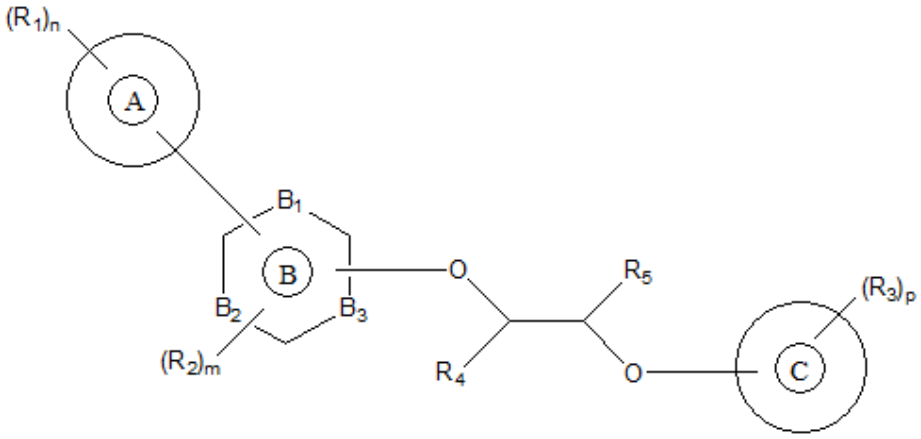
There is therefore a need to provide compounds that inhibit ICMT, and overcome, or at least ameliorate, one or more of the disadvantages described above.

## Summary

The present disclosure provides a compound having the following Formula (I):




(I)

and/or tautomers, enantiomers, solvates, hydrates, prodrugs and pharmaceutically acceptable salts thereof;

wherein:

 represents an aromatic ring system;

Ring A is a 5- or 6- membered carbocyclic ring system, wherein 1 to 4 carbon atoms may be optionally replaced with a heteroatom;

$B_1$, $B_2$ and $B_3$ are independently selected from C, CH, or N;

Ring C is a 5- or 6- membered carbocyclic ring system, wherein 1 to 3 carbon atoms may be optionally replaced with a heteroatom;

$R_1$, $R_2$, and $R_3$ are independently absent or selected from H, OH, cyano, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

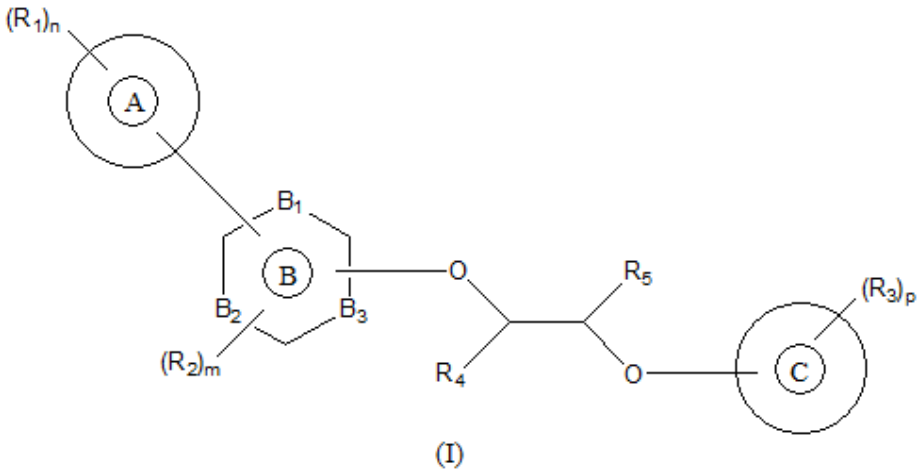
$R_4$ and $R_5$ are independently selected from H or aliphatic;

n is an integer selected from 0 to 5, wherein when n is more than 1, each $R_1$ substituted on Ring A may be the same or different;

m is an integer selected from 0 to 4, wherein when m is more than 1, each $R_2$ substituted on Ring B may be the same or different; and

p is an integer selected from 0 to 5, wherein when p is more than 1, each $R_3$ substituted on Ring C may be the same or different.

The present disclosure also provides a compound having the following Formula (I):




(I)

and/or tautomers, enantiomers, solvates, hydrates, prodrugs and pharmaceutically acceptable salts thereof;

wherein:

 represents an aromatic ring system;

Ring A is a 5- or 6- membered carbocyclic ring system, wherein 1 to 4 carbon atoms may be optionally replaced with a heteroatom;

$B_1$, $B_2$ and $B_3$ are independently selected from C, CH, or N, wherein when one of $B_1$, $B_2$ or $B_3$ is N, the remaining $B_1$, $B_2$ or $B_3$ is C or CH;

Ring C is a 5- or 6- membered carbocyclic ring system, wherein 1 to 3 carbon atoms may be optionally replaced with a heteroatom;

$R_1$ is absent or selected from H, OH, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted

cycloalkenyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

$R_2$ is absent or selected from H, OH, cyano, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

$R_3$ is absent or selected from H, OH, cyano, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, or optionally substituted aryl;

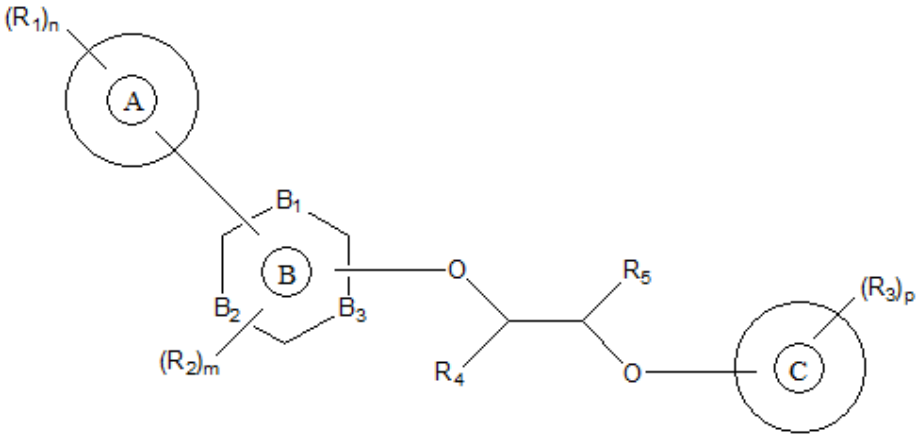
$R_4$ and $R_5$ are independently selected from H or aliphatic;

n is an integer selected from 0 to 5, wherein when n is more than 1, each $R_1$ substituted on Ring A may be the same or different;

m is an integer selected from 0 to 4, wherein when m is more than 1, each $R_2$ substituted on Ring B may be the same or different, and m is 1 when $R_2$ is halogen; and

p is an integer selected from 0 to 5, wherein when p is more than 1, each $R_3$ substituted on Ring C may be the same or different.

In one aspect of the present disclosure, there is provided a compound having the following Formula (I):




(I)

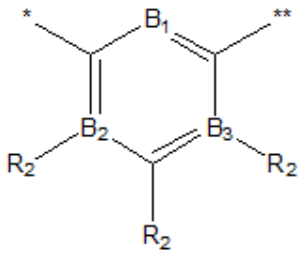
and/or tautomers, enantiomers, solvates, hydrates, prodrugs and pharmaceutically acceptable salts thereof;

wherein:

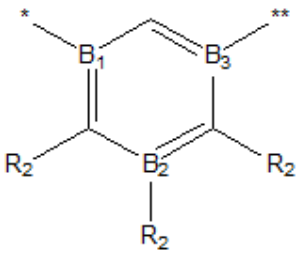
 represents an aromatic ring system;

Ring A is a 5- or 6- membered carbocyclic ring system, wherein 1 to 4 carbon atoms may be optionally replaced with a heteroatom;

Ring B is of formula (bb1) or formula (bb2):




(bb1)




(bb2)

wherein:

* represents the point of attachment to Ring A, and

** represents the point of attachment to the –O(CHR4)- moiety of formula (I);

Ring C is a 5- or 6- membered carbocyclic ring system, wherein 1 to 3 carbon atoms may be optionally replaced with a heteroatom;

$R_1$ is absent or selected from H, OH, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl;

$R_2$ is absent or selected from H, OH, cyano, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted

cycloalkenyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

$R_3$ is absent or selected from H, OH, cyano, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, or optionally substituted aryl;

$R_4$ and $R_5$ are independently selected from H or aliphatic;

n is an integer selected from 0 to 5, wherein when n is more than 1, each $R_1$ substituted on Ring A may be the same or different;

m is an integer selected from 0 to 4, wherein when m is more than 1, each $R_2$ substituted on Ring B may be the same or different, and m is 1 when $R_2$ is halogen; and

p is an integer selected from 0 to 5, wherein when p is more than 1, each $R_3$ substituted on Ring C may be the same or different.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable form or prodrug thereof, and a pharmaceutically acceptable excipient.

