gene deletions) or conditions (e.g., addition of oleic and palmitoleic acid) were replaced as indicated below.

Yeast were cultured using standard techniques in complete synthetic media (CSM) and yeast nitrogen base supplemented with 2% (w/v) carbon source (glucose, raffinose, or galactose) to regulate the expression of the toxic disease protein. An initial starter culture was inoculated in 3 mL CSM-Glucose media and incubated overnight in a 30°C shaker incubator (225 rpm). Saturated morning cultures were then diluted 1:20 in fresh CSM-Raffinose media and grown for 6 h to an OD_{600} (optical density) of ~0.4-0.8 at 30°C with shaking.

Compound stocks (10 mM in 100% DMSO) were arrayed into 384 round well, v-bottom polypropylene plates and diluted according to indicated dilution factors. Compound administration was performed in two separate steps. First, 15 µL of CSM-Galactose (induces expression of toxic protein) was dispensed into clear 384 well assay plates using a MULTIDROP™ Combi reagent dispenser. The diluted compound stock plates were then applied to the assay plates using an automated workstation (Perkin Elmer JANUS™) outfitted with a 384 pin tool containing slotted pins that deliver 100 nL of compound. The cultures described above were then diluted to a 2x concentration (0.03 and 0.08 for alpha-synuclein and ApoE, final OD_{600} of 0.015 and 0.04) in CSM-Galactose. For wild-type and Ole1/SCD1/SCD5 plasmid-containing strains, the 2x cell density was 0.02. In all experiments, 15 µL culture was then dispensed into the pinned assay plate to achieve 30 µL of the 1x OD_{600} culture and a top drug concentration of 33.3 µM. For 96-well assays (Figs. 1A and 1B), compound dilutions in DMSO were generated in 96 well plates and 1 µL was manually pipetted into 96 well clear bottom assay plates.

For experiments with oleic and palmitoleic acid supplementation (Figs. 2A, 2B, 4, and 5), TWEEN®-20 was first added to culture media at a concentration of 0.01%. Oleic and palmitoleic acid were both then added at the indicated concentrations (0.08 to 0.5 mM) and mixed thoroughly prior to compound pinning or the addition of yeast.

For experiments using a plasmid-borne copy of Ole1, SCD1, or SCD5 (Figs. 3B, 6, and 7), media lacking uracil (SX-Ura, where X is glucose, raffinose, or galactose), was used for all steps of the compound profiling protocol to ensure its maintenance throughout the assay.

After yeast delivery, assay plates were incubated under humidified conditions at 30°C for 24 to 40 h. ApoE4 rescue experiments were stopped at 24 h, aSyn experiments at 40 h, Ole1 at 24 h, and SCD1/SCD5 at 40 h. The growth of yeast was monitored by reading the OD_{600} of each well using a microplate reader (Perkin Elmer EnVision™). Data were analyzed as follows. For model rescue experiments, raw data were processed by background subtracting and calculating a fold-change relative to DMSO control [(EXP-0.035)/(DMSO-0.035) – where 0.035 is the OD_{600} contributed by an empty well containing 30 µL of media alone]. For growth inhibition of wild-type cells, raw data were processed by background subtracting and converting values to a percent of the nontreated condition for that strain [(EXP-0.035)/(DMSO-0.035) x 100%].

Compound Sources

Compounds were sourced as follows: cycloheximide (Sigma Aldrich), A939572 (Abcam), CAY10566 (Abcam), MF-438 (Calbiochem), MK-8245 (Selleckchem), oleic acid (Sigma Aldrich), palmitoleic acid (Acros organics), mycophenolic acid (Sigma Aldrich), and tunicamycin (Cayman Chemical).

Drug Resistant Mutant Selection

Strains GMYF and W-erg3 were grown to saturation in CSM-glucose, centrifuged, resuspended in phosphate-buffered Saline (PBS), and plated at a density of 10^7 cells/plate on solid 15cm petri dishes containing CSM with 2% galactose (w/v), 2% (w/v) agar, and 10 µM Compound 155, and incubated at 30°C. Resistant colonies were isolated after 5-7 days, re-streaked on the same media, and resistance reconfirmed. Cultures of validated strains were then inoculated for genomic DNA isolation using a YeaStar™ yeast genomic DNA kit (Zymo Research).

Libraries were prepared for sequencing using the Illumina NEXTERA™ library prep kit and sequenced via Illumina HiSeq™ 2500 1X50 bp (single end reads). Sequences were aligned to the *S. cerevisiae* reference genome (S288CCR64-1-1, Saccharomyces Genome Database (SGD)) using Burrows-Wheeler Aligner (BWA, see, e.g., Li et al. *Bioinformatics* 25:1754-1760, 2009; Li et al. *Bioinformatics* 2010, Epub (PMID 20080505)). The BWA output SAI files were converted to SAM files using BWA. The SAM files were sorted using SAMtools 1.3.1 (Li et al. *Bioinformatics* 25:2079-2079, 2009). Variants (single-nucleotide polymorphisms (SNPs), indels) were identified using Freebayes (see, e.g., arXiv:1207.3907). Variant locations were summarized using snpEFF (Cingolani et al. *Fly* (Austin) 6(2):80-92, 2012).

Quantitative Lipid Profiling

Overnight cultures of yeast strain W303 *pdr1*Δ *pdr3*Δ were diluted into CSM media with 2% (w/v) raffinose, OD_{600} 0.25, and grown for 4 h before resuspending at an OD_{600} of 0.2 in CSM media with 2% (w/v) galactose and adding Compound 95 or DMSO at the indicated concentrations. Cells were grown for the indicated timepoints before centrifugation, washing once in PBS, and freezing pellets. Lipids were extracted from pellets by resuspending the pellets in 600 µL methanol, 300 µL water, and 400 µL chloroform, followed by cell lysis by vortexing with glass beads for 1 min. Samples were then centrifuged at 10,000 x g for 10 min, and the bottom layer that formed (organic/lipids) was moved into a new tube and evaporated. Samples were then analyzed by LC/MS/MS using a Thermo Scientific Q Exactive™ Orbitrap™ coupled to a Dionex UltiMate® 3000 ultra-high performance liquid chromatography system, following the method described in Tafesse et al. *PLoS Pathog.* 11(10): e1005188, 2015.

B. Results

The effect of 1,2,4-oxiadiazoles on cell growth was assessed in a control condition and in a yeast model for ApoE4 toxicity (see International Patent Application Publication No. WO 2016/040794). The control condition was growth of the ApoE4 strain under non-inducing conditions using raffinose as the carbon source. The 1,2,4-oxadiazoles exhibited a bell-shaped rescue curve in the ApoE4 model (Fig. 1A,

top panel). At higher concentrations, these compounds inhibited the growth in the control condition (Fig. 1B, bottom panel). The potency of model rescue correlated well with the potency of growth inhibition across the entire series of 1,2,4-oxadiazoles tested (Fig. 1B). These relationships indicate that the growth inhibition arises from an "on-target" activity, i.e., over activation or inhibition of a target that results in slowed growth.

Drug-resistant mutants can be used to identify the target of the compounds, for example, by preventing or reducing drug binding, and therefore allowing growth under inhibitory doses of 1,2,4-oxadiazole concentrations. Twenty drug-resistant mutants were isolated, and the mutants were subjected to whole-genome sequencing in order to identify genetic lesions associated with the drug resistance. Surprisingly, all mutations identified in the drug resistant mutants localized to OLE1 (YGL055W), the sole stearoyl-CoA desaturase (SCD; also referred to as Δ9-desaturase) in yeast (Fig. 9). The drug resistant mutants specifically conferred resistance to 1,2,4-oxadiazoles, but were not cross-resistant to other toxic compounds. The *ole1* mutations identified included indels and substitution mutations, including A305V, L118Δ, S190T, A305T, I301N, A91T, S190T, P123T, and E118Q. These mutations are relative to the wild-type OLE1 sequence provided below.

MPTSGTTIELIDDQFPKDDSASSGIVDEVDLTEANILATGLNKKAPRIVNGFGSLMGSKE
MVSVEFDKKGNEKKSNLDRLLEKDNQEKEEAKTKIHISEQPWTLNNWHQHLNWLNMVLVC
GMPMIGWYFALSGKVPLHLNVFLFSVFYYAVGGVSITAGYHRLWSHRSYSAHWPLRLFYA
IFGCASVEGSAKWWGHSHRIHHRYTDTLRDPYDARRGLWYSHMGWMLLKPNPKYKARADI
TDMTDDWTIRFQHRHYILLMLLTAFVIPTLICGYFFNDYMGGLIYAGFIRVFVIQQATFC
INSLAHYIGTQPFDDRRTPRDNWITAIVTFGEGYHNFHHEFPTDYRNAIKWYQYDPTKVI
IYLTSLVGLAYDLKKFSQNAIEEALIQQEQKKINKKKAKINWGPVLTDLPMWDKQTFLAK
SKENKGLVIISGIVHDVSGYISEHPGGETLIKTALGKDATKAFSGGVYRHSNAAQNVLAD
MRVAVIKESKNSAIRMASKRGEIYETGKFF (SEQ ID NO: 1)

These data strongly suggest that Ole1 is the target of 1,2,4-oxadiazoles. Additionally, addition of exogenous oleic acid reversed both growth inhibition of wild-type cells and rescue of toxicity in a yeast disease model of alpha-synuclein toxicity (Figs. 2A and 2B, respectively). Likewise, these effects were specific for 1,2,4-oxadiazoles, but not other toxic compounds.

Drug-resistant Ole1 mutations reduced 1,2,4-oxadiazole-induced growth inhibition in control conditions (Fig. 3A). The same mutations also increased the EC50 (concentration that gives half-maximal response) in the context of the alpha-synuclein model, which is consistent with reduced binding to the target. These shifts in does response were specific for 1,2,4-oxadiazoles. These data further support that Ole1/SCD is the target for both growth inhibition and rescue of toxicity in disease models.

The *OLE1* gene is essential in *Saccharomyces cerevisiae*. However, strains deleted for *OLE1* (*ole1*Δ) are viable if their growth media is supplemented with oleic/palmitoleic acid. The *ole1*Δ strain supplemented with exogenous fatty acids was fully resistant to 1,2,4-oxadiazoles (Fig. 4). In other words, in the absence of the target, Ole1, the 1,2,4-oxadiazoles do not have growth inhibition activity. Independently, a chemical genetics approach identified *MGA2*, the transcription factor that regulates Ole1. Genetic deletion of *MGA2* (mga2Δ) phenocopied the effects of 1,2,4-oxadiazoles (Fig. 5). mga2Δ cells have reduced Ole1 levels, which itself rescues toxicity in the yeast disease models (e.g., the ApoE4

model). Supplementation of the growth media with oleic acid reversed this effect, similar to the results described above. Consistent with these data, treatment of yeast cells with the 1,2,4-oxadiazole Compound 95 inhibited lipid desaturation (Figs. 8A-8D). Overall, these data provide still further evidence that Ole1/SCD is the target of 1,2,4-oxadiazoles.

Humanized yeast strains expressing the human SCD proteins SCD1 or SCD5 were generated by genetic deletion of *OLE1* and expressing human SCD1 or SCD5 on a plasmid. Yeast expressing *OLE1* were resistant to known SCD1/SCD5 inhibitors such as A939572, CAY10566, MF-438, and MK-8245 (Fig. 6), suggesting that they do not target the yeast enzyme. In marked contrast, in the SCD1 and SCD5 humanized strains, the known SCD1/SCD5 inhibitors were extremely potent, with low nanomolar half-maximal inhibitory concentration (IC50) values (Fig. 6).

The effect of 1,2,4-oxadiazoles was also evaluated in both of the humanized SCD1 and SCD5 models. 1,2,4-oxadiazoles inhibited the growth of the SCD1 and/or SCD1 yeast strains, and differences in the structure-activity relationship (SAR) between the three SCD proteins was observed (Fig. 7). Some compounds inhibited the growth of both the SCD1 and the SCD5 strains. Other compounds appeared to target only the yeast enzyme. Out of a total of 250 1,2,4-oxadiazoles tested, approximately 50% exhibited activity against the human enzymes. The divergent SAR provides additional strong evidence for SCD being the target of 1,2,4-oxadiazoles.

Finally, treatment of yeast cells with the 1,2,4-oxadiazole Compound 95 inhibited lipid desaturation (Figs. 8A-8D), providing additional confimatory evidence that SCD is the target of 1,2,4-oxadiazoles.

Taken together, these data demonstrate that Ole1/SCD is the target of 1,2,4-oxadiazoles, and that these compounds inhibit Ole1/SCD.

Example 160. Inhibition of Ole1, SDC1, and SCD5 by Compounds of the Invention

Using the methods described above, the inhibition of Ole1, SCD1, and SCD5 was tested for compounds of the invention. The results are shown in Table 5.

