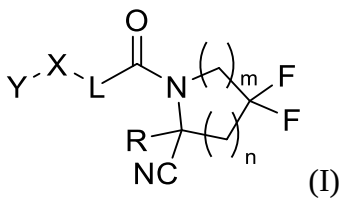
2016; Cohen, S.J., et al., Pancreas, 2008. 37(2): p. 154-8; Ju, M.J., et al., Am J Clin Pathol, 2009. 131(4): p. 498-510) and in colon cancer, increased FAP expression has been associated with a more aggressive disease (Henry, L.R., et al., Clin Cancer Res, 2007. 13(6): p. 1736-41). Purportedly, FAPα on CAFs has critical roles in regulating antitumor immune response by inducing tumor-promoting inflammation (Chen, L., et al., Biochem Biophys Res Commun, 2017; Wen, X., et al., Oncol Res, 2016; Hugo, W., et al., Cell, 2016. 165(1): p. 35-44).

[6] Val-boroPro (Talabostat, PT-100) is the only FAP inhibitor that reached clinical stages. This compound was originally developed as a DPPIV inhibitor and subsequently evaluated as a FAP inhibitor regardless of its lack of selectivity (Cunningham, C.C., Expert Opin Investig Drugs, 2007. 16(9): p. 1459-65). This agent was tested in Phase II in a variety of cancers in combination with standard cytotoxic chemotherapy, however endpoints for efficacy were not met (Eager, R.M., et al., BMC Cancer, 2009. 9: p. 263; Narra, K., et al., Cancer Biol Ther, 2007. 6(11): p. 1691-9; Eager, R.M., et al., Clin Oncol R Coll Radiol, 2009. 21(6): p. 464-72). Two Phase III trials were early terminated, apparently because of both safety and efficacy concerns (Jansen, K., et al., J Med Chem, 2014. 57(7): p. 3053-74). Since Val-boroPro rapidly loses protease inhibitory activity due to cyclization upon standing in pH 7.8, effective concentrations were difficult to achieve in patients given the clinical toxicities seen with this agent at higher doses (Narra, K., et al., Cancer Biol Ther, 2007. 6(11): p. 1691-9).

[7] There is scope to improve FAP inhibitor selectivity and the properties of the inhibitors to improve safety and efficacy *in vivo*.

SUMMARY

[8] Provided herein are compounds, salts thereof, pharmaceutical compositions of the foregoing and methods of making and using the same. In one ~~aspect~~example, the present disclosure refers to a compound of formula (I):

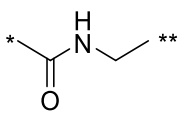
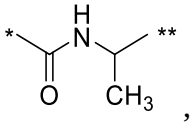
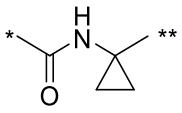
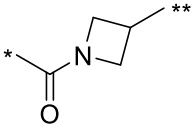
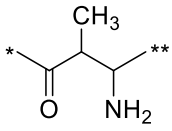
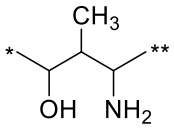
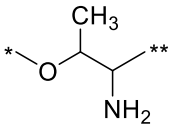
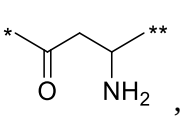
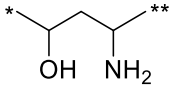
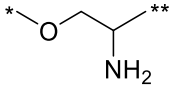
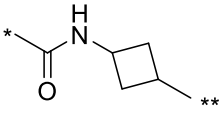
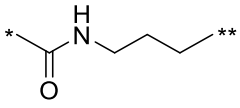


(I)

or a pharmaceutically acceptable salt thereof, wherein:

(b) 6- to 10-membered heteroaryl optionally substituted by R^{12}, such as a pyridinyl or pyrimidinyl substituted by at least one R^{12}; or

(c) 3- to 12-membered heterocyclyl optionally substituted by R^{13}, such as a piperidinyl substituted by at least one R^{13}.

[10] In another example is provided a compound of formula (I), or a salt thereof, wherein the -X-L- moiety is selected from the group consisting of , , , , , , , , , , , and ; wherein * represents the point of attachment to the Y moiety, and ** represents the point of attachment to the remainder of the molecule.

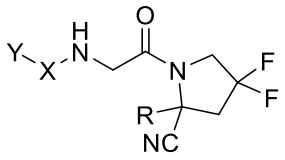
[11] Also provided is a pharmaceutical composition comprising a compound of any formula herein, including formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~**[11a]** In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.~~

[12] Also provided is a method of treating a disease or disorder mediated by fibroblast activation protein (FAP) in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound as detailed herein, including but not limited to a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such compound or salt. Such disease or disorder in one example is characterized by proliferation, tissue remodeling, chronic inflammation, obesity, glucose intolerance, or insulin insensitivity. In one example, the disease or disorder is breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone sarcoma, connective tissue sarcoma, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, leukemia, skin cancer, soft tissue cancer, liver cancer, gastrointestinal carcinoma, or adenocarcinoma. In a particular example, the disease or disorder is metastatic kidney cancer, chronic lymphocytary leukemia, pancreatic

adenocarcinoma, or non-small cell lung cancer. In a further example, the disease or disorder is a fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation, atherosclerotic disease, Crohn's disease, or Type II diabetes. In another particular example is provided a method of reducing tumor growth, tumor proliferation, or tumorigenicity in an individual in need thereof, comprising administering to the individual a compound as detailed herein, such as a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the foregoing.

[12a] In an aspect of the present disclosure, there is provided a compound of formula (I):



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R are independently optionally substituted by R^d;

X is -C(=O)-, -O-, -CH(OH)-, -S-, -S(=O)-, or -$S(=O)_2$-;

Y is 8yridine-4-yl substituted by R^{12} in the 3-position, wherein

R^{12} independently at each occurrence is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_4-C_8 cycloalkenyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, halogen, cyano, oxo, -OR^{14}, -$NR^{15}R^{16}$, -SR^{14}, -NO_2, -C=NH(OR^{14}), -C(O)R^{14}, -OC(O)R^{14}, -C(O)OR^{14}, -C(O)$NR^{15}R^{16}$, -NR^{14}C(O)R^{15}, -NR^{14}C(O)OR^{15}, -NR^{14}C(O)$NR^{15}R^{16}$, -S(O)R^{14}, -$S(O)_2R^{14}$, -NR^{14}S(O)R^{15}, -$NR^{14}S(O)_2R^{15}$, -S(O)$NR^{15}R^{16}$, -$S(O)_2NR^{15}R^{16}$, or -P(O)(OR^{15})(OR^{16}), wherein each R^{12} is independently optionally substituted by R^L;

each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, and 3- to 12-membered heterocyclyl of R^{14} are independently optionally substituted by halogen, -OH, oxo, cyano, or C_1-C_6 alkyl optionally substituted by halogen, -OH, or oxo;

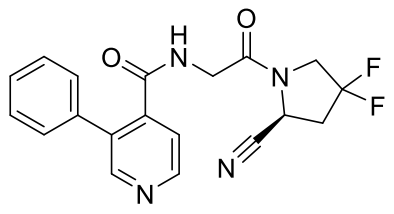
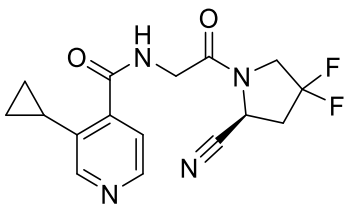
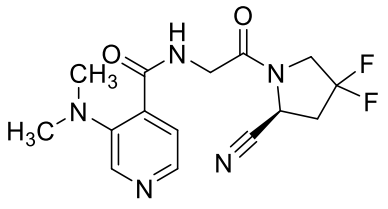
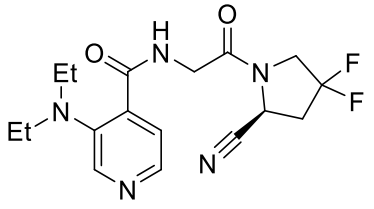
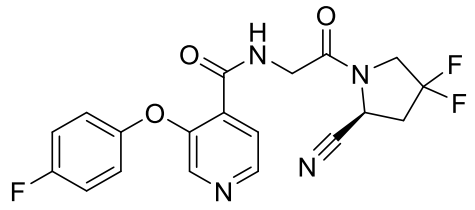
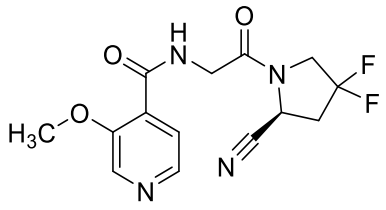
R^{15} and R^{16}, independently of each other and independently at each occurrence, are hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, and 3- to 12-membered heterocyclyl of R^{15} and R^{16} are independently optionally substituted by halogen, -OH, oxo, cyano, or C_1-C_6 alkyl, optionally substituted by halogen, -OH, or oxo,