The present disclosure also provides a method of inhibiting methylation of isoprenylated cysteine or isoprenylcysteine caused by isoprenylcysteine carboxyl methyltransferase (ICMT) comprising contacting the compound as defined herein, or a pharmaceutical composition as defined herein, with ICMT.

The present disclosure further provides a method of inhibiting ICMT in a cell comprising contacting said cell with a compound as defined herein, or a pharmaceutically acceptable form or prodrug thereof, or a pharmaceutical composition as defined herein.

The present disclosure also provides a method of treating a ICMT-related disorder comprising administering to a subject in need of treatment a compound as defined herein, or pharmaceutical, or a composition as defined herein.

In a further aspect of the present disclosure, there is provided a compound as defined herein, or a pharmaceutically form or prodrug thereof, or a composition as defined herein for use in therapy.

In another aspect of the present disclosure, there is provided a use of a compound as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for inhibiting methylation of isoprenylated cysteine or isoprenylcysteine caused by isoprenylcysteine carboxyl methyltransferase (ICMT).

The present disclosure also provides a compound as defined herein, or a pharmaceutically form or prodrug thereof, or a composition as defined herein for use in the treatment and/or prevention of cancer and/or progeroid diseases.

The present disclosure further provides a compound as defined herein, or a pharmaceutically form or prodrug thereof, or a composition as defined herein, for use in the treatment of a ICMT-related disorder.

The present disclosure also provides a use of a compound as defined herein, or a pharmaceutically form or prodrug thereof, or a composition as defined herein, in the manufacture of a medicament for the treatment and/or prevention of cancer and/or progeroid diseases.

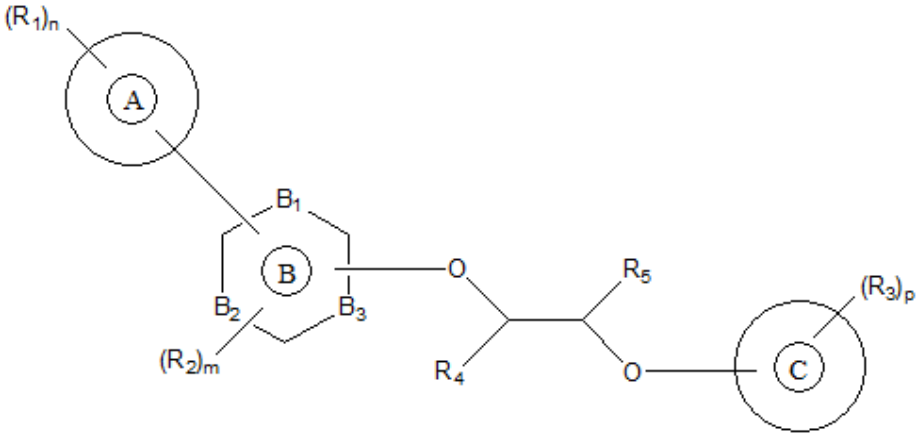
The present disclosure further provides a use of a compound as defined herein, or a pharmaceutically form or prodrug thereof, or a composition as defined herein, in the manufacture of a medicament for the treatment of a ICMT-related disorder.

In yet another aspect of the present disclosure, there is provided a process for synthesizing a compound as defined herein, comprising:

(a) reacting a compound of formula (III):

# CLAIMS

1. A compound having the following Formula (I):




(I)

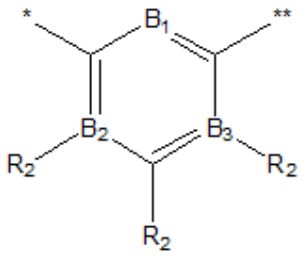
and/or tautomers, enantiomers, solvates, hydrates, prodrugs and pharmaceutically acceptable salts thereof;

wherein:

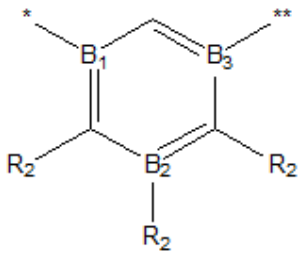
 represents an aromatic ring system;

Ring A is a 5- or 6- membered carbocyclic ring system, wherein 1 to 4 carbon atoms may be optionally replaced with a heteroatom;

Ring B is of formula (bb1) or formula (bb2):




(bb1)




(bb2)

wherein:

* represents the point of attachment to Ring A, and

** represents the point of attachment to the –O($CHR_4$)- moiety of formula (I);

Ring C is a 5- or 6- membered carbocyclic ring system, wherein 1 to 3 carbon atoms may be optionally replaced with a heteroatom;

$R_1$ is absent or selected from H, OH, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl;

$R_2$ is absent or selected from H, OH, cyano, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl;

$R_3$ is absent or selected from H, OH, cyano, halogen, optionally substituted alkyl, haloalkyl, $CF_3$, $CHF_2$, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycloalkyl, or optionally substituted aryl;

$R_4$ and $R_5$ are independently selected from H or aliphatic;

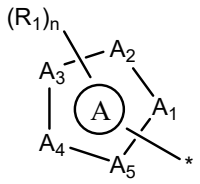
n is an integer selected from 0 to 5, wherein when n is more than 1, each $R_1$ substituted on Ring A may be the same or different;

m is an integer selected from 0 to 4, wherein when m is more than 1, each $R_2$ substituted on Ring B may be the same or different, and m is 1 when $R_2$ is halogen; and

p is an integer selected from 0 to 5, wherein when p is more than 1, each $R_3$ substituted on Ring C may be the same or different.

2. The compound of claim 1, wherein Ring A is selected from the group consisting of formulas (aa), (ab), (ac), and (a1) to (a10):

- Formula (aa)




(aa)

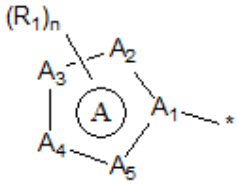
wherein:

* represents the point of attachment to Ring B;

$A_1$, $A_2$, $A_3$, $A_4$ and $A_5$ are independently selected from C, CH, N, O or S; and

$R_1$ and n are as defined in claim 1,

- formula (ab):




(ab)

wherein:

* represents the point of attachment to Ring B;

$A_1$ is N or C;

$A_2$ is N, S, CH or C;

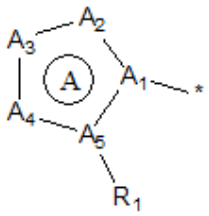
$A_3$ is C, CH, N, or O;

$A_4$ is N;

$A_5$ is C, CH, O, or N; and

$R_1$ and n are as defined in claim 1,

- formula (ac):




(ac)

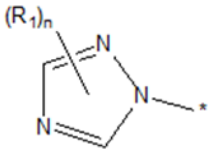
wherein:

* represents the point of attachment to Ring B;

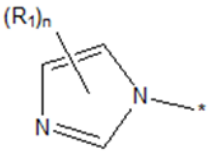
$A_1$, $A_2$, $A_3$, $A_4$ and $A_5$ are independently selected from C, CH, N, O or S; and

$R_1$ is as defined in claim 1,

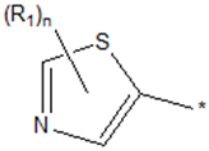
- formulas (a1) to (a8):



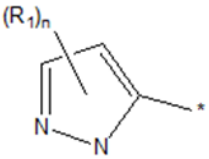

(a1)



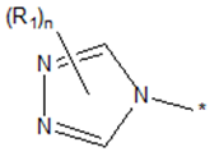

(a2)



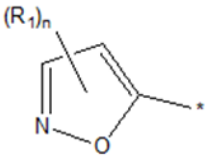

(a3)



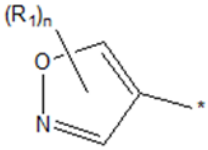

(a4)



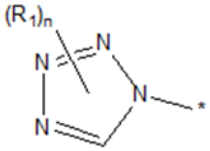

(a5)




(a6)




(a7)

