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;

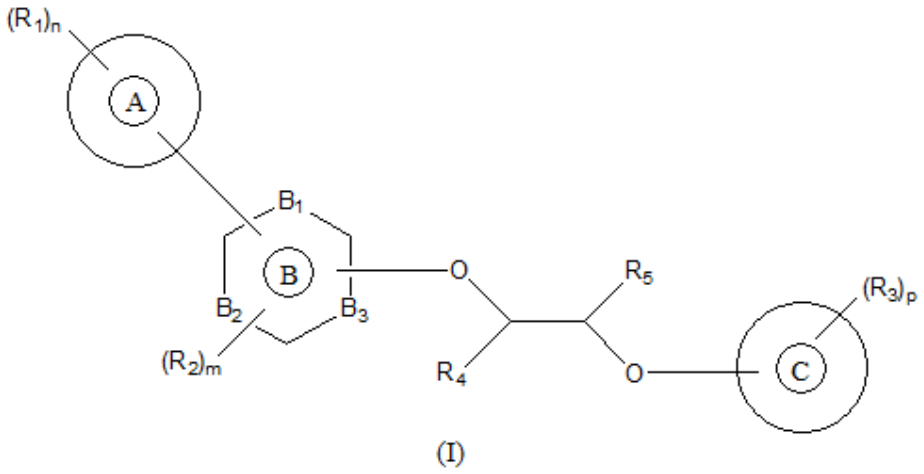
R_4 and R_5 are independently selected from H or aliphatic;

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)

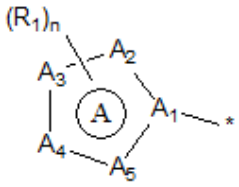
and/or tautomers, enantiomers, solvates, hydrates, prodrugs and pharmaceutically acceptable salts thereof;

wherein:

 represents an aromatic ring system;

Ring A is selected from the group consisting of formulas (ab), (a1) to (a8), and (a1') to (a10''):

- formula (ab):



(ab)

wherein:

* represents the point of attachment to Ring B;

A_1 is N or C;

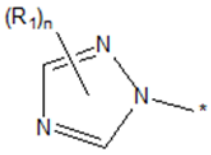
A_2 is N, S, or CH;

A_3 is CH or N;

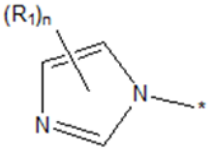
A_4 is N; and

A_5 is C, CH, O, or N;

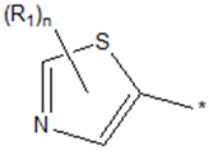
- formulas (a1) to (a8):



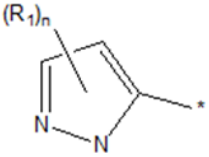
(a1)



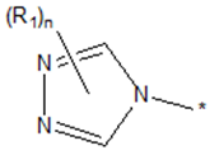
(a2)



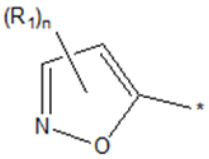
(a3)



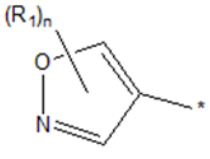
(a4)



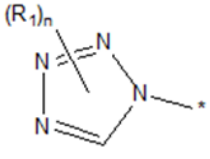
(a5)



(a6)



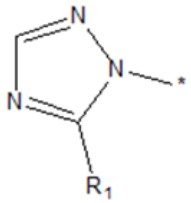
(a7)



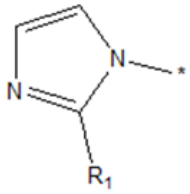
(a8)

wherein * represents the point of attachment to Ring B;

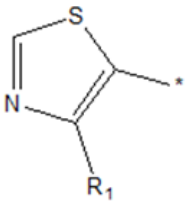
- formulas (a1') to (a8'):



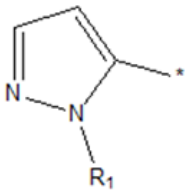
(a1')



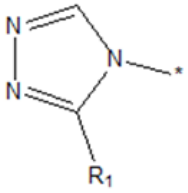
(a2')



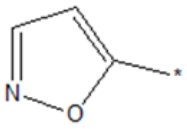
(a3')



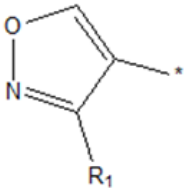
(a4')



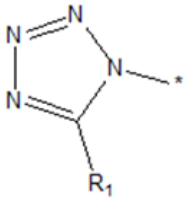
(a5')



(a6')



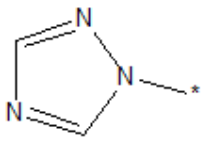
(a7')



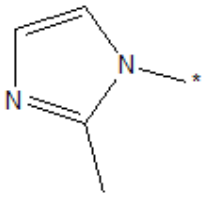
(a8')

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

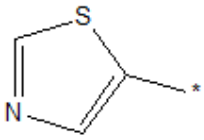
- formulas (a1'') to (a10''):



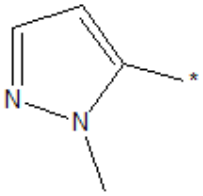
(a1'')



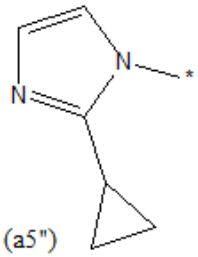
(a2'')



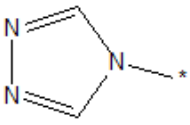
(a3'')



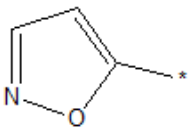
(a4'')



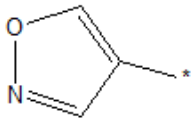
(a5'')



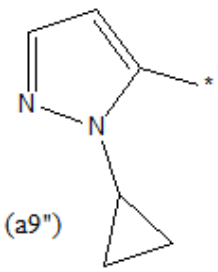
(a6'')



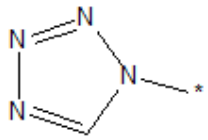
(a7'')



(a8'')



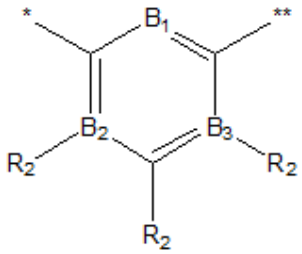
(a9")



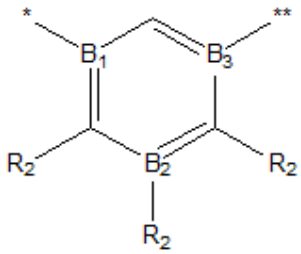
(a10")

wherein * represents the point of attachment to Ring B;

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



(bb1)



(bb2)

wherein:

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

* 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 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, alkyl, haloalkyl, CF_3, CHF_2, alkenyl, alkynyl, alkoxy, amino, acyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heteroaryl;

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

R_3 is absent or selected from H, OH, cyano, halogen, alkyl, haloalkyl, CF_3, CHF_2, alkenyl, alkynyl, alkoxy, amino, acyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or 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 treating an ICMT-related disorder, wherein the disorder is selected from the group consisting of 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.

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.

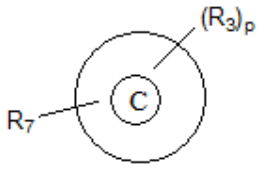
The present disclosure further provides a use of a compound as defined herein, or a pharmaceutically form or prodrug thereof, or a composition as defined herein, in the manufacture of a medicament for the treatment of a ICMT-related disorder.

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):

wherein R_1, R_2, R_4, R_5, B_1, B_2, B_3, n and m are as defined herein, and R_6 is OH orO$^-$,

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 herein, and R_7 is halogen.