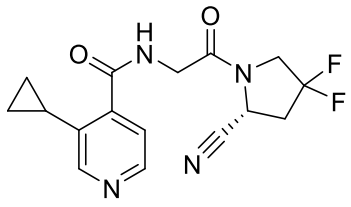
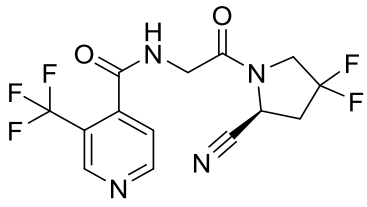
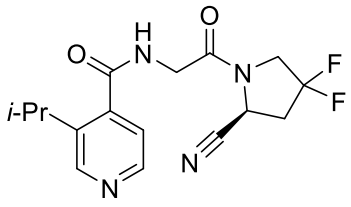
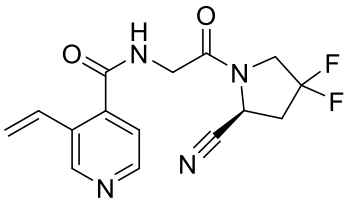
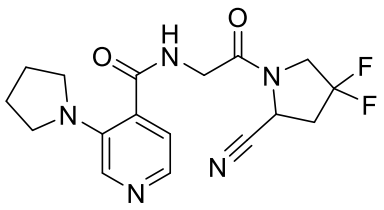
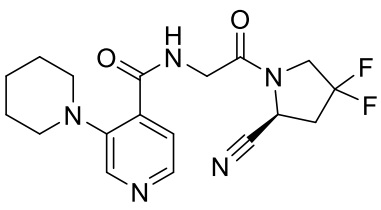
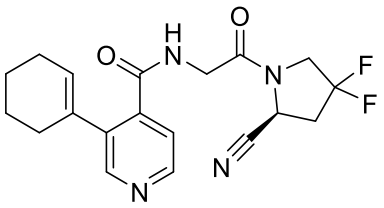
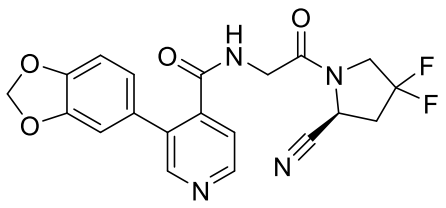
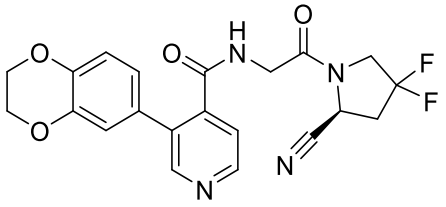
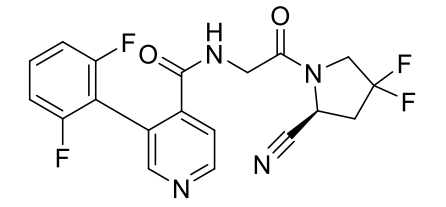
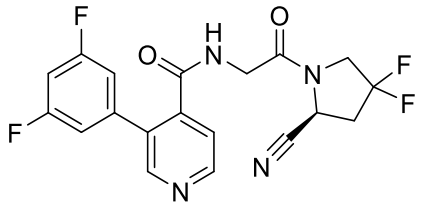
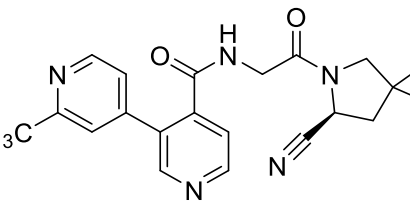
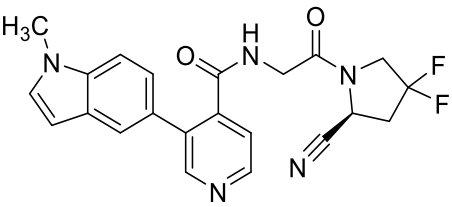
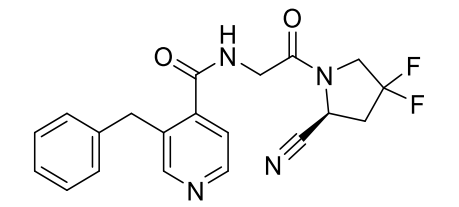
or R^{15} and R^{16} are taken together with the atom to which they are attached to form a 3- to 6-membered heterocyclyl optionally substituted by halogen, oxo, cyano, or C_1-C_6 alkyl optionally substituted by halogen, -OH, or oxo;

R^d is halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, 3- to 12-membered heterocyclyl, $-OR^{14}$, $-NR^{15}R^{16}$, cyano, or nitro; and

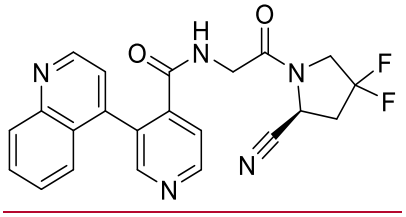
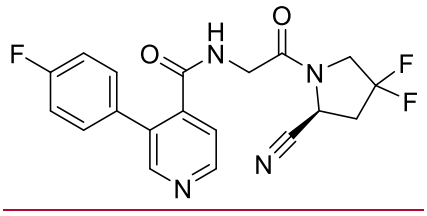
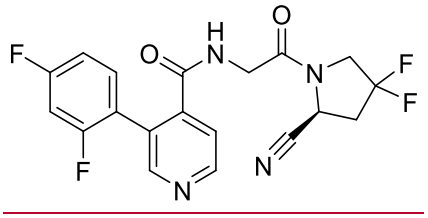
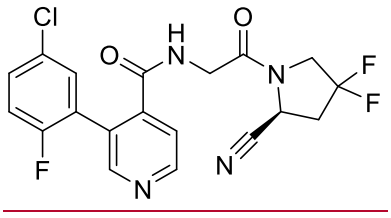
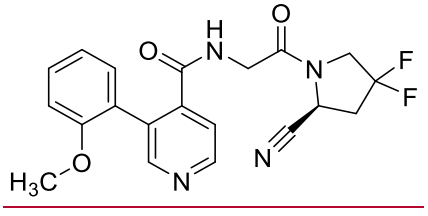
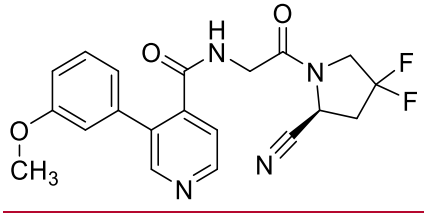
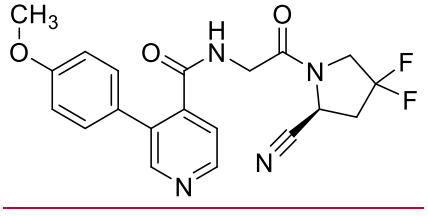
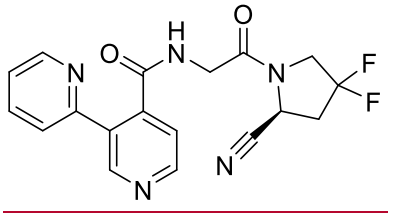
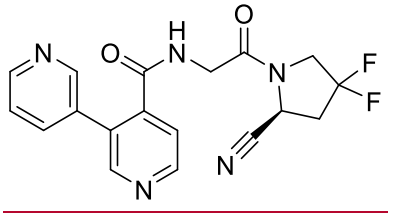
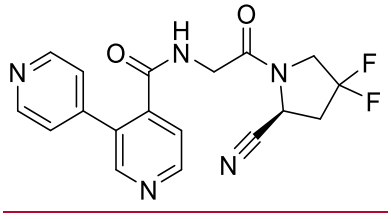
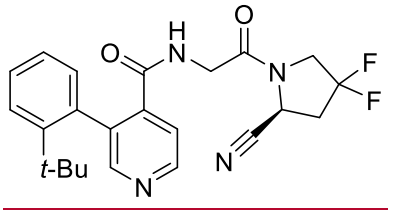
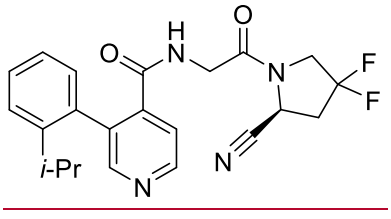
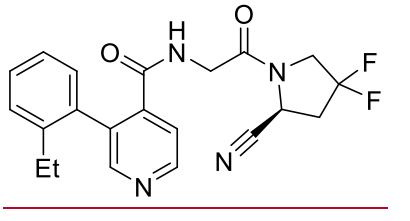
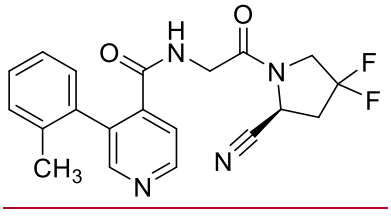
each R^L is independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, 3- to 12-membered heterocyclyl, $-OR^{14}$, $-C(O)R^{14}$, $-NR^{15}R^{16}$, cyano, oxo, or nitro.

[12b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of

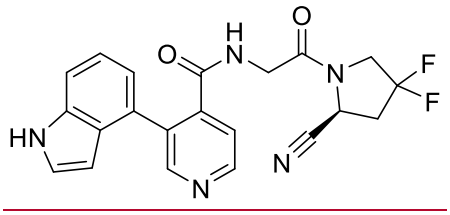
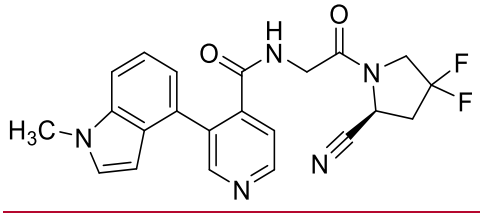
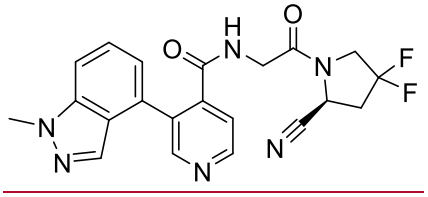
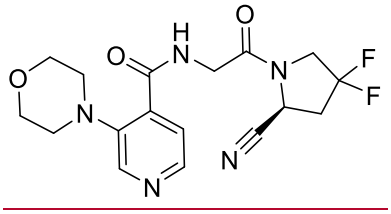
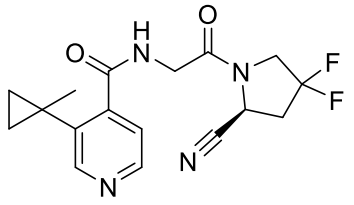
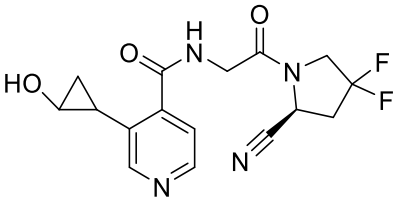
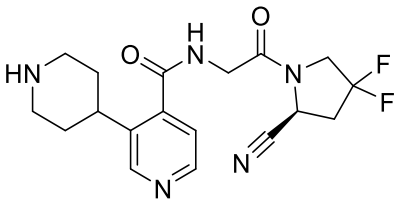
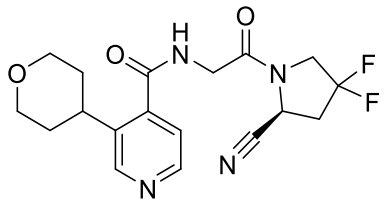
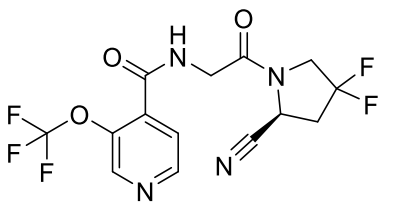
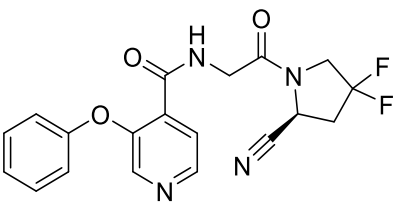
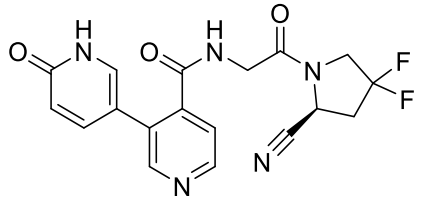
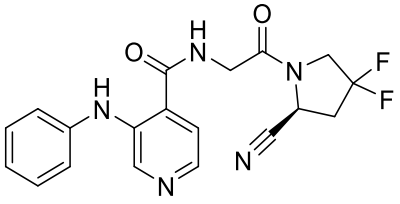
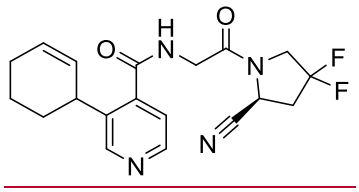
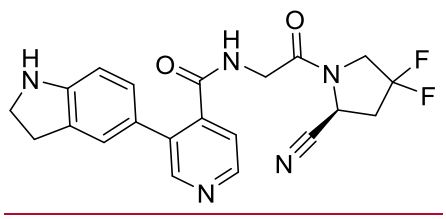
	