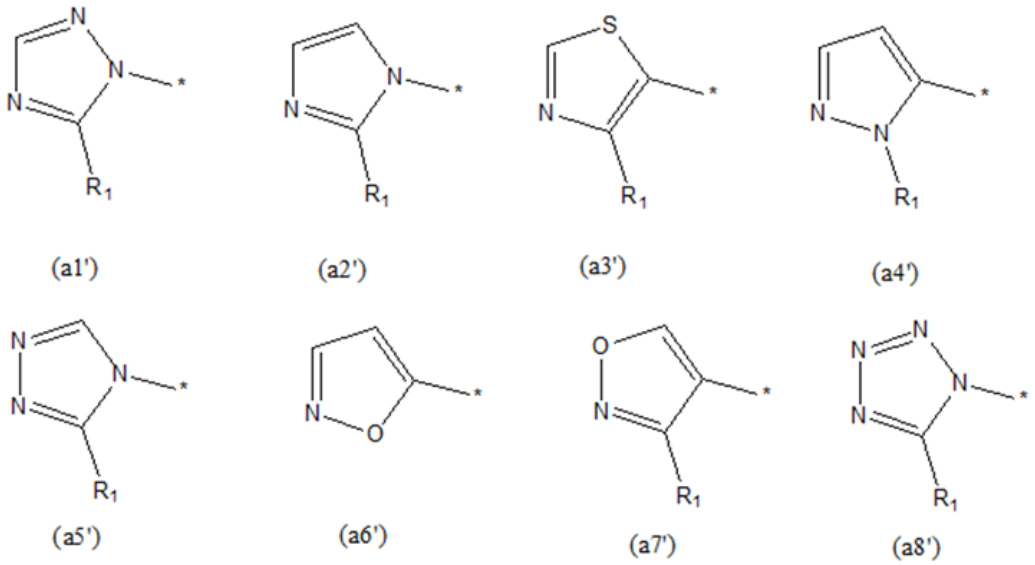



(a8)

wherein * represents the point of attachment to Ring B; and

$R_1$ and n are as defined in claim 1, and

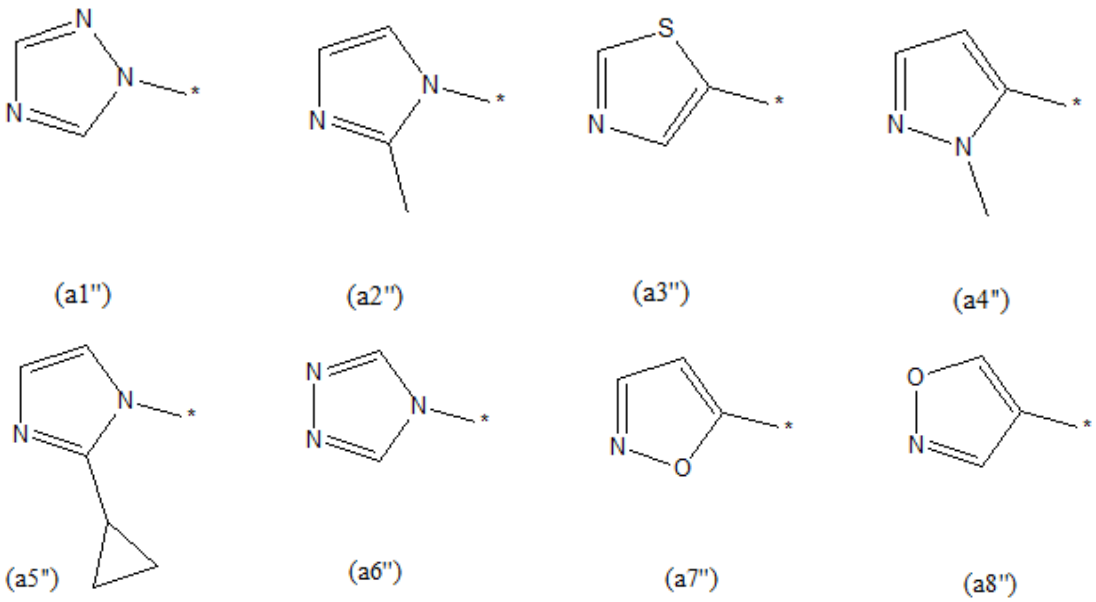
- formulas (a1') to (a8'):

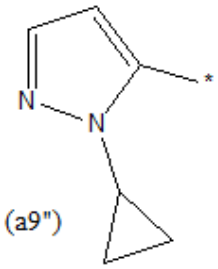



wherein * represents the point of attachment to Ring B; and

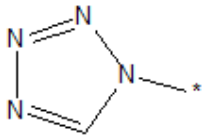
$R_1$ is as defined in claim 1.

3. The compound of claim 1 or claim 2, wherein Ring A is selected from the group consisting of formulas (a1'') to (a10''):






(a9")

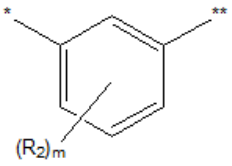



(a10")

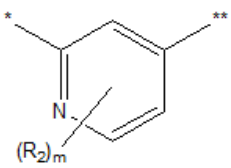
wherein * represents the point of attachment to Ring B.

4. The compound of any one of claims 1 to 3, wherein $R_1$ is alkyl or cycloalkyl, preferably methyl or cyclopropyl.

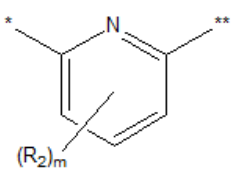
5. The compound of any one of claims 1 to 4, wherein Ring B is selected from the group consisting of formulas (b1) to (b5):



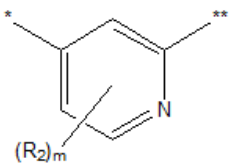

(b1)



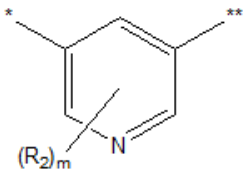

(b2)




(b3)




(b4)




(b5)

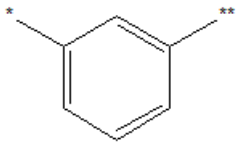
wherein:

* represents the point of attachment to Ring A;

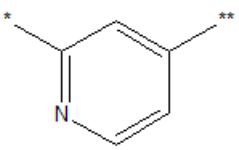
** represents the point of attachment to the –O(CHR4)- moiety of formula (I); and

$R_2$ and m are as defined in claim 1.

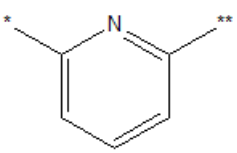
6. The compound of any one of claims 1 to 5, wherein Ring B is selected from the group consisting of formulas (b1') to (b9'):



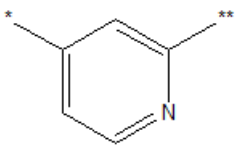
(b1')



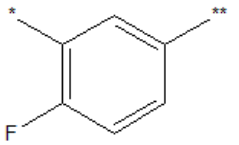
(b2')



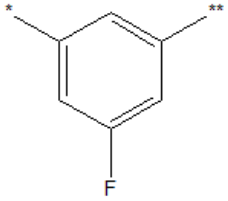
(b3')



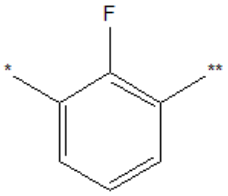
(b4')



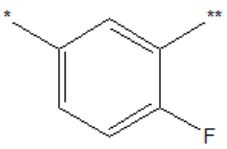
(b5')



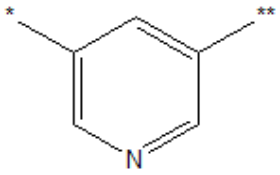
(b6')



(b7')



(b8')



(b9')

wherein:

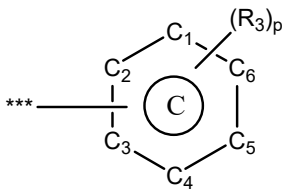
* represents the point of attachment to Ring A; and

** represents the point of attachment to the –O(CHR4)- moiety of formula (I).

7. The compound of any one of claims 1 to 6, wherein $R_2$ is H or F.

8. The compound of any one of claims 1 to 7, wherein Ring C is selected from the group consisting of formulas (ca), (cb), (cc), (c1) to (c4), and (c1') to (c6'):

- formula (ca):



(ca)

wherein:

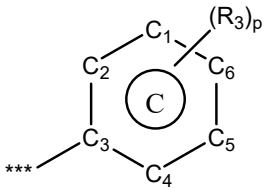

represents an aromatic ring system;

*** represents the point of attachment to the –O(CHR$_5$)- moiety of formula (I);

$C_1$, $C_2$, $C_3$, $C_4$, $C_5$ and $C_6$ are independently selected from C, CH, or N; and

$R_3$ and p are as defined in claim 1,

- formula (cb):




(cb)

wherein:


represents an aromatic ring system;