Table 5. Inhibition of Ole1, SCD1, and SCD5 by Compounds of the Invention

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
1	77.42	40.32	13.31	>45	6.34	>45
2	89.46	>45	39.07	>45	6.07	>45
3	82.44	38.49	22.77	>45	18.19	>45
4	97.53	>45	82.28	>45	5.61	>45
5	4.18	>45	72.44	>45	38.42	24.45
6	64.04	39.15	72.55	>45	77.35	41.10
7	3.03	>45	50.66	39.16	8.11	>45
8	16.92	>45	1.03	>45	2.16	>45
9	104.24	>45	115.64	>45	62.24	>45
10	18.99	>45	18.39	>45	6.06	>45
11	78.50	>45	74.99	>45	35.13	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
12	98.37	>45	70.29	>45	77.40	>45
13	5.69	>45	70.42	>45	25.88	>45
14	14.56	>45	90.98	>45	51.85	27.53
15	9.81	>45	21.78	>45	0.80	>45
16	82.88	>45	66.57	37.11	3.55	>45
17	94.17	>45	71.38	>45	23.21	>45
18	5.70	>45	74.70	41.00	22.66	>45
19	12.81	>45	28.21	>45	4.13	>45
20	112.10	>45	38.25	>45	6.14	>45
21	105.47	>45	87.64	39.94	12.90	>45
22	51.46	40.47	64.47	41.00	74.04	30.02
23	92.36	>45	61.05	33.58	40.64	>45
24	99.70	>45	66.31	>45	67.98	30.03
25	3.45	>45	70.78	>45	51.67	39.44
26	23.82	>45	82.66	>45	50.25	24.46
27	1.78	>45	0.90	>45	-0.86	>45
27	2.82	>45	13.09	>45	3.95	>45
28	4.80	>45	98.15	>45	79.98	>45
29	91.00	>45	69.52	>45	74.10	>45
30	100.46	>45	80.58	>45	74.17	>45
31	79.60	>45	81.19	>45	24.26	25.37
32	108.22	>45	84.16	>45	80.17	>45
33	1.55	>45	8.14	>45	24.10	>45
34	76.89	>45	42.55	>45	5.37	>45
35	3.66	>45	79.23	>45	68.57	>45
36	17.70	>45	64.67	30.02	63.86	>45
37	9.99	>45	81.44	>45	74.18	>45
38	20.26	>45	72.81	>45	64.24	41.03
39	110.89	>45	77.01	>45	79.10	>45
40	1.26	>45	41.70	>45	0.43	>45
40	0.80	>45	47.19	>45	4.73	>45
40	4.9	>45	57.7	>45	13.7	>45
41	85.45	>45	55.28	38.72	43.51	>45
42	95.43	>45	90.77	>45	47.40	>45
43	107.35	>45	76.52	>45	65.66	>45
44	93.69	>45	17.96	>45	10.99	>45
46	87.95	>45	70.27	>45	72.35	>45
47	109.20	>45	73.30	>45	74.25	>45
48	8.16	>45	63.58	39.27	75.26	>45
49	34.89	>45	61.29	>45	63.18	>45
50	98.10	>45	67.05	41.00	46.80	>45
51	102.56	>45	76.83	>45	6.59	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
52	11.78	>45	1.65	>45	-1.01	>45
53	98.51	>45	79.96	>45	2.94	>45
54	85.34	>45	82.41	>45	47.60	>45
55	114.12	>45	74.99	33.67	74.78	>45
56	10.04	>45	59.58	>45	70.33	30.00
57	82.47	>45	80.82	>45	63.17	41.10
58	92.35	>45	101.47	>45	66.93	>45
59	105.25	>45	79.13	>45	59.32	>45
60	2.91	>45	72.03	>45	57.19	41.10
61	71.50	40.87	2.37	>45	13.18	>45
62	86.77	>45	28.73	>45	5.75	>45
63	101.06	>45	62.04	33.67	9.39	>45
64	115.95	>45	32.39	>45	42.05	>45
65	4.02	>45	83.43	>45	73.43	>45
66	99.71	>45	94.04	>45	19.53	>45
67	85.79	>45	54.45	40.71	4.32	>45
68	9.74	>45	22.28	>45	3.75	>45
69	105.31	>45	60.59	>45	8.06	>45
70	74.02	>45	39.36	>45	22.44	>45
71	97.50	>45	67.35	>45	46.73	>45
72	85.17	>45	41.97	27.27	52.89	32.98
73	83.83	>45	61.02	33.67	5.84	>45
74	85.96	>45	51.32	31.26	5.68	>45
75	91.51	>45	80.18	>45	63.65	30.05
78	87.89	38.34	86.39	>45	86.12	>45
79	104.92	>45	81.83	>45	76.87	>45
80	46.71	>45	98.34	>45	15.53	>45
81	13.12	>45	13.86	>45	3.39	>45
82	107.01	>45	83.67	>45	75.72	>45
83	3.73	>45	7.65	>45	1.65	>45
85	64.87	>45	88.05	>45	16.38	>45
86	2.85	>45	84.44	>45	66.85	33.33
88	16.29	>45	63.82	33.46	5.70	>45
89	119.71	>45	106.83	>45	87.41	>45
90	23.20	>45	107.22	>45	3.66	>45
91	3.64	>45	97.20	>45	32.20	>45
92	107.87	>45	80.31	>45	83.38	>45
93	5.46	>45	97.21	>45	8.16	>45
94	29.00	>45	90.84	>45	61.78	39.28
95	5.72	>45	58.05	39.20	7.46	>45
96	3.94	>45	12.37	>45	1.38	>45
97	10.45	>45	81.79	>45	78.75	30.01

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
98	92.44	>45	74.79	>45	52.40	41.10
99	64.73	>45	13.74	>45	8.85	>45
100	23.98	>45	54.37	32.84	6.56	>45
101	12.74	>45	29.81	>45	29.09	>45
102	24.90	>45	60.33	>45	6.56	>45
103	5.27	>45	93.33	>45	68.60	>45
104	110.40	>45	76.89	>45	77.11	>45
105	34.19	>45	41.38	>45	13.93	>45
106	35.35	>45	78.19	>45	71.22	>45
107	4.55	>45	73.32	>45	74.80	>45
108	72.04	>45	72.79	>45	64.66	>45
109	87.87	>45	84.36	>45	89.75	>45
110	96.31	>45	66.85	>45	65.07	>45
111	38.26	>45	76.39	>45	32.73	>45
112	3.16	>45	66.76	>45	21.21	>45
113	5.55	>45	55.33	40.72	27.28	>45
114	90.17	>45	74.54	>45	77.66	>45
115	101.68	>45	77.36	>45	77.85	>45
116	12.75	>45	71.12	>45	8.35	>45
117	92.97	>45	95.94	>45	54.63	36.14
118	87.29	>45	93.37	>45	32.21	27.53
119	111.86	>45	86.22	>45	93.93	>45
120	119.08	>45	99.80	>45	96.39	>45
121	111.12	>45	94.06	>45	98.38	>45
122	109.89	>45	92.73	>45	90.04	>45
123	3.12	>45	73.59	>45	9.69	>45
124	4.55	>45	88.87	>45	96.23	>45
125	92.36	>45	77.68	>45	94.83	>45
126	73.29	>45	69.80	>45	79.08	30.00
127	99.27	>45	66.46	>45	88.59	>45
128	81.43	>45	1.12	>45	1.89	>45
128	60.60	45	23.56	>45	3.32	>45
129	3.25	>45	75.60	>45	93.05	>45
130	2.75	>45	97.82	>45	99.82	>45
131	39.81	25.79	96.48	>45	98.92	>45
132	7.45	>45	115.10	>45	94.34	>45
133	26.72	>45	61.21	37.29	74.75	>45
134	93.94	>45	107.77	>45	98.55	>45
135	99.53	>45	92.42	>45	91.64	>45
136	73.60	>45	34.33	>45	17.07	>45
137	96.83	>45	90.19	>45	50.61	22.33
138	3.94	>45	54.49	37.32	4.57	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
139	25.30	>45	87.50	>45	75.11	>45
140	3.96	>45	77.37	>45	3.46	>45
140	4.98	>45	75.00	45	10.16	1.30
141	1.77	>45	86.53	>45	78.91	>45
142	1.11	>45	80.83	>45	26.00	>45
143	95.01	>45	79.38	>45	96.06	>45
144	100.96	>45	79.00	>45	84.27	>45
145	51.17	15.85	78.31	>45	86.51	>45
146	3.28	>45	60.81	37.75	25.62	>45
147	9.34	>45	74.14	>45	86.70	>45
148	99.90	>45	79.55	>45	86.53	>45
149	90.68	>45	69.75	>45	38.72	>45
150	5.16	>45	74.48	>45	86.15	>45
151	2.67	>45	75.63	>45	20.68	>45
152	2.37	>45	83.39	>45	60.91	>45
153	2.75	>45	75.76	>45	87.51	>45
154	1.20	>45	68.90	>45	3.25	>45
155	1.65	>45	98.25	>45	67.35	33.77
156	63.63	37.08	72.58	>45	22.37	>45
157	91.55	>45	80.54	>45	72.54	>45
158	89.93	>45	78.34	>45	91.96	>45
159	46.92	>45	70.17	38.85	10.25	13.86
160	71.55	36.23	63.44	40.70	28.51	24.31
162	100.35	>45	84.54	>45	76.89	>45
163	71.84	>45	55.99	36.51	24.77	>45
164	96.96	>45	102.20	>45	73.90	>45
165	2.01	>45	94.44	>45	80.23	>45
166	105.73	>45	90.07	>45	68.87	>45
167	57.28	38.39	6.11	>45	2.38	>45
168	4.90	>45	114.58	>45	1.99	>45
168	8.34	>45	74.07	45	14.85	>45
169	99.67	>45	78.78	>45	84.20	>45
170	67.97	40.39	103.19	>45	85.13	>45
171	6.77	>45	74.21	40.42	-0.14	>45
172	3.99	>45	89.39	>45	68.80	41.10
173	99.75	>45	78.07	>45	42.09	29.77
174	89.17	>45	79.07	>45	10.95	>45
175	3.00	>45	77.47	>45	77.96	>45
176	3.62	>45	107.22	>45	83.50	>45
177	40.70	>45	97.88	>45	86.13	>45
178	7.39	>45	114.07	>45	85.67	>45
179	76.70	38.71	106.53	>45	85.02	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
180	107.78	>45	102.85	>45	82.28	>45
181	20.70	>45	88.32	>45	81.40	>45
182	124.27	>45	113.27	>45	79.82	>45
183	101.71	>45	101.67	>45	84.88	>45
184	3.07	>45	86.33	>45	2.41	>45
184	0.87	>45	50.65	45	11.92	>45
185	93.51	>45	97.91	>45	72.91	>45
186	35.40	>45	86.16	>45	73.51	30.01
187	97.42	>45	72.13	>45	2.91	>45
188	4.70	>45	78.63	>45	4.51	>45
189	98.14	>45	88.10	>45	68.58	>45
190	100.94	>45	83.53	>45	19.31	>45
191	89.31	>45	81.79	>45	6.72	>45
192	95.03	>45	84.60	>45	76.82	>45
193	89.35	>45	80.72	>45	85.76	>45
194	60.71	>45	74.07	>45	63.24	>45
195	3.86	>45	75.08	>45	9.78	>45
196	93.87	>45	86.58	>45	75.88	>45
197	4.80	>45	66.87	>45	61.44	>45
198	2.96	>45	71.25	>45	36.45	>45
199	24.34	>45	27.85	>45	3.87	>45
200	2.69	>45	79.67	>45	64.72	41.10
201	85.29	>45	79.67	>45	65.14	32.88
202	94.93	>45	74.09	>45	74.20	>45
203	100.03	>45	84.83	>45	80.12	>45
204	79.30	>45	30.36	>45	0.25	>45
204	50.38	>45	21.99	>45	2.95	>45
205	94.02	>45	31.70	>45	1.01	>45
206	5.25	>45	93.66	>45	19.89	>45
207	5.39	>45	86.42	>45	72.56	>45
208	96.63	>45	14.04	>45	5.68	>45
209	3.74	>45	101.51	>45	78.88	>45
210	2.27	>45	30.48	>45	3.39	>45
211	2.65	>45	39.99	>45	6.95	>45
212	100.82	>45	76.79	>45	76.28	>45
213	94.72	>45	86.35	>45	85.33	>45
214	15.08	>45	65.73	41.00	74.58	>45
215	48.68	>45	88.23	>45	78.96	>45
216	61.84	35.11	83.82	>45	75.59	>45
217	10.39	>45	57.90	36.93	12.62	>45
218	4.63	>45	48.31	>45	25.15	>45
219	3.50	>45	95.22	>45	89.83	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
220	3.10	>45	87.27	>45	13.65	>45
221	113.54	>45	100.56	>45	93.18	>45
222	3.59	>45	40.42	>45	1.92	>45
223	2.22	>45	68.23	40.65	67.37	40.97
224	2.54	>45	26.70	>45	1.12	>45
225	20.97	>45	94.06	>45	88.95	>45
226	1.24	>45	33.20	>45	0.69	>45
227	1.24	>45	63.76	38.33	6.17	>45
228	21.30	>45	51.80	41.00	2.72	>45
229	89.56	>45	66.51	>45	71.18	>45
230	2.63	>45	78.48	>45	44.00	>45
231	29.53	>45	80.00	>45	3.11	>45
232	4.20	>45	81.04	>45	51.17	41.10
233	18.46	>45	73.65	>45	74.91	>45
234	84.80	>45	68.91	>45	76.83	>45
235	84.04	>45	74.46	>45	87.47	>45
236	8.46	>45	77.23	>45	3.14	>45
237	18.53	>45	71.76	>45	45.34	32.63
238	4.93	>45	70.06	>45	69.63	30.00
239	29.21	>45	75.58	>45	6.02	>45
240	4.30	>45	66.85	>45	12.95	>45
241	6.15	>45	91.61	>45	16.97	>45
242	95.59	>45	101.23	>45	79.22	>45
243	94.60	>45	94.50	>45	72.11	>45
244	3.34	>45	15.54	>45	2.85	>45
244	1.29	>45	8.51	>45	2.47	>45
245	95.26	>45	77.70	>45	66.96	>45
246	13.06	>45	77.22	>45	66.03	>45
247	98.49	>45	79.89	>45	72.46	>45
248	73.12	>45	3.09	>45	13.59	>45
249	88.69	>45	80.12	>45	61.88	41.67
250	4.41	>45	86.09	>45	14.48	>45
251	7.80	>45	83.15	>45	20.59	>45
252	27.85	>45	80.73	>45	39.69	>45
253	106.42	>45	62.07	>45	63.11	>45
254	92.77	>45	69.80	>45	83.13	>45
255	96.25	>45	72.70	>45	64.50	30.02
256	4.16	>45	76.04	>45	72.11	>45
261	94.41	>45	73.42	>45	82.31	>45
262	23.99	>45	41.84	>45	10.38	>45
263	8.71	>45	18.81	>45	7.20	>45
264	15.52	>45	56.37	40.76	7.97	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
265	103.04	>45	76.74	>45	10.96	>45
265	83.99	45	54.38	45	3.97	>45
266	7.17	>45	12.42	>45	9.90	>45
267	4.64	>45	58.58	37.75	11.33	>45
268	4.39	>45	79.03	>45	8.68	>45
268	0.14	>45	65	45	2.67	>45
269	6.62	>45	38.78	>45	8.38	>45
269	4.57	>45	25.11	>45	5.30	>45
270	63.00	41.85	82.42	>45	12.30	>45
271	11.7	>45	67.9	>45	53.6	>45
272	40.3	>45	70.8	>45	51.9	>45
273	78.7	>45	67.9	>45	55.0	>45
274	75.9	>45	75.3	>45	67.0	>45
275	11.24	>45	76.51	>45	78.05	>45
276	6.27	>45	61.16	>45	18.81	14.51
277	94.36	>45	76.49	>45	74.99	>45
278	21.08	>45	32.22	>45	10.55	>45
279	83.07	>45	43.86	>45	21.97	>45
280	17.18	>45	11.48	>45	8.86	>45
281	60.23	33.84	84.97	>45	18.03	>45
281	32.09	>45	68.90	45	12.39	>45
282	110.18	>45	90.54	>45	56.23	28.87
283	24.43	>45	34.91	34.65	9.83	>45
284	12.40	>45	4.81	>45	6.80	>45
285	105.26	>45	45.62	>45	30.09	>45
286	5.18	>45	13.04	>45	8.76	>45
286	4.35	>45	14.44	>45	9.55	>45
287	93.89	>45	72.51	>45	66.81	>45
288	7.14	>45	8.71	>45	7.52	>45
289	45.87	>45	62.01	>45	77.71	>45
290	20.6	>45	3.3	>45	8.8	>45
291	15.6	>45	5.0	>45	8.5	>45
291	3.95	>45	0.30	>45	3.29	>45
292	13.6	>45	9.5	>45	10.2	>45
293	66.4	34.9	12.3	>45	11.9	>45
294	4.5	>45	16.6	>45	7.8	>45
294	2.84	>45	23.31	>45	6.57	>45
295	18.4	>45	14.4	>45	9.2	>45
296	99.1	>45	86.6	>45	22.6	>45
297	42.0	25.2	5.7	>45	9.2	>45
298	6.6	>45	92.3	>45	21.3	>45
299	17.5	>45	89.6	>45	30.1	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
299	13.58	>45	62.80	45	22.61	>45
300	79.7	>45	78.1	>45	36.0	>45
301	99.4	>45	96.2	>45	21.0	>45
302	6.7	>45	71.1	36.1	9.4	>45
302	5.26	>45	50.17	45	10.64	>45
303	14.2	>45	94.3	>45	15.6	>45
303	8.50	>45	65	45	20.68	>45
304	14.7	>45	74.9	>45	51.6	>45
305	6.6	>45	73.2	>45	18.4	>45
305	4.23	>45	55.27	45	5.95	>45
306	33.2	>45	67.6	>45	17.6	>45
306	36.88	>45	63.32	45	5.23	>45
307	7.8	>45	78.2	>45	52.5	>45
307	4.08	>45	70.58	45	27.45	>45
308	63.7	>45	81.6	>45	15.5	>45
308	49.30	27.20	61.05	45	6.81	>45
309	8.0	>45	80.6	>45	14.7	>45
310	7.1	>45	71.2	>45	66.6	>45
311	90.8	>45	72.9	>45	60.5	>45
316	89.26	45	69.01	45	80	45
317	8.3	>45	30.0	>45	20.6	>45
318	89.1	>45	77.6	>45	33.7	>45
319	74.25	>45	97.10	>45	4.96	>45
319	63.83	>45	89.16	>45	10.94	>45
319	86.3	>45	81.7	>45	19.6	>45
319	84.75	45	75.42	45	4.56	>45
320	28.5	>45	74.7	>45	76.0	>45
321	14.0	>45	71.6	>45	74.1	>45
322	9.0	>45	73.6	>45	29.8	>45
323	89.1	>45	76.1	>45	73.5	>45
324	90.5	>45	74.9	>45	68.7	>45
325	79.2	>45	73.7	>45	67.2	>45
326	7.5	>45	77.1	>45	26.5	>45
327	74.8	>45	66.5	>45	68.0	>45
328	21.9	>45	86.6	>45	80.5	>45
329	12.5	>45	16.2	>45	13.4	>45
331	13.7	>45	41.9	>45	24.9	>45
332	77.0	>45	59.7	>45	31.5	>45
333	81.2	>45	55.6	>45	62.3	>45
334	84.4	>45	49.3	>45	66.7	>45
335	81.5	>45	54.0	>45	61.2	>45
336	86.7	>45	56.9	>45	74.1	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
337	86.4	>45	49.6	>45	61.6	>45
338	85.2	>45	60.0	>45	76.3	>45
339	85.7	>45	56.1	>45	75.4	>45
340	88.9	>45	55.0	>45	65.9	>45
341	91.7	>45	45.2	>>45	45.6	>45
342	80.9	>45	75.9	>45	43.5	>45
343	84.7	>45	59.1	>45	23.2	>45
344	7.14	>45	n/a	n/a	1.1	>45
345	6.63	>45	n/a	n/a	2.2	>45
346	12.12	>45	n/a	n/a	1.1	>45
348	74.78	>45	n/a	n/a	59.2	45
349	84.00	>45	n/a	n/a	0.2	>45
350	71.00	>45	n/a	n/a	56.3	45
351	68.60	>45	n/a	n/a	57.3	45
352	71.57	>45	n/a	n/a	44.5	>45
354	NT	NT	30.16	>45	4.29	>45
355	NT	NT	71.31	>45	3.68	>45
356	NT	NT	51.18	>45	2.88	>45
357	NT	NT	64.32	>45	2.31	>45
358	NT	NT	59.61	>45	4.53	>45
359	NT	NT	55.70	>45	0.81	>45
360	NT	NT	64.03	>45	2.38	>45
361	NT	NT	67.22	>45	0.95	>45
362	NT	NT	67.00	>45	2.26	>45
363	NT	NT	64.44	>45	1.99	>45
364	NT	NT	70.82	>45	2.22	>45
365	NT	NT	58.08	>45	23.74	>45
484	92.09	>45	75.84	>45	81.46	>45
485	75.19	>45	62.60	>45	65.42	30.03
486	103.51	>45	76.95	>45	72.76	>45
487	103.20	>45	83.76	>45	70.73	40.19
488	90.53	>45	75.87	>45	72.82	>45
489	94.30	>45	68.84	41.00	61.11	41.10
490	96.38	>45	63.84	38.76	50.39	35.13
491	107.15	>45	118.81	>45	83.61	>45
492	106.45	>45	83.92	>45	75.64	>45
493	91.16	>45	68.84	>45	60.28	30.20
494	92.28	>45	79.67	>45	73.76	>45
495	NT	NT	-	>45	-	1.917
496	NT	NT	-	>45	-	0.445
497	NT	NT	-	>45	-	11.33
498	NT	NT	-	>45	-	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
499	NT	NT	-	>45	-	1.103
500	NT	NT	-	>45	-	>45
501	NT	NT	-	12.16	-	21.27
502	NT	NT	-	>45	-	38.94
503	NT	NT	-	>45	-	0.316
504	NT	NT	-	>45	-	14.84
505	NT	NT	-	>45	-	0.669
506	NT	NT	-	>45	-	0.81
507	NT	NT	-	>45	-	2.443
508	NT	NT	-	>45	-	>45
509	NT	NT	-	>45	-	>45
510	NT	NT	-	>45	-	4.16
511	NT	NT	-	>45	-	3.39
512	NT	NT	-	>45	-	>45
513	NT	NT	-	>45	-	>45
514	NT	NT	-	>45	-	>45
515	NT	NT	-	16.53	-	>45
516	NT	NT	-	>45	-	>45
517	NT	NT	-	>45	-	>45
518	NT	NT	-	>45	-	2.95
519	NT	NT	-	>45	-	>45
520	NT	NT	-	>45	-	>45
521	NT	NT	-	>45	-	8.794
522	NT	NT	-	>45	-	>45
523	NT	NT	-	>45	-	>45
524	NT	NT	-	>45	-	2.499
525	NT	NT	-	>45	-	>45
526	NT	NT	-	>45	-	>45
527	NT	NT	-	0.958	-	1.46
528	NT	NT	-	>45	-	>45
529	NT	NT	-	>45	-	>45
530	NT	NT	-	>45	-	>45
531	NT	NT	-	>45	-	>45
532	NT	NT	-	>45	-	2.15
533	NT	NT	-	>45	-	3.331
534	NT	NT	-	>45	-	36.8
535	NT	NT	-	>45	-	>45
536	NT	NT	-	>45	-	>45
537	NT	NT	-	>45	-	>45
538	NT	NT	-	>45	-	>45
539	NT	NT	-	>45	-	>45
540	NT	NT	-	>45	-	>45