	
	

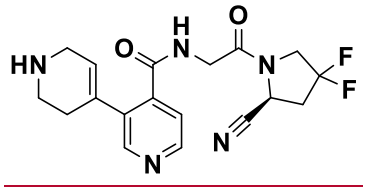
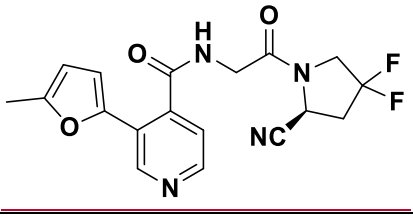
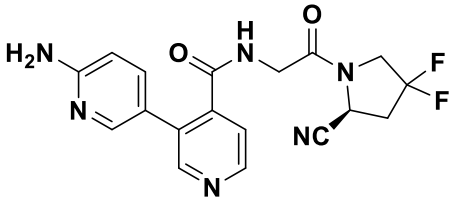
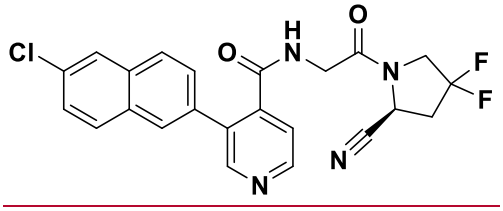
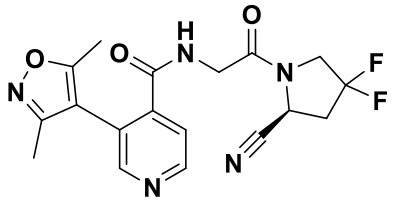
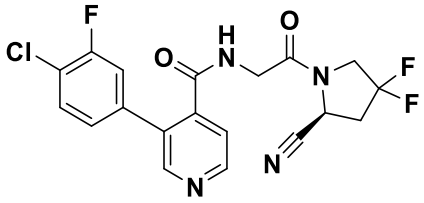
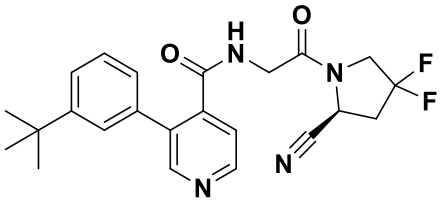
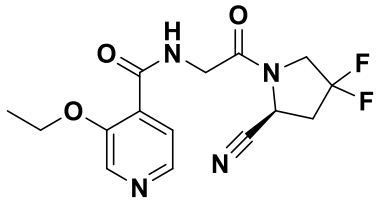
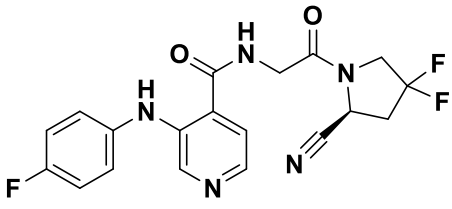
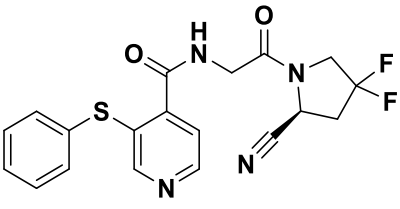
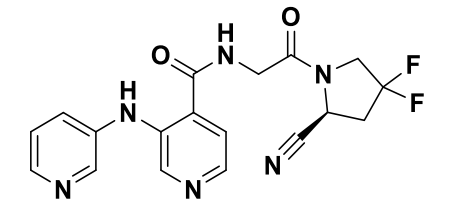
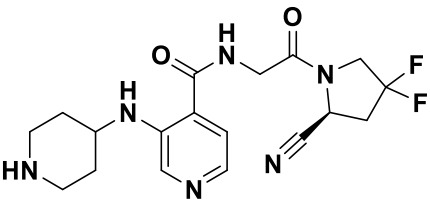
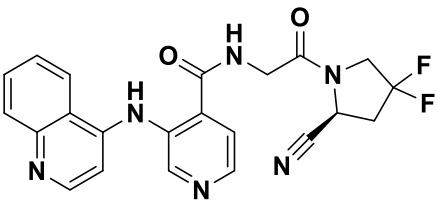
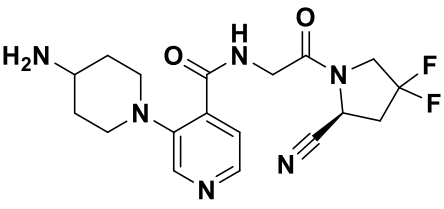
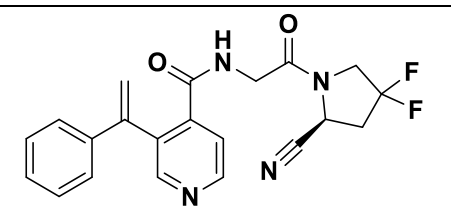
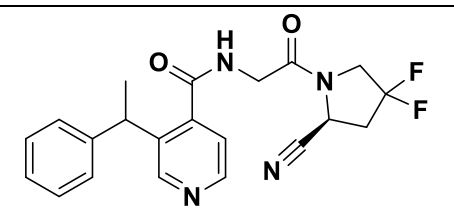
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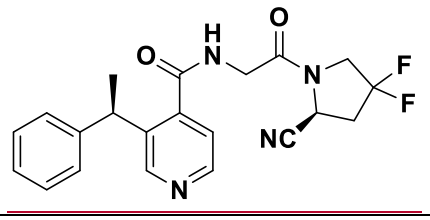
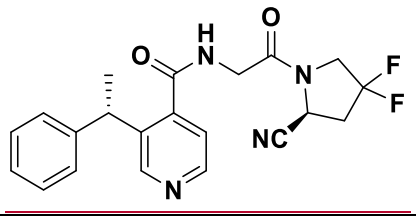
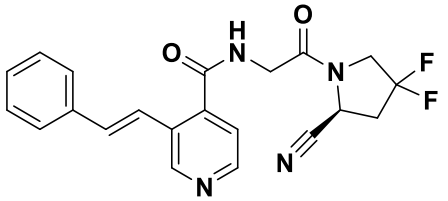
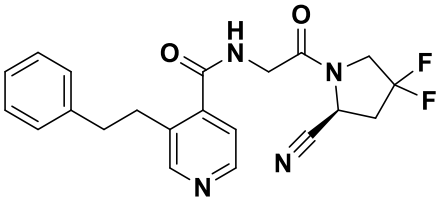
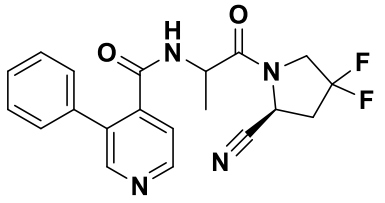
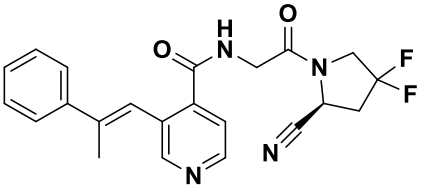
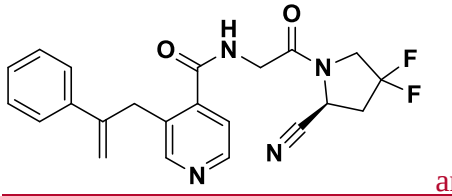
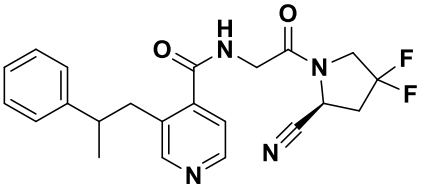
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8e

	
	
	
 and	

, or a pharmaceutically acceptable salt thereof

[12c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier

[~~12a~~12d] In another aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in therapy.

[~~12b~~12e] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease or disorder mediated by fibroblast activation protein (FAP) in an individual in need thereof, or for treating a disease or disorder characterized by proliferation, tissue remodeling, chronic inflammation, obesity, glucose intolerance, or insulin insensitivity in an individual in need thereof.