*** represents the point of attachment to the –O(CHR$_5$)- moiety of formula (I);

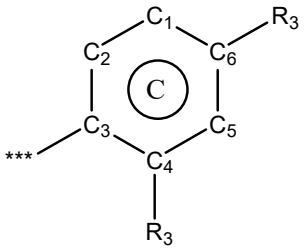
$C_1$ and $C_2$ are independently C, CH or N;

$C_4$, $C_5$, and $C_6$ are C or CH;

$C_3$ is C; and

$R_3$ and p are as defined in claim 1,

- formula (cc):




(cc)

wherein:


represents an aromatic ring system;

*** represents the point of attachment to the –O(CHR$_5$)- moiety of formula (I);

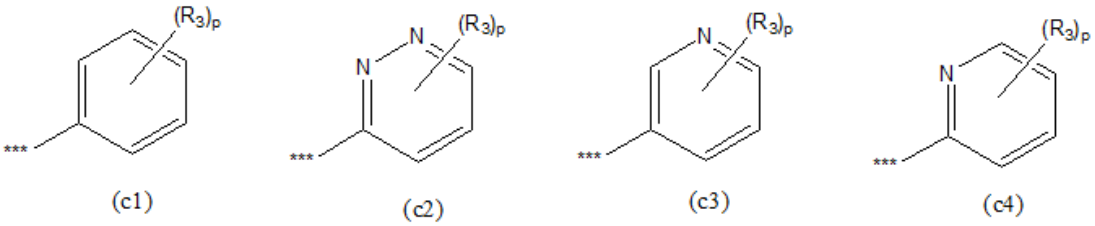
$C_1$ and $C_2$ are independently CH or N;

$C_5$ is CH;

$C_3$, $C_4$, and $C_6$ are C; and

$R_3$ is as defined in claim 1,

- formulas (c1) to (c4):

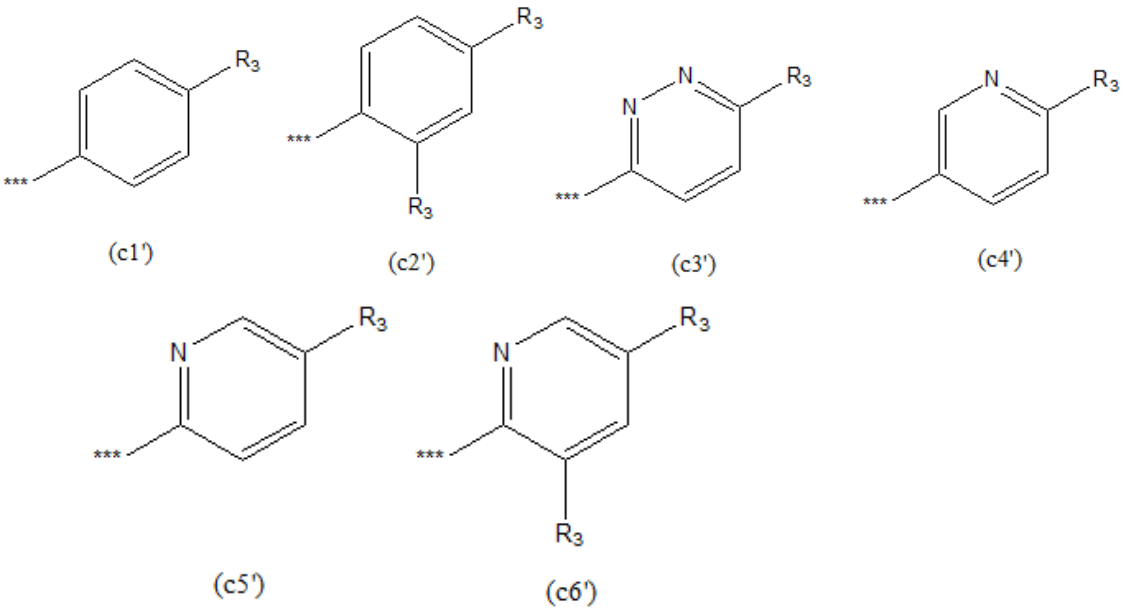



wherein:

*** represents the point of attachment to the –O(CHR$_5$)- moiety of formula (I); and

$R_3$ and p are as defined in claim 1, and

- formulas (c1') to (c6'):

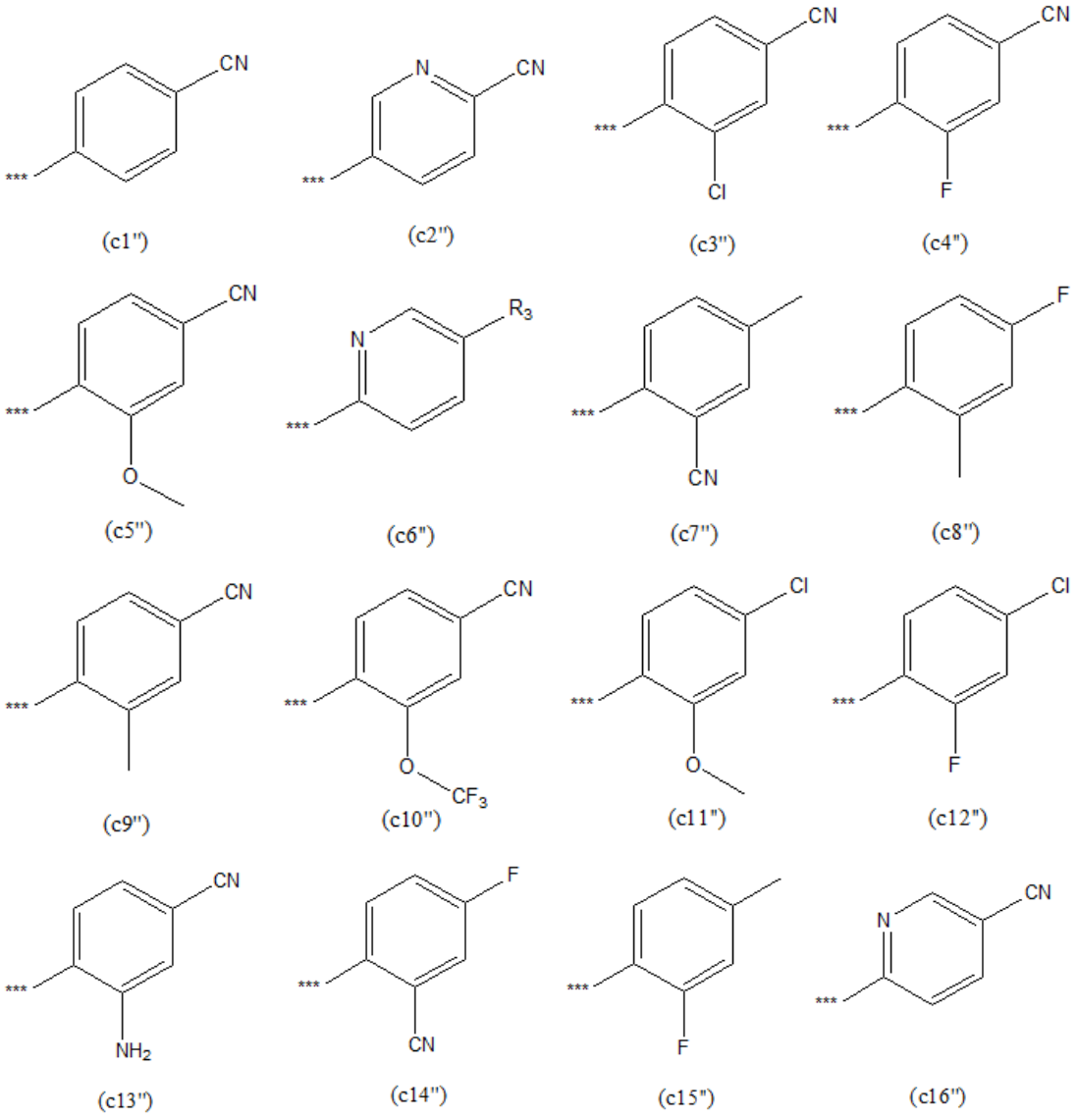


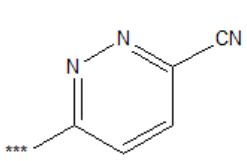
wherein:

*** represents the point of attachment to the –O(CHR$_5$)- moiety of formula (I); and

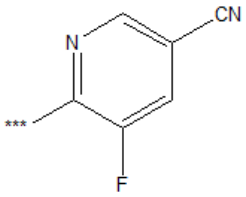
R$_3$ is as defined in claim 1.