Advantageously, the compounds of the present disclosure and pharmaceutical compositions comprising them may inhibit ICMT effectively at low concentrations. Said compounds and pharmaceutical compositions comprising them may be useful for the prophylaxis and/or treatment of diseases linked to ICMT. Advantageously, the compounds or pharmaceutical compositions comprising them may offer a treatment to cancer, premature ageing, or Hutchinson-Gilford progeria syndrome (HGPS), including without limitation a cancer linked to mutant Ras overactivity such as hepatocellular carcinoma cancer, breast cancer, ovarian cancer, colorectal carcinoma, lung cancer, pancreatic cancer or leukaemia, and other diseases linked to high ICMT expression.

Advantageously, compared to known compounds of the prior art, the compounds of the present disclosure may show high effectiveness in ICMT inhibition combined with a desirable excellent anti-proliferative and anti-ageing activity. The compounds of the present disclosure can further be processed well into formulation for further drug testing.

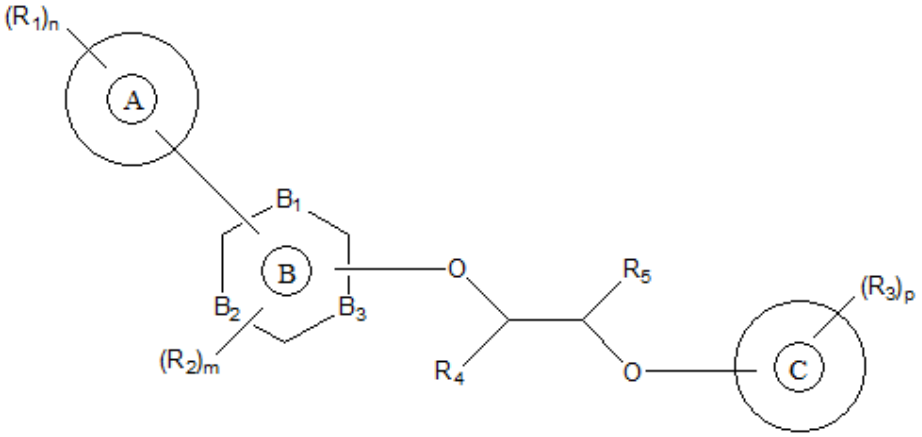
Definitions

The following words and terms used herein shall have the meaning indicated:

"Acyl" means an R-C(=O)- group in which the R group may be an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl group as defined herein. Examples of acyl include acetyl, benzoyl and amino acid derived aminoacyl. The group may be a terminal group or a bridging group. If the group is a

CLAIMS

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



(I)

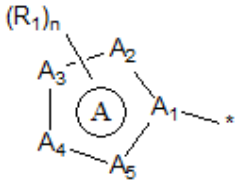
and/or tautomers, enantiomers, solvates, hydrates, prodrugs and pharmaceutically acceptable salts thereof;

wherein:

 represents an aromatic ring system;

Ring A is selected from the group consisting of formulas (ab), (a1) to (a8), and (a1') to (a10''):

- formula (ab):



(ab)

wherein:

* represents the point of attachment to Ring B;

A_1 is N or C;

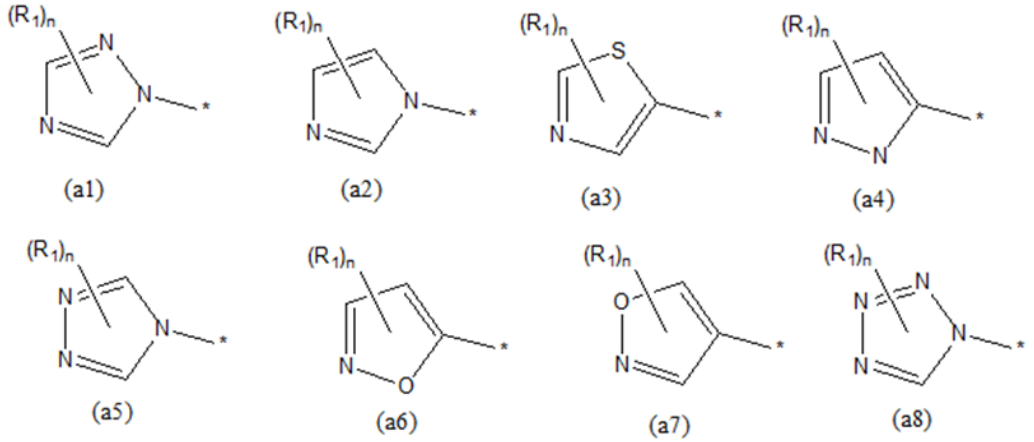
A_2 is N, S, or CH;

A_3 is CH or N;

A_4 is N; and

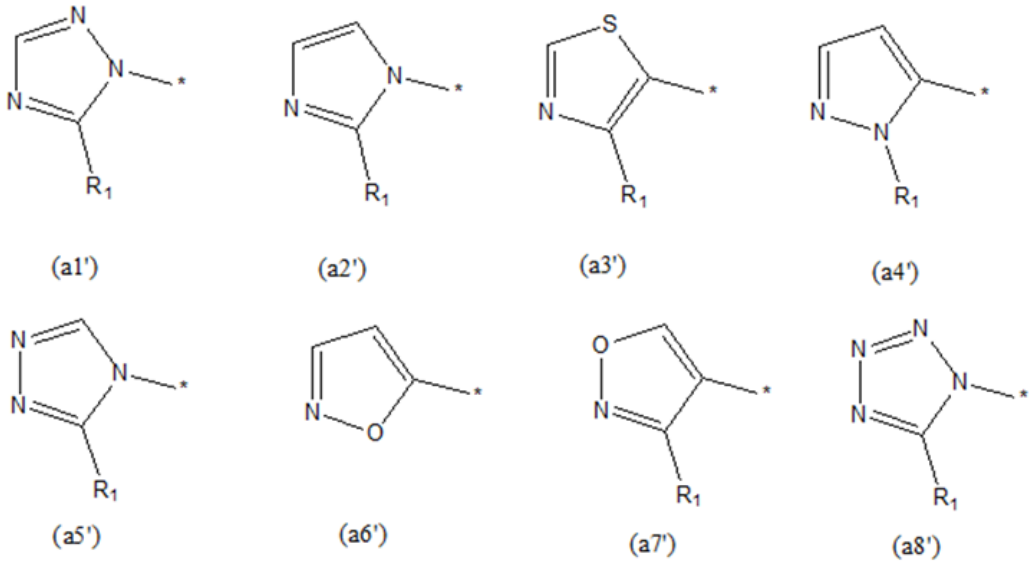
A_5 is C, CH, O, or N;

- formulas (a1) to (a8):



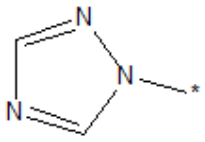
wherein * represents the point of attachment to Ring B;

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

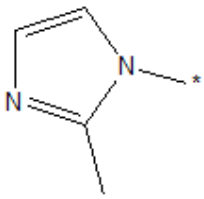


wherein * represents the point of attachment to Ring B; and

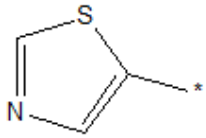
- formulas (a1'') to (a10''):



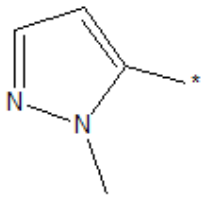
(a1'')



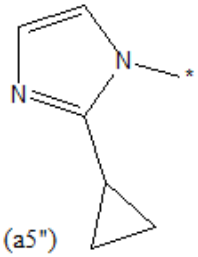
(a2'')