[~~12c~~12f] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as

disclosed herein, in the manufacture of a medicament for treating a disease or disorder selected from fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation, atherosclerotic disease, Crohn's disease, or Type II diabetes.

[~~12d~~12g] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for reducing tumor growth, tumor proliferation, or tumorigenicity in an individual in need thereof.

[~~12e~~12h] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting FAP in an individual.

[~~12f~~12i] In another aspect, the present disclosure refers to a method of inhibiting FAP in a cell, tumor or plasma ex vivo, comprising administering or delivering to the cell, tumor or plasma a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, ~~or a metabolite of the foregoing,~~ wherein the cell is optionally a fibroblast, or wherein the cell is optionally a cancer associated fibroblast (CAF) or a reactive stromal fibroblast.

[~~12g~~12j] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for enhancing an immune response in an individual, wherein (a) an immune checkpoint inhibitor and (b) the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein are to be administered.

[~~12h~~12k] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for increasing the level of FGF21 expression in an individual.

[~~12i~~12l] In another aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the prevention of a disorder or disease mediated by FAP.

BRIEF DESCRIPTION OF THE DRAWINGS

[13] FIG. 1A shows PRXS-AMC degradation over time by rhFAP. FIG. 1B shows Z-Gly-Pro-AMC degradation over time by rhFAP.

[14] FIG. 2A shows PRXS-AMC degradation over time by rhPREP. FIG. 2B shows Z-Gly-Pro-AMC degradation over time by rhPREP.

[15] FIG. 3A shows PRXS-AMC degradation over time by rhDPPIV. FIG. 3B shows PRXS-AMC degradation over time by rhDPP9.

[16] FIG. 4 shows FAPα activity in plasma of mice dosed with compound 13 after various time points post-administration.

[17] FIG. 5 shows DPPIV activity in plasma of mice dosed with compound 13 after various time points post-administration.

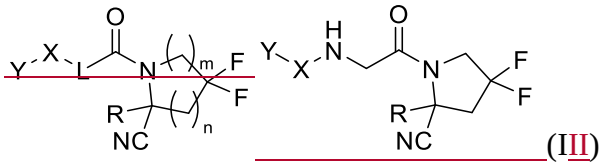
[18] FIG. 6A shows FAP activity in plasma of mice dosed with an exemplary compound after various time points post-administration. FIG. 6B shows DPPIV activity in plasma of mice dosed with an exemplary compound after various time points post-administration. FIG. 6C shows a comparison of FAP activity over time and the compound exposure as measured in in plasma of mice dosed with an exemplary compound.

[19] FIG. 7 shows the volume of a MC38 colon cancer cell line-derived xenograft tumor in C57/BL6 mice after oral administration (on day 7) of test compound 24 (50 mg/kg, twice daily) or a vehicle control. FIG. 8 shows body weight gain of the C47/BL6 mice with the MC38 colon cancer cell line-derived xenograft tumor after administration (day 7) of test compound 24 (50 mg/kg, twice daily) or a vehicle control. FIG. 9 shows individual recordings of tumor volume

CLAIMS

What is claimed is:

1. A compound of formula (I):



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R are independently optionally substituted by R^d;

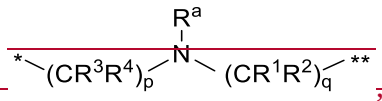
~~m is 0, 1, 2, 3, or 4;~~

~~n is 0, 1, 2, 3, or 4,~~

~~wherein m + n is 1, 2, 3, or 4;~~

X is -C(=O)-, -O-, -CH(OH)-, -S-, -S(=O)-, or -S(=O)$_2$-;

~~L is~~

~~(a)~~  ~~, wherein~~

~~* represents the point of attachment to the Y-X- moiety,~~

~~** represents the point of attachment to the remainder of the molecule,~~

~~R^a is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R^a are independently optionally substituted by R^e,~~

R^1 and R^2, independently of each other and independently at each occurrence, are hydrogen, C_1-C_2 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R^1 and R^2 are independently optionally substituted by R^f,

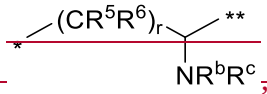
or R^1 and R^2 are taken together with the carbon atom or atoms to which they are attached to form a 3- to 8-membered cycloalkylene optionally substituted by R^f,

q is 1, 2, or 3,

R^3 and R^4, independently of each other and independently at each occurrence, are hydrogen, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R^3 and R^4 are independently optionally substituted by R^g,

or R^3 and R^4 are taken together with the carbon atom to which they are attached to form a 3- to 8-membered cycloalkylene optionally substituted by R^g, and

p is 0, 1, or 2;

(b) 
, wherein

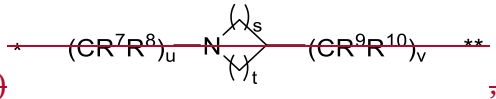
* represents the point of attachment to the Y-X- moiety,

** represents the point of attachment to the remainder of the molecule,

R^5 and R^6, independently of each other and independently at each occurrence, are H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R^5 and R^6 are independently optionally substituted by R^h,

R^b and R^c are independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, or $-C(=O)OR^{17}$, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R^b and R^c are independently optionally substituted by R^i, and

r is 1, 2, or 3; or

(c)  , wherein

* represents the point of attachment to the Y-X- moiety,

** represents the point of attachment to the remainder of the molecule,

R^7 and R^8, independently of each other and independently at each occurrence, are hydrogen, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R^7 and R^8 are independently optionally substituted by R^j,

or R^7 and R^8 are taken together with the carbon atom to which they are attached to form a 3- to 8-membered cycloalkylene optionally substituted by R^j,

R^9 and R^{10}, independently of each other and independently at each occurrence, are H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, or C_6-C_{14} aryl, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, and C_6-C_{14} aryl of R^9 and R^{10} are independently optionally substituted by R^k,

s is 1, 2, or 3,

t is 1, 2, or 3,

wherein s + t is 2, 3, or 4,

u is 0 or 1, and

~~v is 0 or 1;~~

Y is pyridin-4-yl substituted by R^{12} in the 3-position~~C_6-C_9 aryl optionally substituted by R^{11}, 6- to 10-membered heteroaryl optionally substituted by R^{12}, or 3- to 12-membered heterocyclyl optionally substituted by R^{13}, wherein when Y is phenyl or naphthyl, the phenyl or naphthyl of Y is substituted by at least one R^{11}, and wherein when L is * -NH-CH_2- ** and Y is optionally substituted quinolinyl, the optionally substituted quinolinyl of Y is connected to the parent structure at the 2-, 3-, 5-, 6-, 7-, or 8-position~~, wherein

~~R^{11},~~ R^{12}~~, and R^{13}, independently of each other and~~ independently at each occurrence~~, are~~ is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_4-C_8 cycloalkenyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, halogen, cyano, oxo, $-OR^{14}$, $-NR^{15}R^{16}$, $-SR^{14}$, $-NO_2$, $-C{=}NH(OR^{14})$, $-C(O)R^{14}$, $-OC(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{15}R^{16}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}C(O)OR^{15}$, $-NR^{14}C(O)NR^{15}R^{16}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-NR^{14}S(O)R^{15}$, $-NR^{14}S(O)_2R^{15}$, $-S(O)NR^{15}R^{16}$, $-S(O)_2NR^{15}R^{16}$, or $-P(O)(OR^{15})(OR^{16})$, wherein each ~~R^{11},~~ R^{12}~~, and R^{13}~~ is independently optionally substituted by R^L;

each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, and 3- to 12-membered heterocyclyl of R^{14} are independently optionally substituted by halogen, -OH, oxo, cyano, or C_1-C_6 alkyl optionally substituted by halogen, -OH, or oxo;

R^{15} and R^{16}, independently of each other and independently at each occurrence, are hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, and 3- to 12-membered heterocyclyl of R^{15} and R^{16} are independently optionally substituted by halogen, -OH, oxo, cyano, or C_1-C_6 alkyl, optionally substituted by halogen, -OH, or oxo,

or R^{15} and R^{16} are taken together with the atom to which they are attached to form a 3- to 6-membered heterocyclyl optionally substituted by halogen, oxo, cyano, or C_1-C_6 alkyl optionally substituted by halogen, -OH, or oxo;

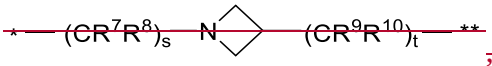
R^d~~, R^e, R^f, R^g, R^h, R^i, R^j, and R^k, independently of each other and independently at each occurrence, are~~ is halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, 3- to 12-membered heterocyclyl, -OR^{14}, -$NR^{15}R^{16}$, cyano, or nitro; and

each R^L is independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, 3- to 12-membered heterocyclyl, -OR^{14}, -$C(O)R^{14}$, -$NR^{15}R^{16}$, cyano, oxo, or nitro.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is -C(=O)-, -O- or -CH(OH)-.

~~3. The compound of claim 1 or 2, or a salt thereof, wherein L is -NH-CR^1R^2-, preferably, -NH-CH_2-, optionally wherein R^1 and R^2 are taken together with the carbon atom to which they are attached to form a 3- to 8-membered cycloalkylene, preferably a cyclopropylene.~~

~~4. The compound of claims 1 or 2, or a salt thereof, wherein L is -CR^5R^6-$CH(NR^bR^c)$-.~~

~~5. The compound of claim 1 or 2, or a salt thereof, wherein L is~~  ~~, wherein L is optionally~~  ~~, wherein * represents the point of attachment to the Y-X- moiety, and ** represents the point of attachment to the remainder of the molecule.~~

~~6. The compound of any one of claims 1 to 5, or a salt thereof, wherein Y is 6- to 10-membered heteroaryl optionally substituted by R^{12}, or 3- to 12-membered heterocyclyl optionally substituted by R^{13}.~~

~~7. The compound of claim 1, or a salt thereof, wherein Y is C_6-C_9 aryl optionally substituted by R^{11}, wherein when Y is phenyl or naphthyl, the phenyl or naphthyl of Y is substituted by at least one R^{11}; wherein Y is optionally selected from (a) phenyl substituted by 1 to 5 R^{11}, which are~~

independently selected from halogen, trihalomethyl, cyano, and -C(=O)NH_2; or (b) unsubstituted 2,3-dihydro-1*H*-inden-2-yl.

