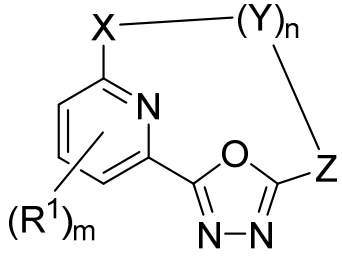
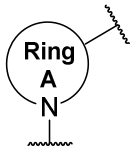
CLAIMS

1. A compound selected from compounds of Formula **I**:



I,

and deuterated derivatives and pharmaceutically acceptable salts thereof, wherein:

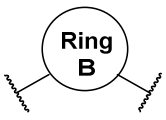
X is selected from -N($\mathbf{R^{X1}}$)- and 

;

Ring A is a 4- to 6-membered heterocyclyl optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl and oxo;

$\mathbf{R^{X1}}$ is selected from H, C_1-C_6 alkyl (optionally substituted with 1-3 groups independently selected from hydroxy, oxo, -O$\mathbf{R^{X2}}$, and -N($\mathbf{R^{X2}}$)$_2$), and C_3-C_8 cycloalkyl;

each $\mathbf{R^{X2}}$ is independently selected from H and C_1-C_6 alkyl;

each **Y** is independently selected from -C($\mathbf{R^{Y}}$)$_2$-, -O-, -CO-, -N$\mathbf{R^{YN}}$-, and 

, wherein each $\mathbf{R^{YN}}$ is independently selected from H, C_1-C_4 alkyl, and $CO_2\mathbf{R^{YN1}}$, wherein each $\mathbf{R^{YN1}}$ is independently selected from C_1-C_4 alkyl and C_3-C_6 cycloalkyl;

each $\mathbf{R^{Y}}$ is independently selected from hydrogen, hydroxy, halogen, C_1-C_6 alkyl (optionally substituted with 1-3 groups independently selected from hydroxy, C_1-C_6 alkoxy, and **Q**), C_3-C_8 cycloalkyl, C_6-C_{10} aryl (optionally substituted with 1-3 groups independently selected from halogen), 5- to 10-membered heteroaryl, -O$\mathbf{R^{Y1}}$, -$CO_2\mathbf{R^{Y1}}$, -CO$\mathbf{R^{Y1}}$, -CON($\mathbf{R^{Y1}}$)$_2$, and -N($\mathbf{R^{Y1}}$)$_2$;

or two $\mathbf{R^{Y}}$ on the same atom are taken together to form a ring selected from C_3-C_8 cycloalkyl and 3- to 7-membered heterocyclyl; or two $\mathbf{R^{Y}}$, one of which is on one atom and the second of which is on an adjacent atom, are taken together to form a pi bond;

each $\mathbf{R^{Y1}}$ is independently selected from hydrogen and C_1-C_6 alkyl, or two $\mathbf{R^{Y1}}$ bonded to the same nitrogen taken together form a 3- to 6-membered heterocyclyl;

Ring B is selected from:

- C_6-C_{10} aryl (optionally substituted with 1-3 groups independently selected from halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy),
- C_3-C_8 cycloalkyl,
- 5- to 10-membered heteroaryl, and
- 3- to 6-membered heterocyclyl (optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl);

each **Q** is independently selected from:

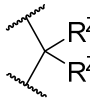
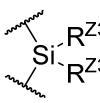
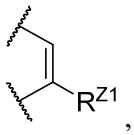
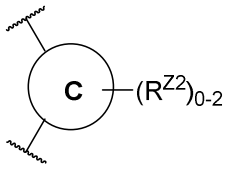
- C_1-C_6 alkyl optionally substituted with 1-3 groups independently selected from:
  - halogen,
  - oxo,
  - C_6-C_{10} aryl (optionally substituted with 1-3 groups independently selected from halogen and -OCF_3), and
  - C_3-C_8 cycloalkyl,
- C_3-C_8 cycloalkyl optionally substituted with 1-3 groups independently selected from:
  - halogen,
  - CN,
  - C_1-C_6 alkyl (optionally substituted with 1-3 groups independently selected from halogen, -NH_2, and -NHCOMe),
  - C_1-C_6 alkoxy,
  - C_6-C_{10} aryl (optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl), and
  - C_3-C_8 cycloalkyl,
- C_6-C_{10} aryl optionally substituted with 1-3 groups independently selected from:
  - halogen,
  - CN,
  - C_1-C_6 alkyl (optionally substituted with 1-3 groups independently selected from halogen and hydroxy),

- C_1-C_6 alkoxy optionally substituted with 1-4 groups independently selected from:
  - halogen,
  - C_3-C_8 cycloalkyl (optionally substituted with CF_3),
- C_3-C_8 cycloalkyl (optionally substituted with 1-3 groups independently selected from halogen, CF_3, OCF_3, and C_1-C_6 alkyl), and
- C_6-C_{10} aryl,