9. The compound of any one of claims 1 to 8, wherein Ring C is selected from the group consisting of (c1'') to (c22''):

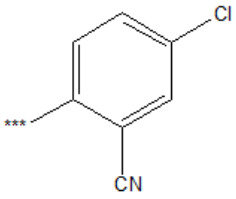




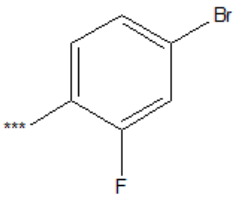

(c17")



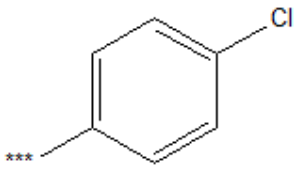

(c18")



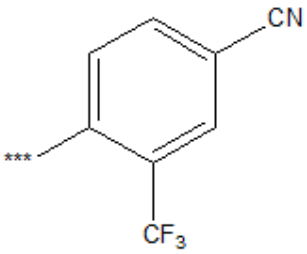

(c19")




(c20")




(c21")




(c22")

wherein:

*** represents the point of attachment to the –O(CHR$_5$)- moiety of formula (I).

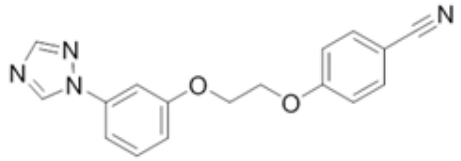
10. The compound of any one of claims 1 to 9, wherein R$_3$ is halogen, -CN, alkoxy, amino, haloalkyl, haloalkyloxy, or alkyl.

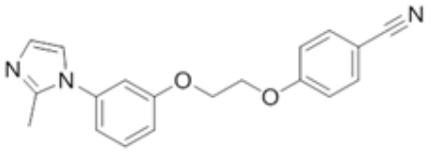
11. The compound of any one of claims 1 to 10, wherein R$_3$ is fluoro, chloro, bromo, -CN, methoxy, methyl, -NH$_2$, -OCF$_3$, CF$_3$, or CHF$_2$.

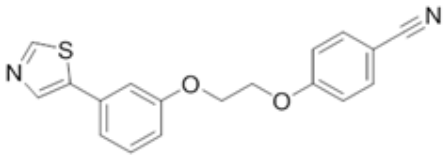
12. The compound of any one of claims 1 to 11, wherein R$_4$ and R$_5$ are independently H or alkyl, preferably wherein R$_4$ and R$_5$ are independently H, methyl, ethyl, propyl, or butyl.

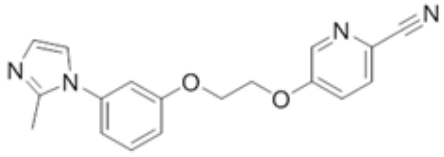
13. The compound of any one of claims 1 to 12, wherein R$_4$ and R$_5$ are H; or R$_4$ is H and R$_5$ is methyl; or R$_4$ is methyl and R$_5$ is H; or R$_4$ is methyl and R$_5$ is methyl.

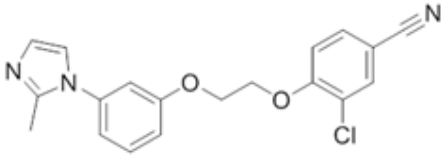
14. A compound of any one of claims 1 to 13, selected from the group consisting of:

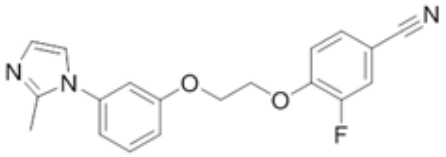


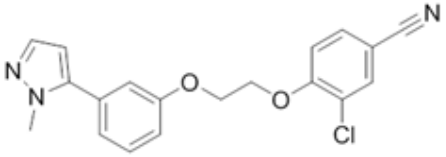


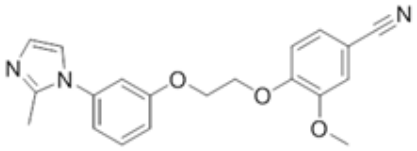






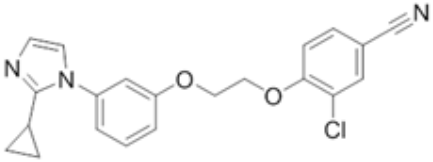


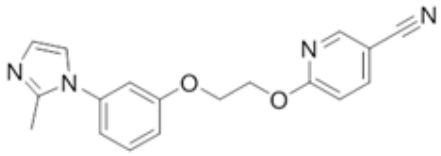


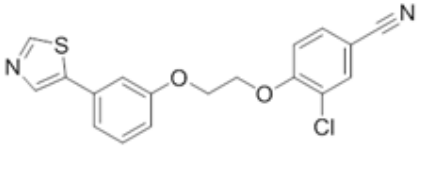


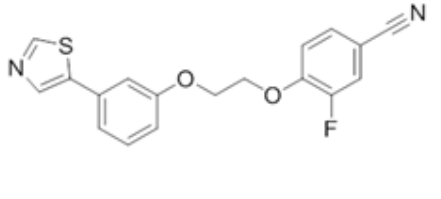


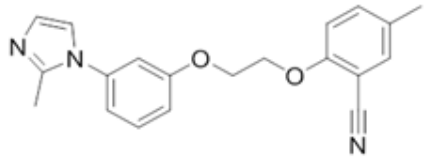


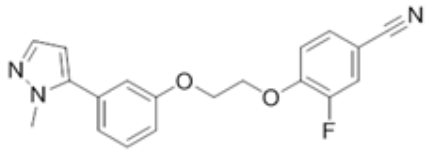


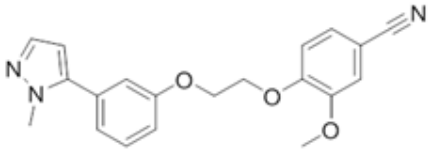


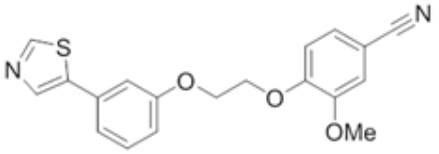


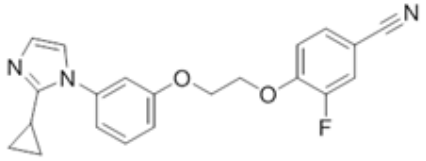


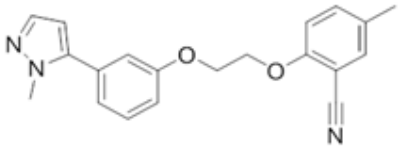


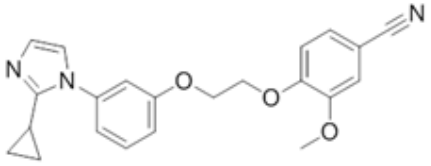


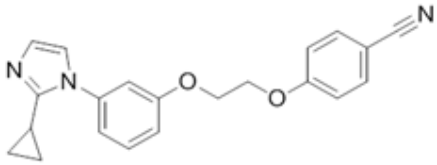


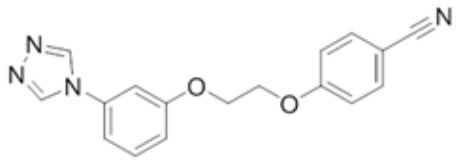


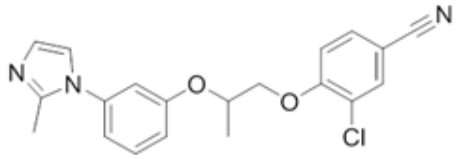


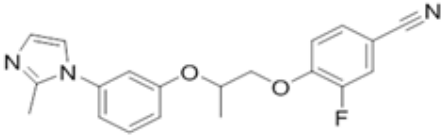


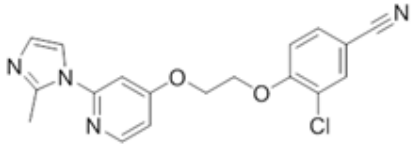


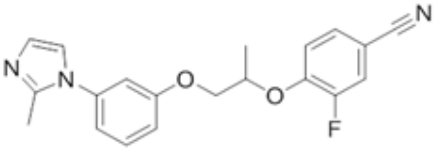


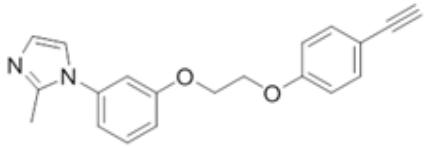


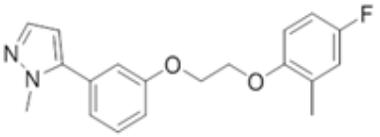


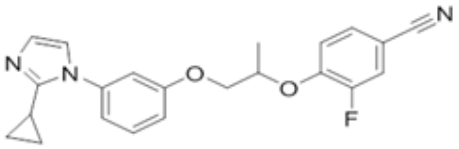


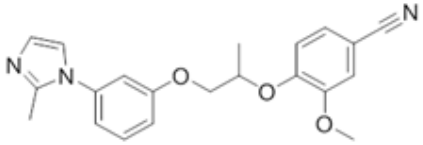


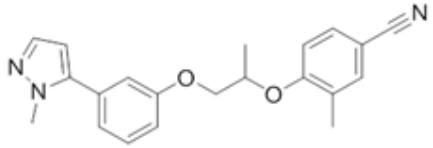


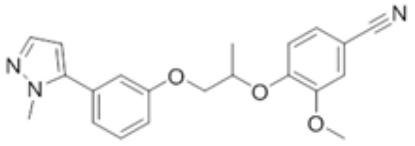


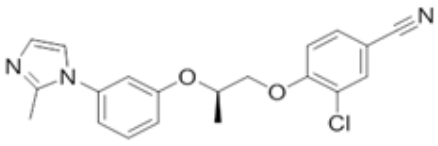




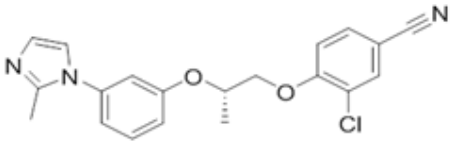


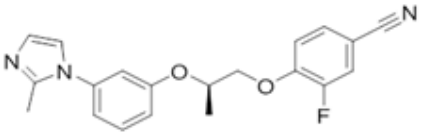


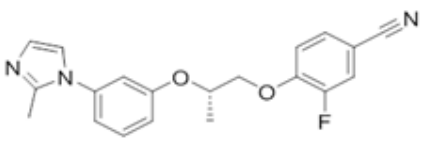


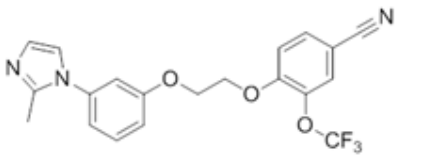


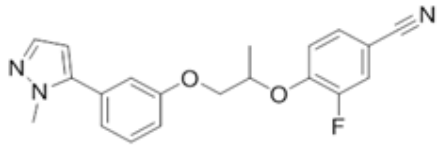


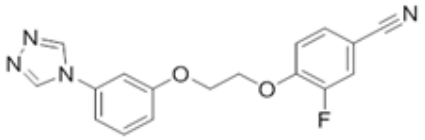


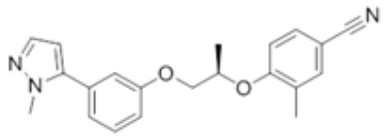


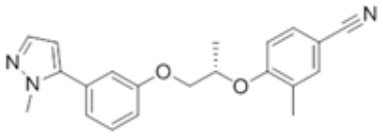


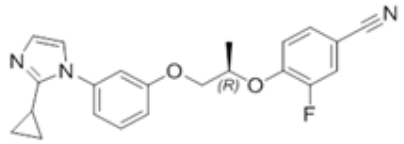


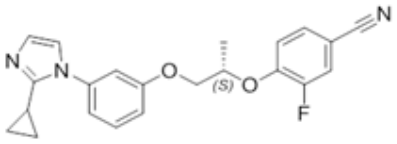


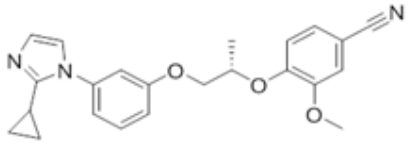


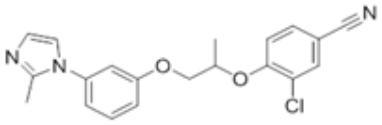


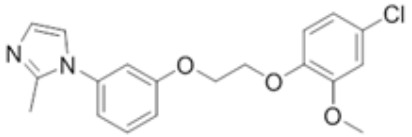


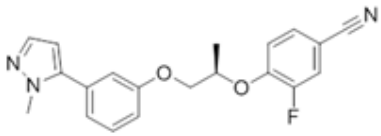






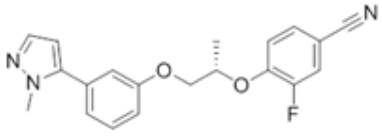


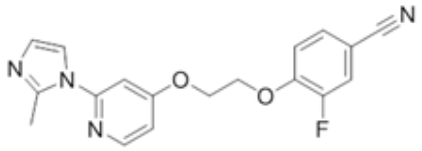


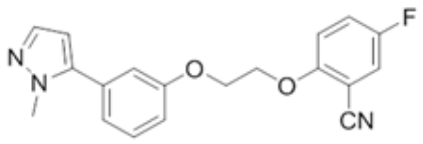


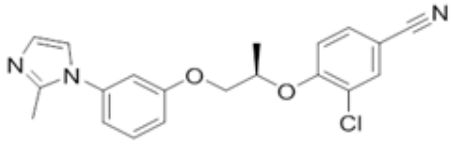


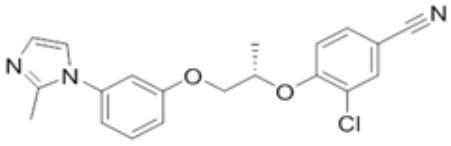


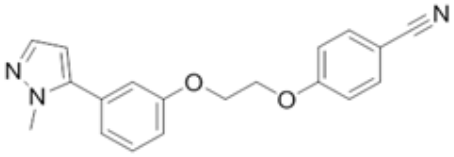


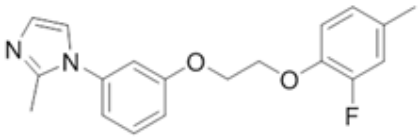


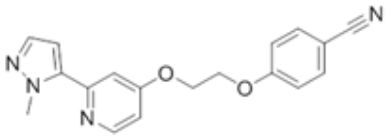


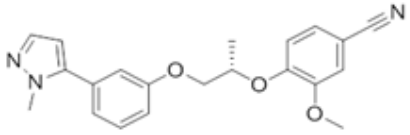


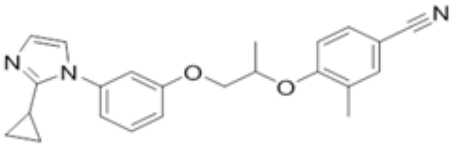


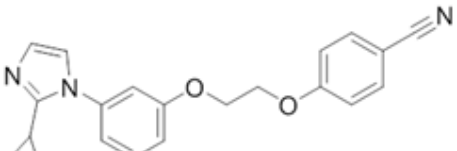


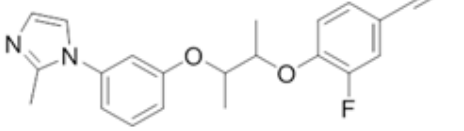