8. The compound of claim 6, or a salt thereof, wherein Y is 6- to 10-membered heteroaryl optionally substituted by R^{12}, wherein when L is *-NH-CH_2-** and Y is optionally substituted quinolinyl, the optionally substituted quinolinyl of Y is connected to the parent structure at the 2-, 3-, 5-, 6-, 7-, or 8-position, optionally wherein either:

(a) L is *-CH_2-CH(NH_2)-** or *-CH(CH_3)-CH(NH_2)-** and Y is quinolin-4-yl optionally substituted by R^{12}; or

(b) L is *-NH-CH_2-**, Y is quinolin-6-yl optionally substituted by R^{12}, which R^{12} is independently selected from -OH and phenyl.

9. The compound of claim 8, or a salt thereof, wherein Y is pyridin-4-yl substituted by R^{12} in the 3-position.

10. The compound of claim 9, or a salt thereof, wherein either:

(a) R^{12} is pyridinyl optionally substituted by C_1-C_6 alkyl; or

(b) R^{12} is indolyl optionally substituted by C_1-C_6 alkyl; or

(c) R^{12} is phenyl optionally substituted by C_1-C_6 alkyl, halogen, or C_1-C_6 alkoxy.

11. The compound of claim 8, or a salt thereof, wherein Y is pyrimidin-4-yl optionally substituted by R^{12} and optionally fused to C_6-C_{14} aryl or C_5-C_{10} cycloalkyl, wherein C_6-C_{14} aryl and C_5-C_{10} cycloalkyl are optionally substituted by R^{12}, optionally wherein either:

(a) Y is pyrimidin-4-yl fused to C_6-C_{14} aryl, wherein C_6-C_{14} aryl is optionally substituted by R^{12}; or

(b) Y is optionally substituted pyridin-3-yl, unsubstituted quinazolin-4-yl or unsubstituted 6,7-dihydro-5*H*-cyclopenta[d]pyrimidin-4-yl; or

~~(c) Y is 2*H*-pyran-2-on-5-yl optionally substituted by R^{12} and optionally fused to C_6-C_{14} aryl, which C_6-C_{14} aryl is optionally substituted by R^{12}, preferably wherein Y is 1*H*-isochromen-1-on-4-yl optionally substituted by halogen.~~

~~12. The compound of claim 8, or a salt thereof, wherein Y is pyridin-2(1*H*)-on-5-yl optionally substituted by R^{12} and optionally fused to C_6-C_{14} aryl or 5- to 10-membered heterocyclyl, which C_6-C_{14} aryl or 5- to 10-membered heterocyclyl, independently of each other and independently at each occurrence, are optionally substituted by R^{12}, optionally wherein Y is either:~~

~~(a) pyridin-2(1*H*)-on-5-yl optionally substituted by C_1-C_6 alkyl or C_6-C_{14} aryl; or~~

~~(b) Y is unsubstituted 7,8,9,10-tetrahydropyrido[1,2-a]azepin-4(6*H*)-on-1-yl; or~~

~~(c) Y is isoquinolin-1(2*H*)-on-4-yl optionally substituted by halogen, C_1-C_6 alkyl, C_6-C_{14} aryl, or C_3-C_8 cycloalkyl.~~

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{12} is C_3-C_8 cycloalkyl that is optionally substituted by R^L.

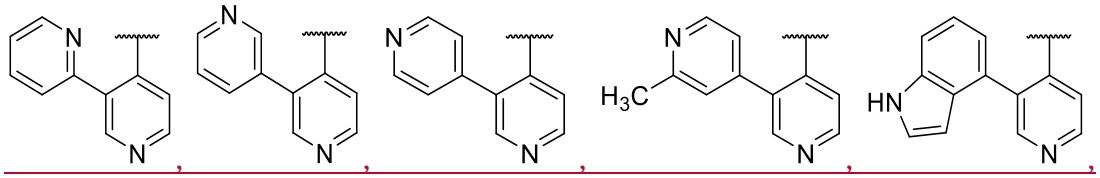
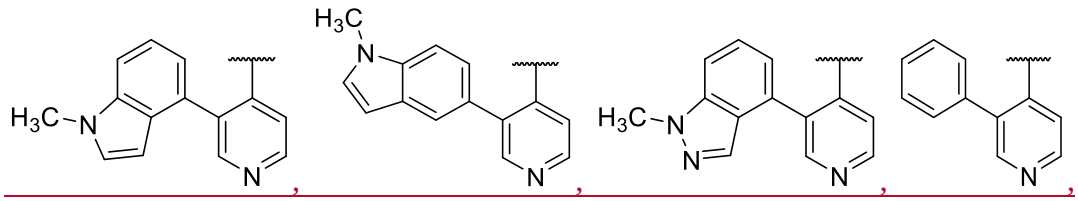
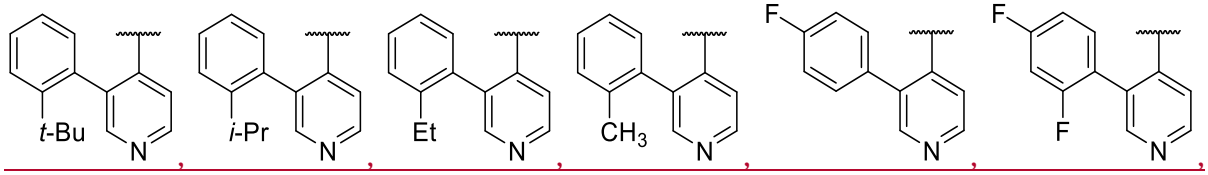
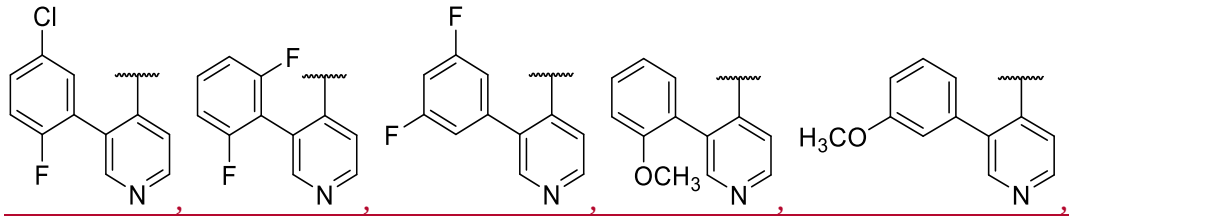
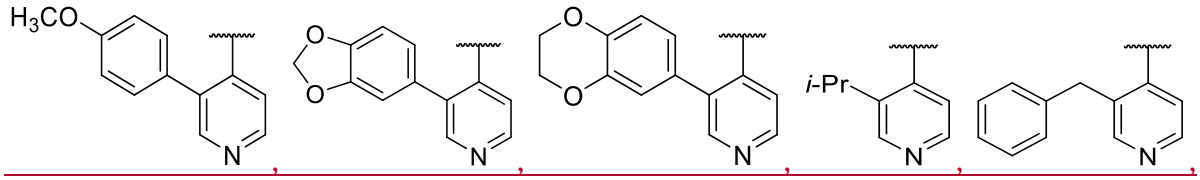
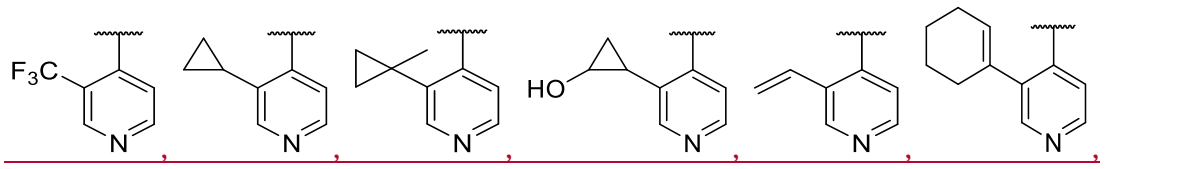
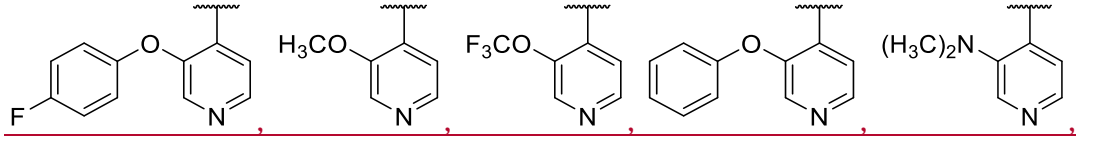
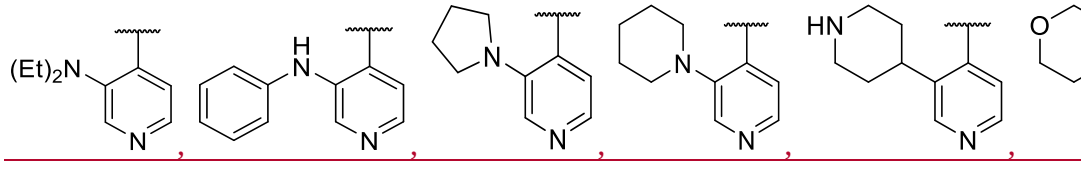
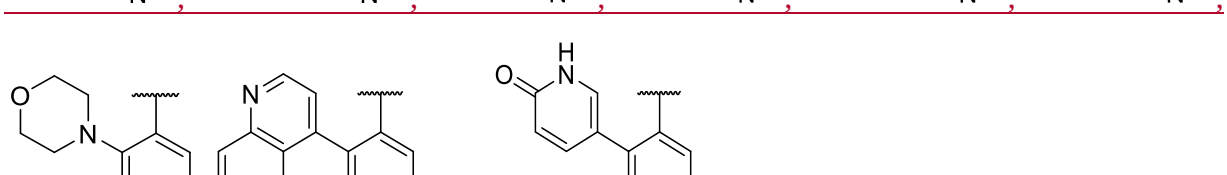
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{12} is C_4-C_8 cycloalkenyl that is optionally substituted by R^L.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{12} is 3- to 12-membered heterocyclyl that is optionally substituted by R^L.