- 5- to 10-membered heteroaryl optionally substituted with 1-3 groups independently selected from:
  - halogen,
  - C_1-C_6 alkyl (optionally substituted with 1-3 groups independently selected from halogen),
  - C_3-C_8 cycloalkyl (optionally substituted with 1-3 CF_3 groups), and
  - 3- to 10-membered heterocyclyl,
- 3- to 10-membered heterocyclyl optionally substituted with 1-3 groups independently selected from:
  - C_1-C_6 alkyl (optionally substituted with 1-3 groups independently selected from oxo and C_3-C_8 cycloalkyl), and
  - oxo;

each $\mathbf{R^1}$ is independently selected from halogen, C_1-C_6 fluoroalkyl, C_1-C_6 alkyl (optionally substituted with a group selected from hydroxy, C_6-C_{10} aryl, and 5- to 6-membered heteroaryl), -O$\mathbf{R^2}$, -N($\mathbf{R^2}$)$_2$, -$CO_2\mathbf{R^2}$, -CO-N($\mathbf{R^2}$)$_2$, -CN, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 5- to 6-membered heteroaryl (optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl), 3- to 6-membered heterocyclyl, -B(O$\mathbf{R^2}$)$_2$, -$SO_2\mathbf{R^2}$, -S$\mathbf{R^2}$, -SO$\mathbf{R^2}$, -PO(O$\mathbf{R^2}$)$_2$, and -PO($\mathbf{R^2}$)$_2$;

each $\mathbf{R^2}$ is independently selected from hydrogen, C_1-C_6 alkyl (optionally substituted with 1-6 groups independently selected from halogen), C_1-C_6 fluoroalkyl, and C_6-C_{10} aryl (optionally substituted with 1-3 groups independently selected from C_1-C_6 fluoroalkyl and C_1-C_6 fluoroalkoxy);

Z is selected from , , , and ; wherein

Ring C is selected from C_6-C_{10} aryl and 5- to 10-membered heteroaryl;

$\mathbf{R^{Z1}}$ is selected from hydrogen, -CN, C_1-C_6 alkyl (optionally substituted with 1-3 hydroxy), C_1-C_6 fluoroalkyl, 3- to 6-membered heterocyclyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, and 5- to 6-membered heteroaryl;

$\mathbf{R^{Z2}}$ is selected from hydrogen, halogen, hydroxy, NH_2, NH(CO)(C_1-C_6 alkyl), and C_1-C_6 alkoxy (optionally substituted with 1-3 groups independently selected from C_3-C_{10} cycloalkyl),

or $\mathbf{R^{Z1}}$ and $\mathbf{R^{Z2}}$ taken together form a group selected from oxo and =N-OH;

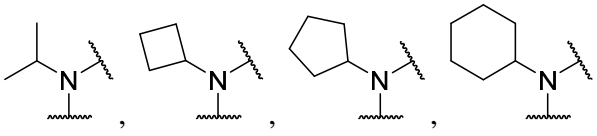
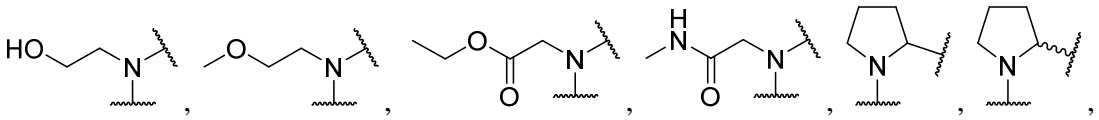
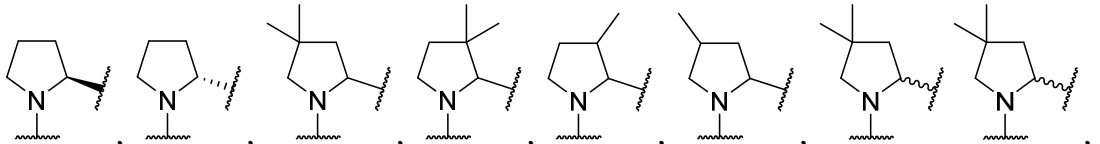
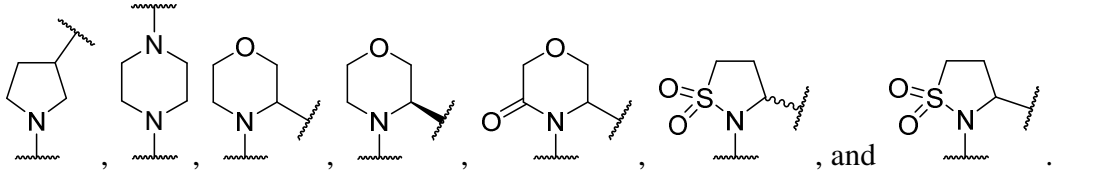
each $\mathbf{R^{Z3}}$ is independently selected from hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and C_6-C_{10} aryl; or two $\mathbf{R^{Z3}}$ are taken together to form a 3- to 6-membered heterocyclyl;

n is selected from 4, 5, 6, 7, and 8; and

m is selected from 0, 1, 2, and 3.

2. The compound, deuterated derivative, or pharmaceutically acceptable salt according to claim 1, wherein **X** is -N($\mathbf{R^{X1}}$)-.

3. The compound, deuterated derivative, or pharmaceutically acceptable salt according to claim 1, wherein **X** is selected from:

-NH-, -N(CH_3)-, -N(CH_2CH_3)-, , , , , and .

4. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein:

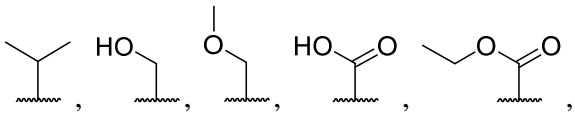
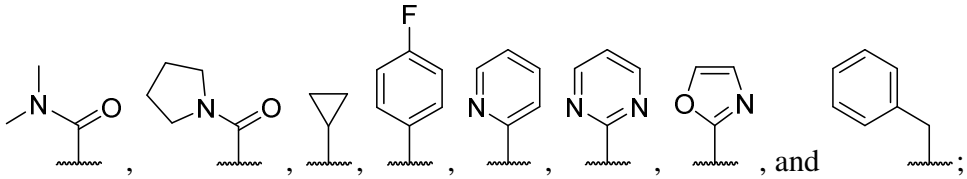
each $\mathbf{R^Y}$ is independently selected from hydrogen, hydroxy, halogen, C_1-C_6 alkyl (optionally substituted with 1-3 groups independently selected from hydroxy, C_1-C_6 alkoxy, and **Q**), C_3-C_8 cycloalkyl, C_6-C_{10} aryl (optionally substituted with 1-3 groups independently selected from halogen), 5- to 10-membered heteroaryl, $-CO_2\mathbf{R^{Y1}}$, and $-CON(\mathbf{R^{Y1}})_2$;

or two $\mathbf{R^Y}$ on the same atom are taken together to form a ring selected from C_3-C_8 cycloalkyl and 3- to 7-membered heterocyclyl;

or two $\mathbf{R^Y}$, one of which is on one atom and the second of which is on an adjacent atom, are taken together to form a pi bond.

5. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 4, wherein:

each $\mathbf{R^Y}$ is independently selected from:

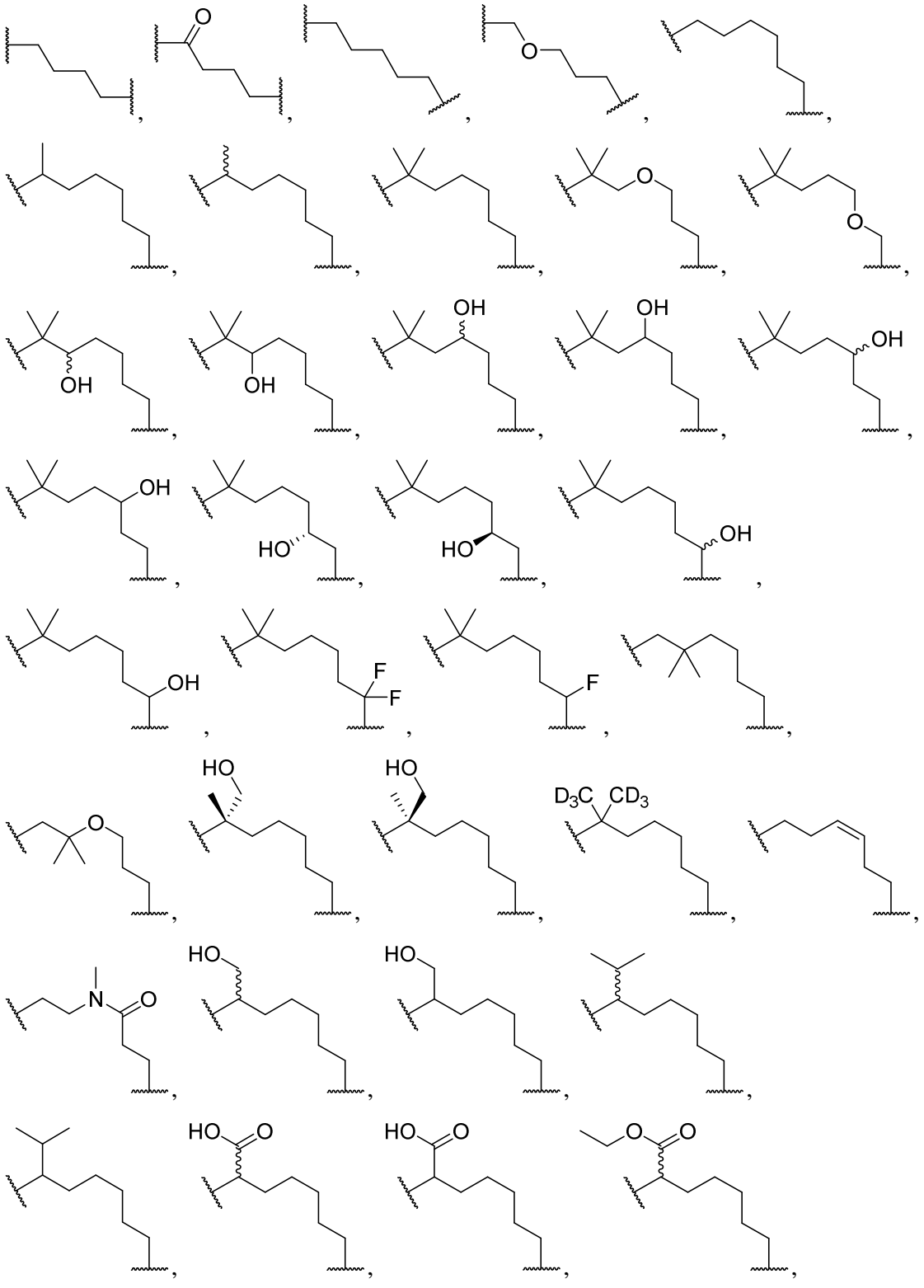
hydrogen, hydroxy, $-CH_3$, $-CD_3$, $-CH_2CH_3$, , , and ;