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
541	NT	NT	-	>45	-	>45
542	NT	NT	-	>45	-	7.331
543	NT	NT	-	>45	-	45
544	NT	NT	-	>45	-	10.03
545	NT	NT	-	>45	-	18.95
546	NT	NT	-	>45	-	0.019
547	NT	NT	-	>45	-	44.3
548	NT	NT	-	>45	-	0.01
549	NT	NT	-	>45	-	1.211
550	NT	NT	-	>45	-	>45
551	NT	NT	-	>45	-	>45
552	NT	NT	-	>45	-	>45
553	NT	NT	-	5.708	-	0.885
554	NT	NT	-	4.079	-	1.071
555	NT	NT	-	>45	-	>45
556	NT	NT	-	>45	-	>45
557	NT	NT	-	>45	-	6.03
558	NT	NT	-	>45	-	1.072
559	NT	NT	-	>45	-	1.191
560	NT	NT	-	>45	-	>45
561	NT	NT	-	>45	-	29.43
562	NT	NT	-	>45	-	1.496
563	NT	NT	-	>45	-	>45
564	NT	NT	-	>45	-	4.234
565	NT	NT	-	>45	-	>45
567	NT	NT	-	>45	-	>45
568	NT	NT	-	>45	-	>45
569	NT	NT	-	>45	-	>45
570	NT	NT	-	>45	-	26.35
571	NT	NT	-	>45	-	>45
572	NT	NT	-	>45	-	14.99
573	NT	NT	-	>45	-	5.601
574	NT	NT	-	>45	-	2.282
575	NT	NT	-	>45	-	4.681
576	NT	NT	-	>45	-	0.028
577	NT	NT	-	>45	-	>45
578	NT	NT	-	8.457	-	1.487
579	NT	NT	-	>45	-	>45
580	NT	NT	-	14.08	-	0.022
581	NT	NT	-	>45	-	>45
582	NT	NT	-	>45	-	0.176
583	NT	NT	-	>45	-	0.989

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
584	NT	NT	-	>45	-	5.338
585	NT	NT	-	>45	-	1.807
586	NT	NT	-	>45	-	3.768
587	NT	NT	-	>45	-	4.92
588	NT	NT	-	>45	-	1.861
589	NT	NT	-	>45	-	0.356
590	NT	NT	-	>45	-	>45
591	NT	NT	-	>45	-	>45
592	NT	NT	-	>45	-	>45
593	NT	NT	-	>45	-	>45
594	NT	NT	-	>45	-	11.8
595	NT	NT	-	>45	-	>45
596	NT	NT	-	>45	-	>45
597	NT	NT	-	>45	-	>45
598	NT	NT	-	>45	-	>45
599	NT	NT	-	>45	-	>45
600	NT	NT	-	>45	-	>45
601	NT	NT	-	>45	-	5.686
602	NT	NT	-	15.94	-	2.744
603	NT	NT	-	7.258	-	2.411
604	NT	NT	-	>45	-	6.12
605	NT	NT	-	31.84	-	0.513
606	NT	NT	-	>45	-	0.737
607	NT	NT	-	>45	-	0.511
608	NT	NT	-	>45	-	>45
609	NT	NT	-	>45	-	>45
610	NT	NT	-	>45	-	2.157
611	NT	NT	-	>45	-	7.479
612	NT	NT	-	>45	-	2.385
613	NT	NT	-	>45	-	>45
614	NT	NT	-	>45	-	13.92
615	NT	NT	-	0.848	-	1.878
616	NT	NT	-	>45	-	>45
617	NT	NT	-	>45	-	0.121
618	NT	NT	-	>45	-	0.101
619	NT	NT	-	>45	-	0.291
620	NT	NT	-	>45	-	0.013
621	NT	NT	-	>45	-	0.042
622	NT	NT	-	>45	-	1.614
623	NT	NT	-	>45	-	0.854
624	NT	NT	-	>45	-	0.222
625	NT	NT	-	>45	-	0.122

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
626	NT	NT	-	>45	-	2.75
627	NT	NT	-	>45	-	6.686
628	NT	NT	-	>45	-	0.01
629	NT	NT	-	>45	-	0.03
630	NT	NT	-	10.24	-	0.014
631	NT	NT	-	>45	-	>45
632	NT	NT	-	>45	-	>45
633	NT	NT	-	>45	-	0.214
634	NT	NT	-	>45	-	45
635	NT	NT	-	>45	-	0.397
636	NT	NT	-	>45	-	1.801
637	NT	NT	-	>45	-	>45
638	NT	NT	-	>45	-	>45
639	NT	NT	-	>45	-	4.791
640	NT	NT	-	>45	-	3.98
641	NT	NT	-	>45	-	6.72
642	NT	NT	-	>45	-	0.211
643	NT	NT	-	>45	-	0.01
644	NT	NT	-	>45	-	>45
645	NT	NT	-	17.92	-	4.473
646	NT	NT	-	>45	-	1.184
647	NT	NT	-	>45	-	9.371
648	NT	NT	-	>45	-	>45
649	NT	NT	-	>45	-	0.259
650	NT	NT	-	4.359	-	0.013
651	NT	NT	-	>45	-	18.43
652	NT	NT	-	>45	-	>45
653	NT	NT	-	>45	-	>45
654	NT	NT	-	>45	-	>45
655	NT	NT	-	>45	-	>45
656	NT	NT	-	>45	-	>45
657	NT	NT	-	>45	-	9.109
658	NT	NT	-	>45	-	0.089
659	NT	NT	-	>45	-	4.201
660	NT	NT	-	>45	-	14.62
661	NT	NT	-	>45	-	1.541
662	NT	NT	-	>45	-	>45
663	NT	NT	-	>45	-	0.01
664	NT	NT	-	23.48	-	0.023
665	NT	NT	-	>45	-	5.006
666	NT	NT	-	>45	-	>45
667	NT	NT	-	>45	-	0.87

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
668	NT	NT	-	>45	-	0.719
669	NT	NT	-	>45	-	>45
670	NT	NT	-	>45	-	3.789
671	NT	NT	-	>45	-	>45
672	NT	NT	-	>45	-	0.441
673	NT	NT	-	>45	-	33.85
674	NT	NT	-	>45	-	>45
675	NT	NT	-	>45	-	0.01
676	NT	NT	-	>45	-	0.013
677	NT	NT	-	>45	-	>45
678	NT	NT	-	>45	-	3.868
679	NT	NT	-	>45	-	>45
680	NT	NT	-	>45	-	>45
681	NT	NT	-	>45	-	>45
682	NT	NT	-	>45	-	0.01
683	NT	NT	-	>45	-	10.15
684	NT	NT	-	>45	-	>45
685	NT	NT	-	>45	-	0.184
686	NT	NT	-	>45	-	>45
687	NT	NT	-	>45	-	>45
688	NT	NT	-	>45	-	1.504
689	NT	NT	-	>45	-	0.657
690	NT	NT	-	>45	-	0.131
691	NT	NT	-	>45	-	>45
692	NT	NT	-	>45	-	0.492
693	NT	NT	-	>45	-	1.666
694	NT	NT	-	>45	-	>45
695	NT	NT	-	>45	-	2.394
696	NT	NT	-	>45	-	0.08
697	NT	NT	-	>45	-	0.059
698	NT	NT	-	>45	-	0.026
699	NT	NT	-	>45	-	7.647
700	NT	NT	-	>45	-	0.703
701	NT	NT	-	>45	-	>45
702	NT	NT	-	>45	-	>45
703	NT	NT	-	>45	-	0.121
704	NT	NT	-	>45	-	1.677
705	NT	NT	-	14.37	-	0.174
706	NT	NT	-	>45	-	>45
707	NT	NT	-	>45	-	14.53
708	NT	NT	-	>45	-	>45
709	NT	NT	-	>45	-	4.774