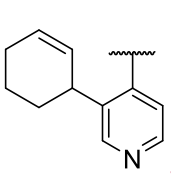
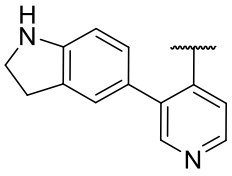
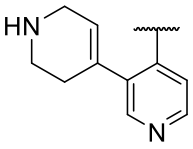
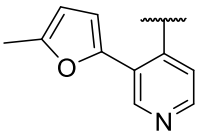
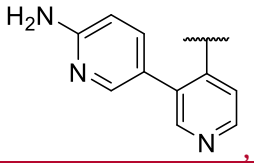
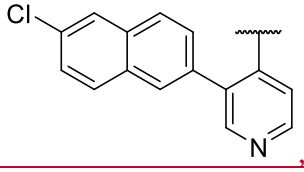
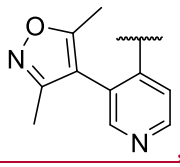
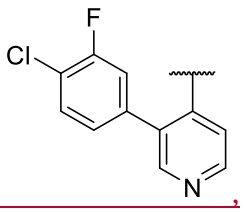
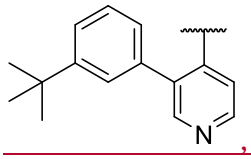
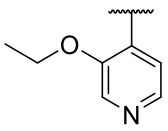
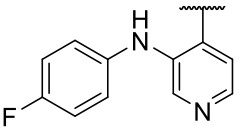
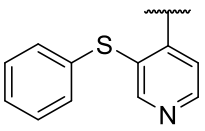
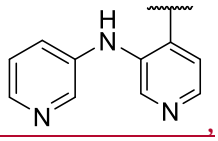
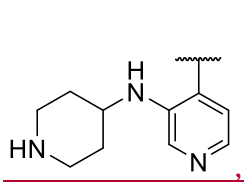
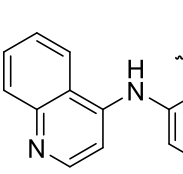
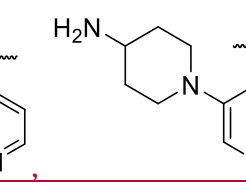
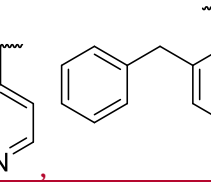
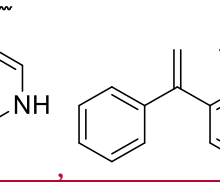
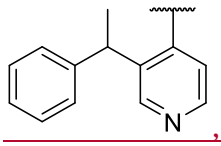
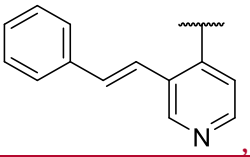
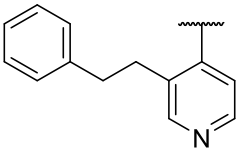
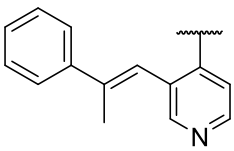
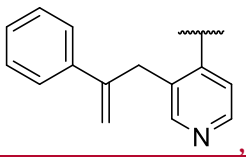
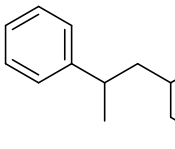
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{12} is 5- to 10-membered heteroaryl that is optionally substituted by R^L.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{12} is C_6-C_{14} aryl that is optionally substituted by R^L.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is selected from the group consisting of:

and

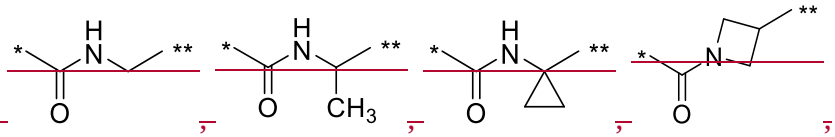
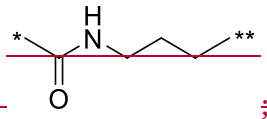
9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is selected from the group consisting of: , , , , , , , , , , , , , , , , , , , , , , , , , , , ,  and .

~~13. The compound of claim 6, or a salt thereof, wherein Y is 3- to 12-membered heterocyclyl optionally substituted by R^{13}, optionally wherein either:~~

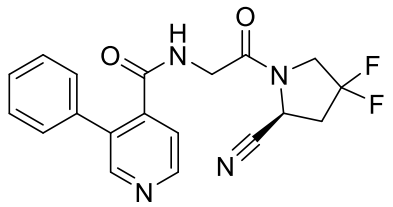
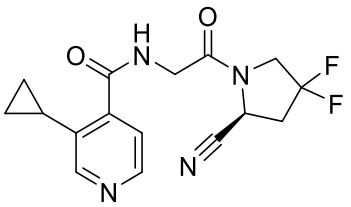
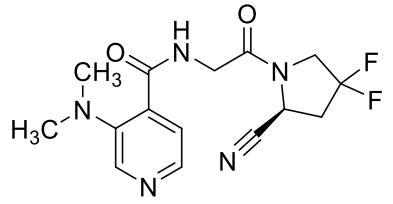
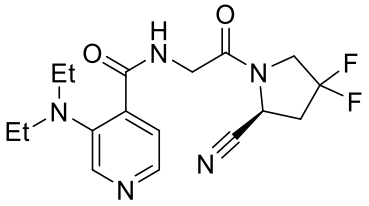
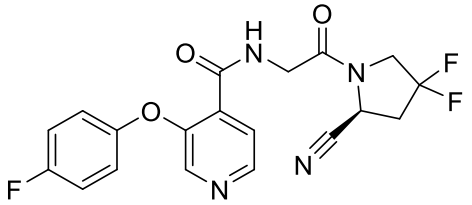
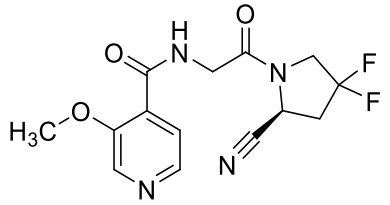
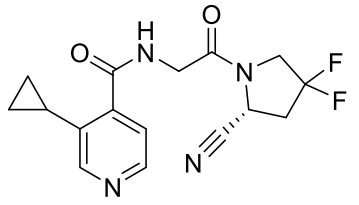
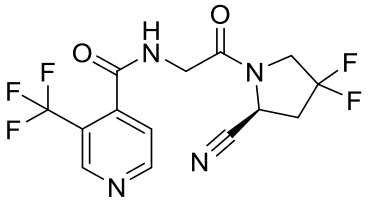
~~(a) Y is unsubstituted isoindolin-2-yl; or (b) Y is piperidin-2-on-5-yl optionally substituted by C_1-C_6-alkyl or C_6-C_{14}-aryl.~~

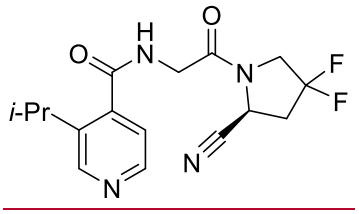
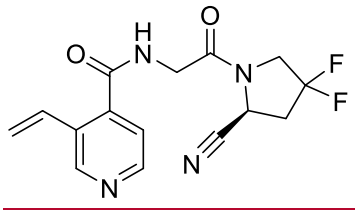
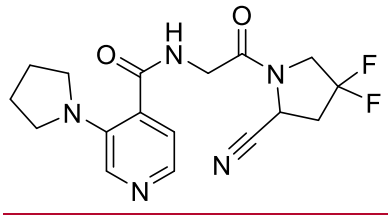
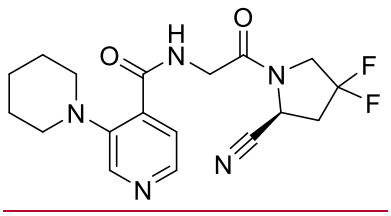
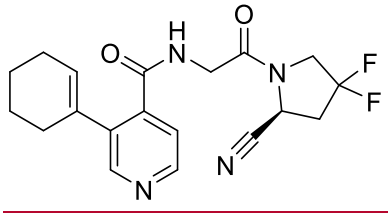
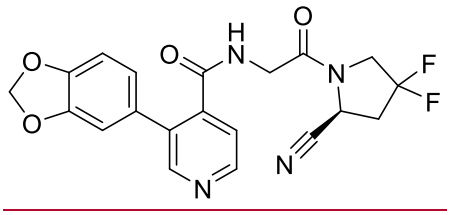
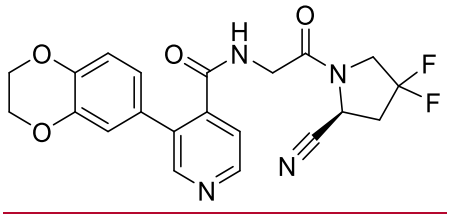
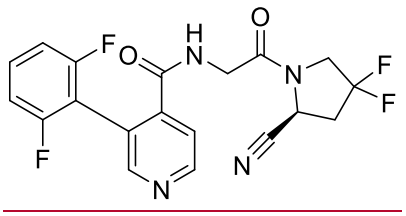
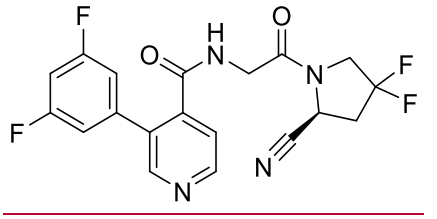
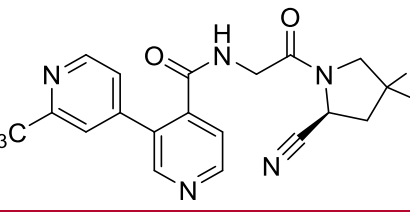
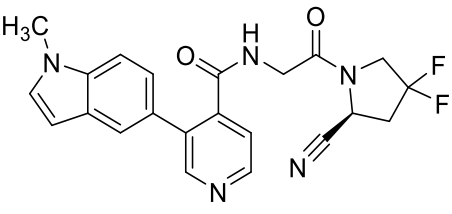
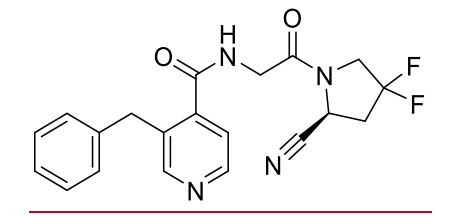
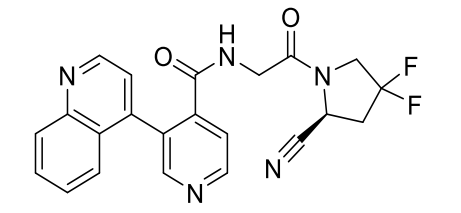
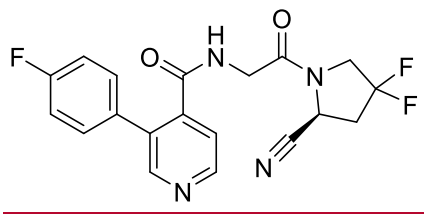
~~14. The compound of any one of claims 1 to 13, or a salt thereof, wherein m = n = 1.~~