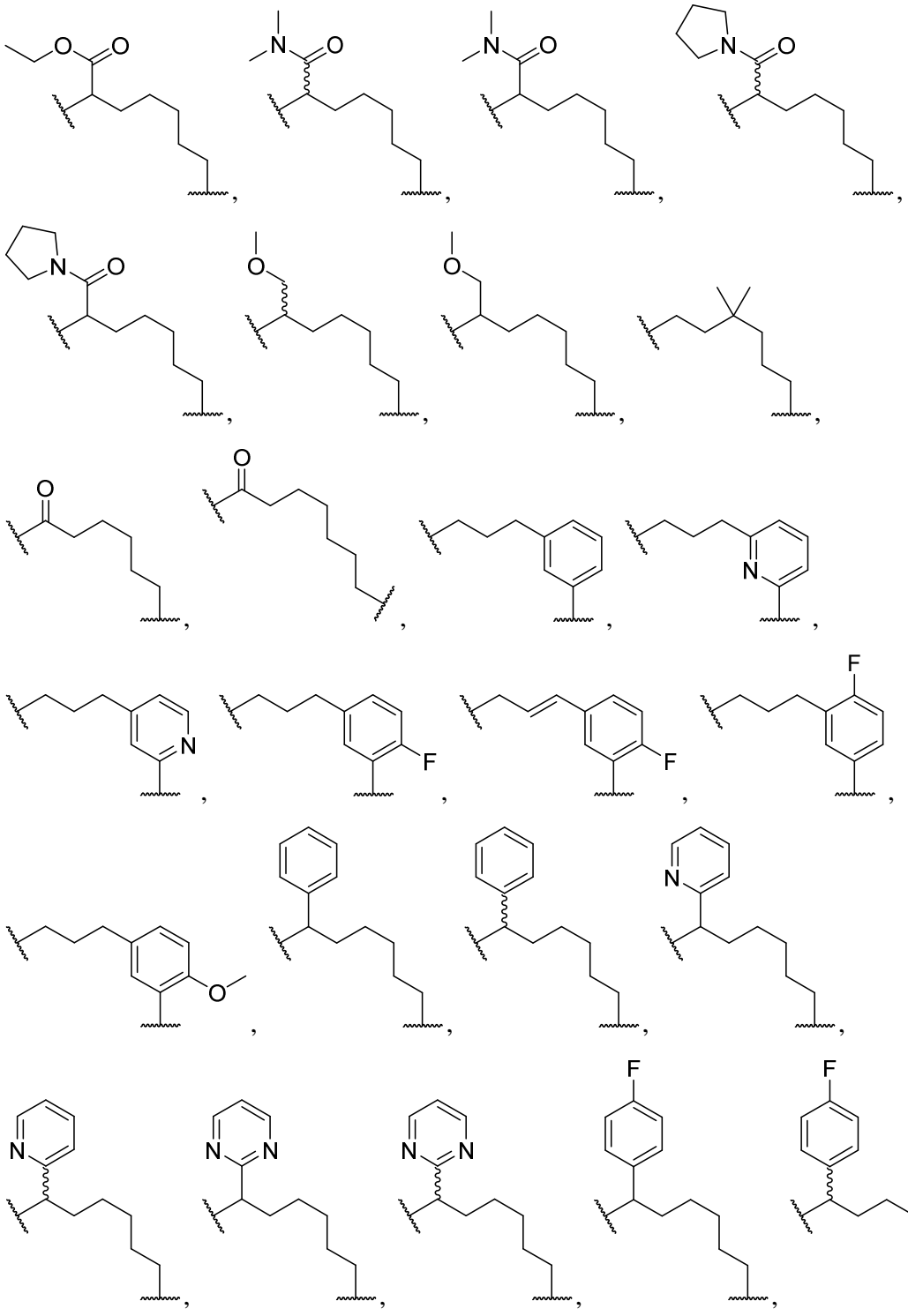
or two $\mathbf{R^Y}$ on the same atom are taken together to form a ring selected from cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyryl, and tetrahydrofuryl;