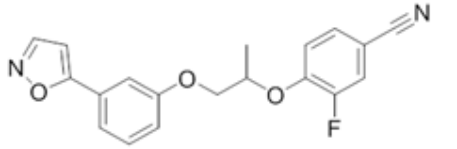


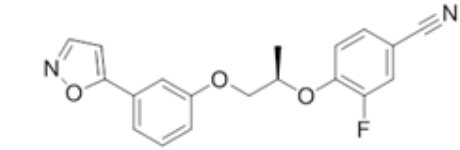


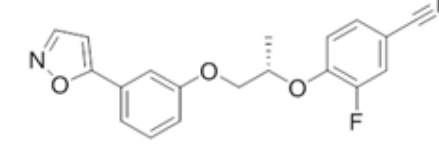


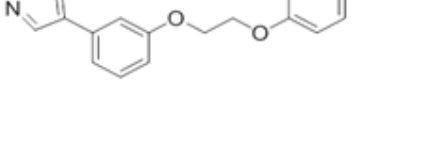




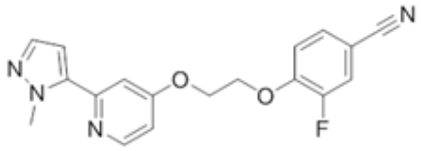


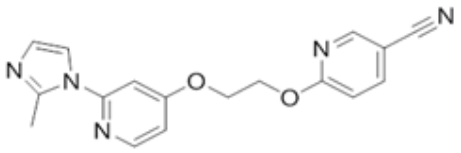


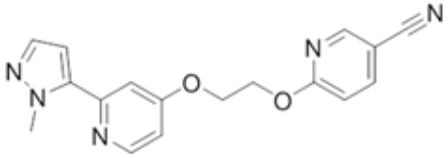


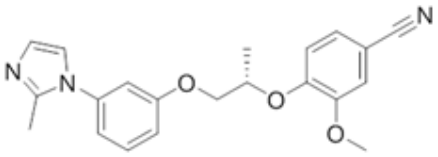


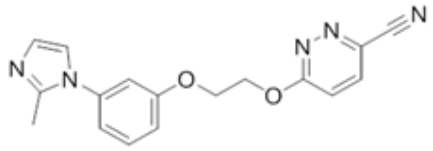


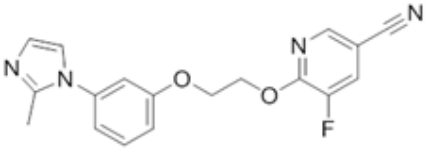


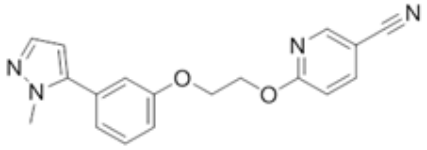


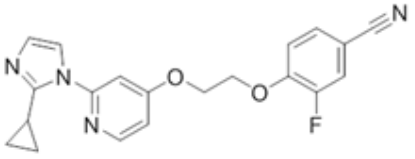


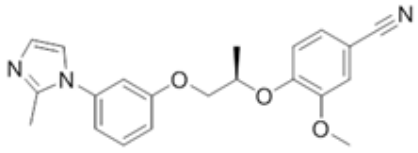


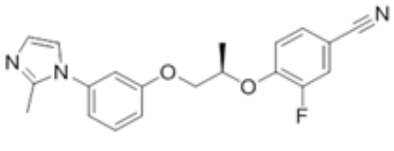


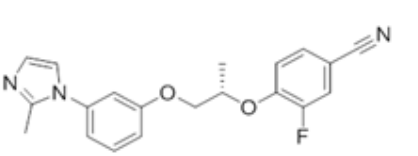


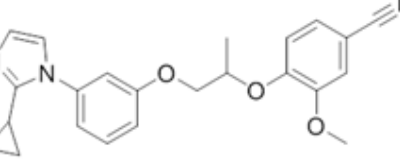






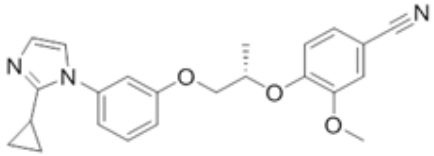


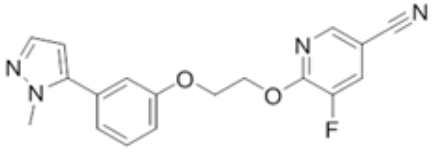


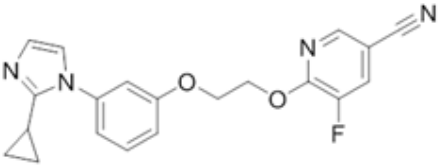


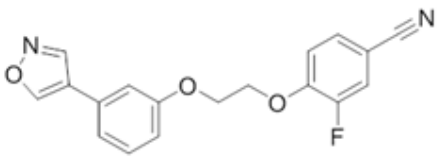


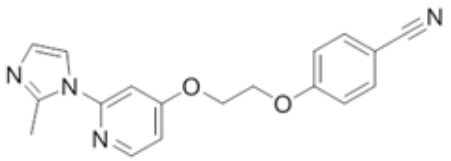


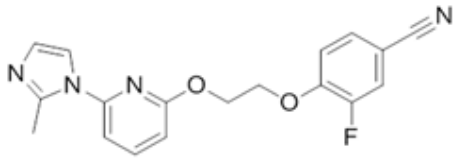


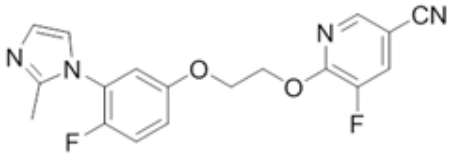


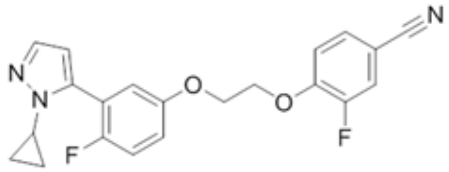


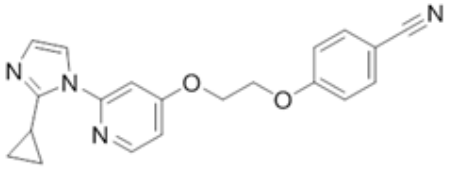


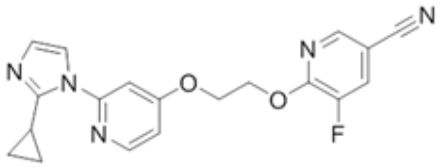


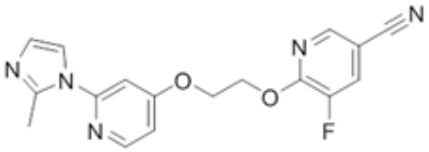


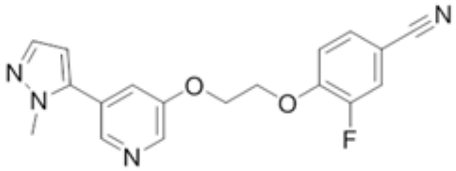


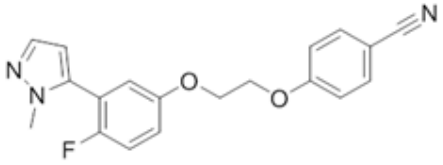


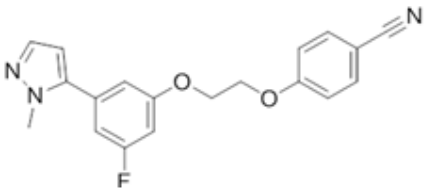


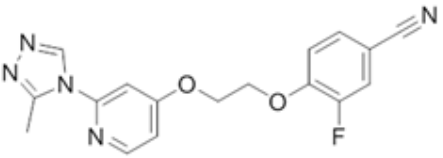


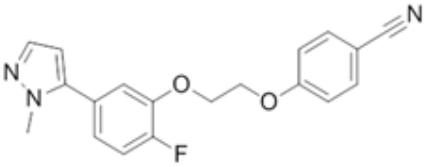


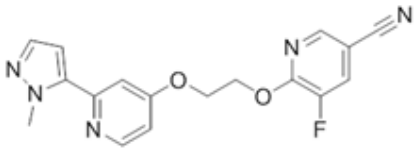


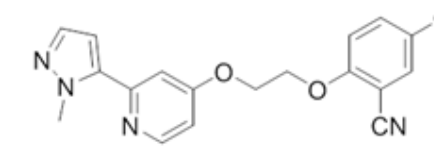


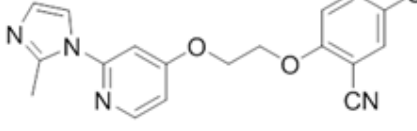


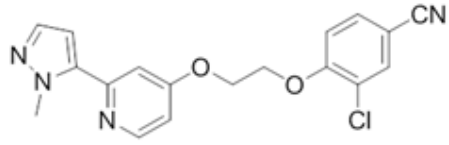


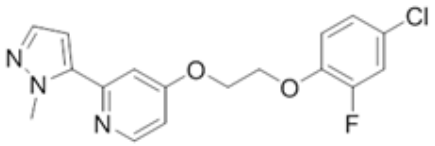


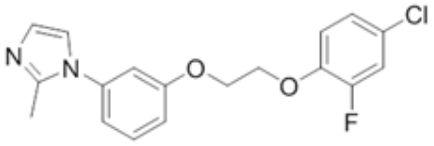


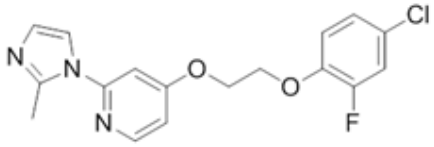


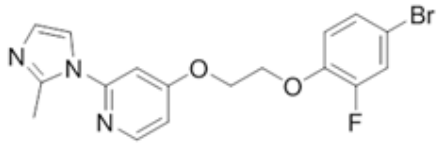


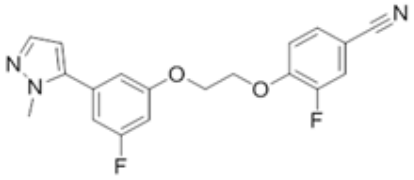


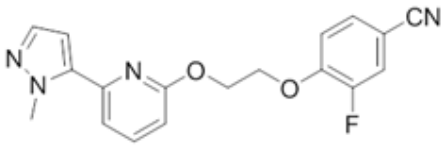


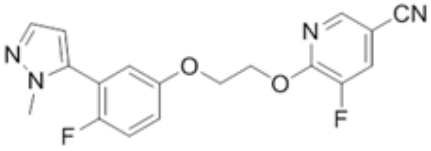


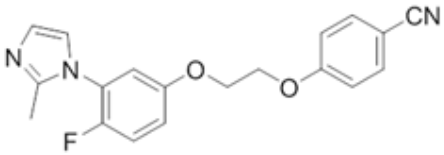


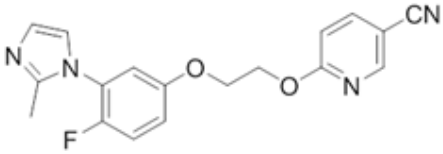


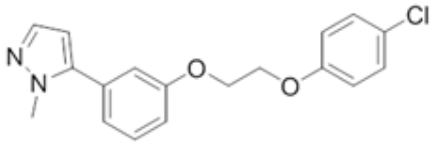


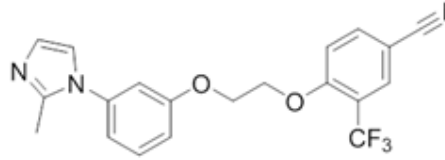


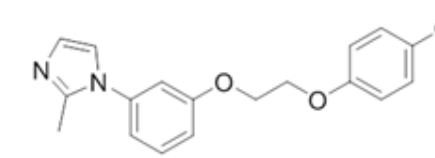






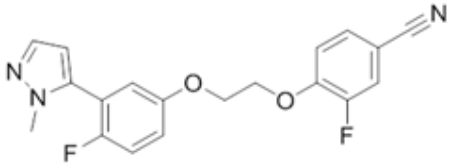


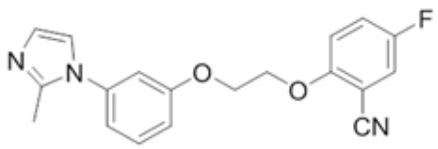


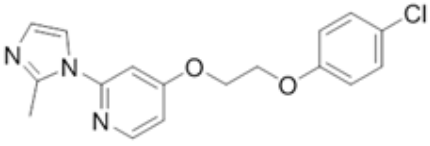


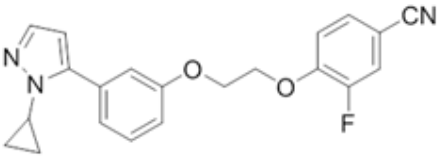


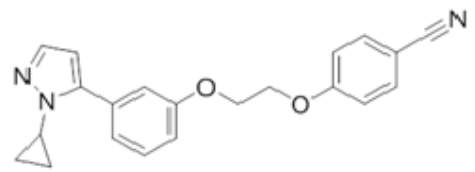