Compound #	OLE1 % Max Inhibition	OLE1 IC50	SCD1 % Max Inhibition	SCD1 IC50 (μM)	SCD5 % Max Inhibition	SCD5 IC50 (μM)
710	NT	NT	-	>45	-	0.05
711	NT	NT	-	>45	-	>45
712	NT	NT	-	>45	-	0.016
713	NT	NT	-	5.583	-	0.01
714	NT	NT	-	>45	-	0.23
715	NT	NT	-	>45	-	0.048
716	NT	NT	-	>45	-	>45
717	NT	NT	-	>45	-	1.698
718	NT	NT	-	>45	-	0.635
719	NT	NT	-	>45	-	>45
720	NT	NT	-	>45	-	1.966
721	NT	NT	-	>45	-	1.653
722	NT	NT	-	>45	-	1.374
723	NT	NT	-	>45	-	>45
724	NT	NT	-	>45	-	1.249
725	NT	NT	-	5.99	-	0.011
726	NT	NT	-	5.65	-	0.01
727	NT	NT	-	>45	-	>45
728	NT	NT	-	>45	-	0.126
729	NT	NT	-	>45	-	>45
730	NT	NT	-	>45	-	0.718
731	NT	NT	-	>45	-	>45
732	NT	NT	-	>45	-	31.82
733	NT	NT	-	>45	-	2.727
734	NT	NT	-	>45	-	>45
735	NT	NT	-	3.99	-	0.01
736	NT	NT	-	32.65	-	0.26
737	NT	NT	-	>45	-	>45
738	NT	NT	-	>45	-	>45
739	NT	NT	-	>45	-	>45
740	NT	NT	-	>45	-	1.43
741	NT	NT	-	>45	-	7.756
742	NT	NT	-	>45	-	5.048
743	NT	NT	-	>45	-	14.78
744	NT	NT	-	>45	-	>45
745	NT	NT	-	>45	-	>45

Table 6. Inhibition of SCD1 and SCD5 by Compounds of the Invention

#	**SCD1 IC50** (μM)	**SCD5 IC50** (μM)	#	**SCD1 IC50** (μM)	**SCD5 IC50** (μM)
747	>45	26.801	858	>45	0.262
748	>45	2.140	859	>45	>4
749	>45	20.798	860	>45	0.478

#	SCD1 IC50 (μM)	SCD5 IC50 (μM)	#	SCD1 IC50 (μM)	SCD5 IC50 (μM)
750	3.25	0.010	861	14.96	0.010
751	>45	>45	862	33.83	0.010
752	>45	>45	863	>45	>45
753	>45	0.585	864	>45	>45
754	>45	16.472	865	>45	0.010
755	>45	5.413	866	>45	4.607
756	>45	4.363	867	>45	1.915
757	>45	4.951	868	>45	0.967
758	>45	5.271	869	>45	1.64
759	>45	>45	870	>45	4.26
760	>45	>45	871	>45	9.54
761	>45	>45	872	>45	8.06
762	>45	5.253	873	>45	41.27
763	29.49	18.001	874	>45	0.05
764	>45	16.700	875	>45	0.02
765	32.91	19.277	876	>45	0.01
766	>45	>45	877	>45	0.08
767	>45	0.010	878	>45	0.005
768	>45	>45	879	5.50	0.01
769	>45	>45	880	>45	0.010
770	>45	>45	881	>45	0.01
771	>45	>45	882	6.56	1.91
772	>45	>45	883	>45	1.00
773	>45	21.475	884	>45	0.01
774	>45	>45	885	25.38	0.01
775	>45	0.022	886	10.62	0.06
776	>45	0.025	887	>45	0.01
777	4.16	0.010	888	>45	0.01
778	>45	0.012	889	13.31	1.90
779	>45	15.285	890	22.69	0.01
780	>45	0.027	891	>45	0.01
781	>45	4.800	892	>45	0.01
782	>45	0.149	893	>45	0.01
783	>45	>45	894	>45	0.07
784	0.95	0.010	895	>45	0.01
785	9.21	0.041	896	>45	0.01
786	>45	>45	897	>45	0.06
787	31.50	0.108	898	>45	0.07
788	>45	6.218	899	>45	25.98

#	SCD1 IC50 (μM)	SCD5 IC50 (μM)	#	SCD1 IC50 (μM)	SCD5 IC50 (μM)
789	>45	0.010	900	>45	13.08
790	>45	0.053	901	>45	>45
791	>45	0.010	902	>45	0.01
792	8.83	0.010	903	>45	0.01
793	>45	>45	904	>45	7.62
794	>45	>45	905	>45	>45
795	>45	0.010	906	>45	0.89
796	>45	1.589	907	>45	0.04
797	>45	0.133	908	>45	0.19
798	>45	>45	909	>45	2.85
799	>45	0.010	910	>45	0.01
801	>45	0.363	911	>45	>45
802	>45	14.209	912	>45	1.98
803	12.88	0.679	913	>45	13.79
804	>45	>45	914	>45	6.17
805	>45	9.360	915	>45	10.12
806	>45	>45	916	1.96	0.01
807	>45	0.247	917	>45	0.10
808	>45	5.816	918	>45	0.80
809	>45	0.124	919	>45	0.18
810	>45	2.497	920	11.67	0.10
811	>45	0.679	921	>45	3.40
812	>45	0.010	922	>45	6.56
813	>45	0.010	923	>45	>45
814	>45	>45	924	>45	4.09
815	>45	>45	925	>45	>45
816	>45	7.186	926	>45	>45
817	4.13	0.010	927	>45	0.14
818	>45	0.560	928	>45	0.01
819	>45	3.725	929	>45	4.42
820	>45	3.744	930	>45	0.20
821	>45	5.058	931	>45	>45
822	>45	0.111	932	>45	0.01
823	>45	0.119	933	>45	0.20
824	>45	0.932	934	>45	0.01
825	>45	9.490	935	>45	>45
826	>45	1.990	936	>45	3.45
827	>45	>45	937	>45	>45
828	>45	0.067	938	>45	>45

#	SCD1 IC50 (μM)	SCD5 IC50 (μM)	#	SCD1 IC50 (μM)	SCD5 IC50 (μM)
829	>45	2.202	939	>45	10.91
830	>45	>45	940	>45	31.18
831	>45	1.202	941	>45	20.36
832	>45	11.644	942	>45	9.16
833	>45	>45	943	>45	>45
834	>45	>45	944	>45	2.22
835	>45	>45	945	>45	5.29
836	>45	1.438	946	>45	4.11
837	>45	12.527	947	>45	>45
838	>45	0.021	948	>45	>45
839	>45	0.035	949	>45	>45
840	>45	20.683	950	>45	>45
841	>45	0.209	951	>45	>45
842	>45	0.010	952	15.60	9.22
843	>45	0.033	953	>45	0.01
844	>45	0.015	954	>45	2.86
845	>45	0.637	955	>45	>45
846	>45	0.040	956	>45	2.46
847	>45	>45	957	27.91	0.01
848	>45	0.010	958	>45	34.53
849	>45	0.644	959	>45	>45
850	>45	0.010	960	20.36	0.01
851	>45	0.065	961	>45	>45
852	>45	5.358	962	>45	0.01
853	>45	0.010	963	>45	0.16
854	14.57	0.010	964	0.31	0.03
855	>45	>45	965	>45	0.01
856	>45	>45	966	>45	0.15
857	>45	26.801			

Table 7. Inhibition of SCD1 and SCD5 by Compounds of the Invention

#	SCD1 IC50 (μM)	SCD5 IC50 (μM)	#	SCD1 IC50 (μM)	SCD5 IC50 (μM)
967	>45	1.52	1082	>45	0.359
968	>45	2.83	1083	>45	0.033
969	>45	1.42	1084	>45	0.027
970	8.50	0.00196	1085	>45	0.532
971	>45	0.089	1086	>45	0.019
972	>45	4.44	1087	>45	0.041
973	>45	>45	1088	>45	2.52

#	SCD1 IC50 (μM)	SCD5 IC50 (μM)	#	SCD1 IC50 (μM)	SCD5 IC50 (μM)
974	>45	0.010	1089	>45	4.68
975	>45	0.010	1090	>45	0.540
976	>45	5.33	1091	>45	3.62
977	>45	5.94	1092	32.333	0.010
978	>45	>45	1093	>45	0.00253
979	>45	0.168	1094	>45	17.4
980	>45	0.877	1095	>45	11.1
981	>45	0.045	1096	>45	0.00101
982	0.010	0.327	1097	>45	0.020
983	>45	1.51	1098	>45	0.062
984	>45	>45	1099	>45	1.88
985	>45	2.56	1100	>45	0.738
986	>45	0.048	1101	27.15	16.6
987	>45	>45	1102	>45	>45
988	>45	0.024	1103	>45	23.397
989	>45	>45	1104	>45	0.01
990	>45	0.010	1105	>45	0.54915098
991	>45	>45	1106	>45	2.955
992	>45	0.081	1107	>45	0.01
993	>45	3.81	1108	>45	>45
994	>45	>45	1109	>45	0.0500
995	>45	>45	1110	>45	0.01
996	>45	5.04	1111	>45	0.179
997	>45	0.022	1112	>45	0.193
998	>45	4.13	1113	>45	0.494
999	>45	0.010	1114	>45	0.116
1000	>45	0.650	1115	>45	10.609
1001	>45	15.6	1116	>45	1.409
1002	>45	5.05	1117	>45	>45
1003	>45	0.457	1118	>45	>45
1004	>45	0.297	1119	>45	>45
1005	>45	0.010	1120	>45	32.764
1006	>45	0.637	1121	>45	15.516
1007	>45	>45	1122	>45	13.164
1008	>45	2.02	1123	>45	6.640
1009	>45	9.51	1124	>45	>45
1010	>45	0.816	1125	>45	0.523
1011			1126	>45	2.738

#	SCD1 IC50 (μM)	SCD5 IC50 (μM)	#	SCD1 IC50 (μM)	SCD5 IC50 (μM)
1012	15.0	0.010	1127	>45	1.465
1013	>45	0.367	1128	>45	>45
1014	>45	4.82	1129	>45	>45
1015	>45	0.429	1130	>45	9.898
1016	>45	0.0614	1131	>45	0.207
1017	17.1	0.010	1132	>45	>45
1018	20.3	0.010	1133	>45	>45
1019	12.2	0.010	1134	>45	0.0269
1020	14.6	0.170	1135	>45	0.188
1021	>45	0.223	1136	>45	0.01
1022	>45	0.010	1137	>45	0.0522
1023	>45	0.295	1138	>45	0.761
1024	>45	0.010	1139	>45	0.0960
1025	>45	0.010	1140	>45	0.0613
1026	3.98	0.200	1141	>45	0.865
1027	>45	3.16	1142	>45	>45
1028	0.953	0.010	1143	>45	>45
1029	>45	0.010	1144	1.78	0.01
1030	>45	11.0	1145	>45	11.139
1031	>45	1.13	1146	>45	0.380
1032	>45	4.10	1147	>45	5.461
1033	>45	3.91	1148	>45	19.415
1034	>45	0.639	1149	>45	0.01
1035	>45	0.265	1150	>45	>45
1036	>45	0.010	1151	>45	1.0917
1037	10.23	0.457	1152	>45	0.01
1038	>45	2.30	1153	1.939	0.840
1039	15.68	0.010	1154	>45	0.0157
1040	>45	0.791	1155	>45	>45
1041	>45	0.010	1156	>45	0.493
1042	>45	0.079	1157	>45	>45
1043	>45	0.011	1158	>45	3.501
1044	>45	0.593	1159	>45	>45
1045	45	0.935	1160	>45	>45
1046	45	0.010	1161	>45	0.0363
1047	45	0.010	1162	17.236	0.0206
1048	>45	0.016	1163	>45	>45
1049	>45	0.012	1164	>45	0.540

#	SCD1 IC50 (μM)	SCD5 IC50 (μM)	#	SCD1 IC50 (μM)	SCD5 IC50 (μM)
1050	>45	0.020	1165	>45	>45
1051	>45	7.50	1166	>45	>45
1052	>45	0.253	1167	>45	>45
1053	>45	0.00118	1168	>45	>45
1054	>45	0.010	1169	15.362	>45
1055	>45	0.00488	1170	>45	0.402
1056	>45	0.00469	1171	1.140	0.0311
1057	>45	0.023	1172	45	9.893
1058	>45	0.00367	1173	45	23.382
1059	>45	0.00223	1174	>45	10.38
1060	>45	0.184	1175	>45	0.21
1061	>45	0.010	1176	>45	0.14
1062	29	0.010	1177	>45	0.84
1063	>45	3.44	1178	>45	0.63
1064	>45	3.44	1179	>45	0.11
1065	>45	0.000386	1180	>45	0.06
1066	>45	0.000681	1181	>45	0.47
1067	>45	0.00498	1182	0.83	0.72
1068	>45	0.00375	1183	>45	>45
1069	>45	0.000862	1184	>45	>45
1070	>45	0.081	1185	>45	>45
1071	>45	0.00303	1186	10.00	6.08
1072	>45	0.021	1187	>45	>45
1073	8.36	0.00252	1188	>45	>45
1074	5.43	1.96	1189	>45	7.72
1075	4.40	0.010	1190	>45	0.06
1076	>45	1.030	1191	>45	1.36
1077	>45	0.300	1192	>45	0.04
1078	>45	0.033	1193	>45	>45
1079	>45	0.911	1194	>45	>45
1080	>45	0.501	1195	>45	>45
1081	>45	2.43			

Other Embodiments

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed

examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

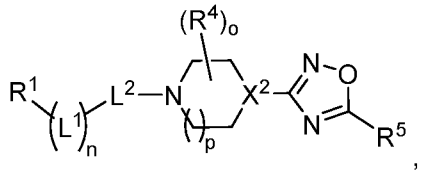
All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

Other embodiments are in the claims.

What is claimed is:

CLAIMS

1. A compound having the structure of **Formula VII**:



Formula VII

wherein

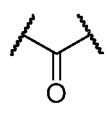
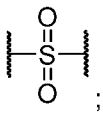
n is 0 or 1;

o is 0, 1, 2, or 3;

p is 1 or 2;

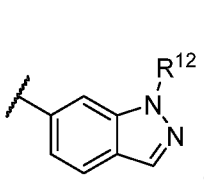
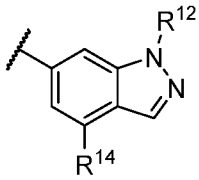
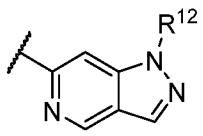
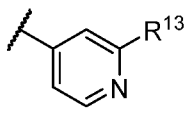
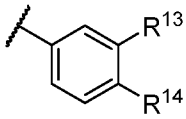
R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heterocycle, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl;

L^1 is –O–;

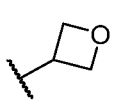
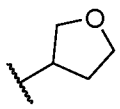
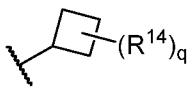
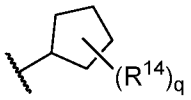
L^2 is  or  ;

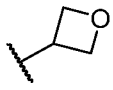
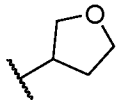
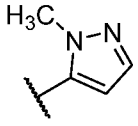
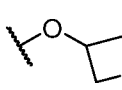
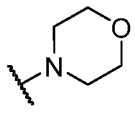
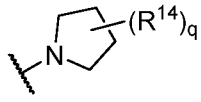
each R^4 is, independently, halogen or optionally substituted C_1-C_6 alkyl;

X^2 is N or CH;

R^5 is  ,  ,  ,  , or  ,

wherein

R^{12} is  ,  ,  , or  ;

R^{13} is  ,  ,  ,  ,  , or  ;

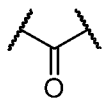
q is 0, 1, 2, or 3; and

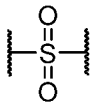
R^{14} is halogen, hydroxyl, or optionally substituted C_1-C_6 alkyl,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein X^2 is CH.