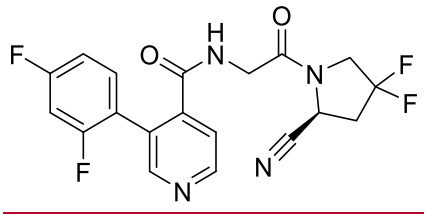
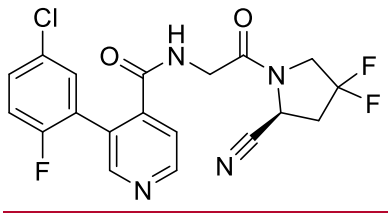
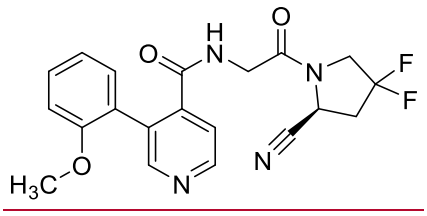
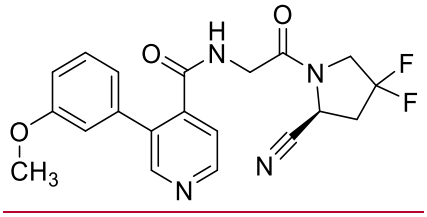
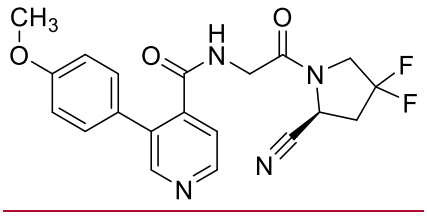
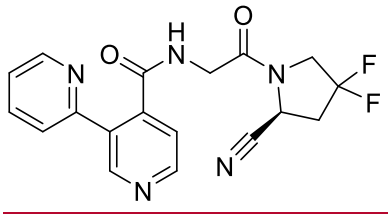
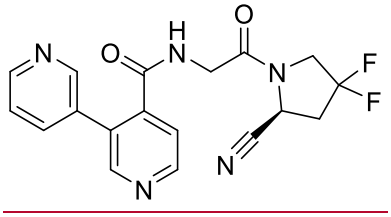
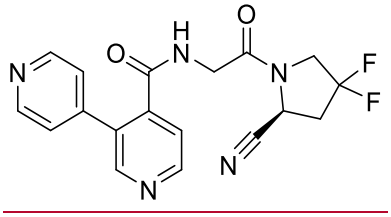
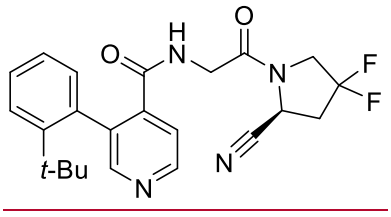
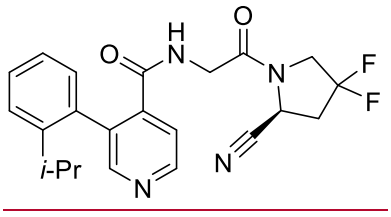
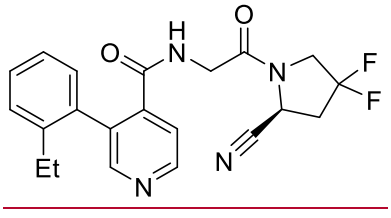
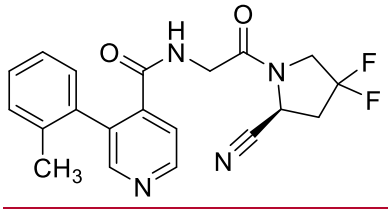
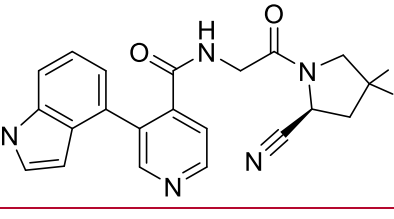
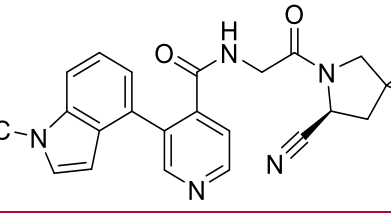
~~15~~10. The compound of any one of claims 1 to ~~14~~9, or a pharmaceutically acceptable salt thereof, wherein R is hydrogen.

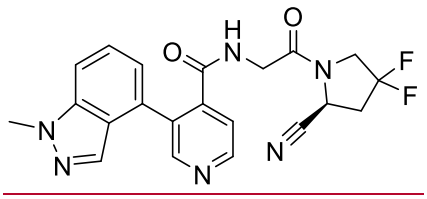
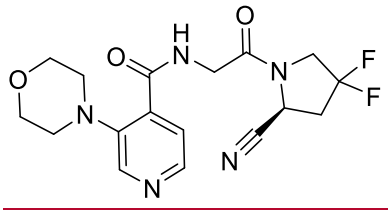
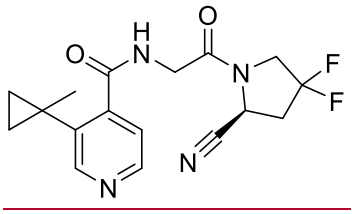
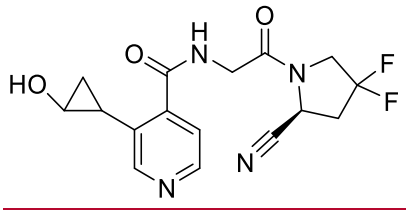
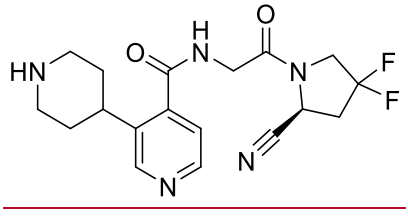
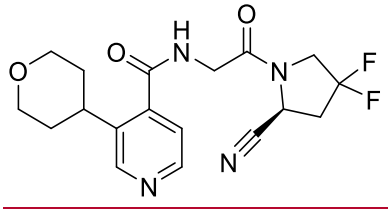
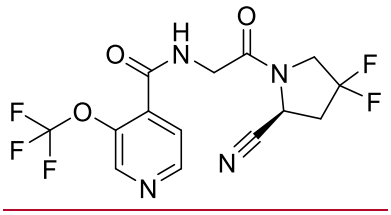
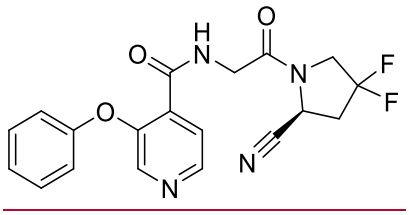
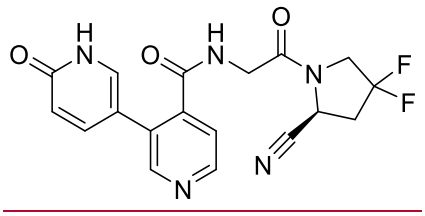
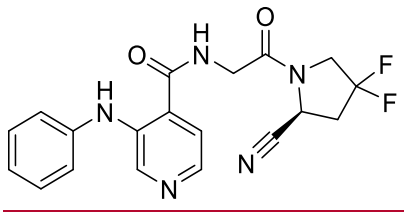
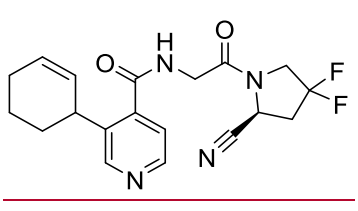
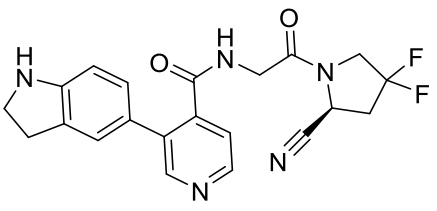
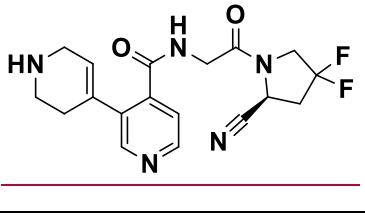
~~16. The compound of claim 1, or a salt thereof, wherein the -X-L- moiety is selected from the group consisting of~~  ~~, and~~  ~~; wherein * represents the point of attachment to the Y moiety, and ** represents the point of attachment to the remainder of the molecule.~~