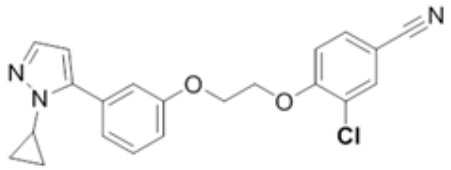
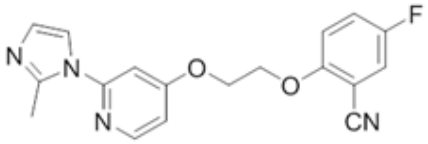
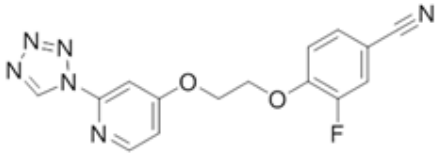
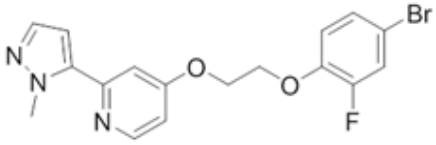










15. A pharmaceutical composition comprising a compound of any one of claims 1 to 14, or a pharmaceutically acceptable form or prodrug thereof, and a pharmaceutically acceptable excipient.

16. A compound according to any one of claims 1 to 14, or a pharmaceutically form or prodrug thereof, or a composition according to claim 15, for use in therapy.

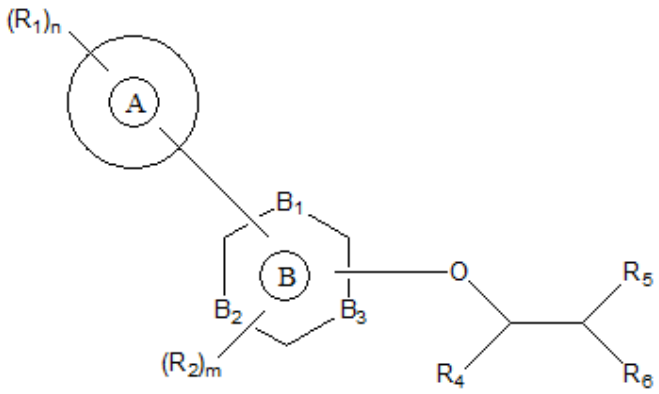
17. Use of a compound of any one of claim 1 to 14, or a pharmaceutical composition according to claim 15, in the manufacture of a medicament for inhibiting methylation of isoprenylated cysteine or isoprenylcysteine caused by isoprenylcysteine carboxyl methyltransferase (ICMT).

18. The use according to claim 17, wherein the disorder is selected from the group consisting of an ICMT-related disorder, cancer, premature ageing, Hutchinson-Gilford progeria syndrome (HGPS), cancer linked to mutant Ras overactivity, hepatocellular carcinoma cancer, breast cancer, ovarian cancer, colorectal carcinoma, lung cancer, pancreatic cancer and leukemia.

19. The compound of any one of claims 1 to 14, having an ICMT $IC_{50}$ of less than about 5 μM, preferably ICMT $IC_{50}$ of about 0.001 μM to about 5 μM.

20. A process for synthesizing a compound according to any one of claims 1 to 14, comprising:

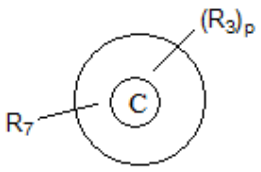
(a) reacting a compound of formula (III):




(III)

wherein $R_1$, $R_2$, $R_4$, $R_5$, $B_1$, $B_2$, $B_3$, n and m are as defined in claim 1, and $R_6$ is a leaving group,

in an organic solvent in the presence of a base with a compound of formula (IV):

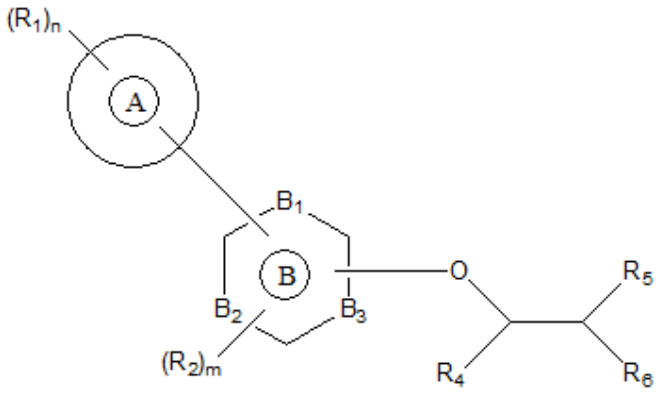



(IV)

wherein $R_3$ and p are as defined in claim 1, and $R_7$ is -OH;

or

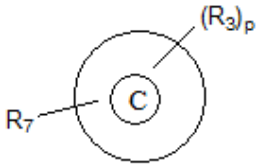
(b) reacting a compound of formula (III):




(III)

wherein $R_1$, $R_2$, $R_4$, $R_5$, $B_1$, $B_2$, $B_3$, n and m are as defined in claim 1, and $R_6$ is OH or an alkoxide,

in an organic solvent in the presence of a base with a compound of formula (IV):




(IV)

wherein $R_3$ and p are as defined in claim 1, and $R_7$ is halogen.