3. The compound of claim 1, wherein X^2 is N.

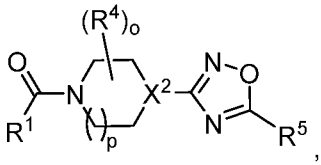
4. The compound of any one of claims 1-3, wherein L^2 is  .

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

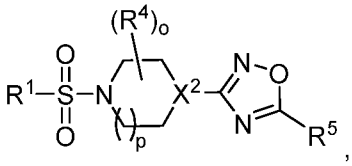
6. The compound of any one of claims 1-5, wherein n is 0.

7. The compound of any one of claims 1-4, wherein n is 1.

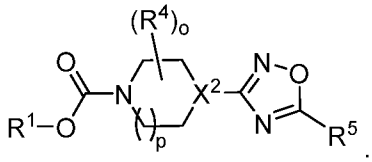
8. The compound of any one of claims 1-7, wherein the compound has the structure of **Formula VIIa**, **FormulaVIIb**, or **Formula VIIc**:

 ,

Formula VIIa

 , or

Formula VIIb

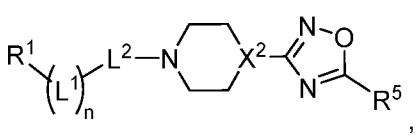
 .

Formula VIIc

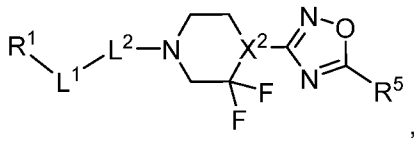
9. The compound of any one of claims 1-8, wherein o is 0, 1, or 2.

10. The compound of claims 1-9, wherein p is 1 or 2.

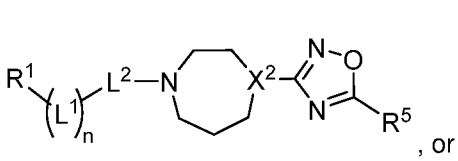
11. The compound of any one of claims 1-10, wherein the compound has the structure of **Formula VIId**, **Formula VIIe**, **Formula VIIf**, or **Formula VIIg**:

 ,

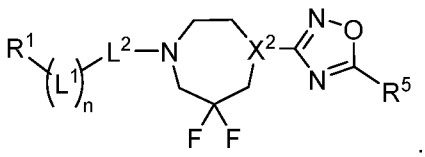
Formula VIId

 ,

Formula VIIe

 , or

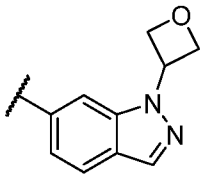
Formula VIIf

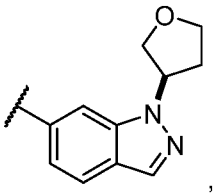
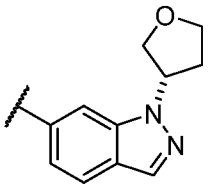
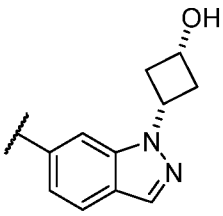
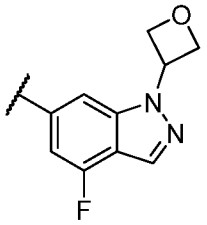
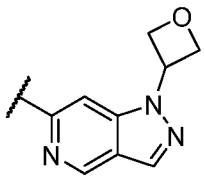
 .

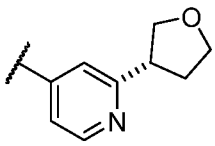
Formula VIIg

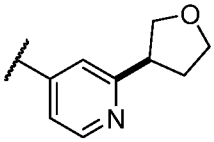
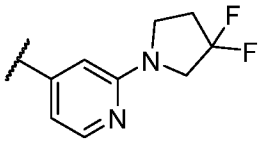
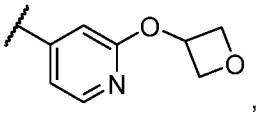
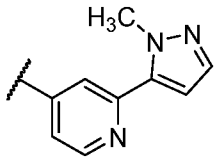
12. The compound of any one of claims 1-11, wherein q is 0 or 1.

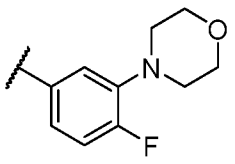
13. The compound of any one of claims 1-12, wherein R^{14} is halogen or hydroxyl.

14. The compound of any one of claims 1-13, wherein R^5 is  ,

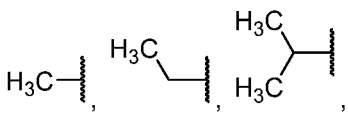
 ,  ,  ,  , or  .

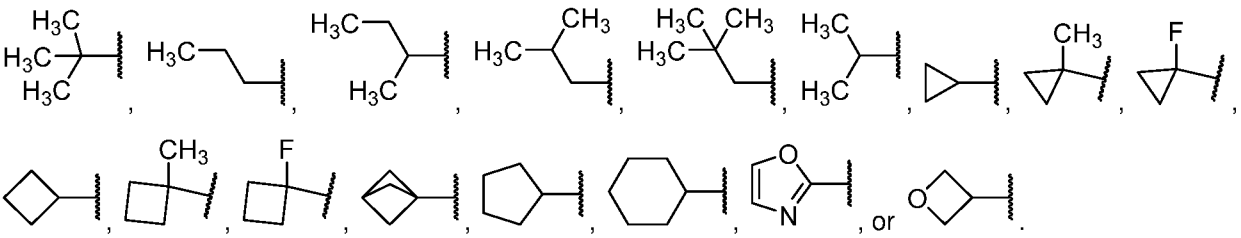
15 The compound of any one of claims 1-13, wherein R^5 is  ,

 ,  ,  , or  .

16. The compound of any one of claims 1-13, wherein R^5 is  .

17. The compound of any one of claims 1-16, wherein R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heterocycle, or optionally substituted C_2-C_9 heteroaryl.

18. The compound of any one of claims 1-17, wherein R^1 is  ,

 .

19. A compound, or pharmaceutically acceptable salt thereof, having the structure of any one of compounds 156-746 in Table 1.

20. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-19 and a pharmaceutically acceptable excipient.

21. A method of treating a neurological disorder in a subject in need thereof, the method comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-19 or a pharmaceutical composition of claim 20.

22. A method of inhibiting toxicity in a cell related to a protein, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 19.

23. The method of claim 22, wherein the toxicity is α-synuclein-related toxicity.

24. The method of claim 22, wherein the toxicity is ApoE4-related toxicity.

25. The method of any one of claims 22 to 24, wherein the cell is a mammalian neural cell.

26. A method of treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 19 or a pharmaceutical composition of claim 20.

27. A method of treating cancer in a subject in need thereof, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 19 or a pharmaceutical composition of claim 20.

28. The method of claim 27, wherein the cancer is esophageal cancer, pancreatic cancer, endometrial cancer, kidney cancer, hepatoma, thyroid cancer, gallbladder cancer, prostate cancer, leukemia (e.g., lymphomas and myelomas), ENT-related cancer, brain cancer, colon cancer, rectal cancer, colorectal cancer, ovarian cancer, uterine cancer, breast cancer, skin cancer, or prostate cancer.

FIG. 1A

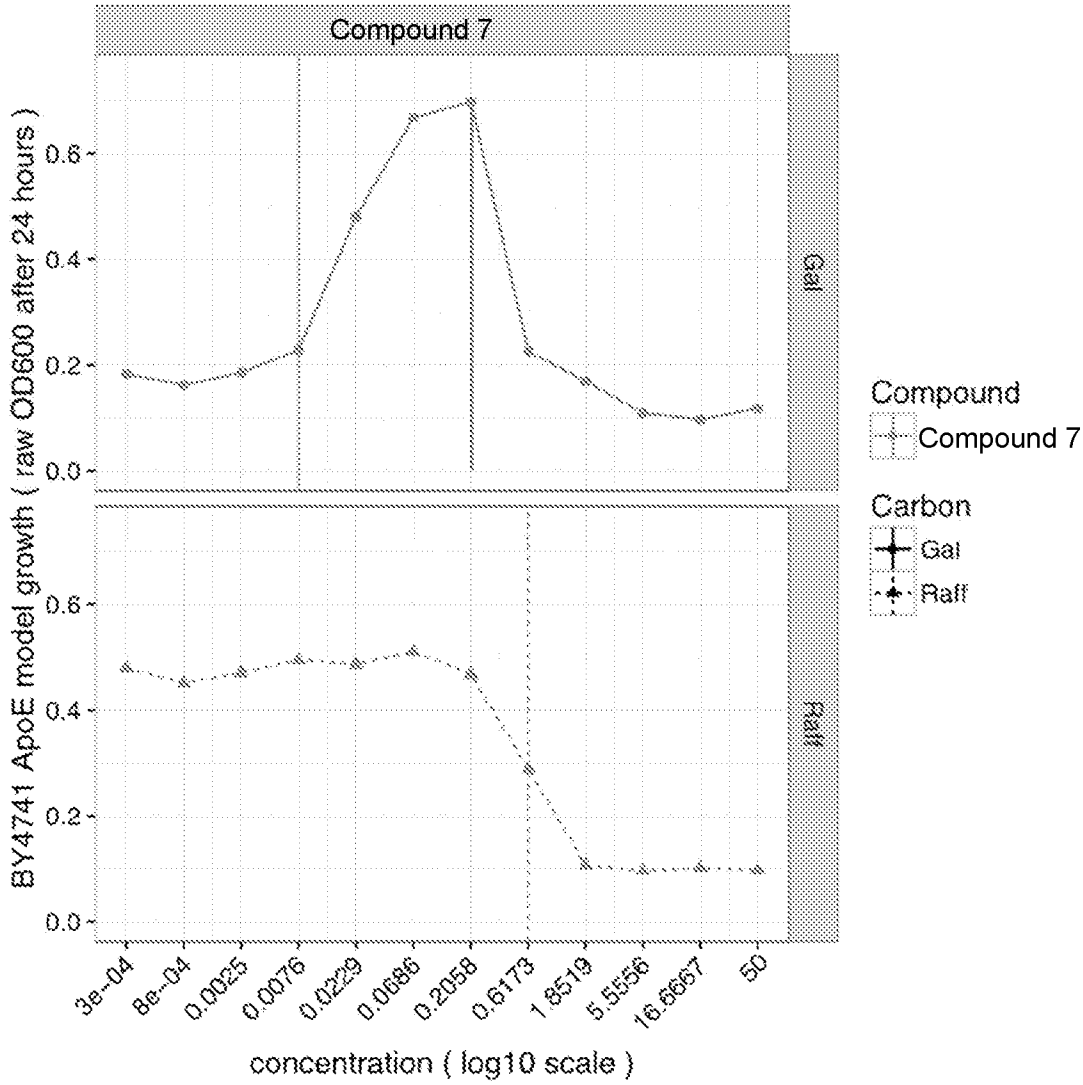

Compound 7
Gal
Raff
BY4741 ApoE model growth (raw OD600 after 24 hours)
0.0
0.2
0.4
0.6
3e−04
8e−04
0.0025
0.0076
0.0229
0.0686
0.2058
0.6173
1.8519
5.5556
16.6667
50
concentration (log10 scale)
Compound
Compound 7
Carbon
Gal
Raff

FIG. 1B

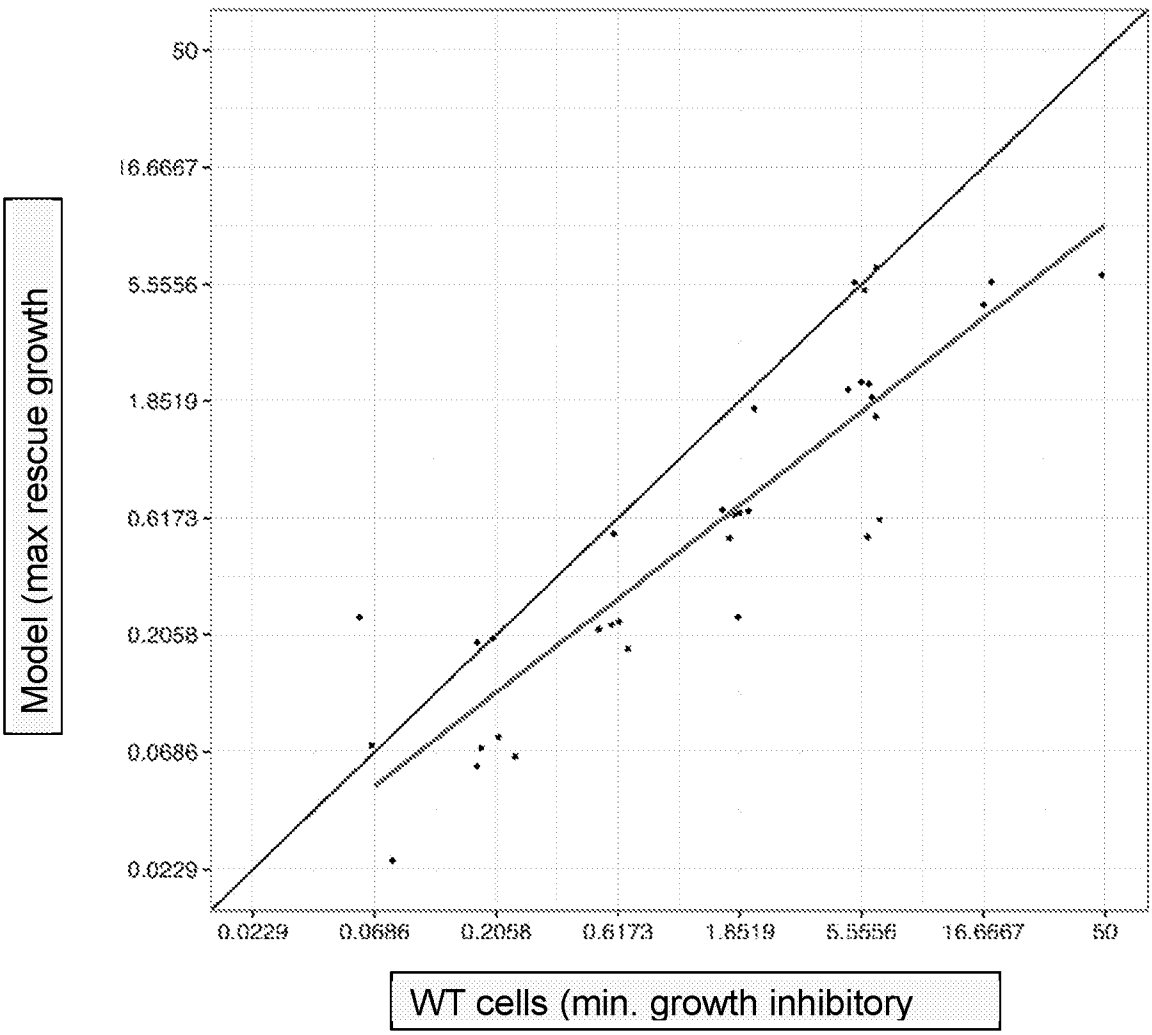

Model (max rescue growth
50
16.6667
5.5556
1.8519
0.6173
0.2058
0.0686
0.0229
0.0229
0.0686
0.2058
0.6173
1.8519
5.5556
16.6667
50
WT cells (min. growth inhibitory