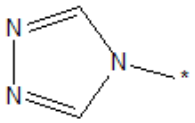
(a3'')



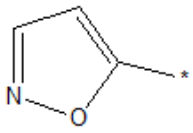
(a4'')



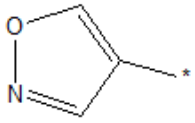
(a5'')



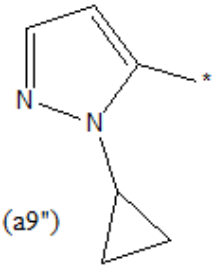
(a6'')



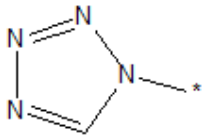
(a7'')



(a8'')



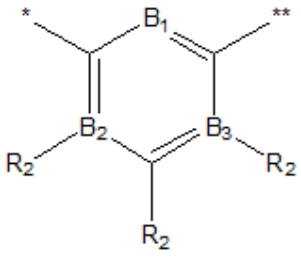
(a9'')



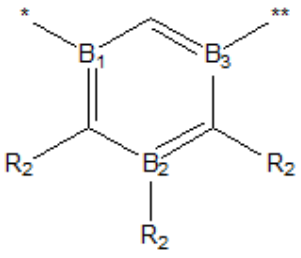
(a10'')

wherein * represents the point of attachment to Ring B;

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



(bb1)



(bb2)

wherein:

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

* 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 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, alkyl, haloalkyl, CF_3, CHF_2, alkenyl, alkynyl, alkoxy, amino, acyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heteroaryl;

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

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

R_4 and R_5 are independently selected from H or aliphatic;

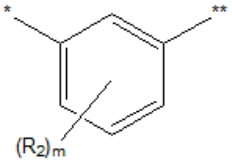
n is an integer selected from 0 to 5, wherein when n is more than 1, each R_1 substituted on Ring A may be the same or different;

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

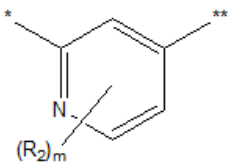
p is an integer selected from 0 to 5, wherein when p is more than 1, each R_3 substituted on Ring C may be the same or different.

2. The compound of claim 1, wherein R_1 is alkyl or cycloalkyl, preferably methyl or cyclopropyl.

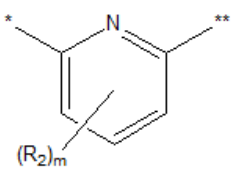
3. The compound of claim 1 or 2, wherein Ring B is selected from the group consisting of formulas (b1) to (b5):



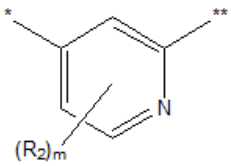
(b1)



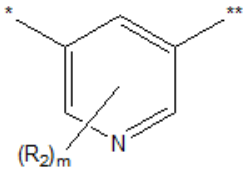
(b2)



(b3)



(b4)



(b5)

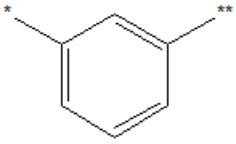
wherein:

* represents the point of attachment to Ring A;

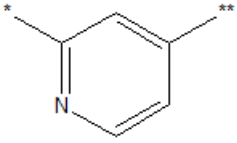
** represents the point of attachment to the –O(CHR4)- moiety of formula (I); and

R2 and m are as defined in claim 1.

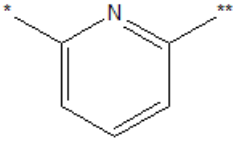
4. The compound of any one of claims 1 to 3, wherein Ring B is selected from the group consisting of formulas (b1') to (b9'):



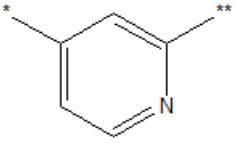
(b1')



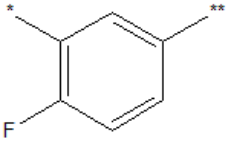
(b2')



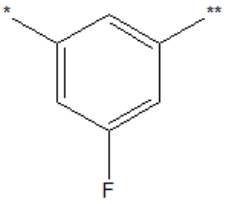
(b3')



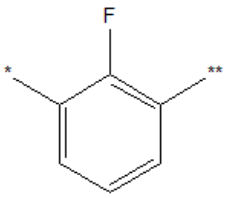
(b4')



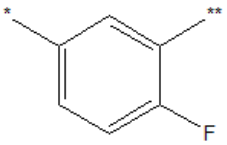
(b5')



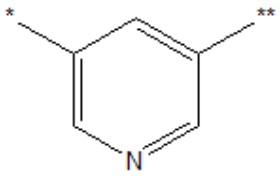
(b6')



(b7')



(b8')



(b9')

wherein:

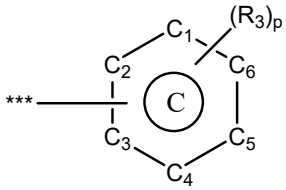
* represents the point of attachment to Ring A; and

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

5. The compound of any one of claims 1 to 4, wherein R_2 is H or F.

6. The compound of any one of claims 1 to 5, 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:

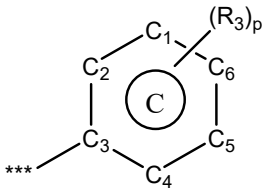
◯ represents an aromatic ring system;

*** represents the point of attachment to the –O(CHR5)- 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);

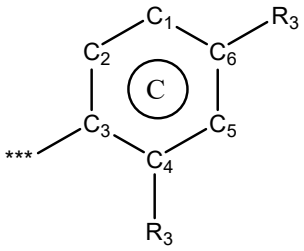
C$_1$ and C$_2$ are independently C, CH or N;

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);

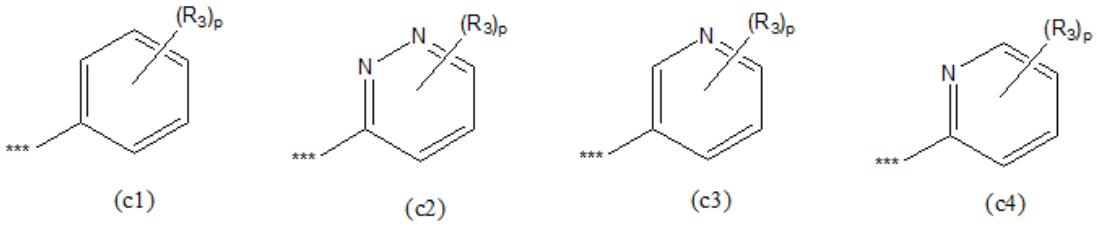
C$_1$ and C$_2$ are independently CH or N;

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):