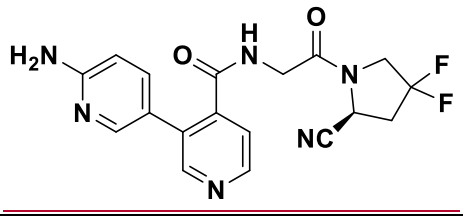
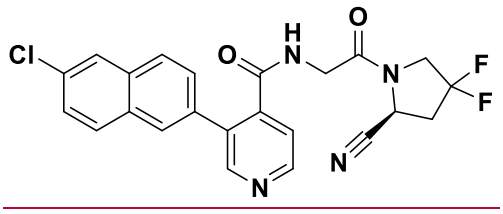
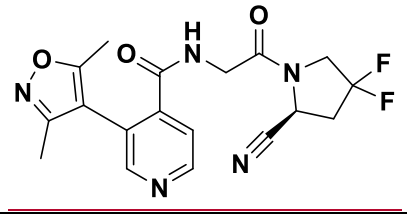
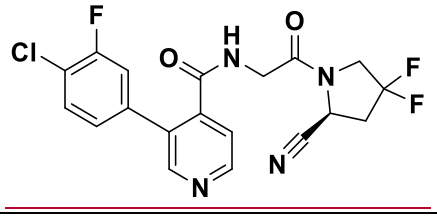
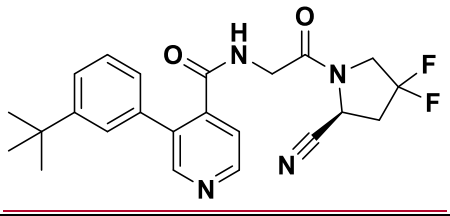
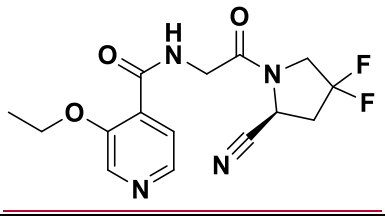
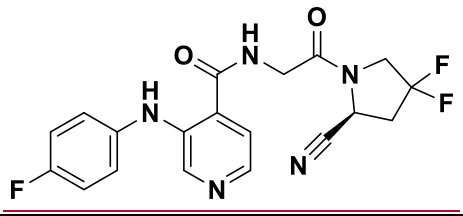
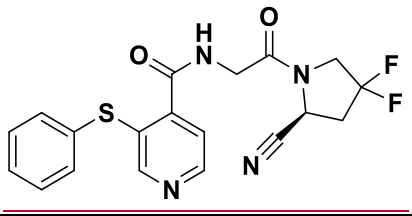
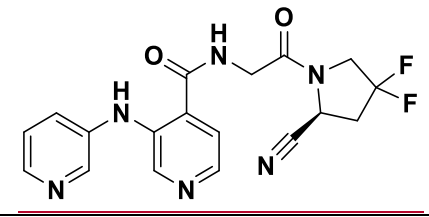
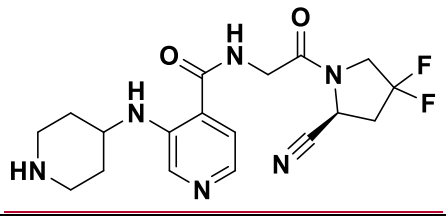
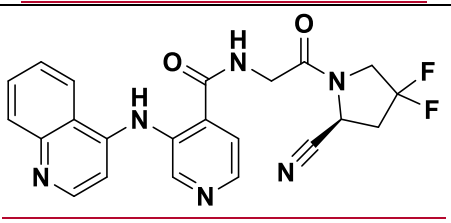
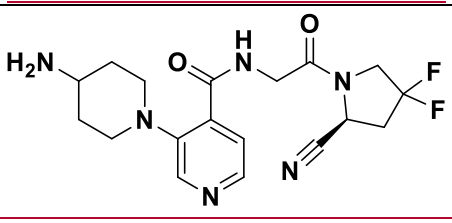
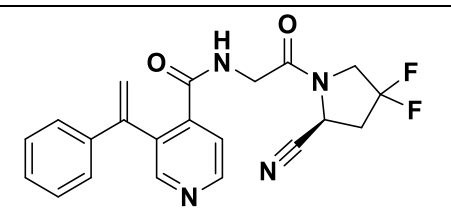
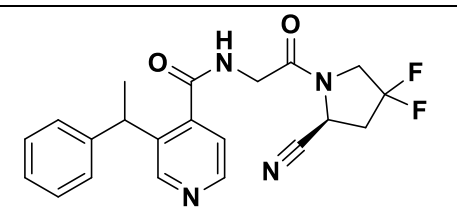
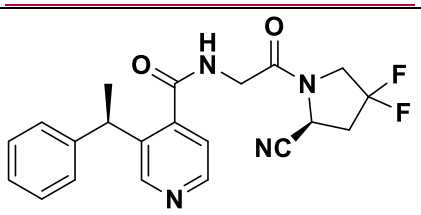
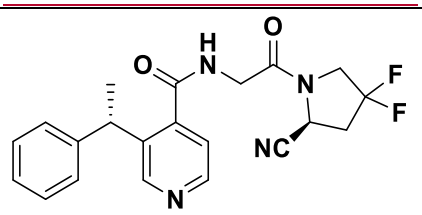
11. A compound selected from the group consisting of

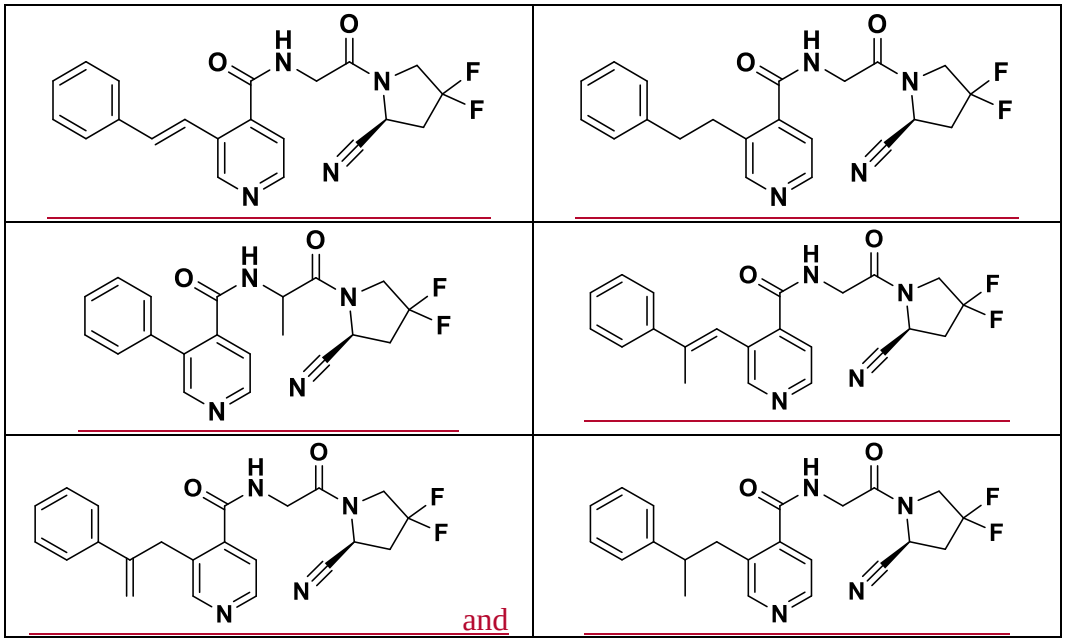
	
	
	
	



and

, or a pharmaceutically acceptable salt thereof.

~~17~~12. A pharmaceutical composition comprising a compound of any one of claims 1-~~16~~11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~18~~13. A compound according to any one of claims 1 to ~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~17~~12, for use in therapy.

~~19~~14. Use of a compound according to any one of claims 1 to ~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~17~~12, in the manufacture of a medicament for treating a disease or disorder mediated by fibroblast activation protein (FAP) in an individual in need thereof, or for treating a disease or disorder characterized by proliferation, tissue remodeling, chronic inflammation, obesity, glucose intolerance, or insulin insensitivity in an individual in need thereof.

~~20~~15. The use according to claim ~~19~~14, wherein the disease or disorder is breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone sarcoma, connective tissue sarcoma, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, leukemia, skin cancer, soft tissue cancer, liver cancer, gastrointestinal carcinoma, or adenocarcinoma, optionally wherein the disease or disorder is metastatic kidney cancer, chronic lymphocytary leukemia, pancreatic adenocarcinoma, or non-small cell lung cancer.

~~21~~16. Use of a compound according to any one of claims 1 to ~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~17~~12, in the manufacture of a medicament for treating a disease or disorder selected from fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation, atherosclerotic disease, Crohn's disease, or Type II diabetes.

~~22~~17. Use of a compound according to any one of claims 1 to ~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~17~~12, in the manufacture of a medicament for reducing tumor growth, tumor proliferation, or tumorigenicity in an individual in need thereof.

~~23~~18. Use of a compound according to any one of claims 1 to ~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~17~~12, in the manufacture of a medicament for inhibiting FAP in an individual.

~~24~~19. A method of inhibiting FAP in a cell, tumor or plasma ex vivo, comprising administering or delivering to the cell, tumor or plasma a compound of any one of claims 1-~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim ~~17~~12, ~~or a metabolite of the foregoing,~~ wherein the cell is optionally a fibroblast, or wherein the cell is optionally a cancer associated fibroblast (CAF) or a reactive stromal fibroblast.

~~25~~20. Use of a compound according to any one of claims 1 to ~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~17~~12, in the manufacture of a medicament for enhancing an immune response in an individual, wherein (a) an immune checkpoint inhibitor and (b) the compound of any one of claims 1-~~16~~11, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim ~~17~~ 12 are to be administered.

~~26~~21. Use of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17, in the manufacture of a medicament for increasing the level of FGF21 expression in an individual.

~~27~~22. The use according to claim 26, wherein an inducer of FGF21 expression, preferably, PPARα agonist, and further preferably, fibrate or fenofibrate, is to be further administered.

~~28~~23. Use of a compound according to any one of claims 1 to ~~16~~11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim ~~17~~12, in the manufacture of a medicament for the prevention of a disorder or disease mediated by FAP.