FIG. 2A

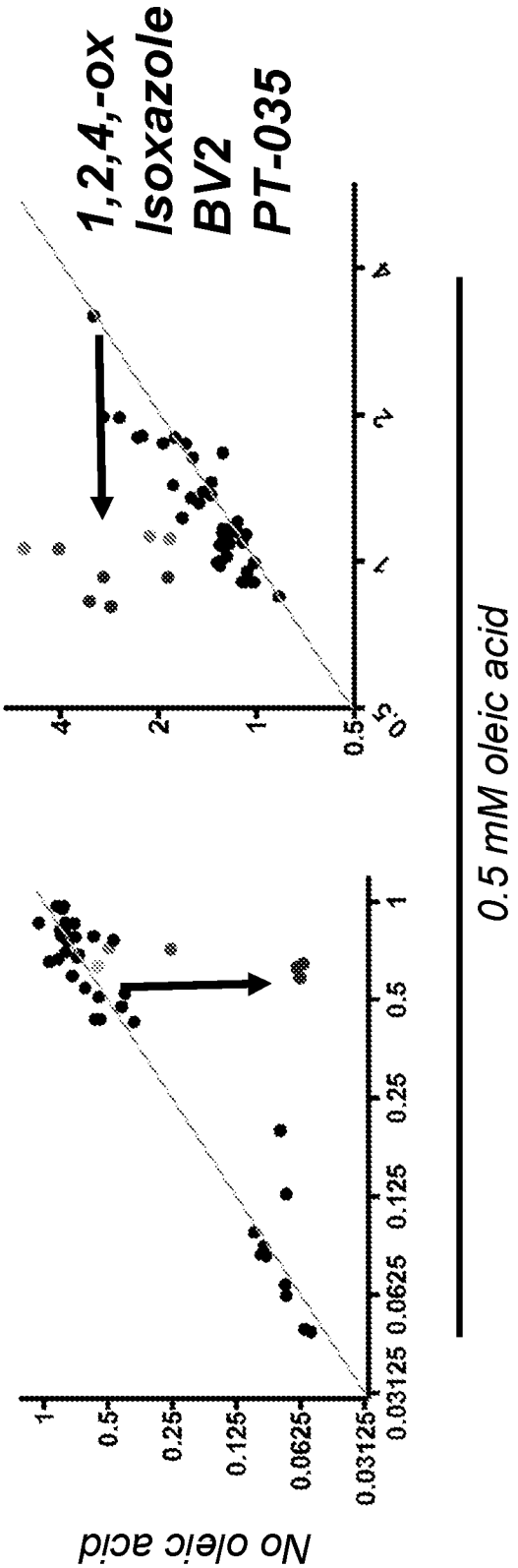

Growth Inhibition
Rescue (aSyn)
1,2,4,-ox
Isoxazole
BV2
PT-035
No oleic acid
0.5 mM oleic acid
1
0.5
0.25
0.125
0.0625
0.03125
0.03125
0.0625
0.125
0.25
0.5
1
0.5
1
2
4

FIG. 2B

FIG. 3A

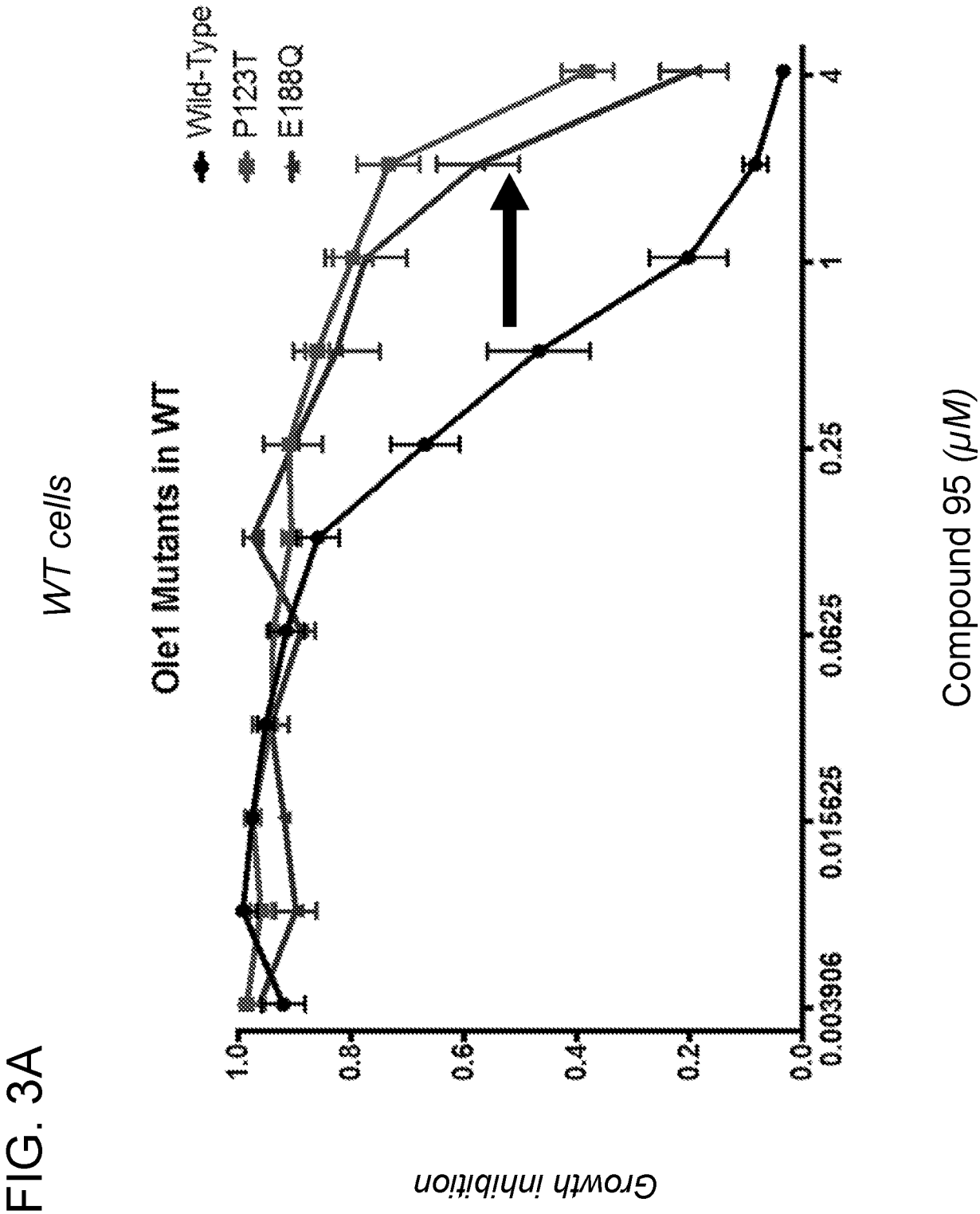

WT cells
Ole1 Mutants in WT
Wild-Type
P123T
E188Q
Growth inhibition
1.0
0.8
0.6
0.4
0.2
0.0
0.003906
0.015625
0.0625
0.25
1
4
Compound 95 (μM)

FIG. 3B

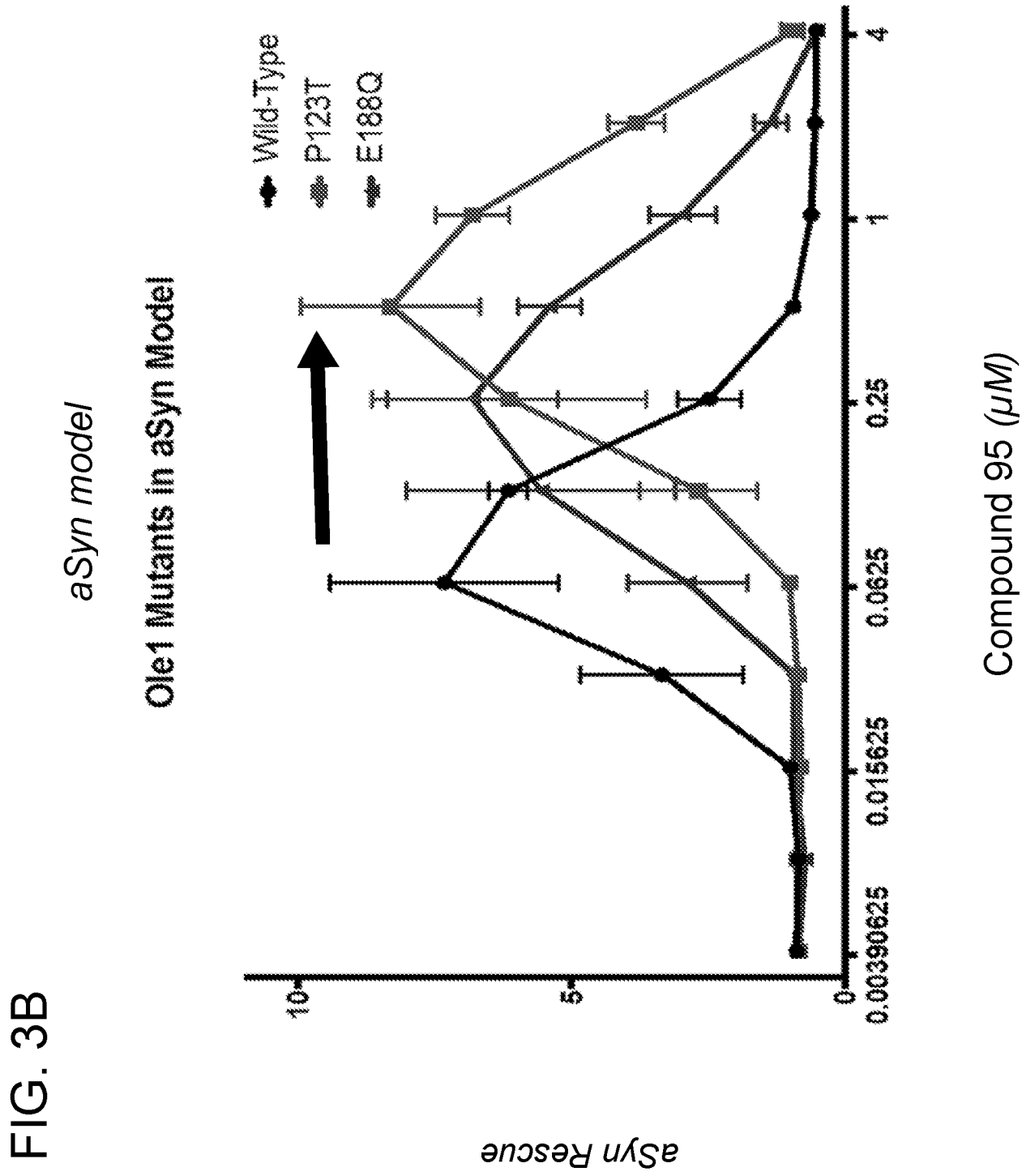

aSyn model
Ole1 Mutants in aSyn Model
Wild-Type
P123T
E188Q
aSyn Rescue
10
5
0
0.00390625
0.015625
0.0625
0.25
1
4
Compound 95 (μM)

FIG. 4

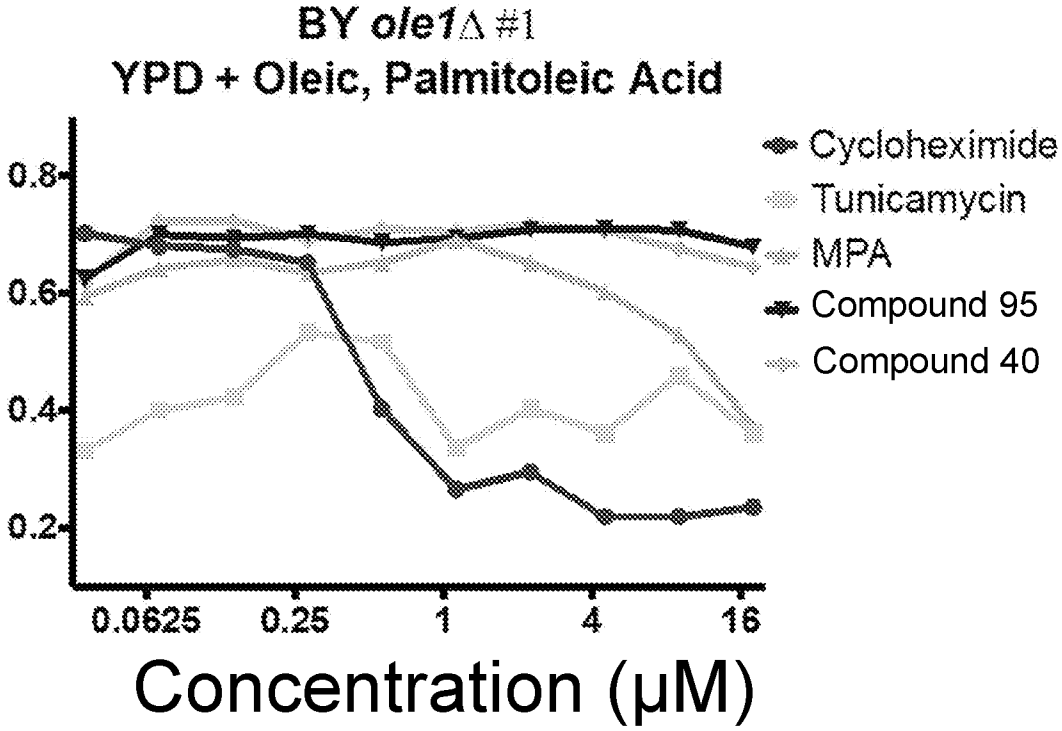

BY ole1Δ #1
YPD + Oleic, Palmitoleic Acid
Cycloheximide
Tunicamycin
MPA
Compound 95
Compound 40
0.8
0.6
0.4
0.2
0.0625
0.25
1
4
16
Concentration (μM)