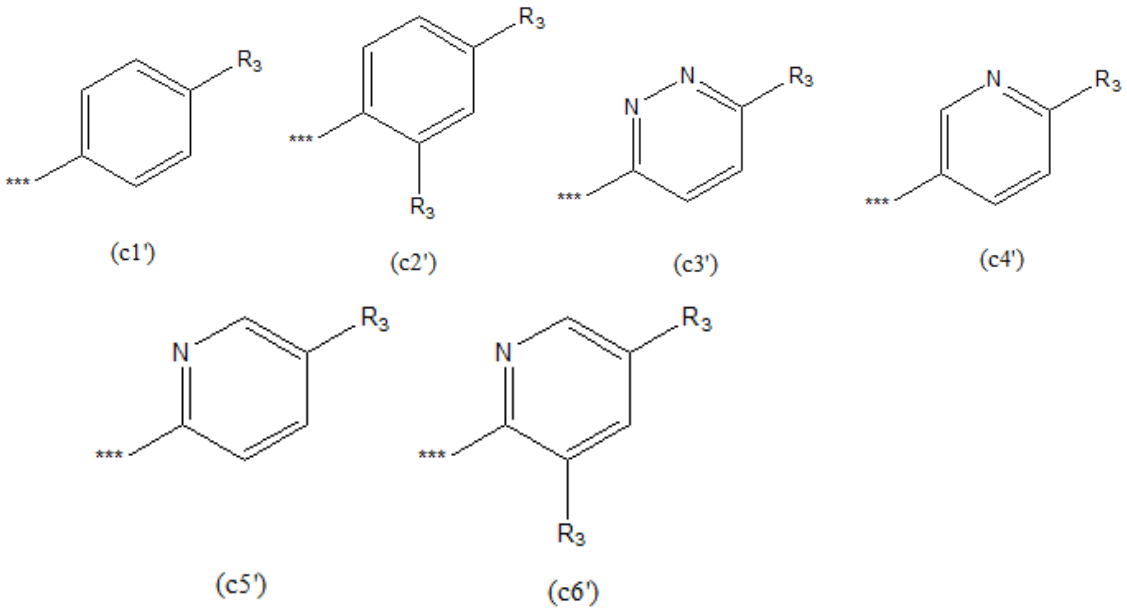
(c1) (c2) (c3) (c4)

wherein:

*** represents the point of attachment to the –O(CHR5)- moiety of formula (I); and

R3 and p are as defined in claim 1, and

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



(c1') (c2') (c3') (c4')

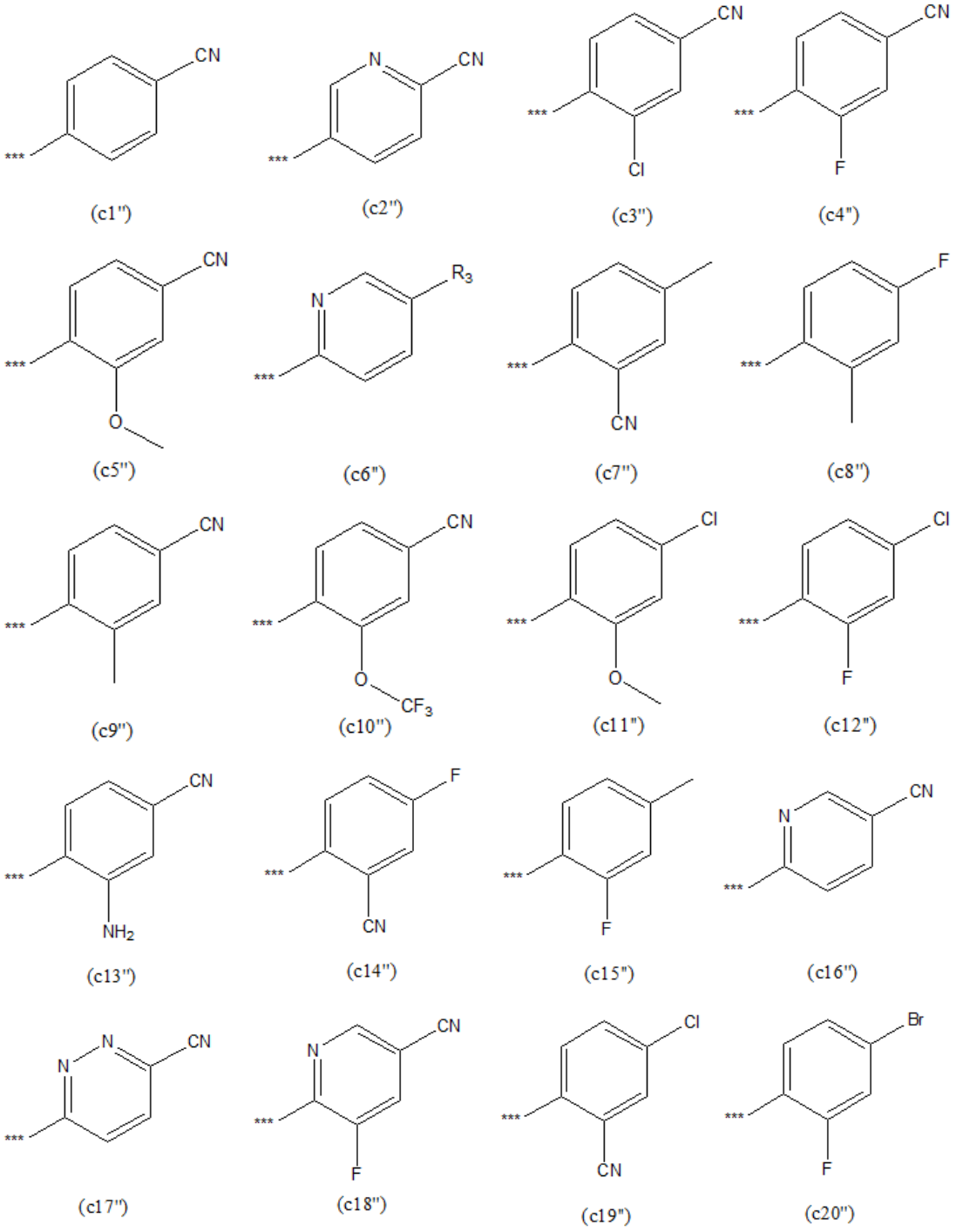
(c5') (c6')

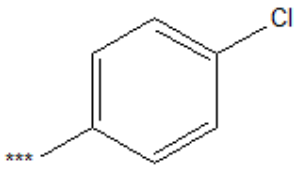
wherein:

*** represents the point of attachment to the –O(CHR5)- moiety of formula (I); and

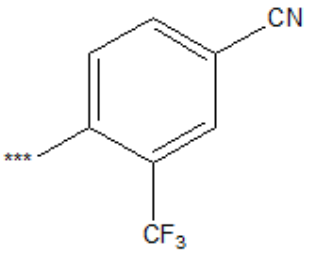
R3 is as defined in claim 1.

7. The compound of any one of claims 1 to 6, wherein Ring C is selected from the group consisting of (c1'') to (c22''):





(c21")



(c22")

wherein:

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

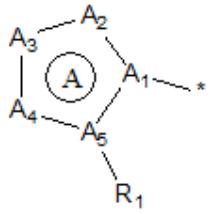
8. The compound of any one of claims 1 to 7, wherein R$_3$ is halogen, -CN, alkoxy, amino, haloalkyl, haloalkyloxy, or alkyl.

9. The compound of any one of claims 1 to 8, wherein R$_3$ is fluoro, chloro, bromo, -CN, methoxy, methyl, -NH$_2$, -OCF$_3$, CF$_3$, or CHF$_2$.

10. The compound of any one of claims 1 to 9, 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.

11. The compound of any one of claims 1 to 10, 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.

12. The compound of any one of claims 1 to 11, wherein Ring A is of formula (ac):



(ac)

wherein:

* represents the point of attachment to Ring B;

A$_1$ is N or C;

A_2 is N, S, or CH;

A_3 is CH or N;

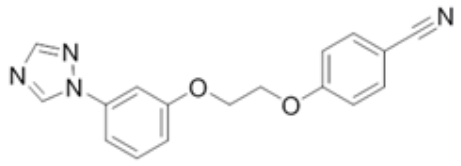
A_4 is N;

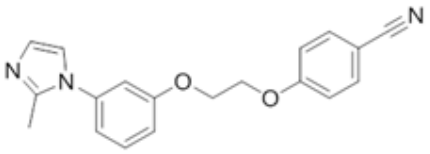
A_5 is C or N; and

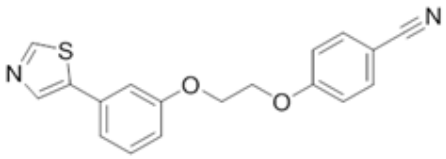
R_1 is alkyl or cycloalkyl.