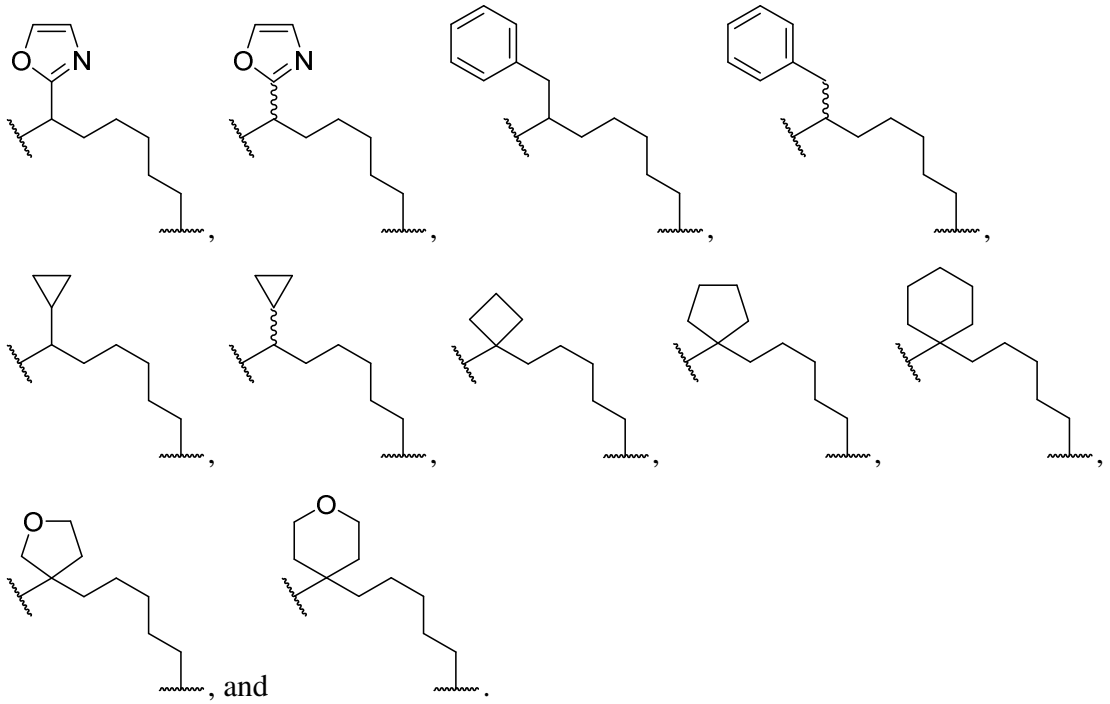
or two $\mathbf{R^Y}$, one of which is on one atom and the second of which is on an adjacent atom, are taken together to form a pi bond.

6. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 5, wherein **n** is selected from 4, 5, 6, and 7.

7. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 6, wherein $-(\mathbf{Y})_n-$ is a group selected from:





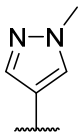
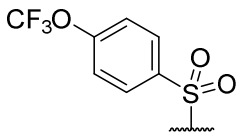
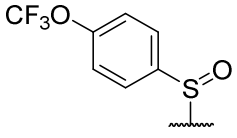
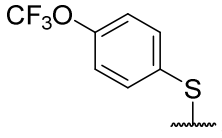


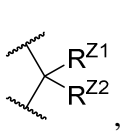
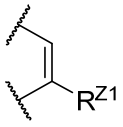
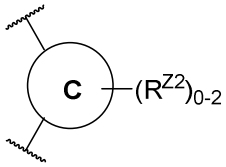
, and .

8. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 7, wherein each $\mathbf{R^1}$ is independently selected from halogen, C_1-C_6 fluoroalkyl, C_1-C_6 alkyl (optionally substituted with a group selected from C_6-C_{10} aryl), -O$\mathbf{R^2}$, -N($\mathbf{R^2}$)$_2$, -$CO_2\mathbf{R^2}$, -CO-N($\mathbf{R^2}$)$_2$, -CN, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 5- to 6-membered heteroaryl (optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl), 3- to 6-membered heterocyclyl, -B(O$\mathbf{R^2}$)$_2$, -$SO_2\mathbf{R^2}$, -S$\mathbf{R^2}$, -SO$\mathbf{R^2}$, and -PO($\mathbf{R^2}$)$_2$.

9. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein each $\mathbf{R^2}$ is independently selected from hydrogen and C_6-C_{10} aryl (optionally substituted with 1-3 groups independently selected from C_1-C_6 fluoroalkoxy).

10. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 9, wherein each $\mathbf{R^1}$ is independently selected from -Br, -CF_3, -NH_2, -CH_3, -$CH(CH_3)_2$, -CN, -OH, -OCH_3, -$NH(CH_3)$, -$NH(CH_2CH_3)$, -$CONH_2$,

-CO_2CH_3, -SO_2CH_3, -SO_2Ph, $PO(CH_3)_2$, $B(OH)_2$, phenyl, pyridyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, cyclohexyl, imidazolyl, , , , and .

11. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 10, wherein **Z** is selected from , , and ; wherein **Ring C** is selected from C_6-C_{10} aryl.

12. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 11, wherein $\mathbf{R^{Z1}}$ is selected from hydrogen, C_1-C_6 alkyl (optionally substituted with 1-3 hydroxy), C_1-C_6 fluoroalkyl, 3- to 6-membered heterocyclyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, and 5- to 6-membered heteroaryl.

13. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 12, wherein $\mathbf{R^{Z2}}$ is selected from hydrogen, halogen, hydroxy, and C_1-C_6 alkoxy (optionally substituted with 1-3 groups independently selected from C_3-C_{10} cycloalkyl).

14. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 13, wherein:

$\mathbf{R^{Z1}}$ is selected from hydrogen, C_1-C_6 alkyl (optionally substituted with 1-3 hydroxy), C_1-C_6 fluoroalkyl, 3- to 6-membered heterocyclyl, C_3-C_6 cycloalkyl, and C_6-C_{10} aryl; and

$\mathbf{R^{Z2}}$ is selected from hydrogen, halogen, and hydroxy;

or $\mathbf{R^{Z1}}$ and $\mathbf{R^{Z2}}$ taken together form a group selected from oxo and =N-OH.

15. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 14, wherein:

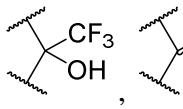
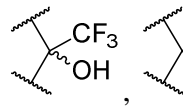
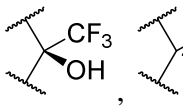
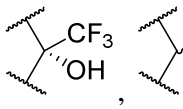
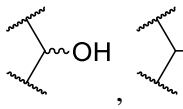
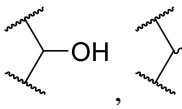
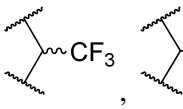
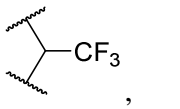
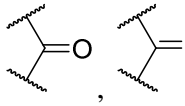
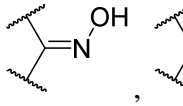
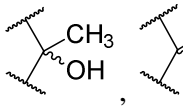
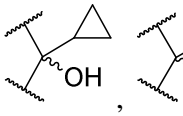
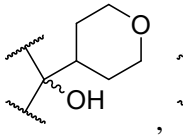
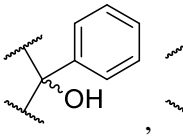
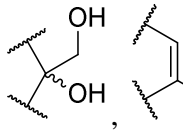
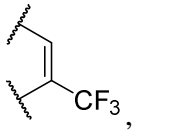
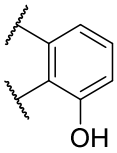
$\mathbf{R^{Z1}}$ is selected from hydrogen, CH_3, CF_3, CH_2OH, phenyl, cyclopropyl, and tetrahydropyranyl; and

$\mathbf{R^{Z2}}$ is selected from hydrogen, halogen, and hydroxy;

or $\mathbf{R^{Z1}}$ and $\mathbf{R^{Z2}}$ taken together form a group selected from oxo and =N-OH.

16. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 15, wherein $\mathbf{R^{Z2}}$ is hydroxy.

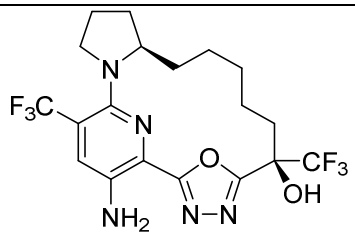
17. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 16, wherein **Z** is selected from:

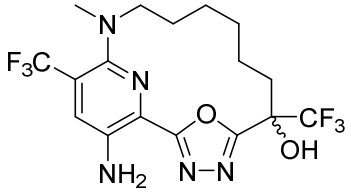
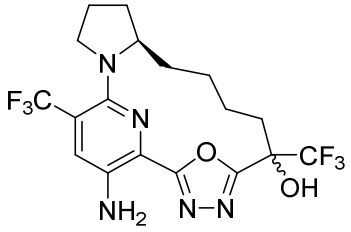
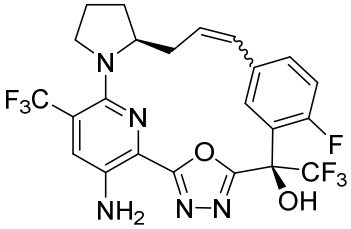
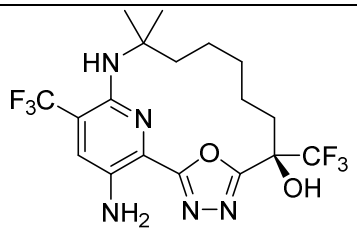
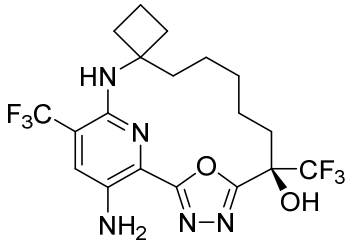
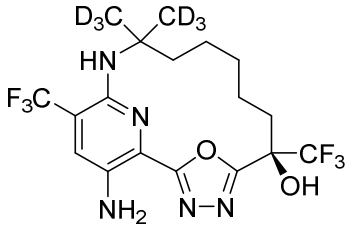
















and .

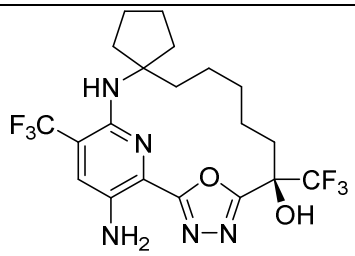
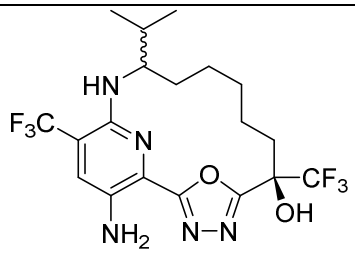
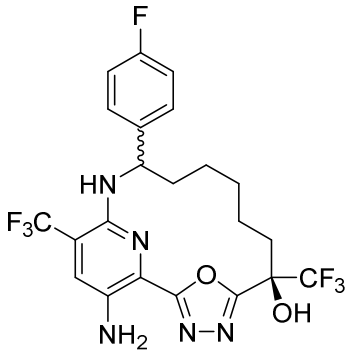
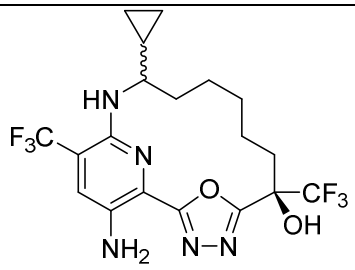
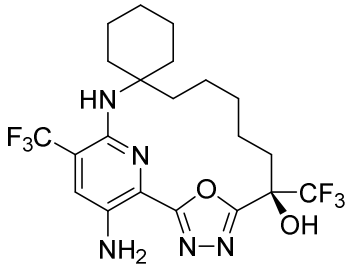
18. The compound, deuterated derivative, or pharmaceutically acceptable salt according to any one of claims 1 to 17, wherein **m** is selected from 1 and 2.