FIG. 5

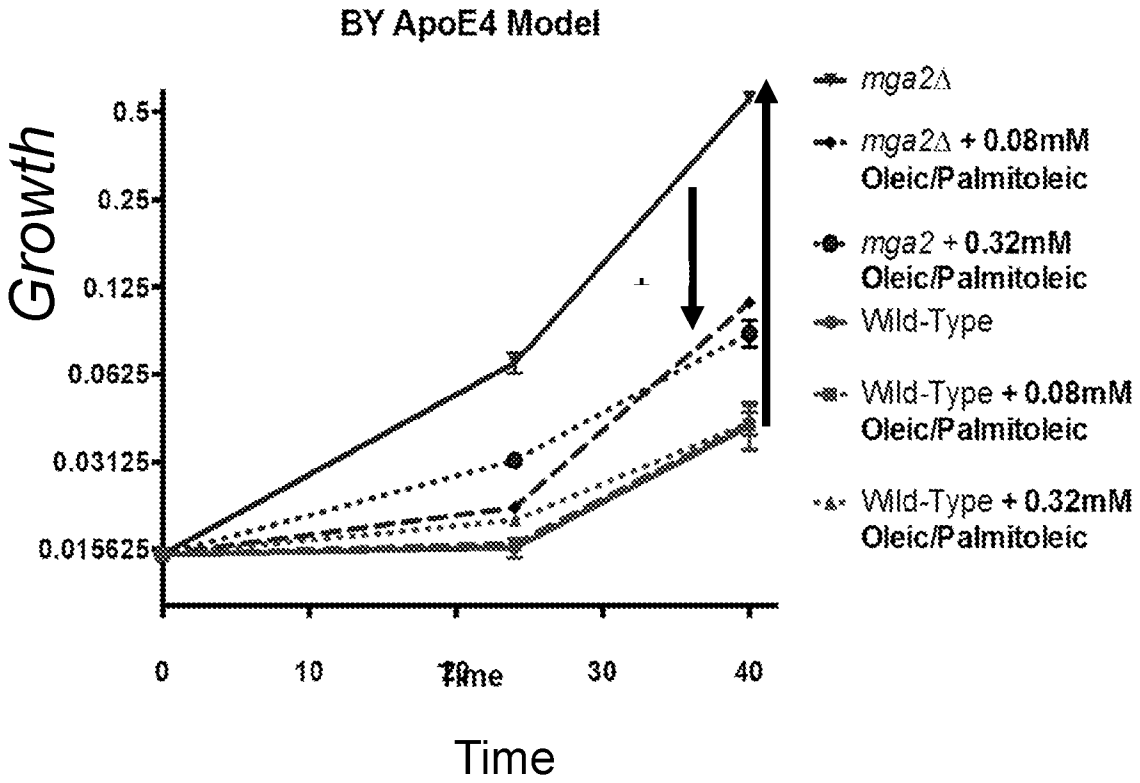

BY ApoE4 Model
Growth
0.5
0.25
0.125
0.0625
0.03125
0.015625
0
10
20
30
40
Time
mga2Δ
mga2Δ + 0.08mM Oleic/Palmitoleic
mga2 + 0.32mM Oleic/Palmitoleic
Wild-Type
Wild-Type + 0.08mM Oleic/Palmitoleic
Wild-Type + 0.32mM Oleic/Palmitoleic

FIG. 6

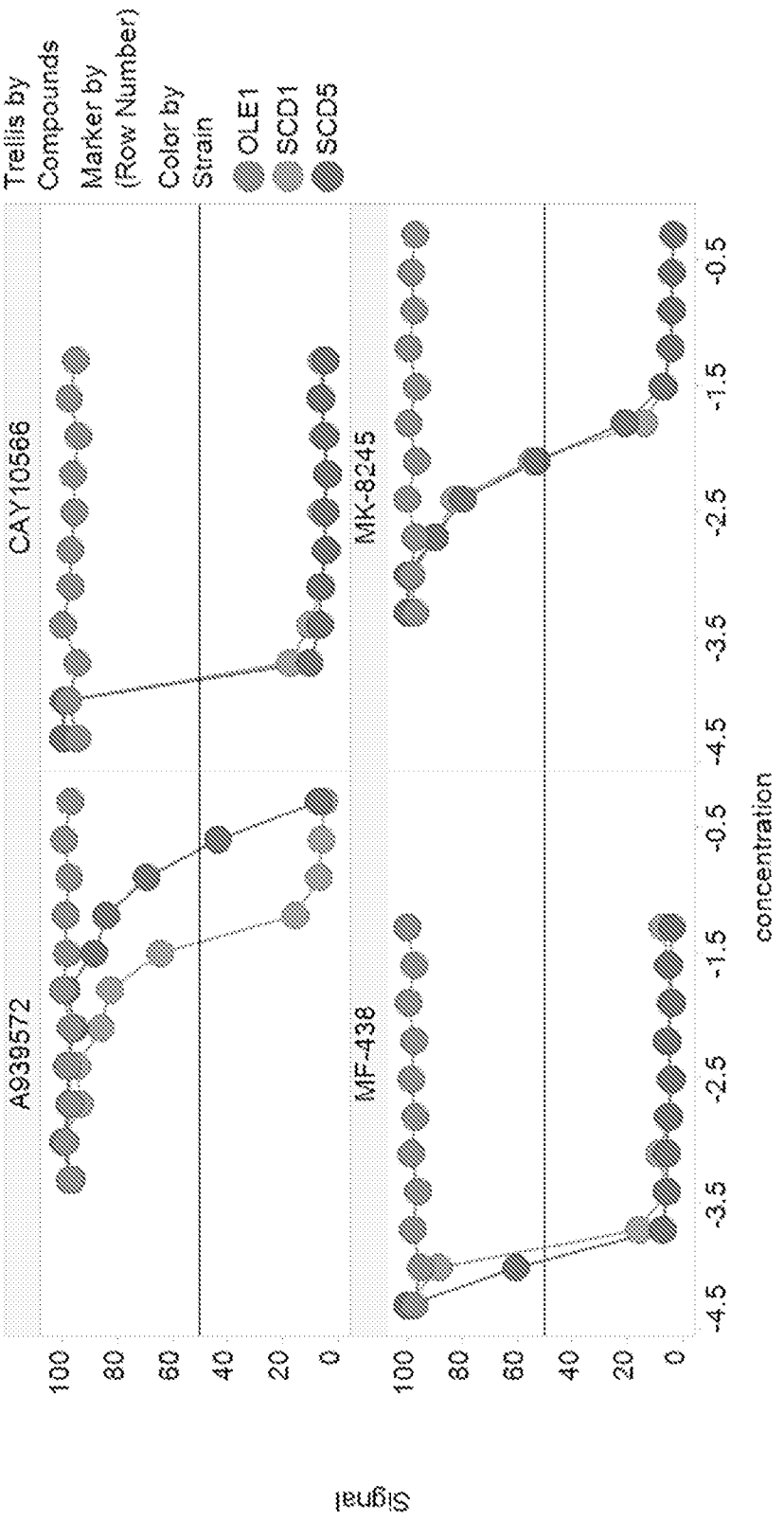

Trellis by Compounds
Marker by (Row Number)
Color by Strain
OLE1
SCD1
SCD5
A939572
CAY10566
MF-438
MK-8245
Signal
concentration
100
80
60
40
20
0
-4.5
-3.5
-2.5
-1.5
-0.5

FIG. 7

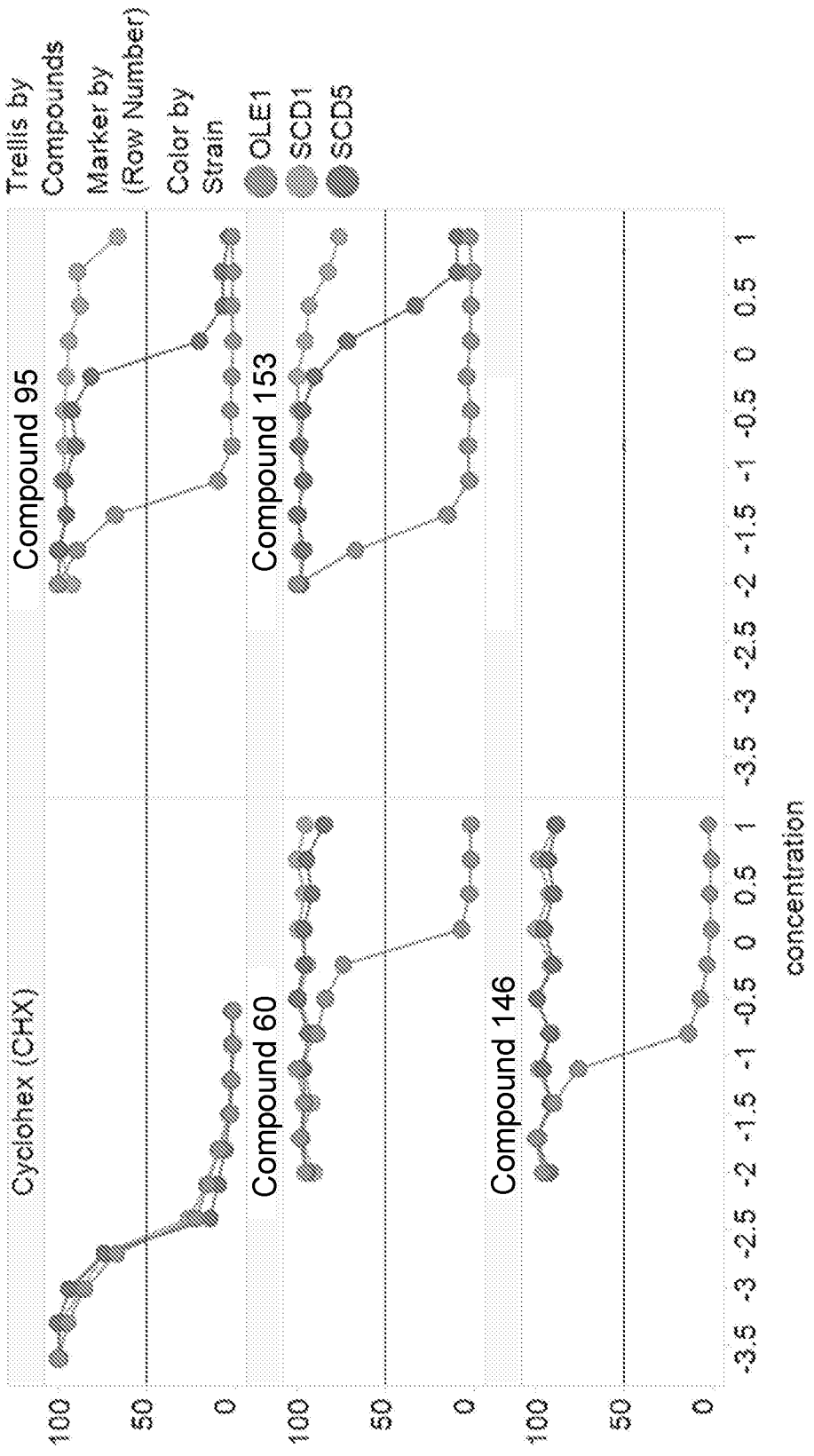

Trellis by Compounds
Marker by (Row Number)
Color by Strain
OLE1
SCD1
SCD5
Cyclohex (CHX)
Compound 95
Compound 153
Compound 60
Compound 146
100
50
0
-3.5 -3 -2.5 -2 -1.5 -1 -0.5 0 0.5 1
concentration

Fig. 8A

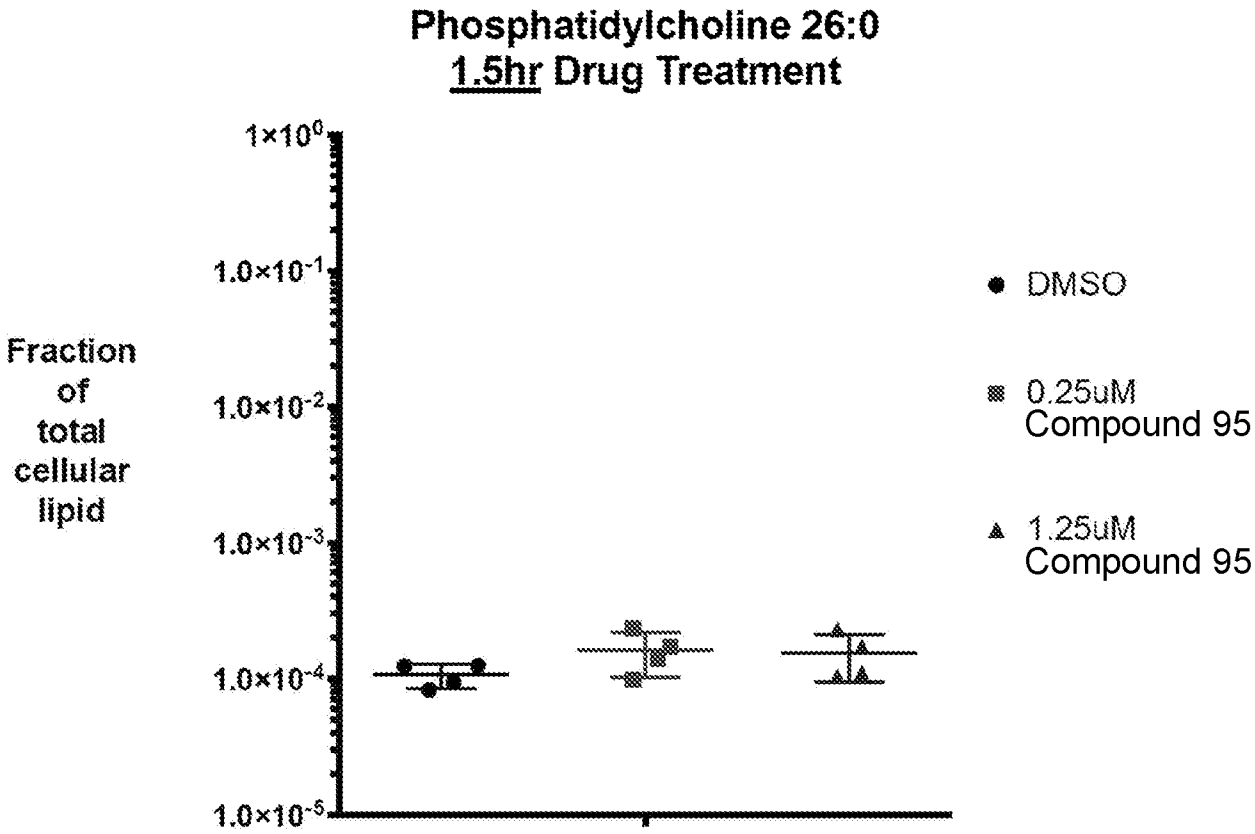

Phosphatidylcholine 26:0
1.5hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
1.0×10^-4
1.0×10^-5
DMSO
0.25uM Compound 95
1.25uM Compound 95