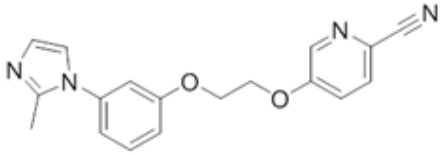
13. The compound of any one of claims 1 to 12, wherein R_3 is halogen or cyano.

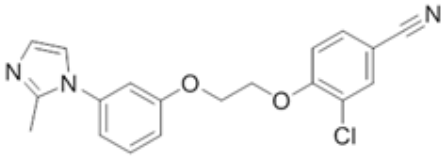
14. A compound of any one of claims 1 to 13, selected from the group consisting of:

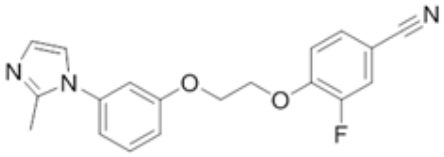


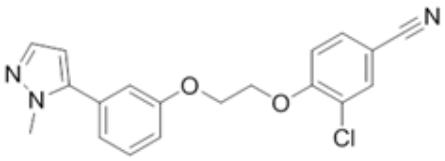


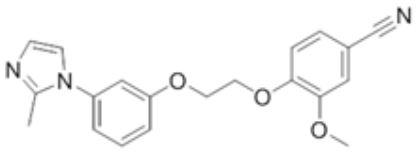


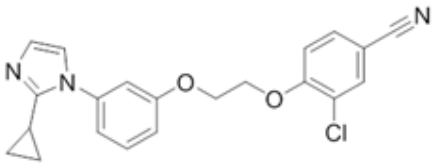


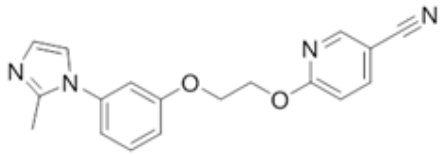


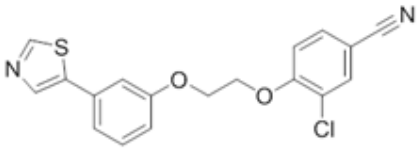


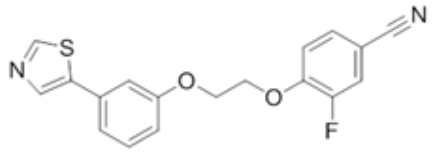


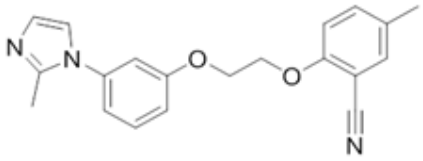


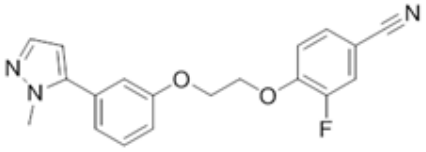


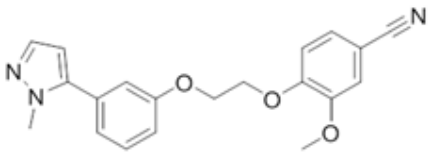


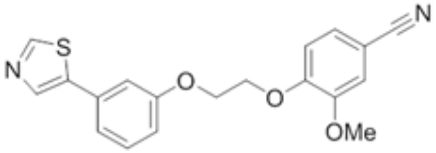


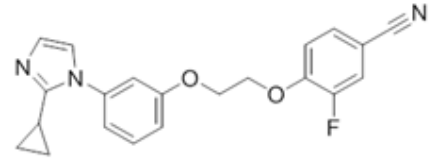


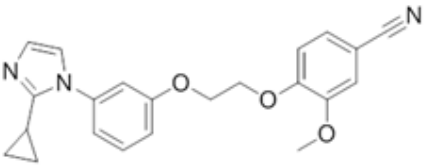


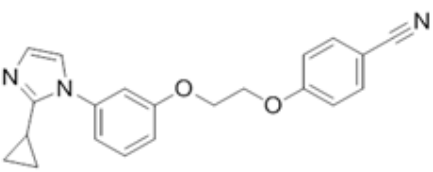


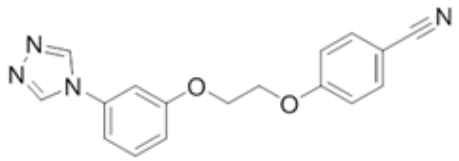


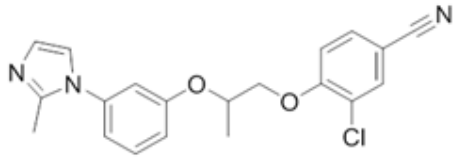


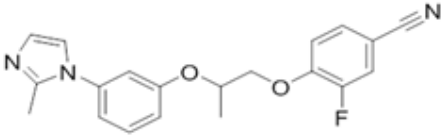


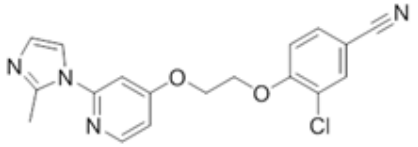


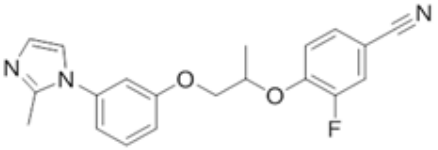


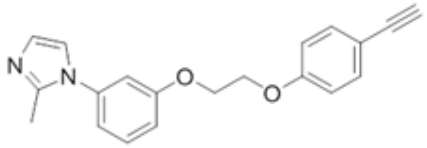


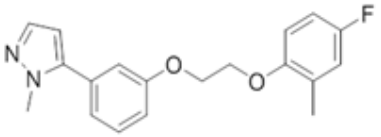


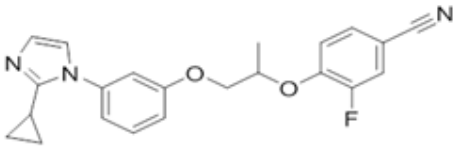


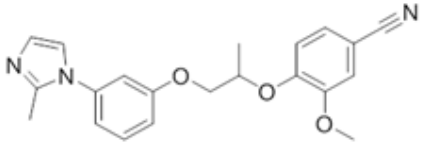


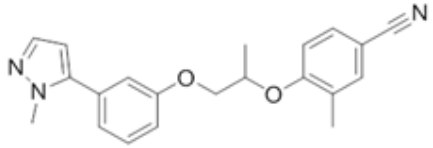


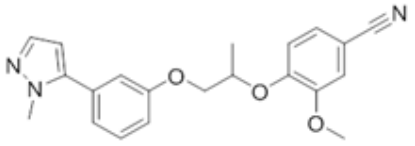


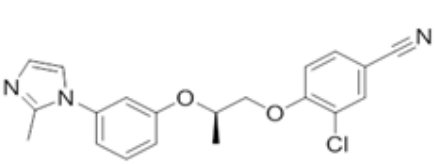


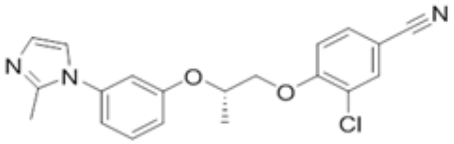


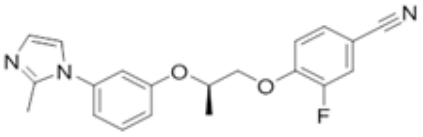


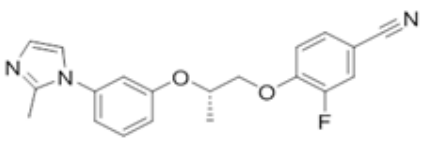


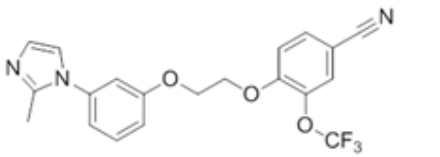