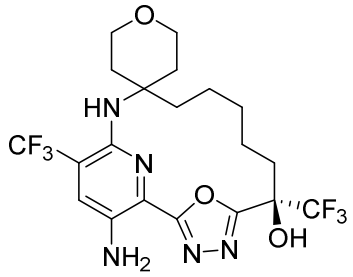
19. A compound selected from compounds of Table 10, pharmaceutically acceptable salts thereof, and deuterated derivatives of any of the foregoing.

20. A compound according to claim 19, wherein the compound is selected from:

Comp. No.	**Structure**
4	

Comp. No.	Structure
19	
32	
138	
163	
173	
176	

Comp. No.	Structure
177	
178	
182	
192	
193	

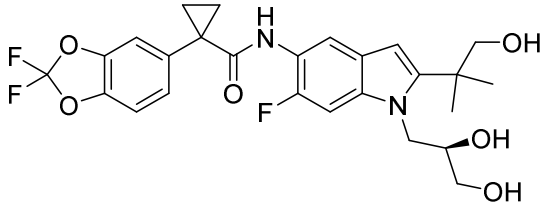
Comp. No.	Structure
205	

21. A pharmaceutical composition comprising a compound, salt, or deuterated derivative of any one of claims 1 to 20 and a pharmaceutically acceptable carrier.

22. The pharmaceutical composition according to claim 21, wherein the pharmaceutical composition further comprises at least one CFTR corrector.

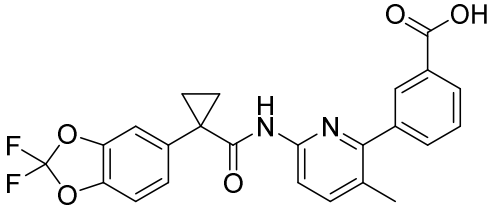
23. The pharmaceutical composition according to claim 22, wherein the at least one CFTR corrector is selected from:

(*R*)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-*N*-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1*H*-indol-5-yl)cyclopropanecarboxamide (Compound **II**):



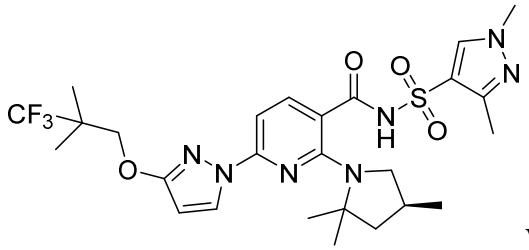
II,

3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Compound **IV**):



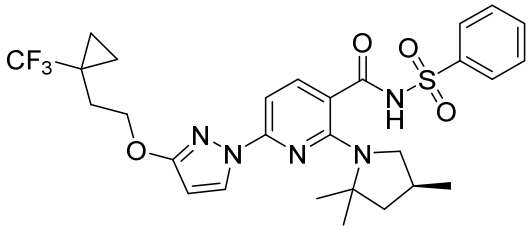
IV,

N-(1,3-dimethylpyrazol-4-yl)sulfonyl-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-[(4*S*)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (Compound **V**):



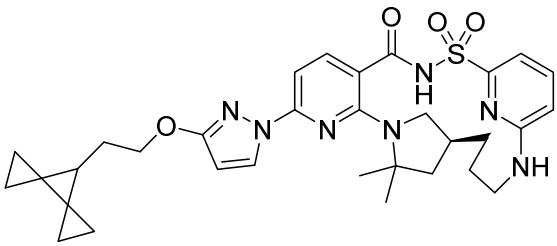
V,

N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl) cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4*S*)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (Compound **VI**):



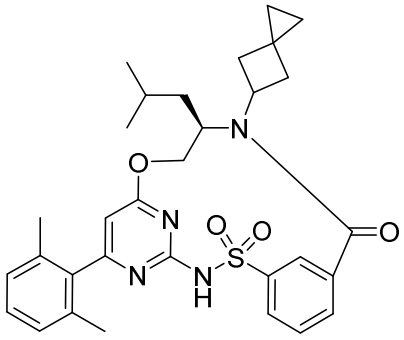
VI,

(14*S*)-8-[3-(2-{dispiro[2.0.2.1]heptan-7-yl}ethoxy)-1*H*-pyrazol-1-yl]-12,12-dimethyl-2λ^6-thia-3,9,11,18,23-pentaazatetracyclo [17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione (Compound **VII**):