Fig. 8B

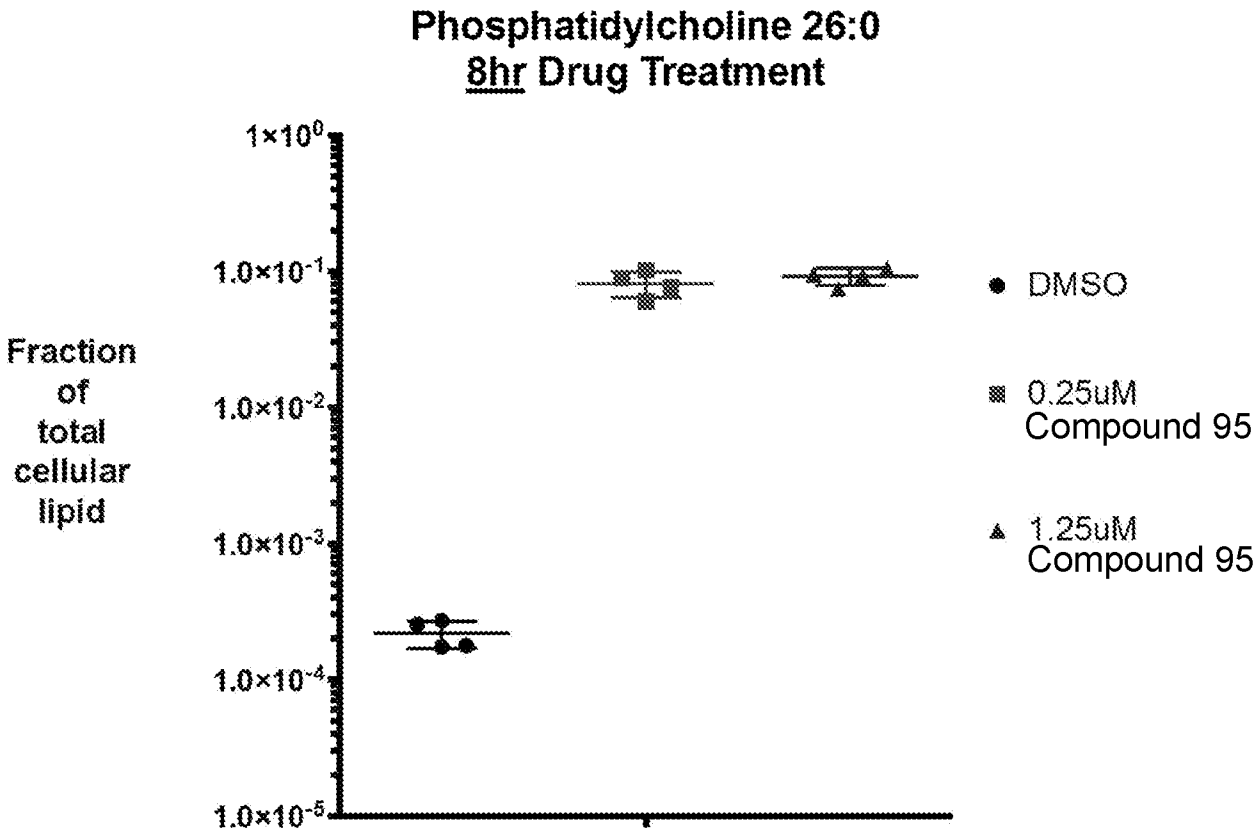

Phosphatidylcholine 26:0
8hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
1.0×10^-4
1.0×10^-5
DMSO
0.25uM Compound 95
1.25uM Compound 95

Fig. 8C

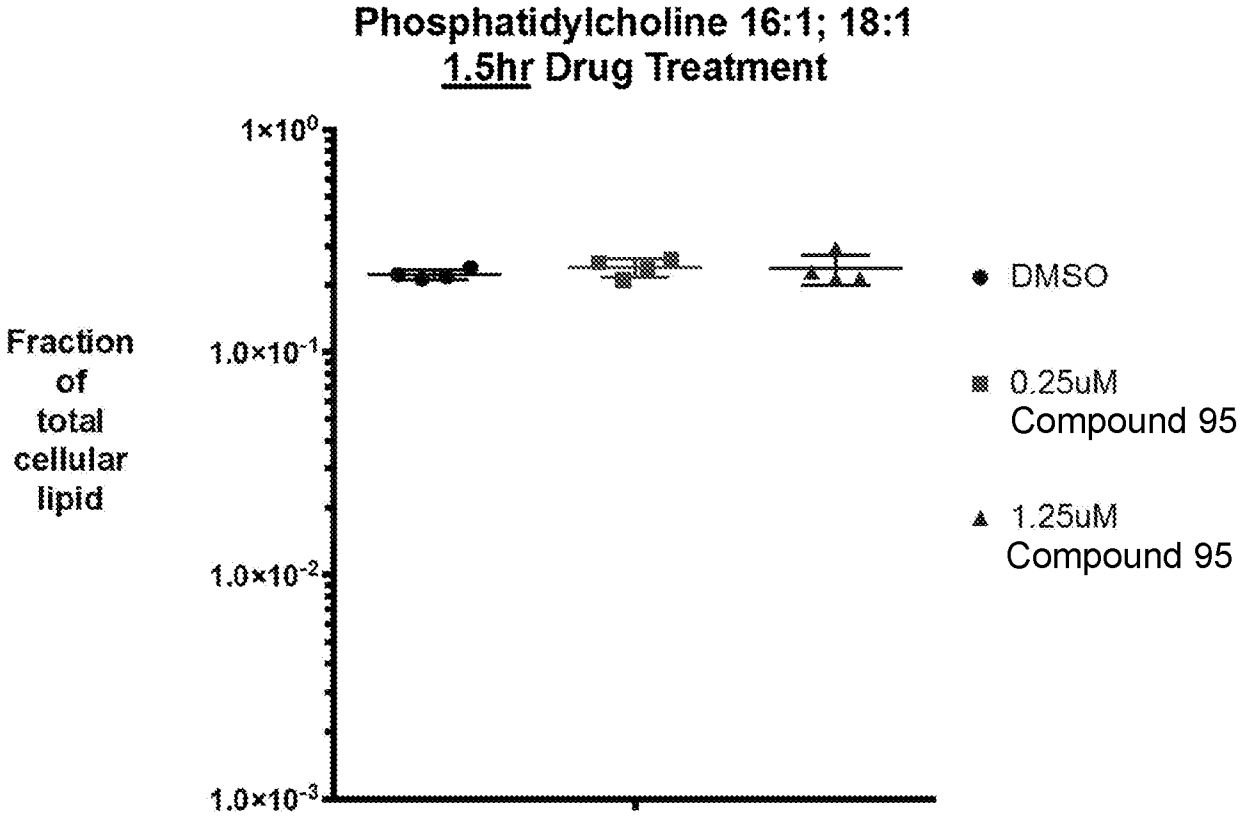

Phosphatidylcholine 16:1; 18:1
1.5hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
DMSO
0.25uM Compound 95
1.25uM Compound 95

Fig. 8D

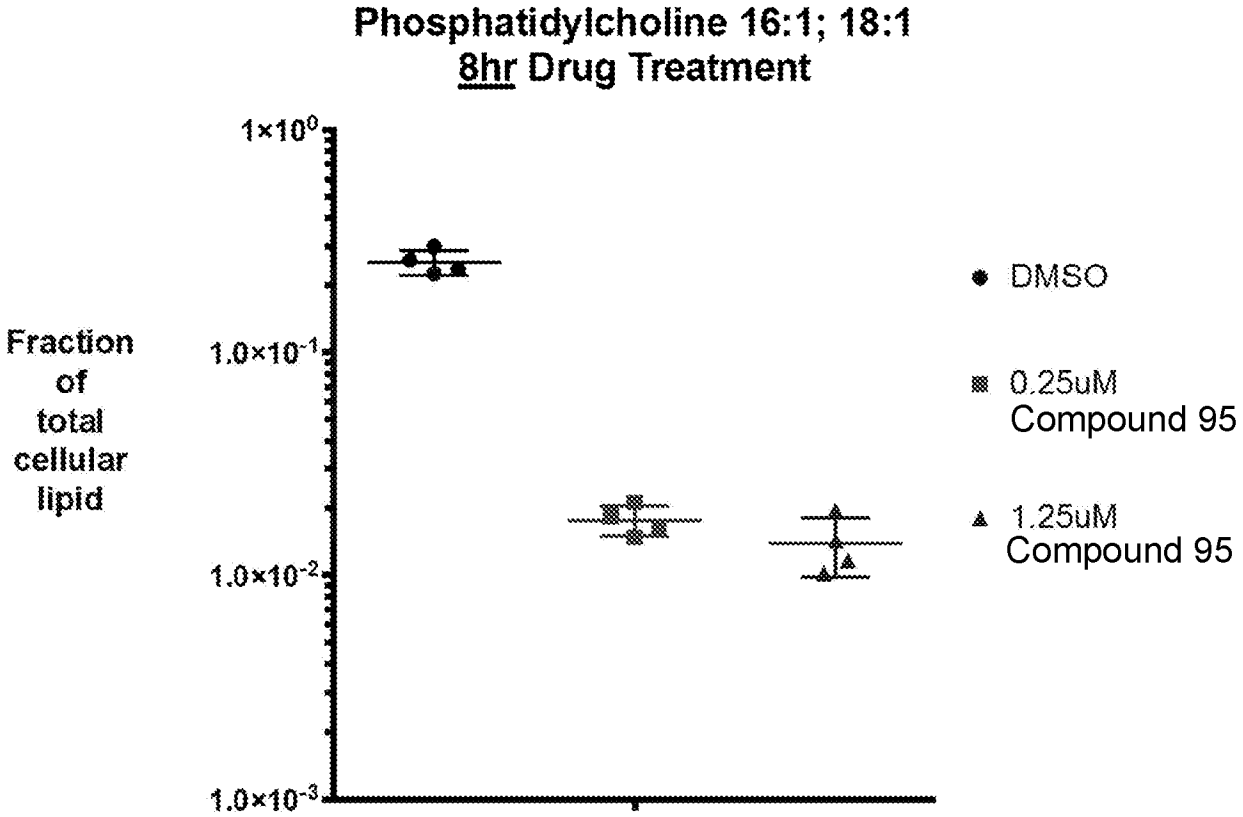
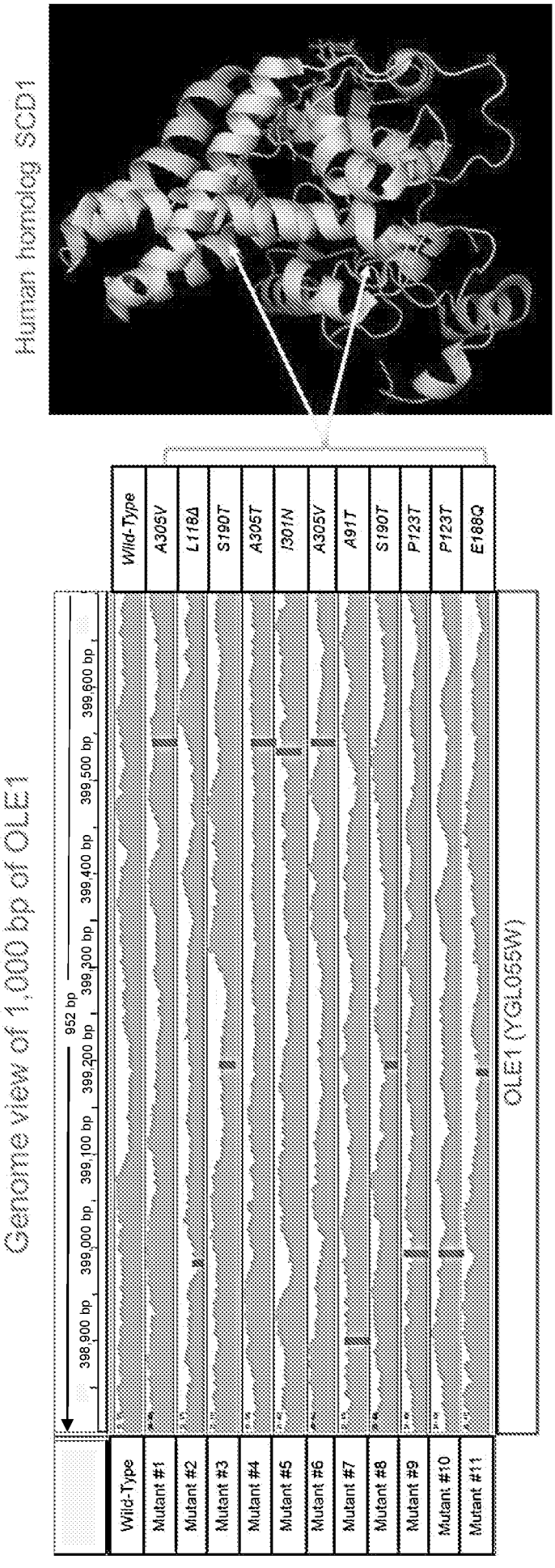

Phosphatidylcholine 16:1; 18:1
8hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
DMSO
0.25uM Compound 95
1.25uM Compound 95

Fig. 9


Human homolog SOD1
Genome view of 1,000 bp of OLE1
398,900 bp
399,000 bp
399,100 bp
952 bp
399,200 bp
399,300 bp
399,400 bp
399,500 bp
399,600 bp
Wild-Type
Mutant #1
Mutant #2
Mutant #3
Mutant #4
Mutant #5
Mutant #6
Mutant #7
Mutant #8
Mutant #9
Mutant #10
Mutant #11
Wild-Type
A305V
L118Δ
S190T
A305T
I301N
A305V
A91T
S190T
P123T
P123T
E188Q
OLE1 (YGL055W)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/43136

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/41, 31/495 (2018.01)
CPC - A61K 31/41, 31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0021028 A1 (SWINNEN, D et al) 24 January 2008; abstract; paragraphs [0166], [0220], [0437], [0960], [1006]	1-3, 4/1-3, 5/1-3
Y	US 2015/0051206 A1 (IRM LLC) 19 February 2015; paragraphs [0140], [0290]	1-3, 4/1-3, 5/1-3
Y	WO 2007/120702 A2 (ARENA PHARMACEUTICALS, INC) 25 October 2007; page 18, lines 25-30; page 99, lines 5-10, 15-20	19
Y	US 2015/0252032 A1 (ACTELION PHARMACEUTICALS LTD) 10 September 2015; abstract; paragraphs [0007], [0822]	19
Y	US 2012/0196844 A1 (ALPER, PB et al) 2 August 2012; paragraphs [0051], [0240]-[0241]	5/1-3
Y	WO 2010/022055 A2 (AMGEN INC) 25 February 2010; abstract; page 154, lines 24-26;	2, 4/2, 5/2
Y	JARVIS, MF et al. A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. Proceedings of the National Academy of Sciences of the United States of America, Vol. 104, No. 20, 15 May 2007, pp. 8520–8525; abstract	2, 4/2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2018 (26.09.2018)	10 OCT 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/43136

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-18, 20-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.