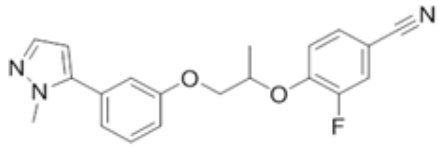


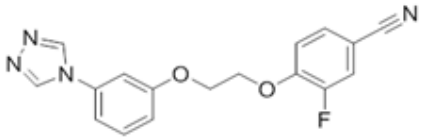


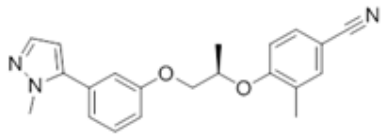


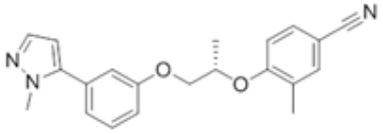


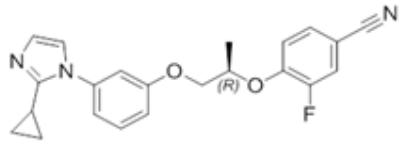


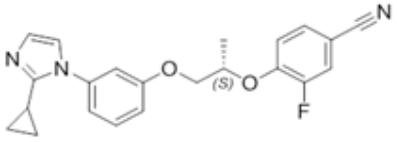


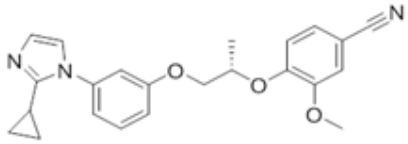


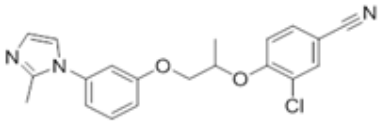


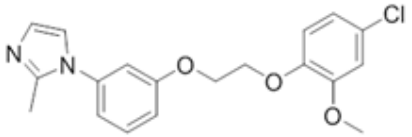


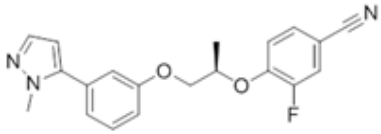


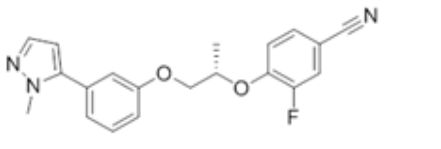


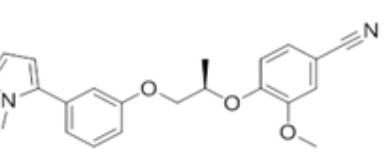


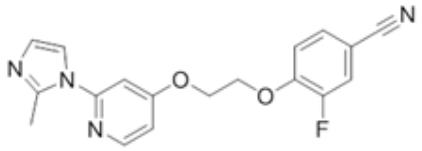


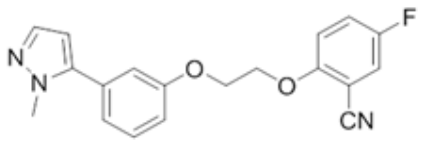


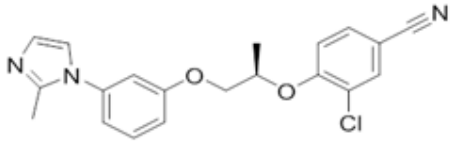


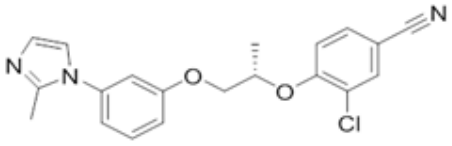


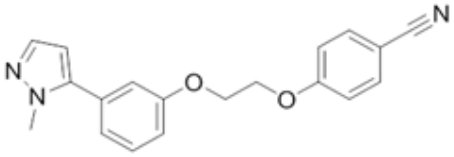


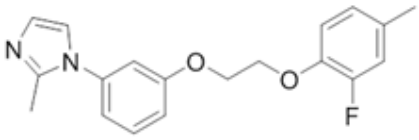


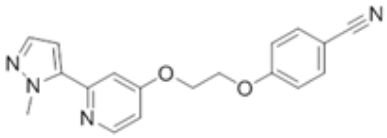


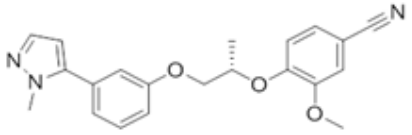


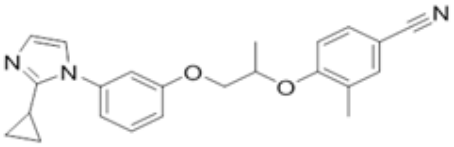


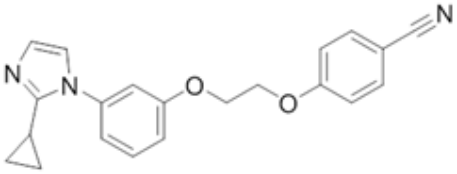


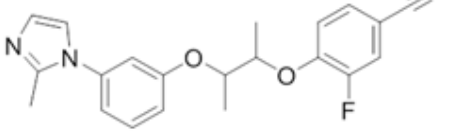


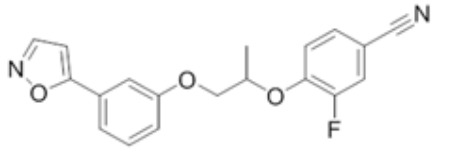


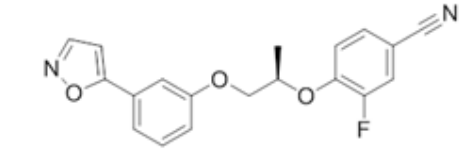


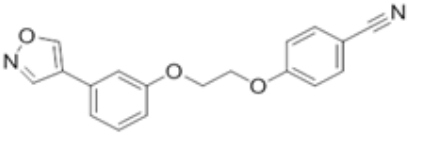


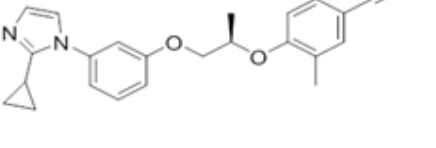


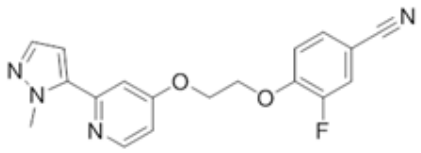


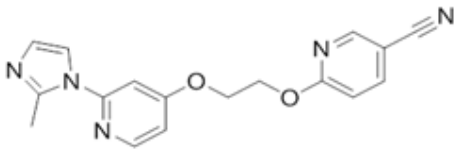


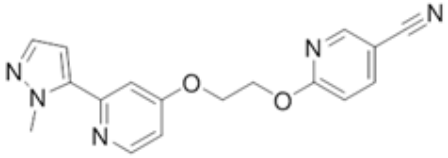


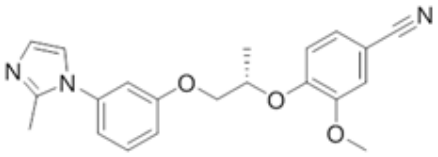


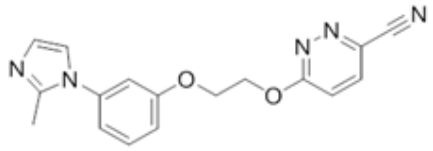


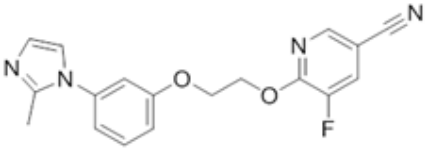


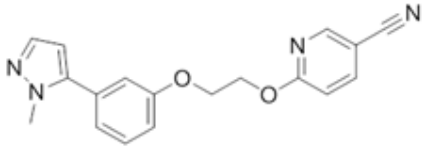


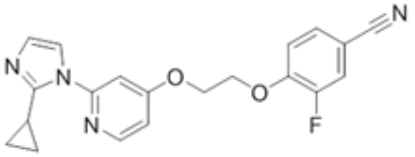


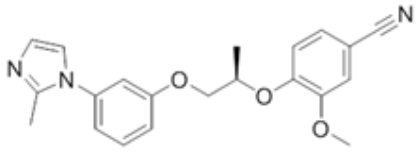