VII,

(11*R*)-6-(2,6-dimethylphenyl)-11-(2-methylpropyl)-12-{spiro[2.3]hexan-5-yl}-9-oxa-2λ^6-thia-3,5,12,19-tetraazatricyclo[12.3.1.14,8]nonadeca-1(17),4(19),5,7,14(18),15-hexaene-2,2,13-trione (Compound **VIII**):



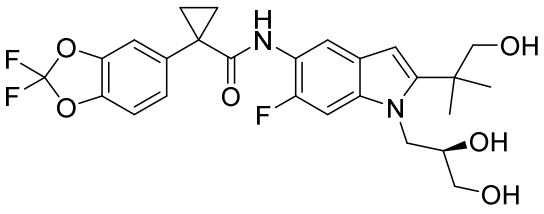
VIII,

PTI-428, ABBV-2222, ABBV-2851, GLPG2737, ABBV-3221, ABBV-3748, ABBV-3903, ABBV-119, FDL-169, ARN5562, ARN21586, ARN22081, ARN22652, ARN23765, ARN23766, and PTI-801.

24. Use of the compound, salt, or deuterated derivative according to any one of claims 1 to 20 or the pharmaceutical composition according to any one of claims 21 to 23, in the manufacture of a medicament for the treatment of cystic fibrosis.

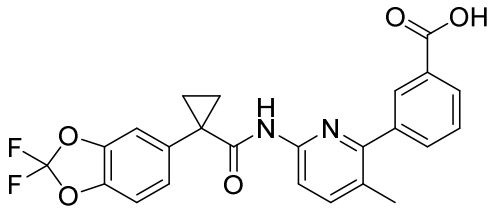
25. The use according to claim 24, wherein the medicament is to be conjointly administered with at least one CFTR corrector.

26. The use according to claim 25, wherein the at least one CFTR corrector is selected from: (*R*)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-*N*-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1*H*-indol-5-yl)cyclopropanecarboxamide (Compound **II**):



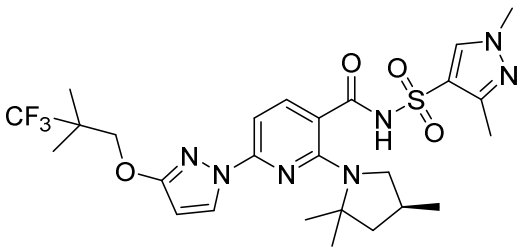
Compound **II**,

3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Compound **IV**):



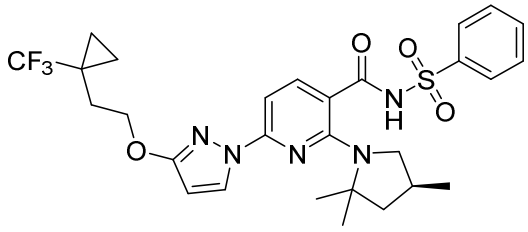
Compound **IV**,

N-(1,3-dimethylpyrazol-4-yl)sulfonyl-6-[3-(3,3,3-trifluoro-2,2-dimethyl-propoxy)pyrazol-1-yl]-2-[(4*S*)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (Compound **V**):



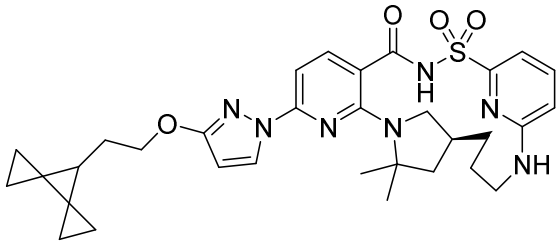
Compound **V**,

N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl) cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4*S*)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (Compound **VI**):



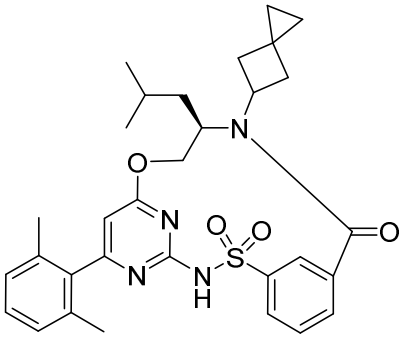
Compound **VI**,

(14*S*)-8-[3-(2-{dispiro[2.0.2.1]heptan-7-yl}ethoxy)-1*H*-pyrazol-1-yl]-12,12-dimethyl-2λ^6-thia-3,9,11,18,23-pentaazatetracyclo [17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione (Compound **VII**):



Compound **VII**,

(11*R*)-6-(2,6-dimethylphenyl)-11-(2-methylpropyl)-12-{spiro[2.3]hexan-5-yl}-9-oxa-2λ^6-thia-3,5,12,19-tetraazatricyclo[12.3.1.14,8]nonadeca-1(17),4(19),5,7,14(18),15-hexaene-2,2,13-trione (Compound **VIII**):



Compound **VIII**,

PTI-428, ABBV-2222, ABBV-2851, GLPG2737, ABBV-3221, ABBV-3748, ABBV-3903, ABBV-119, FDL-169, ARN5562, ARN21586, ARN22081, ARN22652, ARN23765, ARN23766, and PTI-801.

27. The compound, salt, or deuterated derivative of any one of claims 1 to 20 or the pharmaceutical composition according to any one of claims 21 to 23, for use in therapy.