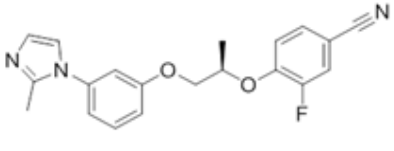


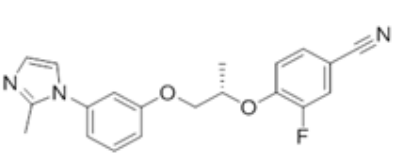


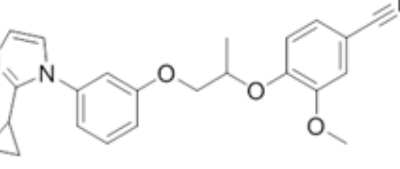


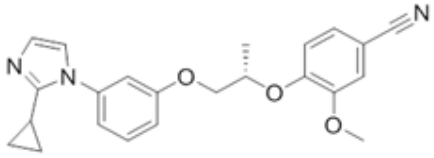


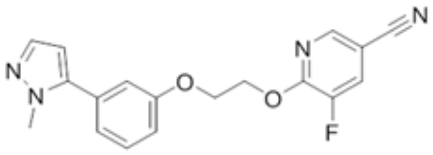


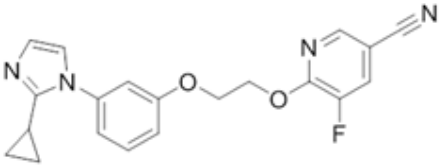


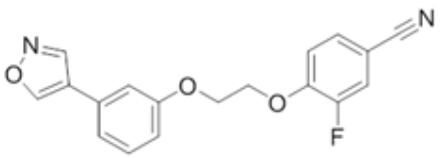


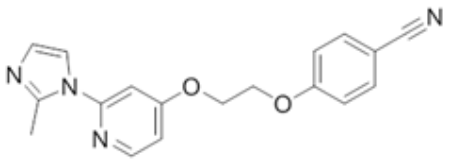


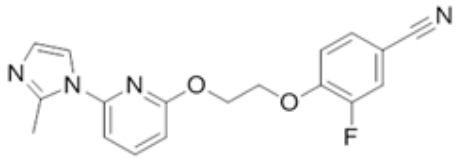


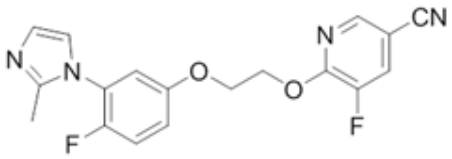


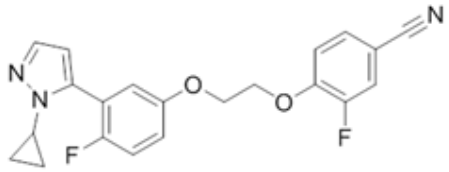


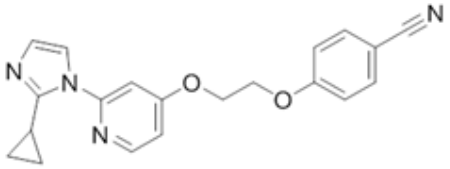


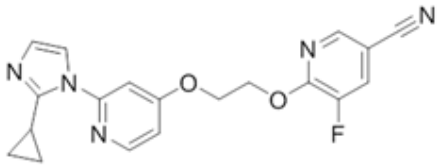


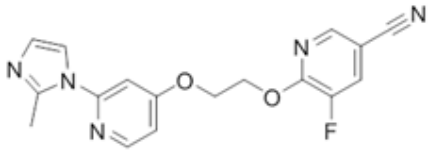


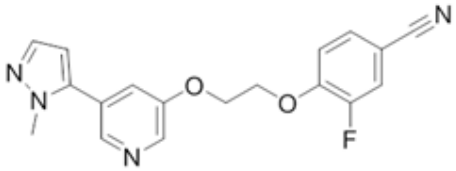


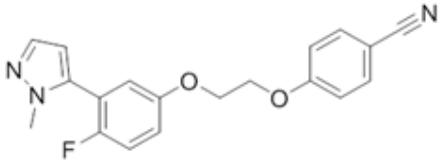


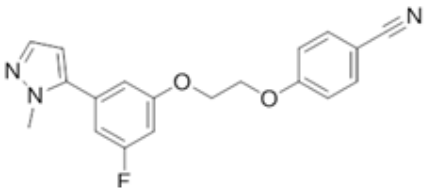


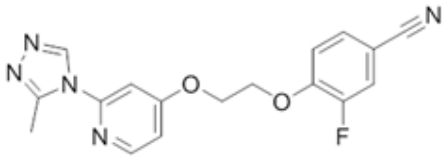


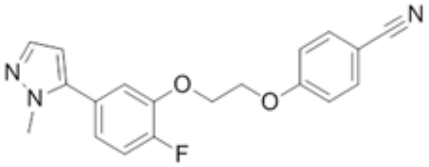


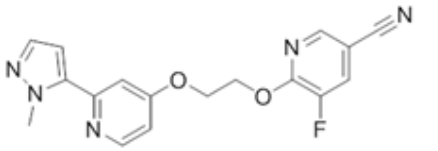


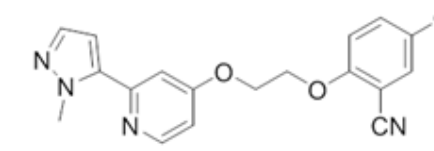


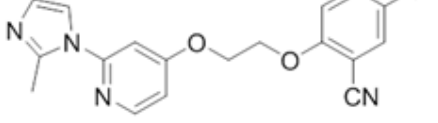


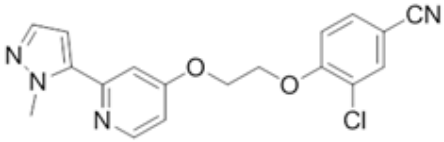


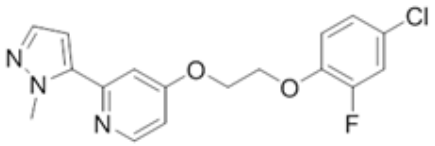


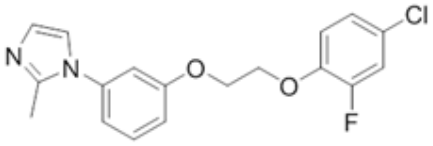


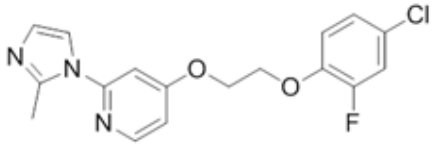


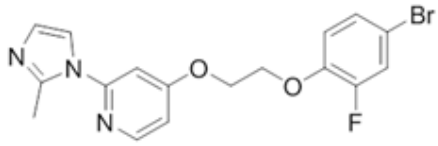


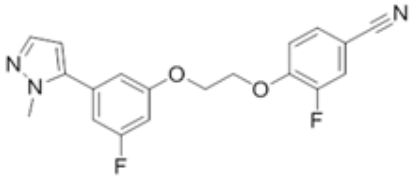


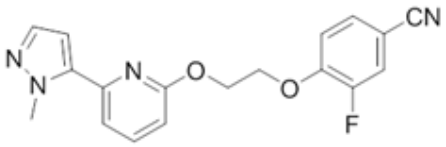


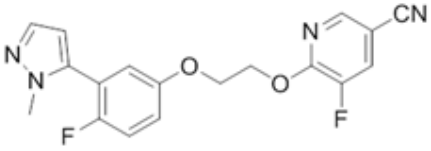


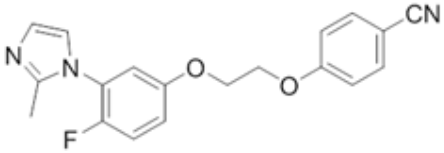


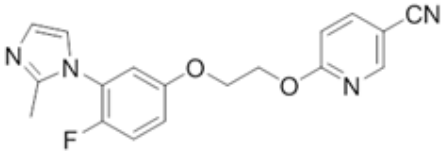


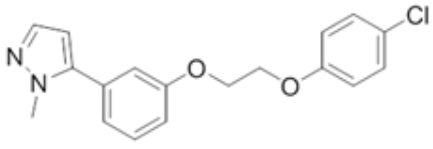


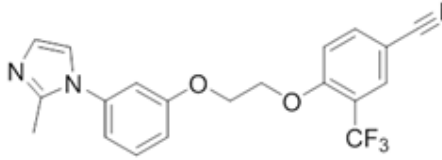


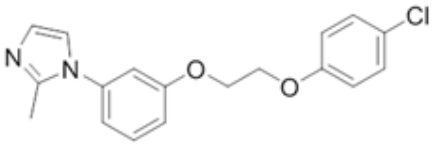


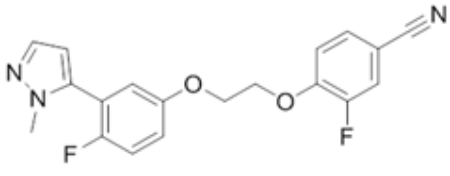


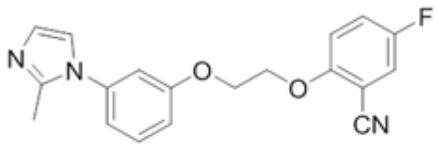


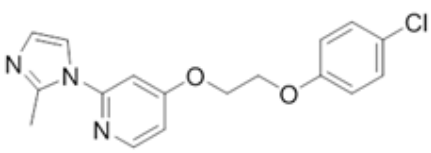


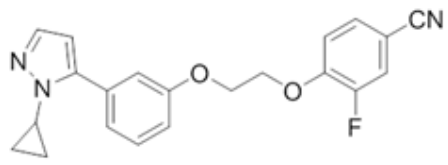


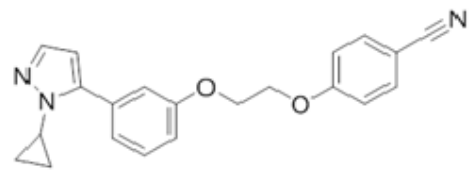
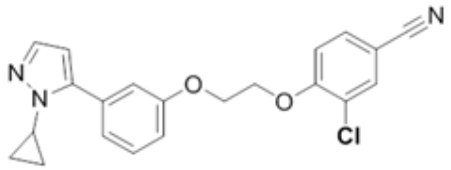
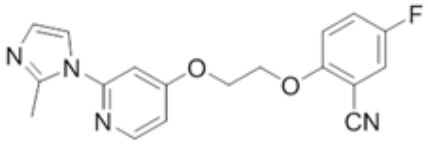
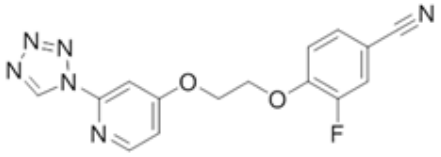
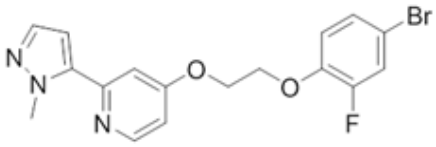










15. A pharmaceutical composition comprising a compound of any one of claims 1 to 14, or a pharmaceutically acceptable form or prodrug thereof, and a pharmaceutically acceptable excipient.

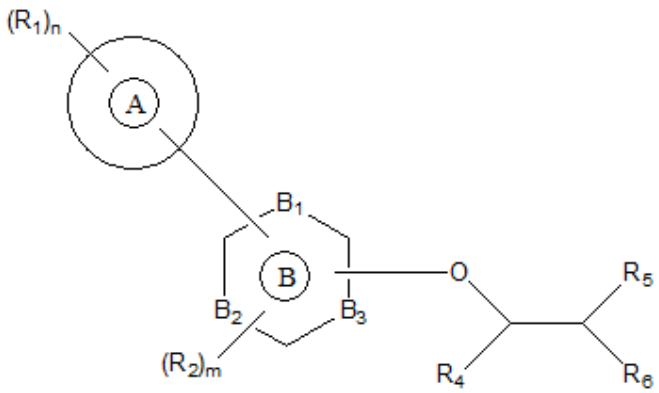
16. A compound according to any one of claims 1 to 14, or a pharmaceutically form or prodrug thereof, or a composition according to claim 15, for use in therapy.

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 treating an ICMT-related disorder, wherein the disorder is selected from the group consisting of 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.

18. 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 0.001 μM to 5 μM.

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

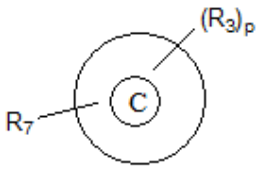
(a) reacting a compound of formula (III):



(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):

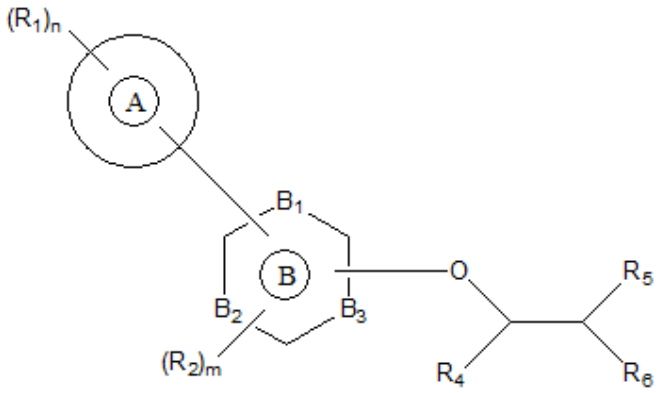


(IV)

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

or

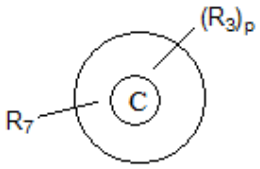
(b) reacting a compound of formula (III):



(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 O^-,

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.